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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A

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Review

Diffuse optical imaging

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Diffuse optical imaging is a medical imaging technique that is beginning to move from the laboratory to the hospital. It is a natural extension of near-infrared spectroscopy (NIRS), which is now used in certain niche applications clinically and particularly for physiological and psychological research. Optical imaging uses sophisticated image reconstruction techniques to generate images from multiple NIRS measurements. The two main clinical applications—functional brain imaging and imaging for breast cancer—are reviewed in some detail, followed by a discussion of other issues such as imaging small animals and multimodality imaging. We aim to review the state of the art of optical imaging.

Keywords: diffuse optical tomography; diffuse optical imaging; medical imaging; biomedical optics

1. Introduction

The ability of light to penetrate tissue was first exploited by Bright (1831), who noted that light could be transmitted through the head of a child with hydrocephalus. Hydrocephalus is an increase in the volume of cerebro-spinal fluid (CSF) in the head, and transillumination became an accepted diagnostic technique for hydrocephalus and intraventricular haemorrhage before the development of transcranial ultrasound. CSF is relatively transparent and, more importantly, does not significantly scatter light. In an extension of the same concept, Curling (1843) used transillumination to investigate a build-up of clear fluid in the testis, a condition known as hydrocele.

The overwhelming degree of scatter in biological tissue at optical wavelengths (650–1000 nm) prevents the use of simple transillumination techniques across significant thicknesses of tissue. Transillumination of the breast was attempted by Cutler (1929) using an electric lamp. He concluded that transillumination was a valuable aid to diagnosis for a wide range of conditions but that the results varied between women. The ensuing history of breast transillumination

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or 'diaphanography' was reviewed by Hebden & Delpy (1997), who concluded that, despite improvements in optical source and detector technology, clinical trials demonstrated that optical transillumination was inferior to X-ray mammography for the diagnosis of breast disease. This was primarily due to the relatively low spatial resolution, which is typically in the range of 6–10 mm (Pogue *et al.* 2006).

Despite the relative lack of success of transillumination, optical techniques were making an impact in blood oximetry, which takes advantage of the different absorption spectra of oxy- and deoxyhaemoglobin (HbO and HHb, respectively) to assess blood oxygenation. This demonstrated that biomedical optics could provide clinically useful information by examination of the *absorption* of tissue, provided that the confounding effects of *scatter* were minimized, by examining either small body parts (e.g. oximetry of the finger or earlobe) or exploiting conditions indicated by low scatter (e.g. hydrocephalus and hydrocele). Perhaps the most significant breakthrough in optical imaging was made by Jöbsis (1977, 1999), who used the 'near-infrared window' between approximately 700 and 1000 nm, at which the overall absorption and scatter of tissue is relatively low, to measure the oxygenation status of both haemoglobin and cytochrome oxidase, an enzyme that is an indicator of cell metabolism.

Jöbsis' technique became known as *near-infrared spectroscopy* (NIRS; Hoshi 2003; Hamaoka *et al.* 2007; Wolf *et al.* 2007). It is a valuable technique that has been used to investigate brain function and pathology in both neonates and adults (Obrig & Villringer 2003). Despite its inherent high signal contrast, one limitation of NIRS is its inability to provide spatial information, and it is natural to consider combining multiple NIRS measurements in order to localize the source of signals in the brain; this approach was taken by Gratton *et al.* (1995) to provide the first optical topographic images.

Since Gratton's first diffuse optical images, more than 2000 breast images have been obtained from women in more than 12 centres (Leff *et al.* 2007), as well as hundreds of brain images and countless images of small animals. In this review, we examine the current clinical state of optical imaging, look at the most significant recent developments, and make some attempts to predict the future clinical roles of diffuse optical imaging.

First, we define the scope of this review. *Optical imaging* describes many methods that cover a wide range of scales and many different applications. Higher-resolution methods, such as direct imaging of the surface, the different forms of microscopy and optical coherence tomography, rely on minimizing or ignoring the effects of scatter (Hillman 2007) and instead record absorption or refractive index of superficial layers. Physiological events tend to manifest themselves as changes in chromophore concentration and therefore as changes in optical absorption. Anatomical regions such as layers in the skin or retina may appear as regions of different refractive index. However, scatter begins to dominate once light has travelled 1 mm or so into tissue, so these methods are unable to probe much deeper than this. The physics of light transport in tissue has been reviewed by Boas *et al.* (2001*a*) and Dunsby & French (2003).

If we want to image larger volumes, we need to accept that scatter will dominate (the reduced scatter coefficient μ'_s is typically 100 times greater than the absorption coefficient μ_a) and use lower-resolution methods, which acquire images from light that has travelled diffusively across centimetres of tissue.

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These methods are referred to as *diffuse optical imaging* (DOI) and form the subject of this review. DOI has been reviewed previously (Boas *et al.* 2001*a*; Gibson *et al.* 2005). Here, we concentrate on its emerging clinical applications.

Successful clinical use of DOI depends intimately on the type of instrumentation (Hebden *et al.* 1997) and the image reconstruction procedure employed (Arridge & Hebden 1997; Arridge 1999; Boas *et al.* 2001*a*; Schweiger *et al.* 2003). In a very general sense, two main approaches are taken, but the boundaries between these applications are blurred (Gibson *et al.* 2005). We take *optical topography* to refer to imaging a few centimetres of tissue (the separation between source and detector is generally <4 cm). The typical application is imaging haemodynamic changes in the cortex of the brain, where we are interested in imaging a change in optical properties with a time course of a few seconds. Such systems generally employ continuous-wave (CW) instrumentation with laser diode sources modulated at a few kilohertz and lock-in detectors (e.g. Yamashita *et al.* 1999). Images are usually reconstructed using a linear approach and presented as a two-dimensional slice parallel to the plane of sources and detectors.

Imaging larger volumes of tissue generally requires more sophisticated instrumentation and reconstruction techniques. We refer to such techniques as *optical tomography*, where data are obtained from light that has travelled across the diameter of the object under examination. More powerful sources and more sensitive detectors are used and acquisition times are longer. Nonlinear image reconstruction methods (Arridge 1999), which attempt to separate the effects of absorption and scatter, are typically used to generate three-dimensional images of the whole tissue volume. This in turn requires measurements of both the intensity and the mean flight time (or, equivalently, phase) of the transmitted light because (in the absence of prior information) measurements of intensity only are unable to distinguish between absorption and scatter at a single wavelength (Arridge & Lionheart 1998). Optical tomography systems therefore often use phase-domain or time-domain measurements (Chance *et al.* 1998*a*).

2. Optical mammography

(*a*) *The clinical question*

Imaging the breast is currently one of the most demanding problems in medical imaging. Screening requires good spatial resolution, high specificity and low cost, while imaging for staging cancer or determining the progress of the disease requires good physiological information and a high level of safety, as repeated imaging may be necessary. Currently, X-ray mammography is the method of choice for screening (Fletcher & Elmore 2003), but the specificity (approx. 97%), while high, still leads to a large number of false positives when used for screening a large population. Ultrasound and magnetic resonance imaging (MRI) are used for investigating known tumours, but ultrasound provides little physiological information and MRI is often prohibitively expensive. It is natural to ask whether optical imaging can play a role.

Tumours are generally associated with increased vascularization (Rice & Quinn 2002), although some advanced tumours may be avascular and anoxic (Zhou *et al.* 2006). The ability of optical mammography to measure blood volume and oxygenation is clearly relevant to determining the presence and stage of

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a tumour. Typically, breast cancer is reported as having approximately twice the haemoglobin content of healthy tissue, and reduced oxygen content (Leff *et al.* 2007).

The technology used for optical mammography can be split into three main groups: imaging the compressed breast; imaging the uncompressed breast; and using a hand-held scanner. We examine each of these in turn.

(*b*) *Optical mammography of the compressed breast*

It is natural to consider imaging the compressed breast. This provides images that appear familiar to radiographers from X-ray mammography. It also reduces the attenuation of light (by compressing the tissue and therefore reducing its overall thickness), allowing faster imaging and lower-cost sources and detectors than are required to detect signals transmitted across the uncompressed breast. Generally, however, the breast is compressed much more gently than in X-ray mammography due to the longer scanning time required. While compressing the breast is a solution to a number of potential problems, the effect of compression on the distribution of blood in the breast must be considered, since the role of breast compression on the pathophysiology of the tumour and the surrounding tissue is not known (Boverman *et al.* 2007).

Groups in Berlin and Milan have imaged more than 300 women using time-resolved compressed optical mammography systems as part of a European consortium called Optimamm (Hebden & Rinneberg 2005). Both groups reported identifying 80–85 per cent of radiologically confirmed tumours (Grosenick *et al.* 2004; Taroni *et al.* 2004*a*) and both groups have gone on to develop systems with improved spatial and spectral performance, which are expected to increase detection further.

Recently, there has been interest in the dynamic optical properties of the compressed breast. Initial concerns that breast compression may squeeze blood out of the breast, removing the mechanism of contrast, appear unfounded. Moreover, it appears that the rate of inflow of blood into the breast following relaxation after compression provides additional information beyond static imaging alone (Jiang *et al.* 2003; Carp *et al.* 2008; Fang *et al.* 2009), and it is likely that such dynamic changes may provide a sensitive indicator of cancer.

The functional information available from optical images complements the anatomical information from X-ray mammography. Work aimed at combining the strengths of both methods is reviewed in §6.

(*c*) *Optical mammography of the uncompressed breast*

If breast compression can be avoided, this is more comfortable for the patient, and the breast can be imaged with no disruption to the blood flow to the tumour. This approach has been led by the group at Dartmouth College (Hanover, NH, USA), who have imaged more than 50 women using a frequency-domain system at a number of different wavelengths (Dehghani *et al.* 2003; Srinivasan *et al.* 2006). The group at UCL has used a time-resolved system to obtain images of the uncompressed breast in 38 women (Enfield *et al.* 2007).

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(*d*) *The state of optical mammography*

A number of studies have shown that optical mammography is capable of identifying the increased vascularization associated with malignant lesions compared to normal tissue in approximately 85 per cent of cases (Leff *et al.* 2007). However, small (<10 mm) malignant tumours are more difficult to identify, as are non-malignant tumours such as fibroadenomas. Using more wavelengths to improve the separation between chromophores (Srinivasan *et al.* 2006) and multimodality imaging (Ntziachristos *et al.* 2000; Zhang *et al.* 2005; Carpenter *et al.* 2007) may improve identification of these more demanding cases.

One application that could provide an excellent clinical niche for optical mammography is monitoring neoadjuvant chemotherapy. This work (Choe *et al.* 2005; Tromberg *et al.* 2005) exploits the strength of optical imaging (physiological contrast and safety) while minimizing the implications of low spatial resolution by focusing on pre-diagnosed lesions.

Tromberg *et al.* (2005) have developed a hand-held optical probe for breast cancer, which can be used as an adjunct to other investigations and which is undergoing clinical trials. Optical imaging of the breast may have reached a point where the next stage is high-quality clinical trials of carefully selected niche applications (Tromberg *et al.* 2008). One obvious difficulty is to settle on a single optimal system to be trialled.

3. Functional brain imaging

(*a*) *Optical topography of brain function*

When imaging the brain, the clinical question is very different from that for the breast. Rather than detecting a static change that is constant during the examination, which is the case when imaging a tumour, we are more interested in the brain's response to a stimulus over a period of a few seconds. We therefore choose to use faster imaging systems and linear reconstruction, which generates images of the *change* in optical properties.

Arguably the most successful series of studies has been that performed by the Hitachi Medical Corporation (Tokyo, Japan) using their ETG-100 system (Koizumi *et al.* 2003). This optical topography system (Yamashita *et al.* 1999) uses eight laser diodes at 780 nm and eight at 830 nm and eight avalanche photodiode lock-in detectors. CW measurements are taken from 24 distinct source–detector pairs held in a regular grid pattern. Researchers at Hitachi have examined the healthy brain in situations such as language development (Watanabe *et al.* 1998) and the emotional response to music (Suda *et al.* 2008), and in pathological conditions such as epilepsy (Watanabe *et al.* 2002), post-traumatic stress disorder (Matsuo *et al.* 2003) and cognitive function in patients with motor neuron disease (Fuchino *et al.* 2008).

The physiological and clinical applications of the Hitachi system have been successful despite (or possibly because of) using a simple CW system, which has a small number of connectors in a fixed pattern and which uses a very simple image reconstruction method. Other researchers have used more sophisticated systems and more complex image reconstruction methods and have demonstrated

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extremely good images, but generally from more controlled laboratory volunteers rather than patients. It remains to be seen whether the more sophisticated methods can be translated effectively and robustly into the clinic.

(*b*) *Developments beyond the basic system*

(i) *Optimal wavelength selection*

The range of wavelengths that can be used is restricted to the near-infrared window between approximately 700 and 1000 nm, where tissue transparency is relatively high. However, within that range, certain wavelengths prove to be more effective for spectroscopic imaging than others. Typically, two wavelengths at approximately 780 and 830 nm have been chosen, as they lie either side of the isosbestic point where the absorptions of HbO and HHb are equal. In practice, the choice of wavelength may depend on the availability of appropriate sources rather than on any theoretical considerations (Cope 1991), although new technologies may provide more precisely controllable wavelengths (Wang *et al.* 2008).

However, recently, researchers have proposed methods for selecting the optimal wavelengths experimentally or theoretically. Well-chosen wavelengths should minimize cross-talk between HHb and HbO, and minimize noise but interrogate similar regions of tissue. A consensus seems to be developing that the shorter of the two wavelengths should be even shorter, between 660 and 770 nm, and the longer of the two should remain at approximately 830 nm (Yamashita *et al.* 2001; Strangman *et al.* 2003; Boas *et al.* 2004; Sato *et al.* 2004; Uludag *et al.* 2004).

Choosing more than two wavelengths allows more chromophores to be identified (Pifferi *et al.* 2003; Taroni *et al.* 2004*b*; Srinivasan *et al.* 2006) and may reduce cross-talk. This is particularly the case if images of the chromophores are reconstructed directly rather than following the method that has been used traditionally, which has been to reconstruct wavelength-specific absorption (and scatter) images and then extract the chromophore concentrations (and scatter size and density) in post-processing (Corlu *et al.* 2003; Dehghani *et al.* 2003; Li *et al.* 2004).

(ii) *Software-encoded detectors*

Each source in Hitachi's ETG-100 system is modulated at a different frequency between 1 and 8.7 kHz. Each detector is then connected to a bank of lock-in amplifiers that can identify which source the light came from by measuring its modulation frequency. This allows each source to be illuminated simultaneously, so that images can be acquired rapidly (Yamashita *et al.* 1999).

This approach, however, has two limitations: first, cross-talk can occur between channels because all sources and detectors are always active; and second, demodulating the signal using hardware limits the flexibility. The CW4 system (Culver *et al.* 2003*c*; Franceschini *et al.* 2003) overcame the second of these problems by demodulating the signals in software rather than hardware. A similar system built by Everdell *et al.* (2005) allowed for both time and frequency encoding in software, potentially allowing for great flexibility using frequency encoding and reduced cross-talk using time encoding.

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(iii) *High connector density*

Zeff *et al.* (2007) introduced a new optical topography system with 24 sources and 28 detectors embedded in a small (13×6 cm) probe array, giving a remarkably high connector density. To take advantage of this, the system was specifically designed to have a wide dynamic range with 24-bit analogue-to-digital converters and a mix of time and frequency encoded detection, allowing for a total of 348 measurements above the noise floor. They used this system to image the visual cortex, successfully mapping different stimuli to different parts of the visual cortex (White *et al.* 2008). The images obtained using this system have arguably the highest spatial resolution of any diffuse optical images and it is likely that more systems similar to this will be built.

(iv) *Image reconstruction*

A large part of the success of using a higher connector density is the use of formal image reconstruction techniques. First-generation systems, which were designed and used as multiple single-channel NIRS systems, tended to present images by assuming that a change in intensity resulted from a change in optical properties originating midway between the relevant source and detector. The measured changes were mapped directly into the image as a colour change. This approach means that the spatial resolution cannot be smaller than the spacing between connectors and means that only simple, regular patterns of connectors can be used.

One of the most significant improvements in image quality in optical topography came when image reconstruction techniques borrowed from optical tomography were used to reconstruct images (see Dehghani *et al.* 2009). A forward model is set up that describes the geometry and the baseline optical properties of the head and is used to calculate the amount by which each measurement would change given a small change in optical properties of each pixel. These values are assembled into a sensitivity matrix. The sensitivity matrix is inverted and multiplied by the measured data to give an image. This process is not straightforward, as the sensitivity matrix is ill-posed and underdetermined (Arridge 1999; Boas *et al.* 2001*a*; Schweiger *et al.* 2003; Gibson *et al.* 2005).

Formal image reconstruction allows multiple measurements to contribute to each pixel, leading to improvements in spatial resolution, spatial accuracy and quantitative accuracy of up to a factor of two, and was first used by Bluestone *et al.* (2001), Boas *et al.* (2001*b*) and Yamamoto *et al.* (2002). Furthermore, image reconstruction from multiple source–detector spacing allows some limited depth discrimination (Bluestone *et al.* 2001; Culver *et al.* 2003*c*; Blasi *et al.* 2007; Zeff *et al.* 2007).

(v) *Frequency-domain imaging*

Measurements of intensity alone cannot distinguish between changes in optical absorption and scatter in the absence of prior information (Arridge & Lionheart 1998). In addition, intensity measurements are particularly sensitive to surface effects such as changes in the contact between the connector and

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the scalp. These limitations have been addressed by systems that measure the intensity of light as well as either the change in phase or the time taken for light to travel across the medium.

Time-domain imaging requires measurements of individual photon flight time, usually using time-correlated single photon counting hardware, and is suited to measurements taken at low flux levels. It has therefore not been actively pursued for optical topography, which requires fast measurements of high-flux signals. The notable exception has been the work of Selb *et al.* (2005, 2006), who used a time-domain system specifically to identify late-arriving photons, which, on average, will have probed deeper volumes of tissue.

Frequency-domain systems (Chance *et al.* 1998*b*) have been somewhat more widely used (Danen *et al.* 1998; Franceschini *et al.* 2000). The instrumentation is more complex and expensive than a CW system, so one approach, taken by Culver *et al.* (2003*a*), has been to combine many CW measurements, to provide high spatial resolution, with a smaller number of frequency-domain measurements, for quantitative accuracy.

(*c*) *Other applications*

Optical imaging is uniquely suited to imaging brain function in babies and infants. It is safe, comfortable, relatively insensitive to motion, and it can be used in a natural, relaxed environment. Some of the earliest studies by Hitachi examined spontaneous and evoked haemodynamic changes in babies and infants (Taga *et al.* 2000, 2003). Optical topography is following the path taken by NIRS by beginning to be accepted as a method of choice for studies of brain development in infants. For example, Tsujimoto *et al.* (2004) used the Hitachi ETG-100 to show that the lateral prefrontal cortex is responsible for short-term memory in both preschool children and adults, and Blasi *et al.* (2007) used UCL's topography system (Everdell *et al.* 2005) to demonstrate an increase in brain activation in four-month-old infants when looking at faces compared to random images. Both of these studies have provided new insights into brain development that would have been difficult or impossible using other, more established, imaging modalities.

The relationship between optical measurements and the underlying physiology is a close one—given some underlying assumptions, changes in the intensity of the measured light are close to being inversely proportional to changes in the concentration of oxy- and deoxyhaemoglobin. This means that optical measurements can play a vital role in determining underlying brain physiology. In particular, optical imaging has been used to investigate neurovascular coupling, the relationship between neuronal activity and haemodynamics, following some brain activity in both small animals (Siegel *et al.* 2003) and humans (Strangman *et al.* 2002; Huppert *et al.* 2006). This is important for a number of reasons, not least to direct the interpretation of functional MRI (fMRI) images. fMRI is the most commonly used method for imaging brain function, at least in adults, but the measurement, known as the blood oxygenation-level dependent (BOLD) signal, depends indirectly on the change in concentration of deoxyhaemoglobin. It is unclear whether an increase in neuronal activity leads to an increase or a decrease in deoxyhaemoglobin concentration (Raichle & Mintun 2006). Results from optical imaging suggest that the positive and negative BOLD fMRI signals correspond to excitation and inhibition of neuronal activity, respectively (Devor *et al.* 2007).

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Finally, a small number of studies have used optical tomography to image the full three-dimensional volume of babies' heads using light that has travelled through deep regions of the brain. Two groups have published such results, both using time-resolved imaging systems. The first, seminal, work used a relatively simple instrument (Benaron *et al.* 1994*a*) and image reconstruction algorithms (Benaron *et al.* 1994*b*). Images were generated showing both pathology and functional activation, which agreed with computed tomography and ultrasound images (Benaron *et al.* 2000).

More recently, researchers at University College London, including one of the authors of this review, have used a 32-channel time-resolved imaging system (Schmidt *et al.* 2000) and a nonlinear image reconstruction algorithm based on the finite-element method (Arridge *et al.* 2000) to image the brains of premature and term infants. The first results showed a haemorrhage in a premature baby, which correlated with ultrasound (Hebden *et al.* 2002). Following this, we imaged changes in brain oxygenation during changes in inspired oxygen and carbon dioxide in a ventilated infant (Hebden *et al.* 2004). The measured changes agreed quantitatively with the expected physiological changes. We have also used the system to image motor-evoked responses in six premature babies (Gibson *et al.* 2006). This work has been reviewed in detail by Austin *et al.* (2006).

4. Other organs

Perhaps the next most developed application after breast and brain imaging is imaging the arthritic finger, which has been pioneered over a decade by Hielscher (e.g. Hielscher *et al.* 2004). The particular difficulty of imaging the finger is that it is so small that the diffusion approximation does not hold. This is a particular problem because the purpose of the study is to examine the volume of the synovial fluid, which is a clear, non-scattering region. Hielscher noted earlier that the only way of robustly imaging the finger joint is to use the full radiative transport equation rather than the diffusion approximation. This led to a programme of work developing reliable image reconstruction methods using the more complex and far more computationally expensive transport equation (Klose & Hielscher 1999).

The muscle is commonly examined using NIRS in sports and rehabilitation medicine to determine its oxygen consumption when working. It has been infrequently studied using DOI (Maris *et al.* 1994). For example, the forearm has been imaged mainly as a simple, near cylindrical, well-controlled test case (Graber *et al.* 2000; Hillman *et al.* 2001).

5. Small animal imaging

Perhaps the greatest impact of DOI to date has been in small animal imaging. This is partly because the optical signal strength is greater when measured across small volumes such as the mouse or rat brain, and the effect of scatter is reduced. But more importantly, a wide range of biologically relevant molecules can be tagged with an equally broad choice of optical contrast agents, leading to great flexibility in both the mechanism for contrast and the measurement approach.

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Many techniques for optical imaging in small animals rely on non-diffuse light. These techniques, such as imaging the exposed cortex, different forms of microscopy, and optical coherence tomography (Fercher *et al.* 2003), have made a significant impact in oncology and neurophysiology and have been reviewed elsewhere (Weisslader & Ntziachristos 2003; Hillman 2007).

Traditional NIR techniques, where intrinsic chromophores, particularly oxy- and deoxyhaemoglobin but also cytochrome oxidase, are imaged using optical topography and optical tomography, have been used to image animal models (e.g. Culver *et al.* 2003*b*; Siegel *et al.* 2003) but arguably the real benefits of optical imaging come when extrinsic chromophores are used to specifically target molecules of interest. Two particular approaches that are commonly taken are fluorescence imaging and imaging bioluminescence (Weisslader & Ntziachristos 2003; Cherry 2004). Both methods are commonly used with relatively simple instrumentation based on a charge-coupled device camera where the emitted light is imaged directly. Here, we concentrate on more sophisticated methods whereby data are collected from a number of projections, allowing tomographic imaging approaches to localize the fluorescent or bioluminescent source within the three-dimensional volume.

Fluorescence imaging relies on an external source of light to excite the target molecule, which then emits light at a longer wavelength, which is detected. Many different fluorescent probes have been developed (Weisslader & Ntziachristos 2003) to target conditions such as infection, apoptosis (programmed cell death) and, in particular, cancer, including tumour growth, metastasis formation and gene expression. Bioluminescence, on the other hand, relies on introducing genes that code for a protein, such as luciferase, which catalyses a reaction that emits light. Bioluminescence does not require an external light source but the signal tends to be weaker than fluorescent signals, requiring more sensitive detectors. Both approaches are well established on a microscopic scale, for imaging cells *in vitro* and for imaging superficial features using microscopic techniques (Weisslader & Pittet 2008).

Optical tomography of fluorescent and bioluminescent sources is being researched, initially in simulation (Ntziachristos *et al.* 2002*a*) and in phantoms (Godovarty *et al.* 2004), and increasingly *in vivo* (Ntziachristos *et al.* 2002*b*; Chaudhari *et al.* 2005). Some technical advances that need to be addressed include the use of the radiative transport equation instead of the diffusion equation due to the small volume being imaged and the use of prior anatomical information (Klose *et al.* 2004). A particularly significant advance is the development of experimental and theoretical methods that allow non-contact imaging. Typically, the surface of the animal is found by photogrammetry and the propagation of light through the body and through free space to the camera is modelled (Schulz *et al.* 2004).

A great advantage of using optical techniques for molecular imaging is that there are natural routes to translate them from imaging small animals into clinical practice. A number of groups have already demonstrated fluorescent breast imaging, including Godovarty *et al.* (2004) and Corlu *et al.* (2008). These early clinical results, supported by results from simulation and phantom studies, suggest that it is possible to detect useful fluorescent signals through large volumes such as the breast (Hawrysz & Sevick-Muraca 2000; Ntziachristos *et al.* 2002*a*).

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A new approach to DOI of intermediate volumes (depths approx. 10 mm) is provided by photoacoustic imaging (Xu & Wang 2006). Here, NIR light illuminates the volume of interest and is preferentially absorbed by chromophores, particularly haemoglobin. Energy is absorbed where there is an increased chromophore density and that region heats up and expands, emitting a short pulse of ultrasound. By detecting the ultrasound, functional images can be reconstructed with the spatial resolution of ultrasound. To date, this method has primarily been used to image small animals (Wang *et al.* 2003) but there have been some attempts to translate the method to imaging the breast (Manohar *et al.* 2007; Pramanik *et al.* 2008).

6. Multimodality methods

Optical images provide high sensitivity to functional changes in the brain or in oncology. The main drawback is the relatively low spatial resolution. The effective spatial resolution can be enhanced by combining optical imaging with anatomical imaging methods. This has a secondary effect of improving the quantitative accuracy by reducing the partial volume effect. Prior information can be incorporated into the image reconstruction procedure as part of either the forward problem or the inverse problem (Gibson *et al.* 2005).

Perhaps the most natural modality to combine with optical methods is magnetic resonance (MR). Optical probes can easily be made to be MR-compatible and optical imaging provides complementary information to MR. The most straightforward approach is to simply compare images acquired using the different modalities. For example, optical images of the brain have been compared with MR images in order to investigate neurovascular coupling as discussed in §3*c* (Strangman *et al.* 2002; Devor *et al.* 2007). This is a valuable approach but does not attempt to use the anatomical information to improve the optical reconstruction. It is possible to segment an anatomical MR image and use it to constrain the forward or inverse problem (e.g. Schweiger & Arridge 1999; Ntziachristos *et al.* 2002*c*; Brooksby *et al.* 2003). This leads to improved optical image quality, and allows the optical image to be directly registered onto the anatomical MR image, much as functional MR images are presented mapped onto an anatomical MR image.

X-ray mammography is the method of choice for screening for breast cancer but its specificity varies, leading to unnecessary biopsies (Fletcher & Elmore 2003). It is natural to consider whether adding the functional information available from optical imaging to the anatomical information obtained from an X-ray mammogram may lead to improved specificity (Li *et al.* 2003). Preliminary results are encouraging (Zhang *et al.* 2005). For more information, see a thorough review by Fang *et al.* (2008).

Finally, there have been some attempts to combine optical imaging with ultrasound, either at the data acquisition stage by photoacoustics (Xu & Wang 2006) or by modulating the light (Wang *et al.* 1995), or at the image reconstruction stage by using ultrasound to improve spatial localization (e.g. Zhu *et al.* 2008).

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7. Conclusion

After almost 15 years of development, optical imaging is still firmly a research tool, but clinical studies are beginning to appear in the literature. We need to move the field from a research subject for physicists and engineers to a practical, working clinical tool. It is unlikely that optical imaging will replace any of the established imaging methods. It is hard to see how optical mammography, for example, will replace X-ray mammography for breast screening, as it is unlikely ever to be sensitive to the smallest tumours and microcalcifications. Similarly, fMRI is established as a gold standard for functional brain imaging, and positron emission tomography imaging for detection and staging of cancer.

However, many niche applications exist where optical imaging could have a significant impact as a stand-alone tool, or in conjunction with other methods. The most established of these at the moment is probably optical topography of babies and infants, where other methods all have significant drawbacks and optical imaging can draw on the existing expertise in NIR spectroscopy. In breast cancer, while X-ray mammography is a sound tool for screening, it is not well suited for imaging younger women, or for repeated imaging for monitoring. In these two areas, optical mammography could play a significant role. In particular, the use of optical methods to investigate new drug treatments and an individual's response to treatment (Cerussi *et al.* 2007; Tromberg *et al.* 2008) could provide a genuine clinical role for optical imaging.

References

Arridge, S. R. 1999 Optical tomography in medical imaging. *Inverse Probl.* **15**, R41–R93. (doi:10.1088/0266-5611/15/2/022)

Arridge, S. R. & Hebden, J. C. 1997 Optical imaging in medicine: II. Modelling and reconstruction. *Phys. Med. Biol.* **42**, 841–853. (doi:10.1088/0031-9155/42/5/008)

Arridge, S. R. & Lionheart, W. R. B. 1998 Nonuniqueness in diffusion-based optical tomography. *Opt. Lett.* **23**, 882–884. (doi:10.1364/OL.23.000882)

Arridge, S. R., Hebden, J. C., Schweiger, M., Schmidt, F. E. W., Fry, M. E., Hillman, E. M. C., Dehghani, H. & Delpy, D. T. 2000 A method for 3D time-resolved optical tomography. *Int. J. Imaging Syst. Technol.* **11**, 2–11. (doi:10.1002/(SICI)1098-1098(2000)11:1<2::AID-IMA2>3.0.CO;2-J)

Austin, T., Gibson, A. P., Branco, G., Yusof, R. M., Arridge, S. R., Meek, J. H., Wyatt, J. S., Delpy, D. T. & Hebden, J. C. 2006 Three-dimensional optical imaging of blood volume and oxygenation in the neonatal brain. *Neuroimage* **31**, 1426–1433. (doi:10.1016/j.neuroimage.2006.02.038)

Benaron, D. A., Ho, D. C., Spilman, S. D., van Houten, J. C. & Stevenson, D. K. 1994*a* Tomographic time-of-flight optical imaging device. *Adv. Exp. Med. Biol.* **361**, 207–214.

Benaron, D. A., Ho, D. C., Spilman, S. D., van Houten, J. C. & Stevenson, D. K. 1994*b* Non-recursive linear algorithms for optical imaging in diffusive media. *Adv. Exp. Med. Biol.* **361**, 215–222.

Benaron, D. A. *et al.* 2000 Noninvasive functional imaging of human brain using light. *J. Cerebr. Blood Flow Metab.* **20**, 469–477. (doi:10.1097/00004647-200003000-00005)

Blasi, A. *et al.* 2007 Investigation of depth dependent changes in cerebral haemodynamics during face perception in infants. *Phys. Med. Biol.* **52**, 6849–6864. (doi:10.1088/0031-9155/52/23/005)

Bluestone, A. Y., Abdouleav, G., Schmitz, C. H., Barbour, R. L. & Hielscher, A. H. 2001 Three-dimensional optical tomography of hemodynamics in the human head. *Opt. Exp.* **9**, 272–286.

Downloaded from rsta.royalsocietypublishing.org on 6 November 2009

Boas, D. A., Brooks, D. H., Miller, E. L., DiMarzio, C. A., Kilmer, M., Gaudette, R. J. & Zhang, Q. 2001*a* Imaging the body with diffuse optical tomography. *IEEE Signal Process. Mag.* **18**, 57–75. (doi:10.1109/79.962278)

Boas, D. A., Gaudette, T., Strangman, G., Cheng, X., Marota, J. J. & Mandeville, J. B. 2001*b* The accuracy of near infrared spectroscopy and imaging during focal changes in cerebral hemodynamics. *Neuroimage* **13**, 76–90. (doi:10.1006/nimg.2000.0674)

Boas, D. A., Chen, K., Grebert, D. & Franceschini, M. A. 2004 Improving the diffuse optical imaging spatial resolution of the cerebral hemodynamic response to brain activation in humans. *Opt. Lett.* **29**, 1506–1508. (doi:10.1364/OL.29.001506)

Boverman, G., Fang, Q., Carp, S. A., Miller, E. L., Brooks, D. H., Selb, J., Moore, R. H., Kopans, D. B. & Boas, D. A. 2007 Spatio-temporal imaging of the hemoglobin in the compressed breast with diffuse optical tomography. *Phys. Med. Biol.* **52**, 3619–3641. (doi:10.1088/0031-9155/52/12/018)

Bright, R. 1831 *Diseases of the brain and nervous system*, vol. 2, p. 431. London, UK: Longman.

Brooksby, B., Dehghani, H., Pogue, B. W. & Paulsen, K. D. 2003 Near infrared (NIR) tomography breast image reconstruction with *a priori* structural information from MRI: algorithm development for reconstructing heterogeneities. *IEEE Quant. Electron.* **9**, 199–209. (doi:10.1109/JSTQE.2003.813304)

Carp, S. A., Selb, J., Fang, Q., Moore, R., Kopans, D., Rafferty, E. & Boas, D. A. 2008 Dynamic functional and mechanical response of breast tissue to compression. *Opt. Exp.* **16**, 16 064–16 078. (doi:10.1364/OE.16.016064)

Carpenter, C. M. *et al.* 2007 Image-guided optical spectroscopy provides molecular-specific information *in vivo*: MRI-guided spectroscopy of breast cancer hemoglobin, water, and scatterer size. *Opt. Lett.* **32**, 933–935. (doi:10.1364/OL.32.000933)

Cerussi, A., Hsiang, D., Shah, N., Mehta, R., Durkin, A., Butler, J. & Tromberg, B. J. 2007 Predicting response to breast cancer neoadjuvant chemotherapy using diffuse optical spectroscopy. *Proc. Natl Acad. Sci. USA* **104**, 4014–4019. (doi:10.1073/pnas.0611058104)

Chance, B. *et al.* 1998*a* A novel method for fast imaging of brain function, non-invasively, with light. *Opt. Exp.* **2**, 411–423.

Chance, B., Cope, M., Gratton, E., Ramirez, N. & Tromberg, B. J. 1998*b* Phase measurement of light absorption and scatter in human tissue. *Rev. Sci. Instrum.* **69**, 3457–3481. (doi:10.1063/1.1149123)

Chaudhari, A. J., Darvas, F., Bading, J. R., Moats, R. A., Conti, P. S., Smith, D. J., Cherry, S. R. & Leahy, R. M. 2005 Hyperspectral and multispectral bioluminescence optical tomography for small animal imaging. *Phys. Med. Biol.* **50**, 5421–5441. (doi:10.1088/0031-9155/50/23/001)

Cherry, S. R. 2004 *In vivo* molecular and genomic imaging: new challenges for imaging physics. *Phys. Med. Biol.* **49**, R13–R48. (doi:10.1088/0031-9155/49/3/R01)

Choe, R. *et al.* 2005 Diffuse optical tomography of breast cancer during neoadjuvant chemotherapy: a case study with comparison to MRI. *Med. Phys.* **32**, 1128–1139. (doi:10.1118/1.1869612)

Cope, M. 1991 The application of near infrared spectroscopy to non invasive monitoring of cerebral oxygenation in the newborn infant. PhD thesis, University of London.

Corlu, A., Durduran, T., Choe, R., Schweiger, M., Hillman, E. M. C., Arridge, S. R. & Yodh, A. G. 2003 Uniqueness and wavelength optimization in continuous-wave multispectral diffuse optical tomography. *Opt. Lett.* **28**, 2339–2431. (doi:10.1364/OL.28.002339)

Corlu, A., Choe, R., Durduran, T., Rosen, M. A., Schweiger, M., Arridge, S. R., Schnall, M. D. & Yodh, A. G. 2008 Three-dimensional *in vivo* fluorescence diffuse optical tomography of breast cancer in humans. *Opt. Exp.* **15**, 6696–6716. (doi:10.1364/OE.15.006696)

Culver, J. P., Choe, R., Holboke, M. J., Zubkov, L., Durduran, T., Slemp, A., Ntziachristos, V., Chance, B. & Yodh, A. G. 2003*a* Three-dimensional diffuse optical tomography in the parallel plane transmission geometry: evaluation of a hybrid frequency domain/continuous wave clinical system for breast imaging. *Med. Phys.* **30**, 235–247. (doi:10.1118/1.1534109)

Downloaded from rsta.royalsocietypublishing.org on 6 November 2009

Culver, J. P., Durduran, T., Furuya, D., Cheung, C., Greenberg, J. H. & Yodh, A. G. 2003*b* Diffuse optical tomography of cerebral blood flow, oxygenation and metabolism in rat during focal ischaemia. *J. Cereb. Blood Flow Metab.* **23**, 911–924. (doi:10.1097/01.WCB.0000076703.71231.BB)

Culver, J. P., Siegel, A. M., Stott, J. J. & Boas, D. A. 2003*c* Volumetric diffuse optical tomography of brain activity. *Opt. Lett.* **28**, 2061–2063. (doi:10.1364/OL.28.002061)

Curling, T. B. 1843 *A practical treatise on the diseases of the testis and of the spermatic cord and scrotum*, pp. 125–181. London, UK: Samuel Highley.

Cutler, M. 1929 Transillumination as an aid in the diagnosis of breast lesions. *Surg. Gynecol. Obstet.* **48**, 721–728.

Danen, R. M., Wang, Y., Li, X. D., Thayer, W. S. & Yodh, A. G. 1998 Regional imager for low resolution functional imaging of the brain with diffusing near-infrared light. *Photochem. Photobiol.* **67**, 33–40. (doi:10.1111/j.1751-1097.1998.tb05162.x)

Dehghani, H., Pogue, B. W., Poplack, S. P. & Paulsen, K. D. 2003 Multiwavelength three-dimensional near-infrared tomography of the breast: initial simulation, phantom and clinical results. *Appl. Opt.* **42**, 135–145. (doi:10.1364/AO.42.000135)

Dehghani, H, Srinivasan, S., Pogue, B. W. & Gibson, A. 2009 Numerical modelling and image reconstruction in diffuse optical tomography. *Phil. Trans. R. Soc. A* **367**, 3073–3093. (doi:10.1098/rsta.2009.0090)

Devor, A. *et al.* 2007 Suppressed neuronal activity and concurrent arteriolar vasoconstriction may explain negative blood oxygenation level-dependent signal. *J. Neurosci.* **27**, 4452–4459. (doi:10.1523/JNEUROSCI.0134-07.2007)

Dunsby, C. & French, P. M. W. 2003 Techniques for depth-resolved imaging through turbid media including coherence gated imaging. *J. Phys. D: Appl. Phys.* **36**, R207–R227. (doi:10.1088/0022-3727/36/14/201)

Enfield, L. C. *et al.* 2007 Three-dimensional time-resolved optical mammography of the uncompressed breast. *Appl. Opt.* **46**, 3628–3638. (doi:10.1364/AO.46.003628)

Everdell, N., Gibson, A. P., Tullis, I. D. C., Vaithianathan, T., Hebden, J. C. & Delpy, D. T. 2005 A frequency multiplexed near-infrared topography system for imaging functional activity in the brain. *Rev. Sci. Instrum.* **76**, 093705. (doi:10.1063/1.2038567)

Fang, Q., Carp, S. A., Selb, J. & Boas, D. A. 2008 Optical imaging and X-ray imaging. In *Translational multimodality optical imaging* (eds F. S. Azar & X. Intes), pp. 752–765. London, UK: Artech House.

Fang, Q. *et al.* 2009 Combined optical imaging and mammography of the healthy breast: optical contrast derived from breast structure and compression. *IEEE Trans. Med. Imaging* **28**, 30–42. (doi:10.1109/TMI.2008.925082)

Fercher, A. F., Drexler, W., Hitzenberger, C. W. & Lasser, T. 2003 Optical coherence tomography—principles and applications. *Rep. Prog. Phys.* **66**, 239–303. (doi:10.1088/0034-4885/66/2/204)

Fletcher, S. W. & Elmore, J. G. 2003 Mammographic screening for breast cancer. *New Engl. J. Med.* **348**, 1672–1680. (doi:10.1056/NEJMcp021804)

Franceschini, M. A., Toronov, V., Filiaci, M. E., Gratton, E. & Fantini, S. 2000 On-line optical imaging of the human brain with 160 ms temporal resolution. *Opt. Exp.* **6**, 49–57.

Franceschini, M. A., Fantini, S., Thompson, J. H., Culver, J. P. & Boas, D. A. 2003 Hemodynamic evoked response of the sensorimotor cortex measured noninvasively with near-infrared optical imaging. *Psychophysiology* **40**, 548–560. (doi:10.1111/1469-8986.00057)

Fuchino, Y. *et al.* 2008 High cognitive function of an ALS patient in the totally locked-in state. *Neurosci. Lett.* **435**, 85–89. (doi:10.1016/j.neulet.2008.01.046)

Gibson, A. P., Hebden, J. C. & Arridge, S. R. 2005 Recent advances in diffuse optical imaging. *Phys. Med. Biol.* **50**, R1–R43. (doi:10.1088/0031-9155/50/4/R01)

Gibson, A. P., Austin, T., Everdell, N., Schweiger, M., Arridge, S. R., Meek, J. H., Wyatt, J. S., Delpy, D. T. & Hebden, J. C. 2006 Three-dimensional whole-head optical tomography of passive motor evoked responses in the neonate. *Neuroimage* **30**, 521–528. (doi:10.1016/j.neuroimage.2005.08.059)

Downloaded from rsta.royalsocietypublishing.org on 6 November 2009

Godovarty, A., Thompson, A. B., Roy, R., Gurfinkel, M., Eppstein, M., Zhang, C. & Sevick-Muraca, E. M. 2004 Diagnostic imaging of breast cancer using fluorescence-enhanced optical tomography: phantom studies. *J. Biomed. Opt.* **9**, 488–496. (doi:10.1117/1.1691027)

Graber, H. L., Zhong, S., Pei, Y., Arif, I., Hira, J. & Barbour, R. L. 2000 Dynamic imaging of muscle activity by optical tomography. In *OSA Biomedical Topical Meeting, Technical Digest*, pp. 407–408. Washington, DC: Optical Society of America.

Gratton, G., Corballis, P. M., Cho, E., Fabiani, M. & Hood, D. C. 1995 Shades of grey matter: noninvasive optical images of human brain responses during visual stimulation. *Psychophysiology* **32**, 505–509. (doi:10.1111/j.1469-8986.1995.tb02102.x)

Grosenick, D. *et al.* 2004 Time domain optical mammography on 150 patients: hemoglobin concentration and blood oxygen saturation of breast tumours. In *OSA Biomedical Topical Meeting, Miami*, paper ThB2. Washington, DC: Optical Society of America.

Hamaoka, T., McCully, K. K., Quaresima, V., Yamamoto, K. & Chance, B. 2007 Near-infrared spectroscopy/imaging for monitoring muscle oxygenation and oxidative metabolism in healthy and diseased humans. *J. Biomed. Opt.* **12**, 062 105. (doi:10.1117/1.2805437)

Hawrysz, D. J. & Sevick-Muraca, E. M. 2000 Developments towards diagnostic breast cancer imaging using near-infrared optical measurements and fluorescent contrast agents. *Neoplasia* **2**, 388–417. (doi:10.1038/sj.neo.7900118)

Hebden, J. C. & Delpy, D. T. 1997 Diagnostic imaging with light. *Br. J. Radiol.* **70**, S206–S214.

Hebden, J. C. & Rinneberg, H. 2005 Optical mammography: imaging and characterization of breast lesions by pulsed near-infrared laser light (OPTIMAMM). *Phys. Med. Biol.* **50**, 2428. (doi:10.1088/0031-9155/50/11/E01)

Hebden, J. C., Arridge, S. R. & Delpy, D. T. 1997 Optical imaging in medicine: I. Experimental techniques. *Phys. Med. Biol.* **42**, 825–840. (doi:10.1088/0031-9155/42/5/007)

Hebden, J. C., Gibson, A. P., Yusof, R. M., Everdell, N., Hillman, E. M., Delpy, D. T., Austin, T., Meek, J. & Wyatt, J. S. 2002 Three-dimensional optical tomography of the premature infant brain. *Phys. Med. Biol.* **47**, 4155–4166. (doi:10.1088/0031-9155/47/23/303)

Hebden, J. C., Gibson, A. P., Austin, T., Yusof, R. M., Everdell, N., Delpy, D. T., Arridge, S. R., Meek, J. H. & Wyatt, J. S. 2004 Imaging changes in blood volume and oxygenation in the newborn infant brain using three-dimensional optical tomography. *Phys. Med. Biol.* **49**, 1117–1130. (doi:10.1088/0031-9155/49/7/003)

Hielscher, A. H., Klose, A. D., Scheel, A. K., Moa-Anderson, B., Backhaus, M., Netz, U. & Beuthan, J. 2004 Sagittal laser optical tomography for imaging of rheumatoid finger joints. *Phys. Med. Biol.* **49**, 1147–1163. (doi:10.1088/0031-9155/49/7/005)

Hillman, E. M. C. 2007 Optical brain imaging *in-vivo*: techniques and applications from animal to man. *J. Biomed. Opt.* **12**, 051402. (doi:10.1117/1.2789693)

Hillman, E. M. C., Hebden, J. C., Schweiger, M., Dehghani, H., Schmidt, F. E., Delpy, D. T. & Arridge, S. R. 2001 Time resolved optical tomography of the human forearm. *Phys. Med. Biol.* **46**, 1117–1130. (doi:10.1088/0031-9155/46/4/315)

Hoshi, Y. 2003 Functional near-infrared optical imaging: utility and limitations in human brain mapping. *Psychophysiology* **40**, 511–520. (doi:10.1111/1469-8986.00053)

Huppert, T. J., Hoge, R. D., Diamond, S., Franceschini, M. A. & Boas, D. A. 2006 A temporal comparison of BOLD, ASL and NIRS hemodynamic responses to motor stimuli in adult humans. *Neuroimage* **29**, 368–382. (doi:10.1016/j.neuroimage.2005.08.065)

Jiang, S., Pogue, B. W., Paulsen, K. D., Kogel, C. & Poplack, S. P. 2003 *In vivo* near-infrared spectral detection of pressure-induced changes in breast tissue. *Opt. Lett.* **28**, 1212–1214. (doi:10.1364/OL.28.001212)

Jöbsis, F. F. 1977 Noninvasive infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* **198**, 1264–1267. (doi:10.1126/science.929199)

Jöbsis, F. F. 1999 Discovery of the near-infrared window into the body and the early development of near infrared spectroscopy. *J. Biomed. Opt.* **4**, 392–396. (doi:10.1117/1.429952)

Klose, A. D. & Hielscher, A. H. 1999 Iterative reconstruction scheme for optical tomography based on the equation of radiative transfer. *Med. Phys.* **28**, 1698–1707. (doi:10.1118/1.598661)

Downloaded from rsta.royalsocietypublishing.org on 6 November 2009

Klose, A. D., Ntziachristos, V. & Hielscher, A. H. 2004 Experimental validation of a fluorescence tomography algorithm based on the equation of radiative transfer. In *OSA Biomedical Topical Meeting, Miami*, paper SA6. Washington, DC: Optical Society of America.

Koizumi, H., Yamamoto, T., Maki, A., Yamashita, Y., Sato, H., Kawaguchi, H. & Ichikawa, N. 2003 Optical topography: practical problems and new applications. *Appl. Opt.* **42**, 3054–3062. (doi:10.1364/AO.42.003054)

Leff, D. R., Warren, O., Enfield, L. C., Gibson, A. P., Athanasiou, T., Pattern, D. K., Hebden, J. C., Yang, G. Z. & Darzi, A. 2007 Diffuse optical imaging of the healthy and diseased breast: a systematic review. *Breast Cancer Res. Treat.* **108**, 9–22. (doi:10.1007/s10549-007-9582-z)

Li, A. *et al.* 2003 Tomographic optical breast imaging guided by three-dimensional mammography. *Appl. Opt.* **42**, 5181–5190. (doi:10.1364/AO.42.005181)

Li, A., Zhang, Q., Culver, J. P., Miller, E. L. & Boas, D. A. 2004 Reconstructing chromophore concentration images directly by continuous wave diffuse optical tomography. *Opt. Lett.* **29**, 256–258. (doi:10.1364/OL.29.000256)

Manohar, S., Vaartjes, S. E., van Hespen, J. C. G., Klaase, J. M., van den Engh, F. M., Steenbergen, W. & van Leeuwen, T. G. 2007 Initial results of *in vivo* non-invasive cancer imaging in the human breast using near-infrared photoacoustics. *Opt. Exp.* **15**, 12 277–12 285. (doi:10.1364/OE.15.012277)

Maris, M., Gratton, E., Maier, J., Mantulin, W. & Chance, B. 1994 Functional near-infrared imaging of deoxygenated hemoglobin during exercise of the finger extensor muscles using the frequency-domain technique. *Bioimaging* **2**, 174–183. (doi:10.1002/1361-6374(199412)2:4<174::AID-BIO2>3.3.CO;2-H)

Matsuo, K. *et al.* 2003 Activation of the prefrontal cortex to trauma-related stimuli measured by near-infrared spectroscopy in posttraumatic stress disorder due to terrorism. *Psychophysiology* **40**, 492–500. (doi:10.1111/1469-8986.00051)

Ntziachristos, V., Yodh, A. G., Schnall, M. & Chance, B. 2000 Concurrent MRI and diffuse optical tomography of breast after indocyanine green enhancement. *Proc. Natl Acad. Sci. USA* **97**, 2767–2772. (doi:10.1073/pnas.040570597)

Ntziachristos, V., Ripoll, J., Weisslader, R. 2002*a* Would near-infrared fluorescence signals propagate through large human organs for clinical studies? *Opt. Lett.* **27** 333–335. [Erratum in *Opt. Lett.* **27**, 1652.] (doi:10.1364/OL.27.000333)

Ntziachristos, V., Tung, C.-H., Bremer, C. & Weisslader, R. 2002*b* Fluorescence molecular tomography resolves protease activity *in vivo*. *Nat. Med.* **8**, 757–760. (doi:10.1038/nm729)

Ntziachristos, V., Yodh, A. G., Schnall, M. & Chance, B. 2002*c* MRI-guided diffuse optical spectroscopy of malignant and benign breast lesions. *Neoplasia* **4**, 347–354. (doi:10.1038/sj.neo.7900244)

Obrig, H. & Villringer, A. 2003 Beyond the visible—imaging the human brain with light. *J. Cereb. Blood Flow Metab.* **23**, 1–18. (doi:10.1097/00004647-200301000-00001)

Pifferi, A., Taroni, P., Torricelli, A., Messina, F. & Cubeddu, R. 2003 Four-wavelength time-resolved optical mammography in the 680–980 nm range. *Opt. Lett.* **28**, 1138–1140. (doi:10.1364/OL.28.001138)

Pogue, B. W., Davis, S. C., Song, X., Brooksby, B. A., Dehghani, H. & Paulsen, K. D. 2006 Image analysis methods for diffuse optical tomography. *J. Biomed. Opt.* **11**, 033 001–033 016. (doi:10.1117/1.2209908)

Pramanik, M., Ku, G., Li, C. & Wang, L. V. 2008 Design and evaluation of a novel breast cancer detection system combining both thermoacoustic (TA) and photoacoustic (PA) tomography. *Med. Phys.* **35**, 2218–2223. (doi:10.1118/1.2911157)

Raichle, M. E. & Mintun, M. A. 2006 Brain work and brain imaging. *Annu. Rev. Neurosci.* **29**, 449–476. (doi:10.1146/annurev.neuro.29.051605.112819)

Rice, A. & Quinn, C. M. 2002 Angiogenesis, thrombospodin, and ductal carcinoma *in situ* of the breast. *J. Clin. Pathol.* **55**, 569–574. (doi:10.1136/jcp.55.8.569)

Downloaded from rsta.royalsocietypublishing.org on 6 November 2009

Sato, H., Kiguchi, M., Kawaguchi, F. & Maki, A. 2004 Practicality of wavelength selection to improve signal-to-noise ratio in near-infrared spectroscopy. *Neuroimage* **21**, 1554–1562. (doi:10.1016/j.neuroimage.2003.12.017)

Schmidt, F. E. W., Fry, M. E., Hillman, E. M. C., Hebden, J. C. & Delpy, D. T. 2000 A 32-channel time-resolved instrument for medical optical tomography. *Rev. Sci. Instrum.* **71**, 256–265. (doi:10.1063/1.1150191)

Schulz, R. B., Ripoll, J. & Ntziachristos, V. 2004 Experimental fluorescence tomography of tissues with noncontact measurements. *IEEE Trans. Med. Imaging* **23**, 492–500. (doi:10.1109/TMI.2004.825633)

Schweiger, M. & Arridge, S. R. 1999 Optical tomographic reconstruction in a complex head model using *a priori* region boundary information. *Phys. Med. Biol.* **44**, 2703–2721. (doi:10.1088/0031-9155/44/11/302)

Schweiger, M., Gibson, A. P. & Arridge, S. R. 2003 Computational aspects of diffuse optical tomography. *IEEE Comput. Sci. Eng.* **5**, 33–41. (doi:10.1109/MCISE.2008.1238702)

Selb, J., Stott, J. J., Franceschini, M. A., Sorensen, A. G. & Boas, D. A. 2005 Improved sensitivity to cerebral hemodynamics during brain activation with a time-gated optical system: analytical model and experimental validation. *J. Biomed. Opt.* **10**, 011013. (doi:10.1117/1.1852553)

Selb, J., Joseph, D. K. & Boas, D. A. 2006 Time-gated optical system for depth-resolved functional brain imaging. *J. Biomed. Opt.* **11**, 044008. (doi:10.1117/1.2337320)

Siegel, A. M., Culver, J. P., Mandeville, J. B. & Boas, D. A. 2003 Temporal comparison of functional brain imaging with diffuse optical tomography and fMRI during rat forepaw stimulation. *Phys. Med. Biol.* **48**, 1391–1403. (doi:10.1088/0031-9155/48/10/311)

Srinivasan, S. *et al.* 2006 *In vivo* hemoglobin and water concentrations, oxygen saturation, and scattering estimates from near-infrared breast tomography using spectral reconstruction. *Acta Radiol.* **13**, 195–202. (doi:10.1016/j.acra.2005.10.002)

Strangman, G., Culver, J. P., Thompson, J. H. & Boas, D. A. 2002 A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. *Neuroimage* **17**, 719–731. (doi:10.1016/S1053-8119(02)91227-9)

Strangman, G., Franceschini, M. A. & Boas, D. A. 2003 Factors affecting the accuracy of near-infrared spectroscopy calculations for focal changes in oxygenation parameters. *Neuroimage* **18**, 865–879. (doi:10.1016/S1053-8119(03)00021-1)

Suda, M., Morimoto, K., Obata, A., Koizumi, H. & Maki, A. 2008 Emotional responses to music: towards scientific perspectives on music therapy. *Neuroreport* **19**, 75–78. (doi:10.1097/WNR.0b013e3282f3476f)

Taga, G., Konishi, Y., Maki, A., Tachibana, T., Fujiwara, M. & Koizumi, H. 2000 Spontaneous oscillation of oxy- and deoxy- hemoglobin changes with a phase difference throughout the occipital cortex of newborn infants observed using non-invasive optical topography. *Neurosci. Lett.* **282**, 101–104. (doi:10.1016/S0304-3940(00)00874-0)

Taga, G., Asakawa, K., Maki, A., Konishi, Y. & Koizumi, H. 2003 Brain imaging in awake infants by near-infrared optical topography. *Proc. Natl Acad. Sci. USA* **100**, 10 722–10 727. (doi:10.1073/pnas.1932552100)

Taroni, P., Danesini, G., Torricelli, A., Pifferi, A., Spinelli, L. & Cubeddu, R. 2004*a* Clinical trial of time-resolved scanning optical mammography at 4 wavelengths between 683 and 975 nm. *J. Biomed. Opt.* **9**, 464–473. (doi:10.1117/1.1695561)

Taroni, P., Pallaro, L., Pifferi, A., Spinelli, L., Torricelli, A. & Cubeddu, R. 2004*b* Multi-wavelength time-resolved optical mammography. In *OSA Biomedical Topical Meeting, Miami*, paper ThB3. Washington, DC: Optical Society of America.

Tromberg, B. J., Cerussi, A., Shah, N., Compton, M., Durkin, A., Hsiang, D., Butler, J. & Mehta, R. 2005 Diffuse optics in breast cancer: detecting tumours in pre-menopausal women and monitoring neoadjuvant chemotherapy. *Breast Cancer Res.* **7**, 279–285. (doi:10.1186/bcr1358)

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Tromberg, B. J., Pogue, B. W., Paulsen, K. D., Yodh, A. G., Boas, D. A. & Cerussi, A. E. 2008 Assessing the future of diffuse optical imaging technologies for breast cancer management. *Med. Phys.* **35**, 2443–2451. (doi:10.1118/1.2919078)

Tsujimoto, S., Yamamoto, T., Kawaguchi, H., Koizumi, H. & Sawaguchi, T. 2004 Prefrontal cortical activation associated with working memory in adults and preschool children: an event-related optical topography study. *Cereb. Cortex* **14**, 703–712. (doi:10.1093/cercor/bhh030)

Uludag, K., Steinbrink, J., Villringer, A. & Obrig, H. 2004 Separability and cross-talk: optimizing dual wavelength combinations for near-infrared spectroscopy of the adult head. *Neuroimage* **22**, 583–589. (doi:10.1016/j.neuroimage.2004.02.023)

Wang, J., Davis, S. C., Srinivasan, S., Jiang, S., Pogue, B. W. & Paulsen, K. D. 2008 Spectral tomography with diffuse near-infrared light: inclusion of broadband frequency domain spectral data. *J. Biomed. Opt.* **13**, 041 305–041 310. (doi:10.1117/1.2952006)

Wang, L., Jacques, S. L. & Zhao, X. 1995 Continuous-wave ultrasonic modulation of scattered laser light to image objects in turbid media. *Opt. Lett.* **20**, 629–631. (doi:10.1364/OL.20.000629)

Wang, X., Pang, Y., Ku, G., Xie, X., Stoica, G. & Wang, L. V. 2003 Noninvasive laser-induced photoacoustic tomography for structural and functional *in vivo* imaging of the brain. *Nat. Biotechnol.* **21**, 803–806. (doi:10.1038/nbt839)

Watanabe, E., Maki, A., Kawaguchi, F., Takashiro, K., Yamashita, Y., Koizumi, H. & Mayanagi, Y. 1998 Non-invasive assessment of language dominance with near-infrared spectroscopic mapping. *Neurosci. Lett.* **256**, 49–52. (doi:10.1016/S0304-3940(98)00754-X)

Watanabe, E., Nagahori, Y. & Mayanagi, Y. 2002 Focus diagnosis of epilepsy using near-infrared spectroscopy. *Epilepsia* **43**(Suppl. 9), 50–55. (doi:10.1046/j.1528-1157.43.s.9.12.x)

Weisslader, R. & Ntziachristos, V. 2003 Shedding light onto live molecular targets. *Nat. Med.* **9**, 123–128. (doi:10.1038/nm0103-123)

Weisslader, R. & Pittet, M. J. 2008 Imaging in the era of molecular oncology. *Nature* **452**, 580–589. (doi:10.1038/nature06917)

White, B. R., Zeff, B., Schlagger, B. L., Dehghani, H. & Culver, J. P. 2008 Phase-encoded retinotopic mapping in humans with DOT. *OSA Biomedical Topical Meeting, Technical Digest*, paper BME3. Washington, DC: Optical Society of America.

Wolf, M., Ferrari, M. & Quaresima, V. 2007 Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. *J. Biomed. Opt.* **12**, 062104. (doi:10.1117/1.2804899)

Xu, M. & Wang, L. V. 2006 Photoacoustic imaging in biomedicine. *Rev. Sci. Instrum.* **77**, 041101. (doi:10.1063/1.2195024)

Yamamoto, T., Maki, A., Kadoya, T., Tanikawa, Y., Yamada, Y., Okada, E. & Koizumi, H. 2002 Arranging optical fibres for the spatial resolution improvement of topographical images. *Phys. Med. Biol.* **47**, 3429–3440. (doi:10.1088/0031-9155/47/18/311)

Yamashita, Y., Maki, A. & Koizumi, H. 1999 Measurement system for noninvasive dynamic optical topography. *J. Biomed. Opt.* **4**, 414–417. (doi:10.1117/1.429940)

Yamashita, Y., Maki, A. & Koizumi, H. 2001 Wavelength dependence of the precision of noninvasive optical measurement of oxy-, deoxy-, and total-haemoglobin concentration. *Med. Phys.* **28**, 1108–1114. (doi:10.1118/1.1373401)

Zeff, B., White, B. R., Dehghani, H., Schlagger, B. L. & Culver, J. P. 2007 Retinotopic mapping of adult human visual cortex with high-density diffuse optical tomography. *Proc. Natl Acad. Sci. USA* **104**, 12 169–12 174. (doi:10.1073/pnas.0611266104)

Zhang, Q. *et al.* 2005 Co-registered tomographic X-ray and optical breast imaging: initial results. *J. Biomed. Opt.* **10**, 024033. (doi:10.1117/1.1899183)

Zhou, J., Schmid, T., Schnitzer, S. & Bruene, B. 2006 Tumor hypoxia and cancer progression. *Cancer Lett.* **237**, 10–21. (doi:10.1016/j.canlet.2005.05.028)

Zhu, Q., Tannenbaum, S., Hegde, P., Kane, M., Xu, C. & Kurtzman, S. H. 2008 Noninvasive monitoring of breast cancer during neoadjuvant chemotherapy using optical tomography with ultrasound localization. *Neoplasia* **10**, 1028–1040.