

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 propagation 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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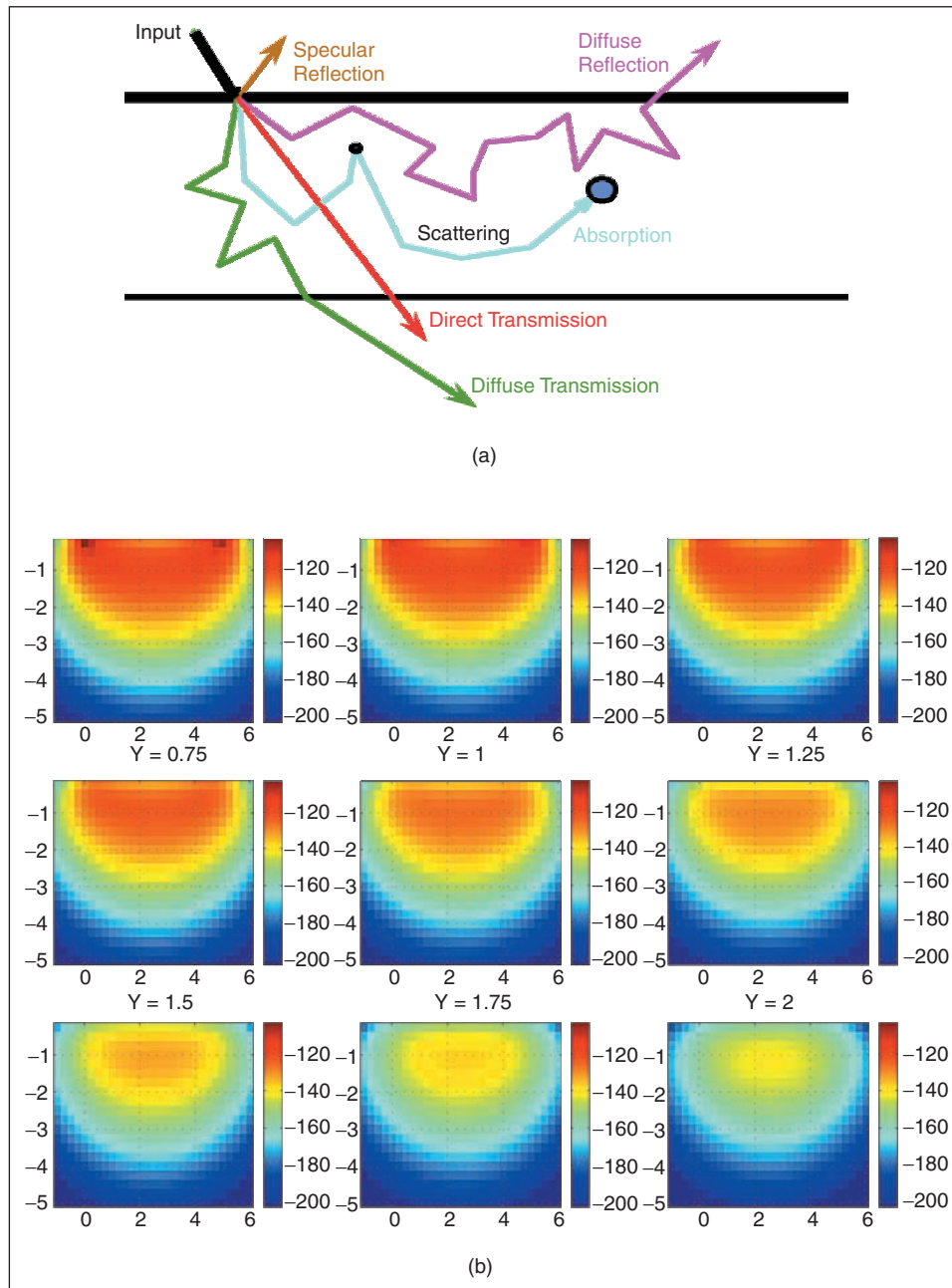
among the numerous implementations that have been investigated for the DOT inverse problem, with an emphasis on signal processing. We summarize with some specific recent results as examples of the current state of DOT research. Given the widespread interdisciplinary activity in DOT, we recognize that 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

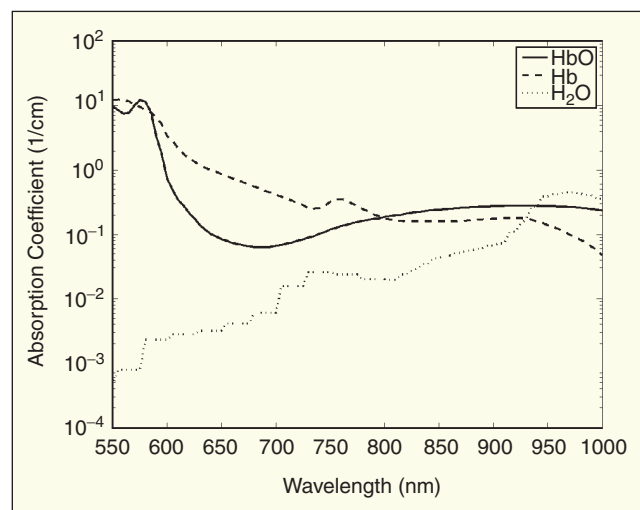
Advances in our understanding of light migration through tissue, the development of tomography algorithms, and experimental verification in phantom systems have shown that DOT is possible.

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-flowmetry, 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

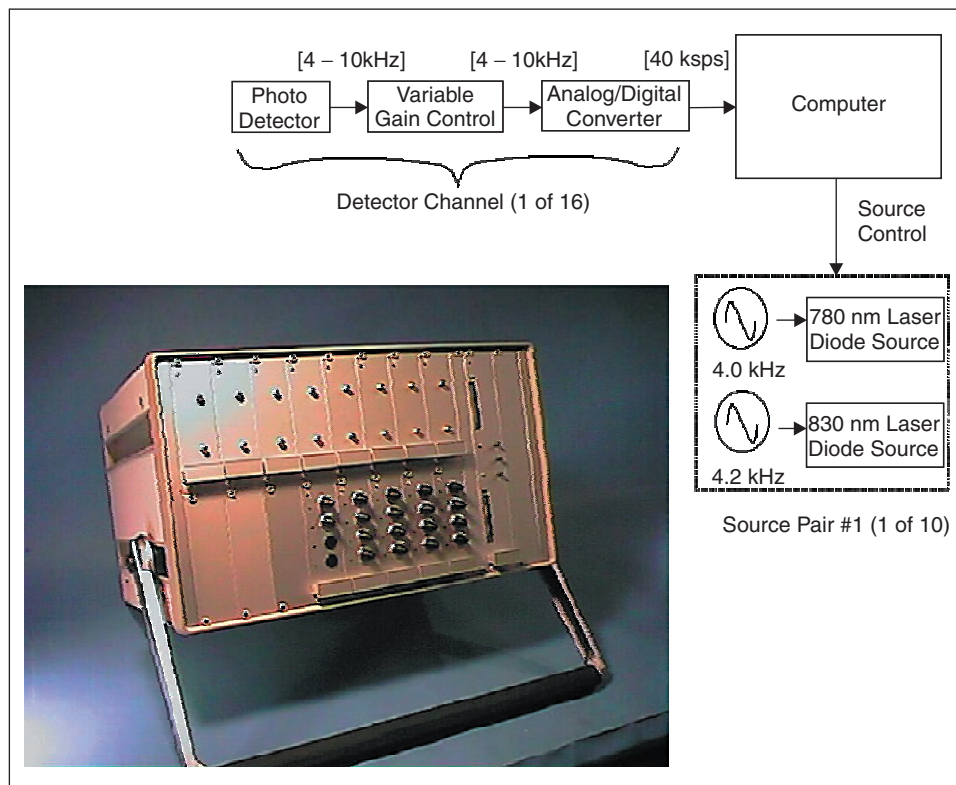
each detector operates independently of the others. The sources, on the other hand, all introduce light into the tissue, which thus must be done using an encoding or multiplexing strategy to allow the individual source signals to be distinguished at each detector. The most common method is time-division, i.e., turning one source on at a time. Fig. 3 shows a block diagram and photograph of a frequency encoded CW imaging system with 18 lasers and 16 detectors developed at Massachusetts General Hospital (MGH). This system is being extended to 32 lasers (intensities modulated at 32 different frequencies) and 32 detectors. The lasers are currently divided into nine at 785 nm (Sanyo, DL7140-201) and nine at 830 nm (Hitachi, HL8325G), although they can be divided among as many different wavelengths as desired. The detectors are avalanche photo-diodes (APDs, Hamamatsu C5460-01). A master clock generates the 18 distinct frequencies between 4.0 kHz and 7.4 kHz in approximately 200 Hz steps. These frequencies are then used to drive the individual lasers with current stabilized square-wave modulation. Following each APD module is a bandpass filter, with a cut-on frequency of 500 Hz to reduce $1/f$ noise and the 60 Hz room light signal, and a cut-off frequency of 10 kHz to reduce the third harmonics of the square-wave signals. After the bandpass filter is a programmable gain stage to match the signal levels with the acquisition level on the analog-to-digital converter within the computer. Each detector is digitized at 40 kHz and individual signals due to each source are then separated by use of a digital bandpass filter, for example a discrete Fourier transform or an infinite impulse response filter.

DOT Imaging

The basic idea of DOT imaging is to illuminate the tissue with an array of light sources and to measure the light leaving the tissue with an array of detectors. For each source location, one records an image of the light reaching each detector from that particular source. A model of the propagation of light in tissue is developed and parameterized in terms of the unknown scattering and/or absorption as a function of position in the tissue. Then, using the model together with the ensemble of images over all the sources, one attempts to “invert” the propagation model to recover the parameters of interest, or, in other words, to estimate the scattering and/or absorption parameters out of the data, using the model.

Optical Characteristics of Biological Tissue

All DOT models depend on an understanding of the optical characteristics of biological tissues. Particularly important is the fact that optical absorption coefficient, at wavelengths of interest, is primarily affected by the concentration and type of hemoglobin present in the tissue being examined. Prahl [41] compiled data from a variety of sources to present the absorption coefficient of whole oxy-hemoglobin and deoxy-hemoglobin versus wavelength, as shown in Fig. 2. Also important are the optical absorption coefficient, the optical scattering coefficient, and the mean cosine of the scattering phase function. The latter two together lead to what is known as the reduced scattering coefficient. Among other studies reported, Mitic et al. [42] found bulk optical absorption coefficients of slightly compressed breast tissue in the range of $0.017\text{--}0.032\text{ cm}^{-1}$. If we assume that the absorption coefficient is entirely due to hemoglobin, then the absorption coefficient of tissue for a given blood volume and oxygenation can be computed using the optical coefficients for pure blood. Mitic et al. [42] also reported a reduced scattering coefficient of $7.2\text{--}10.0\text{ cm}^{-1}$ at 800 nm in breast tissue, while Bevilacqua et al. [43] reported similar results for human brain. Cheong et al. [44] compiled a comprehensive set of optical parameter coefficients from a large number of earlier publications. Cerussi et al. recently published a more comprehensive analysis of the optical properties of human breast tissue measured in vivo [45]. We note for fu-



▲ 3. Photograph of MGH CW4 imaging device with illustration of operation.

ture reference that these results show that the reduced scattering coefficient is more than two orders of magnitude greater than the absorption coefficient.

Some Options in DOT Imaging

Within this modeling framework there are a number of variations and modifications of the imaging problem that are of interest:

▲ *The source and detector geometry:* The three most common geometries are transmissive, in which the sources are on one surface of a region of tissue and the detectors on the other side; reflective, in which both are interspersed on the same tissue boundary; and annular, in which the (generally interspersed) sources and detectors form one or more rings around the region of tissue.

▲ *Frequency or time domain:* In frequency-domain imaging, the light sources are either CW or amplitude modulated at an RF frequency. The resulting light can be conceived of as a DPDW, since the photon density in the tissue will follow the amplitude variation of the source [46]-[50]. DPDWs are a type of scalar, damped, traveling wave which arises formally in any diffusive system that is driven by an oscillating source [51], such as heat conduction [52] and chemical waves [53]. In time-domain imaging, the early-arriving light from a short pulse is measured with one of several mechanisms for time-gating. Due to the high degree of scattering, few if any ballistic (direct-path) photons are measured, but the first arriving photons can be assumed to have followed close to a direct path (few scattering events) through the tissue. If the mean and standard deviation of the random scattering length l are both much smaller than the source-detector separation, even near-ballistic photon arrivals will be rare events, well into the tail of the distribution. Since the SNR of the measurements is related to the number of photons arriving in an (integrated) measurement interval, short integration intervals and high SNRs are difficult to combine and time-domain systems must deal with inherently low SNR. The advantage of time-domain imaging is additional information about path length; its disadvantage is greatly increased expense of the opto-electronics required on both the source and detector side, although the cost of pulsed systems has recently decreased significantly.

▲ *Placement of virtual sources:* One way to improve imaging would be to place optical sources inside the tissue to be probed. Clearly this is not practical in many situations, but one new technology tries to place “virtual sources” at desired locations through acoustic modulation of the DPDW frequency [54]-[57]. In particular, a focused ultrasound beam has been found to modulate the DPDW frequency, and the resultant scattered light can in turn be discriminated at the detectors from light whose origin is not at the focus location by its acoustically-altered modulation frequency. This opens up the possibility of using ultrasound to place distinguishable DPDW “sources” at depth inside the tissue.

▲ *Additional imaging parameters:* In addition to framing the parameterization of the tissue’s optical properties in terms of absorption and scattering coefficients, in some applications the true goal is to recover concentration of oxygenated and de-oxygenated hemoglobin (HbO from Hb) or other functional or metabolic properties of the tissue. This may impose additional imaging requirements, such as the use of more than one wavelength of illuminating light or the use of fluorescent dyes. For instance, to distinguish HbO from Hb one needs a minimum of two wavelengths; knowing the absorption spectra of these two molecules (as a function of wavelength) and with an estimate of the background scattering and absorption, then from an estimate of the space-varying absorption coefficients of the tissue at two wavelengths one can reconstruct the concentration profiles of both molecules. More than two wavelengths may be required to obtain reliable estimates, to estimate the background absorption more accurately, to also estimate scattering coefficients, etc. One advantage of using fluorescent dyes, beyond the ability to tag specified types of molecules, is that they can be selectively imaged by filtering at the detector, since the fluorescent wavelength is generally different from the illumination wavelength. Thus the effect of the scattering from illumination source to fluorescent source on the fluorescent image is ameliorated. Much of the basics of DOT imaging with fluorescent dyes is similar to imaging without these dyes; in this article we do not treat fluorescence imaging in detail, for further information consult [58]-[63].

▲ *Propagation modeling:* As we describe below, a wide variety of linear and nonlinear propagation models can be used in inverse solutions.

Difficulties in DOT Imaging

Given a description of the geometry, a forward propagation model, a model of measurement noise, and a model of the measurements themselves, one then attempts to solve mathematically for the parameters of interest. We explain below why DOT is a nonlinear ill-posed inverse scattering problem, and we list some difficulties which are typical of these problems, as well as others which stem from the particular nature of DOT.

▲ Tissue is a *turbid* medium with strong scattering; thus light follows an extremely complicated path, the signal strength attenuates rapidly, and propagation is inherently 3-D.

▲ In frequency-domain imaging, even with amplitude modulation at hundreds of megahertz, the wavelength of the DPDW is tens of centimeters, much longer than the size of objects of interest, so DOT requires near-field imaging.

▲ In time-domain imaging, ballistic photons have vanishingly small probability, and photons which experience relatively few scattering events are rare, so that expensive electro-optics and small signal strength present difficulties.

▲ The background properties are generally unknown and may be difficult to measure. In addition there are “coupling coefficients,” themselves unknown in practice, which describe the efficiency of the sources at penetrating into the tissue and of the detectors at recording the transmitted light, and which affect interpretation of measurements as well as their use in inverse reconstructions [64].

▲ Noise models may be complicated because sources of noise include both thermal noise in the amplifiers and shot noise due to the quantum nature of the sources.

▲ The information of interest in the measured signal (for instance, in perturbative models, the “scattered wave”) may be several orders of magnitude smaller than the background response (the “incident wave” in perturbative models).

▲ The relationship between the observed field amplitude, phase, or timing, and the absorption and/or scattering coefficients of interest is nonlinear. Thus inverse solutions, as is typical of this class of inverse problems, must either use linearized approximations such as the Born or Rytov or deal with the increased numerical burden of nonlinear forward models. Moreover, the geometry may be complex and may include dramatically different conditions of light propagation, for instance highly scattering brain tissue which is surrounded by lightly scattering cerebro-spinal fluid (CSF).

▲ Due to the physics of the propagation, the inverse problem is ill-posed [65], [66]; this means that relatively large changes in the parameters of interest tend to result in relatively small changes in the measurements. Thus inverse solutions must amplify these small differences; as a consequence measurement noise and model error will be amplified as well, causing inverse solutions to be wildly erratic and nonphysical unless constrained by additional a priori knowledge or assumptions, and solutions, even if theoretically unique, are typically numerically nonunique.

▲ In addition, if one wishes to image a full 3-D volume with a realistic geometry and useful spatial resolution, the resulting ill-posed inverse problem will also generally be under-determined; the number of locations in space (“voxels”) at which one wishes to estimate the absorption or scattering coefficients may well be one or two orders of magnitude greater than the number of measurements. This becomes another source of nonuniqueness of solutions.

In the rest of this article we focus on a subset of the DOT imaging problem; in particular we concentrate on frequency-domain imaging without fluorescence where the absorption coefficient is the particular parameter of interest. The reader interested in more detail about other variants is encouraged to consult the cited papers.

Modeling of Photon Propagation in Highly Scattering Media

In this section we describe some common computational models for the propagation of light in diffusive tissue which are useful for DOT imaging, as well as briefly discuss noise modeling. Computational propagation and

noise models not only are important to understand the physics behind DOT, and to simulate DOT measurements, but also are an essential ingredient of imaging itself—one obvious requirement for DOT reconstructions is that they correspond to the detected fluence, and to check this requirement one needs a practical method to estimate the detected fluence corresponding to a particular reconstruction.

The Radiative Transport Equation

Propagation of light is usually modeled either directly on Maxwell’s equations or using geometric optics. Neither of these models is feasible, however, when the number of distinct interactions is very large, as in turbid media such as a cloud, milk, or tissue; light propagation in this regime behaves more like erratically moving photons migrating on average through the medium than like a propagating wave or a ray. Thus we require a technique that models the large number of interactions by some aggregate approach. One such technique is linear transport theory [67], [68]. In this approach light is treated as composed of distinct particles, photons, propagating through a medium modeled as a background which has constant or variable scattering and absorption characteristics, possibly containing discrete, bounded regions of absorption and/or scattering inhomogeneity. We model interactions only between light particles and the medium and not among light particles themselves. Thus there is no correlation between the fields the particles represent; consequently powers, instead of fields, are additive. This model also does not take into account polarization effects. (A model that does take into account polarization is available [68] but it is not typically employed in the derivation of the diffusion equation for light propagation in a diffusive medium.) Thus a conservation of radiance equation results, known as the radiative transport or Boltzmann transport equation:

$$\begin{aligned} \frac{1}{v} \frac{\partial L(\mathbf{r}, \hat{\Omega}, t)}{\partial t} + \nabla \cdot L(\mathbf{r}, \hat{\Omega}, t) \hat{\Omega} + \mu_t L(\mathbf{r}, \hat{\Omega}, t) \\ = \mu_s \int_{4\pi} f(\hat{\Omega}, \hat{\Omega}') L(\mathbf{r}, \hat{\Omega}', t) d\hat{\Omega}' + Q(\mathbf{r}, \hat{\Omega}, t), \end{aligned} \quad (1)$$

where $L(\mathbf{r}, \hat{\Omega}, t)$ is the radiance (the power per unit area and unit solid angle) at position \mathbf{r} in the direction $\hat{\Omega}$ at time t , $\mu_t = \mu_s + \mu_a$ are the optical transport, scattering, and absorption coefficients respectively, $f(\hat{\Omega}, \hat{\Omega}')$ is the scattering phase function, $Q(\mathbf{r}, \hat{\Omega}, t)$ is the radiant source function, and v is the electromagnetic propagation speed in the medium. If we consider a small element in phase space, that is a small volume around position \mathbf{r} over a small solid angle around $\hat{\Omega}$ at time t , the left-hand side of (1) accounts for photons leaving the small element, and the right-hand side accounts for photons entering it. The first term on the left-hand side is the time derivative of the radiance, which equals the net number of photons enter-

ing the element. The second term accounts for the flux of photons along the direction $\hat{\Omega}$. The third term accounts for the scattering and absorption of photons within the phase element. Photons scattered from an element in phase space are balanced by the scattering into another element in phase space. The balance is handled by the integral on the right-hand side of (1) which accounts for photons at position \mathbf{r} being scattered from all directions $\hat{\Omega}'$ into direction $\hat{\Omega}$. The second term on the right-hand side is the photon source.

Although the linear transport equation is applicable to a wide range of media, analytical solutions are only available for simple scenarios because of the integro-differential structure of the equation. Numerical solutions to the linear transport equation are computationally intensive [69] due to the dependence on space, angle, and time.

Photon Diffusion Equation

If the scattering probability is much larger than that of absorption within the medium, we can use a simpler approximation based on diffusion theory. The approximation depends on the reduced scattering coefficient being small compared to the absorption coefficient. This reduced scattering coefficient, μ'_s , is the equivalent scattering rate that would be required to achieve a uniformly (that is, isotropically) random scattering function. Detailed derivations of the photon diffusion equation from the linear transport equation are given in Ishimaru [68], Haskell et al. [70], Boas [71], and Arridge [12], among others. The basic idea is that if the reduced scattering coefficient is much greater than the absorption coefficient, the radiance can be approximated as a weighted sum of two components, the photon fluence rate $\Phi(\mathbf{r}, t)$, which is the integral of the radiance without respect to direction, and the photon flux $\mathbf{J}(\mathbf{r}, t)$, the first-order directional component of the radiance. This approximation is valid when the radiance is almost angularly uniform, having only a relatively small flux in any particular angular direction. As a physical model one can imagine observing the light from a city on a snowy night from a low-flying airplane: the dominant behavior of the light is isotropic, i.e., it looks the same whether you look up or down, although there is clearly a small angle-dependent gradient of the radiance, or a photon flux, coming up from below. Expressing the radiance in this form, with some other reasonable assumptions [12], allows for the simplification of the linear transport equation to the variable-scattering form of what is known as the photon diffusion equation:

$$-\nabla \cdot D \nabla \Phi(\mathbf{r}, t) + \nu \mu_a \Phi(\mathbf{r}, t) + \frac{\partial \Phi(\mathbf{r}, t)}{\partial t} = \nu S(\mathbf{r}, t). \quad (2)$$

where $S(\mathbf{r}, t)$ is the equivalent isotropic source and D is the diffusion coefficient, $D = \nu / (3\mu'_s)$. (There has been discussion in the field as to whether the denominator of the diffusion coefficient should also contain an additive term

$3\mu_a$ [72], [73].) If the scattering can be treated as constant, D can be moved outside of the Laplacian operator, simplifying the photon diffusion equation even further.

Several aspects of this model deserve additional discussion. Near a boundary such as an air-tissue interface, photons which scatter out of the medium will not be scattered back in. Thus here the diffusion approximation does not hold, and so this must be handled as a special boundary condition; a number of models have been proposed and studied, trading off accuracy for computational ease [70], [74]. DOT sources are typically laser beams incident on the diffuse medium, creating a complex source function, usually dealt with by treating collimated sources as isotropic diffuse sources displaced one transport mean free path $l_{tr} = 1/\mu'_s$ into the scattering medium [70], [71]. Additionally, the distance between sources and detectors should be much greater than the mean transport length $1/(\mu'_s + \mu_a)$ so that enough scattering events occur to generate a diffuse field. (See [75] for a discussion of imaging in diffuse tissue when the source-detector separation is small.) Finally, explicit use of the linear transport equation [76] or a suitable approximation such as radiosity [77]-[79] may be required when some region of the medium being interrogated is not diffuse, for example the cerebral spinal fluid in the head [80].

Frequency-Domain Photon Diffusion Equation

Taking the Fourier transform of the constant scattering form of (2) with respect to time gives the frequency-domain photon diffusion equation which is in the form of the Helmholtz equation:

$$[\nabla^2 + k^2] \Phi(\mathbf{r}, \omega) = \frac{-\nu}{D} S(\mathbf{r}, \omega), \quad (3)$$

where k is the complex wavenumber given by

$$k^2 = \frac{-\nu \mu_a + j\omega}{D} = 3\mu'_s \left(-\mu_a + j \frac{\omega}{\nu} \right). \quad (4)$$

(Note that for consistency with the DOT literature (4) is presented using the Fourier transform defined as $F(\omega) = \int_{-\infty}^{\infty} f(t) e^{j\omega t} dt$. This is a slightly different form than is commonly used in engineering texts in that the $j\omega t$ term is positive, with the consequence that the Fourier transform of the time derivative term becomes $-j\omega \Phi(r, \omega)$ instead of $j\omega \Phi(r, \omega)$.)

Noise Models

Understanding and characterizing noise in DOT imagers is important both to design better imagers, especially important because of noise sensitivity due to the ill-posed nature of the imaging problem, but also because the optical nature of DOT implies noise models which may require modification of standard simulation approaches and prewhitening for some reconstruction algorithms [81]. CW systems will have additive noise on the ampli-

tude of the measured fluence, while RF systems will have noise on both the amplitude and phase (for a discussion of phase noise see [71]). There are several sources of noise in the amplitude of the detected DOT signal, including thermal noise, shot noise, partition noise, and $1/f$ noise, which can be divided into two types, signal independent and signal dependent [82]. The former is generally electronic noise, modeled as Gaussian distributed, white, with equal variance at each sensor, while the latter is primarily shot noise, usually modeled as Poisson distributed or as Gaussian distributed, uncorrelated between sensors, but with a variance proportional to the total fluence rate detected at that detector (i.e., with a signal-dependent variance). The total noise power is the RMS combination of the two noise types, and the SNR is defined in terms of this total noise power.

Numerical Modeling of the Diffusion Equation Forward Problem

To study the propagation of light in diffuse tissue, and also to be able to solve the inverse problem for optical parameters, one requires a means to numerically model the so-called “forward problem,” that is to predict the measured fluence at the detectors given a geometric model of the optical parameters, background parameters, and source and detector locations and functionality. There is a wide variety of approaches that one can take. Perhaps the two most direct are analytical solutions that can be applied in certain restricted geometries and Monte Carlo simulations. A useful case of the former has been the spherical harmonic solution developed by Boas et al. [71], [83] for the case where a spherical inhomogeneity is present in an infinite medium. They developed a closed-form infinite series solution which can be truncated and obtained good agreement with experimental measurements. The method was extended to a cylindrical inhomogeneity by Walker et al. [84]. In Monte Carlo methods, photons are treated as distinct particles with a certain probability of scattering, perhaps angle dependent, and absorption, at every point in a discrete geometry [85], [86]. Many photons are “injected” into the medium at every source, and aggregate statistical sample results are collected at the detectors.

As alternatives to the direct approaches, which are limited either by their geometric applicability or their extreme computational intensity, standard methods for numerical approximation of partial differential equations (PDEs) have been used. These include direct numerical integral or differential methods such as finite difference and finite element and truncated series approximations based on perturbative approaches, such as the Born and Rytov, higher-order extensions of these methods such as the n th order Born, distorted Born, iterative Born, etc. These methods depend on modeling the fields in the medium as a superposition of incident and scattered waves. In particular, with a perturbative method the signal reaching the detector is considered to be a superposition of the DPDW

that traveled through a homogeneous system, plus the first-order scattering of DPDWs from optical inhomogeneities, plus the second order, etc. The optical properties of the background/homogeneous medium are usually taken to be the average or most common optical properties. For computational purposes one generally divides the region of interest into voxels, and the first-order scattered DPDW is then the scattering of the incident DPDW from each voxel. If the optical properties of the voxel are the same as the background then no wave is scattered from that voxel. The voxels are chosen to be small enough so that the scattered DPDW can be linearized, and the amplitude of the scattered wave is then assumed to be linearly proportional to the change in μ_a and μ'_s . Using only this first-order term gives the Born or Rytov approximations; higher order, iterative, and distorted methods take into account interactions between once-scattered waves and the medium in distinct ways. Perturbation expansions are used for the relevant quantities; for details see [87] or the papers cited here. The resulting solutions often employ a Green’s function approach modified for an appropriate set of boundary conditions.

Inverse Solutions

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. From these maps other biological characteristics, such as a map of blood volume or oxygen concentration, can be derived. In this section we first describe some recent work on DOT imaging and then give some examples of the current state of DOT reconstructions.

Recent Work on DOT Inverse Solutions

We concentrate here on methods that have been proposed to solve some of the problems previously described. In particular, DOT is a nonlinear, ill-posed, and generally underdetermined imaging problem. Each of these factors contributes to both theoretical and practical difficulties in finding a reliable and unique solution, and the methods described differ primarily in how they approach these problems. Among the signal-processing tools employed are regularization, optimization, statistical modeling, and parametric representations. Regularization techniques are used to stabilize inversion of forward models against ill-conditioning caused by the ill-posedness of the inverse problem [65], [66], [88]. In brief, regularization consists of adding a second term to be minimized in defining a “good solution” to a standard least-squares fit of the estimate to the data; for example, if we are only interested in imaging the absorption coefficient μ_a , using fluence measurements y and forward model $h(\mu_a)$, we solve

$$\hat{\mu}_a = \operatorname{argmin}_{\mu_a} \|y - h(\mu_a)\|_2^2 + \lambda^2 R(\mu_a), \quad (5)$$

where the first term enforces the fit of the solution to the measured fluence, the second enforces a constraint based on an a priori assumption about how a reasonable solution should behave, and λ is called the regularization parameter and governs the tradeoff between the two terms. Typically R is a norm or the norm of a derivative so as to penalize solutions that are too large or too rough. Choosing the value of λ is often critical and sensitive, and there is a vast literature on this topic (see [66], for instance, for a discussion). Regularization-type formulations can be posed in a variety of optimization frameworks and thus solved by a corresponding variety of optimization methods. Statistical modeling is important to accurately deal with the differing types of noise sources and can also provide an alternative formulation for regularization. Parametric modeling, in particular of the geometric structure of the reconstruction, can serve to reduce or eliminate under-determinedness and ill-posedness as well as to provide attractive new formulations for constraints for regularization. Our discussion must necessarily be brief and omits many contributions. We emphasize recent work and organize the presentation into three general themes: new approaches to reconstruction with linear models, new formulations of forward models for inverse solutions, and two novel approaches based on statistical regularization and parametric geometric representations, respectively.

Reconstruction with Linear Models

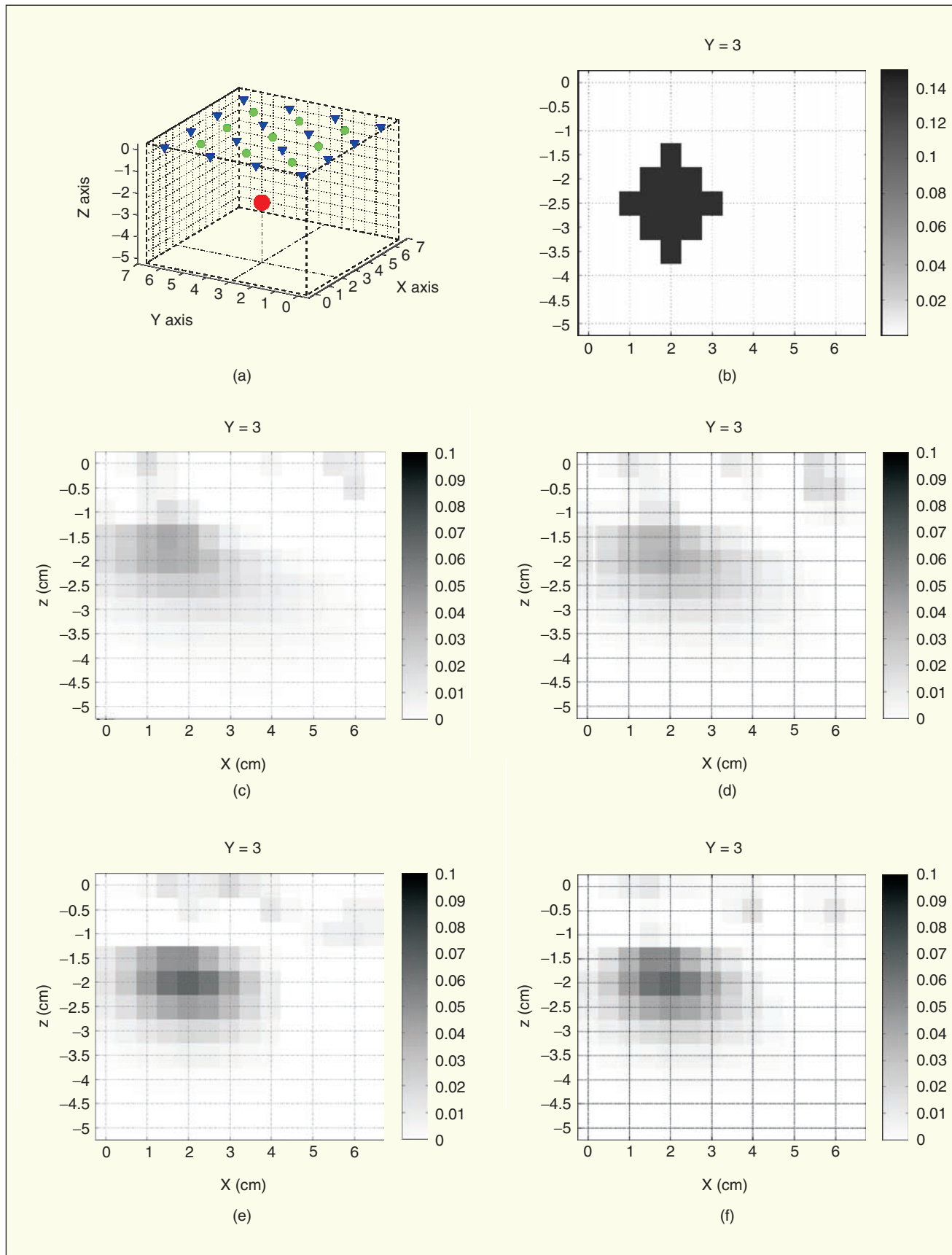
In linear regularization, the functional relationship $b(\mu_a)$ in (5) is approximated as a matrix, $b(\mu_a) \approx H\mu_a$. In addition to the wide use of common linear models, since many nonlinear methods are essentially an iterative succession of solutions to updated linearizations, linear regularization may play a role in nonlinear formulations as well. Standard approaches to regularization of linear-model DOT reconstruction have been reported using a variety of techniques, including the ART, SIRT, and SART algebraic algorithms common in tomography [89]-[91] and subspace algorithms such as truncated singular value decomposition (TSVD), truncated conjugate gradient (TCG), and regularized total least squares [92]-[95]. A direct comparison of ART, SIRT, TSVD, and TCG for a reflection geometry was reported in [81]. One variation on regularization that has been applied to DOT is to allow the relative weight given to the two error terms to vary with space [96], in other words to weight the data more in some locations and the constraint more in others. The goal is to combat reconstruction artifacts which commonly occur near the source and detector locations, as illustrated in Fig. 4. Another method to achieve a “regularization-like” objective is to formulate the reconstruction as an admissible solution problem, where each constraint (including one on the difference between forward-projected “data estimate” and the measured fluence) is seen as describing a constraint set in the solution space. An admissible solution is then one which

meets all constraints being employed. Such problems can be placed in an optimization context and, if the class of constraints employed is restricted to be convex, solved by convex optimization techniques. Both projection on convex sets (POCS) [92] and the ellipsoid algorithm [97] have been tested for DOT. Using either these approaches or more direct regularization, a number of nonstandard constraints have been applied on reconstructions, including positivity of the reconstructed absorption inhomogeneity or limitation of the magnitude of its deviation from the background [89], [90], [93], [97], rescaling of the forward matrix as a normalization constraint [93], [98], and a total variation-type constraint [97] to attempt to concentrate the inhomogeneity in a small number of regions. Finally, three quite different attempts to solve linearized problems have been reported recently, all of which derive new analytic representations of the problem. One, for the time-domain problem, uses an “elliptic systems method” for solving a differential version of the diffusion equation [99], [100]. The other two use a reformulation of the solution as a Fourier-Laplace equation [101], [102] or derive an analytic SVD of the forward operator [103].

Forward Modeling for Inverse Solutions

As described earlier, the two key issues in forward modeling for DOT inverse solutions are the use of the diffusion equation to approximate the transport equation and treating the nonlinearity of the diffusion equation. Two scenarios in which the diffusion equation approximation itself may break down are when source-detector separations are small in comparison with the mean transport length, which is not generally a concern in DOT imaging, and when the tissue region of interest contains nondiffusing regions, as for CSF in brain imaging [80], [104]. Two approaches to this problem have been reported recently. One [76] attempts to model directly the transport equation, but the computational difficulties are nontrivial. The other attempts to fuse two distinct forward models, each applied to an appropriate subregion, the diffusion equation for turbid regions and a radiosity approach, which uses a straight-line ray propagation model, in clear regions.

The limitations of linearized perturbative models when inhomogeneities are large in size or amplitude is well known [87]. One approach to nonlinear inverse solutions has been based on extensions of the Born and Rytov approaches such as iterative Born and distorted Born [105]-[108], which perform an iterative sequence of linearizations by updating the background model, a Green’s function-based propagation model, or both. An interesting feature of [108] is that by careful derivation of the appropriate Frechet derivative, needed to update the Green’s function, the authors found a particular weighting of the current estimate of the unknowns used to update the model. Recent work by Boas et al. [109] reports on expansion of the forward model to include as



▲ 4. Reconstruction examples for four linear reconstruction techniques at 20 dB SNR. Panel (a) shows computational volume with location of inhomogeneity, and (b) shows a vertical slice through the center of the true image. Each subsequent image shows the same vertical slice through a reconstruction using the following algorithms: (c) the ART algorithm, (d) the SIRT algorithm result, (e) the TSVD algorithm, and (f) the TCG algorithm.

unknowns the “coupling coefficients” that model the efficiency of transfer of light from source to tissue and from tissue to detector. These coefficients are multiplicatively related to the detected fluence, so that even a linear model becomes nonlinear, but by use of the Rytov approximation (which employs a logarithmic transformation of an exponential model of the perturbation relationship) they become linear and can be incorporated within a linear reconstruction method. Another variation is to include fluence from more than one illumination wavelength (since at least two are required to determine chromophore concentrations) into a joint inverse problem and estimate the results simultaneously, taking advantage for instance of similarities in spatial structure [110].

Statistical and Parametric Inverse Models

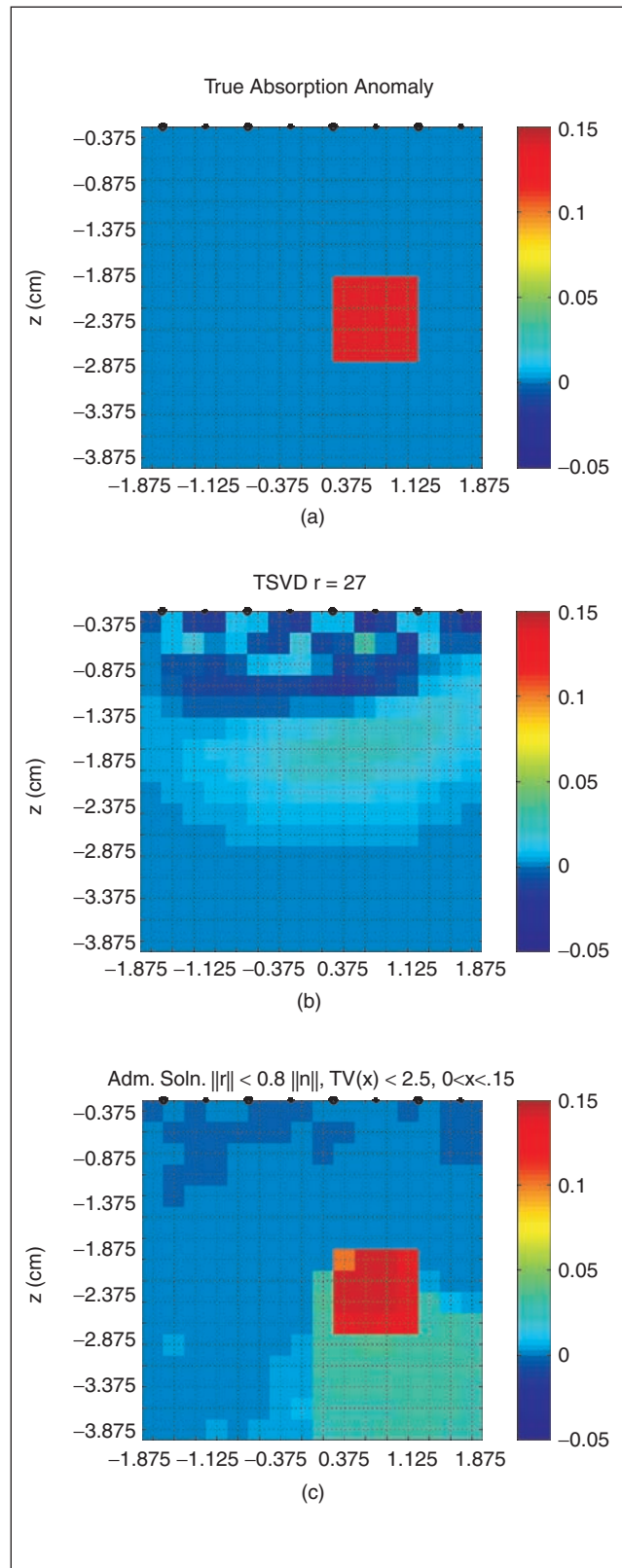
When a statistical prior model is assumed for the unknown parameters, a Bayesian maximum a posteriori (MAP) solution has formal similarity to a regularization solution, but offers extended possibilities for both algorithms and modeling. In [61], Eppstein et al. use this approach to pose the reconstruction as an extended Kalman filter, a scheme which they originally developed for geohydrology. They impose upper and lower limits on the prior probabilities via a transformation from a true beta density to a more tractable Gaussian approximation and reduce the number of unknowns at each iteration by grouping like voxels together into a large voxel with the same properties, thus ameliorating the under-determinedness.

The latter goal, reducing the number of unknowns, has also been the goal of recent work based on a sparse parameterization of the reconstruction domain. Two groups have published articles in this area, with similar but distinct approaches [111]-[115]. These methods divide the tissue region into background regions and inhomogeneities, assume that both the background and inhomogeneities can be modeled by some low-order variation (i.e., constant, linear, etc.), and assume that the boundaries of the regions are either known or can themselves be expanded as a small set of basis functions (trigonometric or B-spline polynomials). Thus the unknowns are reduced from the parameters of interest at every voxel to the coefficients of the background and inhomogeneity models and the location of the boundaries.

Some Examples of DOT Reconstructions

Below we present some reconstruction results drawn from our work, illustrating aspects of the discussion above. These are not intended to be a comprehensive presentation of the state-of-the-art, but rather to give the reader a visual impression of the abilities, limitations, and possibilities of some current approaches.

To illustrate the possibilities and problems of standard regularized DOT reconstructions, in Fig. 4 we show a particular simulated computational volume in a reflection imaging scenario with an absorption

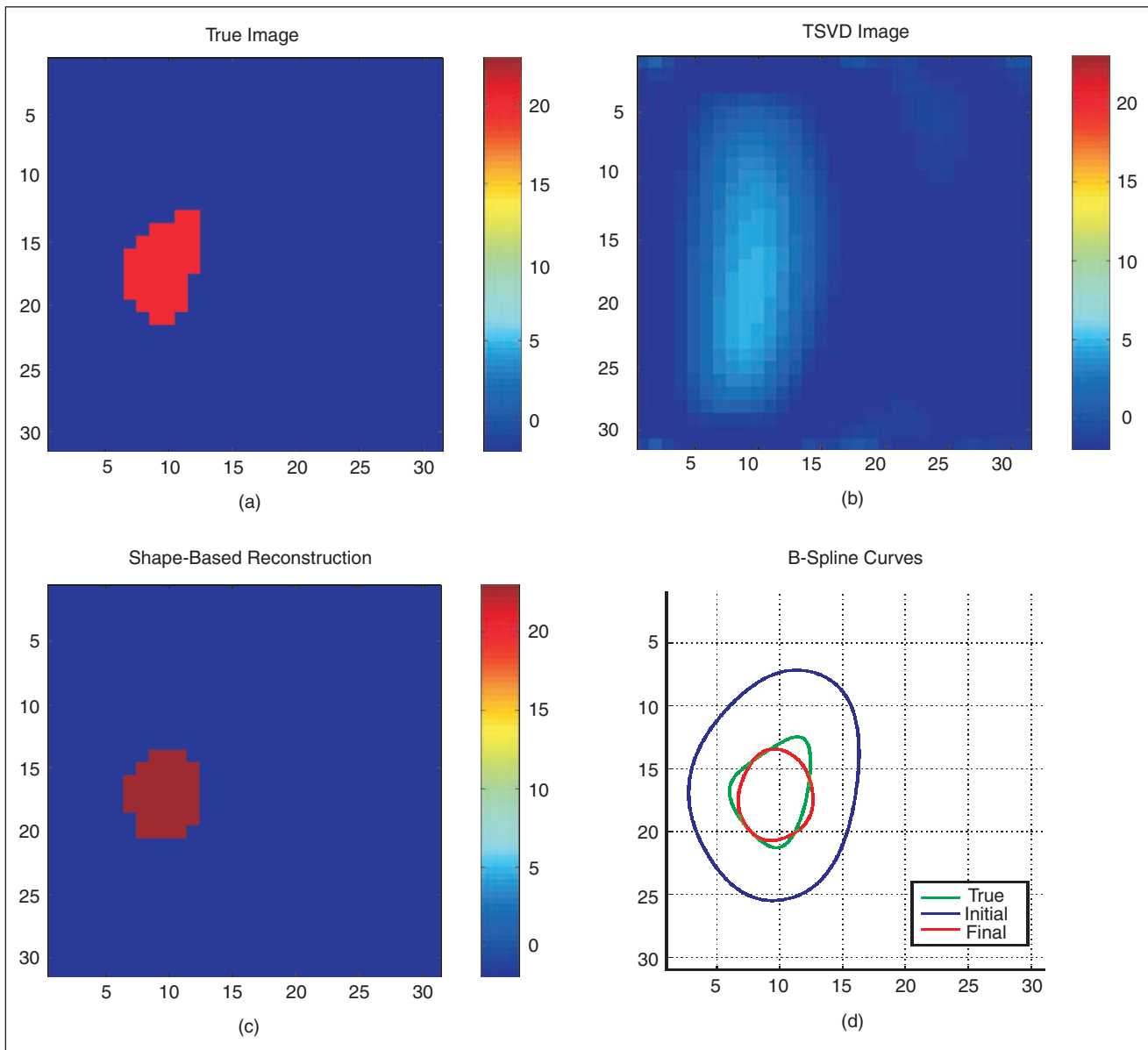


▲ 5. Comparison of the use of nonstandard constraints on the solution is shown, using an admissible-solution optimization approach in a 2-D absorption inhomogeneity simulation model. The upper left panel shows the true distribution of the absorption coefficient, the upper right shows a TSVD reconstruction, and the lower left shows an admissible solution reconstruction using constraints on the residual of the scattered fluence and the total variation and max and min deviations of the absorption.

inhomogeneity as shown (for details, see [81]), along with reconstructions using four linear methods (ART, SIRT, TSVD, and TCG) at 20 dB SNR. Although the subspace methods are better able to reconstruct the object than the algebraic methods are, the reconstructions nonetheless suffer from artifacts (mostly near the surface) and underestimation of amplitude and depth. To illustrate the improvements possible with some of the methods described above we present results from 2-D simulations using two of the different approaches we have described. The first, using an admissible solution formulation and the ellipsoid algorithm, and employing total variation and max and min deviation constraints [97], is shown in Fig. 5, compared to TSVD. The ability of the additional constraints to suppress many of the artifacts in the reconstruction can be seen in the figure. In

Fig. 6 we present a 2-D example of a parametric basis function approach, in which the region is modeled as consisting of a constant background with constant inhomogeneity, and the inhomogeneous region is bounded by a B-spline curve. The values of the absorption in each region and the shape of the boundaries are found through iterative updates which are locally optimal. The improvement over TSVD is illustrated in the figure, and objective measures such as mean square error confirm the result. Details can be found in [115].

We also present one example of reconstruction from measured data using a phantom built at MGH and the reconstruction scheme outlined above for recovering both the coupling and absorption coefficients. The phantom consisted of a highly scattering solution of Intralipid [116] mixed with India ink to produce optical properties of



▲ 6. A 2-D example of a shape-based reconstruction. The upper left panel shows the true model of the inhomogeneity. The upper right panel shows a truncated SVD reconstruction, while the lower left panel shows a shape-based reconstruction. The lower right panel shows the outline of the true object along with the initial guess at the outline and the final outline reconstructed by the shape-based method. In all four panels the x and y axes are marked in centimeters.

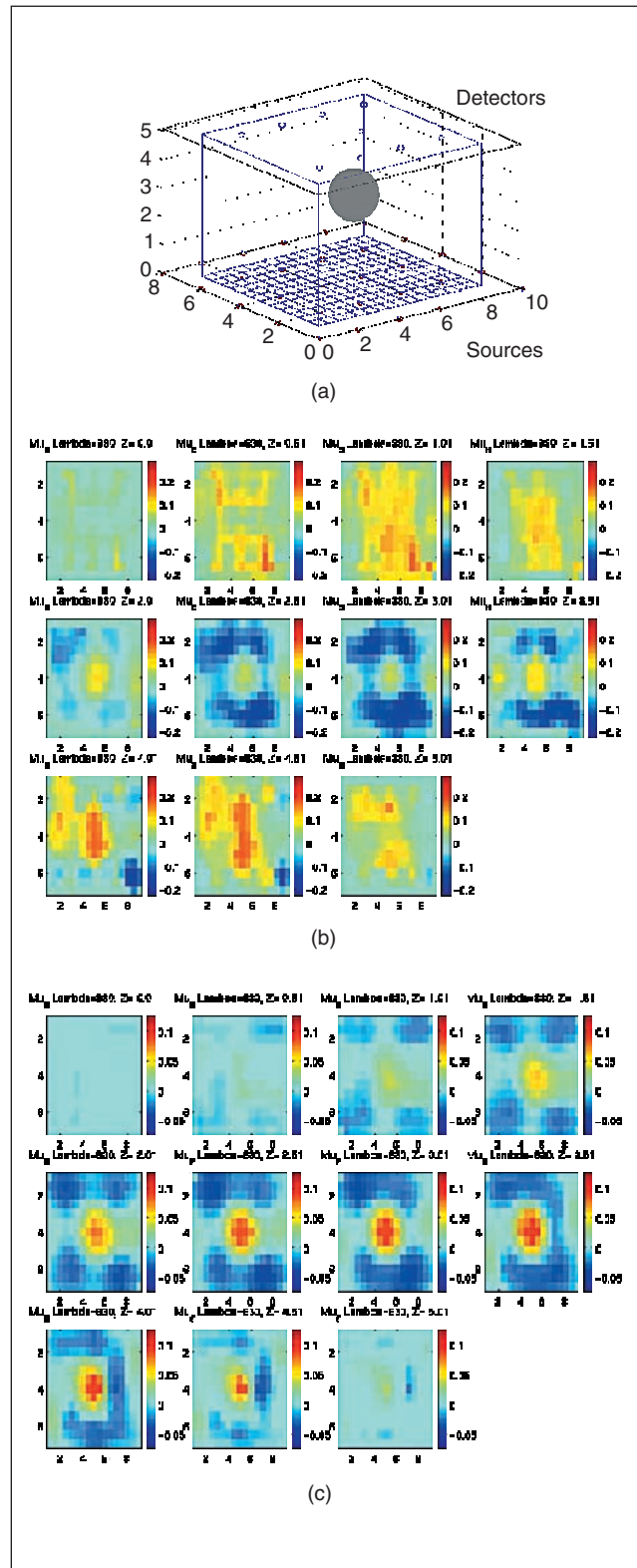
$\mu'_s = 5 \text{ cm}^{-1}$ and $\mu_a = 0.025 \text{ cm}^{-1}$. Thirty sources were placed on one XY boundary of the phantom at $z=0$, while nine detectors were placed on the other XY boundary at $z=5.1 \text{ cm}$. The sources and detectors spanned $8 \times 10 \text{ cm}$ in the XY planes. A spherical absorber ($\mu_a > 0.2 \text{ cm}^{-1}$) with a diameter of 2 cm with the same scattering as the background medium was centered in the phantom. The arrangement of the source and detectors relative to the absorbing sphere are shown in Fig. 7(a). Note that this imager is different from the one pictured earlier. Measurements were made with an RF system, 830 nm illumination wavelength and 70 MHz intensity modulation, and both amplitude and phase of the detected signals were measured. Three-dimensional images were reconstructed from the 270 independent measurements. Fig. 7(b) shows the image reconstructed from the actual measured fluence with an approximate calibration of the source and detector amplitudes made prior to the phantom experiment. The absorbing object can be discerned within the center of the image, but it is overshadowed by large amplitude fluctuations near the source and detector planes. These artifacts near the surfaces result from errors in the calibration. In Fig. 7(c) we show a reconstruction from the same data after including the coupling coefficients of each source and detector in the inverse problem.

Conclusions

As both imaging technology and our understanding of the physical modeling of propagation of scattered light have developed over the last decade, DOT has become increasingly able to take advantage of sophisticated signal processing for both acquisition and reconstruction. The current challenge is twofold: in the near-term the challenge is to provide compelling evidence of its potential on clearly relevant applications such as detection of breast tumors and functional imaging of the brain. In parallel with this effort, in the longer-term the challenge is to develop better imaging devices, physical models, inverse reconstructions, and associated efficient algorithms, to extract the information which the multiply-scattered light is now known to possess. In particular, we believe there may be a role to play for many sophisticated image reconstruction and signal modeling techniques developed in the signal processing community for other purposes. Careful attention must be paid, however, to the integration of such techniques with appropriate models of light propagation to achieve useful and reliable results.

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▲ 7. A diagram of the configuration of a phantom with 30 sources, nine detectors, and the absorbing sphere is shown in (a). All reconstructions in panels (b) and (c) are done using data measured by this experimental setup. The sequence in panel (b) shows an absorption image reconstructed without source/detector amplitude fitting. XY slices are shown at different z levels. Axes are labeled in centimeters. The sequence in (c) shows the same image reconstructed simultaneously with the source/detector amplitude factors.

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