Fluorescence Photon Migration by the Boundary Element Method

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June 24, 2004

Abstract

The use of the boundary element method (BEM) is explored as an alternative to the finite element method (FEM) solution methodology for the elliptic equations used to model the generation and transport of fluorescent light in highly scattering media, without the need for an internal volume mesh. The method is appropriate for domains where it is reasonable to assume the fluorescent properties are regionally homogeneous, such as when using highly-specific molecularly targeted fluorescent contrast agents in biological tissues. In comparison to analytical results on a homogeneous sphere, BEM predictions of complex emission fluence are shown to be more accurate and stable than those of the FEM. Emission fluence predictions made with the BEM using a 708-node mesh, with roughly double the internode spacing of boundary nodes as in a 6956-node FEM mesh, match experimental frequency-domain fluorescence emission measurements acquired on a 1087 cm^3 breast-mimicking phantom as well as those of the FEM, but require only 1/8 to 1/2 the computation time.

1 Introduction

Imaging plays a central part of cancer diagnosis, therapy, and prognosis primarily through the detection of anatomically defined abnormalities. With the wealth of information provided by the now maturing areas of genomics and proteomics, the identification of molecular markers and targets now promises contrast-enhanced, diagnostic imaging with specificity and sensitivity that is not otherwise possible with conventional, anatomical imaging. Molecular imaging promises to improve diagnostic imaging and to impact the quality of cancer patient care.

Near-infrared (NIR) light between the wavelengths of 700-900 nm propagates deeply through tissues and provides a unique approach for molecularly-based diagnostic imaging. In the past decade, significant progress has been made in developing molecularly targeted fluorescent dyes for molecular imaging [1, 2, 3, 4, 5, 6, 7]. With near-infrared excitable fluorescent contrast agents that can be conveniently conjugated with a targeting or reporting moiety, there is potential clinical opportunity for using non-ionizing radiation with these non-radioactive contrast agents for "homing in" on early metastatic lesions, performing sentinel lymph node mapping, and following the progress of therapy.

Direct imaging of fluorescence is possible in small animal and near-surface applications. However, in order to quantify fluorochrome concentrations and/or to image fluorescent targets deeper into tissues, where the rapid decay of light renders the diffuse signal weak and noisy, tomographic reconstruction is necessary. Three dimensional fluorescence tomography has recently been demonstrated in both small volumes [8, 9] and larger, clinically-relevant volumes [10, 11, 12, 13, 14, 15], from experimentally acquired measurements. However, especially in large volumes, there remain a number of challenges for obtaining reliably quantitative and highly resolved image reconstructions, as outlined below.

In NIR fluorescence-enhanced tomography [16], the tissue surface is illuminated with excitation light and measurements of fluorescent light emission are collected at the tissue surface. A forward model of fluorescent light generation and transport through tissue is used to predict the observable states (e.g., emission fluence) at the measurement locations, based on the known excitation light source and an estimate of spatially distributed optical properties of the tissue volume. A computational implementation of the forward model is typically used repeatedly within an inverse (tomography) method, wherein estimates of spatially distributed optical properties of the tissue are iteratively updated until the predictions match the observations sufficiently well, or some other convergence criteria is achieved. Consequently, a rapid and accurate implementation of the forward model is critical for a rapid and accurate tomography code.

In clinically relevant volumes of highly scattering media, the forward problem of fluorescent light generation and transport can be effectively approximated as a diffusive process. The generation and propagation of fluorescent light through highly-scattering media (such as biological tissues) is often modeled by a pair of second order, elliptic, partial differential equations [17, 18, 19]. The first

equation represents propagation of excitation light (subscript x) and the second models the generation and propagation of fluorescently emitted light (subscript m). Herein, we focus on frequency domain measurements using intensity modulated illumination, because a) these time-dependent measurements permit the implementation of fluorescence lifetime tomography [15], and b) frequency domain measurements have some advantages over time domain measurements approaches, including that ambient light rejection is automatic and does not require background subtraction. In the frequency domain, the diffusion approximations to the radiative transport equation over a three-dimensional (3-D) bounded domain Ω are

$$-\nabla \cdot (D_x \nabla \Phi_x) + k_x \Phi_x = S_x \quad (1)$$

$$-\nabla \cdot (D_m \nabla \Phi_m) + k_m \Phi_m = \beta \Phi_x \quad (2)$$

subject to the Robin boundary conditions on the domain boundary $\partial\Omega$ of

$$\overrightarrow{n} \cdot (D_x \nabla \Phi_x) + b_x \Phi_x = p_x \quad (3)$$

$$\overrightarrow{n} \cdot (D_m \nabla \Phi_m) + b_m \Phi_m = 0 \quad (4)$$

where ∇ is the three dimensional (3×1) grad operator and $\overrightarrow{n}$ is the three dimensional (3×1) vector normal to the boundary. In fluorescence tomography the light source is localized on the surface and thus it can be modelled either by an appropriate definition of excitation light source S_x ($Watts/cm^3$) or as a source flux p_x ($Watts/cm^2$) on the surface boundary. Sources are intensity modulated with sinusoidal frequency ω (rad/s), and propagate through the media resulting in the AC component of complex photon fluence at the excitation wavelength of Φ_x ($Watts/cm^2$). The diffusion ($D_{x,m}$), decay ($k_{x,m}$), and emission source (β) coefficients, as shown below,

$$\begin{cases} D_x = \frac{1}{3\left(\mu_{axi}+\mu_{axf}+\mu_{sx}^{'}\right)} \\ D_m = \frac{1}{3\left(\mu_{ami}+\mu_{amf}+\mu_{sm}^{'}\right)} \end{cases} ; \begin{cases} k_x = \frac{i\omega}{c} + \mu_{axi} + \mu_{axf} \\ k_m = \frac{i\omega}{c} + \mu_{ami} + \mu_{amf} \end{cases} ; \beta = \frac{\phi \mu_{axf}}{1 - i\omega\tau} \quad (5)$$

are functions of absorption coefficients due to non-fluorescing chromophore (μ_{axi}, μ_{ami}), absorption coefficients due to fluorophore (μ_{axf}, μ_{amf}), and isotropic (reduced) scattering coefficients ($\mu_{sx}^{'}$, $\mu_{sm}^{'}$) at the two wavelengths (all in units of cm^{-1}), fluorescence quantum efficiency (ϕ), and fluorescence lifetime (τ, in s). Here, $i = \sqrt{-1}$, and c is the speed of light in the media (cm/s). The Robin boundary coefficients (b_x, b_m) are governed by the reflection coefficients (R_x, R_m), which range from 0 (no reflectance) to 1 (total reflectance):

$$b_x = \frac{1 - R_x}{2\left(1 + R_x\right)}; \; b_m = \frac{1 - R_m}{2\left(1 + R_m\right)}. \quad (6)$$

In diffuse fluorescence tomography, the forward model is commonly computationally implemented using the finite element method (FEM) [20, 12, 21]. Despite the fact that all excitation sources and detected measurements are restricted to the tissue surface, in the FEM the entire volume must be discretized into nodes and 3D elements. The internal FEM mesh makes it straightforward to implement the internally distributed emission source term ($\beta\Phi_x$). Unfortunately, the internal FEM mesh introduces discretization error that can render the method unstable, unless a fine enough mesh is employed. In biological tissues, the rate of decay (k, dominated by the absorption coefficients μ_a) is typically much larger than the rate of diffusion (D, dominated by the inverse of the scattering coefficients $\mu_s^{'}$, where $\mu_s^{'} >> \mu_a$), so fine internal volume meshes are required in order to achieve a smooth and stable result. Furthermore, the spatial resolution of small internal targets is governed by the internal mesh discretization in a FEM model. In a tomography algorithm, where the target locations are unknown in advance, fine target resolution in an FEM-based tomography code will require either a uniformly fine mesh, or some sort of adaptive meshing scheme, both of which add to the computational complexity of the model. If the optical parameters to be estimated in a tomographic reconstruction are associated with internal nodes or elements, the inverse problem of FEM-based tomographic reconstruction algorithm will be highly under-determined, since the number of nodes or elements in an adequately resolved FEM mesh typically far exceeds the number of surface measurements available for inversion [11, 13, 14]. In fluorescence tomography applications for large volumes this problem is exacerbated because a very fine mesh resolution imposes large computational memory and time requirements that may be impractical, and because the signal-to-noise of fluorescence emission measurements in large volumes is extremely low and highly spatially-variant [10, 11], thereby rendering the inverse problem even more ill-posed. There have been a variety of weighting and damping approaches proposed for regularization of ill-posed FEM tomography codes [10, 22, 23, 24, 25], as well as methods that explicitly reduce the dimensionality of the parameter space in various FEM-based tomographic applications, including (i) use of *a priori* structural information from co-registered magnetic resonance images to reduce the number of uncertain optical parameters [26], (ii) use of clustering algorithms to dynamically merge spatially adjacent uncertain parameters based on their evolving estimates between iterations (aka data-driven zonation) [10, 27, 28], and (iii) use of adaptive mesh refinement to enable use of a relatively coarse mesh in the background while increasing spatial resolution inside regions of interest, based on evolving estimates [29]. Although these regularization approaches have made FEM-based fluorescence tomography possible, it must be noted that accuracy of FEM-based tomography is sensitive to the regularization imposed.

These difficulties associated with FEM-based fluorescence tomography motivate us to explore boundary element method (BEM) -based tomography, wherein the BEM [30] is used as an alternative numerical approach for solving the diffusion approximations to excitation and emission radiative transport (1) and (2).

In the 3D BEM, the domain is modeled with a finite number of spatially coherent 3D regions, each of which is considered homogeneous. Only the boundaries of these subdomains must be discretized into nodes and two-dimensional (2D) elements. Inside each subdomain analytical solutions are employed, with compatibility and equilibrium constraints enforced on shared boundaries between subdomains [30]. For domains in which it is reasonable to assume that parameters can be modeled with a relatively small number of regionally homogeneous subdomains, the BEM thus requires many fewer nodes and elements than the FEM, and is subject to less discretization error. In a BEM-based tomography code, the number of unknowns can be inherently much lower than the number of measurements, even for large domains, assuming a relatively few number of internal subdomains. For example, unknowns can be limited to the locations of nodes on internal boundaries and the uncertain optical parameters inside the various subdomain regions, as demonstrated in electrical impedance BEM tomography [31, 32]. Such a BEM-based tomography code would be overdetermined, and hence should yield more accurate parameter estimates, that are less sensitive to selection of regularization parameters, than in an FEM-based tomography code.

One difficulty with a BEM-based tomography code, however, is that one must predetermine an upper limit on the number of internally distinct subdomains to model. An approach that has proven successful in electrical impedance tomography using the BEM alternates several generations of a genetic algorithm with several iterations of a gradient-based local optimizer, to dynamically determine the number, locations, and geometries of internal subdomains [32]. Other approaches that may prove effective for providing an initial estimate of target numbers and locations for subsequent refinement with a BEM tomographic reconstruction include (i) extracting approximate parameter structure from the result of a small number of iterations of an FEM tomographic reconstruction, (ii) using an artificial neural network (e.g., a radial basis function neural network [33]) for rapid initial approximation of parameter structure, or (iii) using *a priori* parameter structure estimates from other co-registered imaging modalities, such as PET or MRI.

As previously stated, the BEM treats optical properties as regionally homogeneous. We postulate that this may be appropriate for some biomedical fluorescence tomography applications using highly-selective molecularly-targeting and reporting dyes. When using receptor-targeted fluorescent markers, fluorescent properties such as absorption and lifetime will tend to be highly localized (e.g., on the surface of a discrete tumor) and may therefore be conducive to BEM modeling. While endogenous optical absorption and scattering will remain much more spatially heterogeneous that the distribution of fluorophore, the change in time-dependent measurements with physiological absorption and scattering contrast is insignificant in comparison to the change owing to the fluorescence decay kinetics. Indeed, signal perturbations due to endogenous levels of scattering and absorption contrast can be within the measurement error of time-dependent measurements. Prior computational studies using synthetic data have confirmed that tomographic inversion of fluorescence emission fluence

is relatively insensitive to a wide range of unmodeled variability in background absorption and scattering [28].

There are reports in the literature of successful applications of the BEM to the optical excitation equation (1)[34] and to the electrical impedance diffusion equation [31, 32]. In these applications, implementation of the BEM is relatively straightforward, since all sources and detectors are located on the surface of the domain, where the BEM must be discretized in any case. However, modeling fluorescently generated light, emitted from an internal target, is not straightforward with the BEM. In this case, the source term for the emission equation (2) is internally distributed; it is non-zero wherever there is non-zero fluorescence absorption coefficient (μ_{axf}, μ_{amf}). Modeling this internal source term without an explicit internal volume mesh makes application of the BEM non-trivial. We have found no prior references to the BEM for the coupled excitation/emission equations (1) and (2), or other similarly coupled systems.

Ultimately, we plan to explore various approaches for a practical BEM implementation for 3D fluorescence tomography, as well as BEM-FEM hybrid approaches. As a first step towards BEM-based fluorescence tomography, we herein report on the derivation, implemention, and validation of a prototype BEM forward model of the generation and propagation of fluorescent light through highly-scattering media.

2 BEM formulation for the Governing Equations

The governing equations (1) and (2) are only coupled in one direction; that is, the solution to equation (2) depends on the solution to equation (1), but not *vice versa*. Consequently, it is possible to solve these equations sequentially. To predict fluorescence emission fluence Φ_m at surface detectors (generated in response to an excitation source S_x also at the tissue surface), one first solves the excitation equation (1) with the boundary conditions (3), to predict excitation fluence Φ_x at all the nodes in the domain volume Ω. The predicted excitation fluence is subsequently used in the source term ($\beta\Phi_x$) for solving the emission equation (2), subject to boundary conditions (4), for emission fluence Φ_m. Since an internal discretization of the entire volume Ω is already a requirement of the FEM, the internally distributed source term for equation (2) requires no special accommodation. However, if a sequential solution approach were employed in a BEM formulation, this would necessitate the creation of an internal mesh for the BEM in order to represent the internally distributed fluorescent source. This approach would eliminate many of the potential advantages of the BEM over the FEM.

Alternatively, one can entirely preclude the need of an internal volume mesh discretization when using BEM if the governing equations (1) and (2) are solved simultaneously, rather than sequentially. We recast the governing equations into the following matrix form

$$-\underline{\underline{\nabla}}^T \left(\underline{\underline{\mathbf{D}}}\, \underline{\underline{\nabla}}\, \underline{\mathbf{\Phi}}\right) + \underline{\underline{\mathbf{k}}}\, \underline{\mathbf{\Phi}} = \underline{\mathbf{S}} \qquad on\ \Omega. \tag{7}$$

Similarly, the boundary conditions (3) and (4) are represented by the matrix equation

$$\underline{\mathbf{n}}^{\mathrm{T}}\left(\underline{\underline{\mathbf{D}}}\underline{\underline{\nabla}}\,\underline{\mathbf{\Phi}}\right)+\underline{\underline{\mathbf{r}}}\,\underline{\mathbf{\Phi}}=\underline{\mathbf{p}}\qquad on\ \partial\Omega. \tag{8}$$

Here, we distinguish vector quantities with a single underbar and matrix quantities with a double underbar and we use the following matrix definitions

$$\left\{\begin{array}{c} \underset{(6\times2)}{\underline{\underline{\nabla}}}=\begin{bmatrix}\nabla & \underline{0}\\ \underline{0} & \nabla\end{bmatrix};\ \underset{(6\times2)}{\underline{\underline{\mathbf{n}}}}=\begin{bmatrix}\overrightarrow{n} & \underline{0}\\ \underline{0} & \overrightarrow{n}\end{bmatrix};\ \underset{(6\times6)}{\underline{\underline{\mathbf{D}}}}=\begin{bmatrix}D_x\underline{\underline{\mathbf{I}}} & \underline{\underline{0}}\\ \underline{\underline{0}} & D_m\underline{\underline{\mathbf{I}}}\end{bmatrix};\\ \underset{(2\times2)}{\underline{\underline{\mathbf{k}}}}=\begin{bmatrix}k_x & 0\\ -\beta & k_m\end{bmatrix};\ \underset{(2\times2)}{\underline{\underline{\mathbf{r}}}}=\begin{bmatrix}b_x & 0\\ 0 & b_m\end{bmatrix};\\ \underset{(2\times1)}{\underline{\mathbf{\Phi}}}=\begin{bmatrix}\Phi_x\\ \Phi_m\end{bmatrix};\ \underset{(2\times1)}{\underline{\mathbf{S}}}=\begin{bmatrix}S_x\\ 0\end{bmatrix};\ \underset{(2\times1)}{\underline{\mathbf{p}}}=\begin{bmatrix}p_x\\ 0\end{bmatrix}.\end{array}\right. \tag{9}$$

where the sizes of each matrix are shown for clarity. Note that in the matrix formulation above we have moved the emission source term ($\beta\Phi_x$) to the left hand side of the emission equation. We first present a BEM solution to system (7) on homogeneous domains, and then extend this to the case of non-homogeneous domains.

2.1 Homogenous domains

By assuming a homogenous domain, where the matrices $\underline{\underline{\mathbf{D}}}, \underline{\underline{\mathbf{k}}}, \underline{\underline{\mathbf{b}}}$ are spatially constant inside the domain Ω, we can rewrite Eqs. (7) as follows

$$-\nabla^2\underline{\mathbf{\Phi}}+\underline{\underline{\mathbf{K}}}\,\underline{\mathbf{\Phi}}=\underline{\mathbf{S}}\qquad on\ \Omega \tag{10}$$

with

$$\underset{(2\times2)}{\underline{\underline{\mathbf{K}}}}=\left[\underline{\underline{\mathbf{D}}}^{-1}\underline{\underline{\mathbf{k}}}\right],\qquad \underset{(2\times1)}{\underline{\tilde{\mathbf{S}}}}=\left[\underline{\underline{\mathbf{D}}}^{-1}\underline{\mathbf{S}}\right]. \tag{11}$$

Here, $\underline{\underline{\mathbf{X}}}^{-1}$ indicates the inverse of the matrix $\underline{\underline{\mathbf{X}}}$.

We now define an arbitrary matrix of functions $\underline{\underline{\mathbf{\Psi}}}$

$$\underset{(2\times2)}{\underline{\underline{\mathbf{\Psi}}}}=\begin{bmatrix}\Psi_{xx} & \Psi_{xm}\\ \Psi_{mx} & \Psi_{mm}\end{bmatrix}. \tag{12}$$

Multiplying equation (10) by the transpose of $\underline{\underline{\mathbf{\Psi}}}$ and integrating over the entire domain Ω yields

$$\int_\Omega \underline{\underline{\mathbf{\Psi}}}^T\left(-\boldsymbol{\nabla}^2\underline{\mathbf{\Phi}}+\underline{\underline{\mathbf{K}}}\,\underline{\mathbf{\Phi}}\right)d\underline{\mathbf{x}}=\int_\Omega \underline{\underline{\mathbf{\Psi}}}^T\underline{\tilde{\mathbf{S}}}\,d\underline{\mathbf{x}} \tag{13}$$

where superscript T indicates the transpose operator. Integrating by parts twice and incorporating the boundary conditions (8) gives

$$\int_{\Omega}\left(-\boldsymbol{\nabla}^2\underline{\underline{\boldsymbol{\Psi}}}+\underline{\underline{\mathbf{K}}}^T\underline{\underline{\boldsymbol{\Psi}}}\right)^T\boldsymbol{\Phi}\;d\underline{\mathbf{x}}+\int_{\partial\Omega}\left(-\underline{\underline{\boldsymbol{\Psi}}}^T\frac{\partial\underline{\boldsymbol{\Phi}}}{\partial\overrightarrow{n}}+\frac{\partial\underline{\underline{\boldsymbol{\Psi}}}^T}{\partial\overrightarrow{n}}\underline{\boldsymbol{\Phi}}\right)d\underline{\mathbf{x}}=\int_{\Omega}\underline{\underline{\boldsymbol{\Psi}}}^T\underline{\tilde{\mathbf{S}}}\;d\underline{\mathbf{x}} \tag{14}$$

We now define the matrix $\underline{\underline{\boldsymbol{\Psi}}}$ such that the following adjoint equation is satisfied, that is

$$-\boldsymbol{\nabla}^2\underline{\underline{\boldsymbol{\Psi}}}+\underline{\underline{\mathbf{K}}}^T\underline{\underline{\boldsymbol{\Psi}}}=\underline{\underline{\Delta_j}}. \tag{15}$$

We define $\rho=\left|\underline{\mathbf{x}}-\underline{\mathbf{x}}_j\right|$ to be the distance for any arbitrary point $\underline{\mathbf{x}}$ in the domain to the j^{th} node, $\underline{\mathbf{x}}_j$.Then, $\underline{\underline{\Delta_j}}$ is a 2×2 diagonal matrix of Dirac delta functions centered at node j.

$$\underset{(2\times2)}{\underline{\underline{\Delta_j}}}=\begin{bmatrix}\delta(\rho) & 0\\ 0 & \delta(\rho)\end{bmatrix}. \tag{16}$$

Hereafter $\underline{\underline{\boldsymbol{\Psi}}}$ is called the Green matrix of the 3-D diffusion equations (7) in an infinite domain (equivalent to the Green's function for the scalar case).

Equation (14) then simplifies as follows

$$\underline{\boldsymbol{\Phi}}(\underline{\mathbf{x}}_d)+\int_{\partial\Omega}\left(-\underline{\underline{\boldsymbol{\Psi}}}^T\frac{\partial\underline{\boldsymbol{\Phi}}}{\partial\overrightarrow{n}}+\frac{\partial\underline{\underline{\boldsymbol{\Psi}}}^T}{\partial\overrightarrow{n}}\underline{\boldsymbol{\Phi}}\right)d\underline{\mathbf{x}}=\int_{\Omega}\underline{\underline{\boldsymbol{\Psi}}}^T\underline{\tilde{\mathbf{S}}}\;d\underline{\mathbf{x}}. \tag{17}$$

A modal decomposition procedure is applied to solve the system (15) (see Appendix A for details) which yields, for the case of fluorescence photon migration, the following analytical expression for $\underline{\underline{\boldsymbol{\Psi}}}$

$$\underline{\underline{\boldsymbol{\Psi}}}=\begin{bmatrix}G\left(\sqrt{-\frac{k_x}{D_x}}\rho\right) & \frac{G\left(\sqrt{-\frac{k_x}{D_x}}\rho\right)-G\left(\sqrt{-\frac{k_m}{D_m}}\rho\right)}{\frac{D_m}{\beta}\left(\frac{k_x}{D_x}-\frac{k_m}{D_m}\right)}\\ 0 & G\left(\sqrt{-\frac{k_m}{D_m}}\rho\right)\end{bmatrix} \tag{18}$$

Note that, for the fluorescence photon migration case, the component Ψ_{mx} of the matrix $\underline{\underline{\boldsymbol{\Psi}}}$ is zero, reflecting the asymmetry in the governing equations (1) and (2); that is, Φ_x influences Φ_m, but not vice versa. In equation 18, $G\left(\sqrt{-\lambda}\rho\right)$ is the scalar Green's function satisfying the Helmholtz equation

$$\nabla^2G-\lambda G+\delta(\rho)=0,\qquad \lambda=\frac{k_x}{D_x},\frac{k_m}{D_m}. \tag{19}$$

For 3D domains, the function G is defined as:

$$G(\sqrt{-\lambda}\rho)=\frac{1}{4\pi\rho}\exp\left(-i\sqrt{-\lambda}\rho\right). \tag{20}$$

(See Appendix A for the 2D case). The integral equation (17) can be solved by BEM discretization as follows. We first consider a triangular mesh discretization

Υ_h of the boundary $\partial\Omega$. Without loss of generality, we employ linear elements. Over the boundary $\partial\Omega$, we define the real finite functional space

$$V_h = \{u \in C^0(\partial\Omega)\ \ u\,|_K\ \ \textit{is a linear polynomial}\} \tag{21}$$

where $K \in \Upsilon_h$ is the generic surface triangular element and $h = \max_{K\,\epsilon\Upsilon_h} diam(K)$ is the maximal dimension of the element. We define the global bases for $V_h(\partial\Omega)$ as $\{N_1, N_2, ..., N_n\}$ where n is the number of nodes. The generic basis elements are defined such that $N_i(\underline{\mathbf{x}}_j) = \delta_{ij}$ with δ_{ij} the Kronecker symbol. By means of these bases, $\underline{\mathbf{\Phi}}$, its normal derivative $\underline{\mathbf{q}} = \frac{\partial\underline{\mathbf{\Phi}}}{\partial n}$ and the boundary flux $\underline{\mathbf{p}}$ can be approximated as

$$\underline{\mathbf{\Phi}}(\underline{\mathbf{x}}) = \sum_{k=1}^{n} N_k(\underline{\mathbf{x}})\underline{\mathbf{\Phi}}_k; \qquad \underline{\mathbf{q}}(\underline{\mathbf{x}}) = \sum_{k=1}^{n} N_k(\underline{\mathbf{x}})\underline{\mathbf{q}}_k; \qquad \underline{\mathbf{p}}(\underline{\mathbf{x}}) = \sum_{k=1}^{n} N_k(\underline{\mathbf{x}})\underline{\mathbf{p}}_k \tag{22}$$

where $\underline{\mathbf{\Phi}}_k$,$\underline{\mathbf{q}}_k$ and $\underline{\mathbf{p}}_k$ indicate values relative to the node k. Using these approximations and choosing $\underline{\mathbf{x}}_j$ to span all the nodes of the surface Υ_h, i.e. $\underline{\mathbf{x}}_j = \underline{\mathbf{x}}_i\ \forall\ i = 1, ...n$, the equations (17) and (8) give respectively the following set of algebraic equations

$$\underline{\underline{\mathbf{H}}}\,\underline{\mathcal{U}} + \underline{\underline{\mathbf{G}}}\,\underline{\mathcal{V}} = \underline{\mathcal{S}} \tag{23}$$

$$\underline{\mathcal{V}} = -\underline{\underline{\mathbf{R}}}\,\underline{\mathcal{U}} + \underline{\mathbf{P}}. \tag{24}$$

The matrix $\underline{\underline{\mathbf{R}}}$ is block-diagonal of dimension $(2n \times 2n)$, with n the number of nodes, as follows

$$\underset{(2n\times 2n)}{\underline{\underline{\mathbf{R}}}} = \begin{bmatrix} \underline{\underline{\mathbf{r}}} & & & \\ & \underline{\underline{\mathbf{r}}} & \cdots & \\ & & \cdots & \\ & & & \underline{\underline{\mathbf{r}}} \end{bmatrix}. \tag{25}$$

with $\underline{\underline{\mathbf{I}}}$ the (2×2) identity matrix. We define $\underline{\mathcal{U}}$, $\underline{\mathcal{V}}$, $\underline{\mathbf{P}}$ and $\underline{\mathcal{S}}$ as the column vectors of the nodal values of the fluence $\underline{\mathbf{\Phi}}$, its normal derivative $\underline{\mathbf{q}}$, the prescribed boundary flux $\underline{\mathbf{p}}$ and the volume source $\underline{\mathbf{S}}$ respectively. These are vectors of dimension $(2n \times 1)$, i.e.

$$\underset{(2n\times 1)}{\underline{\mathcal{U}}} = \begin{bmatrix} \underline{\mathbf{\Phi}}_1 \\ \cdots \\ \cdots \\ \underline{\mathbf{\Phi}}_n \end{bmatrix}, \underset{(2n\times 1)}{\underline{\mathcal{V}}} = \begin{bmatrix} \underline{\mathbf{q}}_1 \\ \cdots \\ \cdots \\ \underline{\mathbf{q}}_n \end{bmatrix}, \underset{(2n\times 1)}{\underline{\mathbf{P}}} = \begin{bmatrix} \underline{\mathbf{p}}_1 \\ \cdots \\ \cdots \\ \underline{\mathbf{p}}_n \end{bmatrix}, \underset{(2n\times 1)}{\underline{\mathcal{S}}} = \begin{bmatrix} \underline{\mathbf{s}}_1 \\ \cdots \\ \cdots \\ \underline{\mathbf{s}}_n \end{bmatrix} \tag{26}$$

where the (2×1) vector component $\underline{\mathbf{s}}_j$ at each node j is given by

$$\underset{(2\times 1)}{\underline{\mathbf{s}}_j} = -\int_\Omega \underline{\underline{\mathbf{\Psi}}}^T(\rho)\underline{\mathbf{S}}(\underline{\mathbf{x}})d\Omega. \tag{27}$$

In the case of a point source located on the surface of a 3D domain, we effectively use a lumped mass matrix to concentrate the source at a specific point $\underline{\mathbf{x}}_s$ located

one scattering length inside and normal to the surface beneath the point source, so the integral in equation (27) disappears as follows:

$$\underset{(2x1)}{\underline{\mathbf{s}}_j} = -\underline{\underline{\mathbf{\Psi}}}^T(\left|\underline{\mathbf{x}}_j - \underline{\mathbf{x}}_s\right|)\underline{\mathbf{S}}(\underline{\mathbf{x}}_s) \tag{28}$$

By relocating the point source just inside the domain (so $\underline{\mathbf{x}}_j \neq \underline{\mathbf{x}}_s$, $\forall j, s$) we avoid singularities arising from source locations that coincide with a boundary node (i.e., $\underline{\mathbf{x}}_j = \underline{\mathbf{x}}$ implies $G(0) = \infty$ per equation 20, and therefore $\underline{\underline{\mathbf{\Psi}}} = \infty$ per equation 18). The BEM matrices $\underline{\underline{\mathbf{H}}}$, $\underline{\underline{\mathbf{G}}}$ are partitioned as

$$\underset{(2n\times 2n)}{\underline{\underline{\mathbf{H}}}} = \begin{bmatrix} \underline{\underline{\mathbf{h}}}_{11} & \underline{\underline{\mathbf{h}}}_{12} & \cdots & \underline{\underline{\mathbf{h}}}_{1n} \\ & \cdots & \cdots & \\ & \cdots & \underline{\underline{\mathbf{h}}}_{jk} & \cdots \\ & & \cdots & \underline{\underline{\mathbf{h}}}_{nn} \end{bmatrix}, \underset{(2n\times 2n)}{\underline{\underline{\mathbf{G}}}} = \begin{bmatrix} \underline{\underline{\mathbf{g}}}_{11} & \underline{\underline{\mathbf{g}}}_{12} & \cdots & \underline{\underline{\mathbf{g}}}_{1n} \\ & \cdots & \cdots & \\ & \cdots & \underline{\underline{\mathbf{g}}}_{jk} & \cdots \\ & & \cdots & \underline{\underline{\mathbf{g}}}_{nn} \end{bmatrix} \tag{29}$$

where the block elements are computed as follows

$$\underset{(2\times 2)}{\underline{\underline{\mathbf{h}}}_{jk}} = \underset{(2\times 2)}{\underline{\underline{\mathbf{I}}}}\,\delta_{jk} + \int_{\partial\Omega} \frac{\partial \underline{\underline{\mathbf{\Psi}}}^T(\rho)}{\partial \overrightarrow{n}} N_k(\underline{\mathbf{x}}) d\underline{\mathbf{x}} \tag{30}$$

$$\underset{(2\times 2)}{\underline{\underline{\mathbf{g}}}_{jk}} = -\int_{\partial\Omega} \underline{\underline{\mathbf{\Psi}}}^T(\rho) N_k(\underline{\mathbf{x}}) d\underline{\mathbf{x}} \tag{31}$$

Remark 1 *Note that, since the component Ψ_{mx} of the Green matrix $\underline{\underline{\mathbf{\Psi}}}$ is zero [see Eq. (18)], it results that the matrices $\underline{\underline{\mathbf{H}}}$ and $\underline{\underline{\mathbf{G}}}$ are 3/4 populated $2n \times 2n$ matrices, where n is the number of nodes in the BEM mesh. By defining $\underline{\mathbf{\Phi}}_x$ and $\underline{\mathbf{\Phi}}_m$ as column vectors of the nodal values of the fluences Φ_x and Φ_m, the vectors $\underline{\mathcal{U}}$ and $\underline{\mathcal{V}}$ can be rearranged as follows*

$$\underset{(2n\times 1)}{\underline{\mathcal{U}}} = \begin{bmatrix} \underline{\mathbf{\Phi}}_x \\ \underline{\mathbf{\Phi}}_m \end{bmatrix}, \underset{(2n\times 1)}{\underline{\mathcal{V}}} = \begin{bmatrix} \underline{\mathbf{q}}_x \\ \underline{\mathbf{q}}_m \end{bmatrix} \tag{32}$$

and one finds that the matrices $\underline{\underline{\mathbf{H}}}$ and $\underline{\underline{\mathbf{G}}}$ in Equation (23) have the following structure

$$\underline{\underline{\mathbf{H}}} = \begin{bmatrix} \underline{\underline{\mathbf{H}}}_{xx} & \underline{\underline{\mathbf{0}}} \\ \underline{\underline{\mathbf{H}}}_{xm} & \underline{\underline{\mathbf{H}}}_{mm} \end{bmatrix}, \underline{\underline{\mathbf{G}}} = \begin{bmatrix} \underline{\underline{\mathbf{G}}}_{xx} & \underline{\underline{\mathbf{0}}} \\ \underline{\underline{\mathbf{G}}}_{xm} & \underline{\underline{\mathbf{G}}}_{mm} \end{bmatrix}. \tag{33}$$

For a given surface mesh, the size of the BEM matrices is smaller (dimensioned by number of boundary nodes times 2) than the size of the FEM matrices for the excitation and emission equations (dimensioned by number of nodes in the FEM volume mesh). The computation of the matrix block element entries (equations (30) and (31)) can be done using Gauss integration (we used 7 collocation points inside each triangular element) as long as node k does not coincide with one of the nodes attached to any of the triangular elements attached to

node $\underline{\mathbf{x}}_j$. In this case the integrals appearing in equations (30) and (31) are regular. Otherwise the integrals are singular and special computation is required, as discussed in Appendix B. Substituting equations (24) into (23) yields

$$\left(\underline{\underline{\mathbf{H}}} - \underline{\underline{\mathbf{GR}}}\right)\underline{\mathcal{U}} = \underline{\mathcal{S}} - \underline{\underline{\mathbf{G}}}\underline{\mathbf{P}}. \tag{34}$$

This is a single equation to solve for all boundary nodal values of the light fluence $\underline{\mathcal{U}}$ (comprising both excitation and emission fluence).

2.2 Inhomogenous domains

2.2.1 Definition of the problem and BEM formulation

Assume that a domain volume Ω, with boundary $\partial\Omega$, comprises an inner subdomain Ω_i, with boundary $\partial\Omega_i$, and outer subdomain Ω_o, with boundary $\partial\Omega_o = \partial\Omega_i \cup \partial\Omega$ (Figure 1). The internal properties of the volume Ω_i are characterized by the matrices $\underline{\underline{\mathbf{D}}}_i, \underline{\underline{\mathbf{k}}}_i$ whereas the outer volume Ω_o is defined by the matrices $\underline{\underline{\mathbf{D}}}_o, \underline{\underline{\mathbf{k}}}_o$. The Robin boundary conditions (8) still apply on $\partial\Omega$. Inside each volume Ω_i (inner) and Ω_o (outer) we define $\underline{\mathbf{\Phi}}_i$ and $\underline{\mathbf{\Phi}}_o$ as the inner and outer light fluences defined on the boundary nodes directly touching each domain (note that nodes defining the boundary of the inner volume Ω_i are shared). Equation (17) still holds since each volume is defined as being internally homogenous and two integral equations (inner and outer equations respectively) can be defined as follows

$$\underline{\mathbf{\Phi}}_i(\underline{\mathbf{x}}_d) + \left\langle -\underline{\underline{\mathbf{\Psi}}}_i^T \frac{\partial \underline{\mathbf{\Phi}}_i}{\partial \overrightarrow{n}_i} + \frac{\partial \underline{\underline{\mathbf{\Psi}}}_i^T}{\partial \overrightarrow{n}_i} \underline{\mathbf{\Phi}}_i \right\rangle_{\partial\Omega_i} = \underline{\mathbf{0}} \qquad \underline{\mathbf{x}}_d \in \partial\Omega_i \tag{35}$$

$$\underline{\mathbf{\Phi}}_o(\underline{\mathbf{x}}_d) + \left\langle -\underline{\underline{\mathbf{\Psi}}}_o^T \frac{\partial \underline{\mathbf{\Phi}}_o}{\partial \overrightarrow{n}_o} + \frac{\partial \underline{\underline{\mathbf{\Psi}}}_o^T}{\partial \overrightarrow{n}_o} \underline{\mathbf{\Phi}}_o \right\rangle_{\partial\Omega_o} = \left\langle \underline{\underline{\mathbf{\Psi}}}_o^T \underline{\mathbf{S}} \right\rangle_{\Omega_o} \qquad \underline{\mathbf{x}}_d \in \partial\Omega_o. \tag{36}$$

Here, $\underline{\underline{\mathbf{\Psi}}}_i$ and $\underline{\underline{\mathbf{\Psi}}}_o$ are the Green matrices relative to the domain Ω_i and Ω_o, respectively. Note that according to the inner normal $\overrightarrow{n}_i$ the flux leaving the inner volume, through the inner boundary $\partial\Omega_i$, is $\underline{\underline{\mathbf{D}}}_i \frac{\partial \underline{\mathbf{\Phi}}_i}{\partial \overrightarrow{n}_i}$ whereas the flux entering the outer volume is $-\underline{\underline{\mathbf{D}}}_i \frac{\partial \underline{\mathbf{\Phi}}_i}{\partial \overrightarrow{n}_o}$. We can now define the following matching boundary conditions required at the shared nodes along the internal boundary $\partial\Omega_i$

$$\underline{\mathbf{\Phi}}_i(\underline{\mathbf{x}}) = \underline{\mathbf{\Phi}}_o(\underline{\mathbf{x}}), \qquad \underline{\mathbf{x}} \in \partial\Omega_i \tag{37}$$

$$\underline{\underline{\mathbf{D}}}_i \frac{\partial \underline{\mathbf{\Phi}}_i(\underline{\mathbf{x}})}{\partial \overrightarrow{n}_i} = -\underline{\underline{\mathbf{D}}}_o \frac{\partial \underline{\mathbf{\Phi}}_o(\underline{\mathbf{x}})}{\partial \overrightarrow{n}_o}, \qquad \underline{\mathbf{x}} \in \partial\Omega_i. \tag{38}$$

These conditions impose the continuity of the light fluence (37) and the conservation of the light flux (38) at the nodes on the shared boundary $\partial\Omega_i$. Consider a triangular mesh discretization for both the boundaries $\partial\Omega_i$ and $\partial\Omega_o = \partial\Omega_i \cup \partial\Omega$. In the following, the subscript I or O indicates quantities relative to the nodes

of the inner boundary $\partial\Omega_i$ or the outer boundary $\partial\Omega_o$ respectively, whereas the superscript (i) or (o) indicates properties relative to the inner volume Ω_i or outer volume Ω_o. We use linear elements as we did for the homogenous case (see equation (22)) and indicate with n_I and n_O the number of nodes of the inner and outer boundaries respectively and $n_T = n_I + n_O$ the total number of nodes. The BEM discretization of the inner and outer equations are, respectively

$$\underset{(2n_I\times 2n_I)}{\underline{\underline{\mathbf{H}}}^{(i)}}\ \underset{(2n_I\times 1)}{\underline{\mathcal{U}_I^{(i)}}} + \underset{(2n_I\times 2n_I)}{\underline{\underline{\mathbf{G}}}^{(i)}}\ \underset{(2n_I\times 1)}{\underline{\mathcal{V}_I^{(i)}}} = \underset{(2n_I\times 1)}{\underline{\mathbf{0}}} \tag{39}$$

and

$$\underset{(2n_T\times 2n_T)}{\underline{\underline{\mathbf{H}}}^{(o)}}\ \underset{(2n_T\times 1)}{\underline{\mathcal{U}^{(o)}}} + \underset{(2n_T\times 2n_T)}{\underline{\underline{\mathbf{G}}}^{(o)}}\ \underset{(2n_T\times 1)}{\underline{\mathcal{V}^{(o)}}} = \underset{(2n_T\times 1)}{\underline{\mathcal{S}^{(o)}}}\ . \tag{40}$$

where the sizes of matrices and vectors are shown for clarity. Here, $\underline{\mathcal{U}^{(o)}}$ and $\underline{\mathcal{V}^{(o)}}$ and $\underline{\mathcal{S}^{(o)}}$ are defined as follows

$$\underset{(2n_T\times 1)}{\underline{\mathcal{U}^{(o)}}} = \begin{bmatrix} \underset{(2n_I\times 1)}{\underline{\mathcal{U}_I^{(o)}}} \\ \underset{(2n_O\times 1)}{\underline{\mathcal{U}_O^{(o)}}} \end{bmatrix}, \qquad \underset{(2n_T\times 1)}{\underline{\mathcal{V}^{(o)}}} = \begin{bmatrix} \underset{(2n_I\times 1)}{\underline{\mathcal{V}_I^{(o)}}} \\ \underset{(2n_O\times 1)}{\underline{\mathcal{V}_O^{(o)}}} \end{bmatrix}, \qquad \underset{(2n_T\times 1)}{\underline{\mathcal{S}^{(o)}}} = \begin{bmatrix} \underset{(2n_I\times 1)}{\underline{\mathbf{0}}} \\ \underset{(2n_O\times 1)}{\underline{\mathcal{S}_O^{(o)}}} \end{bmatrix}, \tag{41}$$

and $\underline{\mathcal{U}_I^{(i)}}$ and $\underline{\mathcal{V}_I^{(i)}}$ refer to the nodal values of the inner fluence $\underline{\mathbf{\Phi}}_i$ and its normal derivative along the inner boundary $\partial\Omega_i$. The vectors $\underline{\mathcal{U}_I^{(o)}}$ and $\underline{\mathcal{V}_I^{(o)}}$ are relative to the nodal values of the outer fluence $\underline{\mathbf{\Phi}}_o$ and its normal derivative along the inner boundary $\partial\Omega_i$, respectively, whereas $\underline{\mathcal{U}_O^{(o)}}$ and $\underline{\mathcal{V}_O^{(o)}}$ are vectors relative to the nodal values of the outer boundary $\partial\Omega_o$. Note that both the elements of the matrices $\underline{\underline{\mathbf{H}}}^{(i)}$ and $\underline{\underline{\mathbf{G}}}^{(i)}$, as well as the matrices $\underline{\underline{\mathbf{H}}}^{(o)}$ and $\underline{\underline{\mathbf{G}}}^{(o)}$, are computed using equations (30) and (31), with $\partial\Omega_i$ and $\partial\Omega_o$ as boundary contours for the integrations, respectively.

Because of the matching conditions (37) and (38) we need to impose the nodal conditions

$$\underline{\mathcal{U}_I^{(o)}} = \underline{\mathcal{U}_I^{(i)}} \tag{42}$$

$$\underline{\underline{\mathcal{D}}^{(o)}}\,\underline{\mathcal{V}_I^{(o)}} = -\underline{\underline{\mathcal{D}}^{(i)}}\,\underline{\mathcal{V}_I^{(i)}}. \tag{43}$$

where $\underline{\underline{\mathcal{D}}^{(o)}}$ and $\underline{\underline{\mathcal{D}}^{(i)}}$ are block-diagonal matrices defined as follows

$$\underset{(2n_I\times 2n_I)}{\underline{\underline{\mathcal{D}}^{(o)}}} = \begin{bmatrix} \underline{\underline{\mathbf{D}_o}} & & & \\ & \cdots & & \\ & & \cdots & \\ & & & \underline{\underline{\mathbf{D}_o}} \end{bmatrix}, \qquad \underset{(2n_I\times 2n_I)}{\underline{\underline{\mathcal{D}}^{(i)}}} = \begin{bmatrix} \underline{\underline{\mathbf{D}_i}} & & & \\ & \cdots & & \\ & & \cdots & \\ & & & \underline{\underline{\mathbf{D}_i}} \end{bmatrix}. \tag{44}$$

From Eq. (39) and the matching conditions (42) and (43) we derive a relation between the vectors $\underline{\mathcal{V}^{(o)}}$ and $\underline{\mathcal{U}^{(o)}}$ that is equivalent to a discretized Robin

boundary condition as in Eq. (24) for the homogenous case. Since the matrix $\underline{\underline{\mathbf{G}^{(i)}}}$ is non singular, from equation (39) one obtains

$$\underline{\mathcal{V}_I^{(i)}} = -\left(\underline{\underline{\mathbf{G}^{(i)}}}\right)^{-1} \underline{\underline{\mathbf{H}^{(i)}}}\,\underline{\mathcal{U}_I^{(i)}}. \tag{45}$$

Applying the matching condition (43), equation (45) yields

$$\underline{\underline{\mathcal{D}^{(o)}}}\,\underline{\mathcal{V}_I^{(o)}} = \underline{\underline{\mathcal{D}^{(i)}}}\left(\underline{\underline{\mathbf{G}^{(i)}}}\right)^{-1} \underline{\underline{\mathbf{H}^{(i)}}}\,\underline{\mathcal{U}_I^{(i)}}. \tag{46}$$

Because of the matching condition (42), the following equation holds

$$\underline{\mathcal{V}_I^{(o)}} = \left(\underline{\underline{\mathcal{D}^{(o)}}}\right)^{-1} \underline{\underline{\mathcal{D}^{(i)}}}\left(\underline{\underline{\mathbf{G}^{(i)}}}\right)^{-1} \underline{\underline{\mathbf{H}^{(i)}}}\,\underline{\mathcal{U}_I^{(o)}}. \tag{47}$$

This is a relation between the vector $\underline{\mathcal{V}_I^{(o)}}$ of the nodal normal derivatives of the outer fluence $\underline{\mathbf{\Phi}_o}$ and the vector $\underline{\mathcal{U}_I^{(o)}}$ of the nodal values of the fluence $\underline{\mathbf{\Phi}_o}$ on the inner boundary $\partial\Omega_i$. The discretization of the Robin boundary condition on the outer boundary $\partial\Omega$ (see equation (8)) is defined the same as in equation (23) for the homogenous case, that is

$$\underline{\mathcal{V}_O^{(o)}} = -\underline{\underline{\mathbf{R}}}\,\underline{\mathcal{U}_O^{(o)}} + \underline{\mathbf{P}}. \tag{48}$$

Using the vector definitions (41), the equations (46) and (48) can be recast together in the following block form

$$\underline{\mathcal{V}^{(o)}} = -\underline{\underline{\mathcal{R}}}\,\underline{\mathcal{U}^{(o)}} + \underline{\mathcal{P}} \tag{49}$$

where we have defined

$$\underset{(\ 2n_T\times 2n_T\ )}{\underline{\underline{\mathcal{R}}}} = \begin{bmatrix} \left(\underline{\underline{\mathcal{D}^{(o)}}}\right)^{-1} \underline{\underline{\mathcal{D}^{(i)}}}\left(\underline{\underline{\mathbf{G}^{(i)}}}\right)^{-1} \underline{\underline{\mathbf{H}^{(i)}}} & \underline{\underline{\mathbf{0}}} \\ \underline{\underline{\mathbf{0}}} & \underline{\underline{\mathbf{R}}} \end{bmatrix}, \qquad \underset{(2n_T\times 1)}{\underline{\mathcal{P}}} = \begin{bmatrix} \underline{\mathbf{0}} \\ \underline{\mathbf{P}} \end{bmatrix}. \tag{50}$$

Substituting equation (49) into equation (40) yields the following system

$$\left(\underline{\underline{\mathbf{H}^{(o)}}} - \underline{\underline{\mathbf{G}^{(o)}}}\,\underline{\underline{\mathcal{R}}}\right)\underline{\mathcal{U}^{(o)}} = \underline{\mathcal{S}^{(o)}} - \underline{\underline{\mathbf{G}^{(o)}}}\,\underline{\mathcal{P}}. \tag{51}$$

Equation (51) has the same matrix structure as the equation (34) for the homogenous case. Extension to multiple non-overlapping inner domains is straightforward.

3 Experiments

3.1 Comparison to FEM and Analytical Solution on a Homogeneous Sphere

Both the proposed BEM formulation and the FEM (see [21] for a detailed description of our vectorized finite element implementation) were implemented in

Matlab Version 6.5 [35] on a 2.2 GHz Pentium IV. In order to test the proposed BEM formulation, we first consider the propagation of light through a homogenous sphere of radius Γ. For the following axisymmetric boundary conditions

$$D_x \frac{\partial \Phi_x}{\partial \overrightarrow{n}} = P_\eta, \qquad D_m \frac{\partial \Phi_m}{\partial \overrightarrow{n}} = 0 \tag{52}$$

the analytical solution of the coupled equations (10) in scalar form has expression as follows (see Appendix C for derivation)

$$\Phi_x = \frac{P_\eta \, j_\eta \left(\sqrt{\frac{-k_x}{D_x}} \rho \right)}{d_x \, j_\eta^{'} \left(\sqrt{\frac{-k_x}{D_x}} \Gamma \right)} \tag{53}$$

$$\Phi_m = P_\eta \frac{\beta D_m}{\left(\frac{k_x}{D_x} - \frac{k_m}{D_m} \right)} \left[\frac{j_\eta \left(\sqrt{\frac{-k_m}{D_m}} \rho \right)}{D_m \sqrt{\frac{-k_m}{D_m}} \, j_\eta^{'} \left(\sqrt{\frac{-k_m}{D_m}} \Gamma \right)} - \frac{j_\eta \left(\sqrt{\frac{-k_x}{D_x}} \rho \right)}{D_x \, \sqrt{\frac{-k_x}{D_x}} \, j_\eta^{'} \left(\sqrt{\frac{-k_x}{D_x}} \Gamma \right)} \right] \tag{54}$$

Here, P_η are the Legendre polynomials, $j_\eta(x)$ are the spherical Bessel functions of first kind of order η and $j_\eta^{'}(x)$ is the derivative of $j_\eta(x)$.

The case of $\eta = 0$ corresponds to a uniform imposed flux on the surface of the sphere, and hence the analytic solution is also homogenous on the surface of the sphere, rendering this a good test case for the accuracy and stability of numerical solutions. We have solved this problem using the BEM formulation (34) on 10 cm diameter spheres with 9 levels of surface mesh discretization, using triangular elements with linear basis functions. Specifications for the coarsest, medium, and finest of these nine sphere meshes are detailed in Table 1 and depicted in Figure 2. For these experiments, we selected optical property values consistent with the background properties employed in human breast phantom studies, assuming the presence of low levels of the fluorescent contrast agent Indocyanine Green [11], as shown in Table 2, and assumed a modulation frequency of 100 MHz. The FEM discretizations used the same surface meshes as did the BEM but had additional discretization of the internal volume of the sphere into tetrahedral elements, also using linear basis functions.

For both the FEM and BEM we define the prediction error as the analytical solution minus the numerical prediction, at all surface nodes on the sphere, for both real and imaginary components of the predicted fluence (Φ). Results were assessed by two metrics: (i) the root mean square error of the prediction error (RMSE) was used to indicate accuracy – this metric includes residual bias in the predictions, and (ii) the standard deviation (σ) of the prediction error was used to indicate smoothness – this metric excludes bias in the predictions.

As previously mentioned, for relatively low diffusion coefficients and high decay coefficients (as in biological tissues) FEM mesh discretization must be relatively fine in order to achieve smooth, numerically stable results. In contrast, since the BEM employs internal analytic solutions and therefore has no discretization error associated with an internal volume mesh, we hypothesized that the BEM would be less sensitive to the relative magnitudes of diffusion

and decay coefficients. In order to test this, we compared both the BEM and FEM for accuracy (by RMSE) and smoothness (by σ) of the results, relative to analytic results on the homogeneous sphere, again using the optical properties shown in Table 2, but where the resulting diffusion coefficients (D_x, D_m) were then multiplied by a factor $Dfac$ of 1, 10, and 100.

3.2 Comparison to FEM and Experimental Data from a Non-homogeneous Breast Phantom

In order to test the BEM on a non-homogeneous domain, we compared predictions from the BEM formulation (51) to experimentally acquired measurements. In prior work [11, 13, 14, 15], we experimentally collected measurements of frequency domain fluorescence emission fluence (Φ_m) from the surface of a breast shaped tissue-mimicking phantom (a 10 cm diameter hemispherical "breast" atop a 20 cm diameter cylindrical portion of the "chest wall"). The instrumentation and data collection protocol is outside the scope of this paper, but is fully described elsewhere [11]. By incorporating a finite element model [21] of this phantom into the Bayesian approximate extended Kalman filter [10, 11, 27, 28] image reconstruction algorithm, we have successfully performed 3-D tomographic reconstructions of both fluorescence absorption (μ_{axf}) [11, 13, 14] and fluorescence lifetime (τ) [15]. Herein, we compare the model mismatch of the FEM and BEM forward models to an 11-source experimentally acquired data set [11], with background optical properties as shown in Table 2, and a 1 cc fluorescent target with 100:1 target:background contrast in μ_{axf}, with centroid located 1.4 cm from the surface of the phantom breast. This data set comprised 401 measurements of Φ_m, selected from 704 measurements at 64 spatially distributed optical collection fibers in response to 11 spatially distributed sequential point source illuminations (only those measurements above the noise floor were retained, as described in [11]).

The coarsest FEM mesh that we have found to adequately resolve a 1 cc target and achieve acceptable model match contains 6956 nodes, and is shown in Figure 3a. This is the mesh that was used for the image reconstructions reported in [11, 13, 15]. However, because the BEM requires more memory than the FEM, we were not able to run the BEM using the surface mesh shown in Figure 3a. Consequently, we implemented a much coarser 708 node BEM mesh to model the breast phantom, as shown in Figure 3b, where the inter-node spacing on the domain surface is approximately double that used in the FEM. Note that the geometry and location of the cubic target can be very accurately represented in even a course BEM mesh, because a) the surface mesh of the internal target is independent of the coarseness of the mesh on the outer domain surface, and b) the shape of the internal surface is not constrained by the locations of nodes in an internal volume discretization, as in the FEM. We remind the reader that in this manuscript we are only addressing the forward problem, where the target

location, size, and shape are known. In the inverse problem, the locations of internal target surface nodes could be iteratively estimated, (e.g., as in [32]).

Experimental measurements are referenced, in order to account for instrument effects and unknown source strength. Here, the experimental measurements are referenced by dividing each measurement of emission fluence by the measurement at a designated reference detector [11], for each source illumination. Our FEM and BEM predictions were thus similarly referenced for comparison to the experimental data. Prediction errors are therefore defined as the real and imaginary components of the measured minus predicted *referenced* Φ_m. The distribution of the prediction error is an indication of bias and variance in the combined model and measurement error (aka "model mismatch").

4 Results

4.1 Comparison to Analytical Sphere Solutions

In comparison to the analytical solution on the homogeneous sphere using biologically realistic optical properties, the BEM outperformed the FEM in both accuracy (RMSE) and smoothness (σ) of the predictions, and this effect became increasingly pronounced on finer meshes. On the finest sphere mesh used (Figure 2c), the BEM was over an order of magnitude more accurate and smoother than the FEM (Figure 4). Both convergence and stability of the BEM solutions increase faster than those of the FEM, as the meshes get more refined (Figure 5). These results imply that we may be able to achieve BEM predictions from coarser meshes that are more accurate than FEM predictions with finer meshes.

When we reran the sphere model with diffusion coefficients that were 10 and 100 times higher than in those in biological tissues, both the accuracy and smoothness of the FEM improved, and converged on results similar to those of the BEM. This is exemplified by the results shown in Table 3 for the sphere with medium discretization shown in Figure 2b. Results for the other sphere discretizations followed a similar pattern. These results underscore that the noisy predictions of the FEM on the homogeneous sphere test case (e.g., Figure 5) were not caused by a flaw in our implementation of the FEM, but were due to numerical instabilities on these FEM meshes for the low diffusion-to-decay ratios that result from tissue-like optical properties. Since the BEM has no internal volume mesh, the BEM predictions are smooth and stable. We infer that the optical properties of biological tissues are such that the resulting diffusion coefficients (D_x, D_m) are in a range that is challenging for the FEM and requires a very fine FEM mesh, but may be modeled accurately with the BEM, even with a relatively coarse mesh.

4.2 Comparison to Experimental Data from Breast Phantom

The observed frequency distributions of model mismatch between the model predictions, for both FEM and BEM, and the experimentally acquired data, are shown in Figure 6, for both real and imaginary components of the fluorescence emission fluence. Although the inter-node spacing on the domain surface in the BEM mesh approximately double that of the FEM mesh (Figure 3), the BEM predictions matched the data at least as well as the FEM data, as shown in Figure 6, where it can be seen that the magnitudes of bias and variance of the model mismatch are similar for the two forward models, and in most cases are slightly lower in the BEM predictions than in the FEM predictions. The FEM system matrices are large and sparse, while the BEM system matrix is relatively small but $\frac{3}{4}$ dense (see equations 33). In fact, although the BEM breast mesh had an order of magnitude fewer nodes than the FEM mesh, it had an order of magnitude more non-zero elements in its system matrix (Table 4), thus requiring more memory. Despite this, total prediction time for all 11 source illuminations on these breast models took about half the time with the BEM than with the FEM. If the portions of the system matrix associated with the outer mesh ($\underline{\underline{\mathbf{H}^{(o)}}}$ and $\underline{\underline{\mathbf{G}^{(o)}}}$) were pre-computed, the BEM only took one eighth the time of the FEM (Table 4). Pre-computing the outer mesh may be a practical approach in a BEM tomography application where the background properties and geometry of outer domain are held constant, and only the locations, sizes, shapes, and values of internal targets are estimated. Since this was a prototype implementation of the BEM and used a direct solver, we anticipate that further implementation improvements will yield additional speedups for the BEM.

5 Summary and Conclusions

Finite element method (FEM) approaches to fluorescence tomography in clinically relevant volumes have proven feasible [11, 13, 14, 15], but are highly under-determined. Consequently FEM-based tomographic reconstructions are dependent on, and sensitive to, regularization schemes. In contrast, boundary element method (BEM) based tomography may afford high resolution imaging of internal targets, in the context of an over-determined problem. While FEM models may be necessary for modeling domains with a large degree of continuously varying heterogeneity, the BEM method is appropriate for applications in which the domain can be modeled with a small number of homogeneous subdomains. One such potential application is when modeling fluorescence from molecularly-targeting dyes that exhibit highly-localized spatial accumulation (e.g., on discrete tumors). Using the BEM, only the external boundary and the internal target boundaries require discretization, and regional solutions are solved analytically. The BEM can accurately model the geometries of internal subdomains, independent of the degree of surface discretization, in contrast to the FEM. Unfortunately, the application of a BEM forward model to the flu-

orescence diffusion equations is not straight-forward, because of the internally-distributed fluorescent emission source caused by embedded fluorophore.

In this contribution, we have developed a 3D BEM formulation that allows the simultaneous solution of the excitation and emission equations that describe the generation and propagation of fluorescent light through turbid media, without the need for an internal volume mesh. This formulation is based on a derivation of the fundamental solution to the coupled system of excitation and emission equations. The BEM is shown to be more accurate and more stable than the FEM, when compared to an analytic solution on a spherical homogeneous domain using optical properties consistent with those of biological tissues, owing to the lower internal discretization error inherent in the BEM. For a given inter-node spacing in the mesh, the BEM requires more memory and runtime than the FEM. However, the BEM with a coarser mesh gives more accurate and stable results, and takes less computer time, than the FEM with a fine mesh. Emission fluence predictions made with the BEM using a 708-node boundary mesh, with roughly double the inter-node spacing of boundary nodes as in a 6956-node FEM volume mesh, match experimental frequency-domain fluorescence emission measurements acquired on a non-homogeneous 1087 cm^3 breast-mimicking phantom as well as those of the FEM, but required only 1/8 to 1/2 the computation time. These encouraging results on the BEM forward model of fluorescence photon migration motivate us to pursue BEM-based fluorescence tomography in future work.

6 Appendix A: Analytical derivation of the Green matrix $\underline{\underline{\mathbf{\Psi}}}$

A modal decomposition procedure is applied to solve for the fundamental solution ($\underline{\underline{\mathbf{\Psi}}}$) of the coupled adjoint system (15), as follows. Set $\underline{\underline{\tilde{\mathbf{K}}}} = \underline{\underline{\mathbf{K}^T}}$ in equation (15) as

$$\underline{\underline{\tilde{\mathbf{K}}}} = \begin{bmatrix} \tilde{K}_x & \tilde{K}_{xm} \\ 0 & \tilde{K}_m \end{bmatrix}$$

where

$$\tilde{K}_x = \frac{k_x}{D_x}, \quad \tilde{K}_{xm} = -\frac{\beta}{D_m}, \quad \tilde{K}_m = \frac{k_m}{D_m}.$$

In order to solve the adjoint system (15), define a generic non singular matrix $\underline{\underline{\mathbf{V}}}$ and the variable transformation

$$\underline{\underline{\mathbf{\Psi}}} = \underline{\underline{\mathbf{V}}}\,\underline{\underline{\mathbf{U}}}. \tag{55}$$

The new differential equation satisfied by the transformed variable $\underline{\underline{\mathbf{U}}}$ is readily derived from equation (10) as follows

$$\boldsymbol{\nabla}^2\underline{\underline{\mathbf{U}}} - (\underline{\underline{\mathbf{V}}}^{-1}\underline{\underline{\tilde{\mathbf{K}}\mathbf{V}}})\underline{\underline{\mathbf{U}}} + \underline{\underline{\mathbf{V}}}^{-1}\underline{\underline{\Delta_j}} = \underline{\underline{\mathbf{0}}}. \tag{56}$$

We now choose $\underline{\underline{\mathbf{V}}}$ to be the matrix having as column entries the eigenvectors of the matrix $\underline{\underline{\tilde{\mathbf{K}}}}$. It follows that $\underline{\underline{\mathbf{V}}}^{-1}\underline{\underline{\tilde{\mathbf{K}}}}\underline{\underline{\mathbf{V}}} = \underline{\underline{\mathbf{\Lambda}}}$ with $\underline{\underline{\mathbf{\Lambda}}}$ the diagonal matrix of the eigenvalues and equation (56) simplifies

$$\boldsymbol{\nabla}^2\underline{\underline{\mathbf{U}}} - \underline{\underline{\mathbf{\Lambda}}}\underline{\underline{\mathbf{U}}} + \underline{\underline{\mathbf{V}}}^{-1}\underline{\underline{\Delta_j}} = \underline{\underline{\mathbf{0}}}. \tag{57}$$

Here,

$$\underline{\underline{\mathbf{\Lambda}}} = \begin{bmatrix} \tilde{K}_x & 0 \\ 0 & \tilde{K}_m \end{bmatrix}, \qquad \underline{\underline{\mathbf{V}}} = \begin{bmatrix} 1 & \alpha \\ 0 & 1 \end{bmatrix}, \qquad \underline{\underline{\mathbf{V}}}^{-1} = \begin{bmatrix} 1 & -\alpha \\ 0 & 1 \end{bmatrix} \tag{58}$$

where

$$\alpha = \frac{\tilde{K}_{xm}}{\tilde{K}_m - \tilde{K}_x} = \frac{\frac{\beta}{D_m}}{\frac{k_x}{D_x} - \frac{k_m}{D_m}} \tag{59}$$

From the matrix equation (57) the following scalar equations for the entries U_{ij} of the matrix $\underline{\underline{\mathbf{U}}}$ can be derived

$$\begin{cases} \nabla^2 U_{11} - \tilde{K}_x U_{11} + \delta(\rho) = 0 \\ \nabla^2 U_{12} - \tilde{K}_x U_{12} - \alpha\ \delta(\rho) = 0 \\ \nabla^2 U_{21} + \tilde{K}_m U_{21} = 0 \\ \nabla^2 U_{22} - \tilde{K}_m U_{22} + \delta(\rho) = 0. \end{cases} \tag{60}$$

Note that the component U_{21} is zero and the analytical expression of the matrix $\underline{\underline{\mathbf{U}}}$ is readily obtained

$$\underline{\underline{\mathbf{U}}} = \begin{bmatrix} G\left(\sqrt{-\tilde{K}_x}\ \rho\right) & -\alpha\ G\left(\sqrt{-\tilde{K}_x}\ \rho\right) \\ 0 & G\left(\sqrt{-\tilde{K}_m}\ \rho\right) \end{bmatrix} \tag{61}$$

where $G\left(\sqrt{-\lambda}r\right)$ satisfies the Helmholtz-type equation

$$\nabla^2 G - \lambda G + \delta(\rho) = 0 \qquad \lambda = \tilde{K}_x, \tilde{K}_m. \tag{62}$$

The following radiation boundary condition at infinity needs to be satisfied in order to guarantee decay-outgoing solutions from the location $\underline{\mathbf{x}} = \underline{\mathbf{x}}_j$, i.e.

$$\lim_{\rho\to\infty}\left(\frac{\partial G}{\partial \rho} - i\sqrt{-\lambda}G\right) = 0. \tag{63}$$

In two dimensions

$$G(\sqrt{-\lambda}\rho) = \frac{i}{4}H_0^1\left(\sqrt{-\lambda}\rho\right) \tag{64}$$

where $H_0^1(x)$ is the Hankel function of first kind and order 0, whereas in three dimensions

$$G(\sqrt{-\lambda}\rho) = \frac{1}{4\pi\rho}\exp\left(-i\sqrt{-\lambda}\rho\right). \tag{65}$$

Using the transformation (55) the Green matrix $\underline{\underline{\mathbf{\Psi}}}$ has the general expression as follows:

$$\underline{\underline{\mathbf{\Psi}}} = \begin{bmatrix} G\left(\sqrt{-\tilde{K}_x}\rho\right) & -\alpha\, G\left(\sqrt{-\tilde{K}_x}\rho\right) + \alpha\, G\left(\sqrt{-\tilde{K}_m}\rho\right) \\ 0 & G\left(\sqrt{-\tilde{K}_m}\rho\right) \end{bmatrix}. \tag{66}$$

7 Appendix B: Computation of the matrices $\underline{\underline{\mathbf{H}}}$ and $\underline{\underline{\mathbf{G}}}$

Equations (30) and (31) are required to compute the element entries of the matrices $\underline{\underline{\mathbf{H}}}$ and $\underline{\underline{\mathbf{G}}}$ (equations (29)), and are repeated below:

$$\underset{(2\times2)}{\underline{\underline{\mathbf{h}}}_{jk}} = \underset{(2\times2)}{\underline{\underline{\mathbf{I}}}}\,\delta_{jk} + \int_{\partial\Omega} \frac{\partial \underline{\underline{\mathbf{\Psi}}}^T(\rho)}{\partial \overrightarrow{n}} N_k(\underline{\mathbf{x}}) d\underline{\mathbf{x}} \tag{67}$$

$$\underset{(2\times2)}{\underline{\underline{\mathbf{g}}}_{jk}} = -\int_{\partial\Omega} \underline{\underline{\mathbf{\Psi}}}^T(\rho) N_k(\underline{\mathbf{x}}) d\underline{\mathbf{x}} \tag{68}$$

Special computation is required if the node k coincides with one of the nodes attached to any of the triangular elements attached to node $\underline{\mathbf{x}}_j$. In this case, Gauss quadrature gives poor approximations. In order to compute these integrals, we set a polar coordinate system (ρ, θ) at $\underline{\mathbf{x}}_j$. Since $\rho = \left|\underline{\mathbf{x}} - \underline{\mathbf{x}}_j\right|$, equations (67) and (68), in the polar system, transform to

$$\underset{(2\times2)}{\underline{\underline{\mathbf{h}}}_{jk}} = \underset{(2\times2)}{\underline{\underline{\mathbf{I}}}}\,\delta_{jk} + \int_{\partial\Omega} \underline{\underline{\mathbf{\Psi}}}^T(\rho)\, N_k(\rho,\theta)\rho\, d\rho d\theta, \tag{69}$$

$$\underset{(2\times2)}{\underline{\underline{\mathbf{g}}}_{jk}} = -\int_{\partial\Omega} \frac{\partial \underline{\underline{\mathbf{\Psi}}}^T}{\partial\rho} \frac{\partial\rho}{\partial \overrightarrow{n}}\, N_k(\rho,\theta)\rho\, d\rho d\theta. \tag{70}$$

Here, the integral in (69) is regular, since $\underline{\underline{\mathbf{\Psi}}} \sim \frac{1}{\rho}$ and can be easily computed by numerical quadrature in the domain (ρ, θ). The integral in (70) is weakly singular, since $\frac{\partial \underline{\underline{\mathbf{\Psi}}}}{\partial\rho} \sim \frac{1}{\rho^2}$. In order to compute it, we consider an external small spherical surface $\partial\Omega_\epsilon$ of radius ϵ centered at node $\underline{\mathbf{x}}_j$ (Figure 7). The integral splits into two components, as follows:

$$\underset{(2\times2)}{\underline{\underline{\mathbf{g}}}_{jk}} = -\int_{\partial\Omega_\epsilon} \frac{\partial \underline{\underline{\mathbf{\Psi}}}^T}{\partial\rho} \frac{\partial\rho}{\partial \overrightarrow{n}} N_k(\rho,\theta)\rho\, d\rho d\theta - \int_{\partial\Omega\setminus\partial\Omega_\epsilon} \frac{\partial \underline{\underline{\mathbf{\Psi}}}^T}{\partial\rho} \frac{\partial\rho}{\partial \overrightarrow{n}} N_k(\rho,\theta)\rho\, d\rho d\theta \tag{71}$$

Note that the second component of (71) vanishes, since $\frac{\partial \rho}{\partial \overline{n}} = 0$ in $\partial\Omega \backslash \partial\Omega_\epsilon$. Consequently, the integral simplifies as follows:

$$\underset{(2\times 2)}{\underline{\underline{\mathbf{g}}}_{jk}} = -\int_{\partial\Omega_\epsilon} \frac{\partial \underline{\underline{\mathbf{\Psi}}}^T}{\partial \rho} N_k(\rho,\theta)\rho \; d\rho d\theta \tag{72}$$

In the limit as $\epsilon \to 0$, it holds that $N_k(\rho,\theta) \to \delta_{jk} + o(\epsilon)$, and (72) simplifies to:

$$\underset{(2\times 2)}{\underline{\underline{\mathbf{g}}}_{jk}} = -\delta_{jk} \underset{(2x2)}{\underline{\underline{\mathbf{I}}}} \; \vartheta_j + o(\epsilon). \tag{73}$$

Here, $\underline{\underline{\mathbf{I}}}$ is the $(2x2)$ identity matrix and ϑ_j is the internal solid angle with respect to the normal direction facing the outside of the boundary $\partial\Omega$ at the node $\underline{\mathbf{x}}_j$ (Figure 7). If the surface is flat the solid angle at the node is equal to $\frac{1}{2}$.

8 Appendix C: Analytic Solution to Homogeneous Domain

We derived the analytic solution of the coupled system (10) as follows. Using a similar procedure as applied to derive the Green matrix as described in Appendix A, one can obtain the following eigenfunction expansion for the equations in system (10). Using spherical coordinates ρ, ϕ, and θ,

$$\Phi_x(\rho,\phi,\theta) = \sum A_{\eta\zeta} \exp(i\zeta\theta) P_\eta^\zeta(\phi) \, j_\eta\left(\sqrt{-\frac{k_x}{D_x}}\rho\right) \tag{74}$$

$$\Phi_m(\rho,\phi,\theta) = \sum \exp(i\zeta\theta) P_\eta^\zeta(\phi) \left[B_{\eta\zeta} \, j_\eta\left(\sqrt{-\frac{k_m}{D_m}}\rho\right) - \chi A_{\eta\zeta} j_\eta\left(\sqrt{-\frac{k_x}{D_x}}\rho\right)\right] \tag{75}$$

Here, $A_{\eta\zeta}$ and $B_{\eta\zeta}$ depend upon the boundary conditions, $P_\eta^\zeta(\phi)$ are the Legendre functions (for $\zeta = 0$ they become the Legendre polynomials $P_\eta(\phi)$), $j_\eta(x)$ is the spherical Bessel function of first kind of order η

$$j_\eta(x) = \frac{J_{\left(\eta+\frac{1}{2}\right)}(x)}{\sqrt{x}} \tag{76}$$

where $J_\eta(x)$ is the Bessel function of first kind of order η. The parameter χ is defined as follows

$$\chi = \frac{\beta D_m}{\left(\frac{k_x}{D_x} - \frac{k_m}{D_m}\right)}.$$

The boundary conditions (52) impose axisymmetry, i.e. $\zeta = 0$, and from equations (74) and (75) the two following equations are obtained

$$A_\eta \, D_x \sqrt{-\frac{k_x}{D_x}} j_\eta^{'} \left(\sqrt{-\frac{k_x}{D_x}} \rho \right) = 1 \quad (77)$$

$$B_\eta \sqrt{-\frac{k_m}{D_m}} j_\eta^{'} \left(\sqrt{-\frac{k_m}{D_m}} \rho \right) - \chi A_\eta \sqrt{-\frac{k_x}{D_x}} j_\eta^{'} \left(\sqrt{-\frac{k_x}{D_x}} \rho \right) = 0. \quad (78)$$

where $j_\eta^{'}(x)$ is the derivative of $j_\eta(x)$. Then one can solve for the coefficients A_η and B_η and the solutions for the homogeneous sphere (53) and (54) are readily derived.

9 Acknowledgments

This work was supported in part by NIH R01 EB 002763 and the Vermont Genetics Network through NIH 1 P20 RR16462 from the BRIN program of the NCRR.

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11 Figure Legends

1. Figure 1. Geometry and notation of inhomogeneous domain showing a) the outer subdomain Ω_o and b) one inner subdomain Ω_i (illustrated in 2D, for clarity).

2. Figure 2. The surface mesh for the a) coarsest, b) medium, and c) finest discretizations of the nine sphere meshes used (see Table 1).

3. Figure 3. Cut-away views of the discretizations used for the breast phantom simulations. a) Finite element mesh, and b) boundary element mesh showing internal target. See Table 4 for additional specifications.

4. Figure 4. FEM and BEM prediction errors (analytical minus predicted) using the finest sphere discretization (Figure 2c, Table 1), for the a) real and b) imaginary components of emission fluence.

5. Figure 5. Error metrics for both FEM and BEM predictions, in comparison to the analytical solution on the homogeneous sphere, as a function of maximum distance between nodes in each of the nine sphere discretizations.

6. Figure 6. Observed frequency distribution of model mismatch (measured – predicted) for the referenced experimental data collected on the non-homogeneous breast phantom, for the a) real and b) imaginary components of referenced emission fluence, using the FEM with the mesh shown in Figure 3a and the BEM with the mesh shown in Figure 3b. The mean of the model mismatch is used as an indication of bias.

7. Figure 7. Local geometry of a node, showing the spherical surface $\partial\Omega_\epsilon$ centered at node $\underline{\mathbf{x}}_j$, and the internal solid angle ϑ_j, described in Appendix B.

12 Table Legends

1. Table 1. Three of the nine mesh discretizations of the 10 cm diameter sphere.

2. Table 2. Optical parameter values used in all simulations at the excitation wavelength (λ_x) and the emission wavelength (λ_m).

3. Table 3. Error metrics on the mesh shown in the table above as diffusion coefficients increase by a factor of $Dfac$ on the sphere with medium discretization (Table 1, Figure 2b).

4. Table 4. Computational requirements of two breast meshes used (Figure 3).