Imaging the Body with Diffuse Optical Tomography

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Diffuse optical tomography (DOT) is an emerging medical imaging modality in which tissue is illuminated by near-infrared light from an array of sources, the multiply-scattered light which emerges is observed with an array of detectors, and then a model of the progation physics is used to infer the localized optical properties of the illuminated tissue. The three primary absorbers at these wavelengths, water and both oxygenated and deoxygenated hemoglobin, all have relatively weak absorption. This fortuitous fact provides a spectral window through which we can attempt to localize absorption (primarily by the two forms of hemoglobin) and scattering in the tissue. The most important current applications of DOT are detecting tumors in the breast and imaging the brain. The greater blood supply of tumors compared to surrounding tissue provides a target absorption inhomogeneity to image. A similar idea allows us to image bleeding in the brain, while the same association between cerebral activity and increased oxygen supply which underlies functional magnetic resonance imaging (fMRI) also allows functional imaging with DOT. The modality has seen a tremendous upsurge in interest over the last ten years but still presents a number of significant technological and signal processing challenges.

In this article we introduce the basic idea of DOT and briefly review the history of optical methods in medicine as relevant to the development of DOT. We then detail the concept of DOT, including a brief review of tissue optical properties, modes of operation for DOT, and the challenges which the development of DOT must overcome. The next sections review the basics of modeling the DOT forward problem and some current issues

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among the numerous implementations that have been investigated for the DOT inverse problem, with an emphasis on signal processing. We summarize with some specific recent results as examples of the current state of DOT research. Given the widespread interdisciplinary activity in DOT, we recognize that any relatively short article such as this cannot do justice to many valuable contributors, and we apologize in advance to those whose work we may have inadvertently neglected. We also refer the reader to a longer tutorial article by Arridge [12], which has an emphasis on the mathematical physics of DOT.

Introduction

If you shine a flashlight onto your hand you can clearly see that light can travel through centimeters of tissue and still be detected. So why not use light to "see," or image, inside the body? The same simple experiment with a flashlight illustrates the major difficulty with this idea—the significant scattering that light experiences while traversing centimeters of tissue. This scattering generally complicates imaging of tissue structure and function; since transmitted or reflected light re-emerging from the tissue has followed a very complicated path, any localization of absorption or scattering or other optical parameters is lost when we simply observe the light as it exits the tissue. If we conceptualize the distance that a photon travels between two scattering events as a random variable l, and if the distance between a light source and a detector is significantly greater than the mean free path, i.e., than the expected value of l, the vast majority of photons reaching that detector will have followed a *meandering* trajectory through the tissue. In Fig. 1 we visualize the situation; (a) illustrates how photons may travel in tissue. The bottom panel shows a simulation of relative probability of photon paths in a rectangular block of tissue. The source and detector are on the top surface of the block, and the various images show vertical slices at a sequence of horizontal displacements from the line connecting the source-detector pair. We note that there is a rather broad spatial sensitivity profile from the source to the detector.

The result of this highly scattered light propagation is that we only detect a blurry image of the underlying structures. For this reason, acquiring quantitative structural and functional information is difficult. Using light to image an aggregate quantity has long been the basis of a common clinical tool, the pulse oximeter [1]-[4], which mea-
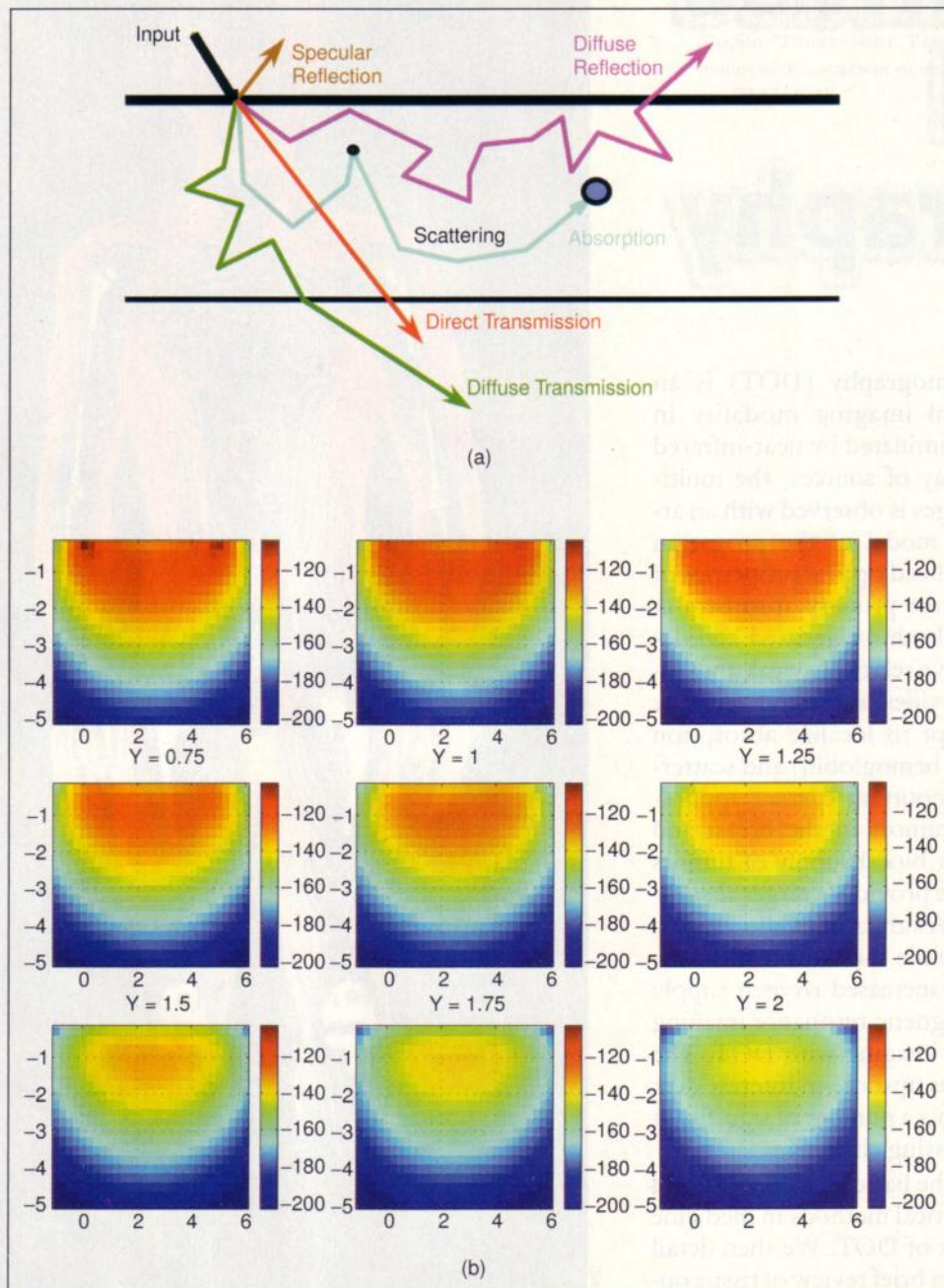
▲ 1. (a) visualizes paths of photons through tissue, and (b) shows how probability of photon travel is distributed in a 3-D volume computational model with source and detector on the top. Source and detector are separated by 5 cm, each image shows a vertical slice, and distances shown are displacement of vertical slice from the line connecting the source/detector pair.

sures the average oxygen saturation of arterial blood, for instance in a finger or toe (see "Historical Overview" for a brief description). But differentiation of the optical properties of *localized* regions within the illuminated tissue was long thought to be impractical. Recent advances in our understanding of light migration through tissue, however, the resulting development of tomography algorithms, and subsequent experimental verification in phantom systems have shown that imaging with diffuse light, known as DOT, is possible. (As this technology has developed, it has been known as photon migration imaging (PMI), diffuse photon density wave (DPDW) imaging, and DOT; the phenomenology behind these names should become clear to the reader through the course of the article.) Furthermore, current results strongly motivate the further development of both basic research and specific clinical applications. The most significant applications for DOT are the screening, diagnosis, and basic research of breast cancer, and the study of the brain, including stroke, hemorrhage, and brain function. The upsurge in interest in DOT has produced a tremendous growth in research activity, resulting in a special issue of the *Journal of the Optical Society of America* in 1997, a special issue of Optics Express in December 2000, and many sessions at relevant conferences run by the Optical Society of America (OSA) and SPIE.

The simultaneous region of relatively weak absorption at near-infrared wavelengths of water, oxygenated hemoglobin (HbO), and deoxygenated hemoglobin (Hb), the three primary absorbers in tissue, as shown in Fig. 2, is what creates an opportunity for optical imaging at centimeter depths. (Note that the actual absorption coefficient is mediated by the molar fractions of the three absorbers in a given region of tissue, but the figure gives an accurate illustration of the effect described.) At frequencies higher than those shown in the figure, the absorption by water increases rapidly, so that what this graph illustrates is a spectral "window" allowing us to "see" the hemoglobin. Moreover, within this window the spectra of oxy- and deoxy-hemoglobin are distinct enough to offer the possibility of performing spectroscopy: illuminating with several wavelengths and recovering separate concentrations of both types of molecules. Different tissue types often have distinct scattering properties, and thereby we can hope to image this distinction as well. Thus DOT offers the opportunity to image three-dimensional (3-D) spatial variations in blood parameters, particularly hemoglobin concentration and oxygen saturation, and thus metabolic factors which these concentrations reflect, along with tissue scattering characteristics. The instrumentation is noninvasive, nonionizing, inexpensive, and portable (at least with one of the two main classes of sources and detectors), making possible widespread use for ambulatory and emergency room diagnoses as well as continuous bedside monitoring. These combined features will likely have a significant impact on a number of scenarios in

Advances in our understanding of light migration through tissue, the development of tomography algorithms, and experimental verification in phantom systems have shown that DOT is possible.

breast and brain care, particularly stroke, as well as during and following brain surgery.

Some Potential Applications of DOT
Breast Imaging
X-ray mammography has greatly increased the detection of breast tumors at early, treatable stages. Advances are being made with X-ray, ultrasound, electrical impedance tomography (EIT), and magnetic resonance imaging (MRI) techniques to further improve the characterization of breast tumors. Of particular interest is the recent interest in functional characterization of tumors through MRI [5] and positron emission tomography (PET), which provides fundamentally new and different information than traditional structural images. In particular, one gains access to direct physiologically relevant information such as metabolism, blood flow, blood volume, and oxygen saturation. These parameters are modified by tumor angiogenesis and are also important for following tumor response to therapeutic intervention. Recent advances in molecular contrast agents will eventually enable molecular imaging [6], [7]. DOT has unique capabilities for imaging these functional parameters. Tumors generally are more highly vascularized than surrounding tissue,
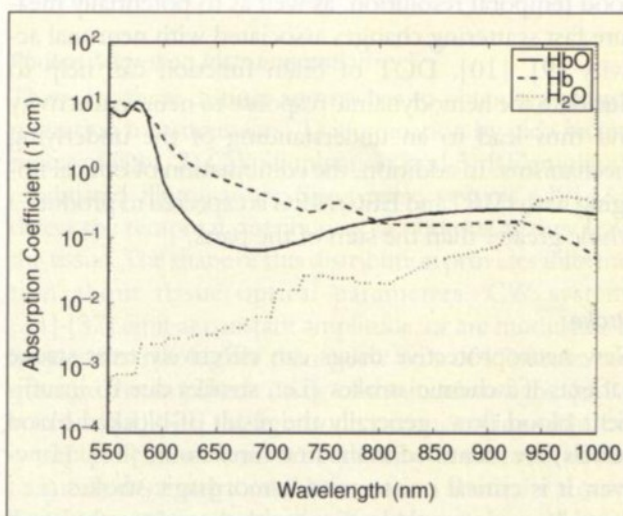
▲ 2. Hemoglobin and water absorption coefficients per mole as a function of wavelength. Note the relatively low absorption between 700 and 1000 nm and the crossover point around 800 nm. Data taken from Prahl [41]. The apparent discontinuities in the water spectrum reflect the resolution of the data when plotted at this scale and not true spectroscopic features.

> **The usual goal of DOT imaging is to reconstruct a spatial map of the optical scattering coefficient, absorption coefficient, or both, from fluence measurements, using a forward model of the photon propagation.**

thus leading to differential light absorption properties, and in addition relative Hb/HbO concentration may not only differentiate tumors from background tissue but also may discriminate among tumors with different activity rates (i.e., degree of malignancy).

Brain Function

DOT of brain function complements PET, fMRI, EIT, electroencephalography (EEG), and magnetoencephalography (MEG) [8]. PET directly images changes in metabolic activity, but has poor temporal and spatial resolution. fMRI images blood flow and the concentration of deoxy-hemoglobin with high spatial resolution and good temporal resolution, but cannot also simultaneously measure oxy-hemoglobin concentration. EEG and MEG monitor neural activity with much better temporal resolution (100 to 1 kHz), but localization of the origin of electrical and magnetic sources is difficult and spatial resolution is poor compared to fMRI. With DOT, although its spatial resolution is also inferior to fMRI, it is possible to simultaneously measure concentrations of oxy- and deoxy-hemoglobin as well as blood volume with good temporal resolution, as well as to potentially measure fast scattering changes associated with neuronal activity [9], [10]. DOT of brain function can help to elucidate the hemodynamic response to neuronal activity and thus lead to an understanding of the underlying mechanisms. In addition, the combination of optical imaging with fMRI and EEG/MEG is expected to produce a whole greater than the sum of the parts.

Stroke

New neuroprotective drugs can effectively treat stroke patients if ischemic strokes (i.e., strokes due to insufficient blood flow, generally the result of blocked blood vessels) are identified in the first three hours [11]. However, it is critical not to treat hemorrhagic strokes (i.e., those due to internal bleeding) with these drugs, as it will lead to rapid death. DOT can potentially enable the necessary early diagnosis/discrimination between ischemic and hemorrhagic stroke. Furthermore, DOT may allow continuous bedside monitoring of the evolution of a stroke as well as its response to treatment.

Monitoring Brain Trauma and Surgical Interventions

Patient outcome during a brain hemorrhage due to trauma or subsequent to surgery can be greatly improved if the hemorrhage is detected early. Presently cognitive tests and invasive monitors (e.g., intracranial pressure gauges) are used in addition to periodic CT scans. DOT could have advantages over these techniques if used bedside as a continuous monitor, providing real-time information on the location and size of bleeds. Monitoring is also important during brain surgery to minimize collateral damage. EEG during surgery can successfully monitor interference with critical functions but requires painstaking and time-consuming electrode placement; fMRI is also being used for planning *prior* to surgery, but since the brain can move within the cranium, accurate path registration is critical and complicated. Intra-operative magnets are in the developmental stage but require a special operating room with an expensive magnet. DOT combined with an optical surface imaging technique could offer an inexpensive alternative.

The Development of DOT Technology

In this section we first give a brief history of some applications of optics in medicine that has led to the development of diffuse optical imaging. We then summarize the basic experimental apparatus and conceptual framework of DOT imaging along with presenting a variety of important imaging parameters, followed by a discussion of some of the important challenges that DOT imaging faces.

Historical Overview
Early Optical Breast Imaging (Diaphanography)—1929 to 1990

The use of continuous wave (CW) light to detect breast lesions was first proposed by Cutler in 1929 [13], but the light intensity required caused overheating of the patient's skin. Repeated attempts to improve the technique were unsuccessful, and it was temporarily abandoned in the 1940s. In 1973, Gros et al. [14] introduced "diaphanography," in which the breast was positioned between a visible or near-infrared light source and the physician. "Images" were perceived by the physician's eye alone. Substantial improvements were made in the following decade, including the use of video cameras as detectors, and in 1982 Carlsen [15] published a seminal paper that included spectral analysis and real-time live viewing. A 1990 Swedish study [16] found that light scanning was inferior to traditional methods of breast imaging; the probability of detection was low for small cancers and the probability of false alarm was almost three times as high as that of other breast imaging methods. Optical breast imaging was consequently abandoned again in the early nineties. Developments in the understanding of light propagation in breast tissue and in time-resolved techniques in tissue spectroscopy led to renewed interest in optical breast imaging later in the nineties. These recent developments were preceded by and evolved from the de-

velopment of pulse oximetry, laser Doppler blood-flow-metry, and near infrared spectroscopy.

Pulse Oximetry—From the 1930s

Pulse oximeters are widely used to monitor patient well being [1]-[4], as they provide accurate information on arterial blood oxygen saturation. The advantage of optical oximeters over oxygen tension monitors (which measure the partial pressure of oxygen in-line in the blood stream or from extracted blood samples) is that they provide a rapid response to changes in blood oxygenation and yet are noninvasive. The first oximeter used in a clinical environment was an ear oximeter, in which the transmission through the ear lobe was measured by a lamp and photocell attached to the ear [1]. It measured average hemoglobin oxygen saturation across vascular compartments. It eventually evolved into the more robust pulse oximeter, whose mathematical model is based on an arterial pulse-triggered measurement of the intensity of the light passing through the tissue. After each heartbeat the arteries expand, increasing the volume fraction of blood and therefore increasing the absorption of light in the tissue, and thus the fraction of light attenuated by the blood varies as a function of this pumping action of the heart. By measuring the maximum and minimum of the absorption, the differential can be related mathematically to arterial oxygen saturation.

Laser Doppler Blood Flowmetry—1960s

The advent of the laser quickly led to its use in medical applications. In the 1970s, the laser was already being used for laser Doppler studies of blood flow [17]-[19]. When a beam of laser light with uniform intensity is incident on a rough surface, the reflection of the beam will not have a uniform intensity but will instead be composed of many bright and dark spots, called speckles, because light reflected in many different directions interferes constructively and destructively at the detector. The same happens for light that has migrated through a highly scattering sample. If the rough surface or scattering particles (e.g., red blood cells) in the turbid medium are moving, the speckle pattern will fluctuate with a time scale which depends on the motion.

Near Infrared Spectroscopy—From the 1970s

Pulse oximetry and laser Doppler blood-flowmetry generally were unable to measure hemodynamics within the brain through the intact skull because of photodetector bandwidth limits and photon limits respectively. Near infrared spectroscopy (NIRS) evolved in the 1970s [20] to monitor baseline changes in total cerebral oxygenation (i.e., an average of arterial, capillary, and venous blood) as revealed by the average intensity of diffusely reflected light. (For a detailed description of NIRS, see [21] and [22].) Briefly, NIRS quantifies changes in chromophore concentration within highly scattering tissue by measur-

ing the change in the photon density of light diffusely transported through it. The measured change in photon density is proportionally related to the concentration change by the extinction coefficient of the chromophore(s) and the effective pathlength through the tissue. The extinction coefficient is an intrinsic property of each chromophore, but the effective pathlength, technically, must be estimated for each measurement as it depends on the measurement geometry and optical properties of the tissue. Research in the use of NIRS for monitoring cerebral oximetry continued through the 1980s [23], [24]. The major limitation of NIRS is its inability to provide an absolute measure of oxygenated and deoxygenated hemoglobin concentration without calibration of the optical pathlength through the tissue. In the late 1980s, pico-second pulsed lasers and time-resolved measurements were used to measure directly the optical pathlength and thus the absorption coefficient and related hemoglobin parameters [25]. Instrumentation expense and complexity were burdensome, and thus investigators quickly introduced the use of inexpensive and relatively simple radio-frequency (RF) modulated lasers and measurements of the phase delay of the amplitude modulated light [26], which provided a measure of the mean tissue optical pathlength and subsequently of the hemoglobin parameters.

Photon Migration Imaging—Late 1980s

It was soon realized that photon migration spectroscopy measurements could be extended to imaging by solving the inverse problem as is done with X-ray computed tomography. Research investigating this possibility began in the late 1980s and was reviewed in 1993 by Arridge [27] and Barbour et al. [28]. We provide more details of these developments later.

Photon Migration Instrumentation

There are three distinct approaches to obtaining photon migration measurements: 1) illumination by pico-second pulses of light, 2) CW illumination, and 3) RF amplitude modulated illumination. Short-pulse systems [29]-[33] detect the temporal distribution of photons as they leave the tissue. The shape of this distribution provides information about tissue optical parameters. CW systems [34]-[37] emit at constant amplitude, or are modulated at frequencies not higher than a few tens of kilohertz, and measure the amplitude decay of the incident light. In RF systems [38]-[40] the light source is on continuously, but is amplitude-modulated at frequencies on the order of tens to hundreds of megahertz. Information about the absorption and scattering properties of tissue are obtained by recording amplitude decay and phase shift (delay) of the detected signal with respect to the incident one [26].

In principle, an imaging instrument will be a simple extension of an NIRS system to include more sources and detectors. Adding more detectors is straightforward as