1 Introduction

In the developed world, a major cause of death or handicap in the newborn is cerebral hypoxic-ischaemic injury. In the full term infant, this is thought to be responsible for at least one-third of all deaths (PAPE and WIGGLESWORTH, 1979) and in the preterm infant it is estimated to be the cause of neurodevelopmental abnormality in up to two-thirds of survivors (STEWART et al., 1983). Cerebral tissue damage can be seen noninvasively using ultrasound, X-ray CT or NMR imaging techniques only after a few weeks, when generalised tissue loss occurs leading to the formation of porencephalic cysts. What is urgently needed is a technique for continuously monitoring cerebral ischaemia/hypoxia which would then allow one to intervene successfully to prevent irreversible damage. Near-infra-red spectroscopy (NIRS) appears to be such a technique, being both safe, noninvasive and applicable at the bedside.

The technique, which was first reported by JÖNSSON, (1977), relies on the relative transparency of tissues to light in the near infra-red, and the presence in this wavelength

![Absorption spectrum of haemoglobin solution. Units for absorption coefficient are quoted per millimolar of haemoglobin solution (molecular weight 64 500) per cm pathlength (WRAY et al., 1988)](image1)

**Fig. 1** Absorption spectrum of haemoglobin solution. Units for absorption coefficient are quoted per millimolar of haemoglobin solution (molecular weight 64 500) per cm pathlength (WRAY et al., 1988)

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**Hb** ---**HbO₂**

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**System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by near infra-red transillumination**

M. Cope  D. T. Delpy

Department of Medical Physics & Bioengineering, University College London, 1st floor, Shropshire House, 11–20 Capper Street, London WC1E 6JA, UK

Abstract—The technique of near-infra-red spectroscopy allows safe continuous monitoring of changes in blood and tissue oxygenation on an intact organ. This is made possible by observing spectral changes in the tissues caused by oxygenated haemoglobin (HbO₂), deoxygenated haemoglobin (Hb) and cytochrome aa₃ (Cyt aa₃). The paper describes the design and performance of an instrument that has been developed to apply this technique to the monitoring of the brain in newborn infants. The instrument monitors optical transmission changes across a newborn infant’s brain at four wavelengths. A standard deviation in error of 1 per cent (0.01 optical density OD) is achieved on measurements of transmission changes at 20 s intervals. This performance is obtained at a mean attenuation of 10 OD, the approximate attenuation across a term infant’s head. Long-term monitoring is possible as instrumental drift is less than 0.004 OD per hour.

Keywords—Cerebral, Cytochrome aa₃, Haemoglobin, Near infra-red, Oxygenation, Spectroscopy, Transillumination

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![Absorption spectrum of purified cytochrome aa₃ enzyme (BRUNORI et al., 1981). Units for absorption coefficient are quoted per millimolar of cytochrome aa₃ solution (two haemoglobin groups, molecular weight approximately 140 000) per cm pathlength](image2)

**Fig. 2** Absorption spectrum of purified cytochrome aa₃ enzyme (BRUNORI et al., 1981). Units for absorption coefficient are quoted per millimolar of cytochrome aa₃ solution (two haemoglobin groups, molecular weight approximately 140 000) per cm pathlength

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region of two natural chromophores having oxygenation dependent absorptions. The two compounds are haemoglobin and cytochrome aa3, and both exhibit different absorption properties depending upon whether they are in their oxygenated or deoxygenated form (Fig. 1 and 2). Haemoglobin is only present in the red blood cell, and its oxygenation state is therefore an indicator of blood oxygenation. Cytochrome aa3 is the terminal electron accepting enzyme in the oxidative metabolic pathway, and hence its oxidation state is an indicator of tissue oxygenation.

2 Equipment requirements

Light traversing tissue suffers a loss in intensity due to the effects of both scattering and absorption. For brain tissue in the wavelength region 700-1300 nm the loss in intensity is approximately one order of magnitude per centimetre (one optical density OD per cm). This increases with shorter wavelengths to three OD per cm at 514 nm in the green (Svaaasand and Ellingsen, 1983). In discussing this attenuation, it is important to note the angular distribution and the area of the input light beam and the detecting optics used for the measurements. Normally a combination of either a collimated laser or an optical fibre is used as the input beam, and an optical fibre for the detection optics. The fall in intensity within the tissue has been shown (Svaaasand, 1981) to occur in two stages. The first stage is very rapid as scattering converts the initially collimated input beam into a diffuse beam. The second stage occurs after a few millimetres of tissue and shows a less rapid fall because scattering does not attenuate a diffuse beam as strongly, and absorption by chromophores becomes a more significant part of the total attenuation.

The full term infant has a head diameter of approximately 10 cm, equivalent to 10 OD if measured in the transillumination mode. Problems of light detection across such large optical densities have led some workers to monitor reflected rather than transmitted light (Ferrari et al., 1986; Brazy et al., 1985). With light source and detector at angles of less than 180° the amount of attenuation decreases with decreasing angle as light can 'cut corners' due to its diffuse distribution in the tissue. The reduced attenuation is a direct consequence of the shorter average optical path length. There are two problems in using this reflection technique. First, because the optical path length is shorter, the attenuation change at the detector produced by a change in concentration of an absorber will be less and hence more difficult to detect. Secondly, the optical path taken by the photons is very difficult to predict and may change substantially with changing absorption. We are presently modelling light transmission through tissue using a Monte Carlo technique, and preliminary results indicate that it may be possible to calculate an average optical path length in the case of transmission (Van der Zee and Delpy, 1987; 1988). These calculations also indicate that, in transmission mode, average path length is only slightly affected by variations in tissue absorption and scattering coefficient, whereas in reflection there is a substantial and nonlinear dependence on these factors. We intend to verify these calculations experimentally by using picosecond light pulses to determine the photon time of flight (Arridge et al., 1986).

To assess the sensitivity required from a monitoring system, it is instructive to calculate the theoretical absorption changes caused by haemoglobin and cytochrome aa3 at concentration levels expected in brain tissue using the assumption that the Beer-Lambert Law will apply and that no scattering occurs in the tissues, the pathlength of the light being equal to the diameter of the head. The absorption calculated in this manner will represent the minimum absorption due to the chromophores. The scattering that does occur in tissue will lead to an increase in pathlength and hence an increase in the observed absorption (Wray et al., 1988). The average blood volume in the brain of the human adult is approximately 5 per cent v/v (Sakai et al., 1985). Assuming a normal haemoglobin concentration in whole blood of 150 g l⁻¹, a molecular weight of 64 500 (for the tetrahaem molecule) and the millimolar absorption coefficients of haemoglobin in Fig. 1, then at 800 nm absorption per centimetre of brain tissue is

\[ \text{absorption [Hb]} (\text{OD cm}^{-1}) = aC \]
\[ = 0.88 \times \frac{150 \times 10^3}{64 500} \times 5 \text{ per cent} \]
\[ = 0.10 \text{ OD cm}^{-1} \]

where

\[ a = \text{millimolar extinction coefficient} \]

\[ C = \text{molar concentration in millimoles} \]

Similarly for cytochrome aa3, cytochrome a concentrations are given as 22 μmolar in the human brain (Purves, 1972). Assuming a 1:1 ratio of cytochrome a to cytochrome aa3 then cytochrome aa3 is also 22 μmolar. Using absorption data for oxygenated cytochrome from Bruno et al., 1981 (Fig. 2) we find that absorption per centimetre of brain tissue at the absorption peak of 825 nm is

\[ \text{absorption [Cyt aa3]} (\text{OD cm}^{-1}) = aC \]
\[ = 3.4 \times 22 \times 10^{-3} \]
\[ = 0.07 \text{ OD cm}^{-1} \]

The effects of NIR absorption due to other chromophores in the blood and tissue have been ignored in this calculation. If these chromophores show no oxygen-dependent change in their absorption characteristics they will only represent a static background absorption. Chromophores having an oxygen dependent absorption (e.g. the remaining respiratory enzymes; Porter, 1966; Gilvvedt et al., 1984) are either present at insignificant concentration or have negligible NIR absorption.

Given the order of magnitude of the calculated absorption changes, and the resolution needed clinically, we have designed and constructed an instrument capable of measuring changes in absorption across an equivalent of 10 OD. The instrument can resolve changes of less than 0.02 OD, with a time resolution of 20 s, drift being less than 0.004 OD per hour.

3 Instrument design

To be able to measure absorption changes across as thick a tissue section as possible, we have chosen to employ high-power pulsed laser diodes as our light sources. For similar reasons, we are using a photomultiplier tube detector operating in the photon counting mode. The whole instrument is controlled by a microcomputer which monitors the intensity of each incident laser diode pulse in addition to the transmitted intensity through the tissues. The system can therefore compensate in software for a change in laser diode output energy. Fig. 3 is a schematic diagram of the instrument, and the important details of each element are discussed below.