Light Propagation through Biological Tissue and Other Diffusive Media: Theory, Solutions, and Validations

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and Other Diffusive Media

THEORY, SOLUTIONS, AND VALIDATION

SECOND EDITION

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To our families

"We shall not cease from exploration and the end of our exploring will be to arrive where we started and know the place for the first time."

T. S. Eliot

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Tiziano Binzoni

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List of Acronyms

Acronym	Description
CW	Continuous wave
DA	Diffusion approximation
DE	Diffusion equation
DOT	Diffuse optical tomography
EBC	Extrapolated boundary condition
EBPC	Extrapolated boundary partial current
FD	Frequency-domain
FWHM	Full width half maximum
GRTE	Generalized radiative transfer equation
HG	Henyey and Greenstein
MC	Monte Carlo
NIRS	Near infrared spectroscopy
PCBC	Partial current boundary condition
pdf	Probability density function (or probability distribution function)
RR	Russian roulette
RTE	Radiative transfer equation
SAA	Small angle approximation
TCSPC	Time correlated single photon counting
TD	Time-domain
TE	Telegrapher equation
TPSF	Temporal point spread function
TR	Time-resolved
ZBC	Zero boundary condition

List of Symbols

Warning: In a few exceptional cases, a symbol may temporarily acquire a second meaning, different than the one presented in the following tables. However, the context of its utilization eliminates any possible misunderstanding.

Mathematical conventions

Notation	Description
$d\aleph$	Differential of $\aleph$
$\aleph_G$	$\aleph$ is a Green's function
$\langle\aleph\rangle$	Mean value of $\aleph$
$\langle\aleph^n\rangle$	n^{th}-order moment of $\aleph$
$\delta\aleph$	Small perturbation of $\aleph$
$\hat{\aleph}$	$\aleph$ is a unit vector
(x, y, z)	Cartesian coordinates
(ρ, θ, z)	Cylindrical coordinates
(ρ, θ, ψ)	Spherical coordinates

Special symbols

Notation	Description
	Supplemental materials

Latin-based

Notation	Description
a	Radius of the sphere
a'	Extrapolated radius of the sphere
A	Coefficient for the extrapolated boundary condition
c	Speed of light in vacuum
$\langle d_k^2\rangle$	Mean square distance from the source after k scattering events
E	Energy
V	Volume, domain
$\mathcal{P}$	Power
D	Diffusion coefficient

(*continued*)

Latin-based Notation	Description
E_2, E_3, E_4	Coefficients for the boundary condition between two diffusive media
$f_1(\theta)$, $f_2(\varphi)$, $f_3(z)$	Probability distribution functions for the photon's scattering
$\mathcal{F}$	Fourier transform
F	Cumulative probability function
$F(\theta_e)$	Angular dependence of the outgoing radiance
g	Asymmetry factor
G	Green's function
h	Planck's constant
$\mathcal{H}$	Hankel transform
I	Radiance or specific intensity
I_n	Modified Bessel function of order n
$\vec{J}$	Flux vector
J_n	Bessel functions of order n
K_n	Modified Bessel function of order n
$\langle k \rangle$	Mean number of scattering events undergone by photons
$\mathcal{L}$	Laplace transform
$l_{\max}$	Maximum length of a photon trajectory
$\ell_s = 1/\mu_s$	Scattering mean free path
$\ell_a = 1/\mu_a$	Absorption mean free path
$\ell_t = 1/\mu_t$	Extinction mean free path
$\ell' = 1/\mu'_s$	Transport mean free path
$\langle l \rangle$	Mean pathlength of photons
$\langle l_R \rangle$	Mean pathlength for the total reflectance
$\langle l_T \rangle$	Mean pathlength for the total transmittance
L_x, L_y, L_z	Dimensions for the parallelepiped
L	Radius of the cylinder
L'	Extrapolated radius of the cylinder
n	Refractive index
n_i	Refractive index of the diffusive medium
n_e	Refractive index of the external medium
n_r	Relative refractive index
N	Particle concentration
N_{ln}	Normalizing factor for the two-layer cylinder solution
$p(\theta)$	Scattering phase function (also called phase function)
$p(z)$	Penetration depth of photons
P	Impinging power of a light beam or detected power
P_n	Legendre polynomials
$Q_a = C_a/C_g$	Absorption efficiency
$Q_s = C_s/C_g$	Scattering efficiency

(*continued*)

Latin-based Notation	Description
$Q_s' = Q_s(1-g)$	Reduced scattering efficiency
r	Radius of particles
$\vec{r}$	Position of the receiver
$\vec{r}_0$	Position of the source
$\vec{r}_2$	Position of the inhomogeneity
$\vec{r}_3$	Position of the detector
$\vec{r}_m^{\,+}, \vec{r}_m^{\,-}$	Sources positions with the method of images for the slab
$\vec{r}_s$	Position vector (x_s, y_s, z_s) of the real source
$\vec{r}\,'$	Position of the source
R	Reflectance
R_F	Fresnel reflection coefficient for unpolarized light
s	Thickness of the slab
$\hat{s}$	Direction of observation of radiance
S^{virt}	Virtual source term
t	Current observation time
t'	Emission time of the source
$\langle t \rangle$	Mean time of flight of photons
$\langle t^n \rangle$	n^{th}-order moment
t_0	Time of flight for ballistic photons
$\langle t_i \rangle$	Mean time of flight spent inside a layer i
T	Transmittance
u	Energy density
v	Speed of light inside the medium
w_{mp}	Contribution to the TPSF of the m^{th} trajectory
$x = 2\pi r/\lambda$	Size parameter
$\langle x_k \rangle, \langle y_k \rangle, \langle z_k \rangle$	Mean photon's coordinates after k scattering events
$Z_e = 2AD$	Extrapolated distance
$Z_{\max}$	Maximum penetration depth
$Z_{\max,i}$	Maximum penetration depth of the trajectory i
$\bar{z}_{\max}$	Average penetration depth
$\bar{z}_{\max,i}$	Average penetration depth of the trajectory i
z_0	Light source position at depth $1/\mu_s'$ along the z axis.
z_s	Light source position along the z axis

Greek-based Notation	Description
α	Angular range of the field of view of the receiver
β_m	Positive roots of the equation $J_m(\beta_m L') = 0$
Γ	Gamma function

(*continued*)

Greek-based Notation	Description
$\delta\Phi = \Phi^{\mathrm{pert}} - \Phi^0$	Perturbation for the fluence rate
$\delta\Phi^a$	Absorption perturbation for the fluence rate
$\delta\Phi^D$	Scattering perturbation for the fluence rate
δR^a	Absorption perturbation for the reflectance
δR^D	Scattering perturbation for the reflectance
δT^a	Absorption perturbation for the transmittance
δT^D	Scattering perturbation for the transmittance
∂V	External physical boundary of a domain V
ϵ	Infinitesimal real value
ε	Source term of the radiative transfer equation
ε_0	Source term of the diffusion equation
θ	Polar angle
$\Theta(x)$	Step function (0 for $x < 0$ and 1 for $x \geq 0$)
λ	Wavelength
Λ	Single-scattering albedo
λ_n	Eigenvalues
$\mu = \cos(\theta)$	Cosine of the scattering angle θ
μ_a	Absorption coefficient
μ_s	Scattering coefficient
$\mu_t = \mu_a + \mu_s$	Extinction coefficient
$\mu_s' = \mu_s(1 - g)$	Reduced scattering coefficient
μ_{eff}	Effective attenuation coefficient
ξ_n	Eigenfunctions
ρ	Distance of the receiver from the pencil light beam
ρ_v	Volume fraction of particles
σ	Standard deviation
$\bar{\sigma}$	Standard error
σ_a	Absorption cross-section
σ_s	Scattering cross-section
σ_g	Geometrical cross-section
Σ	Area, surface
Σ	Cross-section of the light beam
τ	Optical thickness or decay time
φ	Azimuthal angle
Φ	Fluence rate
Φ^0	Unperturbed fluence rate
Φ^{pert}	Perturbed fluence rate
Ω	Solid angle
Ω_d	Acceptance solid angle of the detection system

Preface

This manual is intended as an in-depth introduction to light propagation through biological tissues and diffusive media. After having treated the general theory of light diffusion and its physical and biological interpretation, the text presents the derivation of tens of already reported and newly derived analytical and/or semi-analytical solutions. These solutions are "ready to use" and represent the most employed algorithms appearing in tissue optics and related fields, where light is used to probe the optical and/or biological properties of diffusive media. By studying these examples, the readers should be able to directly apply the solutions to real laboratory problems or to develop their own specific solutions.

In a dedicated part of the manual, the solutions are tested against "gold standard" reference data, and their domain of validity is carefully discussed. This part also serves as a tutorial explaining how to generate suitable reference data and how to test new algorithms obtained, e.g., by the reader.

The text is particularly well suited for skilled master students but also for advanced scientists searching for rapid solutions, eliminating the problem of repeating cumbersome calculations in diffusive optics, and bypassing the need to search among hundreds of published papers.

Thus, to summarize, the present manual offers: **I**) A general introduction to the theory of photon migration; **II**) Ready-to-use analytical and/or semi-analytical solutions, derived from the general theory of photon migration, associated with problems typically encountered in biomedical optics and related domains; **III**) A validation of the proposed solutions by means of comparisons with Monte Carlo (MC) simulations; **IV**) A tutorial software package, implementing the most representative analytical and semi-analytical solutions of the manual (see supplemental material 🔗) and **V**) A set of pre-calculated MC data serving as a gold-standard reference and allowing the reader to personally check the presented exact/approximated solutions (see 🔗).

New to this edition

The manual is a completely revised version of the former published book titled *Light Propagation through Biological Tissue and other Diffusive Media: Theory, Solutions and Software*.[1] The new text wants to get closer to the novelties of the theoretical modeling in photon transport that have appeared in recent years, thus putting the reader in the ideal conditions to comprehend the recent evolution of the theoretical modeling techniques. For this reason, together with an in-depth revision and expansion of the old chapters, eight new chapters have been included, covering new solutions and new aspects of the theory.

Theoretical Background

A simplifying hypothesis

The theoretical background of this book is the general theory of photon transport. The propagation of light through turbid media (i.e., media with scattering and absorption properties) can be accurately described in the mesoscopic and macroscopic scales with the radiative transfer equation (RTE). The RTE is a complex integro-differential equation of which analytical solutions are available for some geometries of practical interest.[2] Such solutions usually suffer from longer computation times and higher complexity compared to the solutions of other approximated theories such as the diffusion equation (DE). The DE is obtained from the RTE by making some simplifying assumptions. Compared to the solutions obtained with the RTE, the solutions derived from the DE, for the same problem, are certainly more efficient but may be approximated. For this reason, for each application in which the DE solutions are used, it is necessary to check their accuracy to ensure that the approximations are sufficiently small. This check can be performed by comparing the approximate solutions against the correspondent reference solutions obtained with the RTE (usually solved by the "gold standard" MC methods).

Why then the diffusion equation?

At this point, the obvious question remains: why to adopt the DE instead of an exact RTE? Diffusive media are turbid media for which the solutions of the DE provide a sufficiently accurate description of light propagation. Through these media, photons propagate in a diffusive regime. In fact, the paths followed by these photons, migrating, e.g., from a source to a detector, look like a random walk (zigzag trajectory). Thus, when these photons undergo a sufficiently high number of scattering events (generating the zigzag trajectory), we obtain a diffusive regime. The important point here is that in daily life we can find a long list of media for which a diffusive regime of propagation can be assumed. This list includes, for example, highly scattering media such as biological tissues, agricultural products, wood, paper, plastic materials, sugar, salt, and milk, for which the diffusive regime can be reached even when the volume of the medium is smaller than a cubic centimeter. The list can also include slightly scattering media, such as clouds of gas and dust in the interstellar medium; in these cases, an extremely large volume is necessary to obtain the diffusive regime. This book is devoted to the study of light propagation through scattering media with a special emphasis on biological tissues and diffusive media. This is the reason why the DE becomes of fundamental interest. Moreover, the diffusive regime of light propagation is a reference and limit regime under which forward solvers can be obtained with extraordinary simplified characteristics. We will see that the above described limits of the DE actually represent its main advantages, which can be fruitfully used in applied science.

Why present solutions in the time domain?

In our study we have given special emphasis to studying light propagation in the time domain,[3] i.e., providing solutions of the DE for a temporal Dirac delta source, and this fact requires a comment. This choice is motivated by the fact that this domain of analysis is widely spread in many applications where short-pulsed laser sources are used. However, the literature includes commonly used solutions in other transformed domains such as the temporal-frequency and spatial-frequency Fourier domains[4,5] where temporal and spatial modulated sources are used. It is important to note that solutions in other transformed domains, such as the temporal-frequency and spatial-frequency domains, can be fully reconstructed by making use of the solutions in the time domain and in the continuous wave (CW) domain[3] (a "special" case of the time domain where a continuously emitting source is used).[5] Thus, the solutions presented in this book can, in principle, cover all the domains of analysis.

For the time domain, it is also finally important to note that it has, in principle, the maximum information content since absorption and scattering effects can be more easily decoupled while studying the RTE in this domain. Indeed, when looking at measurable time-domain quantities, such as time-resolved detected light, the absorption and scattering terms can be identified as affecting very different and independent parts of the measured temporal profile. In fact, absorption interactions are progressively affecting late times, while scattering strongly affects the early part of the detected signal. This fact can lead to an evident advantage in terms of understanding the different physical phenomena and the measurement techniques of the optical properties. For this reason, the time domain represents a primary regime for studying and understanding photon transport. However, the time domain and CW domain can be extremely accurate in measuring the optical properties of diffusive media, showing that through designed experiments absorption and scattering can be decoupled also in the CW domain.[6,7] In this book, the time domain (including the special CW case) is the background for studying photon transport. In any case, for tutorial purposes, in this manual few examples of solutions will be discussed in the other domains.

Note that the expressions “time (temporal) domain” and “CW domain,” utilized for simplicity in this manual, in general should be more precisely written with the longer expressions “spatial time (temporal) domain” and “spatial CW domain.”

Using this manual in everyday practice

Solutions of photon transport can find a natural use in the assessment of the optical properties (absorption and scattering) of scattering media. In fact, these measurements often need, in the inversion procedure, a forward model that describes the dependence of the detected light on the values of the optical properties. Moreover, in the biological domain, the optical properties may in turn be linked to biological quantities important for the understanding of related underlying physiological mechanisms (see Fig. 1). The latter biological application is made possible by the fact that near-infrared light (typical light utilized for biological measurement) can penetrate deeply into tissues (some centimeters) and is sensitive to several tissue constituents.

More specifically, any biological tissue represents a complex random medium wherein light undergoes many scattering events and where, in many practical cases, its propagation may be suitably described as a diffusion process. The interaction of the near-infrared light with a biological tissue is dominated, with few exceptions, by scattering effects (the distance between two subsequent scattering events is on the order of ≈100 μm). However, most of the physiological information is led by the absorption of chromophores (e.g., oxy- or deoxy-hemoglobin) naturally present in the tissues. The

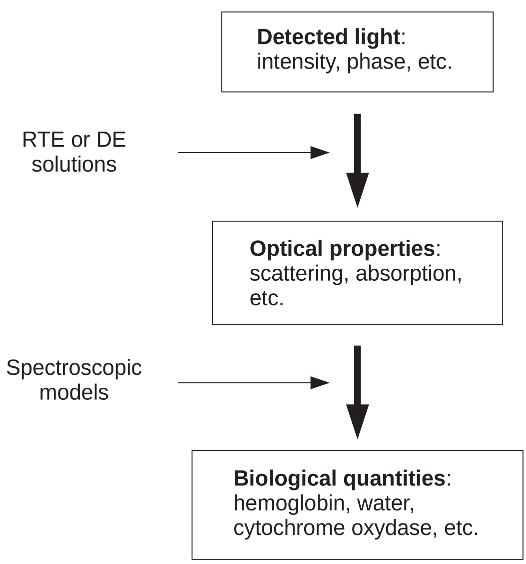

Figure 1 General approach allowing one to extract biological quantities from light that has traveled through a tissue.

possibility to treat this problem as a diffusion process, allows us to assess the small contribution of the absorption by isolating it in a very efficient manner from scattering. It is in this sense that the DE solutions proposed in this manual may represent a very powerful tool for the physiologist, the medical doctor or the engineer involved in the development of new instrumentation for biomedical optics.[3,8,9] These reasons are also why the solutions reported in this manual are already at the core of well-known instrumentation, such as near-infrared spectroscopy (NIRS) and diffuse optical tomography (DOT).[10,11]

Organization of the Manual

The text is organized in three main parts: I) General theory of photon migration; II) Analytic and semi-analytic solutions; and III) Validation of the solutions.

Part I

Part I introduces the whole book and describes the theories that will be used. This part ranges from Ch. 1 to Ch. 4.

- In Ch. 1, the general concepts and the physical quantities necessary to describe light propagation through absorbing and scattering media are introduced.
- In Ch. 2, the RTE and its main properties are described and discussed.
- In Ch. 3, the DE is derived starting from the RTE, and the reader is introduced to the general properties of the DE.
- In Ch. 4, the classic anisotropic diffusion equation (ADE) is derived from the anisotropic generalized RTE.

Part II

In part II, specific analytical and semi-analytical solutions derived from the theories presented in part I are carefully described. This part ranges from Ch. 5 to Ch. 14.

- Chapter 5 is devoted to solutions of the DE for homogeneous media.
- Chapter 6 is dedicated to ballistic and quasi-ballistic radiation and to a heuristic solution designed to model the effect of scattering in ballistic photon detection.
- Chapter 7 provides a general introduction to the calculation of the penetration depth in scattering media delivering analytical solutions for a diffusive slab.
- Chapter 8 focuses on the radial and lateral penetration depth in a homogeneous slab.

- Chapter 9 analyzes the detector-free propagation of light through a scattering and absorbing medium.
- Chapter 10 represents a special topic: hybrid solutions for a homogeneous slab, based on solutions of the RTE and the telegrapher equation.
- In Ch. 11, a solution of the DE for a two-layer medium is described.
- In Ch. 12, solutions for *N*-layered media are presented.
- In Ch. 13, solutions of the perturbed DE, when small defects are introduced into the medium, are obtained with the Born approximation.
- In Ch. 14, time-domain DE solutions for the Raman and the fluorescence signals are presented.

Part III

In part III, the obtained solutions are validated by means of comparisons with the results of reference MC simulations. This part ranges from Ch. 15 to Ch. 18.

- In Ch. 15, elementary MC methods typically utilized to describe photon migration in biomedical optics and, in general, in turbid media are presented.
- In Ch. 16, the different MC codes implemented to generate the reference data utilized to test the analytical and semi-analytical solutions proposed in this manual are carefully described in detail.
- Chapter 17 is dedicated to the validation of the solutions presented in part II. The validations are done by means of comparisons with the MC reference data of Ch. 16, and the results of the comparisons are described and discussed.
- In Ch. 18, the software included in 🔗 is described (MATLAB functions). The collection of MATLAB functions estimates almost all the solutions of photon transport presented in the manual. A large set of reference MC data (Excel *.xlsx format), which can be used as a standard reference, is also included in 🔗. Note that the old software named *Diffusion&Perturbation* together with the FORTRAN codes of the solutions of Ref. 1 can always be found in 🔗.

Beyond Photon Migration and Biomedical Optics

It is worthwhile at this point to conclude this preface by recalling that diffusive processes can be placed in a more general context that goes beyond biomedical optics. This fact may be better appreciated by noting that mathematical equations are in a way quite similar to words; i.e., they acquire their real meaning only when immersed in a precise context. This appears to be also the case for the DE. In fact, many media (agricultural products, wood, food, plastic materials, paper, pharmaceutical products, etc.) have optical properties at visible and/or near-infrared wavelengths for which light propagation in the diffusive regime can be established. Therefore, the same techniques used to study biological tissues can be applied to the monitoring of industrial processes, for quality control,[12–17] or in completely different fields.

Indeed, the theories presented in this manual, i.e., the RTE and the DE, arise from the more general transport theory.[18,19] Transport theory concerns the transport of "particles" through a "background medium" and is used in several applications where the transported particles and the host medium can have a very *different nature* and be represented by very *different physical quantities*. Thus, in general, the transport equation takes its sense depending on the physical phenomenon we want to describe. The advent of personal computers has made several numerical methods affordable to solve transport theory, and the availability of numerical solutions has further encouraged the use of this theory to solve a panoply of practical problems. The list of applications is surprisingly long and eclectic. Duderstadt and Martin[19] summarized for us some of the most relevant applications of transport theory:

> Neutron transport in nuclear reactors, Shielding of radioactive sources, Penetration of X-ray through matter, Brownian motion, Sound propagation, Propagation of light through the atmosphere, Propagation of light through stellar matter, Gas dynamics, Plasma dynamics, Transport of natural aerosols in the atmosphere, Diffusion of molecules in gases and fluids, Multiple scattering of electrons, Diffusion of holes and electrons in semiconductors, Photon transport through biological tissues, Transport of particles air pollution, Traffic flow, etc.

Thus, despite the different kinds of particles (neutrons, gas molecules, atoms of plasma, electrons, photons) or quantities that may be involved in the transport processes, all of these phenomena can be studied and described by using the same basic equation. When the transport process becomes diffusive, the transport equation can be simplified through the DE. Given a physical quantity u representative of the physical process studied (for instance, the particle density), whenever u is described by the equation

$$\frac{\partial}{\partial t}u(\vec{r},t) - k_1\nabla^2 u(\vec{r},t) + k_2 u(\vec{r},t) = 0, \tag{1}$$

we are dealing with a diffusive process. The coefficient k_1 is related to the spatial and temporal scale of the diffusive phenomenon studied, and the coefficient k_2 is related to the probability that the transported particles will be absorbed.

For example, for radiative transfer processes, k_1 will be related to the transport coefficient or diffusion coefficient of photons through the medium. For neutron transport processes, k_1 will be related to the transport coefficient of neutrons through the medium. For the diffusion of electrons and holes in semiconductors, k_1 will be related to the electrical conductivity. For the diffusion of molecules in gases, k_1 will be related to the transport coefficient of the molecules through the gas. The above equation with $k_2 = 0$ can be also used to describe the conduction of heat in solid isotropic materials, where u will be the temperature of the medium, and k_1 will be the thermometric conductivity of the substance, i.e., a material-specific quantity depending on the thermal conductivity, the density, and the specific heat of the substance.[20] The same equation is thus associated with very different physical concepts.

Usually, a diffusion process is associated with the random movement of a certain kind of particles. However, in some situations this is not so evident, as in the case of the physical diffusion of heat or the diffusion of fluids through porous materials.[21] This fact manifests the dichotomous nature of the diffusion process.[21] The dichotomous nature of diffusion theory has been noted by Narasimhan,[21] who showed how the equations of physical diffusion, i.e., Fourier theory of heat conduction,[22] and stochastic diffusion, derived from the Laplace theory of probability,[23] arose. Later, Albert Einstein obtained a single molecular-kinetic heat theory[24,25] wherein the equivalence between the diffusion coefficient of the physical process and of the random event was used. In physics, the work of Fourier inspired the use of the diffusion equation to study electricity phenomena, diffusion of molecules, and fluid flow.[21] The probability theory of Laplace inspired, at the end of the nineteenth century, scientists, economists, and statisticians to formulate a stochastic diffusion equation wherein the concept of probability density was used.[21] Given the high number of diffusion processes that can be observed in natural phenomena, we can view diffusion as a multi-fold theory that can assume very different physical meanings depending on the nature of the processes.

The above few examples and comments clearly show us that with the same mathematical tool different physical processes can be studied; however, given the intrinsic differences between the physical processes involved, each one requires a different physical interpretation of Eq. (1). These considerations want to emphasize that the solutions presented in this manual may have a quite larger field of use than that of tissue optics. Indeed, it is a characteristic of nature to show sometimes similar physical laws when processes involve different physical quantities.

We finally point out that the theories and solutions presented in this book have been obtained with reference to media illuminated by unpolarized light. However, the solutions are also applicable to media illuminated by polarized light, which commonly occurs when laser sources are used. In fact, multiple scattering randomly changes the polarization of scattered light so that light detected after a sufficiently large number of scattering events is completely depolarized. The previous state of polarization only remains near the source where photons arrive after a small number of scattering events. It has been shown with numerical simulations[26,27] and experiments[27] that when propagation occurs in the diffusive regime (i.e., when the solutions presented in this book become applicable), received photons have lost almost all traces of the initial state of polarization, and the results for polarized light become almost identical to those obtained for unpolarized light.

Thousands of papers on the diffusion of light have been published in scientific journals. For this reason, the references presented in this manual cannot *a fortiori* be exhaustive. Thus, we will mention only a few good introductory references, such as the monograph dedicated to the diffusion of light by Ripoll.[4] This reference, mainly refers to publications in the field of biomedical optics and more precisely to the field of NIRS and diffuse optical tomography. In order to have a more complete view of photon transport, we also suggest the reader to refer to other books on light propagation.[18,19,28–33]

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