A Heuristic Superiorization-Like Approach to Bioluminescence Tomography

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Abstract— **Bioluminescence tomography (BLT) is a powerful molecular imaging technology designed for the localization and quantification of bioluminescent sources *in vivo*. With the forward process modeled by the diffusion approximation equation, BLT is the inverse problem to reconstruct the distribution of internal bioluminescent sources subject to Cauchy data. Due to the non-uniqueness of BLT in general, adequate prior information such as nonnegativity and source support constraints must be utilized to obtain a physically favorable BLT solution. Iterative algorithms such as the well-known Expectation Maximization (EM) algorithm and the Landweber algorithm which are suitable for incorporating these knowledge-based constraints are widely used in practice. In the current work, we investigate the application of a superiorization-like approach to BLT. A superiorization-like version of prototypical iterative algorithms for BLT in a general framework, denoted by S-BLT, is presented. For the EM algorithm as the underlying iterative algorithms for BLT and S-BLT, superiorized by the total variation (TV) merit function, preliminary simulation results for a heterogeneous phantom are reported to demonstrate the viability of the approach and evaluate the performance of the proposed algorithm. It is found that total variation superiorization of BLT can significantly improve the visualization effect of the reconstruction with the sources set as a particular case of radial basis functions.**

Keywords— **Superiorization-like, bioluminescence tomography (BLT), total variation (TV).**

I. Introduction

Bioluminescence imaging (BLI) is an important molecular imaging modality to reveal physiological and pathological processes at cellular and molecular levels [1]. It is an optical technique capable of detecting bioluminescent sources *in vivo* generated through a chemical reaction by a combination of luciferases, the substrate luciferin, oxygen, Adenosine triphosphate (ATP) and other factors [2]. In small animal studies, a large fraction of bioluminescent photons can escape the attenuating environment and the emitting light can be captured externally using a highly sensitive charge-coupled device (CCD) camera [3]. BLI is playing an increasingly important role in the areas of gene therapy, drug discovery, immunology and cancer research [4][5]. However, BLI only works in 2D imaging mode which is mainly qualitative and incapable of 3D imaging in practice. To overcome limitations of BLI, bioluminescence tomography (BLT) was introduced [6] to perform quantitative 3D reconstruction of bioluminescent source distributions *in vivo* and has undergone intensive research since [7][8][9][10][11].

A fundamental difficulty with the BLT problem is the solution uniqueness question, studied in [12], where it is proved that BLT is not uniquely solvable in general and the solution uniqueness is established with the solution space restricted to a subspace of bioluminescent source distributions such as radial basis functions. An improvement of the solution uniqueness results is further investigated and established with the multi-spectral bioluminescence tomography (MSBLT) [13]. Mathematically, BLT is a source inversion problem of partial differential equations (PDEs) which is highly ill-posed *per se*. In our previous studies [7][9], prior knowledge such as nonnegativity and source support constrains (also termed permissible source region in another context [8]) were utilized to enhance numerical stability and efficiency. However, a general regularization model for BLT is difficult to handle in the absence of guidance in determining the regularization parameter optimally.

In the current work, we investigate the application of a superiorization-like methodology to BLT. Instead of seeking an optimal solution for the optimization problem based on regularization, it should obtain a superior solution with respect to a given merit function, which is computationally-efficient and circumvents the need to select a regularization parameter. The potential usefulness of superiorization has been demonstrated in several iterative algorithms for inverse problems in image reconstruction which generally belong to the class of convex feasibility problems (CFP) [14][15][16][17]. The fundamental principle, mathematical formulations and a general framework for the superiorization methodology are summarized in [18]. Although the set of all the solutions to BLT is a closed convex set, BLT is mathematically an inverse source problem of PDEs which is of a different setting than CFP. Our main conclusion is that the superiorization-like method is instrumental for BLT. It can provide preferable reconstruction and weaken the strong prior information required by current BLT reconstruction methods.

II. Materials and methods

A. Formulation of BLT

Let $\Omega \subset \mathbb{R}^3$ be a bounded domain containing the object to be imaged with its boundary denoted by Γ. Generally, the BLT problem can be stated as the following inverse source problem of PDE [12]: Given the incoming light g^- and outgoing radiance g on Γ, find a source q_0 with the corresponding diffusion approximation u_0 such that

$$\text{(BLT)} \quad \begin{cases} -\nabla\cdot(D\nabla u_0)+\mu_a u_0 = q_0, \quad x\in\Omega \\ u_0(x)+2D(x)\dfrac{\partial u_0(x)}{\partial \nu} = g^-(x), \quad x\in\Gamma \\ D(x)\dfrac{\partial u_0}{\partial \nu} = -g(x), \quad x\in\Gamma \end{cases} \tag{1}$$

where D and μ_a are diffusion and absorption coefficients of the media, respectively. Based on the theory of Sobolev spaces and elliptical partial differential equations of second order, we can reformulate the BLT problem into operator form. Let $\mathscr{L}$ be the differential operator

$$\mathscr{L}[u_0] = -\nabla\cdot(D\nabla u_0)+\mu_a u_0, \tag{2}$$

with γ_0 and γ_1 as the boundary value maps

$$\gamma_0[u_0] = u_0|_\Gamma \quad \text{and} \quad \gamma_1[u_0] = D\frac{\partial u_0}{\partial \nu}|_\Gamma. \tag{3}$$

Given $f\in H^{\frac{1}{2}}(\Omega)$, define a linear operator by the Dirichlet-to-Neumann map $\mathscr{N}: H^{\frac{1}{2}}(\Gamma)\to H^{-\frac{1}{2}}(\Gamma)$

$$\mathscr{N}[f] = \gamma_1[w_1], \tag{4}$$

with w_1 the solution of the following boundary value problem (BVP)

$$\begin{aligned} \mathscr{L}[w_1] &= 0, \quad \text{in } \Omega \\ \gamma_0[w_1] &= f, \quad \text{on } \Gamma \end{aligned} \tag{5}$$

Define another linear operator $\Lambda : L^2(\Omega)\to H^{\frac{1}{2}}(\Gamma)$

$$\Lambda[q_0] = -\gamma_1[w_2], \tag{6}$$

with w_2 the solution of the following BVP

$$\begin{aligned} \mathscr{L}[w_2] &= q_0, \quad \text{in } \Omega \\ \gamma_0[w_2] &= 0, \quad \text{on } \Gamma \end{aligned} \tag{7}$$

It is proved in [12] that q_0 is a solution to BLT if and only if

$$\Lambda[q_0] = b, \tag{8}$$

where $b = \mathscr{N}[g^- + 2g] + g$.

B. Iterative algorithms for BLT

Generally, iterative algorithms for the problem (8) are based on the minimization of either the least squares (LS) or the Kullback-Leibler (KL) divergence [19][20] as follows,

$$\mathscr{F}(q_0) = \begin{cases} \text{LS}: \dfrac{1}{2}\|\Lambda[q_0]-b\|^2_{L^2(\Gamma)} \\ \text{KL}: \displaystyle\int_\Gamma b\log\frac{b}{\Lambda[q_0]} + \Lambda[q_0] - b \, d\Gamma \end{cases} \tag{9}$$

which is actually equivalent to maximizing the likelihood in the Gaussian or Poisson environments, respectively. Then the inverse problem of BLT can be modeled by the following optimization

$$\min_{q_0\in C} \mathscr{F}(q_0) \tag{10}$$

where C denotes the constraints set which is usually convex. As in our previous study [7][9], we can naturally formulate the constrained Landweber (CL) scheme and a variant of the expectation maximization (EM) method as follows,

$$\begin{aligned} q_0^{(n+1)} &= \text{BLT}(q_0^{(n)}) \\ &= \begin{cases} \text{CL}: P_C\left\{q_0^{(n)} + \tau_n\Lambda^*\left[b-\Lambda[q_0^{(n)}]\right]\right\} \\ \text{EM}: \dfrac{1}{\Lambda^*[1]}\cdot q_0^{(n)}\cdot\Lambda^*\left[\dfrac{b}{\Lambda[q_0^{(n)}]}\right] \end{cases} \end{aligned} \tag{11}$$

which are both essentially gradient-based algorithms corresponding to the minimization of LS and KL distance, respectively. The operators Λ and Λ^* can be calculated numerically by computing two forward BVP problems of PDE [7] with τ_n as relaxation parameters for the Landweber scheme.

C. A "superiorization-like" approach to BLT

Due to the inherent ill-posedness of BLT, regularization is necessary to stabilize the solution, yielding the following optimization problem

$$\min_{q_0\in C}\{\mathscr{F}(q_0)+\gamma\phi(q_0)\} \tag{12}$$

which includes a convex merit function ϕ for regularization. However, the optimization problem is computationally expensive and there is no general guidance for selecting an optimal regularization parameter. A superiorization-like method can be introduced for the purpose of solving the problem at hand.

Instead of seeking an optimal solution for the constrained optimization problem at hand, superiorization takes advantage of the perturbation resilience of some computationally-efficient feasibility-seeking iterative algorithms, so that a superior solution, according to some criterion, which is not necessarily optimal, is obtained at a low computational cost. Based on the general framework of the superiorization methodology proposed in [18], we formulate the following superiorized version, denoted by S-BLT, of our iterative algorithms for BLT. The S-BLT algorithm thus mimics the "Superiorized version of algorithm $\boldsymbol{P}$" on page 6 of [18]. Here we replace the computationally-efficient inner-loop algorithmic operator $\boldsymbol{P}$ there by our BLT algorithmic operator of (11), for the proximity function $\mathscr{P}r_T$ there we use here the function $\mathscr{F}$ of (9), and for the convex merit function by which to superiorize we use the TV of bioluminescent source distributions. Since in this report we do not present any mathematical results necessary to validate our S-BLT algorithm we rather use the expression "superiorization-like" to describe the method.

Algorithm: S-BLT

Initilization: $q_0^{(0)}$

while $(\mathscr{F}(q_0^{(n+1)}) - \mathscr{F}(q_0^{(n)}))/\mathscr{F}(q_0^{(n)}) > \varepsilon$

  set $g^{(n)} \in \partial\phi(q_0^{(n)})$

  super_logic := false

  exit_logic := false

  while $\sim$ super_logic & $\sim$ exit_logic

    $y^{(n)} := q_0^{(n)} + \beta_n g^{(n)}$

    if $\phi(y^{(n)}) \leq \phi(q_0^{(n)})$

      if $\mathscr{F}(\mathrm{BLT}(y^{(n)})) < \mathscr{F}(q_0^{(n)})$

        $q_0^{(n+1)} := \mathrm{BLT}(y^{(n)})$

        super_logic := true

      else

        $\beta_n := \beta_n/2$

    else

      $\beta_n := \beta_n/2$

    if $\beta_n < \eta$

      exit_logic := true

  end

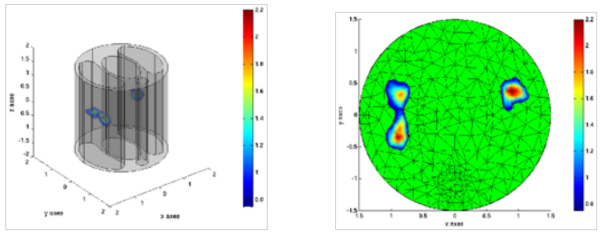
  if $\sim$ super_logic

    $q_0^{(n+1)} = \mathrm{BLT}(q_0^{(n)})$

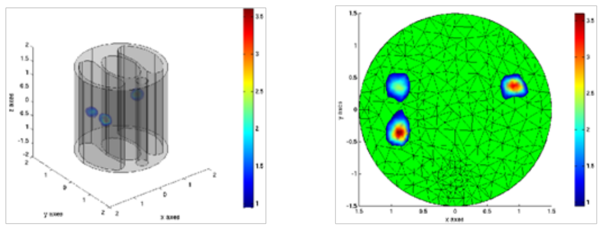
end

III. Results

The configuration of the phantom and form of sources used for numerical experiments are the same as in our previous study [9]. Due to the limited space, we only report representative reconstruction results of S-BLT with the EM algorithm as the underlying inner-loop iterative algorithm.

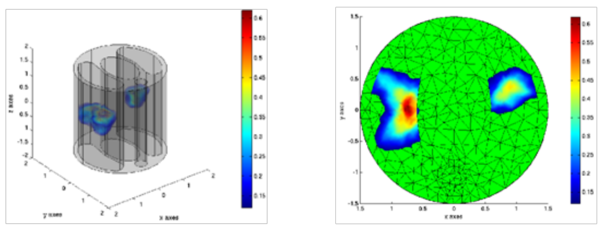


(a)

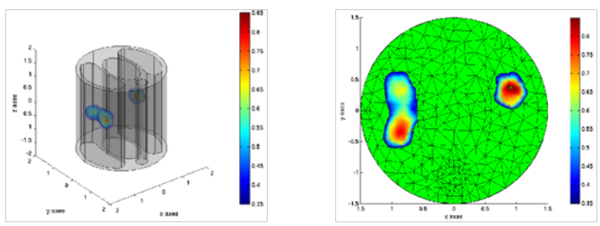


(b)

Fig. 1: Reconstruction results with the source support set as S1



(a)



(b)

Fig. 2: Reconstruction results with the source support set as S2

Reconstruction results for two kinds of supports, denoted by S1 and S2 as given below, are presented in Fig. 1 and Fig. 2.

$$S1 = \{(x,y,z) : 0.8 < (x^2+y^2)^{1/2} < 1.2, -0.15 < z < 0.15\}$$

$$S2 = \{(x,y,z) : 0.65 < (x^2+y^2)^{1/2} < 1.35, -0.25 < z < 0.25\}$$

Similar results can be obtained with Landweber algorithm but the effect of superiorization depend on relaxation parameters.

IV. Discussion

To the best of our knowledge, this superiorization-like methodology is introduced into the field of BLT for the first time here. With the EM algorithm as the underlying iterative algorithm for BLT and S-BLT, numerical simulation results based on a heterogeneous phantom are presented to demonstrate the viability of the approach and evaluate the performance of the proposed algorithm. When the form of sources used for simulation is set as a particular case of radial basis functions, which are piecewise constant, then total variation superiorization-like of BLT is able to present reconstructions that are visually preferable over the current BLT. The following points need to be further studied and verified quantitatively: (1) More precise localization of the reconstructed sources; (2) Increased strength of the reconstructed sources; (3) More compactly distributed support size of the reconstructed sources; and (4) Enhancing image resolution when the source support constraint is relaxed. In general, preferable reconstruction is obtained by S-BLT while the strong prior information can be weakened in the sense that S-BLT can obtain better reconstruction when the source support is enlarged.

Various mathematical issues with the proposed algorithm remain to be investigated. Bounded perturbation resilience of the given iterative algorithms for BLT are still open and left for further investigation. From the physical perspective, the multi-spectral technique for BLT which promises to improve the solution uniqueness of BLT under certain assumptions [13] can also be combined with the superiorization-like methodology. In addition, our formulation can be naturally extended to the partial boundary measurement case which usually occurs in practice due to physical limitations. Further experimental work and evaluation of the proposed algorithm is also underway.

V. Conclusion

Formulation of the problem of BLT and related iterative algorithms is reviewed. A superiorized-like version of the prototypical iterative algorithms for BLT in a general framework is presented. Preliminary simulation results based on a heterogeneous phantom are reported. Several open issues that require further research are highlighted.

Acknowledgements

This work is supported in part by the National Basic Research Program of China (973 Program) (2011CB809105), the National Science Foundation of China (60325101, 60872078), Key Laboratory of Machine Perception (Ministry of Education) of Peking University, and Microsoft Research of Asia. The work of Y. Censor is partially supported by United States-Israel Binational Science Foundation (BSF) Grant number 200912 and by U.S. Department of Army Award number W81XWH-10-1-0170.

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