

Shedding light on the brain

Clare Elwell and Paul Beard (Biomedical Optics Research Laboratory, Department of Medical Physics and Bioengineering, University College London, UK. E-mail: celwell@medphys.ucl.ac.uk)

Every year approximately 1 in 500 infants sustain long-term disability due to brain injury at or around the time of birth. The most common causes are damage related to extreme prematurity or some interruption to blood (and therefore oxygen) supply to the brain. Similarly, traumatic brain injury is a leading cause of mortality in the first four decades of life. Although techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) can be used to provide information on the structure and function of the brain they cannot be used on critically ill patients undergoing life support, particularly newborn infants. Non-invasive, bedside methods of studying the brain which can be used in an intensive care setting are of vital importance in helping us understand the mechanisms of brain damage and develop strategies to improve long-term neurological outcome.

Since the original paper in 1977 describing the first *in vivo* measurements in an intact brain,¹ near infrared (NIR) spectroscopy has been widely used to monitor oxygen and blood levels in biological tissue. In the NIR the major constituent of tissue, water, exhibits relatively low absorption [Figure 1(a)], enabling multiply scattered light to penetrate several centimetres into tissue allowing optical interrogation of layers below the surface, e.g. the human brain cortex. NIR spectroscopy exploits this relative transparency to make spectroscopic measurements of the concentration of two dominant tissue chromophores, oxyhaemoglobin (HbO₂) and deoxyhaemoglobin (HHb), found in the blood [Figure 1(b)]. Another sig-

nificant NIR chromophore is the enzyme oxidised cytochrome c oxidase (CCO) which provides information about the utilisation of oxygen at a cellular level. Figure 1(c) shows the absorption spectra for the oxidised and reduced forms of this enzyme. Unlike haemoglobin, the total concentration of the enzyme is unlikely to change over the course of a measurement and the difference spectra is used to provide information on cellular wellbeing. Spectroscopic measurements of tissue in the NIR therefore provide information about levels of blood oxygenation (from the relative amounts of HbO₂ and HHb), blood volume [derived from the concentration of total haemoglobin (HbO₂+HHb)] and cellular oxygen metabolic status (from the relative amounts of oxidised and reduced CCO). These measurements have enabled a wide range of basic science and applied clinical questions to be addressed.

A major advantage of the technique is its non-invasive and continuous nature—the light intensity levels used being well below those associated with tissue damage. Systems are portable and measurements can be made easily and repeatedly, by clinical staff at the bedside. Early NIR spectroscopy instrumentation used a single emitter and detector (optodes) allowing a specific region of the brain to be monitored. The geometry and relative transparency of the heads of premature infants led to the clinical application of NIR spectroscopy in the early 1980s to the investigation of neonatal brain damage. This allowed specific clinical questions to be addressed including the effects of the drug administration and the relationship between the severity of brain injury

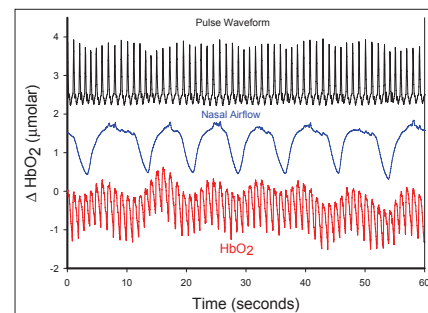


Figure 2. Changes in blood oxygenation due to cardiac (pulse waveform) and respiratory (nasal airflow) related fluctuations are clearly seen in the NIR spectroscopy measured HbO₂ signal in the adult head.

and long-term neurodevelopmental outcome.

By the early 1990s the application of NIR spectroscopy had extended to measurements in the adult brain. A major concern in performing measurements in adults is the contribution from tissues outside the brain, e.g. skin and skull, and this has been addressed using a combination of mathematical modelling and experimental methods. NIR spectroscopy has since been used to investigate a number of different adult patient groups including those with acute brain injury, stroke, depression, dementia and epilepsy.

The high temporal resolution of NIR spectroscopy enables rapid changes in blood oxygenation and volume to be monitored (Figure 2). This feature led to one of the most important developments in NIR spectroscopy research—the measurement of changes in blood

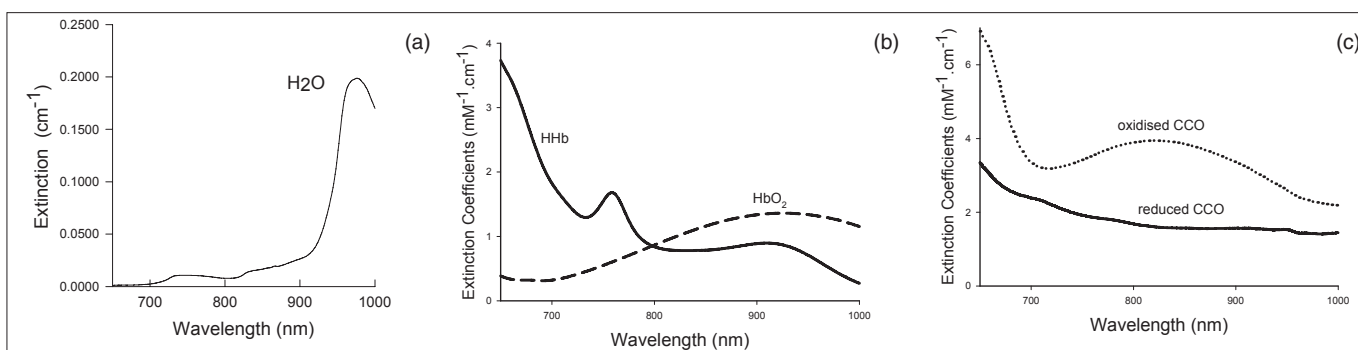


Figure 1. NIR Absorption spectra of the major tissue chromophores (a) water, (b) oxyhaemoglobin (HbO₂) and deoxyhaemoglobin (HHb) and (c) oxidised and reduced cytochrome c oxidase (CCO).

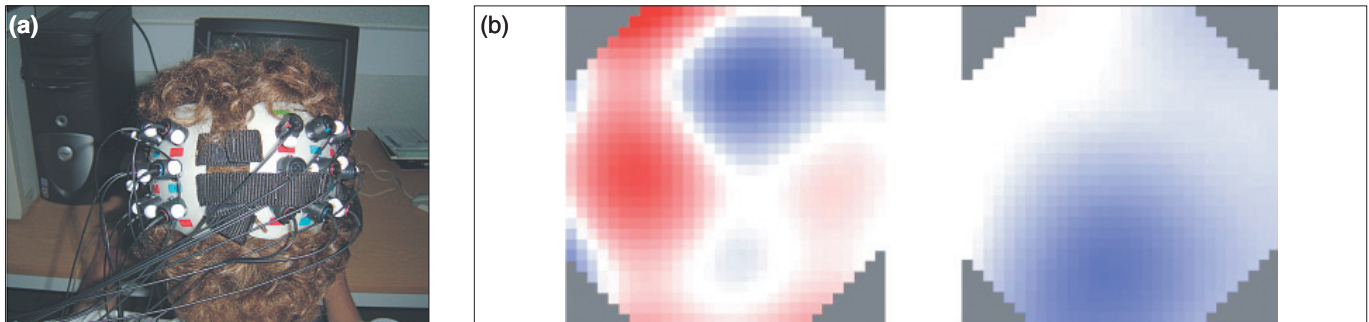


Figure 3. (a) A 24-channel NIR spectroscopy topography system (Hitachi Medical Systems) attached to an adult head and (b) the resulting oxygenation maps showing the distribution of HbO₂ (red) and Hb (blue) over the left and right hemispheres as the subject performs a calculation task.

volume and oxygen in response to localised activation of the brain. For example, if a subject is asked to view an image on a screen the area of the brain responsible for processing this visual information experiences a rapid influx of oxygenated blood (required to fuel the relevant neurons). NIR spectroscopy systems, usually operating at acquisition rates between 5 and 10 Hz, can be used to detect this localised change in blood oxygenation and hence determine which region of the brain is responsible for processing specific visual tasks. So-called functional NIR spectroscopy, is now used to investigate a wide range of processing tasks. Spatial resolution in functional NIR spectroscopy has been improved with the development of multichannel array topographic imaging systems which provide surface maps of the distribution of oxygen and blood in the brain (Figure 3). These systems are currently being used to monitor brain function in subjects of all ages including studies to investigate whether preterm babies feel pain, how young infants process visual information (e.g. familiar and unfamiliar faces) and the origin of visual disturbances associated with migraine.

Technical advances have also led to the development, at UCL, of the first 32-channel, time-resolved optical tomographic imaging system which provides three-dimensional images of the infant brain.² The device measures the flight times of photons transmitted between pairs of points on the surface of the head using very short pulses of laser light and 32 parallel time-resolved detectors. This project has also involved the development of highly sophisticated image reconstruction algorithms which enable the internal distribution of optical properties of the tissue (namely the absorption and scattering coefficients) to be derived from the experimental measurements. Initial imaging studies have utilised plastic, foam-lined helmets custom-built for each individual infant [Figure 4(a)]. Most recently, the system has been used to provide 3D images of the distribution of oxygena-

tion blood in newborn infants' brains during functional activation of the motor cortex (the area of the brain responsible for controlling limb motion).³ The brain of the infant and young child undergoes rapid development, and functional NIR spectroscopy can provide a safe and non-invasive method of characterising the pattern of neurodevelopment in normal babies and detecting abnormalities in infants who may have suffered brain damage.

Looking to the future, technical developments are likely to be aimed at further exploiting the obvious advantages of NIR spectroscopy technology such as its low cost, relatively high temporal

resolution, portability and compatibility with other imaging/monitoring modalities. There is now evidence that, using optical systems with increased temporal resolution (acquisition rates ≈ 100 Hz), it may be possible to measure changes in optical properties of brain tissue associated with firing of neurons (occurring over the first 50–100 ms after stimulation of the brain). This information, combined with the simultaneously measured haemodynamic response, may be particularly valuable in investigating conditions such as epilepsy and migraine.

The future is also likely to herald the introduction of a promising new hybrid NIR technique based upon the photoacoustic effect. In this approach, broadband (tens of MHz) ultrasonic waves are excited at depth within the tissue by the absorption of low-energy nanosecond laser pulses. The photoacoustic signals are then detected at the surface with a 2D array of ultrasound transducers. By measuring the time-of-arrival of the detected photoacoustic signals, and with knowledge of the speed of sound in tissue, a 3D image based upon the absorption and scattering properties of the tissues can be reconstructed. In common with "conventional" NIR spectroscopy, the technique can exploit the wavelength dependence of haemoglobin absorption to determine blood oxygenation. However, because the information is conveyed on an acoustic wave, which compared to NIR light, propagates with relatively little scatter in soft tissues, there is the potential to achieve significantly higher spatial resolution than purely optical methods. [In essence, the technique provides the high spectroscopic-based specificity offered by optical methods with the high spatial resolution available to ultrasound.] Although the technique is in its infancy, it has already been shown to be capable of providing impressive 2D *in vivo* images of the rat brain⁴ showing both the distribution of blood vessels and haemodynamic changes in response to localised functional activation (whisker stimulation). It has further been shown through laboratory studies using tis-

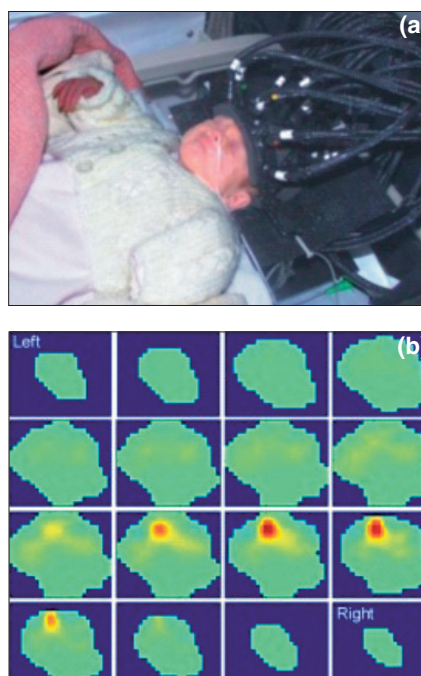


Figure 4. (a) A custom-built helmet for optical tomography of the neonatal brain attached to the head of a 10-day-old, 30 weeks gestation infant, (b) sagittal slices across a 3D image of absorption change in infant brain due to passive movement of left arm showing localised changes in the motor cortex.

sue mimicking phantoms (materials which simulate the optical properties of biological tissues) that the technique has the potential to spectroscopically quantify the blood oxygenation levels⁵ *in vivo*. Such spectroscopic methods also provide the opportunity to characterise biological processes at a cellular or molecular level by externally administering a contrast agent of distinct spectral characteristics that is designed to bind to a specific molecular or cellular receptor. Termed molecular imaging this provides a means of characterising the underlying molecular pathways of disease in order to develop and evaluate new therapies, particularly in drug discovery. Beyond its substantial use in small animal imaging, there exists the exciting prospect of using photoacoustic techniques to image the neonatal brain by making measurements through the fontanel (the acoustically transparent region of the newborn skull). The

ultimate aim of this clinical application will be to provide, non-invasively and at the bedside, high-resolution, quantitative images of brain oxygenation and haemodynamics which can be used to determine cerebral well being in this vulnerable patient group.

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continued from page 27

the stand-alone instrument to a computer. By connecting the gun to a cellular phone, data can be transferred in real-time to a computer at a control centre which may be located many kilometres away from the orchard. As with the KBA, many calibration packages for Brix and acid measurements of many fruits are provided. The users can also develop their own calibration equations from the calibration software packed with the instrument. Besides fruits and vegetables, FANTEC is now extending the applications of this gun into many areas. The measuring head (interactance) which is fitted to the round surface of many fruits can be replaced to fit products that have flat surfaces such as fish or bananas. Transmittance measurement is also available by extending the measuring head with the light source arm so that the physical pathlength is adjustable. The company can provide many parts that will allow you to measure spectra of many products such as leaves, eggs or samples in Petri dishes or test tubes.

Astem Company provides a hand-held instrument called the "Amaika AMC-77", which illuminates fruits by an emission diode instead of a conventional halogen lamp. The instrument weighs only 400g and can detect Brix in many kinds of fruits with thin peel. The acquisition time is only 1.5s, however, the use of an emission diode restricts the instrument to a limited wavelength range. Another fixed wavelength instrument is the "Optical Taster TD-2000C" developed by a joint research between Aomori Advanced Industrial Technology Center and Towa Denki Company. This instrument is also small (1.2kg) and

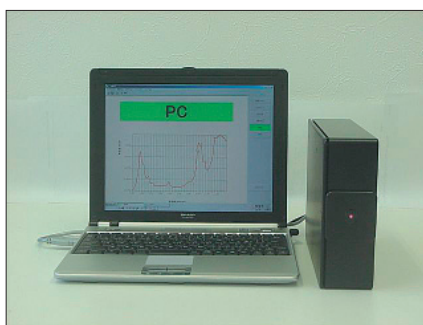


Figure 3. The "PlaScan-W" for plastic identification before recycling.

cheap. You can even rent it for a month for less than \$100, however, the instrument can work only for Brix determination of apples.

The final Japanese portable instruments in this report are the "OptScan-W" and "PlaScan-W" from Opt. Research Company. These are different from the ones used for fruits and vegetables, which utilise a diode array detector, because they use an acousto-optical tunable filter (AOTF). The instruments have one huge advantage in that they can measure spectra from 900 to 3400nm for the OptScan and from 1300 to 2600nm for the PlaScan. However, the AOTF system makes them more expensive. At present, 30% of their market is plastic identification (with calibration packages). Another 30% is the classification of raw materials for pharmaceutical and chemical products in order to meet the ISO 14001 requirement. The rest of their applications are for research, including detection of skin burn, typical skin condition, poisons, biodegradable polymers and quality detection of foods and petrochemical materials. The dimensions of the OptScan

are 57(H)×235(L)×153(W)mm and it weighs 1.6kg (Figure 3). It can provide data in the spc format that is accessible by many commercial chemometric software packages.

Even if this article is about the NIR instruments in Japan, there is one from Spectron Tech, Korea, that should not be omitted; it is the "HN1100". This instrument also works in the long wavelength region from 1100 to 1750nm with an InGaAs diode array. It is relatively heavy (6kg) but still portable. Many publications have shown the ability of this instrument for medical applications, such as evaluation of skin and nail moisture content, detections of hydrogen peroxide in whitening patches for teeth and in antiseptic solutions. The instrument may have a promising future with beauty and cosmetic companies such as Shiseido who are co-publishing a paper for nail moisture determination using this instrument.

Now, you can see that the market for portable NIR instruments in Japan is very active. Many manufacturers are competing in reducing both the size and cost of the instruments. Probably, in the next five years, the sweetness of fruits will be determined by a device that is somewhat similar to a laser pointer we use nowadays in the lecture theatre.

Acknowledgement

The authors express their appreciation to each manufacturer for providing useful information.

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