AD_____

Award Number: DAMD17-99-1-9130

TITLE: Finite Element Based Photon Migration Imaging

PRINCIPAL INVESTIGATOR: Huabei Jiang, Ph.D.

CONTRACTING ORGANIZATION: Clemson University
Clemson, South Carolina 29634-0978

REPORT DATE: May 2002

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	May 2002	Annual (1 May 01 - 30 Apr 02)

4. TITLE AND SUBTITLE
Finite Element Based Photon Migration Imaging

5. FUNDING NUMBERS
DAMD17-99-1-9130

6. AUTHOR(S) :
Huabei Jiang, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Clemson University
Clemson, South Carolina 29634-0978

E-Mail: HJIANG@clemson.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

This research is aimed at developing a new optical approach, called "Photon Migration Imaging", for breast cancer detection and diagnosis. The project will develop computer software and conduct phantom experiments to achieve the proposed goals. During the third year of this project, we have implemented and evaluated the 2D image enhancing schemes especially in the areas of boundary conditions and source/detector models. We have also started to implement the 3D reconstruction algorithms that were proposed to occur in Year 4 of the project. We have conducted extensive simulation and phantom experiments for optical and fluorescence lifetime imaging. The successful experiments have confirmed the imaging capability of our reconstruction software.

14. SUBJECT TERMS
Breast Cancer, photon migration imaging

15. NUMBER OF PAGES
11

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Introduction

The ability of near-infrared (NIR) light-based techniques to noninvasively image and analyze tissue structure and function promises their great potential for detection and diagnosis of breast cancer. Optical diagnostic techniques allow us to not only enhance the existing capabilities, but to eliminate the need for physical biopsies. In addition, optical imaging is inexpensive and portable, which indicates that optical imaging could be an ideal candidate for routine breast screening. However, since the scattering properties of tissues convolute re-emitted NIR signals, the extraction of pertinent information continues to remain elusive. An understanding of light propagation and light-tissue interaction is required before the optical technologies can substantially impact diagnostic medicine.

Research efforts in the Biomedical Optics Laboratory at Clemson University are focused on the biophysics of light propagation and light-tissue interaction in order to engineer appropriate approaches for noninvasive breast imaging and spectroscopy. Specifically, we are developing indirect optical/fluorescence approaches using photon migration measurements in the continuous-wave and frequency domains. These indirect optical/fluorescence approaches or image reconstructions are computationally based on the powerful finite element methods. A CCD-based optical spectroscopic imaging system is already operational in our laboratory for continuous-wave tomographic photon migration measurements, while a frequency-domain system is still under construction. Using these optical systems coupled with our finite element based reconstruction algorithms, we will be able to extract spatial/spectroscopic maps of tissue optical properties, lifetime and/or yield of endogenous and exogenous fluorescent probes. Since metabolic tissue states can be identified by our approaches, diagnostic information is also obtained in addition to detection of tumor.

This Career Development application for support of Dr. Huabei Jiang will facilitate the establishment/continuation of these research activities. Interdisciplinary interactions with the Greenville Hospital System (Greenville, SC) will be enhanced, which insures the direction of research towards a clinically pertinent and feasible system.

Body

This report describes work accomplished during the third year of a proposed four-year study. This Career Award supports Dr. Jiang's research on optical and fluorescence imaging using both continuous-wave and frequency-domain measurements. The focus of the proposed work in Year 3 is the implementation and evaluation of image enhancing schemes in the areas of boundary conditions and source./detector models; continued phantom studies of image reconstructions with dye-free or dye-laden phantom background; initial implementation of 3D reconstruction algorithms.

Software work: We have implemented and evaluated important image enhancing schemes in the areas of boundary conditions and source/detector models. We have also derived a photon diffusion equation that considers the impact of tissue refractive index. Extensive simulation and phantom experiments have been conducted to complete these software developments. The results from these studies have been

published in a recent conference proceeding of Optical Society of America (OSA) (see a manuscript provided in the *Appendix* to the Summary Report). We have started to implement the 3D reconstruction algorithms which was proposed to take place during the fourth year of the project.

Phantom Experiments: Using our frequency-domain imaging system, we have conducted extensive phantom experiments for both optical and fluorescence reconstruction with dye-free background and dye-laden background. Our experimental setup used was the automated multi-channel frequency-domain system mentioned above. The system employed a radio-frequency intensity-modulated near-infrared beam. The laser beam was sent to the phantom by 16 fiber optic bundles coupled with a high precision moving stage. The diffused radiation was received by another 16 channel fiber optic bundles and delivered to a thermo-electric cooled PMT. A second PMT was used to record the reference signal. These PMTs were supplied at a radio-frequency modulated current with 0.1-1KHz shift. The intermediary frequency signal obtained from the PMTs was processed using a National Instruments board. For every source position, 16 measurements for each detector were made, taking alternatively 100 ms samples for sample and reference signals. Fluorescence signals were obtained through an 830nm interference filter placed in front of the detection PMT. dc, ac intensity and phase shift between reference and sample signals were obtained using FFT Labview routines. The total data collection time for 256 measurements was 8 minutes.

Solid phantom was used to mimic the human tissue. It was made of agar, Intralipid, black ink and fluorescent dyes. The absorption and the reduced scattering coefficients are linear with the ink and Intralipid concentrations, respectively. While ICG and DTTCI dyes were continually used in these experiments, we have also used oxygen-sensitive dyes including Pd chlorin e6 and Pd meso-tetra (4-carboxyphenyl) chlorin. Agar was used to make the phantom solid. The absorption and fluorescent emission peaks of these two dyes are about 635 nm and 660nm, respectively. The solid phantom consisted of a cylindrical background and a cylindrical heterogeneity. These experiments show that we may be able to obtain the tissue oxygen concentration images by the use of oxygen-sensitive dyes. This could provide optical imaging a unique capability to distinguish between benign and malignant breast tumors because the oxygen concentration in these two types of tumors often is distinct. While a manuscript is currently in preparation based on these studies, some of the image results have been published in the OSA proceeding (see the second manuscript provided in the *Appendix* to this Summary Report).

Key Research Accomplishments

1. We have implemented and evaluated the 2D image enhancing schemes especially in the areas of boundary conditions and source/detector models. We have also started to implement the 3D reconstruction algorithms that were proposed to occur in Year 4 of the project.
2. We have conducted extensive phantom experiments for optical and fluorescence lifetime imaging. The successful experiments have confirmed the imaging capability of our reconstruction software.

Reportable Outcomes (see the Appendix to this Summary Report)

Conclusions

We have made a significant progress that has exceeded the statement of work proposed for Year 3 of this project. Given the successful Years 1-3, we will be able to fulfil or exceed the work statement for Year 4.

Appendix

1. Q. Lu, Y. Xu, H. Jiang, "The diffusion approximation model for turbid media with a spatially varying refractive index: impact of skin on optical breast imaging", *Proc. OSA Biomedical Topical Meetings: Advances in Optical Imaging and Photon Migration*, 93-95(2002).

2. E. Shives, Y. Xu, N. Iftimia, H. Jiang, "Fluorescent lifetime tomography using frequency-domain data", *Proc. OSA Biomedical Topical Meetings: Advances in Optical Imaging and Photon Migration*, 519-520(2002).

The Diffusion Approximation Model for Turbid Media with a Spatially Varying Refractive Index: Impact of Skin on Optical Breast Imaging

Qi Lu, Yong Xu, Huabei Jiang
Department of Physics and Astronomy, Clemson University, SC 29634

Abstract: We present a study based on the diffusion approximation model which includes the spatial variation of the refractive index of turbid media. In optical imaging, the refractive index has been assumed as a constant to date. But in fact, the refractive index of the skin is much lager than that of the underlying tissue. We simulated with the skin thickness varying from 1 to 3mm and the refractive index of skin from 1.40 to 1.55. Our simulations show that both the refractive index and thickness of skin have significant impact on the reconstructed images. We are currently conducting phantom experiments to confirm the findings from simulations.

Theory

For many random media such as biological tissue, its refractive index is not a constant; even the refractive index within a single cell is spatially dependent. Meanwhile the diffusion equation has been the most powerful model for describing photon propagation in turbid media. We therefore establish the diffusion approximation model that includes the spatial variation of the refractive index of turbid media to quantitatively image tissues more accurately. The derivation is started from a radiative transfer equation that considers a spatially varying refractive index. And it ends up with the equation as follows:

$$-\frac{n}{c}\frac{\partial\Phi(r,t)}{\partial t}+\nabla\cdot D\nabla\Phi(r,t)+\frac{2D}{n}\nabla n\cdot\Phi(r,t)-\mu_a\Phi(r,t)=-S_0(t)\delta(r-r_0)$$

where $\Phi(r,t)$ is the photon density, D is the diffusion coefficient, n is the refractive index, μ_a is the absorption coefficient, c is the wave speed in the medium, and $S_0(t)\delta(r-r_0)$ is a point excitation source.

Simulation

Measured data of photon density in our simulations were generated with the forward diffusion model mentioned above and then were fed into a finite-element-based algorithm that reconstructed the spatial maps of the optical properties (absorption coefficient μ_a and reduced scattering coefficient μ_s').

A circular geometry with an off-centered target used in this study is shown in figure 1. The skin is represented by a boundary ring with various thickness (d) from 1 to 3mm. The refractive index of the skin (n_2) is selected between 1.40 and 1.55 and a refractive index of 1.35 is used for the underlying tissue (n_1). The embedded small circular region indicates the target, the center of which is located at (-5,-6) when the center of the two concentric circles are considered as the origin. The optical properties used for the background and skin regions are: μ_a=0.005mm^{-1}, μ_s'=1.0mm^{-1}; and the ones for the target area are: μ_a=0.010mm^{-1}, μ_s'=2.0mm^{-1}.

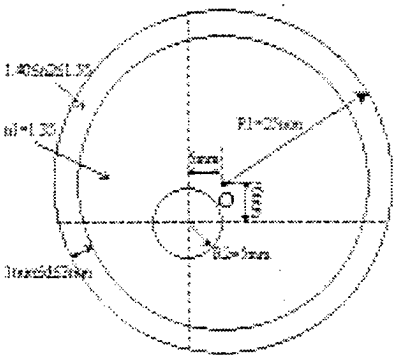


Fig. 1. Test Geometry

Results

Figure 2 shows some representative reconstructed images where different skin thickness and refractive index are used. We can see that the center locations of the targets are clearly shifted and that the target shape is distorted due to the increased refractive index of the skin.

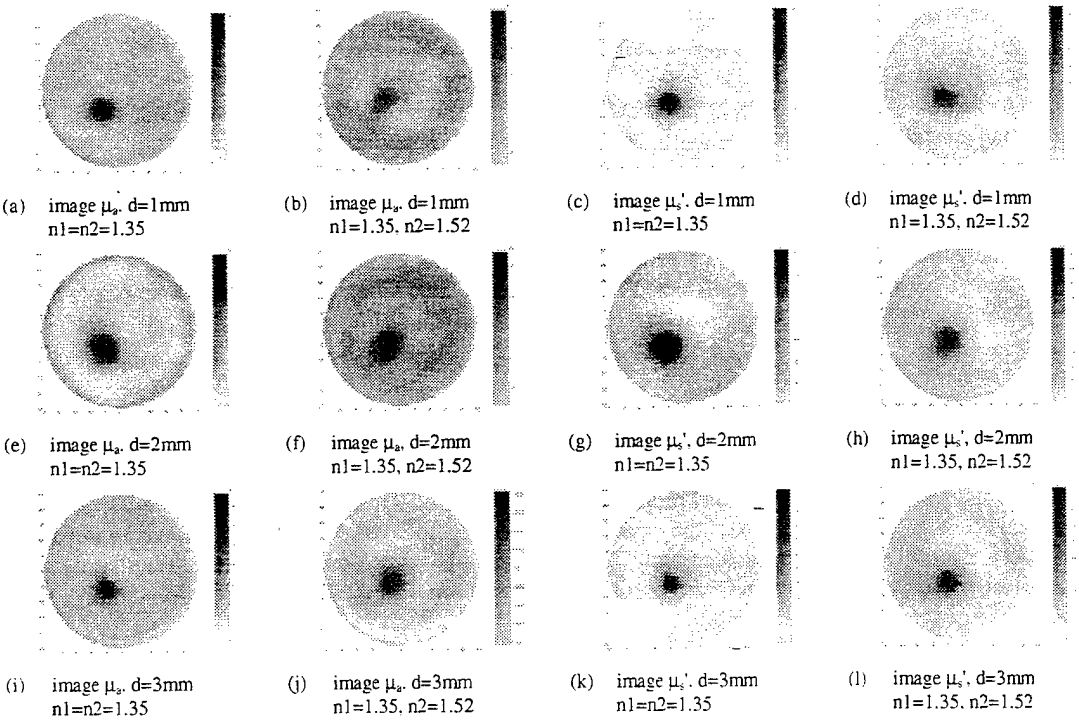
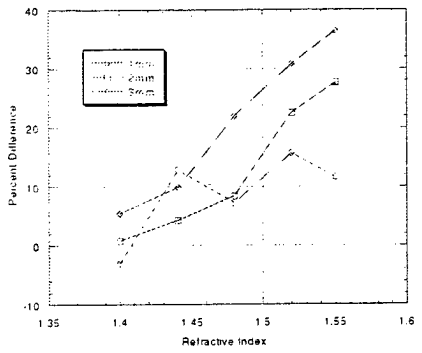


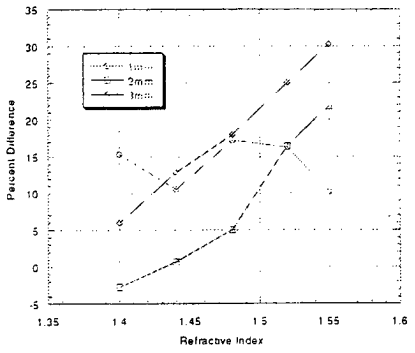
Fig.2. Reconstructed images of different cases in terms of the thickness and the refractive index of the skin.

Figure 3 presents the shift of the target centers for the cases with increased refractive index relative to the homogeneous case. The location of a target center was determined by calculating the full-width at half maximum (FWHM). Different skin thickness was considered. It can be concluded from figure 3 that, in general, the thicker the skin is and the greater refractive index the skin has, the greater shift of the target center is.

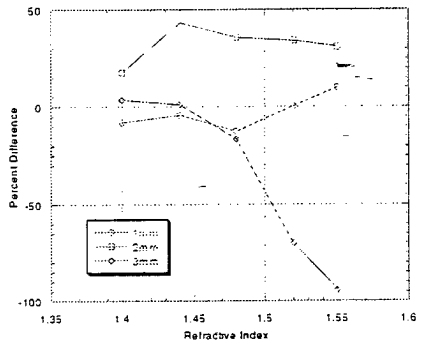
The phantom experiments are currently underway. If the resulting images also show a significant difference due to the skin layer as what we've seen in simulations, we might, in our future study, have to take into account of the impact of the skin. We will present the results at the meeting.



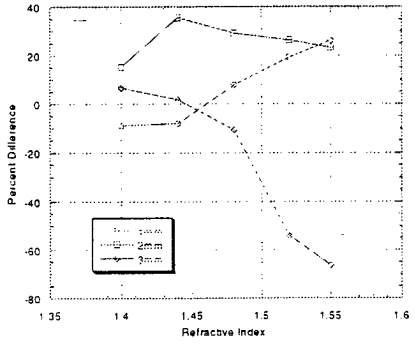
(a) x direction shift of μ_a images



(b) y direction shift of μ_a images



(c) x direction shift of μ_s' images



(d) y direction shift of μ_s' images

Fig. 3. Shift of the target centers

Acknowledgements

This research is supported in part by grants from the National Institute of Health (NIH) (CA 78334) and the Department of Defense (DOD) (BC 980050).

Fluorescence Lifetime Tomography using Frequency-domain Data

Eric Shives, Yong Xu, Nic Iftimia, and Huabei Jiang
Biomedical Optics Lab
Department of Physics & Astronomy
Clemson University
Clemson, SC 29634-0978

Abstract: We present here fluorescence lifetime image reconstructions for heterogeneous lifetimes in a phantom study for two cases: lifetime varied with two different dyes and varied with two different oxygen concentrations with the same dye.

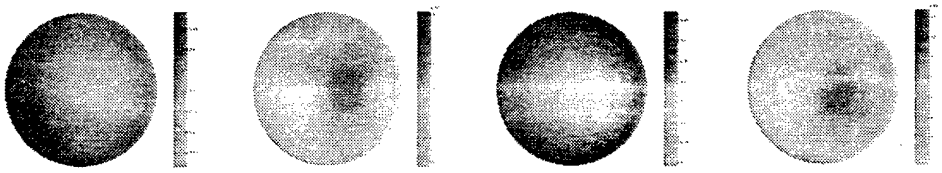
OCIS codes: (170.5280) photon migration, (170.6960) tomography

Introduction: In the past ten years there has been an increased interest in the field of fluorescence lifetime tomography and its clinical applications of breast cancer detection and tissue functional mapping.[1] Cancerous tissue and normal tissue have different properties such as DNA concentration, oxygen concentration, pH, and glucose level. A dye's fluorescence lifetime will change with these differing properties and, that change, may be detected by fluorescence lifetime tomography.[2] It has been shown that a fluorescent dye will have a different lifetime[3,4] and quantum yield in the environment change from normal tissue to cancerous tissue. We modeled this in two cases. In the first case, we used the fluorescent dyes 3,3'-diethylthiatricarbocyanine iodide (DTTCI) and indocyanine green (ICG) that have similar fluorescent spectra but have different lifetimes. By using two dyes with different lifetimes, we are able to simulate a tumor (heterogeneous lifetime) by placing one dye (ICG) in the target and the second dye (DTTCI) in the background. It has also been shown that different oxygen concentration will change the lifetime[5] and quantum yield of an oxygen sensitive fluorescent dye. We will show in this paper that it is possible using frequency-domain data to reconstruct a lifetime image where there is a heterogeneity in lifetime and quantum yield. We also hope to show that it is possible to reconstruct a lifetime image based on the lifetime change of a dye in the environment change of different oxygen concentrations (in progress).

Experimental Set-up: Our frequency-domain system uses a single modulated near-infrared (785 nm wavelength) laser diode for the light source. The light is passed though 16 different source positions around the phantom and collected from 16 different detector positions. An interferential filter was used to collect the fluorescence signals. AC, DC intensities, and phase shift changes between reference and diffused light were obtained.

Experimental Method: A solid phantom consisting of agar, water, and intralipid, was used to simulate human tissue. The cylindrical diameter of the phantom was 50 mm and the diameter of the target was 15 mm. 0.2 μM of DTTCI was used in the background and 1 and 3 μM of ICG were used in the target in order to simulate a tumor and the lifetime and quantum yield change. The lifetime[6] of DTTCI and ICG in water are 1.18 ns and 0.56 ns respectively. The second part of our experiment using oxygen concentration is in progress .

Experimental Results: The figures show that it is possible to accurately reconstruct an image from the heterogeneity in the fluorescence lifetime and quantum yield values. Fig.'s 2a and 2c show the lifetime and quantum yield images respectively for the case of the 1 μM ICG target. Fig.'s 2c and 2d show the lifetime and quantum yield images respectively for the case of the 2.5 μM ICG target. The position of the target is correct in all cases, but the quantum yield image gave a better size resolution. The lifetime image correctly shows that the lifetime of the dye (ICG) in the target is less than the lifetime of the dye (DTTCI) in the background.



(a) lifetime (b) quantum yield (c) lifetime (d) quantum yield

Fig. 2 (Reconstructed lifetime images of the phantom. ICG concentration is 1 μM in a and b and 2.5 μM in c and d)

Results for the second part of our experiment are in progress.

Reference:

1. Jiang, H. *Applied Optics* 1998. **37**. 5337
2. Bambot. S.; Lakowitz. J. and Rao. G. *Trands Biotechnology* 1993. **13**. 106
3. Pradham. A.; Das. B. B.; Yoo. K. M.; Cleary. J.; Prudente, R.; Celmer. E.; and Alfano. R.R. *Lasers Life Science* 1992. **4**, 225-234
4. Tata. D. B.; Foresti. M.; Cordero, J and Tomashfpsky. P. *Biophys. Journal* 1986. **50**. 463-469
5. Vinogradov, S. A.; Lo, L.; Jenkins. W. T.; Evans. S. M.; Koch. C. and Wilson, D. F. *Biophysical Journal 1996*, **70**, 1609-1617
6. Muraca. E. M.; Lopez. G.; Reynolds, J. S.; Troy, T. L.; and Hutchinson. C. L. *Photochemistry and Photobiology* 1997. **66**, 55-64