EXHIBIT 2008

Photoplethysmography (PPG) is a noninvasive optical method accepted in the clinical use fo
oxygen saturation. It is widely believed that the light intensity after interaction with the bio
modulated at the heartbeat frequency mainly due to pulsatile variations of the light absorpt
volume pulsations. Here we report experimental observations, which are not consistent wit
the importance of elastic deformations of the capillary bed in the formation of the PPG wav
new insight on light interaction with live tissue. To explain the observations we propose a n
pulse oscillations of the arterial transmural pressure deform the connective-tissue compon
periodical changes of both the light scattering and absorption. These local changes of the li
are detected as variations of the light intensity returned to a photosensitive camera. Theref
indirectly monitored even by using the light, which slightly penetrates into the biological ti

Introduction

It is commonly accepted that photoplethysmography (PPG) is a non-invasive optical metho
blood volume changes in the microvascular bed of tissue[1,2,3]. PPG waveforms are used for ca
saturation and heart rate determination in pulse oximeters which are widely accepted for r
Conventional pulse oximeters operate at the red and infrared light, and use the transmissio
photoplethysmography in which the light source and photodetector are situated at the opp
across a fingertip or an earlobe[2,4]. Such geometry provides efficient interaction of the light
includes the optical processes of multiple scattering, absorption, reflection, and transmissi
the light intensity received by the photodetector are the blood volume, blood vessel wall m
of red blood cells[7,8,9]. The general consensus is that the PPG waveform originates from puls
optical density caused by arterial pulsations which are the most significant[9,10]. Capillaries a
variations of their size[11].

Imaging photoplethysmography (iPPG) is a non-contact imaging method for mapping cardia
iPPG usually operate in reflection mode where both the illuminating light source and photo
alongside each other. In the reflection-mode PPG, light interaction wit
the illuminating light. Attempts to develop imaging pulse oximeter wer
which penetrates into the tissue for several millimetres, e.g., 2.5 mm at
researchers from different groups reported observation of a large-amp
modulation of the PPG waveform under green light illumination (wavel
photoplethysmography[15,16,17,18,19,20,21,22]. This observation is difficult to

observations.

Results

Mapping the areas with maximal PPG amplitude

The measurements were carried out with 58 healthy subjects. Mapping the PPG signal ampl areas was done by using an iPPG system with lock-in pixel amplification referred to as Bloo which was developed in our group[20,25]. Before measurement the subject placed his palm on comfort position the subject was asked to avoid hand movements during 30 seconds of vide green light (wavelength of 525 nm) for illumination of the subject's arm.

Two typical examples of the PPG-amplitude distribution are shown in Fig. 1a,b where the ar with the initial camera image to provide an anatomic reference of the respective subject. Th calculated as an AC/DC ratio of the PPG waveform where AC and DC refer to the alternatin and average (slowly varying) portions of the detected photo-signals, respectively. The ampli pseudo colours so that the red colour corresponds to the higher amplitude. It is evident fro pulsations are unevenly distributed over the subjects' arms. We found that these maps vary subject to another. Evidently, for each subject we can find an area with the maximal PPG-ar position in the arm. We map the position of these spots in respect to the anatomical schem separately for the left (Fig. 1c) and right (Fig. 1d) hands. In these maps, each hot spot belong subjects. It is clearly seen that the most of hot spots are situated near either radial or ulnar are subjects in whom the hottest spots are in the thumb or in the little finger. Anyway, the h observed in the vicinity of arteries. The amplitude of the blood pulsations in the hottest spo 5.7%. Note that these values represent the AC/DC ratio, i.e. the amplitude of the alternating at the heartbeat frequency in relation to the magnitude of the slowly varying mean PPG sign the hottest spot over all subjects was 2.2% (standard deviation, STD = 0.9%) for the left hand right hand.

Two examples of spatial distribution of the PPG amplitude (**a**) and (**b**) overlaid with raw camera images measured in two positions of the spots in which we observed the maximal PPG amplitude for the left hand (**c**) and for the right hand (**d**) as black circle for one subject. The colour scale on the right shows the pulsation amplitude as the AC/DC ratio of the PPG wa

Counter phase PPG waveforms

Experimental observation of the PPG waveforms pulsating in the counter phase was recentl taking an advantage of the BPI system to visualize the spatial distribution of the relative pha current study, we considerably extended the cohort of subjects and confirmed that all of th adjacent areas in which the PPG waveforms oscillate with the same heart rate but in the co of such signals is shown in Fig. 2 where in Fig. 2a we show the map of PPG-amplitude for a s amplitude is situated nearby the radial artery. An enlarged image patch of the area containi shown in Fig. 2b. A fragment of the PPG phase distribution of the same area is shown in Fig. phase difference between pulsations in the adjacent areas within the black circle is equal to show three dimensional (3D) plot of the pulsation-amplitude distribution considering the re the area within the black circle in Fig. 2b,c. Note that two hot spots within this circle are se only 3.3 mm.

and position as the patch (**b**). Distribution of PPG pulsations (**d**) considering their relative phase in the area within the bl
waveforms (**e**) calculated in ROIs of 3 × 3 pixels chosen in the points with extreme amplitude within the black circle. The
pulsations maps are in degrees and in per cents for phase and amplitude PPG maps, respectively.

After determination the positions of the hot spots in the PPG-amplitude map in Fig. 2a, we
regions of interest (ROI) in the points where two extremes of the amplitude were found. In
PPG signals by the spatial averaging the pixel values within the ROIs of the size 3 × 3 pixels,
area of 0.75 × 0.75 mm^2 at the palm. These waveforms are shown in Fig. 2e. By convention us
photoplethysmography literature[3,5], all PPG waveforms in this paper are inverted in sign so
with varying transmural pressure. Therefore, the negative extremes of the PPG waveform c
phase. As one can see, the PPG signals in these adjacent areas indeed oscillate in the counte
that the red curve in Fig. 2e has a typical saw-tooth shape with the faster transition from th
always observed in measurements of the arterial blood pressure waveforms[5,26]. In contrast,
time and its shape clearly contradicts with behaviour of the arterial pressure. Erroneously,
counter-phase PPG waveforms were attributed with asynchronous blood supply to the adja
to explain their origin in the frames of the commonly accepted model of PPG in which the s
variation in the tissue optical density due to the blood-volume pulsations in arteries[10]. In th
the new model of the PPG signal formation suggesting indirect impact of arterial blood puls
modulation.

Influence of the external local pressure

The experimental data presented in Figs. 1 and 2 were obtained in conditions when the subj
contact. In the next experiment we studied the influence of the mechanical contact on the
end, a subject was asked to put his hand on the glass table while the illuminator (green light
and recording camera were settled under the table. To exclude direct reflections from the g
polarized light and a polarization filter installed before the camera with orthogonal orientat
polarization of the incident light. There were three steps of iPPG recordings. First recordin
contact of the skin with glass. In the second step, the contact of the pa
additional weight of 1.7 kg was applied to the hand in the third step. An
this weight to the skin in the areas of the contact with the glass was es

The results of the experiment are shown in Fig. 3 where spatial distribu
steps 1, 2, and 3 are presented by images a, b, and c, respectively. As or

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