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Photon Diffusion in Biological Tissues

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Abstract

The use of laser-based optical techniques for medical imaging is an attractive alternative to other methods that utilize ionizing radiation. Beside being non-carcinogenic, it is non-invasive, the equipment is transportable, and the methodology can be used to examine properties of soft tissue. However, unlike x-ray photons, optical photons generated in the near-infrared suffer significant amounts of scattering by heterogeneous bodies (e.g., organelles) found in biological tissue. Thus, theory is required to interpret experimental data which appear in the form o spatially or temporally varying light patterns on the skin surface. There is a wide range of parameters over which either diffusion theory or the theory of lattice random walks can be called on to translate optical data into medically significant information embodied in optical parameters of the tissue. We discuss several problems in diffusion theory arising in the analysis of optical measurements, for tissues modeled by a semi-infinite or slab geometry, having either isotropic or anisotropic optical parameters. The measured quantities are related to the intensity of light re-emitted on the tissue surface. A brief discussion is given related to the telegrapher's equation, which has been suggested as a simple way of incorporating the effects of forward scattering. Mention is made of calculations related to layered media which frequently occur in tissues such as skull and esophagus. Finally, we briefly discuss discrete random walk models for photon migration. These have recently been used to provide parameters conveying information related to the region interrogated by photons constrained to reappear on skin surface.

1 Introduction

The seminal works by Einstein and Smoluchowski, [1, 2], in understanding and generalizing Brownian motion and diffusion, appeared near a century ago. These studies were

motivated by problems in statistical mechanics. Early applications of diffusion theory were therefore almost exclusively focused on the motion of matter particles dissolved in a liquid. An early example is that of Brownian motion seen in pollen in solution which may even have been observed by van Leeuwenhoek, the inventor of the microscope. Today the ambit of diffusion is a much broader one. A field of applications being investigated by a large number of scientific groups is that of the transport of photons through turbid media. A good general, and not too technical, overview of this area of research is to be found in an article by Yodh and Chance, [3].

One motivation for the study of many varieties of optical technology is that light, at the intensities used for diagnostic purposes, is not carcinogenic, in contrast to those of imaging modalities based on ionizing radiation. Consequently, when optical techniques can be suitably adapted for uses in medical imaging, they are preferable to techniques based on x-rays. A further motivation for the use of optical techniques based on photons in the near-infrared (NIR) is that these are potentially sensitive to information related to metabolic processes and blood flow. This can often enable a distinction to be made between different types of soft tissues that may be unobservable by other imaging modalities. However, in contrast to x-rays, photons in the NIR suffer the drawback of being significantly scattered in tissue, which has the effect of randomizing photon trajectories and leading to a blurring of images produced in applications.

A holy grail in the use of optical techniques is that of replacing x-ray mammography by optical methods. To accomplish this goal it would be necessary to have a spatial resolution on the order of millimeters. It is also necessary to generate a sufficient number of photons at the given wavelength without increasing the laser beam intensity to a point where it poses a danger to tissue. A first experiment in the use of optical techniques for breast imaging was described by Cutler in 1929, [4]. Little useful information was obtained from this early experiment because the necessary technological infrastructure simply didn't exist at that time. However, it did indicate the significant amount of blurring resulting from photon scattering. A not necessarily exhaustive, but nevertheless excellent, summary of available techniques in optical imaging up to 1997 is to be found in a review by Hebden et al, [5]. A major update of this material has appeared in a recent review article by Gibson et al, [6].

The many potential applications of optical imaging and spectroscopy suggest that a heavy investment in the development of suitable theory is required to optimize experimental design as well as to interpret data obtained from optical measurements. This is by no means a trivial requirement. Even restricting oneself to a purely phenomenological analysis, it is necessary to deal with a transport equation, [7], whose solution can only be found numerically. A rigorous analysis ideally starts from a model of photons in terms of waves, which can be shown to eventually approach a description of photon motion in terms of diffusion in the long-wavelength limit. A lengthy and thorough discussion of some of the subtleties involved in developing a theory of motion in a disordered medium is to be found in an enlightening review by van Rossum and Nieuwenhuizen, [8].

Several problems will be discussed that arise in translating optical data on a surface into useful information relating to optical properties of tissue interior to the surface. The simplest problems require only elementary and straightforward applications of diffusion theory. These will be generalized to deal with effects on standard experimental measure-

ments when the tissue has optical properties that are anisotropic with respect to a boundary. We further discuss two techniques for deriving information related to photon trajectories which are not themselves directly observable. Our analysis will be phrased either in terms of diffusion theory or the theory of lattice random walks, [9]-[11]. There are mainly minor differences between the two theories, but occasionally one or the other picture is found to be the more appropriate technique. The problems to be discussed here will be described in the context of biomedical applications. Because literature on the subject is by now so vast, this review can only describe a small fraction of the theory, mainly to give the reader an idea of the kinds of questions posed by medical applications.

2 Diffusion models

2.1 Isotropic media

Three main categories of measurements in use today are (1) time-gated measurements, (2) continuous-wave (CW) measurements, and (3) frequency-domain measurements. In the first of these, a pulse of light generated by a laser beam enters the tissue and measurements of light intensity due to photons re-emitted at the tissue surface are collected as a function of time. In CW measurements a continuous beam of light impinges on the tissue surface and the resulting reflected light intensity is measured along an external surface separating the tissue from the environment. Such measurements are made as a function of the distance between the source and detecting optodes. Finally, in frequency domain measurements, a periodically modulated beam enters the tissue and the data consist of measurements of amplitude and phase shifts as a function of frequency. Penetration depths of photons in biological tissues may range up to approximately 100 mm but most measurements explore considerably shorter depths . Not all of the input photons eventually reach the surface since some are absorbed internally which means that they disappear from the system and are never otherwise measured.

The three types of measurements just mentioned are far from exhaustive but constitute the set of techniques for whose analysis diffusion-like models have been extensively applied. Roughly speaking, this is because internal photon scattering randomizes the directions of motion. This brings the central-limit theorem into play, [12], and leads to the Gaussian propagator (in free space) which justifies the use of diffusion theory. One notable example in which diffusion theory is inapplicable is that of Optical Coherence Tomography (OCT) which registers effects of only a single scattering event. This technique produces images resolved with extremely high accuracy, [13, 14], but the depth explored by the photons is quite small. It is generally believed that something on the order of ten scattering events validates analysis based on diffusion theory. The depth of tissue generally explored in the diffusion range is of the order of 100 mm or less, while in OCT measurements, since photons are scattered once (approximately) it is from 2 to 4 mm.

Two geometric structures are most often used to model the tissue; a semi-infinite space bounded by a plane (figure 1a) and a slab (figure 1b). Very little is known about effects of curvature on results derivable from planar models since the mathematical analysis required

for dealing with this problem is extremely complicated. In both models, the semi-infinite tissue and the slab, in which the interface between the tissue and its surroundings is planar, optical properties of the tissue are generally assumed to be homogeneous and isotropic. Results for this simple case are needed as a backdrop for analyzing more sophisticated models.

The simplest set of problems to be discussed require dealing with three optical parameters, μ_s, μ_a and $g = \langle \cos\theta \rangle$, which are, respectively, the scattering coefficient, the absorption coefficient, and the average of the cosine of the angle, θ, through which a photon is scattered in a single scattering event in an unbounded space. The inverse of μ_s is the average distance between successive scatterings, that of μ_a is the average distance between successive internal absorptions. Very often experimentalists combine g and μ_s and deal with the so-called transport-corrected scattering coefficient, $\mu_s' = \mu_s(1-g)$. This parameter combination is a crude and empirical way of incorporating forward scattering effects into the analysis. Typical orders of magnitude of these parameters for healthy human tissues or oxygenated blood obtained using laser radiation whose wavelength is between 540 and 633 nm are $\mu_s \approx 1$ mm^{-1}, $\mu_a \approx 0.01$ mm^{-1} and $g \approx 0.8$, [15]. The range of wavelengths generally used for biologically useful measurements at the present time is from approximately 400 to 900 nm.

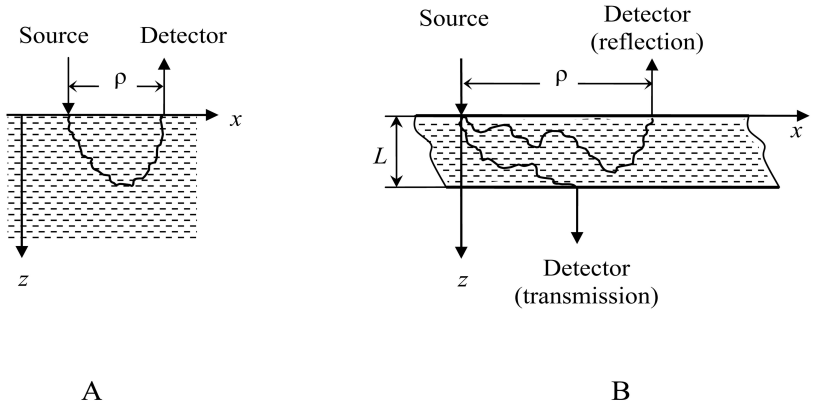

Figure 1: Geometric structures most often used to model the tissue. a) A semi-infinite space bounded by a flat plane. b) A slab of finite thickness and unbounded surfaces. In both cases ρ is the distance between the laser beam and the detector.

2.2 The propagator and the light intensity

The simplest model calculation requires us to find an expression for the reflectance in a CW experiment on a semi-infinite medium with isotropic optical properties. When optical properties of the tissue are assumed to be isotropic the object of our calculations is that of finding an expression for the light intensity on the planar surface as a function of the

distance ρ separating the point at which the laser beam enters the tissue and the point on the surface at which it leaves. Denote an arbitrary point in the tissue by $\mathbf{r} = (x, y, z)$ where $z > 0$ corresponds to points in the tissue, and let $-\infty < x, y < \infty$ be the coordinates in any plane perpendicular to the z-axis.

Let $p(\mathbf{r}; t|\mathbf{r}_0)$ be the propagator, i.e., the probability density for the position of the photon, **r**, at time t, given that it was initially at $\mathbf{r}_0$. In the diffusion formulation this function satisfies

$$\frac{\partial p}{\partial t} = D\nabla^2 p - \mu_a p \tag{1}$$

where, in units in which the speed of light in the tissue is equal to 1, the diffusion constant is related to the scattering and absorption coefficients by $D = [3(\mu_s' + \alpha\mu_a)]^{-1}$ where α is a constant whose exact value is not agreed upon (cf. [16], the references therein and more recently in [17]), but is of the order of one. However, since for normal tissues the ratio of μ_a/μ_s' is of the order of 10^{-2}, the term $\alpha\mu_a$ is negligible compared to μ_s' so that $D \approx (3\mu_s')^{-1}$ is often used. Internal absorption is assumed to follow the Beer-Lambert law which is implied in Eq.(1) so that the probability, $S(t)$, that a photon diffuses through an unbounded tissue for a time t without being absorbed is equal to $\exp(-\mu_a t)$. The rate at which the photon changes direction as it is scattered is $k = c\mu_s'$. Our results will be expressed in terms of the dimensionless time $\tau = kt$ so that the survival probability written in terms of dimensionless time is

$$S(\tau) = \exp(-\nu\tau) \tag{2}$$

where $\nu = \mu_a/\mu_s'$.

The interface, $z = 0$, is assumed to be an absorbing plane, so that for a tissue the propagator satisfies the boundary condition

$$p(x, y, 0; t|\mathbf{r}_0) = 0 \tag{3}$$

We note that some authors suggest the use of an extrapolated boundary condition, [18], which sets the boundary at some other value of z_{e} found in terms of the solution of the Milne equation. However,this has been disputed, [19], and there is no clear evidence that Eq.(3) leads to results that are significantly incorrect. Another possible boundary condition has been investigated, the so-called radiation boundary condition, which is written

$$\left.\frac{\partial p}{\partial z}\right|_{z=0} = \kappa p(x, y, 0; t|\mathbf{r}_0) \tag{4}$$

where κ is a constant, [20]. The results produced by solving Eq.1 with this boundary condition do not differ significantly from those produced by setting $\kappa = \infty$, except at points close to the input point where the use of a diffusion model is questionable in any case. With this in mind, and to keep the analysis as simple as possible, we will always use the absorbing boundary condition in Eq.(3). As the final ingredient in formulating the diffusion model we specify the initial condition by setting $\mathbf{r}_0 = (0, 0, z_0)$ where z_0 is a scattering length, $z_0 = 1/\mu_s'$.

Following standard practice in applications of diffusion theory, the surface intensity will be identified with the flux found using Fick's law

$$I(\rho,0;t|\mathbf{r}_0) = -D\left.\frac{\partial p}{\partial z}\right|_{z=0} \tag{5}$$

in which $\rho = (x,y)$. In our pursuit of the question of characterizing the region visited by photons we can ask for the information obtainable from the solution to the problem as so far stated. There are at least two functions of space which furnish some information about photon trajectories, and which are easily found. The first is the expected time to absorption at a distance on the surface, ρ, from the laser beam, and the second is the maximum depth reached by the photon trajectory conditional on reaching the surface.

Let $p^{(F)}(\mathbf{r};\tau|\mathbf{r}_0)$ be the propagator in an unbounded space. The propagator in the presence of an absorbing boundary can be written in terms of this propagator as

$$\begin{aligned} p(\mathbf{r};\tau|\mathbf{r}_0) &= p^{(F)}(x,y,z-z_0;\tau|0,0,z_0) - p^{(F)}(x,y,z+z_0;\tau|0,0,z_0) \\ &= \frac{1}{(4\pi D\tau)^{3/2}}\exp\left(-\frac{\rho^2}{4D\tau}-\nu\tau\right)\left[\exp\left\{-\frac{(z-z_0)^2}{4D\tau}\right\}\right. \\ &\quad \left.-\exp\left\{-\frac{(z+z_0)^2}{4D\tau}\right\}\right] \end{aligned} \tag{6}$$

where $\rho^2 = x^2+y^2$. Because we have assumed that the optical properties of the tissue are isotropic the intensity of interest is not assumed to be a point, which corresponds to the propagator in Eq.(6), but rather the intensity detected in an annulus centered at ρ. This will be denoted by $\Gamma(\rho;\tau)$:

$$\Gamma(\rho;\tau) = 2\pi\rho I(\rho;\tau) = \frac{z_0\rho}{8\left(\pi D^3\tau^5\right)^{1/2}}\exp\left(-\frac{\rho^2}{4D\tau}-\nu\tau\right) \tag{7}$$

This result is the function needed to interpret data obtained either from CW or time-gated measurements. It is seen to have a single maximum as a function of τ. This is located at

$$\tau_{\max} = \frac{1}{8D\nu}\{\sqrt{100D^2+16D\nu\rho^2}\} - 10D \tag{8}$$

Typical values of the time at which the maximum of the intensity occurs are of the order of hundreds of picoseconds.

For healthy tissue the parameter ν will generally be small, of the order of 10^{-2}, so that we can expand this expression around $\nu = 0$, retaining the lowest order term. This simplifies the expression for $\tau_{\max}$ to

$$\tau_{\max} \approx \frac{\rho^2}{10D} \tag{9}$$

so that when the scattering rate k is known and $\tau_{\max}$ is measured, the diffusion constant can be found by plotting $\tau_{\max}$ as a function of ρ^2 to find the multiplicative coefficient. The

function measured in a CW experiment is

$$\Gamma(\rho) = \int_0^\infty \Gamma(\rho;\tau)d\tau = \frac{z_0}{2\rho^2}\left[1+\rho\sqrt{\frac{\nu}{D}}\right]\exp\left(-\rho\sqrt{\frac{\nu}{D}}\right) \tag{10}$$

While this diverges at $\rho = 0$ the diffusion model is not correct at short distances because of the implicit requirement that photons need to undergo a large number of collisions to validate the use of a diffusion picture. Hence one cannot expect Eq.10 to be accurate in the immediate neighborhood of $\rho = 0$.

A second quantity of interest in the context of describing the photon trajectory is the average time for a photon to reach a distance ρ from the source. This is a possible measure of how much of the tissue has been explored, but it is a rather crude one. Later we discuss alternatives to this characterization. When the speed of light in tissue is assumed constant, this function is defined by

$$\langle\tau|\rho\rangle = \int_0^\infty \tau\Gamma(\rho;\tau)d\tau \Big/ \int_0^\infty \Gamma(\rho;\tau)d\tau = \frac{\rho^2}{\sqrt{4D\nu}\left[\rho+\sqrt{\frac{D}{\nu}}\right]} \tag{11}$$

so that if ν is held fixed, and ρ tends to infinity, $\langle\tau|\rho\rangle \approx \rho/\sqrt{4D\nu}$ as derived originally by the random walk analysis in [21]. This proportionality to the first power of ρ reflects the fact that when the internal absorption differs from zero the trajectory approaches a straight line to minimize, as far as possible, the possibility of absorption.

Since scattering photon trajectories are random, the problem of characterizing the region interrogated by photons is of some importance. One approach to this problem is to calculate the local time in some region of the tissue, [22]. Consider the trajectory of a photon moving in a semi-infinite medium. In the present context the conditional density, or conditional local time, spent at point $\mathbf{r} = (x, y, z)$, of a diffusing particle that is absorbed at $\mathbf{R} = (X, Y, 0)$ at time t, will be defined as the fraction of time spent at $\mathbf{r}$ during $(0, t)$ conditional on reaching $\mathbf{R}$ at time t. This problem was initially investigated in terms of a lattice random walk, [23]. Here we give the result that follows in the corresponding diffusion picture. Let $h(\mathbf{r}|\mathbf{R}, t)$ be this density. It can be expressed in terms of the propagator as

$$h(\mathbf{r}|\mathbf{R},t) = \frac{\int_0^t p(\mathbf{R},t-\tau|\mathbf{r})p(\mathbf{r},\tau|\mathbf{r}_0)d\tau}{tp(\mathbf{R},\tau|\mathbf{r}_0)} \tag{12}$$

Since both the numerator and denominator in this expression vanish because $z = 0$ at the point $\mathbf{R}$, it is necessary to use L'Hô pitals rule, [24] to evaluate the equation. Without going into the detailed calculations, which are straightforward but tedious, we note that the local time at z units of length from the surface reduces to

$$h(\mathbf{r}|\mathbf{R},t) = \frac{2z}{Dt}\exp\left(-\frac{z^2}{Dt}\right) \tag{13}$$

which is independent of both $\mathbf{R}$ and ν. Since the term $\exp(-\nu\tau)$ appears as a multiplier in both the numerator and denominator of Eq.12, it cancels out. This is no longer true for CW

measurements, since, for example, the denominator in Eq. 12 must account for the number of photons which reach $\mathbf{R}$,which must clearly be a function of ν. Similarly, ν appears in the numerator as term shown in greater detail in [24].

2.3 Anisotropic media

The standard formulation of diffusion theory has recently been extended to take into account tissues whose optical parameters are anisotropic. This development was motivated by the existence of tissues having this property such as skin, [25], white matter in the brain, collagen, and dentin, [26]. The extension of the theory in the diffusion framework replaces the single diffusion constant by a 3×3 diffusion matrix as first suggested by Heino, Arridge and Sommersalo, [27]. This is based on a heuristic argument, but also can be derived directly from a continuous-time random walk (CTRW) picture, [9]. Further work in this area was done in [28] and [29], which discusses the problem of estimating the angular dependence of optical parameters in terms of surface intensity measurements.

The analysis itself is straightforward, except for the requirement that the resulting equations must satisfy the boundary conditions. We outline the analysis for time-gated measurements made on a semi-infinite medium. Figure 2 is a schematic diagram of an anisotropic system, drawn for simplicity in two dimensions. The optical parameters lie along the dashed lines which are at an angle θ with respect to the z-axis. Describing the system necessitates utilizing two sets of coordinates. In the laboratory, or observable coordinates a point is denoted by $\mathbf{r} = (x, y, z)$ and in the skewed coordinates, defined by the anisotropy of the optical parameters, a point is denoted by $\mathbf{r}' = (x', y', z')$. For simplicity we consider only the special case in which the diffusion matrix is

$$\mathbf{D}' = \begin{pmatrix} D_{x'} & 0 & 0 \\ 0 & D_{x'} & 0 \\ 0 & 0 & D_{z'} \end{pmatrix} = D_{x'} \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & B \end{pmatrix} \tag{14}$$

where $B = D_{z'}/D_{x'}$ is a measure of bias, so that $B = 1$ corresponds to an isotropic medium.

The anisotropy is embodied in two angles, φ and θ, where φ represents a rotation around the z axis while θ is an angle of rotation around the x' axis as illustrated in figure 2. We will use a compact notation for the trigonometric functions by writing $c_\theta = \cos\theta$, $s_\theta = \sin\theta$, and $t_\theta = \tan\theta$. The two coordinate systems are related by a linear transformation $\mathbf{r}' = \mathbf{M}_\theta \mathbf{M}_\varphi \mathbf{r}$ where

$$\mathbf{M}_\theta = \begin{pmatrix} 1 & 0 & 0 \\ 0 & c_\theta & s_\theta \\ 0 & -s_\theta & c_\theta \end{pmatrix}, \; \mathbf{M}_\varphi = \begin{pmatrix} c_\varphi & s_\varphi & 0 \\ -s_\varphi & c_\varphi & 0 \\ 0 & 0 & 1 \end{pmatrix} \tag{15}$$

The diffusion equation, written in skewed coordinates is

$$\frac{\partial p}{\partial \tau} = \nabla' \cdot \mathbf{D} \cdot \nabla' p - \nu\tau \tag{16}$$

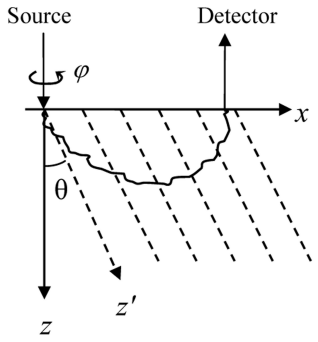

Figure 2: Schematic diagram of an anisotropic system, drawn for simplicity in two dimensions. The optical parameters lie along the dashed lines which are at an angle θ with respect to the z-axis.

which is to be solved subject to the initial condition $\mathbf{r}_0 = (0, 0, z_0)$ in laboratory coordinates or $\mathbf{r}'_0 = (0, z_0 s_\theta, z_0 c_\theta)$ in the skewed coordinates. The solution is also required to satisfy the boundary condition $p(\mathbf{r}; \tau|\mathbf{r}_0) = 0$ at $z = 0$ in laboratory coordinates. By appealing to the rotation matrices in Eq. 15 we find that the plane at $z = 0$ is equivalent to $z' = -y' t_\theta$ in skewed coordinates. The solution to Eq. 16 in free space, i.e., with no boundaries, is

$$\begin{aligned} p^{(F)}(\mathbf{r}'; \tau|\mathbf{r}'_0) &= \frac{1}{(4\pi D_z \tau)^{3/2}} \frac{1}{B^{1/2}} exp[-\frac{1}{4D_z\tau}[(x')^2 + (y' - z_0 s_\theta)^2 \\ &\quad +(z' - z_0 c_\theta^2/B)] - \nu\tau] \end{aligned} \tag{17}$$

To satisfy the boundary condition it is necessary to generalize the method of images by subtracting a function from Eq.17 that satisfies both the diffusion equation and the boundary condition. We therefore propose a solution which is written $p(\mathbf{r}'; \tau|\mathbf{r}'_0) = p^{(F)}(\mathbf{r}'; \tau|\mathbf{r}'_0) - q(\mathbf{r}'; \tau|\mathbf{r}'_0)$ where the function q will be assumed to have the form

$$\begin{aligned} q(\mathbf{r}'; \tau|\mathbf{r}'_0) &= \frac{1}{(4\pi D_z \tau)^{3/2}} \frac{1}{B^{1/2}} \exp\left\{-\frac{1}{4D_z\tau}\left[(x')^2 + (y' - z_0 U)^2 \right.\right. \\ &\quad \left.\left. +(y' t_\theta + z_0 V)^2/B\right] - \nu\tau\right\} \end{aligned} \tag{18}$$

where U and V are constants chosen so that the propagator vanishes on the boundary. Notice that $z_0 U$ and $z_0 V$ can be regarded as the coordinates of image points. After some algebra one finds that U and V can be expressed in terms of the parameter $\Omega = 1 - 1/B$ as

$$U = \frac{s_\theta\left[\Omega(1 + c_\theta^2) - 1\right]}{1 - \Omega s_\theta^2}, \; V = \frac{c_\theta\left[1 + \Omega s_\theta^2\right]}{1 - \Omega s_\theta^2} \tag{19}$$

Although we have written the propagator in terms of skewed coordinates, these are not

directly observable by the experimenter, and must be transformed back into laboratory coordinates using the rotation matrices in Eq.15.

Any information related to optical properties within the tissue is found from the intensity as measured on the planar surface. In the diffusion formulation the intensity at $\mathbf{R} = (X, Y, 0)$ can be calculated in terms of the propagator in skewed coordinates, leading to

$$I(\mathbf{R};\tau) = -D_z(s_\theta \frac{\partial p}{\partial y'} + c_\theta \frac{\partial p}{\partial y'})_{z'=-y't_\theta} \tag{20}$$

Although an exact expression is available, [29], it is quite complicated. However, the expression can be simplified by observing that the scattering length, z_0, is generally small as compared to other lengths that describe the system. With this observation one can write the expression for the intensity in laboratory coordinates as

$$I(\mathbf{R};\tau) \approx z_0 \frac{\exp\left(-\frac{1}{4D_z\tau}\mathbf{RQR}' - \nu\tau\right)}{(4\pi D_z\tau)^{3/2}\left(1 + B\Omega c_\theta^2\right)\tau^{5/2}} \tag{21}$$

where $\mathbf{Q}$ is a symmetric 2×2 matrix, $\mathbf{R}'$ is the transpose of $\mathbf{R}$ and the expression for $\mathbf{RQR}'$ is

$$\mathbf{RQR}' = X^2\left(1 - \Omega s_\theta^2 s_\varphi^2\right) + 2XY\Omega s_\theta^2 c_\varphi s_\varphi + Y^2\left(1 - \Omega s_\theta^2 c_\varphi^2\right) \tag{22}$$

The equation $\mathbf{RQR}' =$ constant is a quadratic form for an ellipse, from whose location and orientation one can derive enough relations from which the optical parameters can be estimated, [29]. Some sample results generated for contours of equal intensity are shown in figure 3.

More recently we have developed a comparable theory for anisotropic diffusion in a slab geometry, [30]. In this work we considered the problem of determining the parameters allowing one to estimate the angles defining the anisotropy, directional bias of diffusive spreading and scattering and absorbing coefficients from data obtained from time-gated measurements of the light transmitted through a slab of thickness L. The proposed model can be solved exactly, the end result being expressed as an infinite series, which although exact, is extremely complicated. However, a physically reasonable approximation, allows us to simplify the result to a considerable degree. As in the case of the semi-infinite model, measured values of the surface intensity are elliptical. In addition to the effects of rotation and change in the eccentricity of the ellipse as a function of the angles θ and φ observed in the semi-infinite model (figure 3) the slab geometry also allows for a shift of the center of the ellipse as a function of slab thickness, L. The parameters of the ellipses suffice to estimate properties of the tissue interior.

2.4 The telegrapher's equation

Another extension of the diffusion equation, first suggested as partially accounting for forward scattering effects by Ishimaru, [31], is the telegraphers equation (TE), [32] which dates back at least to the time of Maxwell, [33]. This equation has the form

$$\frac{\partial^2 p}{\partial t^2} + \frac{1}{T}\frac{\partial p}{\partial t} = c^2\nabla^2 p \tag{23}$$

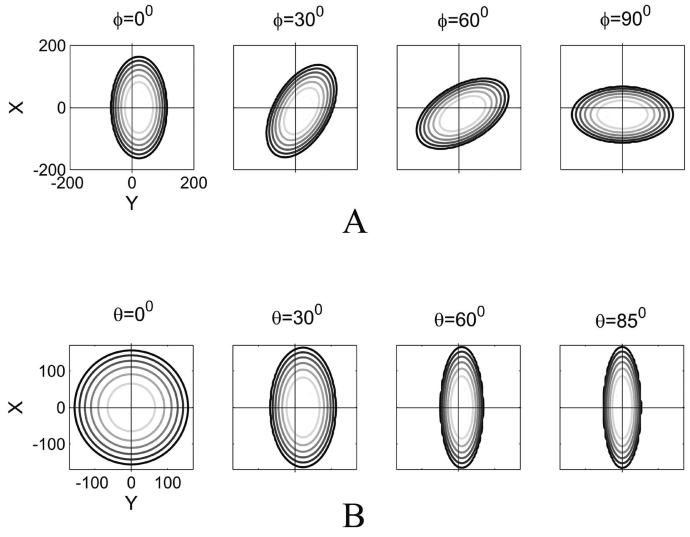

Figure 3: Equi-intensity contours of the logarithmic intensity of the light detected at the surface of a half-infinite anisotropic medium corresponding to an ellipse. The variation in the shades of gray from light to dark corresponds to a change in intensity from strong to weak. a) Rotation of the ellipse as a function of angle φ when the angle θ is held fixed at 30°, $B = 0.1$, $\tau = 10$. b). Change in the eccentricity of the ellipse as a function of θ when $\varphi = 0$, with all other parameter values the same as in figure 1a.

which reduces to the diffusion equation in the limits $T \to 0$, $c^2T \to D$ as well as in the asymptotic limit, $t \to \infty$ for arbitrary values of c and D. The TE can be derived as a first-order term in an expansion of the transport equation in a series by assuming that any single scattering event results in only a small deviation of the trajectory prior to the scattering, [34]. The TE has one advantage over the diffusion equation in that the speed of signal transmission is finite, rather than being infinite. However, there is one difficulty in applying the TE, to wit: rigorous boundary conditions are known only in one dimension, [35]. Even so, the application to optical problems has been pursued with heuristic boundary conditions, e.g., [36]. The resulting theory yields qualitative, but not quantitative, agreement with other properties known to be valid in describing photon transport in turbid media, [37].

2.5 Layered tissues

To this point we have considered tissue models in which the optical properties of tissue are taken to be completely homogeneous. However, there are tissues which are inherently layered, and which require that some account be taken of this layering. Tissues which can have significant amounts of layering are bladder, esophagus, intestine, skin and stomach. One example which has been investigated experimentally by a number of workers relates to measurements of oxygenation of the brain, [38]-[40]. Experiments on the degree to which layered tissues can effect measurements of optical properties of biological tissue have been carried out by many research groups, e.g., [41, 42].

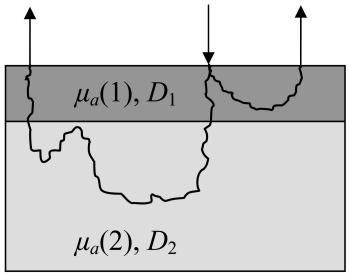

Figure 4: A schematic diagram of a two-layered system.

It is quite straightforward to derive the equations governing reflectance or transilluminination (penetration of photons through a slab), taking into account any number of layers [43, 44]. Very often these are solvable in terms of a combination of Fourier and Laplace transforms, but these are difficult to invert except numerically. Figure 4 is a schematic diagram of a two layer system in which the optical properties in both strata are assumed to be isotropic. Several aspects of such configurations have been investigated. One of these relates to estimating the thickness of the uppermost of the two layers in terms of data obtained from CW reflectance measurements on a semi-infinite model tissue. A motivation for this specific problem is, for example, that of estimating the thickness of a melanoma, or

of a layer of burn tissue. This was first investigated by Nossal et al, [45] who formulated the problem in terms of a lattice random walk requiring a numerical solution.

However, the problem can equally well be formulated in terms of a diffusion model, [46]. The original model made the fortuitous assumption that the scattering coefficients in the two layers were equal but had different absorption coefficients. This assumption was also made in formulating the diffusion model. The main assumption is that the two diffusion constants are equal, $D_1 = D_2 = D$. The diffusion equation in each of the strata is just that given in Eq. 1, supplemented by formulae that connect the propagators in each stratum, p_1 and p_2, as well as the fluxes at the interface $z = L$. These require that the two propagators and fluxes be equal at the break point $z = L$. More exactly, if n_i is the index of refraction in stratum i then the propagators were assumed to satisfy

$$\frac{p_1(\rho, L; t)}{p_2(\rho, L; t)} = \left(\frac{n_1}{n_2}\right)^2 \approx 1 \tag{24}$$

since the index of refraction of a number of tissues is generally within a few percent of 1.4, [47]. The surface intensity is identified with the flux as in Eq. 5. If the two layers have absorption coefficients $\mu_a(i)$ $i = 1, 2$ it was found that when $\mu_a(1) > \mu_a(2)$ the curves of $\log[\rho I(\rho)]$ separate into uniformly spaced lines as indicated in figure 5 thereby providing a tool for estimating the width L. When the converse holds, this uniformity of layer separation no longer holds and there seem to be no qualitative differences between the curves of $\log[\rho I(\rho)]$ for different L. These results followed from the simulations, a heuristic argument, [48], and a diffusion equation analysis, [46]. It has also been recently shown that the qualitative separation as a function of L of $\log[\rho I(\rho)]$ depends crucially on the assumption that the diffusion constants in the two strata are equal, [49].

A very careful and detailed investigation of a multilayered model of photon diffusion in skin was made by Schmitt et al, [50], who also studied factors influencing the estimation of the scattering and absorption coefficients in the two layers. They used a diffusion model taking into account the finite (circular) dimensions of the source and detector. Results of the analysis were checked experimentally by means of phantoms. These proved to be in very good agreement with the theoretical predictions. While it is not difficult to solve the n-layer diffusion problem in terms of transforms, the inversion taking these results back into space and time is computationally demanding as mentioned earlier. Hence large numbers of studies of this more general class of problems have been carried out by simulation methods. An interesting variant of the 2-layer model has been used to estimate the absorption and scattering coefficients and the width of the upper layer, [51]. The analysis was based on frequency-domain reflectance, which we will not discuss in the present paper. Of course the accuracy of the estimates depends on the number of parameters that are dealt with, so that the analysis may be problematic when five parameters are to be estimated. A slightly less general investigation was described based on time-resolved reflectance in which the width of the upper layer was assumed known by Kienle and his collaborators, [52]. Their study was based on a diffusion model, and the results were verified using phantoms.

Diffusion models are convenient for studying problems in which optical properties of tissue are either homogeneous or close to homogeneous. They are not generally useful

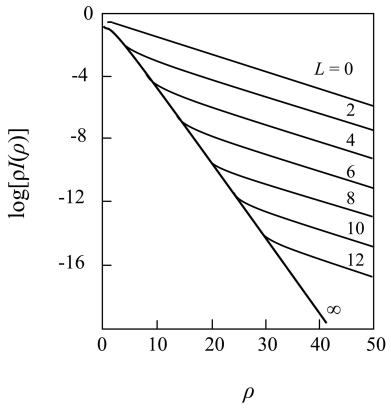

Figure 5: Layered tissue : typical curves of $\log[\rho \cdot I(\rho)]$ illustrating the separation due to changing the width of the upper layer. The absorptivities used to generate the curves were $\mu_{\rm a}(1) = 0.2$ and $\mu_{\rm a}(2) = 0.01$. The data were generated using the exact enumeration method.

when, for example, there are small inclusions in the tissue, which is certainly a significant class of models in the context of optical imaging schemes. Some progress can be made in attacking these problems through the use of perturbation schemes, as in [53], but the majority of problems which cannot easily be formulated in terms of perturbations, are otherwise extremely difficult. In the problems reviewed in this section, the boundaries have always been assumed to be planar. However, this is not generally true when there are tissue inclusions. However, there are solvable models that can be formulated in terms of random walks that incorporate the effects of inclusions, e.g., [54].

Finally, a major defect of diffusion modelling is that it cannot be accurate at very short times because at those times there will not have been enough scattering events to validate the implicit use of the central-limit theorem. On the other hand, the short-time regime is most likely to provide accurate information because the perturbation of photon trajectories are the least affected by scattering events. In this regime in time, a description of photon trajectories requires the solution of a full transport equation which generally can only be done numerically. In consequence, problems related to parameter estimation from data at short times pose severe problems.

3 Lattice random walk models

3.1 The lattice propagator

In this section we briefly discuss one approach to characterizing the region explored by a photon, basing our analysis on lattice random walks as opposed to the diffusion analysis in

the last section. The utility of lattice random walks is that very often they can be solved in closed form in terms of generating functions rather than by more complicated analytical tools that involve the solution of a diffusion equation. A second reason for dealing with this class of models is suggested by the general problem of estimating the region interrogated by photons in the course of optical measurements. This is important both in imaging and in applications of photodynamic therapy. As already stated, this is not a well-defined problem in a continuum since photons are point particles, which rules out the use of a volume to characterize what one means by the term "region". However, a natural definition is available in the framework of the lattice random walk, namely, the number of distinct sites visited by an n-step random walk (or the number of distinct sites visited in time t when time is continuous).

Properties of lattice random walks are, in many aspects, closely related to those based on diffusion theory. For example, early techniques for solving diffusion equations numerically replaced the continuum by a lattice and allowed the investigator to solve the resulting set of differential equations defined on points of the lattice. This is equivalent to solving the problem of a random walk on the set of lattice points. A random walk is simply a sum of random variables each of which represents the magnitude and direction of a single step. This identification together with the central-limit theorem leads us to the expectation that many photon migration problems are solvable in the framework of random walks or diffusion theory. In the former it is necessary to pass to the limit of zero spacing of the lattice points to bring the two solutions into coincidence. However, there is a class of problems not easily formulated in terms of a diffusion model which can be phrased perfectly sensibly in terms of random walks. Briefly stated, these are problems in which one can enumerate a set of configurations on a lattice where there is no continuum formulation or where an analytic solution to the continuum formulation is otherwise extremely difficult to derive.

In all applications of random walk formalism to optical problems to date, the structure is assumed to be a simple cubic lattice, in which the lattice point is assumed to consist of a vector of integers (figure 6). The dimensionless coordinate can be converted to the physical coordinate, $\mathbf{r}_{\rm ph}$, by the relation $\mathbf{r}_{\rm ph} = \mathbf{r}\sqrt{2}/\mu_s'$ as follows from an argument given in [55]. There are two formulations of the random walk model. In the first, time is measured in discrete units, so that a propagator is denoted by $p_n(\mathbf{r}|\mathbf{r}_0)$ which is the probability that a random walker, initially at $\mathbf{r}_0$, is found at $\mathbf{r}$ after n steps have been made. Thus, the units of time are uniformly spaced. In the CTRW the units of time are continuous and the times between two successive steps are random variables. We do not discuss the CTRW model in this article except to note that with suitably defined transition probabilities and probability density of the jump time it is possible to derive an exact solution for the propagator, [56].

The formalism in both cases is based on an exact integral representation of the propagator. We start from the discrete random walk in which $p(\mathbf{j})$ is the probability that the displacement of the random walker in a single step is equal to **j**. We further define a generating function $\hat{p}(\theta)$ as

$$\hat{p}(\theta) = \sum_{\mathbf{j}} p(\mathbf{j}) e^{i\mathbf{j}\cdot\theta} \tag{25}$$

where the sum is taken over all lattice points. When the steps of the random walk are

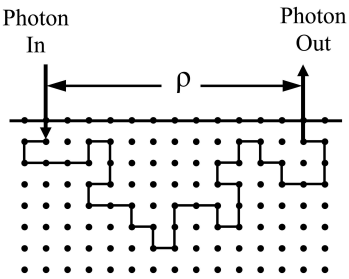

Figure 6: Lattice random walk

independent random variables the propagator in free space can be written

$$p_n^{(F)}(\mathbf{r}|\mathbf{r}_0) = \frac{1}{(2\pi)^3}\iiint_{-\pi}^{\pi} \hat{p}^n(\theta) e^{-i(\mathbf{r}-\mathbf{r}_0)\cdot\theta} d\theta_1\, d\theta_2\, d\theta_3 \tag{26}$$

When a constraint exists, such as an absorbing or reflecting plane, the expression for the propagator must be modified to incorporate effects of the constraint. As an example, consider a nearest-neighbor random walk in the presence of an absorbing boundary at $z = 0$. By a nearest-neighbor random walk we mean one in which a random walker can only make one of the six steps $(x, y, z) \rightarrow (x \pm 1, y \pm 1, z \pm 1)$. If the random walk is isotropic so that the probability of any single step is 1/6, the photons emitted at a surface point $(X, Y, 0)$ at step n is $p_{n-1}(X, Y, 1|\mathbf{r}_0)/6$, i.e., a probability rather than a flux, or a derivative, as is natural in continuum diffusion. There is some experimental evidence to indicate that using the concentration near the surface as an absorbing boundary condition leads to more accurate results in calculating the surface intensity than the use of the continuum flux, [58].

3.2 The generating function

As will be seen later, the generating function formed from the set of propagators plays an important role in applications. The generating function with respect to step number, n, is defined by

$$\hat{p}_\xi(\mathbf{r}|\mathbf{r}_0) = \sum_{n=0}^{\infty} p_n(\mathbf{r}|\mathbf{r}_0)\xi^n = \frac{1}{(2\pi)^3}\iiint_{-\pi}^{\pi} \frac{e^{-i(\mathbf{r}-\mathbf{r}_0)\cdot\theta}}{1-\xi\hat{p}(\theta)} d\theta_1\, d\theta_2\, d\theta_3 \tag{27}$$

found directly from Eq. 26. Many asymptotic properties (e.g., the behavior of $p_n(\mathbf{r}|\mathbf{r}_0)$ at large n) can be found by the application of the formalism of Abelian and Tauberian theorems to the generating function, [57]. These relate the (small, large)-n behavior of $p_n(\mathbf{r}|\mathbf{r}_0)$ to the (large, small)-ξ behavior of $\hat{p}_\xi(\mathbf{r}|\mathbf{r}_0)$. A second important function in applications is the first-passage time, $f_n(\mathbf{r}|\mathbf{r}_0)$, which is the probability that a random walker, initially at $\mathbf{r}_0$, arrives at $\mathbf{r}$ for the first time at step n, never having reached that point before step n.

Again, for simplicity, we restrict ourselves to a random walk in free space, and show that the generating function for the f 's can be expressed in terms of the generating function for the p's. Let **s** be the target point. We may then express the relations between the two sets of functions in the step-number domain as

$$p_n(\mathbf{s}|\mathbf{r}_0) = \delta_{n,0}\delta_{\mathbf{s},\mathbf{r}_0} + \sum_{j=1}^{n} f_j(\mathbf{s}|\mathbf{r}_0)p_{n-j}(\mathbf{s}|\mathbf{s}) \tag{28}$$

This is derived by noting that a random walker arriving at **s** at step n either have been there initially, or arrived there at step $j \geq 1$, and arrived there again after $n - j$ steps. Since this equation is in the form of a discrete convolution, forming the generating function of both sides and solving for $\hat{f}_\xi(\mathbf{s}|\mathbf{r}_0)$ from the resulting equation leads us to

$$\hat{f}_\xi(\mathbf{s}|\mathbf{r}_0) = \frac{\hat{p}_\xi(\mathbf{s}|\mathbf{r}_0) - \delta_{\mathbf{s},\mathbf{r}_0}}{\hat{p}_\xi(\mathbf{s}|\mathbf{s})} \tag{29}$$

A function that embodies the notion of the region visited by a photon, can be modeled in terms of a lattice random walk. This is the number of distinct sites visited by a random walk constrained to be absorbed on the surface at a specific site at step n. The distinct number of sites visited in n steps is a random variable, the calculation of whose properties generally presents extremely difficult mathematical problems, [59]. However, it has been known for at least forty years that the generating function of the first moment is relatively simple to calculate, and, by means of a Tauberian theorem, furnishes large-n asymptotics. We describe this calculation for a semi-infinite medium and a random walker initially at $\mathbf{r}_0 = (0, 0, 1)$ which is constrained to reach $\mathbf{R} = (X, Y, 0)$ at step n, [60].

Let $\langle N_n(\mathbf{R}|\mathbf{r}_0)\rangle$ be the expected number of distinct sites visited by the random walker before reaching the surface at $\mathbf{R}$, conditional on the random walker reaching that site at step n. The joint probability that site **r** has been visited at time $n' \leq n$ and that it is later absorbed at step n will be denoted by $Q_n(\mathbf{r}|\mathbf{r}_0)$. The function of interest, $\langle N_n(\mathbf{R}|\mathbf{r}_0)\rangle$, is related to $Q_n(\mathbf{r}|\mathbf{r}_0)$ by

$$\langle N_n(\mathbf{R}|\mathbf{r}_0)\rangle = \frac{\sum_{\mathbf{r}} Q_n(\mathbf{r}|\mathbf{r}_0)}{p_n(\mathbf{R}|\mathbf{r}_0)} \tag{30}$$

The function $Q_n(\mathbf{r}|\mathbf{r}_0)$ can, in turn, be expressed in terms of the first-passage time probabilities as

$$Q_n(\mathbf{r}|\mathbf{r}_0) = \sum_{l=0}^{n} f_l(\mathbf{r}|\mathbf{r}_0)p_{n-l}(\mathbf{R}|\mathbf{r}) \tag{31}$$

since the random walker first moves from its initial position to **r** in l steps and from that point to its final destination **R** in the remaining $n - l$ steps. Since $Q_n(\mathbf{r}|\mathbf{r}_0)$ is seen to be a convolution, its generating function, $\hat{Q}_\xi(\mathbf{r}|\mathbf{r}_0)$, is a product, $\hat{Q}_\xi(\mathbf{r}|\mathbf{r}_0) = \hat{f}_\xi(\mathbf{r}|\mathbf{r}_0)\hat{p}_\xi(\mathbf{R}|\mathbf{r})$. But, $\hat{f}_\xi(\mathbf{r}|\mathbf{r}_0)$ satisfies the relation in Eq. 29 so that

$$\hat{N}_\xi(\mathbf{R}|\mathbf{r}_0) = \frac{\hat{p}_\xi(\mathbf{r}|\mathbf{r}_0)\hat{p}_\xi(\mathbf{R}|\mathbf{r})}{\hat{p}_\xi(\mathbf{r}|\mathbf{r})} \tag{32}$$

Consider first the denominator of the last expression. This will be expressed in terms of the generating function for the free-space propagator. The method of images allows us to write $\hat{p}_\xi(\mathbf{r}|\mathbf{r}) = \hat{p}_\xi^{(F)}(0,0,0) - \hat{p}_\xi^{(F)}(0,0,2z_0)$. Further, since $\hat{p}_\xi^{(F)}(0,0,2z_0)$ decreases monotonically with z_0 , we will approximate to $\hat{p}_\xi(\mathbf{r}|\mathbf{r})$ by dropping $\hat{p}_\xi^{(F)}(0,0,2z_0)$ in comparison with $\hat{p}_\xi^{(F)}(0,0,0)$. The validity of this approximation has been checked numerically for a solvable model, [60], and also leads to final results in good agreement with simulated data. The mathematical advantage gained from this approximation is that there is no longer an $\mathbf{r}$ -dependent term in the denominator of Eq. 32.

The final step in the calculation is to sum over all $\mathbf{r}$. For this purpose we note the identity

$$p_n(\mathbf{R}|\mathbf{r}_0) = \sum_{\mathbf{r}} p_{n'}(\mathbf{R}|\mathbf{r}) p_{n-n'}(\mathbf{r}|\mathbf{r}_0) \tag{33}$$

Thus an approximate expression for the expected number of distinct sites visited in n steps is

$$\langle N_n(\mathbf{R}|\mathbf{r}_0)\rangle \approx n/\hat{p}_\xi^{(F)}(0,0,0) \tag{34}$$

which is exactly the asymptotic result for a random walk in free space, [9, 10]. This was checked for 30,000 replications of two random walks, one starting from $z_0 = 10$ and one from $z_0 = 15$. In both cases the slope estimated from simulated data agreed with the prediction in Eq.34 to within 2%. While this result might appear to be surprising, it is due to the fact that random walkers initially near the origin tend to be trapped quite rapidly, while Eq 34 requires that n be large.

4 Concluding remarks

We have seen that the analysis of optical methods in biomedical applications requires the consideration of many different forms of diffusion theory as well as the theory of random walks. The present article has only skimmed the surface of a rich collection of problems, at least some of them unsolvable using presently available analytical techniques. For a much wider sampling of these problems the reader is directed to the Proceedings of meetings of the SPIE which appear yearly. The currently most pressing problem in the area of photon diffusion is that of developing a theory valid at short times during which photon trajectories tend to be least affected by scattering events.

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References

[1] A. Einstein, Ann. Phys. (Leipzig) **17**, 549 (1905).
[2] M. von Smoluchowskii, Ann. Phys. (Leipzig) **21**, 756 (1906).
[3] A. Yodh and B. Chance, Phys. Today, **48**, 34 (1995).
[4] M. Cutler, Surg. Gynec. Obstet. **48**, 721 (1929).
[5] J.C. Hebden, S.R. Arridge and D.T. Delpy, Phys. Med. Biol. **42**, 925 (1997).
[6] A.P. Gibbson, J.C. Hebden and S.R. Arridge, Phys. Med. Biol. **50**, R1 (2005).
[7] S.R. Arridge and J.C. Hebden, Phys. Med. Biol. **42**, 841 (1997).
[8] M.C.W. van Rossum and Th.M. Nieuwenhuizen, Rev. Mod. Phys. **71**, 313 (1999).
[9] G.H. Weiss, *Aspects and Applications of the Random Walk* (North-Holland, Amsterdam, 1994).
[10] B.D. Hughes, *Random Walks and Random Environments.* vol. 1 (Clarendon Press-Oxford, 1995).
[11] J. Rudnick and G. Gaspari, *Elements of the Random Walk* (Cambridge University Press, Cambridge, UK, 2004).
[12] W. Feller, *An Introduction to Probability Theory and its Applications.* vol. 1, 3'rd ed. (John Wiley, New York, 1968).
[13] D.A. Benaron, W. Cheong and D.K. Stevenson, Science, **276**, 2002 (1997).
[14] G.J. Tearney, M.E. Brezinski, B.E. Bouma, S.A. Boppart, C. Pitris, J.F. Southern and J.G. Fujimoto, Science **276**, 2037 (1997).
[15] B.C. Wilson in *Optical-Thermal Response of Laser-irradiated Tissue* ed. A.J. Welch and M.J.C. Gemert (Plenum, New York, 1995) p.233: W.-F. Cheong, *ibid*, p.275.
[16] R. Aronson and N. Corngold, J. Opt. Soc. Am. A **14**, 1066 (1999).
[17] R. Elaloufi, R. Carminati and J-J. Greffet, J. Opt. Soc. Am. **20**, 678 (2003).
[18] P.M. Morse and H. Feshbach, *Methods of Theoretical Physics*, vol. 1 (McGraw-Hill, New York, 1953).
[19] I. Freund, Phys. Rev. A **45**, 8854 (1992).
[20] D. ben-Avraham, H. Taitelbaum and G.H. Weiss, Lasers in the Life Sciences, **4**, 29 (1991).
[21] R.F. Bonner, R. Nossal, S. Havlin and G.H. Weiss, J. Opt. Soc. Am. **4** A, 423 (1987).
[22] S. Karlin and H.M. Karlin, *A Second Course in Stochastic Processes* (Academic Press, New York, 1981).
[23] G.H. Weiss, R. Nossal and R.F. Bonner, J. Mod. Opt. **36**, 349 (1989).
[24] D.J. Bicout and G.H. Weiss, Opt. Comm. **158**, 213 (1998).
[25] S. Nickell, M. Herman, M. Ehrenpreis, T.J. Farrell, U. Krämer and M.S. Patterson, Phys. Med. Biol. **45**, 2873 (2000).
[26] A. Kienle, F.K. Forster, R. Diebolder and R. Hibst, Phys. Med. Biol. **48**, N7 (2003).
[27] J. Heino, S. Arridge and E. Sommersalo, Tech. Dig. OSA Biomed. Top. Mtgs. 18 (2002).
[28] L. Dagdug, G.H. Weiss and A.H. Gandjbakhche, Phys. Med. Biol. **48**, 1361 (2003).

[29] O.K. Dudko, G.H. Weiss, V. Chernomordik and A.H. Gandjbakhche, Phys. Med. Biol. **49**, 3979 (2004).
[30] O.K. Dudko and G.H. Weiss, Biophys. J. **88**, (2005).
[31] A.J. Ishimaru, Appl. Opt. **28**, 2210 (1989).
[32] G.H. Weiss, Physica A **311**, 381 (2002).
[33] J.C. Maxwell, Trans. Royal Soc. Lond. **157**, 49 (1867).
[34] A.J. Ishimaru, J. Opt. Soc. Am. **68**, 1045 (1978).
[35] J. Masoliver, J.M. Porrà and G.H. Weiss, Phys. Rev. E **48**, 939 (1993).
[36] D.J. Durian and J. Rudnick, J. Opt. Soc. Am. A **14**, 235 (1997).
[37] J.M. Porrà, J. Masoliver and G.H. Weiss, Phys. Rev. E **55** 7771 (1997).
[38] F.F. Jöbsis, Science **19**, 1264 (1977).
[39] B. Chance, J.S. Leigh, H. Miyaka, D.S. Smith, D.S. Niola, P. Greenfeld, M. Finander, K. Kaufman, W. Levy, M. Young, P. Cohen, P. Yoshioka and R. Boretsky, Proc. Natl. Acad. Sci. USA **85**, 4971 (1988).
[40] D.A. Benaron, W.E. Benitz, R.L. Ariagno and D.K. Stevenson, Clin. Pediatr. **31**, 258 (1992).
[41] S. Homma, T. Fukunaga and A. Kagaya, J. Biomed. Opt. **1**, 418 (1996).
[42] K. Yamamoto, M. Niwayama, T. Shiga, L. Lin, N. Kudo and K. Shimizu. in *Selected Proceedings from the International Symposium on Non-invasive Optical Diagnosis*, 37 (1996).
[43] S. Takatani and M.D. Graham, Trans. Biomed. Eng. **26**, 656 (1979).
[44] M. Keijzer, W.M. Star and P.R.M. Storchi, Appl. Opt. **27**, 1820 (1988).
[45] R. Nossal, J.E. Kiefer, G.H. Weiss, R.F. Bonner, H. Taitelbaum and S. Havlin, Appl. Opt. **27**, 3382 (1988).
[46] I. Dayan, S. Havlin and G.H. Weiss, J. Mod. Opt. **39**, 1567 (1992).
[47] F.P. Bolin, I.E. Preuss, R.C. Taylor and R.J. Ference, Appl. Opt. **28**, 2297 (1989).
[48] H. Taitelbaum, S. Havlin and G.H. Weiss, Appl. Opt. **28**, 2245 (1989).
[49] M. Dishon, H. Taitelbaum and G.H. Weiss, J. Mod. Opt. **50**, 2727 (2003).
[50] J.M. Schmitt, G.X. Zhou, E.C. Walker and R.T. Wall, J. Opt. Soc. Am. **7**, 2141 (1990).
[51] T.H. Pham, T. Spott, L.O. Svaasand and B.J. Tromberg, Appl. Opt. **39**, 4733 (2000).
[52] A. Kienle, T. Glanzmann, G. Wagnières and H. van den Bergh, Appl. Opt. **37**, 6852 (1998).
[53] S. De Nicola, R. Esposito, M. Lepore and P.L. Indovina, Phys. Rev. E **69**, 031901 (2004).
[54] A.H. Gandjbakhche, R.F. Bonner, R. Nossal and G.H. Weiss Appl. Opt. **35**, 1767 (1996).
[55] A.H. Gandjbakhche, R.F. Bonner and R. Nossal, J. Stat. Phys. **69**, 35 (1992).
[56] G.H. Weiss, J.M. Porrà and J. Masoliver, Opt. Comm. **146**, 268 (1998).
[57] A.I. Saichev and W.A. Woyczyński, *Distributions in the Physical and Engineering Sciences*, vol. 1 (Birkhäuser, Boston, 1997).
[58] B.B. Das, F. Liu and R.R. Alfano, Rep. Prog. in Phys. **60**, 227 (1997).

[59] F. den Hollander and G.H. Weiss, in *Contemporary Problems in Statistical Physics*, ed. G.H. Weiss (SIAM, Philadelphia, 1994).
[60] L. Dagdug, A.M. Berezhkovskii and G.H. Weiss, Phys. Rev. E **66**, 012901 (2002).