DIFFUSE OPTICAL IMAGING OF THE NEWBORN INFANT BRAIN

Jeremy C. Hebden,[1] Marta Varela,[1] Salavat Magazov,[1] Nick Everdell,[1]
Adam Gibson,[1] Judith Meek,[2] Topun Austin[3]

[1]. Department of Medical Physics & Bioengineering, University College London,
Gower Street, London WC1E 6BT, UK
[2]. Institute for Women's Health, University College London Hospitals NHS Foundation Trust,
235 Euston Road, London NW1 2BU, UK
[3]. The Rosie Hospital, Cambridge University Hospitals NHS Foundation Trust,
Hills Road, Cambridge CB2 0QQ, UK

ABSTRACT

Diffuse optical imaging has been developed at University College London (UCL) as a new method of assessing cerebral function and pathology in the newborn infant brain. The technique exploits the relative transparency of biological tissue to near-infrared light (700-1000nm) and the wavelength dependent absorption characteristics of hemoglobin, which vary with oxygenation. Methods have been developed to localize rapid hemodynamic changes resulting from functional activation of the cerebral cortex, and to generate three-dimensional images representing the spatial variation in cerebral blood volume and oxygenation. Previous studies have also been made of the brains of infants with intraventricular hemorrhage, hypoxic-ischemic injury, and epileptic seizures. This paper summarizes preliminary measurements performed with a new time-resolved system.

Index Terms— Diffuse optical imaging, medical imaging, optical tomography, infant brain imaging.

1. INTRODUCTION

The head of a newborn infant, by virtue of its small size and thin skull, is ideally suited for interrogation using methods based on the transmission of near-infrared (NIR) light. Monitoring cerebral oxygenation and hemodynamics in the neonate by exploiting the different NIR signatures of oxy- and deoxy-hemoglobin has been a focus of research at UCL since the pioneering studies by Wyatt *et al*. in 1986 [1]. Diffuse optical imaging systems have subsequently been developed at UCL and elsewhere to produce spatial maps (in two or three dimensions) of blood volume and oxygenation in the newborn brain [2-6].

Recently, diffuse optical imaging studies at UCL have focused on infants diagnosed with seizures [6]. Unexpected large fluctuations in cortical blood volume were identified in several infants treated with anticonvulsant medication, which were not exhibited in the healthy controls. These studies were performed using a continuous-wave system based on an array of avalanche photodiode detectors and laser diode sources (at two wavelengths) [7]. Meanwhile a new multi-channel time-resolved imaging system has been developed based on photomultiplier tubes and a tunable super-continuum laser. This has been built to replace a previous time-resolved imager [8], offering advantages in terms of improved portability, speed of data acquisition, and availability of wavelengths. The new system and results of preliminary measurements on newborn infants are outlined below.

2. INSTRUMENTATION

A schematic of the new UCL time-resolved imaging system is shown below.

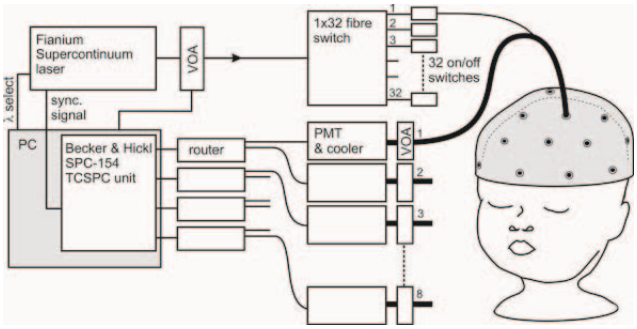


Figure 1: UCL time-resolved imaging system.

Although it is designed to accommodate 32 independent detectors, infant studies performed with the system so far

have only used 8 detecting channels as illustrated. The source consists of a supercontinuum laser (Fianium, UK), which emits powerful broadband picosecond pulses, coupled to a pair of acousto-optic tunable filters (AOTFs; one for each orthogonal polarization) which allow wavelengths to be selected over the range 600-1100 nm. The laser output is coupled to an array of optical fibers via a 32-way fiber switch and 32 on/off fiber switches. The average laser power at the surface of the head is a few milliwatts illuminating an area of about 30 mm^2, and therefore well within the limits for both eye and skin safety. The ends of the source fibers are co-located on a probe array with 3-mm diameter fiber bundles which collect the diffusely reflected light from the surface of the infant head. Each detector bundle is coupled to a photomultipler tube (PMT; Hamamatsu H8224P-50) via a computer-controlled variable optical attenuator (VOA) which is designed to reduce the amount of light reaching the PMT when a source is illuminated close to the corresponding detector. Each custom-made VOA consists of a 12-segment disk of variably-exposed x-ray film mounted on a stepper motor which provides attenuation of up to 3.7 neutral densities. The PMT outputs are routed to a time-correlated single photon counting module (TCSPC; Becker & Hickl SPC-630) which records the photon flight times relative to a synchronization pulse derived directly from the laser. The result is a distribution of flight times (known as the temporal point spread function, or TPSF) for each source-detector combination.

3. MEASUREMENTS

Preliminary measurements with the new time-resolved system in an 8-detector configuration have been performed on four newborn infants in the UCL Hospital neonatal intensive care unit (postmenstrual ages in the range 38-42 weeks). The source fibers and detector bundles are coupled to the infant head via a simple array probe illustrated in figure 2 (each of the numbered locations represents a source and detector). The probe consists of a thin flexible silicone rubber sheet lined with soft black foam.

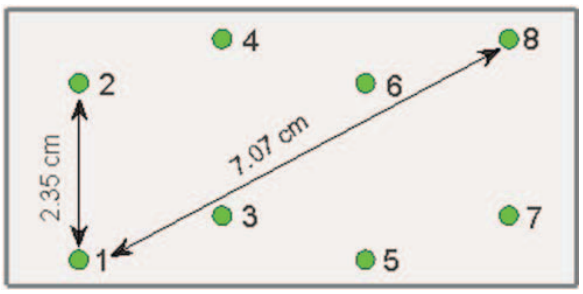


Figure 2: Schematic of optical imaging probe.

Following tests of the instrument on tissue-equivalent phantoms, initial measurements were performed on the infants using a simple passive motor stimulus. The probe was held in contact with the head immediately over the expected location of the motor cortex while either the left or right arm of the infant was passively flexed at the elbow. Data were recorded during 15 seconds of activation and again, after a 5 second delay, for 15 seconds during rest. This was repeated for up to 15 minutes. Each infant slept throughout the study. In addition, a sequence of back-reflection measurements from the skin surface were acquired for each source/detector pair, which were later used to deconvolve the impulse response of the system [9]. The preliminary measurements reported here were recorded at a single wavelength of 780 ± 2 nm.

After excluding the TPSF measurements with very low signal, two so-called datatypes were derived from each TPSF: the log amplitude (log A) and phase (ϕ) at a Fourier frequency of 120 MHz. Sets of data corresponding to "activation" and "rest" were then used to reconstruct a three-dimensional (3D) image representing the changes in optical properties occurring in the head directly below the array. A linear image reconstruction algorithm was used, based on the Rytov approximation [10]. Internal changes in the tissue absorption and transport scattering coefficients ($\Delta\mu_a$, $\Delta\mu_s'$) are computed from the differences between the datatypes using the matrix equation:

$$\Delta(\log A, \phi) = \mathbf{J} \,.\Delta(\mu_a,\mu_s') \qquad (1)$$

where **J** is the Jacobian or sensitivity matrix. The Jacobian is calculated using the TOAST software package [10] by solving the time-dependent diffusion equation for a spherical finite element model representing the approximate head geometry, assuming uniform optical properties ($\mu_s' = 1.0$ mm^{-1} and $\mu_a = 0.03$ mm^{-1}). An image representing the 3D distribution of the change in absorption or scatter is generated by inverting **J**. This is achieved using Tikhonov regularization of the Moore-Penrose generalized inverse:

$$\Delta(\mu_a,\mu_s') = \mathbf{J}^T (\mathbf{J}\mathbf{J}^T + \lambda\mathbf{I})^{-1} \Delta(\log A, \phi) \qquad (2)$$

where the regularization parameter λ was set to 10% of the largest singular value of $\mathbf{J}\mathbf{J}^T$, and **I** is the identity matrix.

4. RESULTS

The image displayed in figure 3 corresponds to a slice across a 3D image representing the change in absorption coefficient occurring in the head of an infant during the passive stimulus of the infant's right arm. The displayed slice is extracted across the spherical model at a depth of 6 mm below the center of the probe. The displayed greyscale corresponds to a change of absorption coefficient relative to background (μ_a = 0.03 mm^{-1}) from about -2% (black) to +2% (white).

The black cross in figure 3 corresponds to the estimated position of the left side of the motor cortex, according to the 10:20 anatomical system. The image exhibits the expected increase in absorption resulting from a local increase in blood volume. Less expected is the substantial decrease on the right side, which may be artifact, or may be evidence of vascular steal, when blood from surrounding vessels is recruited to supply the activated region. Some evidence of vascular steal has been observed in previous optical imaging studies of functional activation in infants [11].

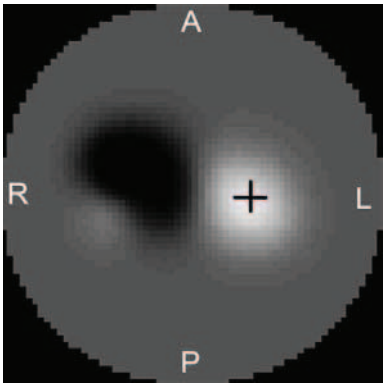


Figure 3: An image representing the change in absorption coefficient in an infant head at a depth of 6 mm below the surface, in response to activation of the motor cortex.

Inevitably the position of the probe relative to the underlying neuroanatomy involves some uncertainty. This problem is being addressed by utilizing photogrammetry techniques which enable the probe position to be related to suitable anatomical landmarks, and by combining with other anatomical imaging data (e.g. MRI images) when available.

5. DISCUSSION

Preliminary studies using a new multi-channel time-resolved system have been used to acquire images of functional activation in the newborn infant brain. Unlike a previous time-resolved system developed at UCL [8], data may be collected continuously with no "dead-time" required for storage of data between source switching. Furthermore, the system is more portable, avoids detector crosstalk by utilizing separate PMTs, and has the facility to collect data over a broad range of wavelengths. Modifications are in progress to allow data to be collected at four user-selected wavelengths simultaneously. The AOTFs will be programmed to switch at roughly 1 kHz, while data recorded at each wavelength are stored in different memory pages on the TCSPC modules.

6. ACKNOWLEDGEMENTS

The work has been supported by funding from the EC seventh framework programme under Grant Agreement No. FP7-HEALTH-2007-201076.

7. REFERENCES

[1] J. S. Wyatt, D.T. Delpy, M. Cope, S. Wray, and E.O.R. Reynolds, "Quantification of cerebral oxygenation and haemodynamics in sick newborn infants by near-infrared spectrophotometry," *Lancet* **328**, 1063-1066, 1986.

[2] J.P. Van Houten, D.A. Benaron, S. Spilman, and D.K. Stevenson, "Imaging brain injury using time-resolved near-infrared light scanning," *Pediatr. Res*. **39**, 470-476, 1996.

[3] J.C. Hebden, A.P. Gibson, R.Md. Yusof, N. Everdell, E.M.C. Hillman, D.T. Delpy, S. Arridge, T. Austin, J.H. Meek, and J.S. Wyatt, "Three-dimensional optical tomography of the premature infant brain," *Phys. Med. Biol*. **47**, 4155-4166, 2002.

[4] G. Taga, K. Asakawa, A. Maki, Y. Konishi, and H. Koizumi, "Brain imaging in awake infants by near-infrared optical topography," *Proc. Nat. Acad. Sci. USA* **100**, 10722-10727, 2003.

[5] J. Heiskala, P. Hiltunen, and I. Nissila, "Significance of background optical properties, time-resolved information and optode arrangement in diffuse optical imaging of term neonates," *Phys. Med. Biol*. **54**, 535-554, 2009.

[6] R.J. Cooper, J.C. Hebden, H. O'Reilly, S. Mitra, A.W.Michell, N.L. Everdell, A.P. Gibson, and T. Austin, "Transient haemodynamic events in neurologically compromised infants: a simultaneous EEG and diffuse optical imaging study," *Neuroimage* **55**, 1610-1616, 2011.

[7] N. L. Everdell, A. P. Gibson, I. D. C. Tullis, T. Vaithianathan, J. C. Hebden, and D. T. Delpy, "A frequency multiplexed near infrared topography system for imaging functional activation in the brain," *Rev. Sci. Instrumen*. **76**, 093705, 2005.

[8] F. E. W. Schmidt, M. E. Fry, E. M. C. Hillman, J. C. Hebden, and D. T. Delpy, "A 32-channel time-resolved instrument for medical optical tomography," *Rev. Sci. Instrumen*. **71**, 256-265, 2000.

[9] J. C. Hebden, F. M. Gonzalez, A. Gibson, E. M. C. Hillman, R. Md. Yusof, N. Everdell, D. T. Delpy, G. Zaccanti, and F. Martelli, "Assessment of an in situ temporal calibration method for time-resolved optical tomography," *J. Biomed. Opt*. **8**, 87-92, 2003.

[10] S. R. Arridge, "Optical tomography in medical imaging," *Inverse Problems* **15**, R41-R93, 1999.

[11] A. P. Gibson, T. Austin, N. L. Everdell, M. Schweiger, S. R. Arridge, J. H. Meek, J. S. Wyatt, D. T. Delpy, and J. C. Hebden, "Three-dimensional whole-head optical tomography of passive motor evoked responses in the neonate," *Neuroimage* **30**, 521-528, 2006.