The British Journal of Radiology, 70 (1997), S206–S214

Diagnostic imaging with light

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Abstract. This paper reviews the evolution of optical imaging in diagnostic radiology and examines recent progress. Although the idea has been around for many decades, interest in the development of an effective method has never been so great. Optical imaging presents several potential advantages over existing radiological techniques. First, the radiation is non-ionizing and therefore reasonable doses can be repeatedly employed without harm to the patient. Second, optical methods offer the potential to differentiate between soft tissues with different optical absorption or scatter, but which are indistinguishable using other modalities. And third, specific absorption by natural chromophores (such as haemoglobin) allows functional information to be obtained. Principal clinical applications include a means of detecting breast disease and a cerebral imaging modality for mapping oxygenation and haemodynamics in the brain of newborn infants or cortical functional activity in adults. Past attempts to image tissues with light have been severely restricted by the overwhelming scatter which occurs when optical radiation spreads through tissue: however, recent innovations in technology have suggested once again that it may be a practical possibility.

Introduction

When playing with an electric torch many children are amused to discover that their fingers glow red when illuminated from behind by the beam. However, it is always a disappointment that they are unable to discern bones or other anatomical structures below the skin. Unfortunately the light is scattered so profusely that a parallel beam becomes diffuse after penetrating only a millimetre or so. It is impossible to resolve internal structures whose dimensions are much smaller than the total thickness of the tissue. Regardless of this considerable obstacle, the possibility of a diagnostic imaging method based on optical radiation has been discussed for more than 70 years. Despite occasional encouraging results, sometimes accompanied by unrealistic claims of significant clinical utility, development of a successful method has continued to be elusive. However, substantial recent progress suggests that optical imaging might finally evolve into a viable clinical modality within the next two or three years. In this paper we will examine the history, summarize the recent advancements and consider the likely prospects for optical imaging in diagnostic radiology.

There are several very significant advantages that optical imaging might offer over existing radiological techniques. The most obvious attractive feature is that radiation at optical wavelengths (ranging from visible to infrared) is non-ionizing and therefore patients can be exposed repeatedly without the harm associated with an accumulated dose of X-rays. As with ultrasound, the only significant hazard arises from tissue heating, which can be avoided with reasonable care. Optical methods have potential diagnostic value for two reasons: (1) they could make it possible to differentiate between soft tissues, which possess different absorption or scatter at optical wavelengths, but are indistinguishable using any other technique, including MRI; (2) specific absorption by natural chromophores (such as haemoglobin) allows functional information to be obtained. In this respect, optical imaging may enable functional images to be recorded without the use of radioisotopes or other contrast agents. Furthermore, such monitoring could, if required, be performed continuously at the bedside.

To appreciate the severity of the problem of diagnostic imaging with light, one must consider the nature of the interactions that occur between light and tissue. By far the most dominant interaction at optical wavelengths is elastic scattering. The scatter coefficient μ_s (the mean number of scatters per unit length) of many soft tissues has been measured at a variety of optical wavelengths, and is typically within the range 10–100 mm^{-1} [1]. As a consequence, measurements of transmitted intensity through more than a few millimetres of tissue are dominated by scattered light. Imaging contrast is largely governed by photon interactions at the surface. The choice of wavelength is complicated by the need to consider the relative optical characteristics of the different tissues under investigation, the availability of suitable sources and the sensitivity of the detector. The characteristic scatter of tissues is commonly expressed in terms of the transport scatter coefficient $\mu_s' = \mu_s(1-g)$, where g is the mean cosine of the single scatter phase function. Typically

μ_s' is about 1 mm^{-1} for breast and neonate brain tissues, but is larger for muscle and the adult brain. The other important fundamental characteristic of tissue is the absorption coefficient μ_a. Very strong absorption by haemoglobin in blood at wavelengths less than 600 nm limits the radiation that can be used for imaging through several centimetres of tissue to the red and near-infrared (NIR) region, illustrated in Figure 1. A steady decrease in scatter also favours the use of longer wavelengths, although significant absorption by water, the dominant component in most soft tissues [2], prevents the use of wavelengths in excess of about 1 μm.

Several possible clinical applications have been proposed for NIR imaging. Potentially the most important is the development of a means of screening for breast cancer, particularly if a specificity and sensitivity exceeding those of X-ray mammography can be achieved. Screening demands a spatial resolution of a few millimetres or better in order to distinguish tumours from surrounding healthy tissue while they are still small in size, before metastasis occurs and treatment becomes more difficult. This has been the main focus of interest in the optical imaging of tissue since the idea of transillumination was first mooted more than 70 years ago, and the history of developments is given below.

The second principal goal is to develop a method of brain imaging for mapping structure and function in newborn infants, and possibly adults too. This represents a natural extension of NIR spectroscopy [3, 4] which has already been established as a valuable clinical technique. It would not require such high spatial resolution as breast imaging; 10 mm would probably be adequate. Recent work on neonatal brain imaging is summarised below, and this section is followed by another short section describing a few additional clinical situations where optical imaging may have some utility.

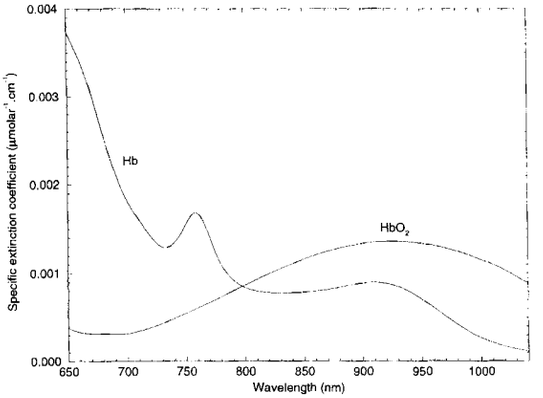

Figure 1. The absorption spectra of oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (Hb).

In the field of NIR imaging, there is also considerable interest in the development of methods to obtain sub-millimetre resolution images of tissue a few millimetres in thickness. The technique known as optical coherence tomography has been employed for both tissue microscopy and ocular imaging, and is reviewed by Fercher [5]. But, coherence techniques are no use for imaging through the larger thicknesses of tissues required for diagnostic radiology, and are not discussed in this review.

Breast transillumination

History

Transillumination of the female breast as a means of diagnosing lesions was first described by Dr Max Cutler [6] in 1929. However, Dr Cutler himself attributes the idea for this work to Dr Ewing, and the performance of the first studies to Dr Frank Adair. As Cutler reports, the transillumination technique was "relatively simple":

> "The examination is made in a totally dark room with the patient sitting in a revolving chair opposite the examiner. The [electric] lamp is placed against the under surface of the breast and gradually moved as different areas in the breast are inspected successively, the object being to place the particular portion in question directly between the light and the examiner's eye."

Even these early experiments revealed that the multiple scattering which occurs when light propagates through tissue causes features below the surface to appear extremely blurred. Yet Cutler did make a number of valuable discoveries, the most important of which was the dominant role played by blood concentration in the degree of opacity of a given tissue. He found that solid tumours often appeared to be opaque, although it was not possible to differentiate between benign and malignant tumours. Low inherent spatial resolution clearly resulted in very poor sensitivity and specificity. Although Cutler was generally positive about the potential of transillumination for certain classes of breast pathology, and a small number of further papers were published on the subject in the 1930s, the technique did not catch on.

In fact only sporadic interest was shown over the following 40 years, until 1972, when Gros reported the use of a water-cooled probe with a high-intensity white light source [7]. This device provided sufficient transmitted intensity to record the images on colour film. These researchers were also responsible for coining the term "diaphanography" to describe transillumination of the breast, derived from the Greek words *dia* (through) and

phanes (showing). Nevertheless, the new technology still exhibited poor sensitivity [8].

It then occurred to some researchers that, because of the very high absorption by blood, the vast majority of the optical radiation emitted by a white light source was achieving little except heating the tissue. In 1980, Ohlsson and his colleagues employed NIR sources and infrared-sensitive film, which considerably improved their ability to identify carcinoma, and a 95% accuracy was claimed [9]. This development, in conjunction with the employment of video cameras and recorders, led to a minor explosion of interest [10–17]. The study which probably generated the greatest optimism during the early 1980s was that of Carlsen [10] in 1982, who reported results obtained using a commercial instrument designed and marketed by Spectrascan Inc. This device recorded transmission images of the breast using two (red and NIR) wavelength regions simultaneously, and displayed their relative intensity on a monitor. Carlsen also reported a sensitivity better than 90%, and an overall performance comparable to that of X-ray mammography. It was discovered that dysplastic tissue of high radiodensity, which prevents visualization of embedded tumours using X-rays, is apparently insensitive to optical radiation [10, 11], which encouraged the development of transillumination. Although some initial evaluations of the Spectrascan device were reasonably positive [11, 13], subsequent detailed comparisons between transillumination and X-ray mammography were generally unfavourable. Geslien et al [15] reported a sensitivity of only 58% (compared to 97% for X-ray mammography) and deduced that the performance was inadequate for screening. Even some tumours larger than 1 cm in diameter were not detectable. An equally thorough assessment of breast transillumination which produced very similar results was reported by Monsees et al in 1987 [16, 17].

Time-resolved imaging

Not surprisingly, enthusiasm for transillumination among the radiological community dwindled rapidly following these negative reports. Nevertheless, scientific contemplation of the fundamental limitations of transillumination methods continued. For the first time, consideration was given to the idea of improving the resolution and contrast by either reducing the influence of scatter, or exploiting some knowledge of its statistical behaviour. In general, researchers have approached the task of improving the performance of transillumination in two ways. The so-called indirect approach is based on the assumption that, given a set of measurements of transmitted light between pairs of points on the surface of an object, there exists a unique three-dimensional distribution of internal scatterers and absorbers which would yield that set [18]. Because of its particular relevance to transverse imaging of the brain, we will discuss this idea further in the next section.

The second (direct) approach is based on a reasonable assumption that photons which are least scattered provide inherently better spatial resolution and contrast since they propagate closest to a straight line through the tissue [19]. Imaging therefore involves appropriate filtering, or "gating", to isolate this transmitted component from the majority of the multiply-scattered light. This is illustrated schematically in Figure 2.

A broad variety of gating techniques have been proposed and tested experimentally. The simplest filtering method which has been widely investigated is the rejection of transmitted light which emerges from the tissue at large angles with respect to the incident beam. This simply requires a collimated detector aligned co-axially with a collimated source. Several experimental systems were developed which achieved modest results for various *ex vivo* tissue samples and model media [20–22]. A dual-wavelength scanning laser beam system employing a degree of collimated detection was constructed for breast imaging studies by Kaneko et al [23]. There were some quite enthusiastic claims of the usefulness of this system in detecting certain tumours, but the spatial resolution and the demonstrated specificity were both poor [24]. Computer simulations have shown that unfortunately the collimated detection method ceases to be effective when all light entering the tissue becomes diffuse, which for soft tissues implies a limiting thickness of just a few millimetres [25]. Similar restrictions apply to proposed gating

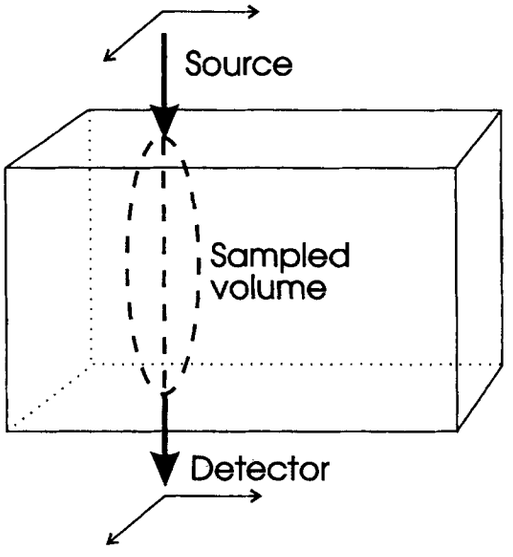

Figure 2. The direct imaging method. Contrast and/or spatial resolution is improved by generating images with a select fraction of the transmitted radiation.

methods which rely on a fraction of photons being able to propagate without loss of initial coherence [26] or polarization state [27].

By the mid-1980s new technologies were becoming available which enabled researchers to investigate the possibility of gating transmitted photons according to the lengths of their paths, or more precisely, their time of flight within the tissue. Perhaps the first explicit description of time-gated imaging can be credited to Maarek et al [28], who examined its potential using computer simulations. The time gating method involves illuminating the tissue with a source of very short pulses and measuring their arrival time using an ultrafast detector. The temporal distribution of photons produced when a pulse of a few picoseconds is transmitted through a highly scattering medium is generally known as the temporal point spread function (TPSF). For several centimetres of soft tissue, the TPSF will extend over several nanoseconds. However, for a transillumination geometry, the intensity of transmitted light measured over some very small period of time after the photons first emerge from the tissue will be dependent upon the optical properties of the tissue contained within a small volume element surrounding the line-of-sight between the source and detector. Images are constructed by sampling multiple lines-of-sight. The shorter the temporal sampling period, the narrower the volume element and the greater the spatial resolution. This idea was studied intensively by numerous investigators during the late 1980s and early 1990s.

An experimental time-gated system based on the Kerr cell was actually described by Martin et al [29] a few years before the suggestion of Maarek and colleagues [28]. Although the former employed their system to image samples of biological tissue, they only considered recording *reflection* images, which has a limited, if any, clinical application. The Kerr cell acts as a very fast shutter, whose optical transmission can vary from about 0.01% to about 20% over the period of a few picoseconds. By recording the light transmitted through the cell electronically or using conventional photography, high-resolution images through scattering media may be obtained by selectively sampling the transmitted photons with the shortest flight times. The breast imaging potential of this technology has been investigated thoroughly by Professor Alfano and coworkers [30, 31]. Unfortunately, the performance of Kerr gate imaging techniques is ultimately limited by the dynamic range of the transmission opacity of the cell. A centimetre or so of tissue would appear to be the maximum thickness for which Kerr gating would be an effective method of isolating photons with shorter flight times. Other fast-shutter methods, summarized elsewhere [19], have demonstrated similar deficiencies.

The ideal time gate detector is one which can sample transmitted photons over any temporal window without contamination by photons arriving outside the window. The device which comes nearest to this ideal is the optical streak camera. Streak cameras, which are able to record entire TPSFs along a single line-of-sight with a temporal resolution of 10 ps or better, have been widely used to explore the potential and limitations of time-gated methods and their application to breast imaging in particular. For example, Mitic et al [32] recently obtained a series of breast TPSF measurements, enabling *in vivo* optical properties of breast tissue to be derived. The results have been used to construct realistic tissue-equivalent phantoms which have allowed more meaningful evaluations of imaging performance [33]. The streak camera is able to isolate least-scattered photons through many centimetres of tissue with excellent precision. In order to sample many lines of sight using a streak camera's small collection area (typically 1 mm^2) either the detector must record TPSFs consecutively, which is too slow, or multiple detectors must be employed, which is too expensive. The most practical current option for a time-resolved imaging system is one based upon technology known as time-correlated single-photon counting (TCSPC). An example of this is described by Berg et al [34], whose system consists of a microchannel plate photomultiplier tube (MCP-PMT) and a time-to-amplitude converter (TAC). As described in our final section, a time-resolved imaging system based on an array of similar detectors is being constructed at University College London (UCL) [35].

Frequency domain imaging

As a general mathematical principle, any measurement in the time domain can be equivalently expressed in the frequency domain. Scientists have therefore sought to develop imaging techniques which acquire transmitted light information in the frequency domain directly. This involves illuminating tissue with an intensity-modulated beam, and measuring the AC modulation amplitude and phase shift of the transmitted signal [36]. The fundamental imaging work performed with such systems is reviewed elsewhere [19]. The principal advantage over time domain measurement is that continuous light sources and detectors can be employed, which are generally less expensive.

Although relatively little information appears in the published literature, some industrial companies are known to have already built breast imaging devices based on frequency-domain measurement.

Separate preliminary clinical trials have already been performed, using prototypes, at Carl Zeiss and at Siemens in Germany. The breast imaging system at Carl Zeiss is briefly described by Kaschke et al [37], who present a preliminary image of a normal female breast obtained at 690 nm. Data are acquired by scanning a collinear source and detector over a two-dimensional plane in the direct manner illustrated in Figure 2. A study of 42 patients using the system is described by Moesta et al [38]. They claim that the sensitivity is greater than that of conventional transillumination, although the ability to observe minimal cancers located in the centre of the breast has not yet been assessed systematically.

Following extensive studies of the *in vivo* optical properties of breast tissue [32], a group at Siemens has also built a frequency-domain breast imaging system. However, the specifications of the system and the results of clinical trials have not yet been widely published.

Despite the growing amount of clinical data, there is still no clear evidence that current frequency-domain imaging systems represent an effective tool for breast imaging. Unfortunately, no sources capable of providing significant power at very high frequencies are yet available. Most experimental work performed so far has utilized frequencies of a few hundred MHz, which is equivalent to a temporal resolution of a few nanoseconds.

NIR functional imaging of the brain

The community of scientists and engineers who have developed NIR spectroscopy into a very successful method of acquiring functional and physiological data non-invasively . has long regarded the development of an optical imaging modality as their ultimate goal. NIR spectroscopy is now used regularly to monitor brain oxygenation changes in newborn infants [39, 40], adults [41] and the fetus during labour [42]. Absolute quantification of cerebral physiological parameters such as blood flow [43] and blood volume [44] has also been achieved. Recently, detection of brain activity through evoked response to mental tasks and external stimuli has been reported [45–48].

Because of the very low transmitted flux, imaging the entire adult brain is an unrealistic goal. Research has consequently concentrated on mapping of the adult cortex with an array of sources and detectors placed over the surface of the head [46, 47]. It is however feasible to transilluminate the head of a premature infant and obtain an entire cross-sectional image. Currently there is no diagnostic imaging modality which can be continuously and safely employed on the many neonates in intensive care who suffer from dysfunction in cerebral oxygenation and other brain pathologies. Optical methods have the potential to provide images at the cotside with no risk to the infant. Characteristic absorption by haemoglobin provides a natural contrast agent to study oxygenation, blood volume, and dynamic processes, including evoked responses. The artificial contrast agent indocyanine green has also been administered to monitor blood flow optically [49]. Near-infrared imaging also offers the facility to map cerebral blood volume and the variation in myelination. The fact that the neonatal head, and especially its surface tissues, are relatively transparent to light has been known for a long time, and transillumination of the head has been widely used to observe abnormalities near the brain surface, development of hydrocephalus, and subdural haemorrhage [50, 51].

Obtaining a transverse image of a neonatal brain requires the indirect imaging approach briefly mentioned in the previous section and comprehensively reviewed by Arridge and Hebden [18]. Indirect methods generally involve detecting transmitted radiation at multiple sites for each source position. The most common sampling configuration is shown in Figure 3, where detectors are arranged around the circumference of the tissue and a source is moved to successive points around the same circumference. Imaging becomes a task of solving an inverse problem using complex mathematical algorithms which include some knowledge of the statistical behaviour of light in tissue. In principle, the measurements employed by the algorithms could be of any type, even total transmitted intensity. However, because of the overwhelming dependence of total intensity on interactions at the surface, the measurement of one or more characteristics of the temporal distribution of transmitted light, or an equivalent in the frequency domain, is considered more suitable.

Although the indirect imaging approach has been widely tested on model media, the only clinical studies published to date are those using the multichannel TAC system built at Stanford University by Dr Benaron and colleagues [52–55].

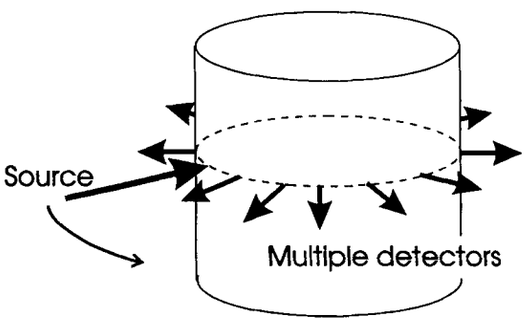

Figure 3. The indirect imaging method. Multiple sources and detectors are placed around the circumference.

Neonate images revealing severe brain haemorrhage were reconstructed from temporal measurements using various analytical methods [54, 55]. The Stanford system is currently very inefficient in terms of data collection, requiring acquisition times of several hours, which is impractical for routine clinical use in many situations. However, this imaging approach shows much promise and developments over the next year or two could lead to a significant clinical impact. At least two further multichannel systems are currently under construction, including the UCL system described below, and another 64-channel system being built in Japan [45, 56].

Additional clinical applications

It is interesting to note that when Cutler reported the first breast imaging results in 1929, transillumination was already known as a means of diagnosing inflammatory diseases of the sinuses and of differentiating between solid tumours of the testis and hydrocele [6]. The applications proposed for the current time and frequency domain system include the study of extremities, including the response of muscle to exercise, assessment of tissue viability and diagnosis of peripheral vascular disease [57–59]. The first *in vivo* image acquired with a frequency domain system was that of a human hand, described by Gratton et al [60]. The authors claimed, rather optimistically perhaps, that the images revealed internal structures such as bones and blood vessels with millimetre resolution. This work was soon followed by reports of the first functional images using frequency domain measurements [61]. Maps of the dorsal surface of the adult forearm were produced before, during and after isotonic exercise of the finger muscles. The images, generated from the difference in signals obtained during exercise, respond to the increased absorption of deoxygenated haemoglobin resulting from increased oxygen metabolism during the exercise. Earlier NIR images of the human forearm were presented by Araki and Nashimoto [62, 63], which revealed a two-dimensional distribution of the oxygenation state at the surface. Although these potential applications have not been a major motivation for the development of optical imaging methods, a successful device could have significant impact in many areas of clinical diagnosis.

Summary of current prospects

The steadily increasing number of international conferences [64–69] and scientific journals that are devoted to biomedical optics shows what a flourishing research area it is. The development of a diagnostic imaging modality is arguably its most ambitious goal, and is given so much attention that it looks as if success is either imminent or else inherently unachievable. Imaging systems designed for clinical use based on time domain and frequency domain technologies are in various stages of development in Europe, the USA, and Japan. In addition to those already mentioned, industrial systems are currently being evaluated by researchers at Philips Research Laboratories in the Netherlands [70] and Imaging Diagnostic Systems in the USA [71].

At UCL, we have adopted the philosophy that one should aim to gain as much information as possible from the light transmitted through the tissue, and that one cannot do better than detect every photon and measure its flight time with the highest temporal resolution. In an attempt to achieve this as closely as current technology allows, a multichannel time-resolved system has been designed, based on state-of-the-art TCSPC instrumentation. The system, described in detail elsewhere [35], is illustrated in Figure 4. Light from a source of NIR pulses is coupled successively into a series of optical fibres so that the point of illumination on the tissue surface is varied *sequentially*. Meanwhile the transmitted light is collected by 32 detector fibre bundles *simultaneously*. The source and detector fibres are arranged at equal intervals around the circumference of the breast or neonatal head. Each of the 32 detector fibre bundles is coupled to the cathode of a MCP-PMT via a variable optical attenuator. The attenuators ensure that the intensity of detected light does not saturate or damage the MCP-PMT, and the flux

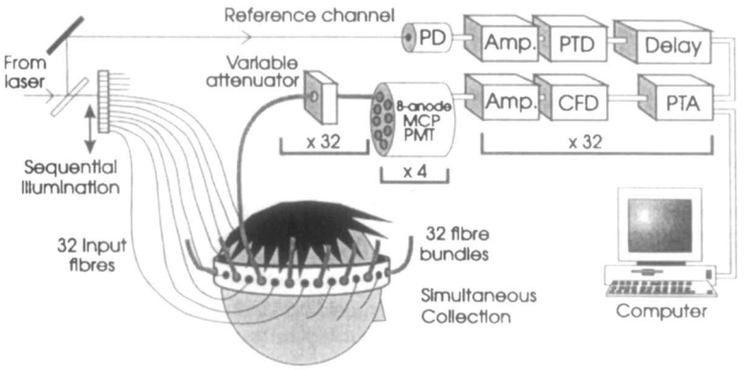

Figure 4. The UCL multichannel time-resolved imaging system.

of photons is sufficiently small to prevent detection of multiple photons during each electronic cycle. The system employs four 8-anode MCP-PMTs. Electronic pulses generated each time a photon is detected are sampled by a sophisticated electronic system manufactured by EG&G ORTEC. By measuring the delay between these pulses and a reference signal received directly via the laser, histograms of photon flight times (*i.e.* TPSFs) are gradually built up within the storage memory of the device. For 32 separate source positions, the instrument acquires a total of 1024 TPSFs. The instrument is known as the Multi-channel Opto-electronic Near-infrared System for Time-resolved Image Reconstruction (MONSTIR). As it is contained in a rack 1.8 m high and 0.9 m deep, the acronym appears appropriate for its size. However, the MONSTIR is designed to be fully portable and will be able to operate at the cotside in neonatal intensive care units. The system is currently being tested in the laboratory. Initial clinical studies are due to begin in the summer of 1997.

Of course, the success of the MONSTIR and clinical systems elsewhere will depend as much upon the reconstruction algorithms as upon the instrumentation. At UCL, the theoretical reconstruction effort is led by Dr Arridge [18]. Assuming initial results are encouraging, it is likely that the development of algorithms will undergo a period of extensive evolution as occurred in the development of X-ray computed tomography and MRI. However, optical imaging for both principal applications is very unlikely to approach the spatial resolution of either X-rays or MRI. The overall performance may be more like that of the radioisotope imaging modalities such as PET and SPECT. An analogy with these techniques is appropriate because the emphasis of optical imaging is on the display of function rather than structure. The optical imaging problem is significantly more complex than any previously tackled in diagnostic radiology. Although the current prognosis is very positive, the jury remains out for a short while longer.

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