Discretization Error Analysis for Fluorescence Diffuse Optical Tomography

Laurel Reilly-Raska[a], Murat Guven[a], Birsen Yazici[a]

[a]Rensselaer Polytechnic Institute, Troy, NY, USA

ABSTRACT

In fluorescence diffuse optical tomography, the error due to discretization of the forward and inverse problems leads to an error in the reconstructed image. Using a Galerkin formulation, we consider zeroth and first order Tikhonov regularization terms and analyze the forward and inverse problems under an optimization formulation which incorporates *a priori* information. We derive error estimates to describe the impact that discretization of the forward and inverse problems due to finite element method has on the accuracy of the reconstructed optical absorbtion image.

Keywords: discretization, error, analysis, optical imaging, fluorescence

1. INTRODUCTION

Fluorescence diffuse optical tomography (FDOT) is an imaging modality which capitalizes on light propagating at near infrared (NIR) spectral ranges in tissues in which a fluorescent agent has been introduced.[2] Measurements collected on the boundary of the domain are used to reconstruct a three-dimensional image of the underlying tissue and its properties. This functional image can lead to identification of diseased tissue for use in non-invasive clinical diagnosis[7] and other various medical applications.[?] Furthermore, recent developments in fluorescent contrast agents means that specific events, cellular receptors,[5] or tissue properties can be readily targeted.

The key challenge in fluorescence imaging rests with the image reconstruction algorithms. There are two main issues, computational complexity and accuracy. Our desire is to reduce the complexity while maintaining the highest possible accuracy in the reconstructed image. This is a difficult undertaking, as higher accuracy generally comes at the expense of computational efficiency. Typically, image reconstruction in fluorescence tomography occurs through a two loop system. The outer loop consists of solving the coupled system of partial differential equations defining the forward problem to determine the light field. The inner loop solves the nonlinear inverse problem for parameter estimation by applying various inversion techniques. This usually consists of a discrete numerical approximation algorithm, such as the finite element method used in this paper, which introduces an error into the reconstructed image based on the discretization employed. Clearly, poor choice of discretization can lead to errors in the reconstruction.

The main premise of this work is to analyze the error in fluorescence optical imaging due to discretization. We identify the key factors specific to the imaging problem that show how discretization impacts the accuracy of the reconstructed optical absorption image.

There is a vast degree of work describing the impact of discretization in reconstructed optical imaging[8911].[10] Applying approximation error estimates allows the use of lower than normal mesh densities thus increasing computational efficiency.[1] Numerous studies have been performed on the discretization error of PDEs but less is known about the error as it applies to estimation. One recent study applied discretization error estimates on diffuse optical tomography.[13] It was shown that developing an optimal adaptive mesh for each of the forward and inverse solutions yielded greater clarity in the final reconstruction. In that paper, the application of linear basis functions employed in the collocation method worked well with diffuse optical tomography although trouble arises in applying the same method to FDOT because a second derivative operator which eliminates the linear basis functions occurs in the analysis. Choosing other basis functions or employing a finite difference method on the resultant equations, as was done in[3] are both options to handle the second derivative operator. However, the

Send correspondence to Birsen Yazici: E-mail: yazici@ecse.rpi.edu

Multimodal Biomedical Imaging III, edited by Fred S. Azar, Xavier Intes,
Proc. of SPIE Vol. 6850, 68500B, (2008)
1605-7422/08/$18 · doi: 10.1117/12.763724

finite difference method introduces its own error and it is possible to find tighter error bounds by reformulating the analysis from[?] under the Galerkin methodology.

In this study, we model the forward problem as a coupled set of PDEs and ultimately consider the variational form, as we apply a finite element method for solving the problem. The inverse problem is a nonlinear integral equation which we linearize using an iterative method, where zeroth and first order Tikhonov regularization terms are selected to address the ill-posedness of the resulting linear integral equation. Next, we establish the inverse problem as an optimization problem using a variational formulation. We discretize the forward and inverse problems using a finite element expansion of linear Lagrange basis functions. We analyze the error due to discretized forward problem when there is no discretization due to the inverse problem and compute an upper bound on this error. Next we examine the error due to discretization of the inverse problem and obtain another error bound. We discuss the major implications established by these bounds and the overall effect on the reconstructed images.

We note that the error analysis presented in this work can be used to design adaptive mesh refinement schemes in order to reduce error in the final reconstructed image.

2. FORWARD PROBLEM

2.1. Notational Conventions

In this paper we denote operators by capital cursive Latin letters ($\boldsymbol{\mathcal{A}}$), finite element matrices by bold capital Latin letters ($\mathbf{A}$) and finite element approximations of a function (f) by capital letters (F). Functions are denoted by lowercase Latin and Greek letters. For a function g, we employ the following notational definitions: g^* indicates the adjoint, $\overline{g}$ indicates complex conjugate, $\boldsymbol{g}$ (bold) denotes vectorized quantities. Table 1 provides a summary of key variables and function spaces used throughout the paper.

Table 1. Definition of function spaces and norms.

Notation	Explanation
$C(\Omega)$	Space of continuous complex-valued functions on Ω
$L^\infty(\Omega)$	$L^\infty(\Omega) = \{f \vert\ ess \sup_\Omega \vert f(\mathbf{x})\vert < \infty\ \}$
$L^p(\Omega)$	$L^p(\Omega) = \{f\vert\ (\int_\Omega \vert f(\mathbf{x})\vert^p d\mathbf{x})^{1/p} < \infty\ \}$, $p \in [1, \infty)$
$H^p(\Omega)$	$H^p(\Omega) = \{f\vert\ (\sum_{\vert z\vert \le p} \Vert D_w^z f\Vert_0^2)^{1/2} < \infty\ \}$, $p \in [1, \infty)$
$\Vert f\Vert_0$	The $L^2(\Omega)$ norm of f
$\Vert f\Vert_p$	The $H^p(\Omega)$ norm of f
$\Vert f\Vert_{p*}$	The norm of f in the dual space $H^{p*}(\Omega)$
$\Vert f\Vert_\infty$	The $L^\infty(\Omega)$ norm of f
$\Vert f\Vert_{L^p(\Omega)}$	The $L^p(\Omega)$ norm of f
$\Vert f\Vert_{0,m}$	The L^2 norm of f over the m^{th} finite element Ω_m

2.2. Forward problem derivation

We start with the coupled diffusion equations which describe the light transport in a fluorescent medium of a bounded domain $\Omega \subset R^3$ with Lipschitz boundary $\partial\Omega$

$$\nabla \cdot [D_x(\boldsymbol{r})\nabla\phi_x(\boldsymbol{r},\omega)] - [\mu_{ax}(\boldsymbol{r}) + j\omega/c]\phi_x(\boldsymbol{r},\omega) = 0, \tag{1}$$

$$\nabla \cdot [D_m(\boldsymbol{r})\nabla\phi_m(\boldsymbol{r},\omega)] - [\mu_{am}(\boldsymbol{r}) + j\omega/c]\phi_m(r,\omega) = -\phi_x(\boldsymbol{r})\eta\mu_{axf}(\boldsymbol{r})\frac{1 - j\omega\tau(\boldsymbol{r})}{1 + (\omega\tau(\boldsymbol{r}))^2}, \tag{2}$$

where $\boldsymbol{r} = [r_1, r_2, r_3] \in \Omega$, subscripts x, m denote the excitation and emission wavelengths, $\phi_{x,m}$ represent the optical fields, $D_{x,m}$ represent the isotropic diffusion coefficients. We assume the diffusion coefficients are known and that they are identical during both the excitation and emission for all points in the closed domain; this implies $D(\boldsymbol{r}) := D_x(\boldsymbol{r}) = D_m(\boldsymbol{r})$. The quantum efficiency is denoted by η, μ_{axf} is the absorbtion coefficient of the fluorophore, $\tau(\boldsymbol{r})$ is the lifetime of the fluorophore. Later, subsequent developments can be extended to include multiple frequencies where τ is known. However, for the sake of exposition, we make the following simplifying assumption that the frequency $\omega = 0$. The quantities μ_{ax} and μ_{am} represent the absorption coefficient of the medium at the excitation and emission wavelengths, respectively. Typically these are represented as

$$\mu_{ax}(\boldsymbol{r}) = \mu_{axe}(\boldsymbol{r}) + \mu_{axf}(\boldsymbol{r}), \tag{3}$$

$$\mu_{am}(\boldsymbol{r}) = \mu_{ame}(\boldsymbol{r}) + \mu_{amf}(\boldsymbol{r}), \tag{4}$$

where the subscript e denotes endogenous properties and f denotes exogenous properties.

Let N_S be the number of point sources at position $\boldsymbol{r}_i$ for $i = 1...N_S$ along the boundary $\partial\Omega$. Based on the assumptions stated above, we use the following boundary value problem to model NIR light propagation at the excitation wavelength due to the ith source,

$$\nabla \cdot [D(\boldsymbol{r})\nabla\phi_x(\boldsymbol{r},\boldsymbol{r}_i)] - \mu_{ax}(\boldsymbol{r})\phi_x(\boldsymbol{r},\boldsymbol{r}_i) = 0, \tag{5}$$

$$\nabla \cdot [D(\boldsymbol{r})\nabla\phi_m(\boldsymbol{r},\boldsymbol{r}_i)] - \mu_{am}(\boldsymbol{r})\phi_m(\boldsymbol{r},\boldsymbol{r}_i) = -\phi_x(\boldsymbol{r},\boldsymbol{r}_i)\eta\mu_{axf}(\boldsymbol{r}), \tag{6}$$

where $\boldsymbol{r} \in \Omega$. The Robin-type boundary conditions are

$$2D(\boldsymbol{r})\frac{\partial\phi_x(\boldsymbol{r},\boldsymbol{r}_i)}{\partial n} + \rho\phi_x(\boldsymbol{r},\boldsymbol{r}_i) = -S(\boldsymbol{r}_i), \tag{7}$$

$$2D(\boldsymbol{r})\frac{\partial\phi_m(\boldsymbol{r},\boldsymbol{r}_i)}{\partial n} + \rho\phi_m(\boldsymbol{r},\boldsymbol{r}_i) = 0, \tag{8}$$

where $\boldsymbol{r}, \boldsymbol{r}_i \in \partial\Omega$, ρ is a parameter governing the internal reflection at the boundary $\partial\Omega$, and $\partial/\partial n$ denotes the directional derivative along the unit normal vector on the boundary. In this work, $S(\boldsymbol{r}_i)$ represents the ith point source on the boundary, which is modeled by a Gaussian function centered at source position.[13]

In order to simplify the analysis of later sections, we make use of the adjoint problem associated with (6) and (8). Let N_D be the number of detectors. Then, for a detector located at $\boldsymbol{r}_j \in \partial\Omega, j = 1...N_D$

$$\nabla \cdot [D(\boldsymbol{r})\nabla g_m^*(\boldsymbol{r},\boldsymbol{r}_j)] - \mu_{am}(\boldsymbol{r})g_m^*(\boldsymbol{r},\boldsymbol{r}_j) = 0, \quad \boldsymbol{r} \in \Omega, \tag{9}$$

$$2D(\boldsymbol{r})\frac{\partial g_m^*(\boldsymbol{r},\boldsymbol{r}_j)}{\partial n} + \rho g_m^*(\boldsymbol{r},\boldsymbol{r}_j) = S^*(\boldsymbol{r}_j), \quad \boldsymbol{r} \in \partial\Omega, \tag{10}$$

where S^* is the adjoint source. For a point adjoint source located at the detector position $\boldsymbol{r}_j$,

$$g_m^*(\boldsymbol{r},\boldsymbol{r}_j) = g_m(\boldsymbol{r}_j,\boldsymbol{r}), \boldsymbol{r} \in \Omega, \tag{11}$$

where g_m is the Green's solution to (6). Note that in this paper, we model the point adjoint source by a Gaussian function with sufficiently low variance, centered at $\boldsymbol{r}_j$.

The emission field at $\boldsymbol{r}_j$ due to the source at $\boldsymbol{r}_i$ is given by the following nonlinear integral equation:

$$\phi_m(\boldsymbol{r}_j,\boldsymbol{r}_i) = \int_\Omega g_m^*(\boldsymbol{r},\boldsymbol{r}_j)\phi_x(\boldsymbol{r},\boldsymbol{r}_i)\eta\mu_{axf}(\boldsymbol{r})d\boldsymbol{r}. \tag{12}$$

The relationship between ϕ_m and μ_{axf} defined in (14) is nonlinear because g_m^* is dependent on μ_{amf} which in turn is related to μ_{axf}. We assume that μ_{ax} can be determined independently of μ_{axf}. The nonlinearity is therefore due entirely to the dependence of g_m^* on μ_{amf}.

In the next section, we formally state the inverse problem and address the nonlinearity by using an iterative linearization scheme based on first order Frechet derivatives.

3. INVERSE PROBLEM

Given N_S sources and N_D detectors, we define $\Gamma_{i,j}$ to be the measurement for a detector at position $r_j, j = 1...N_D$ due to a source at $r_i, i = 1...N_S$. The individual measurements can be grouped into the vector form,

$$\mathbf{\Gamma} := [\Gamma_{1,1}, ...\Gamma_{1,N_D}, \Gamma 2, 1, ...\Gamma_{N_S,N_D}]^T , \tag{13}$$

where the (i, j)th measurement satisfies the following model:

$$\Gamma_{i,j} = \int_{\Omega} g_m^*(\boldsymbol{r}, \boldsymbol{r}_j)\phi_x(\boldsymbol{r}, \boldsymbol{r}_i)\eta\mu_{axf}(\boldsymbol{r})d\boldsymbol{r}. \tag{14}$$

Our objective is to recover the quantity μ_{axf} using the measurement vector $\mathbf{\Gamma}$ based on the nonlinear integral equation (14) for each (i, j)th pair.

In the next section, to address the problem of nonlinearity in (14), we select an iterative linearization scheme based on first order Frechet derivatives. Next, to address the ill-posedness, we discuss regularization in an optimization framework and incorporation of *a priori* information about the unknown image μ_{axf}. Then, by taking the derivative of the resulting optimization problem and defining appropriate boundary conditions, we convert it into a boundary value problem. In the final subsection, we show the variational formulation of the boundary value problem and comment on the existence and uniqueness of the solution.

3.1. Iterative linearization

Consider an infinitestimal perturbation on μ_{axf},[19,20]

$$\mu_{axf} \leftarrow \mu_{axf} + \delta\mu_{axf} \tag{15}$$

Then the corresponding perturbation $\delta\phi_m$ at each linearization step at detector position $\boldsymbol{r}_j$ due to the source at $\boldsymbol{r}_i$ is given by the following linear integral equation

$$\delta\phi_m(\boldsymbol{r}_j, \boldsymbol{r}_i) = \int_{\Omega} g_m^*(\boldsymbol{r}, \boldsymbol{r}_j)\phi_x(\boldsymbol{r}, \boldsymbol{r}_i)\eta\delta\mu_{axf}(\boldsymbol{r})d\boldsymbol{r} \tag{16}$$

where g_m^* is the solution to the boundary value problem (9)-(10). To simplify notation, we introduce $\delta\mu(\boldsymbol{r}) := \eta\delta\mu_{axf}(\boldsymbol{r})$ which represents the unknown perturbed fluorophore absorption coefficient scaled by the quantum efficiency. Furthermore, noting that the emission and excitation subscripts are fixed for the duration of this analysis, we represent $g_j^*(\boldsymbol{r}) := g_m^*(\boldsymbol{r}, \boldsymbol{r}_j)$ and $\phi_i(\boldsymbol{r}) := \phi_x(\boldsymbol{r}, \boldsymbol{r}_i)$, suppressing the x, m dependence of these functions.

We define $\delta\Gamma_{i,j}$ to be the differential measurement at the ith source and jth detector normalized to the known background fluorophore absorption. Let $H_{ij}(\boldsymbol{r}) = g_j^*(\boldsymbol{r})\phi_i(\boldsymbol{r})$. Using (16) we model $\delta\Gamma_{i,j}$ as follows:

$$\delta\Gamma_{i,j} = \int_{\Omega} H_{ij}(\boldsymbol{r})\delta\mu(\boldsymbol{r})d\boldsymbol{r}, \tag{17}$$

$$:= (\boldsymbol{\mathcal{A}}\delta\mu)_{ij}. \tag{18}$$

We represent individual source-detector pairs as elements of a vector

$$\delta\mathbf{\Gamma} := [\delta\Gamma_{1,1}, \cdots, \delta\Gamma_{1,N_D}, \delta\Gamma_{2,1}, \cdots, \delta\Gamma_{N_S,N_D}]^T \tag{19}$$

$$:= \boldsymbol{\mathcal{A}}\delta\mu \tag{20}$$

where $\boldsymbol{\mathcal{A}} : L^2(\Omega) \to \mathbb{R}^{N_S \times N_D}$ is a vector of operators whose (i, j)th entry acting on $\delta\mu$ corresponds to (18). Although all norms on a finite dimensional space are equivalent, we select the norm on the range of $\boldsymbol{\mathcal{A}}$ to be the l^1 norm as this proves useful in later analysis. Then, an upper bound for the linear operator can be given by

$$\|\boldsymbol{\mathcal{A}}\|_{L^2(\Omega)\to l^1} \leq \sum_{i,j}^{N_D,N_S} \|g_j\phi_i\|_0. \tag{21}$$

The boundedness and the finite-dimensional range of operator $\boldsymbol{\mathcal{A}}$ means it is compact.[12]

We define the adjoint* operator $\boldsymbol{\mathcal{A}}^* : \mathbb{R}^{N_S \times N_D} \to L^2(\Omega)$ acting on a general function $w \in \mathbb{R}^{N_S \times N_D}$ as

$$[\boldsymbol{\mathcal{A}}^* w](\boldsymbol{r}) = [H_{11}^*(\boldsymbol{r}) \dots H_{N_S 1}^*(\boldsymbol{r}) \dots H_{N_S N_D}^*(\boldsymbol{r})]w \tag{22}$$

where $H_{ij}^*(\boldsymbol{r}) = g_j^*(\boldsymbol{r})\phi_i(\boldsymbol{r})$ for $j = 1, .., N_D$ and $i = 1, .., N_S$.

Let $\mathcal{B} = \boldsymbol{\mathcal{A}}^*\boldsymbol{\mathcal{A}} : L^2(\Omega) \to L^2(\Omega)$

$$(\mathcal{B}\delta\mu)(\boldsymbol{r}) \quad := \quad \int_\Omega \kappa(\boldsymbol{r}, \acute{\boldsymbol{r}})\delta\mu(\acute{\boldsymbol{r}})d\acute{\boldsymbol{r}}, \tag{23}$$

where

$$\kappa(\boldsymbol{r}, \acute{\boldsymbol{r}}) := \sum_{i,j}^{N_D, N_S} H_{ij}^*(\boldsymbol{r})H_{ij}(\acute{\boldsymbol{r}}). \tag{24}$$

Then, an alternate form of (20) can be expressed as follows:

$$\gamma(\boldsymbol{r}) = (\mathcal{B}\delta\mu)(\boldsymbol{r}), \tag{25}$$

where $\gamma = \boldsymbol{\mathcal{A}}^*\delta\boldsymbol{\Gamma}$. Note that $\mathcal{B}$ is compact since $\boldsymbol{\mathcal{A}}$ is compact. Therefore, (25) is ill-posed.

In the next section, we address the ill-posedness in an optimization framework by incorporating regularization terms.

3.2. Inverse problem as an optimization problem and regularization

In this section, we address the ill-posedness of (25) through regularization in the optimization framework which provides a suitable means for the incorporation of *a priori* information about the solution. In this respect, we consider the following minimization problem where we seek a solution $\delta\hat{\mu} \in H^1(\Omega)$:

$$\delta\hat{\mu} \quad = \quad \min_{\delta\mu \in H^1(\Omega)} J\left(\delta\mu, \nabla\delta\mu\right), \tag{26}$$

where the $H^1(\Omega)$ smoothness on the solution is imposed through the use of appropriate regularization terms. The functional J in (26) can be decomposed into two parts, J_L and J_R as follows:

$$J(\delta\mu, \nabla\delta\mu) = J_L(\delta\mu) + J_R(\delta\mu, \nabla\delta\mu), \tag{27}$$

where J_L measures the difference between the predicted and actual measurements

$$J_L(\delta\mu) = \|\Gamma - \mathcal{A}\delta\mu\|_{l^2}^2, \tag{28}$$

and the regularization term J_R contains the *a priori* information. In this work, we assume that *a priori* information on the image and image gradient is available. To make use of such *a priori* information, we use both zeroth- and first-order Tikhonov regularization terms simultaneously,[13] ,[21] ,

$$J_R(\delta\mu, \nabla\delta\mu) \quad = \quad \lambda_1 \int_\Omega \left[\delta\mu(\boldsymbol{r}) - \beta_1(\boldsymbol{r})\right]^2 d\boldsymbol{r} + \lambda_2 \int_\Omega |\nabla\delta\mu(\boldsymbol{r}) - \beta_2(\boldsymbol{r})|^2 d\boldsymbol{r}, \tag{29}$$

where $\nabla\delta\mu$ is the image gradient and $\lambda_1, \lambda_2 > 0$ are regularization parameters. Using (28) and (29), the minimization problem (26) can be rewritten as follows:

$$\delta\hat{\mu} = \min_{\delta\mu \in H^1(\Omega)} \left(\sum_{j,i}^{N_D, N_S} \left[\delta\Gamma_{j,i} - (\mathcal{A}\delta\mu)_{j,i}\right]^2 + \lambda_1 \int_\Omega \left[\delta\mu(\boldsymbol{r}) - \beta_1(\boldsymbol{r})\right]^2 d\boldsymbol{r} \right.$$
$$\left. + \lambda_2 \int_\Omega \left|\nabla\delta\mu(\boldsymbol{r}) - \beta_2(\boldsymbol{r})\right|^2 d\boldsymbol{r} \right). \tag{30}$$

*For the definition of adjoint operators in Banach spaces see.[12]

There are a number of methods in choosing appropriate regularization parameters,[22] .[23] In this work, we assume that λ_1 and λ_2 are properly chosen and focus on deriving discretization error estimates. In the next section, after defining appropriate boundary conditions, we consider the equivalent variational formulation of the minimization problem in (30).

3.3. Inverse problem as boundary value problem and variational formulation

In this work, we follow a finite element method for the discretization of the inverse problem. Due to incorporation of the regularization term on the gradient of the solution, a natural step is to formulate the minimization problem as a variational one. In this section, we describe the derivation of the variational problem formulation of the inverse problem by first considering the first order optimality condition for the minimization problem (30). Next, with the aid of properly chosen boundary conditions, we transform the optimization problem into a boundary value problem (BVP), which is followed by the variational formulation of the BVP. Finally, we show that a unique solution exists to the variational formulation of the regularized inverse problem.

The solution of (30) satisfies $\partial J/\partial\delta\mu(\delta\mu, \nabla_q\delta\mu) = 0$ where ∇_q is the gradient with respect to the r_qth direction for $q = 1, 2, 3$. In particular, if $J = \int u(\boldsymbol{r}, \delta\mu, \partial\delta\mu/\partial r_q)d\boldsymbol{r}$, the Gâteaux derivative[18] is defined by

$$\frac{\partial J}{\partial\delta\mu} = \frac{\partial u}{\partial\delta\mu} - \sum_q \frac{\partial}{\partial r_q}\left(\frac{\partial u}{\partial\delta\mu_q}\right). \tag{31}$$

Taking the Gâteaux derivative of (30) with respect to $\delta\mu$ and setting it equal to zero yields:

$$\mathcal{B}\delta\mu(\boldsymbol{r}) + \lambda_1\delta\mu(\boldsymbol{r}) - \lambda_2\nabla^2\delta\mu(\boldsymbol{r}) = f(\boldsymbol{r}), \tag{32}$$

where

$$f(\boldsymbol{r}) := \gamma(\boldsymbol{r}) + \lambda_1\beta_1(\boldsymbol{r}) + \lambda_2\beta_2(\boldsymbol{r}). \tag{33}$$

Note that $f(\boldsymbol{r})$ is composed of known terms from *a priori* information and measurements.

We consider (32) with the following Neumann boundary condition:

$$\frac{\partial\delta\mu}{\partial\hat{n}}(\boldsymbol{r}) = 0, \quad \boldsymbol{r} \in \partial\Omega. \tag{34}$$

where $\partial\delta\mu/\partial\hat{n}$ is the directional derivative of $\delta\mu$ along the unit normal at the boundary $\partial\Omega$. The boundary condition in (34) implies that no changes in the pertubated fluorophore concentration occur across the boundary.

At this point, one can consider a finite difference scheme for the solution of the inverse problem which is posed as a boundary value problem (32)-(34). However, as our goal in this paper is to apply a finite element scheme for the discretization of the BVP, we obtain the corresponding variational (weak) problem. Hence, we multiply both sides of (32) by a test function $\psi \in H^1(\Omega)$, and integrate over Ω. Applying Green's first theorem to the last term on the left and using of the boundary condition in (34), we obtain

$$\int_\Omega \psi(\boldsymbol{r})\left[(\mathcal{B}\delta\mu)(\boldsymbol{r}) + \lambda_1\delta\mu(\boldsymbol{r})\right]d\boldsymbol{r} + \lambda_2\int_\Omega \nabla\psi(\boldsymbol{r})\cdot\nabla\delta\mu(\boldsymbol{r})d\boldsymbol{r} = \int_\Omega \psi(\boldsymbol{r})f(\boldsymbol{r})d\boldsymbol{r}. \tag{35}$$

A more convenient way to express (35) is through a bilinear form. Thus, we define

$$\mathcal{F}(\psi, \delta\mu) := (\psi, \mathcal{B}\delta\mu) + \lambda_1(\psi, \delta\mu) + \lambda_2(\nabla\psi, \nabla\delta\mu) \tag{36}$$

$$\mathcal{G}(\psi) := (\psi, f), \tag{37}$$

where the inner product is defined by

$$(k, l) := \int_\Omega k(\boldsymbol{r})l(\boldsymbol{r})d\boldsymbol{r}.$$

Hence, (35) can be expressed as

$$\mathcal{F}(\psi, \delta\mu) = \mathcal{G}(\psi). \tag{38}$$

It can be shown that the bilinear form (36) is bounded and coercive. Thus, by the Lax-Milgram lemma, we can conclude that a unique solution exists for the problem (38),.[12, 15] For an explicit statement of the Lax-Milgram lemma, see Appendix II.

In the following section, we describe the discretization methods selected in this paper for each of the separate forward and inverse discretizations as well as the combined forward and inverse discretization.

4. DISCRETIZATION BY FINITE ELEMENT METHOD OF THE FORWARD AND INVERSE PROBLEMS

In the following sections, we first discuss the variational formulation and finite element discretization of the forward problem. In practice, for arbitrary domains and background optical properties, no analytical solutions exist for the forward problem when defined in a variational form. Thus, we discretize the forward problem and obtain finite dimensional approximations of g_j^* and ϕ_i, for $j = 1, \cdots, N_D$, $i = 1, \cdots, N_S$.

Next, we use the finite element solutions of the forward problem in the inverse problem formulation, which implies an approximation to the inverse problem. The resulting inverse problem in general does not possess a closed form solution. Therefore, finding the solution calls for numerical techniques. We discuss the discretization of the resulting approximate inverse problem using projection by Galerkin method.

4.1. Discretization of the Forward Problem

In this section, we discuss the forward problem discretization. We express the coupled PDEs in their variational form in order to apply a finite element method.

To do so we multiply (5) by a test function $\chi_1 \in H^1(\Omega)$, and apply Green's theorem to the second derivative term. Then, using the boundary condition in (7) we have

$$\int_\Omega (\nabla\chi_1 \cdot D\nabla\phi_i + \mu_{ax}\chi_1\phi_i)d\boldsymbol{r} + \frac{1}{2\rho}\int_{\partial\Omega} \chi_1\phi_i dl \quad = \quad \frac{1}{2\rho}\int_{\partial\Omega} \chi_1 S_i dl. \tag{39}$$

It can be shown that a unique solution for (39) exists and is bounded.[12] Similarly, for a test function $\chi_2 \in H^1(\Omega)$, the variational form for the adjoint forward problem (9)-(10) becomes

$$\int_\Omega \left(\nabla\chi_2 \cdot D\nabla g_j^* - \mu_{am}\chi_2 g_j^*\right) d\boldsymbol{r} + \frac{1}{2\rho}\int_{\partial\Omega} \chi_2 g_j^* dl = \frac{1}{2\rho}\int_{\partial\Omega} \chi_2 S_i^* dl \tag{40}$$

for which it is possible to show that a unique, bounded solution exists as well.

Let L_k be the piecewise linear Lagrange basis functions, and $Y_i \subset H^1(\Omega)$ be the finite-dimensional subspace spanned by $\{L_k\}$, $i = 1, \ldots, N_i$ for $j = 1, \ldots, N_D$ which are associated with the set of points $\{\boldsymbol{r}_p\}$, $p = 1, \ldots, N_i$, on Ω. Similarly, we define $Y_j^* \subset H^1(\Omega)$ as the finite-dimensional subspace spanned by L_k, for $k = 1, \ldots, N_j$ for $j = 1, \ldots, N_S$ associated with a set of N_j points.

Next, the functions χ_1, ϕ_i in (39) and χ_2, g_j^* in (40) are replaced by their finite-dimensional counterparts

$$\Xi_2(\boldsymbol{r}) := \sum_{k=1}^{N_i} p_k L_k(\boldsymbol{r}), \quad \Phi_i^{N_i} := \sum_{k=1}^{N_i} c_k L_k(\boldsymbol{r}). \tag{41}$$

$$\Xi_1(\boldsymbol{r}) := \sum_{k=1}^{N_j} p_k L_k(\boldsymbol{r}), \quad G_j^{*,N_j} := \sum_{k=1}^{N_j} d_k L_k(\boldsymbol{r}) \tag{42}$$

The representation $\Phi_i^{N_i}$ (G_j^{*,N_j}) is an approximation to the function ϕ_i (g_j^*) for each source (detector). This means that for each source and detector the dimension of the solution can be different; the parameters N_i, N_j can vary for each i and j, respectively. The finite dimensional expansions are therefore dependent on the parameters

N_i, N_j as represented by the superscript. However, we suppress this cumbersome notation as the dependence is clearly understood.

Substitution of (42)-(41) into the variational forward problem (39)-(40) yields the matrix equations

$$\mathbf{M}\mathbf{c}_i = \mathbf{q}_i, \tag{43}$$
$$\mathbf{M}^*\mathbf{d}_j^* = \mathbf{q}_j^*, \tag{44}$$

for $\mathbf{c}_i = [c_1, c_2, ..., c_{Ni}]^T$ and $\mathbf{d}_j^* = [d_1, d_2, ..., d_{Nj}]^T$. Here $\mathbf{M}$ and $\mathbf{M}^*$ are the finite element matrices and $\mathbf{q}_i$ and $\mathbf{q}_j^*$ are the load vectors resulting from the finite element discretization of the forward problem.

The $H^1(\Omega)$ boundedness of the solutions g_j^* and ϕ_i implies that the finite element discretization errors $e_j^* := g_j^* - G_j^*$ and $e_i := \phi_i - \Phi_i$ in the forward problem solutions are bounded. Let $\{\Omega_{ni}\}$ denote the set of linear elements used to discretize (39) for $n = 1, \ldots, N_\Delta^i$, where N_Δ^i is the number of elements for the ith source such that $\bigcup_n^{N_\Delta^i} \Omega_{ni} = \Omega$ for all $i = 1, \ldots N_S$. Similarly, let $\{\Omega_{mj}\}$ denote the set of linear elements used to discretize (40) for $m = 1, \ldots, N_\Delta^{*j}$ where N_Δ^{*j} is the number of elements for the jth detector such that $\bigcup_m^{N_\Delta^{*j}} \Omega_{mj} = \Omega$ for all $j = 1, \ldots N_D$.

A bound for e_j^* and e_i on each finite element can be given by (Theorem 4.4.4 in[15]):

$$\|e_j^*\|_{0,mj} \leq C\|g_j^*\|_{1,mj} h_{mj}, \tag{45}$$
$$\|e_i\|_{0,ni} \leq C\|\phi_i\|_{1,ni} h_{ni}, \tag{46}$$

where C is a positive constant, $\|\cdot\|_{0,mj}$ ($\|\cdot\|_{0,ni}$) and $\|\cdot\|_{1,mj}$ ($\|\cdot\|_{1,ni}$) are respectively the L^2 and H^1 norms on Ω_{mj} (Ω_{ni}), and h_{mj} (h_{ni}) is the diameter of the smallest ball containing the finite element Ω_{mj} (Ω_{ni}) in the solution G_j^* (Φ_i).

In the next section, these approximate solutions to the forward problem are substituted into the inverse problem operator. The error is estimated based on the resulting operators with approximations.

4.2. Simultaneous discretization of the inverse and forward problems

We substitute the forward problem expansions (42)-(41) into $H_{i,j}, H_{i,j}^*$ in the operators $\mathcal{A}, \mathcal{A}^*$ defined by (20) and (22). The resulting operators are denoted by tildes ($\tilde{\mathcal{A}}$, $\tilde{\mathcal{A}}^*$), indicating a finite element solutions of the forward problem are used. By so doing, we arrive at the approximate variational problem formulation:

$$\tilde{\mathcal{F}}(\psi, \tilde{\delta}\mu) = \tilde{\mathcal{G}}(\psi). \tag{47}$$

In (47), $\tilde{\mathcal{F}}(\psi, \tilde{\delta}\mu)$ and $\tilde{\mathcal{G}}(\psi)$ are given respectively by

$$\tilde{\mathcal{F}}(\psi, \tilde{\delta}\mu) := (\psi, \tilde{\mathcal{B}}\tilde{\delta}\mu) + \lambda_1(\psi, \tilde{\delta}\mu) + \lambda_2(\nabla\psi, \nabla\tilde{\delta}\mu) \tag{48}$$
$$\tilde{\mathcal{G}}(\psi) := (\psi, \tilde{f}), \tag{49}$$

where

$$\begin{aligned}(\tilde{\mathcal{B}}\tilde{\delta}\mu)(\boldsymbol{r}) &:= \int_\Omega \tilde{\kappa}(\boldsymbol{r}, \boldsymbol{r}')\tilde{\delta}\mu(\boldsymbol{r}')d\boldsymbol{r}' \\ &= \sum_{j,i}^{N_D,N_S} G_j^*(\boldsymbol{r})\Phi_i(\boldsymbol{r}) \int_\Omega G_j^*(\boldsymbol{r}')\Phi_i(\boldsymbol{r}')\tilde{\delta}\mu(\boldsymbol{r}')d\boldsymbol{r}'\end{aligned}$$

and

$$\begin{aligned}\tilde{f}(\boldsymbol{r}) &:= \tilde{\gamma}(\boldsymbol{r}) + \lambda_1\beta_1(\boldsymbol{r}) + \lambda_2\beta_2(\boldsymbol{r}), \\ &= \sum_{j,i}^{N_D,N_S} G_j^*(\boldsymbol{r})\Phi_i(\boldsymbol{r})\Gamma_{i,j} + \lambda_1\beta_1(\boldsymbol{r}) + \lambda_2\beta_2(\boldsymbol{r}).\end{aligned}$$

Next, we discretize the functions ψ and $\tilde{\delta}\mu$ by representing them in their finite element expansions. Let $V_n \subset H^1(\Omega)$ denote a sequence of finite-dimensional subspaces of dimension n, spanned by the first-order Lagrange basis functions $\{L_1, \ldots, L_n\}$ which are associated with the set of points $\{\boldsymbol{r}_p\}$, $p = 1, \ldots, n$, on Ω. We replace ψ and $\tilde{\delta}\mu$ in (38) by their respective, finite dimensional counterparts $\Psi^n \in V_n$ and $\tilde{\Delta}\mu^n \in V_n$

$$\Psi^n := \sum_{k=1}^{n} p_k L_k(\boldsymbol{r}), \tag{50}$$

$$\tilde{\Delta}\mu^n := \sum_{k=1}^{n} m_k L_k(\boldsymbol{r}), \tag{51}$$

where p_k and m_k are unknown coefficients. As it is clear that the finite-dimensional expansions are dependent on the parameter n, this dependence is hereafter suppressed. Substituting (50)-(51) into (47) arriving at

$$\tilde{\mathcal{F}}(\Psi, \tilde{\Delta}\mu) = \tilde{G}(\Psi). \tag{52}$$

This can be transformed to a matrix equation

$$\mathbf{F}_n \boldsymbol{m} = \mathbf{G}_n, \tag{53}$$

where $\boldsymbol{m} = [m_1, \cdots, m_n]^T$ represents the unknown coefficients in the finite expansion of (51) and $\mathbf{F}_n$ and $\mathbf{G}_n$ are respectively the finite element matrix and the load vector resulting from the projection of (38) by Galerkin method.

5. ANALYSIS OF THE ERROR IN FLUORESCENCE IMAGING DUE TO DISCRETIZATION

In this work, we consider the solution of the problem stated in (38) to be exact since there is no introduction of finite element methods contained in the formulation. It is our desire to examine the error in fluorescence absorption imaging due to finite element discretization of the forward and inverse problems. We then use the error analysis to design an adaptive mesh based on these error estimates that could reduce the total error in the reconstructed image.

We have divided this section into two subsections. In the first, we derive an estimate for the error in fluorescence absorption imaging due to forward problem discretization as described in the previous section. We employ tildes to denote errors due to forward problem discretization; the resulting approximated problem is given by (47). Note that the solution, $\tilde{\delta}\mu$ satisfies this approximated equation and is different from $\delta\mu$, which is the exact solution of (38). Thus, the first error we find is the difference $e = \delta\mu - \tilde{\delta}\mu$. Note that the inverse problem has not been discretized for this case.

In the second subsection, we analyze the fluorescence absorption imaging error due to finite element discretization for the inverse problem by examining the approximated equation given by (52). In this formulation, the statement of the problem has been fully discretized. Here, we describe the error in fluorescence absorption imaging due to discretization of the inverse problem by comparing the solutions of (47) to (52), $E = \tilde{\delta}\mu - \tilde{\Delta}\mu$. We define the total error as the difference between the solutions of (38) and (52) in terms of two contributors:

$$\delta\mu - \tilde{\Delta}\mu = e + E. \tag{54}$$

Each of the error estimates are presented as theorems with proofs given in the appendices.

5.1. Error in fluorescence imaging due to forward problem discretization

Theorem 1:

Let $\{\Omega_{ni}\}$ denote the set of linear elements used to discretize (39) for $n = 1, \ldots, N^i_\Delta$; such that $\bigcup_n^{N^i_\Delta} \Omega_{ni} = \Omega$ and h_{ni} be the diameter of the smallest ball that contains the nth element in the solution Φ_i, for all $i = 1, \ldots N_S$. Similarly, let $\{\Omega_{mj}\}$ denote the set of linear elements used to discretize (40) for $m = 1, \ldots, N^{*j}_\Delta$; such that $\bigcup_m^{N^{*j}_\Delta} \Omega_{mj} = \Omega$ and h_{mj} be the diameter of the smallest ball that contains the mth element in the solution G^*_j, for all $j = 1, \ldots N_D$. Then, a bound for the error between the solution $\delta\mu$ of (38) and the solution $\tilde{\delta}\mu$ of (47) due to the approximations $\tilde{\mathcal{F}}$ and $\tilde{\mathcal{G}}$ is given by:

$$\begin{aligned} \|\delta\mu - \tilde{\delta}\mu\|_1 \quad \leq \quad & \frac{C}{\min(\lambda_1, \lambda_2)} \max_{i,j} \|g^*_j \phi_i\|_0 \\ & \times \left(\sum_{i=1}^{N_S} \sum_{n,j}^{N^{*j}_\Delta, N_D} (2\|g^*_j \delta\mu\|_{0,ni} + \|g^*_j\|_{\infty,ni} \|\alpha\|_0) \|\phi_i\|_{1,ni} h_{ni} \right. \\ & \left. + \sum_{j=1}^{N_D} \sum_{m,i}^{N^i_\Delta, N_S} (2\|\phi^*_i \delta\mu\|_{0,mj} + \|\phi_i\|_{\infty,mj} \|\alpha\|_0) \|g^*_j\|_{1,mj} h_{mj} \right), \end{aligned} \tag{55}$$

where $\alpha \in L^2(\Omega)$ satisfies (25).

Proof: See[24]here. □

Theorem 1 provides two main implications. First, it shows the specific effect that the forward problem discretization has on the accuracy of the reconstruction. This suggests that the forward problem discretization scheme should take into account the inverse problem discretization accuracy, as it directly effects the error bound. Second, this theorem suggests the regions where an adaptive mesh may be optimally refined. Clearly, using a small value for h_{ni} is useful in places where contributing terms due to the jth detector $(2\|g^*_j \delta\mu\|_{0,ni} + \|g^*_j\|_{\infty,ni} \|\alpha\|_0)$ are large. Similarly, restricting the size of h_{mj} reduces the error where the source term contribution $(2\|\phi^*_i \delta\mu\|_{0,mj} + \|\phi_i\|_{\infty,mj} \|\alpha\|_0)$ is large. Note also that the values of $\|g^*_j\|$ $(\|\phi_i\|)$ are higher close to the jth detector (ith source). Keeping h_{mj} (h_{ni}) small near the detector (source) can counter this effect.

Furthermore, it is clear that other details can contribute to a higher error. The regularization parameters scale the sum of terms. Choosing smaller values for λ_1, λ_2 can result in a higher error estimate since the regularization parameters enter as a reciprocal. Additionally, the solutions to the forward problem $\|g^*_j \phi_i\|_0$ scale the result of the error estimate. Note too that since the error is a sum over all sources and detectors, increasing the number of either can impact the error estimate. Finally, we note this error estimate shows a dependence not only on the finite-element discretization error for the forward problem solutions but also on the location of the the heterogeneity with respect to the sources and detectors due to g^*_j being large near the jth detector. Thus, simply reducing the error of the finite element discretization may not automatically ensure accuracy in the reconstructed image because the accuracy depends on the location of the heterogeneity.

5.2. Error in fluorescence imaging due to inverse problem discretization

Theorem 2:

Consider the Galerkin projection of the variational problem (47) on a finite dimensional subspace $V_n \subset H^1(\Omega)$ using a set $\{\Omega_t\}$ of linear finite elements, for $t = 1, \cdots, N_\Delta$ whose vertices are at $\{r_p\}$, $p = 1, \cdots, n$ such that $\bigcup_t^{N_\Delta} \Omega_t = \Omega$, and let h_t be the diameter of the smallest ball that contains the t^{th} element. Assume that the solution $\tilde{\delta}\mu$ of (47) also satisfies $\tilde{\delta}\mu \in H^2(\Omega)$. Then, a bound for the error E due to Galerkin projection of (47) with respect to the solution $\tilde{\delta}\mu$ of (47) can be given by

$$\begin{aligned} \|\tilde{\delta}\mu - \tilde{\Delta}\mu\|_1 \leq \frac{C}{\min(\lambda_1, \lambda_2)} & \left(\max_{i,j} \|G^*_j \Phi_i\|_0 \sum_t^{N_\Delta} \sum_{i,j}^{N_S, N_D} \|\Phi_i G^*_j\|_{0,t} \|\tilde{\delta}\mu\|_{2,t} h_t^2 \right. \\ & \left. + \lambda_1 \sum_t^{N_\Delta} \|\tilde{\delta}\mu\|_{2,t} h_t^2 + \lambda_2 \sum_t^{N_\Delta} \|\tilde{\delta}\mu\|_{2,t} h_t \right), \end{aligned} \tag{56}$$

where $\lambda_1, \lambda_2 > 0$ are regularization parameters.

Proof: [24] □

We discuss the error estimate and possible implications on the reconstructed image here. The finite-element solutions to the forward problem $\|G_j^* \Phi_i\|_{0,t}$ scale $\|\tilde{\delta}\mu\|_{2,t}$ in (56). This demonstrates that the forward problem solution is spatially dependent on the inverse problem discretization. It further implies that the error bound is dependent on the location of the heterogeneity with respect to the sources and detectors as the forward problem solutions are larger close to the sources and detectors. Note also that the number of sources and detectors, as well as the number of terms in the finite element discretization all effect the error estimate. Similarly to Theorem 1, the regularization parameters have a reciprocal multiplicative effect on all terms in the error. However, in the last two terms the regularization parameters λ_1, λ_2 effect the second and third term, respectively. Finally, the mesh parameter h_t^2 should be kept small over regions where $\|\tilde{\delta}\mu\|_{2,t}$ is large. As in the previous theorem, simply keeping the mesh parameter small may not ensure a reduction of the error in the reconstructed image because of the dependence on the location of the heterogeneity. However, this can be countered by refining the mesh size when the following terms are large: $\|G_j^* \Phi_i\|_{0,t}$ and $\|\Phi_i G_j^*\|_{0,t}$.

Combining results of Theorems 1 and 2 and rearranging the terms, both error estimates can be viewed in a single equation. Let $\|G_j^* \Phi_i\|_0 \leq \|g_j^* \phi_i\|_0$ for all $i = 1, \cdots, N_S$ and $j = 1, \cdots, N_D$. Then,

$$\|\delta\mu - \tilde{\Delta}\mu\|_1 \leq \frac{C}{\min(\lambda_1, \lambda_2)} \max_{i,j} \|g_j^* \phi_i\|_0 \sum_{i,j}^{N_S, N_D} \left(\sum_n^{N_\Delta^{*j}} (2\|g_j^* \delta\mu\|_{0,ni} + \|g_j^*\|_{\infty,ni} \|\alpha\|_0) \|\phi_i\|_{1,ni} h_{ni} \right.$$
$$\left. + \sum_m^{N_\Delta^i} (2\|\phi_i^* \delta\mu\|_{0,mj} + \|\phi_i\|_{\infty,mj} \|\alpha\|_0) \|g_j^*\|_{1,mj} h_{mj} + \sum_t^{N_\Delta} \|\Phi_i G_j^*\|_{0,t} \|\tilde{\delta}\mu\|_{2,t} h_t^2 \right)$$
$$+ \frac{C}{\min(\lambda_1, \lambda_2)} \left(\lambda_1 \sum_t^{N_\Delta} \|\tilde{\delta}\mu\|_{2,t} h_t^2 + \lambda_2 \sum_t^{N_\Delta} \|\tilde{\delta}\mu\|_{2,t} h_t \right). \tag{57}$$

6. CONCLUSION

In this work, we analyzed the effect of discretization on the accuracy of fluorescence optical tomography. We summarized the results of our analysis in two theorems which present bounds on the error in the reconstructed fluorophore absorption coefficient resulting from discretization of the forward and inverse problems. These error bounds show that the error in the reconstructed image due to the discretization of each problem depends on the smoothness of both the forward and inverse problem solutions, their positions with respect to each other, and the source-detector configuration.

REFERENCES

1. S R Arridge, J P Kaipio, V Kolehmainen, M Schweiger, E Somersalo, T Tarvainen and M Vauhkonen, “Approximation errors and model reduction with an application in optical diffusion tomography”, *Inverse Problems* **22**:175-195, 2006
2. S R Arridge. Optical tomography in medical imaging. *Inverse Problems* **15**:R41-93, 1999.
3. J. P. Kaipio. and E. Somersalo, Statistical and computational inverse problems, Springer Verlag, New York, 2005.
4. A B Milstein, S Oh, K J Webb, C A Bouman, Q Zhang, D A Boas, and R P Millane. Fluorescence optical diffusion tomography. *Applied Optics* **42**(16):3081-3094, 2003
5. J E Bugaj, S Achilefu, R B Dorshow, and R Rajagopalan. Novel fluorescent contrast agents for optical imaging of *in vivo* tumors based on receptor-targeted dy-peptide conjugate platform. *J. Biomed. Opt.* **6**:122-133, 2001

6. A P Gibson, J C Hebden and S R Arridge. Recent advances in diffuse optical imaging. *Phys. Med. Biol.* **50**:R1-R43, 2005
7. V. Ntziachristos, A. G. Yodh, M. Schnall, and B. Chance. Concurrent MRI and diffuse optical tomography of breast after indocyanine green enhancement. *PNAS* **97**(6):2767-2772, 2000
8. I. Babuška and W. C. Rheinboldt. Error estimates for adaptive finite element computations. *SIAM Journal on Numerical Analysis* **15**:736-754, 1978.
9. I. Babuška, O. C. Zienkieqics, J. Gago, and E.R. de A. Oliveira. *Accuracy Estimates and Adaptive Refinements in Finite Element Computations* John Wiley and Sons, 1986.
10. T. Strouboulis and K. A Hague. Recent experiences with error estimation and adaptivity, part I: Review of error estimators for scalar elliptic problems. *Computer Methods in Applied Mechanics and Engineering* **97**:399-436, 1992
11. R. Verfurth. *A Review of A Posteriori Error Estimation and Adaptive Mesh Refinement Techniques* Tuebner-Wiley, 1996
12. R. Kress. *Linear Integral Equations*, volume 82 of *Applied Mathematical Sciences.* Springer-Verlag, 1999
13. M. Guven, B. Yazici, K. Kwon, E. Giladi, and X. Intes. Effect of discretization error and adaptive mesh generation in diffuse optical absorption imaging: Part I. *Inverse Problems*, volume **23**, pages 1115-1133, 2007.
14. M. Guven, B. Yazici, K. Kwon, E. Giladi, and X. Intes. Effect of discretization error and adaptive mesh generation in diffuse optical absorption imaging: Part II, *Inverse Problems*, volume **23**, 1135-1160, 2007.
15. S. Brenner and L. Scott. *The Mathematical Theory of Finite Element Methods.* Springer-Verlag, 2002
16. M. J. Eppstein, D. E. Dougherty, D. J. Hawrysz, and E. M. Sevick-Muraca. Three-dimensional Bayesian optical image reconstruction with domain decomposition. *IEEE Trans on Medical Imaging,* **20**(3): 147-163, 2001
17. A. Joshi, W. Bangerth, and E.M. Sevick-Muraca. Adaptive finite element based tomography for fluorescence optical imaging in tissue. *Optics Express*, **12**(22):5402-5417, 2004.
18. G. Aubert and P. Kornprobst. *Mathematical Problems in Image Processing*, Springer-Verlag, 2002
19. F. Fedele, J.P. Laible, M.J. Eppstein. Coupled complex adjoint sensitivities for frequency-domain fluorescence tomography: theory and vectorized implementation. *J Comp Phys.* **187**: 597-619, 2003
20. M.J. Eppstein, F. Fedele, J.P. Laible, C. Zhang, A. Godavarty, E.M. Sevick-Muraca. A comparison of exact and approximate adjoint sensitivies in fluorescence tomography. *IEEE Trans. Med. Imag.*
21. Y. Lin, H. Gao, O Nalcioglu, and G. Gulsen. Fluorescence diffuse optical tomography with functional and anatomical a priori information: feasibility study. *Phys. Med. Biol.* **52** 5569-5585, 2007
22. S.J. Reeves, R.M. Mersereau. Optimal regularization parameter estimation for image restoration. in *Proc. SPIE: Image Processing Algorithms and Techniques II* **1452** p. 127-138, 1991
23. A. M. Urmanov, A. V. Gribok, H. Bozdogan, J. W. Hines and R. E. Uhrig, "Information complexity-based regularization parameter selection for solution of ill conditioned inverse problems", *Inverse Problems* **18**(2) L1-L9, 2002
24. L. Reilly-Raska, M. Guven and B. Yazici, "Discretization Error Analysis and Adaptive Meshing Algorithms for Fluorescence Diffuse Optical Tomography", to be submitted to IEEE Transactions on Medical Imaging.

Acknowledgment

This work was supported by US Army Medical Research-W81XWH-04-1-0559 and by the Center for Subsurface Sensing and Imaging Systems, under the Engineering Research Centers Program of the National Science Foundation (Award Number EEC-9986821). Any opinions, findings, conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation.