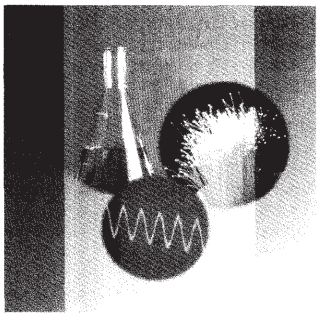

# Optical Oximetry Sensors for Whole Blood and Tissue

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The oxygen saturation of hemochromes such as hemoglobin, myoglobin, and cytochromes yield useful information for evaluation of patients in various clinical settings. In particular, clinical measurements of hemoglobin saturation in major vessels and cardiac chambers have been reported during catheterization for detection of cardiac shunts [1-2], for estimation of cardiac output from arterio-venous oxygen difference via Fick's principle [3], and for monitoring patients with various cardiac diseases [4-6]. During surgical procedures and recovery from anesthesia, hemoglobin oxygen saturation has been utilized for early detection of hypoxia [7-8]. And in the care of fetuses and neonates, oxygen saturation data are useful [9-12].

The measurement of oxygen saturation in humans goes back to the 1940s, when Millikan devised an instrument to measure arterial saturation from the forehead [13]. This was followed by various workers including Brinkman, Wood, Sekelj, Tait, et al., who noninvasively estimated arterial saturation as well as tissue oxygen saturation [14-17]. The works by Wood and co-workers resulted in ear oximeters, and the contributions by Sekelj, et al. advanced this device. In the 1960s, solid state devices such as the light emitting diode and photodiode were introduced to make a miniature skin reflectance sensors and also intravascular measurement systems by utilizing fiber optic guides. The fiber optic intravascular oximeter developed by Polanyi and Hehir [18] became the basis for the modern invasive oximeter.

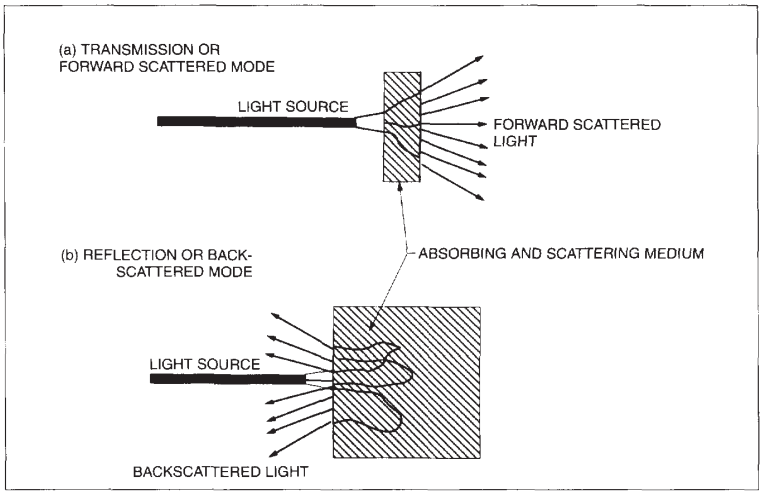
In the 1970s, Cheung and Reynolds [19-20] modeled the optical fiber system in blood, based on the photon diffusion theory developed by Johnson [21]. Noninvasive skin and tissue reflectance oximeters were also developed by Cohen and Takatani [22-23] in the late 1970s, with optical propagation in the medium modeled utilizing one-dimensional and three-dimensional photon diffusion theory. Contrary to the transport theory approach, Lubbers, et al. [24-25] utilized the multi-component approach in combination with Monte-Carlo simulation in analyzing the tissue spectra. However, problems of the earlier workers included 1) lack of adequate calibration procedure in vivo, 2) unknown distribution of arterial-to-venous blood volume in tissue, 3) unknown optical path-length in tissue, and 4) lack of an appropriate mathematical relation to calculate tissue hemoglobin saturation in vivo.

In the early 1980s, the innovative approach of pulse oximetry, which combined the principle of conventional optical oximetry with the plethysmographic principle, offered a means of noninvasively estimating arterial blood oxygen saturation [26-30]. This instrument assumes that the forward scattered plethymographic pulsatile signals are due to arterial blood, and noninvasively measures arterial saturation from the finger tip or the ear lobe. Most operating rooms and intensive care units today are equipped with this device. Another innovative approach is the use of a very narrow light pulse (on the order of picoseconds) or ultra high frequency signal (on the order of 500 MHz) to measure transit time of light signals through tissues. These techniques characterize the tissue optical properties of absorption and scattering, from which absolute tissue oxygen saturation can be estimated [31-34]. Although this approach is still in the experimental state, it offers an absolute determination of tissue oxygen saturation as well as an image of the tissue oxygen field in a three dimensions [35-36].

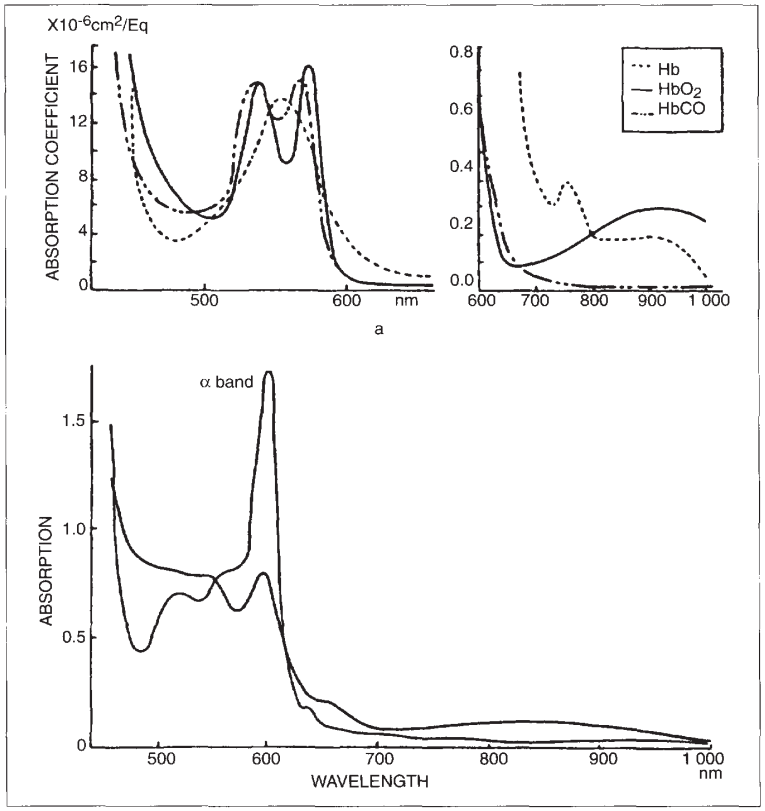
This article reviews the optical techniques applied to the determination of intravascular hemoglobin oxygen saturation as well as the noninvasive estimation of arterial and tissue saturation. Although in skeletal muscles and brain tissues myoglobin and cytochrome analyses have been demonstrated [37-38], their effects upon absorption and reflection spectra of tissues are small. Thus, this review is focused only upon measurement of hemoglobin saturation.

## Basis of Optical Oximetry

Optical oximetry can be classified into a) transmission or forward scattering and b) reflection or back scattering type (Fig. 1). In forward scattering, a target area is illuminated with a light source, and transmitted or forward scattered light is analyzed. In the reflection mode,




**1. Principle of (a) transmission or forward scattered, and (b) reflection or backward scattered optical spectroscopy.**




**2. Absorption spectra of hemoglobin, myoglobin, bilirubin and cytochrome aa3 in visible and near-infrared wavelength.**

backscattered light from the specimen is sampled to estimate the oxygen saturation. In both methods, absorption (K) and scattering (S) properties of the tissue sample plays a major role. In particular, wavelength dependent absorption properties of various species such as hemoglobin, myoglobin, cytochrome aa3 contained in the tissue sample will affect the measured transmittance and reflectance.

Figure 2 shows the absorption spectra of these hemochromes in the visible and near-infrared regions [39-40]. In normal tissue, when the transmission and reflection spectra are examined, they strongly depend on the absorption spectra of hemoglobin, since the concentration is much greater than other species.

### Absorption Constant

In relation to blood and tissue oximetry, absorption of light by hemoglobin in the wavelength ranges between 450 and 550 nm is significantly larger (about 10 times) in comparison to the wavelength range between 650-1000 nm (Fig. 2). Bench top oximeters usually sample absorption spectra at around 550 nm, while intravascular and tissue oximetry utilize the wavelength range of 650-1000 nm. The wavelength of 805 nm is called isosbestic, where there is no absorption difference between the oxy- and deoxy-hemoglobin.

As the hemoglobin is contained inside the red blood cells (RBC), a microscopic absorption cross section of RBCs, $\sigma$ in $\mu^2$, is usually used to describe absorption properties, either as oxygenated cross section, so or deoxygenated, $\sigma_r$. Microscopic absorption cross section of RBCs can be derived from the specific absorption coefficients of hemoglobin using the known absorption cross section at a specific wavelength. The macroscopic absorption constant of blood, $K_b$ in $mm^{-1}$ is obtained by multiplying the microscopic cross section, $\sigma$, by concentration of RBCs (hematocrit, $H/\overline{V}$), i.e., $K_b = H\sigma/\overline{V}$. For a given oxygen saturation $SO_2$ of whole blood, $K_b$ is expressed as a linear sum of $\sigma_o$ and $\sigma_r$ as follows:

$$K_b = H\frac{\sigma}{\overline{V}} = \frac{H}{\overline{V}}(\sigma_o\, SO_2 + \sigma_r\,(1-SO_2)) \qquad (1)$$

A compound system of tissue can be treated as a homogeneous mixture of blood and blood-less tissue, and blood volume fraction, $V_b$, can be used to obtain the net absorption constant of tissue, $K_T$, as follows:

$$K_T = K_t\,(1-V_b) + K_b V_b \qquad (2)$$

where, $K_t$ is the macroscopic absorption constant of the blood-less tissue. Typical $K_t$ values of various tissues range from 0.03 to 10.0 $mm^{-1}$ [37, 41-46]. Further,

blood in tissue can be treated as a sum of arterial and venous blood, and $V_b$ can be given as:

$$V_b = V_a + V_v \tag{3}$$

where $V_a$ and $V_v$ are the arterial and venous fractional blood volume in tissue, respectively. Equation 1 can be divided into a component for arterial saturation, $S_aO_2$, and the one for venous saturation $S_vO_2$ as follows:

$$K_{ba} = \frac{H}{V}(\sigma_o S_a O_2 + \sigma_r(1-S_a O_2)) \tag{4}$$

$$K_{bv} = \frac{H}{V}(\sigma_o S_v O_2 + \sigma_r(1-S_v O_2)) \tag{5}$$

where $K_{ba}$ and $K_{bv}$ are the macroscopic absorption constants of arterial and venous blood, respectively. Then, The net absorption constant due to mixture of the arterial and venous blood, $K_b'$ becomes:

$$K_b' = K_{ba}V_{ba} + K_{bv}V_{bv} \tag{6}$$

Thus, the net absorption constant of the tissue becomes

$$K_T = K_t\,[1-(V_a+V_v)] + K_b' \tag{7}$$

The net tissue oxygen saturation, $SO_{2T}$, averaged over the arterial and venous blood, can be expressed as:

$$SO_{2T} = S_a O_2 V_a + S_v O_2 V_v \tag{8}$$

This is the oxygen saturation of tissue when transmitted or reflected light from tissue is analyzed. When we discuss tissue oxygenation utilizing time resolved spectroscopy, $SO_{2T}$ is the target measurement from which venous saturation and arterial to venous blood volume distribution can be derived.

### Scattering Constant

Scattering of light by red blood cells and tissue components takes place at interfaces where there is a change in the index of refraction. This scattering is due to microscopic fluctuations in the refractive index of the tissue, corresponding to physical inhomogeneities. The angles through which the light is scattered and the scatter coefficient depend on the size and shape of the optical inhomogeneities relative to the wavelength, and to differences in the refractive index between the inhomogeneities and the surrounding medium. Scattering from molecules or structures whose size is much less than the wavelength (Rayleigh scattering), is weak, nearly equal in all directions (isotropic scattering), and rapidly decreases with wavelength. When the wavelength and inhomogeneities are about the same size, the scattering is stronger, is more forward-directed, and decreases roughly inversely with the wavelength. Scattering from large inhomogeneities is highly forward-directed and only weakly dependent on wavelength (Mie scattering).

The RBC is biconcave in shape, with outer diameter of about 8 μm and average thickness of about 1 μm. The average volume of a human RBC is about 87 $\mu m^3$. Again, the microscopic scattering cross section of a RBC is defined as $\sigma_s$, where this value denotes total scattering cross section and comprises forward scattering cross sections $\sigma_s^+$, and backscattering cross section $\sigma_s^-$. The index of anisotropicity is defined as: $w = (\sigma_s^+ - \sigma_s^-)/(\sigma_s^+ + \sigma_s^-)$. When the particle is totally forward scattering, w = 1, while totally backscattering, w= -1. The w of RBC ranges from 0.7 to 0.967, and is strongly forward scattering. The scattering characteristics of RBC and tissue components are wavelength dependent. The backscattering cross section of RBC in the visible and near-infrared regions is approximately constant. In the near-infrared region above 800 nm, since the absorption by the hemoglobin is smaller, the light particle can propagate deeper into tissue. Scattering cross sections of the RBCs have been described theoretically using a sphere model by Mie theory [19,20,47], a disk model by the Rayleigh-Gans method [19,20], and a more complicated discoid model by a WKB method [48]. These values have been compared against experimental values and used to explain experimental results.

Again, the macroscopic scattering constant of the blood can be given by:

$$S_b = \frac{H}{V}\sigma_s \tag{9}$$

where $\sigma_s$ is the total scattering cross section given by $\sigma = \sigma_s^+ + \sigma_s^-$. However, in a single phase material there will be no scattering, i.e., when RBCs are packed (H = 100%) or when there are no RBCs (H = 0). Thus, Eq. 8 is usually multiplied by (1 - H) [49], giving:

$$S'_b = S_b(1-H) = \frac{H}{V}(1-H)\sigma \tag{10}$$

For a compound system such as tissue, the linear treatment used in the absorption analysis is also applicable. Thus, the net scattering constant of tissue, $S_T$, is expressed as:

$$S_T = S_t(1-V_b) + S_b'V_b \tag{11}$$

Here, $S_t$ is the scattering constant of the bloodless tissue component. Usually, since the absorption constant of arterial and venous blood do not deviate significantly, that is oxygen saturation does not affect scattering properties of RBCs, Eq. 11 can be used to express the macroscopic scattering constant of compound tissue.

## Theoretical Analysis of Optical Propagation in Tissue

Theoretical analysis of optical propagation can be divided into 1) absorbing but no scattering, and 2) both absorbing and scattering.

### Absorbing but Non-Scattering Medium

In the case of non-scattering but absorbing medium, the simple Beer-Lambert Law can be applied to analyze the transmitted light intensity in terms of various species concentrations. Here, the transmitted intensity of light, $I_t$, is related to the incident light intensity, $I_o$, by:

$$I_t = I_o e^{-\alpha C t} \tag{12}$$

$$OD = \ln(I_o/I_t) = \alpha C t \tag{13}$$

where α is the absorption coefficient, C the concentration of the absorber, and t is the optical pathlength. This equation can be applied to a homogeneous and non-scattering solution. In Eq. 13, OD is the optical density, a linear function of concentration, C, when optical pathlength, t, is fixed. Bench top oximeters usually utilize from 2 to 4 wavelengths, depending on the number of components involved in the system. Equation 13 is utilized to solve for the concentration of the species, from which saturation can be derived. For example, when two wavelengths are used, from Eq. 13, concentrations of oxy- and deoxy-hemoglobin, $C_{HbO2}$ and $C_{Hb}$, are given as:

$$C_{Hb} = \frac{n}{d}$$

where

$$n = OD(\lambda_1)\alpha(\lambda_2 Hb) - OD(\lambda_2)\alpha(\lambda_1 Hb)$$

and

$$d = t\,[\alpha(\lambda_1 HbO2)\alpha(\lambda_2 Hb) - \alpha(\lambda_2 HBO2)\alpha(\lambda_1 Hb)] \tag{14}$$

$$C_{Hb} = \frac{n}{d}$$

where

$$n = OD\,(\lambda_1)\alpha(\lambda_2 HbO2) - OD(\lambda_2)\,\alpha(\lambda_1 HbO2)$$

and

$$d = t\,[\alpha(\lambda_1 Hb)\,\alpha(\lambda_2 HbO2) - \alpha(\lambda_2 Hb)\,\alpha(\lambda_1 HbO2)] \tag{15}$$

In Eqs. 14 and 15, $\alpha(\lambda_1 Hb)$ and $\alpha(\lambda_1 HbO2)$ are the absorption coefficients of Hb and HbO2, respectively, at wavelength $\lambda_1$, and $\alpha(\lambda_2 Hb)$ and $\alpha(\lambda_2 HbO2)$ are the absorption coefficients of Hb and HbO2, respectively, at wavelength $\lambda_2$. Then, from Eqs. 14 and 15, the oxygen saturation can be derived as:

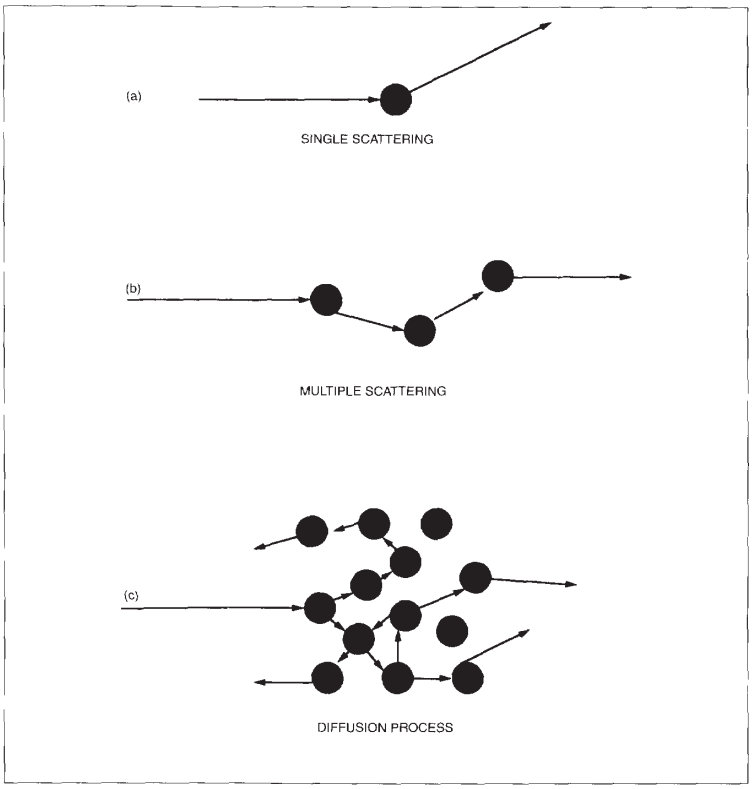
$$SO_2 = \frac{C_{HbO2}}{C_{HbO2} + C_{Hb}}$$

### Absorbing and Scattering Medium

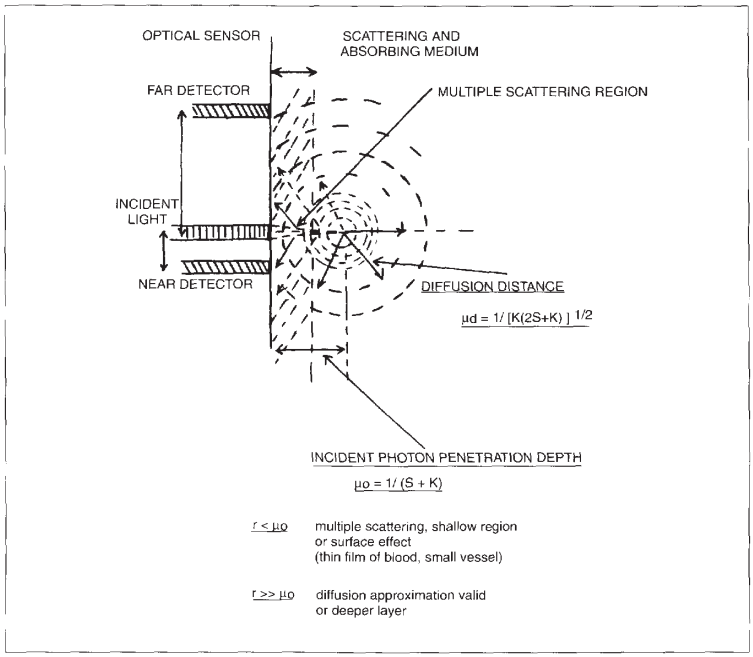
When the medium is both scattering and absorbing, the non-liner effect of scattering becomes important and the result deviates from Eq. 13. The first theoretical treatment of scattering in a random medium was given in 1903 by Schuster [50], who described interactions of radiation with the foggy atmosphere. This one-dimensional theory was based on phenomenological observations of intensity transfer in the medium. It was further heuristically developed in 1931 by Kubelk and Munk [51], by which time it was called the "two-flux theory." Based on the concept of forward and backward traveling fluxes, it adequately describes optical propagation in a medium if the illumination is diffuse and the medium is dull so that light is diffusely scattered (Fig. 3). However, because of its phenomenological and heuristic nature, as well as its one-dimensionality, the theory has serious limitations when applied to optical processes in whole blood and tissue.

The optical process can be classified into a) single scattering, b) multiple scattering and 3) diffusion, depending on the concentration of scatterers as shown in Fig. 4. Various scattering theories are available for a single particle, including Mie theory, which deals with scattering of light by a sphere; and Rayleigh-Gans theory for scattering by a disk. When the particle concentration increases, a phenomenon called "multiple scattering" occurs. The light goes through multiple scatterings because of the existence of numerous particles in the medium. In application to biological samples, such as whole blood and tissue, Twersky developed a forward scattering theorem [49]. It includes both absorption and scattering terms in a modification of Eq. 12, and as given by:

$$I_t = I_o e^{-ST} + q(1-e^{-ST})e^{-\alpha Ct} \qquad (16)$$




**3. Schematic drawing of (a) single scattering, (b) multiple scattering, and (c) diffusion processes.**




**4. Diffusion process in the medium, and underlying assumptions for diffusion process.**

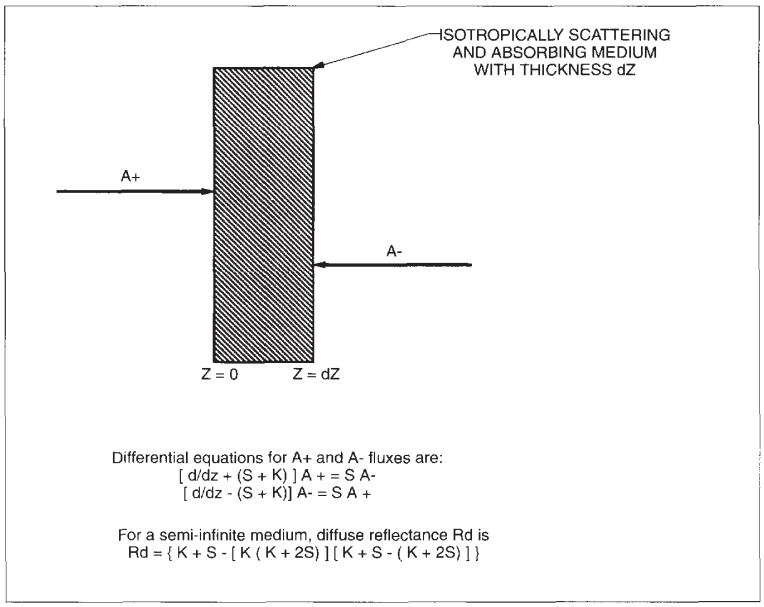
Then, OD becomes:

$$OD = B + \alpha Ct \quad (17)$$

Here, B is the term related to scattering and the second term is related to absorption. For the multiple scattering analysis to be applicable, the medium thickness must be very thin or the concentration of the particles must be very low, so that the coherence of the incoming light is not lost. Equation 16 has been successfully applied to analysis of light transmitted through a small vessel, through a frozen tissue sample, and in the vicinity of the optical fiber tips.

When the particle concentration increases above 5%, or the medium thickness becomes large so that light will go through repeated multiple scattering, then the coherence of the incident light is lost and it is said the light becomes diffused [52]. This was confirmed in whole blood with an immersed optical fiber. As the hematocrit of blood increased, the light patterns became more and more centered around the tip of optical fiber, and coherence of the incident light was completely lost [21].

Thus, as shown in Fig. 5, diffusion takes place, when the medium satisfies the conditions of a) scattering particle concentration above the critical value, and b) the medium thickness becomes large. We can define two parameters to evaluate the underling assumptions of diffusion theory. First, incident photon penetration depth, $\delta_o$, and defined as 1/(S + K), will indicate the average depth, $t_D$ in which the light can penetrate into a particular medium before losing coherence. Thus, it is entirely function of the medium and excitation wavelength, $\lambda$. The second parameter is the diffusely scattering condition, called albedo, and defined as S/(S + K). The albedo, as S and K are also wavelength dependent, is determined by the medium and the excitation wavelength . When the albedo of the medium is greater than 0.5, diffusion will take place. When the medium satisfies both conditions, diffusion analysis is valid. Diffusion analysis is a heuristic approach derived from transport theory. Its application to biological media such as whole blood and tissues has been employed by several researchers. The diffusion approach can be divided into two phases: a) steady state continuous case, and b) a time resolved or pulse diffusion case.




**5. Two flux analysis**

## Diffusion analysis

*a. Steady state diffusion equation*

For the steady state case, the diffusion equation was derived from the transport theory and given in the cylindrical coordinate by [21]:

$$(\Delta^2 - f_a / D)\, \rho_s(r,\theta,z) = So(r,\theta,z) \quad (18)$$

where So is a source function and $\rho_s$ is the scattered photon density, c is the velocity of light, D is the diffusion constant given by $D = 1/3\,[f_a+(1 - w)f_s]$, $f_a$ and $f_s$ are the absorption and scattering coefficient and related to K and S by

$$c\,K = f_a \quad (19)$$

$$c\,S = f_s \quad (20)$$

The solutions of Eq. 18 for both isotropic and an-isotropic scattering with various boundary conditions have been solved and successfully applied to design fiber optic oximeters in whole blood. The solution obtained by Reynolds for isotropically scattering homogeneous medium is [20]:

$$R(r_a) = (2/d)[S/(S+K)]\times \sum A_n\left[1 - e^{-d/\delta o}(-1)^n\right]\times [1-(2r/b)\,M_1N_1] \quad (21)$$

This equation gives diffuse reflectance for an illuminating optical fiber radius of b separated from the receiving fiber by $r_a$ as a function of tissue thickness, d, and scattering and absorption constants, S and K. M1 and N1 are the first order Bessel functions. This equation can give quantitative diffuse reflectance from an isotropically scattering homogeneous medium such as whole blood.

In application to tissue, one-dimensional solution was applied to reflectance oximetry in blood and tissue by Longini, Cohen, et al. [53-54]. A three-dimensional solution for a two-layer tissue model was obtained by Takatani and Graham for application to reflectance oximetry from gut mucosa [55]. This solution was further extended by Schmitt to a multi-layer model application in pulse oximetry [56].

*b. Time resolved case*

When a narrow width light pulse, on the order of picoseconds, is injected into the medium, the transmitted pulse's shape and amplitude indicate the scattering and absorbing characteristics of the medium. The diffusion equation for a narrow width pulse through the medium can be written as [57]:

$$[(1/Dc)(\delta/\delta t) - (\Delta^2 - f_a/D)]\rho_s(r,\theta,z,t) = S'(r,\theta,z,t) \quad (22)$$

where, scattered photon density, $\rho_s(r,\theta,z,t)$, is now expressed as a time varying function. The local diffuse reflectance, R (r,t), from a semi-infinite medium irradiated by a pencil beam is given by [57];

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