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Sparsity-Promoting Fluorescence Molecular Tomography with Iteratively Reweighted Regularization

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***Abstract*— Fluorescence molecular tomography has become a promising technique for *in vivo* small animal imaging, and has many potential applications. Due to the ill-posed and the ill-conditioned nature of the problem, Tikhonov regularization is generally adopted to stabilize the solution. However, the result is usually over-smoothed. In this study, the sparsity of the fluorescent source is used as *a priori* information. We replace Tikhonov method with an iteratively reweighted scheme. By dynamically updating the weight matrix, L0- or L1-norm regularization can be approximated which can promote the sparsity of the solution. Simulation study shows that this method can preserve the sparsity of the fluorescent source within heterogeneous medium, even with very limited measurement data.**

I. INTRODUCTION

In vivo small animal molecular imaging has become an important and rapidly developing method for biomedical research, and has been widely used for cancer detection, drug discovery, and gene expression visualization [1]. Among molecular imaging modalities, fluorescence molecular tomography (FMT) has become a promising technique which can three-dimensionally resolve molecular processes by measuring the photons on the animal surface and reconstructing the distribution of fluorescent probes.

In recent years, much effort has been put into the reconstruction of FMT. FMT is often an ill-posed inverse problem since only the photon distribution on the surface is measurable. This can be alleviated by increasing the measurement data sets. However, even if sufficient measurements can be obtained, the problem may still be ill-conditioned, which means that it is unstable and is sensitive to noises. To compute a meaningful approximate solution, various regularization methods are generally incorporated to make this problem less sensitive to perturbations. Among different regularization methods, Tikhonov regularization is a popular method that has been widely adopted in optical tomography problems [2], [3], [4]. Tikhonov method assumes that the "size" of the solution should not be very large, and adds L2-norm constraint of the solution to the original problem. The advantage of Tikhonov regularization is that the optimization problem is simple and can be solved efficiently by now-standard minimization tools. However, the solution is often over-smoothed with the localized features lost during the reconstruction process [5].

To improve the quality of the reconstructed image, more *a priori* information should be included. Fortunately, for FMT problems, the domains of the fluorescent sources are often very small and sparse compared with the entire reconstruction domain [6]. This can be considered as valuable *a priori* information for FMT. A straightforward way to incorporate sparsity constraint is to replace the Tikhonov regularization with L0-norm regularization. However, the problem becomes NP-hard if L0-norm is utilized, and cannot be solved efficiently. Fortunately, it is proved that when the solution is sufficiently sparse, L0-norm can be replaced by L1-norm, which is convex and can be solved by standard optimization tools, such as pursuit algorithms [7]. In recent years, several reconstruction algorithms incorporating L1-norm regularization have been reported [6], [8], [9].

In this paper, an iteratively reweighted regularization method is proposed for the FMT problem. Based on the basic idea of FOCUSS algorithm which is used in MEG reconstruction [10], we extend Tikhonov method by incorporating a weighting matrix. By iteratively updating the weighting matrix, L0- or L1-norm regularization can be approximated which tends to promote the sparsity of the solution. The advantage of the proposed method is that the optimization problem remains simple and can be solved by many minimization algorithms, such as the Newton method. Besides, this method is very easy to implement. Experimental results on simulated data demonstrate the performance of the proposed method.

II. SPARSITY-PROMOTING FLUORESCENCE MOLECULAR TOMOGRAPHY

A. Photon propagation model

In the near infrared spectral window, the photon propagation model for steady-state FMT with point excitation sources can be depicted using the following coupled diffuse equations:

$$\begin{cases} \nabla D_x(r)\nabla\Phi_x(r) - \mu_{ax}(r)\Phi_x(r) = -\Theta_s\delta(r-r_l) \\ \nabla D_m(r)\nabla\Phi_m(r) - \mu_{am}(r)\Phi_m(r) = -\Phi_x(r)\eta\mu_{af}(r) \end{cases} \quad (1)$$

where subscripts x and m denote the excitation and emission wavelengths, respectively. $\Phi_{x,m}$ is the photon density, $\mu_{ax,am}$ is the absorption coefficient and $D_{x,m}$ is the diffusion coefficient. $\eta\mu_{af}(r)$ denotes the fluorescent yield which is

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to be reconstructed. In this forward model, the excitation light is implemented as isotropic point sources located one mean free path of photon transport beneath the surface at different locations $r_l (l = 1, 2, ..., L)$ with the amplitude Θ_s. These equations are complemented by Robin-type boundary conditions on the boundary $\partial\Omega$ of the domain Ω:

$$2D_{x,m}\partial\Phi_{x,m}/\partial\vec{n} + q\Phi_{x,m} = 0 \quad (2)$$

where $\vec{n}$ denotes the outward normal vector to the surface and q is a constant depending on the optical reflective index mismatch at the boundary.

B. Finite element discretization

Instead of solving Eqs. (1) and (2) directly, they are posed in their weak solution forms. Discretizing the domain with tetrahedron elements and employing the base functions as the test functions, the FMT problem can be linearized and the following matrix-form equations can be obtained. The detailed derivation can be found in [2].

$$[K_x]\{\Phi_x\} = \{S_x\} \quad (3)$$

$$[K_m]\{\Phi_m\} = [F]\{X\} \quad (4)$$

where K_x and K_m are the system matrices. Matrix F is obtained by discretizing the unknown fluorescent yield distribution. Vector X denotes the fluorescent yield to be reconstructed.

For each excitation point source at r_l $(l = 1, 2, ..., L)$, Φ_x can be directly obtained by solving Eq. (3). Considering the *inverse crime* problem, Φ_x is calculated on a fine mesh using 2nd order Lagrange elements. Then, it is projected onto a coarse mesh which is used for the reconstruction of X with linear elements.

As K_m is symmetrical positive definite, Eq. (4) can be transformed into $\{\Phi_{m,l}\} = [K_{m,l}^{-1}][F]\{X\} = [B_l]\{X\}$. Removing the unmeasurable entries in Φ_m and corresponding rows in B, we can obtain the following matrix equation:

$$\{\Phi_{m,l}^{meas}\} = [A_l]\{X\} \quad (5)$$

Then, we assemble Eq. (5) for different excitation locations and obtain the following matrix-form equation:

$$\{\Phi_m^{meas}\} = [A]\{X\} \quad (6)$$

where

$$\Phi_m^{meas} = \begin{Bmatrix} \Phi_{m,1}^{meas} \\ \Phi_{m,2}^{meas} \\ \vdots \\ \Phi_{m,L}^{meas} \end{Bmatrix}, \ A = \begin{bmatrix} A_1 \\ A_2 \\ \vdots \\ A_L \end{bmatrix} \quad (7)$$

C. Iteratively reweighted regularization

Due to the ill-posed and the ill-conditioned nature of the FMT problem, regularization method is always utilized to make the solution more reasonable, which can be considered as a kind of *a priori* information. Here, we extend Tikhonov regularization by incorporating a weighting matrix W:

$$\min_{X \geq 0} J(X) = \frac{1}{2}||AX - \Phi_m^{meas}||_2^2 + \frac{\lambda^2}{2}||WX||_2^2 \quad (8)$$

where λ^2 is the regularization parameter that balances the two terms, and W is a diagonal matrix. In this paper, we always assume that X is non-negative. This energy function $J(X)$ can be efficiently minimized by iterative minimization tools, such as Newton method.

It is evident that the desirable norms $||X||_0$ and $||X||_1$ can be represented using $||WX||_2^2$ by choosing the weighting matrix W as follows:

$$W_0(i,i) = \begin{cases} 1/X(i) & X(i) > 0 \\ 0 & X(i) = 0 \end{cases} \quad (9)$$

$$W_1(i,i) = \begin{cases} 1/\sqrt{X(i)} & X(i) > 0 \\ 0 & X(i) = 0 \end{cases} \quad (10)$$

However, both W_0 and W_1 depend on X and are unknown in advance. To resolve this problem, we assume that for every two adjacent iterations $n-1$ and n during the minimization process, $||X_n - X_{n-1}||_2$ is relatively small compared with $||X_{n-1}||_2$, which means that we can use X_{n-1} to approximate X_n to some extent. Therefore, for every new iteration n, we can construct the sparsity-promoting regularizers $||X||_0$ and $||X||_1$ using the current solution X_{n-1}. Based on this, we redefine the two diagonal weighting matrices W_0 and W_1 as follows to approximate L0- and L1-norm regularization, which are termed as L0- and L1-like regularization, respectively:

$$W_0(i,i) = \begin{cases} 1/X_{n-1}(i) & X_{n-1}(i) > 0 \\ 0 & X_{n-1}(i) = 0 \end{cases} \quad (11)$$

$$W_1(i,i) = \begin{cases} 1/\sqrt{X_{n-1}(i)} & X_{n-1}(i) > 0 \\ 0 & X_{n-1}(i) = 0 \end{cases} \quad (12)$$

where X_{n-1} is the reconstructed solution from the last iteration.

For the first few iterations of the minimization algorithm, the solution X_n may vary rapidly, which violates our basic assumption. To resolve this problem, Tikhonov method is firstly used for several iterations to provide a rough initial guess. The number of iterations can be set in advance or be determined dynamically. Then, L0- or L1-like regularization starts from the initial guess to compute a sparse solution.

III. SIMULATION RESULTS

In this section, heterogeneous simulation experiments were conducted to verify the sparsity-promoting characteristic of the proposed method. Fig. 1 shows the heterogeneous cylindrical phantom we used, which was of 20mm in diameter and 20mm in height. The phantom consisted of four kinds of materials, which is illustrated in Fig. 2, to represent muscle (M), lung (L), heart (H), and bone (B), respectively. The optical parameters can be found in [11]. Three spherical fluorescent sources of 2mm in diameter centered in $z = 0$ plane were placed in the left and the right lungs. The fluorescent yield was set to be 8.

Fluorescence measurement was implemented in transillumination mode. For each excitation source, which was modeled as an isotropic point source located one mean free path of photon transport beneath the surface in $z = 0$ plane,

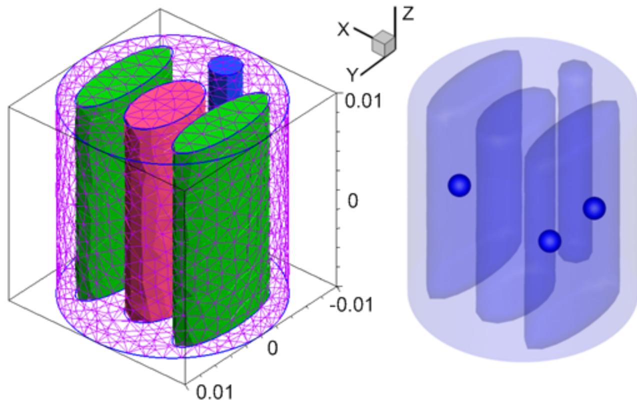
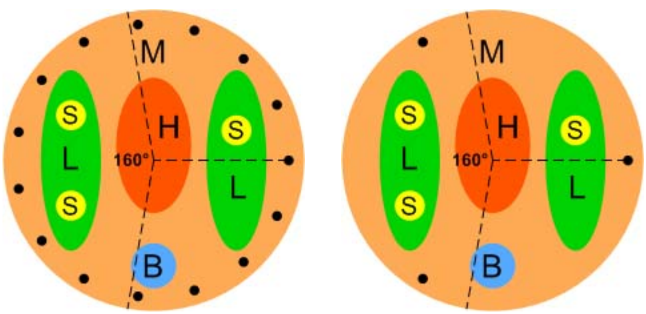


Fig. 1. Mouse-mimicking heterogeneous phantom with three spherical fluorescent sources of 2mm in diameter centered in $z = 0$ plane.



(a) 15 excitation sources (b) 3 excitation sources

Fig. 2. Slice images of the phantom in $z = 0$ plane. The black dots represent the locations of the excitation point sources. For each excitation location, fluorescence is measured from the opposite cylindrical side within 160° field of view.

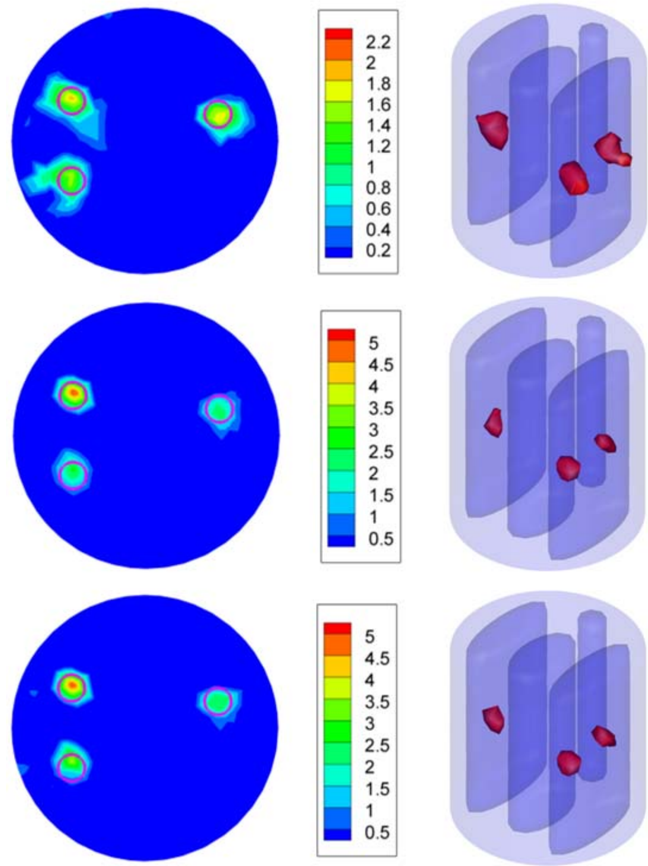


Fig. 3. Reconstruction results using 15 measurement data sets with Tikhonov (top row), L1-like (middle row) and L0-like (bottom row) regularizations, respectively. These results are presented in the form of slice images in $z = 0$ plane (left column) and iso-surfaces for 30% of the maximum value (right column). The small circles in the slice images denote the real positions of the fluorescent sources.

measurement of the emitted fluorescence on the surface was taken from the opposite cylindrical side within 160° field of view (FOV), which is illustrated in Fig. 2. It means that all the nodes on the cylindrical side within this FOV were considered to be measurable. Besides, 5% guassian noise was added to the measurement data to simulate the real case.

Newton method was adopted to iteratively compute the solution. To provide an initial guess, Tikhonov method was used for the first 10 iterations. Then, L0- or L1-like regularization proceeded the reconstruction from the initial guess. The maximum iteration number was set to be 300. The regularization parameter λ^2 plays an important role for the inverse problem. However, finding the optimal λ^2 is itself a very challenging task and will not be covered in this paper. Instead, we sampled the range between 1e-2 and 1e-6 which was sufficient for this experiment, and performed reconstructions using these sampled values. The best value for λ^2 was chosen by visual inspection of the results and quantitative comparison of reconstructed location errors.

In the first experiment, fluorescence was excited by point sources from 15 different locations in sequence, which is illustrated in Fig. 2(a). Measurements were taken every 24° and a total of 15 data sets were acquired for the reconstruction of the fluorescent yield. To show the merit of the proposed method, L0- and L1-like regularizations were compared with Tikhonov method. Fig. 3 shows the reconstruction results which are presented in the form of slice images in $z = 0$ plane and iso-surfaces for 30% of the maximum value. The small circles in the slice images denote the real positions of the fluorescent sources. From Fig. 3 we can clearly see that, the result obtained using the Tikhonov regularization is over-smoothed with reduced intensities. On the contrary, both L0-like and L1-like regularizations can preserve the sparsity characteristic of the fluorescent sources very well, and the reconstructed intensities are greater.

Next, we reduced the amount of measurement data to simulate a much worse case. This is possible when long-time measurement is not appropriate or feasible. For instance, when imaging small animals like mice, the artifacts caused by movements must be taken into consideration. Besides, long-time measurement can cause the bleaching effect of the fluorescent probes and affect the accuracy of the reconstruction results. One way to resolve this problem is to reduce the number of fluorescence measurements. This requires that we should be able to reconstruct the fluorescent sources from very limited data. It has been shown in bioluminescence to-

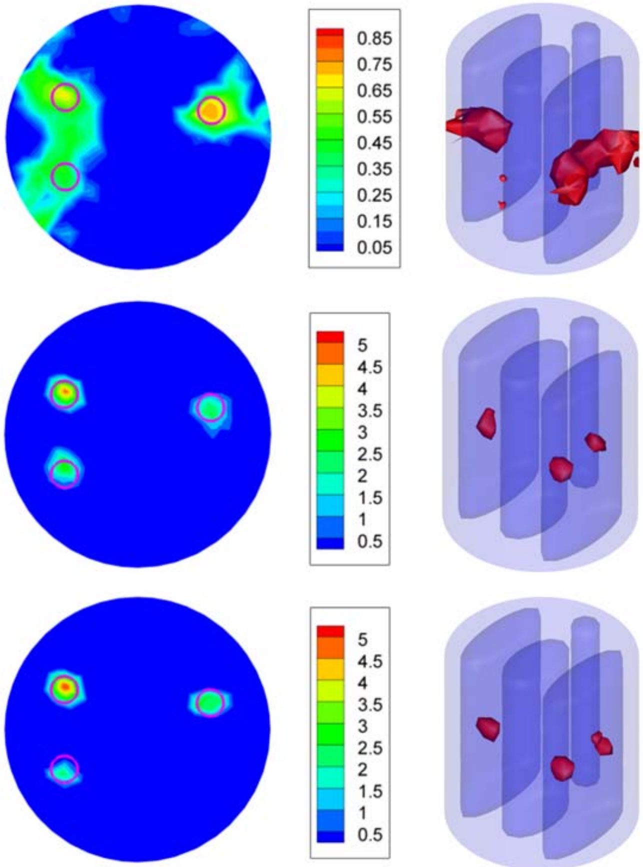


Fig. 4. Reconstruction results using 3 measurement data sets with Tikhonov (top row), L1-like (middle row) and L0-like (bottom row) regularizations, respectively. These results are presented in the form of slice images in $z = 0$ plane (left column) and iso-surfaces for 30% of the maximum value (right column). The small circles in the slice images denote the real positions of the fluorescent sources.

mography that, by using L1-norm regularization, satisfactory results can still be achievable even with very limited imaging data [5]. Here, we only retained 3 measurement data sets, which is illustrated in Fig. 2(b). Fig. 4 shows the reconstruction results using Tikhonov regularization and the proposed method. From these results we can clearly see that, due to the badly ill-posed situation and the over-smooth effect, the two sources in the left lung cannot be separated from the result when using Tikhonov regularization. However, the proposed method can still preserve the sparsity of the sources very well. This demonstrates the applicability of the proposed method under more ill-posed conditions.

IV. CONCLUSIONS

In this paper, we have incorporated the sparsity characteristic of the fluorescent sources into the FMT problem as *a priori* information, and proposed a sparsity-promoting reconstruction algorithm. The algorithm is based on an iteratively reweighted scheme which can approximate L0- or L1-norm regularization. The advantage of the proposed method is that the optimization problem remains simple and can be solved efficiently. The extra work is merely the construction of a diagonal weighting matrix at each iteration, which is a relatively cheap operation. For the evaluation of this method, heterogeneous simulation experiments have been conducted. Compared with Tikhonov method, more reasonable and satisfactory results can be obtained when using L0- or L1-like regularization, even with very limited measurement data. This demonstrates the applicability of the proposed method for the early detection of tumors which are usually small and sparse at this stage. Of course, there are situations in which the assumption that the solution will be sparse cannot hold, e.g. a large tumor or broadly distributed fluorescence signal, and the proposed method may fail in those cases.

Although the diffuse equation has been utilized to describe photon propagation in biological tissues, yet it is not applicable in certain regions, such as void or more absorptive regions. Several improved models, e.g. higher order approximation to radiative transfer equation, have been proposed to resolve the problem. Since FMT reconstruction is a linear inverse problem in nature, the proposed method can potentially be utilized in these improved models.

In conclusion, we have developed a sparsity-promoting reconstruction method for FMT. Numerical simulations show the merits of our method. In vivo mouse studies using the proposed method will be reported in the future.

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