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-off 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 signal. 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. Prah [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 0.017-0.032 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 7.2-10.0 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-
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 diffuse medium.) Thus a conservation of radiance equation results, known as the radiative transport or Boltzmann transport equation:

\[
\frac{1}{r} \frac{\partial I(r,\Omega,t)}{\partial t} + \nabla \cdot I(r,\Omega,t)\Omega + \mu_s I(r,\Omega,t) \\
= \mu_s \int_{\Omega} f(\Omega',\Omega')L(r,\Omega',t)d\Omega' + Q(r,\Omega,t),
\]

(1)

where \(L(r,\Omega,t)\) is the radiance (the power per unit area and unit solid angle) at position \(r\) in the direction \(\Omega\) at time \(t\), \(\mu_s\) is the optical transport, scattering, and absorption coefficients respectively, \(f(\Omega,\Omega')\) is the scattering phase function, \(Q(r,\Omega,t)\) is the radiant source function, and \(r\) is the electromagnetic propagation speed in the medium. If we consider a small element in phase space, that is a small volume around position \(r\) over a small solid angle around \(\Omega\) 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 \( \Omega \). 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 \( r \) being scattered from all directions \( \Omega' \) into direction \( \Omega \). 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, \( \mu'_s \), 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 \( \Phi(r, t) \), which is the integral of the radiance without respect to direction, and the photon flux \( J(r, t) \), 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:

\[
- \nabla \cdot D \Phi(r, t) + \nu \mu_a \Phi(r, t) + \frac{\partial \Phi(r, t)}{\partial t} = \nu S(r, t).
\]  

where \( S(r, t) \) 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 \( 1/\mu'_s \) 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:

\[
\left[ \nabla^2 + k^2 \right] \Phi(r, \omega) = \frac{-\nu}{D} S(r, \omega),
\]

where \( k \) is the complex wavenumber given by

\[
k^2 = \frac{-\nu \mu_a}{D} + i \frac{\omega}{\nu} = 3 \mu'_s \left( -\mu_a + \frac{\omega}{D} \right).
\]

(Note that for consistency with the DOT literature [4] is presented using the Fourier transform defined as \( F(\omega) = \int f(r) e^{-j \omega \cdot r} \, dr \). This is a slightly different form than is commonly used in engineering texts in that the \( j \omega \) 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 nth 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 $\mu_s$ and $\mu'_s$. 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 $\mu_s$, using fluence measurements $y$ and forward model $b(\mu_s)$, we solve

$$\hat{\mu}_s = \arg\min_{\mu_s} \|y - b(\mu_s)\|_2^2 + \lambda^2 R(\mu_s),$$

(5)