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APPLICATION OF NEAR INFRARED SPECTROSCOPY TO PULSE OXIMETRY AND TUMOUR OXIMETRY

Sonnia M. López Silva
Instituto Universitario de Microelectrónica Aplicada, Universidad de Las Palmas de Gran Canaria, Spain

Introduction

Jöbsis [1] first showed that near infrared (NIR) radiation has the characteristic of excellent penetration through biological tissues and could be used to monitor the degree of oxygenation of certain metabolites. Since then many works have been devoted to the application of NIR spectroscopy (NIRS) to tissue oxygenation clinical monitoring and the instrumental development of this technique [2].

Wavelength dependent absorption properties of various natural chromophores make possible the quantification of blood and tissues oxygenation by optical spectroscopy. In Figure 1 are shown the variations of the millimolar extinction coefficient of the oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (RHb), the two major blood haemoglobin derivatives, from 600 to 1000 nm [3]. One of the most important parameters related to the blood' oxygenation is the oxygen saturation. Oxygen saturation (So_2) refers by definition to the part of the haemoglobin concentration in the blood that can combine reversibly with oxygen. Consequently [4]:

$$So_2 = \frac{c_{HbO_2}}{c_{tHb} - c_{dHb}} = \frac{c_{HbO_2}}{c_{RHb} + c_{HbO_2}} \tag{1}$$

being C_{tHb}, C_{dHb}, C_{HbO2} and C_{RHb} the concentrations of total haemoglobin, dyshaemoglobins, oxyhaemoglobin and deoxyhaemoglobin, respectively. In the case of a non-scattering but absorbing medium containing two blood haemoglobin derivatives (HbO_2 and RHb), it is possible to apply the Bouguer-Lambert-Beer law and through simple transformations for a two components system measured at two wavelengths (λ_1 and λ_2) to obtain [3]:

$$So_2 = \frac{\varepsilon_{RHb}^{\lambda_1} - \varepsilon_{RHb}^{\lambda_2}\left(A^{\lambda_1}/A^{\lambda_2}\right)}{\varepsilon_{RHb}^{\lambda_1} - \varepsilon_{HbO_2}^{\lambda_1} - \left(\varepsilon_{RHb}^{\lambda_2} - \varepsilon_{HbO_2}^{\lambda_2}\right)\left(A^{\lambda_1}/A^{\lambda_2}\right)} \tag{2}$$

expression that relates So_2 with $\varepsilon_{RHb}^{\lambda_1}, \varepsilon_{HbO_2}^{\lambda_1}, \varepsilon_{RHb}^{\lambda_2}, \varepsilon_{HbO_2}^{\lambda_2}$ - the millimolar extinction coefficients of RHb and HbO_2 at wavelengths λ_1 and λ_2 respectively.

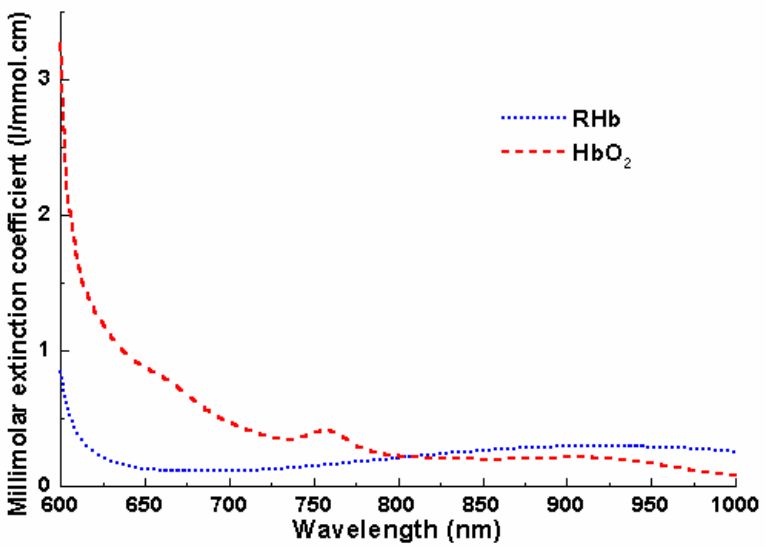

Fig. 1. Absorption spectra of oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (RHb) [3].

Pulse oximetry

Pulse oximetry is widely used for the non-invasive monitoring of arterial blood' haemoglobin oxygen saturation (So_2) and heart rate [5-7]. This technique is based on the differential absorption of the oxy- (HbO_2) and deoxyhaemoglobin (RHb) (Figure 1) and the time variable optical attenuation by a vascular bed associated to the cardiac cycle (Figure 2). The So_2 value is derived by analysing the pulsatile component with respect to the corresponding non-pulsatile component of the time variable signals or photoplethysmograms (PPG) at two specific wavelengths. The pulsatile component (E_{AC}) results from the expansion and relaxation of the arterial bed. The non-pulsatile component (E_{DC}) of the PPG is related to the attenuation by nonpulsatile arterial blood, venous blood and tissue. The available pulse oximeters use light emitting diodes (LEDs) with emissions in two regions of the optical spectrum, in the red (630-660 nm) and in the infrared (880-940 nm), as sources. In the last years have been proposed changes in the traditional wavelengths [8-13] mainly toward an effective application of reflectance pulse oximetry to fetal monitoring [9, 11]. With the aim of apply the NIRS advantages to pulse oximetry, has been developed and improved an optical sensor based on two laser diodes [14-21], a signal processing algorithm [14-17], as well as an alternative calibration procedure [20-21].

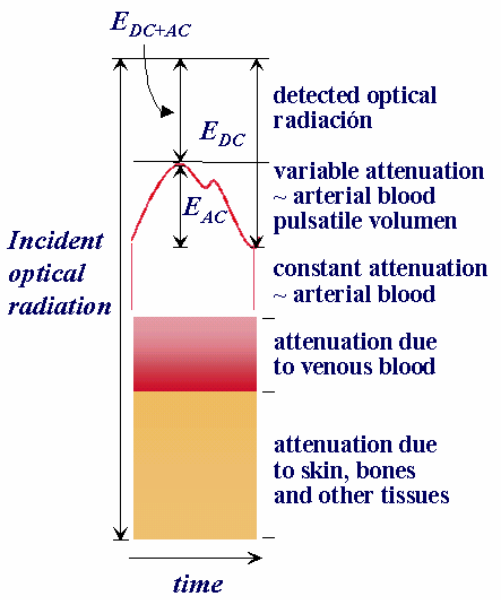

Fig. 2. Pulse oximetry principles: the variable and constant components of a photoplethysmogram.

The optical sensor consists of the light sources, optical detectors and detectors pre-amplifier. The light sources are two laser diodes (LDs) with peak wavelengths close to 750 nm and 850 nm. In particular, at 760 nm there is a clear maximum differential absorption between HbO_2 and RHb spectra (Figure 1). This property has been exploited [14-21] to substitute the red LED typically used in pulse oximetry. As detectors are used BPW34 p-i-n silicon photodiodes (PDs) connected in parallel, for the purpose of increase the detection area. The sensor configuration corresponds to the transmission mode and according to that the LDs and the PDs are situated in opposite sides, in close contact with the surface of the finger. The measurement system also comprises the sensor electronics, an acquisition board (DAQ) and a personal computer (PC). The sensor electronics generates separated pulses to energise the LDs alternately through the driver during 1 or 5 μs with a repetition rate of 1 kHz. The output current from the PDs is first converted to a proportional voltage and the amplified output voltage is decomposed into separated channels using sample-and-hold circuits (S&H) synchronously triggered with respect to the pulse driving the corresponding LD. The outputs of the S&H are fed into the analogue inputs of the DAQ. The timing board of the sensor electronics also generates the trigger and conversion signals for the DAQ.

The attenuation of the radiation by a human body pulsatile bed is due to the RHb and HbO_2 absorption, but is also caused by multiple scattering in the tissue structures and red blood cells. Because of that, the relationship used for calibration and So_2 calculation could have the form [22]:

$$So_2 = \frac{K_1 + K_2 \cdot q}{K_3 + K_4 \cdot q} \tag{3}$$

where K_1, K_2, K_3 and K_4 are coefficients derived from the pulse oximeter calibration procedure that are related to the HbO_2 and RHb millimolar extinction coefficients (Equation 2), and q is [17]:

$$q = \frac{\log(1 - \frac{E_{AC}^{750}}{E_{DC}^{750}})}{\log(1 - \frac{E_{AC}^{850}}{E_{DC}^{850}})} \approx \frac{\frac{E_{AC}^{750}}{E_{DC}^{750}}}{\frac{E_{AC}^{850}}{E_{DC}^{850}}} \tag{4}$$

The main difficulties in the extraction of the information from the PPG signals for each wavelength are the little value of the signals variation with respect to their constant values and the presence in the signals of artefacts caused by movements of the part under analysis. The signal processing algorithm [14-17, 21] for the calculation of q (Equation 4) relies on a numeric separation of the E_{AC} and E_{DC} signals for both wavelengths (750 and 850 nm) and a non-linear filtering.

Patients ranging in age from 50 to 86 years old, with respiratory failure conditions were monitored as a part of the calibration procedure in order to cover a wide range of So_2 values. A calibration curve has been derived [20, 21] according to Equation 3 through the in vitro arterial So_2 determination with a significant quantity of experimental points (41) ranging from 60 to 95 %.

Tumour oximetry

Tumour hypoxia is a major factor influencing the clinical response of many tumours to therapy [26]. Ischemia and hypoxia in tumours lead to radiotherapy and chemotherapy resistance and additionally predisposes the cancer cells to a physiologic selection that encourages the increase in cellular variants with more aggressive potential [27]. Knowledge of low tumour oxygenation status has high clinical value as it is an adverse prognostic factor [27] and oxygenation increases would be advantageous for maximising the effectiveness of treatment [28]. Tumours are usually heterogeneous, existing a strong heterogeneity between individual tumours and within individual tumour with respect to therapy relevant biological parameters, cell proliferation, distribution of blood vessels and others.

The physically dissolved oxygen in the interstitial fluid corresponds to the availability of O_2 at the cellular level. The oxygen partial pressure (pO_2) can be directly measured in tumours using polarographic microelectrodes based systems [26, 29]. The needle probes consist of sterile electrodes with stainless steel shafts 300 μm in diameter. The sharply ground tips of the probes contain a membranized polarographic, recessed microcathode in the form of a gold wire 12 or 17 μm in diameter. The absolute reading depends on the O_2 diffusion properties and solubility of the volume surrounding the electrode tip. Has been estimated that 12 μm probe will "see" a 3-cell thick hemisphere of about 50 cells in front of the electrode, whereas for the 17 μm electrode the hemisphere would be 5-4 cells thick containing around 550 cells. Calibration is required before and after the measurements. Measurements are made while driving the probe through the tumour in a stepwise manner. In this way, the pO_2 values for each stopping point in the electrode track through the tumour are monitored. No time dependent changes in pO_2 from a single location can be monitor due to the electrode O_2 consumption by electrochemical reduction. It causes continuos signal decrease with time, which can result in underestimation of the pO_2 level with this technique. Another problem is that it cannot accurately detect the very small electrical currents associated with low O_2 concentrations in the most hypoxic and radiobiologically interesting tumour areas.

In the last years has been marketed fibre-optic oxygen sensing devices [28, 30]. Blue light pulses carried by an optical fibre induce pulsatile fluorescence of a ruthenium luminophor incorporated into a silicone rubber polymer at the probe tip. The lifetime of the fluorescent pulses is inversely proportional to pO_2 in the tip. This rapidly equilibrates with the pO_2 in the surrounding medium and continuos readout of tissue pO_2 can be obtained. If it assumed that the luminophor is hemispherical in shape and has the same diameter as the fibre (230 μm), then it would be in immediate contact with about 400 cells (each cell is assumed to be 15 μm in diameter). It will presumably sample the oxygen content of these cells and their surrounding medium. One problem of this type of device is the non-linear relationship of the sensor response versus the O_2 concentration, so the probe has to be calibrated against known O_2 solutions. Errors in fluorescence lifetime determination are more serious at high O_2 concentrations than at low concentrations. As from a radiological point of view the interest is in the low end of the curve, the

linearity and high sensitivity in this region (0-15 mm Hg) is advantageous. However, because of its inherent non-linearity there may be a tendency for the probe to bring weighted average of pO_2 values where the more hypoxic regions predominate.

Several attempts have been made for the application of optical spectroscopy to tumour oximetry. Guichard et al [31] developed an instrument, which evaluated the relative proportion of HbO_2 and RHb in tissue by measuring the blood's absorption at two wavelengths. Two light emitting diodes with emissions at 660 nm and 940 nm were coupled to optical fibres, which were applied on the tumour and a third fibre collected the light backscattered. The tests carried out both on mice and on a human patient showed that the technique was reliable. More recently, Kim et al [32] measured relative changes in HbO_2 and total Hb in tumour vasculature and tumour tissue pO_2 simultaneously using non-invasive NIRS and needle type electrode respectively. The studies on a phantom solution and on a rat tumour showed that NIR technology could provide an efficient approach to monitoring tumour physiology, which is compatible with additional techniques.

NIR spectroscopy provides an estimate of average vascular oxygenation encompassing arterial, venous and capillary compartments based on the optical characteristics of HbO_2 and RHb, but parameters only derived from the blood Hb do not reflect the decisive terminal pathway of O_2 transport in tissue adequately. However NIRS also could provide an estimate of the intracellular tissue oxygenation through the analysis of other natural chromophores.

Cytochrome oxidase (CtOx) is the terminal enzyme in the cellular respiratory chain and is located in the mitochondrial membrane. Changes in CtOx redox state could be useful markers for the oxygenation state of tissue due to its redox changes in response to oxygen availability at the cellular level. CtOx has a broad absorption band in the NIR region, with a maximum around 830 nm in oxidised CtOx, which is missing in the reduced enzyme. Since the total tissue CtOx concentration does not vary in the short term, in vivo NIR measurements need only be made of the change in redox state, and therefore it is only necessary to know the difference spectrum between the oxidised and reduced forms of the enzyme. The difference spectrum, shown in Figure 3 [33], contains a small contribution from cytochromes, other than cytochrome oxidase found in tissue. Difficulties could arise from the fact that the contribution of cytochrome to overall absorption in tissue is considerably less than that of haemoglobin because of its lower concentration. Typically, the neonatal brain will have 40-60 micromoles of haemoglobin and 2-3 micromoles of cytochrome oxidase. For useful physiological measurements, one should expect to resolve changes of 1 micromole in haemoglobin and 0.1 micromoles of cytochrome oxidase [33].

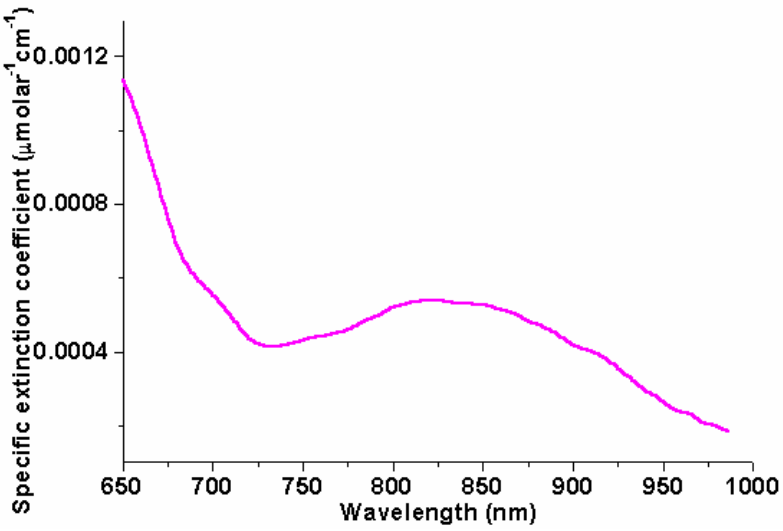

Figure 3: The difference absorption spectrum between the oxidised and reduced forms of CtOx [33].

NIR noninvasive spectroscopy has been implemented in a wide range scanner system in reflection mode [34] with a scan frequency of 400 Hz in the 400 to 1200 nm range and spectroscopy resolution less than 1 nm. The absolute quantities of oxygen saturation, oxygenated and deoxygenated haemoglobin and total

haemoglobin for blood volume could be measured. It has been also possible the cytochromes detection [35]. Studies of oxygenation in different tumours have been performed with this system [34, 36].

Discussion and conclusions

Pulse oximetry relies on the assumption that no other haemoglobin derivatives different from HbO_2 and RHb are present in the arterial blood, but in some cases other haemoglobin derivatives that have lose (temporarily or permanently) the ability to combine with oxygen are also present. Of the dyshaemoglobins, the carboxyhaemoglobin (HbCO) is the most dangerous as it is fairly common. At 660 nm the HbCO specific absorption coefficient is as high as the HbO_2 one [23]. One expected advantage of the 750-760 nm wavelength with respect to the classical red one (630-660 nm) is the small optical absorption of HbCO. Consequently, the error of the measured oxygen saturation value in the presence of such haemoglobin derivative could be negligible if the red wavelength is substituted by 750-760 nm. Beside this, the combination of measurement at wavelengths in (at least) three regions like 630-660 nm, 750-760 nm and 800-950 nm, could lead to the detection of the presence of the HbCO, if not to its quantification.

The assumption in pulse oximetry about the equality of the optical path lengths for the red wavelengths (630-660 nm) and the traditional infrared (880-940 nm) fails at low saturation values. It has been demonstrated for the case of reflectance that choosing two wavelengths closer to each other permit to equalise the penetration depth into the tissue and thus the sampling area [10, 13]. The results obtained through numerical simulation studies predicted that reflectance sensors fabricated with 735-760 nm and 890 nm emitters [10] or with 730-770 nm / 880-910 nm combinations [13] should be more accurate at low saturation than sensors made with conventional 660 and 900 nm band emitters. That was confirmed experimentally by animal testing with reflectance sensors based on 735 nm / 890 nm [12] and 730 nm / 880 nm [13] LEDs. This improvement of the pulse oximetry technique for low saturation values in the case of reflectance could be also valid, in some way, for the case of transmittance pulse oximetry. Nevertheless, the good performance of pulse oximeters at low saturation values also depends upon an appropriate calibration procedure, as numerical modelling cannot replace the empirical calibration.

From the point of view of the differences in HbO_2 and RHb specific absorption characteristics the wavelengths pair 750 nm / 850 nm has lower So_2 sensitivity in comparison to 630-660 nm / 880-940 nm. In the 750-760 nm band vicinity (Figure 1) there is a pronounced changes and a steep slope RHb curve respect to the HbO_2 one, which justifies the use of a LD. For the second wavelength was used an 850 nm LD, although the sensitivity could be improved using an emitter of the region 880-940 nm where the differences between HbO_2 and RHb spectra are bigger. It should be noted also that the curves around the 850 nm are flatter, and any shift in the emitter centre wavelength causes a smaller error than would be generated by the same shift in the 750-760 nm band. Although the LD have a narrow emission wavelength only a few nanometers in wide, the shape of the emission spectra as well as the peak wavelength are slightly temperature dependent. Avoidance of wavelength errors involves either temperature control of the LDs or measurement of the temperature with software compensation for the wavelength shift. It should be evaluated for a particular LD structure in regions like the 750-760 nm the magnitude of the error in pulse oximeter saturation readings as result of a LD wavelength shift associated to temperature variations.

Some works have been devoted to the development and application of multiwavelength pulse oximetry with different purposes [24, 25]. Taking into account the specific characteristics of other haemoglobin derivatives for its determination or quantification by optical methods it is necessary to carry out measurements at several wavelengths. The development of multiwavelength specific systems for non-invasive measurement needs the use of narrow emission bandwidths. The LDs exhibit narrow emissions and also have other advantages, like their high external efficiency and that are suitable for high frequency modulation. High external efficiency and wavelength specificity imply less thermal effects on the tissues under analysis. It is also possible to minimise the thermal effects by activating the LDs with short pulses.

As NIR radiation suffers less attenuation it could be more suitable to develop transmittance pulse oximeter sensor improved for measurements in pulsating beds thicker than normal finger tips, or in infant foot. From the point of view of the silicon photodiodes detection capabilities, the 750-760 nm band corresponds to higher values in comparison to 630-660 nm wavelengths, and in the order of the 850 nm. It lets to optimise the amplification process as the detected photocurrents could be of the same order.

The fact that a part of the processing is carried out via software instead of hardware brings a higher degree of flexibility to the measurement system. A potential possibility is to use the same sensor and sensor electronics for different kind of measurements or measurements in different places. For example: to measure the absolute saturation value in a pulsating bed or to record the relative variations of HbO_2 and RHb in a non-pulsating bed. Once acquired the raw signals, the processing by software would correspond to the type of measurement.

The obtained results [14-21] demonstrate the feasibility of using a sensor with laser diodes emitting at specific near infrared wavelengths for transmittance pulse oximetry and that it is possible to apply the proposed system to monitor a wide range of oxygen saturation levels.

Despite the attempts made for the application of NIRS to tumour oximetry [31, 32, 34-36], no method has become established in routine clinical practice. Due to it diagnostic and therapeutics consequences it is desirable the use, improvement and development of techniques for the rapid and continuos measurement of tumour oxygenation. It would be useful to develop instruments, equipment or devices accurate at low oxygen levels, with no time consuming or tedious calibration procedures and capable to differentiate, discriminate or recognise healthy, tumour and necrotic tissues. It would be necessary the utilisation of probes for interstitial measurements of needle type or for catheter insertion and probes for surface measurements. The purpose of using such techniques for tumour oximetry would be to measure the absolute value at a single location, the distribution in a given volume and the average value in that volume.

The use of NIRS and fibre optics offers interesting possibilities to measure the tumour oxygenation related parameters in a minimally invasive way and to combine this determination with others also based on optical principles, but a number of open question have to be solved. The development of such a project implies, among others: i) define the more appropriate fibre optic probe configuration for the detection of the optical signals; ii) study the optical characteristics of healthy and tumour tissues in vivo and of samples from these tissues; and iii) establish the oxygenation level, vasculature and blood' flow parameters, as well as histo-pathological characteristics of the tissues of interest by the standard reference methods and procedures. Toward the quantification of oxygen level in tumours it would be also necessary: i) define the wavelengths that better reflex the changes of HbO_2, RHb and CtOx related to tumour O_2 level; ii) establish the relationships and processing algorithms that permit to convert the diffuse optical reflectance signals detected at different wavelengths in parameters related to tumour O_2 levels; and iii) consider and compensate the interference caused by other natural components and structures of the analysed medium.

Acknowledgments

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