Direct Reconstruction of Pharmacokinetic Rate Images of Indocyanine Green in Fluorescence Molecular Tomography

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Abstract: We propose a two-compartment model to present the pharmacokinetics of ICG around a tumor region. We introduce a method to directly reconstruct ICG pharmacokinetic rate images from boundary photon flux measurements using extended Kalman filtering.

OCIS codes :(100.0100) Image processing; (100.3010) Image reconstruction techniques

1. Introduction

Hemoglobin being an endogeneous contrast agent is incapable of providing high contrast. Thus, a new technique, fluorescence diffuse optical tomography (FDOT), whose theory is a straightforward expansion of that of diffuse optical tomography (DOT) have been proposed as an efficient means for increasing optical contrast. In FDOT, rather than endogenous contrast agents, NIR-excitable exogenous fluorescent contrast agents are investigated in terms of their optical properties. In FDOT, after discretizing the domain, the concentrations of the fluorochromes inside the tissue are reconstructed for each voxel from the boundary photon flux measurements [1]. The spatially and temporally resolved concentration images can then be used to form spatially resolved pharmacokinetic rates based on compartmental modeling [4]. In this study, we propose a method to reconstruct pharmacokinetic rate images of ICG directly from the boundary photon flux measurements based on extended Kalman filtering framework. We used a two-compartment model for indocyanine green (ICG) pharmacokinetics in a domain around the tumor region and coupled this model with the FDOT forward model to form a state space model which is then iteratively solved by extended Kalman filtering algorithm.

2. Methodology

2.1 Forward Problem in Fluorescence Diffuse Optical Tomography

In this work, we used a coupled system of diffusion equations to model fluorescence light propagation in tissue [1]. The quantity, we wish to estimate is the spatially varying pharmacokinetic rate parameters which are directly related to the absorption coefficient of the fluorophore at the excitation wavelength. Based on the coupled diffusion equation, the forward model for FDOT can be expressed as:

$$\Psi = f(\mu_a) \quad . \tag{1}$$

where μ_a is the absorption coefficient vector and Ψ is the boundary flux measurement vector and f is a nonlinear function defined by the coupled diffusion equation. Note that the absorption coefficient vector includes the absorption due to endogenous background and exogenous fluorochromes. Under the assumption that the exogenous optical properties has no effect on endogenous optical properties, (1) can be linearized to obtain

$$\Psi_n = W\mu_{af} \tag{2}$$

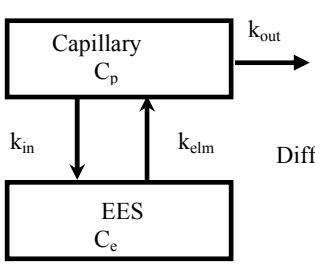
where Ψ_n is the normalized Born measurements, μ_{af} is the absorption coefficient of the fluorochromes and W is the weight (Jacobian) matrix. The absorption coefficient μ_{af} of the fluorophore is related to the bulk ICG concentration m as follows:

$$\mu_{af} = \ln 10 \times \varepsilon_\lambda \times m \tag{3}$$

where ε_λ is the wavelength dependent molar extinction coefficient of the fluorophore at the emission wavelength.

2.2 The Two-compartment Model for ICG Pharmacokinetics and Inverse Problem

ICG pharmacokinetics has the potential to provide diagnostic information for tumor differentiation [2,3]. In this study, we define pharmacokinetics as the rate of change of ICG concentration in vascular tumors and use a compartmental modeling approach to capture the ICG transition between different compartments. We assume that the tumor region is composed of two compartments; namely, the plasma and extracellular extravascular space (EES), [2,3]. Figure 1 illustrates the two-compartment model for ICG kinetics and ICG model equations. C_p and C_e represent the ICG concentrations in the plasma and EES, respectively. The parameters k_{in} and k_{out} govern the leakage into and the drainage out of the EES. The parameter k_{elm} describes the ICG elimination from the body through kidneys and livers. The parameters v_p and v_e are the plasma and EES volume fractions, respectively.



$$\frac{dC_p(t)}{dt} = -(k_{in} + k_{elm})C_p(t) + k_{out}C_e(t)$$

$$\frac{dC_e(t)}{dt} = k_{in}C_p(t) - k_{out}C_e(t)$$

$$m(t) = v_pC_p(t) + v_eC_e(t)$$

Fig. 1. The representation of the two-compartment model.

In this work, we want to reconstruct the pharmacokinetic rate images in a domain composed of voxels. In order to do so, we extend the compartmental model equations given above to spatially resolved case: Let *m(r,t)*, denote the bulk ICG concentration at location *r* and time *t*, and $C_{e,p}(r,t)$ denote the ICG concentration at location *r* and time *t* in the EES and plasma concentrations, respectively. For *N* voxels, we form

$$\begin{bmatrix} m(r_1,t) \\ \vdots \\ m(r_N,t) \end{bmatrix}_{Nx1} = \begin{bmatrix} v_e(r_1) & v_p(r)_1 & 0 & 0 \\ 0 & \ddots & \ddots & 0 \\ 0 & 0 & v_e(r_N) & v_p(r_N) \end{bmatrix}_{Nx2N} \begin{bmatrix} C_e(r_1,t) \\ \vdots \\ C_p(r_N,t) \end{bmatrix} + \overline{\eta}(r,t) \tag{4}$$

where r_j denotes the location of the j[th] voxel and $v_e(r_j)$, $v_p(r_j)$ are plasma and EES volume fractions; and *η(r,t)* is zero mean Gaussian process representing the noise in the measurements. The differential equations describing the transition between the plasma and EES for spatially resolved case is given by

$$\begin{bmatrix} \dot{C}_e(r_1,t) \\ \vdots \\ \dot{C}_p(r_N,t) \end{bmatrix}_{2Nx1} = \begin{bmatrix} K^1_{2x2} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & K^N_{2x2} \end{bmatrix}_{2Nx2N} \begin{bmatrix} C_e(r_1,t) \\ \vdots \\ C_p(r_N,t) \end{bmatrix}_{2Nx1} + \overline{\omega}(r,t) \tag{5}$$

where *ω(r,t)* can be thought of as a zero mean Gaussian process *and* K^j is the matrix describing the transition between the two compartments for the j^{th} voxel given by

$$K^j = \begin{bmatrix} -k^j_{out} & k^j_{in} \\ k^j_{out} & -(k^j_{in} + k^j_{elm}) \end{bmatrix} . \tag{6}$$

The implicit form of the equations (4) and (5) are given by

$$\overline{m}(r,t)_{Nx1} = \overline{V}_{Nx2N}\overline{C}(r,t)_{2Nx1} + \overline{\eta}(r,t)_{Nx1} \tag{7}$$

$$\dot{\overline{C}}(r,t)_{2Nx1} = \overline{K}_{2Nx2N}\overline{C}(r,t)_{2Nx1} + \overline{\omega}(r,t)_{2Nx1} . \tag{8}$$

Next we combine the linearized FDOT model given in equation (2), (3) AND the spatially resolved compartmental model in equation (7) to obtain

$$\overline{\Psi}(r,t)_{Mx1} = \overline{W}_{MxN}\mu_{af}m(r,t)_{Nx1} = \overline{W}_{MxN}\varepsilon_{\lambda}.\overline{m}(r,t) = \varepsilon\overline{W}_{MxN}\overline{V}_{Nx2N}\overline{C}(r,t)_{2Nx1} + \overline{W}_{MxN}\overline{\eta}(r,t)_{Nx1} . \tag{9}$$

The state space presentation form which is used for direct reconstruction of pharmacokinetic rate images are given by

$$\dot{\overline{C}}(r,t)_{2Nx1} = \overline{K}_{2Nx2N}\overline{C}(r,t)_{2Nx1} + \overline{\omega}(r,t)_{2Nx1} \quad (10)$$

$$\overline{\Psi}(r,t)_{Mx1} = \overline{\Gamma}_{Mx2N}\overline{C}(r,t)_{2Nx1} + \overline{W}_{MxN}\overline{\eta}(r,t)_{Nx1} \quad (11)$$

where the matrix Γ is given by $\varepsilon_\lambda WV$.

We reconstruct the pharmacokinetic rate images recursively using the extended Kalman filtering framework. The details of the algorithm can be found in [2]. Here it is important to note that, to get improved estimates, we introduce a Markov random field model on pharmacokinetic rates. This model imposes a spatial correlation between the values of the neighboring voxels.

3. Simulations and Results

To validate the EKF method, we performed a simulation study. Using physiologically reasonable values for pharmacokinetic rates, k_{in}, k_{out}, k_{elm}, and volume fractions, v_e, v_p, around the tumor region, a set of time series data, $\Psi(r,t)$, was generated from a simulated domain with tissue-like characteristics. To generate the synthetic measurements, the diffusion equation was solved numerically using FEM algorithm with Robin type boundary conditions. The simulation used a modulation frequency 300 MHz. The phantom is 6cm by 6cm in size, and it is discretized into 8 by 8 voxels of each of size 0.75cm by 0.75cm. The 8 sources and 8 detectors are arranged throughout the boundary sequentially. The maximum transition rates of k_{in} and k_{out} is created in the center of the image of size 1.5cm by 1.5cm and smoothly decreased through boundaries. Figures 2a and 3a displays the true images of pharmacokinetic rates k_{in} and k_{out}. Figures 2b and 3b displays the reconstructed images of these rates. The percent error between the true images and the reconstructed images are calculated using the ratio of the norm of the error and the norm of the true image. The percent error is calculated to be 12.74 % for k_{in}, and 13.65 % for k_{out}. Here, k_{elm}, presenting the elimination of ICG from the body is not imaged since it is nearly same for all voxels.

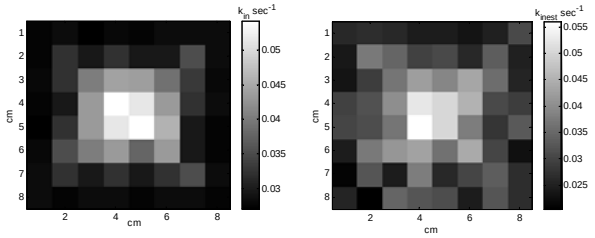


Fig 2. Pharmacokinetic rate images of k_{in} : (a) true, and (b) reconstructed.

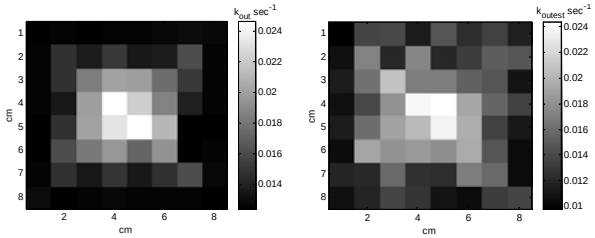


Fig 3. Pharmacokinetic rate images of k_{out} : (a) true, and (b) reconstructed.

4. Conclusion

In this paper, we reconstructed pharmacokinetic rate images of ICG directly from boundary photon flux measurements. We performed a simulation study using a digital phantom. Reconstructed images with small errors show that the algorithm can be used for real data analysis. In the near feature, we are planning to apply the proposed algorithm using the ICG concentration data acquired from breast tumors.

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