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A fast solver for an inverse problem arising in bioluminescence tomography

Rongfang Gong [a,*], Xiaoliang Cheng [b], Weimin Han [c]

[a] Department of Mathematics, Nanjing University of Aeronautics and Astronautics, Nanjing 211106, China
[b] Department of Mathematics, Zhejiang University, Hangzhou 310027, China
[c] Department of Mathematics, University of Iowa, Iowa City, IA 52242, USA

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ABSTRACT

Bioluminescence tomography (BLT) is a new method in biomedical imaging, with a promising potential in monitoring non-invasively physiological and pathological processes *in vivo* at the cellular and molecular levels. The goal of BLT is to quantitatively reconstruct a three dimensional bioluminescent source distribution within a small animal from two dimensional optical signals on the surface of the animal body. Mathematically, BLT is an under-determined inverse source problem and is severely ill-posed, making its numerical treatments very challenging. In this paper, we provide a new Tikhonov regularization framework for the BLT problem. Compared with the existing reconstruction methods about BLT, our new method uses an energy functional defined over the whole problem domain for measuring the data fitting, associated with two related but different boundary value problems. Based on the new formulation, a fast solver is introduced by transforming the proposed optimization model into a system of partial differential equations. Moreover, a finite element method is used to obtain a regularized discrete solution. Finally, numerical results show that the fast solver for BLT is feasible and effective.

1. Introduction

With the accomplishment of human genome sequence and the coming of post-genome era, it is urgent to explore the mechanism of occurrence and development of various diseases (especially malignant diseases) at the cellular, molecular and gene levels, so that we can detect diseases before the appearance of clinical symptoms and enhance therapeutic effect through their early alarm and treatment. Molecular imaging is a rapidly developing biomedical imaging technique for this purpose; see e.g. [1–5] and references therein. Molecular imaging is broadly based on three technologies: nuclear imaging [6,7], magnetic resonance imaging (MRI) [8,9], and optical imaging [10,11]. As an optical molecular imaging, bioluminescence tomography (BLT) is a recently developed promising modality and attracts more and more attention [12–16]. The goal of BLT is to quantitatively reconstruct a three dimensional bioluminescent source distribution within a small animal from two dimensional optical signals on the surface of the animal body. Currently, BLT is mainly used to cellular, molecular and gene expression imaging in studies of small animals, especially mice, but the success of this research will facilitate disease studies, drug development and therapeutic intervention [17,3,10].

Mathematically, BLT is an under-determined inverse source problem and is severely ill-posed, making its numerical treatments very challenging. Light propagation in biological tissue is governed by the radiative transfer equation (RTE) [18].

* Corresponding author.
E-mail addresses: grf_math@nuaa.edu.cn (R. Gong), xiaoliangcheng@zju.edu.cn (X. Cheng), weimin-han@uiowa.edu (W. Han).

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However, the RTE is highly dimensional and presents a serious challenge for its accurate numerical simulations given the current level of development in computer software and hardware. Experimental evidence shows that the range of light emission peaks is 460–630 nm for characterized luciferase enzymes [19], which is very small compared to the size of a typical object in this context. For this spectral range, scattering dominates for the photons in the tissue, and usually a diffusion approximation of the RTE is employed [20,21].

Let $\Omega \subset \mathbb{R}^d$ be the biological medium with the boundary $\Gamma = \partial\Omega$. Although the dimension $d = 3$ for applications, the method we develop here is valid for any dimension. Without going into detail, the BLT problem based on the diffusion approximation is the determination of a light source function p in the differential equation

$$-\operatorname{div}(D\nabla u) + \mu_a u = p\chi_{\Omega_0} \quad \text{in } \Omega \tag{1.1}$$

with the following boundary condition

$$u + 2AD\frac{\partial u}{\partial n} = g^- \quad \text{on } \Gamma \tag{1.2}$$

from measurement data g on the boundary Γ:

$$g = -D\frac{\partial u}{\partial n} \quad \text{on } \Gamma. \tag{1.3}$$

Here, $D = [3(\mu_a + \mu')]^{-1}$, μ_a and μ' are given absorption and reduced scattering coefficients; $\partial/\partial n$ stands for the outward normal derivative; the function g^- is an incoming flux on the boundary Γ, and $A(x) = (1 + R(x))/(1 - R(x))$; $R(x) \approx -1.4399\gamma(x)^{-2} + 0.7099\gamma(x)^{-1} + 0.6681 + 0.0636\gamma(x)$ with $\gamma(x)$ the refractive index of the medium at $x \in \Gamma$. Moreover, Ω_0 is a measurable subset of Ω, called the permissible region, χ_{Ω_0} is the characteristic function of Ω_0, i.e., its value is 1 in Ω_0 and is 0 outside Ω_0.

Based on the diffusion approximation equation (1.1), many theoretical analysis and numerical methods about BLT have been explored, see e.g. [22,12,23–29] and references therein. To improve the accuracy of the reconstructed light source function, multispectral systems are developed [30–33]. We refer to [34,35] for the BLT problem with enhancement of knowledge of the optical properties. In these works, Tikhonov regularization methods are used, with which various a priori information of a light source can be incorporated conveniently, and the BLT problems are transferred into optimization ones.

Conventionally, an L^2-norm functional is used on a part of or the whole boundary Γ to measure the data fitting, and then gradient-type iterative algorithms are adopted to find the minimizers, see [22,30,12,31,23,32,24,15,25,34,35,33,26,27,29] and so on. Alternatively, in this work, a Kohn–Vogelius type energy functional is used for our source function reconstruction. In general, Kohn–Vogelius functionals are expected to lead to more robust optimization procedures [36]. In the literature, these functionals have been used for a long time in the electrical impedance tomography [37]. However, to the best of our knowledge, they have not been used in the BLT problem. In this study, we give a new reconstruction framework based on a Kohn–Vogelius type energy functional. Moreover, instead of using usual gradient-type iterative algorithms for the optimal solution, with a priori information about the light source location, a fast solver is given to compute the density of inner light source function. By using our method, the proposed optimization model is transformed into a system of partial differential equations. As a result, issues occurring in iterative methods such as the choice of initial guess, convergence of iteration and stop criterion are avoided, and then the computation efficiency of light source reconstruction is enhanced.

We end this section with a description of the structure for the rest of this work. In Section 2, an optimization framework based on an energy functional is established for BLT. Section 3 introduces a fast solver for the proposed optimization problem via adjoint theory in such a way that the BLT problem is transferred into a system of partial differential equations. In Section 4, discretization of the system of equations by the finite element method is discussed. Several numerical examples are presented in Section 5 to demonstrate the feasibility and efficiency of the proposed method.

2. An optimization framework based on an energy functional

We first introduce notations for function spaces and sets. Assume the boundary Γ is Lipschitz continuous. For a set G (e.g., Ω, Ω_0 or Γ), we denote by $W^{m,s}(G)$ the standard Sobolev spaces with norm $\|\cdot\|_{m,s,G}$, $W^{0,s}(G) = L^s(G)$. Particularly, $H^m(G)$ represents $W^{m,2}(G)$ with corresponding inner product $(\cdot,\cdot)_{m,G}$ and norm $\|\cdot\|_{m,G}$. Let $V = H^1(\Omega)$ and $Q = L^2(\Omega_0)$. Moreover, we assume $D \in L^\infty(\Omega)$ such that $D \geq D_0$ for some positive constant D_0, $\mu_a \in L^\infty(\Omega)$, $\mu_a \geq 0$ and μ_a is positive in a subset of Ω with a positive measure. Also we assume $g^-,\ g \in L^2(\Gamma)$.

From the Neumann boundary condition (1.2) and the Robin boundary condition (1.3), we derive a Dirichlet boundary condition

$$u = g_1 := g^- + 2Ag \quad \text{on } \Gamma. \tag{2.1}$$

Note that only two of the three boundary conditions (1.2), (1.3) and (2.1) are independent. Usually, to determine the source function p, we may associate one of the above three boundary conditions (1.2), (1.3) and (2.1) with the differential equation (1.1) to form a boundary value problem (BVP) while choosing one of the remaining boundary conditions for data matching in forming the inverse problem for p. For instance, in [25], (1.1) and (1.3) are used for the boundary value problem while (2.1) for the measurement matching. Then, because of the ill-posedness of the pointwise formulation of BLT, the following regularized problem is studied.