Estimation of Kinetic Model Parameters in Fluorescence Optical Diffusion Tomography

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We present a technique for reconstructing the spatially dependent dynamics of a fluorescent contrast agent in turbid media. The dynamic behavior is described by linear and nonlinear parameters of a compartmental model, or some other model with a deterministic functional form. The method extends our previous work in fluorescence optical diffusion tomography by parametrically reconstructing the time-dependent fluorescent yield. The reconstruction uses a Bayesian framework and parametric iterative coordinate descent optimization, which is closely related to Gauss-Seidel methods. We demonstrate the method with a simulation study. © 2005 Optical Society of America

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1. Introduction

In optical imaging of diseased tissue, the use of fluorescent agents in imaging diseased tissue has attracted considerable interest due to the potential for high specificity and contrast.\textsuperscript{1} Injected fluorophores may accumulate in diseased tissue due to the increased vascular density\textsuperscript{2} or selective targeting.\textsuperscript{3,4,5,6} As in positron emission tomography,\textsuperscript{7} the reconstruction of optical contrast agent kinetics can provide useful physiological information. Several groups of researchers have measured the dynamic behavior of injected optical contrast agents in animal or human subjects.\textsuperscript{8,9,10,11,12,13} Gurfinkel \textit{et al}.\textsuperscript{11} have used an intensified CCD camera
to measure the pharmacokinetics of fluorescent agents in a canine with mammary tumors and fit the image sequence to a biexponential decay function which arises from a compartmental model. The study employed indocyanine green (ICG), which is believed to act as a nonselective blood pool agent, and carotene-conjugated 2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide (HPPH-car), a photosensitizer which is believed to accumulate selectively in diseased tissue. A model parameter related to the dye’s uptake rate showed significant contrast between diseased and surrounding tissue for HPPH-car, but not for ICG. Cuccia et al.\textsuperscript{13} have measured the dynamics of two light-absorbing dyes, ICG and methylene blue (MB), in an adenocarcinoma rat tumor model by use of an optical probe with magnetic resonance imaging coregistration. Due to its small molecular weight of 373.9 Da, the MB temporal dynamics were dominated by blood flow effects. From the MB measurements, the authors observed variations in perfusion within the rat tumor. In contrast, ICG binds to albumin in the blood, with a resulting effective molecular weight of 66 kDa. Hence, ICG’s temporal dynamics are dominated by the movement of albumin across the capillary membrane between the plasma and the extravascular, extracellular space (EES). The authors used ICG dynamics to compute a physiologic parameter related to capillary permeability.

In optical diffusion tomography (ODT), volume images of the absorption coefficient, the scattering coefficient, or the fluorescent yield and lifetime parameters are reconstructed from several optical measurements made on the surface.\textsuperscript{14} Fluorescence optical diffusion tomography (FODT) refers specifically to the reconstruction of the fluorescence parameters.\textsuperscript{15} Laser or light emitting diode sources inject light into the tissue at the fluorophore’s excitation wavelength. The light is modulated with a short pulse, modulated with an RF sinewave, or unmodulated. The fluorophore absorbs the incident light and then decays to its ground state with some characteristic time constant, emitting some of the light at a longer
wavelength. The emitted photons are then measured by an array of detection devices. From the data, one can reconstruct images of the fluorescent yield (a measure of the fluorescence efficiency) and the fluorescence lifetime (the fluorescent decay parameter). Multiple photon scattering in tissue must be properly accounted for in the reconstruction.\textsuperscript{16,17} Diffusion or radiative transport models are used to describe the propagation of light through the highly scattering domain.\textsuperscript{18} As a result of the multiple scattering of light, FODT must be used to accurately quantify drug concentration in tissue regions which are not directly under the skin surface.

Previously, the time-varying absorption coefficient has been reconstructed in a cylindrical phantom\textsuperscript{19} and in the human brain\textsuperscript{20} by solving the inverse problem separately for each image in a time sequence. However, in some cases, the unknown image may not reasonably be considered constant over the instrument’s measurement time. In addition, independent reconstruction of each image in the sequence ignores correlations in the image over time. Kolehmainen et al. have presented a state-estimation approach to the time-varying optical diffusion tomography problem which models the unknown image as a stochastic process governed by a stochastic difference equation.\textsuperscript{21} This method solves the inverse problem by using extended Kalman filter and Kalman smoother techniques. The authors demonstrate their method with synthetic data from a two-dimensional phantom and, in a subsequent investigation, on real hemodynamic data from the human motor cortex.\textsuperscript{22} This approach has shown promise for dynamic imaging problems where the time variation cannot be accurately parameterized by a known, deterministic model alone. However, in practical three-dimensional imaging problems, reconstructing a time sequence of images and updating large estimator covariance matrices may pose some difficulty, due to storage and computation requirements. Other dynamic imaging approaches have been investigated, including space/time regular-
ization operators,\textsuperscript{23,24,25} principal components analysis,\textsuperscript{26} and temporal B-splines,\textsuperscript{27,28,29} In many tracer experiments, a compartmental model\textsuperscript{30,7} can accurately describe tracer kinetics by use of a system of first order differential equations. Previously, maximum likelihood approaches for direct reconstruction of kinetic model parameter images from PET data have been presented.\textsuperscript{31,32} Recently, Kamasak \textit{et al.}\textsuperscript{33} have presented a Bayesian approach for dynamic PET which directly reconstructs images of the compartmental model’s parameter images using all the data, while imposing spatial regularization. This approach results in substantially improved accuracy compared with previous dynamic imaging methods which do not directly reconstruct the kinetic parameter images.

Here, we present a Bayesian, three-dimensional reconstruction approach for time-varying fluorescence optical diffusion tomography problems with nonlinear parameterizations of some known functional form. We demonstrate the method in a simulation study for the important case of a double exponential model, where the unknown parameters are the two amplitude coefficients and the two rate constants. This case can arise from a compartmental model in some applications, and it is similar to the behavior observed by Gurfinkel \textit{et al.}\textsuperscript{11} and Cuccia \textit{et al.}\textsuperscript{13} The reconstruction approach is closely related to the methods of Kamasak \textit{et al.}\textsuperscript{33} in that it uses a statistical framework to directly reconstruct kinetic model parameters and a similar optimization scheme. We use all of the measured data to reconstruct the model parameter images directly, rather than reconstructing and storing a time sequence of fluorescence images. Our approach explicitly accounts for the fact that different sources are illuminated at different times. We also draw upon our recent work, in which we presented a nonlinear Bayesian inversion approach for the ODT/FODT problems and applied it to experimental data.\textsuperscript{34,15,35,36} We use parametric iterative coordinate descent (PICD) optimization,\textsuperscript{33,37,34} which is efficient and convenient for enforcing non-negativity
constraints, and we use the generalized Gaussian Markov random field (GGMRF) prior model\textsuperscript{38} for spatial regularization in the parameter images.

2. Forward Problem

A. Diffusion Model

Here, we briefly review the forward model for the FODT problem which we have presented before.\textsuperscript{15,34} In applications where scattering dominates over absorption, the transport of light modulated at an RF frequency $\omega$ through a scattering medium can be modeled using the photon transport equation.\textsuperscript{18,39} For $e^{j\omega t}$ time variation, it is given by:

$$\nabla \cdot [D(r)\nabla \phi(r,\omega)] - [\mu_a(r) + j\omega/c] \phi(r,\omega) = -\delta(r - s_k),$$

(1)

where $\phi(r,\omega)$ (W/cm\textsuperscript{2}) is the complex modulation envelope of the photon flux, $s_k$ is the location of a point source, and $\delta(r)$ is the Dirac function. The diffusion coefficient $D(r)$ (cm) is inversely related to the scattering coefficient, and $\mu_a(r)$ (cm\textsuperscript{-1}) is the absorption coefficient.

For the case where the scattering medium contains a fluorophore, the fluorophore is excited with light at wavelength $\lambda_x$, and emits light at a longer wavelength $\lambda_m$. We use two coupled diffusion equations to describe a fluorescence measurement, with the first to represent $\lambda_x$ excitation and the second to represent the emitted $\lambda_m$ photons:\textsuperscript{16,17,40}

$$\nabla \cdot [D_x(r)\nabla \phi_x(r,\omega)] - [\mu_{ax}(r) + j\omega/c] \phi_x(r,\omega) = -\phi_x(r,\omega)\eta_{\mu_{ax}}(r) \frac{1 - j\omega\tau(r)}{1 + [\omega\tau(r)]^2},$$

(2)

$$\nabla \cdot [D_m(r)\nabla \phi_m(r,\omega)] - [\mu_{am}(r) + j\omega/c] \phi_m(r,\omega)$$

$$= -\phi_x(r,\omega)\eta\mu_{ax} \phi_x(r,\omega) \frac{1 - j\omega\tau(r)}{1 + [\omega\tau(r)]^2},$$

(3)
where the subscripts $x$ and $m$ denote excitation and emission wavelengths $\lambda_x$ and $\lambda_m$, respectively. The fluorescent lifetime, $\tau(r) \ (s)$, is the fluorophore’s characteristic exponential decay constant. The fluorescent yield $\eta \mu_a(r) \ (\text{cm}^{-1})$ incorporates the fluorophore’s quantum efficiency $\eta$ and its absorption coefficient $\mu_a$. We will use the notation $\eta$, rather than $\eta \mu_a$, for brevity.

B. Time Varying Fluorescence

Suppose the fluorescent yield $\eta(r, t)$ varies with time, on a scale comparable to the total acquisition time of the tomography instrument. The time variation might be a result of drug kinetics, which may be of physiological interest. Here, we consider the case where $\eta(r, t)$ can be expressed as a (possibly nonlinear) function of $U$ parameters which do not vary in time:

$$\eta(r, t) = \bar{\eta}(\gamma_1(r), \cdots, \gamma_U(r), t), \quad (4)$$

where $\bar{\eta}$ is a known function.

One important case which follows this framework is the compartmental model. In a compartmental model, the body consists of a number of compartments, conceptual regions where the drug’s concentration is assumed to be uniform. A system of differential equations describes the exchange of the drug among the different compartments. Previously, the pharmacokinetics of ICG in animal subjects has been described by use of a three-compartment model, depicted in Figure 1. The compartments were the plasma, the tissue (the extracellular, extravascular space), and the kidneys and liver, which tend to clear the fluorophore out of the blood pool. Let $c_P(t)$ and $c_T(t)$ be the concentration of fluorophore in the plasma and tissue compartments, respectively. Cuccia et al. initially assumed a biexponential decay model for $c_P(t)$, but ultimately observed only single exponential behavior in their experiment due to the relatively long elimination time of ICG.
compared with their measurement duration. Hence, we will assume single exponential decay for $c_P(t)$:

$$c_P = A \exp(-\kappa_3 t)$$

(5)

where $A$ is taken to be the initial fluorophore concentration in the plasma and $\kappa_3$ is the rate constant for fluorophore elimination. We assume that the plasma input function does not vary throughout the imaging domain, i.e., that $c_T(t)$ is not large enough to significantly effect the overall rate of elimination. A similar assumption was made by Cuccia et al.\textsuperscript{13} We also let $\kappa_1$ and $\kappa_2$ be the rate constants for ICG entering and leaving the tissue. Then the concentrations are obtained by solving a differential equation for $c_T(t)$:

$$\frac{dc_T}{dt} = \kappa_1 c_P - \kappa_2 c_T.$$  

(6)

To obtain a volumetric image, we solve (6) with initial condition $c_T(0) = 0$ to obtain $c_T(t)$ in each voxel:

$$c_T = \left( \frac{\kappa_1 A}{\kappa_2 - \kappa_3} \right) \left[ \exp(-\kappa_3 t) - \exp(-\kappa_2 t) \right].$$

(7)

The experimentally observed fluorescent yield is proportional to the concentration of fluorophore in the imaging domain. Within each voxel, the fluorophore concentration is some weighted sum of the tissue and blood compartments. Hence, we may write $\eta(r, t)$ as

$$\eta(r, t) = w_P(r) c_P(t) + w_T(r) c_T(r, t).$$

(8)

Substituting (5) and (7) into (8) yields the biexponential solution:

$$\eta(r, t) = \gamma_1(r) \exp[-\gamma_4(r)t] - \gamma_2(r) \exp[-\gamma_3(r)t]$$

(9)
where

\[
\begin{align*}
\gamma_1 & = A \left( w_P + \frac{w_T \kappa_1}{\kappa_2 - \kappa_3} \right) \quad (10) \\
\gamma_2 & = A \left( \frac{w_T \kappa_1}{\kappa_2 - \kappa_3} \right) \quad (11) \\
\gamma_3 & = \kappa_2 \quad (12) \\
\gamma_4 & = \kappa_3. \quad (13)
\end{align*}
\]

From \( \gamma_1, \ldots, \gamma_4 \), it is possible to obtain the parameters \( \kappa_2, \kappa_3, (A w_P) \), and \( (A w_T \kappa_1) \). Hence, we directly reconstruct images of the biexponential model parameters \( \gamma_1, \gamma_2, \gamma_3 \), and \( \gamma_4 \). To enforce the spatial independence of \( c_P(t) \), one can constrain \( \gamma_4 \) to be the same everywhere. Alternatively, one can reconstruct \( \gamma_4(r) \) to check the self-consistency of the model.

Strictly speaking, the time-dependence of \( \eta(r, t) \) should correspond with a time-dependent perturbation in \( \mu_{ax} \). In previous work, we have observed that perturbational changes in \( \mu_{ax} \) do not have a strong effect on reconstructed fluorescence.\(^{15} \) Hence, for simplicity, we will not consider the reconstruction of time-varying \( \mu_{ax} \) here.

C. Tomography Problem

Previously, for the stationary case, we have shown how to reconstruct \( \mu_{ax}(r), \mu_m(r), D_x(r), D_m(r), \tau(r), \) and \( \eta(r) \).\(^{34,15} \) Here, we assume that \( \mu_{ax}(r), \mu_m(r), D_x(r), \) and \( D_m(r) \) are known in advance and do not vary with time, and we consider the problem of reconstructing \( \tau(r) \) and \( \eta(r, t) \) in the time-varying case.

Suppose that measurements are recorded at \( C \) measurement times, which we call \( t_1, \ldots, t_C \). At each measurement time, measurements are recorded with one or more sources at wavelength \( \lambda_x \) and detectors filtered at \( \lambda_m \). Figure 2 schematically depicts the measurement, with a source and an array of detectors arranged around the domain at each time. Note that the source and detector geometry may be different at different time indices. In
particular, practical instruments often sequentially illuminate sources one at a time, while all detectors are used simultaneously at all times, and all are fixed in space.

Consider a domain discretized into $N$ volume elements, or voxels. Let $r_i$ denote the position of the $i^{th}$ voxel centroid. Assuming that $\eta(r, t)$ can be expressed using (4), we define the image vector $x$:

$$x = \begin{bmatrix} x^T(0) & x^T(1) & \cdots & x^T(U) \end{bmatrix}^T,$$

where

$$x^T(u) = \begin{bmatrix} x_{(u),1} & \cdots & x_{(u),N} \end{bmatrix}^T,$$

$$x^T(0) = \begin{bmatrix} \tau(1) & \cdots & \tau(N) \end{bmatrix}^T,$$

and, for $1 \leq u \leq U$,

$$x^T(u) = \begin{bmatrix} \gamma_u(r_1) & \cdots & \gamma_u(r_N) \end{bmatrix}^T,$$

with the superscript $T$ denoting the transpose operation. Note that $x$ is of size $(U + 1) \times N$, consisting of $U + 1$ concatenated parameter vectors of size $N$. In the parameterization of (9), $U = 4$.

3. Inverse Problem

A. Bayesian Framework

Let $y$ denote the measurement vector whose ordering will be precisely specified in Section B. Similarly, let $f(x)$ denote the forward model. As previously,\textsuperscript{15,36,35} we address the ill-posed problem of estimating $x$ from $y$ in a Bayesian framework. The maximum a posteriori (MAP) estimate can be computed as:

$$\hat{x}_{MAP} = \arg \max_{x \geq 0} \{ \log p_{Y|X}(y|x) + \log p_X(x) \},$$

9
where \( p_{Y|X}(y|x) \) is the data likelihood and \( p_X(x) \) is the prior density for the image. We impose positivity constraints for \( x \), and also require that \( \eta(r_i, t) \geq 0 \) for all \( r_i \) and \( t \). For \( p_{Y|X}(y|x) \), we use an independent Gaussian distribution derived from a shot noise model: \(^{41}\)

\[
p_{Y|X}(y|x) = \frac{1}{(\pi \alpha)^{P|\Lambda|^{-1}}} \exp \left[ -\frac{||y - f(x)||^2}{\alpha} \right], \tag{19}
\]

where \( \alpha \) is a scalar parameter that scales the noise variance, \( P \) is the number of measurements, \( ||w||^2_\Lambda = w^H \Lambda w \) (where \( H \) denotes Hermitian transpose), and \( \alpha \Lambda^{-1} \) is the covariance matrix given by

\[
\alpha \Lambda^{-1} = \alpha \text{diag} \{ |y_1|, |y_2|, ..., |y_P| \}. \tag{20}
\]

The prior model \( p_X(x) \) is the Gaussian Markov random field (GGMRF) model. \(^{38,41}\) We use upper case to represent the corresponding random variables, and we assume that \( X(0), \cdots, X(U) \) are independent:

\[
p_X(x) = \prod_{u=0}^U p_{X(u)}(x(u)) \tag{21}
\]

\[
= \prod_{u=0}^U \frac{1}{\sigma_N(u, \rho(u))} \exp \left( -\frac{1}{\rho(u)} \sum_{i,j \in \mathcal{N}} b_{i,j} |x(u,i) - x(u,j)|^{p(u)} \right), \tag{22}
\]

where the \( u \) subscripts correspond to (15), \( \mathcal{N} \) consists of all pairs of neighboring (adjacent) nodes in a 26-neighbor system, and \( b_{i,j} \) is the weighting coefficient corresponding to the \( i^{th} \) and \( j^{th} \) nodes. The coefficients \( b_{i,j} \) are assigned to be inversely proportional to the node separation in a cube-shaped node layout, where \( \sum_j b_{i,j} = 1 \). The parameters \( \rho \) and \( \sigma \) control the shape and scale of the distribution, and \( \zeta(\rho) \) is a normalization term.

We incorporate \( \alpha \) into the inverse problem as an unknown instrument parameter, as we have found that this tends to improve the robustness and speed of convergence: \(^{42}\)

\[
\hat{x} = \arg \max_{x \geq 0, \alpha \geq 0} \{ p_{X|Y}(x|y, \alpha) \}. \tag{23}
\]
We form the log posterior probability $l(x)$:

$$l(x) = - P \log \| y - f(x) \|_A^2 - \sum_{u=0}^U \left( \frac{1}{\rho(u)} \sigma(u) \sum_{i,j \in \mathcal{N}} b_{i-j} |x_{(u),i} - x_{(u),j}|^{\rho(u)} \right)$$

and implement its maximization by alternating closed form updates of $\hat{\alpha}$ with updates of $\hat{x}$:

$$\hat{\alpha} \leftarrow \frac{1}{P} \| y - f(\hat{x}) \|_A^2$$

$$\hat{x} \leftarrow \arg \max_{x \geq 0} \{ \log p_Y|X(y, \hat{\alpha}) + \log p_X(x) \}$$

where “$\leftarrow$” denotes assignment and “arg update” denotes an iteration of some optimizer.

The update in (26) is equivalent to reducing a cost function

$$c(x, \hat{\alpha}) = \frac{1}{\hat{\alpha}} \| y - f(x) \|_A^2 + \sum_{u=0}^U \left( \frac{1}{\rho(u)} \sigma(u) \sum_{i,j \in \mathcal{N}} b_{i-j} |x_{(u),i} - x_{(u),j}|^{\rho(u)} \right).$$

(27)

B. Definitions

Define $s_{t_c,k}$ as the location of the $k^{th}$ source at time $t_c$, and $d_{t_c,m'}$ as the location of the $m'^{th}$ detector at time $t_c$, and let $g_x(s_{t_c,k}, d_{t_c,m'}; \omega)$ and $g_m(s_{t_c,k}, d_{t_c,m'}; \omega)$ be the diffusion equation Green’s functions for wavelength $\lambda_x$, and $\lambda_m$, respectively. Also, let $\phi_f(s_{t_c,k}, d_{t_c,m'}; \omega, t_c, x)$ be the fluorescence observed at observation position $d_{t_c,m'}$ for an excitation source at $s_{t_c,k}$, where

$$\phi_f(s_{t_c,k}, d_{t_c,m'}; \omega, t_c, x) =$$

$$\int \eta(r, t_c) \frac{1 - j \omega \tau(r)}{1 + [\omega \tau(r)]^2} g_x(s_{t_c,k}, r; \omega) g_m(r, d_{t_c,m'}; \omega) d^3 r.$$  

(28)
Suppose that at time $t_c$ we have $K_c$ sources and $M_c$ detectors at a modulation frequency of $\omega$. (Typically, $K_c = 1$ for most systems which illuminate sources sequentially.) Let $f_{\omega,t_c}(x)$ be the forward model for the data taken at $t_c$ with $e^{j\omega t}$-modulated light. Then,

$$
\phi_f(s_{t_c,1}, d_{t_c,1}; \omega, t_c, x) \\
\phi_f(s_{t_c,1}, d_{t_c,2}; \omega, t_c, x) \\
\vdots \\
\phi_f(s_{t_c,1}, d_{t_c,M_c}; \omega, t_c, x) \\
\phi_f(s_{t_c,2}, d_{t_c,1}; \omega, t_c, x) \\
\vdots \\
\phi_f(s_{t_c,K_c}, d_{t_c,M_c}; \omega, t_c, x)
$$

Let $Q$ be the number of modulation frequencies used, and $C$ be the number of measurement times times. Then:

$$
f_{t_c}(x) = \left[ f_{\omega_1,t_c}(x)^T, f_{\omega_2,t_c}(x)^T \cdots f_{\omega_Q,t_c}(x)^T \right]^T
$$

$$
f(x) = \left[ f_{t_1}(x)^T, f_{t_2}(x)^T \cdots f_{t_C}(x)^T \right]^T.
$$

Similarly, we define the measurement vector $y$ as:

$$
y_{t_c} = \left[ y_{\omega_1,t_c}^T, y_{\omega_2,t_c}^T \cdots y_{\omega_Q,t_c}^T \right]^T
$$

$$
y = \left[ y_{t_1}^T, y_{t_2}^T \cdots y_{t_C}^T \right]^T
$$

corresponding to the same order used in (31). Note that $g(s_k, d_{m'} \omega)$ = $g(d_{m'}, s_k \omega)$ at $\lambda_x$ and at $\lambda_m$, due to reciprocity.43

We may use matrices to approximate the integration of (28). For consistency, we assume a regular rectangular mesh in the following formulation, although we note that more generic...
finite element formulations of similar problems have been previously presented.\textsuperscript{44} We define

\[ G^x(\omega, t_c) = \begin{bmatrix} g_x(s_{t_c,1}, r_1; \omega) & \cdots & g_x(s_{t_c,1}, r_N; \omega) \\ \vdots & \ddots & \vdots \\ g_x(s_{t_c,K}, r_1; \omega) & \cdots & g_x(s_{t_c,K}, r_N; \omega) \end{bmatrix} \]  

(34)

\[ G^m(\omega, t_c) = \begin{bmatrix} g_m(d_{t_c,1}, r_1; \omega) & \cdots & g_m(d_{t_c,1}, r_N; \omega) \\ \vdots & \ddots & \vdots \\ g_m(d_{t_c,M}, r_1; \omega) & \cdots & g_m(d_{t_c,M}, r_N; \omega) \end{bmatrix} \]  

(35)

We also define \( J_{\omega,t_c} \) as

\[ J_{\omega,t_c} = \begin{bmatrix} G^x_{1,1}(\omega, t_c) G^m_{1,1}(\omega, t_c) & \cdots & G^x_{1,N}(\omega, t_c) G^m_{1,N}(\omega, t_c) \\ \vdots & \ddots & \vdots \\ G^x_{1,1}(\omega, t_c) G^m_{M,1}(\omega, t_c) & \cdots & G^x_{1,N}(\omega, t_c) G^m_{M,N}(\omega, t_c) \\ G^x_{2,1}(\omega, t_c) G^m_{1,1}(\omega, t_c) & \cdots & G^x_{2,N}(\omega, t_c) G^m_{1,N}(\omega, t_c) \\ \vdots & \ddots & \vdots \\ G^x_{K,1}(\omega, t_c) G^m_{M,1}(\omega, t_c) & \cdots & G^x_{K,N}(\omega, t_c) G^m_{M,N}(\omega, t_c) \end{bmatrix} \]  

(36)

where \( V \) is the volume of a voxel. Let

\[ h(x_{(s),i}; \omega, t) = \eta(r_i, t) \frac{1 - j\omega \tau(r_i)}{1 + [\omega \tau(r_i)]^2} \]  

(37)

\[ h_{\omega,t_c}(x) = \begin{bmatrix} h(x_{(s),1}, \omega, t_c) & \cdots & h(x_{(s),N}, \omega, t_c) \end{bmatrix}^T \]  

(38)

Then

\[ f_{\omega,t_c}(x) = J_{\omega,t_c} h_{\omega,t_c}(x) \]  

(39)
if we ignore discretization error. Therefore, (27) is equivalent to:

\[
c(x, \hat{x}) = \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left\| y_{\omega_q, t_c} - J_{\omega_q, t_c} h_{\omega_q, t_c}(x) \right\|_{\Lambda_{\omega_q, t_c}}^2 \\
+ \sum_{u=0}^{U} \frac{1}{\rho(u)^{\sigma(u)}} \sum_{\{i,j\} \in \mathcal{N}} b_{i-j} \left| x_{(u), i} - x_{(u), j} \right|^{\rho(u)}. \tag{40}
\]

The cost function in (40) is used in our image reconstruction.

**C. Parametric Iterative Coordinate Descent**

To optimize (40), we use an algorithm which we call parametric iterative coordinate descent (PICD). It is based on earlier work,\textsuperscript{41} and it is modified to allow for computationally efficient updates of the kinetic model parameters. The voxels are individually updated in random order by optimizing the cost function with respect to the parameters at each voxel position.

The updates enforce the constraints \( x \geq 0 \), and also \( \gamma_1 \geq \gamma_2 \) and \( \gamma_3 \geq \gamma_4 \), which are necessary and sufficient to ensure that each parameter is nonnegative, and that \( \eta(t) \geq 0 \) for all time.

In one update scan for \( \hat{x} \), all of the unknowns \( x_{(u)}, u = 0, \cdots, 4 \) are updated at all \( N \) voxel positions. Let the scalar \( x_{(u), i} \) denote the \( i^{th} \) element of \( x_{(u)} \). With all other image elements fixed, the PICD update for the estimate \( \hat{x}_{(u), i} \) is given by

\[
\hat{x}_{(u), i} \leftarrow \arg \min_{x_{(u), i} \geq 0} \left\{ \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left\| y_{\omega_q, t_c} - J_{\omega_q, t_c} s_i h(x_{(u), i}, \omega_q, t_c) \right\|_{\Lambda_{\omega_q, t_c}}^2 \\
+ \frac{1}{\rho(u)^{\sigma(u)}} \sum_{j \in \mathcal{N}_i} b_{i-j} \left| x_{(u), i} - \hat{x}_{(u), j} \right|^{\rho(u)} \right\}, \tag{41}
\]

where \( \mathcal{N}_i \) is the set of nodes neighboring node \( i \) and \( \rho(u) \) and \( \sigma(u) \) are the prior model parameters for \( X_{(u)} \). In (41), \( J_{\omega_q, t_c} s_i \) denotes the \( i^{th} \) column of \( J_{\omega_q, t_c} \). Suppose we have
an initial guess $\tilde{x}$, and let $z_{\omega_q, t_c} = y_{\omega_q, t_c} - f_{\omega_q, t_c}(\tilde{x})$. Then, (41) is equivalent to

$$
\hat{x}_{(u), i} \leftarrow \arg \min_{x_{(u), i} \geq 0} \left\{ \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left[ \|z_{\omega_q, t_c} - [J_{\omega_q, t_c}]_{s(i)} h(x_{(s) i}, \omega_q, t_c) - h(\tilde{x}_{(s) i}, \omega_q, t_c) \|^2 \right]_{\omega_q, t_c} \\
+ \frac{1}{\rho(u) \sigma(u)} \sum_{j \in N_i} b_{i-j} \|x_{(u) i} - \hat{x}_{(u) j}\|^{\rho(u)} \right\},
$$

$$
= \arg \min_{x_{(u), i} \geq 0} \left\{ \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left[ \theta_{1, \omega_q, t_c} h(x_{(s) i}, \omega_q, t_c) - h(\tilde{x}_{(s) i}, \omega_q, t_c) \\
+ \frac{\theta_{2, \omega_q, t_c}}{2} [h(x_{(s) i}, \omega_q, t_c) - h(\tilde{x}_{(s) i}, \omega_q, t_c)]^2 \right) \\
+ \frac{1}{\rho(u) \sigma(u)} \sum_{j \in N_i} b_{i-j} \|x_{(u) i} - \hat{x}_{(u) j}\|^{\rho(u)} \right\},
$$

where

$$
\theta_{1, \omega_q, t_c} = -2 \text{Re} \left\{ [J_{\omega_q, t_c}]_{s i} H_{\omega_q, t_c} z_{\omega_q, t_c} \right\}
$$

$$
\theta_{2, \omega_q, t_c} = 2 [J_{\omega_q, t_c}]_{s i} H_{\omega_q, t_c} [J_{\omega_q, t_c}]_{s i}.
$$

In (42), $\theta_{1, \omega_q, t_c}$ and $\theta_{2, \omega_q, t_c}$ are not functions of $x_{(u) i}$, and thus do not need to be recomputed during the nonlinear, one-dimensional (1-D) line search over $x_{(u) i}$. This property enables significant computational savings, as repeated computations of $\theta_{1, \omega_q, t_c}$ and $\theta_{2, \omega_q, t_c}$ would require numerous complex multiplications. We perform the minimization over $x_{(u) i}$ by use of a Golden Section search.45

To enforce the constraints $\gamma_1 \geq \gamma_2$, we initially perform minimizations over $x_{(1) i}$ and over $x_{(2) i}$ and observe whether the inequality constraint is satisfied. If $\hat{x}_{(2) i} > \hat{x}_{(1) i}$, we
perform a new line search enforcing $x_{(1),i} = x_{(2),i}$:

$$\hat{x}_{(1),i}, \hat{x}_{(2),i} \leftarrow \arg \min_{x_{(1),i}=x_{(2),i} \geq 0} \left\{ \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left( \theta_{1,\omega_{q},t_{c}} [h(x_{(s),i}, \omega_{q}, t_{c}) - h(\bar{x}_{(s),i}, \omega_{q}, t_{c})] \right) \\
+ \frac{\theta_{2,\omega_{q},t_{c}}}{2} [h(x_{(s),i}, \omega_{q}, t_{c}) - h(\bar{x}_{(s),i}, \omega_{q}, t_{c})]^2 \right) \\
+ \frac{1}{\rho_{(1)} \sigma_{(1)}} \sum_{j \in \mathcal{N}_{i}} b_{i-j} |x_{(1),i} - \bar{x}_{(1),j}|^{\rho_{(1)}} \\
+ \frac{1}{\rho_{(2)} \sigma_{(2)}} \sum_{j \in \mathcal{N}_{i}} b_{i-j} |x_{(2),i} - \bar{x}_{(2),j}|^{\rho_{(2)}} \right\} \quad (45)$$

A similar procedure is used to enforce the $\gamma_3 \geq \gamma_4$ condition.

We implement the joint estimation of $\alpha$ and $x$ iteratively. One iteration consists of a closed form update of $\hat{\alpha}$ using (25), followed by a PICD scan to update $\hat{x}$. Appendix A provides pseudocode for a more detailed specification of the PICD algorithm.

4. Simulation

To validate the method, we performed a simulation study. A synthetic time series of data was generated from a cube-shaped phantom containing two heterogeneities. The background properties were $\mu_{a_x} = \mu_{a_m} = 0.047 \text{ cm}^{-1}$ and $D_x = D_m = 0.027 \text{ cm}$. The heterogeneities had the same $\tau$, but different $\gamma_1$, $\gamma_2$, and $\gamma_3$. The parameter $\gamma_4$ was 0, and was not reconstructed. This corresponds to an assumption that elimination time of fluorophore from the plasma is long compared with the measurement time, which is reasonable in cases where we are most interested in the initial drug uptake behavior. The parameter values were selected to result in uptake behavior on the order of seconds, which may be reasonable for a small animal imaging experiment.13

The phantom was $8 \text{ cm} \times 8 \text{ cm} \times 5.7 \text{ cm}$ in size, and it was discretized into $33 \times 33 \times 17$ voxels of size $0.26 \text{ cm} \times 0.26 \text{ cm} \times 0.38 \text{ cm}$. To generate the synthetic measurements, the
The diffusion equation was solved numerically using multigrid finite differences and extrapolated zero-flux boundary conditions with interpolated source positions as we have described previously. The simulation used a modulation frequency of 78.4 MHz. Figure 3 shows the locations of the sources which were placed on the bottom face of the cube-faced domain. The same positions were used as detector positions on the top face of the domain, simulating a parallel-plate transmission geometry similar to that which has been used for optical mammography previously. The sources were illuminated one at a time at different times, in the order shown in Figure 3, and the data consisted of one complete pass through all of the sources, with 441 measurements in all. Simulated shot noise was added, giving an average signal/noise ratio of 28 dB for all the data. The true phantom is shown in Figure 4, with cross section images through each of the heterogeneities.

For the reconstructions, the hyperparameter $\rho$ was set to 2, corresponding to the Gaussian Markov random field (GMRF) model. Although automatic estimation of the hyperparameters is possible in principle, $\sigma$ was chosen to empirically give the best results, as we have done previously. For this problem the best results were given by $\sigma(0) = 2.75 \times 10^{-10}$, $\sigma(1) = 0.5$, $\sigma(2) = 0.5$, and $\sigma(3) = 0.0125$ (where the units of lifetime are seconds and the units of fluorescence are cm$^{-1}$). The PICD algorithm was run to 50 iterations, which required approximately 2 hours on a 2 GHz AMD Athlon workstation.

The reconstructed parametric images are shown in Fig. 5. The results are accurate, although shadowing effects are apparent in the images. In particular, $\gamma_3$, which is related to a dye’s uptake rate, was reconstructed accurately, enabling a clear distinction between the two objects. Figure 6(a)-(d) shows the true images of $\eta(r, t)$ for the two objects, at 4 different times, and Figure 6(e) shows plots of $\eta(t)$ for a single point near the center of each object. The reconstructed time variation is also accurate, without shadowing artifacts.
The reconstruction $\hat{\eta}(r, t)$ was obtained by substituting $\hat{\gamma}_1(r)$, $\hat{\gamma}_2(r)$, and $\hat{\gamma}_3(r)$ into (9).

The results shown in Figure 7 indicate that all features are nicely captured. Figure 8 shows a convergence plot showing monotone decrease of the cost function versus iteration number. For comparison, we also reconstructed $\eta(r, t)$ by independently reconstructing $\eta(r, t_i)$ at each measurement time $t_i$, using our previous FODT reconstruction algorithm. For the first simulation, we used the same 441 measurements that was used for the results in Figure 9. The reconstructions all used $\rho = 2$, with $\sigma = 0.5$ for $\eta$ and $\sigma = 2.75 \times 10^{-10}$ for $\tau$ (which gave the best empirical results). We performed 21 reconstructions of $\eta(r, t_i)$, using a single source and 21 detectors for each. The results, shown in Figure 9, have poor accuracy. For the second simulation, we greatly increased the number of data, using all 21 sources and 21 detectors for each of the reconstructions of $\eta(r, t_i)$ (i.e., 9261 measurements, with 441 measurements used at each time index). The reconstructions in this simulation used $\rho = 2$, with $\sigma = 0.375$ for $\eta$ and $\sigma = 2.75 \times 10^{-10}$ for $\tau$. The results are shown in Figure 10. With this 21-fold increase in data, the reconstructions accuracy approaches that of the parametric imaging method.

5. Conclusions

We have presented a method for parametric reconstruction of fluorescent drug kinetics by use of fluorescence optical diffusion tomography. The simulation showed that two heterogeneities with different time-dependent behavior could be reconstructed simultaneously, and clearly distinguished based on uptake-related parameters. In principle, receptor-targeted fluorescent probes may have a significantly faster uptake rate in tumors compared with the surrounding tissue. Hence, the ability to reconstruct the drug uptake kinetics could facilitate tumor imaging with high contrast, compared with methods which do not make full use of the drug
dynamics.

The presented approach is flexible, and may be applied to more sophisticated compartmental models. In principle, more complicated kinetic models which incorporate additional compartments or nonlinear saturation effects may be used in the same framework, as they simply increase the complexity of the single-site updates. In addition, the PICD algorithm may be incorporated into a multigrid framework\textsuperscript{48} to improve convergence properties for a wide variety of images.

Experimental demonstration of the approach should be developed in future work. One possibility is that controlled FODT Intralipid phantom experiments using fluorescent contrast agents\textsuperscript{34} could be modified for kinetic imaging work. For example, fluorescent dye could be introduced into the phantom over time, while the FODT instrument’s sources and detectors record measurements. Ultimately, validation on living animal subjects would be required, extending previous kinetic modeling work to full three-dimensional imaging geometries. Recent work with three-dimensional fluorophore localization and molecular imaging with animal tissues\textsuperscript{49,1,50} could be applied to the kinetic imaging problem.

A. Pseudocode for Inversion Algorithm

\begin{verbatim}
main {

1. Form $G_x^{(s)}$ and $G_m^{(d)}$

2. Repeat until converged: {

(a) $\hat{\alpha}_f \leftarrow \frac{1}{T_f} \| y_f - f_f(\hat{x}_f, \hat{x}_x, \hat{x}_m) \|^2_{\Lambda_f}$

(b) $\hat{x}_f \leftarrow \text{ICD\_update}(\hat{x}_f, \hat{\alpha}_f, G_x^{(s)}, G_m^{(d)})$

}

\end{verbatim}
\[ \hat{x} \leftarrow \text{ICD}_\text{update}(\hat{x}, \hat{\alpha}, G^{(s)}, G^{(d)}; x) \]

1. For \( c = 1, \ldots, C \) \{
   (a) For \( q = 1, \ldots, Q \) \{
      i. \( z_{\omega_q, t_c} \leftarrow y_{\omega_q, t_c} - f_{\omega_q, t_c}(\hat{x}) \)
   \}
\}

2. For \( i = 1, \ldots, N \) (in random order), \{
   (a) \( \tilde{x}_i \leftarrow \hat{x}_i \)
   (b) For \( c = 1, \ldots, C \) \{
      i. For \( q = 1, \ldots, Q \) \{
      A. Compute \( [J_{\omega_q, t_c}]_{\star(i)} \), by taking the \( i^{th} \) column in (36)
      B. \( \theta_{1, \omega_q, t_c} \leftarrow -2 \text{Re} \{ [J_{\omega_q, t_c}]_{\star(i)} \Lambda_{\omega_q, t_c} z_{\omega_q, t_c} \} \)
      C. \( \theta_{2, \omega_q, t_c} \leftarrow 2([J_{\omega_q, t_c}]_{\star(i)} \Lambda_{\omega_q, t_c} [J_{\omega_q, t_c}]_{\star(i)} \}
      \}
   \}
   (c) \( \hat{\tau} \leftarrow \arg\min_{x(0), i \geq 0} \{ \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} (\theta_{1, \omega_q, t_c}[h(x(\ast)), i, \omega_q, t_c] - h(\bar{x}(\ast)), i, \omega_q, t_c]) \\
               + \frac{\theta_{2, \omega_q, t_c}}{2} [h(x(\ast), i, \omega_q, t_c) - h(\bar{x}(\ast)), i, \omega_q, t_c]^2] \\
               + \frac{1}{\rho(0) \sigma(0)} \sum_{j \in N_i} b_{i-j} |x(0), i - \bar{x}(0), j|^{\rho(0)} \} \} \)
\[
\begin{align*}
&\text{(d) } \hat{\gamma}_1 \leftarrow \arg \min_{x(1),i \geq 0} \left\{ \right. \\
&\quad \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left( \theta_{1,\omega_q,t_c} [h(x(s),i,\omega_q,t_c) - h(\bar{x}(s),i,\omega_q,t_c)] \\
&\quad + \frac{\theta_{2,\omega_q,t_c}}{2} [h(x(s),i,\omega_q,t_c) - h(\bar{x}(s),i,\omega_q,t_c)]^2 \right) \\
&\quad + \frac{1}{\rho_{(1)} \sigma_{(1)}^{\rho_{(1)}}} \sum_{j \in N_i} b_{i-j} |x(1),i - \bar{x}(1),j|^{\rho_{(1)}} \left. \right\} \\
&\text{(e) } \hat{\gamma}_2 \leftarrow \arg \min_{x(2),i \geq 0} \left\{ \right. \\
&\quad \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left( \theta_{1,\omega_q,t_c} [h(x(s),i,\omega_q,t_c) - h(\bar{x}(s),i,\omega_q,t_c)] \\
&\quad + \frac{\theta_{2,\omega_q,t_c}}{2} [h(x(s),i,\omega_q,t_c) - h(\bar{x}(s),i,\omega_q,t_c)]^2 \right) \\
&\quad + \frac{1}{\rho_{(2)} \sigma_{(2)}^{\rho_{(2)}}} \sum_{j \in N_i} b_{i-j} |x(2),i - \bar{x}(2),j|^{\rho_{(2)}} \left. \right\} \\
&\text{(f) if } (\hat{\gamma}_2 > \hat{\gamma}_1) \{ \\
&\quad \hat{\gamma}_1, \hat{\gamma}_2 \leftarrow \arg \min_{x(1),i = x(2),i \geq 0} \left\{ \right. \\
&\quad \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left( \theta_{1,\omega_q,t_c} [h(x(s),i,\omega_q,t_c) - h(\bar{x}(s),i,\omega_q,t_c)] \\
&\quad + \frac{\theta_{2,\omega_q,t_c}}{2} [h(x(s),i,\omega_q,t_c) - h(\bar{x}(s),i,\omega_q,t_c)]^2 \right) \\
&\quad + \frac{1}{\rho_{(1)} \sigma_{(1)}^{\rho_{(1)}}} \sum_{j \in N_i} b_{i-j} |x(1),i - \bar{x}(1),j|^{\rho_{(1)}} \\
&\quad + \frac{1}{\rho_{(2)} \sigma_{(2)}^{\rho_{(2)}}} \sum_{j \in N_i} b_{i-j} |x(2),i - \bar{x}(2),j|^{\rho_{(2)}} \left. \right\} \\
&\text{ } \\
&\text{(g) } \hat{\gamma}_3 \leftarrow \arg \min_{x(3),i \geq 0} \left\{ \right. \\
&\quad \frac{1}{\alpha} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left( \theta_{1,\omega_q,t_c} [h(x(s),i,\omega_q,t_c) - h(\bar{x}(s),i,\omega_q,t_c)] \\
&\quad + \frac{\theta_{2,\omega_q,t_c}}{2} [h(x(s),i,\omega_q,t_c) - h(\bar{x}(s),i,\omega_q,t_c)]^2 \right) \\
&\quad + \frac{1}{\rho_{(3)} \sigma_{(3)}^{\rho_{(3)}}} \sum_{j \in N_i} b_{i-j} |x(3),i - \bar{x}(3),j|^{\rho_{(3)}} \left. \right\} \\
&\text{(h) } \hat{\gamma}_4 \leftarrow \arg \min_{x(4),i \geq 0} \left\{ \\
\end{align*}
\]
\[
\frac{1}{n} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left( \theta_{1, \omega_q, t_c} [h(x(s), i, \omega_q, t_c) - h(\tilde{x}(s), i, \omega_q, t_c)] \\
+ \frac{\theta_{2, \omega_q, t_c}}{2} [h(x(s), i, \omega_q, t_c) - h(\tilde{x}(s), i, \omega_q, t_c)]^2 \right) \\
+ \frac{1}{\rho(4) \sigma(4)} \sum_{j \in N_i} b_{i-j} [x(4), i - \tilde{x}(4), j]^{\rho(4)} \right) \}
\]

(i) if \( \dot{\gamma}_4 > \dot{\gamma}_3 \)

\[
\dot{\gamma}_3, \dot{\gamma}_4 \leftarrow \text{arg min}_{x(3), i = x(4), i \geq 0} \left\{ \right. \\
\frac{1}{n} \sum_{c=1}^{C} \sum_{q=1}^{Q} \left( \theta_{1, \omega_q, t_c} [h(x(s), i, \omega_q, t_c) - h(\tilde{x}(s), i, \omega_q, t_c)] \\
+ \frac{\theta_{2, \omega_q, t_c}}{2} [h(x(s), i, \omega_q, t_c) - h(\tilde{x}(s), i, \omega_q, t_c)]^2 \right) \\
+ \frac{1}{\rho(3) \sigma(3)} \sum_{j \in N_i} b_{i-j} [x(3), i - \tilde{x}(3), j]^{\rho(3)} \\
+ \frac{1}{\rho(4) \sigma(4)} \sum_{j \in N_i} b_{i-j} [x(4), i - \tilde{x}(4), j]^{\rho(4)} \left\} \}
\]

(j) \( \hat{x}(0), \hat{x}(2), \hat{x}(3), \hat{x}(4) \) \leftarrow [\hat{x}, \hat{\gamma}_1, \hat{\gamma}_2, \hat{\gamma}_3] \]

(k) For \( c = 1, \ldots, C \) \{

i. For \( q = 1, \ldots, Q \) \{

A. \( z_{\omega_q, t_c} \leftarrow z_{\omega_q, t_c} + [J_{\omega_q, t_c}]_{x_i} [h(\tilde{x}(s), i, \omega_q, t_c) - h(\tilde{x}(s), i, \omega_q, t_c)] \)

\}

\}

\}
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References


32. J. Matthews, D. Bailey, P. Price, and V. Cunningham, “The direct calculation of parametric images from dynamic PET data using maximum-likelihood iterative reconstruc-


Fig. 1. Compartmental model describing the exchange of contrast agent between the tissue and the plasma.

Fig. 2. Measurement approach for reconstructing $\eta(t)$ and $\tau$. Note that the measurement geometry may differ at each time.
Fig. 3. Source and detector locations used in the simulations. The sources were on the bottom face of the cube-shaped phantom, while the detectors were on the top. The sources were illuminated in the order shown, with one source used for each measurement time.
Fig. 4. True parameter images describing the time-varying fluorescence in simulation study. Cross sections are shown through the top heterogeneity and the bottom heterogeneity. Note the parameter $\gamma_3$ indicates different uptake rates in the two heterogeneities. In (e), an isosurface of the $\gamma_1$ reconstruction is shown, contoured at $1/3$ the maximum value.
Fig. 5. Reconstructed parameter images describing the time-varying fluorescence in the simulation study. In (e), an isosurface of the $\gamma_1$ reconstruction is shown, contoured at 1/3 the maximum value.
Fig. 6. (a)-(d) True fluorescence versus time $\eta(t)$. (e) $\eta(t)$ for a sample point within each heterogeneity.
Fig. 7. (a)-(d) Fluorescence versus time, reconstructed by parametric ICD method.

(e) \( \eta(t) \) for a sample point within each heterogeneity.
Fig. 8. Convergence for the PICD algorithm in the simulation study.
Fig. 9. (a)-(d) Fluorescence versus time, reconstructed independently at each measurement time, using the same data as the parametric reconstructions. (e) $\hat{\eta}(t)$ for a sample point within each heterogeneity.
Fig. 10. (a)-(d) Fluorescence versus time, reconstructed independently at each measurement time, using a 21-fold increase in data over those used in the parametric reconstructions. (e) $\check{\eta}(t)$ for a sample point within each heterogeneity.