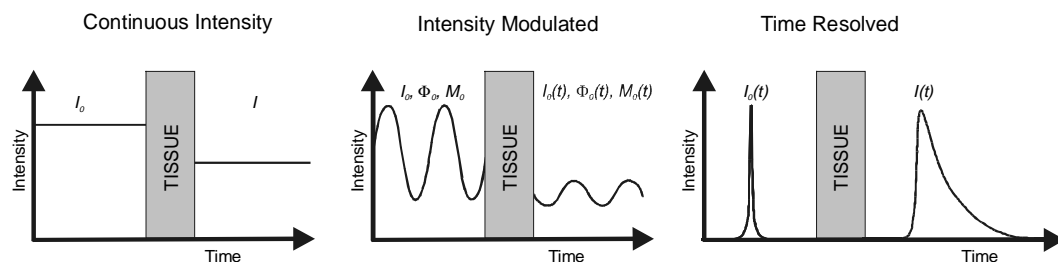


## 5 Current State of Near Infrared Spectroscopy and Imaging

Biomedical optics is a fast growing field of research, both in academia as well as in industrial R&D laboratories. The advantages of using optical techniques in diagnostic procedures are significant and include the complete non-invasiveness, the use of harmless, non-ionising radiation, and the prospects for revealing chemical contrast, which can represent valuable physiological information. One of the most important applications is the monitoring of tissue oxygenation and blood volume using measurements of the tissue absorption at two or more wavelengths. The first section of this chapter introduces different types of instrumentation and their associated measurement methods as they are currently used in Near Infrared Spectroscopy (NIRS) and Imaging (NIRI). NIRS features highly in this chapter since tomographic imaging is in many ways an extension of this established technique, and the types of instrumentation employed are common to both. Non-localised and localised NIRS are outlined in sections 5.2 and 5.3, respectively, while optical imaging is discussed in detail in section 5.4.

### 5.1 Types of instrumentation

A recent review of the subject of quantification and measurement types in NIRS is given by [Delpy 1997]. As described earlier in section 4.1, attenuation of NIR light in tissue is due to absorption and scatter. Absorption is caused by chromophores of both constant (e.g. water), and variable (e.g. HbO<sub>2</sub> and Hb) concentration. The consequence of scattering is that the optical pathlength of individual photons does not equal the geometrical source-detector separation and is also wavelength dependent. It is a function of the absorption and scattering coefficients  $\mu_a$  and  $\mu_s$ , the scattering phase function  $f(\cos\theta)$ , and the tissue and measurement geometry. Hence attenuation measurements alone do not allow quantification of chromophore concentrations.



**Figure 5-1** The three fundamental types of NIR spectroscopy/imaging instrumentation.

Figure 5–1 schematically illustrates the three fundamental types of NIRS and NIRS instrumentation (continuous intensity, intensity-modulated and time-resolved) that will be outlined below with their associated measurement methods.

### 5.1.1 Continuous intensity instruments

Continuous intensity instruments measure changes in attenuation by recording the change in the intensity of light leaving the tissue surface [Jöbsis 1977]. In order to obtain quantitative data, extra information is required which can be provided by the following means.

#### Intensity change at fixed source-detector spacing

One can calculate quantitative *changes* in chromophore concentrations from the measured attenuation changes provided the average optical pathlength the detected light has traversed is known [Giannini 1982, Cope 1988, Cope 1991, Arridge 1992]. Hence it is convenient to define an effective optical pathlength, a quantity called *differential pathlength (DP)*, which relates changes in intensity  $I$  to changes in absorption  $\mu_a$ , such that

$$DP = -\frac{\delta \ln I}{\delta \mu_a} \quad (5.1)$$

The  $DP$  is related to the geometrical pathlength (inter-optode spacing)  $d$  by the *differential pathlength factor (DPF)*.

$$DP = DPF \cdot d \quad (5.2)$$

If the  $DPF$  is known, and can be assumed to be constant over a narrow wavelength range, it is possible to quantify *changes* in chromophore concentrations in non-arbitrary units from attenuation measurements at multiple wavelengths.  $DPF$  values for the newborn infant head have been determined to be approximately 5 [Duncan 1995a]. *Absolute* quantification can be achieved by inducing small known perturbations through controlled physiological changes (e.g. ventilation changes monitored with a pulse oximeter) [Wyatt 1990].

#### Differential spectra at fixed spacing

Broad band transmission spectra in the range 500-1000 nm can be obtained with fibre coupled CCD spectrometers. Because the water concentration of tissue is known accurately it is possible to use spectral measurements and the known optode spacing to determine the optical pathlength. It has been shown that by taking the 2<sup>nd</sup> differential of the spectrum, unknown constant and linearly wavelength dependent features are removed. Knowledge of the pathlength can then be used to quantify changes in concentrations of chromophores that exhibit 2<sup>nd</sup> differential features [Cope 1989, Matcher 1995a, Cooper 1996].

#### Intensity change at multiple spacings

If the intensity of light exiting the tissue surface is measured at *different* inter-optode spacings it is possible to compute  $\mu_a$  and  $\mu_s'$  by fitting data to a light transport model. This method is also referred to as *spatially resolved NIRS* [Groenhuis 1993, Farrell 1992, Matcher 1995b].

### 5.1.2 Intensity-modulated instruments

The first frequency-domain measurements were reported by [Lakowicz 1990]. A source of light (typically a current modulated diode laser) is intensity-modulated at radio frequencies (RF), and the detected intensity ( $I$ ), phase shift ( $\Phi$ ), and modulation depth ( $M$ ) relative to the input signal are measured [Duncan 1993, Chance 1998a]. In practice the RF signal is down-converted to an audio frequency (AF) signal so that standard phase detection

techniques can be applied. The various implementations of this technique for quantifying tissue properties are summarised as follows.

#### Intensity (I), phase ( $\Phi$ ) and modulation (M) at fixed spacing vs. frequency

For tissues probed at low frequencies ( $< 200$  MHz),  $\Phi$  has been shown to be proportional to the average optical pathlength. This allows the calculation of quantified changes in chromophore concentrations from attenuation changes by fitting the data to a diffusion model [Patterson 1989, Arridge 1992]. In order to obtain accurate estimates of  $\mu_a$  and  $\mu_s'$  measurements over a wider frequency range need to be performed, which proves to be more difficult in practice.

#### Intensity, phase and modulation at fixed frequency and fixed spacing

Rather than trying to obtain absolute values of I,  $\Phi$  and M, it is easier to measure (induced) changes and calculate  $\mu_a$  and  $\mu_s'$  from expressions derived from diffusion theory [Kohl 1996]. In this way it is possible to obtain accurate estimates of  $\mu_a$  that are almost independent of scattering.

#### Intensity, phase and modulation change at single frequency and multiple spacing

In analogy to spatially resolved NIRS, changes in I,  $\Phi$  and M vs. optode spacing are measured and  $\mu_a$  and  $\mu_s'$  are obtained by fitting the data to an equation derived from diffusion theory [Fantini 1995].

### **5.1.3 Time-resolved instruments**

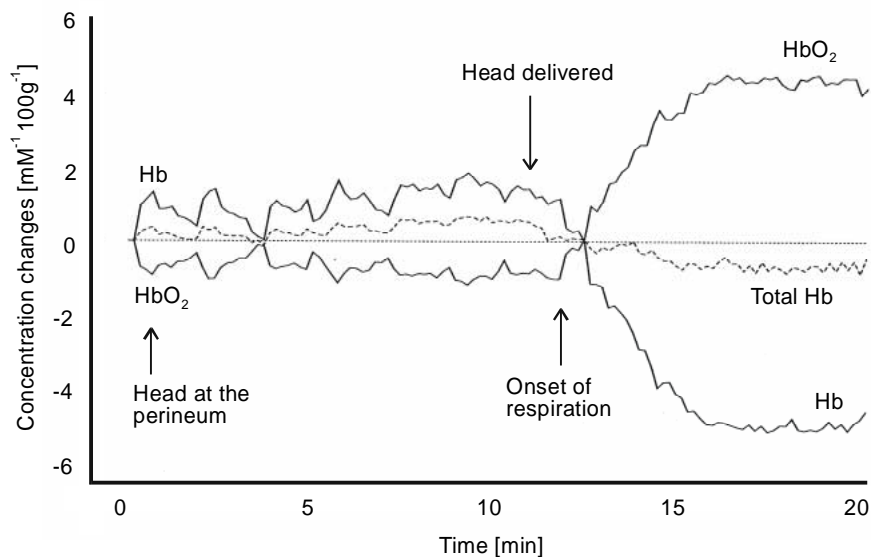
Time-resolved and intensity-modulated data are Fourier transform equivalent. Time-resolved instruments measure the temporal response of tissue to an ultrashort (a few ps) input laser pulse [Chance 1988, Delpy 1988]. The temporal distribution of light emerging from the tissue surface is commonly detected with either a synchroscan streak camera, or a *time-correlated single photon counting* (TCSPC) system. In the latter case a photon counting detector records individual photons and measures their flight times relative to a reference pulse. Thus a histogram of the distribution of arrival times (also called *temporal point spread function*, or TPSF) is built up. TPSFs can be interpreted as the impulse response of the tissue probed for a given source/detector optode arrangement, their shape and temporal offset depending on the optical properties within the medium.

It has been shown that if the complete TPSF is recorded at a fixed optode spacing, values for  $\mu_a$  and  $\mu_s'$  can be obtained from fits to a light transport model [Patterson 1989]. Measurements at multiple wavelengths allow estimates of tissue chromophore concentrations to be made. Methods of recording and extracting information from TPSFs are described in more detail in the context of time-resolved imaging schemes in section 5.4.2 below.

## **5.2 Non-localised NIR spectroscopy**

As described earlier in section 4.1, clinical NIR spectroscopy is possible because human tissues (i) are relatively transparent to light in the NIR region of the spectrum, and (ii) contain compounds whose absorption of light is oxygenation status dependent. It is the aim of non-localised near infrared spectroscopy to perform *global* measurements of the concentrations of tissue chromophores such as oxy- (HbO<sub>2</sub>) and deoxyhaemoglobin (Hb) in order to monitor physiological changes [Jöbsis 1977, Giannini 1982, Cope 1988, Cope 1991, and Delpy 1997]. The first spectroscopic measurements of Hb and HbO<sub>2</sub> were performed early this century on in-vitro blood samples, while the first in-vivo *oximeters*

were developed during the second World War for monitoring the oxygenation of pilots in unpressurised cockpits. The history of oximetry (arterial haemoglobin oxygenation measurement) has been outlined by [Severinghaus 1986]. Oximetry experienced a breakthrough when the more effective *pulse oximeter* was developed in the 1970s. It measures the change in light attenuation, usually across the fingertip or ear, which arises as a result of arterial blood volume changes during each cardiac cycle. Absolute arterial haemoglobin saturation values can be obtained by probing the subject with light at two different wavelengths. Pulse oximeters are now in widespread clinical use, with a wide range of commercial devices available.



**Figure 5–2** NIRS measurements of Hb and HbO<sub>2</sub> concentration *changes* recorded during delivery. These reveal changes in the human foetal brain during the transition from foetal to postnatal life. Also note the periodic changes due to uterine contractions. An optode was positioned against the scalp, and the data were recorded using the continuous intensity Hamamatsu NIRO 500 instrument. (Reproduced from [Peebles 1992]).

NIRS is commonly used today to measure *tissue*, as opposed to *arterial*, haemoglobin saturation (and chromophore concentrations in general) in organs, particularly in the brain and muscles. [Jöbsis 1977] initiated the field of NIRS by first measuring the attenuation spectrum across a cat's head. Since then this area of research has evolved rapidly, with a range of commercial devices available, and a number of instruments in use as clinical research tools. One of its greatest potentials lies perhaps in its application as a general clinical non-invasive bedside monitor of cerebral oxygenation in the newborn infant. However, because the Beer-Lambert law does not apply in its original form, NIRS is not quantitative unless the absorption and scattering of light penetrating the tissue is taken into account. Various approaches to overcome this limitation have been outlined in the previous section on the different instrumentation and measurement types.

As an example, Figure 5–2 shows a NIRS study of the foetal brain during delivery.

### 5.3 Localised NIR spectroscopy

In localised cerebral NIR spectroscopy the objective is usually to correlate changes in chromophore concentrations with the stimulation of particular *regions* of the brain [Maki 1995, Chance 1998b]. It has been possible for some time to obtain non-quantified func-

tional images of brain haemodynamics using the established Positron Emission Tomography (PET) technique and, more recently, functional Magnetic Resonance Imaging (fMRI). Although fMRI combines functional information with high resolution anatomical images (see also Figure 3–8) it has the disadvantage of not being able to provide *absolute* quantitative data. In contrast, NIRS offers the potential of delivering quantified chromophore concentrations – but at a very low spatial resolution.

[Maki 1995] describes NIRS studies in which motor activity (a finger movement stimulus) causes measurable, localised changes in the haemodynamics of the adult human motor cortex. Measurements with a continuous intensity NIRS system were performed at various locations on the head to obtain a topographic map, showing a localised increase in oxy-haemoglobin and total-haemoglobin (CBV), as well as a decrease in deoxy-haemoglobin following motor stimuli. The objective of near infrared imaging is to go one step further and obtain a *tomographic* image of the interior of the brain, rather than a *topographic* map of the brain's surface (the cortex).

## 5.4 Optical imaging

Optical imaging techniques in medicine have recently been reviewed by [Hebden 1997a]. As was pointed out earlier, the potential advantage of optical over established medical imaging techniques is the unique combination of non-ionising radiation, the potential to differentiate between different types of soft tissue, and the possibility to derive functional information from quantitative measurements of chromophore concentrations. Clinical applications on which research in the field is currently focussed include the following.

- Breast cancer: imaging of tumours. Screening requires either high spatial resolution (better than 5 mm) to detect a structural signature, or a characteristic spectroscopic signal. Despite the relatively low spatial resolution achievable with optical imaging (perhaps 5-10 mm for thick sections of tissue), multi-wavelength NIR imaging, or localised NIR spectroscopy, may nevertheless represent a valuable tool for specifying pre-diagnosed abnormalities. These techniques are commonly referred to as *optical mammography* or *optical biopsy*.
- Skin cancer: imaging of the dermis and epidermis for improved differentiation between malignant and benign melanoma.
- Imaging or spectroscopic monitoring of muscle function, which is of particular interest in sports medicine. Functional imaging of the extremities may also be useful to study muscular diseases (e.g. muscular dystrophy), and other conditions such as mitochondrial myopathy or peripheral vascular disease.
- Functional imaging of the adult cortex, which represents an extension of localised NIRS.
- Tomographic neonatal brain imaging of tissue chromophores. Here even a low resolution (approx. 1 cm) would still be clinically very useful.

This section provides a brief historical outline of work done in biomedical optical imaging, discusses various time-resolved imaging schemes, and introduces a range of imaging systems recently developed by other researchers.

### 5.4.1 Historical background

While light is scattered profoundly in tissue, it does penetrate the surface of the skin. This is evident from the observation that the skin appears pinkish, because blood vessels near its surface preferentially transmit longer wavelength (red) light, while strongly absorbing the shorter wavelength (blue, green) components from the visible region of the spectrum (see

also the absorption spectrum of blood in Figure 4–4). In fact, for thousands of years doctors have used the ‘eye-spectrometer’ for visual observations of skin complexion, bruises, etc as an aid to diagnose patients.

An early description of optical transillumination of the human brain has been provided by R. Bright, a lecturer at Guys Hospital, London [Bright 1831]. In 1831, following an examination of a patient suffering from hydrocephalus, he remarked:

“If a candle was held behind his head, or the sun happened to be behind it, the cranium appeared semi-transparent and this was more or less evident till he attained his fourteenth year.”

A few years later T. B. Curling, a surgeon at London Hospital, gave detailed descriptions on how to perform a visual examination of the testes using a simple ‘optical instrument’ [Curling 1843]:

“The mode of making the examination generally adopted is to darken the room, and place a lighted candle so that the tumour may be interposed between the eye and the light. The testis is then readily recognised as an opaque object, and its situation exactly ascertained. In cases in which the parietes of the cysts are unusually thick, or the fluid is very dark coloured, I have sometimes derived considerable assistance from using a wooden tube, about three quarters of an inch in diameter, open at both extremities. One end being placed against the swelling opposite the light, the surgeon on looking through the other, can observe the transparency with great advantage. If a more convenient tube be not at hand, a roll of writing paper will answer the purpose.”

The first clinical results on optical transillumination imaging of the female breast were reported by [Cutler 1929] in the 1920s. By looking at the shadows cast by features beneath the surface he was able to differentiate between normal and pathological tissue. He described the procedure as follows:

“The examination is made in a totally dark room with the patient sitting in a revolving chair opposite the examiner. The 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.”

It was Gros et al (see [Profio 1989]) who in 1972 was first to report the differentiation of benign and malignant tumours using this method, which he termed *diaphanography*. Differences in attenuation of various tissues enable the detection of lesions that look darker (e.g. dense tumours or haematoma) or clearer (e.g. some types of cysts) as compared to surrounding tissues. The contrast can be improved by recording a photographic image of the transilluminated light at NIR wavelengths [Ohlsson 1980]. Since the resolution is very low (about 2 cm), and only very large tumours (or those near the surface) are detectable, conventional transillumination techniques yield a low sensitivity and specificity. Hence diaphanoscopy in its present form is a poor competitor with x-ray mammography and may be useful only as a pre-screening tool.

A related optical imaging technique is *infrared photography* [Jones 1982]. In clinical NIR photography, an image of blood vessels close to the surface (approx. 2.5 mm) is recorded with the use of IR-sensitive film or solid state detectors in the wavelength range of typically 0.7-0.9  $\mu\text{m}$ .

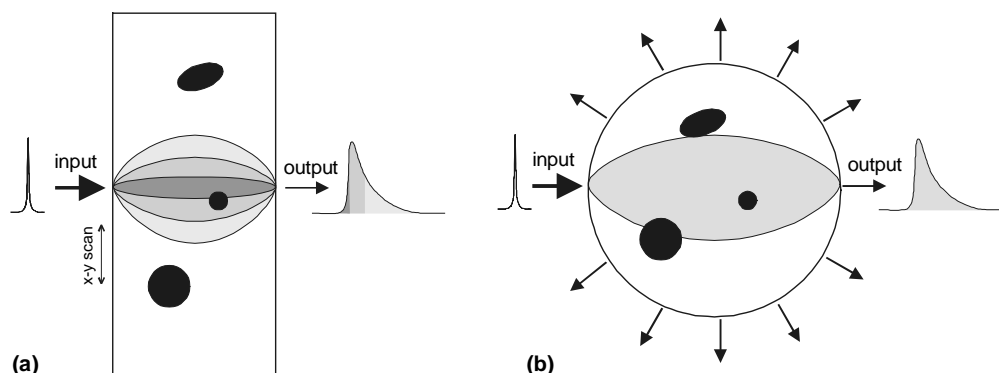
In thermal imaging, or *thermography*, an infrared camera records the radiant emission from the skin surface to obtain an image of the skin surface temperature distribution [Jones

1983]. Infrared cameras usually employ cryogenically cooled semiconductor photon detectors (photoconductive or photovoltaic), arranged in a single or multiple element scanning system. The skin temperature is normally in the range 25–35 °C, whereas temperature changes associated with medical conditions (due to hypervascularisation) are typically of the order 2–3 °C. The spectral distribution of the emitted thermal radiation is represented by Planck's formula, and is in the range 2–50  $\mu\text{m}$ , with a maximum at 10  $\mu\text{m}$ . A range of factors have an effect on surface temperature distribution, in particular blood flow through subcutaneous veins down to about 7 mm. Thermography is useful for arthritis, vascular and metabolic studies, assessment of pain, trauma and malignant disease, especially skin disease, and breast tumours which are located close to the surface.

The evolution of diagnostic imaging with light is outlined by [Hebden 1997b], while the history of medical imaging in general is described by [Webb 1990].

### 5.4.2 Time-resolved imaging schemes

The three basic types of instrumentation used in NIR spectroscopy and imaging (continuous intensity, intensity-modulated and time-resolved) were briefly introduced earlier. In this section, various imaging techniques that utilise photon time-of-flight information are described in more detail.



**Figure 5–3** Diagram illustrating two types of time-resolved imaging schemes: (a) isolating shorter flight time photons (usually in an x-y scanning geometry; early photons are shaded in dark grey), and (b) recording the whole TPSF (using multiple detectors arranged around the surface).

Time-resolved optical imaging schemes can be broadly split into two categories.

- ‘Gating’ methods that aim to isolate shorter flight time photons. Isolating early arriving light provides an improved resolution for transillumination images, as these photons have travelled along a path closer to the optical axis connecting the source and detector positions. Figure 5–3 (a) depicts these short flight time photons and the volume they are confined to by the dark shaded area. A coaxial scanning geometry is commonly chosen for this type of imaging.
- Methods in which the whole TPSF is recorded (see Figure 5–3 (b)), and the image reconstruction performed via an inversion procedure, often using one or several characteristics of the temporal distribution of transmitted light (or Fourier-domain equivalent). The inversion can be performed using backprojection or a more elaborate iterative scheme. Iterative methods are 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. A powerful finite-element diffusion model based iterative

image reconstruction scheme, which has been developed at UCL and is used throughout this project, is briefly described in appendix D.

In the remainder of this section I will list and briefly describe some of the most common techniques used to acquire data suitable for these imaging methods.

### Isolating shorter flight time photons

*Collimated detection* [Jarry 1984, Arridge 1986, Kaneko 1989] is accomplished by spatially filtering the light leaving the tissue surface. This is similar to the method of scatter rejection used in diagnostic x-ray imaging systems. Since this technique relies on filtering out weakly scattered photons, which exit the tissue at relatively shallow angles, it is only effective for imaging a few mm of tissue.

*Polarisation discrimination* [Schmitt 1992] involves eliminating photons whose polarisation is changed as a result of multiple scattering interactions. It is effective up to about 1cm of tissue, as a relatively large number of scattering events are required to completely depolarise a light beam.

*Coherent detection* techniques (also referred to as *coherence gating*) utilise the fact that only unscattered, or weakly scattered, light retains its coherence relative to a reference beam.

- *Holographic gating* [Spears 1989, Hyde 1995, Barry 1997] uses holography as a means of discriminating in favour of relatively weakly scattered light. The emerging light is combined with a reference beam to obtain a hologram that encodes the image information. Depth resolution can be achieved by using a short-coherence-length light source. Ultrashort pulses of laser light are now commonly employed to achieve the gating.
- *Heterodyne detection* [Inaba 1990]. The scattered light is interferometrically combined with a frequency modulated reference beam. By isolating the modulated component of the signal the incoherent component from multiply scattered photons is effectively rejected.
- *Nonlinear techniques*. Coherent interference within a nonlinear-medium produces a signal at a different wavelength which contains information about the coherent, weakly or unscattered component. Anti-Stokes Raman scattering [Reintjes 1993], or degenerate four wave mixing [Sappey 1994] are nonlinear processes that have been used.

Although techniques based on coherence discrimination are limited to tissue thicknesses of up to a few millimetres, the very high spatial resolution (including depth resolution) has led to considerable research into the development of so called Optical Coherence Tomography (OCT) instruments [Fercher 1996]. Apart from being employed for imaging through thin sections of strongly scattering tissue [Yadlowsky 1995], OCT is also used to perform ocular scans [Huang 1991].

*Ultrafast shuttering*, also called *time-gating*, aims to isolate early light by using a nonlinear sub-nanosecond shutter. Images can only be obtained through several mm of tissue because of the limited dynamic range and the inherently small number of early photons.

- A *Kerr gate* [Martin 1980, Liang 1995] consists of a Kerr cell positioned between crossed polarisers. Gating is achieved by optically inducing birefringence with a reference pulse. A limiting factor, however, is the low dynamic range of the cell (transmission varies between about 0.01% to 20%).
- *Raman amplifiers* [Bashkansky 1993, Reintjes 1993] use stimulated Raman scattering (SRS). The long wavelength Stokes beam (the signal) is amplified by a shorter wavelength pump-beam (generated from the reference beam), the dynamic range being as high as  $10^6$ . As is the case for the Kerr cell, the gating mechanism does not depend on the coherence state of the transmitted light.

- *Second harmonic generation* [Yoo 1991]. The signal and reference beams are interferometrically recombined in a nonlinear crystal to produce frequency-doubled light, which can then be easily isolated. Again this method is independent of coherence, but the small phase-matching acceptance angle makes this technique rather inefficient.
- The *parametric amplifier* [Faris 1994] uses an optical parametric amplifier for sum-frequency generation of the combined signal and frequency-doubled reference beams, but also requires too small an acceptance angle to represent an effective means for the detection of diffuse light.

### Recording the whole TPSF

A *streak camera* with picosecond time resolution can be used to record a whole TPSF [Delpy 1988, Ho 1989, Mitic 1994]. It is then possible to apply a time gate for simple transillumination imaging [Hebden 1991], or one can use information obtained from the TPSF and reconstruct an image using a backprojection algorithm [Hebden 1993, Benaron 1993a], or an iterative scheme ([Schweiger 1993], see also appendix D). Streak cameras exhibit an exceptionally high temporal resolution in the picosecond range, but the disadvantages include the high cost, small collection area (about 1 mm<sup>2</sup>), a relatively low dynamic range (approx. 10<sup>4</sup>), as well as significant temporal nonlinearity that is inherent due to the sinusoidal ramp voltage.

*Time correlated single photon counting* (TCSPC) systems [Anders.-Engels 1990, Berg 1993, Benaron 1993b, Oda 1997, Ntziachristos 1999a] also record the whole TPSF, but measure the arrival times of individual photons by comparison with a reference pulse, for instance using a TAC (Time-to-Amplitude Converter) device. TCSPC systems have a very high dynamic range and excellent temporal linearity. They usually employ PMT or MCP-PMT detectors, which have the additional advantage of a large collection area. An alternative type of detector is the avalanche photodiode (APD) [Kirkby 1996], which is very compact and low cost, but unfortunately suffers from an inherently small detection area. The main drawback of TCSPC systems is a comparatively low temporal resolution, which is typically in the range of tens to hundreds of picoseconds. The UCL imaging system, upon whose development this Ph.D. project is based, uses TCSPC and will be described in detail in chapter 6.

In the preceding discussion a distinction was made between techniques that involve recording the full TPSF, and those that aim to isolate short-pathlength photons. However, researchers have also attempted to improve the spatial resolution of images by recording the full TPSF and use this information to obtain an *estimate* of the short-pathlength photon component.

- *Temporal Extrapolation* [Hebden 1995b] is a method which involves fitting a diffusion theory based model to all or part of the TPSF. The fit is then extrapolated to early times to obtain an estimate of the intensity of short-pathlength photons where measured statistics are poor.
- The *Temporally Extrapolated Absorbance Method* (TEAM) [Yamada 1993, Oda 1996, Hebden 1997c] is based on two difference measurements where the level of scattering can be assumed to be identical (for instance TPSFs recorded at two wavelengths that are sufficiently close). An estimate of the absorption ratio in the absence of any scattering is estimated by temporally extrapolating the time-resolved difference in the absorbance to the shortest flight time.

The above discussion has focussed on time-domain techniques only. In frequency-domain methods [Lakowicz 1990, Sevick 1992, Fishkin 1993, Jiang 1995] an object is illuminated with an intensity-modulated light beam and the amplitude, phase and modulation depth of

the emerging *photon density waves* are measured, usually using a heterodyne detection method. One of the main advantages of frequency-domain systems is the relatively low cost of the light source and detectors. A drawback is that in practice the frequency range is limited to  $< 1$  GHz, which corresponds to a rather low temporal resolution of a few nanoseconds. Nevertheless, it is still possible to accurately compute the mean time from the phase shift [Arridge 1992].

### 5.4.3 Current imaging systems

This section introduces some of the most important medical optical imaging systems that are currently being, or have recently been, developed by other research teams active in the field. However, the focus is entirely on systems designed for imaging through *thick* sections of tissue. Therefore OCT and other types of instrumentation that are designed for imaging thin sections of tissue, such as the skin, are not included in this summary.

In the early 1980s Dr. G. Jarry's group pioneered transillumination imaging through organs by performing simulations [Maarek 1982] and experimental studies using a collimated detection scheme [Jarry 1984]. Another early system based on collimated detection is the laser-scanning breast imager engineered by Hamamatsu (Hamamatsu City, Japan), which has been described by [Kaneko 1989].

Also in Japan, researchers at Hitachi (Tokyo, Japan) have built a continuous intensity system for the topographic mapping of cortical activity [Maki 1995]. They describe NIRS studies in which motor activity (a finger movement stimulus) causes measurable, localised changes in the haemodynamics of the adult human motor cortex. The measurements were performed with a continuous intensity measuring NIRS system, which was successively positioned at various locations on the head to obtain a topographic map. The experiments showed a localised increase in oxy-haemoglobin and total-haemoglobin (CBV), as well as a decrease in deoxy-haemoglobin following motor stimuli. A paper by [Yamashita 1999] describes the latest prototype instrument developed by this group. Elsewhere, Prof. M. Tamura's group from Sapporo University has presented similar data on brain activity measurements [Hoshi 1993].

An advanced 64-channel TCSPC system has been constructed as part of a Japanese MITI funded project that ties together a number of universities and companies. It is a TAC based time-resolved instrument that employs specially developed low power picosecond diode lasers (average power 0.25 mW) and fast PMT detectors [Oda 1997]. The overall system response is reported to be about 150 ps. Backprojection and iterative reconstruction schemes (based on TOAST, see appendix D) are being considered for the image reconstruction. Although the system is time-resolved, only continuous intensity phantom studies have been reported to date [Oda 1998].

A few years earlier, Dr. D. Benaron's group at Stanford University has developed and tested a relatively simple time-of-flight optical tomographic imaging system [Benaron 1993b, Van Houten 1996, Benaron 1997, Hintz 1999]. It utilises pulsed laser diode sources and either a commercially available Optical Time Domain Reflectometer (OTDR) or APDs for the detection. Neonatal brain image data have been recorded in 1-4 h acquisition time, and low resolution images reconstructed from photon mean-flight times using a modified backprojection algorithm.

The group of Prof. B. Chance at the University of Philadelphia, apart from being among the pioneers of NIR spectroscopy, also has a longstanding interest in optical imaging. For instance, they have constructed a continuous intensity light imager that consists of four dual-wavelength detectors and nine light sources arranged in an array. The assembly is placed on the subject's head and allows the topographic mapping of OD variations between

source-detector pairs. Maps of OD variations due to brain functional activity in response to various stimuli, as well as the detection of intracranial and epidural haematoma, have been reported [Chance 1997]. The detectors are based on the RUNMAN tissue oximeter, a commercially engineered version of which has also been used for the monitoring of physiological conditions in sports medicine [Shiga 1995]. [Chance 1997] has also reported a frequency-domain imaging system using the same configuration. Another system developed in Prof. Chance's group is an 8-channel time-resolved TCSPC instrument reported by [Ntziachristos 1998 and Ntziachristos 1999a]. The system employs pulsed laser diodes at 780 and 830 nm to perform spatially resolved NIR spectroscopy for monitoring motor cortex activity, as well as performing tomographic breast phantom studies. The overall temporal response of the system is of the order of 400 ps, and separate absorption and scattering images were reconstructed from difference data. Accuracy and performance limits of time-resolved measurements performed with this type of system are discussed by [Ntziachristos 1999b].

Meanwhile, Dr. H. Jiang from Dartmouth College (New Hampshire) reports both continuous intensity and frequency-domain phantom studies using laboratory-based imaging systems [Jiang 1995, Jiang 1998]. Absorption and scattering images were reconstructed using a finite-element based diffusion model. Another American group, led by Prof. R. Barbour at the State University of New York, has recently developed an 18-channel continuous intensity system called the IRIS-OPTiscanner. It uses a fibre-coupled CCD camera as the detector, and incorporates a mechanically adjustable iris for bringing optodes into contact with the tissue surface [Barbour 1998]. Phantom and preliminary arm imaging studies were reported.

A time-domain single-channel scanning optical mammography instrument has been reported by Prof. H. Rinneberg's group at the Physikalisch-Technische Bundesanstalt in Berlin [Rinneberg 1998, Grosenick 1999]. The compressed breast is scanned with a 5 mW diode laser producing pulses of 400 ps duration at 785 nm. The reconstruction algorithm uses the total integrated intensity, intensity in different temporal windows and other quantities to generate images. Large diameter (> 1 cm) tumours were detected with this system in clinical trials.

The company Siemens (Munich, Germany) has developed a frequency-domain optical mammography system, which has undergone clinical trials. The system consists of four laser diodes at different wavelengths, and records amplitude and phase data over several minutes of integration time. A rather unsatisfactory specificity in the detection of breast tumours has apparently led to a halt in the project. At about the same time, another frequency-domain mammography system was built by Carl Zeiss (Oberkochen, Germany). It records amplitude and phase data for obtaining the spatial distribution of normalised, edge-effect corrected, attenuation values based on a diffusion model [Kaschke 1994]. Two wavelengths (690 and 810 nm) are used at 110 MHz modulation frequency. The company reports a significant improvement as compared to conventional continuous intensity laser transillumination mammography systems, and evaluation of the system is continued by Dr. E. Gratton's research group at the University of Illinois (Urbana-Champaign) [Fantini 1996]. In the meantime in Holland, Philips (Eindhoven) have developed and evaluated frequency-domain [Papaioannou 1995] and continuous intensity [Colak 1997] mammography systems. The latter consists of a large number of sources and detectors arranged in a cone shape. The image reconstruction scheme is based on a modified backprojection algorithm that deconvolves the broadened image with a spatially variant point-spread function, and performs nonlinearity corrections for the curved photon paths. They claim an improvement in resolution as a result of these image processing techniques by nearly an order of magnitude. In America, the relatively small venture capital firm Imaging Diagnos-

tic Systems (Plantation, FL) has developed an optical mammography system that employs a solid state picosecond pulsed laser and an array of APD detectors arranged in a scanning configuration [Grable 1997]. Data from continuous intensity and time-resolved measurements are used in a filtered backprojection scheme for the reconstruction of phantom and clinical images. The device is currently undergoing clinical trials.

Meanwhile here at University College London Dr. J. Hebden, before initiating the project on which this thesis is based, has imaged solid breast phantoms with embedded scattering and absorption inhomogeneities using a streak camera based time-resolved system [Hebden 1995c, Hall 1995]. The image resolution could be substantially improved using the temporal extrapolation method that was briefly described in the preceding section. He concludes that sub-centimetre resolution imaging of low-contrast tumours in the breast is feasible. The new UCL time-resolved TCSPC system is described in chapter 6.



