FAST LOCALIZE THE BIOLUMINESCENT SOURCE VIA GRAPH CUTS

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ABSTRACT

Bioluminescence imaging (BLI) and bioluminescence tomography (BLT) make it possible to elucidate cellular signatures to better understand the effects of human disease in small animal *in vivo*. However, to the best of our knowledge, the existing gradient-type reconstruction methods in BLT are not very efficient, and often require a relatively small volume of interest (VOI) for feasible results. In this paper, a fast graph cuts based reconstruction method for BLT is presented, which is to localize the bioluminescent source in heterogeneous mouse atlas via max-flow/min-cut algorithm. Since the original graph cuts theory can only handle graph-representable problem, the quadratic pseudo-boolean optimization is incorporated to make the graph tractable. The internal light source can be reconstructed from the whole domain, so *a priori* knowledge of VOI can be avoided in this method. In the experiments, the proposed method is validated in a heterogeneous mouse atlas, and the source can be localized reliably and efficiently by graph cuts; and compared with a gradient-type method, graph cuts is about 25-50 times faster.

Index Terms— Bioluminescence tomography (BLT), inverse problem, light propagation in tissues, diffusion equation

1. INTRODUCTION

Bioluminescence imaging (BLI) has become an promising modality in cancer research, cell trafficking and drug development [1, 2]. There is no inherent tissue autofluorescence generated by external excitation light, making it extremely sensitive. Furthermore, bioluminescence tomography (BLT) can make use of the information obtained from BLI data measured on the surface of a small animal in reference to a corresponding micro-CT volume of the same small animal, and localize the bioluminescent source deep in tissue.

Over the past few years, many reconstruction methods for BLT have been developed. To the best of our knowledge, they are mainly gradient-type methods [3, 4]. Since it has to execute many steps of iteration and calculate the gradient in every iteration until reliable results are obtained, the time cost during the reconstruction is relatively expensive [4]. Parallel computation is one way to improve the reconstruction efficiency, but it needs expensive and complex hardware to support the corresponding algorithm [5]. Furthermore, many of the existing methods are apt to adopt relatively small volume of interest (VOI), which is known prior to the BLT reconstruction. Nevertheless, it is not always reliable or feasible to define such a region effectively. Especially, for the cases on a large VOI or even on the whole region, the results may be trapped in local extremum and be very far from the optimal solutions. Here, a gradient-free reconstruction method is presented, which is called graph cuts. It is emerging as an increasingly useful method for energy minimization in computer vision including segmentation, image restoration and stereo [6, 7]. With respect to this BLT problem, firstly, a directed graph with nonnegative edge weights is constructed. And then, a max-flow/min-cut approach is applied to localize the bioluminescent source. Because the max-flow/min-cut is not dependent on gradient any more, it can perform efficiently. Moreover, by restricting graph representable, we can often find global optimal solutions in polynomial time [6]. Therefore, for the BLT problem, graph cuts method can provide both fast and exact solutions.

The outline of the paper is as follows. In the nest section, we present the reconstruction methodology for BLT. The forward diffusion equation is briefly introduced. And then, the graph cuts based reconstruction method is elaborately formulated. In Section 3, the numerical experiments are demonstrated to verify the proposed method. Reconstruction comparisons between graph cuts and a gradient-type method indicate the efficiency and reliability of the proposed method in a heterogeneous mouse atlas. Finally, we conclude the paper in the last section.

2. METHODOLOGY

In the steady-state domain, the forward problem of light propagation for BLT can be modeled as a diffusion equation in

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steady state [3], which is given by

$$-\nabla \cdot \Big(D(\mathbf{r})\nabla(\Phi(\mathbf{r}) \Big) + \mu_a(\mathbf{r})\Phi(\mathbf{r}) = \mathcal{X}(\mathbf{r}) \;\; (\mathbf{r} \in \Omega) \tag{1}$$

with a Robin-type boundary condition:

$$\Phi(\mathbf{r}) + 2\kappa(\mathbf{r})D(\mathbf{r})\Big(\mathbf{v}(\mathbf{r}) \cdot \nabla\Phi(\mathbf{r})\Big) = 0 \;\; (\mathbf{r} \in \partial\Omega) \tag{2}$$

Here Φ is the photon density, $\mathcal{X}$ is an isotropic source term; κ is a boundary term that incorporates the refractive index mismatch at the tissue-air boundary; $\mathbf{v}$ is the unit outward normal on $\partial\Omega$; D and μ_a are the optical diffusion and absorption coefficients, respectively.

Due to the highly ill-posed nature, BLT is an extremely intractable inverse problem. The common approach is to use the output-least-squares formulation incorporated with a regularization term. The solution can be determined by minimizing the energy function:

$$E(\mathcal{X}) = \|\mathcal{M}\mathcal{X} - \mathbf{b}\|^2 + \lambda\|\mathcal{X}\|^2 \tag{3}$$

where $\mathbf{b}$ denotes the measured photon density on the boundary, $\mathcal{M}$ the system matrix in finite element formulation of (1) and (2), and λ the regularization parameter. As said above, the existing reconstruction methods are mainly gradient-type in BLT. Since the calculation of gradient operation is needed in each iteration, the time cost during the reconstruction is relatively expansive. When it executes on a large VOI or even on the whole region, the variables may be trapped in local extremum and the results may be very far from the global optimum. In this paper, a gradient-free reconstruction method-graph cuts is reported, which can provide both a fast and an exact solution [6]. First of all, a directed graph $\mathcal{G} = (\mathcal{V}, \mathcal{A})$ is needed to be created, where set $\mathcal{V}$ denotes nodes in the finite-element grid of VOI, and set $\mathcal{A}$ represents edges (Fig. 1(a)). Then, energy function (3) is reformulated into the graph framework as follows:

$$\begin{aligned} E(\mathcal{X}) &= \|\mathcal{M}\mathcal{X} - \mathbf{b}\|^2 + \lambda\|\mathcal{X}\|^2 \\ &= \theta_{const} + \sum_{i \in \mathcal{V}} \theta_i(x_i) + \sum_{(i,j) \in \mathcal{A}} \theta_{ij}(x_i, x_j) \end{aligned} \tag{4}$$

where

$$\mathcal{M} = \begin{bmatrix} \mathbf{m}_1, & \mathbf{m}_2, & \ldots, & \mathbf{m}_N \end{bmatrix} \tag{5}$$

and

$$\theta_{const} = \mathbf{b}^T\mathbf{b} \tag{6}$$

$$\theta_i(x_i) = (\mathbf{m}_i^T\mathbf{m}_i + \lambda)x_i^2 - 2(\mathbf{b}^T\mathbf{m}_i)x_i \tag{7}$$

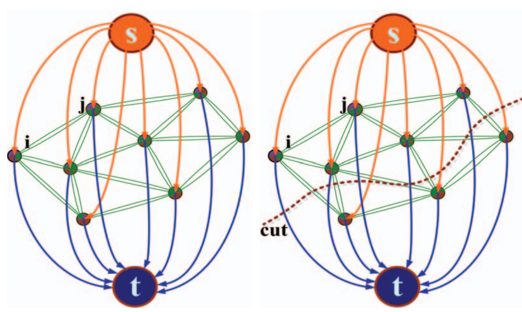
$$\theta_{ij}(x_i, x_j) = 2(\mathbf{m}_i^T\mathbf{m}_j)x_i x_j \tag{8}$$

Here, $\mathcal{X} = \{x_i\}$, N denotes the number of nodes, θ_{const} is the constant term of the energy, $\theta_i(\cdot)$ are the unary terms, and $\theta_{ij}(\cdot, \cdot)$ are the pairwise terms.

Unfortunately, graph cuts can only be used for minimizing *submodular* energy functions, i.e. functions whose pairwise terms satisfy [7]

$$\theta_{ij}(0,0) + \theta_{ij}(1,1) \le \theta_{ij}(0,1) + \theta_{ij}(1,0) \tag{9}$$

In order to minimize energy functions with both *submodular* and *supermodular* terms ($\theta_{ij}(1,1) + \theta_{ij}(0,0) > \theta_{ij}(0,1) + \theta_{ij}(1,0)$) via graph theory, the quadratic pseudo-boolean optimization is employed [7]. It has four useful properties: a) *Persistency* which implies that the energy never goes up. b) *Partial optimality* which guarantees there exists global minimum $\mathcal{X}^*$ of energy (4) such that $x_i = x_i^*$ for all labeled nodes i. c) This algorithm is invariant with respect to "flipping" a subset of nodes $\mathcal{U} \subset \mathcal{V}$, which means that flipping transforms *supermodular* terms between $\mathcal{U}$ and $\mathcal{V} \backslash \mathcal{U}$ into *submodular*. d) If all terms of the energy are *submodular*, then the algorithm will label all nodes.



(a) (b)

Figure 1: An irregular directed graph. A similar graph-cut construction was used in computer vision [6], except that the graph used here is irregular. (a)A graph $\mathcal{G}$. (b)A cut on $\mathcal{G}$.

Motivated by the properties aforementioned, the original graph can be revised as follows. For each node $i \in \mathcal{V}$ there will be two nodes i and $\bar{i}$. Node $\bar{i}$ can be associated with variable $x_{\bar{i}}$. In addition, there are two special nodes, source s and sink t, which are called the terminals. Therefore, $V = \{i, \bar{i} | i \in \mathcal{V}\} \bigcup \{s, t\}$. Moreover, for every non-zero term of $\theta_{ij}(\cdot, \cdot)$, two edges are added to the set A [7]. Then the generalized graph represents energy E' expressed as a function of old variables $\mathcal{X}$ and new variables $\bar{\mathcal{X}} = \{x_{\bar{i}}\}$ [7]:

$$\begin{aligned} E'(\mathcal{X}, \bar{\mathcal{X}}) &= \theta_{const} + \frac{1}{2}\sum_{i \in \mathcal{V}} \big[\theta_i(x_i) + \theta_i(1 - x_{\bar{i}})\big] \\ &+ \sum_{(i,j) \in Sub} \frac{1}{2}\big[\theta_{ij}(x_i, x_j) + \theta_{ij}(1 - x_{\bar{i}}, 1 - x_{\bar{j}})\big] \\ &+ \sum_{(i,j) \in Super} \frac{1}{2}\big[\theta_{ij}(x_i, 1 - x_{\bar{j}}) + \theta_{ij}(1 - x_{\bar{i}}, x_j)\big] \end{aligned} \tag{10}$$

Now, a new directed graph $G_q = (V, A)$ has been created and the size of the graph is doubled. Here, Sub and $Super$ denote the sets in which the terms are *submodular* and *supermodular*, respectively. According to the properties above, a global minimum of the energy would be obtained via graph cuts. In addition, since the new energy $E^{'}$ of variables $\{x_i, x_{\bar{i}}\}$ is enforced to be *submodular*, it can be minimized in polynomial time [6].

According to the theorem of Ford and Fulkerson [8], the computation of the min-cut is equivalent to computing the max-flow from the source to the sink. Several algorithms can compute this flow [9, 6]. One of the powerful graph cuts is Boykov-Kolmogorov's algorithm, which belongs to augmenting path-based type. Normally, it starts a new search for $s \rightarrow t$ paths as soon as all paths of a given length are exhausted [6]. It is noted that, for certain optimization problems like BLT, max-flow/min-cut algorithms provide both a fast and an exact solution.

The algorithm presented here involves three parts: graph construction, min-cut/max-flow, and postprocessing, as shown in Fig. 2. Firstly, graph should be constructed by setting unary and pairwise terms, and setting up the neighborhood system. It needs to be emphasized that unlike the graphs used in the context of computer vision and image segmentation, etc. [6, 7], the graphs in optics are usually irregular in three dimension (Fig. 1(a)), so adjacent connections of the nodes via edges should be built up and more memory is needed. Secondly, min-cut/max-flow is executed by literately repeating three stages: growth stage, augmentation stage, and adoption stage. The details could be found in [6]. After the adoption stage is completed, it returns to the growth stage. The algorithm terminates when the search trees on the graph cannot grow and the graph is separated by saturated edges. This implies that a maximum flow is achieved, and the corresponding min-cut is generated, as shown in Fig. 1(b). Finally, the results are analyzed and output.

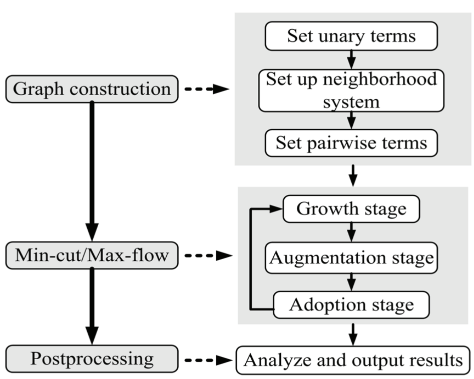


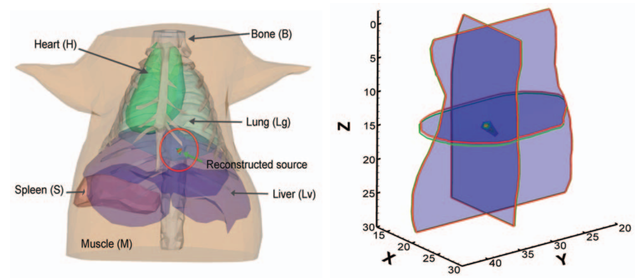
Figure 2: The graph cuts algorithmic structure used for BLT reconstruction.

3. RESULTS

Before reconstructions, an atlas of the BALB/c mouse was developed using our micro-CT system and cone-beam reconstruction algorithm (Fig. 3(a))[10]. By using image processing and interactive segmentation methods, some primary organs were delineated, and the optical coefficients for each organ are listed in Table 1. And then, the mouse atlas was discreted into volumetric mesh. This discreted mesh contains 4614 nodes and 25783 tetrahedral elements. The actual source is located in liver, with the center at (21.45, 33.65, 14.52), the diameter of 1.48mm, and the depth of about 7mm from mouse surface.

Table 1: Optical coefficients for each organ in the mouse atlas. The units are mm^{-1}.

	H	Lg	Lv	M	B	S
μ_a	0.022	0.071	0.128	0.032	0.0024	0.075
μ_s'	1.129	2.305	0.646	0.586	0.935	2.178



(a) (b)

Figure 3: The tomography results based on graph cuts on the whole region (4614 nodes). (a) The mouse atlas used for reconstruction. The arrow points to the reconstructed source in liver. (b) The results in cross-sections. The red and green boundaries are the center position of actual and reconstructed sources respectively.

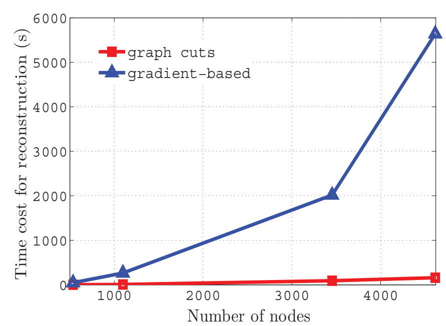


Figure 4: Time cost comparisons between graph cuts and a gradient-type method for BLT reconstructions. The execution time of the proposed method grows much more slowly with the number of nodes than that of the latter.

In the numerical reconstructions, three cases with different size of VOI were considered (Table 2), and a a constrained Newton-type optimization method was selected as the gradient-based method to compare with graph cuts [11]. In all cases of graph cuts, the location error from the real source is within 0.5mm, and the diameter of the recovered also fairly matches with that of real one. Even on the whole

Table 2: Comparisons of reconstruction results between graph cuts and a gradient-type method.

	Nodes	Edges	Recons. Loc. Center (mm)	Loc. Error (mm)	Dimension (mm)	Recons. Time (s)
Graph Cuts	536	1183	(21.53, 33.56, 14.97)	0.47	1.26	1.55
Grad.-type			(23.34, 34.98, 14.30)	2.44	2.36	46.35
Graph Cuts	1097	3989	(21.53, 33.56, 14.97)	0.47	1.29	7.24
Grad.-type			(23.34, 34.98, 14.23)	2.33	2.46	264.42
Graph Cuts	3453	21372	(21.53, 33.56, 14.97)	0.47	1.29	80.35
Grad.-type			(27.03, 33.31, 14.07)	5.61	4.18	2087.32
Graph Cuts	4614	30880	(21.33, 33.54, 14.88)	0.39	1.22	148.78
Grad.-type			(27.56, 33.66, 15.47)	6.74	3.88	5639.25

atlas, which means none *a priori* knowledge about source distribution is incorporated (Fig. 3), the position and diameter of the source can still be accurately recovered by graph cuts. In contrast, the reconstructed locations using gradient-type method deviate more from the real one, and when the VOI enlarges, the deviation becomes greater, or even the recovered position is too far away to be acceptable.

Moreover, compared with gradient-type, graph cuts is about 25-50 times faster, and according to the reconstruction time (the total time for the three parts in Fig. 2) in Table 2, the efficiency of graph cuts becomes increasingly remarkable as more and more nodes and edges appear. It is significative that the reconstruction time is comparable to that for data acquisition even on whole region. All reconstructions were performed on a desktop computer with Intel Core 2 Duo 1.86GHz CPU and 3GB RAM.

4. CONCLUSION

We have presented a novel graph cuts approach for localizing the bioluminescent source in heterogeneous mouse atlas. We stress that this technique performs well based on irregular grid in complex geometry.

In the experiments, reconstruction comparisons between graph cuts and the gradient-type method demonstrate accuracy and efficiency of the proposed method. Based on graph cuts, even no *a priori* knowledge about source distribution is used, the results can still be desirably reconstructed. Because of its fine performance, the method has the potential for practical mouse study in BLT and other optical imaging modalities.

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