Exhibit 9

US006175752B1

(12) **United States Patent**
Say et al.

(10) **Patent No.: US 6,175,752 B1**
(45) **Date of Patent: Jan. 16, 2001**

(54) **ANALYTE MONITORING DEVICE AND METHODS OF USE**

(75) Inventors: **James Say**, Alameda; **Michael F. Tomasco**, Cupertino, both of CA (US); **Adam Heller**, Austin, TX (US); **Yoram Gal**, Kibbutz Yagur (IL); **Behrad Aria**, Alameda, CA (US); **Ephraim Heller**, Oakland, CA (US); **Phillip John Plante**, Sunnyvale, CA (US); **Mark S. Vreeke**, Alameda, CA (US); **Keith A. Friedman**, Austin, TX (US); **Fredric C. Colman**, Berkeley, CA (US)

(73) Assignee: **Therasense, Inc.**, Alameda, CA (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/070,677**

(22) Filed: **Apr. 30, 1998**

(51) **Int. Cl.**[7] **A61B 5/05**

(52) **U.S. Cl.** **600/345**; 600/365; 128/903

(58) **Field of Search** 600/300–301, 600/346, 306–309, 345–365, 372, 385–390; 604/174–180; 128/897–898, 903, 904, 920

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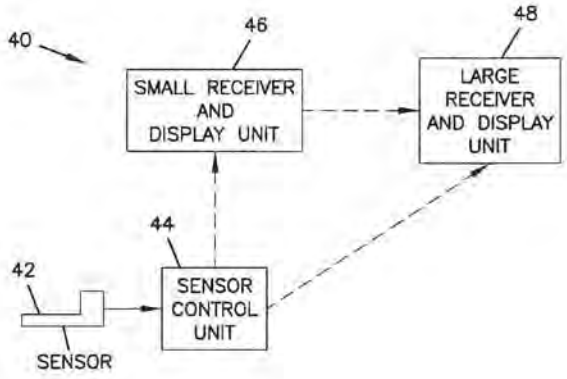
Primary Examiner—Cary O'Connor
Assistant Examiner—Michael Astorino
(74) *Attorney, Agent, or Firm*—Merchant & Gould P.C.

(57) **ABSTRACT**

An analyte monitor includes a sensor, a sensor control unit, and a display unit. The sensor has, for example, a substrate, a recessed channel formed in the substrate, and conductive material disposed in the recessed channel to form a working electrode. The sensor control unit typically has a housing adapted for placement on skin and is adapted to receive a portion of an electrochemical sensor. The sensor control unit also includes two or more conductive contacts disposed on the housing and configured for coupling to two or more contact pads on the sensor. A transmitter is disposed in the housing and coupled to the plurality of conductive contacts for transmitting data obtained using the sensor. The display unit has a receiver for receiving data transmitted by the transmitter of the sensor control unit and a display coupled to the receiver for displaying an indication of a level of an analyte. The analyte monitor may also be part of a drug delivery system to alter the level of the analyte based on the data obtained using the sensor.

94 Claims, 26 Drawing Sheets



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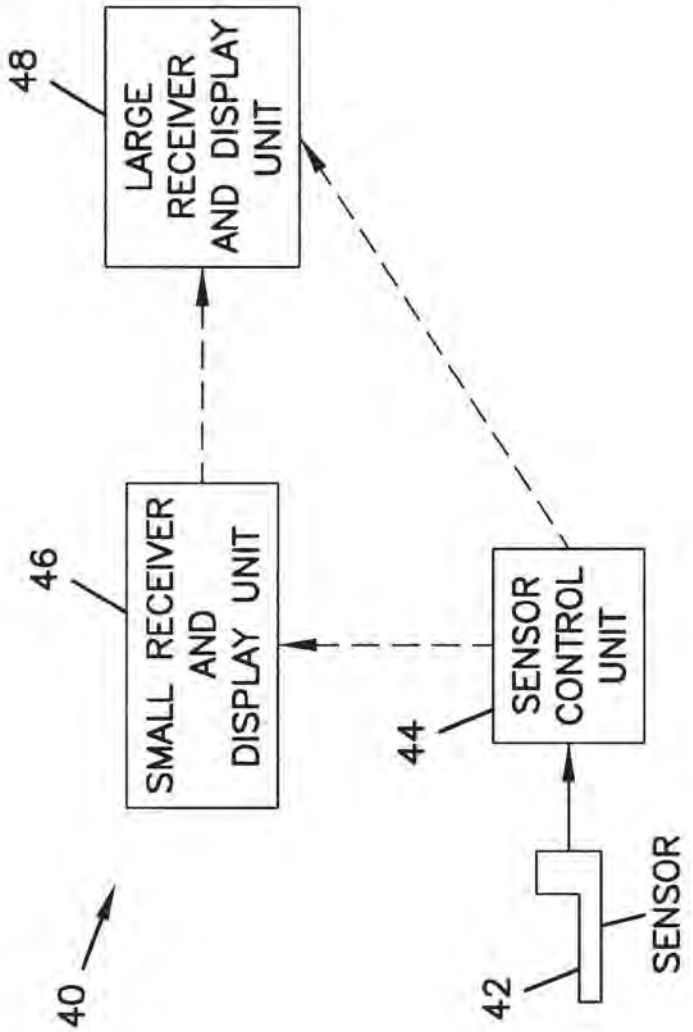


FIG. 1

FIG. 2

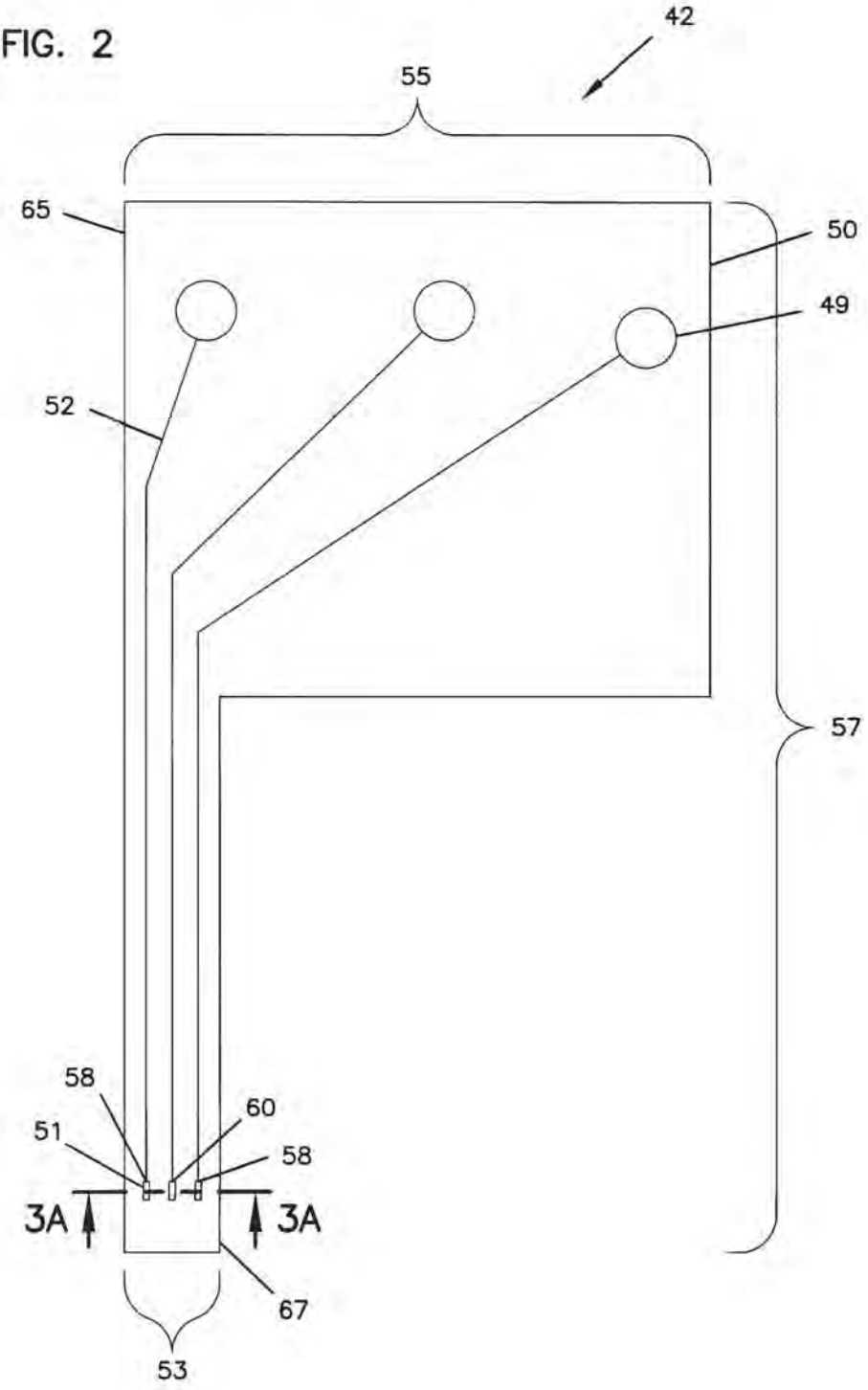


FIG. 3A

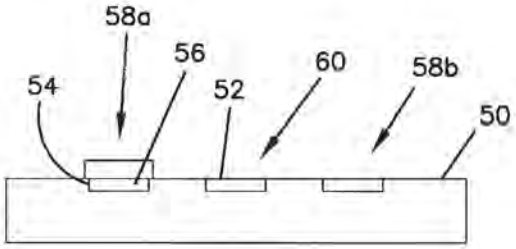


FIG. 3B

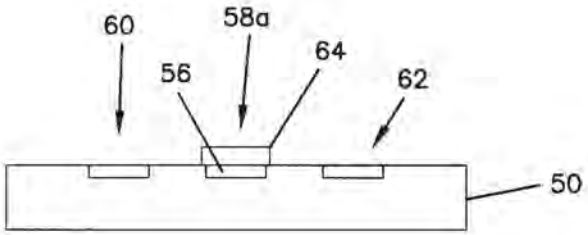


FIG. 9

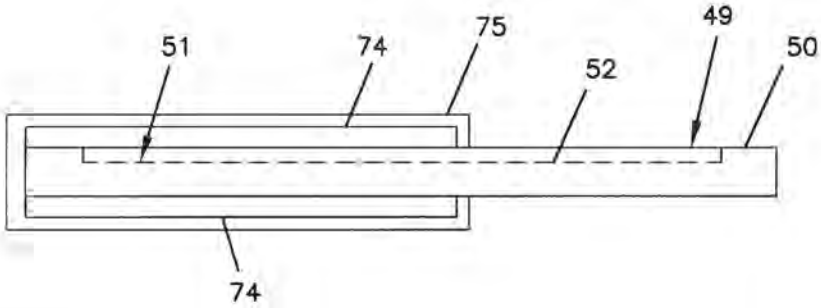


FIG. 4A

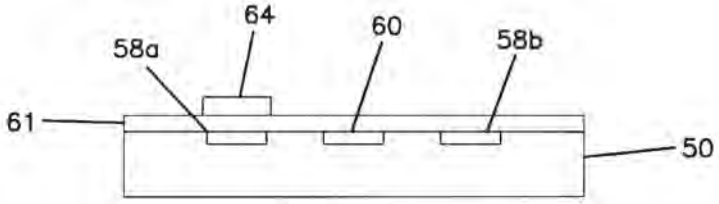


FIG. 4B

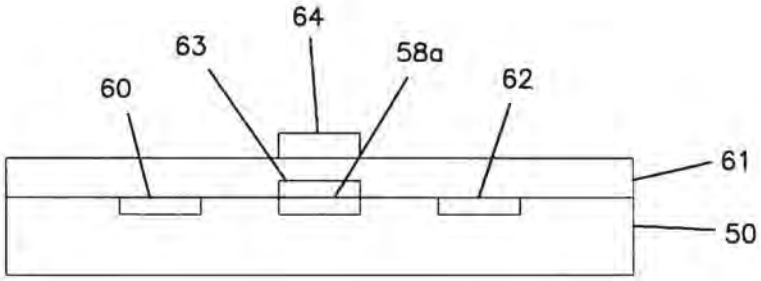


FIG. 5

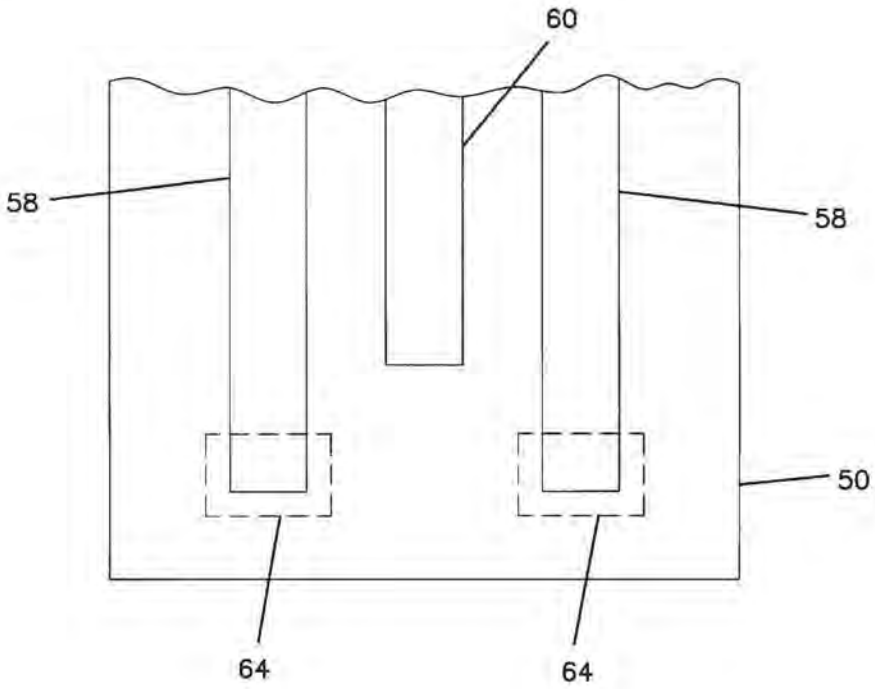


FIG. 6

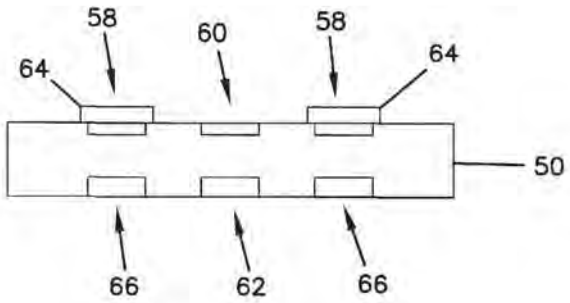


FIG. 7

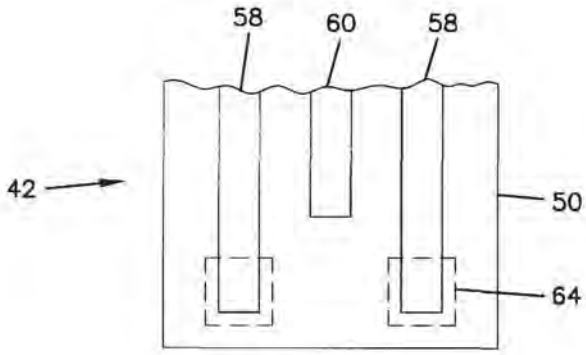


FIG. 8

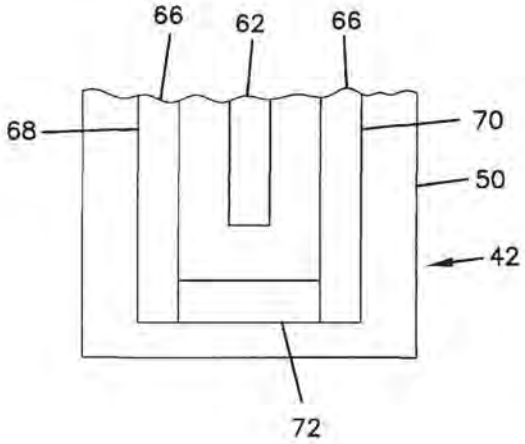


FIG. 10

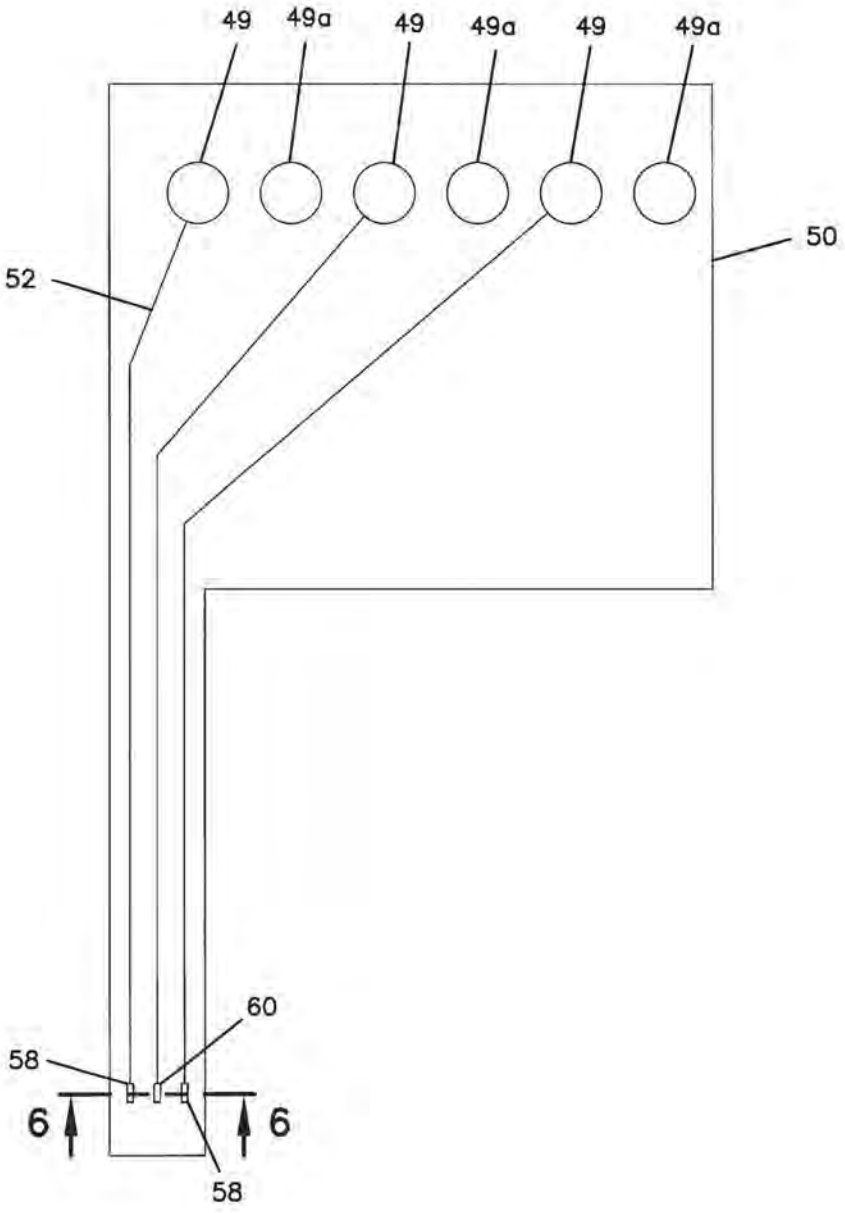


FIG. 11

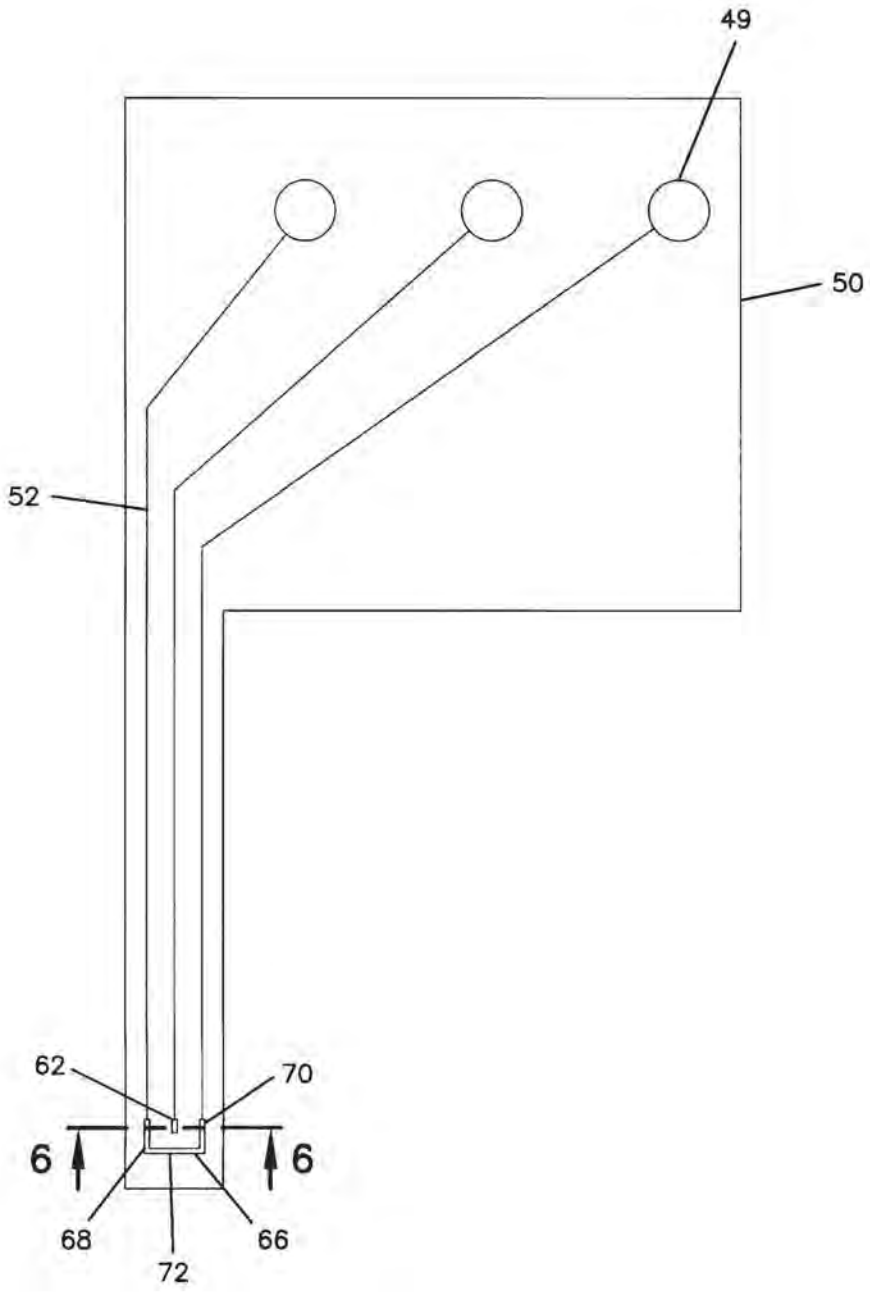


FIG. 12

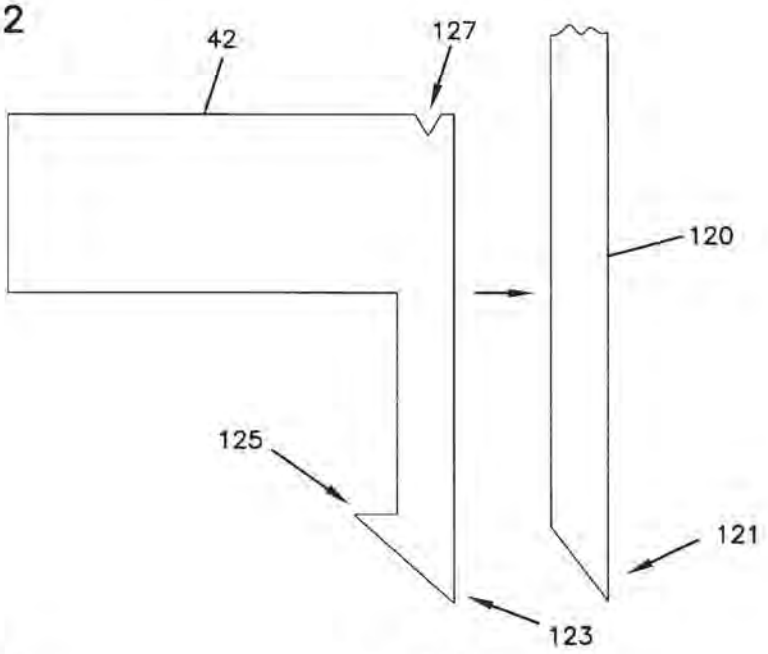


FIG. 13A

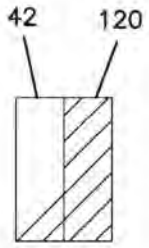


FIG. 13B

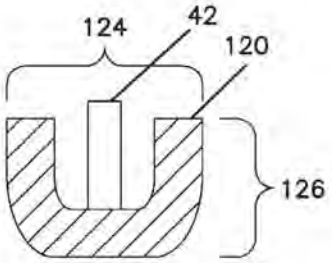


FIG. 13C

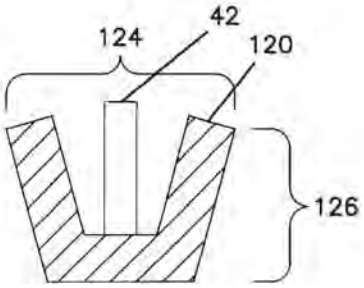


FIG. 15

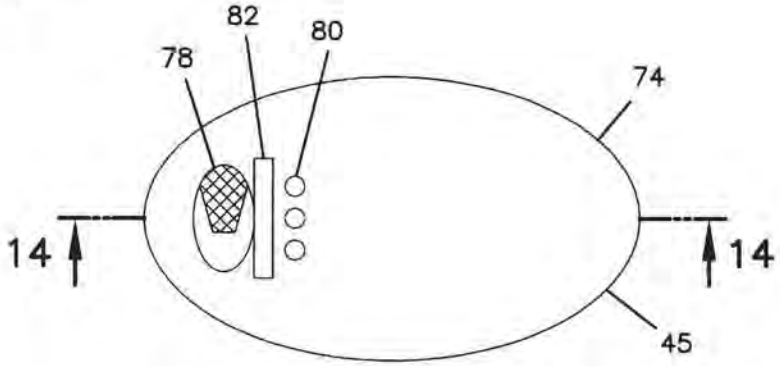


FIG. 16

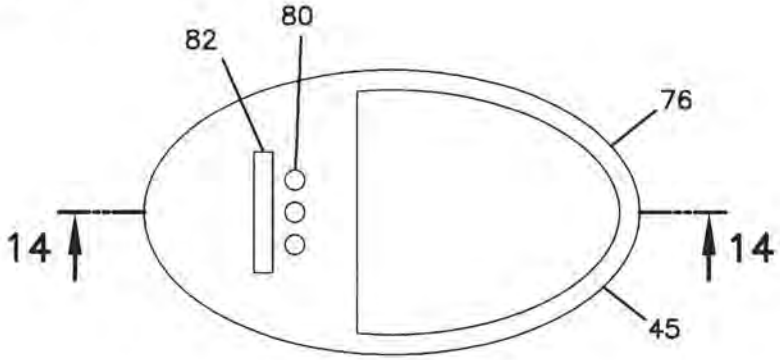


FIG. 14

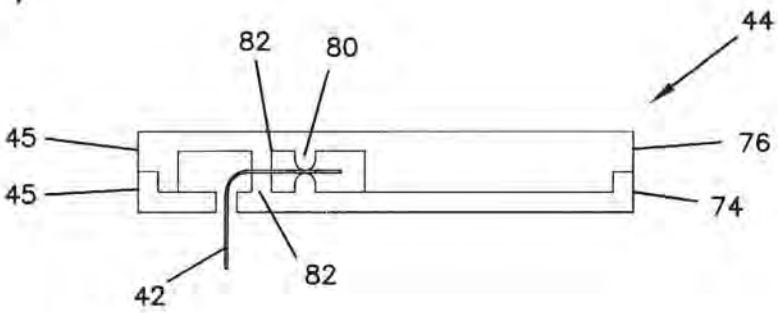


FIG. 17

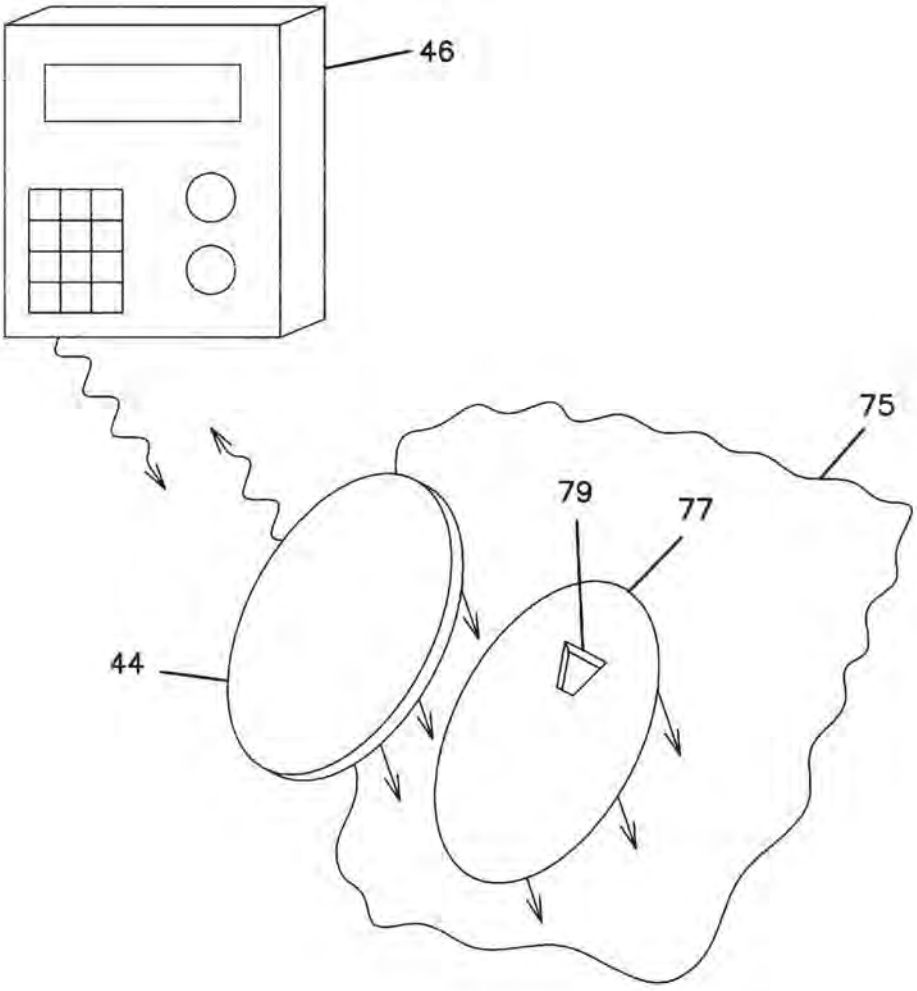


FIG. 18A

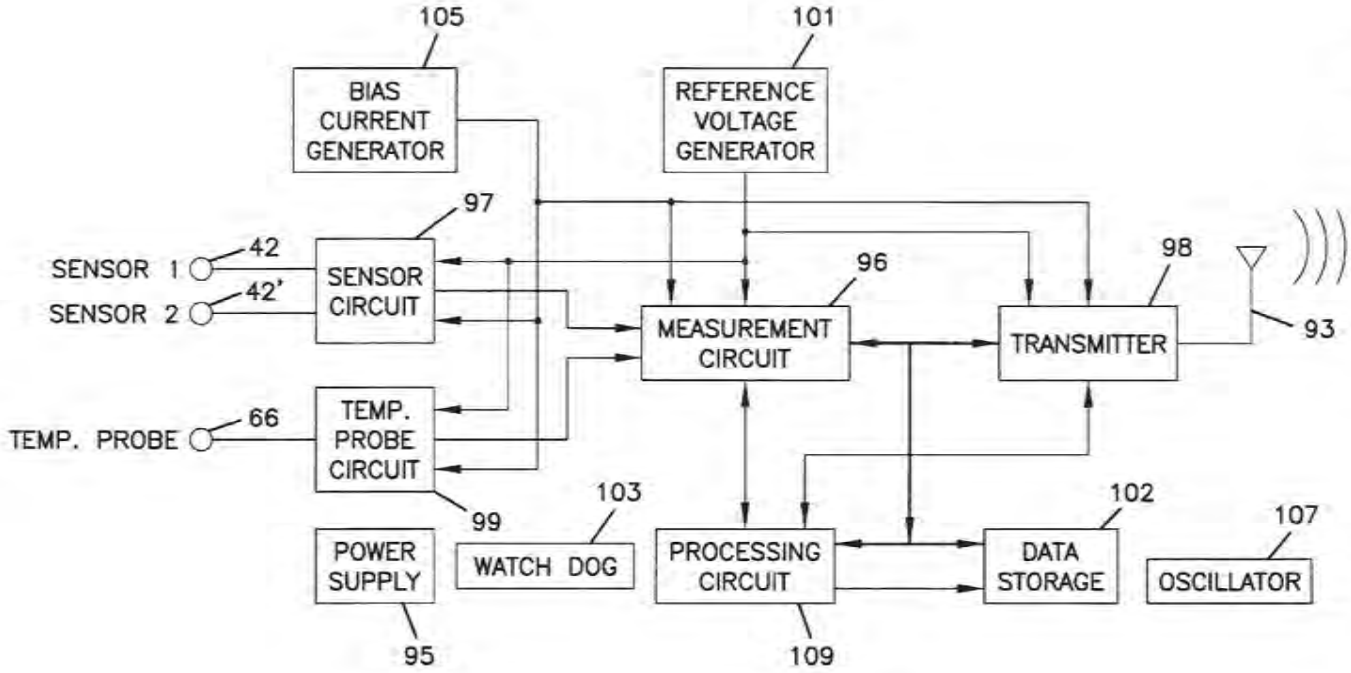


FIG. 18B

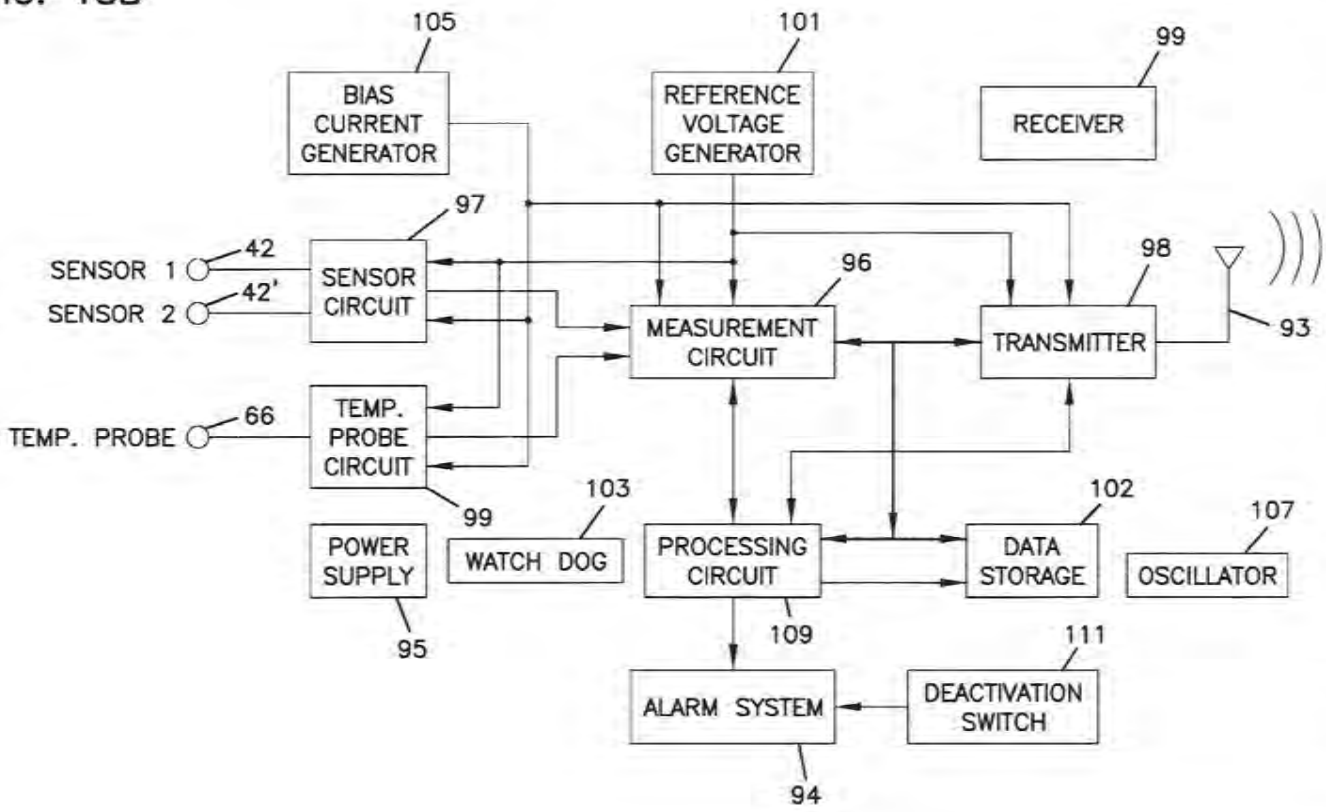


FIG. 19A

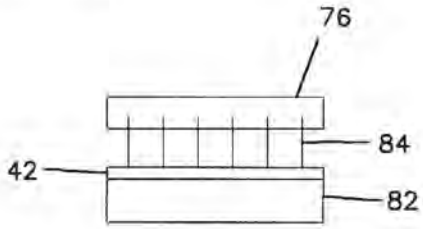


FIG. 19B

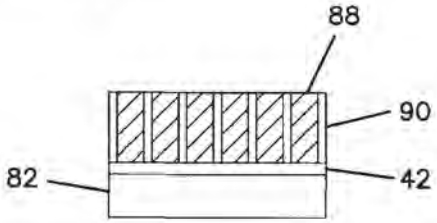


FIG. 19C

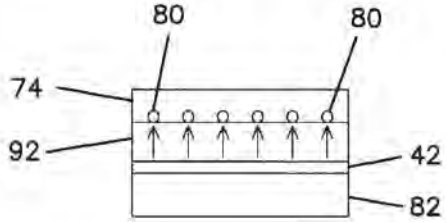


FIG. 19D

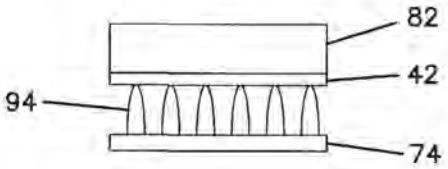


FIG. 19E

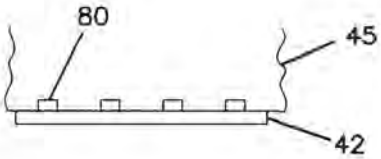


FIG. 19F

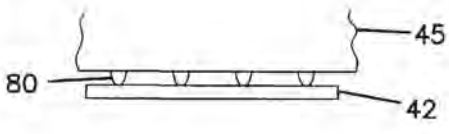


FIG. 20A

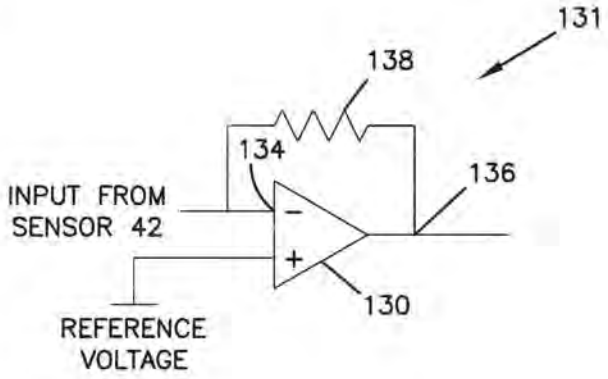
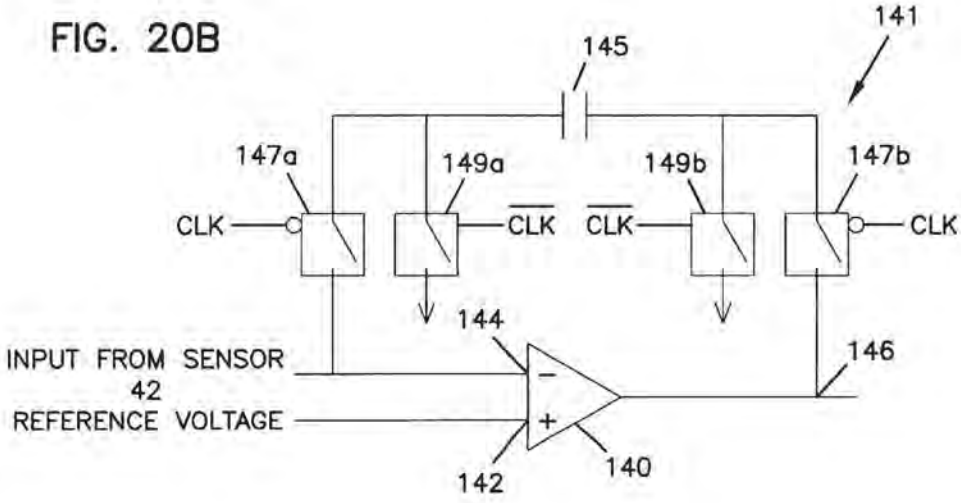


FIG. 20B



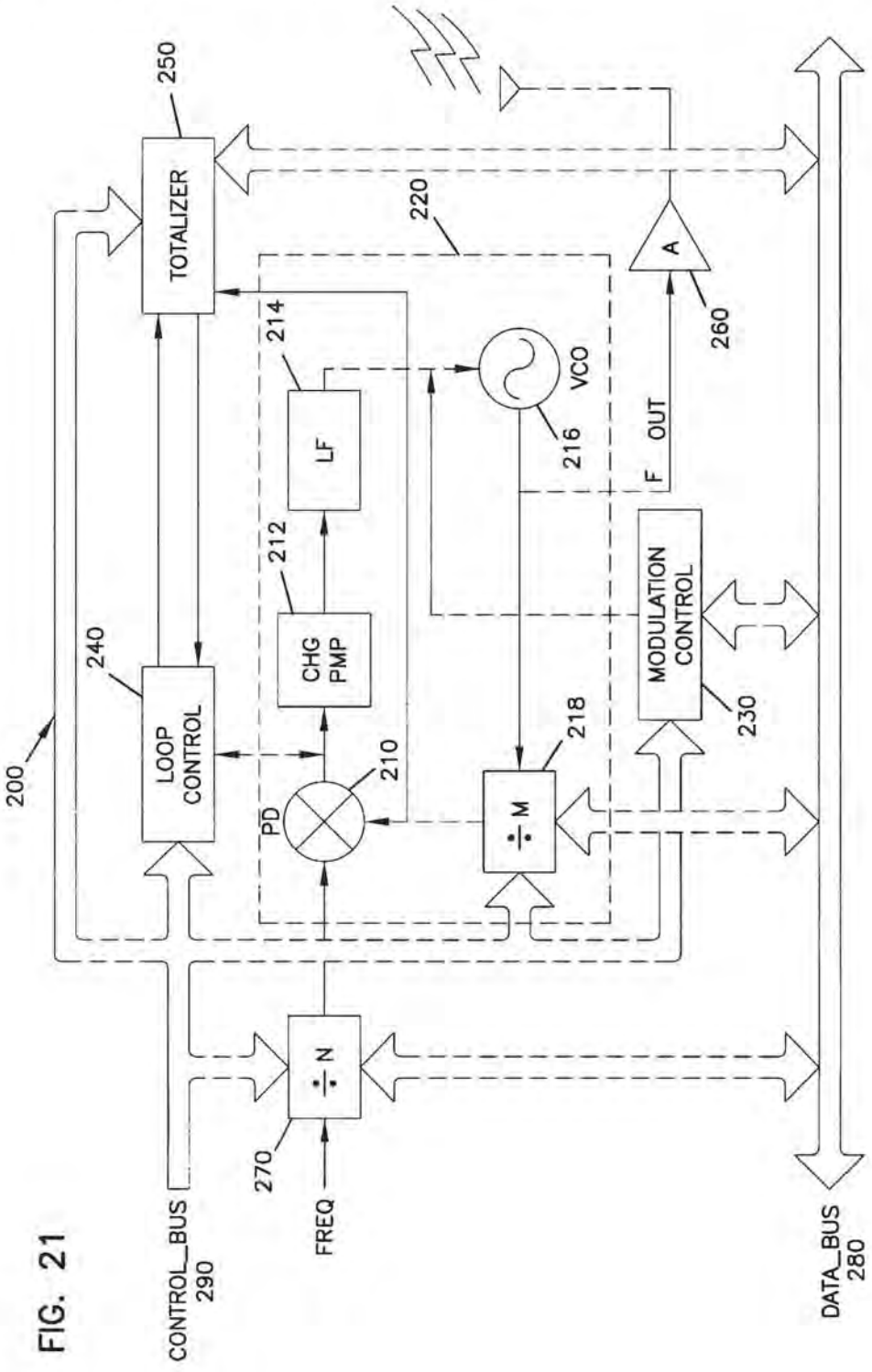


FIG. 21

FIG. 22

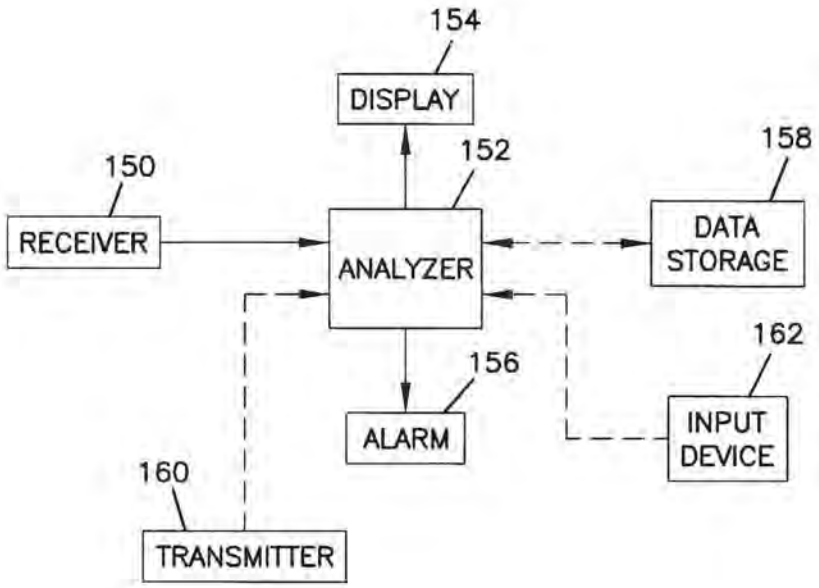


FIG. 23

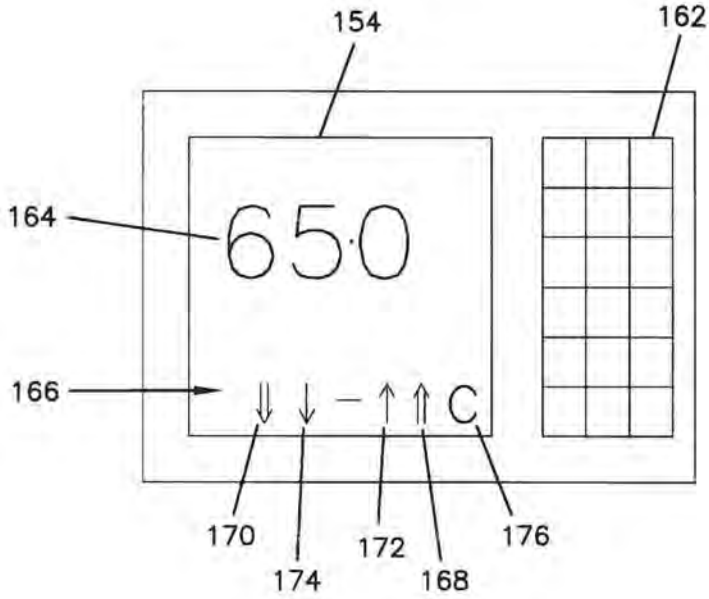
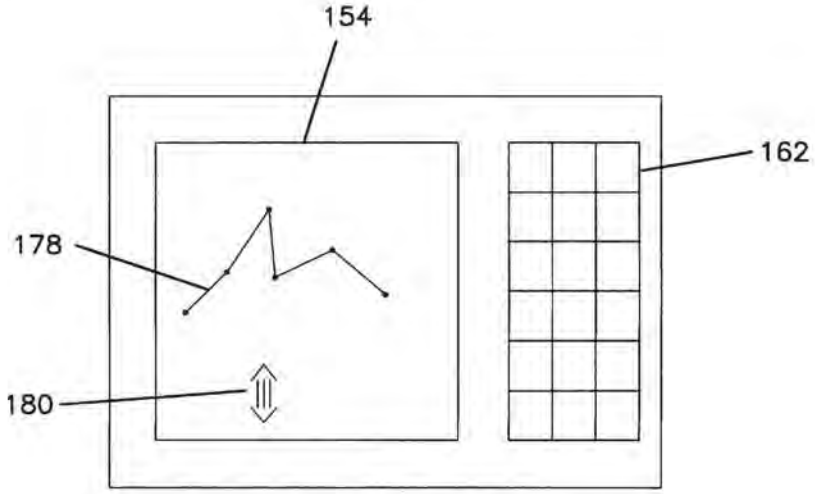


FIG. 24



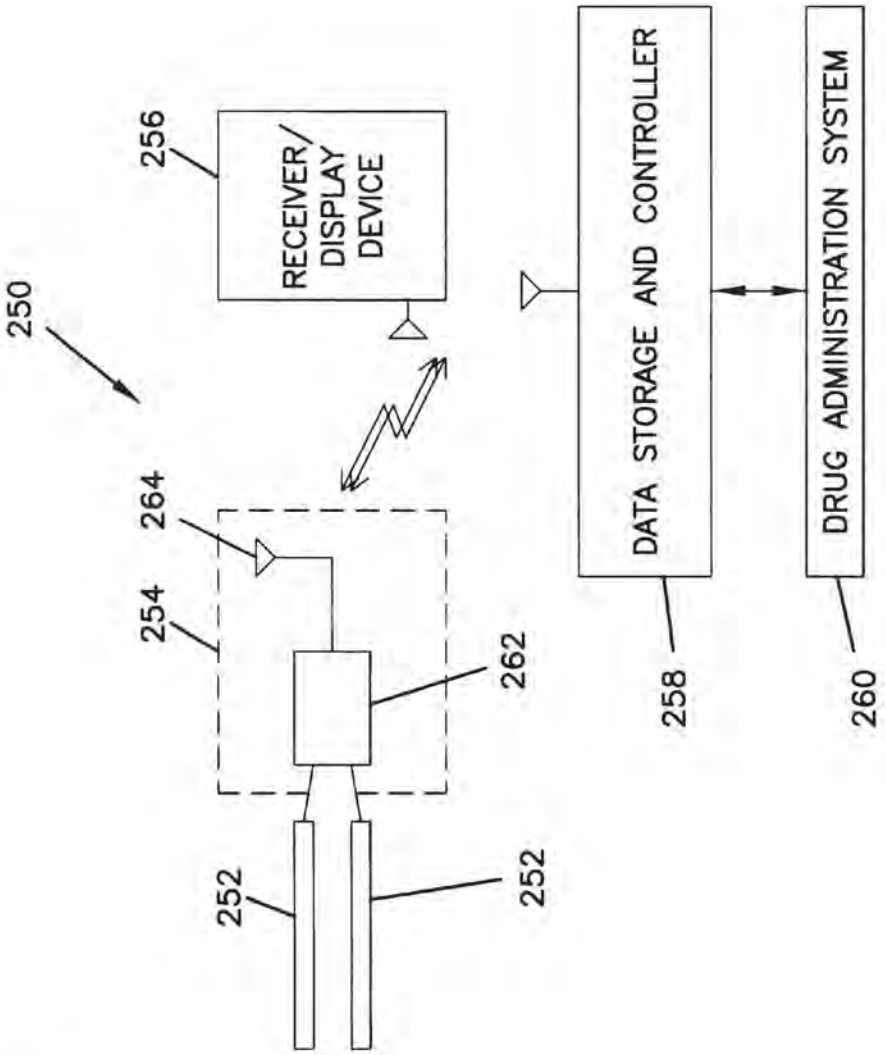


FIG. 25

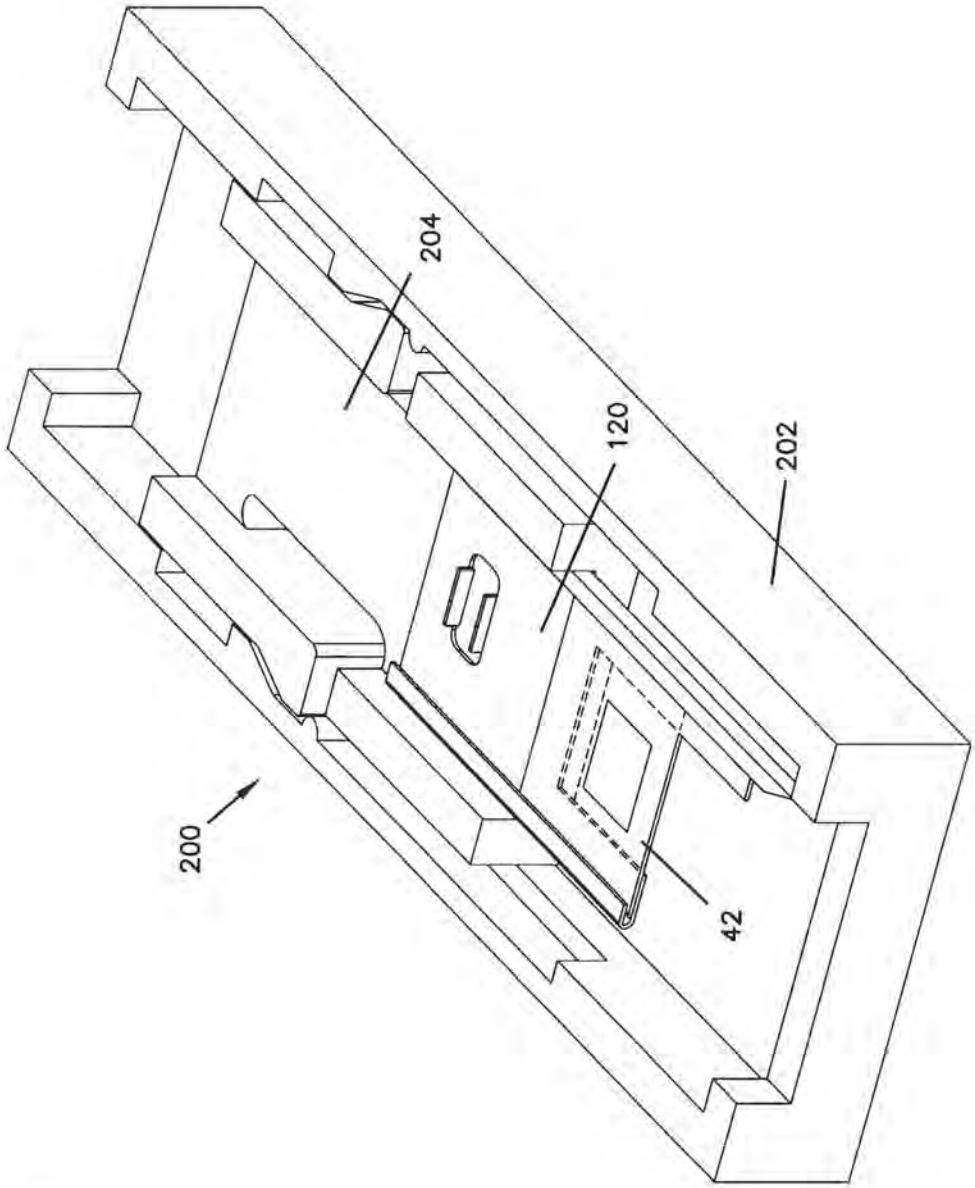


FIG. 26

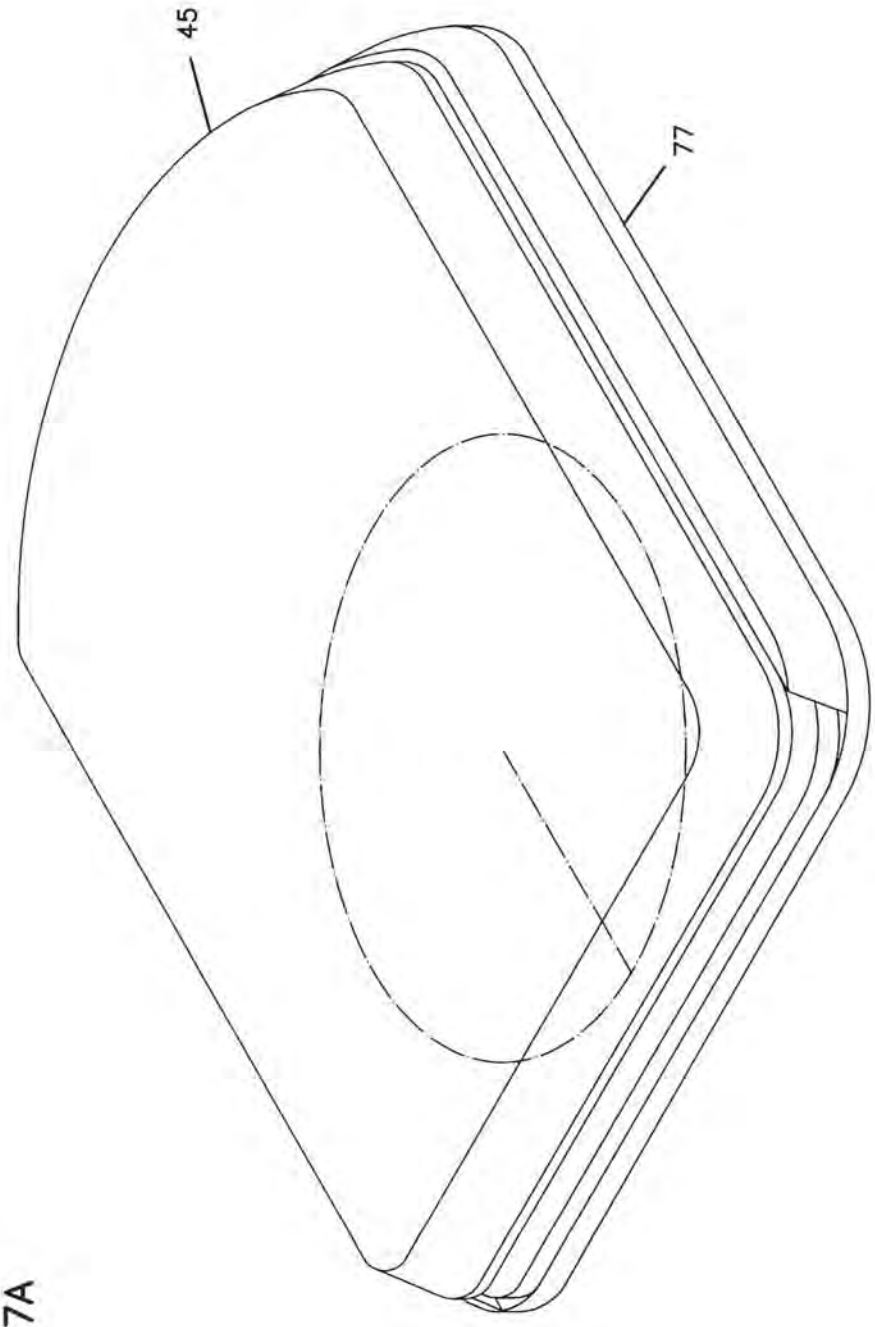


FIG. 27A

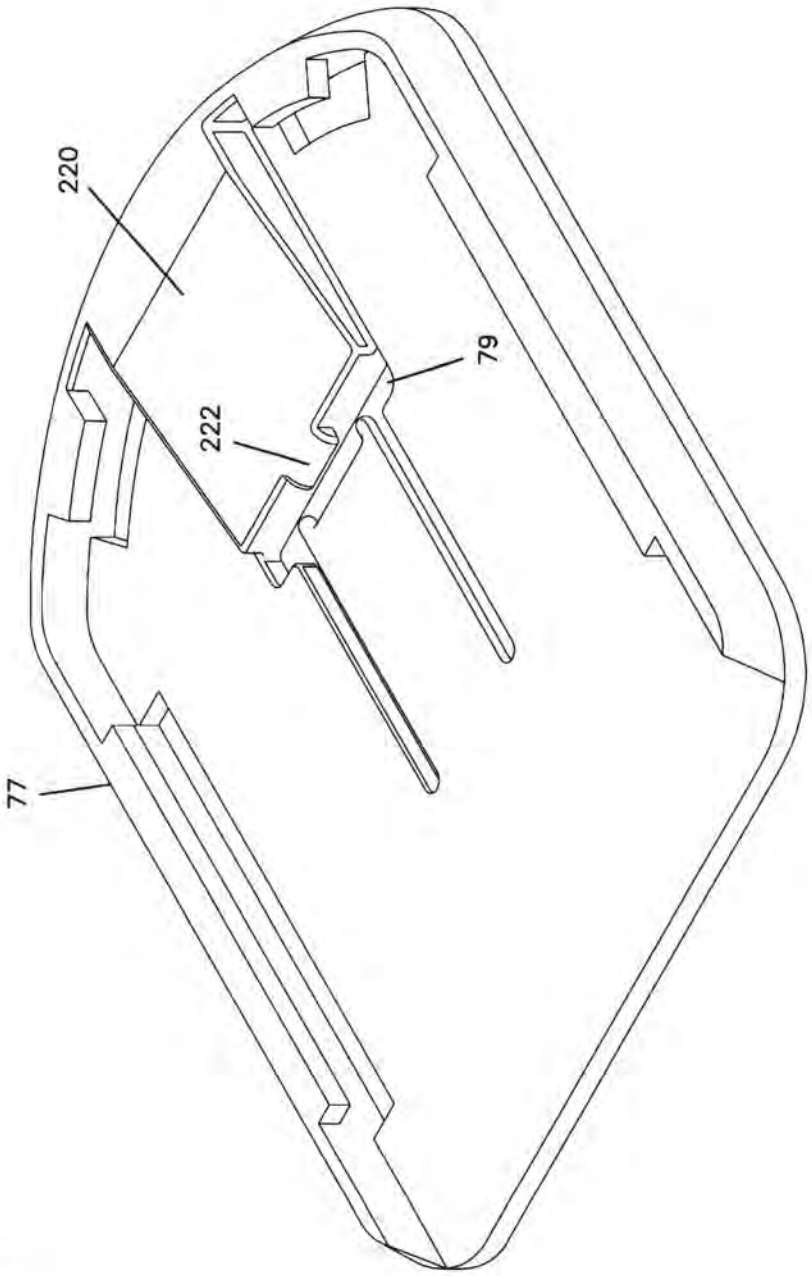


FIG. 27B

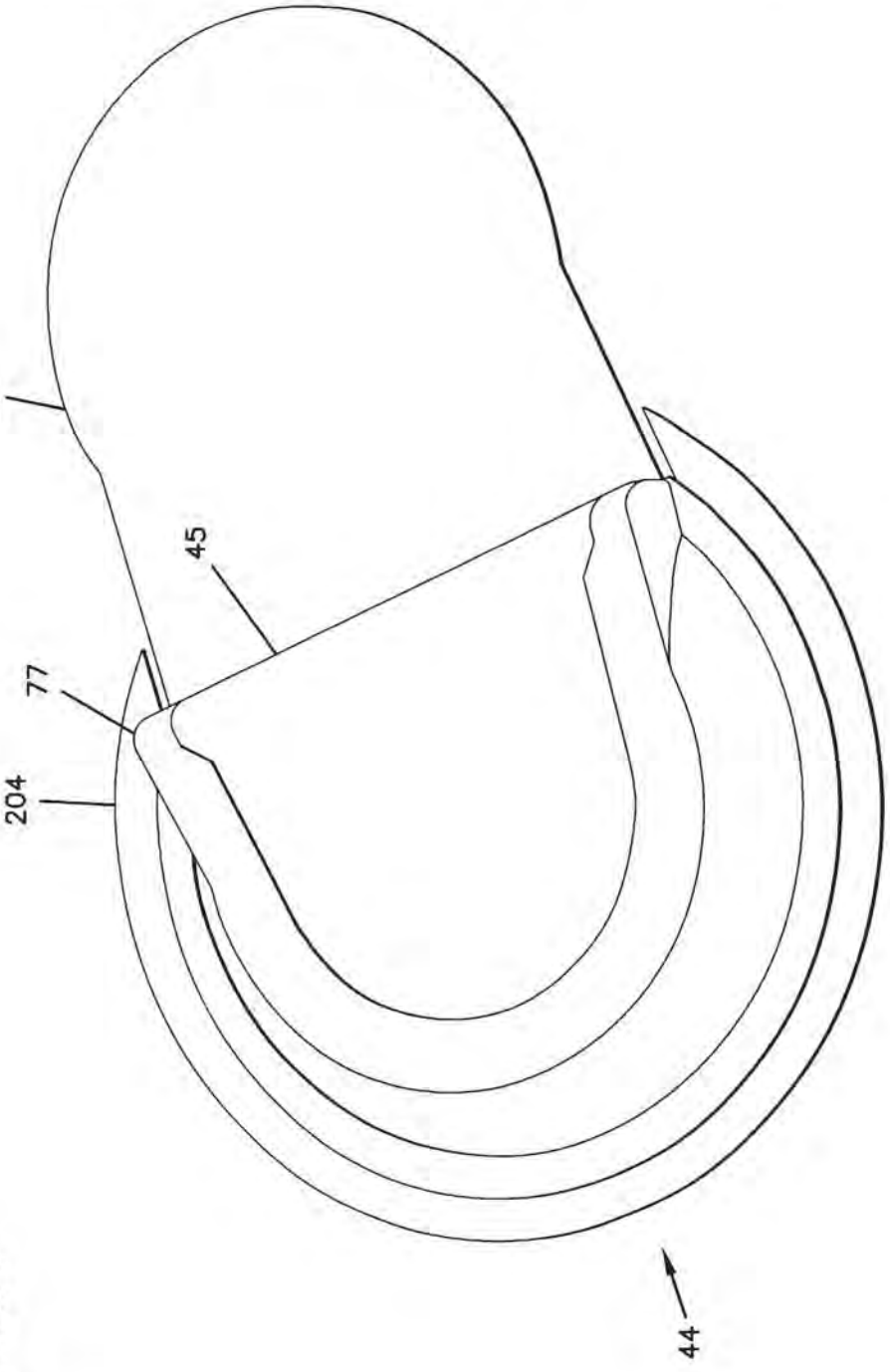


FIG. 28A

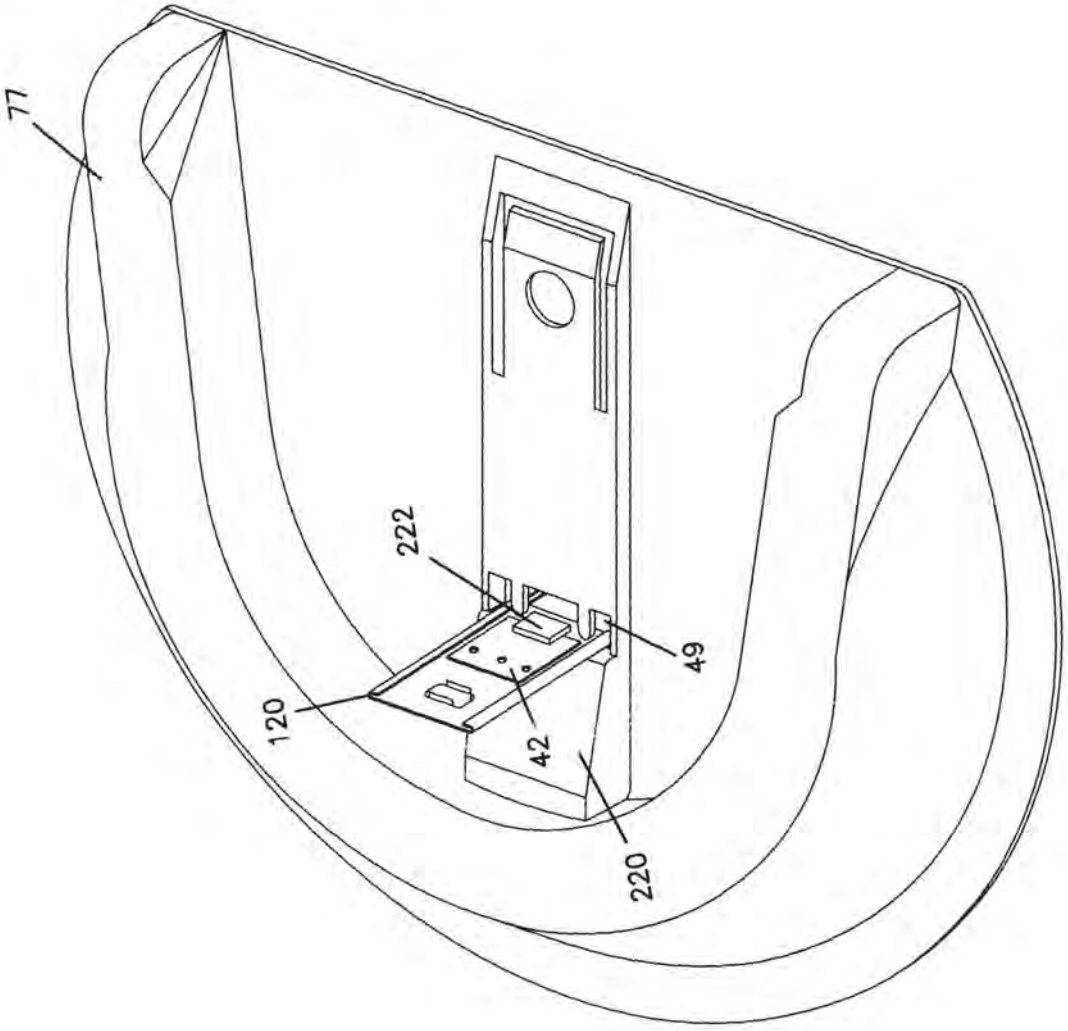


FIG. 28B

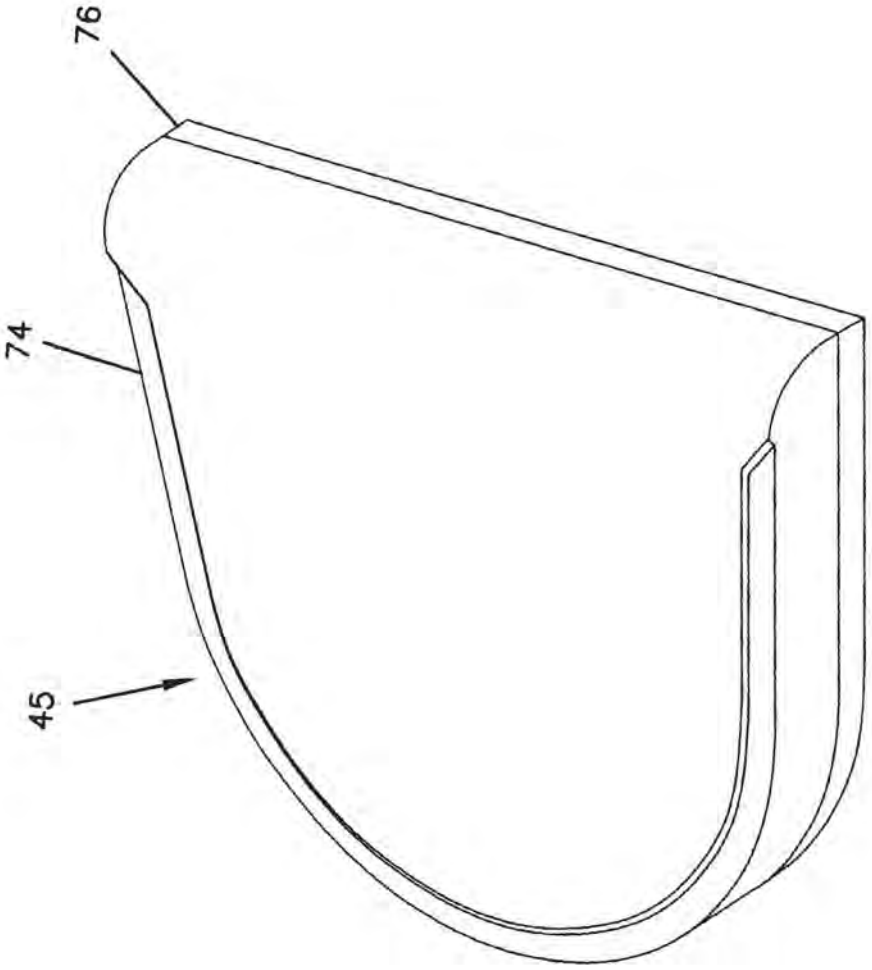


FIG. 28C

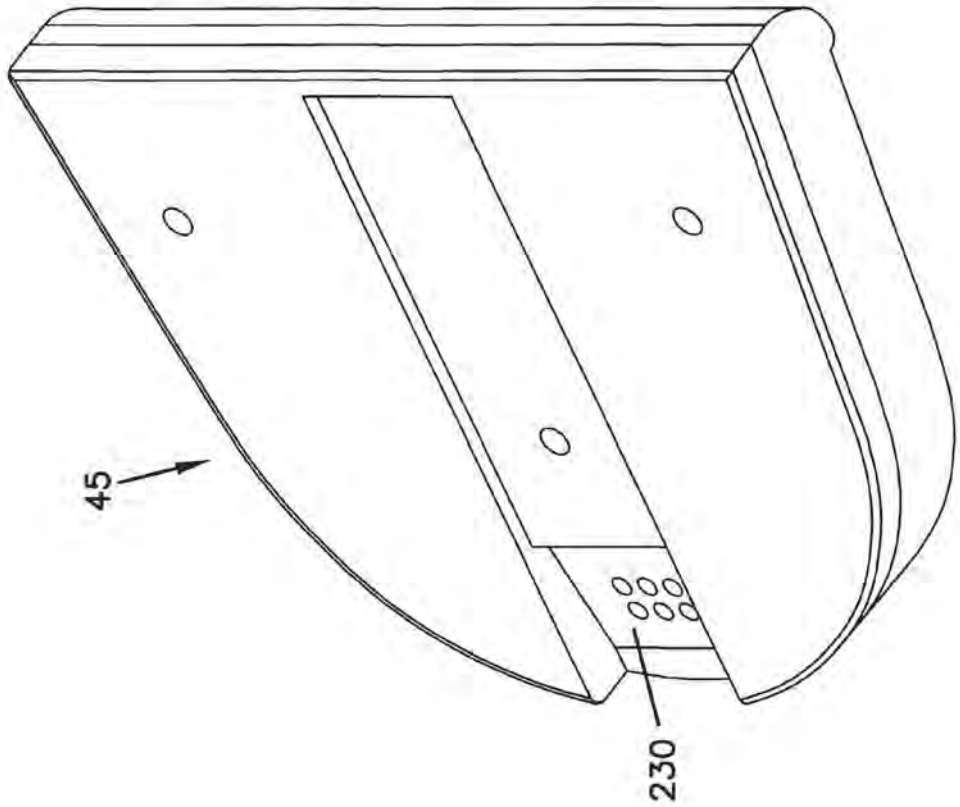


FIG. 28D

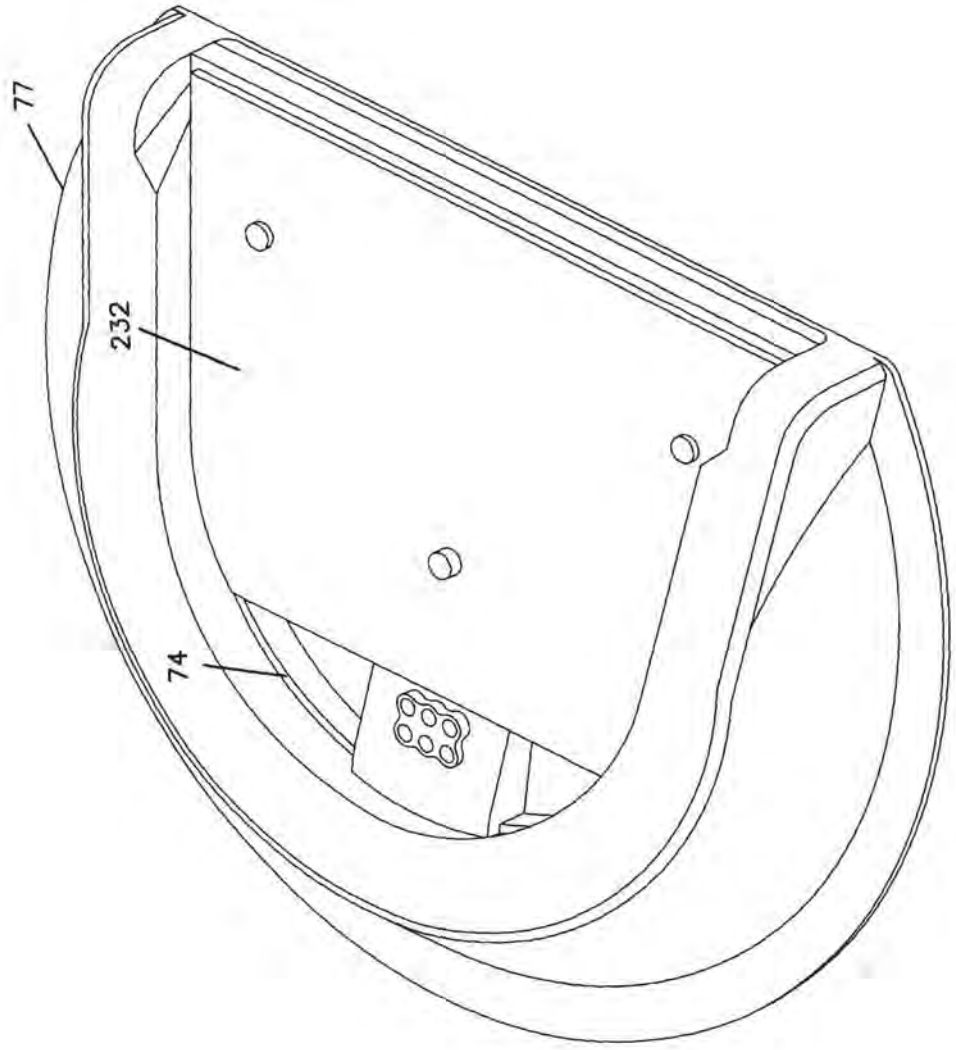


FIG. 28E

ANALYTE MONITORING DEVICE AND METHODS OF USE

FIELD OF THE INVENTION

The present invention is, in general, directed to devices and methods for the in vivo monitoring of an analyte, such as glucose or lactate. More particularly, the present invention relates to devices and methods for the in vivo monitoring of an analyte using an electrochemical sensor to provide information to a patient about the level of the analyte.

BACKGROUND OF THE INVENTION

The monitoring of the level of glucose or other analytes, such as lactate or oxygen, in certain individuals is vitally important to their health. High or low levels of glucose or other analytes may have detrimental effects. The monitoring of glucose is particularly important to individuals with diabetes, as they must determine when insulin is needed to reduce glucose levels in their bodies or when additional glucose is needed to raise the level of glucose in their bodies.

A conventional technique used by many diabetics for personally monitoring their blood glucose level includes the periodic drawing of blood, the application of that blood to a test strip, and the determination of the blood glucose level using calorimetric, electrochemical, or photometric detection. This technique does not permit continuous or automatic monitoring of glucose levels in the body, but typically must be performed manually on a periodic basis. Unfortunately, the consistency with which the level of glucose is checked varies widely among individuals. Many diabetics find the periodic testing inconvenient and they sometimes forget to test their glucose level or do not have time for a proper test. In addition, some individuals wish to avoid the pain associated with the test. These situations may result in hyperglycemic or hypoglycemic episodes. An in vivo glucose sensor that continuously or automatically monitors the individual's glucose level would enable individuals to more easily monitor their glucose, or other analyte, levels.

A variety of devices have been developed for continuous or automatic monitoring of analytes, such as glucose, in the blood stream or interstitial fluid. A number of these devices use electrochemical sensors which are directly implanted into a blood vessel or in the subcutaneous tissue of a patient. However, these devices are often difficult to reproducibly and inexpensively manufacture in large numbers. In addition, these devices are typically large, bulky, and/or inflexible, and many can not be used effectively outside of a controlled medical facility, such as a hospital or a doctor's office, unless the patient is restricted in his activities.

Some devices include a sensor guide which rests on or near the skin of the patient and may be attached to the patient to hold the sensor in place. These sensor guides are typically bulky and do not allow for freedom of movement. In addition, the sensor guides or the sensors include cables or wires for connecting the sensor to other equipment to direct the signals from the sensors to an analyzer. The size of the sensor guides and presence of cables and wires hinders the convenient use of these devices for everyday applications. There is a need for a small, compact device that can operate the sensor and provide signals to an analyzer without substantially restricting the movements and activities of a patient.

The patient's comfort and the range of activities that can be performed while the sensor is implanted are important considerations in designing extended-use sensors for continuous or automatic in vivo monitoring of the level of an analyte, such as glucose. There is a need for a small, comfortable device which can continuously monitor the level of an analyte, such as glucose, while still permitting the patient to engage in normal activities. Continuous and/or automatic monitoring of the analyte can provide a warning to the patient when the level of the analyte is at or near a threshold level. For example, if glucose is the analyte, then the monitoring device might be configured to warn the patient of current or impending hyperglycemia or hypoglycemia. The patient can then take appropriate actions.

SUMMARY OF THE INVENTION

Generally, the present invention relates to methods and devices for the continuous and/or automatic in vivo monitoring of the level of an analyte using a subcutaneously implantable sensor. Many of these devices are small and comfortable when used, thereby allowing a wide range of activities. One embodiment is a sensor control unit having a housing adapted for placement on skin. The housing is also adapted to receive a portion of an electrochemical sensor. The sensor control unit includes two or more conductive contacts disposed on the housing and configured for coupling to two or more contact pads on the sensor. A transmitter is disposed in the housing and coupled to the plurality of conductive contacts for transmitting data obtained using the sensor. The sensor control unit may also include a variety of optional components, such as, for example, adhesive for adhering to the skin, a mounting unit, a receiver, a processing circuit, a power supply (e.g., a battery), an alarm system, a data storage unit, a watchdog circuit, and a measurement circuit. Other optional components are described below.

Another embodiment of the invention is a sensor assembly that includes the sensor control unit described above. The sensor assembly also includes a sensor having at least one working electrode and at least one contact pad coupled to the working electrode or electrodes. The sensor may also include optional components, such as, for example, a counter electrode, a counter/reference electrode, a reference electrode, and a temperature probe. Other components and options for the sensor are described below.

A further embodiment of the invention is an analyte monitoring system that includes the sensor control unit described above. The analyte monitoring system also includes a sensor that has at least one working electrode and at least one contact pad coupled to the working electrode or electrodes. The analyte monitoring system also includes a display unit that has a receiver for receiving data from the sensor control unit and a display coupled to the receiver for displaying an indication of the level of an analyte. The display unit may optionally include a variety of components, such as, for example, a transmitter, an analyzer, a data storage unit, a watchdog circuit, an input device, a power supply, a clock, a lamp, a pager, a telephone interface, a computer interface, an alarm or alarm system, a radio, and a calibration unit. Further components and options for the display unit are described below. In addition, the analyte monitoring system or a component of the analyte monitoring system may optionally include a processor capable of determining a drug or treatment protocol and/or a drug delivery system.

Yet another embodiment of the invention is an insertion kit for inserting an electrochemical sensor into a patient. The insertion kit includes an inserter. A portion of the inserter has a sharp, rigid, planer structure adapted to support the sensor during insertion of the electrochemical sensor. The insertion kit also includes an insertion gun having a port configured to

accept the electrochemical sensor and the inserter. The insertion gun has a driving mechanism for driving the inserter and electrochemical sensor into the patient, and a retraction mechanism for removing the inserter while leaving the sensor within the patient.

Another embodiment is a method of using an electrochemical sensor. A mounting unit is adhered to skin of a patient. An insertion gun is aligned with a port on the mounting unit. The electrochemical sensor is disposed within the insertion gun and then the electrochemical sensor is inserted into the skin of the patient using the insertion gun. The insertion gun is removed and a housing of the sensor control unit is mounted on the mounting base. A plurality of conductive contacts disposed on the housing is coupled to a plurality of contact pads disposed on the electrochemical sensor to prepare the sensor for use.

One embodiment of the invention is a method for detecting failures in an implanted analyte-responsive sensor. An analyte-responsive sensor is implanted into a patient. The analyte-responsive sensor includes N working electrodes, where N is an integer and is two or greater, and a common counter electrode. Signals generated at one of the N working electrodes and at the common counter electrode are then obtained and the sensor is determined to have failed if the signal from the common counter electrode is not N times the signal from one of the working electrodes, within a predetermined threshold limit.

Yet another embodiment is a method of calibrating an electrochemical sensor having one or more working electrodes implanted in a patient. A signal is generated from each of the working electrodes. Several conditions are tested to determine if calibration is appropriate. First, the signals from each of the one or more working electrodes should differ by less than a first threshold amount. Second, the signals from each of the one or more working electrodes should be within a predetermined range. And, third, a rate of change of the signals from each of the one or more working electrodes should be less than a second threshold amount. A calibration value is found assaying a calibration sample of a patient's body fluid. The calibration value is then related to at least one of the signals from the one or more working electrodes if the conditions described above are met.

A further embodiment is a method for monitoring a level of an analyte. A sensor is inserted into a skin of a patient and a sensor control unit is attached to the skin of the patient. Two or more conductive contacts on the sensor control unit are coupled to contact pads on the sensor. Then, using the sensor control unit, data is collected regarding a level of an analyte from signals generated by the sensor. The collected data is transmitted to a display unit and an indication of the level of the analyte is displayed on the display unit.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The Figures and the detailed description which follow more particularly exemplify these embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention may be more completely understood in consideration of the following detailed description of various embodiments of the invention in connection with the accompanying drawings, in which:

FIGS. **1**, **1A**, **1B** is a block diagram of one embodiment of a subcutaneous analyte monitor using a subcutaneously implantable analyte sensor, according to the invention;

FIG. **2** is a top view of one embodiment of an analyte sensor, according to the invention;

FIGS. **3**, **3A** is a cross-sectional view of the analyte sensor of FIG. **2**;

FIG. **3B** is a cross-sectional view of another embodiment of an analyte sensor, according to the invention;

FIG. **4A** is a cross-sectional view of a third embodiment of an analyte sensor, according to the invention;

FIG. **4B** is a cross-sectional view of a fourth embodiment of an analyte sensor, according to the invention;

FIGS. **5A–5D** is an expanded top view of a tip portion of the analyte sensor of FIG. **2**;

FIG. **6** is a cross-sectional view of a fifth embodiment of an analyte sensor, according to the invention;

FIG. **7** is an expanded top view of a tip-portion of the analyte sensor of FIG. **6**;

FIG. **8** is an expanded bottom view of a tip-portion of the analyte sensor of FIG. **6**;

FIG. **9** is a side view of the analyte sensor of FIG. **2**;

FIG. **10** is a top view of the analyte sensor of FIG. **6**;

FIG. **11** is a bottom view of the analyte sensor of FIG. **6**;

FIG. **12** is an expanded side view of one embodiment of a sensor and an insertion device, according to the invention;

FIGS. **13A**, **13B**, **13C** are cross-sectional views of three embodiments of the insertion device of FIG. **12**;

FIG. **14** is a cross-sectional view of one embodiment of a on-skin sensor control unit, according to the invention;

FIG. **15** is a top view of a base of the on-skin sensor control unit of FIG. **14**;

FIG. **16** is a bottom view of a cover of the on-skin sensor control unit of FIG. **14**;

FIG. **17** is a perspective view of the on-skin sensor control unit of FIG. **14** on the skin of a patient;

FIG. **18A** is a block diagram of one embodiment of an on-skin sensor control unit, according to the invention;

FIG. **18B** is a block diagram of another embodiment of an on-skin sensor control unit, according to the invention;

FIGS. **19A**, **19B**, **19C**, and **19D** are cross-sectional views of four embodiments of conductive contacts disposed on an interior surface of a housing of an on-skin sensor control unit, according to the invention;

FIGS. **19E** and **19F** are cross-sectional views of two embodiments of conductive contacts disposed on an exterior surface of a housing of an on-skin sensor control unit, according to the invention;

FIGS. **20A** and **20B** are schematic diagrams of two embodiments of a current-to-voltage converter for use in an analyte monitoring device, according to the invention;

FIG. **21** is a block diagram of one embodiment of an open loop modulation system for use in an analyte monitoring device, according to the invention;

FIG. **22** is a block diagram of one embodiment of a receiver/display unit, according to the invention;

FIG. **23** is a front view of one embodiment of a receiver/display unit;

FIG. **24** is a front view of a second embodiment of a receiver/display unit;

FIG. **25** is a block diagram of one embodiment of a drug delivery system, according to the invention;

FIG. **26** is a perspective view of the internal structure of an insertion gun, according to the invention;

FIG. **27A** is a top view of one embodiment of an on-skin sensor control unit, according to the invention;

FIG. **27B** is a top view of one embodiment of a mounting unit of the on-skin sensor control unit of FIG. **27A**;

FIG. **28**A is a top view of another embodiment of an on-skin sensor control unit after insertion of an insertion device and a sensor, according to the invention;

FIG. **28**B is a top view of one embodiment of a mounting unit of the on-skin sensor control unit of FIG. **28**A;

FIG. **28**C is a top view of one embodiment of a housing for at least a portion of the electronics of the on-skin sensor control unit of FIG. **28**A;

FIG. **28**D is a bottom view of the housing of FIG. **28**C; and

FIG. **28**E is a top view of the on-skin sensor control unit of FIG. **28**A with a cover of the housing removed.

While the invention is amenable to various modifications and alternative forms, specifics thereof have been shown by way of example in the drawings and will be described in detail. It should be understood, however, that the intention is not to limit the invention to the particular embodiments described. On the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention as defined by the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is applicable to an analyte monitoring system using an implantable sensor for the in vivo determination of a concentration of an analyte, such as glucose or lactate, in a fluid. The sensor can be, for example, subcutaneously implanted in a patient for the continuous or periodic monitoring an analyte in a patient's interstitial fluid. This can then be used to infer the glucose level in the patient's bloodstream. Other in vivo analyte sensors can be made, according to the invention, for insertion into a vein, artery, or other portion of the body containing fluid. The analyte monitoring system is typically configured for monitoring the level of the analyte over a time period which may range from days to weeks or longer.

The following definitions are provided for terms used herein:

A "counter electrode" refers to an electrode paired with the working electrode, through which passes a current equal in magnitude and opposite in sign to the current passing through the working electrode. In the context of the invention, the term "counter electrode" is meant to include counter electrodes which also function as reference electrodes (i.e., a counter/reference electrode).

An "electrochemical sensor" is a device configured to detect the presence and/or measure the level of an analyte in a sample via electrochemical oxidation and reduction reactions on the sensor. These reactions are transduced to an electrical signal that can be correlated to an amount, concentration, or level of an analyte in the sample.

"Electrolysis" is the electrooxidation or electroreduction of a compound either directly at an electrode or via one or more electron transfer agents.

A compound is "immobilized" on a surface when it is entrapped on or chemically bound to the surface.

A "non-leachable" or "non-releasable" compound or a compound that is "non-leachably disposed" is meant to define a compound that is affixed on the sensor such that it does not substantially diffuse away from the working surface of the working electrode for the period in which the sensor is used (e.g., the period in which the sensor is implanted in a patient or measuring a sample).

Components are "immobilized" within a sensor, for example, when the components are covalently, ionically, or coordinatively bound to constituents of the sensor and/or are entrapped in a polymeric or sol-gel matrix or membrane which precludes mobility.

An "electron transfer agent" is a compound that carries electrons between the analyte and the working electrode, either directly, or in cooperation with other electron transfer agents. One example of an electron transfer agent is a redox mediator.

A "working electrode" is an electrode at which the analyte (or a second compound whose level depends on the level of the analyte) is electrooxidized or electroreduced with or without the agency of an electron transfer agent.

A "working surface" is that portion of the working electrode which is coated with or is accessible to the electron transfer agent and configured for exposure to an analyte-containing fluid.

A "sensing layer" is a component of the sensor which includes constituents that facilitate the electrolysis of the analyte. The sensing layer may include constituents such as an electron transfer agent, a catalyst which catalyzes a reaction of the analyte to produce a response at the electrode, or both. In some embodiments of the sensor, the sensing layer is non-leachably disposed in proximity to or on the working electrode.

A "non-corroding" conductive material includes non-metallic materials, such as carbon and conductive polymers.

Analyte Sensor Systems

The analyte monitoring systems of the present invention can be utilized under a variety of conditions. The particular configuration of a sensor and other units used in the analyte monitoring system may depend on the use for which the analyte monitoring system is intended and the conditions under which the analyte monitoring system will operate. One embodiment of the analyte monitoring system includes a sensor configured for implantation into a patient or user. For example, implantation of the sensor may be made in the arterial or venous systems for direct testing of analyte levels in blood. Alternatively, a sensor may be implanted in the interstitial tissue for determining the analyte level in interstitial fluid. This level may be correlated and/or converted to analyte levels in blood or other fluids. The site and depth of implantation may affect the particular shape, components, and configuration of the sensor. Subcutaneous implantation may be preferred, in some cases, to limit the depth of implantation of the sensor. Sensors may also be implanted in other regions of the body to determine analyte levels in other fluids. Examples of suitable sensor for use in the analyte monitoring systems of the invention are described in U.S. patent application, Ser. No. 09/034,372, incorporated herein by reference.

One embodiment of the analyte monitoring system **40** for use with an implantable sensor **42**, and particularly for use with a subcutaneously implantable sensor, is illustrated in block diagram form in FIG. **1**. The analyte monitoring system **40** includes, at minimum, a sensor **42**, a portion of which is configured for implantation (e.g., subcutaneous, venous, or arterial implantation) into a patient, and a sensor control unit **44**. The sensor **42** is coupled to the sensor control unit **44** which is typically attached to the skin of a patient. The sensor control unit **44** operates the sensor **42**, including, for example, providing a voltage across the electrodes of the sensor **42** and collecting signals from the sensor **42**. The sensor control unit **44** may evaluate the signals from the sensor **42** and/or transmit the signals to one or more optional receiver/display units **46**, **48** for evaluation. The sensor control unit **44** and/or the receiver/display units

46, 48 may display or otherwise communicate the current level of the analyte. Furthermore, the sensor control unit 44 and/or the receiver/display units 46, 48 may indicate to the patient, via, for example, an audible, visual, or other sensory-stimulating alarm, when the level of the analyte is at or near a threshold level. In some embodiments, a electrical shock can be delivered to the patient as a warning through one of the electrodes or the optional temperature probe of the sensor. For example, if glucose is monitored then an alarm may be used to alert the patient to a hypoglycemic or hyperglycemic glucose level and/or to impending hypoglycemia or hyperglycemia.

The Sensor

A sensor 42 includes at least one working electrode 58 formed on a substrate 50, as shown in FIG. 2. The sensor 42 may also include at least one counter electrode 60 (or counter/reference electrode) and/or at least one reference electrode 62 (see FIG. 8). The counter electrode 60 and/or reference electrode 62 may be formed on the substrate 50 or may be separate units. For example, the counter electrode and/or reference electrode may be formed on a second substrate which is also implanted in the patient or, for some embodiments of the implantable sensors, the counter electrode and/or reference electrode may be placed on the skin of the patient with the working electrode or electrodes being implanted into the patient. The use of an on-the-skin counter and/or reference electrode with an implantable working electrode is described in U.S. Pat. No. 5,593, 852, incorporated herein by reference.

The working electrode or electrodes 58 are formed using conductive traces 52 disposed on the substrate 50. The counter electrode 60 and/or reference electrode 62, as well as other optional portions of the sensor 42, such as a temperature probe 66 (see FIG. 8), may also be formed using conductive traces 52 disposed on the substrate 50. These conductive traces 52 may be formed over a smooth surface of the substrate 50 or within channels 54 formed by, for example, embossing, indenting or otherwise creating a depression in the substrate 50.

A sensing layer 64 (see FIGS. 3A and 3B) is often formed proximate to or on at least one of the working electrodes 58 to facilitate the electrochemical detection of the analyte and the determination of its level in the sample fluid, particularly if the analyte can not be electrolyzed at a desired rate and/or with a desired specificity on a bare electrode. The sensing layer 64 may include an electron transfer agent to transfer electrons directly or indirectly between the analyte and the working electrode 58. The sensing layer 64 may also contain a catalyst to catalyze a reaction of the analyte. The components of the sensing layer may be in a fluid or gel that is proximate to or in contact with the working electrode 58. Alternatively, the components of the sensing layer 64 may be disposed in a polymeric or sol-gel matrix that is proximate to or on the working electrode 58. Preferably, the components of the sensing layer 64 are non-leachably disposed within the sensor 42. More preferably, the components of the sensor 42 are immobilized within the sensor 42.

In addition to the electrodes 58, 60, 62 and the sensing layer 64, the sensor 42 may also include a temperature probe 66 (see FIGS. 6 and 8), a mass transport limiting layer 74 (see FIG. 9), a biocompatible layer 75 (see FIG. 9), and/or other optional components, as described below. Each of these items enhances the functioning of and/or results from the sensor 42, as discussed below.

The Substrate

The substrate 50 may be formed using a variety of non-conducting materials, including, for example, polymeric or plastic materials and ceramic materials. Suitable materials for a particular sensor 42 may be determined, at least in part, based on the desired use of the sensor 42 and properties of the materials.

In some embodiments, the substrate is flexible. For example, if the sensor 42 is configured for implantation into a patient, then the sensor 42 may be made flexible (although rigid sensors may also be used for implantable sensors) to reduce pain to the patient and damage to the tissue caused by the implantation of and/or the wearing of the sensor 42. A flexible substrate 50 often increases the patient's comfort and allows a wider range of activities. Suitable materials for a flexible substrate 50 include, for example, non-conducting plastic or polymeric materials and other non-conducting, flexible, deformable materials. Examples of useful plastic or polymeric materials include thermoplastics such as polycarbonates, polyesters (e.g., Mylar™ and polyethylene terephthalate (PET)), polyvinyl chloride (PVC), polyurethanes, polyethers, polyamides, polyimides, or copolymers of these thermoplastics, such as PETG (glycol-modified polyethylene terephthalate).

In other embodiments, the sensors 42 are made using a relatively rigid substrate 50 to, for example, provide structural support against bending or breaking. Examples of rigid materials that may be used as the substrate 50 include poorly conducting ceramics, such as aluminum oxide and silicon dioxide. One advantage of an implantable sensor 42 having a rigid substrate is that the sensor 42 may have a sharp point and/or a sharp edge to aid in implantation of a sensor 42 without an additional insertion device.

It will be appreciated that for many sensors 42 and sensor applications, both rigid and flexible sensors will operate adequately. The flexibility of the sensor 42 may also be controlled and varied along a continuum by changing, for example, the composition and/or thickness of the substrate 50.

In addition to considerations regarding flexibility, it is often desirable that implantable sensors 42 should have a substrate 50 which is non-toxic. Preferably, the substrate 50 is approved by one or more appropriate governmental agencies or private groups for in vivo use.

The sensor 42 may include optional features to facilitate insertion of an implantable sensor 42, as shown in FIG. 12. For example, the sensor 42 may be pointed at the tip 123 to ease insertion. In addition, the sensor 42 may include a barb 125 which assists in anchoring the sensor 42 within the tissue of the patient during operation of the sensor 42. However, the barb 125 is typically small enough that little damage is caused to the subcutaneous tissue when the sensor 42 is removed for replacement.

Although the substrate 50 in at least some embodiments has uniform dimensions along the entire length of the sensor 42, in other embodiments, the substrate 50 has a distal end 67 and a proximal end 65 with different widths 53, 55, respectively, as illustrated in FIG. 2. In these embodiments, the distal end 67 of the substrate 50 may have a relatively narrow width 53. For sensors 42 which are implantable into the subcutaneous tissue or another portion of a patient's body, the narrow width 53 of the distal end 67 of the substrate 50 may facilitate the implantation of the sensor 42. Often, the narrower the width of the sensor 42, the less pain the patient will feel during implantation of the sensor and afterwards.

For subcutaneously implantable sensors 42 which are designed for continuous or periodic monitoring of the analyte during normal activities of the patient, a distal end 67 of the sensor 42 which is to be implanted into the patient has

a width **53** of 2 mm or less, preferably 1 mm or less, and more preferably 0.5 mm or less. If the sensor **42** does not have regions of different widths, then the sensor **42** will typically have an overall width of, for example, 2 mm, 1.5 mm, 1 mm, 0.5 mm, 0.25 mm, or less. However, wider or narrower sensors may be used. In particular, wider implantable sensors may be used for insertion into veins or arteries or when the movement of the patient is limited, for example, when the patient is confined in bed or in a hospital.

Returning to FIG. **2**, the proximal end **65** of the sensor **42** may have a width **55** larger than the distal end **67** to facilitate the connection between contact pads **49** of the electrodes and contacts on a control unit. The wider the sensor **42** at this point, the larger the contact pads **49** can be made. This may reduce the precision needed to properly connect the sensor **42** to contacts on the control unit (e.g., sensor control unit **44** of FIG. **1**). However, the maximum width of the sensor **42** may be constrained so that the sensor **42** remains small for the convenience and comfort of the patient and/or to fit the desired size of the analyte monitor. For example, the proximal end **65** of a subcutaneously implantable sensor **42**, such as the sensor **42** illustrated in FIG. **1**, may have a width **55** ranging from 0.5 mm to 15 mm, preferably from 1 mm to 10 mm, and more preferably from 3 mm to 7 mm. However, wider or narrower sensors may be used in this and other in vivo applications.

The thickness of the substrate **50** may be determined by the mechanical properties of the substrate material (e.g., the strength, modulus, and/or flexibility of the material), the desired use of the sensor **42** including stresses on the substrate **50** arising from that use, as well as the depth of any channels or indentations formed in the substrate **50**, as discussed below. Typically, the substrate **50** of a subcutaneously implantable sensor **42** for continuous or periodic monitoring of the level of an analyte while the patient engages in normal activities has a thickness of 50 to 500 μm and preferably 100 to 300 μm. However, thicker and thinner substrates **50** may be used, particularly in other types of in vivo sensors **42**.

The length of the sensor **42** may have a wide range of values depending on a variety of factors. Factors which influence the length of an implantable sensor **42** may include the depth of implantation into the patient and the ability of the patient to manipulate a small flexible sensor **42** and make connections between the sensor **42** and the sensor control unit **44**. A subcutaneously implantable sensor **42** for the analyte monitor illustrated in FIG. **1** may have a length ranging from 0.3 to 5 cm, however, longer or shorter sensors may be used. The length of the narrow portion of the sensor **42** (e.g., the portion which is subcutaneously inserted into the patient), if the sensor **42** has narrow and wide portions, is typically about 0.25 to 2 cm in length. However, longer and shorter portions may be used. All or only a part of this narrow portion may be subcutaneously implanted into the patient. The lengths of other implantable sensors **42** will vary depending, at least in part, on the portion of the patient into which the sensor **42** is to be implanted or inserted.

Conductive Traces

At least one conductive trace **52** is formed on the substrate for use in constructing a working electrode **58**. In addition, other conductive traces **52** may be formed on the substrate **50** for use as electrodes (e.g., additional working electrodes, as well as counter, counter/reference, and/or reference electrodes) and other components, such as a temperature probe. The conductive traces **52** may extend most of the distance along a length **57** of the sensor **50**, as illustrated in FIG. **2**, although this is not necessary. The placement of the conductive traces **52** may depend on the particular configuration of the analyte monitoring system (e.g., the placement of control unit contacts and/or the sample chamber in relation to the sensor **42**). For implantable sensors, particularly subcutaneously implantable sensors, the conductive traces typically extend close to the tip of the sensor **42** to minimize the amount of the sensor that must be implanted.

The conductive traces **52** may be formed on the substrate **50** by a variety of techniques, including, for example, photolithography, screen printing, or other impact or non-impact printing techniques. The conductive traces **52** may also be formed by carbonizing conductive traces **52** in an organic (e.g., polymeric or plastic) substrate **50** using a laser. A description of some exemplary methods for forming the sensor **42** is provided in U.S. patent application Ser. No. 09/034,422, incorporated herein by reference.

Another method for disposing the conductive traces **52** on the substrate **50** includes the formation of recessed channels **54** in one or more surfaces of the substrate **50** and the subsequent filling of these recessed channels **54** with a conductive material **56**, as shown in FIG. **3A**. The recessed channels **54** may be formed by indenting, embossing, or otherwise creating a depression in the surface of the substrate **50**. Exemplary methods for forming channels and electrodes in a surface of a substrate can be found in U.S. patent application Ser. No. 09/034,422. The depth of the channels is typically related to the thickness of the substrate **50**. In one embodiment, the channels have depths in the range of about 12.5 to 75 μm (0.5 to 3 mils), and preferably about 25 to 50 μm (1 to 2 mils).

The conductive traces are typically formed using a conductive material **56** such as carbon (e.g., graphite), a conductive polymer, a metal or alloy (e.g., gold or gold alloy), or a metallic compound (e.g., ruthenium dioxide or titanium dioxide). The formation of films of carbon, conductive polymer, metal, alloy, or metallic compound are well-known and include, for example, chemical vapor deposition (CVD), physical vapor deposition, sputtering, reactive sputtering, printing, coating, and painting. The conductive material **56** which fills the channels **54** is often formed using a precursor material, such as a conductive ink or paste. In these embodiments, the conductive material **56** is deposited on the substrate **50** using methods such as coating, painting, or applying the material using a spreading instrument, such as a coating blade. Excess conductive material between the channels **54** is then removed by, for example, running a blade along the substrate surface.

In one embodiment, the conductive material **56** is a part of a precursor material, such as a conductive ink, obtainable, for example, from Ercon, Inc. (Wareham, Mass.), Metech, Inc. (Elverson, Pa.), E.I. du Pont de Nemours and Co. (Wilmington, Del.), Emca-Remex Products (Montgomeryville, Pa.), or MCA Services (Melbourn, Great Britain). The conductive ink is typically applied as a semi-liquid or paste which contains particles of the carbon, metal, alloy, or metallic compound and a solvent or dispersant. After application of the conductive ink on the substrate **50** (e.g., in the channels **54**), the solvent or dispersant evaporates to leave behind a solid mass of conductive material **56**.

In addition to the particles of carbon, metal, alloy, or metallic compound, the conductive ink may also contain a binder. The binder may optionally be cured to further bind the conductive material **56** within the channel **54** and/or on the substrate **50**. Curing the binder increases the conductivity of the conductive material **56**. However, this is typically not necessary as the currents carried by the conductive material **56** within the conductive traces **52** are often rela-

tively low (usually less than 1 μA and often less than 100 nA). Typical binders include, for example, polyurethane resins, cellulose derivatives, elastomers, and highly fluorinated polymers. Examples of elastomers include silicones, polymeric dienes, and acrylonitrile-butadiene-styrene (ABS) resins. One example of a fluorinated polymer binder is Teflon® (DuPont, Wilmington, Del.). These binders are cured using, for example, heat or light, including ultraviolet (UV) light. The appropriate curing method typically depends on the particular binder which is used.

Often, when a liquid or semiliquid precursor of the conductive material **56** (e.g., a conductive ink) is deposited in the channel **54**, the precursor fills the channel **54**. However, when the solvent or dispersant evaporates, the conductive material **56** which remains may lose volume such that the conductive material **56** may or may not continue to fill the channel **54**. Preferred conductive materials **56** do not pull away from the substrate **50** as they lose volume, but rather decrease in height within the channel **54**. These conductive materials **56** typically adhere well to the substrate **50** and therefore do not pull away from the substrate **50** during evaporation of the solvent or dispersant. Other suitable conductive materials **56** either adhere to at least a portion of the substrate **50** and/or contain another additive, such as a binder, which adheres the conductive material **56** to the substrate **50**. Preferably, the conductive material **56** in the channels **54** is non-leachable, and more preferably immobilized on the substrate **50**. In some embodiments, the conductive material **56** may be formed by multiple applications of a liquid or semiliquid precursor interspersed with removal of the solvent or dispersant.

In another embodiment, the channels **54** are formed using a laser. The laser carbonizes the polymer or plastic material. The carbon formed in this process is used as the conductive material **56**. Additional conductive material **56**, such as a conductive carbon ink, may be used to supplement the carbon formed by the laser.

In a further embodiment, the conductive traces **52** are formed by pad printing techniques. For example, a film of conductive material is formed either as a continuous film or as a coating layer deposited on a carrier film. This film of conductive material is brought between a print head and the substrate **50**. A pattern on the surface of the substrate **50** is made using the print head according to a desired pattern of conductive traces **52**. The conductive material is transferred by pressure and/or heat from the film of conductive material to the substrate **50**. This technique often produces channels (e.g., depressions caused by the print head) in the substrate **50**. Alternatively, the conductive material is deposited on the surface of the substrate **50** without forming substantial depressions.

In other embodiments, the conductive traces **52** are formed by non-impact printing techniques. Such techniques include electrophotography and magnetography. In these processes, an image of the conductive traces **52** is electrically or magnetically formed on a drum. A laser or LED may be used to electrically form an image. A magnetic recording head may be used to magnetically form an image. A toner material (e.g., a conductive material, such as a conductive ink) is then attracted to portions of the drum according to the image. The toner material is then applied to the substrate by contact between the drum and the substrate. For example, the substrate may be rolled over the drum. The toner material may then be dried and/or a binder in the toner material may be cured to adhere the toner material to the substrate.

Another non-impact printing technique includes ejecting droplets of conductive material onto the substrate in a desired pattern. Examples of this technique include ink jet printing and piezo jet printing. An image is sent to the printer which then ejects the conductive material (e.g., a conductive ink) according to the pattern. The printer may provide a continuous stream of conductive material or the printer may eject the conductive material in discrete amounts at the desired points.

Yet another non-impact printing embodiment of forming the conductive traces includes an ionographic process. In the this process, a curable, liquid precursor, such as a photopolymerizable acrylic resin (e.g., Solimer 7501 from Cubital, Bad Kreuznach, Germany) is deposited over a surface of a substrate **50**. A photomask having a positive or negative image of the conductive traces **52** is then used to cure the liquid precursor. Light (e.g., visible or ultraviolet light) is directed through the photomask to cure the liquid precursor and form a solid layer over the substrate according to the image on the photomask. Uncured liquid precursor is removed leaving behind channels **54** in the solid layer. These channels **54** can then be filled with conductive material **56** to form conductive traces **52**.

Conductive traces **52** (and channels **54**, if used) can be formed with relatively narrow widths, for example, in the range of 25 to 250 μm, and including widths of, for example, 250 μm, 150 μm, 100 μm, 75 μm, 50 μm, 25 μm or less by the methods described above. In embodiments with two or more conductive traces **52** on the same side of the substrate **50**, the conductive traces **52** are separated by distances sufficient to prevent conduction between the conductive traces **52**. The edge-to-edge distance between the conductive traces is preferably in the range of 25 to 250 μm and may be, for example, 150 μm, 100 μm, 75 μm, 50 μm, or less. The density of the conductive traces **52** on the substrate **50** is preferably in the range of about 150 to 700 μm/trace and may be as small as 667 μm/trace or less, 333 μm/trace or less, or even 167 μm/trace or less.

The working electrode **58** and the counter electrode **60** (if a separate reference electrode is used) are often made using a conductive material **56**, such as carbon. Suitable carbon conductive inks are available from Ercon, Inc. (Wareham, Mass.), Metech, Inc. (Elverson, Pa.), E.I. du Pont de Nemours and Co. (Wilmington, Del.), Emca-Remex Products (Montgomeryville, Pa.), or MCA Services (Melbourn, Great Britain). Typically, the working surface **51** of the working electrode **58** is at least a portion of the conductive trace **52** that is in contact with the analyte-containing fluid (e.g., implanted in the patient).

The reference electrode **62** and/or counter/reference electrode are typically formed using conductive material **56** that is a suitable reference material, for example silver/silver chloride or a non-leachable redox couple bound to a conductive material, for example, a carbon-bound redox couple. Suitable silver/silver chloride conductive inks are available from Ercon, Inc. (Wareham, Mass.), Metech, Inc. (Elverson, Pa.), E.I. du Pont de Nemours and Co. (Wilmington, Del.), Emca-Remex Products (Montgomeryville, Pa.), or MCA Services (Melbourn, Great Britain). Silver/silver chloride electrodes illustrate a type of reference electrode that involves the reaction of a metal electrode with a constituent of the sample or body fluid, in this case, Cl^-.

Suitable redox couples for binding to the conductive material of the reference electrode include, for example, redox polymers (e.g., polymers having multiple redox centers.) It is preferred that the reference electrode surface be non-corroding so that an erroneous potential is not measured. Preferred conductive materials include less corrosive metals, such as gold and palladium. Most preferred

are non-corrosive materials including non-metallic conductors, such as carbon and conducting polymers. A redox polymer can be adsorbed on or covalently bound to the conductive material of the reference electrode, such as a carbon surface of a conductive trace **52**. Non-polymeric redox couples can be similarly bound to carbon or gold surfaces.

A variety of methods may be used to immobilize a redox polymer on an electrode surface. One method is adsorptive immobilization. This method is particularly useful for redox polymers with relatively high molecular weights. The molecular weight of a polymer may be increased, for example, by cross-linking.

Another method for immobilizing the redox polymer includes the functionalization of the electrode surface and then the chemical bonding, often covalently, of the redox polymer to the functional groups on the electrode surface. One example of this type of immobilization begins with a poly(4-vinylpyridine). The polymer's pyridine rings are, in part, complexed with a reducible/oxidizable species, such as $[Os(bpy)_2Cl]^{+/2+}$ where bpy is 2,2'-bipyridine. Part of the pyridine rings are quaternized by reaction with 2-bromoethylamine. The polymer is then crosslinked, for example, using a diepoxide, such as polyethylene glycol diglycidyl ether.

Carbon surfaces can be modified for attachment of a redox species or polymer, for example, by electroreduction of a diazonium salt. As an illustration, reduction of a diazonium salt formed upon diazotization of p-aminobenzoic acid modifies a carbon surface with phenylcarboxylic acid functional groups. These functional groups can then be activated by a carbodiimide, such as 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride. The activated functional groups are then bound with a amine-functionalized redox couple, such as the quaternized osmium-containing redox polymer described above or 2-aminoethylferrocene, to form the redox couple.

Similarly, gold can be functionalized by an amine, such as cystamine,. A redox couple such as $[Os(bpy)_2(pyridine\text{-}4\text{-}carboxylate)Cl]^{0/+}$ is activated by 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride to form a reactive O-acylisourea which reacts with the gold-bound amine to form an amide.

In one embodiment, in addition to using the conductive traces **52** as electrodes or probe leads, two or more of the conductive traces **52** on the substrate **50** are used to give the patient a mild electrical shock when, for example, the analyte level exceeds a threshold level. This shock may act as a warning or alarm to the patient to initiate some action to restore the appropriate level of the analyte.

The mild electrical shock is produced by applying a potential between any two conductive traces **52** that are not otherwise connected by a conductive path. For example, two of the electrodes **58**, **60**, **62** or one electrode **58**, **60**, **62** and the temperature probe **66** may be used to provide the mild shock. Preferably, the working electrode **58** and the reference electrode **62** are not used for this purpose as this may cause some damage to the chemical components on or proximate to the particular electrode (e.g., the sensing layer on the working electrode or the redox couple on the reference electrode).

The current used to produce the mild shock is typically 0.1 to 1 mA. Higher or lower currents may be used, although care should be taken to avoid harm to the patient. The potential between the conductive traces is typically 1 to 10 volts. However, higher or lower voltages may be used depending, for example, on the resistance of the conductive traces **52**, the distance between the conductive traces **52** and the desired amount of current. When the mild shock is delivered, potentials at the working electrode **58** and across the temperature probe **66** may be removed to prevent harm to those components caused by unwanted conduction between the working electrode **58** (and/or temperature probe **66**, if used) and the conductive traces **52** which provide the mild shock.

Contact Pads

Typically, each of the conductive traces **52** includes a contact pad **49**. The contact pad **49** may simply be a portion of the conductive trace **52** that is indistinguishable from the rest of the trace **52** except that the contact pad **49** is brought into contact with the conductive contacts of a control unit (e.g., the sensor control unit **44** of FIG. **1**). More commonly, however, the contact pad **49** is a region of the conductive trace **52** that has a larger width than other regions of the trace **52** to facilitate a connection with the contacts on the control unit. By making the contact pads **49** relatively large as compared with the width of the conductive traces **52**, the need for precise registration between the contact pads **49** and the contacts on the control unit is less critical than with small contact pads.

The contact pads **49** are typically made using the same material as the conductive material **56** of the conductive traces **52**. However, this is not necessary. Although metal, alloys, and metallic compounds may be used to form the contact pads **49**, in some embodiments, it is desirable to make the contact pads **49** from a carbon or other non-metallic material, such as a conducting polymer. In contrast to metal or alloy contact pads, carbon and other non-metallic contact pads are not easily corroded if the contact pads **49** are in a wet, moist, or humid environment. Metals and alloys may corrode under these conditions, particularly if the contact pads **49** and contacts of the control unit are made using different metals or alloys. However, carbon and non-metallic contact pads **49** do not significantly corrode, even if the contacts of the control device are metal or alloy.

One embodiment of the invention includes a sensor **42** having contact pads **49** and a control unit **44** having conductive contacts (not shown). During operation of the sensor **42**, the contact pads **49** and conductive contacts are in contact with each other. In this embodiment, either the contact pads **49** or the conductive contacts are made using a non-corroding, conductive material. Such materials include, for example, carbon and conducting polymers. Preferred non-corroding materials include graphite and vitreous carbon. The opposing contact pad or conductive contact is made using carbon, a conducting polymer, a metal, such as gold, palladium, or platinum group metal, or a metallic compound, such as ruthenium dioxide. This configuration of contact pads and conductive contacts typically reduces corrosion. Preferably, when the sensor is placed in a 3 mM, and more preferably, in a 100 mM, NaCl solution, the signal arising due to the corrosion of the contact pads and/or conductive contacts is less than 3% of the signal generated by the sensor when exposed to concentration of analyte in the normal physiological range. For at least some subcutaneous glucose sensors, the current generated by analyte in a normal physiological range ranges from 3 to 500 nA.

Each of the electrodes **58**, **60**, **62**, as well as the two probe leads **68**, **70** of the temperature probe **66** (described below), are connected to contact pads **49** as shown in FIGS. **10** and **11**. In one embodiment (not shown), the contact pads **49** are on the same side of the substrate **50** as the respective electrodes or temperature probe leads to which the contact pads **49** are attached.

In other embodiments, the conductive traces **52** on at least one side are connected through vias in the substrate to contact pads **49***a* on the opposite surface of the substrate **50**, as shown in FIGS. **10** and **11**. An advantage of this configuration is that contact between the contacts on the control unit and each of the electrodes **58**, **60**, **62** and the probe leads **68**,**70** of the temperature probe **66** can be made from a single side of the substrate **50**.

In yet other embodiments (not shown), vias through the substrate are used to provide contact pads on both sides of the substrate **50** for each conductive trace **52**. The vias connecting the conductive traces **52** with the contact pads **49***a* can be formed by making holes through the substrate **50** at the appropriate points and then filling the holes with conductive material **56**.

Exemplary Electrode Configurations

A number of exemplary electrode configurations are described below, however, it will be understood that other configurations may also be used. In one embodiment, illustrated in FIG. **3**A, the sensor **42** includes two working electrodes **58***a*, **58***b* and one counter electrode **60**, which also functions as a reference electrode. In another embodiment, the sensor includes one working electrode **58***a*, one counter electrode **60**, and one reference electrode **62**, as shown in FIG. **3**B. Each of these embodiments is illustrated with all of the electrodes formed on the same side of the substrate **50**.

Alternatively, one or more of the electrodes may be formed on an opposing side of the substrate **50**. This may be convenient if the electrodes are formed using two different types of conductive material **56** (e.g., carbon and silver/silver chloride). Then, at least in some embodiments, only one type of conductive material **56** needs to be applied to each side of the substrate **50**, thereby reducing the number of steps in the manufacturing process and/or easing the registration constraints in the process. For example, if the working electrode **58** is formed using a carbon-based conductive material **56** and the reference or counter/reference electrode is formed using a silver/silver chloride conductive material **56**, then the working electrode and reference or counter/reference electrode may be formed on opposing sides of the substrate **50** for ease of manufacture.

In another embodiment, two working electrodes **58** and one counter electrode **60** are formed on one side of the substrate **50** and one reference electrode **62** and a temperature probe **66** are formed on an opposing side of the substrate **50**, as illustrated in FIG. **6**. The opposing sides of the tip of this embodiment of the sensor **42** are illustrated in FIGS. **7** and **8**.

Sensing Layer

Some analytes, such as oxygen, can be directly electrooxidized or electroreduced on the working electrode **58**. Other analytes, such as glucose and lactate, require the presence of at least one electron transfer agent and/or at least one catalyst to facilitate the electrooxidation or electroreduction of the analyte. Catalysts may also be used for those analyte, such as oxygen, that can be directly electrooxidized or electroreduced on the working electrode **58**. For these analytes, each working electrode **58** has a sensing layer **64** formed proximate to or on a working surface of the working electrode **58**. Typically, the sensing layer **64** is formed near or on only a small portion of the working electrode **58**, often near a tip of the sensor **42**. This limits the amount of material needed to form the sensor **42** and places the sensing layer **64** in the best position for contact with the analyte-containing fluid (e.g., a body fluid, sample fluid, or carrier fluid).

The sensing layer **64** includes one or more components designed to facilitate the electrolysis of the analyte. The sensing layer **64** may include, for example, a catalyst to catalyze a reaction of the analyte and produce a response at the working electrode **58**, an electron transfer agent to indirectly or directly transfer electrons between the analyte and the working electrode **58**, or both.

The sensing layer **64** may be formed as a solid composition of the desired components (e.g., an electron transfer agent and/or a catalyst). These components are preferably non-leachable from the sensor **42** and more preferably are immobilized on the sensor **42**. For example, the components may be immobilized on a working electrode **58**. Alternatively, the components of the sensing layer **64** may be immobilized within or between one or more membranes or films disposed over the working electrode **58** or the components may be immobilized in a polymeric or sol-gel matrix. Examples of immobilized sensing layers are described in U.S. Pat. Nos. 5,262,035, 5,264,104, 5,264,105, 5,320,725, 5,593,852, and 5,665,222, U.S. patent application Ser. No. 08/540,789, and PCT Patent Application No. US98/02403 entitled "Soybean Peroxidase Electrochemical Sensor", filed on Feb. 11, 1998, incorporated herein by reference.

In some embodiments, one or more of the components of the sensing layer **64** may be solvated, dispersed, or suspended in a fluid within the sensing layer **64**, instead of forming a solid composition. The fluid may be provided with the sensor **42** or may be absorbed by the sensor **42** from the analyte-containing fluid. Preferably, the components which are solvated, dispersed, or suspended in this type of sensing layer **64** are non-leachable from the sensing layer. Non-leachability may be accomplished, for example, by providing barriers (e.g., the electrode, substrate, membranes, and/or films) around the sensing layer which prevent the leaching of the components of the sensing layer **64**. One example of such a barrier is a microporous membrane or film which allows diffusion of the analyte into the sensing layer **64** to make contact with the components of the sensing layer **64**, but reduces or eliminates the diffusion of the sensing layer components (e.g., a electron transfer agent and/or a catalyst) out of the sensing layer **64**.

A variety of different sensing layer configurations can be used. In one embodiment, the sensing layer **64** is deposited on the conductive material **56** of a working electrode **58***a*, as illustrated in FIGS. **3**A and **3**B. The sensing layer **64** may extend beyond the conductive material **56** of the working electrode **58***a*. In some cases, the sensing layer **64** may also extend over the counter electrode **60** or reference electrode **62** without degrading the performance of the glucose sensor. For those sensors **42** which utilize channels **54** within which the conductive material **56** is deposited, a portion of the sensing layer **64** may be formed within the channel **54** if the conductive material **56** does not fill the channel **54**.

A sensing layer **64** in direct contact with the working electrode **58***a* may contain an electron transfer agent to transfer electrons directly or indirectly between the analyte and the working electrode, as well as a catalyst to facilitate a reaction of the analyte. For example, a glucose, lactate, or oxygen electrode may be formed having a sensing layer which contains a catalyst, such as glucose oxidase, lactate oxidase, or laccase, respectively, and an electron transfer agent that facilitates the electrooxidation of the glucose, lactate, or oxygen, respectively.

In another embodiment, the sensing layer **64** is not deposited directly on the working electrode **58***a*. Instead, the sensing layer **64** is spaced apart from the working electrode **58***a*, as illustrated in FIG. **4**A, and separated from the working electrode **58***a* by a separation layer **61**. The sepa-

ration layer **61** typically includes one or more membranes or films. In addition to separating the working electrode **58***a* from the sensing layer **64**, the separation layer **61** may also act as a mass transport limiting layer or an interferent eliminating layer, as described below.

Typically, a sensing layer **64**, which is not in direct contact with the working electrode **58***a*, includes a catalyst that facilitates a reaction of the analyte. However, this sensing layer **64** typically does not include an electron transfer agent that transfers electrons directly from the working electrode **58***a* to the analyte, as the sensing layer **64** is spaced apart from the working electrode **58***a*. One example of this type of sensor is a glucose or lactate sensor which includes an enzyme (e.g., glucose oxidase or lactate oxidase, respectively) in the sensing layer **64**. The glucose or lactate reacts with a second compound (e.g., oxygen) in the presence of the enzyme. The second compound is then electrooxidized or electroreduced at the electrode. Changes in the signal at the electrode indicate changes in the level of the second compound in the fluid and are proportional to changes in glucose or lactate level and, thus, correlate to the analyte level.

In another embodiment, two sensing layers **63**, **64** are used, as shown in FIG. **4**B. Each of the two sensing layers **63**, **64** may be independently formed on the working electrode **58***a* or in proximity to the working electrode **58***a*. One sensing layer **64** is typically, although not necessarily, spaced apart from the working electrode **58***a*. For example, this sensing layer **64** may include a catalyst which catalyzes a reaction of the analyte to form a product compound. The product compound is then electrolyzed in the second sensing layer **63** which may include an electron transfer agent to transfer electrons between the working electrode **58***a* and the product compound and/or a second catalyst to catalyze a reaction of the product compound to generate a signal at the working electrode **58***a*.

For example, a glucose or lactate sensor may include a first sensing layer **64** which is spaced apart from the working electrode and contains an enzyme, for example, glucose oxidase or lactate oxidase. The reaction of glucose or lactate in the presence of the appropriate enzyme forms hydrogen peroxide. A second sensing layer **63** is provided directly on the working electrode **58***a* and contains a peroxidase enzyme and an electron transfer agent to generate a signal at the electrode in response to the hydrogen peroxide. The level of hydrogen peroxide indicated by the sensor then correlates to the level of glucose or lactate. Another sensor which operates similarly can be made using a single sensing layer with both the glucose or lactate oxidase and the peroxidase being deposited in the single sensing layer. Examples of such sensors are described in U.S. Pat. No. 5,593,852, U.S. patent application Ser. No. 08/540,789, and PCT Patent Application No. US98/02403 entitled "Soybean Peroxidase Electrochemical Sensor", filed on Feb. 11, 1998, incorporated herein by reference.

In some embodiments, one or more of the working electrodes **58***b* do not have a corresponding sensing layer **64**, as shown in FIGS. **3**A and **4**A, or have a sensing layer (not shown) which does not contain one or more components (e.g., an electron transfer agent or catalyst) needed to electrolyze the analyte. The signal generated at this working electrode **58***b* typically arises from interferents and other sources, such as ions, in the fluid, and not in response to the analyte (because the analyte is not electrooxidized or electroreduced). Thus, the signal at this working electrode **58***b* corresponds to a background signal. The background signal can be removed from the analyte signal obtained from other working electrodes **58***a* that are associated with fully-functional sensing layers **64** by, for example, subtracting the signal at working electrode **58***b* from the signal at working electrode **58***a*.

Sensors having multiple working electrodes **58***a* may also be used to obtain more precise results by averaging the signals or measurements generated at these working electrodes **58***a*. In addition, multiple readings at a single working electrode **58***a* or at multiple working electrodes may be averaged to obtain more precise data.

Electron Transfer Agent

In many embodiments, the sensing layer **64** contains one or more electron transfer agents in contact with the conductive material **56** of the working electrode **58**, as shown in FIGS. **3**A and **3**B. In some embodiments of the invention, there is little or no leaching of the electron transfer agent away from the working electrode **58** during the period in which the sensor **42** is implanted in the patient. A diffusing or leachable (i.e., releasable) electron transfer agent often diffuses into the analyte-containing fluid, thereby reducing the effectiveness of the electrode by reducing the sensitivity of the sensor over time. In addition, a diffusing or leaching electron transfer agent in an implantable sensor **42** may also cause damage to the patient. In these embodiments, preferably, at least 90%, more preferably, at least 95%, and, most preferably, at least 99%, of the electron transfer agent remains disposed on the sensor after immersion in the analyte-containing fluid for 24 hours, and, more preferably, for 72 hours. In particular, for an implantable sensor, preferably, at least 90%, more preferably, at least 95%, and most preferably, at least 99%, of the electron transfer agent remains disposed on the sensor after immersion in the body fluid at 37° C. for 24 hours, and, more preferably, for 72 hours.

In some embodiments of the invention, to prevent leaching, the electron transfer agents are bound or otherwise immobilized on the working electrode **58** or between or within one or more membranes or films disposed over the working electrode **58**. The electron transfer agent may be immobilized on the working electrode **58** using, for example, a polymeric or sol-gel immobilization technique. Alternatively, the electron transfer agent may be chemically (e.g., ionically, covalently, or coordinatively) bound to the working electrode **58**, either directly or indirectly through another molecule, such as a polymer, that is in turn bound to the working electrode **58**.

Application of the sensing layer **64** on a working electrode **58***a* is one method for creating a working surface for the working electrode **58***a*, as shown in FIGS. **3**A and **3**B. The electron transfer agent mediates the transfer of electrons to electrooxidize or electroreduce an analyte and thereby permits a current flow between the working electrode **58** and the counter electrode **60** via the analyte. The mediation of the electron transfer agent facilitates the electrochemical analysis of analytes which are not suited for direct electrochemical reaction on an electrode.

In general, the preferred electron transfer agents are electroreducible and electrooxidizable ions or molecules having redox potentials that are a few hundred millivolts above or below the redox potential of the standard calomel electrode (SCE). Preferably, the electron transfer agents are not more reducing than about −150 mV and not more oxidizing than about +400 mV versus SCE.

The electron transfer agent may be organic, organometallic, or inorganic. Examples of organic redox species are quinones and species that in their oxidized state have quinoid structures, such as Nile blue and indophenol.

Some quinones and partially oxidized quinhydrones react with functional groups of proteins such as the thiol groups of cysteine, the amine groups of lysine and arginine, and the phenolic groups of tyrosine which may render those redox species unsuitable for some of the sensors of the present invention because of the presence of the interfering proteins in an analyte-containing fluid. Usually substituted quinones and molecules with quinoid structure are less reactive with proteins and are preferred. A preferred tetrasubstituted quinone usually has carbon atoms in positions 1, 2, 3, and 4.

In general, electron transfer agents suitable for use in the invention have structures or charges which prevent or substantially reduce the diffusional loss of the electron transfer agent during the period of time that the sample is being analyzed. The preferred electron transfer agents include a redox species bound to a polymer which can in turn be immobilized on the working electrode. The bond between the redox species and the polymer may be covalent, coordinative, or ionic. Useful electron transfer agents and methods for producing them are described in U.S. Pat. Nos. 5,264,104; 5,356,786; 5,262,035; and 5,320,725, incorporated herein by reference. Although any organic or organometallic redox species can be bound to a polymer and used as an electron transfer agent, the preferred redox species is a transition metal compound or complex. The preferred transition metal compounds or complexes include osmium, ruthenium, iron, and cobalt compounds or complexes. The most preferred are osmium compounds and complexes. It will be recognized that many of the redox species described below may also be used, typically without a polymeric component, as electron transfer agents in a carrier fluid or in a sensing layer of a sensor where leaching of the electron transfer agent is acceptable.

One type of non-releasable polymeric electron transfer agent contains a redox species covalently bound in a polymeric composition. An example of this type of mediator is poly(vinylferrocene).

Another type of non-releasable electron transfer agent contains an ionically-bound redox species. Typically, this type of mediator includes a charged polymer coupled to an oppositely charged redox species. Examples of this type of mediator include a negatively charged polymer such as Nafion® (DuPont) coupled to a positively charged redox species such as an osmium or ruthenium polypyridyl cation. Another example of an ionically-bound mediator is a positively charged polymer such as quaternized poly(4-vinyl pyridine) or poly(1-vinyl imidazole) coupled to a negatively charged redox species such as ferricyanide or ferrocyanide. The preferred ionically-bound redox species is a highly charged redox species bound within an oppositely charged redox polymer.

In another embodiment of the invention, suitable non-releasable electron transfer agents include a redox species coordinatively bound to a polymer. For example, the mediator may be formed by coordination of an osmium or cobalt 2,2'-bipyridyl complex to poly(1-vinyl imidazole) or poly (4-vinyl pyridine).

The preferred electron transfer agents are osmium transition metal complexes with one or more ligands, each ligand having a nitrogen-containing heterocycle such as 2,2'-bipyridine, 1,10-phenanthroline, or derivatives thereof. Furthermore, the preferred electron transfer agents also have one or more ligands covalently bound in a polymer, each ligand having at least one nitrogen-containing heterocycle, such as pyridine, imidazole, or derivatives thereof. These preferred electron transfer agents exchange electrons rapidly between each other and the working electrodes **58** so that the complex can be rapidly oxidized and reduced.

One example of a particularly useful electron transfer agent includes (a) a polymer or copolymer having pyridine or imidazole functional groups and (b) osmium cations complexed with two ligands, each ligand containing 2,2'-bipyridine, 1,10-phenanthroline, or derivatives thereof, the two ligands not necessarily being the same. Preferred derivatives of 2,2'-bipyridine for complexation with the osmium cation are 4,4'-dimethyl-2,2'-bipyridine and mono-, di-, and polyalkoxy-2,2'-bipyridines, such as 4,4'-dimethoxy-2,2'-bipyridine. Preferred derivatives of 1,10-phenanthroline for complexation with the osmium cation are 4,7-dimethyl-1,10-phenanthroline and mono, di-, and polyalkoxy-1,10-phenanthrolines, such as 4,7-dimethoxy-1,10-phenanthroline. Preferred polymers for complexation with the osmium cation include polymers and copolymers of poly(1-vinyl imidazole) (referred to as "PVI") and poly(4-vinyl pyridine) (referred to as "PVP"). Suitable copolymer substituents of poly(1-vinyl imidazole) include acrylonitrile, acrylamide, and substituted or quaternized N-vinyl imidazole. Most preferred are electron transfer agents with osmium complexed to a polymer or copolymer of poly(1-vinyl imidazole).

The preferred electron transfer agents have a redox potential ranging from −100 mV to about +150 mV versus the standard calomel electrode (SCE). Preferably, the potential of the electron transfer agent ranges from −100 mV to +150 mV and more preferably, the potential ranges from −50 mV to +50 mV. The most preferred electron transfer agents have osmium redox centers and a redox potential ranging from +50 mV to −150 mV versus SCE.

Catalyst

The sensing layer **64** may also include a catalyst which is capable of catalyzing a reaction of the analyte. The catalyst may also, in some embodiments, act as an electron transfer agent. One example of a suitable catalyst is an enzyme which catalyzes a reaction of the analyte. For example, a catalyst, such as a glucose oxidase, glucose dehydrogenase (e.g., pyrroloquinoline quinone glucose dehydrogenase (PQQ)), or oligosaccharide dehydrogenase, may be used when the analyte is glucose. A lactate oxidase or lactate dehydrogenase may be used when the analyte is lactate. Laccase may be used when the analyte is oxygen or when oxygen is generated or consumed in response to a reaction of the analyte.

Preferably, the catalyst is non-leachably disposed on the sensor, whether the catalyst is part of a solid sensing layer in the sensor or solvated in a fluid within the sensing layer. More preferably, the catalyst is immobilized within the sensor (e.g., on the electrode and/or within or between a membrane or film) to prevent unwanted leaching of the catalyst away from the working electrode **58** and into the patient. This may be accomplished, for example, by attaching the catalyst to a polymer, cross linking the catalyst with another electron transfer agent (which, as described above, can be polymeric), and/or providing one or more barrier membranes or films with pore sizes smaller than the catalyst.

As described above, a second catalyst may also be used. This second catalyst is often used to catalyze a reaction of a product compound resulting from the catalyzed reaction of the analyte. The second catalyst typically operates with an electron transfer agent to electrolyze the product compound to generate a signal at the working electrode. Alternatively, the second catalyst may be provided in an interferent-eliminating layer to catalyze reactions that remove interferents, as described below.

One embodiment of the invention is an electrochemical sensor in which the catalyst is mixed or dispersed in the

conductive material **56** which forms the conductive trace **52** of a working electrode **58**. This may be accomplished, for example, by mixing a catalyst, such as an enzyme, in a carbon ink and applying the mixture into a channel **54** on the surface of the substrate **50**. Preferably, the catalyst is immobilized in the channel **53** so that it can not leach away from the working electrode **58**. This may be accomplished, for example, by curing a binder in the carbon ink using a curing technique appropriate to the binder. Curing techniques include, for example, evaporation of a solvent or dispersant, exposure to ultraviolet light, or exposure to heat. Typically, the mixture is applied under conditions that do not substantially degrade the catalyst. For example, the catalyst may be an enzyme that is heat-sensitive. The enzyme and conductive material mixture should be applied and cured, preferably, without sustained periods of heating. The mixture may be cured using evaporation or UV curing techniques or by the exposure to heat that is sufficiently short that the catalyst is not substantially degraded.

Another consideration for in vivo analyte sensors is the thermostability of the catalyst. Many enzymes have only limited stability at biological temperatures. Thus, it may be necessary to use large amounts of the catalyst and/or use a catalyst that is thermostable at the necessary temperature (e.g., 37° C. or higher for normal body temperature). A thermostable catalyst may be defined as a catalyst which loses less than 5% of its activity when held at 37° C. for at least one hour, preferably, at least one day, and more preferably at least three days. One example of a thermostable catalyst is soybean peroxidase. This particular thermostable catalyst may be used in a glucose or lactate sensor when combined either in the same or separate sensing layers with glucose or lactate oxidase or dehydrogenase. A further description of thermostable catalysts and their use in electrochemical inventions is found in U.S. Pat. No. 5,665,222 U.S. patent application Ser. No. 08/540,789, and PCT Application No. US98/02403 entitled "Soybean Peroxidase Electrochemical Sensor", filed on Feb. 11, 1998.

Electrolysis of the Analyte

To electrolyze the analyte, a potential (versus a reference potential) is applied across the working and counter electrodes **58**, **60**. The minimum magnitude of the applied potential is often dependent on the particular electron transfer agent, analyte (if the analyte is directly electrolyzed at the electrode), or second compound (if a second compound, such as oxygen or hydrogen peroxide, whose level is dependent on the analyte level, is directly electrolyzed at the electrode). The applied potential usually equals or is more oxidizing or reducing, depending on the desired electrochemical reaction, than the redox potential of the electron transfer agent, analyte, or second compound, whichever is directly electrolyzed at the electrode. The potential at the working electrode is typically large enough to drive the electrochemical reaction to or near completion.

The magnitude of the potential may optionally be limited to prevent significant (as determined by the current generated in response to the analyte) electrochemical reaction of interferents, such as urate, ascorbate, and acetaminophen. The limitation of the potential may be obviated if these interferents have been removed in another way, such as by providing an interferent-limiting barrier, as described below, or by including a working electrode **58***b* (see FIG. **3**A) from which a background signal may be obtained.

When a potential is applied between the working electrode **58** and the counter electrode **60**, an electrical current will flow. The current is a result of the electrolysis of the analyte or a second compound whose level is affected by the analyte. In one embodiment, the electrochemical reaction occurs via an electron transfer agent and the optional catalyst. Many analytes B are oxidized (or reduced) to products C by an electron transfer agent species A in the presence of an appropriate catalyst (e.g., an enzyme). The electron transfer agent A is then oxidized (or reduced) at the electrode. Electrons are collected by (or removed from) the electrode and the resulting current is measured. This process is illustrated by reaction equations (1) and (2) (similar equations may be written for the reduction of the analyte B by a redox mediator A in the presence of a catalyst):

$$nA(ox) + B \xrightarrow{\text{catalyst}} nA(red) + C \quad (1)$$

$$nA(red) \xrightarrow{\text{electrode}} nA(ox) + ne^- \quad (2)$$

As an example, an electrochemical sensor may be based on the reaction of a glucose molecule with two non-leachable ferricyanide anions in the presence of glucose oxidase to produce two non-leachable ferrocyanide anions, two hydrogen ions, and gluconolactone. The amount of glucose present is assayed by electrooxidizing the non-leachable ferrocyanide anions to non-leachable ferricyanide anions and measuring the current.

In another embodiment, a second compound whose level is affected by the analyte is electrolyzed at the working electrode. In some cases, the analyte D and the second compound, in this case, a reactant compound E, such as oxygen, react in the presence of the catalyst, as shown in reaction equation (3).

$$D + E \xrightarrow{\text{catalyst}} F + G \quad (3)$$

The reactant compound E is then directly oxidized (or reduced) at the working electrode, as shown in reaction equation (4)

$$nE(red) \xrightarrow{\text{electrode}} nE(ox) + ne^- \quad (4)$$

Alternatively, the reactant compound E is indirectly oxidized (or reduced) using an electron transfer agent H (optionally in the presence of a catalyst), that is subsequently reduced or oxidized at the electrode, as shown in reaction equations (5) and (6).

$$nH(ox) + E \rightarrow nH(red) + I \quad (5)$$

$$nH(red) \xrightarrow{\text{electrode}} nH(ox) + ne^- \quad (6)$$

In either case, changes in the concentration of the reactant compound, as indicated by the signal at the working electrode, correspond inversely to changes in the analyte (i.e., as the level of analyte increase then the level of reactant compound and the signal at the electrode decreases.)

In other embodiments, the relevant second compound is a product compound F, as shown in reaction equation (3). The product compound F is formed by the catalyzed reaction of analyte D and then be directly electrolyzed at the electrode or indirectly electrolyzed using an electron transfer agent and, optionally, a catalyst. In these embodiments, the signal arising from the direct or indirect electrolysis of the product compound F at the working electrode corresponds directly to the level of the analyte (unless there are other sources of the

product compound). As the level of analyte increases, the level of the product compound and signal at the working electrode increases.

Those skilled in the art will recognize that there are many different reactions that will achieve the same result; namely the electrolysis of an analyte or a compound whose level depends on the level of the analyte. Reaction equations (1) through (6) illustrate non-limiting examples of such reactions.

Temperature Probe

A variety of optional items may be included in the sensor. One optional item is a temperature probe **66** (FIGS. **8** and **11**). The temperature probe **66** may be made using a variety of known designs and materials. One exemplary temperature probe **66** is formed using two probe leads **68**, **70** connected to each other through a temperature-dependent element **72** that is formed using a material with a temperature-dependent characteristic. An example of a suitable temperature-dependent characteristic is the resistance of the temperature-dependent element **72**.

The two probe leads **68**, **70** are typically formed using a metal, an alloy, a semimetal, such as graphite, a degenerate or highly doped semiconductor, or a small-band gap semiconductor. Examples of suitable materials include gold, silver, ruthenium oxide, titanium nitride, titanium dioxide, indium doped tin oxide, tin doped indium oxide, or graphite. The temperature-dependent element **72** is typically made using a fine trace (e.g., a conductive trace that has a smaller cross-section than that of the probe leads **68**, **70**) of the same conductive material as the probe leads, or another material such as a carbon ink, a carbon fiber, or platinum, which has a temperature-dependent characteristic, such as resistance, that provides a temperature-dependent signal when a voltage source is attached to the two probe leads **68**, **70** of the temperature probe **66**. The temperature-dependent characteristic of the temperature-dependent element **72** may either increase or decrease with temperature. Preferably, the temperature dependence of the characteristic of the temperature-dependent element **72** is approximately linear with temperature over the expected range of biological temperatures (about 25 to 45° C.), although this is not required.

Typically, a signal (e.g., a current) having an amplitude or other property that is a function of the temperature can be obtained by providing a potential across the two probe leads **68**, **70** of the temperature probe **66**. As the temperature changes, the temperature-dependent characteristic of the temperature-dependent element **72** increases or decreases with a corresponding change in the signal amplitude. The signal from the temperature probe **66** (e.g., the amount of current flowing through the probe) may be combined with the signal obtained from the working electrode **58** by, for example, scaling the temperature probe signal and then adding or subtracting the scaled temperature probe signal from the signal at the working electrode **58**. In this manner, the temperature probe **66** can provide a temperature adjustment for the output from the working electrode **58** to offset the temperature dependence of the working electrode **58**.

One embodiment of the temperature probe includes probe leads **68**, **70** formed as two spaced-apart channels with a temperature-dependent element **72** formed as a cross-channel connecting the two spaced-apart channels, as illustrated in FIG. **8**. The two spaced-apart channels contain a conductive material, such as a metal, alloy, semimetal, degenerate semiconductor, or metallic compound. The cross-channel may contain the same material (provided the cross-channel has a smaller cross-section than the two spaced-apart channels) as the probe leads **68**, **70**. In other embodiments, the material in the cross-channel is different than the material of the probe leads **68**, **70**.

One exemplary method for forming this particular temperature probe includes forming the two spaced-apart channels and then filling them with the metallic or alloyed conductive material. Next, the cross-channel is formed and then filled with the desired material. The material in the cross-channel overlaps with the conductive material in each of the two spaced-apart channels to form an electrical connection.

For proper operation of the temperature probe **66**, the temperature-dependent element **72** of the temperature probe **66** can not be shorted by conductive material formed between the two probe leads **68**, **70**. In addition, to prevent conduction between the two probe leads **68**, **70** by ionic species within the body or sample fluid, a covering may be provided over the temperature-dependent element **72**, and preferably over the portion of the probe leads **68**, **70** that is implanted in the patient. The covering may be, for example, a non-conducting film disposed over the temperature-dependent element **72** and probe leads **68**, **70** to prevent the ionic conduction. Suitable non-conducting films include, for example, Kapton™ polyimide films (DuPont, Wilmington, Del.).

Another method for eliminating or reducing conduction by ionic species in the body or sample fluid is to use an ac voltage source connected to the probe leads **68**, **70**. In this way, the positive and negative ionic species are alternately attracted and repelled during each half cycle of the ac voltage. This results in no net attraction of the ions in the body or sample fluid to the temperature probe **66**. The maximum amplitude of the ac current through the temperature-dependent element **72** may then be used to correct the measurements from the working electrodes **58**.

The temperature probe can be placed on the same substrate as the electrodes. Alternatively, a temperature probe may be placed on a separate substrate. In addition, the temperature probe may be used by itself or in conjunction with other devices.

Another embodiment of a temperature probe utilizes the temperature dependence of the conductivity of a solution (e.g., blood or interstitial fluid). Typically, the conductivity of an electrolyte-containing solution is dependent on the temperature of the solution, assuming that the concentration of electrolytes is relatively constant. Blood, interstitial fluid, and other bodily fluids are solutions with relatively constant levels of electrolytes. Thus, a sensor **42** can include two or more conductive traces (not shown) which are spaced apart by a known distance. A portion of these conductive traces is exposed to the solution and the conductivity between the exposed portions of the conductive traces is measured using known techniques (e.g., application of a constant or known current or potential and measurement of the resulting potential or current, respectively, to determine the conductivity).

A change in conductivity is related to a change in temperature. This relation can be modeled using linear, quadratic, exponential, or other relations. The parameters for this relationship typically do not vary significantly between most people. The calibration for the temperature probe can be determined by a variety of methods, including, for example, calibration of each sensor **42** using an independent method of determining temperature (e.g., a thermometer, an optical or electrical temperature detector, or the temperature probe **66**, described above) or calibrating one sensor **42** and using that calibration for all other sensors in a batch based on uniformity in geometry.

Biocompatible Layer

An optional film layer **75** is formed over at least that portion of the sensor **42** which is subcutaneously inserted into the patient, as shown in FIG. **9**. This optional film layer **74** may serve one or more functions. The film layer **74** prevents the penetration of large biomolecules into the electrodes. This is accomplished by using a film layer **74** having a pore size that is smaller than the biomolecules that are to be excluded. Such biomolecules may foul the electrodes and/or the sensing layer **64** thereby reducing the effectiveness of the sensor **42** and altering the expected signal amplitude for a given analyte concentration. The fouling of the working electrodes **58** may also decrease the effective life of the sensor **42**. The biocompatible layer **74** may also prevent protein adhesion to the sensor **42**, formation of blood clots, and other undesirable interactions between the sensor **42** and body.

For example, the sensor may be completely or partially coated on its exterior with a biocompatible coating. A preferred biocompatible coating is a hydrogel which contains at least 20 wt. % fluid when in equilibrium with the analyte-containing fluid. Examples of suitable hydrogels are described in U.S. Pat. No. 5,593,852, incorporated herein by reference, and include crosslinked polyethylene oxides, such as polyethylene oxide tetraacrylate.

Interferent-Eliminating Layer

An interferent-eliminating layer (not shown) may be included in the sensor **42**. The interferent-eliminating layer may be incorporated in the biocompatible layer **75** or in the mass transport limiting layer **74** (described below) or may be a separate layer. Interferents are molecules or other species that are electroreduced or electrooxidized at the electrode, either directly or via an electron transfer agent, to produce a false signal. In one embodiment, a film or membrane prevents the penetration of one or more interferents into the region around the working electrodes **58**. Preferably, this type of interferent-eliminating layer is much less permeable to one or more of the interferents than to the analyte.

The interferent-eliminating layer may include ionic components, such as Nafion®, incorporated into a polymeric matrix to reduce the permeability of the interferent-eliminating layer to ionic interferents having the same charge as the ionic components. For example, negatively charged compounds or compounds that form negative ions may be incorporated in the interferent-eliminating layer to reduce the permeation of negative species in the body or sample fluid.

Another example of an interferent-eliminating layer includes a catalyst for catalyzing a reaction which removes interferents. One example of such a catalyst is a peroxidase. Hydrogen peroxide reacts with interferents, such as acetaminophen, urate, and ascorbate. The hydrogen peroxide may be added to the analyte-containing fluid or may be generated in situ, by, for example, the reaction of glucose or lactate in the presence of glucose oxidase or lactate oxidase, respectively. Examples of interferent eliminating layers include a peroxidase enzyme crosslinked (a) using glutaraldehyde as a crosslinking agent or (b) oxidation of oligosaccharide groups in the peroxidase glycoenzyme with $NaIO_4$, followed by coupling of the aldehydes formed to hydrazide groups in a polyacrylamide matrix to form hydrazones are describe in U.S. Pat. Nos. 5,262,305 and 5,356,786, incorporated herein by reference.

Mass Transport Limiting Layer

A mass transport limiting layer **74** may be included with the sensor to act as a diffusion-limiting barrier to reduce the rate of mass transport of the analyte, for example, glucose or lactate, into the region around the working electrodes **58**. By limiting the diffusion of the analyte, the steady state concentration of the analyte in the proximity of the working electrode **58** (which is proportional to the concentration of the analyte in the body or sample fluid) can be reduced. This extends the upper range of analyte concentrations that can still be accurately measured and may also expand the range in which the current increases approximately linearly with the level of the analyte.

It is preferred that the permeability of the analyte through the film layer **74** vary little or not at all with temperature, so as to reduce or eliminate the variation of current with temperature. For this reason, it is preferred that in the biologically relevant temperature range from about 25° C. to about 45° C., and most importantly from 30° C. to 40° C., neither the size of the pores in the film nor its hydration or swelling change excessively. Preferably, the mass transport limiting layer is made using a film that absorbs less than 5 wt. % of fluid over 24 hours. This may reduce or obviate any need for a temperature probe. For implantable sensors, it is preferable that the mass transport limiting layer is made using a film that absorbs less than 5 wt. % of fluid over 24 hours at 37° C.

Particularly useful materials for the film layer **74** are membranes that do not swell in the analyte-containing fluid that the sensor tests. Suitable membranes include 3 to 20,000 nm diameter pores. Membranes having 5 to 500 nm diameter pores with well-defined, uniform pore sizes and high aspect ratios are preferred. In one embodiment, the aspect ratio of the pores is preferably two or greater and more preferably five or greater.

Well-defined and uniform pores can be made by track etching a polymeric membrane using accelerated electrons, ions, or particles emitted by radioactive nuclei. Most preferred are anisotropic, polymeric, track etched membranes that expand less in the direction perpendicular to the pores than in the direction of the pores when heated. Suitable polymeric membranes included polycarbonate membranes from Poretics (Livermore, Calif., catalog number 19401, 0.01 μm pore size polycarbonate membrane) and Corning Costar Corp. (Cambridge, Mass., Nucleopore™ brand membranes with 0.015 μm pore size). Other polyolefin and polyester films may be used. It is preferred that the permeability of the mass transport limiting membrane changes no more than 4%, preferably, no more than 3%, and, more preferably, no more than 2%, per ° C. in the range from 30° C. to 40° C. when the membranes resides in the subcutaneous interstitial fluid.

In some embodiments of the invention, the mass transport limiting layer **74** may also limit the flow of oxygen into the sensor **42**. This can improve the stability of sensors **42** that are used in situations where variation in the partial pressure of oxygen causes non-linearity in sensor response. In these embodiments, the mass transport limiting layer **74** restricts oxygen transport by at least 40%, preferably at least 60%, and more preferably at least 80%, than the membrane restricts transport of the analyte. For a given type of polymer, films having a greater density (e.g., a density closer to that of the crystalline polymer) are preferred. Polyesters, such as polyethylene terephthalate, are typically less permeable to oxygen and are, therefore, preferred over polycarbonate membranes.

Anticlotting Agent

An implantable sensor may also, optionally, have an anticlotting agent disposed on a portion the substrate which is implanted into a patient. This anticlotting agent may reduce or eliminate the clotting of blood or other body fluid

around the sensor, particularly after insertion of the sensor. Blood clots may foul the sensor or irreproducibly reduce the amount of analyte which diffuses into the sensor. Examples of useful anticlotting agents include heparin and tissue plasminogen activator (TPA), as well as other known anticlotting agents.

The anticlotting agent may be applied to at least a portion of that part of the sensor **42** that is to be implanted. The anticlotting agent may be applied, for example, by bath, spraying, brushing, or dipping. The anticlotting agent is allowed to dry on the sensor **42**. The anticlotting agent may be immobilized on the surface of the sensor or it may be allowed to diffuse away from the sensor surface. Typically, the quantities of anticlotting agent disposed on the sensor are far below the amounts typically used for treatment of medical conditions involving blood clots and, therefore, have only a limited, localized effect.

Sensor Lifetime

The sensor **42** may be designed to be a replaceable component in an in vivo analyte monitor, and particularly in an implantable analyte monitor. Typically, the sensor **42** is capable of operation over a period of days. Preferably, the period of operation is at least one day, more preferably at least three days, and most preferably at least one week. The sensor **42** can then be removed and replaced with a new sensor. The lifetime of the sensor **42** may be reduced by the fouling of the electrodes or by the leaching of the electron transfer agent or catalyst. These limitations on the longevity of the sensor **42** can be overcome by the use of a biocompatible layer **75** or non-leachable electron transfer agent and catalyst, respectively, as described above.

Another primary limitation on the lifetime of the sensor **42** is the temperature stability of the catalyst. Many catalysts are enzymes, which are very sensitive to the ambient temperature and may degrade at temperatures of the patient's body (e.g., approximately 37° C. for the human body). Thus, robust enzymes should be used where available. The sensor **42** should be replaced when a sufficient amount of the enzyme has been deactivated to introduce an unacceptable amount of error in the measurements.

Insertion Device

An insertion device **120** can be used to subcutaneously insert the sensor **42** into the patient, as illustrated in FIG. **12**. The insertion device **120** is typically formed using structurally rigid materials, such as metal or rigid plastic. Preferred materials include stainless steel and ABS (acrylonitrile-butadiene-styrene) plastic. In some embodiments, the insertion device **120** is pointed and/or sharp at the tip **121** to facilitate penetration of the skin of the patient. A sharp, thin insertion device may reduce pain felt by the patient upon insertion of the sensor **42**. In other embodiments, the tip **121** of the insertion device **120** has other shapes, including a blunt or flat shape. These embodiments may be particularly useful when the insertion device **120** does not penetrate the skin but rather serves as a structural support for the sensor **42** as the sensor **42** is pushed into the skin.

The insertion device **120** may have a variety of cross-sectional shapes, as shown in FIGS. **13**A, **13**B, and **13**C. The insertion device **120** illustrated in FIG. **13**A is a flat, planar, pointed strip of rigid material which may be attached or otherwise coupled to the sensor **42** to ease insertion of the sensor **42** into the skin of the patient, as well as to provide structural support to the sensor **42** during insertion. The insertion devices **120** of FIGS. **13**B and **13**C are U- or V-shaped implements that support the sensor **42** to limit the amount that the sensor **42** may bend or bow during insertion. The cross-sectional width **124** of the insertion devices **120** illustrated in FIGS. **13**B and **13**C is typically 1 mm or less, preferably 700 μm or less, more preferably 500 μm or less, and most preferably 300 μm or less. The cross-sectional height **126** of the insertion device **120** illustrated in FIGS. **13**B and **13**C is typically about 1 mm or less, preferably about 700 μm or less, and more preferably about 500 μm or less.

The sensor **42** itself may include optional features to facilitate insertion. For example, the sensor **42** may be pointed at the tip **123** to ease insertion, as illustrated in FIG. **12**. In addition, the sensor **42** may include a barb **125** which helps retain the sensor **42** in the subcutaneous tissue of the patient. The barb **125** may also assist in anchoring the sensor **42** within the subcutaneous tissue of the patient during operation of the sensor **42**. However, the barb **125** is typically small enough that little damage is caused to the subcutaneous tissue when the sensor **42** is removed for replacement. The sensor **42** may also include a notch **127** that can be used in cooperation with a corresponding structure (not shown) in the insertion device to apply pressure against the sensor **42** during insertion, but disengage as the insertion device **120** is removed. One example of such a structure in the insertion device is a rod (not shown) between two opposing sides of an insertion device **120** and at an appropriate height of the insertion device **120**.

In operation, the sensor **42** is placed within or next to the insertion device **120** and then a force is provided against the insertion device **120** and/or sensor **42** to carry the sensor **42** into the skin of the patient. In one embodiment, the force is applied to the sensor **42** to push the sensor into the skin, while the insertion device **120** remains stationary and provides structural support to the sensor **42**. Alternatively, the force is applied to the insertion device **120** and optionally to the sensor **42** to push a portion of both the sensor **42** and the insertion device **120** through the skin of the patient and into the subcutaneous tissue. The insertion device **120** is optionally pulled out of the skin and subcutaneous tissue with the sensor **42** remaining in the subcutaneous tissue due to frictional forces between the sensor **42** and the patient's tissue. If the sensor **42** includes the optional barb **125**, then this structure may also facilitate the retention of the sensor **42** within the interstitial tissue as the barb catches in the tissue.

The force applied to the insertion device **120** and/or the sensor **42** may be applied manually or mechanically. Preferably, the sensor **42** is reproducibly inserted through the skin of the patient. In one embodiment, an insertion gun is used to insert the sensor. One example of an insertion gun **200** for inserting a sensor **42** is shown in FIG. **26**. The insertion gun **200** includes a housing **202** and a carrier **204**. The insertion device **120** is typically mounted on the carrier **204** and the sensor **42** is pre-loaded into the insertion device **120**. The carrier **204** drives the sensor **42** and, optionally, the insertion device **120** into the skin of the patient using, for example, a cocked or wound spring, a burst of compressed gas, an electromagnet repelled by a second magnet, or the like, within the insertion gun **200**. In some instances, for example, when using a spring, the carrier **204** and insertion device may be moved, cocked, or otherwise prepared to be directed towards the skin of the patient.

After the sensor **42** is inserted, the insertion gun **200** may contain a mechanism which pulls the insertion device **120** out of the skin of the patient. Such a mechanism may use a spring, electromagnet, or the like to remove the insertion device **120**.

The insertion gun may be reusable. The insertion device **120** is often disposable to avoid the possibility of contami-

nation. Alternatively, the insertion device **120** may be sterilized and reused. In addition, the insertion device **120** and/or the sensor **42** may be coated with an anticlotting agent to prevent fouling of the sensor **42**.

In one embodiment, the sensor **42** is injected between 2 to 12 mm into the interstitial tissue of the patient for subcutaneous implantation. Preferably, the sensor is injected 3 to 9 mm, and more preferably 5 to 7 mm, into the interstitial tissue. Other embodiments of the invention, may include sensors implanted in other portions of the patient, including, for example, in an artery, vein, or organ. The depth of implantation varies depending on the desired implantation target.

Although the sensor **42** may be inserted anywhere in the body, it is often desirable that the insertion site be positioned so that the on-skin sensor control unit **44** can be concealed. In addition, it is often desirable that the insertion site be at a place on the body with a low density of nerve endings to reduce the pain to the patient. Examples of preferred sites for insertion of the sensor **42** and positioning of the on-skin sensor control unit **44** include the abdomen, thigh, leg, upper arm, and shoulder.

An insertion angle is measured from the plane of the skin (i.e., inserting the sensor perpendicular to the skin would be a 90° insertion angle). Insertion angles usually range from 10 to 90°, typically from 15 to 60°, and often from 30 to 45°.

On-Skin Sensor Control Unit

The on-skin sensor control unit **44** is configured to be placed on the skin of a patient. The on-skin sensor control unit **44** is optionally formed in a shape that is comfortable to the patient and which may permit concealment, for example, under a patient's clothing. The thigh, leg, upper arm, shoulder, or abdomen are convenient parts of the patient's body for placement of the on-skin sensor control unit **44** to maintain concealment. However, the on-skin sensor control unit **44** may be positioned on other portions of the patient's body. One embodiment of the on-skin sensor control unit **44** has a thin, oval shape to enhance concealment, as illustrated in FIGS. **14–16**. However, other shapes and sizes may be used.

The particular profile, as well as the height, width, length, weight, and volume of the on-skin sensor control unit **44** may vary and depends, at least in part, on the components and associated functions included in the on-skin sensor control unit **44**, as discussed below. For example, in some embodiments, the on-skin sensor control unit **44** has a height of 1.3 cm or less, and preferably 0.7 cm or less. In some embodiments, the on-skin sensor control unit **44** has a weight of 90 grams or less, preferably 45 grams or less, and more preferably 25 grams or less. In some embodiments, the on-skin sensor control unit **44** has a volume of about 15 cm^3 or less, preferably about 10 cm^3 or less, more preferably about 5 cm^3 or less, and most preferably about 2.5 cm^3 or less.

The on-skin sensor control unit **44** includes a housing **45**, as illustrated in FIGS. **14–16**. The housing **45** is typically formed as a single integral unit that rests on the skin of the patient. The housing **45** typically contains most or all of the electronic components, described below, of the on-skin sensor control unit **44**. The on-skin sensor control unit **44** usually includes no additional cables or wires to other electronic components or other devices. If the housing includes two or more parts, then those parts typically fit together to form a single integral unit.

The housing **45** of the on-skin sensor control unit **44**, illustrated in FIGS. **14–16**, may be formed using a variety of materials, including, for example, plastic and polymeric materials, particularly rigid thermoplastics and engineering thermoplastics. Suitable materials include, for example, polyvinyl chloride, polyethylene, polypropylene, polystyrene, ABS polymers, and copolymers thereof. The housing **45** of the on-skin sensor control unit **44** may be formed using a variety of techniques including, for example, injection molding, compression molding, casting, and other molding methods. Hollow or recessed regions may be formed in the housing **45** of the on-skin sensor control unit **44**. The electronic components of the on-skin sensor control unit **44**, described below, and/or other items, such as a battery or a speaker for an audible alarm, may be placed in the hollow or recessed areas.

In some embodiments, conductive contacts **80** are provided on the exterior of the housing **45**. In other embodiments, the conductive contacts **80** are provided on the interior of the housing **45**, for example, within a hollow or recessed region.

In some embodiments, the electronic components and/or other items are incorporated into the housing **45** of the on-skin sensor control unit **44** as the plastic or polymeric material is molded or otherwise formed. In other embodiments, the electronic components and/or other items are incorporated into the housing **45** as the molded material is cooling or after the molded material has been reheated to make it pliable. Alternatively, the electronic components and/or other items may be secured to the housing **45** using fasteners, such as screws, nuts and bolts, nails, staples, rivets, and the like or adhesives, such as contact adhesives, pressure sensitive adhesives, glues, epoxies, adhesive resins, and the like. In some cases, the electronic components and/or other items are not affixed to the housing **45** at all.

In some embodiments, the housing **45** of the on-skin sensor control unit **44** is a single piece. The conductive contacts **80** may be formed on the exterior of the housing **45** or on the interior of the housing **45** provided there is a port **78** in the housing **45** through which the sensor **42** can be directed to access the conductive contacts **80**.

In other embodiments, the housing **45** of the on-skin sensor control unit **44** is formed in at least two separate portions that fit together to form the housing **45**, for example, a base **74** and a cover **76**, as illustrated in FIGS. **14–16**. The two or more portions of the housing **45** may be entirely separate from each other. Alternatively, at least some of the two or more portions of the housing **45** may be connected together, for example, by a hinge, to facilitate the coupling of the portions to form the housing **45** of the on-skin sensor control unit **44**.

These two or more separate portions of the housing **45** of the on-skin sensor control unit **44** may have complementary, interlocking structures, such as, for example, interlocking ridges or a ridge on one component and a complementary groove on another component, so that the two or more separate components may be easily and/or firmly coupled together. This may be useful, particularly if the components are taken apart and fit together occasionally, for example, when a battery or sensor **42** is replaced. However, other fasteners may also be used to couple the two or more components together, including, for example, screws, nuts and bolts, nails, staples, rivets, or the like. In addition, adhesives, both permanent or temporary, may be used including, for example, contact adhesives, pressure sensitive adhesives, glues, epoxies, adhesive resins, and the like.

Typically, the housing **45** is at least water resistant to prevent the flow of fluids into contact with the components in the housing, including, for example, the conductive contacts **80**. Preferably, the housing is waterproof. In one

embodiment, two or more components of the housing **45**, for example, the base **74** and the cover **76**, fit together tightly to form a hermetic, waterproof, or water resistant seal so that fluids can not flow into the interior of the on-skin sensor control unit **44**. This may be useful to avoid corrosion currents and/or degradation of items within the on-skin sensor control unit **44**, such as the conductive contacts, the battery, or the electronic components, particularly when the patient engages in such activities as showering, bathing, or swimming.

Water resistant, as used herein, means that there is no penetration of water through a water resistant seal or housing when immersed in water at a depth of one meter at sea level. Waterproof, as used herein, means that there is no penetration of water through the waterproof seal or housing when immersed in water at a depth of ten meters, and preferably fifty meters, at sea level. It is often desirable that the electronic circuitry, power supply (e.g., battery), and conductive contacts of the on-skin sensor control unit, as well as the contact pads of the sensor, are contained in a water resistant, and preferably, a waterproof, environment.

In addition to the portions of the housing **45**, such as the base **74** and cover **76**, there may be other individually-formed pieces of the on-skin sensor control unit **44**, which may be assembled during or after manufacture. One example of an individually-formed piece is a cover for electronic components that fits a recess in the base **74** or cover **76**. Another example is a cover for a battery provided in the base **74** or cover **76**. These individually-formed pieces of the on-skin sensor control unit **44** may be permanently affixed, such as, for example, a cover for electronic components, or removably affixed, such as, for example, a removable cover for a battery, to the base **74**, cover **76**, or other component of the on-skin sensor control unit **44**. Methods for affixing these individually-formed pieces include the use of fasteners, such as screws, nuts and bolts, staples, nails, rivets, and the like, frictional fasteners, such as tongue and groove structures, and adhesives, such as contact adhesives, pressure sensitive adhesives, glues, epoxies, adhesive resins, and the like.

One embodiment of the on-skin sensor control unit **44** is a disposable unit complete with a battery for operating the unit. There are no portions of the unit that the patient needs to open or remove, thereby reducing the size of the unit and simplifying its construction. The on-skin sensor control unit **44** optionally remains in a sleep mode prior to use to conserve the battery's power. The on-skin sensor control unit **44** detects that it is being used and activates itself. Detection of use may be through a number of mechanisms. These include, for example, detection of a change in resistance across the electrical contacts, actuation of a switch upon mating the on-skin sensor control unit **44** with a mounting unit **77** (see FIGS. **27**A and **28**A). The on-skin sensor control unit **44** is typically replaced when it no longer operates within threshold limits, for example, if the battery or other power source does not generate sufficient power. Often this embodiment of the on-skin sensor control unit **44** has conductive contacts **80** on the exterior of the housing **45**. Once the sensor **42** is implanted in the patient, the sensor control unit **44** is placed over the sensor **42** with the conductive contacts **80** in contact with the contact pads **49** of the sensor **42**.

The on-skin sensor control unit **44** is typically attached to the skin **75** of the patient, as illustrated in FIG. **17**. The on-skin sensor control unit **44** may be attached by a variety of techniques including, for example, by adhering the on-skin sensor control unit **44** directly to the skin **75** of the patient with an adhesive provided on at least a portion of the housing **45** of the on-skin sensor control unit **44** which contacts the skin **75** or by suturing the on-skin sensor control unit **44** to the skin **75** through suture openings (not shown) in the sensor control unit **44**.

Another method of attaching the housing **45** of the on-skin sensor control unit **44** to the skin **75** includes using a mounting unit, **77**. The mounting unit **77** is often a part of the on-skin sensor control unit **44**. One example of a suitable mounting unit **77** is a double-sided adhesive strip, one side of which is adhered to a surface of the skin of the patient and the other side is adhered to the on-skin sensor control unit **44**. In this embodiment, the mounting unit **77** may have an optional opening **79** which is large enough to allow insertion of the sensor **42** through the opening **79**. Alternatively, the sensor may be inserted through a thin adhesive and into the skin.

A variety of adhesives may be used to adhere the on-skin sensor control unit **44** to the skin **75** of the patient, either directly or using the mounting unit **77**, including, for example, pressure sensitive adhesives (PSA) or contact adhesives. Preferably, an adhesive is chosen which is not irritating to all or a majority of patients for at least the period of time that a particular sensor **42** is implanted in the patient. Alternatively, a second adhesive or other skin-protecting compound may be included with the mounting unit so that a patient, whose skin is irritated by the adhesive on the mounting unit **77**, can cover his skin with the second adhesive or other skin-protecting compound and then place the mounting unit **77** over the second adhesive or other skin-protecting compound. This should substantially prevent the irritation of the skin of the patient because the adhesive on the mounting unit **77** is no longer in contact with the skin, but is instead in contact with the second adhesive or other skin-protecting compound.

When the sensor **42** is changed, the on-skin sensor control unit **44** may be moved to a different position on the skin **75** of the patient, for example, to avoid excessive irritation. Alternatively, the on-skin sensor control unit **44** may remain at the same place on the skin of the patient until it is determined that the unit **44** should be moved.

Another embodiment of a mounting unit **77** used in an on-skin sensor control unit **44** is illustrated in FIGS. **27**A and **27**B. The mounting unit **77** and a housing **45** of an on-skin sensor control unit **44** are mounted together in, for example, an interlocking manner, as shown in FIG. **27**A. The mounting unit **77** is formed, for example, using plastic or polymer materials, including, for example, polyvinyl chloride, polyethylene, polypropylene, polystyrene, ABS polymers, and copolymers thereof. The mounting unit **77** may be formed using a variety of techniques including, for example, injection molding, compression molding, casting, and other molding methods.

The mounting unit **77** typically includes an adhesive on a bottom surface of the mounting unit **77** to adhere to the skin of the patient or the mounting unit **77** is used in conjunction with, for example, double-sided adhesive tape or the like. The mounting unit **77** typically includes an opening **79** through which the sensor **42** is inserted, as shown in FIG. **27**B. The mounting unit **77** may also include a support structure **220** for holding the sensor **42** in place and against the conductive contacts **80** on the on-skin sensor control unit **42**. The mounting unit **77**, also, optionally, includes a positioning structure **222**, such as an extension of material from the mounting unit **77**, that corresponds to a structure (not shown), such as an opening, on the sensor **42** to facilitate proper positioning of the sensor **42**, for example, by aligning the two complementary structures.

In another embodiment, a coupled mounting unit **77** and housing **45** of an on-skin sensor control unit **44** is provided on an adhesive patch **204** with an optional cover **206** to protect and/or confine the housing **45** of the on-skin sensor control unit **44**, as illustrated in FIG. **28**A. The optional cover may contain an adhesive or other mechanism for attachment to the housing **45** and/or mounting unit **77**. The mounting unit **77** typically includes an opening **49** through which a sensor **42** is disposed, as shown in FIG. **28**B. The opening **49** may optionally be configured to allow insertion of the sensor **42** through the opening **49** using an insertion device **120** or insertion gun **200** (see FIG. **26**). The housing **45** of the on-skin sensor control unit **44** has a base **74** and a cover **76**, as illustrated in FIG. **28**C. A bottom view of the housing **45**, as shown in FIG. **28**D, illustrates ports **230** through which conductive contacts (not shown) extend to connect with contact pads on the sensor **42**. A board **232** for attachment of circuit components may optionally be provided within the on-skin sensor control unit **44**, as illustrated in FIG. **28**E.

In some embodiments, the adhesive on the on-skin sensor control unit **44** and/or on any of the embodiments of the mounting unit **77** is water resistant or waterproof to permit activities such as showering and/or bathing while maintaining adherence of the on-skin sensor control unit **44** to the skin **75** of the patient and, at least in some embodiments, preventing water from penetrating into the sensor control unit **44**. The use of a water resistant or waterproof adhesive combined with a water resistant or waterproof housing **45** protects the components in the sensor control unit **44** and the contact between the conductive contacts **80** and the sensor **42** from damage or corrosion. An example of a non-irritating adhesive that repels water is Tegaderm (3M, St. Paul, Minn.).

In one embodiment, the on-skin sensor control unit **44** includes a sensor port **78** through which the sensor **42** enters the subcutaneous tissue of the patient, as shown in FIGS. **14** to **16**. The sensor **42** may be inserted into the subcutaneous tissue of the patient through the sensor port **78**. The on-skin sensor control unit **44** may then be placed on the skin of the patient with the sensor **42** being threaded through the sensor port **78**. If the housing **45** of the sensor **42** has, for example, a base **74** and a cover **76**, then the cover **76** may be removed to allow the patient to guide the sensor **42** into the proper position for contact with the conductive contacts **80**.

Alternatively, if the conductive contacts **80** are within the housing **45** the patient may slide the sensor **42** into the housing **45** until contact is made between the contact pads **49** and the conductive contacts **80**. The sensor control unit **44** may have a structure which obstructs the sliding of the sensor **42** further into the housing once the sensor **42** is properly positioned with the contact pads **49** in contact with the conductive contacts **80**.

In other embodiments, the conductive contacts **80** are on the exterior of the housing **45** (see e.g., FIGS. **27**A–**27**B and **28**A–**28**E). In these embodiments, the patient guides the contacts pads **49** of the sensor **42** into contact with the conductive contacts **80**. In some cases, a guiding structure may be provided on the housing **45** which guides the sensor **42** into the proper position. An example of such a structure includes a set of guiding rails extending from the housing **45** and having the shape of the sensor **42**.

In some embodiments, when the sensor **42** is inserted using an insertion device **120** (see FIG. **12**), the tip of the insertion device **120** or optional insertion gun **200** (see FIG. **26**) is positioned against the skin or the mounting unit **77** at the desired insertion point. In some embodiments, the insertion device **120** is positioned on the skin without any guide. In other embodiments, the insertion device **120** or insertion gun **200** is positioned using guides (not shown) in the mounting unit **77** or other portion of the on-skin sensor control unit **44**. In some embodiments, the guides, opening **79** in the mounting unit **77** and/or sensor port **78** in the housing **45** of the on-skin sensor control unit **44** have a shape which is complementary to the shape of the tip of the insertion device **120** and/or insertion gun **200** to limit the orientation of the insertion device **120** and/or insertion gun **200** relative to the opening **79** and/or sensor port **78**. The sensor can then be subcutaneously inserted into the patient by matching the complementary shape of the opening **79** or sensor port **78** with the insertion device **120** and/or insertion gun **200**.

In some embodiments, the shapes of a) the guides, opening **79**, or sensor port **78**, and (b) the insertion device **120** or insertion gun **200** are configured such that the two shapes can only be matched in a single orientation. This aids in inserting the sensor **42** in the same orientation each time a new sensor is inserted into the patient. This uniformity in insertion orientation may be required in some embodiments to ensure that the contact pads **49** on the sensor **42** are correctly aligned with appropriate conductive contacts **80** on the on-skin sensor control unit **44**. In addition, the use of the insertion gun, as described above, may ensure that the sensor **42** is inserted at a uniform, reproducible depth.

The sensor **42** and the electronic components within the on-skin sensor control unit **44** are coupled via conductive contacts **80**, as shown in FIGS. **14**–**16**. The one or more working electrodes **58**, counter electrode **60** (or counter/reference electrode), optional reference electrode **62**, and optional temperature probe **66** are attached to individual conductive contacts **80**. In the illustrated embodiment of FIGS. **14**–**16**, the conductive contacts **80** are provided on the interior of the on-skin sensor control unit **44**. Other embodiments of the on-skin sensor control unit **44** have the conductive contacts disposed on the exterior of the housing **45**. The placement of the conductive contacts **80** is such that they are in contact with the contact pads **49** on the sensor **42** when the sensor **42** is properly positioned within the on-skin sensor control unit **44**.

In the illustrated embodiment of FIGS. **14**–**16**, the base **74** and cover **76** of the on-skin sensor control unit **44** are formed such that, when the sensor **42** is within the on-skin sensor control unit **44** and the base **74** and cover **76** are fitted together, the sensor **42** is bent. In this manner, the contact pads **49** on the sensor **42** are brought into contact with the conductive contacts **80** of the on-skin sensor control unit **44**. The on-skin sensor control unit **44** may optionally contain a support structure **82** to hold, support, and/or guide the sensor **42** into the correct position.

Non-limiting examples of suitable conductive contacts **80** are illustrated in FIGS. **19**A–**19**D. In one embodiment, the conductive contacts **80** are pins **84** or the like, as illustrated in FIG. **19**A, which are brought into contact with the contact pads **49** on the sensor **42** when the components of the on-skin sensor control unit **44**, for example, the base **74** and cover **76**, are fitted together. A support **82** may be provided under the sensor **42** to promote adequate contact between the contact pads **49** on the sensor **42** and the pins **84**. The pins are typically made using a conductive material, such as a metal or alloy, for example, copper, stainless steel, or silver. Each pin has a distal end that extends from the on-skin sensor control unit **44** for contacting the contact pads **49** on the sensor **42**. Each pin **84** also has a proximal end that is coupled to a wire or other conductive strip that is, in turn,

coupled to the rest of the electronic components (e.g., the voltage source **95** and measurement circuit **96** of FIGS. **18**A and **18**B) within the on-skin sensor control unit **44**. Alternatively, the pins **84** may be coupled directly to the rest of the electronics.

In another embodiment, the conductive contacts **80** are formed as a series of conducting regions **88** with interspersed insulating regions **90**, as illustrated in FIG. **19**B. The conducting regions **88** may be as large or larger than the contact pads **49** on the sensor **42** to alleviate registration concerns. However, the insulating regions **90** should have sufficient width so that a single conductive region **88** does not overlap with two contact pads **49** as determined based on the expected variation in the position of the sensor **42** and contact pads **49** with respect to the conductive contacts **80**. The conducting regions **88** are formed using materials such as metals, alloys, or conductive carbon. The insulating regions **90** may be formed using known insulating materials including, for example, insulating plastic or polymer materials.

In a further embodiment, a unidirectional conducting adhesive **92** may be used between the contact pads **49** on the sensor **42** and conductive contacts **80** implanted or otherwise formed in the on-skin sensor control unit **44**, as shown in FIG. **19**C.

In yet another embodiment, the conductive contacts **80** are conductive members **94** that extend from a surface of the on-skin sensor control unit **44** to contact the contact pads **49**, as shown in FIG. **19**D. A variety of different shapes may be used for these members, however, they should be electrically insulated from each other. The conductive members **94** may be made using metal, alloy, conductive carbon, or conducting plastics and polymers.

Any of the exemplary conductive contacts **80** described above may extend from either the upper surface of the interior of the on-skin sensor control unit **44**, as illustrated in FIG. **19**A–**19**C, or from the lower surface of the interior of the on-skin sensor control unit **44**, as illustrated in FIG. **19**D, or from both the upper and lower surfaces of the interior of the on-skin sensor control unit **44**, particularly when the sensor **42** has contact pads **49** on both sides of the sensor.

Conductive contacts **80** on the exterior of the housing **45** may also have a variety of shapes as indicated in FIGS. **19**E and **19**F. For example, the conductive contacts **80** may be embedded in (FIG. **19**E) or extending out of (FIG. **19**F) the housing **45**.

The conductive contacts **80** are preferably made using a material which will not corrode due to contact with the contact pads **49** of the sensor **42**. Corrosion may occur when two different metals are brought in contact. Thus, if the contact pads **49** are formed using carbon then the preferred conductive contacts **80** may be made using any material, including metals or alloys. However, if any of the contact pads **49** are made with a metal or alloy then the preferred conductive contacts **80** for coupling with the metallic contact pads are made using a non-metallic conductive material, such as conductive carbon or a conductive polymer, or the conductive contacts **80** and the contact pads **49** are separated by a non-metallic material, such as a unidirectional conductive adhesive.

In one embodiment, electrical contacts are eliminated between the sensor **42** and the on-skin sensor control unit **44**. Power is transmitted to the sensor via inductive coupling, using, for example, closely space antennas (e.g., facing coils) (not shown) on the sensor and the on-skin sensor control unit. Changes in the electrical characteristics of the sensor control unit **44** (e.g., current) induce a changing magnetic field in the proximity of the antenna. The changing magnetic field induces a current in the antenna of the sensor. The close proximity of the sensor and on-skin sensor control unit results in reasonably efficient power transmission. The induced current in the sensor may be used to power potentiostats, operational amplifiers, capacitors, integrated circuits, transmitters, and other electronic components built into the sensor structure. Data is transmitted back to the sensor control unit, using, for example, inductive coupling via the same or different antennas and/or transmission of the signal via a transmitter on the sensor. The use of inductive coupling can eliminate electrical contacts between the sensor and the on-skin sensor control unit. Such contacts are commonly a source of noise and failure. Moreover, the sensor control unit may then be entirely sealed which may increase the waterproofing of the on-skin sensor control unit.

An exemplary on-skin sensor control unit **44** can be prepared and used in the following manner. A mounting unit **77** having adhesive on the bottom is applied to the skin. An insertion gun **200** (see FIG. **26**) carrying the sensor **42** and the insertion device **120** is positioned against the mounting unit **77**. The insertion gun **200** and mounting unit **77** are optionally designed such that there is only one position in which the two properly mate. The insertion gun **200** is activated and a portion of the sensor **42** and optionally a portion of the insertion device **120** are driven through the skin into, for example, the subcutaneous tissue. The insertion gun **200** withdraws the insertion device **200**, leaving the portion of the sensor **42** inserted through the skin. The housing **45** of the on-skin control unit **44** is then coupled to the mounting unit **77**. Optionally, the housing **45** and the mounting unit **77** are formed such that there is only one position in which the two properly mate. The mating of the housing **45** and the mounting unit **77** establishes contact between the contact pads **49** (see e.g., FIG. **2**) on the sensor **42** and the conductive contacts **80** on the on-skin sensor control unit **44**. Optionally, this action activates the on-skin sensor control unit **44** to begin operation.

On-Skin Control Unit Electronics

The on-skin sensor control unit **44** also typically includes at least a portion of the electronic components that operate the sensor **42** and the analyte monitoring device system **40**. One embodiment of the electronics in the on-skin control unit **44** is illustrated as a block diagram in FIG. **18**A. The electronic components of the on-skin sensor control unit **44** typically include a power supply **95** for operating the on-skin control unit **44** and the sensor **42**, a sensor circuit **97** for obtaining signals from and operating the sensor **42**, a measurement circuit **96** that converts sensor signals to a desired format, and a processing circuit **109** that, at minimum, obtains signals from the sensor circuit **97** and/or measurement circuit **96** and provides the signals to an optional transmitter **98**. In some embodiments, the processing circuit **109** may also partially or completely evaluate the signals from the sensor **42** and convey the resulting data to the optional transmitter **98** and/or activate an optional alarm system **94** (see FIG. **18**B) if the analyte level exceeds a threshold. The processing circuit **109** often includes digital logic circuitry.

The on-skin sensor control unit **44** may optionally contain a transmitter **98** for transmitting the sensor signals or processed data from the processing circuit **109** to a receiver/display unit **46**, **48**; a data storage unit **102** for temporarily or permanently storing data from the processing circuit **109**; a temperature probe circuit **99** for receiving signals from and operating a temperature probe **66**; a reference voltage gen-

erator **101** for providing a reference voltage for comparison with sensor-generated signals; and/or a watchdog circuit **103** that monitors the operation of the electronic components in the on-skin sensor control unit **44**.

Moreover, the sensor control unit **44** often includes digital and/or analog components utilizing semiconductor devices, such as transistors. To operate these semiconductor devices, the on-skin control unit **44** may include other components including, for example, a bias control generator **105** to correctly bias analog and digital semiconductor devices, an oscillator **107** to provide a clock signal, and a digital logic and timing component **109** to provide timing signals and logic operations for the digital components of the circuit.

As an example of the operation of these components, the sensor circuit **97** and the optional temperature probe circuit **99** provide raw signals from the sensor **42** to the measurement circuit **96**. The measurement circuit **96** converts the raw signals to a desired format, using for example, a current-to-voltage converter, current-to-frequency converter, and/or a binary counter or other indicator that produces a signal proportional to the absolute value of the raw signal. This may be used, for example, to convert the raw signal to a format that can be used by digital logic circuits. The processing circuit **109** may then, optionally, evaluate the data and provide commands to operate the electronics.

FIG. **18**B illustrates a block diagram of another exemplary on-skin control unit **44** that also includes optional components such as a receiver **99** to receive, for example, calibration data; a calibration storage unit **100** to hold, for example, factory-set calibration data, calibration data obtained via the receiver **99** and/or operational signals received, for example, from a receiver/display unit **46**, **48** or other external device; an alarm system **104** for warning the patient; and a deactivation switch **111** to turn off the alarm system.

Functions of the analyte monitoring system **40** and the sensor control unit **44** may be implemented using either software routines, hardware components, or combinations thereof. The hardware components may be implemented using a variety of technologies, including, for example, integrated circuits or discrete electronic components. The use of integrated circuits typically reduces the size of the electronics, which in turn may result in a smaller on-skin sensor control unit **44**.

The electronics in the on-skin sensor control unit **44** and the sensor **42** are operated using a power supply **95**. One example of a suitable power supply **95** is a battery, for example, a thin circular battery, such as those used in many watches, hearing aids, and other small electronic devices. Preferably, the battery has a lifetime of at least 30 days, more preferably, a lifetime of at least three months, and most preferably, a lifetime of at least one year. The battery is often one of the largest components in the on-skin control unit **44**, so it is often desirable to minimize the size of the battery. For example, a preferred battery's thickness is 0.5 mm or less, preferably 35 mm or less, and most preferably 0.2 mm or less. Although multiple batteries may be used, it is typically preferred to use only one battery.

The sensor circuit **97** is coupled via the conductive contacts **80** of the sensor control unit **44** to one or more sensors **42**, **42'**. Each of the sensors represents, at minimum, a working electrode **58**, a counter electrode **60** (or counter/reference electrode), and an optional reference electrode **62**. When two or more sensors **42**, **42'** are used, the sensors typically have individual working electrodes **58**, but may share a counter electrode **60**, counter/reference electrode, and/or reference electrode **52**.

The sensor circuit **97** receives signals from and operates the sensor **42** or sensors **42**, **42'**. The sensor circuit **97** may obtain signals from the sensor **42** using amperometric, coulometric, potentiometric, voltammetric, and/or other electrochemical techniques. The sensor circuit **97** is exemplified herein as obtaining amperometric signals from the sensor **42**, however, it will be understood that the sensor circuit can be appropriately configured for obtaining signals using other electrochemical techniques. To obtain amperometric measurements, the sensor circuit **97** typically includes a potentiostat that provides a constant potential to the sensor **42**. In other embodiments, the sensor circuit **97** includes an amperostat that supplies a constant current to the sensor **42** and can be used to obtain coulometric or potentiometric measurements.

The signal from the sensor **42** generally has at least one characteristic, such as, for example, current, voltage, or frequency, which varies with the concentration of the analyte. For example, if the sensor circuit **97** operates using amperometry, then the signal current varies with analyte concentration. The measurement circuit **96** may include circuitry which converts the information-carrying portion of the signal from one characteristic to another. For example, the measurement circuit **96** may include a current-to-voltage or current-to-frequency converter. The purpose of this conversion may be to provide a signal that is, for example, more easily transmitted, readable by digital circuits, and/or less susceptible to noise contributions.

One example of a standard current-to-voltage converter is provided in FIG. **20**A. In this converter, the signal from the sensor **42** is provided at one input terminal **134** of an operational amplifier **130** ("op amp") and coupled through a resistor **138** to an output terminal **136**. This particular current-to-voltage converter **131** may, however, be difficult to implement in a small CMOS chip because resistors are often difficult to implement on an integrated circuit. Typically, discrete resistor components are used. However, the used of discrete components increases the space needed for the circuitry.

An alternative current-to-voltage converter **141** is illustrated in FIG. **20**B. This converter includes an op amp **140** with the signal from the sensor **42** provided at input terminal **144** and a reference potential provided at input terminal **142**. A capacitor **145** is placed between the input terminal **144** and the output terminal **146**. In addition, switches **147***a*, **147***b*, **149***a*, and **149***b* are provided to allow the capacitor to charge and discharge at a rate determined by a clock (CLK) frequency. In operation, during one half cycle, switches **147***a* and **147***b* close and switches **149***a* and **149***b* open allowing the capacitor **145** to charge due to the attached potential VI. During the other half cycle, switches **147***a* and **147***b* open and switches **149***a* and **149***b* close to ground and allow the capacitor **145** to partially or fully discharge. The reactive impedance of the capacitor **145** is analogous to the resistance of the resistor **138** (see FIG. **20**A), allowing the capacitor **145** to emulate a resistor. The value of this "resistor" depends on the capacitance of the capacitor **145** and the clock frequency. By altering the clock frequency, the reactive impedance ("resistance value") of the capacitor changes. The value of the impedance ("resistance") of the capacitor **145** may be altered by changing the clock frequency. Switches **147***a*, **147***b*, **149***a*, and **149***b* may be implemented in a CMOS chip using, for example, transistors.

A current-to-frequency converter may also be used in the measurement circuit **96**. One suitable current-to-frequency converter includes charging a capacitor using the signal

from the sensor **42**. When the potential across the capacitor exceeds a threshold value, the capacitor is allowed to discharge. Thus, the larger the current from the sensor **42**, the quicker the threshold potential is achieved. This results in a signal across the capacitor that has an alternating characteristic, corresponding to the charging and discharging of the capacitor, having a frequency which increases with an increase in current from the sensor **42**.

In some embodiments, the analyte monitoring system **40** includes two or more working electrodes **58** distributed over one or more sensors **42**. These working electrodes **58** may be used for quality control purposes. For example, the output signals and/or analyzed data derived using the two or more working electrodes **58** may be compared to determine if the signals from the working electrodes agree within a desired level of tolerance. If the output signals do not agree, then the patient may be alerted to replace the sensor or sensors. In some embodiments, the patient is alerted only if the lack of agreement between the two sensors persists for a predetermined period of time. The comparison of the two signals may be made for each measurement or at regular intervals. Alternatively or additionally, the comparison may be initiated by the patient or another person. Moreover, the signals from both sensors may be used to generate data or one signal may be discarded after the comparison.

Alternatively, if, for example, two working electrodes **58** have a common counter electrode **60** and the analyte concentration is measured by amperometry, then the current at the counter electrode **60** should be twice the current at each of the working electrodes, within a predetermined tolerance level, if the working electrodes are operating properly. If not, then the sensor or sensors should be replaced, as described above.

An example of using signals from only one working electrode for quality control includes comparing consecutive readings obtained using the single working electrode to determine if they differ by more than a threshold level. If the difference is greater than the threshold level for one reading or over a period of time or for a predetermined number of readings within a period of time then the patient is alerted to replace the sensor **42**. Typically, the consecutive readings and/or the threshold level are determined such that all expected excursions of the sensor signal are within the desired parameters (i.e., the sensor control unit **44** does not consider true changes in analyte concentration to be a sensor failure).

The sensor control unit **44** may also optionally include a temperature probe circuit **99**. The temperature probe circuit **99** provides a constant current through (or constant potential) across the temperature probe **66**. The resulting potential (or current) varies according to the resistance of the temperature dependent element **72**.

The output from the sensor circuit **97** and optional temperature probe circuit is coupled into a measurement circuit **96** that obtains signals from the sensor circuit **97** and optional temperature probe circuit **99** and, at least in some embodiments, provides output data in a form that, for example can be read by digital circuits. The signals from the measurement circuit **96** are sent to the processing circuit **109**, which in turn may provide data to an optional transmitter **98**. The processing circuit **109** may have one or more of the following functions: 1) transfer the signals from the measurement circuit **96** to the transmitter **98**, 2) transfer signals from the measurement circuit **96** to the data storage circuit **102**, 3) convert the information-carrying characteristic of the signals from one characteristic to another (when, for example, that has not been done by the measurement circuit **96**), using, for example, a current-to-voltage converter, a current-to-frequency converter, or a voltage-to-current converter, 4) modify the signals from the sensor circuit **97** using calibration data and/or output from the temperature probe circuit **99**, 5) determine a level of an analyte in the interstitial fluid, 6) determine a level of an analyte in the bloodstream based on the sensor signals obtained from interstitial fluid, 7) determine if the level, rate of change, and/or acceleration in the rate of change of the analyte exceeds or meets one or more threshold values, 8) activate an alarm if a threshold value is met or exceeded, 9) evaluate trends in the level of an analyte based on a series of sensor signals, 10) determine a dose of a medication, and 11) reduce noise and/or errors, for example, through signal averaging or comparing readings from multiple working electrodes **58**.

The processing circuit **109** may be simple and perform only one or a small number of these functions or the processing circuit **109** may be more sophisticated and perform all or most of these functions. The size of the on-skin sensor control unit **44** may increase with the increasing number of functions and complexity of those functions that the processing circuit **109** performs. Many of these functions may not be performed by a processing circuit **109** in the on-skin sensor control unit **44**, but may be performed by another analyzer **152** in the receiver/display units **46**, **48** (see FIG. **22**).

One embodiment of the measurement circuit **96** and/or processing circuit **109** provides as output data, the current flowing between the working electrode **58** and the counter electrode **60**. The measurement circuit **96** and/or processing circuit **109** may also provide as output data a signal from the optional temperature probe **66** which indicates the temperature of the sensor **42**. This signal from the temperature probe **66** may be as simple as a current through the temperature probe **66** or the processing circuit **109** may include a device that determines a resistance of the temperature probe **66** from the signal obtained from the measurement circuit **96** for correlation with the temperature of the sensor **42**. The output data may then be sent to a transmitter **98** that then transmits this data to at least one receiver/display device **46**,**48**.

Returning to the processing circuit **109**, in some embodiments processing circuit **109** is more sophisticated and is capable of determining the analyte concentration or some measure representative of the analyte concentration, such as a current or voltage value. The processing circuit **109** may incorporate the signal of the temperature probe to make a temperature correction in the signal or analyzed data from the working electrode **58**. This may include, for example, scaling the temperature probe measurement and adding or subtracting the scaled measurement to the signal or analyzed data from the working electrode **58**. The processing circuit **109** may also incorporate calibration data which has been received from an external source or has been incorporated into the processing circuit **109**, both of which are described below, to correct the signal or analyzed data from the working electrode **58**. Additionally, the processing circuit **109** may include a correction algorithm for converting interstitial analyte level to blood analyte level. The conversion of interstitial analyte level to blood analyte level is described, for example, in Schmidtke, et al., "Measurement and Modeling of the Transient Difference Between Blood and Subcutaneous Glucose Concentrations in the Rat after Injection of Insulin", Proc. of the Nat'l Acad. of Science, 95, 294–299 (1998) and Quinn, et al., "Kinetics of Glucose Delivery to Subcutaneous Tissue in Rats Measured with 0.3

mm Amperometric Microsensors", Am. J. Physiol., 269 (Endocrinol. Metab. 32), E155–E161 (1995), incorporated herein by reference.

In some embodiments, the data from the processing circuit **109** is analyzed and directed to an alarm system **94** (see FIG. **18B**) to warn the user. In at least some of these embodiments, a transmitter is not used as the sensor control unit performs all of the needed functions including analyzing the data and warning the patient.

However, in many embodiments, the data (e.g., a current signal, a converted voltage or frequency signal, or fully or partially analyzed data) from processing circuit **109** is transmitted to one or more receiver/display units **46**, **48** using a transmitter **98** in the on-skin sensor control unit **44**. The transmitter has an antenna **93**, such as a wire or similar conductor, formed in the housing **45**. The transmitter **98** is typically designed to transmit a signal up to about 2 meters or more, preferably up to about 5 meters or more, and more preferably up to about 10 meters or more, when transmitting to a small receiver/display unit **46**, such as a palm-size, belt-worn receiver. The effective range is longer when transmitting to a unit with a better antenna, such as a bedside receiver. As described in detail below, suitable examples of receiver/display units **46**, **48** include units that can be easily worn or carried or units that can be placed conveniently on, for example, a nightstand when the patient is sleeping.

The transmitter **98** may send a variety of different signals to the receiver/display units **46**, **48**, typically, depending on the sophistication of the processing circuit **109**. For example, the processing circuit **109** may simply provide raw signals, for example, currents from the working electrodes **58**, without any corrections for temperature or calibration, or the processing circuit **109** may provide converted signals which are obtained, for example, using a current-to-voltage converter **131** or **141** or a current-to-frequency converter. The raw measurements or converted signals may then be processed by an analyzer **152** (see FIG. **22**) in the receiver/display units **46**, **48** to determine the level of an analyte, optionally using temperature and calibration corrections. In another embodiment, the processing circuit **109** corrects the raw measurements using, for example, temperature and/or calibration information and then the transmitter **98** sends the corrected signal, and optionally, the temperature and/or calibration information, to the receiver/display units **46**, **48**. In yet another embodiment, the processing circuit **109** calculates the analyte level in the interstitial fluid and/or in the blood (based on the interstitial fluid level) and transmits that information to the one or more receiver/display units **46**, **48**, optionally with any of the raw data and/or calibration or temperature information. In a further embodiment, the processing circuit **109** calculates the analyte concentration, but the transmitter **98** transmits only the raw measurements, converted signals, and/or corrected signals.

One potential difficulty that may be experienced with the on-skin sensor control unit **44** is a change in the transmission frequency of the transmitter **98** over time. To overcome this potential difficulty, the transmitter may include optional circuitry that can return the frequency of the transmitter **98** to the desired frequency or frequency band. One example of suitable circuitry is illustrated in FIG. **21** as a block diagram of an open loop modulation system **200**. The open loop modulation system **200** includes a phase detector (PD) **210**, a charge pump (CHGPMP) **212**, a loop filter (L.F.) **214**, a voltage controlled oscillator (VCO) **216**, and a divide by M circuit (÷M) **218** to form the phase-locked loop **220**.

The analyte monitoring device **40** uses an open loop modulation system **200** for RF communication between the transmitter **98** and a receiver of, for example, the one or more receiver/display units **46**, **48**. This open loop modulation system **230** is designed to provide a high reliability RF link between a transmitter and its associated receiver. The system employs frequency modulation (FM), and locks the carrier center frequency using a conventional phase-locked loop (PLL) **220**. In operation, the phase-locked loop **220** is opened prior to the modulation. During the modulation the phase-locked loop **220** remains open for as long as the center frequency of the transmitter is within the receiver's bandwidth. When the transmitter detects that the center frequency is going to move outside of the receiver bandwidth, the receiver is signaled to stand by while the center frequency is captured. Subsequent to the capture, the transmission will resume. This cycle of capturing the center frequency, opening the phase-locked loop **220**, modulation, and recapturing the center frequency will repeat for as many cycles as required.

The loop control **240** detects the lock condition of the phase-locked loop **220** and is responsible for closing and opening the phase-locked loop **220**. The totalizer **250** in conjunction with the loop control **240**, detects the status of the center frequency. The modulation control **230** is responsible for generating the modulating signal. A transmit amplifier **260** is provided to ensure adequate transmit signal power. The reference frequency is generated from a very stable signal source (not shown), and is divided down by N through the divide by N block (÷N) **270**. Data and control signals are received by the open loop modulation system **200** via the DATA BUS **280**, and the CONTROL BUS **290**.

The operation of the open loop modulation system **200** begins with the phase-locked loop **220** in closed condition. When the lock condition is detected by the loop control **240**, the phase-locked loop **220** is opened and the modulation control **230** begins generating the modulating signal. The totalizer **250** monitors the VCO frequency (divided by M), for programmed intervals. The monitored frequency is compared to a threshold programmed in the totalizer **250**. This threshold corresponds to the 3dB cut off frequencies of the receiver's intermediate frequency stage. When the monitored frequency approaches the thresholds, the loop control **240** is notified and a stand-by code is transmitted to the receiver and the phase-locked loop **220** is closed.

At this point the receiver is in the wait mode. The loop control **240** in the transmitter closes the phase-locked loop **220**. Then, modulation control **230** is taken off line, the monitored value of the totalizer **250** is reset, and the phase-locked loop **220** is locked. When the loop control **240** detects a lock condition, the loop control **240** opens the phase-locked loop **220**, the modulation control **230** is brought on line and the data transmission to the receiver will resume until the center frequency of the phase-locked loop **220** approaches the threshold values, at which point the cycle of transmitting the stand-by code begins. The ÷N **270** and ÷M **218** block set the frequency channel of the transmitter.

Accordingly, the open loop modulation system **200** provides a reliable low power FM data transmission for an analyte monitoring system. The open loop modulation system **200** provides a method of wide band frequency modulation, while the center frequency of the carrier is kept within receiver bandwidth. The effect of parasitic capacitors and inductors pulling the center frequency of the transmitter is corrected by the phase-locked loop **220**. Further, the totalizer **250** and loop control **240** provide a new method of center frequency drift detection. Finally, the open loop modulation system **200** is easily implemented in CMOS process.

The rate at which the transmitter **98** transmits data may be the same rate at which the sensor circuit **97** obtains signals and/or the processing circuit **109** provides data or signals to the transmitter **98**. Alternatively, the transmitter **98** may transmit data at a slower rate. In this case, the transmitter **98** may transmit more than one datapoint in each transmission. Alternatively, only one datapoint may be sent with each data transmission, the remaining data not being transmitted. Typically, data is transmitted to the receiver/display unit **46, 48** at least every hour, preferably, at least every fifteen minutes, more preferably, at least every five minutes, and most preferably, at least every one minute. However, other data transmission rates may be used. In some embodiments, the processing circuit **109** and/or transmitter **98** are configured to process and/or transmit data at a faster rate when a condition is indicated, for example, a low level or high level of analyte or impending low or high level of analyte. In these embodiments, the accelerated data transmission rate is typically at least every five minutes and preferably at least every minute.

In addition to a transmitter **98**, an optional receiver **99** may be included in the on-skin sensor control unit **44**. In some cases, the transmitter **98** is a transceiver, operating as both a transmitter and a receiver. The receiver **99** may be used to receive calibration data for the sensor **42**. The calibration data may be used by the processing circuit **109** to correct signals from the sensor **42**. This calibration data may be transmitted by the receiver/display unit **46, 48** or from some other source such as a control unit in a doctor's office. In addition, the optional receiver **99** may be used to receive a signal from the receiver/display units **46, 48**, as described above, to direct the transmitter **98**, for example, to change frequencies or frequency bands, to activate or deactivate the optional alarm system **94** (as described below), and/or to direct the transmitter **98** to transmit at a higher rate.

Calibration data may be obtained in a variety of ways. For instance, the calibration data may simply be factory-determined calibration measurements which can be input into the on-skin sensor control unit **44** using the receiver **99** or may alternatively be stored in a calibration data storage unit **100** within the on-skin sensor control unit **44** itself (in which case a receiver **99** may not be needed). The calibration data storage unit **100** may be, for example, a readable or readable/writeable memory circuit.

Alternative or additional calibration data may be provided based on tests performed by a doctor or some other professional or by the patient himself. For example, it is common for diabetic individuals to determine their own blood glucose concentration using commercially available testing kits. The results of this test is input into the on-skin sensor control unit **44** either directly, if an appropriate input device (e.g., a keypad, an optical signal receiver, or a port for connection to a keypad or computer) is incorporated in the on-skin sensor control unit **44**, or indirectly by inputting the calibration data into the receiver/display unit **46, 48** and transmitting the calibration data to the on-skin sensor control unit **44**.

Other methods of independently determining analyte levels may also be used to obtain calibration data. This type of calibration data may supplant or supplement factory-determined calibration values.

In some embodiments of the invention, calibration data may be required at periodic intervals, for example, every eight hours, once a day, or once a week, to confirm that accurate analyte levels are being reported. Calibration may also be required each time a new sensor **42** is implanted or if the sensor exceeds a threshold minimum or maximum value or if the rate of change in the sensor signal exceeds a threshold value. In some cases, it may be necessary to wait a period of time after the implantation of the sensor **42** before calibrating to allow the sensor **42** to achieve equilibrium. In some embodiments, the sensor **42** is calibrated only after it has been inserted. In other embodiments, no calibration of the sensor **42** is needed.

The on-skin sensor control unit **44** and/or a receiver/display unit **46, 48** may include an auditory or visual indicator that calibration data is needed, based, for example, on a predetermined periodic time interval between calibrations or on the implantation of a new sensor **42**. The on-skin sensor control unit **44** and/or receiver display/units **46, 48** may also include an auditory or visual indicator to remind the patient that information, such as analyte levels, reported by the analyte monitoring device **40**, may not be accurate because a calibration of the sensor **42** has not been performed within the predetermined periodic time interval and/or after implantation of a new sensor **42**.

The processing circuit **109** of the on-skin sensor control unit **44** and/or an analyzer **152** of the receiver/display unit **46, 48** may determine when calibration data is needed and if the calibration data is acceptable. The on-skin sensor control unit **44** may optionally be configured to not allow calibration or to reject a calibration point if, for example, 1) a temperature reading from the temperature probe indicates a temperature that is not within a predetermined acceptable range (e.g., 30 to 42° C. or 32 to 40° C.) or that is changing rapidly (for example, 0.2° C./minute, 0.5° C./minute, or 0.7° C./minute or greater); 2) two or more working electrodes **58** provide uncalibrated signals that are not within a predetermined range(e.g., within 10% or 20%) of each other; 3) the rate of change of the uncalibrated signal is above a threshold rate (e.g., 0.25 mg/dL per minute or 0.5 mg/dL per minute or greater); 4) the uncalibrated signal exceeds a threshold maximum value (e.g., 5, 10, 20, or 40 nA) or is below a threshold minimum value (e.g., 0.05, 0.2, 0.5, or 1 nA); 5) the calibrated signal exceeds a threshold maximum value (e.g., a signal corresponding to an analyte concentration of 200 mg/dL, 250 mg/dL, or 300 mg/dL) or is below a threshold minimum value (e.g., a signal corresponding to an analyte concentration of 50 mg/dL, 65 mg/dL, or 80 mg/dL); and/or 6) an insufficient among of time has elapsed since implantation (e.g., 10 minutes or less, 20 minutes or less, or 30 minutes or less).

The processing circuit **109** or an analyzer **152** may also request another calibration point if the values determined using the sensor data before and after the latest calibration disagree by more than a threshold amount, indicating that the calibration may be incorrect or that the sensor characteristics have changed radically between calibrations. This additional calibration point may indicate the source of the difference.

The on-skin sensor control unit **44** may include an optional data storage unit **102** which may be used to hold data (e.g., measurements from the sensor or processed data) from the processing circuit **109** permanently or, more typically, temporarily. The data storage unit **102** may hold data so that the data can be used by the processing circuit **109** to analyze and/or predict trends in the analyte level, including, for example, the rate and/or acceleration of analyte level increase or decrease. The data storage unit **102** may also or alternatively be used to store data during periods in which a receiver/display unit **46, 48** is not within range. The data storage unit **102** may also be used to store data when the transmission rate of the data is slower than the acquisition rate of the data. For example, if the data acqui-

sition rate is 10 points/min and the transmission is 2 transmissions/min, then one to five points of data could be sent in each transmission depending on the desired rate for processing datapoints. The data storage unit **102** typically includes a readable/writeable memory storage device and typically also includes the hardware and/or software to write to and/or read the memory storage device.

The on-skin sensor control unit **44** may include an optional alarm system **104** that, based on the data from the processing circuit **109**, warns the patient of a potentially detrimental condition of the analyte. For example, if glucose is the analyte, than the on-skin sensor control unit **44** may include an alarm system **104** that warns the patient of conditions such as hypoglycemia, hyperglycemia, impending hypoglycemia, and/or impending hyperglycemia. The alarm system **104** is triggered when the data from the processing circuit **109** reaches or exceeds a threshold value. Examples of threshold values for blood glucose levels are about 60, 70, or 80 mg/dL for hypoglycemia; about 70, 80, or 90 mg/dL for impending hypoglycemia; about 130, 150, 175, 200, 225, 250, or 275 mg/dL for impending hyperglycemia; and about 150, 175, 200, 225, 250, 275, or 300 mg/dL for hyperglycemia. The actual threshold values that are designed into the alarm system **104** may correspond to interstitial fluid glucose concentrations or electrode measurements (e.g., current values or voltage values obtained by conversion of current measurements) that correlate to the above-mentioned blood glucose levels. The analyte monitor device may be configured so that the threshold levels for these or any other conditions may be programmable by the patient and/or a medical professional.

A threshold value is exceeded if the datapoint has a value that is beyond the threshold value in a direction indicating a particular condition. For example, a datapoint which correlates to a glucose level of 200 mg/dL exceeds a threshold value for hyperglycemia of 180 mg/dL, because the datapoint indicates that the patient has entered a hyperglycemic state. As another example, a datapoint which correlates to a glucose level of 65 mg/dL exceeds a threshold value for hypoglycemia of 70 mg/dL because the datapoint indicates that the patient is hypoglycemic as defined by the threshold value. However, a datapoint which correlates to a glucose level of 75 mg/dL would not exceed the same threshold value for hypoglycemia because the datapoint does not indicate that particular condition as defined by the chosen threshold value.

An alarm may also be activated if the sensor readings indicate a value that is beyond a measurement range of the sensor **42**. For glucose, the physiologically relevant measurement range is typically about 50 to 250 mg/dL, preferably about 40–300 mg/dL and ideally 30–400 mg/dL, of glucose in the interstitial fluid.

The alarm system **104** may also, or alternatively, be activated when the rate of change or acceleration of the rate of change in analyte level increase or decrease reaches or exceeds a threshold rate or acceleration. For example, in the case of a subcutaneous glucose monitor, the alarm system might be activated if the rate of change in glucose concentration exceeds a threshold value which might indicate that a hyperglycemic or hypoglycemic condition is likely to occur.

The optional alarm system **104** may be configured to activate when a single data point meets or exceeds a particular threshold value. Alternatively, the alarm may be activated only when a predetermined number of datapoints spanning a predetermined amount of time meet or exceed the threshold value. As another alternative, the alarm may be activated only when the datapoints spanning a predetermined amount of time have an average value which meets or exceeds the threshold value. Each condition that can trigger an alarm may have a different alarm activation condition. In addition, the alarm activation condition may change depending on current conditions (e.g., an indication of impending hyperglycemia may alter the number of datapoints or the amount of time that is tested to determine hyperglycemia).

The alarm system **104** may contain one or more individual alarms. Each of the alarms may be individually activated to indicate one or more conditions of the analyte. The alarms may be, for example, auditory or visual. Other sensory-stimulating alarm systems may be used including alarm systems which heat, cool, vibrate, or produce a mild electrical shock when activated. In some embodiments, the alarms are auditory with a different tone, note, or volume indicating different conditions. For example, a high note might indicate hyperglycemia and a low note might indicate hypoglycemia. Visual alarms may use a difference in color, brightness, or position on the on-skin sensor control device **44** to indicate different conditions. In some embodiments, an auditory alarm system is configured so that the volume of the alarm increases over time until the alarm is deactivated.

In some embodiments, the alarm may be automatically deactivated after a predetermined time period. In other embodiments, the alarm may be configured to deactivate when the data no longer indicate that the condition which triggered the alarm exists. In these embodiments, the alarm may be deactivated when a single data point indicates that the condition no longer exists or, alternatively, the alarm may be deactivated only after a predetermined number of datapoints or an average of datapoints obtained over a given period of time indicate that the condition no longer exists.

In some embodiments, the alarm may be deactivated manually by the patient or another person in addition to or as an alternative to automatic deactivation. In these embodiments, a switch **101** is provided which when activated turns off the alarm. The switch **101** may be operatively engaged (or disengaged depending on the configuration of the switch) by, for example, operating an actuator on the on-skin sensor control unit **44** or the receiver/display unit **46**, **48**. In some cases, an actuator may be provided on two or more units **44**, **46**, **48**, any of which may be actuated to deactivate the alarm. If the switch **101** and or actuator is provided on the receiver/display unit **46**, **48** then a signal may be transmitted from the receiver/display unit **46**, **48** to the receiver **98** on the on-skin sensor control unit **44** to deactivate the alarm.

A variety of switches **101** may be used including, for example, a mechanical switch, a reed switch, a Hall effect switch, a Gigantic Magnetic Ratio (GMR) switch (the resistance of the GMR switch is magnetic field dependent) and the like. Preferably, the actuator used to operatively engage (or disengage) the switch is placed on the on-skin sensor control unit **44** and configured so that no water can flow around the button and into the housing. One example of such a button is a flexible conducting strip that is completely covered by a flexible polymeric or plastic coating integral to the housing. In an open position the flexible conducting strip is bowed and bulges away from the housing. When depressed by the patient or another person, the flexible conducting strip is pushed directly toward a metal contact and completes the circuit to shut off the alarm.

For a reed or GMR switch, a piece of magnetic material, such as a permanent magnet or an electromagnet, in a flexible actuator that is bowed or bulges away from the housing **45** and the reed or GMR switch is used. The reed or

GMR switch is activated (to deactivate the alarm) by depressing the flexible actuator bringing the magnetic material closer to the switch and causing an increase in the magnetic field within the switch.

In some embodiments of the invention, the analyte monitoring device **40** includes only an on-skin control unit **44** and a sensor **42**. In these embodiments, the processing circuit **109** of the on-skin sensor control unit **44** is able to determine a level of the analyte and activate an alarm system **104** if the analyte level exceeds a threshold. The on-skin control unit **44**, in these embodiments, has an alarm system **104** and may also include a display, such as those discussed below with respect to the receiver/display units **46**, **48**. Preferably, the display is an LCD or LED display. The on-skin control unit **44** may not have a transmitter, unless, for example, it is desirable to transmit data, for example, to a control unit in a doctor's office.

The on-skin sensor control unit **44** may also include a reference voltage generator **101** to provide an absolute voltage or current for use in comparison to voltages or currents obtained from or used with the sensor **42**. An example of a suitable reference voltage generator is a band-gap reference voltage generator that uses, for example, a semiconductor material with a known band-gap. Preferably, the band-gap is temperature insensitive over the range of temperatures that the semiconductor material will experience during operation. Suitable semiconductor materials includes gallium, silicon and silicates.

A bias current generator **105** may be provided to correctly bias solid-state electronic components. An oscillator **107** may be provided to produce a clock signal that is typically used with digital circuitry.

The on-skin sensor control unit **44** may also include a watchdog circuit **103** that tests the circuitry, particularly, any digital circuitry in the control unit **44** to determine if the circuitry is operating correctly. Non-limiting examples of watchdog circuit operations include: a) generation of a random number by the watchdog circuit, storage of the number in a memory location, writing the number to a register in the watchdog circuit, and recall of the number to compare for equality; b) checking the output of an analog circuit to determine if the output exceeds a predetermined dynamic range; c) checking the output of a timing circuit for a signal at an expected pulse interval. Other examples of functions of a watchdog circuit are known in the art. If the watchdog circuit detects an error that watchdog circuit may activate an alarm and/or shut down the device.

Receiver/Display Unit

One or more receiver/display units **46**, **48** may be provided with the analyte monitoring device **40** for easy access to the data generated by the sensor **42** and may, in some embodiments, process the signals from the on-skin sensor control unit **44** to determine the concentration or level of analyte in the subcutaneous tissue. Small receiver/display units **46** may be carried by the patient. These units **46** may be palm-sized and/or may be adapted to fit on a belt or within a bag or purse that the patient carries. One embodiment of the small receiver/display unit **46** has the appearance of a pager, for example, so that the user is not identified as a person using a medical device. Such receiver/display units may optionally have one-way or two-way paging capabilities.

Large receiver/display units **48** may also be used. These larger units **48** may be designed to sit on a shelf or nightstand. The large receiver/display unit **48** may be used by parents to monitor their children while they sleep or to awaken patients during the night. In addition, the large receiver/display unit **48** may include a lamp, clock, or radio for convenience and/or for activation as an alarm. One or both types of receiver/display units **46**, **48** may be used.

The receiver/display units **46**, **48**, as illustrated in block form at FIG. **22**, typically include a receiver **150** to receive data from the on-skin sensor control unit **44**, an analyzer **152** to evaluate the data, a display **154** to provide information to the patient, and an alarm system **156** to warn the patient when a condition arises. The receiver/display units **46**, **48** may also optionally include a data storage device **158**, a transmitter **160**, and/or an input device **162**. The receiver/display units **46**,**48** may also include other components (not shown), such as a power supply (e.g., a battery and/or a power supply that can receive power from a wall outlet), a watchdog circuit, a bias current generator, and an oscillator. These additional components are similar to those described above for the on-skin sensor control unit **44**.

In one embodiment, a receiver/display unit **48** is a bedside unit for use by a patient at home. The bedside unit includes a receiver and one or more optional items, including, for example, a clock, a lamp, an auditory alarm, a telephone connection, and a radio. The bedside unit also has a display, preferably, with large numbers and/or letters that can be read across a room. The unit may be operable by plugging into an outlet and may optionally have a battery as backup. Typically, the bedside unit has a better antenna than a small palm-size unit, so the bedside unit's reception range is longer.

When an alarm is indicated, the bedside unit may activate, for example, the auditory alarm, the radio, the lamp, and/or initiate a telephone call. The alarm may be more intense than the alarm of a small palm-size unit to, for example, awaken or stimulate a patient who may be asleep, lethargic, or confused. Moreover, a loud alarm may alert a parent monitoring a diabetic child at night.

The bedside unit may have its own data analyzer and data storage. The data may be communicated from the on-skin sensor unit or another receiver/display unit, such as a palm-size or small receiver/display unit. Thus, at least one unit has all the relevant data so that the data can be downloaded and analyzed without significant gaps.

Optionally, the beside unit has an interface or cradle into which a small receiver/display unit may be placed. The bedside unit may be capable of utilizing the data storage and analysis capabilities of the small receiver/display unit and/or receive data from the small receiver/display unit in this position. The bedside unit may also be capable of recharging a battery of the small receiver/display unit.

The receiver **150** typically is formed using known receiver and antenna circuitry and is often tuned or tunable to the frequency or frequency band of the transmitter **98** in the on-skin sensor control unit **44**. Typically, the receiver **150** is capable of receiving signals from a distance greater than the transmitting distance of the transmitter **98**. The small receiver/display unit **46** can typically receive a signal from an on-skin sensor control unit **44** that is up to 2 meters, preferably up to 5 meters, and more preferably up to 10 meters or more, away. A large receiver/display unit **48**, such as a bedside unit, can typically receive a receive a signal from an on-skin sensor control unit **44** that is up to 5 meters distant, preferably up to 10 meters distant, and more preferably up to 20 meters distant or more.

In one embodiment, a repeater unit (not shown) is used to boost a signal from an on-skin sensor control unit **44** so that the signal can be received by a receiver/display unit **46**, **48** that may be distant from the on-skin sensor control unit **44**. The repeater unit is typically independent of the on-skin

sensor control unit **44**, but, in some cases, the repeater unit may be configured to attach to the on-skin sensor control unit **44**. Typically, the repeater unit includes a receiver for receiving the signals from the on-skin sensor control unit **44** and a transmitter for transmitting the received signals. Often the transmitter of the repeater unit is more powerful than the transmitter of the on-skin sensor control unit, although this is not necessary. The repeater unit may be used, for example, in a child's bedroom for transmitting a signal from an on-skin sensor control unit on the child to a receiver/display unit in the parent's bedroom for monitoring the child's analyte levels. Another exemplary use is in a hospital with a display/receiver unit at a nurse's station for monitoring on-skin sensor control unit(s) of patients.

The presence of other devices, including other on-skin sensor control units, may create noise or interference within the frequency band of the transmitter **98**. This may result in the generation of false data. To overcome this potential difficulty, the transmitter **98** may also transmit a code to indicate, for example, the beginning of a transmission and/or to identify, preferably using a unique identification code, the particular on-skin sensor control unit **44** in the event that there is more than one on-skin sensor control unit **44** or other transmission source within range of the receiver/display unit **46**, **48**. The provision of an identification code with the data may reduce the likelihood that the receiver/display unit **46**, **48** intercepts and interprets signals from other transmission sources, as well as preventing "crosstalk" with different on-skin sensor control units **44**. The identification code may be provided as a factory-set code stored in the sensor control unit **44**. Alternatively, the identification code may be randomly generated by an appropriate circuit in the sensor control unit **44** or the receiver/display unit **46**, **48** (and transmitted to the sensor control unit **44**) or the identification code may be selected by the patient and communicated to the sensor control unit **44** via a transmitter or an input device coupled to the sensor control unit **44**.

Other methods may be used to eliminate "crosstalk" and to identify signals from the appropriate on-skin sensor control unit **44**. In some embodiments, the transmitter **98** may use encryption techniques to encrypt the datastream from the transmitter **98**. The receiver/display unit **46**, **48** contains the key to decipher the encrypted data signal. The receiver/display unit **46**, **48** then determines when false signals or "crosstalk" signals are received by evaluation of the signal after it has been deciphered. For example, the analyzer **152** in the one or more receiver/display units **46**, **48** compares the data, such as current measurements or analyte levels, with expected measurements (e.g., an expected range of measurements corresponding to physiologically relevant analyte levels). Alternatively, an analyzer in the receiver/display units **46**, **48** searches for an identification code in the decrypted data signal.

Another method to eliminate "crosstalk", which is typically used in conjunction with the identification code or encryption scheme, includes providing an optional mechanism in the on-skin sensor control unit **44** for changing transmission frequency or frequency bands upon determination that there is "crosstalk". This mechanism for changing the transmission frequency or frequency band may be initiated by the receiver/display unit automatically, upon detection of the possibility of cross-talk or interference, and/or by a patient manually. For automatic initiation, the receiver/display unit **46**, **48** transmits a signal to the optional receiver **99** on the on-skin sensor control unit **44** to direct the transmitter **98** of the on-skin sensor control unit **44** to change frequency or frequency band.

Manual initiation of the change in frequency or frequency band may be accomplished using, for example, an actuator (not shown) on the receiver/display unit **46**, **48** and/or on the on-skin sensor control unit **44** which a patient operates to direct the transmitter **98** to change frequency or frequency band. The operation of a manually initiated change in transmission frequency or frequency band may include prompting the patient to initiate the change in frequency or frequency band by an audio or visual signal from the receiver/display unit **46**, **48** and/or on-skin sensor control unit **44**.

Returning to the receiver **150**, the data received by the receiver **150** is then sent to an analyzer **152**. The analyzer **152** may have a variety of functions, similar to the processor circuit **109** of the on-skin sensor control unit **44**, including 1) modifying the signals from the sensor **42** using calibration data and/or measurements from the temperature probe **66**, 2) determining a level of an analyte in the interstitial fluid, 3) determining a level of an analyte in the bloodstream based on the sensor measurements in the interstitial fluid, 4) determining if the level, rate of change, and/or acceleration in the rate of change of the analyte exceeds or meets one or more threshold values, 5) activating an alarm system **156** and/or **94** if a threshold value is met or exceeded, 6) evaluating trends in the level of an analyte based on a series of sensor signals, 7) determine a dose of a medication, and 7) reduce noise or error contributions (e.g., through signal averaging or comparing readings from multiple electrodes). The analyzer **152** may be simple and perform only one or a small number of these functions or the analyzer **152** may perform all or most of these functions.

The output from the analyzer **152** is typically provided to a display **154**. A variety of displays **154** may be used including cathode ray tube displays (particularly for larger units), LED displays, or LCD displays. The display **154** may be monochromatic (e.g., black and white) or polychromatic (i.e., having a range of colors). The display **154** may contain symbols or other indicators that are activated under certain conditions (e.g., a particular symbol may become visible on the display when a condition, such as hyperglycemia, is indicated by signals from the sensor **42**). The display **154** may also contain more complex structures, such as LCD or LED alphanumeric structures, portions of which can be activated to produce a letter, number, or symbol. For example, the display **154** may include region **164** to display numerically the level of the analyte, as illustrated in FIG. **23**. In one embodiment, the display **154** also provides a message to the patient to direct the patient in an action. Such messages may include, for example, "Eat Sugar", if the patient is hypoglycemic, or "Take Insulin", if the patient is hyperglycemic.

One example of a receiver/display unit **46**, **48** is illustrated in FIG. **23**. The display **154** of this particular receiver/display unit **46**, **48** includes a portion **164** which displays the level of the analyte, for example, the blood glucose concentration, as determined by the processing circuit **109** and/or the analyzer **152** using signals from the sensor **42**. The display also includes various indicators **166** which may be activated under certain conditions. For example, the indicator **168** of a glucose monitoring device may be activated if the patient is hyperglycemic. Other indicators may be activated in the cases of hypoglycemia (**170**), impending hyperglycemia (**172**), impending hypoglycemia (**174**), a malfunction, an error condition, or when a calibration sample is needed (**176**). In some embodiments, color coded indicators may be used. Alternatively, the portion **164** which displays the blood glucose concentration may also include a

composite indicator **180** (see FIG. **24**), portions of which may be appropriately activated to indicate any of the conditions described above.

The display **154** may also be capable of displaying a graph **178** of the analyte level over a period of time, as illustrated in FIG. **24**. Examples of other graphs that may be useful include graphs of the rate of change or acceleration in the rate of change of the analyte level over time. In some embodiments, the receiver/display unit is configured so that the patient may choose the particular display (e.g., blood glucose concentration or graph of concentration versus time) that the patient wishes to view. The patient may choose the desired display mode by pushing a button or the like, for example, on an optional input device **162**.

The receiver/display units **46**, **48** also typically include an alarm system **156**. The options for configuration of the alarm system **156** are similar to those for the alarm system **104** of the on-skin sensor control unit **44**. For example, if glucose is the analyte, than the on-skin sensor control unit **44** may include an alarm system **156** that warns the patient of conditions such as hypoglycemia, hyperglycemia, impending hypoglycemia, and/or impending hyperglycemia. The alarm system **156** is triggered when the data from the analyzer **152** reaches or exceeds a threshold value. The threshold values may correspond to interstitial fluid glucose concentrations or sensor signals (e.g., current or converted voltage values) which correlate to the above-mentioned blood glucose levels.

The alarm system **156** may also, or alternatively, be activated when the rate or acceleration of an increase or decrease in analyte level reaches or exceeds a threshold value. For example, in the case of a subcutaneous glucose monitor, the alarm system **156** might be activated if the rate of change in glucose concentration exceeds a threshold value which might indicate that a hyperglycemic or hypoglycemic condition is likely to occur.

The alarm system **156** may be configured to activate when a single data point meets or exceeds a particular threshold value. Alternatively, the alarm may be activated only when a predetermined number of datapoints spanning a predetermined amount of time meet or exceed the threshold value. As another alternative, the alarm may be activated only when the datapoints spanning a predetermined amount of time have an average value which meets or exceeds the threshold value. Each condition that can trigger an alarm may have a different alarm activation condition. In addition, the alarm activation condition may change depending on current conditions (e.g., an indication of impending hyperglycemia may alter the number of datapoints or the amount of time that is tested to determine hyperglycemia).

The alarm system **156** may contain one or more individual alarms. Each of the alarms may be individually activated to indicate one or more conditions of the analyte. The alarms may be, for example, auditory or visual. Other sensory-stimulating alarm systems by be used including alarm systems **156** that direct the on-skin sensor control unit **44** to heat, cool, vibrate, or produce a mild electrical shock. In some embodiments, the alarms are auditory with a different tone, note, or volume indicating different conditions. For example, a high note might indicate hyperglycemia and a low note might indicate hypoglycemia. Visual alarms may also use a difference in color or brightness to indicate different conditions. In some embodiments, an auditory alarm system might be configured so that the volume of the alarm increases over time until the alarm is deactivated.

In some embodiments, the alarms may be automatically deactivated after a predetermined time period. In other embodiments, the alarms may be configured to deactivate when the data no longer indicate that the condition which triggered the alarm exists. In these embodiments, the alarms may be deactivated when a single data point indicates that the condition no longer exists or, alternatively, the alarm may be deactivated only after a predetermined number of datapoints or an average of datapoints obtained over a given period of time indicate that the condition no longer exists.

In yet other embodiments, the alarm may be deactivated manually by the patient or another person in addition to or as an alternative to automatic deactivation. In these embodiments, a switch is provided which when activated turns off the alarm. The switch may be operatively engaged (or disengaged depending on the configuration of the switch) by, for example, pushing a button on the receiver/display unit **46**, **48**. One configuration of the alarm system **156** has automatic deactivation after a period of time for alarms that indicate an impending condition (e.g., impending hypoglycemia or hyperglycemia) and manual deactivation of alarms which indicate a current condition (e.g., hypoglycemia or hyperglycemia).

The receiver/display units **46**, **48** may also include a number of optional items. One item is a data storage unit **158**. The data storage unit **158** may be desirable to store data for use if the analyzer **152** is configured to determine trends in the analyte level. The data storage unit **158** may also be useful to store data that may be downloaded to another receiver/display unit, such as a large display unit **48**. Alternatively, the data may be downloaded to a computer or other data storage device in a patient's home, at a doctor's office, etc. for evaluation of trends in analyte levels. A port (not shown) may be provided on the receiver/display unit **46**, **48** through which the stored data may be transferred or the data may be transferred using an optional transmitter **160**. The data storage unit **158** may also be activated to store data when a directed by the patient via, for example, the optional input device **162**. The data storage unit **158** may also be configured to store data upon occurrence of a particular event, such as a hyperglycemic or hypoglycemic episode, exercise, eating, etc. The storage unit **158** may also store event markers with the data of the particular event. These event markers may be generated either automatically by the display/receiver unit **46**, **48** or through input by the patient.

The receiver/display unit **46**, **48** may also include an optional transmitter **160** which can be used to transmit 1) calibration information, 2) a signal to direct the transmitter **98** of the on-skin sensor control unit **44** to change transmission frequency or frequency bands, and/or 3) a signal to activate an alarm system **104** on the on-skin sensor control unit **44**, all of which are described above. The transmitter **160** typically operates in a different frequency band than the transmitter **98** of the on-skin sensor control unit **44** to avoid cross-talk between the transmitters **98**, **160**. Methods may be used to reduce cross-talk and the reception of false signals, as described above in connection with the transmitter **100** of the on-skin sensor control unit **44**. In some embodiments, the transmitter **160** is only used to transmit signals to the sensor control unit **44** and has a range of less than one foot, and preferably less than six inches. This then requires the patient or another person to hold the receiver/display unit **46** near the sensor control unit **44** during transmission of data, for example, during the transmission of calibration information. Transmissions may also be performed using methods other than rf transmission, including optical or wire transmission.

In addition, in some embodiments of the invention, the transmitter **160** may be configured to transmit data to

another receiver/display unit **46**, **48** or some other receiver. For example, a small receiver/display unit **46** may transmit data to a large receiver/display unit **48**, as illustrated in FIG. **1**. As another example, a receiver/display unit **46**, **48** may transmit data to a computer in the patient's home or at a doctor's office. Moreover, the transmitter **160** or a separate transmitter may direct a transmission to another unit or to a telephone or other communications device that alerts a doctor or other individual when an alarm is activated and/or if, after a predetermined time period, an activated alarm has not been deactivated, suggesting that the patient may require assistance. In some embodiments, the receiver/display unit is capable of one-way or two-way paging and/or is coupled to a telephone line to send and/or receive messages from another, such as a health professional monitoring the patient.

Another optional component for the receiver/display unit **46**, **48** is an input device **162**, such as a keypad or keyboard. The input device **162** may allow numeric or alphanumeric input. The input device **162** may also include buttons, keys, or the like which initiate functions of and/or provide input to the analyte monitoring device **40**. Such functions may include initiating a data transfer, manually changing the transmission frequency or frequency band of the transmitter **98**, deactivating an alarm system **104**, **156**, inputting calibration data, and/or indicating events to activate storage of data representative of the event.

Another embodiment of the input device **162** is a touch screen display. The touch screen display may be incorporated into the display **154** or may be a separate display. The touch screen display is activated when the patient touches the screen at a position indicated by a "soft button" which corresponds to a desired function. Touch screen displays are well known.

In addition, the analyte monitoring device **40** may include password protection to prevent the unauthorized transmission of data to a terminal or the unauthorized changing of settings for the device **40**. A patient may be prompted by the display **154** to input the password using the input device **152** whenever a password-protected function is initiated.

Another function that may be activated by the input device **162** is a deactivation mode. The deactivation mode may indicate that the receiver/display unit **46**, **48** should no longer display a portion or all of the data. In some embodiments, activation of the deactivation mode may even deactivate the alarm systems **104**, **156**. Preferably, the patient is prompted to confirm this particular action. During the deactivation mode, the processing circuit **109** and/or analyzer **152** may stop processing data or they may continue to process data and not report it for display and may optionally store the data for later retrieval.

Alternatively, a sleep mode may be entered if the input device **162** has not been activated for a predetermined period of time. This period of time may be adjustable by the patient or another individual. In this sleep mode, the processing circuit **109** and/or analyzer **152** typically continue to obtain measurements and process data, however, the display is not activated. The sleep mode may be deactivated by actions, such as activating the input device **162**. The current analyte reading or other desired information may then be displayed.

In one embodiment, a receiver/display unit **46** initiates an audible or visual alarm when the unit **46** has not received a transmission from the on-skin sensor control unit within a predetermined amount of time. The alarm typically continues until the patient responds and/or a transmission is received. This can, for example, remind a patient if the receiver/display unit **46** is inadvertently left behind.

In another embodiment, the receiver/display unit **46**, **48** is integrated with a calibration unit (not shown). For example, the receiver/display unit **46**, **48** may, for example, include a conventional blood glucose monitor. Another useful calibration device utilizing electrochemical detection of analyte concentration is described in U.S. patent application Ser. No. 08/795,767, incorporated herein by reference. Other devices may be used including those that operate using, for example, electrochemical and colorimetric blood glucose assays, assays of interstitial or dermal fluid, and/or non-invasive optical assays. When a calibration of the implanted sensor is needed, the patient uses the integrated in vitro monitor to generate a reading. The reading may then, for example, automatically be sent by the transmitter **160** of the receiver/display unit **46**, **48** to calibrate the sensor **42**.

Integration With a Drug Administration System

FIG. **25** illustrates a block diagram of a sensor-based drug delivery system **250** according to the present invention. The system may provide a drug to counteract the high or low level of the analyte in response to the signals from one or more sensors **252**. Alternatively, the system monitors the drug concentration to ensure that the drug remains within a desired therapeutic range. The drug delivery system includes one or more (and preferably two or more) subcutaneously implanted sensors **252**, an on-skin sensor control unit **254**, a receiver/display unit **256**, a data storage and controller module **258**, and a drug administration system **260**. In some cases, the receiver/display unit **256**, data storage and controller module **258**, and drug administration system **260** may be integrated in a single unit. The sensor-based drug delivery system **250** uses data form the one or more sensors **252** to provide necessary input for a control algorithm/mechanism in the data storage and controller module **252** to adjust the administration of drugs. As an example, a glucose sensor could be used to control and adjust the administration of insulin.

In FIG. **25**, sensor **252** produces signals correlated to the level of the drug or analyte in the patient. The level of the analyte will depend on the amount of drug delivered by the drug administration system. A processor **262** in the on-skin sensor control unit **254**, as illustrated in FIG. **25**, or in the receiver/display unit **256** determines the level of the analyte, and possibly other information, such as the rate or acceleration of the rate in the increase or decrease in analyte level. This information is then transmitted to the data storage and controller module **252** using a transmitter **264** in the on-skin sensor control unit **254**, as illustrated in FIG. **25**, or a non-integrated receiver/display unit **256**.

If the drug delivery system **250** has two or more sensors **252**, the data storage and controller module **258** may verify that the data from the two or more sensors **252** agrees within predetermined parameters before accepting the data as valid. This data may then be processed by the data storage and controller module **258**, optionally with previously obtained data, to determine a drug administration protocol. The drug administration protocol is then executed using the drug administration system **260**, which may be an internal or external infusion pump, syringe injector, transdermal delivery system (e.g., a patch containing the drug placed on the skin), or inhalation system. Alternatively, the drug storage and controller module **258** may provide a the drug administration protocol so that the patient or another person may provide the drug to the patient according to the profile.

In one embodiment of the invention, the data storage and controller module **258** is trainable. For example, the data storage and controller module **258** may store glucose readings over a predetermined period of time, e.g., several weeks. When an episode of hypoglycemia or hyperglycemia is encountered, the relevant history leading to such event

may be analyzed to determine any patterns which might improve the system's ability to predict future episodes. Subsequent data might be compared to the known patterns to predict hypoglycemia or hyperglycemia and deliver the drug accordingly. In another embodiment, the analysis of trends is performed by an external system or by the processing circuit **109** in the on-skin sensor control unit **254** or the analyzer **152** in the receiver/display unit **256** and the trends are incorporated in the data storage and controller **258**.

In one embodiment, the data storage and controller module **258**, processing circuit **109**, and/or analyzer **152** utilizes patient-specific data from multiple episodes to predict a patient's response to future episodes. The multiple episodes used in the prediction are typically responses to a same or similar external or internal stimulus. Examples of stimuli include periods of hypoglycemia or hyperglycemia (or corresponding conditions for analytes other than glucose), treatment of a condition, drug delivery (e.g., insulin for glucose), food intake, exercise, fasting, change in body temperature, elevated or lowered body temperature (e.g., fever), and diseases, viruses, infections, and the like. By analyzing multiple episodes, the data storage and controller module **258**, processing circuit **109**, and/or analyzer **152** can predict the coarse of a future episode and provide, for example, a drug administration protocol or administer a drug based on this analysis. An input device (not shown) may be used by the patient or another person to indicate when a particular episode is occurring so that, for example, the data storage and controller module **258**, processing circuit **109**, and/or analyzer **152** can tag the data as resulting from a particular episode, for use in further analyses.

In addition, the drug delivery system **250** may be capable of providing on-going drug sensitivity feedback. For example, the data from the sensor **252** obtained during the administration of the drug by the drug administration system **260** may provide data about the individual patient's response to the drug which can then be used to modify the current drug administration protocol accordingly, both immediately and in the future. An example of desirable data that can be extracted for each patient includes the patient's characteristic time constant for response to drug administration (e.g., how rapidly the glucose concentration falls when a known bolus of insulin is administered). Another example is the patient's response to administration of various amounts of a drug (e.g., a patient's drug sensitivity curve). The same information may be stored by the drug storage and controller module and then used to determine trends in the patient's drug response, which may be used in developing subsequent drug administration protocols, thereby personalizing the drug administration process for the needs of the patient.

The present invention should not be considered limited to the particular examples described above, but rather should be understood to cover all aspects of the invention as fairly set out in the attached claims. Various modifications, equivalent processes, as well as numerous structures to which the present invention may be applicable will be readily apparent to those of skill in the art to which the present invention is directed upon review of the instant specification. The claims are intended to cover such modifications and devices.

We claim:

1. A sensor control unit comprising:

a housing adapted for placement on skin and adapted to receive a portion of an electrochemical sensor extending out of the skin having a plurality of contact pads;

a plurality of conductive contacts disposed on the housing and configured for coupling to the plurality of contact pads on the electrochemical sensor; and

an rf transmitter disposed in the housing and coupled to the plurality of conductive contacts for transmitting data obtained using the electrochemical sensor.

2. The sensor control unit of claim **1**, further comprising adhesive for adhering the sensor control unit to skin.

3. The sensor control unit of claim **1**, further comprising a mounting unit adapted for coupling with the housing.

4. The sensor control unit of claim **3**, wherein the mounting unit is configured for placement between the housing and the skin of the patient.

5. The sensor control unit of claim **3**, wherein adhesive is disposed on a surface of the mounting unit for adhering the mounting unit and housing to the skin of the patient.

6. The sensor control unit of claim **3**, further comprising a support structure disposed on the mounting unit for aligning the contact pads of the sensor with the conductive contacts of the sensor control unit.

7. The sensor control unit of claim **3**, further comprising an opening in the mounting unit configured for guiding insertion of the electrochemical sensor into the patient.

8. The sensor control unit of claim **1**, wherein the housing comprises a base and a cover.

9. The sensor control unit of claim **8**, wherein the base and cover are configured to form a water resistant seal when coupled.

10. The sensor control unit of claim **1**, wherein the housing is water resistant.

11. The sensor control unit of claim **1**, wherein the conductive contacts are disposed on an interior surface of the housing.

12. The sensor control unit of claim **11**, wherein the housing comprises a port adapted for penetration by the sensor.

13. The sensor control unit of claim **1**, wherein the plurality of conductive contacts are disposed on an exterior surface of the housing.

14. The sensor control unit of claim **1**, wherein a volume of the housing is about 10 cm^3 or less.

15. The sensor control unit of claim **1**, wherein a height of the housing is about 0.7 cm or less.

16. The sensor control unit of claim **1**, wherein a weight of the housing is about 90 grams or less.

17. The sensor control unit of claim **1**, further comprising a battery disposed in the housing.

18. The sensor control unit of claim **17**, wherein the battery is sealed within the housing of the sensor control unit.

19. The sensor control unit of claim **17**, wherein the battery is removable from the housing.

20. The sensor control unit of claim **1**, further comprising an alarm to indicate at least one of hypoglycemia, impending hypoglycemia, hyperglycemia, or impending hyperglycemia.

21. The sensor control unit of claim **20**, further comprising a switch for deactivating the alarm.

22. The sensor control unit of claim **20**, wherein the alarm produces an audible signal when activated.

23. The sensor control unit of claim **22**, wherein a loudness of the alarm increases over time when the alarm is activated.

24. The sensor control unit of claim **20**, wherein the alarm produces a vibration when activated.

25. The sensor control unit of claim **20**, wherein the alarm is configured to indicate at least two of hypoglycemia, impending hypoglycemia, hyperglycemia, or impending hyperglycemia.

26. The sensor control unit of claim **1**, further comprising a receiver disposed in the housing.

27. The sensor control unit of claim 1, further comprising a processing circuit disposed in the housing and coupled to the conductive contacts, the processing circuit is configured for determining a level of an analyte from a signal generated by the sensor.

28. The sensor control unit of claim 27, wherein the processing circuit is configured for determining the level of the analyte in blood from a sensor that is subcutaneously implanted in the patient.

29. The sensor control unit of claim 27, wherein the processing circuit is configured for adjusting the data for temperature using a signal from a temperature probe of the sensor.

30. The sensor control unit of claim 1, wherein the plurality of conductive contacts of the sensor control unit comprise conductive carbon.

31. The sensor control unit of claim 1, further comprising a data storage unit disposed in the housing for keeping data for a period of time.

32. A sensor assembly, comprising:

a sensor having a substrate, at least one recessed channel formed in a surface of the substrate, conductive material disposed in the at least one recessed channel to form at least one working electrode and an individual contact pad for each of the at least one working electrodes; and

a sensor control unit for placement on a skin of an animal, the sensor control unit including

a housing having a port through which the sensor penetrates the housing, and

a plurality of conductive contacts disposed in the housing and configured for coupling with the contact pads of the sensor.

33. A sensor assembly, comprising:

a sensor comprising a flexible substrate with at least one working electrode, at least one counter electrode, and at least one contact pad coupled to each of the working and counter electrodes, the sensor being adapted for implantation of a portion of the sensor comprising the working and counter electrodes through skin; and

a sensor control unit comprising

a housing adapted for placement on skin;

a plurality of conductive contacts disposed on the housing and configured for coupling to the contact pads of the sensor; and

an rf transmitter disposed in the housing and coupled to the plurality of conductive contacts for transmitting data obtained using the sensor.

34. A sensor assembly, comprising:

a sensor comprising at least one working electrode and at least one contact pad coupled to the at least one working electrode; and

the sensor control unit of claim 1.

35. The sensor assembly of claim 34, wherein the plurality of conductive contacts, the plurality of contact pads, or both comprise conductive carbon.

36. The sensor assembly of claim 35, wherein a signal generated by corrosion of the plurality of conductive contacts and the plurality of contact pads when immersed in a 1 mM NaCl solution is 3% or less of a signal generated by the working electrode when exposed to an analyte having a concentration within an expected physiological range.

37. The sensor assembly of claim 35, wherein a signal generated by corrosion of the plurality of conductive contacts and the plurality of contact pads when immersed in a 100 mM NaCl solution is 3% or less of a signal generated by the working electrode when exposed to an analyte having a concentration within an expected physiological range.

38. The sensor assembly of claim 34, further comprising a mounting unit adapted for coupling with the housing.

39. An analyte monitoring system comprising:

a sensor comprising at least one working electrode and at least one contact pad coupled to the at least one working electrode, the sensor being adapted for implantation of a portion of the sensor comprising the working electrode through skin;

the sensor control unit of claim 1; and

a display unit comprising an rf receiver for receiving data from the sensor control unit, and a display coupled to the rf receiver for displaying an indication of the level of an analyte.

40. The analyte monitoring system of claim 39, further comprising a mounting unit adapted for coupling with the housing.

41. The analyte monitoring system of claim 39, wherein the sensor control unit further comprises an rf receiver disposed in the housing and the display unit further comprises an rf transmitter for transmitting to the rf receiver of the sensor control unit.

42. The analyte monitoring system of claim 39, wherein the display unit further comprises an analyzer coupled to the display and the rf receiver for analyzing data from the rf receiver and providing analyzed data to the display.

43. The analyte monitoring system of claim 39, wherein the display unit further comprises a battery coupled to the receiver and display.

44. The analyte monitoring system of claim 39, wherein the display unit further comprises an input device coupled to the display.

45. The analyte monitoring system of claim 39, further comprising a calibrator for providing a calibration value to at least one of the display unit and the sensor control unit.

46. The analyte monitoring system of claim 45, wherein the calibrator is coupled to the receiver of the display unit for providing the calibration value to the sensor control unit.

47. The analyte monitoring system of claim 45, wherein the calibrator provides a calibration value using 1 microliter or less of body fluid.

48. The analyte monitoring system of claim 45, wherein the calibrator comprises a device configured for non-invasive optical assay of analyte.

49. The analyte monitoring system of claim 39, wherein the display unit is portable.

50. The analyte monitoring system of claim 49, wherein the display unit is configured for wearing on a piece of clothing.

51. The analyte monitoring system of claim 49, further comprising a secondary display unit having a power cord for connecting to an electrical outlet, a receiver for receiving data transmitted by the transmitter, and a display coupled to the receiver for displaying the level of the analyte.

52. The analyte monitoring system of claim 51, wherein the display unit and the secondary display unit are configured for exchanging data.

53. The analyte monitoring system of claim 39, wherein the display unit is configured for connection to an electrical outlet.

54. The analyte monitoring system of claim 53, wherein the display unit further comprises at least one of a lamp, a radio, a clock, an interface to a telephone system, an interface to a computer, or a battery backup system.

55. The analyte monitoring system of claim 39, wherein the display unit further comprises an alarm configured for

activation if a signal from the transmitter of the sensor control unit is not received with a predetermined time interval.

56. The analyte monitoring system of claim **39**, wherein the display unit comprises a pager receiver for receiving pages from an external paging system.

57. The analyte monitoring system of claim **56**, wherein the display unit comprises a pager transmitter for sending pages to the external paging system, wherein the pager transmitter is activated when at least one of hypoglycemia, impending hypoglycemia, hyperglycemia, or impending hyperglycemia is indicated.

58. The analyte monitoring system of claim **39**, wherein the display unit is configured for coupling to an external download device to transfer data from the display unit.

59. The analyte monitoring system of claim **39**, further comprising at least one alarm disposed in the display unit and configured to indicate when a level of an analyte exceeds a threshold level.

60. The analyte monitoring system of claim **59**, wherein the alarm is configured to indicate when a level of an analyte is near a threshold level.

61. The analyte monitoring system of claim **60**, wherein the alarm is configured to indicate at least one of hypoglycemia, impending hypoglycemia, hyperglycemia, or impending hyperglycemia.

62. The analyte monitoring system of claim **61**, wherein the alarm is configured to indicate impending hypoglycemia and is deactivated if an impending hypoglycemia condition does not exist.

63. The analyte monitoring system of claim **61**, wherein the alarm is configured to indicate hypoglycemia and is only manually deactivatable.

64. The analyte monitoring system of claim **61**, wherein the alarm is configured to indicate hypoglycemia and the alarm, when activated, produces an audible signal that increases in loudness over time.

65. The analyte monitoring system of claim **59**, wherein the analyte monitoring system comprises at least two alarms, each alarm producing an audible signal, wherein the signals of the at least two alarms are distinguishable.

66. The analyte monitoring system of claim **39**, further comprising a processing circuit in the display unit, the processing circuit being configured to analyze patient-specific data from multiple episodes to predict a patient's response to future episodes.

67. The analyte monitoring system of claim **66**, wherein the patient-specific data comprises a response to a treatment.

68. The analyte monitoring system of claim **67**, wherein the analyte is glucose and the treatment is an administration of insulin.

69. The analyte monitoring system of claim **67**, wherein the display unit further comprises an input device for indicating when a treatment is administered.

70. The analyte monitoring system of claim **66**, wherein the processing circuit is configured to determine a drug administration protocol in response to the patient-specific data.

71. The analyte monitoring system of claim **66**, wherein the patient-specific data is a dosage dependence of a response to a drug.

72. The analyte monitoring system of claim **66**, wherein the display unit further comprises an input device for indicating when food has been injested.

73. The analyte monitoring system of claim **72**, where the input device is configured for indicating an approximate caloric content of the food.

74. The analyte monitoring system of claim **39**, further comprising a temperature measurement device to correct data obtained from the sensor.

75. The analyte monitoring system of claim **74**, wherein the temperature measurement device comprises a temperature probe disposed on the substrate.

76. The analyte monitoring system of claim **39**, wherein the analyte monitoring system further comprises a drug administration system which dispenses a drug based on the level of the analyte.

77. The analyte monitoring system of claim **76**, wherein the drug administration system comprises a receiver for receiving data from at least one of the sensor control unit or display unit to direct dispensing of the drug.

78. The analyte monitoring system of claim **76**, wherein the drug administration system comprises at least one of a needle, syringe, pump, catheter, inhaler, or transdermal patch to administer the drug.

79. The analyte monitoring system of claim **76**, wherein the drug is insulin.

80. A method for monitoring a level of an analyte using the analyte monitoring system of claim **39**, the method comprising:

inserting the sensor into skin of a patient;

attaching the sensor control unit to the skin of the patient;

coupling a plurality of conductive contacts disposed in the sensor control unit to a plurality of contact pads disposed on the sensor;

collecting data, using the sensor control unit, regarding a level of an analyte from signals generated by the sensor;

transmitting the collected data to the display unit using the rf transmitter of the sensor control unit; and

displaying an indication of the level of the analyte on the display of the display unit.

81. The method of claim **80**, wherein collecting data comprises generating signals from the sensor and processing the signals into data.

82. The method of claim **80**, wherein the data comprises the signals from the sensor.

83. The method of claim **80**, further comprising activating an alarm if the data indicates an alarm condition.

84. The method of claim **80**, further comprising administering a drug in response to the data.

85. The method of claim **80**, further comprising obtaining a calibration value from a calibration device to calibrate the data.

86. The method of claim **85**, wherein the calibration device is coupled to the display unit.

87. The method of claim **86**, further comprising transmitting the calibration value from a transmitter in the display unit to a receiver in the sensor control unit.

88. An analyte monitoring system comprising:

(a) a sensor comprising at least one working electrode and at least one contact pad coupled to the at least one working electrode, the sensor being adapted for implantation of a portion of the sensor comprising the working electrode through skin;

(b) a sensor control unit comprising,

(i) a housing adapted for placement on skin and adapted to receive a portion of an electrochemical sensor having a plurality of contact pads;

(ii) a plurality of conductive contacts disposed on the housing and configured for coupling to the plurality of contact pads on the electrochemical sensor; and

(iii) an rf transmitter disposed in the housing and coupled to the plurality of conductive contacts for transmitting data obtained using the electrochemical sensor; and

(c) a display unit comprising a receiver for receiving data from the sensor control unit, and a display coupled to the receiver for displaying an indication of the level of an analyte, wherein the transmitter of the sensor control unit and the receiver of the display unit are capable of transmitting and receiving data when separated by a distance of two meters.

89. A sensor control unit comprising:

a housing adapted for placement on skin and adapted to receive a portion of an independent electrochemical sensor extending out of the skin and having at least one contact pad;

at least one conductive contact configured for coupling to the at least one contact pad on the independent electrochemical sensor; and

an rf transmitter disposed in the housing and coupled to the at least one conductive contact for transmitting data obtained using the independent electrochemical sensor.

90. A method for monitoring a level of an analyte using the analyte monitoring system of claim **39**, the method comprising:

inserting the sensor into skin of a patient;

attaching the sensor control unit to the skin of the patient;

coupling a plurality of conductive contacts disposed in the sensor control unit to a plurality of contact pads disposed on the sensor;

collecting data, using the sensor control unit, regarding a level of an analyte from signals generated by the sensor;

transmitting the collected data to the display unit using the rf transmitter of the sensor control unit;

displaying an indication of the level of the analyte on the display of the display unit; and

replacing the sensor with a new sensor after a period of use.

91. The analyte monitoring system of claim **74**, wherein the analyte monitoring system if configured and arranged to determine a temperature near the sensor using two electrodes of the sensor.

92. The analyte monitoring system of claim **39**, wherein the sensor further comprises an enzyme non-leachably disposed on the at least one working electrode.

93. The analyte monitoring system of claim **39**, wherein the working electrode comprises a mixture of conductive material and an analyte-responsive enzyme.

94. The analyte monitoring system of claim **39**, wherein the sensor further comprises a mass transport limiting membrane disposed over the working electrode, the mass transport limiting member maintaining a rate of permeation of the analyte through the mass transport limiting membrane with a variation of no more than 3% per ° C. at temperatures ranging from 30° C. to 40° C.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,175,752 B1
DATED : January 16, 2001
INVENTOR(S) : Say et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [75] (Inventors:), delete "Behrad Aria, Alameda, CA (US)" and "Fredric C. Colman, Berkeley, CA (US)".

Signed and Sealed this

Twenty-fifth Day of September, 2001

Attest:

Nicholas P. Godici

Attesting Officer

NICHOLAS P. GODICI
Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,175,752 C1
APPLICATION NO. : 90/009497
DATED : December 14, 2010
INVENTOR(S) : James Say et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

AT COL 2, LINE 1:

Please replace -- The patentability of claims 35, 36, 52, 55, 56, 57 and 87 is confirmed. -- with -- The patentability of claims 36, 37, 52, 55, 56, 57 and 87 is confirmed. --

AT COL 2, LINE 4:

Please replace -- Claims 1-34, 37-51, 53-54, 58-86 and 88-94 were not reexamined. -- with -- Claims 1-35, 38-51, 53, 54, 58-86, and 88-94 were not reexamined. --

Signed and Sealed this
Twenty-sixth Day of July, 2011

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

US006175752C1

(12) **EX PARTE REEXAMINATION CERTIFICATE** (7929th)

United States Patent
Say et al.

(10) **Number: US 6,175,752 C1**
(45) **Certificate Issued: Dec. 14, 2010**

(54) **ANALYTE MONITORING DEVICE AND METHODS OF USE**

(75) Inventors: **James Say**, Alameda, CA (US); **Michael F. Tomasco**, Cupertino, CA (US); **Adam Heller**, Austin, TX (US); **Yoram Gal**, Kibbutz Yagur, IL (US); **Behrad Aria**, Alameda, CA (US); **Ephriam Heller**, Oakland, CA (US); **Phillip John Plante**, Sunnyvale, CA (US); **Mark S. Vreeke**, Alameda, CA (US); **Keith A Friedman**, Austin, TX (US); **Fredric C. Colman**, Berkeley, CA (US)

(73) Assignee: **Therasense, Inc.**, Alameda, CA (US)

Reexamination Request:
No. 90/009,497, Jun. 17, 2009

Reexamination Certificate for:

Patent No.:	**6,175,752**
Issued:	**Jan. 16, 2001**
Appl. No.:	**09/070,677**
Filed:	**Apr. 30, 1998**

Certificate of Correction issued Sep. 25, 2001.

(51) **Int. Cl.**
A61B 5/00 (2006.01)

(52) **U.S. Cl.** **600/345**; 600/365; 128/903

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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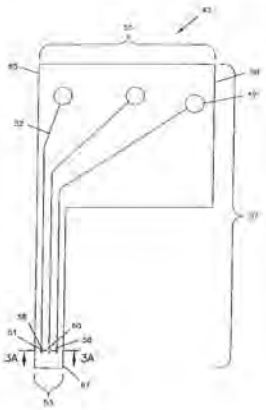

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Primary Examiner—Albert J Gagliardi

(57) **ABSTRACT**

An analyte monitor includes a sensor, a sensor control unit, and a display unit. The sensor has, for example, a substrate, a recessed channel formed in the substrate, and conductive material disposed in the recessed channel to form a working electrode. The sensor control unit typically has a housing adapted for placement on skin and is adapted to receive a portion of an electrochemical sensor. The sensor control unit also includes two or more conductive contacts disposed on the housing and configured for coupling to two or more contact pads on the sensor. A transmitter is disposed in the housing and coupled to the plurality of conductive contacts for transmitting data obtained using the sensor. The display unit has a receiver data transmitted by the transmitter of the sen-

sor control unit and display coupled to the receiver for displaying an indication of a level of an analyte. The analyte monitor may also be part of a drug delivery system to alter the level of the analyte based on the data obtained using the sensor.

At the time of issuance and publication of this certificate, the patent remains subject to pending reexamination control number 90/007,910 filed Feb. 1, 2006. The claim content of the patent may be subsequently revised in the reexamination proceeding.

EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **35**, **36**, **52**, **55**, **56**, **57** and **87** is confirmed.

Claims **1-34**, **37-51**, **53-54**, **58-86** and **88-94** were not reexamined.

* * * * *

Exhibit 10

US005791344A

United States Patent [19]

Schulman et al.

[11] Patent Number: 5,791,344

[45] Date of Patent: *Aug. 11, 1998

[54] **PATIENT MONITORING SYSTEM**

[75] Inventors: **Joseph H. Schulman**, Santa Clarita; **Ronald J. Lebel**, Sherman Oaks; **Joseph Y. Lucisano**, San Diego; **Alfred E. Mann**, Beverly Hills; **Orville Rey Rule, III**; **David I. Whitmoyer**, both of Los Angeles, all of Calif.

[73] Assignee: **Alfred E. Mann Foundation for Scientific Research**, Sylmar, Calif.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,497,772.

[21] Appl. No.: **582,756**

[22] Filed: **Jan. 4, 1996**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 155,737, Nov. 19, 1993, Pat. No. 5,497,772.

[51] **Int. Cl.**[6] **A61B 5/00**

[52] **U.S. Cl.** **128/635**; 204/403; 204/415

[58] **Field of Search** 128/635; 604/64–66; 204/403, 408, 412, 415

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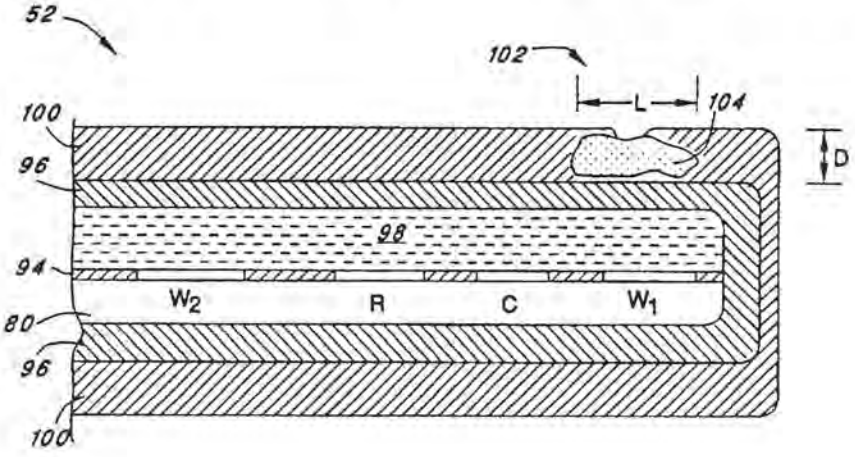
Primary Examiner—Robert L. Nasser

Attorney, Agent, or Firm—Fitch, Even, Tabin & Flannery

[57] **ABSTRACT**

A patient monitoring system measures the concentration of a particular substance in a patient's tissue, blood, or other bodily fluids, provides an indication of the rate of change of such concentration, and determines whether the measured concentration and rate of change are within certain preset limits. If not, an audible and/or visual alarm signal is generated. The patient monitoring system includes at least one enzymatic sensor adapted to be inserted into the patient, where it produces sensor signals related to the concentration of the substance being measured. The sensor signals are delivered through a suitable interconnect cable to a monitor. In one embodiment, the interconnect cable includes a contactless connector that electrically isolates the enzymatic sensor from the monitor, and reduces the number of conductors required to interface with a plurality of sensors. The monitor interprets the sensor signals by applying a previously determined calibration to quantitatively determine the substance concentration value. The substance concentration value thus determined is then processed in order to determine the rate of change, is stored (to create a history or record), and may also be displayed in large, easy-to-read numerals. Rate of change information (trend) may also be numerically or graphically displayed.

33 Claims, 12 Drawing Sheets



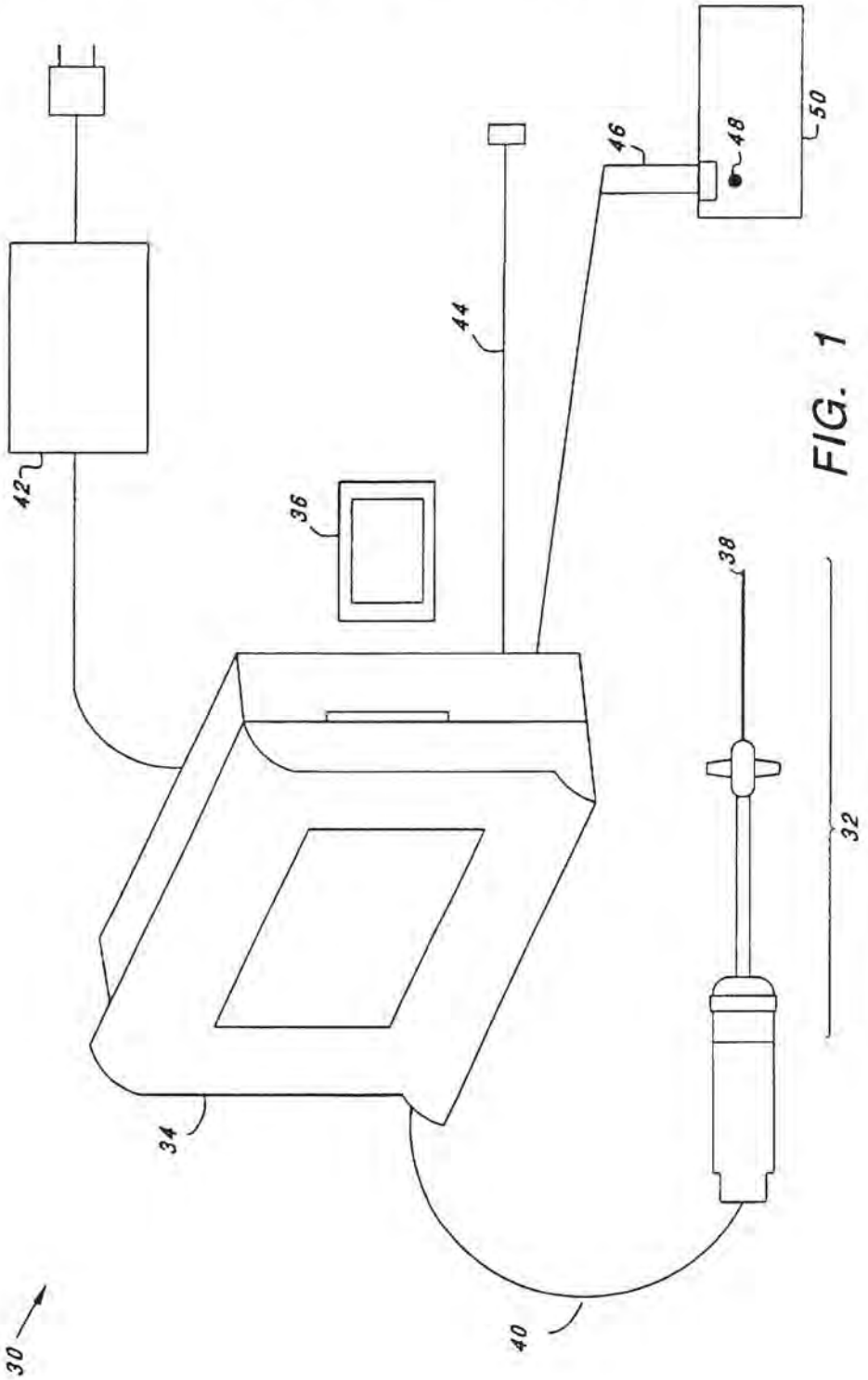


FIG. 1

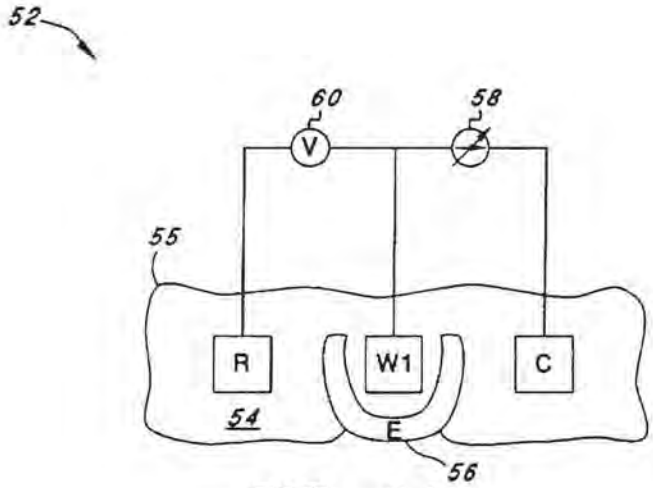


FIG. 2A

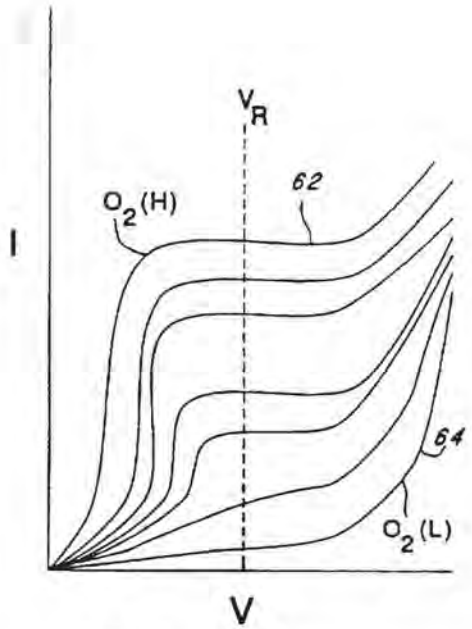


FIG. 2B

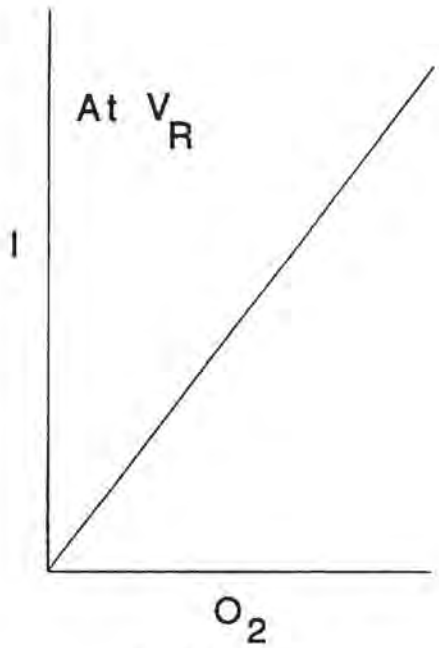


FIG. 2C

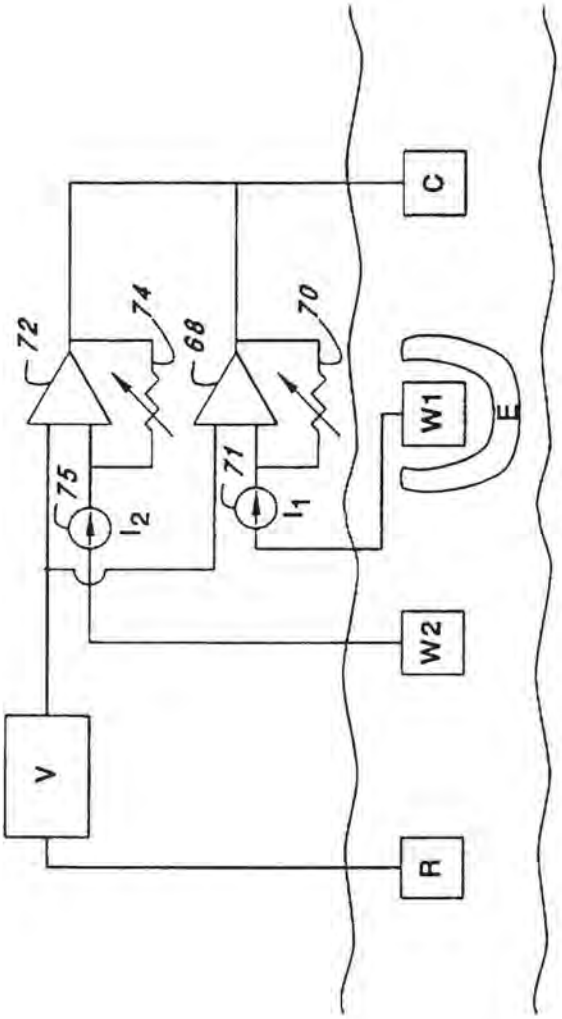


FIG. 3

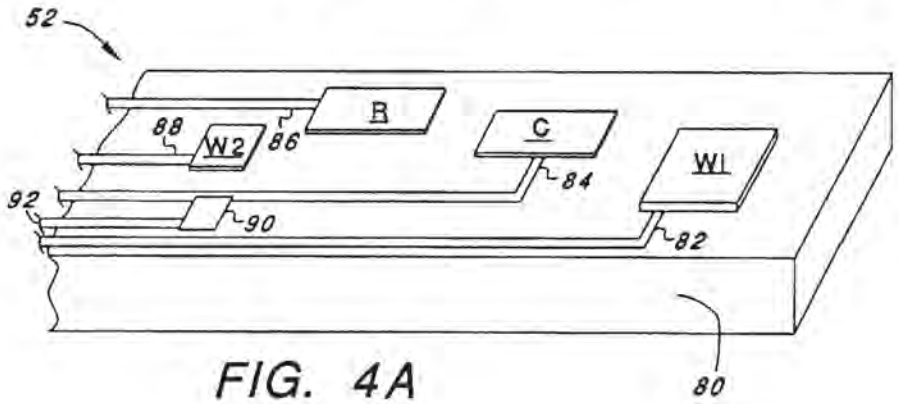


FIG. 4A

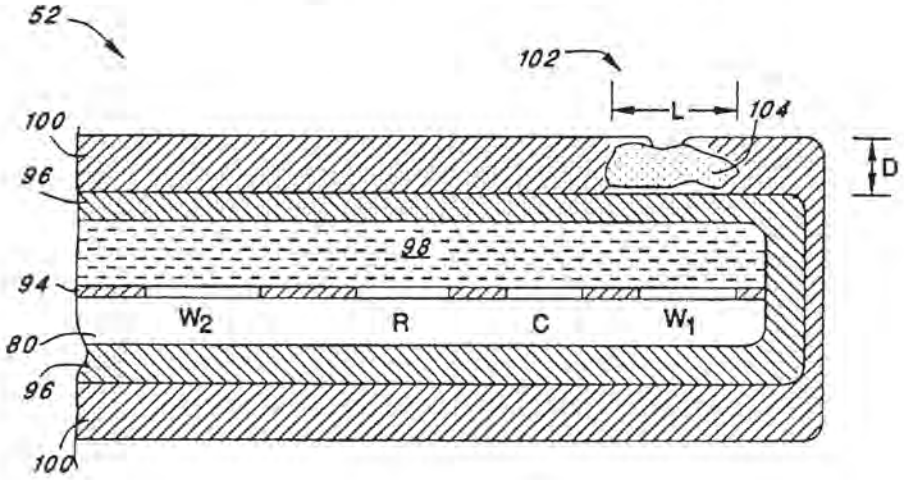


FIG. 4B

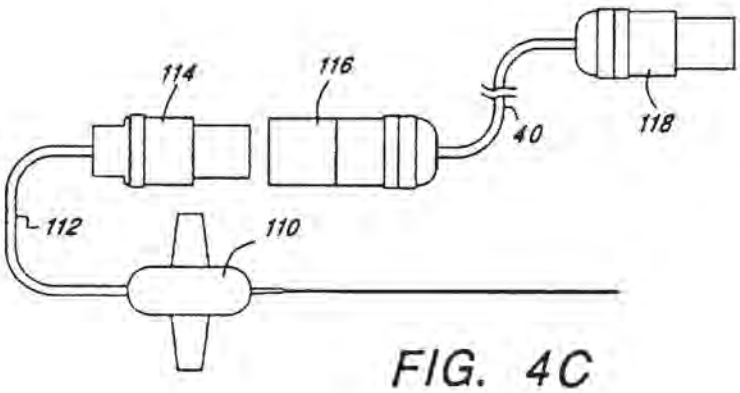


FIG. 4C

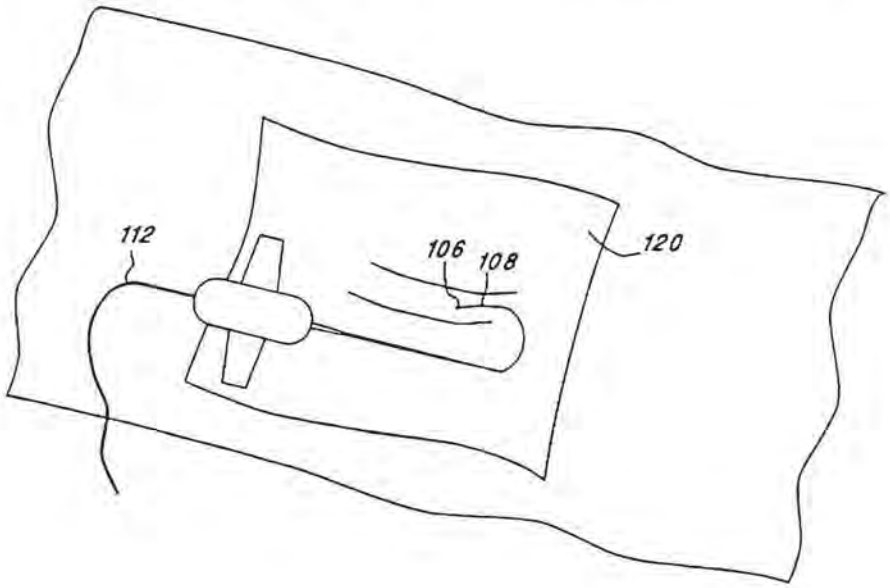

112
106
108
120

FIG. 5

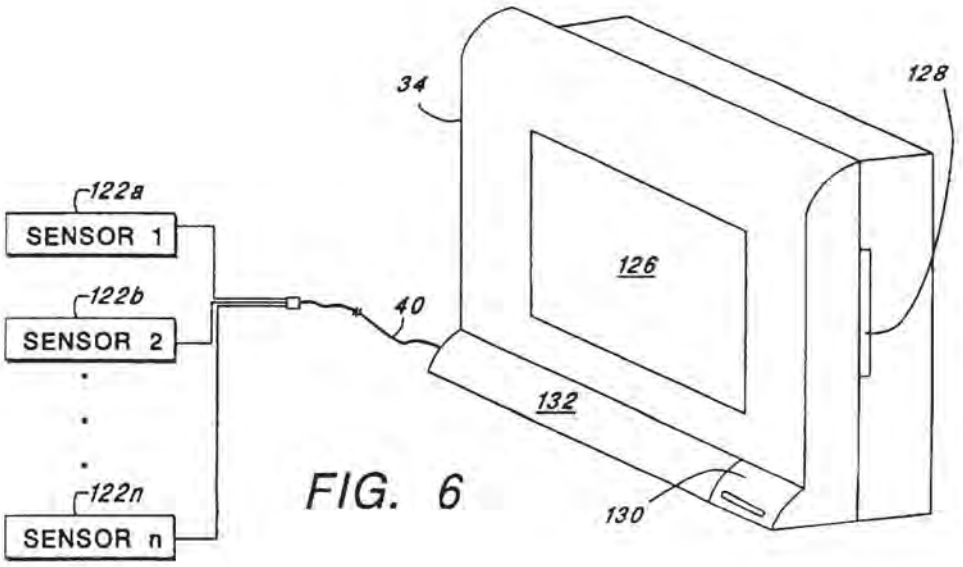

34
128
122a
SENSOR 1
122b
SENSOR 2
122n
SENSOR n
40
126
132
130

FIG. 6

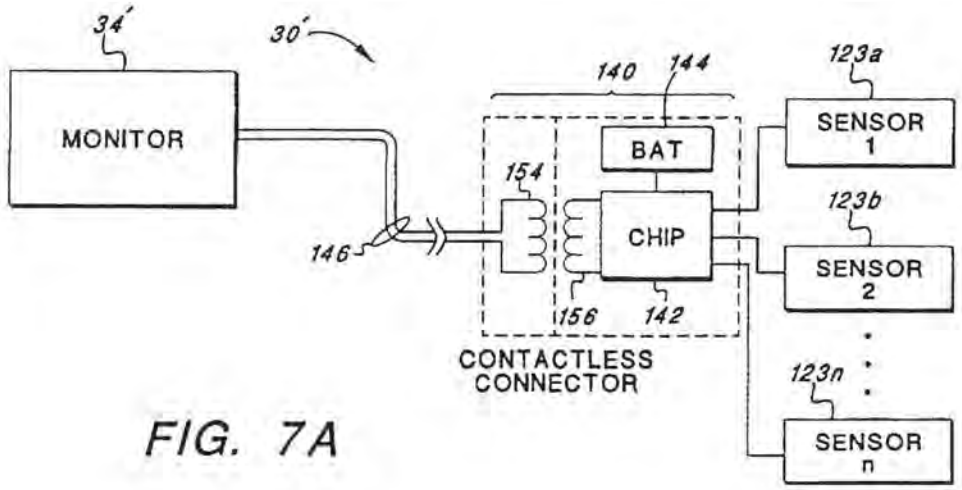


FIG. 7A

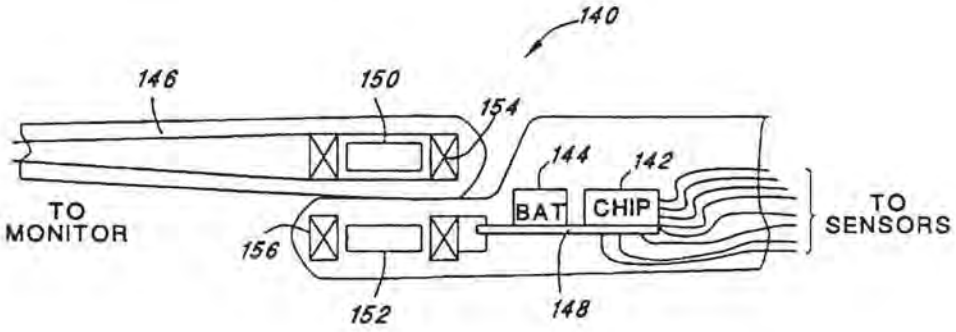


FIG. 7B

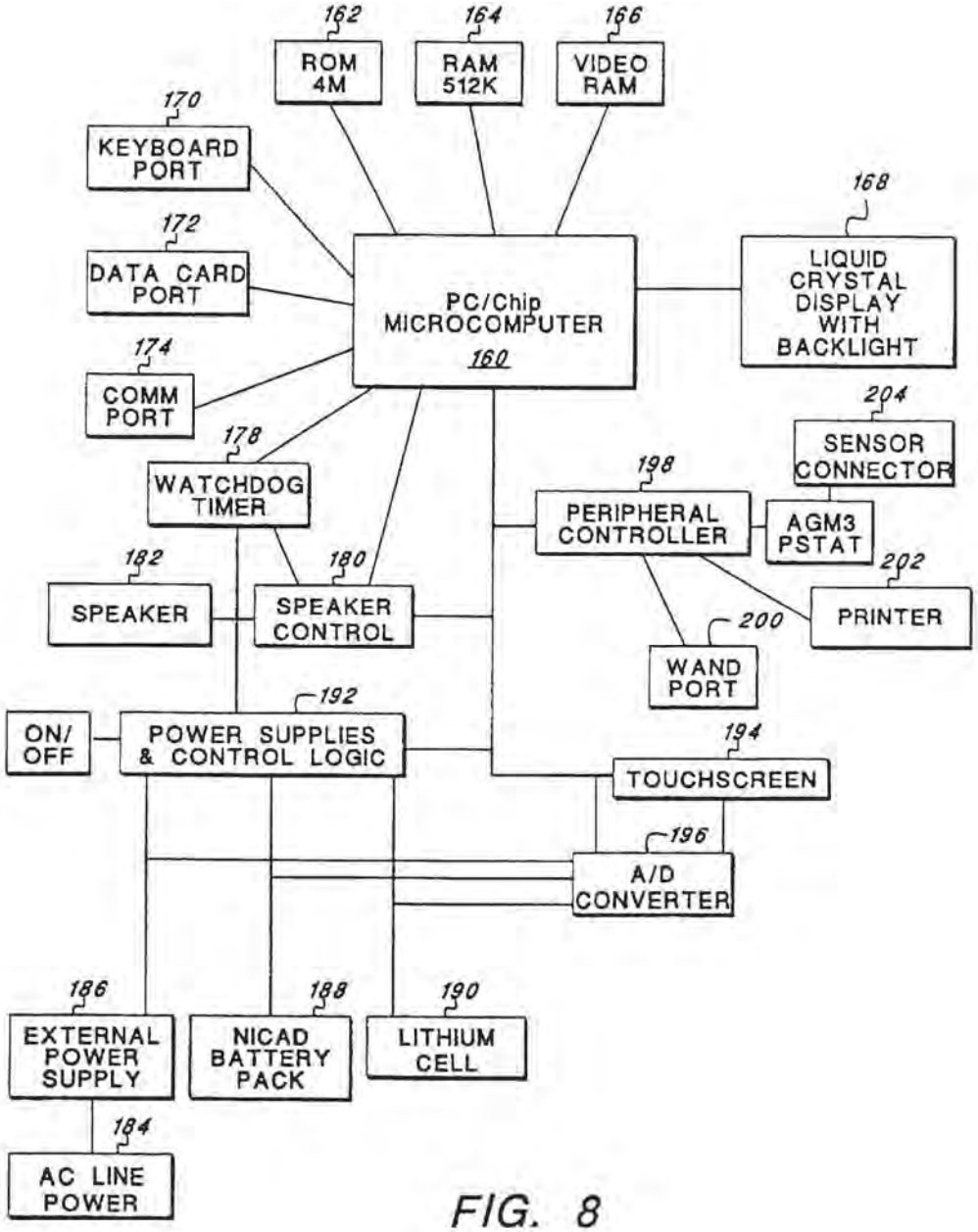


FIG. 8

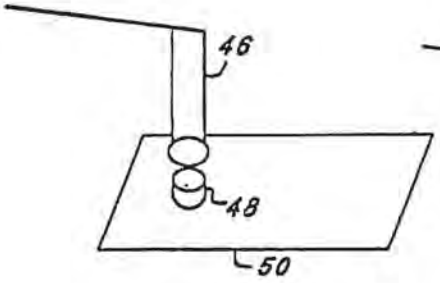


FIG. 9A

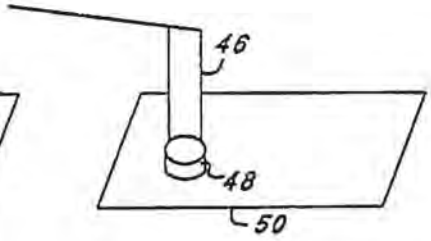


FIG. 9B

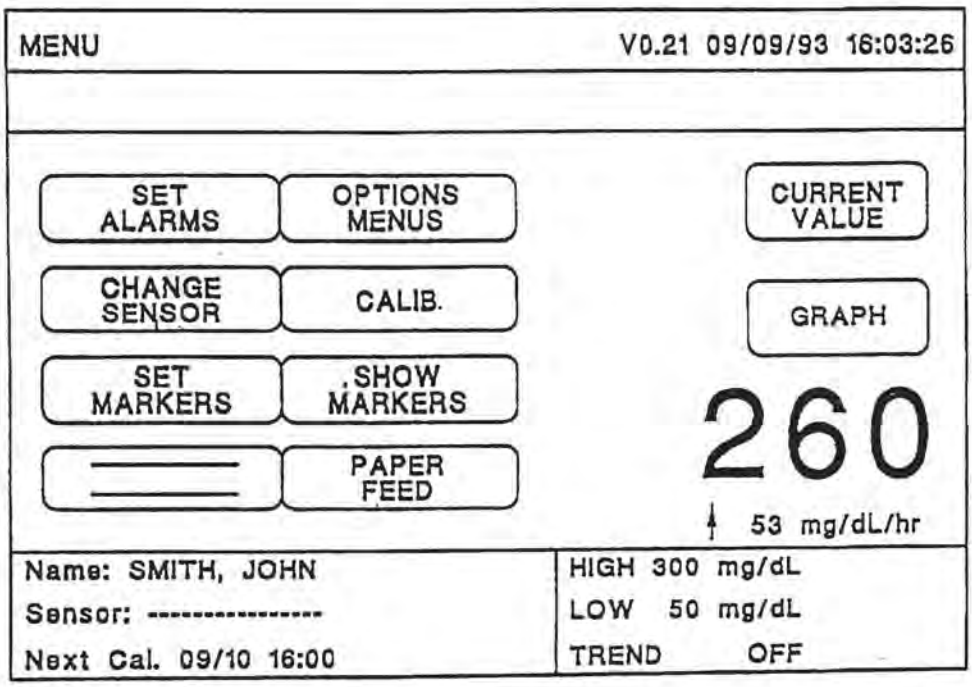


FIG. 10A

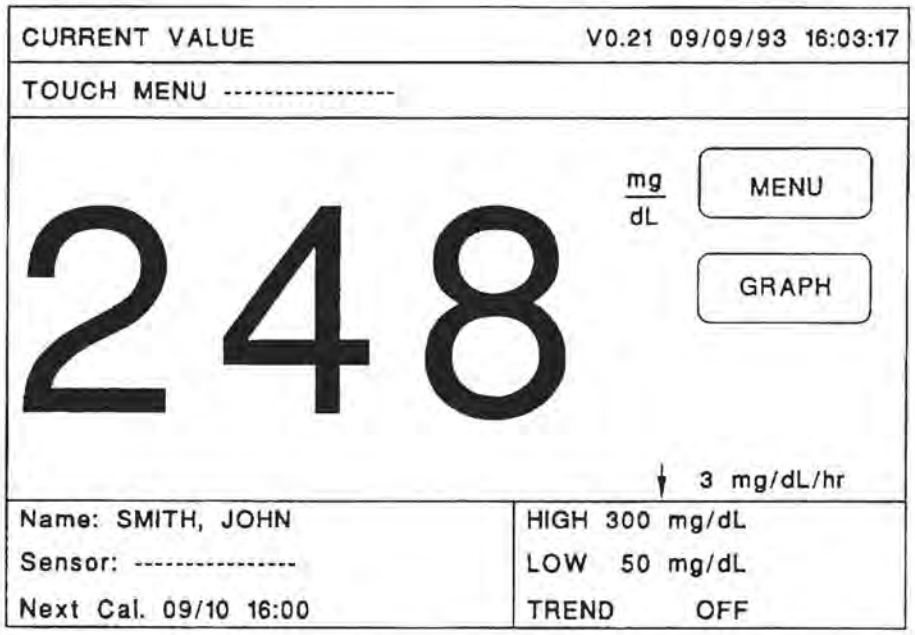


FIG. 10B

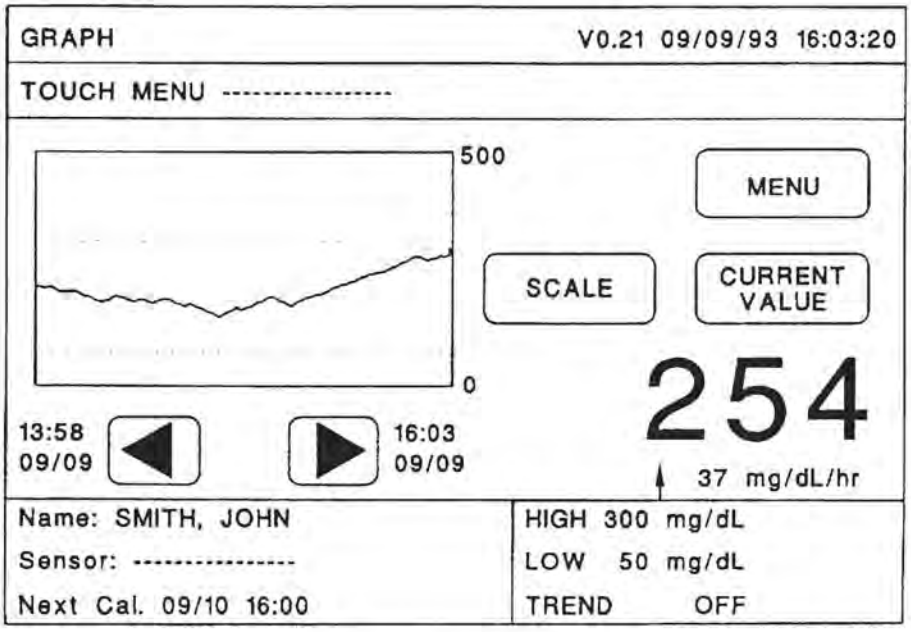


FIG. 10C

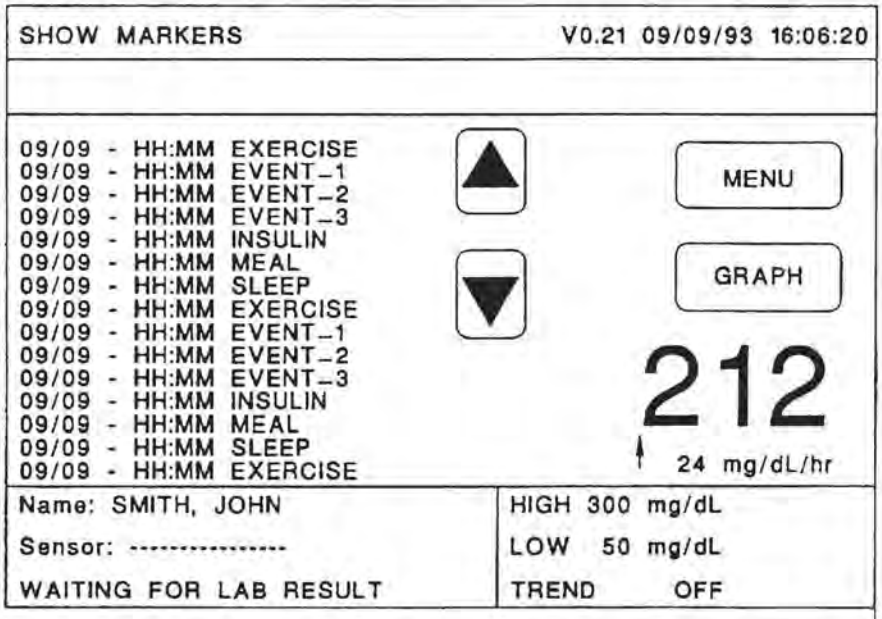


FIG. 10D

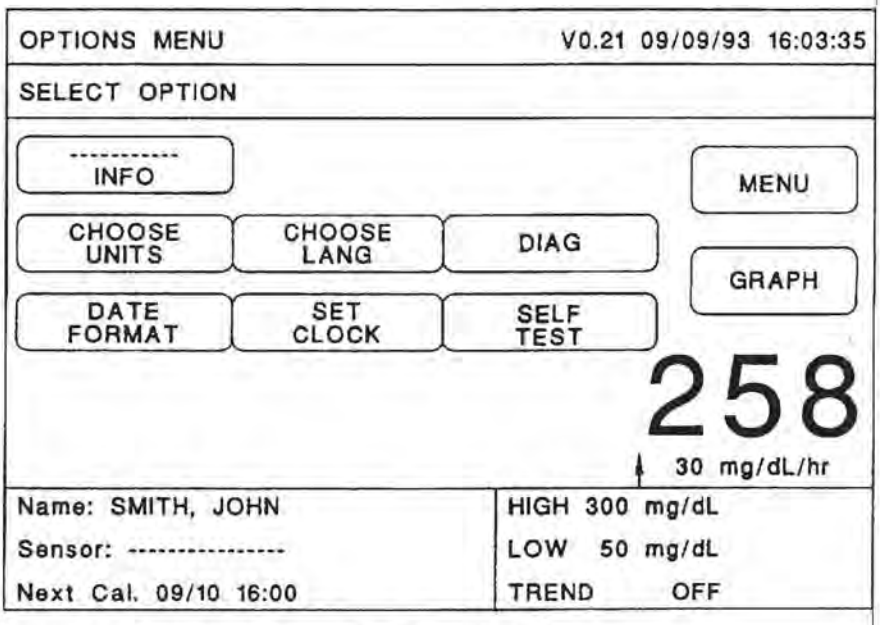


FIG. 10E

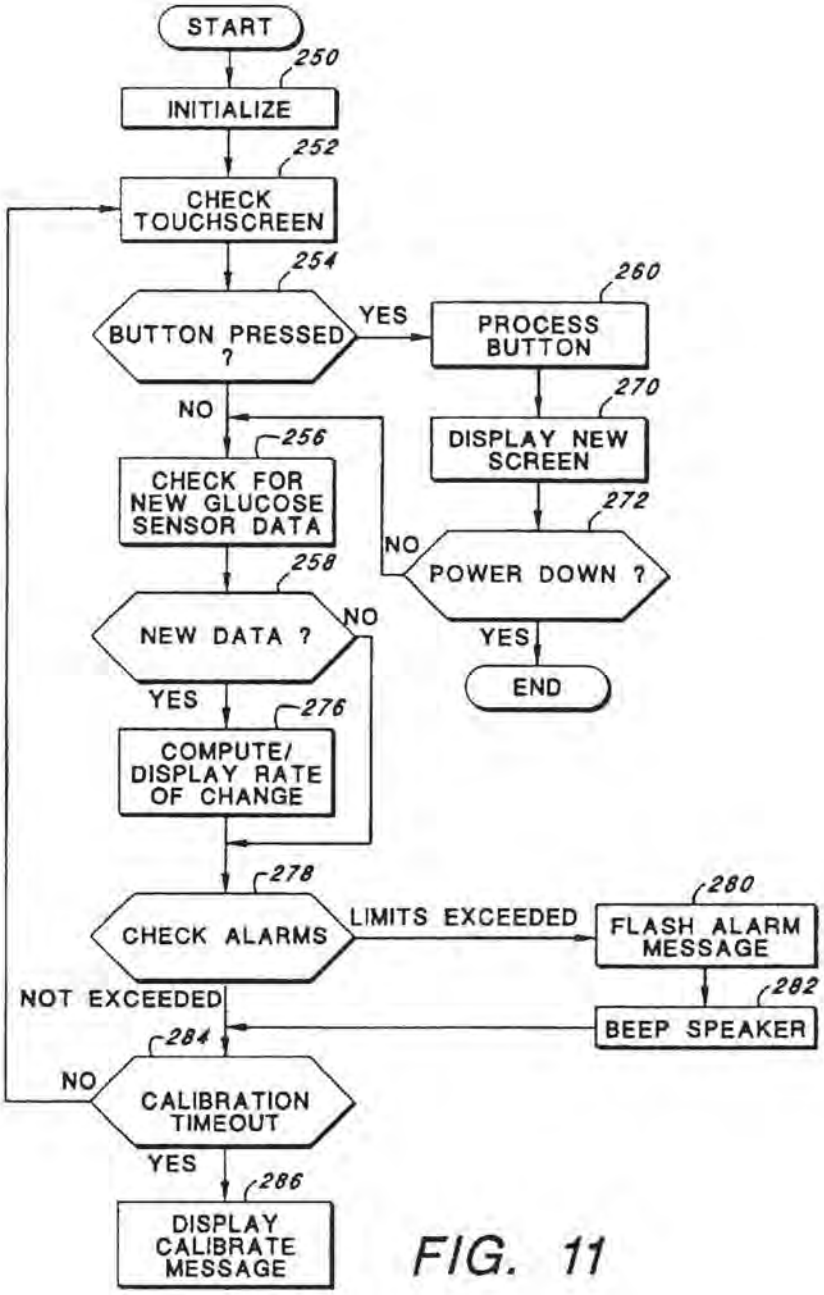


FIG. 11

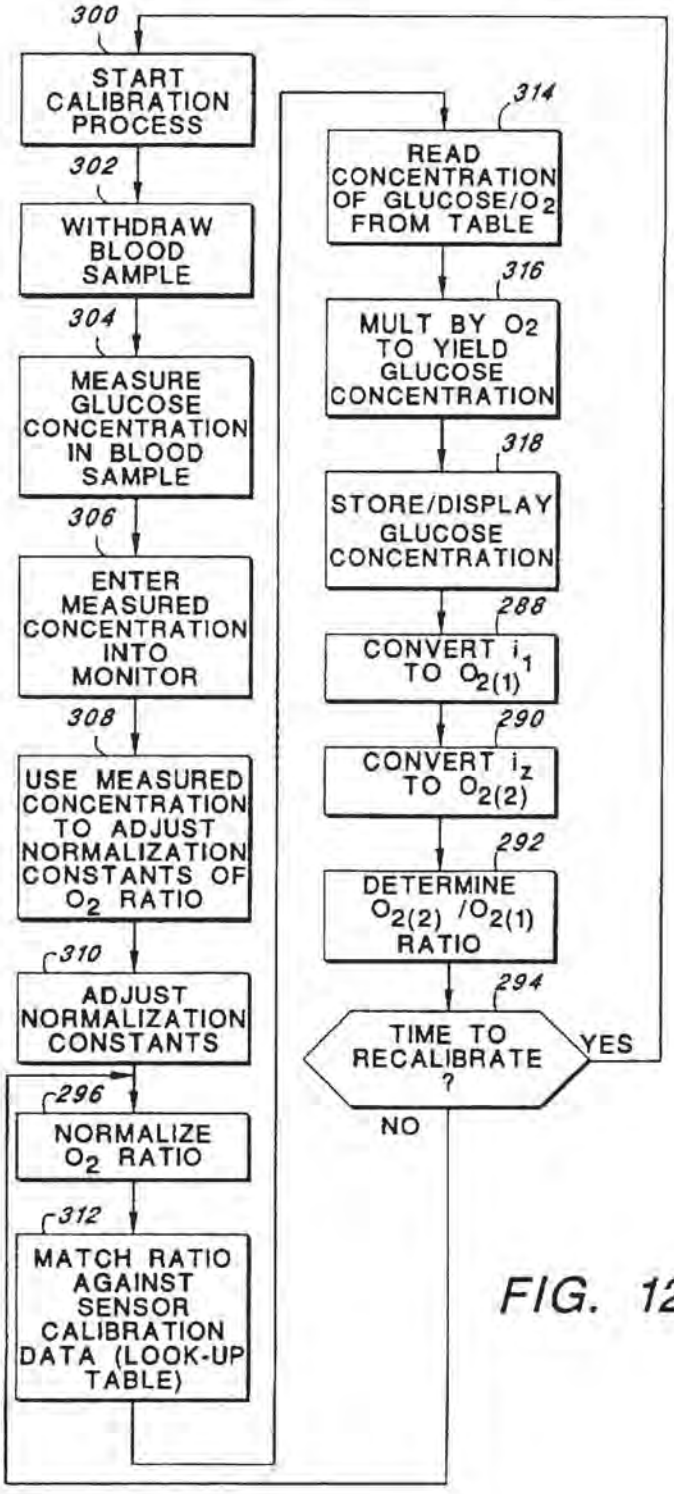


FIG. 12

PATIENT MONITORING SYSTEM

This is a continuation-in-part application of patent application, Ser. No. 08/155,737, filed Nov. 19, 1993, now U.S. Pat. No. 5,497,772.

BACKGROUND OF THE INVENTION

The present invention relates to patient monitoring systems and methods, and more particularly to a system that monitors the amount and rate of change of a specified substance, e.g., glucose, in a patient, providing an easy-to-read display of such monitored information, as well as an alarm if either the amount or rate of change exceeds programmable limits.

The monitoring and measuring of glucose concentrations in a patient's blood is one application of the present invention. Glucose is a simple sugar containing six carbon atoms (a hexose). Glucose is an important source of energy in the body and the sole source of energy for the brain. Glucose is stored in the body in the form of glycogen. In a healthy person, the concentration of glucose in the blood is maintained at around 5 mmol/l by a variety of hormones, principally insulin and glucagon. If the blood-glucose concentration falls below this level neurological and other symptoms may result, such as hypoglycemia. Conversely, if the blood-glucose level is raised above its normal level, e.g., to above about 10 mmol/l, the condition of hyperglycemia develops, which is one of the symptoms of diabetes mellitus. It is thus evident that maintaining the concentration of glucose in the blood at a proper level is critically important for wellness and good health.

Unfortunately, some individuals, either through disease, dramatic and/or sudden changes to the body (such as may be caused by injury or surgery), or for other reasons, are unable to maintain the proper level of glucose in their blood. In such instances, the amount of glucose can usually be altered, as required, in order to bring the glucose concentration to a proper level. A shot of insulin, for example, can be administered in order to decrease the glucose concentration (insulin decreases the amount of glucose in the blood). Conversely, glucose may be added directly to the blood through injection, an intravenous (IV) solution, or indirectly by eating or drinking certain foods or liquids.

Before the glucose concentration can be properly adjusted, however, an attending physician (or the patient himself or herself), must know what the present glucose concentration is and whether such concentration is increasing or decreasing. Unfortunately, the only viable technique heretofore available for measuring glucose concentration has been by drawing a blood sample and directly measuring the amount of glucose therein, or by measuring the amount of sugar in the urine. Both measurement techniques are not only inconvenient for the patient, but also may require significant time, manpower, and the use of expensive laboratory instruments, tools or aides to complete. As a result, it is usually not possible for a physician to know immediately what the glucose concentration of a given patient is. Rather, fluid samples must first be obtained, tested or analyzed, and a report issued. Based on such report, appropriate corrective action can then be taken when needed, e.g., through insulin injections or IV supplements, to move the glucose concentration back to an acceptable level. Unfortunately, however, because of the inherent time delay involved with gathering the fluid samples, performing the analysis, and issuing the report, such corrective action may not be possible until several hours after it is first needed. Even after the report is issued, the report results may be misinterpreted, or (e.g., through transcription or analysis error) may simply be wrong. Hence, it is apparent that what is needed is a way to accurately determine the glucose concentration of a patient immediately, effectively communicate such measured concentration to a physician or other interested person (including the patient) with minimum likelihood of error, and provide a clear indication of whether such concentration is within certain prescribed safe limits.

Even after the glucose concentration is known, the physician must still estimate how much corrective action is required until such time as a direction and rate of change of the glucose concentration level has been established. Unfortunately, to identify a trend in the glucose concentration using existing techniques, i.e., to determine whether the glucose concentration is increasing or decreasing, and at what rate, a series of the above-described body fluid measurements must first be made, and the results then analyzed. Such measuring and analyzing process only further delays any appropriate corrective action. What is clearly needed, therefore, is a glucose measurement system that provides a physician, or other medical personnel (or the patient himself or herself) with a rapid measure or indication of the rate of change of the glucose concentration, thereby immediately informing the physician whether any corrective action is needed.

In addition to glucose, there are other substances or elements within a patient that need to be monitored for medical or other reasons. There is thus a need in the art for measurement systems that accurately and rapidly not only measure such other substances, but also provide an indication of the rate of change or such measured substances. The present invention advantageously addresses the above and other needs.

SUMMARY OF THE INVENTION

The present invention provides a patient monitoring system that continuously measures the concentration of a specified substance, e.g., glucose, in a patient, and provides an indication of the rate of change of such concentration. The system further automatically determines whether the measured concentration and rate of change are within certain preset limits, and if not, generates an alarm signal.

The preferred embodiment of the invention relates to a monitoring system that continuously measures the glucose concentration in the blood of a patient. However, it is to be understood that the invention is not so limited, but also applies to systems, apparatus, and methods for monitoring and measuring the concentration of any substance or element found in a patient's tissue, blood, or other body fluids that needs to be monitored and measured with an appropriate sensor.

The preferred glucose monitoring system includes a glucose sensor that may be inserted into an appropriate body location, such as the venous system, the peritoneal system, or other location of the patient, where it responds to blood glucose or other elements or substances and produces electrical signals that are related to the concentration of glucose or other substances. The electrical signals generated by the sensor ("sensor signals") are delivered through a suitable interconnect cable to a monitor. The monitor interprets the sensor signals by applying a previously determined calibration to quantitatively determine the concentration value of the blood glucose or other substance. The concentration value thus determined is then processed in order to determine the rate of change, is stored (to create a history or

record), and may also be displayed. One selectable display mode displays the measured concentration in large, easy-to-read numerals, with selectable units, e.g., milligrams (mg) per deciliter (dl), or mg/dl. Another selectable display mode displays a graph of the rate of change (trend) in accordance with selected units, such as mg/dl/hr. Such graph provides an easy-to-see representation of the concentration values over a past period of time, e.g., three hours.

The preferred glucose monitor stores the blood glucose value and other data (including the patient name, sensor identification number, start date, etc.) in memory and displays the measured glucose level, updating the displayed level periodically (e.g., once per minute). Such stored data may also advantageously be viewed, as selected, as a graphic display that indicates the last several hours of recorded values, thereby clearly showing any trends in the data over such time period.

In accordance with one aspect of the invention, a plurality of glucose or other sensors, e.g., at least two sensors, are inserted into a vein or other appropriate location of the patient and are coupled to the monitor, with a concentration measurement being provided by each sensor. A prescribed degree of correlation must exist between the readings from each sensor in order to validate the correctness of the concentration measurement that is made. If the prescribed degree of correlation does not exist, then the monitor automatically indicates that a recalibration and/or new sensor(s) is required.

In accordance with a further aspect of the invention, some of the plurality of sensors coupled to the monitor may be other than glucose sensors, e.g., a sensor to detect oxygen, hydrogen peroxide, or other substances or elements of interest that are present in the patient's tissue, blood, or other bodily fluids. The monitor, in such instances, may process and combine the measurements from each sensor, e.g., by combining the measurement from one sensor with the measurement from another sensor, as required, in order to provide an overall evaluation of the condition, well-being and/or health of the patient.

In accordance with another aspect of the invention, the monitor includes a data card port that allows the current data to be stored in a data card that can be selectively removed from the monitor in order to indirectly make such data available to another computer or processor, or to make such data available for analysis at a later time. The monitor may further include, in one embodiment, an RS-232 (serial) port that allows the monitor to be connected directly to a computer network, or other computer equipment, to facilitate the direct transfer of the data to such other computer network or equipment.

In accordance with an additional aspect of the invention, the monitor is controlled via on-screen menus that define the various subroutines or processes carried out by the monitor at any given time. The screen menus are readily accessed, in a preferred embodiment, by simply touching a designated area of a touch sensitive screen. A user of the monitor may readily "jump" between the main menu and any of the subroutines or processes by merely pressing or touching an appropriate MENU button or key displayed on the touch sensitive screen.

In accordance with yet a further aspect of the invention, the patient monitoring system is calibrated with each new sensor. Further, periodically, e.g., once every 24 hours, the system is calibrated against a blood or other tissue sample that has been independently analyzed by a certified reference method for measuring the concentration of a particular element or substance, e.g., glucose, therein.

It is therefore a feature of the invention to provide a monitoring system that continuously monitors the concentration of a specified substance or element within a patient, providing real-time readings and a history of concentration levels of that substance or element for the patient, including the rate at which the concentration is changing. Such system is particularly suited for use in a hospital environment or other in-patient setting. Such system is also adaptable to any language or units of measure.

It is another feature of the invention to provide such a monitoring system that displays the measured concentration in large, easy-to-read numerals that can be seen from across the room, or even from outside of the room (e.g., just by looking into the room where the patient is situated).

It is an additional feature of the invention to provide such a monitoring system that has setable limits above or below which the measured concentration, or the rate of change (trend) of the concentration, may not go without flashing and/or sounding an alarm.

It is a further feature of the invention to provide a glucose or other sensor that is designed to be implanted in the patient, e.g., into the venous system, the peritoneal system, or exposed to other tissue or fluids of the patient, to continuously monitor the presence of a specified substance, e.g., the glucose concentration, and to provide a measurement thereof without having to withdraw a blood or tissue sample (except for an occasional calibration check). Such sensor advantageously provides electrical signals (an electrical current) from which the concentration can be derived.

It is another feature of the invention, in accordance with one embodiment thereof, to provide a monitoring system that couples an implanted or external sensor, e.g., a sensor placed in the venous or peritoneal system of a patient, through a "contactless" connector and two- or three-conductor cable with a monitor. Advantageously, the contactless connector may be purposefully or inadvertently disconnected without harming the patient or the sensor, and without disrupting operation of the sensor (thereby preventing the need for restabilization or recalibration).

It is yet an additional feature of the invention to provide a monitoring system that monitors the blood or other tissue/fluids for the presence of certain substances, and that utilizes the measurements from a plurality of venous, interperitoneal, or other implanted sensors, in order to confirm the correctness of a given determination or measurement. Such system requires, e.g., that the measurements from two or three separate sensors be within certain prescribed limits of each other before a measurement is considered accurate or reliable, or before identifying or confirming the presence and/or concentration of certain substances within the blood or other tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other aspects, features and advantages of the present invention will be more apparent from the following more particular description thereof, presented in conjunction with the following drawings and appendices wherein:

FIG. **1** is a block diagram of a glucose monitoring system made in accordance with the present invention;

FIG. **2A** is an electrical diagram of a glucose sensor;

FIG. **2B** is a graph that qualitatively depicts the relationship between electrical current delivered to the electrodes of the glucose sensor and the voltage applied between the electrodes varies as a function of oxygen content;

FIG. 2C is a graph that qualitatively depicts the approximatly linear relationship that exists at a fixed electrode voltage between the electrical current passing through the electrode of the glucose sensor and the oxygen concentration;

FIG. 3 is an electrical schematic diagram that depicts the use of two working electrodes within the glucose sensor, one to provide a measure of the oxygen that reacts with the glucose in the blood (and thereby used to provide a measure of the glucose in the blood), and another to provide a reference baseline measurement of the background blood oxygen concentration in the blood (used for compensation);

FIG. 4A is a top view of a representative glucose sensor that may be used by the glucose monitoring system of the present invention;

FIG. 4B is a side view of the sensor of FIG. 4A;

FIG. 4C shows a glucose sensor assembly that includes two glucose sensors of the type shown in FIGS. 4A and 4B, which assembly includes a "butterfly" handle to facilitate attaching the assembly to a patient, and appropriate connectors and cables for connecting the sensor assembly to the glucose monitor;

FIG. 5 diagrammatically illustrates a typical dressing placement of the sensor assembly of FIG. 4C in the arm of a patient;

FIG. 6 shows a glucose monitoring system that includes a glucose monitor connected to a plurality of different sensors;

FIG. 7A depicts a glucose monitoring system that is coupled to a plurality of different sensors through a detachable connector that does not use a direct electrical contact (i.e., a "contactless" connector), thereby providing electrical isolation between the glucose monitor and the sensors, and thereby further reducing the number of electrical wires needed within the cable that connects the monitor to the contactless connector;

FIG. 7B is a side view of the contactless connector of FIG. 7A;

FIG. 8 is a block diagram of one embodiment of a glucose monitor used with the present invention;

FIG. 9 depicts the manner in which a wand, coupled to the glucose monitor, determines the glucose sensor identification (ID) and calibration data when a particular sensor is first used within the glucose monitoring system;

FIG. 10A shows the main menu screen displayed by the glucose monitor when in use;

FIG. 10B depicts the current value screen displayed by the monitor when the current value selection is made from the main menu;

FIG. 10C depicts a representative graph of the glucose concentration that is generated and displayed by the glucose monitor when the graphic selection is made from the main menu;

FIG. 10D shows a representative marker screen that is displayed by the glucose monitor when the marker selection is made from the main menu;

FIG. 10E illustrates the options menu screen that is displayed by the glucose monitor when the options selection is made from the main menu;

FIG. 11 shows a flow chart of the main loop of operation carried out by the glucose monitor; and

FIG. 12 is a flow chart of the calibration method used by the glucose monitoring system.

Additional information relative to a preferred Glucose Monitoring System may be found in the Appendices of U.S. patent application, Ser. No. 08/155,737, U.S. Pat. No. 5,497,772 entitle "Glucose Monitoring System," filed Nov. 19, 1993, which application is incorporated herein by reference.

Corresponding reference characters indicate corresponding components throughout the several views of the drawings.

DETAILED DESCRIPTION OF THE INVENTION

The following description is of the best mode presently contemplated for carrying out the invention. This description is not to be taken in a limiting sense, but is made merely for the purpose of describing the general principles of the invention. The scope of the invention should be determined with reference to the claims.

As indicated previously, the present invention relates to a patient monitoring system for monitoring and measuring the concentration of a specified substance or element in the patient's tissue, blood, or other bodily fluids. The preferred embodiment of the invention, described below, relates to a glucose monitoring system that uses one or more glucose sensors inserted into the patient's venous system. However, it is to be understood that the invention is not limited to a glucose monitoring system, but may be used for any application wherein specified substances or elements within a patient's body need to be monitored or measured.

Referring first to FIG. 1, there is shown a block diagram of a glucose monitoring system **30** made in accordance with the present invention. The system **30** includes a glucose sensor assembly **32**, a glucose monitor **34** and a removable data card **36**. A distal tip **38** of the sensor assembly **32** includes a pair of glucose sensors, described below. The distal tip **38** of the sensor assembly **32** is adapted for insertion into a vein (or other body location) of a patient whose blood glucose concentration is to be measured. The sensor assembly **32** is electrically connected to the glucose monitor **34** by means of an interconnect cable **40**. The monitor is powered by a suitable power supply **42** during normal operation. In the event of a power failure, the monitor includes a backup battery that provides sufficient power to operate for up to four hours (without excessive printing).

As explained more fully below, the glucose monitor **34** includes processing circuits, much like a personal computer, that are programmed by a suitable operating program stored in the memory of the monitor or on the removable data card **36**. The data card **36** also provides a means for removable data storage, much like a floppy disk in a personal computer, whereon glucose concentration data measured through the sensor assembly **32** may be stored for later analysis. In some embodiments, a computer industry standard RS-232 serial port, located on the back of the monitor **34**, further allows a communication cable **44** to be connected to the monitor **34** so that glucose concentration data, or other data (e.g., diagnostic data), obtained by or associated with the glucose monitoring system may also be downloaded to a computer. As required, such RS-232 serial port further allows necessary programming data to be uploaded to the monitor **34**, when required.

The monitor **34** further includes an output connector to which an identifier wand **46** may be connected. The identifier wand **46** is used with some types of sensor assemblies to read a memory chip **48**, housed in a round chip package that has the appearance of a "button". Such chip package is placed on a shipping package or carton **50** wherein the sensor assembly **32** is placed during shipping. The memory

chip **48** includes calibration data unique to the particular sensor assembly **32**, which calibration data is used by the monitor **34** as it processes the signals obtained from the sensor assembly **32** in order to accurately and reliably determine the glucose sensor data. Identifier wands **46** and corresponding identifier memory chips **48** are commercially available products that may be obtained from various manufacturers. Other types of sensor assemblies, as explained below, contain the requisite calibration data stored in a small non-volatile memory, powered by a small battery, that is included as part of the sensor assembly. With such sensor assemblies, the monitor automatically reads the calibration data from the chip when a sensor assembly is attached (coupled) to the monitor.

As evident from FIG. **1**, an important element of the monitoring system **30** is the sensor assembly **32**, and more particularly the glucose sensors that form a part thereof. In order to better understand how such a glucose sensor operates, reference is next made to FIG. **2A**, where there is shown a simplified electrical diagram of a glucose sensor **52**. It is noted that there are various types of sensors known in the art, including glucose sensors. See, e.g., U.S. Pat. Nos. 4,484,987; 4,650,547; 4,627,906; 4,671,288; 4,781,798; 4,703,756; and 4,890,620, incorporated herein by reference.

The glucose sensor **52** of FIG. **2A** is based on the "enzyme electrode" principle where an enzyme reaction and an electrochemical detector are utilized to measure the concentration of glucose. The glucose sensor **52** includes at least three electrodes: a first working electrode **W1**, a counter electrode C, and a reference electrode R, submersed in a suitable conductive liquid **54**, such as a saline solution of H_2O, confined by a first membrane **55**. A fixed trim voltage V is applied between the electrode R and the electrodes W1 and C. A suitable enzyme E is immobilized in a second membrane **56** so as to surround the working electrode **W1**. For a glucose sensor, the enzyme E is preferably glucose oxidase (GO). During operation, the sensor **52** is inserted in the venous system so that the enzyme E is exposed to the flow of blood. Glucose and oxygen diffuse from the blood into the membranes **55** and **56** wherein, in the presence of the enzyme, they react as follows:

$$\text{Glucose} + O_2 + H_2O \xrightarrow{GO} \text{gluconic acid} + H_2O_2$$

The rate of the above reaction is directly related to the concentration of glucose in the blood and is monitored by an electrochemical oxygen detector made up of the electrodes W1, R and C, the current source **58** and the voltage source **60**. The working electrode W1 and the counter electrode C are preferably made or coated from platinum (Pt). The reference electrode R is typically made from or coated with silver chloride, Ag_2Cl. When a trim voltage V is placed across the electrodes R and W1, as well as across R and C, a current I tends to flow between the electrodes C and W1. (Assuming the voltage source is an ideal voltage source, with infinite impedance, no current flows through the reference electrode R.) When the above chemical reaction occurs, oxygen is consumed at the working electrode. The amount of oxygen remaining can be determined as a function of the amount of current flowing through the working electrode. More particularly, it can be shown that the relationship between the current (I) that flows and the trim voltage (V) varies as a function of the oxygen concentration as shown qualitatively in FIG. **2B**. For a high concentration of O_2, a curve **62** establishes the relationship between I and V. For a low concentration of O_2, a lower curve **64** establishes the relationship between I and V. For each value of O_2 concentration between the high concentration curve **62** and the low concentration curve **64**, another curve (intermediate the curves **62** and **64**) establishes the current-voltage relationship. Thus, a family of curves exists that establishes the current-voltage relationship, with each curve of the family corresponding to a different O_2 concentration.

To measure the O_2 concentration using a circuit such as is shown in FIG. **2A**, all that need be done is to force the trim voltage V to be a fixed value V_R, where V_R typically ranges between 0.3 and 0.7 volts, e.g., 0.5 volts. This is done by adjusting the current I until the desired trim voltage V_R is obtained. At the voltage V_R, the relationship between the current I and the oxygen O_2 is substantially linear, as depicted qualitatively in FIG. **2C**. Thus, using a sensor such as is functionally depicted in FIG. **2A**, the amount of oxygen remaining at the working electrode W1 is simply a function of the current I required to force the trim voltage V to V_R.

Since the oxygen detector is monitoring the oxygen not consumed by the enzyme reaction, the detector signal, i.e., the current I, is inversely related to the blood glucose concentration. The more glucose in the blood, the less oxygen will be detected by the oxygen detector with the enzyme present.

To improve the accuracy of the oxygen determination made by the detector of FIG. **2A**, and in particular to allow compensation for changes in the background blood oxygen concentration, a second working electrode **W2** is typically employed at a location in the sensor that is not surrounded by the enzyme E, as shown in FIG. **3**. As seen in FIG. **3**, a first adjustable current source is realized from an operational amplifier **68** and a feedback loop **70**. A second adjustable current source is likewise realized from an operational amplifier **72** and a feedback loop **74**. Both the first and second current sources apply their respective currents to the counter electrode C. A measurement of the current I_1 flowing through the first working electrode W1 is provided by current sensing element **71**. Similarly, a measurement of the current I_2 flowing through the second working electrode W2 is provided by current sensing element **75**.

In operation, the trim voltage V is set to the desired fixed trim value V_R, and the currents I_1 and I_2 are measured. The current I_1 provides a measure of the oxygen remaining at the working electrode **W1**, which in turn provides an inverse measure of the glucose concentration in the blood. The current I_2 provides a measure of the background oxygen in the blood, and thus provides a means for compensating the I_1 measurement for background oxygen variations. The absolute quantitative value of the blood glucose level is determined by comparison of the two detector signals, i.e., the two currents I_1 and I_2, and by reference to a previously determined calibration. Appropriate processing to obtain such quantitative measure of the blood glucose level is performed by the processing circuits in the glucose monitor **34** (FIG. **1**).

Turning next to FIGS. **4A** and **4B**, there is shown a diagrammatic top view and side view, respectively, of a representative glucose sensor **52** that may be used by the glucose monitoring system **30** of the present invention. The sensor is fabricated on a suitable ceramic substrate **80**. Appropriate metalized patterns are deposited or etched on the substrate **80** using conventional thin film deposition, or metalized etching techniques, as are common in the printed circuit board and integrated circuit fabrication arts.

In FIG. **4A**, for example, the working electrode **W1** is placed near one end of the substrate area used for the sensor **52**. A metalized trace **82** provides an electrical connection to this working electrode. The counter electrode C is likewise

placed on the substrate, near the working electrode W1. Another metalized trace **84** provides electrical connection to the counter electrode. The reference electrode R is similarly placed on the substrate at a location near the counter electrode C. A metalized trace **86** provides the electrical connection to such reference electrode R. The second working electrode **W2** is placed on the substrate adjacent the reference electrode R. A metalized trace **88** provides the electrical connection to the second working electrode **W2**. Finally, a suitable semiconductor element **90**, such as a germanium chip, is placed so as to be in electrical contact with the metalized trace **84** and another metalized trace **92**. Such element **90** is used as a temperature sensor. That is, the resistivity of the semiconductor chip **90** is highly dependent upon temperature, and the temperature may thus be monitored by measuring the current that flows through the chip **90** when a fixed voltage is applied across the traces **92** and **84**. After stabilization, such temperature of the sensor will be the same as the patient's blood temperature, which is a very useful medical parameter, particularly when it is available continuously. Such temperature measurement may likewise be stored, plotted, graphed or used for other purposes. Other types of temperature sensors, other than a semiconductor chip, may also be mounted on the substrate and used in a similar manner.

As required, a thin layer of titanium, e.g., about 300 Å thick, may be used to bond the metalized patterns to the substrate. The metalized patterns are typically made from, or plated with, the metals indicated above. The patterns are on the order of 1 to 3 mils thick. Note that a complete sensor **52**, including a temperature sensor, requires 5 conductors (traces) or wires in order to make the proper electrical connections with the various electrodes and elements. The conductor or trace **84**, connected to the counter electrode C and to one side of the temperature sensing element **90**, may function as a common conductor.

The sensor **52** shown in FIG. **4**A only shows the substrate, electrodes, temperature sensor, and connecting traces. A complete glucose sensor made in accordance with the invention includes more than just these elements. The additional elements required by the sensor **52** are shown in the side view of the sensor in FIG. **4**B. As seen in FIG. **4**B, a suitable layer of insulation **94**, such as glass or aluminum oxide, AlO_2, is placed between the electrodes W2, W1, C and R, and between the metalized traces. A thin sheath **96** of silicone rubber, e.g., 0.003 inches thick (3 mils), covers the substrate electrodes and traces. This sheath functions as the membrane **55** referenced in FIG. **2**A. A suitable thin pocket or space exists within the sheath **96**, above the electrodes, wherein a suitable conductive fluid **98** may be placed. Such space is on the order of 1 to 3 mils thick, and is filled with a thick "jello" like substance known as "hema", that functions as a conductive solution. The thin inner sheath **96** is covered with a second, much thicker, sheath **100**, also made of silicone rubber, or equivalent substance. A pocket, or "window", **102** is formed in the outer sheath **100** over the first working electrode W1. Such pocket **102** is filled with the enzyme glucose oxidase (GO) **104**. The pocket wherein the enzyme **104** is placed has a length L and a thickness D, as shown in the figure. It is preferred that the ratio between L and D be on the order of about 3 to 1 in order to provide the best linearity between the current I_1 and the glucose concentration measurement. However, this ratio may vary widely from the preferred 3 to 1 ratio and the sensor will still function.

In operation, the silicone rubber sheaths **96** and **100** comprise membranes through which O_2 may pass. Thus, when the entire sensor is inserted in the venous or peritoneal system, the oxygen and glucose in the blood are able to pass into the packet **102** and contact enzyme **104** where the above-described chemical reaction takes place. Excess, unreacted and background oxygen can then be determined allowing the oxygen to be measured by measuring the currents I_1 and I_2, from which the glucose concentration can be determined.

Typically, at least two, and perhaps three, or more, sensors as shown in FIGS. **4**A and **4**B may be included within the same glucose sensor assembly **32** (FIG. **1**). When such multiple sensors are used, they may be fabricated on the same substrate, with the respective "windows" (or pockets wherein the enzyme is placed above the first working electrode) being spaced apart about 0.4 to 1.0 inches along the length of the substrate.

FIG. **4**C illustrates a glucose sensor assembly **32** that includes two glucose sensors **106** and **108** of the type shown in FIGS. **4**A and **4**B. As seen in FIG. **4**C, the two sensors are located near the distal tip of the assembly. Only this area of the assembly includes the substrate within the inner and outer sheaths as described above. The remaining portion of the distal end of the assembly **32** comprises a suitable multi-conductor cable, e.g., 9 or 10 conductor cable, that provides the requisite electrical contact with the 5 conductors or traces of each sensor. (Note, that the two sensors **106** and **108** may share the same "common" line, thereby reducing the number of conductors needed to nine.) Such 9 or 10 conductor cable may be, e.g., a laminated ribbon cable that includes 1 mil conductive wires spaced apart 1–2 mils in a Teflon inner layer, with kapton layers on each side (top and bottom) of the middle Teflon layer.

A butterfly handle **110** facilitates attachment of the assembly **32** to a patient, as depicted in FIG. **5** below. From the butterfly handle **110**, a multi-conductor cable **112** of about 18 inches carries the 9 or 10 conductors to a suitable male connector **114**. An extension cable **40** of about 10 feet in length then provides the electrical connection with the monitor **34**. The extension cable **40** is a flexible, low noise, multi-conductor type of cable. The cable **40** is terminated at each end with a uniquely shaped (keyed) electrical connectors. A female connector **116** is adapted to connect with the male connector **114** of the sensor assembly **32**. A male connector **118** is adapted to connect with the monitor **34**. The cable **40** and its connectors **116** and **118** are designed for multiple connect/disconnects without replacement. The extension cable **40** advantageously allows the monitor **34** to be placed near the patient's bedside, e.g., on a bed pole, yet still allows the patient sufficient movement of his or her arm, where the sensor assembly is typically inserted, so as not to be too restrictive of the patient's movements.

The tip of the sensor assembly **32** may be inserted into the venous system or other body/tissue location using several methods. Typically, the insertion site is sterilized, and an 18 gauge tear-away introducer needle (provided with the sensor assembly) is inserted into a peripheral vein. It is important that the vein selected have sufficient diameter to accommodate the sensor while still allowing blood to flow past the device after it has been inserted. The preferred insertion site in most patients is the antecubital region of the cephalic vein.

After the introducer needle has been inserted into the vein, the sensor is removed from its fluid sheath (in which it is shipped) and the tip of the sensor is kept from contacting any surface in the field. The sensor is inserted through the introducer needle and advanced into the vein about 4 to 6 cm. The introducer is then withdrawn while holding the

sensor assembly to prevent its removal. The sensor is looped on the skin to provide strain relief for the insertion site. The loop and the insertion site are then covered with a transparent dressing, and the butterfly handle **110** is included under the dressing, as shown in FIG. **5**. The sensor is then ready to be connected to the monitor **34**.

Turning next to FIG. **6**, it is seen that the monitoring system of the present invention is not limited to use with one or two sensors. Rather, the monitor **34** may be connected to a plurality of different sensors **122***a*, **122***b*, . . . **122***n*. Each sensor may be a glucose sensor as described above, or some other sensor as is known in the art. The monitor **34** obtains glucose sensor readings from each sensor and requires that there be some specified relationship between the sensor readings before such sensor readings are considered to be valid. For example, when two glucose sensors are used, the readings from each sensor are combined, e.g., averaged, to provide the overall or composite glucose measurement value. However, such combining only occurs if the sensor readings are within 10% of each other over a six minute interval. If not, then the monitor **34** requires a recalibration of the sensors to be made. Should the sensor reading be more than 30% different over a six minute interval, then the monitor **34** requests that the sensors be replaced. If at any time the sensor readings are more than 50% different, then the monitor requires that the sensors be replaced.

In addition to using multiple sensors of the same type, e.g., multiple glucose sensors, the monitoring system of the present invention contemplates that the multiple sensors may be of different types. For example, one sensor may sense oxygen, the other may sense peroxide (H_2O_2). Note peroxide is one of the products of the reaction that takes place in the presence of the enzyme, and therefore making a peroxide measurement represents an alternate way of determining the glucose concentration. An appropriate relationship between the oxygen measurement defines the glucose concentration. If the sensors give conflicting results, then that indicates something is wrong, e.g., a sensor malfunction or contaminants in the blood or other body tissue.

The oxygen sensor described above in FIGS. **2–4** can readily be converted to a peroxide sensor by simply changing the polarity of the trim voltage that is applied to the reference electrode, and by removing the outer and inner rubber sheaths. (Some means must still be used, of course, to keep the enzyme confined to an area near the working electrode.) Thus, a peroxide sensor has its electrodes exposed so that they come in direct contact with the blood or other body tissue/fluids.

Other types of sensors, i.e., used to detect elements or compounds other than O_2 or H_2O_2, may be fabricated by using a different enzyme in the vicinity of the first working electrode. Using such other sensors, alone or in various combinations with other sensors, thus provides versatility in how the present monitor may be used to determine an appropriate measurement, or to determine in real-time the presence of a particular substance, element or contaminant in the tissue, blood, or other bodily fluids of the patient.

Still referring to FIG. **6**, a preferred representation of the monitor **34** is shown in greater detail. The monitor includes a large screen **126** wherein the sensor data, e.g., glucose concentration, rates of change, and history (graphs of concentration over time) may be displayed. A touch screen overlays the display screen and provides a convenient mechanism for entering various commands and selecting various programmable options for use with the monitor **34**. A slot **128** appears on one side of the monitor case wherein the data card **36** (FIG. **1**) may be removably inserted. A printer is included within the monitor **34**, providing a paper tape output that appears from a slot **130**. A removable cover **132** reveals a clip for holding the male connector **118** as it is connected to the monitor **34**.

FIG. **7A** depicts a monitoring system **30'** having a monitor **34'** that is coupled to a plurality of different sensors **123***a*, **123***b*, . . . **123***n* through a detachable connector **140** that does not use a direct electrical contact (a "contactless" connector) between the circuits of the monitor **34'** and the plurality of sensors **123**. Such contactless connector thus provides electrical isolation between the glucose monitor **34'** and the sensors **123**. Moreover, the contactless connector **140** is a "smart" connector, i.e., it includes a processing chip **142**, powered by a battery **144**. The processing chip **142** encodes the data being transferred or transmitted from the sensors to the monitor **34'**. Such encoding allows address data to be included to identify at which sensor of the plurality of sensors the sensor data originated, and to identify different types of data (e.g., temperature data, O_2 data, etc.). Hence, whereas each sensor **123***a*, **123***b*, . . . **123***n* requires, e.g., five conductors for proper operation and monitoring, it is possible by encoding the data and sending it over the same conductor to reduce the number of conductors needed within the cable **146** to, e.g., two conductors.

One advantage of the contactless connector **140** shown in FIG. **7A** is that the connector **140** can be pulled apart, e.g., purposefully (e.g., when a new sensor is inserted) or inadvertently (e.g., by the patient accidentally moving or pulling his or her arm) without causing harm or damage to either the monitor, sensors, or patient. Typically, the sensors, for proper operation, need to be operated continuously (have a current flowing therethrough, which means the sensors must be "wet") without interruption. Such continuous operation does not require large amounts of power. To the contrary, each sensor usually only requires nanoamperes of current for proper operation. Advantageously, the battery **144** included within the sensor-side of the contactless connector **140** provides such power regardless of whether the connector is coupled to the monitor **34'**. Further, such battery **144** may be installed at the factory, and the sensors may thus be operational (assuming they are shipped "wet", i.e., in an appropriate solution) from the time they are shipped, thereby obviating the need for any warm-up or stabilization period after they leave the manufacturing site. Other types of sensors may be operated on a "sampled" basis, which typically requires even less current.

FIG. **7B** is a side view of a representative contactless connector **140**. At the end of the cable **146** (the monitor side of the contactless connector **140**), there is included a magnet **150** and a coil **154**. On the sensor side of the connector **140**, there is likewise included a magnet **152** and a coil **156**. The magnets **150** and **152** attract each other and force a proper alignment between the coils **154** and **156**, and further provide a holding force for holding the connector together (which force is sufficiently strong to maintain the two sides of the connector together, but is not so strong as to prevent the two sides from being pulled apart when desired or needed). The two coils **154** and **156** thus provide transformer (inductive) coupling between the two sides of the connector.

The sensor side of the connector **140** further includes a circuit board **148** on which the battery **144** and the chip **142** are mounted. The chip **142** may be considered as a transmitter chip because it receives all the sensor data from the various sensors, encodes it as required, and transmits it serially through the transformer coupling to the monitor **34'**. The chip **142** further includes a small amount of non-volatile memory that is maintained by the battery wherein calibration data is stored.

A significant advantage of utilizing a transmitter chip as described above is that all of the calibration data needed for proper operation may be within the transmitter chip **142**. Thus, there is no need to use a wand **46** to read a memory identifier element **48** contained on the shipping package **50**. Rather, the monitor will automatically read the calibration data from the chip when a sensor is attached. Further, there is no need for extended stabilization periods to pass before the sensor assembly can be used. All that is required is that the sensor assembly be removed from its shipping carton (which maintains it in a wet environment), be inserted into the venous system or other body location of the patient, and be coupled to the monitor through the contactless connector.

It is noted that while the contactless connector **140** is illustrated in FIGS. 7A and 7B as being realized using transformer coupling, the invention is not intended to be limited to transformer coupling. Other types of contactless coupling, such as optical coupling, may also be used.

Turning next to FIG. **8**, there is shown a block diagram of one embodiment of a monitor **34** that may be used with the monitoring system of the invention. The monitor **34** receives sensor signals from the sensor assembly **32** via the interconnect cable **40**. It analyzes and stores the concentration level at a prescribed interval, e.g., every minute, in a file named for the sensor number. The file also contains the start date and start time. Such file can be transferred to another computer via the data card **36**, or via the RS232 serial port **44**, for more extensive analysis.

The monitor **34** displays the current concentration of the substances being monitored and the trend (the rate of change over a previous period of time, e.g., fifteen minutes). The concentration thus measured is presented as either a digital display of the current value, or as a graph. The concentration value is updated once each minute (or other prescribed interval). In the graphic display mode, the concentration is plotted at user selected intervals, showing periods of 3 to 72 hours. The 15 minute trend value is displayed in small numbers in the bottom right portion of each display. Increasing and decreasing trends are indicated with up (↑) and down (↓) arrows, respectively. In the monitor mode, the concentration of the measured substance is displayed in large numerals that can be easily seen from across the room, as illustrated, e.g., in FIG. **10**B.

As seen in FIG. **8**, at the heart of the monitor **34** is a microcomputer **160**. Connected to the microcomputer **160** are a wide array of peripheral devices and circuits. Such devices and circuits include suitable memory, including ROM **162**, RAM **164**, and a video RAM **166**. Also a LCD display **166** is connected to the microcomputer **160**, as is a keyboard port **170**, a data card port **172**, and a comm port (RS-232 serial port) **174**. With such peripheral devices, the microcomputer **160** is fully equipped to function as a computer or sophisticated signal processor to perform whatever task it is programmed to perform.

To control the monitor as it performs the function of monitoring the concentration of a specified substance, a monitoring operating program is downloaded, or accessed from, a data card that is inserted into the card port **172**. A watchdog timer circuit **178** ensures that all specified events within the operating program occur within specified time limits, else various corrective events are triggered, e.g., putting the monitor into an alarm state where alarms are sounded through a speaker control circuit **180** and speaker **182**, and/or flashed on the display **168**. Foremost of the alarms that sound and/or are displayed is an alarm that signals when the value of the most recent reading is below or above user-set (or, if none, default) low or high limits, or if the trend exceeds the user-set default limits.

Power for the monitor is provided primarily through an ac power line **184** that drives an external power supply **186**. An internal rechargeable nickel cadmium (NiCad) battery **188** is also included. In the event that line power is not available (e.g., during a power outage, or when moving the patient) the NiCad battery provides a minimum of four hours of monitor operation, provided the printer is not used. A lithium battery **190** is also included to maintain the monitor's memory and the time keeping function. Power supply control circuitry **192** selects and applies the appropriate power source to the other circuits of the monitor.

Further included within the monitor **34** is a touch sensitive screen **194** (also referred to as a "touchscreen"). The principal visual element of the monitor **34** is the display screen **168** which, with the touchscreen **194** positioned thereover, is touch sensitive. The screen presents a LCD graphic display of the glucose concentration and allows the user to give commands by touching areas on the screen called "buttons". Such buttons are rounded rectangles with white background and dark letters. There are various types of buttons, including menu option buttons, and data buttons. The menu option buttons change the screen to the selected option or make the monitor do whatever it has been asked to do. Data buttons allow the user to enter information into the monitor memory.

An analog-to-digital (A/D) converter **196** is used in conjunction with the touchscreen **194** in order to provide a digitized grid location whereat a touch of the touchscreen has been sensed. Such grid location is then compared to the known grid locations where the various buttons have been displayed in order to determine which button was touched. The use of touchscreens for entering information and selecting various options in this manner is particularly well suited for a medical device that may be used in a hospital setting, particularly an operating room (OR), because it eliminates the need for bulky keyboards that, in general, must be placed on a horizontal surface, and thereby occupy valuable working surface space.

A peripheral controller circuit further interfaces the microcomputer **160** with a wand port **200**, a printer **202**, and the sensor connector **204**. The sensor connector **204**, in turn, is connected to a potentiostat circuit **206** that controls the trim voltage V_R applied to each sensor, and measures the currents I_1 and I_2 associated with each sensor. Such measurements are digitized by the potentiostat circuit **206**, and provided to the microcomputer **160** for appropriate storage and processing.

An important requirement associated with operation of the monitor **34** is to assure that the proper calibration data for a given sensor assembly **32** is downloaded to the memory **164** for use by the microcomputer **160** as it computes the glucose concentration data. To this end, the wand port **200** allows a suitable sensor identifier wand **50** to read a sensor identifier button **48** that is included on the package **50** in which the sensor assembly is shipped, as seen in FIG. **9**. In operation, the wand **46** is connected to the wand port **200**. Each glucose sensor of the type that is not continually powered (i.e., those sensors that are not used with a contactless connector as shown in FIGS. 7A and 7B) typically has unique factory calibration parameters. These parameters are contained in a sealed stainless steel capsule, or sensor identifier **48**. The sensor identifier **48** is mounted on the outer surface of the sensor package **50**.

The factory assigned serial number of the sensor assembly **32** must be entered into the monitor **34** before the system will operate. Such serial number is entered by touching the appropriate buttons on the menu screen. Once the serial number has been entered, it should be checked for accuracy.

and modified if needed. Once correct, the screen display changes and prompts the user to touch the wand **46** to the sensor identifier button **48** on the sensor package **50**. Touching the wand to the sensor package is carried out as shown in FIG. **9**. That is, the wand is placed above the identifier button **48**, as shown in FIG. **9**(A), and then placed over the button **48**, as shown in FIG. **9**(B). Touching the wand to the button **48** causes the wand to "read" the memory contained therewithin, thereby downloading the calibration data stored within the memory. If the serial number read through the wand matches the serial number that was entered manually, then the screen display advances to the next screen (entering patient ID information.)

Several of the menu screens that are displayed by the glucose monitor **34** are illustrated in FIGS. **10**A–**10**E. The screens shown in FIGS. **10**A–**10**E are not all the screens that may be displayed, but are merely representative of those screens that may be displayed. The various menu buttons on each screen are shown as rectangles with rounded corners. Other data displayed on the screens are shown as numbers.

FIG. **10**A, for example, shows the main menu screen displayed by the glucose monitor when in use. FIG. **10**B depicts the current value screen displayed by the monitor when the current value selection is made from the main menu. Note the large size of the glucose measurement displayed, providing easy-to-read numbers that are several inches high. FIG. **10**C depicts a representative graph of the glucose concentration that is generated and displayed by the glucose monitor when the graphic selection is made from the main menu. A similar graph may be printed by the printer **202**.

FIG. **10**D shows a representative marker screen that is displayed by the glucose monitor when the marker selection is made from the main menu. Markers allow the user to specify at what time certain events occurred, such as sleeping, eating, exercising, and the like. The same information that appears on the marker screen may also be printed.

FIG. **10**E illustrates the options menu screen that is displayed by the glucose monitor when the options selection is made from the main menu. Such options include, for example, the capability of choosing units, choosing a language, performing diagnostic and other tests, setting the date and clock, and the like.

As is evident from the above description, it is seen that the monitor **34** performs four basic functions: (1) system hardware setup, during which alarms are set, and during which time and date, units, language, and date format are established; (2) sensor introduction, during which the sensor is stabilized (for direct contact sensors), the sensor is identified, and the patient is identified; (3) system calibration, during which a blood or tissue sample is taken and time marked, with the blood sample result being input into the monitor so that appropriate sensor calibration may take place; and (4) patient monitoring, during which continuous monitoring of the concentration of a specified substance, e.g., glucose, of the patient is made, including 24 hour recalibration and 72 hour sensor replacement and calibration.

Turning next to FIG. **11**, there is shown a simplified flow chart of the main loop of operation carried out by microcomputer **160** as it performs its basic function of patient monitoring. In the flow chart of FIG. **11**, each main step or process is depicted as a "box" or "block", with each box or block having a reference numeral for reference purposes. The main loop shown in FIG. **11** assumes that glucose is the substance being monitored and that the glucose monitoring system has already been initialized (block **250**). Initialization includes a system hardware setup, during which the alarms are set, and the time and date, units, language, and date format are established. Further, initialization (block **250**) includes sensor introduction, meaning that the sensor is stabilized (if needed), the sensor is identified, and the patient is identified. An initial system calibration is also performed during initialization (block **250**) which involves drawing a blood or tissue glucose sample from the patient, measuring the glucose concentration in the sample using certifiable external equipment, imputing the measurement made into the system, and time marking when the sample was taken. The time marking is important so that the system knows when the next calibration must be performed. In general, the system signals that a new calibration is needed every 24 hours. If a recalibration is not made within 26 hours of the last calibration, then the monitoring system shuts down.

Once all the initialization steps have been completed, the main loop is entered. The main loop first checks the touchscreen (block **252**). If a button on the touchscreen has been touched or pressed (YES branch of block **254**), then such button is processed (block **260**), meaning that whatever action is appropriate for the touched button is carried out. Such action always involves displaying a new screen (block **270**), and may include other process steps (such as printing a graph, making a data calculation, or the like). If the new screen is a power-down screen (block **272**), and if a power down operation is confirmed (YES branch of block **272**), then the main loop terminates, and the monitoring system is powered OFF.

Regardless of whether a process button has been pressed (block **254**), or whether a new screen has been displayed (block **270**), the system next checks (assuming that the system remains powered) for new glucose sensor data (block **256**). The glucose sensor, as explained above, is a continuous sensor. However, the currents I_1 and I_2 from each working electrode of each sensor (making four total current measurements) are only sampled every minute. Based on when the most recent sample has been taken, new glucose data may or may not be available (block **258**). If it is available, then such data is retrieved and displayed (block **274**).

Based on the new or old glucose data, each pass through the main loop also involves a computation and display of the rate of change or "trend" of the glucose data (block **276**). The glucose data, including the computed rate of change is compared to the limits associated with the alarms (block **278**). If any of the alarm limits have been exceeded, then an alarm message is flashed on the screen (block **280**), and the monitor beeps (block **282**). The beeping can be silenced by touching a silence button on the screen, but the flashing alarm message continues until such time as the condition which triggered the alarm is corrected as evidenced by new sensor data.

The alarms are preferably programmable to be different in positive or negative directions, including different rate-of-change alarms for a positive (increasing) change in concentration of the substance being monitored and a negative (decreasing) change in the concentration. This is because, e.g., a sudden negative change in glucose concentration, particularly if starting from an already low level of glucose concentration, can be far more serious than a positive change in glucose concentration, or a negative change that starts from a higher glucose concentration. Hence, the alarm limits may be set to identify the potentially more dangerous low glucose concentration levels, and negative rate of change levels that start from a low level.

In some embodiments of the invention, however, the alarm limits may be symmetrical, without regard to whether the change is positive or negative.

Finally, each time through the main loop shown in FIG. **11**, a determination is made as to whether it is time to recalibrate (block **284**). Recalibration should be performed every 24 hours, and must be performed within 26 hours of the last calibration. If it is time to recalibrate, then a calibration message is displayed (block **286**) and the calibration loop is initiated.

A simplified flow diagram of the calibration loop for a glucose sensor is shown in FIG. **12**. Essentially, the calibration loop is a single point calibration method, meaning that only a single point of glucose data from an external source is needed to perform the calibration method.

Turning to FIG. **12**, when the calibration process is started (block **300**), then the user is instructed to withdraw a blood or other tissue/fluid sample from the patient (block **302**). Such sample is then subjected to a conventional off-line measurement device, and a reading is obtained (block **304**). The off-line reading is then entered into the monitor (block **306**) using a special touchscreen display for such purpose. Such entered value is then used to adjust the normalization constants of the O_2 ratio used in computing the concentration (block **308**), explained below.

During the normal measurement loop, as indicated at the right of FIG. **12**, the current measurements from each sensor, assuming each sensor is a glucose sensor, are obtained and converted to an O_2 measurement. There are actually four current measurements involved, two for each sensor, even though only two current measurements are shown in FIG. **12**. The first current measurement I_1 is converted to an appropriate O_2(**1**) measurement (block **288**). Similarly, the second current measurement I_2 is converted to an O_2(**2**) measurement (block **290**). A ratio is then determined of O_2(**2**)/O_2(**1**) (block **292**). This ratio must be normalized to match the most recent external glucose reading. If it is time to recalibrate (YES branch of block **294**), then such calibration is performed by obtaining the external glucose reading based on a drawn blood sample, as described above. Appropriate normalization constants, determined from the external glucose measurement (block **310**) are then used to normalize the O_2 ratio (block **296**). If it is not time to recalibrate (NO branch of block **294**), then the most recently determined normalization constants are used for the normalization of the O_2 ratio (block **296**).

The normalized O_2 ratio is then matched against sensor calibration data (block **312**) obtained from the factory for the particular sensors that are used. Such calibration data is essentially available in a look-up table that is downloaded to the monitor at the time of initialization using the data wand as described previously. Once the best match is found, then the glucose/O_2 ratio may be determined (block **314**). This ratio is multiplied by the measured O_2 value (block **316**), thereby leaving just the glucose concentration. Such glucose concentration is then stored in the monitor memory, and displayed, as appropriate.

From the preceding description, it is thus seen that the present invention provides a monitoring system that continuously monitors the glucose concentration, or the concentration of another substance, of a patient, providing real-time readings and a history of the concentration of the measured substance, including the rate at which the concentration is changing. It is further seen that the invention provides a way to graphically display the measured concentration, and/or the rate of change of such concentration, in large, easy-to-read numerals or graphs in a format that cannot easily be misunderstood or misinterpreted. Further, the monitoring system thus provided has setable limits above or below which the measured concentration, or the rate of change (trend) of the concentration, may not go without flashing and/or sounding an alarm.

As also seen from the above, the present invention provides a glucose sensor designed for placement into a patient's venous system or other body location so as to continuously monitor in-line the glucose concentration in the patient without the need for withdrawing a blood or tissue sample (except for an occasional, e.g., once every 24 hours, calibration check). The glucose concentration measurement is provided by means of sensor signals that comprise electrical signals (electrical currents). From such electrical signals, the glucose concentration is easily derived using calibration data generated during manufacture of the sensor, as well as the calibration check data obtained once every 24 hours.

It is further seen that the invention provides, in one embodiment thereof, a monitoring system that couples a sensor placed into the venous system, or other body location, of the patient with a monitor through a contactless connector. Such contactless connector advantageously allows for the inadvertent or purposeful disconnection of the monitor from the sensor without harming the patient or the sensor, and without disrupting operation of the sensor (thereby preventing the need for recalibration of the sensor).

Also, it is evident from the above description that the invention provides a monitoring system that utilizes measurements from a plurality of venous or other implanted sensors in order to confirm the correctness of a given determination or measurement.

While the invention herein disclosed has been described by means of specific embodiments and applications thereof, numerous modifications and variations could be made thereto by those skilled in the art without departing from the scope of the invention set forth in the claims.

What is claimed is:

1. A glucose monitoring system comprising:

an enzymatic glucose sensor adapted to be placed within a person whose blood glucose concentration is to be measured, said glucose sensor including means for generating a sensor signal that varies inversely proportional to the concentration of sensed glucose, said glucose sensor comprising an oxygen detector that detects the amount of oxygen in the region of a prescribed enzyme held within said glucose sensor, and wherein glucose and oxygen react with said prescribed enzyme such that the amount of oxygen is inversely proportional to the glucose concentration, and wherein said oxygen detector comprises

a first working electrode, a counter electrode, a reference electrode, and a second working electrode, all of said first and second working electrodes, reference electrode and counter electrode being enclosed within a first membrane wherein an ionic solution is maintained, and said first membrane being enclosed within a second membrane,

said prescribed enzyme being confined to a window region near said first working electrode,

electrical means for causing an electrical current to flow between said counter electrode and said first and second working electrodes, and

means for measuring how much current flows from said first and second working electrodes when a prescribed trim voltage is maintained across said reference electrode and said first and second working electrodes;

sensor signal comprises the ratio of said currents, thereby providing a measure of oxygen in the vicinity of said glucose sensor; and

a glucose monitor electrically coupled to the glucose sensor, said monitor comprising

means for receiving the sensor signal from the signal generating means,

means for processing the sensor signal and generating a glucose concentration data signal therefrom,

means for storing the glucose concentration data signal,

means for monitoring the glucose concentration data signal over a prescribed period of time and generating a rate of change signal that indicates how rapidly the glucose concentration data signal is changing,

means for selectively displaying the glucose concentration data signal and the rate of change signal,

first alarm means for determining if the glucose concentration data signal exceeds a preset level limit, and if so, generating a first alarm signal,

second alarm means for determining if the rate of change signal exceeds a preset trend limit, and if so, generating a second alarm signal,

calibration means for periodically calibrating the sensor so that it provides an accurate measure of the glucose concentration in the blood stream, and

control means for controlling the monitor so that it performs at least one of a plurality of monitoring functions as selected by a user of said monitor.

2. The glucose monitoring system as set forth in claim **1** wherein said prescribed enzyme comprises glucose oxidase.

3. The glucose monitoring system as set forth in claim **1** wherein said calibration means includes means for normalizing a ratio of said currents with a calibration constant, said calibration constant being obtained from an independent measure of the glucose concentration in a tissue/fluid sample taken from the patient.

4. The glucose monitoring system as set forth in claim **3** wherein said glucose monitor further includes means for issuing a calibration message in the event said independent measure of the glucose in the tissue/fluid sample has not been taken within a prescribed period from a prior calibration.

5. The glucose monitoring system as set forth in claim **3** wherein said calibration means further includes means for downloading calibration data to said glucose monitor at the time that a particular glucose sensor is first coupled to said glucose monitor, said calibration data being generated at the time of manufacture of said glucose sensor.

6. The glucose monitoring system as set forth in claim **1** wherein said glucose monitor includes a flat display of at least four inches by four inches overlaid with a touch sensitive screen, and wherein said control means comprises means for displaying one of a plurality of menus on said display, each of said plurality of menus including at least one button labeled with a monitoring function, and wherein said touch sensitive screen includes means for sensing if said display is touched by a user of said glucose monitor at a button of said menu, and if so, carrying out the function specified by said button.

7. The glucose monitoring system as set forth in claim **6** wherein said means for displaying further comprises at least one button for displaying the glucose concentration data signal in large numbers that substantially fill said flat display.

8. The glucose monitoring system as set forth in claim **1** wherein said glucose sensor is electrically coupled to said glucose monitor through a coupling cable that provides direct electrical contact between the glucose monitor and the glucose sensor.

9. The glucose monitoring system as set forth in claim **8** wherein said glucose sensor is coupled to said glucose monitor through a contactless coupling that electrically isolates said glucose sensor from said glucose monitor.

10. The glucose monitoring system as set forth in claim **9** wherein said contactless coupling comprises a transformer coupling.

11. The glucose monitoring system as set forth in claim **9** wherein said contactless coupling comprises an optical coupling.

12. The glucose monitoring system as set forth in claim **9** wherein said contactless coupling includes signal processing means on a sensor side of said coupling, said signal processing means including means for encoding the sensor signals passed through to the glucose monitor with sensor source information, whereby all of the sensor signals passed through to the glucose monitor may share a common set of cables.

13. The glucose monitoring system as set forth in claim **12** wherein said contactless coupling further includes a memory element having calibration data stored therein unique to said sensors, and a battery on the sensor side of said coupling, said battery providing a source of continuous power to said sensors.

14. The glucose monitoring system as set forth in claim **13** wherein said contactless coupling includes at least one magnet and a metal member to which said magnet is attracted, the magnet or metal member being located on the sensor side of the coupling, and the other of the magnet or metal member being located on a monitor side of the coupling, said magnet having a magnetic force field that pulls the magnet toward the metal member, said magnetic force field thereby holding said contactless coupling together.

15. A glucose monitoring system comprising:

a glucose assembly comprising a plurality of glucose sensors, each glucose sensor comprising an enzymatic glucose sensor adapted to be positioned within a person whose glucose concentration is to be measured, each glucose sensor of the glucose assembly providing a respective sensor signal that varies as a function of sensed glucose; and

a glucose monitor electrically coupled to the glucose assembly, said glucose monitor comprising

means for receiving the sensor signal from each glucose sensor,

means for processing the sensor signal received from each glucose sensor, said means for processing including means for comparing the sensor signals obtained from each of said plurality of sensors and generating a composite sensor signal only if the respective sensor signals are within a first prescribed amount of each other,

means for storing the composite sensor signal,

means for monitoring the composite sensor signal over a prescribed period of time and generating a rate of change signal that indicates how rapidly the composite sensor signal is changing,

means for selectively displaying the composite sensor signal and the rate of change signal,

first alarm means for determining if the composite sensor signal exceeds a preset level limit, and if so, generating a first alarm signal,

second alarm means for determining if the rate of change signal exceeds a preset trend limit, and if so, generating a second alarm signal,

calibration means for periodically verifying that each glucose sensor of the sensor assembly provides an accurate measure of the glucose concentration in the blood stream, and

control means for controlling the monitor so that it performs at least one of a plurality of monitoring functions as selected by a user of said monitor.

16. The glucose monitoring system as set forth in claim **15** wherein said processing means further includes means for generating an error message in the event that the respective sensor signals are not within said first prescribed amount of each other, said error message advising a user of said glucose monitor to check said plurality of glucose sensors.

17. The glucose monitoring system as set forth in claim **16** wherein said processing means further includes shutdown means for automatically shutting down said glucose monitor in the event at least one of the sensor signals differs from the others of said sensor signals by more than a second prescribed amount.

18. The glucose monitoring system as set forth in claim **15** further including at least one additional sensor adapted to sense a parameter other than glucose concentration, and wherein said processing means includes means for combining all of the sensor signals in arriving at said composite sensor signal.

19. A method of measuring a glucose concentration in a patient comprising:

(a) inserting a plurality of glucose sensor assemblies into a patient, each of said glucose sensor assemblies having a reference electrode, a counter electrode and first and second working electrodes;

(b) applying a voltage to said electrodes so as to cause first and second electrical currents to flow through said first and second working electrodes, respectively, and measuring said first and second electrical currents, the ratio of said second electrical current to said first electrical current providing a measure of oxygen in the patient;

(c) placing a glucose oxidase enzyme at said first working electrode, said glucose oxidase enzyme reacting with the oxygen and glucose such that the amount of oxygen measured at said first electrode is inversely proportional to the glucose concentration;

(d) determining the glucose concentration based on said measure of oxygen and calibration constants associated with each of said glucose sensors;

(e) comparing the glucose concentration measured by each of said plurality of sensors to determine if the respective plurality of glucose concentration measurements are within a prescribed percentage of each other, and if so, combining the plurality of glucose concentration measurements to form a composite glucose measurement, and if not, rejecting the plurality of glucose measurements as being inaccurate;

(f) storing the composite glucose measurement as a function of time;

(g) computing a rate-of-change signal for the composite glucose measurement that indicates how said composite glucose measurement has varied over a specified period of time;

(h) comparing the composite glucose measurement formed most recently and the rate-of-change signal to preprogrammed limits, and generating an alarm signal in the event the preprogrammed limits are exceeded; and

(i) selectively displaying the composite glucose measurement and rate-of-change signal.

20. The method, as set forth in claim **19**, wherein said glucose assembly is inserted into the peritoneal system of the patient.

21. The method, as set forth in claim **19**, wherein said glucose assembly is placed in contact with body tissue of the patient.

22. A patient monitoring system comprising:

an enzymatic sensor adapted to be inserted into a patient in order to make contact between said sensor and a bodily fluid/tissue of said patient, said sensor including means for generating a sensor signal that varies as a function of concentration of a substance sensed in said bodily fluid/tissue, said sensor comprising a detector that detects the amount of said substance in the region of a prescribed enzyme held within said sensor, and wherein said substance in said bodily fluid/tissue reacts with said prescribed enzyme such that the amount of said substance can be measured, and wherein said detector comprises

a first working electrode, a counter electrode, a reference electrode, and a second working electrode, all of said first and second working electrodes, reference electrode and counter electrode being enclosed within a first membrane wherein an ionic solution is maintained, and said first membrane being enclosed within a second membrane,

said prescribed enzyme being confined to a window region near said first working electrode,

electrical means for causing an electrical current to flow between said counter electrode and said first and second working electrodes, and

means for measuring how much current flows from said first and second working electrodes when a prescribed trim voltage is maintained across said reference electrode and said first and second working electrodes, said measuring means being in communication with said sensor signal generating means, the sensor signal comprising the ratio of said currents and being representative of the substance concentration in said bodily fluid/tissue in the vicinity of said sensor; and

a monitor electrically coupled to the sensor, said monitor comprising

means for receiving the sensor signal,

means for processing the sensor signal and generating a substance concentration data signal therefrom,

means for storing the substance concentration data signal,

means for monitoring the substance concentration data signal over a prescribed period of time and generating a rate of change signal that indicates how rapidly the substance concentration data signal is changing,

means for selectively displaying the substance concentration data signal and the rate of change signal,

first alarm means for determining if the substance concentration data signal exceeds a preset level limit, and if so, generating a first alarm signal,

second alarm means for determining if the rate of change signal exceeds a preset trend limit, and if so, generating a second alarm signal,

calibration means for periodically calibrating the sensor so that it provides an accurate measure of the substance concentration in the bodily fluid/tissue, and

control means for controlling the monitor so that it performs at least one of a plurality of monitoring functions as selected by a user of said monitor.

23. A method of measuring the concentration level of a particular substance within a patient, said method comprising the steps of:

(a) inserting a plurality of sensors into a body location of a patient in order to make contact between said plurality of sensors and body fluid/tissue of the patient, each of said sensors having a reference electrode, a counter electrode and first and second working electrodes, and means for providing a measure of a substance concentration within the patient's body fluid/tissue as a function of the electrical current flowing between said first and second working electrodes;

(b) applying a voltage to said electrodes so as to cause first and second electrical currents to flow through said first and second working electrodes, respectively, and measuring said first and second electrical currents, said first and second electrical currents providing a measure of the substance concentration within the patient's body fluid/tissue;

(c) determining the substance concentration in the body fluid/tissue of the patient based on the first and second electrical currents measured in step (b) for each of said plurality of sensors; and

(d) comparing the substance concentration measured by each of said plurality of sensors to determine if the respective plurality of substance concentration measurements are within a prescribed percentage of each other, and if so, combining the plurality of substance concentration measurements to form a composite substance measurement, and if not, rejecting the plurality of substance measurements as being inaccurate.

24. The method of claim 23 further including:

(a) storing the composite substance measurement as a function of time;

(b) computing a rate-of-change signal for the composite substance measurement that indicates how said composite substance measurement has varied over a specified period of time;

(c) comparing the composite substance measurement formed most recently and the rate-of-change signal to preprogrammed limits, and generating an alarm signal in the event the preprogrammed limits are exceeded; and

(d) selectively displaying the composite substance measurement and rate-of-change signal.

25. An enzymatic sensor adapted to be inserted into a patient in order to make contact with body fluid/tissue of said patient, said sensor comprising:

a first working electrode (W1), a counter electrode (C), a reference electrode (R), and a second working electrode (W2), all of said first and second working electrodes, reference electrode and counter electrode being enclosed within a first membrane wherein an ionic solution is maintained, and said first membrane being enclosed within a second membrane,

said prescribed enzyme being confined to a window region near said first working electrode,

electrical means for causing an electrical current to flow between said counter electrode and said first and second working electrodes, and

means for measuring how much current flows from said first and second working electrodes when a prescribed trim voltage is maintained across said reference electrode and said first and second working electrodes, a ratio of said currents comprising a sensor signal, which sensor signal provides a measure of the substance concentration in said body fluid/tissue in the vicinity of said sensor.

26. A sensor assembly adapted for implantation into the body of a patient to measure the concentration of one or more substances in the patient's blood, said sensor assembly comprising:

a substrate;

first and second sets of sensors spaced apart on said substrate, wherein each set of sensors comprises:

first and second working electrodes bonded to said substrate;

a reference electrode bonded to said substrate;

a counter electrode bonded to said substrate; and

means for making electrical contact with said first and second working electrodes, reference electrode, and counter electrode;

a layer of insulation deposited on said substrate and means for making electrical contact so as to be interspersed between the electrodes bonded to said substrate, a prescribed surface area of each of said electrodes being exposed through said layer of insulation, whereby said first and second working electrodes, reference electrode and counter electrode are all electrically isolated from each other on said substrate;

first membrane means covering said substrate and electrodes;

a saline solution held within said first membrane, said saline solution being in contact with said electrodes bonded to said substrate;

second membrane means covering said first membrane means, said second membrane means having a window pocket therein above the exposed surface area of said first working electrode;

a prescribed enzyme placed within said window pocket; and

means for applying a prescribed reference voltage, within each set of sensors, between said counter electrode and said reference electrode, and between said first and second working electrodes and said reference electrode, and for measuring the electrical current that flows from said first and second working electrodes, within each set of sensors;

whereby when said sensor assembly is inserted in the patient's venous system, oxygen and other substances in the blood of the patient may penetrate said first and second membrane means of each set of sensors and electrochemically react, in the presence of the prescribed enzyme held in said window pocket of each set of sensors, with the current flowing through each of said first working electrodes, and electrochemically react in the absence of said enzyme with the current flowing through each of said second working electrodes;

said currents flowing through said first and second working electrodes of each set of sensors thereby providing a measure of oxygen and other substances in the blood of the patient as a function of the electrochemical reactions that occur at said first and second working electrodes of each set of sensors.

27. The sensor assembly as set forth in claim 26 wherein said prescribed enzyme comprises glucose oxidase.

28. The sensor assembly as set forth in claim 26, wherein said first and second sets of sensors are separated on said substrate such that the window pockets are spaced apart about 0.4 to 1.0 inches along the length of the substrate.

29. The sensor assembly as set forth in claim 26 wherein said first and second sets of sensors further comprise a temperature sensor mounted on said substrate.

30. The sensor assembly as set forth in claim 29 wherein each of said temperature sensors comprises a prescribed semiconductor having a resistivity that varies as a function of temperature, and means for applying a voltage across said semiconductor, whereby the current flowing through said semiconductor provides a measure of the resistivity, and hence the temperature.

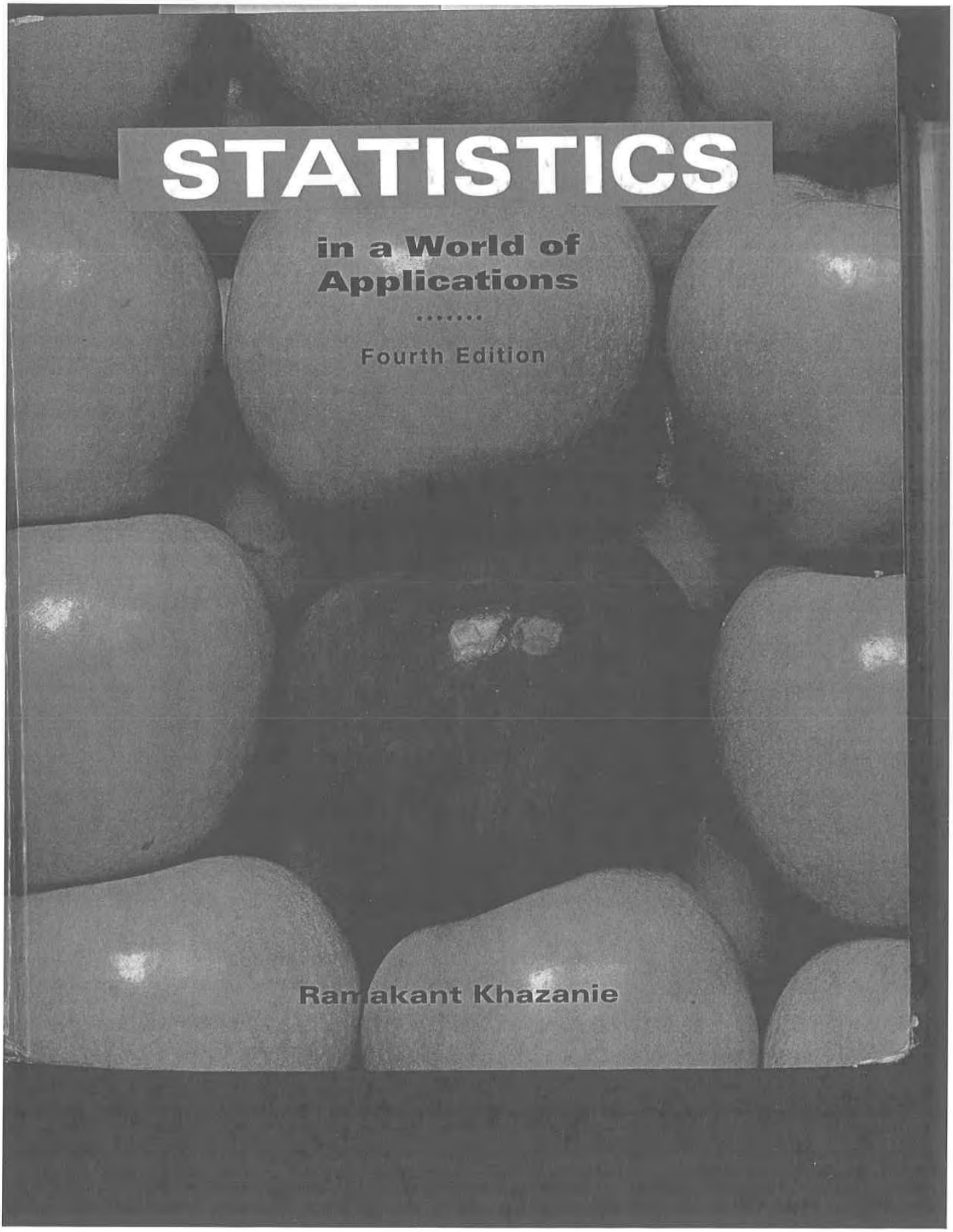
31. The sensor assembly as set forth in claim 29 further including a cable carrying sufficient electrical conductors to make contact with said first and second electrodes, reference electrode, counter electrode and temperature sensor of each of said sets of sensors, said cable terminating in a first contactless connector, said first contactless connector having a battery and a control chip therein that receives and processes the electrical current that flows from the first and second working electrodes of each set of sensors, said control chip including memory means for storing calibration data associated with said sensor assembly, processing means for processing the received electrical current with the calibration data to produce encoded sensor data signals, and transmitting means for transmitting the encoded sensor data signals to a receiver located in a second contactless connector, said second contactless connector being adapted to be coupled to said first contactless connector without making direct electrical contact therewith, whereby electrical isolation is provided between the first and second contactless connectors, said second contactless connector being coupled to a monitoring device whereat said encoded sensor data signals are decoded, displayed and stored.

32. The sensor assembly as set forth in claim 31 wherein said second contactless connector is coupled to said monitoring device through a connection cable having two electrical conductors.

33. The sensor assembly as set forth in claim 31 wherein at least one of said first and second contactless connectors includes a permanent magnet that is attracted to a metallic member in the other contactless connector, and wherein said permanent magnet provides a holding force for maintaining said first and second contactless connectors in close proximity to each other.

* * * * *

Exhibit 11



STATISTICS

in a World of Applications

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Fourth Edition

Ramakant Khazanie
Humboldt State University

HarperCollinsCollegePublishers

To the memory of my grandparents, my father, and my brother, Suresh

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Compositor: Interactive Composition Corporation
Printer and Binder: R. R. Donnelley & Sons Company
Cover Printer: Phoenix Color Corporation

Statistics in a World of Applications, Fourth Edition

Reprinted with correction, July 1997.

Reproduced by Addison-Wesley Publishing Company Inc. from camera-ready copy supplied by the author.

Library of Congress Cataloging-in-Publication Data
Khazanie, Ramakant.
Statistics in a world of applications / Ramakant Khazanie.—4th ed.
p. cm.
Rev. ed. of: Elementary statistics in a world of applications. 3rd ed. c1990.
Includes index.
ISBN 0-673-46768-6
1. Statistics. I. Khazanie, Ramakant. Elementary statistics in a world of applications. II. Title.
QA276.12.K5 1996
519.5—dc20 95-23434

3 4 5 6 7 8 9 10-DOC-01 00 99 98 97

fewer assets than older, more established ones, there's cold comfort in those figures, too: The 1993 median for families headed by someone 45 to 54, for example, was a mere $2,600.

Not only do those figures represent a "woeful low," as characterized by John L. Steffens of Merrill Lynch, which commissioned the analysis, but the low has been getting lower just as the nation's economic pilots have been fretting that their beast is soaring too high. What's going on? Apparently just more of that familiar refrain about the rich getting richer. As the Capital Research Associates study also makes clear, if with some qualifiers, *mean* family wealth jumped smartly during the same two-year span that *median* wealth swooned. In other words, while at least half of all Americans were watching their already shriveled nest eggs diminish even more, there is at least some statistical suggestion that a small minority was growing very much better off.

In this recovery, many more boats seem to have been swamped than lifted.

2-3 MEASURES OF DISPERSION

As useful as the measures of central location are in providing some understanding about the data in a distribution, total reliance on the information conveyed by the mean, the median, and the mode can be misleading, as we now illustrate.

Suppose a test is given to two sections of a class, Section A and Section B. Table 2-2 gives the scores (in points) recorded in the two sections.

TABLE 2-2 Test Scores in Sections A and B

Section A Scores	Section B Scores
56	30
58	35
60	60
60	60
60	60
62	85
64	90

We can verify that both sections have the same mean score (60), the same median score (60), and the same mode (60). Solely on the basis of this information, however, it would be wrong to infer that the two sets of data are similar. In Section A, the group of students is homogeneous, all of them scoring in the vicinity of 60 points. In Section B, on the other hand, the performance is very erratic, from a low of 30 points to a high of 90 points. If we choose a student from Section A, we can assume that the student's score will be close to 60 points. We cannot say the same about a student chosen from Section B.

Often, a revealing picture emerges by considering histograms of the distributions, as in Figure 2-6. The two distributions give the tensile strength of cables manufactured by two processes. In both cases, we have the same mean, median, and mode. However, there is smaller variability in the data for the histogram in Figure 2-6(a) than for the histogram in Figure 2-6(b)

Variability of values in data collected is a very common phenomenon, and its importance should be acknowledged. For instance, a company manufacturing electric bulbs will be interested not only in the average life of the bulbs, but also in how consistent the performance of the bulbs is. The manufacturer interested in marketing bulbs with a mean life of 1000 hours will not

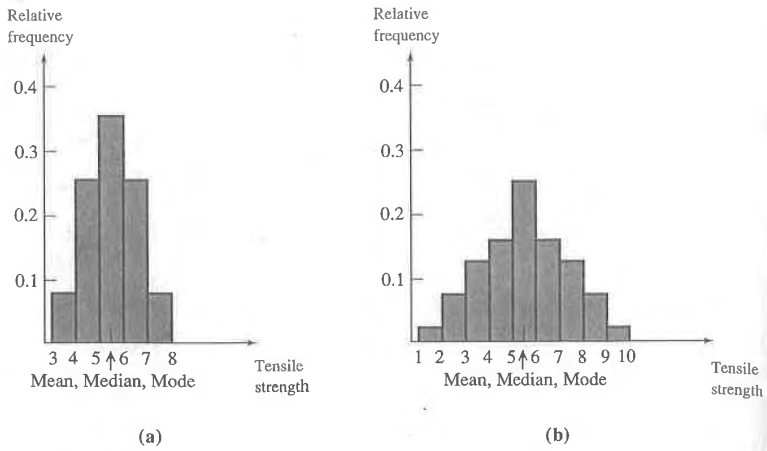


Figure 2-6
Two distributions having the same mean, median, and mode, with the spread of data in (b) more than in (a)

be satisfied even if this goal is realized if, in fact, there is a very high ratio of bulbs that only last for up to 200 hours. In other words, the success of the bulbs will depend upon the variability of life; the smaller the variability the better.

THE RANGE

The simplest measure of dispersion is the **range.** As we saw in Section 1-1, the range is defined as the difference between the largest and smallest value in the data.

$$\textbf{range} = \textbf{largest value} - \textbf{smallest value}$$

A familiar example where range is used as the measure of variability is a weather forecaster's daily temperature report given as, for example, a low of 40 degrees to a high of 70 degrees. The range is $70 - 40$, or 30, degrees.

If we take the highest and the lowest observations, the range is easy to compute. However, it ignores the intermediate values and provides no information at all about the set of observations between the highest and lowest values. Consider, for example, the following two sets of data.

3 7 9 11 16 and 3 12 12 12 16

Each set has the same range, but the two distributions are markedly different. Also, by describing data solely in terms of extreme values, the presence of an unusually extreme value will inflate the range out of proportion. The range, therefore, is the least satisfactory of all measures of dispersion that we consider in this chapter.

MEAN DEVIATION

The variability of the data depends upon the extent to which individual observations are spread about a measure of central tendency. If the values are widely scattered, the variability will be large. On the other hand, if the values are compactly distributed about this measure, the variability will be small. Because the arithmetic mean is by far the most important measure of central tendency, the deviations of the individual observations are usually taken as deviations from the mean $\bar{x}$.

For any value x_i in the data set of n values, $x_i - \bar{x}$ is its deviation from the mean. The n values will give rise to n deviations from the mean. Some of these deviations will be positive, others negative. Their sum, however, is *always* zero, irrespective of the scatter of the data. This is a mathematical fact. Thus we always have

$$\sum (x_i - \bar{x}) = 0$$

Because the sum of the deviations is always zero, $\Sigma (x_i - \bar{x})$ is of no value to us as a measure of variability. But notice that if the mean is 50, then the value 42 is as much removed from the mean as is the value 58, and the two will contribute to the same extent toward the variability. This allows us to overcome the difficulty posed by the fact that $\Sigma (x_i - \bar{x}) = 0$, by giving weight only to the magnitude of each deviation and considering all the deviations positive. These values are called *absolute deviations* from the mean and are denoted as $|x_i - \bar{x}|$. The arithmetic mean of the absolute deviations is customarily called the **mean deviation,** though, perhaps, calling it *mean absolute deviation* would seem more appropriate. It is found by dividing the sum of the absolute deviations by the total number of observations.

MEAN DEVIATION

If $x_1, x_2, \ldots, x_n$ are n values in the data set, then

$$\text{mean deviation} = \frac{\sum |x_i - \bar{x}|}{n}$$

In contrast with the range, the mean deviation takes into account the magnitude of all the observations in the data.

EXAMPLE 1 A secretary typed six letters. The times (in minutes) spent on these letters were 6, 8, 13, 10, 8, and 9. Find the mean deviation.

SOLUTION We see that the mean is

$$\bar{x} = \frac{6 + 8 + 13 + 10 + 8 + 9}{6} = 9.$$

Therefore,

$$\text{mean deviation} = \frac{|6 - 9| + |8 - 9| + |13 - 9| + |10 - 9| + |8 - 9| + |9 - 9|}{6}$$

$$= \frac{3 + 1 + 4 + 1 + 1 + 0}{6} = \frac{5}{3}.$$

VARIANCE AND THE STANDARD DEVIATION

The use of absolute values causes considerable problems in treating mean deviation mathematically. For this reason, mean deviation is not suitable, and we will seldom refer to it again in the remainder of the book. The preferred measures of spread or dispersion of data are **sample variance** and **sample standard deviation**. The sample variance is computed from the deviations $(x_i - \bar{x})$, by squaring them and dividing the sum of these squares by $n - 1$. The deviations are squared because squaring produces positive numbers for both positive and negative deviations. The sample standard deviation is defined as the *positive* square root of the variance. The sample variance is denoted by s^2 and the sample standard deviation by s where s is positive.

SAMPLE VARIANCE AND STANDARD DEVIATION

If a sample consists of n numerical measurements $x_1, x_2, \ldots, x_n$, then the **sample variance** s^2 is defined by

$$s^2 = \frac{\sum (x_i - \bar{x})^2}{(n - 1)}$$

and the **sample standard deviation** s by

$$s = \sqrt{\frac{\sum (x_i - \bar{x})^2}{(n - 1)}}$$

If you analyze the formula for s, the following steps are involved in its computation.

1. Compute the mean.
2. Compute the deviations from the mean. (As a computational check, the sum of these values should be 0.)
3. Square the deviations.
4. Add the squared deviations.

5 Divide the sum of the squared deviations by $n - 1$. In this step we have computed s^2 or the sample variance.

6 Find the *positive* square root. This step yields the standard deviation.

If the observations in the data are too widely spread out, then quite a few of them will be far removed from the mean. For these observations $(x_i - \bar{x})^2$ will be large and, as a consequence, $\Sigma (x_i - \bar{x})^2$ will be large. This will result in making both s^2 and s large. Thus if the data are too scattered, the variance and the standard deviation both will be large.

Rationale for Dividing by $n - 1$

For finding s^2, the sum of squares of deviations from $\bar{x}$ is divided by $n - 1$ instead of by n. The rationale is as follows. Suppose we are told to pick *any* three numbers with the condition that their sum is to be 18. Are we really free to pick three numbers? Of course not. We have freedom to pick only two (that is, $3 - 1$) numbers since the third number is determined automatically by the constraint. About the same sort of thing happens when finding the sample variance. We are told that we have n observations from which to compute the sample variance, but first we must compute the sample mean using these observations since it is involved in the formula. It turns out that we have, in effect, $n - 1$ observations with which to compute the sample variance. The number $n - 1$ is called the *degrees of freedom* (abbreviated *df*) associated with the sample variance.

EXAMPLE 2 The price (in dollars) of a certain commodity on eight trading sessions was as follows.

38 11 8 60 52 68 32 19

Find the variance and standard deviation.

SOLUTION The computations are presented in Table 2-3. Following the steps listed on page 104 we proceed as follows.

1. In Column 1 we first find the mean $\bar{x} = 288/8$, or 36.
2. Then in Column 2 we compute deviations of the prices from the mean price; that is, we compute $x_i - 36$. As a check, notice that the sum of the entries in this column is zero.
3. The third column presents squares of deviations from the mean.
4. Next, we compute the sum of the squares in Column 3. We get

$$\sum (x_i - \bar{x})^2 = 3574$$

5. In this step we obtain the variance. Since $n = 8$, the variance (in dollars^2) is given as

$$s^2 = \frac{\sum (x_i - \bar{x})^2}{n - 1} = \frac{3574}{8 - 1} = 510.57$$

TABLE 2-3 Computation of the Variance of the Price of a Commodity

Price x	Deviation $x - 36$		Square of Deviation $(x - 36)^2$	
38	2		4	
11	−25		625	
8	−28		784	
60	24	Step 2	576	Step 3
52	16		256	
68	32		1,024	
32	−4		16	
19	−17		289	
$\sum x_i = 288$	$\sum (x_i - \bar{x}) = 0$		$\sum (x_i - \bar{x})^2 = 3574$	←Step 4
Step 1→ mean $\bar{x} = 36$				

6. Finally, in this step we find the positive square root of the variance, getting the standard deviation. The standard deviation is expressed in dollars and is given as

$$s = \sqrt{510.5714} = 22.6 \text{ dollars}$$

If you examine Column 3 of squared deviations, the largest squared deviation is 1,024 and is contributed by the data value 68. The other major contributors are 60 and 52 at the upper end, and 8 and 11 at the lower end. All these values are considerably farther from the mean price 36 than the rest of the values.

A Word about Rounding

Retain two decimal places more than in the original data in presenting the sample variance and one decimal place more than in the original data in presenting the standard deviation. Be careful not to find the standard deviation from the rounded variance.

Shortcut Formula

Through some algebraic simplifications, the preceding formula for s leads to the following shortcut formula for the standard deviation and it is convenient for computational purposes.

SHORTCUT FORMULA FOR THE STANDARD DEVIATION

$$s = \sqrt{\frac{1}{(n-1)}\left[\sum x_i^2 - \frac{\left(\sum x_i\right)^2}{n}\right]}$$

In the shortcut formula, you need to compute Σx_i^2 and Σx_i, which is a lot easier than computing the deviations and their squares. In words, the shortcut formula is

$$s = \sqrt{\frac{1}{(n-1)}\left[\begin{pmatrix}\text{sum of squares}\\ \text{of sample values}\end{pmatrix} - \frac{(\text{sum of sample values})^2}{n}\right]}$$

EXAMPLE 3 Compute s for the data in Example 2 using the shortcut formula.

SOLUTION We have determined that $n = 8$ and $\Sigma x_i = 288$. The sum of the squares of the values in the data set is

$$\begin{aligned}\sum x_i^2 &= (38)^2 + (11)^2 + (8)^2 + (60)^2 + (52)^2 + (68)^2 \\ &\quad + (32)^2 + (19)^2 \\ &= 13{,}942\end{aligned}$$

Substituting in the shortcut formula, we then get

$$s = \sqrt{\frac{1}{(8-1)}\left[13{,}942 - \frac{(288)^2}{8}\right]} = 22.6$$

This is the same answer we obtained in Example 2. ●

Use of Pocket Calculators

The statistical function s is built into many scientific pocket calculators and can be obtained simultaneously with the mean $\bar{x}$. Instead of using the definitional formula on page 104, the calculator uses the shortcut formula for computing s. It accumulates n, Σx_i, and Σx_i^2, in three special registers as the data are entered. The calculator uses the accumulated entries in the registers n and Σx to compute the mean when the key for the mean is pressed. It uses the accumulated entries in all the three registers and the shortcut formula to give s when the key for s is pressed. A few authors choose to define the standard deviation by dividing the sum of the squares of the deviations by n instead of by $n - 1$. Some calculators, therefore, have two keys, labeled s_n and s_{n-1}, or σ_n and σ_{n-1}. Since we divide by $n - 1$ in this text, you should use the key s_{n-1} or σ_{n-1} for s.

You will be performing many statistical computations and should own a versatile statistical calculator to save you the drudgery of tedious computations. Also, familiarize yourself thoroughly with the calculator's accompanying manual.

A word about the units to be employed in expressing the variance and the standard deviation Because the variance is based on the sum of squared differences, it is expressed in squared units. The standard deviation is the square root of the variance. Therefore, it is expressed in terms of the units that were employed in measuring the data.

For example, if the data are given in feet, then the units used for expressing the variance are feet squared, abbreviated $(\text{ft})^2$, and those for the standard deviation are feet. In the same way, if the data are expressed in minutes, then the units for expressing the variance are minutes squared, or $(\text{min})^2$, and for the standard deviation the units are minutes.

PROPERTIES OF THE STANDARD DEVIATION

The standard deviation of data has the following two important properties:

1. If a fixed value d is added to each of the observations in the data, then the standard deviation is unchanged, that is,

$$\begin{pmatrix}\text{the standard deviation}\\ \text{of the new data}\end{pmatrix} = \begin{pmatrix}\text{the standard deviation}\\ \text{of the original data}\end{pmatrix}$$

   For example, if the salary of each employee is raised by \$100, then the standard deviation of salaries before the raise is the same as the standard deviation after the raise.

2. If each observation in the data is multiplied by a fixed constant c, then

$$\begin{pmatrix}\text{the standard deviation}\\ \text{of the new data}\end{pmatrix} = c \text{ times } \begin{pmatrix}\text{the standard deviation}\\ \text{of the original data}\end{pmatrix}$$

   For example, suppose the height of students in a classroom is measured in feet and the standard deviation is 0.8 feet. If the height is measured in inches, then the standard deviation will be (12)(0.8), or 9.6 inches.

SIGNIFICANCE OF THE STANDARD DEVIATION

When a researcher analyzes a bulk of numerical data, the two measures that will often be quoted are the mean and the standard deviation. There is a special relationship between these two statistics in communicating considerable information about the extent of the spread of the data. This relationship is explained in the theorem developed by the great Russian mathematician P. L. Chebyshev (1821–1894) and is named after him.

If k is a positive number, an interval which is k standard deviations from the mean is defined as the interval $(\bar{x} - ks, \bar{x} + ks)$ as shown in Figure 2-7. Thus, for example, if $\bar{x} = 16.8$, $s = 1.02$, then an interval which is two standard deviations from the mean is $(16.8 - 2(1.02), 16.8 + 2(1.02))$, that is, $(14.76, 18.84)$

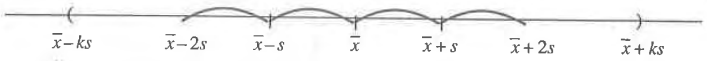


Figure 2-7 An Interval That Is k Standard Deviations from the Mean

For any positive number k, Chebyshev's rule states the minimum percentage of observations that will fall in the interval $(\bar{x} - ks, \bar{x} + ks)$, that is, within k standard deviations of the mean. This percentage is given by $\left(1 - \frac{1}{k^2}\right) \cdot 100$. In the following presentation we interpret the rule for certain values of k.

CHEBYSHEV'S RULE

For any data set, irrespective of its frequency distribution (whether it be symmetric, skewed to the right, skewed to the left, or any other variation) the following is true.

1. *At least* 0 percent of the observations will fall within 1 standard deviation of the mean, that is, in the interval $(\bar{x} - s, \bar{x} + s)$. This assertion is quite obvious.
2. *At least* 75 percent of the observations will fall within 2 standard deviations of the mean, that is, in the interval $(\bar{x} - 2s, \bar{x} + 2s)$.
3. *At least* 89 percent of the observations will fall within 3 standard deviations of the mean, that is, in the interval $(\bar{x} - 3s, \bar{x} + 3s)$.

Chebyshev's rule gives very conservative estimates, as it would have to, since it covers the entire gamut of frequency distributions. If additional information is available about the frequency distribution of the data, then more substantial statements can be made about how many observations will fall within 1, 2, and 3 standard deviations of the mean. For data having an almost symmetric, sort of mound or bell-shaped distribution, where the measurements are concentrated near the center and the histogram is tapering off in either direction from the center, the following Empirical rule is available. It provides a guideline for the *approximate* number of observations. (The basis for the Empirical rule is explained later on in Chapter 5 on page 306.)

THE EMPIRICAL RULE

For a data set with a symmetric frequency distribution as described above, the following hold true.

1. *Approximately* 68.3 percent of the observations will fall in the interval $(\bar{x} - s, \bar{x} + s)$.
2. *Approximately* 95.4 percent of the observations will fall in the interval $(\bar{x} - 2s, \bar{x} + 2s)$.
3. *Approximately* 99.7 percent, that is, practically all the observations will fall in the interval $(\bar{x} - 3s, \bar{x} + 3s)$.

As an illustration, consider the data presented by the dot diagram in Figure 2-8, where each value is denoted by a dot. There are three measurements each equal to 2, one measurement equal to 3, and so on, and altogether there are thirty-six measurements.

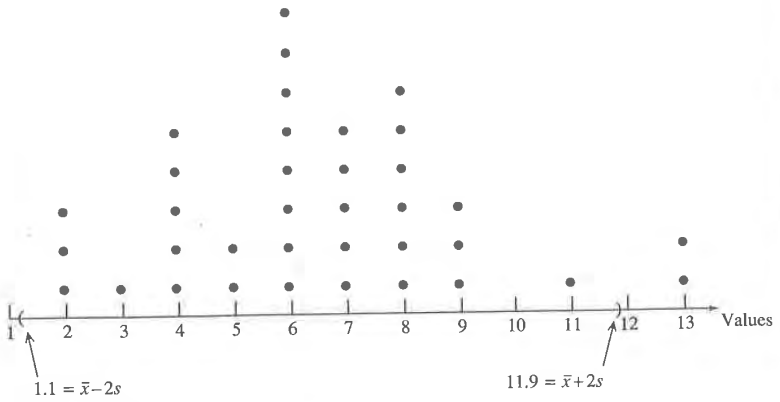


Figure 2-8 Dot Plot.
There are thirty-four values in (1.1, 11.9).

It can be verified that $\bar{x} = 6.5$ and $s = 2.7$. Thus, the interval $(\bar{x} - 2s, \bar{x} + 2s)$ is given by (1.1, 11.9) and the interval $(\bar{x} - 3s, \bar{x} + 3s)$ by $(-1.6, 14.6)$. From the dot diagram it can be seen that there are thirty-four measurements in the interval (1.1, 11.9), that is, 94.4 percent. In the interval $(-1.6, 14.6)$ there are all thirty-six observations, that is, 100 percent. In the following table we present the actual percentages and those predicted by the two rules.

Interval	Chebyshev (at least) %	Empirical (Approx.) %	Actual %
(1.1, 11.9)	75	95.4	94.4
$(-1.6, 14.6)$	89	99.7	100

Notice that the actual percentages are definitely in keeping with the predictions of Chebyshev's rule. Also, the actual percentages are not too far off from those given by the Empirical rule, even though, from the dot diagram, we could not quite say that the distribution was symmetrical and bell-shaped.

EXAMPLE 4 A psychologist claims to have a new instructional method for improving the performance of students. The psychologist tries the instructional method with eighty students and reports the summary of the results as follows: $\bar{x} = 120$ points and $s = 22$ points. What does this information tell us about the student scores?

SOLUTION Of course, we have no idea about the individual scores. But by using Chebyshev's rule we are in a position to make the following statements.

(a) Because $\bar{x} = 120$ and $s = 22$, we have the following.

$$\bar{x} - 2s = 120 - 2(22) = 76$$
$$\bar{x} + 2s = 120 + 2(22) = 164$$

We can infer that at least 75 percent of the eighty students, that is, at least sixty students, had scores between 76 and 164 points.

(b) For three standard deviations from the mean we have the following.

$$\bar{x} - 3s = 120 - 3(22) = 54$$
$$\bar{x} + 3s = 120 + 3(22) = 186$$

We can infer that at least 89 percent of the students, that is, at least seventy-one students, had scores between 54 and 186 points.

If the psychologist adds to the report that the frequency distribution was almost mound shaped, then we could improve our estimates using the Empirical rule as follows.

Approximately 95.4 percent, that is, approximately seventy-six students, had scores between 76 and 164 points. Also, practically every student in the study had a score between 54 and 186 points. ●

Section 2-3 Exercises

1. The scores of six students on a test are as follows.

   75 82 56 69 87 43

   Arrange the data in an ascending order of magnitude and find the range of scores.

2. The amount of time spent on each of ten telephone calls was recorded (in minutes) as follows.

   25 15 8 2 5
   12 34 3 12 3

   Find the range of the time spent on these calls.

3. The altitudes (in feet) of six locations (above or below sea level) are as follows.

   1200 above 140 above 100 below
   10,500 above 400 below 800 above

   Find the range of heights.

4. The minimum daily temperature readings (°F) of a ski resort on eight days were as follows.

22 −18 0 −8 16 30 5 −20

Find the temperature range for these days.

5. If the range of the price of a stock during a week was \$15.75, and if the lowest price was \$82.50, find the highest price during the week.

6. For the set of values 8, 6, 12, 10, and 14, find the following.

(a) $\sum (x_i - \bar{x})$ **(b)** $\sum |x_i - \bar{x}|$ **(c)** The mean deviation

7. The following figures refer to the times (in minutes) that eight customers spent from the time they entered a store to the time they left it.

6 3 2 10 2 5 4 6

Find the following.
(a) The arithmetic mean $\bar{x}$ of the time the customers spent in the store
(b) The absolute deviations
(c) The mean deviation

In Exercises 8–11, compute mean deviations for the given sets of observations.

8. 14, −4, 10, 6, 10, −15, and 7

9. 1.8, 2.8, 2.3, 4.5, and 1.1

10. 6, −7, −5, −4, and 5

11. −8, −7, −6, −5, −10, and −12

12. Seven buses are expected to arrive at the bus depot at 8 A.M., 9 A.M., 10 A.M., 11 A.M., 12 noon, 1 P.M., and 2 P.M. They arrive at 8:04 A.M., 9:10 A.M., 9:52 A.M., 10:56 A.M., 11:55 A.M., 1:10 P.M., and 2:00 P.M., respectively. Find the mean deviation of the amount of time by which a bus is late. (If a bus arrives ahead of schedule, for example, by 4 minutes, then consider the late arrival time is negative, or −4.)

13. The following figures give the price per pound of ground chuck (in dollars) at a supermarket during six weeks.

2.98 2.89 2.80 2.88 2.84 2.95

Find the number of weeks when the price is within one mean deviation of the mean price.

14. For the set of values 18, 19, 16, 12, 7, 10, 23, find the following.
(a) The arithmetic mean $\bar{x}$
(b) The deviations from the mean
(c) The squared deviations
(d) The sample variance
(e) The sample standard deviation

In each of Exercises 15–17 compute the variance and the standard deviation for the given sets of observations.

15. 14, −4, 10, 6, 10, −15, and 7

16. 1.8, 2.8, 2.3, 4.5, and 1.1

17. 6, −7, −5, −4, and 5

18. What is the standard deviation of a set of scores when all the observations are identical?

19. What does it mean when the variance of a set of observed values is zero?

20. If the variable x is measured in ounces, what units should be used in expressing the variance and the standard deviation?

21. The following readings were obtained for the tensile strength (in tons per square inch) of six specimens of an alloy.

2.58 2.65 2.40 2.46 2.44 2.41

Find the mean tensile strength and the standard deviation of the tensile strengths.

22. The heights of four fifth-grade students are 58, 56, 60, and 62 inches, and those of five sixth-grade students are 66, 59, 63, 61, and 66 inches. Which grade has the higher standard deviation?

23. A club has ten members whose weights are $x_1, x_2, \ldots, x_{10}$. Find the mean weight and the variance of the weights if $\Sigma x_i = 1500$ and $\Sigma x_i^2 = 325{,}000$.

24. Five samples of coal, each of which weighs 2.00 grams, lose the following amounts of moisture (in grams) after air drying in an oven.

0.158 0.160 0.156 0.153 0.163

Find the variance of the amount of moisture lost.

25. In a chemistry experiment seven students obtained the following percentages of chlorine in a sample of pure sodium chloride.

60.65 60.68 60.70 60.60
60.64 60.65 60.70

Find the standard deviation of the percentage of chlorine.

26. Using the formula for the variance, find the variance of the data in Part a. From this answer find the variance of the data in Parts b and c.

(a) 7, 8, 6, 8, and 6
(b) 27, 28, 26, 28, and 26
(c) 107, 108, 106, 108, and 106

Hint: The observations in Part b are obtained by adding 20 to each observation in Part a; and those in Part c are obtained by adding 100 to each observation in Part a.

27. After grading a test, Professor Adams announced to the class that the mean score was 68 points with a standard deviation of 12 points. However, a student brought to his attention that one of the questions on the test was incorrect and impossible to solve. As a result, Professor Adams agreed to add 10 points to each student's score. Find the mean, the variance, and the standard deviation of the new set of scores.

28. The mean salary of the employees in a certain company is \$22,300, with a standard deviation of \$2500. The company announces a flat raise of \$1000 for each employee during the following year. Find the mean and the standard deviation of the new salaries.

29. The following data are the chlorophyll content (mg/g) of thirty wheat leaves.

2.6	2.9	3.2	3.0	2.6
3.2	3.2	3.0	2.9	3.0
2.6	2.6	3.0	3.2	2.9
3.2	2.6	2.9	3.2	2.6
3.2	2.8	3.2	3.0	3.0
2.8	2.9	3.2	2.8	2.8

(a) Find the variance and the standard deviation of the chlorophyll content.
(b) How many observations are within two standard deviations of the mean?

30. To show the impact of the increase in federal tax effective October 1, 1993, Mobil Corporation published the following figures for major markets where Mobil does most of its business. The data give federal, state, and local taxes, in cents, that go into the price of gas at the pump.

Gasoline Taxes in Cents per Gallon in Some Key Locations:

Metropolitan Area	Federal Tax	State Excise Tax	Other State and Local Taxes	Total
Chicago	18.63	19.00	21.66	59.29
Long Island, NY	18.63	8.00	26.49	53.12
New Haven, CT	18.63	29.00	5.28	52.91
Buffalo, NY	18.63	8.00	25.79	52.42
Albany, NY	18.63	8.00	25.79	52.42
Los Angeles	18.63	17.00	11.84	47.47
Providence, RI	18.63	28.00	0	46.63
Tampa	18.63	4.00	21.17	43.80
Miami	18.63	4.00	20.17	42.80
Baltimore	18.63	23.50	0	42.13
Philadelphia	18.63	12.00	10.35	40.98
Boston	18.63	21.00	.50	40.13
Fairfax, VA	18.63	17.50	3.13	39.26
Detroit	18.63	15.00	5.61	39.24
Dallas	18.63	20.00	.59	39.22
Phoenix	18.63	18.00	1.00	37.63
Newark, NJ	18.63	10.50	4.04	33.17
St. Louis	18.63	13.00	0	31.63

Average of these areas: 44.13

Source: "Pump Price and Tax Collectors-VI" by Mobil Corporation. Copyright © 1993 Mobil Corporation. Reprinted by permission of Mobil Corporation.

You can verify that the average of 43.958 given at the bottom of the table refers to the mean and that it is computed from the column giving the total taxes. Compute the standard deviation of the total taxes. Without using the actual data any more, what would the mean tax and the standard deviation of the taxes be in the listed areas if the federal tax of 18.63 cents was eliminated?

31. The following data for calcium and oxalic acid contents (in mg/g) of alfalfa meal are reproduced from the article *Oxalic Acid Content of Alfalfa Hays and Its Influence on the Availability of Calcium, Phosphorus, and Magnesium to Ponies,* by H. F. Hintz et al., from the *Journal of Animal Science,* vol. 58, no. 4, 1984. Reprinted by permission of the American Society of Animal Science.

Location	Calcium	Oxalate
Alabama	16.4	3.6
Alabama	15.1	3.7
Ontario, Can.	19.6	3.3
Ontario, Can.	12.3	2.4
Ontario, Can.	14.0	2.8
Colorado	17.2	3.3
Illinois	13.8	4.1
Iowa	15.6	4.3
Iowa	15.2	3.2
Nebr. or Kan.	13.0	3.7
Nebr. or Kan.	16.2	3.7
Nebr. or Kan.	15.1	4.2
Nebr. or Kan.	12.8	6.6
Minnesota	16.3	2.4
Michigan	16.0	2.7
Nebraska	16.8	3.3
Nebraska	14.2	3.8
Ohio	15.7	2.0
Ohio	17.3	2.3
Ohio	13.5	3.5
Texas	12.0	4.7
Washington	14.7	5.1

(a) Prepare stem-and-leaf diagrams for calcium content and oxalic acid content.
(b) Use the stem-and-leaf diagrams to compute the median contents of the two variables.
(c) Construct histograms for the two variables.
(d) Compute the mean and the standard deviation of the two variables.
(e) For each variable locate the mean along the horizontal axis of the histogram and mark the interval that is two standard deviations from the mean.
(f) Compute (*calcium/oxalate*) ratios. Then compute the mean and the standard deviation of the resulting ratios.

32. Benzo(a)pyrine is one of the polycyclic hydrocarbons released into the marine environment by the oil pollution of the seas. The amount of benzo(a)pyrine (μg/kg) in the tissues of mussels, a mollusk, was determined in a coastal region by the spectral luminescence method. Ten samples were analyzed from the unpolluted section of the region and eight samples from the oil-polluted section.

BENZO(a)PYRINE (μ/kg)	
Unpolluted	**Polluted**
0.36	382.1
0.39	292.6
0.35	313.9
0.38	373.8
0.37	322.8
0.37	337.1
0.35	381.2
0.39	351.3
0.38	
0.37	

Calculate the following.

(a) The mean benzo(a)pyrine in the unpolluted section and also in the oil-polluted section

(b) The standard deviation of the benzo(a)pyrine content in each section of the coastal region

33. Three fish-rearing ponds were fertilized with fodder yeast and mineral fertilizer containing superphosphate and ammonium nitrate. Five determinations of dissolved oxygen concentration (mg/l) were made in two of the ponds and four determinations were made in the third pond. The data are shown in the following table.

DISSOLVED OXYGEN (mg/l)		
Pond 1	**Pond 2**	**Pond 3**
5.5	5.3	5.8
5.8	5.2	5.9
5.6	5.4	5.7
5.5	5.1	5.6
5.4	5.3	

In Chapter 12 we will investigate such data in more detail. For now, answer the following questions:

(a) Find the mean dissolved oxygen concentration in each of the three ponds.

(b) Find the overall mean dissolved oxygen concentration in the three ponds taken together. (When different sets of data are regarded as one set, the data are said to be *pooled*.)

(c) Find the mean of the three means you computed in Part a. (*Careful*! Consider Property 1 on page 80.) Is your answer the same as in Part b?

(d) Find the standard deviation of the dissolved oxygen concentration in each of the three ponds.

(e) Find the overall standard deviation of the dissolved oxygen concentration in the three ponds taken together.

34. *Coridothyme capitatus* is a wild spice plant widely distributed in Israel and on the West Bank of the Jordan River. An area of approximately 0.1 hectare was randomly chosen for sample collection. A sample of plant material was gathered by taking one branch of each *C. capitatus* plant growing in the selected area. Essential oil was distilled from each sample separately. The thymol (carvacrol isomer) and carvacrol contents in essential oils of *C. capitatus* from different sites are presented in the following table. [Alexander Fleisher et al., Chemovarieties capitatus I. Rchb. growing in Israel; *J. Sc. Food Agric.* 35 (1984): 495–499.]

Site Location	Thymol Concentration in Essential Oil (%)	Carvacrol Concentration in Essential Oil (%)
Rosh-Hanikra, beach, Western Galilee	49.3	9.8
Haifa, Mt. Carmel	63.6	5.2
Hacarmel beach, coastal plain	55.0	5.1
Kfar Galim, coastal plain	41.7	24.2

Site Location	Thymol Concentration in Essential Oil (%)	Carvacrol Concentration in Essential Oil (%)
Atlit, coastal plain	42.0	22.9
Habonim beach, coastal plain	13.7	55.7
Moshav Habonim, coastal plain Sample A	45.2	10.9
Moshav Habonim, coastal plain Sample B	19.2	46.3
Dor beach, coastal plain	6.7	59.4
Zichron Jaacob, Mt. Carmel	47.5	20.3
Hertzelia beach, coastal plain	48.9	9.5
Umtzafa forest, West Bank	52.8	7.4
Nes-Ziona, inner plain	56.8	5.3
Nablus, West Bank	47.6	19.8
Bet-El, West Bank	51.1	6.6
Bet-Lechem, West Bank	51.8	10.8
Gush-Atzion, West Bank	16.0	44.3
Kibbutz Nativ Halamed Hey, West Bank	43.6	7.7
Beer-Sheva-Arad road, Negev	53.8	5.8
Kibbutz Saad, Negev	61.2	5.0

Compute the following.

(a) The mean thymol and carvacrol concentrations

(b) The standard deviations of thymol and carvacrol concentrations

35. Mr. Chan owns a retail store in a small town. When he checked his computer spreadsheet at the end of the calendar year 1994, there were the following balances (in dollars) in 33 accounts receivable.

52	74	50	57	62	101	57	99	68	114	48
76	84	52	63	97	76	73	64	78	85	95
67	61	82	90	51	75	88	65	25	160	72

(a) Compute the mean balance and the median balance.

(b) Prepare a histogram and locate the mean and the median.

(c) Compute the standard deviation and determine the number of observations in the interval $(\bar{x} - 2s, \bar{x} + 2s)$. Exhibit this interval on the histogram.

36. Fifteen 5- to 6-week-old male rats each weighing approximately 100 grams were fed a test diet containing casein treated with a methanol (HCHO) solution containing 40 grams HCHO/liter. The rats were housed for 14 days in metabolism cages and were fed 10 grams fresh weight of diet per day. During the final 7-day period a total collection of feces and urine was carried out and the samples were analyzed for total N (nitrogen). The following data give figures for N digestibility of the rats.

0.91	0.91	0.94	0.95	0.93
0.93	0.92	0.92	0.91	0.92
0.94	0.92	0.92	0.93	0.92

Determine the following:
(a) The mean nitrogen digestibility of the rats
(b) The median nitrogen digestibility from the stem-and-leaf diagram
(c) The standard deviation of the nitrogen digestibility
(d) The interquartile range. (Provide an interpretation, as well).

37. The following figures give the cost (in cents) for a quart of a particular brand of oil at eight automotive supply centers.

80 85 95 88 92 85 92 95

Find the number of places where the price is within one standard deviation of the mean.

38. When ten 5-gram samples of an alloy were analyzed for silver content by the method of electrodeposition, the following amounts of silver (in grams) were found.

1.273	1.276	1.265	1.276	1.274
1.277	1.273	1.275	1.285	1.278

(a) Find the mean and the standard deviation of the amount of silver.
(b) Determine the interval which represents two standard deviations from the mean.
(c) How many samples have amounts of silver in the interval obtained as the solution to Part b?

39. The following figures give the percentage recovery of chemically reactive lysine in the presence of glucose by a modified trinitrobenzene sulphonic acid procedure.

57.2	79.7	82.7	66.3	64.7
66.1	55.6	67.3	72.1	80.5
64.8	74.0	71.2	71.5	70.7
69.9	73.3	70.9	61.4	78.4
70.2	62.8	74.7	70.0	73.9

(a) Compute the mean percentage recovery.
(b) Compute the variance of the percentage recovery.
(c) Determine the interval $(\bar{x} - 2s, \bar{x} + 2s)$ and compute the percentage of readings that fall in it.
(d) Determine the interval $(\bar{x} - 3s, \bar{x} + 3s)$ and compute the percentage of readings that fall in it.
(e) Are the data described satisfactorily by the Empirical rule?

40. The following data contain figures for the concentration of acid-soluble sulfides (mg/l fresh ooze) in the bottom sediments of a lagoon. Twenty-five samples were analyzed.

998	938	971	949	1013
1000	1021	1002	995	956
1010	1015	967	987	990
954	974	984	988	982
941	976	1047	974	965

(a) Calculate the following.
  i. The mean concentration and the median concentration of sulfides
  ii. The standard deviation

(b) Find the number of observations in these intervals.
  i. $(\bar{x} - 2s, \bar{x} + 2s)$
  ii. $(\bar{x} - 3s, \bar{x} + 3s)$

(c) Are the data described satisfactorily by the Empirical rule?

41. Thirty milk-yielding Ayrshire cows were fed a diet of silage supplemented with a protein concentrate. The figures below refer to the milk fat concentration (g/kg) for each cow.

30.5	28.7	27.3	24.1	42.3
41.5	20.5	36.3	25.5	30.9
26.3	33.6	31.9	34.7	35.0
34.5	30.6	34.0	38.2	42.5
40.3	21.7	35.7	32.7	34.6
35.1	35.9	33.3	37.4	33.3

Calculate the following.

(a) The mean milk fat concentration

(b) The standard deviation of the milk fat concentration

(c) The number of cows with milk yield within two standard deviations of the mean

(d) The interquartile range (Interpret this quantity in terms of the variable under consideration.)

(e) The number of cows with milk yield falling in the interquartile range

42. For the data in Exercise 41 prepare a histogram with 6 classes and discuss its symmetry. Locate the mean and the median on the horizontal axis along the base of the histogram. Comment on the closeness of the mean and the median considering the symmetry of the histogram or the lack of it.

43. Sixty dry cell batteries were tested. It was found that the mean life was 96 hours with a standard deviation of 12 hours. What does this tell you about the lives of the batteries? (*Hint:* Consider Chebyshev's rule and see Example 4 on page 111.)

44. When dopamine levels (nmoles/g) were measured in the brains of 36 rats, the mean amount was 6.18 nmoles/g and the standard deviation was 0.68 nmoles/g. What does this information tell you about the dopamine levels of the 36 rats? (Use the hint for Exercise 43, above.)

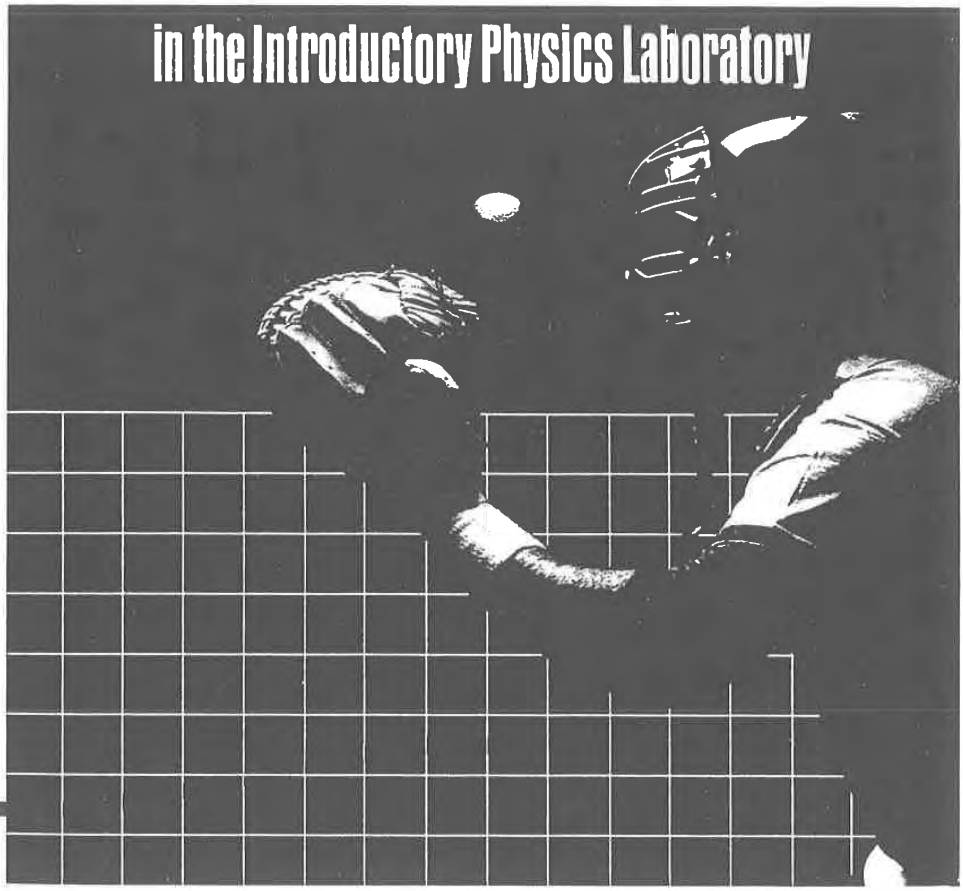
2-4 MEAN AND STANDARD DEVIATION FOR FREQUENCY DISTRIBUTIONS

The basic formula for computing the sample mean and the sample standard deviation have been given in the preceding sections. Now, if the data are given in a frequency table, the formulas can be expressed in the following form.

Exhibit 12

Data and Error Analysis

in the Introductory Physics Laboratory



WILLIAM LICHTEN

Data and Error Analysis in the Introductory Physics Laboratory

WILLIAM LICHTEN

Yale University

Prentice Hall, Upper Saddle River, New Jersey 07458

Library of Congress Cataloging-in- Publication Data
Lichten, William
Data and error analysis in the introductory physics laboratory
William Lichten.
p. cm.
Bibliography: p.
Includes index.
ISBN 0-205-11193-9
1. Statistics. 2. Error analysis (Mathematics). I. Title.
HD30.28.D3785 1996
519.5—dc19 87-26954
CIP

Printed in the United States of America
10 9 8 7 6 5

ISBN 0-205-11193-9

Prentice-Hall International (UK) Limited, London
Prentice-Hall of Australia Pty. Limited, Sydney
Prentice-Hall Canada Inc., Toronto
Prentice-Hall Hispanoamericana, S.A., Mexico
Prentice-Hall of India Private Limited, New Delhi
Prentice-Hall of Japan, Inc., Tokyo
Simon & Schuster Asia Pte. Ltd., Singapore
Editora Prentice-Hall do Brasil, Ltda., Rio de Janeiro

Precision Versus Accuracy: Random and Systematic Errors

Let's go back to the example of the pencil. Suppose everyone in the class uses the same ruler, measures the pencil to the nearest millimeter, and all agree it is 192 mm long. All say that it couldn't be either 191 or 193 mm long. We say that the class has measured the length of the ruler to a *precision* of 1 mm. *Precision* is the reliability or repeatability of a measurement.

Suppose that the instructor now points out, "You all have made the same mistake. You lined up one end of the pencil and one end of the ruler together. The end of the ruler is worn badly; it doesn't begin at zero. Try to remeasure the pencil by putting it in the middle of the ruler. Then find the position of both ends." (see Table 1-1.) "Subtract one value from the other to find the length." Now the class finds that the pencil is 187 mm long! How can this be?

Both measurements are equally precise. The second one is more *accurate* than the first, because a *systematic* error (caused by the worn end of the ruler) is no longer there. A *systematic error* is an effect that changes all measurements by the same amount or by the same percentage.

The class's experience with the ruler is a mirror of the history of science. Systematic errors have often hidden unsuspected in measurements. The only way to eliminate systematic errors is to look carefully for them and to understand well the nature of the experiment or measurement.

Random Errors. Can We Avoid Them? Let's return to the example of the class measurement of the length of a pencil; when measuring to the nearest millimeter, everyone got the same value. Let's try to push the precision further and ask each person to measure to the nearest *tenth* of a millimeter. Now disagreements appear. We find different values: 186.7, 187.0, 187.3 mm, as shown in Table 1-1.

Is someone making a mistake? No, even the most careful and skillful person will come up with values that vary by one- or two-tenths of a millimeter. Now we are at the limit of measurement by use of the naked eye and rulers. The unavoidable change in successive measurements, due to small irregularities in the ruler, difficulty in estimating precisely, and the like, is called a *random error,* or *error* for short.

Your Best Estimate, The Arithmetic Mean. What Is Your Error? At this point, you've been careful not to make any mistakes, you've avoided all systematic errors, and you've narrowed your uncertainty to the random error of measurement. What's next?

Common sense tells you to take the average of several measurements, called the *arithmetic mean* or *mean.* The algebraic expression for the average $\overline{X}$ of N numbers is

$$\overline{X} = \frac{\text{sum}}{N} = \frac{x_1 + x_2 + \cdots + x_N}{N} = \frac{\sum x}{N} \qquad (1\text{-}1)$$

TABLE 1-1 Measurement of the Length of a Pencil.

Left End, L (cm)	Right End, R (cm)	Length (cm) = $R - L$	Deviation from Mean
10.16	28.83	18.67	−0.03
15.87	34.57	18.70	0.00
20.22	38.95	18.73	+0.03

Sum = 56.10 cm; $N = 3$

Average = sum/N = 18.70 cm

Average deviation = (0.03 + 0.0 + 0.03)/3 = 0.02 cm

The data's scatter gives you an idea of the random error of measurement. A handy measure is the *average deviation from the mean,* sometimes shortened to *average deviation.* You can get this by finding the difference between each measurement and the mean and then taking the average. (You count all deviations as positive for this calculation.) An example of these calculations is given in Table 1-1.

The final result is 18.70(2) cm = 18.70 ± 0.02 cm. Note two ways of showing the error: ± precedes the error, or parentheses show the error in the last place. We will see later that, if you take three measurements, the average deviation is a remarkably good estimate of the error of your measurement.

Let's go over this again: *Take three measurements. Take the average as your best estimate of the true value. Take the average deviation as an estimate of the error of measurement.* This is a good rule of thumb that has several advantages. It's simple. It's easy to do the calculations (see Table 1-1); most of the time you can do them in your head or on a very small piece of paper.

1-3 SIGNIFICANT FIGURES

Rounding Off to the Right Number of Significant Figures. Using calculators causes a common problem: What do we do with the long string of digits in the display? Keep them all? Throw out some? If so, how many?

The answer to these questions is: keep only the *significant digits;* round off to the correct number of *significant figures.* Knowing the error of your measurement tells you how many significant figures there are in your result. Thus, you never give a result like 23.343 g when you only can weigh to 0.1 g. The correct value is 23.3(1) g. *The number of significant figures is the number of digits needed to state the result of a measurement,* or a calculation based on that measurement, *without losing any precision.* Thus a measurement of 10.05(1) cm (or 10.05 ± 0.01 cm) has four significant figures.

Exhibit 13

US005672256A

United States Patent [19]

Yee

[11] Patent Number: 5,672,256

[45] Date of Patent: Sep. 30, 1997

[54] **MULTI-ELECTRODE BIOSENSOR AND SYSTEM AND METHOD FOR MANUFACTURING SAME**

[75] Inventor: **Hee-Jin Yee**, Seoul, Rep. of Korea

[73] Assignee: **LG Semicon Co., Ltd.**, Chungcheongbuk-do, Rep. of Korea

[21] Appl. No.: **569,740**

[22] Filed: **Dec. 8, 1995**

[30] **Foreign Application Priority Data**

Dec. 8, 1994 [KR] Rep. of Korea 33335/1994

[51] **Int. Cl.**[6] **G01N 27/26**

[52] **U.S. Cl.** **204/403**; 204/415; 204/412; 204/406; 435/817; 435/289.1

[58] **Field of Search** 204/403, 406, 204/412, 415; 435/817, 288, 291

[56] **References Cited**

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Primary Examiner—Bruce F. Bell

Attorney, Agent, or Firm—Morgan, Lewis and Bockius, LLP

[57] **ABSTRACT**

A multi-electrode biosensor for sensing a material present in a sample includes a substrate, a plurality of working electrodes formed on the substrate, a counter electrode formed on the substrate, and a reference electrode formed on the substrate.

15 Claims, 6 Drawing Sheets

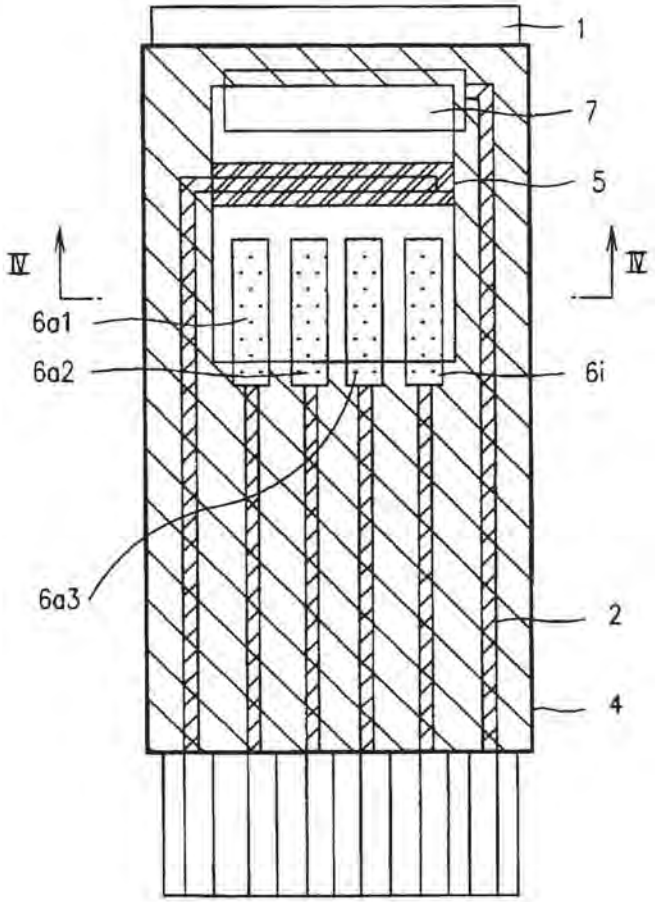


FIG.1
prior art

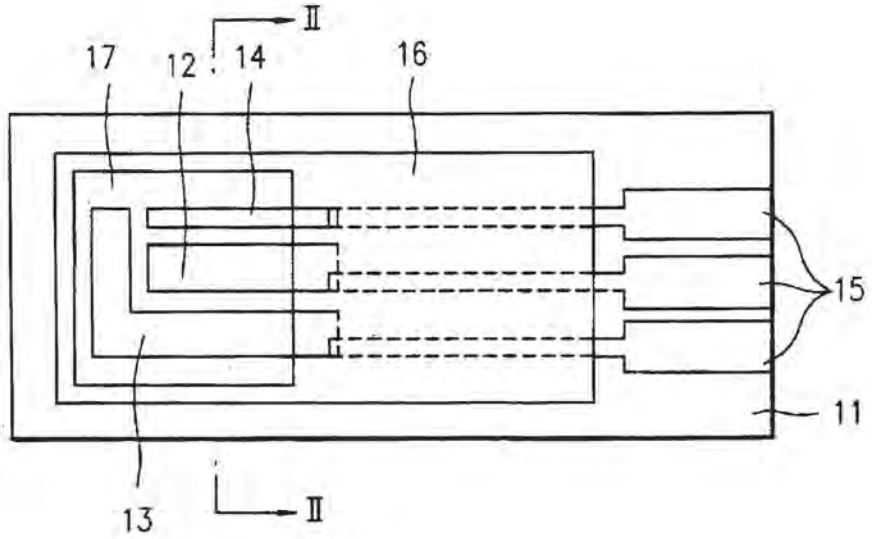


FIG.2
prior art

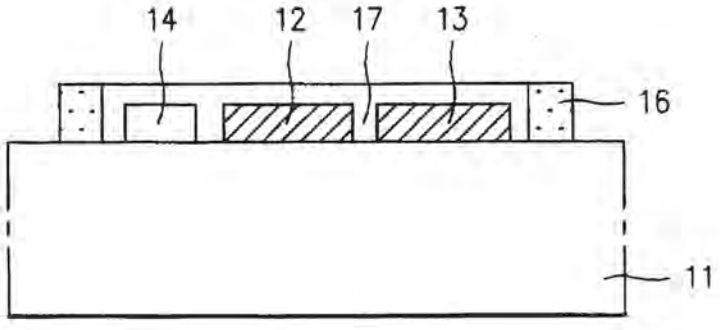


FIG.3

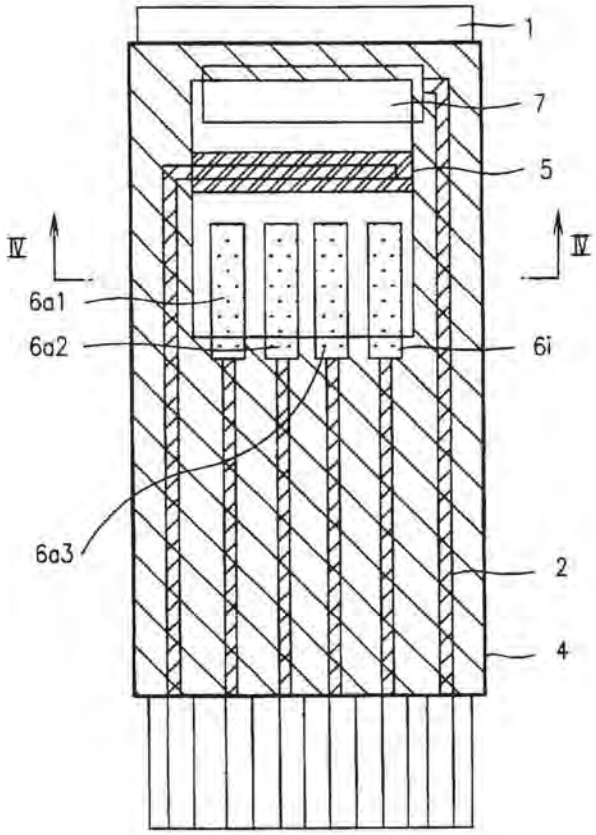


FIG.4

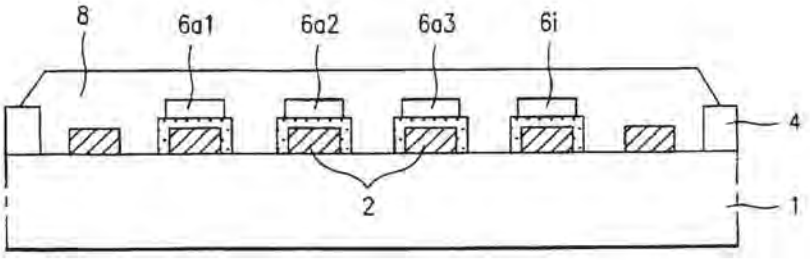
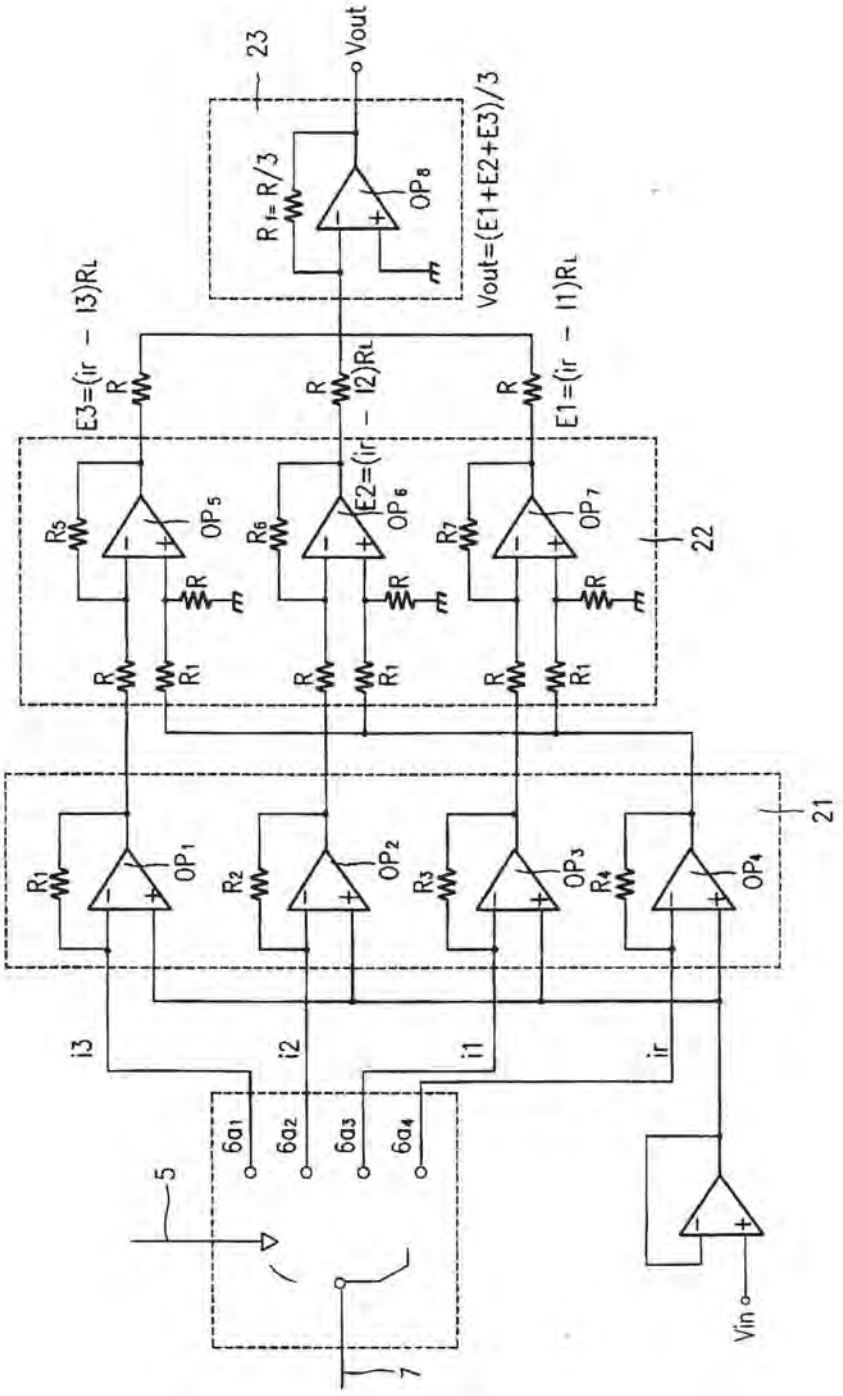
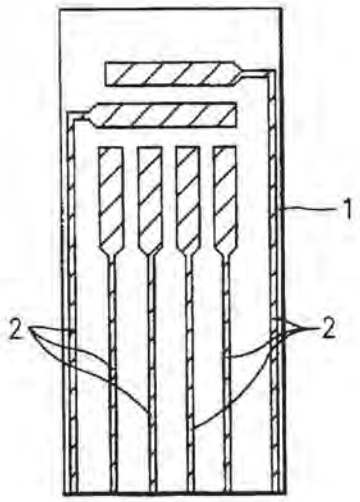


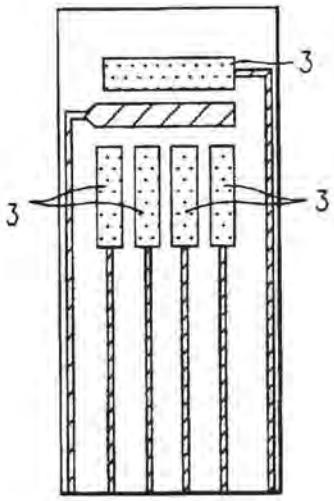
FIG.5



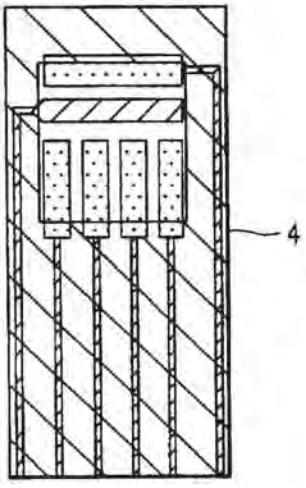
F I G.6a



F I G.6b



F I G.6c



F I G.6d

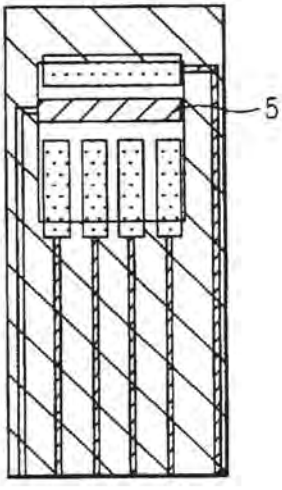


FIG.6e

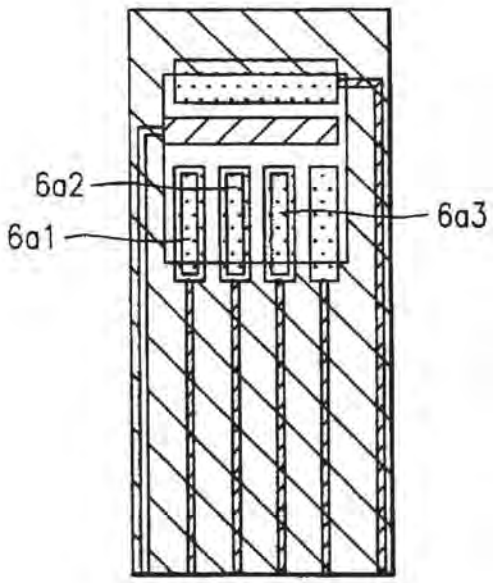


FIG.6f

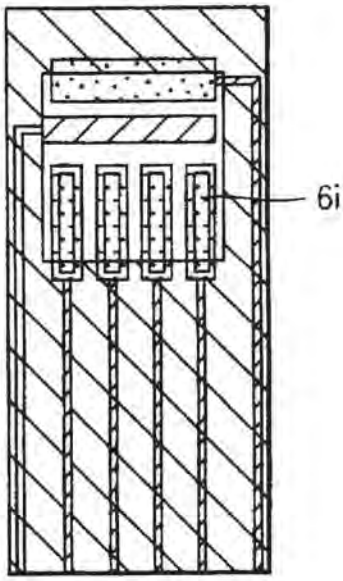


FIG.7

ethanol concentration (ppm)	responsive current(μA)	
	multi-electrode type	none multi-electrode type
21	1.550±0.045(2.90%)	1.590±0.083(5.23%)
167	4.340±0.118(2.73%)	4.440±0.224(5.05%)
665	6.570±0.166(2.90%)	6.430±0.26(4.12%)

$$*\text{relative error}\left(\frac{\text{standard deviation}}{\text{average}} * 100\right)$$

MULTI-ELECTRODE BIOSENSOR AND SYSTEM AND METHOD FOR MANUFACTURING SAME

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a biosensor.

2. Discussion of the Related Art

Generally, a biosensor for measuring a predetermined material includes a biomaterial that selectively reacts with the predetermined material. Such a biosensor has advantages over other physical or chemical sensors. However, due to the instability of biomaterials, the biosensor's reliability is reduced as measurements are repeated, thereby requiring frequent replacement of the sensing film.

Recently, with the introduction of thick-film device technology, mass production of low cost sensors has been achieved. Some sensors are now intended for one-time use and thus disposed after one measurement. One-time biosensors have taken the lead in development of biosensors.

Clinically, the accuracy of a measurement is important when trying to precisely measure a very small amount of a material. Unlike physical or chemical sensors, most biosensors cannot correct themselves after fabrication. Thus, to obtain measurements, sensors of one batch must have exactly the same characteristics. For instance, in the case of a biosensor using an enzyme, when hundreds of sensors are manufactured on a substrate using thick-film device fabrication technology, the respective enzyme sensing films must have exactly the same amount of enzyme and several cofactors. In addition, the relative molecular orientation of the enzymes and the cofactors must be the same.

In reality, these conditions are impossible to meet so that the calibration curve of any biosensor has a permissible error range. Among the products on the market, some have an error range of 10% or higher. A biosensor with an error range of 5–6% is regarded as a commercial success. However, in most cases, the acceptability of such error ranges significantly depends on the user's skills. The meaning of a measurement using an apparatus having an error range of 5–6% may depend on the measurement's peculiarity. For instance, in the case of a blood sugar measuring apparatus, a widely used piece of equipment, a user is interested in whether a measured value deviates is above or below a predetermined value (i.e., high or low blood sugar). Attention is not paid to its intermediate value or how much the measured value deviates from the predetermined value.

If sequential values are clinically important within a predetermined range, the error range available in the above cases cannot ensure its accuracy. In this case, the solution is to average several measurements with several sensors. This inconvenience may be accepted by hospitals but not by general users.

A conventional biosensor will be described with reference to the attached drawings. FIG. **1** is a plan view of a conventional biosensor. FIG. **2** is a sectional view of the conventional biosensor cut along line II—II of FIG. **1**.

The conventional biosensor has a working electrode **12**, a counter electrode **13**, and a reference electrode **14** all formed on an insulating substrate **11**. Here, working electrode **12** is formed at the center, counter electrode **13** and reference electrode **14** are formed on both sides of working electrode **12**, and counter electrode **13** is formed wider than reference electrode **14**.

For insulating substrate **11**, Al_2O_3 or a polymer such as poly Vinyl Chloride (PVC), Polyethylene Terephthalate, polyester, or Polyethylene may be used. For working electrode **12** and counter electrode **13**, a paste containing an electric conductor such as platinum (Pt) or carbon (C) may be printed.

For example, if Pt is used for working electrode **12** and counter electrode **13**, screen printing is performed on an 86×84 mm alumina substrate using a metal screen of 250 mesh. Then, the resultant structure is dried for ten minutes at 100° C. and fired at 1,250° C. For reference electrode **14**, silver (Ag) paste is printed and fired at **850°** C. Otherwise, Ag paste having AgCl may be printed.

The arrangement of working electrode **12**, counter electrode **13**, and reference electrode **14** does not affect their characteristics. But, their areas and distances between one another are important because they greatly affect the electrodes' signal magnitude and noise level.

Sequentially, Ag/Pt paste is printed and fired to form a connection pad **15**. Then, dielectric paste is printed and fired to form an insulating layer **16**. On the insulating layer **16** and on working electrode **12**, counter electrode **13** and reference electrode **14**, immobilized enzyme layer **17** is formed according to a material to be measured.

As an example, to manufacture an ethanol biosensor for measuring the concentration of ethanol, an enzyme solution is prepared in such a manner that 20 mg of alcohol dehydrogenase and 6.6 mg of NAD^+ (β-nicotinamide-adenine dinucleotide) are dissolved in 1 ml of 0.1M phosphate buffer. Then, 1 ml of solution is prepared in which gelatin is 10% (w/v) in 0.1M KCl solution. Here, 1 ml of the previously prepared enzyme solution is mixed at 25° C.

Next, 5 μl of the mixed enzyme solution are dropped on the electrodes of the insulating layer **16**, which is then dried to form immobilized enzyme layer **17** in which the enzyme and cofactors are fixed.

These conventional biosensors have the following drawbacks. As discussed above, the biosensors cannot correct themselves and have reduced reliability because of a single working electrode despite an error range permissible within a predetermined extent. For this reason, if sequential values are important clinically within a predetermined scope, a user inconveniently must average several measured values with the conventional biosensor.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to a multi-electrode biosensor that substantially obviates one or more of the problems due to limitations and disadvantages of the related art.

An object of the present invention is to provide a multi-electrode biosensor in which several working electrodes are formed on a single substrate using a technique of miniaturization and mass production of biosensors so that one measurement produces multiple signals in response to the same measured material. The signals are processed through circuits to determine the average, thereby obtaining a single measurement as accurate as the average of several measurements using different sensors.

Additional features and advantages of the invention will be set forth in the description which follows, and in part will be apparent from the description, or may be learned by practice of the invention. The objectives and other advantages of the invention will be realized and attained by the structure particularly pointed out in the written description and claims hereof as well as the appended drawings.

To achieve these and other advantages and in accordance with the purpose of the present invention, as embodied and broadly described, the multi-electrode biosensor of the

present invention comprises a substrate, a plurality of working electrodes formed on the substrate, a counter electrode formed on the substrate, and a reference electrode formed on the substrate.

To further achieve these and other advantages and in accordance with the purpose of the invention, as embodied and broadly described, the multi-electrode biosensor system of the present invention comprises a multi-electrode biosensor including a substrate, a plurality of working electrodes formed on the substrate, a counter electrode formed on the substrate, and a reference electrode formed on the substrate; and a processing circuit including an average summing portion for averaging signals from selected ones of the plurality of working electrodes.

To still further achieve these and other advantages and in accordance with the present invention, as embodied and broadly described, the method for manufacturing a multi-electrode biosensor of the present invention comprises the steps of forming a plurality of metal conducting paths on the substrate, forming a first base carbon electrode on a first selected one of the plurality of metal conducting paths to provide a counter electrode, forming at least second, third, and fourth base carbon electrodes on respective second, third, and fourth selected ones of the plurality of metal conducting paths, forming a reference electrode from a fifth selected one of the plurality of metal conducting paths, providing a bioactive material on at least the second and third base carbon electrodes to form active working electrodes, and providing a bioinactive material on the fourth base carbon electrode to form an inert working electrode.

In one aspect, the multi-electrode biosensor includes more than two active working electrodes for generating signals by reacting independently with the same material present in a sample, an inert working electrode for correcting a background signal, a counter electrode, and a reference electrode.

In another aspect, the method of fabricating a multi-electrode biosensor includes the steps of printing a metal conducting path on a substrate by a predetermined interval as many as four working electrodes, reference electrode, and counter electrode; thermally processing the substrate, printing a base carbon electrode at the end of the metal conducting paths corresponding to the working electrodes and reference electrode, and thermally processing the resultant structure; forming an insulating layer on the overall surface of the structure with opening a rectangular area of the insulating layer so that the ends of the metal conducting paths serving as the base carbon electrode and reference electrode are exposed; forming the reference electrode at the ends of the metal conducting paths; forming active working electrodes on the three base carbon electrodes corresponding to the working electrode; and forming an inert working electrode on the remaining base carbon electrode corresponding to the working electrode.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are included to provide a further understanding of the invention and are incorporated in and constitute a part of this specification, illustrate embodiments of the invention and together with the description serve to explain the principles of the invention. In the drawings:

FIG. **1** is a plan view of a conventional biosensor;

FIG. **2** is a sectional view of the conventional biosensor;

FIG. **3** is a plan view of one embodiment of a multi-electrode biosensor according to the present invention;

FIG. **4** is a sectional view of the multi-electrode biosensor of FIG. **3**;

FIG. **5** is a circuit diagram for use with the multi-electrode biosensor of FIG. **3**;

FIGS. **6***a*–**6***f* are plan views of the multi-electrode biosensor of FIG. **3** during respective manufacturing steps; and

FIG. **7** is a table comparing the reproducibility of the multi-electrode biosensor of FIG. **3** with that of the conventional biosensor when respective concentrations of ethanol are measured.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Reference will now be made in detail to the preferred embodiment of the present invention, an example of which is illustrated in the accompanying drawings.

Generally, the biosensor of the present invention includes a plurality of electrodes, which simultaneously generate a plurality of respective signals from a single measurement of a sample. The simultaneously generated signals are averaged by a processing circuit, such as a multi-channel potentiostat.

As shown in FIGS. **3** and **4**, one embodiment of the multi-electrode biosensor of the present invention comprises four working electrodes **6***a***1**, **6***a***2**, **6***a***3** and **6***i*, a reference electrode **5**, and a counter electrode **7**. Of the working electrodes, electrodes **6***a***1**, **6***a***2**, and **6***a***3** are active working electrodes and electrode **6***i* is an inert working electrode. A processing circuit for averaging the signals output from the multiple electrodes of the multi-electrode biosensor is shown in FIG. **5**.

As shown in FIG. **5**, the processing circuit comprises an amplifying portion **21** including amplifiers OP**1**, OP**2**, OP**3** and OP**4** and resistors R**1**, R**2**, R**3** and R**4**, which are arranged as shown to amplify the signals output from active working electrodes **6***a***1**, **6***a***2** and **6***a***3** and inert working electrode **6***i* by predetermined gains, a differential amplifying portion **22** including amplifiers OP**5**, OP**6** and OP**7** and resistors R**5**, R**6** and R**7**, which are arranged as shown to differentially amplify the amplified signals of active working electrodes **6***a***1**, **6***a***2** and **6***a***3** using the amplified signal of inert working electrode **6***i* as a reference signal, and an average summing portion **23** including an amplifier OP**8** and resistor Rf, which are arranged as shown to sum the signals output from differential amplifying portion **22** and divide the summed signal by the number of active working electrodes, i.e., three, to thereby output their average. Here, reference signal V_{in} of amplifying portion **21** operates the biosensor and serves to maintain a voltage between reference electrode **5** and the four working electrodes at V_{TN}.

A method of manufacturing the multi-electrode biosensor of FIGS. **3** and **4** will now be described.

As shown in FIG. **6***a*, silver conducting paths **2** are formed on a polyester substrate **1** for the four working electrodes, the reference electrode, and the counter electrode using thick film device technology.

As shown in FIG. **6***b*, the resultant substrate **1** is thermally processed for ten minutes at 110° C., base carbon electrodes **3** are printed at the ends of the silver conducting paths for the working electrodes and counter electrode, and the resultant structure is thermally processed. The base carbon electrode

printed on the end of the silver path for the counter electrode has no layer piled thereon.

As shown in FIG. **6***c*, an insulating layer **4** is formed on the surface of the resultant structure except on at least portions of the base carbon electrodes **3** and except on at least a portion of the end of the silver conducting path for the reference electrode. For example, the open area may be rectangular as shown.

As shown in FIG. **6***d*, the resultant structure is immersed in 100 mM of $FeCl_3$ so that Ag/AgCl is formed at the exposed end of the silver conducting path for the reference electrode to complete the reference electrode **5**.

As shown in FIG. **6***e*, as an ethanol biosensor manufacturing step, for example, 405 mg of alcohol dehydrogenase (ADH), 45 mg of NAD^+, 40 mg of DEAE-dextran, 400 mg of lactitol, and 1.28 g of carbon powder are put into a mortar with 4 ml of 2% hydroxyethyl cellulose. They are homogenized to form a bioactive paste which is printed on three of the base carbon electrodes to form active working electrodes **6***a***1**, **6***a***2**, and **6***a***3**.

As shown in FIG. **6***f*, a bioinactive paste, such as bovine serum albumin having the same amount of the ADH used in FIG. **6***e*, is printed on the remaining base carbon electrode to form inert working electrode **6***i*.

To complete the multi-electrode biosensor for measuring ethanol vapor, a 6% hydroxyethyl cellulose paste is printed on the resulting structure to form an outer layer **8** (FIG. **4**) to be used as a buffered electrolyte system.

FIG. **7** shows a table in which ethanol vapor is measured by the multi-electrode ethanol biosensor using the multi-channel potentiostat in order to examine its reproducibility. The results are compared with measurements using a conventional biosensor (non-multi-electrode type) having a working electrode, reference electrode, and counter electrode. As indicated in the table, the multi-electrode ethanol biosensor of the present invention has a smaller error range than that of the conventional non-multi-electrode biosensor. Therefore, the present invention yields excellent reproducibility.

As described above, in the present invention, several working sensors for generating a signal by reacting with a predetermined material are provided on a single sensor, thereby obtaining the effect of performing several independent measurements through a one-time measurement. This involves no requirement to average several measurements using respective sensors so that a user easily obtains a clinically important measurement value regardless of specialty or skill.

Therefore, the commercially useful scope of health self-diagnosing apparatuses for measuring only a value above or below a discontinuous value can expand to the clinical field which requires higher precision and continuous values become important. In addition, high reliability can be ensured in any precision measurement using a biosensor.

This invention can be employed in a thick-film biosensor using screen printing, a thin-film biosensor in which biomaterials, such as enzymes, antigens, antibodies, nucleic acids, and molecular receptors are fixed on the working electrodes, and in a biosensor having working electrodes with electrochemical, optical, and/or piezoelectric properties.

It will be apparent to those skilled in the art that various modifications and variations can be made in the multi-electrode biosensor and method for manufacturing same of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

What is claimed is:

1. A multi-electrode biosensor comprising:

a substrate;

a plurality of working electrodes formed on the substrate, the plurality of working electrodes including at least two active working electrodes and an inert working electrode, wherein the active working electrode includes a bioactive material and the inert working electrode is bioinactive;

a counter electrode formed on the substrate; and

a reference electrode formed on the substrate.

2. The multi-electrode biosensor according to claim **1**, wherein the biomaterial includes at least one of an enzyme, an antigen, an antibody, a nucleic acid, and a molecular receptor.

3. The multi-electrode biosensor according to claim **1**, wherein the biomaterial has at least one of electrochemical, optical, and piezoelectric properties.

4. A multi-electrode biosensor system comprising:

a multi-electrode biosensor including;

a substrate,

a plurality of working electrodes formed on the substrate, the plurality of working electrodes including at least two active working electrodes and an inert working electrode, wherein the active working electrode includes a bioactive material and the inert working electrode is bioinactive,

a counter electrode formed on the substrate, and

a reference electrode formed on the substrate; and

a processing circuit including an average summing portion for averaging signals from selected ones of the plurality of working electrodes.

5. The multi-electrode biosensor system according to claim **4**, wherein the plurality of working electrodes include at least two active working electrodes, and wherein the average summing portion averages signals from the active working electrodes.

6. The multi-electrode biosensor system according to claim **4**, wherein the average summing portion includes an amplifier and resistor.

7. The multi-electrode biosensor system according to claim **4**, wherein the processing circuit further includes an amplifying portion for amplifying signals from each of the plurality of working electrodes.

8. The multi-electrode biosensor system according to claim **7**, wherein the amplifying portion includes, for each of the plurality of working electrodes, an amplifier and a resistor.

9. The multi-electrode biosensor system according to claim **7**, wherein the processing circuit further includes a differential amplifying portion for differentially amplifying selected ones of the signals amplified by the amplifying portion.

10. The multi-electrode biosensor system according to claim **9**, wherein the plurality of working electrodes include at least two active working electrodes and an inert working electrode, wherein the amplifying portion amplifies signals from the at least two active working electrodes and the inert electrode, and wherein the differential amplifying portion differentially amplifies the amplified signals from the active working electrodes using the amplified signal from the inert working electrode as a reference signal.

11. A method for manufacturing a multi-electrode biosensor on a substrate comprising the steps of:

forming a plurality of metal conducting paths on the substrate;

forming a first base carbon electrode on a first selected one of the plurality of metal conducting paths to provide a counter electrode;

forming at least second, third, and fourth base carbon electrodes on respective second, third, and fourth selected ones of the plurality of metal conducting paths;

forming a reference electrode from a fifth selected one of the plurality of metal conducting paths;

providing a bioactive material on at least the second and third base carbon electrodes to form active working electrodes; and

providing a bioinactive material on the fourth base carbon electrode to form an inert working electrode.

12. The method according to claim 11, further comprising the step of providing an insulating layer except on at least portions of the at least first, second, third, and fourth base carbon electrodes and except on at least a portion of the fifth selected one of the plurality of metal conducting paths.

13. The method according to claim 11, wherein the step of forming the reference electrode includes the step of forming Ag/AgCl on the fifth selected one of the plurality of metal conducting paths.

14. The method according to claim 11, further comprising the step of providing an outer layer to be used as a buffered electrolyte system.

15. The method according to claim 11, wherein the step of providing the bioactive material on at least the second and third base carbon electrodes includes the step of applying a bioactive paste on at least the second and third base carbon electrodes, and wherein the step of providing the bioinactive material on the fourth base carbon electrode includes the step of applying a bioinactive paste on the fourth base carbon electrode.

* * * * *

Exhibit 14

US006540891B1

(12) **United States Patent**
Stewart et al.

(10) **Patent No.: US 6,540,891 B1**
(45) **Date of Patent: Apr. 1, 2003**

(54) **TEST STRIP**

(75) Inventors: **Alan Andrew Stewart**, Berkshire (GB); **Steven Scott**, Andover, MA (US)

(73) Assignee: **Abbott Laboratories**, Abbott Park, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/674,891**

(22) PCT Filed: **May 6, 1999**

(86) PCT No.: **PCT/GB99/01424**

§ 371 (c)(1),
(2), (4) Date: **Jan. 11, 2001**

(87) PCT Pub. No.: **WO99/58709**

PCT Pub. Date: **Nov. 18, 1999**

(30) **Foreign Application Priority Data**

May 8, 1998 (GB) 9809963

(51) **Int. Cl.**[7] **G01N 27/327**

(52) **U.S. Cl.** **204/403.14**; 204/403.01; 204/403.15

(58) **Field of Search** 204/403.01, 403.06, 204/403.1, 403.11, 403.14, 403.15

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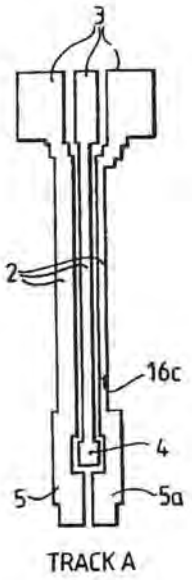
Primary Examiner—T. Tung
Assistant Examiner—Alex Noguerola
(74) *Attorney, Agent, or Firm*—David L. Weinstein

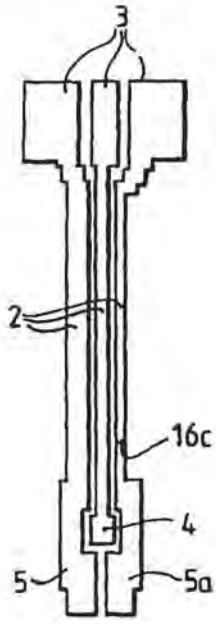
(57) **ABSTRACT**

An improved disposable test strip for use in amperometric measurement of analytes in complex liquid media, such as blood, which has three or more electrodes has been developed. This strip is designed so that different electrical potentials can be maintained between a common pseudo reference/counter electrode and each of the other electrodes upon the imposition of a common potential by an amperometric meter. This capability is imparted to the test strip by providing different circuit resistances for each of these other electrodes. The test strip can be utilized to measure a single analyte such as glucose with a background compensation via a "dummy" electrode or it can be used to measure the concentration of multiple analytes.

22 Claims, 3 Drawing Sheets

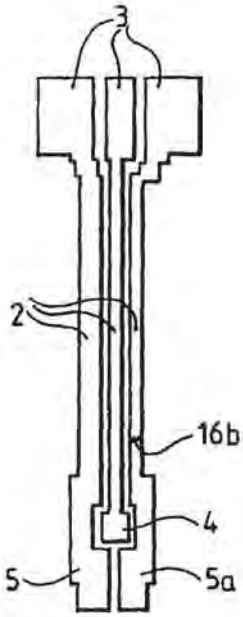


TRACK A



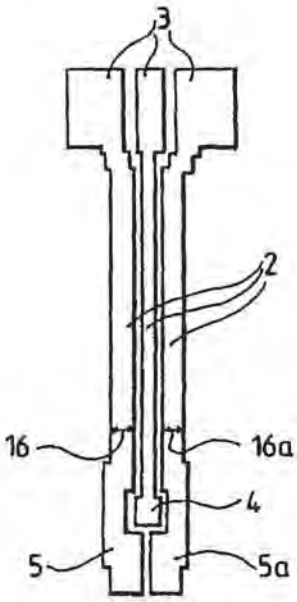
TRACK A

Fig.1a.



TRACK B

Fig.1b.



CONTROL

Fig.2.

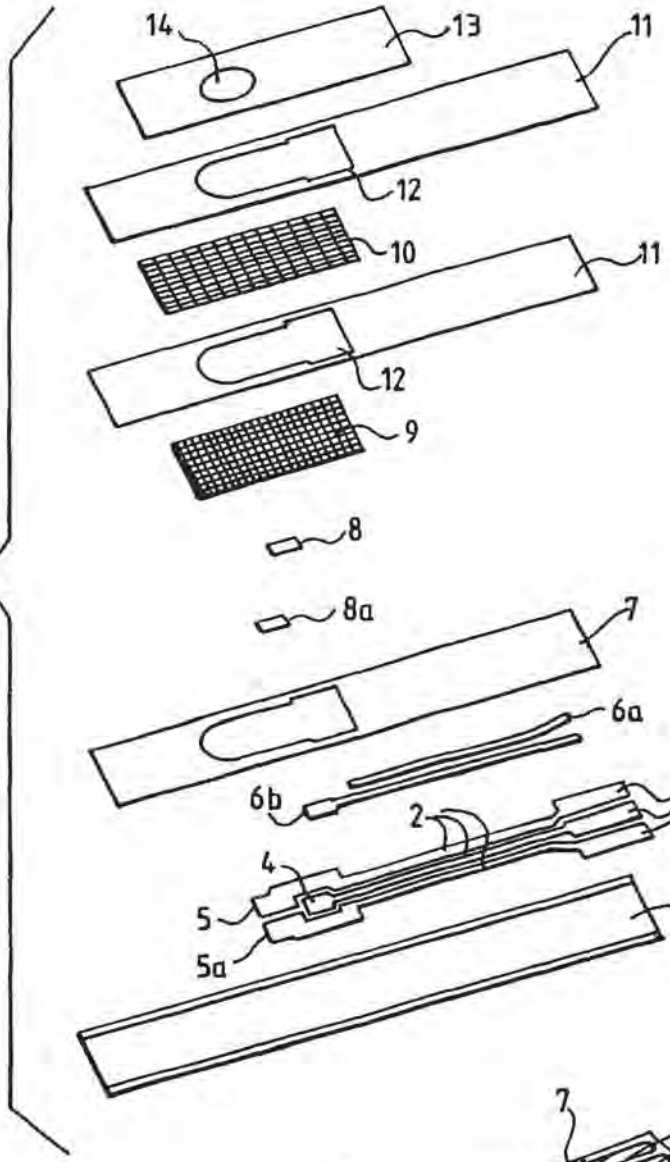


Fig. 3.

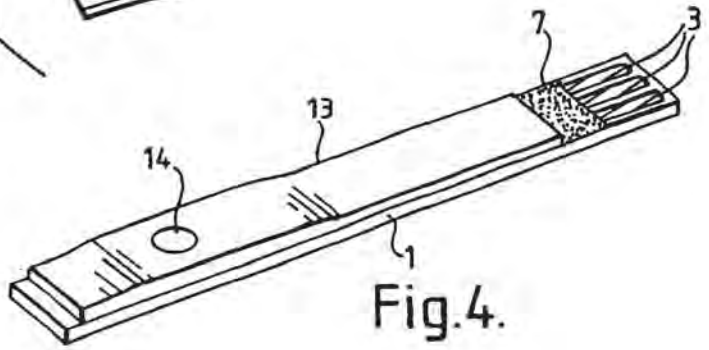


Fig. 4.

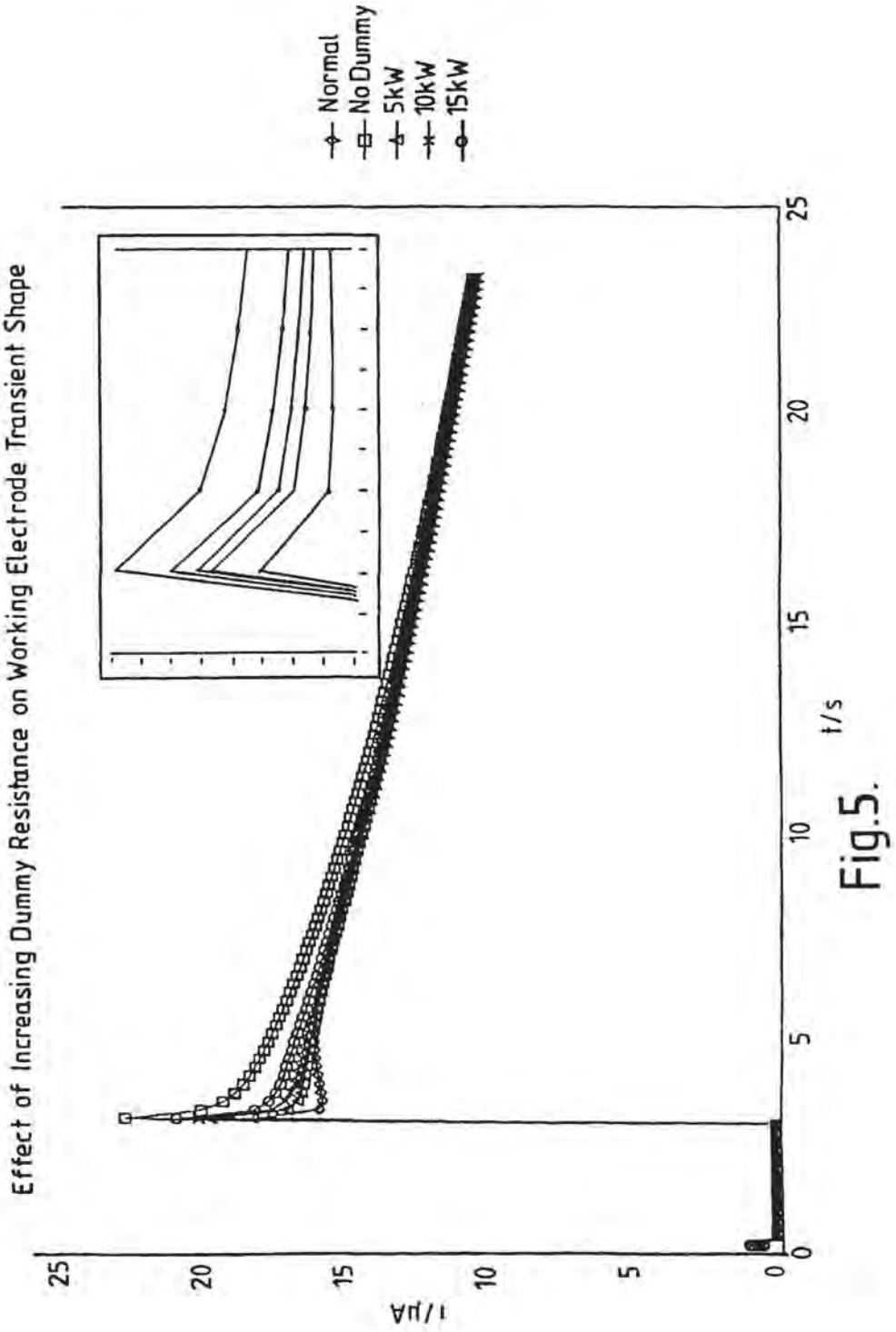

Normal
No Dummy
5kW
10kW
15kW
Effect of Increasing Dummy Resistance on Working Electrode Transient Shape
i/μA
t/s
0
5
10
15
20
25

Fig.5.

TEST STRIP

The measurement of analytes such as glucose in complex liquid media such as human blood by amperometric methods using disposable test strips has become widely used and is currently employed in a number of commercial products. In certain configurations it is advantageous to improve the signal to noise ratio by employing a three electrode system in which one electrode serves as a pseudo reference/counter electrode to establish a reference potential. Typically this is a silver/silver chloride electrode. A second, working electrode is coated with an enzyme which promotes an oxidation or a reduction reaction with the intended analyte and a mediator which transfers electrons between the enzyme and the electrode. The third "dummy" electrode is coated with the mediator but not the enzyme and it provides a measure of the current which arises from other than the oxidation reduction reaction involving the target analyte. An example of such a system is described in U.S. Pat. No. 5,628,980 to Carter, et al. (incorporated by reference herein) and is utilized in the MediSense QID glucose meter.

The three electrode system provides a good way to isolate the current which arises from the oxidation reduction reaction involving the target s analyte such as glucose but it also imposes a higher current load on the pseudo reference/counter electrode. In some testing environments such as glucose meters used by diabetics in their homes it is impractical or impossible to pretreat the samples to remove possible interferants. Thus with home use glucose meters the diabetic simply applies a sample of whole blood. Whole blood typically contains a number of electrochemically active species whose concentration may vary from person to person or even from sample to sample from the same individual. The dummy electrode provides a measure of current arising from the presence of these interferants thus allowing a normalization which removes their contribution to the current measured at the working electrode. However, in such a three electrode configuration the current seen by the pseudo reference/counter electrode includes contributions from both the working electrode and the dummy electrode. Thus in some cases the pseudo reference/counter electrode sees a significantly greater current than it would in a two electrode configuration.

The pseudo reference/counter electrode in such a configuration is, in act, serving two roles which can be inconsistent if the current it sees becomes too great. It serves, on the one hand, to provide a constant half-cell potential, i.e. a reference potential and, on the other hand, it also serves as a counter electrode balancing the electron transfer occurring at the working and dummy electrodes. For instance, in a typical glucose meter,mediator is becoming oxidized at the working and dummy electrodes so a reduction reaction needs to occur at the pseudo reference/counter electrode to balance the electron transfer. With the typical Ag/AgCl pseudo reference/counter electrode this involves the reduction of silver ions thus consuming (or reducing) silver chloride. If too much silver chloride is consumed the pseudo reference/counter electrode can no longer serve its function of providing a source of constant half-cell potential. In other words, the potential difference between the two electrode reactions such as the oxidation of a mediator at the working electrode and the reduction of silver at the pseudo reference/counter electrode will actually shift as the reaction proceeds.

One approach is to redesign the pseudo reference/counter electrode to handle higher current loads without displaying a significant shift in half-cell potential. This would normally mean increasing the size or silver concentration of the pseudo reference/counter electrode relative to the working and dummy electrodes. It is difficult to further reduce the size of the working electrode because its size has already been minimized. It is limited by the economically acceptable procedures for reproducibly manufacturing millions of such disposable test strips. On the other hand, increasing the size or silver concentration of the pseudo reference/counter electrode would significantly increase the cost of such three electrode disposable strips because silver is the most expensive material used in the construction of such strips.

Therefore, there is a need for three electrode disposable test strips for use in amperometric systems whose cost is comparable to two electrode test strips and yet have pseudo reference/counter electrodes with about the same stability as in the two electrode test strips.

It has been discovered that the current load on the pseudo reference/counter counter electrode in a disposable test strip for use in amperometric measurements with a three electrode system can be decreased and therefore its half cell potential better stabilized by increasing the resistance of the dummy electrode. This allows three electrode test strips to give better performance without changing the operating characteristics of the meters in which they are used.

Increasing the resistance of the dummy electrode not only reduces the total current passing through the pseudo reference/counter electrode but it also changes the potential at the dummy electrode's interface with the sample. Thus it is possible to have a three electrode system which can simultaneously measure the concentration of two analytes. The effective potential at the "dummy" electrode with the higher total resistance can be adjusted to be too low to effect an oxidation reduction reaction indicative of the concentration of one of the two target analytes.

It is preferred to have the resistance of the dummy electrode be at least 1000 ohms greater than that of the working electrode and it is especially preferred that the resistance differential be at least about 4000 ohms.

It is also preferred that the resistance of the dummy electrode be increased by putting a resistance in series with the active electrode surface of this electrode. Thus both the area and nature of the active surface of the dummy electrode are kept similar or identical to that of the working electrode. This can readily be achieved by increasing the resistance of the conductive track which connects the active electrode surface to the meter which applies the potential and measures the resulting current. In the typical disposable strip for amperometric analyte measurement three electrode surfaces are present on one end of an elongated flat strip and three contact pads, one for each of the electrode surfaces, are present on the other end of the strip. Each electrode surface is connected to its contact pad by a conductive track. The contact pads serve as the means to establish electrical contact between the strip and the meter which applies the potential and measures the resultant current. The conductive tracks are typically covered by an insulating layer to prevent any short circuits between them.

It is particularly preferred to increase the resistance of the conductive track of the dummy electrode by narrowing its width. If this conductive track is made of the same material as the working electrode's conductive track and has about the same thickness as the conductive track of the working electrode it will have a higher resistance. Such a mechanism of increasing resistance is particularly easy to implement in mass manufacturing.

An example of the present invention will be described in accordance with the accompanying drawings, in which:

FIGS. 1*a* and 1*b* are schematic diagrams depicting the conductive layers of electrodes of disposable test strips

having dummy/second working electrodes with narrowed conductive layers;

FIG. **2** is a schematic diagram depicting the conductive layers of electrodes of a control disposable test strip;

FIG. **3** is an exploded view of a disposable test strip;

FIG. **4** is a perspective view of the assembled strip of FIG. **3**; and

FIG. **5** is a series of plots of current in microamps versus time in seconds for a working electrode subjected to an initial potential of 400 milliVolts in the presence of a glucose containing sample for various dummy electrode configurations.

The three electrode disposable test strip for the amperometric measurement of analytes in complex liquid media is optimized to improve the signal to noise ratio without imposing an excessive current load on the reference/counter electrode by increasing the resistance of the dummy electrode, i.e. the electrode which carries the electrochemical mediator also utilized at the working electrode but which has no enzyme or other reactant selected to engage the analyte in an oxidation reduction reaction. A typical environment for the application of this concept is the three electrode test strip described in U.S. Pat. No. 5,628,890 for the determination of glucose in whole blood samples.

Such a test strip is typically constructed of an elongated strip of a rigid electrically non-conducting material such as plastic. Suitable plastics include PVC, polycarbonate or polyester. Three conductive tracks are laid on this strip so as to establish independent conductive paths from one end to the other. Each track terminates at the end adapted to be proximate to the meter used to apply electrical potential and measure the resulting currents with a contact pad that interfaces with the meter. At the distal end of the strip each track terminates in an electrode adapted to contact the complex liquid medium which carries the analyte to be measured. A typical medium is whole human blood and a typical analyte is glucose.

The working electrode is a pad which is coated with both a substance designed to engage the target analyte in an oxidation-reduction reaction and a mediator adapted to transfer electrons between the pad and the oxidation reduction reaction. A typical substance is an enzyme adapted to promote the oxidation of glucose, such as glucose oxidase, and the mediator is a compound which readily transfers electrons from the oxidation reduction reaction to the pad, such as a ferrocene derivative.

The "dummy" electrode is a pad which preferably has the same surface area as the working electrode and is coated with the same amount of the same mediator as the working electrode. The concept is to provide an environment in the immediate vicinity of this "dummy" electrode which is essentially identical to that of the working electrode except for the substance, typically an enzyme, adapted to react with the target analyte. Then the spurious electrochemical reactions which might occur at the working electrode giving rise to noise are just as likely to occur at the "dummy" electrode. Thus the signal arising from such spurious reactions can be determined by measurement at the "dummy" electrode and subtracted from the total signal measured at the working electrode. This provides an improved signal to noise ratio.

The pseudo reference/counter electrode is a pad with a material such as silver/silver chloride which has both the oxidized and reduced form of a species to provide an essentially constant half-cell potential. So long as the relative proportions of the reduced and oxidized form of this species such as silver and silver chloride are not substantially changed the half-cell potential of this electrochemical couple will remain relatively constant. This facilitates being able to maintain a known constant oxidation or reduction potential at the working electrode. This allows a production batch of disposable test strips to have a common calibration.

In the typical situation the disposable strips are utilized with a meter which functions to correlate the amount of current observed upon the application of an external potential to the contact pads of the disposable strip to the amount of analyte present. This meter is designed to assume certain electrical characteristics will be observed upon the application of this external potential. One such assumption is that the amount of current observed will decrease monotonically with time. If the current does not decay in the expected manner the meter is programmed to abort the test. If the half-cell potential of the pseudo reference/counter electrode such as a silver/silver chloride electrode shifts the current characteristics may indeed fail to meet the expectations programmed into the meter causing an aborted test.

For example the half-cell potential of the silver/silver chloride electrode will shift if the proportion of silver to silver chloride is changed. As current flows through this electrode silver is either reduced or oxidized, depending on the nature of the reaction occurring at the working electrode In the typical meter for sensing glucose concentration glucose is oxidized at the working electrode reducing the mediator. The mediator then transfers the electron or electrons it has gained in this reduction reaction to its electrode pad. These electrons are then taken up at the pseudo reference/counter electrode. In the typical case this is a silver/silver chloride electrode and the electrons are taken up by the reduction of silver ions transforming silver chloride to silver metal.

If a sufficient amount of current passes through such a pseudo reference/counter electrode the proportion of silver to silver chloride will change enough to cause a noticeable change in the half-cell potential of this electrode. If this change becomes large enough the current at the working electrode may no longer decay monotonically. This in turn will cause the meter to sense an error condition and abort the test.

The current at the working electrode arises from the oxidation reduction reaction involving the target analyte and the subsequent transfer of electrons by the mediator. In the typical glucose meter glucose is oxidized by glucose oxidase and the mediator, for instance a ferrocene derivative, then transfers the electrons liberated by the oxidation of the glucose to its electrode pad. In detail the glucose oxidase becomes reduced by oxidizing the glucose in the sample which is exposed to the disposable test strip and then is reoxidized by reducing the mediator. The mediator in turn becomes reoxidized by transferring electrons through its electrode pad to the circuit with the pseudo reference/counter electrode. Normally the current arising from this transfer decays monotonically in accordance with the Cottrell equation as the mediator in reasonable diffusion distance to the electrode pad which was reduced by reaction with glucose oxidase is reoxidized. However, this behavior is dependent upon the potential at the working electrode being held at or above a certain potential relative to the pseudo reference/counter electrode. If the potential at this pseudo reference/counter electrode shifts, the behavior at the working electrode may no longer follow this pattern.

The disposable strips are typically designed so that the pseudo reference/counter electrode does not undergo such a potential shift. For instance this electrode can be made large enough that the current generated by the analyte concentrations typically encountered does not consume enough silver ions to cause such a shift.

The use of a third, "dummy" electrode, however, imposes an additional current load on the pseudo reference/counter electrode. In the typical glucose meter where an oxidation reaction occurs at the working electrode, the reduction reaction occurring at the pseudo reference/counter electrode must balance not only the oxidation reaction at the working electrode but also any oxidation reaction occurring at the "dummy" electrode. This additional burden may be sufficient to shift the half-cell potential of the pseudo reference/counter electrode out of its design range.

This is a particular problem in glucose meters which utilize an initially reduced mediator such as a ferrocene derivative. In such a meter there is an initial high current load as the mediator is oxidized at both the working and "dummy" electrodes. If there is also a high level of glucose in the sample being tested, there will also be a fairly high current load from the reoxidation of mediator initially reduced as a result of the oxidation of the glucose. The combined current load has a tendency to adversely effect the half-cell potential of the pseudo reference/counter electrode.

The total current load on the pseudo reference/counter electrode can be reduced by increasing the resistance in the overall circuit. However, it is impractical to change the resistance in the circuit involving the working electrode. The meters used with the disposable test strips of present concern are calibrated to correlate the level of current in the working electrode circuit after sometime period or over some fixed time interval after exposure of the test strip to the sample to the concentration of target analyte. Then the meters are distributed to a large number of users who expect to use the meters with the disposable test strips for a number of years. Thus it is impractical to make any change in such test strips which would require a corresponding change in the meter with which they are used.

It has, however, been found that the resistance in the "dummy" electrode circuit can be increased without adversely effecting the interaction between the disposable test strip and its meter. The function of the "dummy" electrode is to allow subtraction from the total signal or current at the working electrode of that portion attributable to superious oxidation-reduction reactions with species in the complex liquid medium other than the target analyte. This subtraction is only of concern at the time or over the interval during which the current at the working electrode is measured for correlation to the analyte concentration. Typically such measurements are made after the resistance of the overall system is comparatively high after most of the oxidation at the working electrode has already occurred. It has been discovered that at this point the difference in electrochemical environments at the working and "dummy" electrodes is insufficient to adversely effect the function of the dummy electrode.

The relative difference in electrochemical environment between the working electrode and a "dummy" electrode with added resistance does tend to decrease as a test cycle proceeds. As the mediator subject to reoxidation at the working electrode decreases the effective resistance in the working electrode circuit increases, i.e. there are few species to support electron transfer. Thus although there will always be a fixed difference in resistance between the working and "dummy" electrodes circuits the percentage difference will decrease as the effective resistance in the working electrode circuit increases.

In an alternative embodiment, the three electrode arrangement is used to simultaneously measure the concentration of two analytes. In this case there are two working electrodes and one pseudo reference/counter electrode. The first working electrode is designed to operate with a first substance that engages one of the target analytes in an oxidation reduction reaction at a relatively low potential. The second working electrode is designed to operate with a second substance that engages the other target analyte in an oxidation reduction reaction only at a higher potential. For ease in manufacturing both working electrodes are typically coated with is both substances and appropriate mediators. However, the test strip is designed so that the second substance which is coated on the first working electrode remains inactive. In particular, the electrical resistance in the circuit path from the contact pad connected to the first working electrode through the first working electrode is significantly greatly than the electrical resistance in the circuit path from the contact pad connected to the second working electrode through the working electrode. Thus when a certain electrical potential is applied to the contact pads of both electrodes relative to the pseudo reference/counter electrode, the effective potential at the first working electrode is less than that at the second working electrode, some of the potential drop having been expended traversing the higher circuit resistance.

The two analyte embodiment is applied to the simultaneous measurement of ketones and glucose by utilizing an enzyme mediator system for the ketones which operates at +200 mV and an enzyme mediator system for the glucose which operates at +400 mv. In particular, hydroxy butyrate dehydrogenase (HBDH) with a nicotinamide adenine dinucleotide (NADH) cofactor and a 1,10-phenanthroline quinone (1,10 PQ) mediator is used for the ketones and glucose oxidase with a ferrocene derivative mediator is used for the glucose.

The low operating potential of the HBDH/NADH/1, 10 PQ system is a significant advantage for an analyte like ketones which has a limited linear response range. In the case of ketones a linear response is typically expected only over a range of between about 0 and 8 milli Molar. By operating at a low potential interference from other species which might undergo an oxidation reduction reaction at a higher potential is avoided. In other words, the probability that another chemical species in the sample might become oxidized and deliver electrons to the first working electrode thus making a superious contribution to the current sensed at this electrode is minimized.

The potential at the first working electrode is adjusted so that upon the application of a 400 mV potential between the second working electrode and the reference/counter electrode the potential between this first working electrode and the reference/counter electrode is 200 mV. This adjustment is effected by increasing the resistance of the circuit path involving this electrode relative to that involving the second working electrode by an appropriate amount in one of the ways discussed hereinabove.

The current sensed at the first working electrode is the result of the oxidation of ketones while that sensed at the second working electrode is the result of the oxidation of both ketones and glucose. The amount of current at each electrode can then be employed in a simple simultaneous equation to determine the concentration of ketones and glucose in the same sample.

It is, of course, possible to coat only the first working electrode with the ketones sensitive chemistry and to coat only the second working electrode with only the glucose sensitive chemistry. This would be expected to result in higher manufacturing costs. Typically the disposable test strips are manufactured by a series of printing steps so that applying different chemistries to each working electrode would require additional printing steps.

A particular application of the concept of a high resistance dummy electrode to the measurement of glucose is illustrated in FIGS. **1** through **5**. In the strips illustrated, the working electrode and the dummy electrode each had a surface area of 6.612 square millimeters while the pseudo reference/counter electrode had a surface area of 4.18 square millimeters. The conductive tracks which connect the contact pads to the electrode pads are in most cases 0.801 millimeters. In two cases the conductive track associated with the dummy electrode was narrowed to 0.510 millimeters and 0.305 millimeters, as illustrated in FIGS. **1***a* and **1***b*.

Two different conductive layer prints are illustrated in FIGS. **1***a* (Track A) and **1***b* (Track B). A control conductive layer print, in which the working and dummy electrodes have the same resistance, is shown in FIG. **2**. Referring to FIGS. **1***a*, **1***b* and **2**, the electrode configuration on the sensor strips has three printed layers of electrically conducting carbon ink **2**. The layers define the positions of the pseudo reference/counter electrode **4**, the working electrode **5**, the dummy electrode **5***a* and electrical contacts **3**.

Referring to FIG. **2**, working electrode **5** has a track width **16** that is equal to track width **16***a* of dummy electrode **5***a*. Equal track widths **16** and **16***a* give the working electrode and dummy electrode equal resistances. Referring to FIGS. **1***a* and **1***b*, track widths **16***b* and **16***c* of dummy electrode **5***a* are narrower than track width **16***a* of the control in FIG. **2**. The conductive layer of dummy electrode **5***a* is narrowed in order to increase the resistance of the dummy electrode relative to the working electrode resistance. Track width **16***c* is smaller than track width **16***b*. Thus, the resistance of dummy electrode **5***a* in Track A (FIG. **1***a*) is greater than the resistance of dummy electrode **5***a* in Track B (FIG. **1***b*).

The composition of the conductive layers can also affect the resistance of the electrodes. Generally, the conductive layers of the electrodes are printed at the same time with the same ink. The conductive layers can be printed with a low carbon-content ink or a high carbon-content ink. Low carbon-content had a carbon content of between 30 and 31 weight percent and a resin content of between 7 and 9 weight percent. The high carbon-content ink has a carbon content of between 42 and 45 weight percent, and a resin content of between 7 and 9 weight percent.

A suitable electrode sensor strip is illustrated in FIGS. **3** and **4**. Referring to FIGS. **3** and **4**, the electrode support **1**, an elongated strip of plastic material (e.g., PVC, polycarbonate, or polyester) supports three printed tracks of electrically conducting carbon ink **2**. These printed tracks define the positions of the pseudo reference/counter electrode **4**, of the working electrode **5**, of the dummy electrode **5***a*, and of the electrical contacts **3** that are inserted into an appropriate measurement device (not shown). The conductive layer of dummy electrode **5***a* is narrowed in order to increase the resistance of the dummy electrode relative to the working electrode.

The elongated portions of the conductive tracks are each overlaid with silver/silver chloride particle tracks **6***a* and **6***b*, with the enlarged exposed area overlying **4**, and **6***b* and **4** together forming the pseudo reference/counter electrode. The conductive track or layer for dummy electrode **5***a* is not overlaid with silver/silver chloride. This further increases the resistance of the dummy electrode. The conductive tracks are further overlaid with a layer of hydrophobic electrically insulating material **7** that leaves exposed only the positions of the pseudo reference/counter electrode, the working electrode and the dummy electrode, and the contact areas. This hydrophobic insulating material prevents short circuits. Because this insulating material is hydrophobic, it can confine the sample to the exposed electrodes. A preferred insulating material is available as POLYPLAST□ (Sericol Ltd., Broadstairs, Kent, UK).

The working electrode working area **8** is formed from an ink that includes a mixture of an enzyme, a mediator, and a conductive material. The dummy electrode working area is formed from ink that includes a mixture of a mediator and a conductive material without enzyme. The respective inks are applied to the positions **5** and **5***a* of carbon tracks **2** as discrete areas of fixed length. Alternatively, instead of an enzyme, electrode layer **8** can contain a substrate catalytically reactive with an enzyme to be assayed. The conductive material in a preferred embodiment includes particulate carbon having the redox mediator adsorbed thereon.

A printing ink is formed as an aqueous solution of the conductor and adsorbed redox mediator. For the working electrode, it also includes the enzyme or, alternatively, a substrate. When the analyte to be measured is blood glucose, the enzyme is preferably glucose oxidase, and the redox mediator is a ferrocene derivative.

The ink can be screen printed. The ink can include a polysaccharide (e.g., a guar gum or an alginate), a hydrolyzed gelatin, an enzyme stabilizer (e.g., glutamate or trehalose), a film-forming polymer (e.g., a polyvinyl alcohol), a conductive filler (e.g., carbon), a redox mediator (e.g., ferrocene or a ferrocene derivative), a defoaming agent, a buffer, and an enzyme or a substrate. The ink printed on a dummy electrode lacks the enzyme or the substrate.

The pseudo reference/counter electrode **6***b* is situated relative to the working electrode **8** and dummy electrode **8***a* such that it is in a non-ideal position for efficient electrochemical function. The electrodes are arranged not to minimize the effect of the resistance of the solution on the overall resistance of the circuit (as is conventional). Positioning the pseudo reference/counter electrode downstream of the working electrode has the advantage of preventing completion of a circuit (and thus detection of a response) before the working electrode has been completely covered by sample.

The electrode area is overlaid by a fine grade mesh **9**. This mesh protects the printed components from physical damage. It also helps the sample to wet the pseudo reference/counter electrode and working electrode by reducing the surface tension of the sample, thereby allowing it to spread evenly over the electrodes. Preferably, this mesh layer extends over the whole length of the sample path, between and including, the application point and the electrode area. Preferably, this mesh is constructed of finely woven nylon strands. Alternatively, any woven or non-woven material can be used, provided it does not occlude the surface of the electrode such that normal diffusion is obstructed. The thickness of the mesh is selected so that the resulting sample depth is sufficiently small to produce a high solution resistance. Preferably, the fabric is not more than 70 μm in thickness. Preferably the mesh has a percent open area of about 40 to about 45%, a mesh count of about 95 to about 115 per cm, a fiber diameter of about 20 to about 40 μm, and a thickness of from about 40 to about 60 μm. A suitable mesh is NY64 HC mesh, available from Sefar (formerly ZBF), CH-8803, Ruschlikon, Switzerland.

The mesh can be surfactant coated. This is only necessary if the mesh material itself is hydrophobic (for example, nylon or polyester). If a hydrophilic mesh is used, the surfactant coating can be omitted. Any suitable surfactant can be used to coat the mesh, so long as it allows adequate even spreading of the sample. A preferred surfactant is FC 170C FLUORAD□ fluorochemical surfactant (3M, St. Paul,

Minn.). FLUORAD™ is a solution of a fluoroaliphatic oxyethylene adduct, lower polyethylene glycols, 1,4-dioxane, and water. A preferred surfactant loading for most applications is from about 15–20 μg/mg of mesh. The preferred surfactant loading will vary depending on the type of mesh and surfactant used and the sample to be analyzed. It can be determined empirically by observing flow of the sample through the mesh with different levels of surfactant.

A second layer of coarser surfactant coated mesh **10** is applied over the first mesh. This second mesh layer controls the influx of the sample as it travels from the application point toward the pseudo reference/counter and working electrode areas by providing a space into which the displaced air within the sample transfer path can move as the sample moves preferentially along the lower fine grade mesh layer **9** and partially in mesh layer **10**. The spacing of the larger fibers of the secondary mesh layer, perpendicular to the direction of sample flow, helps to control the sample flow by presenting repeated physical barriers to the movement of the sample as it travels through the transfer path. The regular pattern of the mesh fibers ensures that the sample progresses in stages and that only samples with sufficient volume to generate an accurate response are able to pass all the way along the pathway and reach the pseudo reference/counter electrode.

Preferably, mesh **10** is of a woven construction, so that it presents a regular repeating pattern of mesh fibers both perpendicular to and parallel to the longest aspect of the strip. Generally, the second mesh layer should be substantially thicker than the first mesh, with larger diameter mesh fibers and larger apertures between them. The larger mesh preferably has a thickness of from 100 to 1000 μm, with a thickness of from 100 to 150 μm being most preferred. A preferred mesh has a percent open area of about 50 to about 55%, a mesh count of from about 45 to about 55 per cm, and a fiber diameter of from about 55 to about 65 μm. A preferred mesh is NY151 HC mesh, also available from Sefar, CH-8803, Rushchlikon, Switzerland.

Mesh **10** is also provided with a coating of a suitable surfactant (unless the mesh itself is hydrophilic). Preferably, it is the same surfactant as that on the first mesh layer. The loading of surfactant is lower on mesh **10** than on mesh **9**, providing a further barrier to movement of sample past the transverse fibers of mesh **10**. In general, a loading of 1–10 μg/mg of mesh is preferred.

The mesh layers **9** and **10** are held in place by layers of hydrophobic electrically insulating ink **11**. These layers can be applied by screen printing the ink over a portion of the peripheries of the meshes. Together, the layers and mesh surround and define a suitable sample transfer path **12** for the sample to travel from the application point at the furthest end of the strip towards the working electrode and pseudo reference/counter electrode. The ink impregnates the mesh outside of path **12**. The insulating material thus defines sample transfer path **12** by not allowing sample to infiltrate the area of mesh covered by the layers of insulating material. A preferred insulating ink for impregnating the mesh layers is SERICARD™ (Sericol, Ltd., Broadstairs, Kent, UK).

The upper part of the electrode is enclosed by a liquid/vapor impermeable cover membrane **13**. This can be a flexible tape made of polyester or similar material which includes a small aperture **14** to allow access of the applied sample to the underlying surfactant coated mesh layers. The impermeable cover membrane encloses the exposed working electrode and pseudo reference/counter electrode. Thus, it maintains the available sample space over the electrodes at a fixed height which is equivalent to the thickness of both mesh layers **9** and **10**. This ensures that the solution resistance is kept at a high level. Any sample thickness up to the maximum depth of the two mesh layers is adequate in this respect. Aperture **14** is positioned overlying the furthest end of the open mesh area, remote from the pseudo reference/counter electrode **6***b*, such that the exposed area of mesh beneath the aperture can be used as a point of access or application for the liquid sample to be measured. The aperture can be of any suitable size large enough to allow sufficient volume of sample to pass through to the mesh layers. It should not be so large as to expose any of the area of the electrodes. The aperture is formed in the cover membrane by any suitable method (e.g., die punching). The cover membrane is affixed to the strip along a specific section, not including the electrodes, the sample transfer path or application area, using a suitable method of adhesion. Preferably this is achieved by coating the underside of a polyester tape with a layer of hot melt glue which is then heat welded to the electrode surface. The hot melt glue layer is typically of a coating weight between 10–50 g/m^2, preferably from 20 to 30 g/m^2. Pressure sensitive glues or other equivalent methods of adhesion may also be used. Care should be taken when the tape is applied, the heat and pressure applied to the cover membrane can melt the SERICARD™ and can cause it to smear onto adjoining areas.

The upper surface of the cover membrane can also be usefully provided with a layer of silicone or other hydrophobic coating which helps to drive the applied sample onto the portion of exposed surfactant coated mesh at the application point and thus make the application of small volumes of sample much simpler.

In use, a disposable test strip of the invention is connected, via electrode contacts **3**, to a meter (not shown). A sample is applied to aperture **14**, and moves along the sample transfer path **12**. The progress of the sample is sufficiently impeded by mesh layer **10** to allow the sample to form a uniform front rather than flowing non-uniformly. Air is displaced thorough the upper portion of mesh layer **10** to and through aperture **14**. The sample first covers working electrode **5** in its entirety, and only then approaches and covers pseudo reference/counter electrode **4**. This completes the circuit and causes a response to be detected by the measuring device.

The effect of increasing the resistance of a dummy electrode in a system for measuring glucose in a whole blood sample was electronically modeled. In particular, Medisense G2a disposable test strips which utilize glucose oxidase and a ferrocene mediator were tested using venous blood spiked with glucose to a concentration of 15 mM. The electronics was used to simulate the effect of having a dummy electrode with each of five added resistances from zero to infinity (no dummy electrode). An initial potential relative to the pseudo reference/counter electrode of 400 mV was imposed on the working electrode and the current at the working electrode was monitored over time. The results were reported in FIG. **5**.

FIG. **5** illustrates that as the resistance increases so does the current at the working electrode. This is an indirect indication that the half cell potential of the pseudo reference/counter electrode is being stabilized. In an ideal situation the current at the working electrode should be independent of the resistance of the dummy electrode and should just depend upon the rate at which glucose is oxidized. However, in the real world the extra current load imposed on the pseudo reference/counter electrode by the dummy electrode does cause an observable shift in the half cell potential of the pseudo reference/counter electrode. This in turn has an effect

upon the current observed at the working electrode. As the potential difference between the working and pseudo reference/counter electrodes decreases because of this shift so does the current at the working electrode.

In addition, under some conditions the current decay at the working electrode departs from the expected model. In particular, it is expected the current will decrease monotonicly with time and tend to exhibit the behavior predicted by the Cottrell equation. However, under certain conditions when the dummy electrode is imposing a significant current load on the pseudo reference/counter electrode the current at the working electrode departs from classical behavior and may actually increase with time over some short time period. This is clearly illustrated in the lowest most curve of FIG. **5**, which represents a disposable test strip in which there is no resistance differential between the circuit path involving the working electrode and that involving the dummy electrode.

The glucose meters with which the disposable test strips of present concern are typically used have electronic features designed to detect invalid test results. One of these check features is a monitoring of the current decay at the working electrode. If this decay is not monotonic the meter will report an error condition and abort the test.

Thus increasing the resistance of the dummy electrode has been shown to be effective in decreasing the likelihood of a non-monotonic current decay at the working electrode and the consequent abortion of a test.

We claim:

1. A disposable test strip suitable for attachment to the signal readout circuitry of a meter which performs an amperometric test to detect a current representative of the concentration of an analyte in a complex liquid medium comprising:

(a) a working electrode which comprises an electrode pad coated with both a substance designed to engage said analyte in an oxidation-reduction reaction and a mediator compound which will transfer electrons between the oxidation-reduction reaction and the electrode pad;

(b) a dummy electrode which comprises an electrode pad which is coated with about the same amount of mediator compound as the working electrode but lacks the substance which engages the analyte in the oxidation-reduction reaction;

(c) a pseudo reference/counter electrode which comprises an electrode pad coated with a material which contains both the oxidized and reduced form of a chemical species which is designed to undergo a reduction or oxidation reaction to balance the opposite reaction at the working and dummy electrodes; and

(d) three conductive tracks, each of which extends from a contact pad adapted to interface with said readout circuitry to one of the electrode pads and which is in electrical contact with both its contact pad and its electrode pad;

wherein the electrical resistance in the circuit path from the contact pad connected to the dummy electrode through the dummy electrode is significantly greater than the electrical resistance in the circuit path from the contact pad connected to the working electrode through the working electrode.

2. The disposable test strip of claim **1** wherein the greater electrical resistance in the dummy electrode circuit is provided by increasing the resistance of the conductive track connecting the dummy electrode to its contact pad.

3. The disposable test strip of claim **1**, further comprising an elongate support having a substantially flat, planar surface arranged to be releasably attached to the readout circuitry.

4. The disposable test strip of claim **3** wherein the three conductive tracks are created by coating conductive particles on the elongated support.

5. The disposable test strip of claim **4** wherein the conductive particles comprise carbon.

6. The disposable test strip of claim **4** wherein a greater electrical resistance is imparted to the conductive track connecting the dummy electrode to its contact pad by using a smaller volume of conductive particles in this track as compared to that used in the conductive track connecting the working electrode to its contact pad.

7. The disposable test strip of claim **1** wherein the conductive track connecting the dummy electrode to its contact pad is narrower than the conductive track connecting the working electrode to its contact pad.

8. The disposable test strip of claim **1** wherein the conductive track connecting the dummy electrode to its contact pad is thinner than the conductive track connecting the working electrode to its contact pad.

9. The disposable test strip of claim **1** wherein the conductive track connecting the dummy electrode to its contact pad has a different composition than the conductive track connecting the working electrode to its contact pad.

10. The disposable test strip of claim **9** wherein both the conductive track connected to the dummy electrode and the conductive track connected to the working electrode are comprised of carbon particles but only the latter conductive track is coated with silver.

11. The disposable test strip of claim **1** wherein the conductive track connecting the dummy electrode to its contact pad is longer than the conductive track connecting the working electrode to its contact pad.

12. The disposable test strip of claim **1** wherein the analyte is glucose and the substance engaging the analyte in an oxidation reduction reaction is an enzyme.

13. The disposable test strip of claim **12** wherein the enzyme is glucose oxidase.

14. The disposable test strip of claim **1** wherein the mediator is a ferrocene derivative.

15. The disposable test strip of claim **1** wherein said pseudo reference/counter electrode comprises an electrode pad coated with a mixture of silver and silver chloride.

16. The disposable test strip of claim **1** wherein the electrical resistance in said dummy electrode circuit is at least 1000 ohms greater than in said working electrode circuit path.

17. A disposable test strip suitable for attachment to the signal readout circuitry of a meter which performs an amperometric test to detect currents representative of the concentrations of multiple analytes in a liquid medium comprising:

(a) a first working electrode which comprises an electrode pad coated with both a substance designed to engage one of the multiple analytes in an oxidation-reduction reaction at a first electrical potential difference and a mediator compound which will transfer electrons between its oxidation-reduction reaction and its electrode pad;

(b) a second working electrode which comprises an electrode pad which is coated with both a substance designed to engage another of the multiple analytes in an oxidation-reduction reaction at a second electrical potential difference which is significantly greater than said first electrical potential difference and another mediator compound which will transfer electrons between its oxidation-reduction reaction and its electrode pad;

(c) a pseudo reference/counter electrode which comprises an electrode pad coated with a material which contains both the oxidized and reduced form of a chemical species which is designed to undergo a reduction or oxidation reaction to balance the opposite reactions at the first and second working electrodes; and

(d) three conductive tracks, each of which extends from a contact pad intended to interface with said readout circuitry to one of the electrode pads and which is in electrical contact with both its contact pad and its electrode pad;

wherein the electrical resistance in the circuit path from the contact pad connected to the first working electrode through the first working electrode is significantly greater than the electrical resistance in the circuit path from the contact pad connected to the second working electrode through the second working electrode.

18. The disposable test strip of claim **17** wherein there are only two working electrodes.

19. The disposable test strip of claim **17** wherein the pseudo reference/counter electrode comprises an electrode pad coated with a mixture of silver and silver chloride.

20. The disposable test strip of claim **17** wherein the first working electrode comprises an enzyme system adapted to engage ketones and a suitable mediator and the second working electrode comprises an enzyme suitable to engage glucose and a suitable mediator.

21. The disposable test strip of claim **20** wherein the first working electrode comprises a HBDH/NADH/1, 10 PQ system and the second working electrode comprises a glucose oxidase and a ferrocene based mediator.

22. The disposable test strip of claim **21** wherein the resistance in the first working electrode circuit is such that when a 400 mV potential exists between the second working electrode and the pseudo reference/counter electrode there is a 200 mV potential between the first working electrode and the pseudo reference/counter electrode.

* * * * *

Exhibit 15

United States Patent [19]

Horii

[11] **Patent Number: 5,004,998**

[45] **Date of Patent: Apr. 2, 1991**

[54] **ION-MEASURING APPARATUS FOR USE IN PROCESS**

[75] Inventor: **Yoshio Horii**, Miyanohigashi, Japan

[73] Assignee: **Horiba, Ltd.**, Kyoto, Japan

[21] Appl. No.: **447,221**

[22] Filed: **Dec. 7, 1989**

[30] **Foreign Application Priority Data**

Dec. 14, 1988 [JP] Japan 63-316778

[51] **Int. Cl.**[5] **G08B 21/00**; G01N 27/26

[52] **U.S. Cl.** **340/507**; 204/401; 324/537; 364/497; 364/551.01

[58] **Field of Search** ..... 204/401, 416, 433, 412, 204/406; 364/497, 551.01; 324/438, 512, 537; 73/1 R; 340/506, 537, 507

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Primary Examiner—G. L. Kaplan
Attorney, Agent, or Firm—Price, Gess & Ubell

[57] **ABSTRACT**

An ion-measuring apparatus for use in processes, characterized by comprising 3 or more ion-measuring electrodes for measuring a same one ion contained in a same one sample, means for computing a mean value of measured values obtained by means of said ion-measuring electrodes, an indicating portion for indicating the computed result, means for judging an existence of an abnormality in the ion-measuring electrodes and an alarm for emitting a maintenance alarm when the abnormality occurs in any one of the ion-measuring electrodes so that the ion-measuring electrode, which has been judged to be abnormal, may be excluded to continue a measurement by means of remaining ion-measuring electrodes.

24 Claims, 10 Drawing Sheets

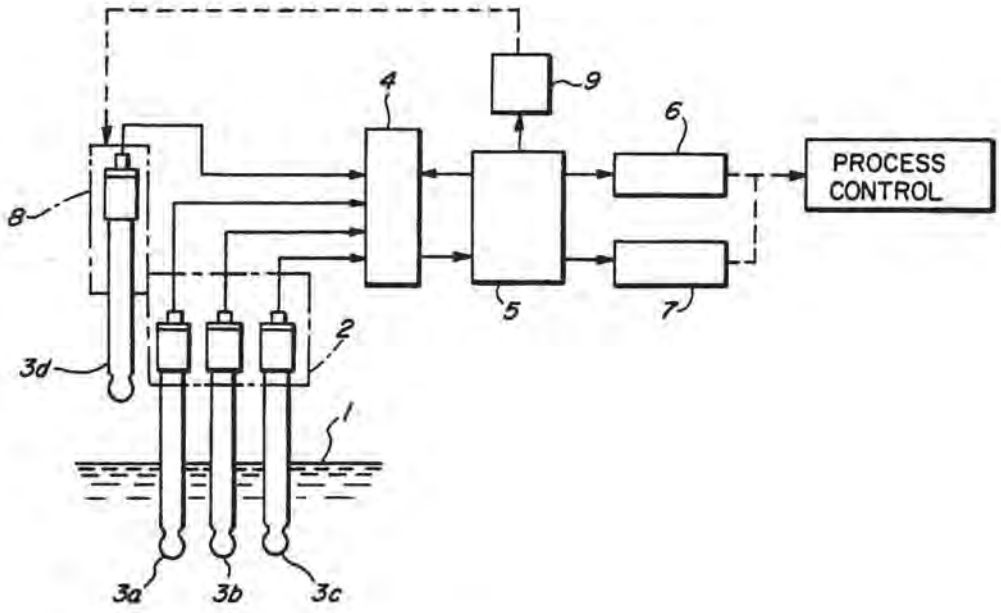


FIG. 1

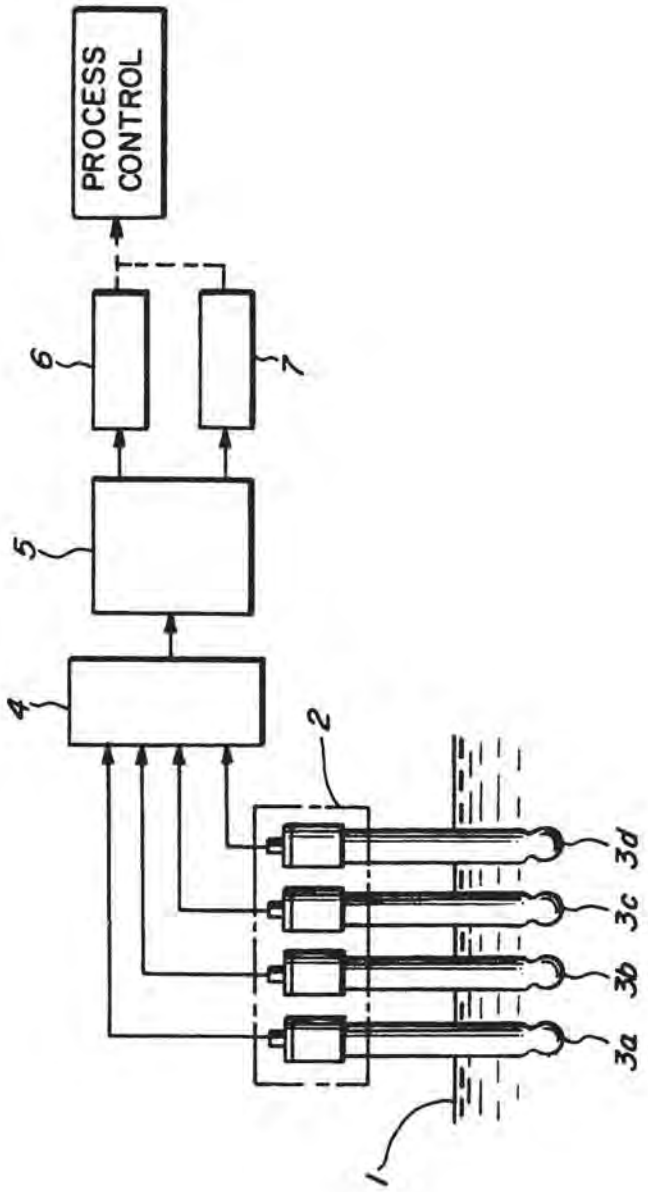


FIG. 2

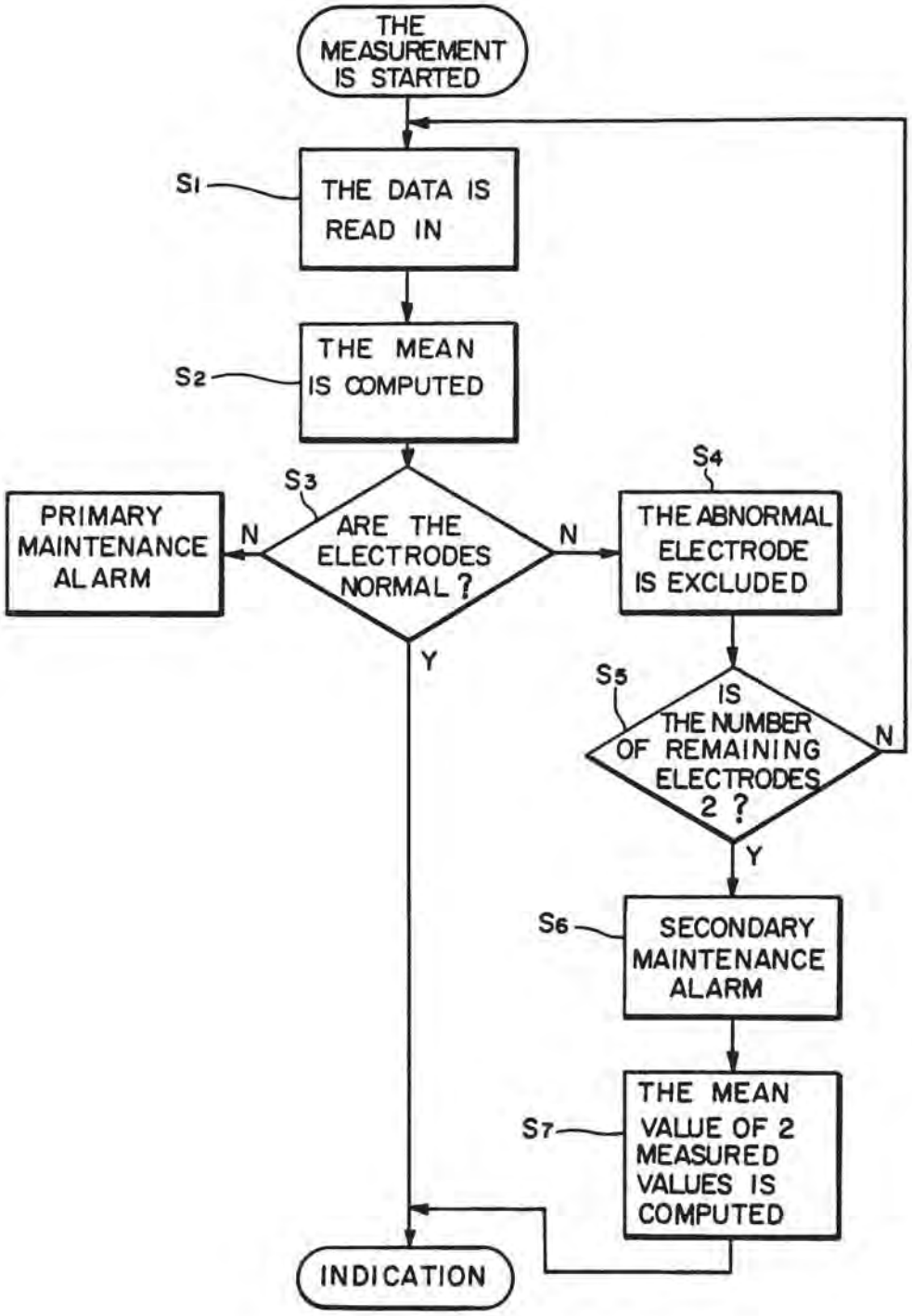


FIG. 3

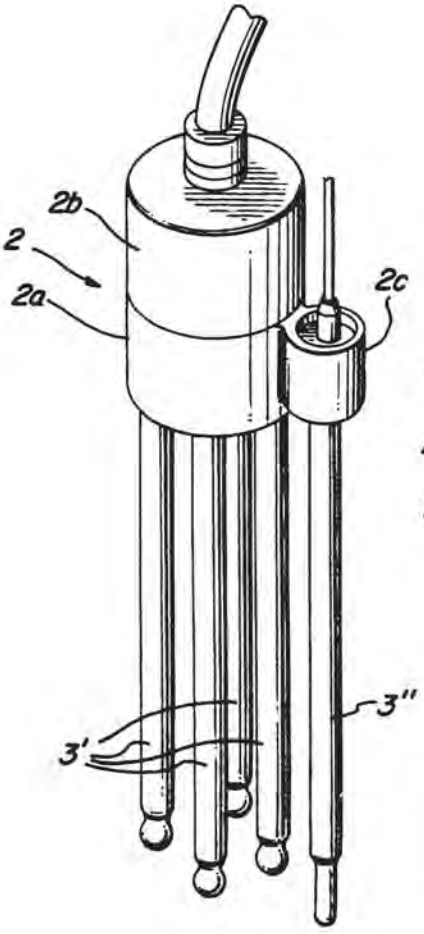


FIG. 4

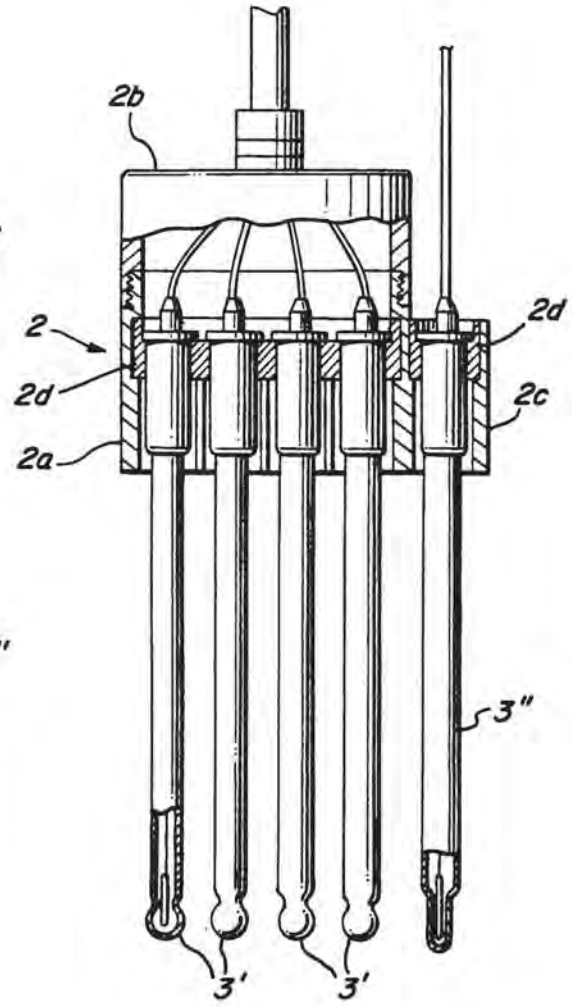


FIG. 5

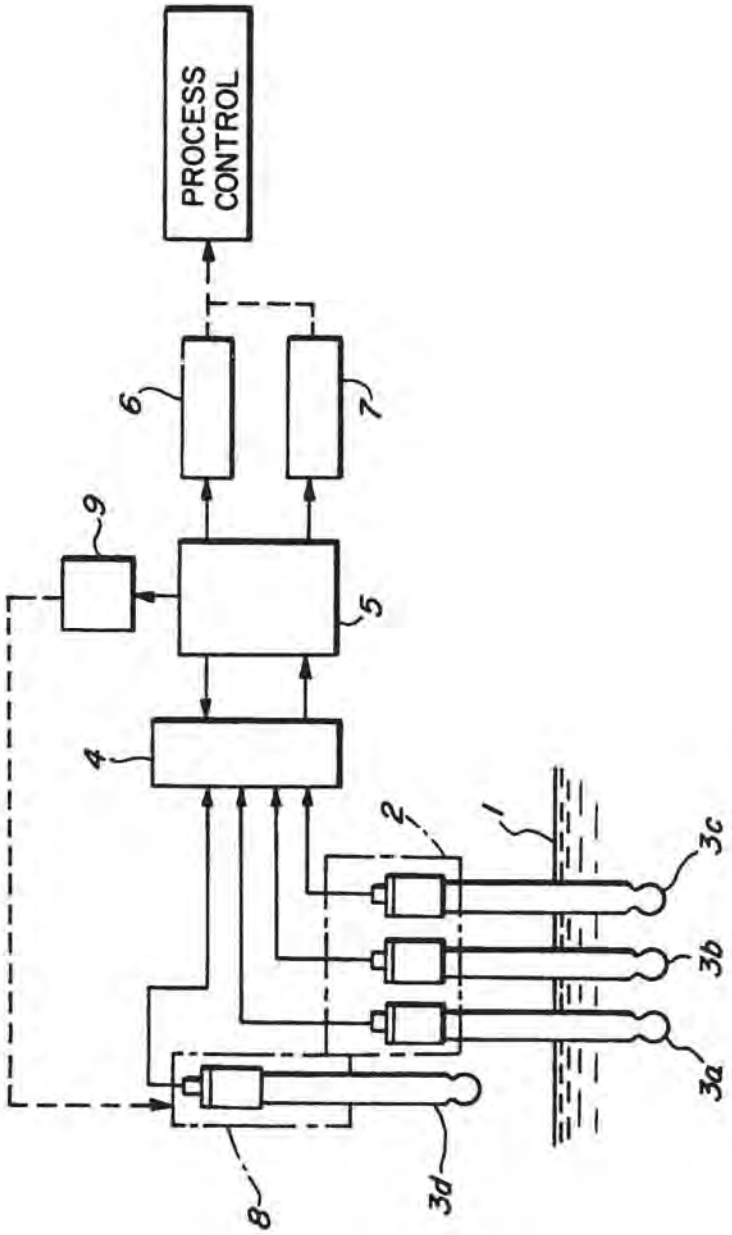


FIG. 6

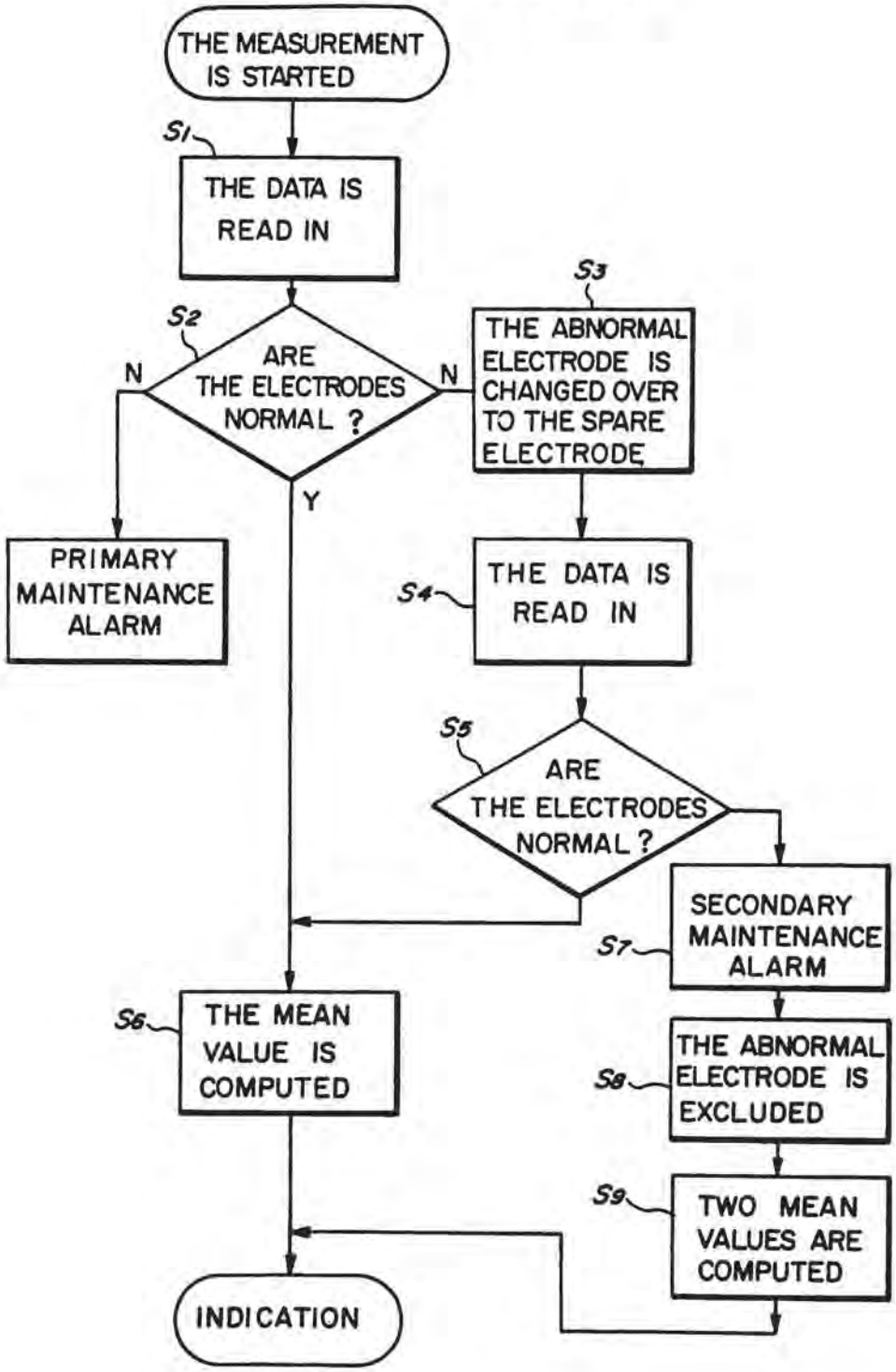


FIG. 7

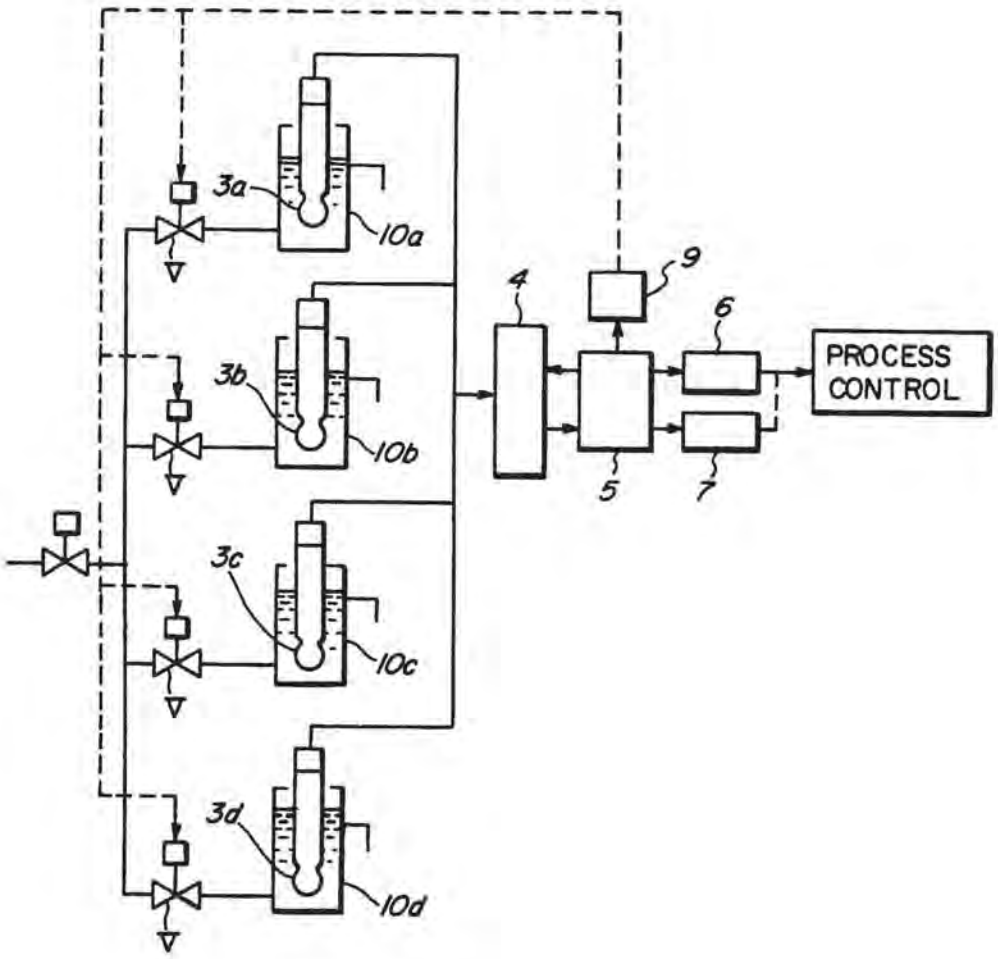


FIG. 8

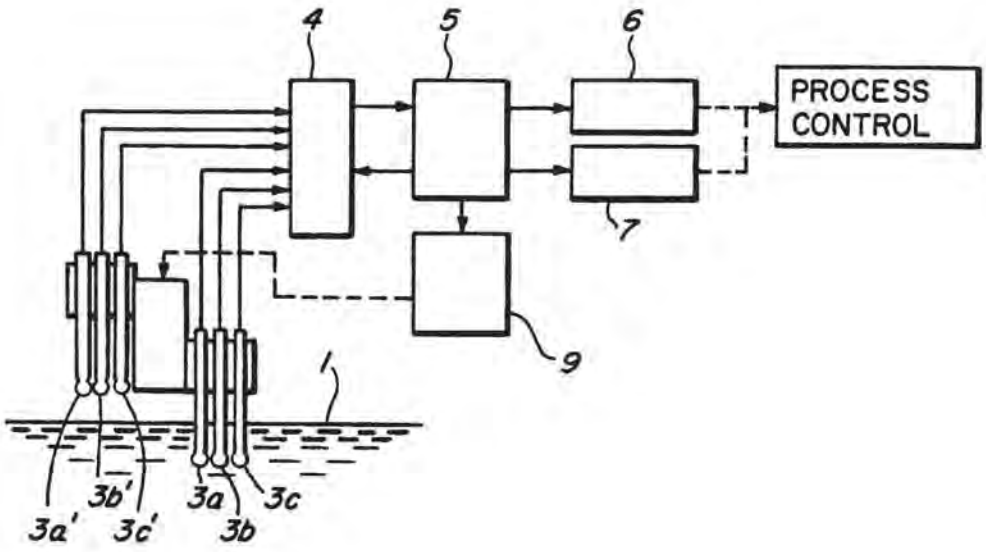


FIG. 9

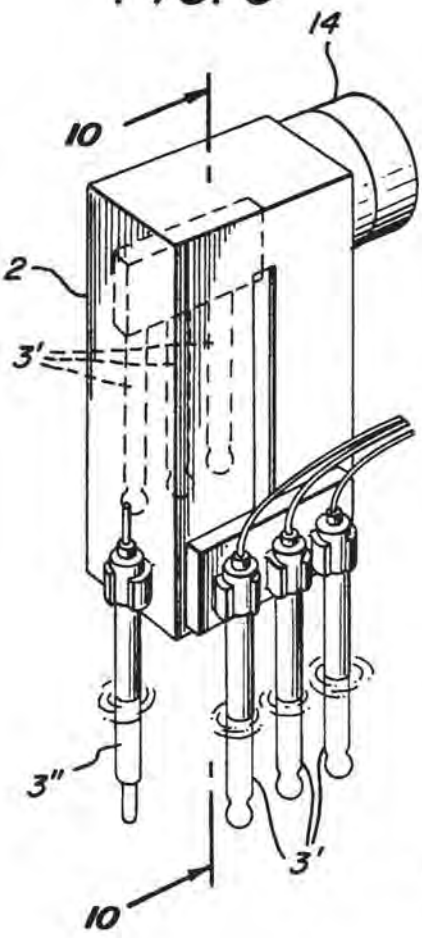


FIG. 10

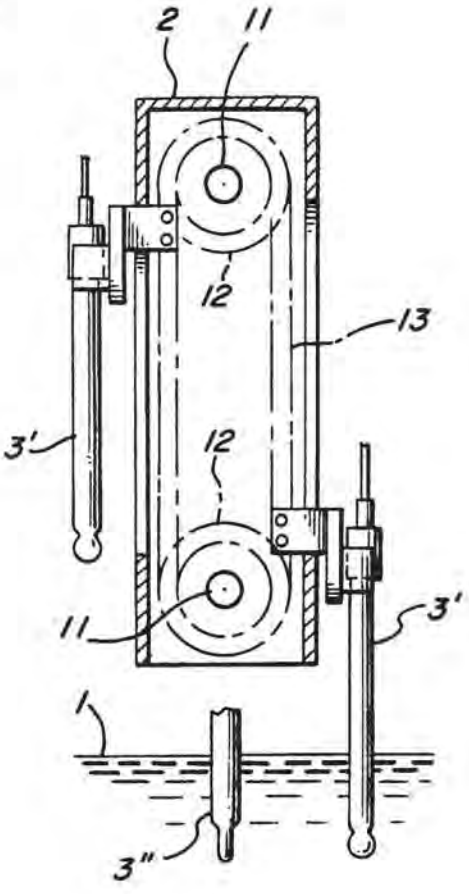


FIG. 11

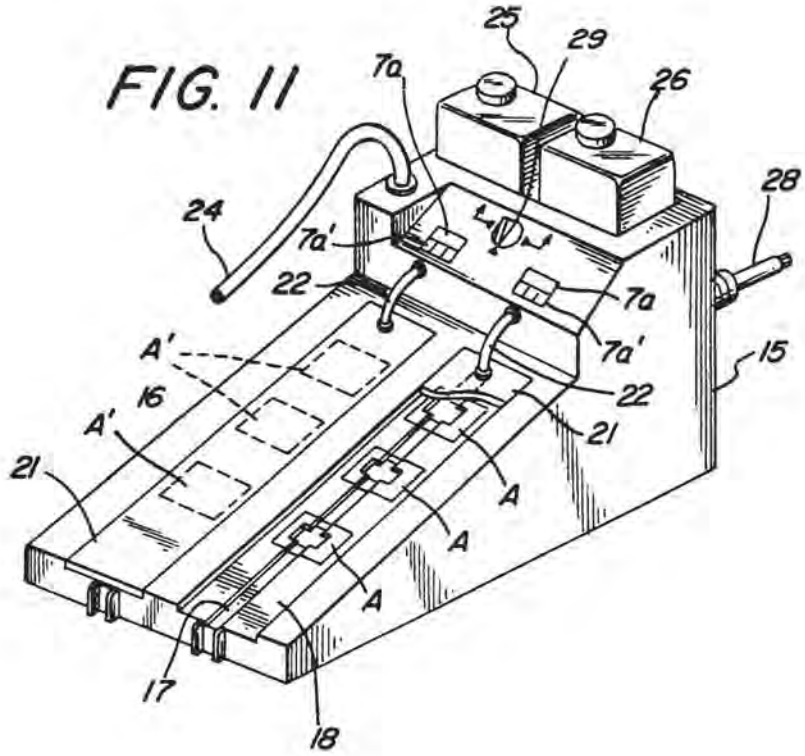


FIG. 12

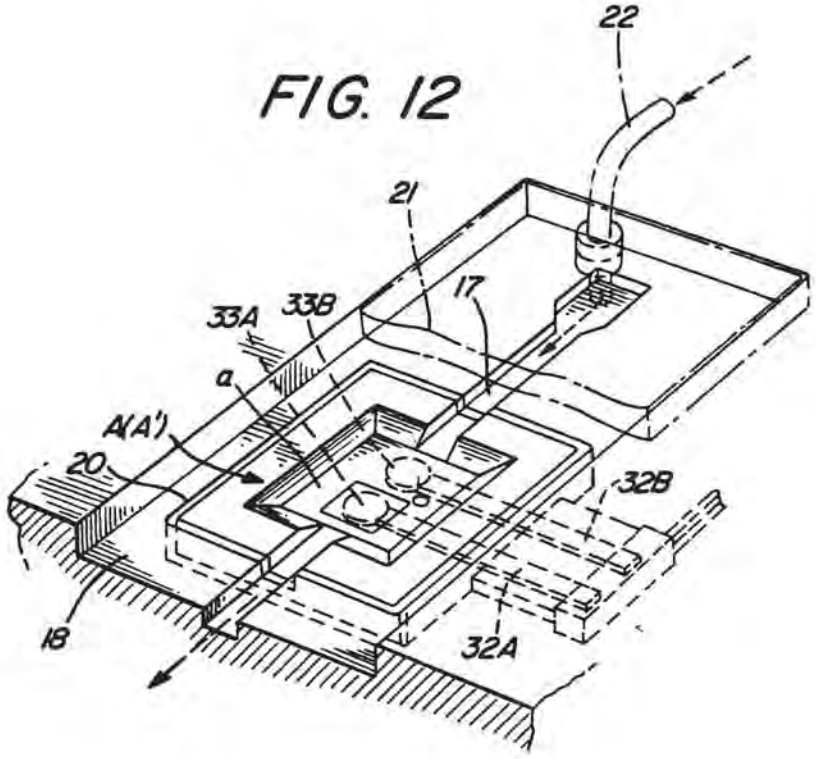


FIG. 13

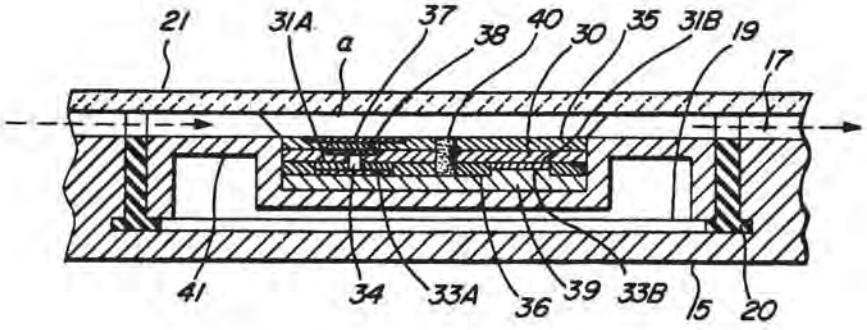
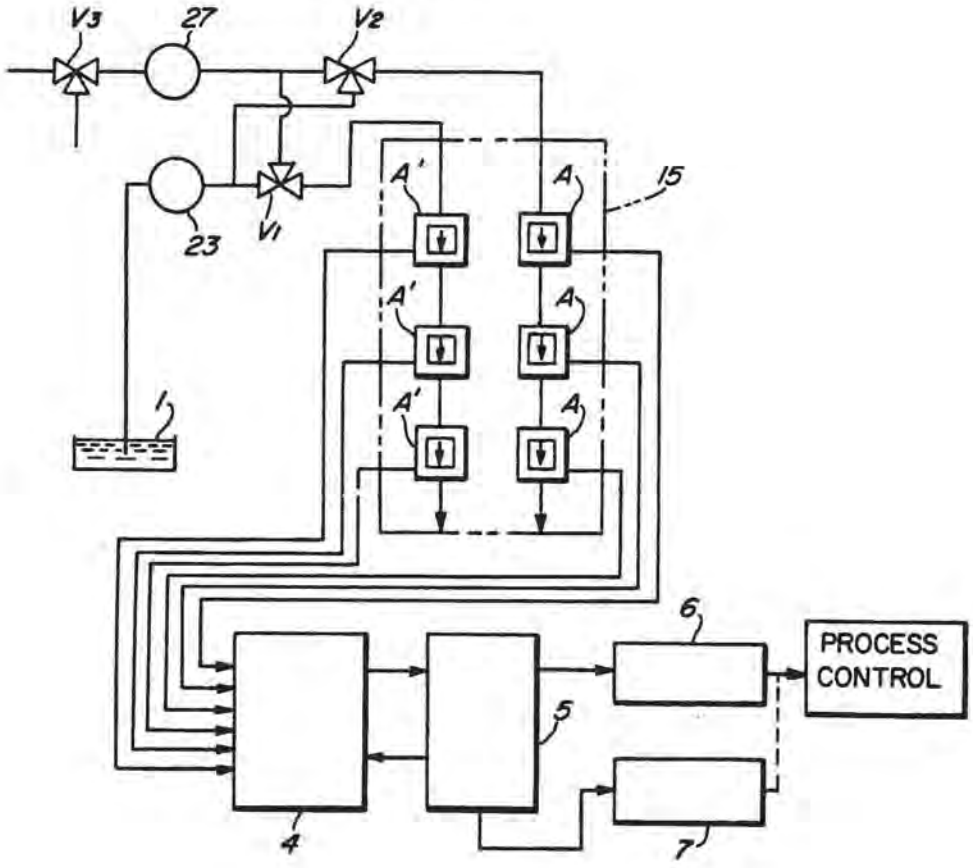


FIG. 14



ION-MEASURING APPARATUS FOR USE IN PROCESS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an ion-measuring apparatus adapted to measure concentrations of H^+, Na^+, K^+or other ions contained in a sample and capable of conducting a process control on the basis of the results of the measurement.

2. Description of the Prior Art

In the conventional ion-measuring apparatus for use in processes, usually not only a calibration of an ion-measuring electrode is periodically conducted but also a manual analysis is conducted by means of a separate measuring apparatus in a periodical maintenance to confirm a reliability of a measured value obtained by the ion-measuring electrode on the basis of a correlation between the measured value and the resulting analytical value.

In the above described conventional example, it is necessary to previously determine a maintenance period and periodically conduct the maintenance of the ion-measuring electrode but this maintenance period has been set considerably early than a useful life time of the ion-measuring electrode in anticipation of considerable safety.

Accordingly, it has been necessary that a worker required for maintenance must go to a measuring spot in a short period, in short before an actual occurrence of abnormality in the ion-measuring electrode, and, in the case where an actual abnormality has occurred in the ion-measuring electrode by the damage, contamination and the like of the ion-measuring electrode, a worker must instantly deal with the abnormality whether it is a holiday or midnight.

SUMMARY OF THE INVENTION

The present invention has been achieved in view of the above described conventional disadvantages and it is an object of the present invention to provide an ion-measuring apparatus for use in processes capable of increasing the maintenance period of the ion-measuring electrode and dealing with the abnormality with time to spare even though the abnormality occurs in the electrode.

It is another object of the present invention to provide an inexpensive ion-measuring apparatus having the above described advantages.

In order to achieve the above described objects, the present invention takes the following technical measures. That is to say, an ion-measuring apparatus for use in processes according to the present invention comprises 3 or more ion-measuring electrodes for measuring the same one ion contained in the same one sample, means for calculating a mean value of measured values by these ion-measuring electrodes, means for indicating a result of the calculation, means for judging an existence of the abnormality in these ion-measuring electrodes and an alarm portion for emitting a maintenance alarm when the abnormality occurs in any one of the ion-measuring electrodes and is characterized in that the ion-measuring electrode, which has been judged to be abnormal, is excluded and the measurement is continued by means of remaining ion-measuring electrodes.

The ion-measuring apparatus according to the present invention may be provided with a spare ion-measuring electrode in addition to the above described construction so that the ion-measuring electrode, which has been judged to be abnormal, may be switched to the spare ion-measuring electrode to continue the measurement by means of said spare ion-measuring electrode and the remaining ion-measuring electrodes.

In addition, the ion-measuring apparatus according to the present may comprise 2 sets of 3 or more ion-measuring electrodes for measuring the same one ion contained in the same one sample, means for alternately changing over 2 sets of ion-measuring electrodes to a measuring condition, in which the ion-measuring electrodes are brought into contact with the sample, and an awaiting condition, in which the ion-measuring electrodes are not brought into contact with the sample, means for calculating a mean value of measured values obtained by the ion-measuring electrodes existing under the measuring condition, a portion for indicating the result of calculation, means for judging an existence of an abnormality in the ion-measuring electrodes existing under the awaiting condition and an alarm portion for emitting a maintenance alarm when the abnormality occurs in any one of the ion-measuring electrodes so that the ion-measuring electrode, which has been judged to be abnormal, may be excluded to continue the measurement by means of the remaining ion-measuring electrodes.

Said ion-measuring electrodes may be rod-like composite electrodes and sheet-like composite electrodes integrally comprising an ion-selective electrode and a reference electrode.

In addition, said 3 or more ion-measuring electrodes may comprise 3 or more ion-selective electrodes and one reference electrode to commonly use one reference electrode for the respective ion-measuring electrodes. Said 2 sets of ion-measuring electrodes may comprise 2 sets of 3 or more ion-selective electrodes and one reference electrode to commonly use one reference electrode for the respective ion-selective electrodes.

With the ion-measuring apparatus for use in processes having the above described construction, if no abnormality occurs in all ion-measuring electrodes, a mean value of the measured values obtained by the respective electrodes is indicated and the process control is conducted on the basis of the indicated mean value.

If the abnormality occurs in any one of the electrodes, the maintenance alarm is emitted but the electrode, which has been judged to be abnormal, is excluded to continue the measurement by means of the remaining normal electrodes or the remaining normal electrodes and the spare electrode.

Accordingly, even though the maintenance alarm is emitted, in short the actual abnormality occurs in the electrode, the process control is not hindered, so that the maintenance of the electrodes can be conducted with a time to spare.

In addition, the maintenance alarm is emitted at a point of time when the actual abnormality occurs in the electrode, so that it is unnecessary to determine the maintenance period so that the maintenance may be conducted before the occurrence of the abnormality in the electrode, whereby the maintenance period can be increased.

BRIEF DESCRIPTION OF THE DRAWINGS

One preferred embodiment of the present invention is shown in FIGS. 1, 2, in which

FIG. 1 is a rough block diagram showing a pH measuring apparatus for use in processes; and

FIG. 2 is a flow chart for describing an operation of the pH-measuring apparatus for use in processes.

Another preferred embodiment of the present invention is shown in FIGS. 3, 4, in which

FIG. 3 is a perspective view showing principal parts; and

FIG. 4 is a partially cut-off front view showing the principal parts.

FIG. 5 is a rough block diagram showing a pH measuring apparatus for use in processes according to another preferred embodiment of the present invention.

FIG. 6 is a flow chart for describing an operation of the apparatus shown in FIG. 5.

FIG. 7 is a rough block diagram showing a pH-measuring apparatus for use in processes according to another preferred embodiment of the present invention.

FIG. 8 is a rough block diagram showing a pH-measuring apparatus for use in processes according to another preferred embodiment of the present invention.

FIG. 9 is a perspective view showing principal parts of the apparatus shown in FIG. 8.

FIG. 10 is a longitudinally sectioned side view showing the principal parts of the apparatus shown in FIG. 8.

Another preferred embodiment of the present invention is shown in FIGS. 11 to 14, in which

FIG. 11 is a perspective view showing a pH-measuring apparatus for use in processes;

FIG. 12 is a perspective view showing principal parts;

FIG. 13 is a longitudinally sectioned front view showing the principal parts; and

FIG. 14 is a rough block diagram showing a pH-measuring apparatus for use in processes.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred embodiments of the present invention will be below described with reference to the drawings.

FIG. 1 shows a pH-measuring apparatus for use in processes and FIG. 2 is a flow chart for describing an operation of said apparatus. Referring now to FIGS. 1, 2, reference numeral 1 designates a sample, reference numeral 2 designating an immersion electrode-holder, and reference numerals 3*a*, 3*b*, 3*c*, 3*d* designating 3 or more (4 in this preferred embodiment) pH-measuring electrode. Said electrodes 3*a*, 3*b*, 3*c*, 3*d* are held by one electrode-holder 2 so as to be separately mounted and detached. All of them are used for the measurement of pH of the same one sample 1. Reference numeral 4 designates changeover means for selectively taking measured signals by the respective electrodes 3*a*, 3*b*, 3*c*, 3*d* in a computing portion 5. Mean value-calculating means is composed of said change-over means 4 and said computing portion 5. That is to say, the measured signals by the respective electrodes 3*a*, 3*b*, 3*c*, 3*d* are put in the computing portion 5 through the changeover means 4 in turn where the mean value of the pH-measured values by the respective electrodes 3*a*, 3*b*, measured values by the respective electrodes 3*a*, 3*b*, 3*c*, 3*d* is computed. And, a signal corresponding to said mean value is put out from an indicating portion 6 and an appointed process control (for example an automatic regulation of pH in a plating bath and the like) is conducted on the basis of said output signal. Said computing portion 5 is provided with means for judging the existence of the abnormality in the electrodes 3*a*, 3*b*, 3*c*, 3*d* on the basis of the measured signals by the respective electrodes a, 3*b*, 3*c*, 3*d*. If the abnormality occurs in any one of the electrodes 3*a*, 3*b*, 3*c*, 3*d*, the electrode, which has been judged to be abnormal, is excluded (the measured signal is cut) and the measurement of pH of said sample 1 is continued by the remaining electrodes. Reference numeral 7 designates an alarm portion composed of a lamp and the like. When the abnormality occurs in any one of the electrodes 3*a*, 3*b*, 3*c*, 3*d*, a primary maintenance alarm (that is a previous warning alarm informing the approach of the maintenance time, for example this is realized by lighting a yellow lamp) is emitted and when the abnormality occurs in two electrodes, in other words merely two electrodes are normal, a secondary maintenance alarm (for example the lighting of a red lamp) is emitted.

Next, an operation of the above described apparatus is described with reference to FIG. 2.

When the apparatus is installed at first, a zero point and a sensitivity are calibrated by the use of two kinds of standard solution (the first standard solution having a pH of 7 and the second standard solution having a pH close to a pH of the sample 1) prior to the measurement. The characteristics of the respective electrodes 3*a*, 3*b*, 3*c*, 3*d* obtained in this calibration, in short an unsymmetrical electric potential (an electromotive force at a pH of 7), a sensitivity and a response time (a time from a point of time when the first standard solution is changed over to the second standard solution until a point of time when the output is stabilized) are memorized in a memory of said computing portion 5 and used as data for judging the useful life time of the respective electrodes in the maintenance which will be conducted later.

After finishing the calibration, all of the electrodes 3*a*, 3*b*, 3*c*, 3*d* are immersed in the sample 1 to start the measurement.

The measured signals (voltages on a mV unit) by four electrodes 3*a*, 3*b*, 3*c*, 3*d* are read in the computing portion 5 in turn through the change-over means 4 (Step S_1).

In the computing portion 5, the mean value (pHm) of the measured values by four electrodes 3*a*, 3*b*, 3*c*, 3*d* is computed (Step S_2).

Subsequently, the existence of the abnormality in the electrodes 3*a*, 3*b*, 3*c*, 3*d* is judged (Step S_3).

This judgment is conducted as follows:

That is to say, a potential difference Δ pHx of the respective electrodes 3*a*, 3*b*, 3*c*, 3*d* relative to the mean value (pHm) computed in the Step S_2 (this is a general name of the potential difference Δ pHa of the electrode 3*a*, the potential difference of Δ pHb of electrode 3*b*, the potential difference Δ pHc of the electrode 3*c* and the potential difference Δ pHd of the electrode 3*d*.)=pHm - pHx is computed and if said potential difference Δ pHx is within an allowable range, the electrode is judged to be normal while if said potential difference exceeds the allowable range, the electrode is judged to be abnormal. For example, Provided that the measured value by a certain electrode 3*a* is pHa when the mean value is pHm, pHm - pHa=Δ pHa is determined and if this is within a previously set allowable range (for example ±0.1 pH corresponding to about ±6 mV), said electrode 3*a* is judged to be normal while if this exceeds the allowable range (±0.1 pH corresponding to about ±6 mV), said electrode 3*a* is judged to be abnormal.

In the case where all of the electrodes 3*a*, 3*b*, 3*c*, 3*d* are judged to be normal, the mean value (pHm) ob-

tained by Step s_2 is converted into a pH unit and put in the indicating portion **6**. The process control is conducted on the basis of the signal put out from the indicating portion **6**.

When any one of the electrodes **3***a*, **3***b*, **3***c*, **3***d* is judged to be abnormal, the primary maintenance alarm is emitted from the alarm portion **7** and simultaneously the electrode, which has been judged to be abnormal, is excluded (the measured signal is cut) (Step S_4)

Then, it is judged whether two electrodes are active or not (Step S_5). In the case where **3** or more electrodes are active, the procedure is returned to Step S_1, so that the measurement by means of **3** or more electrodes is continued through Steps S_2, S_3 and S_4 and the process control is continued on the basis of the signal of the mean value (pHm) put out from the indicating portion **6**.

In the case where **2** electrodes still active, the secondary maintenance alarm is emitted from the alarm portion **7** (Step S_6) and the mean value of the measured values by said **2** electrodes is computed (Step S_7). Subsequently, said mean value is converted into a pH unit and put in the indicating portion **6**. The process control is continued on the basis of the signal put out from the indicating portion **6**.

And, if the secondary maintenance alarm has been activated, the worker required for maintenance goes to the measuring spot to conduct the maintenance, the exchange and the like of the electrode, which has been judged to be abnormal and excluded, without interrupting the continued measurement by means of the 2 remaining electrodes. In this case, it can be determined whether said electrode should be exchanged or not by conducting the calibration by means of the first and second standard solutions to measure the characteristics of the electrode, which has been judged to be abnormal and excluded, (unsymmetric electric potential, sensitivity, response speed), and comparing these with the initial values (the above described data for judging a useful life time) to confirm to what extent these characteristics are varied from the initial values (whether they reach the previously set control values or not).

In addition, although a rod-like composite electrode integrally comprising a glass electrode, which is an ion-selective electrode, and a reference electrode is used as the electrodes **3***a*, **3***b*, **3***c*, **3***d*, respectively, the ion-selective electrode and the reference electrode may be separately used (in the event that the temperature of the sample is not constant, also a temperature compensating electrode is integrated according to circumstances). When the ion-selective electrode and the reference electrode are separately used, said electrodes **3***a*, **3***b*, **3***c*, **3***d* may be composed of **3** or more (**4** in the preferred embodiment shown in the drawing) glass electrodes **3'** and one reference electrode **3''** and one reference electrode **3''** may be commonly used for the respective glass electrodes **3'**, as shown in FIGS. **3** and **4**. With such the construction, not only the expense for the electrodes can be saved but also the standard electric potential can be fixed due to the common use of the reference electrode **3''** and thus the accuracy of measurement can be improved. Referring to FIGS. **3** and **4**, reference numeral **2***a* designates a holder body, reference numeral **2***b* designating a screw type cap, reference numeral **2***c* designating a reference electrode holder provided in said holder body **2***a*, and reference numeral **2***d* designating a packing made of rubber and the like. One electrode holder **2** is composed of said members **2***a*, **2***b*, **2***c* and **2***d*.

FIG. **5** is a rough block diagram showing a pH-measuring apparatus for use in processes according to another preferred embodiment of the present invention. In this pH-measuring apparatus for use in processes, **3** or more (**3** in the preferred embodiment shown in the drawing) pH-measuring electrodes **3***a***3***b*, c having the same one construction and type of spare electrode **3***d* are mounted on an electrode holder **2**, an elevating device **8** for moving said spare electrode d from a position above a sample **1** to a position where the spare electrode **3***d* is immersed in the sample **1** being provided, and the process control being conducted on the basis of a mean value of measured values by said electrodes **3***a*, **3***b*, **3***c*. When an abnormality occurs in any one of these electrodes **3***a*, **3***b*, **3***c*, an alarm **6** emits a primary maintenance alarm and simultaneously an electrode, which has been judged to be abnormal, is automatically changed over to the spare electrode **3***d* to continue the measurement by means of said spare electrode **3***d* and the 2 remaining electrodes. In addition, when an abnormality occurs in any one of the 3 electrodes (the spare electrode and 2 remaining electrodes) used for the measurement under the above described condition, the alarm 6 emits a secondary maintenance alarm. Reference numeral **4** designates a change-over device for selectively taking measured signals by the electrodes **3***a*, **3***b*, **3***c*, **3***d* in a computing portion **4** and reference numeral **9** designates a controller for said elevating device **8**. Other constituent members are same as in the preceding preferred embodiment.

An operation of the above described apparatus is described with reference to FIG. **6** as follows:

All of the electrodes **3***a*, **3***b*, **3***c*, **3***d* are calibrated and the data for judging the useful life time are obtained. Subsequently, the measurement is started by means of **3** electrodes **3***a*, **3***b*, **3***c*.

Measured signals by **3** electrodes **3***a*, **3***b*, **3***c* are read in a computing portion **5** in turn through the change-over device **4** (Step S_1).

In the computing portion **5**, a comparison of the measured signals by the respective electrodes **3***a*, **3***b*, and **3***c* is conducted to judge the existence of any abnormality (Step S_2). That is to say, if the measured signals by the **3** electrodes **3***a*, **3***b*, **3***c* are similar to each other, all of the electrodes are judged to be normal while if merely the measured signal by any one of the electrodes is greatly different from the measured signals by **2** other electrodes, said one electrode is judged to be abnormal and the **2** remaining electrodes are judged to be normal

In the case where all of the electrodes **3***a*, **3***b*, **3***c* are judged to be normal, a mean value of the measured values by these electrodes **3***a*, **3***b*, **3***c* is computed (Step S_6) and the computed mean value is converted into a pH unit to be put in an indicating portion **6**. The process control is conducted on the basis of the signal put out from the indicating portion **6**.

If any one electrode is judged to be abnormal, an alarm **7** emits a primary maintenance alarm and simultaneously the electrode, which has been judged to be abnormal, is changed over to the spare electrode **3***d* (Step S_3). That is to say, the measured signal from the electrode, which has been judged to be abnormal, is suspended and simultaneoulsy the elevating device **8** is operated to descend the spare electrode **3***d* to a position where the spare electrode is immersed in the sample **1**.

Subsequently, the measured signals by the 2 remaining electrodes and the spare electrode 3*d* are read in the computing portion 5 in turn through the change-over device 4 (Step S_4).

In the computing portion 5, a comparison of these 3 electrodes (2 remaining electrodes and the L spare electrode 3*d*') is conducted to judge the existence of abnormality (Step S_5).

In the case where all of the electrodes are judged to be normal, the procedure is made to progress to Step S_6. But, if any one electrode is judged to be abnormal, the alarm 7 emits a secondary maintenance alarm (Step S_7) to electrode, which has been judged to be abnormal, (to cut the measured signal) (Step S_8) and compute a mean value of the measured values by the 2 remaining electrodes (Step S_9). The process control is continued on the basis of this mean value.

And, when the secondary maintenance alarm is emitted, the worker required for maintenance goes to the measuring spot to conduct the maintenance, exchange and the like of the electrode, which has been judged to be abnormal and excluded, within the continued measurement by means of the 2 remaining electrodes.

According to the present preferred embodiment, the spare electrode 3*d* is held under the condition that it is not brought into contact with the sample 1 during the normal measurement by means of the electrodes 3*a*, 3*b*, 3*c* while it is immersed in the sample 1 when it is actually required, so that an advantage occurs in that the deterioration of the spare electrode 3*d* due to hindrances, soils and the like in the sample 1 can be prevented.

In addition, in the case where 4 or more electrodes other than the spare electrode 3*d* are used, a control program, in which the electrodes which have been judged to be abnormal are excluded one by one until 3 electrodes are remained, is added. Although a rod-like composite electrode integrally comprising a glass electrode and a reference electrode is used as the electrodes 3*a*, 3*b*, 3*c*, 3*d*, respectively, in the preferred embodiment shown in the drawing, the glass electrode and the reference electrode may be separated. In addition, similarly to the preferred embodiment described with reference to FIGS. 3 and 4, one reference electrode may be commonly used for the respective glass electrodes. Furthermore, also a flow through type apparatus as shown in FIG. 7 can be used. That is to say, respective electrodes 3*a*, 3*b*, 3*c*, 3*d* are separately installed in respective electrode chambers 10*a*, 10*b*, 10*c*, 10*d* and electro-magnetic valves V are provided in sample-sampling passages communicating with the respective electrode chambers 10*a*, 10*b*, 10*c*, 10*d*. When any one electrode is judged to be abnormal, the electro-magnetic valve V of the electrode chamber corresponding to the electrode, which has been judged to be abnormal, is closed by a signal from a controller 9 and simultaneously the electro-magnetic valve V of the electrode chamber 10*d* for use in the spare electrode 3*d* is opened.

FIGS. 8 and 9 show a further preferred embodiment of the present invention.

An apparatus according to this preferred embodiment comprises 2 sets of 3 or more pH-measuring electrodes 3*a*, 3*b*, 3*c*, 3*a*', 3*b*', 3*c*' having the same type of construction, means for alternately changing over said 2 sets of electrodes (3*a*, 3*b*, 3*c* and 3*a*', 3*b*', 3*c*') to a measuring condition, in which they are brought into contact with a sample 1, and a waiting condition, in which they are not brought into contact with the sample 1, in an appointed period, means for computing a mean value of measured values by the electrodes (3*a*, 3*b*, 3*c* or 3*a*', 3*b*', 3*c*') existing under the measuring condition, an indicating portion 6 for indicating a computed result, means for judging an existence of abnormality in the electrodes (3*a*, 3*b*, 3*c* or 3*a*', 3*b*', 3*c*') and an alarm 7 for emitting a maintenance alarm when the abnormality occurs in any one of the electrodes and is characterized in that the electrode, which has been judged to be abnormal, is excluded to continue the measurement by means of the remaining electrodes. Although various kinds of mechanism can be adopted as the above described 2 condition change over means, in the present preferred embodiment, as shown in FIGS. 9 and 10, an endless belt 13 is extended across wheel members 12, 12 pivotally installed through horizontal shafts 11 above and below an electrode-holder 2 and 2 sets of a group of electrodes are mounted on said endless belt 13 at symmetrical positions of the endless belt 13, and a motor 14, which can be reversibly changed over, being driven on the basis of a signal from a controller 9, whereby the above described 2 condition-change over can be conducted. Other constructions are the same as in the preceding preferred embodiment.

An operation of the above described pH-measuring apparatus for use in processes is substantially the same one as that shown in FIG. 2 excepting that 2 sets of a group of electrodes are automatically changed over to a measuring condition and an awaiting condition in an appointed period, so that its description is omitted.

According to the present preferred embodiment, 2 sets of a group of electrodes are alternately used, so that the sum total of an actual operation time of the respective electrodes occupying in an operation time of the apparatus is reduced to half, whereby the maintenance period can be increased.

In addition, said electrodes 3*a*, 3*b*, 3*c*, 3*a*', 3*b*', 3*c*' may be composite electrodes and a glass electrode and a reference electrode may be separately used. In particular, in the latter case, the above described 2 sets of group of electrodes (3*a*, 3*b*, 3*c*) and (3*a*', 3*b*', 3*c*') are composed of 2 sets of broup of glass electrodes 3' and one reference electrode 3'' to commonly use one reference electrode 3'' as a reference electrode for 2 sets of group of glass electrodes 3', whereby an expense of the electrodes can be reduced, and a standard electric potential of 2 sets of group of electrodes is fixed, so that an accuracy of measurement can be improved.

FIGS. 11 to 14 show a further preferred embodiment of the present invention. The present preferred embodiment is characterized in that 2 condition-change over means for alternately changing over 2 sets of 3 or more sheet-like composite electrodes for use in a measurement of pH A, A' and 2 sets of sheet-like composite electrodes A, A' having the same type of construction to a measuring condition, in which the electrodes are brought into contact with a sample, and an awaiting condition, in which the electrodes are not brought into contact with the sample, in an appointed period, means for computing a mean value of measured values by the sheet-like composite electrodes (A or A') existing ulcer the measuring condition, an indicating portion 6, means for judging an existence of an abnormality in the sheet-like composite electrodes (A or A') existing under the measuring condition and an alarm 7 for emitting a maintenance alarm when the abnormality occurs in any one of the sheet-like composite electrodes are provided and the sheet-like composite electrode, which has been

judged to be abnormal, is excluded to continue the measurement by means of the remaining sheet-like composite electrodes.

The construction of this pH-measuring apparatus for use in processes is in more detail described as follows:

That is to say, reference numeral **15** designates an apparatus body, a pair of right inclined surface **18** and left inclined surface **18** provided with a groove **17** inclined at about 15 to 25° being formed on an upper surface **16** of said apparatus body **15**, and 3 or more (**3** in the preferred embodiment shown in the drawings) concave portions **19** being formed along the groove **17** in the respective inclined surfaces **18**. The respective sheet-like composite electrodes A, A' are detachably inserted into said concave portions **19** so that a sample-receiving concave portion(a) on an upper surface of the respective sheet-like composite electrodes A, A' may be communicated with the groove **17**. Reference numeral **20** designates an elastic packing made of rubber and the like for fixing the sheet-like composite electrodes A, A' and making a circumference watertight. Reference numerals **21**, **21** designate a detachable cover installed so as to be stuck to the inclined surfaces **18**, **18** and to cover the groove **17** and the sample-receiving concave portion (*a*). Tubes **22**, **22** are based through the side of an upper end of the inclination of the covers **21**, **21** so that the continuously sampled sample **1** may be alternately fallen drop by drop from the tubes **22**, **22** in an appointed period to alternately flow the sample **1** through both grooves **17**, **17** in an appointed period (this period is set at an interval of a time required for a calibration which will be mentioned later or more). Reference numeral **23** designates a sampling pump and V_1, V_2 designate three-way electro-magnetic valves for changing over flowing directions toward the right groove **17** and the left groove **17**. These members compose said **2** condition-change over means. Reference numeral **24** designates a tube for sampling the sample **1**, reference numeral **25** designating a tank of a first standard solution, reference numeral **26** designating a bank of a second standard solution, reference numeral **27** designating a pump for supplying the standard solutions, and reference numeral **28** designating a signal-taking out cable for use in a process control. Reference numerals *7a*, *7a* designate lamps composing the alarm **7**. Reference numeral *7a'*, *7a'*designate interchange display lamps provided corresponding to the respective electrodes and they are lighted when a degree of change (deterioration) in characteristic of the respective electrodes measured in the calibration exceeds a previously set control value. V_3 designates a manual three-way valve for changing over the first standard solution and the second standard solution to each other and reference numeral **29** designates an operating portion of said three-way valve V_3.

Said sheet-like composite electrodes A, A', as an external appearance thereof is shown in FIG. **12**, comprise as square portion having a reduced thickness and a terminal plate portion projected form one side of said square portion. The detailed construction is shown in FIG. **13**.

Referring to FIG. **13**, reference numeral **30** designates a substrate formed of material (for example polyethylene terephthalate, silica glass and the like) having a sufficiently high electrical insulating property even though they are immersed in a solution containing electrolytes. Said substrate **30** is provided with at least one pair (two pairs in case of the sheet-like composite electrodes provided with a temperature compensating electrode integrated therewith) of electrodes **31A**, **31B** formed of a metal selected form the group consisting of electrically conductive Ag, Cu, Pt and the like and alloys thereof or pastes containing said metal or semiconductors, such as IrO_2 and SnO_2, formed on a lower surface thereof by physical plating methods, such as the vacuum coating method and the CVD method, or the chemical plating methods, such as the electrolytic method and the electroless plating method, or the printing methods, such as the silk screen printing method, the relief printing method and the flat plate printing method.

And, base end portions positioned at one end edge portion of the substrate **30** of the respective electrodes **31A**, **31B** serve as lead portions **32A**, **32B** as they are, another almost circular pointed end portions positioned in an almost central portion of the substrate **30** being formed in the form of internal electrodes **33A**, **33B** coated with electrode materials, such as AgCl, (by the physical plating methods or the chemical palting methods or the printing methods), and one **33A** of the internal electrodes (on the side of the pH-measuring electrode) being provided with a through hole **34**, of which an inner surface has been subjected to a treatment for making it electrically conductive, as an electrode through hole formed at an almost center thereof. Reference numeral **35** designates a first support layer fixedly mounted on the upper surface of the substrate **30** and reference numeral **36** designates a second support layer fixedly mounted on the lower surface of the substrate **30**. All of the se support layers **35**, **36** are formed of materials having a sufficiently high electrical insulating property (for example polyethylene terephthalate) in the same manner as the substrate **30**. Reference numeral **37** designates a gelatinized internal solution charged in the through hole of the first support layer **35** and is sealed up tightly by means of a flat plate ion-responsive membrane **38** fixedly mounted on the first support layer **35**. The gelatinized internal solution **37** is obtained by adding gelatinizing agents (for example agar-agar, gelatin, glue, alginic acid, various kinds of hygroscopic polymer and the like) and evaporation-preventing agents (for example glycerin, ethylene glycol and the like) to a basic internal solution, which is obtained by adding a phosphoric acid buffer solution to a AgCl-supersaturated 3.3 N-KCl solution, and formed in the form of a thin plate. Reference numeral **39** designates a gelatinized internal solution on the side of the reference electrode having the same chemical composition as the above described gelatinized internal solution **37** and brought into contact with the internal electrode **33B** through a through hole formed in the second support layer **36**. A gel-impregnated hydrophobic high molecular porous member **540** passing through the first support layer **35**, the substrate **30** and the second support layer **36** is provided in the vicinity of the internal electrode **33***b* so as to serve as a liquid junction. Reference numeral **41** designates a case for housing the above described first support layer **35**, substrate **30**, second support layer **36**, gelatinized internal solution **39** and the like therein. Other constructions are the same as in the preferred embodiment shown in FIG. **5**.

An operation of the above described pH-measuring apparatus for use in processes is substantially the same one as that shown in FIG. **2** excepting that 2 sets of a group of sheet-like composite electrodes A, A' are automatically changed over to a measuring condition (a

condition in which the sample is flown through the groove **17**) and an awaiting condition (a condition in which the sample is stopped to flow through the groove **17**).

That is to say, under the condition that the sample is flown through the groove **17** on the right side, the measurement is conducted by means of 3 sheet-like composite electrodes A disposed in said groove **17**, a mean value of measured values by these sheet-like composite electrodes A being computed, potential differences Δ pHx of the respective sheet-like composite electrodes A relative to said mean value being computed, and if said potential differences Δ pHx are within an allowable range (for example ±0.1 pH corresponding to about ±6 mV), said sheet-like composite electrodes are judged to be normal while if they exceed the allowable range, they are judged to be abnormal.

In the case where all of the sheet-like composite electrodes A have been judged to be normal, a mean value (pHm) of these measured values is converted into a pH unit to be put in the indicating portion **6**. The process control is conducted on the basis of a signal put out from the indicating portion **6**.

If any one of the sheet-like composite electrodes A is judged to be abnormal, the alarm **7** emits the maintenance alarm and simultaneously the sheet-like composite electrode, which has been judged to be abnormal, is excluded (the measured signal is cut), the measurement being continued by means of 2 remaining sheet-like composite electrodes A, the mean value being computed, and the process control being continued on the basis of the computed mean value.

And, when the maintenance alarm is emitted, the worker required for maintenance goes to the measuring spot to conduct the maintenance and the like of the sheet-like composite electrode, which has been judged to be abnormal, while the measurement is continued by means of 2 remaining sheet-like composite electrodes A.

In addition, although the measurement is conducted by **3** sheet-like composite electrodes, so that the maintenance alarm is emitted when the abnormality occurs in one sheet-like composite electrode, in the preferred embodiment shown in the drawing, in the case where the measurement is conducted by means of **4** or more sheet-like composite electrodes in the same manner as in the preferred embodiment shown in FIG. **1**, the primary maintenance alarm is emitted at a point of time when the abnormality occurs in any one of the sheet-like composite electrodes, the sheet-like composite electrodes, in which the abnormality has occurred, being excluded in turn, and at a point of time when **2** electrodes remain active the secondary maintenance alarm, in short the original maintenance alarm, is then activated.

Furthermore, the group of the sheet-like composite electrodes existing under the awaiting condition is periodically calibrated. The characteristics (unsymmetrical electric potential, sensitivity, response speed) of the respective electrodes measured in said calibration are compared with the data (unsymmetrical electric potential, sensitivity, response speed) for judging a useful life time of the respective sheet-like composite electrodes obtained by the first calibration conducted when the apparatus was installed to judge whether the electrode should be exchanged or not.

That is to say, when a number of times when the respective groups of the sheet-like composite electrodes are changed over to the awaiting condition reaches an appointed number, said pump **27** is moved and the three-way valve V_3 is changed over, whereby the first standard solution and the second standard solution are flown through the groove **17** on the side of the electrode existing under the awaiting condition in this order, so that every sheet-like composite electrode can be calibrated to a zero point and sensitivity. In this calibration, the electrode characteristics, in short unsymmetrical electric potential, sensitivity and response speed, of every sheet-like composite electrode are measured and compared with the initial values (data for judging a useful life time). And, if the result of comparison (the degree of the change from the initial value) reaches the previously set control value, the exchange display lamp **7***a*' corresponding to said sheet-like composite electrode is lighted.

According to the present preferred embodiment, **2** sets of the group of electrodes are used in the same manner as in the preferred embodiment shown in FIG. **8**, so that the sum total of times during the respective electrodes are actually used occupying in the operating time of the apparatus is reduced to half, whereby the maintenance period can be increased. In addition, an advantage occurs in that the use of the sheet-like composite electrodes can make the measuring apparatus light and compact on the whole.

Besides, although the pH-measuring apparatus was illustrated in the above described respective preferred embodiments, the present invention can be similarly applied also to the ion-measuring apparatus for measuring a concentration of other ions such as Na+and K+.

Effects of the Invention

The present invention has the above described construction, so that the following effects can be given by the present invention.

(1) Since when the abnormality occurs in any one of the electrodes, the maintenance alarm is emitted but the electrode, which has been judged to be abnormal, is excluded to continue the measurement by means of the remaining normal electrodes and the spare electrodes, even though the maintenance alarm was emitted, in short the abnormality actually occurred in the electrode, the process control is not hindered, and as a result, the maintenance of the electrode can be conducted with a time to spare.

(2) Since the maintenance alarm is emitted at a point of time when the abnormality actually occurred in the electrode, it is not necessary to determine the maintenance period in such the manner that the maintenance is conducted before the abnormality occurs in the electrode, whereby the maintenance period can be increased.

(3) According to the invention spare electrode is held a the condition that it is not brought into contact with the sample during the normal measurement and is brought into contact with the sample when it is actually required, so that the deterioration of the spare electrode by hindrances, soils and the like contained in the sample can be prevented, whereby the maintenance period can be effectively increased.

(4) Two sets of the group of electrodes are used, so that the sum total of times during which the respective electrodes are actually used in the operating time of the apparatus is reduced to half, whereby by the maintenance period can be increased. The use of sheet-like composite electrodes can make the measuring apparatus light and compact. Not only the expense of the electrode can be reduced but also the standard electric

potential is fixed by the common use of the reference electrode, whereby improving the accuracy of measurement.

What is claimed is:

1. An ion measuring apparatus for the monitoring of a sample from a production process, comprising:
- a plurality of ion measuring electrodes for respectively measuring the ion content of the sample and providing an output measurement signal based on outputs from each of the electrodes;
- means for determining a failure of one of the electrodes, and
- means for excluding the failed electrode output form the output measurement signal

2. The ion measuring apparatus of claim 11 further including a supplemental ion measuring electrode whose output signal is utilized to replace the output of the failed electrode.

3. The ion measuring apparatus of claim 2 further including means for automatically activating the supplemental ion measuring electrode upon a failure of an electrode.

4. The ion measuring apparatus of claim 2 wherein an initial set of ion measuring electrodes are provided and means are provided to replace the set of ion measuring electrodes with a supplemental set of ion measuring electrodes upon detection of a failure of any one of the set of ion measuring electrodes.

5. The ion measuring apparatus of claim 2 further including means for moving the supplemental ion measuring electrode into the sample after detection of a failure.

6. The ion measuring apparatus of claim 1 wherein the ion measuring electrodes are in the form of sheet electrodes.

7. The ion measuring apparatus of claim 1 wherein the ion measuring electrodes are in the form of rod-like composite electrodes integrally comprising an ion-selective electrode and a reference electrode.

8. The ion measuring apparatus of claim 7 including a second alarm for providing an indication of a second failure of an electrode and means for enabling a second alarm mode of operation after the initial detection of a failure.

9. The ion measuring apparatus of claim 1 further including an alarm that is responsive to a detection of a failure of an electrode.

10. An ion measuring apparatus for continuously monitoring samples form a production process, comprising:
- a plurality of duplicate ion measuring electrodes for measuring a predetermined ion concen.ration characteristic of the sample;
- means for calibrating each of the ion measuring electrodes;
- first means of determining any failure of the electrodes;
- second means, in response to the determination of a failure by the first means, for determining whether a sufficient number of electrodes are still accurately measuring the sample, and
- means for excluding the failed ion measuring electrode and continuing the measurement of the sample when the second determining means indicates that an accurate measurement can be continued with the remaining electrodes.

11. The ion measuring apparatus of claim 10 wherein the plurality of duplicate ion measuring electrodes includes at least one replacement electrode and means for activating the replacement electrode to take the place of the failed electrode.

12. The ion measuring apparatus of claim 10 further including means responsive to the failure determining first means for providing an alarm signal.

13. The ion measuring apparatus of claim 10 further including a supplemental ion measuring electrode whose output signal is utilized to replace the output of the failed electrode.

14. The ion measuring apparatus of claim 10 wherein the ion measuring electrodes are in the form of sheet electrodes.

15. The ion measuring apparatus of claim 10 wherein the ion measuring electrodes are in the form of rod-like composite electrodes integrally comprising an ion-selective electrode and a reference electrode.

16. An ion measuring apparatus for the monitoring of a sample from a production process, comprising:
- a plurality of ion measuring electrodes for respectively measuring the ion content of the sample and providing an output signal from each of the electrodes;
- means for computing a mean value signal from the output signals of each of the electrodes as a measurement signal;
- means for judging a failure of any one of the electrodes to profile a reliable output signal;
- means for excluding the failed ion measuring electrode output signal from the mean value computation;
- warning means for providing an indication of a failure, and
- means for using he output signals from the remaining ion measuring electrodes after the failure judgment to maintain a continuous measurement signal, whereby the production process can continue despite the failed electrode.

17. The ion measuring apparatus of claim 16 wherein the warning means includes a secondary alarm that is enabled after an initial alarm.

18. The ion measuring apparatus of claim 16 further including means for determining whether a sufficient number of electrodes ar still accurately measuring the sample.

19. The ion measuring apparatus of claim 16 further including a supplemental ion measuring electrode whose output signal is utilized to replace the output of the failed electrode.

20. The ion measuring apparatus of claim 19 further including means or automatically activating the supplemental ion measuring electrode upon a failure of an electrode.

21. The ion measuring apparatus of claim 20 further including means for moving the supplemental ion measuring electrode into the sample after detection of a failure.

22. The ion measuring apparatus of claim 16 wherein the ion measuring electrodes are in the form of sheet electrodes.

23. The ion measuring apparatus of claim 16 wherein the ion measuring electrodes are in the form of rod-like composite electrodes integrally comprising an ion-selective electrode and a reference electrode.

24. The ion measuring apparatus of claim 16 wherein an initial set of ion measuring electrodes are provided and means are provided to replace the set of ion measuring electrodes with a supplemental set of ion measuring electrodes upon detection of a failure of any one of the set of ion measuring electrodes.

* * * * *

Exhibit 16

Exhibit 16

Claim 1 of '105 Patent	Nankai ('420) in view of Say ('752)
A method of measuring the concentration of a substance in a sample liquid comprising the steps of:	The combination of references provides the claimed method.
providing a measuring device said device comprising:	Nankai ('420) provides a measuring device at FIG. 12.
a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid;	Nankai ('420): a first working sensor part 43 for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Nankai ('420) at 8:4-14, FIG. 12.
a second working sensor part downstream from said first working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid	Nankai ('420): a second working sensor part 42 downstream from the first working sensor part 43 also for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Nankai ('420) at 8:4-14, FIG. 12.
wherein said first and second working sensor parts are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part are substantially identical to the quantity of said	Nankai ('420): said first and second working sensor parts 43, 42 are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part 43 are substantially identical to the quantity of said charge carriers generated by said second working sensor part 42. This is inherent in Nankai ('420), as its first and second working sensor parts 43, 42 are constructed in the same manner, include the same reagent, and are the same size.

charge carriers generated by said second working sensor part;	*See* Nankai ('420) at 8:4-46, FIG. 12.
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Nankai ('420): a reference sensor part 5 which is a common reference for both the first and second working sensor parts 43, 42. Nankai ('420) at 8:4-52, 4:55-57, FIG. 12. While Nankai ('420) does not explicitly show the reference sensor part 5 being upstream from the first and second working sensor parts 43, 42, such arrangement is merely an unpatentable rearrangement of parts, and in any case would be one of a finite number of identified, predictable solutions having a reasonable expectation of success (and thus obvious to try).
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Nankai ('420): said reference sensor part 5 and said first and second working sensor parts 43, 42 being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part 5 and said first and second working sensor parts 43, 42. Nankai ('420) at 8:4-29, FIG. 12.
wherein said first and second working sensor parts and said reference sensor part are provided on a disposable test strip;	Nankai ('420): said first and second working sensor parts 43, 42 and said reference sensor part 5 are provided on a disposable test strip. Nankai ('420) at 8:37, FIG. 12.
applying the sample liquid to said measuring device;	Nankai ('420) at 8:25-30.

measuring an electric current at each working sensor part proportional to the concentration of said substance in the sample liquid;	Using Patent Owner's construction of "proportional" (*i.e.*, correlated to), Nankai ('420) measures an electric current at each working sensor part proportional to the concentration of said substance in the sample liquid. Nankai ('420) at 8:11-14, 8:30-46.
comparing the electric current from each of the working sensor parts to establish a difference parameter;	Say ('752) discloses that when readings are taken from multiple electrodes, they should be compared to one another to identify errors. *See* Say ('752) at 39:26-46, 40:11, 40:14-16. Incorporating this into Nankai ('420) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	When the comparison in Say ('752) reveals that the difference in readings is outside a predetermined threshold level, the patient is alerted that the sensor is defective. *See* Say ('752) at 39:26-46 and 40:11. Alerting users of the Nankai ('420) device of defects would have been obvious in light of the teachings of Say ('752). This would nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.

Exhibit 17

Exhibit 17

Claim 1 of '105 Patent	Nankai ('420) in view of Schulman ('344)
A method of measuring the concentration of a substance in a sample liquid comprising the steps of:	The combination of references provides the claimed method.
providing a measuring device said device comprising:	Nankai ('420) provides a measuring device at FIG. 12.
a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid;	Nankai ('420): a first working sensor part 43 for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Nankai ('420) at 8:4-14, FIG. 12.
a second working sensor part downstream from said first working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid	Nankai ('420): a second working sensor part 42 downstream from the first working sensor part 43 also for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Nankai ('420) at 8:4-14, FIG. 12.
wherein said first and second working sensor parts are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part are substantially identical to the quantity of said	Nankai ('420): said first and second working sensor parts 43, 42 are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part 43 are substantially identical to the quantity of said charge carriers generated by said second working sensor part 42. This is inherent in Nankai ('420), as its first and second working sensor parts 43, 42 are constructed in the same manner, include the same reagent, and are the same size.

charge carriers generated by said second working sensor part;	*See* Nankai ('420) at 8:4-46, FIG. 12.
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Nankai ('420): a reference sensor part 5 which is a common reference for both the first and second working sensor parts 43, 42. Nankai ('420) at 8:4-52, 4:55-57, FIG. 12. While Nankai ('420) does not explicitly show the reference sensor part 5 being upstream from the first and second working sensor parts 43, 42, such arrangement is merely an unpatentable rearrangement of parts, and in any case would be one of a finite number of identified, predictable solutions having a reasonable expectation of success (and thus obvious to try).
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Nankai ('420): said reference sensor part 5 and said first and second working sensor parts 43, 42 being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part 5 and said first and second working sensor parts 43, 42. Nankai ('420) at 8:4-29, FIG. 12.
wherein said first and second working sensor parts and said reference sensor part are provided on a disposable test strip;	Nankai ('420): said first and second working sensor parts 43, 42 and said reference sensor part 5 are provided on a disposable test strip. Nankai ('420) at 8:37, FIG. 12.
applying the sample liquid to said measuring device;	Nankai ('420) at 8:25-30.

measuring an electric current at each working sensor part proportional to the concentration of said substance in the sample liquid;	Using Patent Owner's construction of "proportional" (*i.e.*, correlated to), Nankai ('420) measures an electric current at each working sensor part proportional to the concentration of said substance in the sample liquid. Nankai ('420) at 8:11-14 and 8:30-46.
comparing the electric current from each of the working sensor parts to establish a difference parameter;	Schulman ('344) at 3:17-28. Incorporating this feature from Schulman ('344) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	Schulman ('344) at 3:17-28. Incorporating this feature from Schulman ('344) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.

Exhibit 18

Exhibit 18

Claim 1 of '105 Patent	Nankai ('420) in view of Khazanie
A method of measuring the concentration of a substance in a sample liquid comprising the steps of:	The combination of references provides the claimed method.
providing a measuring device said device comprising:	Nankai ('420) provides a measuring device at FIG. 12.
a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid;	Nankai ('420): a first working sensor part 43 for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Nankai ('420) at 8:4-14, FIG. 12.
a second working sensor part downstream from said first working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid	Nankai ('420): a second working sensor part 42 downstream from the first working sensor part 43 also for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Nankai ('420) at 8:4-14, FIG. 12.
wherein said first and second working sensor parts are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part are substantially identical to the quantity of said	Nankai ('420): said first and second working sensor parts 43, 42 are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part 43 are substantially identical to the quantity of said charge carriers generated by said second working sensor part 42. This is inherent in Nankai ('420), as its first and second working sensor parts 43, 42 are constructed in the same manner, include the same reagent, and are the same size.

charge carriers generated by said second working sensor part;	*See* Nankai ('420) at 8:4-46, FIG. 12.
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Nankai ('420): a reference sensor part 5 which is a common reference for both the first and second working sensor parts 43, 42. Nankai ('420) at 8:4-52, 4:55-57, FIG. 12. While Nankai ('420) does not explicitly show the reference sensor part 5 being upstream from the first and second working sensor parts 43, 42, such arrangement is merely an unpatentable rearrangement of parts, and in any case would be one of a finite number of identified, predictable solutions having a reasonable expectation of success (and thus obvious to try).
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Nankai ('420): said reference sensor part 5 and said first and second working sensor parts 43, 42 being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part 5 and said first and second working sensor parts 43, 42. Nankai ('420) at 8:4-29, FIG. 12.
wherein said first and second working sensor parts and said reference sensor part are provided on a disposable test strip;	Nankai ('420): said first and second working sensor parts 43, 42 and said reference sensor part 5 are provided on a disposable test strip. Nankai ('420) at 8:37, FIG. 12.
applying the sample liquid to said measuring device;	Nankai ('420) at 8:25-30.

measuring an electric current at each working sensor part proportional to the concentration of said substance in the sample liquid;	Using Patent Owner's construction of "proportional" (*i.e.*, correlated to), Nankai ('420) measures an electric current at each working sensor part proportional to the concentration of said substance in the sample liquid. Nankai ('420) at 8:11-14 and 8:30-46.
comparing the electric current from each of the working sensor parts to establish a difference parameter;	While Nankai ('420) teaches taking multiple readings and calculating a mean value, *see* Nankai ('420) at 8:11-14 and 8:30-46, Khazanie teaches that simply averaging the values of collected data without doing more is an undesirable practice. For example, Khazanie says that "Variability of values in data collected is a very common phenomenon, and its importance should be acknowledged." *See* Khazanie at p. 101. To obtain a better understanding of the collected data, either the mean deviation—or even more preferably the standard deviation—should be computed. *Id.* at pp. 103-105. Thus, when considered in view of Nankai ('420), Khazanie teaches that the electric current from each of the working sensor parts should be compared to establish a difference parameter (*i.e.*, a mean deviation or a standard deviation). This would be nothing more than the combination of prior art elements according to known methods to yield predictable results, and Khazanie's teaching further would have led one of ordinary skill to modify Nankai ('420) to include this step.
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	Because Nankai ('420) teaches that it is important to obtain accurate glucose readings, *see* Nankai ('420) at 1:18-19, 2:64, 4:1-2, 8:43, it would have been obvious to indicate that an error has occurred if the difference parameter is greater than a predetermined threshold (*i.e.*, if the error is impermissible). One of ordinary skill in the art would have been motivated to provide the indication of an error based on the teachings of Nankai ('420) and common sense.

Exhibit 19

Exhibit 19

Claim 1 of '105 Patent	Nankai ('420) in view of Lichten
A method of measuring the concentration of a substance in a sample liquid comprising the steps of:	The combination of references provides the claimed method.
providing a measuring device said device comprising:	Nankai ('420) provides a measuring device at FIG. 12.
a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid;	Nankai ('420): a first working sensor part 43 for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Nankai ('420) at 8:4-14, FIG. 12.
a second working sensor part downstream from said first working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid	Nankai ('420): a second working sensor part 42 downstream from the first working sensor part 43 also for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Nankai ('420) at 8:4-14, FIG. 12.
wherein said first and second working sensor parts are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part are substantially identical to the quantity of said	Nankai ('420): said first and second working sensor parts 43, 42 are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part 43 are substantially identical to the quantity of said charge carriers generated by said second working sensor part 42. This is inherent in Nankai ('420), as its first and second working sensor parts 43, 42 are constructed in the same manner, include the same reagent, and are the same size.

charge carriers generated by said second working sensor part;	*See* Nankai ('420) at 8:4-46, FIG. 12.
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Nankai ('420): a reference sensor part 5 which is a common reference for both the first and second working sensor parts 43, 42. Nankai ('420) at 8:4-52, 4:55-57, FIG. 12. While Nankai ('420) does not explicitly show the reference sensor part 5 being upstream from the first and second working sensor parts 43, 42, such arrangement is merely an unpatentable rearrangement of parts, and in any case would be one of a finite number of identified, predictable solutions having a reasonable expectation of success (and thus obvious to try).
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Nankai ('420): said reference sensor part 5 and said first and second working sensor parts 43, 42 being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part 5 and said first and second working sensor parts 43, 42. Nankai ('420) at 8:4-29, FIG. 12.
wherein said first and second working sensor parts and said reference sensor part are provided on a disposable test strip;	Nankai ('420): said first and second working sensor parts 43, 42 and said reference sensor part 5 are provided on a disposable test strip. Nankai ('420) at 8:37, FIG. 12.
applying the sample liquid to said measuring device;	Nankai ('420) at 8:25-30.

measuring an electric current at each working sensor part proportional to the concentration of said substance in the sample liquid;	Using Patent Owner's construction of "proportional" (*i.e.*, correlated to), Nankai ('420) measures an electric current at each working sensor part proportional to the concentration of said substance in the sample liquid. Nankai ('420) at 8:11-14, 8:30-46.
comparing the electric current from each of the working sensor parts to establish a difference parameter;	While Nankai ('420) teaches taking multiple readings and calculating a mean value, *see* Nankai ('420) at 8:11-14 and 8:30-46, Lichten teaches that simply averaging the values of collected data without doing more is incomplete. Instead, an estimate of error in the measurement should be obtained. *See* Lichten at p. 3. According to Lichten, a "handy measure" of the error is the average deviation from the mean. *Id.* Thus, when considered in view of Nankai ('420), Lichten teaches that the electric current from each of the working sensor parts should be compared to establish a difference parameter (*i.e.*, the average deviation). This would be nothing more than the combination of prior art elements according to known methods to yield predictable results, and Lichten's teaching further would have led one of ordinary skill to modify Nankai ('420) to include this step.
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	Because Nankai ('420) teaches that it is important to obtain accurate glucose readings, *see* Nankai ('420) at 1:18-19, 2:64, 4:1-2, 8:43, it would have been obvious to indicate that an error has occurred if the difference parameter is greater than a predetermined threshold (*i.e.*, if the error is impermissible). One of ordinary skill in the art would have been motivated to provide the indication of an error based on the teachings of Nankai ('420) and common sense.

Exhibit 20

Exhibit 20

Claim 1 of '105 Patent	
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Any deficiency in the arrangement of sensor parts is met by Winarta ('229). Winarta ('229) discloses placing the reference sensor part R upstream from the working sensor parts W, Wo as claimed. Winarta ('229) at 5:59 to 6:10, 7:11-42, FIG. 2. Incorporating this into Nankai ('420) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Any deficiency in the arrangement of sensor parts is met by Winarta ('229). Winarta ('229) discloses placing the reference sensor part R upstream from the working sensor parts W, Wo and unidirectional flow as claimed. Winarta ('229) at 5:59 to 6:10, 7:11-42, FIG. 2. Incorporating this into Nankai ('420) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.

Exhibit 21

Exhibit 21

Claim 1 of '105 Patent	
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Any deficiency in the arrangement of sensor parts is met by Yee ('256). Yee ('256) discloses that the arrangement of electrodes does not affect their characteristics. Yee ('256) at 2:11-13. This further confirms that it would be obvious to place the reference sensor upstream of the working sensor parts, as set forth in claim 1.
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Any deficiency in the arrangement of sensor parts is met by Yee ('256). Yee ('256) discloses that the arrangement of electrodes does not affect their characteristics. Yee ('256) at 2:11-13. This further confirms that it would be obvious to place the reference sensor upstream of the working sensor parts and have unidirectional flow, as set forth in claim 1.

Exhibit 22

Exhibit 22

Claim 1 of '105 Patent	
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	Stewart ('891) at 11:18-23. Incorporating this feature from Stewart ('891) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.

Exhibit 23

Exhibit 23

Claim 1 of '105 Patent	
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	Horii ('998) at Abstract, 4:8-16, 5:5-9, FIG. 2. Incorporating this feature from Horii ('998) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.

Exhibit 24

Exhibit 24

Claim 1 of '105 Patent	Winarta ('229) in view of Say ('752)
A method of measuring the concentration of a substance in a sample liquid comprising the steps of:	The combination of references provides the claimed method.
providing a measuring device said device comprising:	Winarta ('229) provides the claimed measuring device at sensor 10.
a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid;	Winarta ('229): a first working sensor part W for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.
a second working sensor part downstream from said first working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid	Winarta ('229): a second working sensor part Wo downstream from said first working sensor part W also for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.
wherein said first and second working sensor parts are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part are substantially identical to the quantity of said charge carriers generated by said	Winarta ('229): said first and second working sensor parts W, Wo are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part W are substantially identical to the quantity of said charge carriers generated by said second working sensor part Wo. This is inherent in Winarta ('229), as its first and second working sensor parts W, Wo are constructed in the same manner, include the same reagent, and are the same size. *See* Winarta ('229) at 5:37-54, 7:11-42, 9:4-14, FIG. 2.

second working sensor part;	Even if W and Wo are not the same size, one of ordinary skill in the art would have altered the sizing to arrive at a uniform size to take advantage of the Say ('752) disclosure of taking multiple measurements and performing averaging and comparison functions.
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Winarta ('229): a reference sensor part R upstream from said first and second working sensor parts W, Wo which reference sensor part R is a common reference for both the first and second working sensor parts W, Wo. Winarta ('229) at 5:59 to 6:10, 7:23-25, FIG. 2.
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Winarta ('229): said reference sensor part R and said first and second working sensor parts W, Wo being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part R and said first and second working sensor parts W, Wo. Winarta ('229) at 5:59-62, FIG. 2.
wherein said first and second working sensor parts and said reference sensor part are provided on a disposable test strip;	Winarta ('229): said first and second working sensor parts W, Wo and said reference sensor part R are provided on a disposable test strip. Winarta ('229) at Abstract, 11:2-3, FIGs. 1-3.
applying the sample liquid to said measuring device;	Winarta ('229) at 5:59-62, 10:1-67.
measuring an electric current at each working sensor part proportional to the concentration of said substance in the	Say ('752) discloses that readings should be taken from multiple electrodes and compared to one another to identify errors. *See* Say ('752) at 39:26-46, 40:11, 40:14-16. Because the test strip of Winarta ('229) is capable of taking multiple measurements (*i.e.*, using the

sample liquid;	first working sensor part W and the second working sensor part Wo), it would have been obvious to take multiple measurements and obtain an average as taught by Say ('752). This would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
comparing the electric current from each of the working sensor parts to establish a difference parameter;	Say ('752) discloses that when readings are taken from multiple electrodes, they should be compared to one another to identify errors. *See* Say ('752) at 39:26-46, 40:11, 40:14-16. Because the test strip of Winarta ('229) is capable of taking multiple measurements (*i.e.*, using the first working sensor part W and the second working sensor part Wo), it would have been obvious to take multiple measurements and obtain an average as taught by Say ('752). This would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	When the comparison in Say ('752) reveals that the difference in readings is outside a predetermined threshold level, the patient is alerted that the sensor is defective. *See* Say ('752) at 39:26-46, 40:11. Alerting users of the Winarta ('229) device of defects would have been obvious in light of the teachings of Say ('752). This would nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.

Exhibit 25

Exhibit 25

Claim 1 of '105 Patent	Winarta ('229) in view of Horii ('998)
A method of measuring the concentration of a substance in a sample liquid comprising the steps of:	The combination of references provides the claimed method.
providing a measuring device said device comprising:	Winarta ('229) provides the claimed measuring device at sensor 10.
a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid;	Winarta ('229): a first working sensor part W for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.
a second working sensor part downstream from said first working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid	Winarta ('229): a second working sensor part Wo downstream from said first working sensor part W also for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.
wherein said first and second working sensor parts are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part are substantially identical to the quantity of said	Winarta ('229): said first and second working sensor parts W, Wo are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part W are substantially identical to the quantity of said charge carriers generated by said second working sensor part Wo. This is inherent in Winarta ('229), as its first and second working sensor parts W, Wo are constructed in the same manner, include the same reagent, and are the same size.

charge carriers generated by said second working sensor part;	*See* Winarta ('229) at 5:37-54, 7:11-42, 9:4-14, FIG. 2. Even if W and Wo are not the same size, one of ordinary skill in the art would have altered the sizing to arrive at a uniform size to take advantage of the Horii ('998) disclosure of taking multiple measurements and performing comparison functions.
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Winarta ('229): a reference sensor part R upstream from said first and second working sensor parts W, Wo which reference sensor part R is a common reference for both the first and second working sensor parts W, Wo. Winarta ('229) at 5:59 to 6:10, 7:23-25, FIG. 2.
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Winarta ('229): said reference sensor part R and said first and second working sensor parts W, Wo being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part R and said first and second working sensor parts W, Wo. Winarta ('229) at 5:59-62, FIG. 2.
wherein said first and second working sensor parts and said reference sensor part are provided on a disposable test strip;	Winarta ('229): said first and second working sensor parts W, Wo and said reference sensor part R are provided on a disposable test strip. Winarta ('229) at Abstract, 11:2-3, FIGs. 1-3.
applying the sample liquid to said measuring device;	Winarta ('229) at 5:59-62, 10:1-67.
measuring an electric current at each working sensor part proportional	Horii ('998) teaches that multiple measurements should be taken to identify errors. *See* Horii ('998) at Abstract, FIG. 2. Because the test strip of Winarta ('229) is

to the concentration of said substance in the sample liquid;	capable of taking multiple measurements (*i.e.*, using the first working sensor part W and the second working sensor part Wo), it would have been obvious to take multiple measurements as taught by Horii ('998). This would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
comparing the electric current from each of the working sensor parts to establish a difference parameter;	Horii ('998) at Abstract, 3:41 to 4:66, FIG. 2. Incorporating this feature from Horii ('998) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	Horii ('998) at Abstract, 4:8-16, 5:5-9, FIG. 2. Incorporating this feature from Horii ('998) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.

Exhibit 26

Exhibit 26

Claim 1 of '105 Patent	Winarta ('229) in view of Schulman ('344)
A method of measuring the concentration of a substance in a sample liquid comprising the steps of:	The combination of references provides the claimed method.
providing a measuring device said device comprising:	Winarta ('229) provides the claimed measuring device at sensor 10.
a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid;	Winarta ('229): a first working sensor part W for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.
a second working sensor part downstream from said first working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid	Winarta ('229): a second working sensor part Wo downstream from said first working sensor part W also for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.
wherein said first and second working sensor parts are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part are substantially identical to the quantity of said	Winarta ('229): said first and second working sensor parts W, Wo are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part W are substantially identical to the quantity of said charge carriers generated by said second working sensor part Wo. This is inherent in Winarta ('229), as its first and second working sensor parts W, Wo are constructed in the same manner, include the same reagent, and are the same size.

charge carriers generated by said second working sensor part;	*See* Winarta ('229) at 5:37-54, 7:11-42, 9:4-14, FIG. 2. Even if W and Wo are not the same size, one of ordinary skill in the art would have altered the sizing to arrive at a uniform size to take advantage of the Schulman ('344) disclosure of taking multiple measurements and performing comparison functions.
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Winarta ('229): a reference sensor part R upstream from said first and second working sensor parts W, Wo which reference sensor part R is a common reference for both the first and second working sensor parts W, Wo. Winarta ('229) at 5:59 to 6:10, 7:23-25, FIG. 2.
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Winarta ('229): said reference sensor part R and said first and second working sensor parts W, Wo being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part R and said first and second working sensor parts W, Wo. Winarta ('229) at 5:59-62, FIG. 2.
wherein said first and second working sensor parts and said reference sensor part are provided on a disposable test strip;	Winarta ('229): said first and second working sensor parts W, Wo and said reference sensor part R are provided on a disposable test strip. Winarta ('229) at Abstract, 11:2-3, FIGs. 1-3.
applying the sample liquid to said measuring device;	Winarta ('229) at 5:59-62, 10:1-67.
measuring an electric current at each working sensor part proportional	Schulman ('344) teaches that multiple measurements should be taken to identify errors. *See* Schulman ('344) at 3:17-28. Because the test strip of Winarta ('229) is

to the concentration of said substance in the sample liquid;	capable of taking multiple measurements (*i.e.*, using the first working sensor part W and the second working sensor part Wo), it would have been obvious to take multiple measurements as taught by Schulman ('344). This would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
comparing the electric current from each of the working sensor parts to establish a difference parameter;	Schulman ('344) at 3:17-28. Incorporating this feature from Schulman ('344) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	Schulman ('344) at 3:17-28. Incorporating this feature from Schulman ('344) would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.

Exhibit 27

Exhibit 27

Claim 1 of '105 Patent	Winarta ('229) in view of Yee ('256) and Khazanie
A method of measuring the concentration of a substance in a sample liquid comprising the steps of:	The combination of references provides the claimed method.
providing a measuring device said device comprising:	Winarta ('229) provides the claimed measuring device at sensor 10.
a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid;	Winarta ('229): a first working sensor part W for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.
a second working sensor part downstream from said first working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid	Winarta ('229): a second working sensor part Wo downstream from said first working sensor part W also for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.

wherein said first and second working sensor parts are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part are substantially identical to the quantity of said charge carriers generated by said second working sensor part;	Winarta ('229): said first and second working sensor parts W, Wo are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part W are substantially identical to the quantity of said charge carriers generated by said second working sensor part Wo. This is inherent in Winarta ('229), as its first and second working sensor parts W, Wo are constructed in the same manner, include the same reagent, and are the same size. *See* Winarta ('229) at 5:37-54, 7:11-42, 9:4-14, FIG. 2. Even if W and Wo are not the same size, one of ordinary skill in the art would have altered the sizing to arrive at a uniform size to take advantage of the Yee ('256) and Khazanie disclosures of taking multiple measurements and performing averaging and comparison functions.
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Winarta ('229): a reference sensor part R upstream from said first and second working sensor parts W, Wo which reference sensor part R is a common reference for both the first and second working sensor parts W, Wo. Winarta ('229) at 5:59 to 6:10, 7:23-25, FIG. 2.
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Winarta ('229): said reference sensor part R and said first and second working sensor parts W, Wo being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part R and said first and second working sensor parts W, Wo. Winarta ('229) at 5:59-62, FIG. 2.

wherein said first and second working sensor parts and said reference sensor part are provided on a disposable test strip;	Winarta ('229): said first and second working sensor parts W, Wo and said reference sensor part R are provided on a disposable test strip. Winarta ('229) at Abstract, 11:2-3, FIGs. 1-3.
applying the sample liquid to said measuring device;	Winarta ('229) at 5:59-62, 10:1-67.
measuring an electric current at each working sensor part proportional to the concentration of said substance in the sample liquid;	Yee ('256) discloses that, due for example to the construction methods for glucose test strips, error can be expected in test results. *See* Yee ('256) at 1: 21-36. To counter that error, Yee ('256) teaches that multiple measurements should be taken and averaged together. *Id.* at 1:48-51, 2:34-41, 2:49-56. Because the test strip of Winarta ('229) is capable of taking multiple measurements (*i.e.*, using the first working sensor part W and the second working sensor part Wo), it would have been obvious to take multiple measurements and obtain an average as taught by Yee ('256). This would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
comparing the electric current from each of the working sensor parts to establish a difference parameter;	While taking multiple readings is an obvious step as set forth above, Khazanie teaches that simply averaging the values of collected data without doing more is an undesirable practice. For example, Khazanie says that "Variability of values in data collected is a very common phenomenon, and its importance should be acknowledged." Khazanie at p. 101. To obtain a better understanding of the collected data, either the mean deviation—or even more preferably the standard deviation—should be computed. *Id.* at pp. 103-105. Thus, when considered in view of the Winarta ('229) and Yee ('256) combination set forth above, Khazanie teaches that the electric current from each of the working sensor parts should be compared to establish a difference parameter (*i.e.*, a mean deviation or a standard deviation). This would be nothing more than the combination of prior art elements according to

	known methods to yield predictable results, and Khazanie's teaching further would have led one of ordinary skill to modify the prior art references to include this step.
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	Because Winarta ('229) teaches that it is important to obtain accurate glucose readings, *see* Winarta ('229) at 1:13-19 and 3:36-37, and also because Yee ('256) teaches that there is a range of errors that is impermissible, *see* Yee ('256) at 1:33-53, it would have been obvious to indicate that an error has occurred if the difference parameter is greater than a predetermined threshold (*i.e.*, if the error is impermissible). One of ordinary skill in the art would have been motivated to provide the indication of an error based on the teachings of Winarta ('229), the disclosure of Yee ('256), and common sense.

Exhibit 28

Exhibit 28

Claim 1 of '105 Patent	Winarta ('229) in view of Lichten
A method of measuring the concentration of a substance in a sample liquid comprising the steps of:	The combination of references provides the claimed method.
providing a measuring device said device comprising:	Winarta ('229) provides the claimed measuring device at sensor 10.
a first working sensor part for generating charge carriers in proportion to the concentration of said substance in the sample liquid;	Winarta ('229): a first working sensor part W for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.
a second working sensor part downstream from said first working sensor part also for generating charge carriers in proportion to the concentration of said substance in the sample liquid	Winarta ('229): a second working sensor part Wo downstream from said first working sensor part W also for generating charge carriers in proportion to the concentration of said substance in the sample liquid. Winarta ('229) at 7:11-42.
wherein said first and second working sensor parts are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part are substantially identical to the quantity of said	Winarta ('229): said first and second working sensor parts W, Wo are arranged such that, in the absence of an error condition, the quantity of said charge carriers generated by said first working sensors part W are substantially identical to the quantity of said charge carriers generated by said second working sensor part Wo. This is inherent in Winarta ('229), as its first and second working sensor parts W, Wo are constructed in the same manner, include the same reagent, and are the same size.

charge carriers generated by said second working sensor part;	*See* Winarta ('229) at 5:37-54, 7:11-42, 9:4-14, FIG. 2. Even if W and Wo are not the same size, one of ordinary skill in the art would have altered the sizing to arrive at a uniform size to take advantage of the Lichten disclosure of taking multiple measurements and performing averaging and comparison functions.
and a reference sensor part upstream from said first and second working sensor parts which reference sensor part is a common reference for both the first and second working sensor parts,	Winarta ('229): a reference sensor part R upstream from said first and second working sensor parts W, Wo which reference sensor part R is a common reference for both the first and second working sensor parts W, Wo. Winarta ('229) at 5:59 to 6:10, 7:23-25, FIG. 2.
said reference sensor part and said first and second working sensor parts being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part and said first and second working sensor parts;	Winarta ('229): said reference sensor part R and said first and second working sensor parts W, Wo being arranged such that the sample liquid is constrained to flow substantially unidirectionally across said reference sensor part R and said first and second working sensor parts W, Wo. Winarta ('229) at 5:59-62, FIG. 2.
wherein said first and second working sensor parts and said reference sensor part are provided on a disposable test strip;	Winarta ('229): said first and second working sensor parts W, Wo and said reference sensor part R are provided on a disposable test strip. Winarta ('229) at Abstract, 11:2-3, FIGs. 1-3.
applying the sample liquid to said measuring device;	Winarta ('229) at 5:59-62, 10:1-67.
measuring an electric current at each working sensor part proportional	Lichten discloses that, to improve test results, "Common sense tells you to take the average of several elements, called the arithmetic mean or mean." Lichten at p. 2.

to the concentration of said substance in the sample liquid;	Because the test strip of Winarta ('229) is capable of taking multiple measurements (*i.e.*, using the first working sensor part W and the second working sensor part Wo), it would have been obvious to take multiple measurements and obtain an average as taught by Lichten. This would be nothing more than the use of a known technique to improve similar devices/methods in the same way, and the results would be predictable.
comparing the electric current from each of the working sensor parts to establish a difference parameter;	While taking multiple readings is an obvious step as set forth above, Lichten teaches that simply averaging the values of collected data without doing more is incomplete. Instead, an estimate of error in the measurement should be obtained. *See* Lichten at p. 3. According to Lichten, a "handy measure" of the error is the average deviation from the mean. *Id.* Thus, when considered in view of Winarta ('229), Lichten teaches that the electric current from each of the working sensor parts should be compared to establish a difference parameter (*i.e.*, the average deviation). This would be nothing more than the combination of prior art elements according to known methods to yield predictable results, and Lichten's teaching further would have led one of ordinary skill to modify Winarta ('229) to include this step.
and giving an indication of an error if said difference parameter is greater than a predetermined threshold.	Because Winarta ('229) teaches that it is important to obtain accurate glucose readings, *see* Winarta ('229) at 1:13-19 and 3:36-37, and also because Yee ('256) teaches that there is a range of errors that is impermissible, *see* Yee ('256) at 1:33-53, it would have been obvious to indicate that an error has occurred if the difference parameter is greater than a predetermined threshold (*i.e.*, if the error is impermissible). One of ordinary skill in the art would have been motivated to provide the indication of an error based on the teachings of Winarta ('229) and common sense.