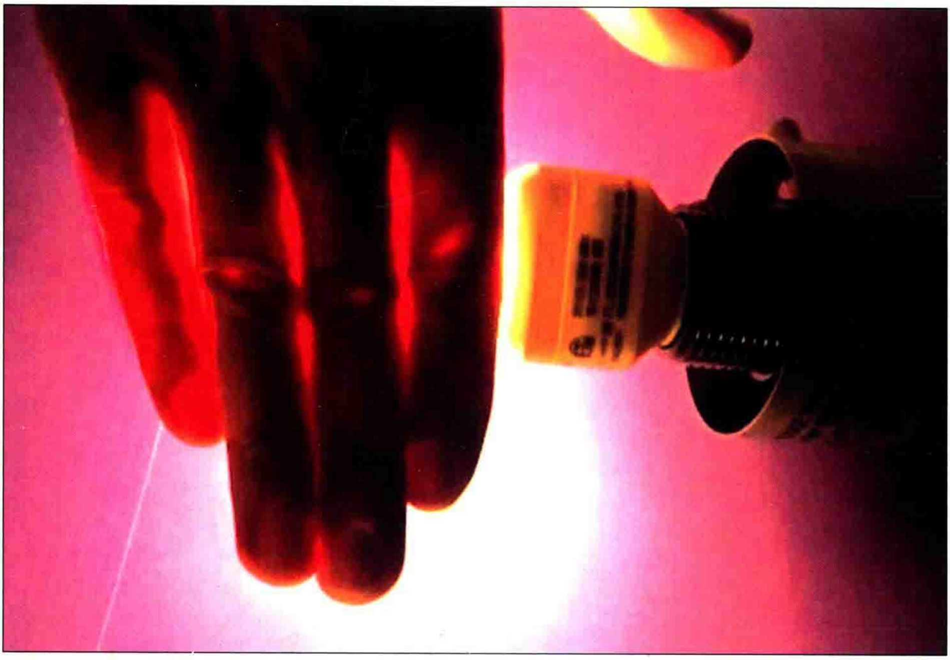
PRINCIPLES OF DIFFUSE LIGHT PROPAGATION

Light Propagation in Tissues with Applications in Biology and Medicine



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To Alicia

Foreword

Probing disease with light is the oldest and still most wide-spread clinical examination method world-wide. Every single day at every hospital in the world, doctors will 'look' at patients to see discolorations and anatomical changes, they will shine light on them with endoscopes or surgical lamps and they will transilluminate them with pulse oximetry devices to obtain blood saturation measurements or to examine the lung of premature newborns. The familiarity of humans with optical imaging usually hides the fact that a significant part of clinical decision making today is still performed with an 'optical imaging' method. It is often believed that whereas a physical examination may be based on a patient visual inspection, more advanced radiological imaging eventually contributes to accurate diagnostics. However, from skin inspection to gastro-intestinal endoscopies, colposcopies and surgical procedures, optical imaging remains a primary diagnostic and theranostic method. Similarly, within the realm of photo-dynamic therapy, light is also employed therapeutically.

In contrast to human vision or photography typically based on light reflected from surfaces, optical imaging of tissues is a significantly more complex procedure which at times can become highly confusing. This is because tissue is not a perfect light reflector; instead, depending on the wavelength employed, a significant proportion of the incident light will distribute in tissues. This portion of light will encounter cellular organelles and interfaces which will change the original direction of propagation leading eventually to light diffusion. Part of this light will encounter absorbing molecules such as hemoglobin or melanin or will excite natural fluorochromes such as NADH or structural proteins. Some will eventually pass through a detection device such as a lens, or a fiber interface. These natural and seemingly straightforward procedures contribute to a physical system that can be very perplexed. The macroscopic appearance of these processes leads to a non-linear problem that, to the experience of many experimentalists, presents multiple challenges when it comes to quantifying such measurements, generating images with them and more importantly leading to accurate medical interpretation. Addressing these challenges requires a thorough theoretical understanding of light propagation in tissues. Using quantitative models of light propagation optical imaging of tissue can gain in terms of diagnostic and theranostic potential, beyond the one achieved today through simple photographic inspection of tissues.

It is when an inspired theoretical physicist in optical diffusion spends many years with the capricious experimental intricacies of diffusive measurements and tomographic reconstructions that you get a book like the one you read now: an account of light propagation in tissues from the view point of the measurement. This book is an account of a large volume of knowledge that has been developed over decades on scattering theory and bio-photonics, including the authors own contributions. However it does not only serve the purpose of presenting the theoretical abstraction but also prioritize this knowledge and present it from the view point of the experimental relevance. I can only simile the development of the book herein in the context of the phenomena it describes, a tortuous move of the author within complex optical definitions and matching experimental measurements. The result is a rigorous theoretical presentation and analysis of light propagation and diffusion that carries the weathering of experimental application of the concepts described to match real-life measurements. Unequivocally a most comprehensive account of diffusion theory for bio-optical imaging; not only for the theorist but more importantly for the experimentalist. I wish I had this book in 1995!

Vasilis Ntziachristos

Preface

I will never forget the moment when, in the context of a meeting, I was with Simon Arridge and mentioned I was writing a book. He smiled and told me a joke, which on general terms sounded something like: 'two scientists meet at a conference and one says to the other "I'm writing a book" and the other one answers "me neither"'. I have to admit that I did not find it that funny. At first. As the months became a year and my book was not even half-way through, I started to panic and thought how exquisitely accurate this joke was, and have been laughing at it ever since. I guess — hope, rather — that this is what happens to all on their first book, where you realize time is not available in the quantities you expected it to be.

Light propagation in biological tissues, and in particular, applications of light diffusion, is a relatively new field that during the past two decades has been causing a strong impact in the fields of medicine and biology, mainly due to its capabilities to image *in-vivo* in small animals and humans. Due to the fact that most of the on-going research in this area is applied, there are very few basic theoretical works in the area of light diffusion. On the other hand, there are numerous peer-reviewed papers dealing solely with numerical simulations or numerical solutions of complex problems applied to diffuse light imaging. This has caused a gap between the basic theory and application, which I hope that this book can cover at least partially. I believe a basic book oriented towards providing the post-graduate student with a strong foundation of the principles of light propagation in biological media is still lacking, showing how several simple, yet extremely useful problems may be approached using analytical expressions.

The main idea behind this book is to present a rigorous derivation of the equations that govern light propagation in highly scattering media, with a particular emphasis in their application in imaging in biology and medicine. I have included the basis for modeling diffuse light propagation starting from the very beginning and have presented, hopefully with enough detail, all the steps leading to the final expressions. The way I conceived this book was so that it could be read from beginning to end, each chapter building on the formulas and knowledge gained in the previous chapters. Even though I have tried hard for this book to be as enjoyable to read as possible, I understand that it takes great skill to manage this, so beforehand my apologies if some (hopefully not all) areas of the book are too dense. So as to make clear what contributions from each chapter are the most relevant, I have included two ways of highlighting those important parts: 'building blocks' and 'important notes'. Building blocks, as their name clearly implies, are the equations and expressions we will be using to arrive to the diffusion equation and to study diffuse light propagation. Important notes refer to issues which are important and are usually not that well-known.

This book provides the basic framework to work with reflection and transmission of diffuse waves at interfaces and their behavior at non-scattering interfaces, in a manner very similar to that taught to undergraduates when working with Electromagnetic propagation (see Born and Wolf (1999), for example). It explains in detail what approximations are taken when deriving the diffusion approximation and their implication, both from a fundamental physics point of view and with respect to their biological and medical applications. It begins with an overview of the problem (Chapters 1 and 2) and thorough step-by-step derivations until the diffusion equation is reached (Chapters 3 to 5). From then on, it concentrates on the basis of diffuse light propagation (Chapters 6 and 7), diffuse light at interfaces (Chapter 8), the ill-posed nature of diffuse waves (Chapter 9), and briefly presents some approximations to solve the inverse problem with analytical expressions (Chapter 10). Since my main concern was to explain in detail the basics of diffuse light propagation, and the subject of solving the inverse problem is such an extensive one, I have unfortunately dedicated very little space to this issue. I hope, however, that enough material and references are presented so that those willing to approach the inverse problem have a solid starting point.

Most of what is explained in this book is in the context of the new emerging field of optical molecular imaging, to which imaging with diffuse light became an integrating part mainly thanks to Vasilis Ntziachristos, who was the first to publish the use of diffuse light to image activatable fluorescent probes *in-vivo*. This technique, which he termed Fluorescence

Molecular Tomography (FMT), makes use of the principles developed for diffuse optical tomography and applies them to image molecular function by using fluorescent probes. In this sense, the physical governing principles are equivalent to fluorescence diffuse optical tomography (fDOT), however it is the whole concept and application to imaging molecular function which was a breakthrough and clearly distinguishes FMT from fDOT as a molecular imaging modality.

Since this book concentrates on the basics of diffuse light propagation, I have opted for not including too many citations and refer the reader, when possible, to complete and thus more comprehensive volumes such as books or Thesis dissertations. In doing so I understand many peer-reviewed papers that have been very important in this field have been omitted. To those that feel that their contribution is not well represented, my sincere apologies. Additionally, since this book is almost entirely based on formulas, I am certain that some errors might have sneaked through my radar. I would be very grateful if you inform me if one of these unfortunate enemies is detected.

One of the things I would like to single out from this book is the explicit use of units. I remember being grilled in college on the importance of units, and I have come to understand why. All quantities, when presented for the first time in each chapter, are always introduced with the appropriate units, and whenever writing any expression I always check to see if the units are correct. If units are incorrect, there is an error in the formula, plain and simple. The reason I go over such an obvious matter is that lately a vast majority of peer-reviewed papers published (at least in our field) have expressions with different units on each side of the equation. I hope this book at least contributes to establishing what units are relevant in diffuse light propagation.

With regards to the technicalities of this book, all figures were generated with Inkscape, an open source vector graphics editor, `http://inkscape.org`; Google Sketchup, a freeware 3D modeling program, `http://sketchup.google.com`; and Octave 3.4.2, an open source high-level interpreted language intended for numerical computations `http://www.gnu.org/software/octave/`, was used to generate all the data. This book was written in LaTex using TeXworks, a TeX front-end program, `http://www.tug.org/texworks/`.

Among the many people I am indebted for help in the preparation of this book, I would like to single out Juan Aguirre for thoroughly studying and commenting on the formulas and explanations in the first four chapters of this book; my father, Pedro Ripoll, for reading and editing the whole book — I can now say that at least two people have read all of it — and my mother, Elena Lorenzo, for formatting and editing; Florian Stuker for his useful comments; Eleftherios Economou, Juan José Saenz and Manuel Nieto-Vesperinas for answering questions regarding the physics and equations in the second chapter on basic electromagnetism; and above all Alicia Arranz for not only editing parts of this book but for her endless help and support. Without her this book would have not been possible.

There are also several researchers from whom I have learned much and have been a direct influence in the material that follows, in particular Manuel Nieto-Vesperinas, Eleftherios N. Economou, Simon Arridge, Arjun Yodh, Rémi Carminati, Frank Scheffold, Juan José Saenz and especially Vasilis Ntziachristos, with whom most of the formulas presented in this book were applied experimentally and who has always been the best at finding both interesting and useful problems. Even though they are completely unaware of it, two great Bills were of great help in the long hours until this book's completion: Bill Evans, for providing the perfect background, and Bill Bryson, for providing the best of distractions and also, the most enjoyable of scientific references (if you have not read 'A short history of nearly everything', I can't recommend it enough).

I would also like to gratefully acknowledge the support of the Institute for Electronic Structure and Laser, from the Foundation for Research and Technology-Hellas, where most of this book developed, and Markus Rudin for hosting me at the ETH-Zürich where the final chapters were written.

Jorge Ripoll Lorenzo
November 2011

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PART 1

Light Propagation in Tissues