

IMAGING WITH DIFFUSE PHOTON DENSITY WAVES

Maureen A. O'Leary

A DISSERTATION

in

PHYSICS

Presented to the Faculties of the University of Pennsylvania in Partial Fulfillment of  
the Requirements for the Degree of Doctor of Philosophy

1996

---

Arjun G. Yodh

Supervisor of Dissertation

---

Robert Hollebeek

Graduate Group Chairperson

COPYRIGHT  
Maureen Ann O'Leary  
1996

## DEDICATION

This work is dedicated to  
Mom, Dad,  
Terry, Stephen, Kathleen,  
and Surge.

## ACKNOWLEDGEMENTS

Because my project has straddled the mutually exclusive worlds of Penn physics and Penn biophysics, it has been my privilege to have had the guidance of two advisors, Dr. Britton Chance from the Biochemistry and Biophysics Department, and Dr. Arjun Yodh from the Physics department.

Arjun Yodh provided me with many of the ideas and helped me learn the physics I needed to solve some difficult problems. I thank him for the many nights and weekends he spent helping me with papers and presentations. In the physics department I took my courses, and exams, and defended this thesis. Dr. Ralf Amado has been a constant support throughout this process. Tony Dinsmore, Peter Kaplan and especially Xingde Li, have been valuable coworkers from the physics department.

But it was in the Department of Biochemistry and Biophysics that I finally felt at home. I thank Dr. Les Dutton for supporting me on his training grant and allowing me to work in his lab. He introduced me to the Biochemistry and Biophysics department, where both men and women can enjoy scientific inquiry without intimidation. He also introduced me to my second advisor, Dr. Britton Chance. Britton Chance, besides being a scientific and athletic legend, is an incredibly supportive advisor and does his best to advance everyone around him. Britton gave me the opportunity to speak at many meetings, and made me known to some of the most influential people in research today.

I also thank him for setting up a terrific group of people who are part of the lab. Although this list is no where near complete, it has been a pleasure to work with Hanli Liu, Shoko Nioka, Mary Leonard, Dot Coleman, Shiyin Zhao, and Henry Williams. Libo He, Ben Duggan and Jian Weng taught me all I needed to know about electronics.

It has been my honor, to have had the opportunity to work for four years with David Boas. Besides being the greatest scientist that I have ever known, he is a good friend and an enthusiastic coworker. Without David, this project would not have been the success that it was, and I probably would not have had the strength to finish it

without David's support.

## **ABSTRACT**

### **IMAGING WITH DIFFUSE PHOTON DENSITY WAVES**

Maureen A. O'Leary

Arjun G. Yodh

Diffusing photons can be used to probe and characterize optically thick turbid samples such as paints, foams and human tissue. In this work, we present experiments which illustrate the properties of diffuse photon density waves. Our observations demonstrate the manipulation of these waves by adjustment of the photon diffusion coefficients of adjacent media. The waves are imaged, and are shown to obey simple relations such as Snell's Law.

Next we present images of heterogeneous turbid media derived from measurements of diffuse photon density waves. These images are the first experimental reconstructions based on frequency-domain optical tomography. We demonstrate images of both absorbing and scattering homogeneities, and show that this method is sensitive to the optical properties of a heterogeneity. The algorithm employs a differential measurement scheme which reduces the effect of errors resulting from incorrect estimations of the background optical properties.

In addition to imaging absorption and scattering changes, we are also able to image the lifetime and concentration profile of heterogeneous fluorescent media.

## Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
1.1	Historical Perspective . . . . .	2
1.2	Photon Diffusion Equation . . . . .	5
1.3	Introduction to Optical Imaging . . . . .	6
1.3.1	Forward Models . . . . .	6
1.3.2	The Inverse Problem . . . . .	10
1.4	Resolution . . . . .	11
1.5	Contrast . . . . .	13
<b>2</b>	<b>Optics for Diffuse Photon Density Waves</b>	<b>17</b>
<b>3</b>	<b>Hardware Specifications</b>	<b>33</b>
3.1	Photon Detection - Photomultiplier tubes . . . . .	34
3.2	Photon Detection - Avalanche Photodiodes . . . . .	39
3.3	Laser diodes . . . . .	42
3.4	Amplitude-phase detector . . . . .	44
3.5	Signal Generators . . . . .	46
3.6	Filters . . . . .	47
3.7	Mixers . . . . .	51
3.8	Summary . . . . .	51
<b>4</b>	<b>Imaging the Absorption Coefficient</b>	<b>55</b>
4.1	The Heterogeneous Diffusion Equation . . . . .	56

4.2	Born Approximation . . . . .	56
4.3	Rytov Approximation . . . . .	58
4.4	Breakdown of the Born and Rytov Approximations . . . . .	59
4.5	Inverting the Solutions to the Heterogeneous Diffusion Equation . . . . .	60
4.6	Singular Value Decomposition . . . . .	64
4.7	Algebraic Reconstruction Techniques . . . . .	69
4.8	Data Analysis . . . . .	72
4.9	Experimental and Computational Results . . . . .	79
4.10	Updating the Weight Functions . . . . .	80
4.11	Resolving Multiple Objects . . . . .	83
4.12	DPDW Imaging Combined With Other Imaging Modalities . . . . .	84
4.13	Finite Systems . . . . .	92
<b>5</b>	<b>Imaging the Scattering coefficient</b>	<b>95</b>
5.1	Born Expansion . . . . .	96
5.2	Rytov Expansion . . . . .	97
5.3	Matrix Equations . . . . .	101
<b>6</b>	<b>Absorption and Scattering</b>	<b>105</b>
6.1	Simulation Results . . . . .	106
<b>7</b>	<b>Imaging Fluorescence</b>	<b>111</b>
7.1	Fluorescent Diffuse Photon Density Wave Theory . . . . .	112
7.2	Localizing Fluorescent Objects . . . . .	116
7.3	Tomographic Imaging of Fluorescent Objects . . . . .	123
<b>8</b>	<b>Summary</b>	<b>133</b>
<b>A</b>	<b>Singular Matrices</b>	<b>135</b>
<b>B</b>	<b>Time Resolved Spectroscopy</b>	<b>137</b>

<b>C Time Domain Fluorescent DPDW Derivation</b>	<b>141</b>
<b>D Back Projection</b>	<b>143</b>
<b>E The Photon Migration Imaging Software Package</b>	<b>147</b>
E.1 Sample PMI scripts . . . . .	149
E.2 PMI Command Summary . . . . .	152
<b>F Parallel Processing</b>	<b>177</b>

## List of Figures

1.1	Absorption spectra of major tissue chromophores. . . . .	3
1.2	A simplified schematic of the RunMan <sup>TM</sup> instrument. . . . .	4
1.3	A typical RunMan <sup>TM</sup> oxygenation trace . . . . .	4
1.4	A reconstruction of two absorbing objects . . . . .	7
1.5	Sample weight distributions for CAT and diffuse photon imaging. . .	8
1.6	Sample weight distributions for a pulsed source on the surface of a semi-infinite medium. . . . .	9
2.1	Experimental DPDW phase contours. . . . .	24
2.2	Refraction of DPDW's. . . . .	27
2.3	Refraction by a spherical surface . . . . .	28
2.4	The amplitude and phase of a simulated phased array . . . . .	29
2.5	The amplitude and phase of scanned phased array . . . . .	30
2.6	Three possible configurations for the phased array measurements. . .	31
3.1	A schematic of the frequency domain instrument. . . . .	34
3.2	The spectral sensitivity and quantum efficiency of the R928 PMT. . .	36
3.3	Experimental setup for testing the amplitude-phase cross-talk of the PMT. . . . .	37
3.4	The dynode structure and position sensitivity of the R928 PMT. . . .	38
3.5	Holding the DC current from the PMT constant reduces the amplitude- phase cross-talk. . . . .	39
3.6	The current versus voltage curve of an ideal zener diode. . . . .	39
3.7	A Zener diode is used to reduce the space-charge effect on the phase.	40

3.8	Schematic of a silicon photo-diode. . . . .	42
3.9	The spectral sensitivity and quantum efficiency of the photodiode in an APD. . . . .	43
3.10	An AC signal is capacitor coupled to the laser diode driving current. . . . .	44
3.11	A schematic of the lock-in amplifier. . . . .	45
3.12	Amplitude-phase cross-talk of the SRS530. . . . .	47
3.13	Twin-T bandpass filter. . . . .	48
3.14	The response of the twin-T band-pass filter at several different Q. . . . .	49
3.15	Amplitude-phase cross-talk of the twin-T filter . . . . .	49
3.16	RLC bandpass filter. . . . .	50
3.17	Amplitude-phase cross-talk of the RLC filter . . . . .	50
3.18	Schematics of sample mixers. . . . .	52
4.1	Schematic of the Born solution to the heterogeneous diffusion equation. . . . .	58
4.2	A comparison of the Born and Rytov approximations. . . . .	60
4.3	A typical scanning geometry and volume digitization. . . . .	62
4.4	Linear algebra definitions for SVD . . . . .	66
4.5	Eigenvalue smoothing algorithm for singular value decomposition . . . . .	68
4.6	Algebraic reconstruction . . . . .	70
4.7	Algebraic reconstruction using noisy or incomplete data . . . . .	71
4.8	Reconstructed absorption images as a function of SIRT iteration . . . . .	72
4.9	Geometry of the reference measurements. . . . .	74
4.10	Reconstructions of absorption when the background absorption is mis-estimated - no SIRT constraints. . . . .	77
4.11	Reconstructions of absorption when the background absorption is mis-estimated - with SIRT constraints. . . . .	78
4.12	Reconstruction of a single perfect absorber. . . . .	80
4.13	Reconstruction of a series of absorbing spheres. . . . .	81
4.14	Resolution of two absorbing spheres . . . . .	85
4.15	An overly simplified breast model. . . . .	86

4.16	1st and 2nd iteration of reconstructed absorption versus the true value, for a single spherical inhomogeneity. . . . .	89
4.17	Simulation with six absorbing inhomogeneities. . . . .	89
4.18	A tissue phantom simulating a human breast . . . . .	91
4.19	A schematic of the image sources and image objects needed to model a semi-infinite boundary condition. . . . .	93
5.1	The reconstruction of a highly scattering sphere. . . . .	102
5.2	Reconstructed scattering images as a function of SIRT iteration . . .	103
6.1	Simultaneous reconstructions of absorption and scattering. . . . .	108
6.2	Effect of absorption versus scattering variation on amplitude and phase.	109
6.3	Reconstruction of absorption and scattering using amplitude and/or phase data . . . . .	110
7.1	A schematic of fluorescent DPDW generation. . . . .	115
7.2	Experimental measurements of fluorescent diffuse photon density waves.	118
7.3	Experimental measurements of fluorescent diffuse photon density waves from a cylindrical object. . . . .	118
7.4	A device for localizing the center of a fluorescent object. . . . .	120
7.5	The estimated position of a reradiator using the fitting algorithm. . .	121
7.6	Localization of a fluorescent object using a phased array. . . . .	122
7.7	Images proportional to fluorophore concentration show spurious voxels with unphysical optical properties. . . . .	126
7.8	A plot of $\tan^{-1}(\omega\tau)$ versus $\omega\tau$ shows the saturation effect for $\omega\tau$ greater than 1. . . . .	127
7.9	Reconstruction of fluorophore lifetime and concentration in a system with no background fluorophore. . . . .	128
7.10	A cartoon describing the breakdown of the background fluorescence problem. . . . .	129

7.11 Reconstruction of fluorophore lifetime and concentration in a system with background fluorophore. . . . .	131
B.1 A schematic of the TRS system . . . . .	138
B.2 Signal processing by the constant fraction discriminator (CFD) . . . . .	138
B.3 Equivalent circuit for the time amplitude converter (TAC). . . . .	138
D.1 The measurement geometry for the NIM back-projection imaging project.	145
D.2 Sample back-projection images for a solid block sample with an em- bedded heterogeneity. . . . .	145
F.1 An overview of the PMI software . . . . .	178
F.2 A block diagram of the flow of the parallel code. . . . .	179
F.3 The CPU times for various homogeneous and heterogeneous systems.	181

## List of Tables

1.1	Popular forward models for photon diffusion imaging. . . . .	10
1.2	Popular inverse models for photon diffusion imaging. . . . .	12
2.1	The optical properties of human tissues. . . . .	18
3.1	Specifications of the Hamamatsu R928 photomultiplier tube. . . . .	35
3.2	Specifications of the Hamamatsu C5658 Avalanche photodiode. . . . .	41
3.3	Specifications of the Sharp LT022MD laser diode. . . . .	43
3.4	Specifications of the SRS530 . . . . .	46
4.1	Reconstruction results for multiple absorbing inhomogeneities. . . . .	90
F.1	The clock and CPU times for 1, 2, 4 and 8 node trials. . . . .	182