Sparse reconstruction for fluorescence molecular tomography via a fast iterative algorithm

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Fluorescence molecular tomography (FMT) is a fast-developing optical imaging modality that has great potential in early diagnosis of disease and drugs development. However, reconstruction algorithms have to address a highly ill-posed problem to fulfill 3D reconstruction in FMT. In this contribution, we propose an efficient iterative algorithm to solve the large-scale reconstruction problem, in which the sparsity of fluorescent targets is taken as useful a priori information in designing the reconstruction algorithm. In the implementation, a fast sparse approximation scheme combined with a stage-wise learning strategy enable the algorithm to deal with the ill-posed inverse problem at reduced computational costs. We validate the proposed fast iterative method with numerical simulation on a digital mouse model. Experimental results demonstrate that our method is robust for different finite element meshes and different Poisson noise levels.

Keywords: Fluorescence molecular tomography; sparse regularization; reconstruction algorithm; least absolute shrinkage and selection operator.

1. Introduction

Fluorescence molecular tomography (FMT) is a promising imaging modality that allows detailed investigations of biological processes, disease progression, and response to therapy at a molecular level within small animals. Compared with plane fluorescence imaging, FMT provides more quantitative and accurate information of spatial location and strength.
of fluorescent sources (usually fluorescent probe tagging the molecule of interest). It has recently gained much attention in the field of pre-clinical studies, such as drug development, early cancer detection and cell-based therapy.\textsuperscript{1–6}

Methodologies or schema for quantitative image reconstruction is the key to the further advancement of FMT. In this paper, we focus on the inverse problem of FMT based on continuous wave fluorescence measurements, i.e., recovery of the 3D distribution of the interior fluorescent source from measurements at the tissue surface based on a photons propagating model.

Due to high degrees of absorption and scattering of photons propagating through biological tissue, the inverse problem of FMT is inherently illposed. Consequently, various regularization strategies become indispensable for the inverse algorithm to obtain a stable solution.\textsuperscript{7} In addition, a priori knowledge regarding solution is usually incorporated into image reconstruction to play an important role in improving the solution quality, e.g., anatomical information,\textsuperscript{10–12} local smoothness,\textsuperscript{13} or sparsity.\textsuperscript{14,15}

To solve the inverse problem, prior knowledge regarding the solution usually presents in the form of a regularizer or a penalty term in the objective function, such as Tikhonov regularization, $l_1$ regularization and total variation (TV) regularization. Typically, the biological mechanisms are locally concentrated within specific areas of interest, which means the fluorescence-labeled targets present a sparse distribution in the volume or the solutions only have a few nonzero coefficients. The $l_1$ norm is a widely used sparsity-inducing norm and recent researches have witnessed that $l_1$ regularization is a preferable choice for sparse images reconstruction of FMT.\textsuperscript{16–22}

In this contribution, the inverse problem of FMT is formulated into a least absolute shrinkage and selection operator (LASSO) problem by $l_1$ regularization and a fast iterative algorithm is developed to reconstruct the fluorophore distribution. Simulations on 3D digital mouse model are performed to evaluate the proposed method.

2. Method

2.1. Inverse model

In continuous wave FMT, the distribution of the fluorophore is recovered from the steady state surface measurements. With the diffusion approximation, the photons propagation through tissue can be described by a set of coupled partial differential equations.\textsuperscript{19–22} By solving the diffusion equation numerically using the finite elements method,\textsuperscript{23–25} we can build a linear relationship between the unknown fluorescence target $x$ and the measured surface fluorescence data $b$:

$$ Ax = b, $$

where $A \in R^{m \times n}$ is the system matrix. Typically, $A$ for FMT is a large size rank-deficient matrix, therefore constraints are necessary to distinguish the meaningful solution from an infinite number of solutions. We take the sparsity as a constraint and formulate the inverse problem of FMT into an $l_1$-norm regularized optimization problem:

$$ \min_x \{L(x) = \|Ax - b\|_2 + \lambda \|x\|_1 \}. \quad (2) $$

The problem in (2) is a LASSO problem,\textsuperscript{26} also known as basis pursuit.\textsuperscript{27} We proposed an efficient iterative algorithm for solving such optimization problem in (2),\textsuperscript{28} which will be referred to as stagewise fast LASSO (SwF-LASSO) in the following section. Here, SwF-LASSO is used to solve the convex optimization problem for FMT.

2.2. Stagewise fast LASSO

Obviously, the objective function in (2) is convex but not differentiable. We define some notations to simplify the objective function. Let the residual vector be $r(x) = Ax - b$, where $r(x) = (r_1(x), \ldots, r_m(x))^T$. Let $\omega = (\omega_1, \ldots, \omega_n)^T$, $\omega_i = \frac{\text{sign}(x_i)}{\alpha_i} \cdot \frac{z_i}{\sqrt{1 + z_i^2}}$, $i = 1, \ldots, n$. Define the sign vector $s(x) = (s_1(x), \ldots, s_m(x))^T$ by

$$ s_i(x) = \begin{cases} 1, & 0 < r_i(x) < \infty \\ -1, & -\infty < r_i(x) < 0 \\ 0, & \text{otherwise} \end{cases}. \quad (3) $$

Then the objective function can be reformulated into

$$ \min_x \{L(x) = x^T A^T A x - 2((A)^T b - \lambda \omega^T / 2)x \}. \quad (4) $$

By setting the deviation of (4) to zero, it is easy to derive the solution of (2) that takes the form of:

$$ \hat{x} = (A^T A)^{-1}(A^T b - \lambda \omega / 2). \quad (5) $$
However, the solution cannot be determined directly with (5) because \( \omega \) depends on \( x \). Moreover, the matrix inversion in (5) is a time-consuming operation for a large-size system matrix \( A \). To avoid matrix inversion, we employ a greedy scheme to solve (4) efficiently, which is inspired by the fast sparse approximation for least squares support vector machine. In the implementation, we regard matrix \( A \) as a basis function dictionary, i.e., \( A = [a_1, a_2, \ldots, a_n] \) is the \( m \times n \) dictionary. Two index sets, \( S \) and \( P \), are used in the proposed algorithm. The algorithm works by initializing index set \( P \) empty and \( S = \{1, 2, \ldots, n\} \). SwF-LASSO iteratively builds the decision function by adding several basis functions (columns of \( A \)) and updates the parameters until the given stopping criterion is satisfied. Once some basis functions are picked from the dictionary \( A \), the corresponding indices will be eliminated from \( S \) and added to set \( P \).

We assume that the index set \( P \) contains \( n_p \) elements at the \( n \)th iteration, which means \( n_p \) basis functions or columns of \( A \) have been selected to form a \( m \times n_p \) sub-matrix of \( A \), denoted by \( A_P \). The components of \( x \) corresponding to \( A_P \) are denoted by vector \( x_P \) and the other components are set to zero. Let us now illustrate how to compute the inverse matrix and update the solution iteratively. Let \( Q^n = (A_P^T A_P)^{-1} \). Given that other \( k \) basis functions are selected at the \((n+1)\)th iteration and be ranged in a sub-matrix \( A_K \). Then

\[
Q^{n+1} = \left( \begin{array}{cc}
A_P^T & A_K
\end{array} \right)^{-1}
\begin{array}{c}
A_P^T A_P \\
A_K^T A_K
\end{array}
\]

\[
= \left( \begin{array}{cc}
A_P^T A_P & A_P^T A_K \\
A_K^T A_P & A_K^T A_K
\end{array} \right)^{-1}
\]

\[
= \left( Q^n \right)^{-1}
\left( \begin{array}{cc}
A_P^T A_P & A_P^T A_K \\
A_K^T A_P & A_K^T A_K
\end{array} \right)
\]

\[
= \left( Q^n \right)^{-1}
\left( \begin{array}{cc}
A_P^T A_P & A_P^T A_K \\
A_K^T A_P & A_K^T A_K
\end{array} \right)
\]

\[
+ \eta \left( \begin{array}{cc}
\rho & 0 \\
0 & 1
\end{array} \right) \left( \begin{array}{c}
\rho^{-1} \\
-1
\end{array} \right)
\left( Q^n \right)^{-1},
\]

where \( \rho = Q^n A_K^T A_K \), \( \eta = (A_K^T A_K - A_K^T A_P \rho)^{-1} \). Combing with (5), the iterative formula for the solution \( x \) is obtained accordingly

\[
(x^{n+1}) = \left( \begin{array}{c}
x_P^{n+1} \\
x_K^{n+1}
\end{array} \right) = Q^{n+1} \left( \begin{array}{c}
A_P^T b - \lambda \omega_P / 2 \\
A_K^T b - \lambda \omega_K / 2
\end{array} \right)
\]

\[
\]

where \( \Delta = \rho^T (A_P^T b - \lambda \omega_P / 2) - A_K^T b + \lambda \omega_K / 2 \).

In fact, the optimization problem in (4) is solved with a greedy scheme, i.e., SwF-LASSO iteratively builds the decision function by adding several basis functions (columns of \( A \)). The criterion for selecting basis functions is to maximize the descending in the objective function caused by adding basis functions to the model. For example, given \( i \in S \), \( \Delta L_i^{n+1} = L_i^{n+1} - L_n \) denotes the descent caused by adding the \( i \)th basis function. Here,

\[
\Delta L_i^{n+1} = L_i^{n+1} - L_n = x_i^T a_i^T a_i + 2x_i
\times \left( (a_i^T A_P x_P) - (b_P^T a_i - \lambda \omega_i / 2) \right).
\]

So the selection of basis functions is equivalent to the following sub-problem:

\[
\min_{x_i} \{ q_i n (a_i^T a_i x_i^2 + 2q_i n x_i) \},
\]

where

\[
q_i = \begin{cases} 
-(b_P^T a_i - \lambda \omega_i / 2) & n = 0 \\
(a_i^T A_P x_P - (b_P^T a_i - \lambda \omega_i / 2) & n > 0.
\end{cases}
\]

It is easy to compute that the optimal solution of (9) is

\[
\Delta L_i^{n+1} = -q_i^2 / a_i^T A_i.
\]

To accelerate the convergence of the algorithm, a stage-wise learning strategy is adopted to select several basis functions at a time. The stage-wise size is adaptively determined based on \( \gamma \) threshold. Specifically, \( \gamma \) threshold is computed by

\[
\gamma = \sqrt{\sum_{i \in S} (\Delta L_i^{n+1})^2 / |S|},
\]

where \( |S| \) represents the cardinality of index set \( S \). According to the stage-wise strategy, the basis functions to be selected are the columns indexed by the elements of

\[
K^{n+1} = \{ i | \nu > |\Delta L_i^{n+1}| > c \cdot \gamma, i \in S \},
\]

where \( \nu \) is the weight coefficient.
where $|\Delta L_{i}^{n+1}|$ denotes the absolute value of $\Delta L_{i}^{n+1}$. $\nu$ and $c$ are two positive constants and their values control the stage-wise size. In the experiments, $c$ ranges from 1 to 3.

The iterations continue until one of the following stopping criteria is met: (1) The index set $S$ is empty; (2) $K^{n+1}$ is empty; (3) $\max_{s \in K^{n+1}} |\Delta L_{i}^{n+1}| < \varepsilon$. If algorithm stops at the $k$th iteration, then the sparse solution of (2) can be approximated by $x^k$.

The flowchart of StF-LASSO algorithm is illustrated in Fig. 1.

![Flowchart of StF-LASSO algorithm](image)

3. Experiments and Results

In this section, the performance of the presented SwF-LASSO approach is experimentally verified and is compared with IVTCG and StOMP. All the experiments are performed on the same 3D digital mouse model. We obtained anatomical information from the mouse model of CT and cryosection data, as shown in Fig. 2(a). The torso section of the mouse atlas with a height of 35 mm is the volume to investigate. A total of 18 point sources were placed around the surface for excitation as shown in Fig. 2(b).

The measurements used in the numerical experiments were obtained by solving the forward model with FEM. To do this, the torso mouse model was discretized into 24,906 nodes and 132,202 tetrahedral elements. But in the reconstruction process, the mesh consisted of 2604 nodes and 12,376 tetrahedral elements, and the maximum and minimum mesh sizes are 3.2 and 0.2 mm, respectively. Swf-Lasso, IVTCG and StOMP are separately employed to solve the FMT inverse problem in (2). Reconstruction performance was evaluated in terms of location error, fluorescent yield and runtime. The quantitative comparison is listed in Table 2. Figure 3 shows the results of the above three methods for single target reconstruction.

From Table 2, we can find that the presented Swf-Lasso algorithm stand as a comparison with StOMP and perform slightly better than IVTCG in the single target setting. The source centers reconstructed by the three methods are identical and the
Table 2. Result for single target reconstruction.

<table>
<thead>
<tr>
<th>Method</th>
<th>Position (mm)</th>
<th>Location error (mm)</th>
<th>Fluorescent yield (mm⁻¹)</th>
<th>Time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SwF-LASSO</td>
<td>11.8, 6.3, 16.0</td>
<td>0.40</td>
<td>0.018</td>
<td>0.87</td>
</tr>
<tr>
<td>IVTCG</td>
<td>11.8, 6.3, 16.0</td>
<td>0.40</td>
<td>0.005</td>
<td>19.37</td>
</tr>
<tr>
<td>StOMP</td>
<td>11.8, 6.3, 16.0</td>
<td>0.40</td>
<td>0.026</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Fig. 3. Comparison of reconstruction results for single target, a red cylinder represents the actual source and the black region means the position of reconstruction.
location error is 0.40 mm. In fact, the reconstructed source center is also the nearest node to the actual source, which means all the three algorithms locate the target accurately. As for the computing time, Swf-Lasso and StOMP run faster than IVTCG.

3.1. Reconstruction of double targets

In the case of double targets reconstruction, two cylinder fluorescent targets of 1.6 mm high by 0.8 mm radius were set in the liver. The center of these targets located in (11.9, 6.4, 16.4 mm) and (11.9, 10.9, 16.4 mm), and the actual fluorescent yield is 0.05 mm$^{-1}$. A total of 18 point sources were placed around the surface for excitation. The comparisons of these methods are shown in Table 3 and Fig. 4.

The quantitative results in Table 3 demonstrate that our algorithm is better than the compared methods. Although, SwF-LASSO runs slightly slower than StOMP, it yields more accurate reconstruction. The location errors for the two targets by our method are 0.60 and 1.03 mm, respectively. In contrast, one of the reconstructed sources with IVTCG and StOMP method deviated from the actual target. Meanwhile, our proposed method obtains satisfied fluorescent yield which is near the actual value.

3.2. Stability analysis

In this part, three groups of experiments are presented to evaluate the robustness and stability of our algorithm.

Firstly, we added different levels (0%, 10%, 20%, 40%) of Poisson noise to boundary measurements. We implemented 60 independent reconstructions for each noise level. The impacts of noise on reconstruction results are shown in Table 4.

As shown in Table 4, for all the noise levels considered, the source locations are identical to that of without noise. Furthermore, we find that the reconstructed power varies very slightly with the increase of noise level, and the maximum deviation of the power occurs at 30% noise level, which possess a maximum 9.4% deviation to the actual power.

<table>
<thead>
<tr>
<th>Method</th>
<th>Position center (mm)</th>
<th>Location error (mm)</th>
<th>Fluorescent yield (mm$^{-1}$)</th>
<th>Time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SwF-LASSO</td>
<td>11.7,10.4,16.5</td>
<td>0.60</td>
<td>0.045</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>11.1,6.8,16.9</td>
<td>1.03</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>IVTCG</td>
<td>11.7,10.4,16.5</td>
<td>0.60</td>
<td>0.018</td>
<td>24.66</td>
</tr>
<tr>
<td></td>
<td>10.3,5.3,16.4</td>
<td>1.26</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>StOMP</td>
<td>11.7,10.4,16.5</td>
<td>0.60</td>
<td>0.022</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>11.3,5.3,16.4</td>
<td>1.26</td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

(a) Swf-Lasso

Fig. 4. Reconstruction results for double targets, two red cylinders represent the actual sources and the black region means the position of reconstruction.
As for location error, the proposed algorithm obtained the same best results under different noise levels. From the view of fluorescent yield, the means of results for different noise levels have a slight fluctuation. Therefore, we can make a conclusion that our proposed method is robust for Poisson noise.

Secondly, we changed different meshes for reconstruction to evaluate the stability of our method. We utilized three different meshes to reconstruct single target separately, i.e., the model were discretized into 1349 nodes and 6036 tetrahedral elements, 2604 nodes and 12,376 tetrahedral elements, 3620 nodes and 17,504 tetrahedral elements, respectively. We computed that the location errors for the best point of these meshes were 1.14, 0.40, 1.22 mm, respectively. Meanwhile, the corresponding initial fluorescent yield on different meshes is 0.05 mm\(^{-1}\). The experimental results on different meshes are shown in Table 5. It is obviously shown in Table 5 that the points of our reconstruction are the best points, respectively on different mesh levels. In conclusion, we can say that our algorithm is stable for different meshes.

At last, we reconstructed the single target on the condition of decreasing excitation sources. Based on the single target experiments, we decrease the number of excitation sources from 18 to 12, 9 and 6, separately. The results of this group experiments are shown in Table 6.

<table>
<thead>
<tr>
<th>Noise level</th>
<th>Position center (mm)</th>
<th>Location error (mm)</th>
<th>Fluorescent yield (mm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>11.8,6.3,16.0</td>
<td>0.40</td>
<td>0.0182 ± 0.0012</td>
</tr>
<tr>
<td>10%</td>
<td>11.8,6.3,16.0</td>
<td>0.40</td>
<td>0.0182 ± 0.0010</td>
</tr>
<tr>
<td>20%</td>
<td>11.8,6.3,16.0</td>
<td>0.40</td>
<td>0.0183 ± 0.0016</td>
</tr>
<tr>
<td>40%</td>
<td>11.8,6.3,16.0</td>
<td>0.40</td>
<td>0.0184 ± 0.0021</td>
</tr>
</tbody>
</table>

As for location error, the proposed algorithm obtained the same best results under different noise levels. From the view of fluorescent yield, the means of results for different noise levels have a slight fluctuation. Therefore, we can make a conclusion that our proposed method is robust for Poisson noise.

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At last, we reconstructed the single target on the condition of decreasing excitation sources. Based on the single target experiments, we decrease the number of excitation sources from 18 to 12, 9 and 6, separately. The results of this group experiments are shown in Table 6.
From Table 6, it is shown that we obtain satisfied result in 18 excitation sources and 12 excitation sources. However, when we decrease them to half or one third of full number, the position of reconstruction deviates from the best point. Moreover, the fluorescent yield declines along with decreasing excitation source.

4. Discussion and Conclusion

In this paper, we propose an efficient reconstruction algorithm for inverse problem of FMT. Considering sparse distribution of fluorescent target in the imaging domain, sparsity regularization is employed to deal with the ill-posedness of tomographic fluorescence imaging problem. To solve the $l_1$-norm regularized objective functions efficiently, a fast iterative algorithm is developed to find stable approximate solution. Numerical experiments with 3D digital mouse model verify that our proposed algorithm is feasible, stable and efficient.

With respect to quantitative indexes and visual qualities of the experimental results, the proposed SwF-LASSO algorithm performs comparable to StOMP and better than the IVTCG in single target reconstruction. Nevertheless, the presented algorithm performs best in double targets reconstruction. The stability tests further demonstrate that the SwF-LASSO algorithm is stable and robust to measure noise and mesh discretization. In addition, SwF-LASSO yields satisfactory reconstruction when we decrease the number of excitation source from 18 to 12, but the results experience a noticeable decline in quality when the number further decreases. Consequently, the number of excitation sources has a degree of impact on reconstruction results.

In conclusion, the presented SwF-LASSO algorithm is a stable and efficient iterative algorithm for tomographic fluorescence imaging problem, and the in vivo evaluation will be reported in future.

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