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Electro-optical Plethysmography for Non-invasive Estimation of Hemoglobin Concentration

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Abstract–**Novel sensors and instrumentation are currently being investigated with the intended application of determining the concentration of hemoglobin and other optically absorbing compounds in blood using non-invasive methods. In order to measure concentration, the mass or amount of a compound must be known in addition to the volume of liquid. In principle, it may be possible to estimate hemoglobin concentration from a change in optical absorbance occurring over the cardiac cycle divided by a corresponding change in measured blood volume during the cycle measured from peripheral tissue, e.g. the finger or ear. Electrical and optical sensors were evaluated *in vitro* using a tissue phantom and an absorbing liquid medium. The effect of changes in optical absorption and pulse pressure on the capacitance and optical absorbance were studied.**

I. Introduction

IRON-deficiency anemia is a common condition affecting approximately two billion people worldwide [1]. It is defined as a less than normal quantity of hemoglobin in the blood or a decrease from the normal size and/or number of red blood cells. The main function of hemoglobin is to carry oxygen from the lungs to the tissues, so anemia leads to hypoxia (lack of oxygen) in organs. Mild anemia is usually symptomless but in moderate cases, sufferers exhibit symptoms of tiredness and lethargy. Severe cases can lead to dizziness, shortness of breath or cardiac arrest. The clinical definition of anemia in adults is a blood concentration of hemoglobin of less than 12-13 mg/L of blood, usually manifested as a lack of red blood cells [2].

Currently, hemoglobin concentration measurement is performed by collecting a venous blood sample or a pinprick of blood from an accessible site such as a finger. The blood is transferred to a disposable cuvette which is then placed in a suitable analyzer and the hemoglobin concentration is measured spectrophotometrically. Various factors are known to affect accuracy, many of which depend on individual sampling techniques [3, 4].

The envisaged system, by contrast to this method would be completely non-invasive, pain-free and may be performed quickly and safely by an operator with minimal training (or by the patient in the home or other non-clinical environment). There would be no risk associated with handling blood and needles, and no need for disposal of biohazard waste. Furthermore, once the probe is applied to the patient, the readout may be continuous which would have useful application during surgery where significant blood loss can occur over a short timescale.

Estimation of hemoglobin concentration depends on the ability to detect the hemoglobin (or red cell) amount as well as the total blood volume (approximately red cells + plasma). Non-invasive estimation of hemoglobin concentration is possible using recently developed commercially available systems based on purely optical methods [5]. These systems show indeterminate accuracy and precision however [6], since the plasma component of the blood is optically transparent and therefore difficult to detect using optical methods alone.

The use of capacitance sensors has been reported already for measurement of hematocrit *in vitro* [7]. Prior to development of a single electro-optical sensor capable of measuring simultaneous time-dependent capacitance and absorbance variations, separate capacitance and optical sensors were designed and developed. The capacitance sensor is sensitive to pulsatile variations in dielectric permittivity of the tissue. An optical photoplethysmography sensor was also developed to measure time-dependent absorbance variations. The two sensors were used to detect changes in capacitance and absorbance occurring in a tissue phantom consisting of elastic tubing simulating arteries filled with a saline and dye solution. Signals from both sensors analyzed and compared for a range of dye concentrations and pulse pressures. The former investigation was designed to assess the system's sensitivity to simulated changes in hemoglobin concentration while the latter was to assess any (undesirable) variation by factors other than hemoglobin concentration, namely blood pressure.

II. Materials and Methods

A. Capacitance sensor and instrumentation

The capacitance sensor is essentially two plates of a parallel plate capacitor so that when it is placed over an extremity, the tissue of the extremity forms the capacitor dielectric. A grounded guard rail was added as shown in Fig. 1 (a), which has the effect of reducing sideways 'leakage' of electric field at the edge of the sensor, i.e. the field lines are effectively straightened at the plate edges.

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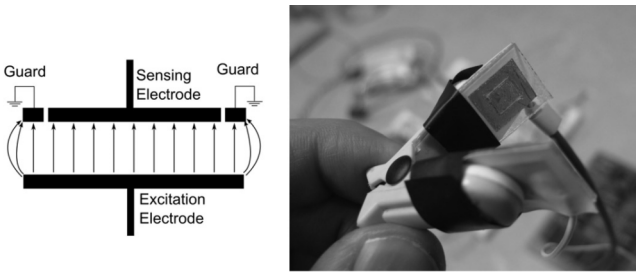
The plates were electrically insulated from the tissue using 0.1 mm thick adhesive cellulose film. The plates were attached to an earlobe pulse oximeter probe shell as shown in the photograph in Fig. 1(b). One plate (the excitation electrode) is attached to a signal generator supplying a 100 kHz sinusoidal signal of 1.5 Vrms amplitude.



(a) (b)

Fig. 1. (a) Diagram of guarded capacitance sensor. (b) Photograph of sensor enclosed within earlobe probe shell.

The sensing electrode was connected via a screened cable to a capacitance-to-voltage (C-V) circuit, shown in the diagram in Fig. 2. It is based on a transimpedance amplifier, or current-to-voltage converter (I-V) converter, where the transimpedance is a capacitance. This circuit is used in electrical capacitance tomography systems. Any capacitive sensor has stray capacitances associated with it which are due to factors such as the screened cable connecting the sensing electrode to the measuring circuit (approximately 100 pF for a 1 metre cable). In the C-V circuit, the stray capacitance C_{s1} is driven by the sine wave voltage source directly and will not affect capacitance measurement. C_{s2} is kept at virtual earth by the operational amplifier, therefore, there is no potential difference across it and no effect on capacitance measurement. Such a circuit is therefore considered, stray capacitance-immune.

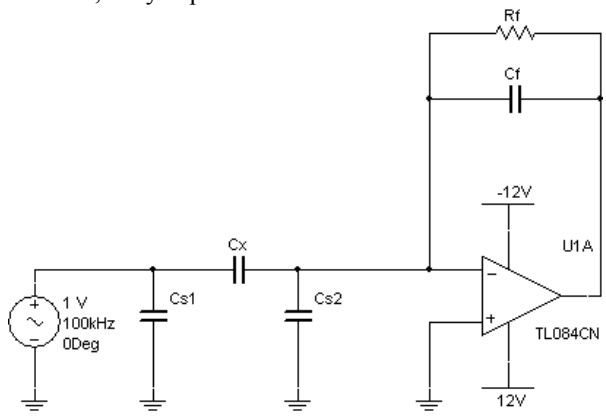


Fig. 2. Circuit diagram of capacitance-voltage circuit for measuring the capacitance *Cx* of the probe.

C_x is the capacitive sensor and C_f is the feedback capacitance. R_f is needed to bias the op-amp to prevent the op-amp output drift, which would eventually saturate the op-amp. The output of the circuit, $V_{out,}$ is given by:

$$V_{out} = \frac{j\omega C_x R_f}{j\omega C_f R_f + 1} V_{in} \quad (1)$$

where ω is the angular frequency of the sine-wave source. If $\left| j\omega C_f R_f \right| \gg 1$ then

$$V_{out} = -\frac{C_x}{C_f} V_{in} \quad (2)$$

The output voltage from the C-V circuit is amplified and the signal passed to a full-wave rectifier to demodulate the slowly-varying (dc) signal from the excitation signal. The rectified signal is low-pass filtered (cut-off frequency 22.5 Hz) to remove mains interference. The dc capacitance signal is tapped at this point, which is used to normalize the pulsatile (ac) capacitance signal. This signal is band pass filtered (0.1 Hz – 22.5 Hz), and the resulting ac signal amplified (gain 54.5). The normalized (ac/dc) capacitance was calculated thus

$$\frac{\Delta C_x}{C_x} = \frac{\Delta V_{out}}{V_{out}} \quad (3)$$

where $\Delta V_{out,}$ is the ac voltage output from the capacitance measurement circuit and $V_{out,}$ is the dc voltage output. This quantity is referred to in the results section as the capacitance plethysmography (CPG) amplitude.

B. Optical sensor and instrumentation

The optical sensor was fabricated using a commercial earlobe pulse oximeter (GE Healthcare, Helsinki, Finland). The red-emitting light-emitting diode and PIN photodiode were utilized to make a single wavelength photoplethysmograph sensor. The LED was driven by a 24mA dc signal, while the photodiode was connected to a transimpedance (I-V) amplifier of gain 6.67 x10^5 VA^{-1} and the signal lowpass filtered to produce a dc output. The signal was also band-pass filtered (0.4 Hz – 15.9 Hz), and amplified to produce an ac output signal. The normalized (ac/dc) absorbance was calculated thus

$$\frac{\Delta A}{A} = \frac{\Delta V'_{out}}{V'_{out}} \quad (4)$$

where $\Delta V'_{out,}$ is the ac voltage output from the optical measurement circuit and $V'_{out,}$ is the dc voltage output. This quantity is referred to in the results section as the photoplethysmography (PPG) amplitude. The capacitance and optical signals were digitized and recorded using a National Instruments Data Acquisition card and recorded to a text file for later analysis using a LabVIEW virtual instrument.

C. In vitro model of perfused tissue

A simple model of the circulation was constructed for the purposes of evaluating the performance of the electrical and optical sensors, which is shown schematically in Fig 3. A

mixture of 0.9% saline containing black pigment dye was pumped using a custom pulsatile pump capable of generating a physiologic arterial pressure waveform of varying pulse pressure (systolic pressure minus diastolic pressure: selectable from 20 to 220 mmHg), at a constant frequency of 1 Hz (60 bpm 'heart rate'). The pump was connected using a short length of stiff arterial pressure catheter tubing to a custom tissue phantom. The phantom consisted of a loop elastic silicone tubing of internal diameter 2.2 mm enclosed within a glass cuvette of dimensions (*h* x *d* x *w)* 35 x 10 x 10 mm. The phantom is thus incompressible, being enclosed in glass. Besides the silicone tubing, the cuvette was otherwise empty containing only air. The temperature of the liquid was

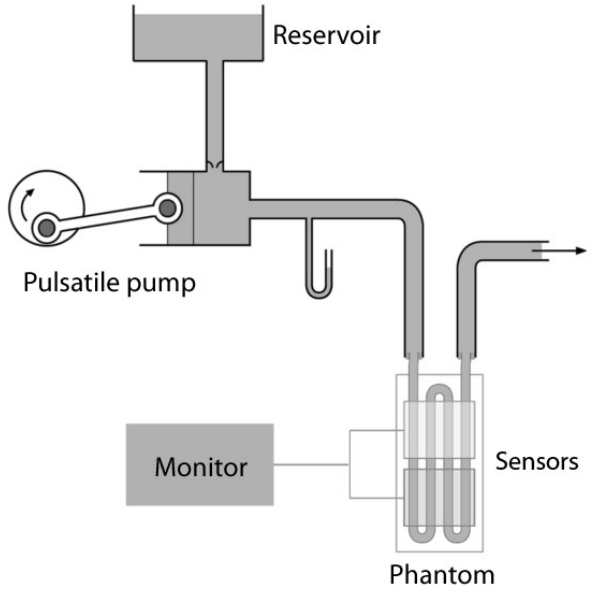


Fig. 3. Schematic diagram of the *in vitro* circulation model and tissue phantom.

The flow rate through the system could be adjusted using a roller clamp downstream of the phantom. The electrical and optical sensors were attached to the phantom adjacent to one another as shown in Fig 3. This configuration allowed recording of simultaneous optical and capacitance measurements to be recorded.

D. Measurements: effect of variable dye concentration

The reservoir was filled with a saline solution containing dye with an optical absorbance (at 660 nm) equivalent to blood with a hemoglobin concentration of 60 g/dL,.A Novaspec 4049 spectrophotometer (LKB-Produkter, Bromma, Sweden) was used to check the absorbance value. The pump was switched on and the tubing purged with the saline dye mixture. The flow rate was maintained at approximately 40 mL per minute through the system and the pulse pressure was maintained at 250 mmHg. Signals were recorded from the capacitance and optical probes for a period of 30 seconds. The normalized 'capacitance plethysmograph' (CPG) and photoplethysmograph (PPG) amplitudes were calculated from the acquired signals using (3) and (4) and averaged over the 30 second measurement period. The dye concentration was adjusted by diluting the contents of the reservoir with an appropriate volume of saline and measurements repeated for a range of dye concentrations.

E. Measurements: effect of variable pulse pressure

A range of measurements were made using a similar protocol but with a constant dye concentration giving an optical absorbance equivalent to blood of hemoglobin concentration 20 g/dL. The pulse pressure however was varied from 20 mmHg to 220 mmHg, keeping diastolic pressure less than 20 mmHg (i.e. the systolic pressure was increased). As before, flow was maintained at approximately 40 mL/minute.

III. Results

It was found that the static capacitance of the probe and phantom was approximately 180 pF when the tubing within the phantom was filled with 0.9% saline. Fig. 4 shows a graph of the peak-to-peak amplitudes of the normalized optical and capacitance signals (PPG and CPG respectively) plotted against equivalent hemoglobin concentration.

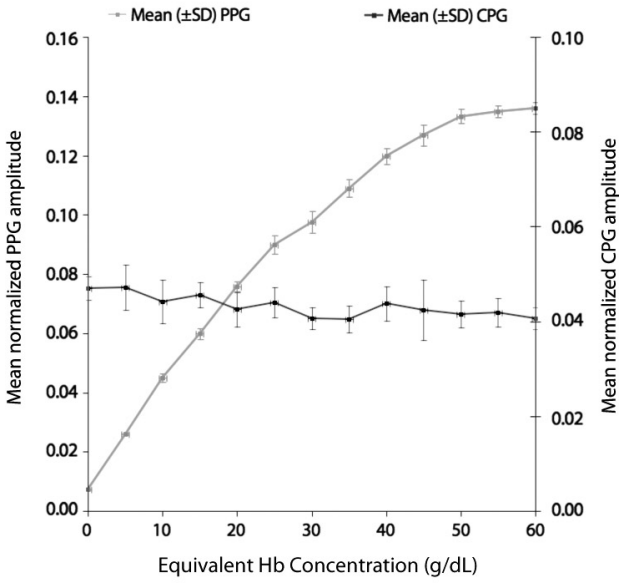


Fig. 4. Graph of mean normalized PPG amplitude (left *y*-axis) and mean normalized CPG amplitude plotted against equivalent blood hemoglobin (Hb) concentration.

It can be seen that the PPG amplitude increases greatly with increasing dye concentration. By contrast, the CPG amplitude changes little, decreasing very slightly, with increasing dye concentration. Fig. 5 shows a graph of the ratio PPG:CPG amplitude against equivalent hemoglobin. It can be seen that this ratio increases with increasing concentration.

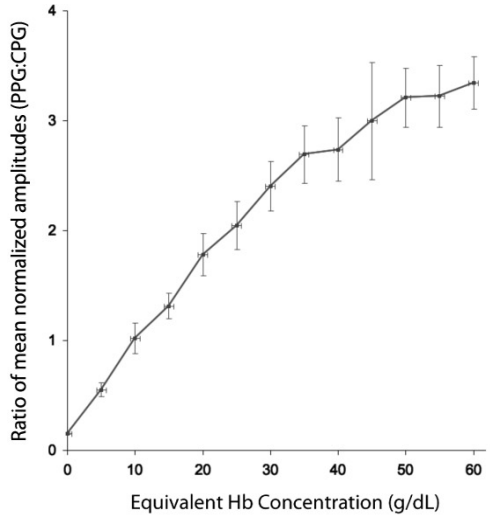


Fig. 5. Graph of ratio of mean normalized amplitudes (PPG:CPG ratio) plotted against equivalent blood hemoglobin (Hb) concentration.

The following results were obtained from the second part of the study: an investigation of the effects of pulse pressure. Both the PPG and CPG signal amplitudes were seen to increase with increasing pulse pressure. Fig. 6 shows a graph of the ratio PPG:CPG amplitude against pulse pressure. It can be seen that this ratio is not affected greatly by changes in pulse pressure.

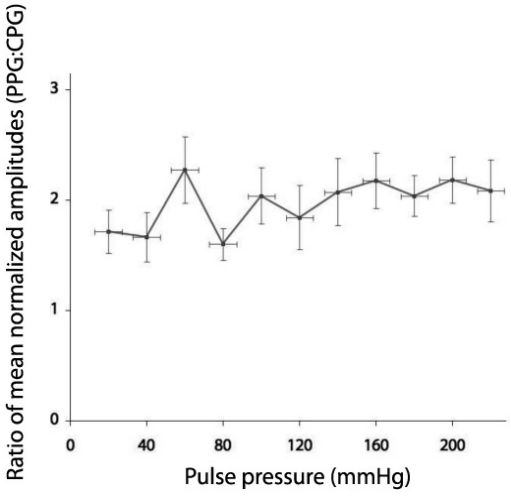


Fig. 6. Graph of ratio of mean normalized amplitudes (PPG:CPG ratio) plotted against pulse pressure.

IV. Discussion

This *in vitro* investigation demonstrated that simultaneous measurements of optical absorbance and capacitance can yield useful information regarding the composition of a blood substitute (saline and dye), namely the concentration of dye, which like hemoglobin and other chromophores is readily detectable using photoplethysmography. However, unlike hemoglobin, the plasma component of blood is more difficult to detect. The slight decrease in capacitance with dye concentration could not be explained. The ratio of PPG amplitude to CPG amplitude was seen to vary with varying dye concentration which suggests that this value may be a useful index of hemoglobin concentration *in vivo*. The result is not surprising since the dye would not be expected to significantly affect the capacitance of the liquid component within the phantom. A major concern would be inter-patient variability caused by physiological factors other than hemoglobin concentration. For this reason the pulse pressure was chosen as an independent variable to further investigate this technique. It was found that the ratio PPG:CPG was invariant to pulse pressure, suggesting that if the technique were to be applied *in vivo*, the probe may be insensitive to blood pressure changes: a desirable property of a hemoglobin monitor.

Further work is needed to validate the technique *in vivo* and to produce a non-invasive device for continuous monitoring of hemoglobin concentration. Early results suggest that the capacitance signal is small and difficult to resolve against background noise and interference in the signal. The instrumentation is currently undergoing revision and improved screening is being added to the measurement system in an attempt to mitigate this effect.

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