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Detailed Terms
Sparse algebraic reconstruction for Fluorescence Mediated Tomography

Arrate Muñoz-Barrutia\textsuperscript{a}, Carlos Pardo-Martin\textsuperscript{b}, Thomas Pengo\textsuperscript{a} and Carlos Ortiz-de-Solorzano\textsuperscript{a}

\textsuperscript{a} Center for Applied Medical Research, University of Navarra, Pamplona, Spain; \textsuperscript{b} Harvard-MIT Division of Health Sciences and Technology, Cambridge, USA

ABSTRACT

In this paper, we explore the use of anatomical information as a guide in the image formation process of fluorescence molecular tomography (FMT). Namely, anatomical knowledge obtained from high resolution computed tomography (micro-CT) is used to construct a model for the diffusion of light and to constrain the reconstruction to areas candidate to contain fluorescent volumes. Moreover, a sparse regularization term is added to the state-of-the-art least square solution to contribute to the sparsity of the localization. We present results showing the increase in accuracy of the combined system over conventional FMT, for a simulated experiment of lung cancer detection in mice.

Keywords: ALG, MICRO, OPT, OT, PHT, SIM.

1. INTRODUCTION

1.1 Fluorescence Mediated Tomography

It has been recently shown that fluorescently tagged gene expression as well as fluorescently labeled proteins can be detected in vivo, within rodents using tomographic devices.\textsuperscript{1} This technology can non-invasively produce 3D images of the distribution of genes or proteins in these animals, which could be instrumental, for instance, to detect and characterize tumors in a minimally invasive way by looking at the distribution of fluorescently labeled tumor biomarkers.\textsuperscript{2,3}

To detect fluorescent signals inside an animal, the common experimental setup uses a laser illumination source adapted to the excitation spectrum of the fluorophore. This highly coherent laser beam traverses the animal, exciting the fluorescence molecules attached to the gene products or proteins of interest. Then the emitted photons that leave the animal are captured at different angles using a CCD camera or an optical fiber array coupled to photomultiplier devices (PMT). In order to determine the amount and precise location of fluorescence sources from the angular projections, a variety of physical models of light propagation in tissues and algebraic reconstruction algorithms can be used.\textsuperscript{4-6}

Further author information: (Send correspondence to A.M.B.)
A.M.B.: E-mail: arrmunoz@unav.es, Telephone: +34 948 194700 ext. 5020
C.P.M.: E-mail: cpardo@mit.edu, Telephone: +1 617 6 503553
T.P.: E-mail: tpengo@unav.es, Telephone: +34 948 194700 ext. 5021
C.O.S.: E-mail: codesolorzano@unav.es, Telephone: +34 948 194700 ext. 5019
1.2 Dual system FMT-CT

Fluorescence Mediated Tomography (FMT) suffers from low spatial resolution, which is an inherent problem to any reporting system relying on light diffusion. Recently, it has been shown that, by incorporating a priori anatomical information into the image formation process, one can increase the accuracy of the diffusion model and that of the reconstruction algorithm. Moreover, the advent of dual animal FMT-Computer Tomography (FMT-CT) systems, call for the development of novel data processing and reconstruction algorithms that make use of the anatomical information provided by the CT to improve the resolution of the FMT. Hyde et al. studied the integration of micro-CT and FMT and established that the dual-modality approach allows for accurate fluorescence localization within the murine brain, as compared to conventional fluorescence tomography. We consider the dual FMT-CT system will also enhance the capability of fluorescence tomography when applied to lung cancer detection.

1.3 Reconstruction algorithms

Hyde et al. developed a parameterized inverse problem relying on an anatomical segmentation. To that end, they introduced two novel regularization techniques. The first technique regularizes individual voxels depending on the contribution of the underlying segments in the reduction of the residual error. This spatially varying regularization improves the solutions of the reconstruction by locating them in the appropriate anatomical regions. The second regularization uses the covariance matrix of a modified diffusion process. In this case, the segmentation information is encoded as regions connected by specified boundary conditions. The basic outcome of a regularization of this type is a relaxation of the treatment of boundary information useful to handle the resolution disparity between modalities. A more detailed analysis of the covariance structure was presented in. This method was developed for the detection of Amyloid-β plaques in a murine Alzheimer’s disease model and for the detection of inflammation in a murine lung. Both applications deal with a considerable fluorescence emission in the whole organ.

1.4 Our approach

We are interested in detecting tumors in a mouse model of lung cancer, which can be modeled as point-like sources of fluorescence inside the lung. This requires a different model from the case used to detect fluorescence emitted from entire organs and, in particular, a sparse solution is more appropriate. The regularizer we choose to enforce sparseness is an anatomically constrained $L_1$-regularizer. In addition, we incorporate CT anatomical information in the construction of the diffusion model to guide the reconstruction. We demonstrate that the combination of both tools results in a sparse and accurate reconstruction of fluorescence emission inside a murine lung compared to the case of using the state-of-the-art least-squares reconstruction with no a-priori anatomical information.

1.5 Structure of the paper

The paper is structured as follows: In Section II, we describe the method that we propose to solve the direct and inverse problem. In Section III, we describe the experimental setup and give qualitative and quantitative measurements of the quality of our reconstruction. We end with some conclusions and a discussion on future work.
2. METHODOLOGY

In this section, we describe the methodology we have used to solve the direct and inverse problem.

2.1 Direct problem

Given a known distribution of fluorescent signals, solving the direct problem for a particular setup consists in calculating the amount of light collected at each detector, for all possible pairs of laser (entry point) and detector. To obtain that information we first need to model the behavior of the light as it transverses the body of our sample.

The propagation of photons within the tissue when the source and the detector are separated by at least a few millimeters can be modeled using the diffusion approximation. Green’s functions solutions to these equations can be computed numerically for complex geometries. In particular, we apply an iterative Finite Differences Method (FDM) to solve the diffusion equation (see the reference for details). To accelerate the convergence, the resulting linear system was solved using a multi-grid approach. We used the normalized Born ratio that divides each emitted fluorescence measurement by its corresponding excitation signal, thereby eliminating the need to explicitly solve the full system of coupled differential equations. The Born ratio corrects for optical inhomogeneities and eliminates the need to determine source and detector coupling coefficients. The use of the normalized Born ratio together with the first order Born approximation allows a single linear system to relate the normalized data signal to the underlying physical distribution of fluorochrome. In particular,

\[ b = Ax + e \]  

where \( b \) is the vector of measures, \( A \) is the linearized forward operator, \( x \) is the vector of fluorescence concentrations and \( e \) represents additive Gaussian noise with zero mean and covariance matrix \( \sigma^2 I \). The \((p, q)\) element of the matrix \( A \) is computed as

\[ A_{p,q} \propto \frac{G(r_s, r_q) \cdot G(r_d, r_q)}{G(r_s, r_d)} \]  

where \( G \) are the Green functions, the index \( p \) represents a pair source-detector and \( q \) a voxel of the phantom interior.

The matrix \( A \), as defined, has a number of rows equal to the number of all possible combinations of lasers and detectors, i.e. the product of the number of lasers by the number of detectors. The number of columns, on the other hand, is the total number of points of the sampling grid that lie in the interior of the model. As a consequence, the total number of elements in the matrix is proportional to at least the cubic power of the lateral dimension, which produces an extremely large matrix for moderate to large discrete phantoms. To simplify the computations, we have regularized the problem by considering only those points in the lung where the intensity in Hounsfield units was within a probable range for tumors. To reduce memory usage even further, we have chosen to compute the elements of the matrix \( A \) on-the-fly using the pre-computed Green matrices as given by equation (2). By combining the above mentioned strategies, we reduce the number of elements of the matrices by a factor of 4 orders of magnitude.
In previous work, we have used Self Consistent Boundary Conditions\textsuperscript{17} for the numerical solution of the diffusion equation. Here we adopted a different approach, where we expand the simulation space and include a highly absorbing and highly scattering material around the mouse: we can therefore reasonably assume Dirichlet boundary conditions by fixing the fluence rate at the boundary to 0.

### 2.2 Inverse problem

The inverse problem consists in calculating the probability distribution of the fluorescence inside the sample $x$, for a set of given measurements $b$. We have chosen to formulate it as an $L_1$-regularized least squares problem to enforce the sparsity of the solution. Namely,

$$
\hat{x} = \arg \max_x \{-\|b - Ax\|_2^2 - \gamma \|x\|_1\}
$$

where $\gamma$ is a regularization parameter.

We solve the equation using the Expectation-Maximization (EM) algorithm,\textsuperscript{18} which is a general method to obtain the maximum penalized log-likelihood estimator (MPLE) by introducing missing data and maximizing the complete penalized log-likelihood. The MPLE corresponding to (3) is

$$
\hat{x} = \arg \max_x \{\log p(b|x) - \gamma \|x\|_1\}
$$

where $p(b|x)$ denotes the likelihood function with $p(b|x) \propto -\|b - Ax\|^2$ and $-\|x\|_1$ is the prior distribution.

We need to introduce a hidden variable $\mu$, which is the noisy version of the true absorption perturbation $x$. The two steps of the iterative algorithm, which alternates until some stopping criterion is met, are:

- **Expectation step (E-step):** Calculate the expected value of the complete log-likelihood function (of $b$ and $\mu$), given the observed data $b$ and the current estimate $\hat{x}^{(k)}$ at iteration $k$:

$$
Q(x, \hat{x}^{(k)}) = E[\log p(b, \mu|x)b, \hat{x}^{(k)}],
$$

which was shown to be equivalent to compute

$$
\hat{\mu}^k = \hat{x}^{(k)} + \frac{\alpha^2}{\sigma^2} A^T (b - A\hat{x}^{(k)})
$$

with $\alpha$ is a positive constant constrained to $\alpha^2 \leq \sigma^2/\beta$ where $\beta$ denotes the largest eigenvalue of $AA^T$.

To avoid having to calculate the entire matrix, we observe that the matrix is always used within a matrix-vector product: we can then create a function that evaluates such products by calculating the values of the matrix on-the-fly, when needed. This technique greatly reduces memory usage but as the values of the matrix have to be calculated on-the-fly it requires an increase in computational time.
Maximization step (M-step): Finds the parameter which maximizes this quantity
\[ \hat{x}^{(k+1)} = \arg \max_x \{ Q(x, \hat{x}^{(k)}) - \gamma \| x \|_1 \} = \arg \max_x \{ -\| x - \hat{\mu}^{(k)} \|^2 - 2\alpha^2 \gamma \| x \|_1 \}. \tag{7} \]

The last equation can be solved separately for each element using a soft-threshold method\(^{19}\)
\[ \hat{x}^{(k+1)} = \text{sgn}(\hat{\mu}^{(k)})(|\hat{\mu}^{(k)}| - \alpha^2 \gamma)_+, \tag{8} \]
where \((x)_+ = \max(x, 0)\) and \(\text{sgn}(x) = 1\) if \(x > 0\) and \(\text{sgn}(x) = -1\) if \(x < 0\).

We refer the reader to reference\(^{18}\) for the details on the derivation of the algorithm.

3. RESULTS

3.1 Experimental Setup

3.1.1 Optical parameters

The optical characteristics of the tissue are: absorption coefficient \(\mu_a = 0.18 \text{ cm}^{-1}\), scattering coefficient \(\mu_s = 19 \text{ cm}^{-1}\) and the anisotropy coefficient \(g = 0.875\). The optical characteristics of the air are: \(\mu_a = 10^{-5} \text{ cm}^{-1}\), \(\mu_s = 10 \text{ cm}^{-1}\) and \(g = 0.90\). The optical characteristics of the bone are: absorption coefficient \(\mu_a = 1 \text{ cm}^{-1}\), \(\mu_s = 1000 \text{ cm}^{-1}\) and \(g = 0.99\). The volume surrounding the mouse has the following optical characteristics: \(\mu_a = 1 \text{ cm}^{-1}\), \(\mu_s = 1000 \text{ cm}^{-1}\) and \(g = 0.99\). The light source used in all the simulation was a monochromatic continuous beam laser with a peak transmission of 600 nm and an emission power of 50 mW. We suppose an integration time of 20 s and a quantum efficiency for the fluorescence (photons emitted per photons received) of 100%. The photomultiplier gain for the excitation and the emission light was fixed to \(10^{-7}\). The resulting simulated SNR was on average 26.8 dB for the excitation light and 7.8 dB for the emission light.

3.1.2 Mouse phantoms

In our experiments, we use two phantoms: a heterogeneous phantom that incorporates CT anatomical information in the definition of the optical matrices governing the diffusion of light and a homogeneous phantom with constant optical properties in the entire mouse chest volume.

- **Heterogeneous phantom**: This phantom is a reconstructed micro X-ray computed tomography image of the chest of a 21 gr. Balb/c mouse. The number of projections used in the reconstruction was 600. The micro-CT volume size was \(581 \times 441 \times 432\) with a voxel size of 92 microns. The size of the volume was reduced to \(64 \times 64 \times 64\) using a cubic interpolation scheme to adapt the phantom to the low resolution typical of FMT systems. The chest image was segmented using a three-level Isodata threshold which differentiated bone, lungs -which we assume to have a similar behaviour to air- and tissue -including tissue within the lungs, such as blood vessels, lung tumors etc.-.

- **Homogeneous phantom**: This phantom is constructed from the mouse chest volume of the resized CT image. All the mouse chest volume was optically characterized as tissue. The size for the homogenous phantom is therefore the same as the size of the heterogenous one.
3.1.3 Light sources and detectors positions

We consider 80 punctual light sources and detectors distributed in the phantom surface. The choice of the subset of laser entry points along the surface and the points where to perform the measurements was done according to the following scheme: if we map our three-dimensional model to a cylindrical coordinate system, all points on the lateral border of the mouse can be identified by two coordinates: the longitudinal axis $z$ and the angle $\theta$. We then sampled the $z$-$\theta$ plane using the Halton point set. Among various possible sampling schemes, this low discrepancy set is designed to have a good uniformity level, as can be qualitatively observed in Figure 1.

3.2 Parameters of the direct and inverse problem resolution

For the heterogeneous phantom, the direct problem is solved using 8 multigrid V-cycles to get an absolute error (i.e. difference between consequent iterations) of $10^{-5}$. The stopping criterion for the EM-reconstruction algorithm is fixed to 5000 iterations or a convergence rate of $10^{-5}$.

For the homogeneous phantom, we use only 6 multigrid V-cycles to obtain the same absolute error. The stopping criterion for the EM-reconstruction algorithm was the same as above.

3.3 Illustration of the reconstruction

Figure 1 shows a qualitative example of the reconstruction of a fluorescent signal using the experimental setup described above. The figure shows the maximum intensity projections at the XY, XZ and YZ planes. We show the position of the sources and detectors using red spots. The distribution probability of the fluorophore location is shown in blue. The real location of the point-like probe is shown in green, although it appears to be light blue due to the overlap with the estimation, which is color-coded in blue. Note the good spatial agreement between the true fluorochrome location and its reconstruction.
Figure 2. Variation of the mismatch between the centroid of the estimated probability distribution and the location of the true loci as a function of the distance from the center axis.

Figure 3. Variation of the precision of the true loci location as a function of the distance from the center axis: (a) x-dimension, (b) y-dimension and (c) z-dimension.
3.4 Localization mismatch and precision

The objective of the following experiment is to characterize the improvement in the estimation of detection of the fluorescence when anatomical information is used. We have simulated the reconstruction of 18 fluorescence sources, considered one at a time, located at arbitrary positions inside the phantom. The results are shown in Figures 2 and 3. The results shown in Figure 2 represent -for both phantoms- the variation of the mismatch between the centroid of the estimated probability distribution and the true location of the fluorophore, as a function of the distance from the center axis. We observe a mismatch about 0.1 cm inferior for the heterogeneous phantom with respect the homogeneous one. Besides, in both cases, the mismatch decreases linearly as the distance to the center axis increases, i.e. the fluorescence signal is located closer to the phantom surface.

Figure 3 represents the indetermination in positioning the fluorophore in the x, y, and z dimensions as a function of the distance to the center axis. To measure the precision of the localization, we calculated a weighted standard deviation of the distance estimation. The formula is (given for the x dimension, but applicable to the other two dimensions as well)

\[ \sigma_x = \sqrt{\frac{\sum_i [(x_i - x_c)(\mu_i - \mu_t)]^2}{\sum_i (\mu_i - \mu_t)}} \]

where \( x_i \) is the x coordinate of the estimation, \( x_c \) is the x coordinate of the true location, \( \mu_i \) is the intensity of \( x_i \) and \( \mu_t \) is the threshold intensity. As can be observed in Figure 2, the trend lines for the two sets are well separated, which suggests that there is a clear improvement of the localization of the fluorophore when we use an heterogeneous model. However, in Figure 3, the difference in the dispersion of the estimation is not evident: this may be due to the small size of the set of points used for the test. Further investigation would need to be done in order to better characterize the difference in performance.

4. CONCLUSIONS

The dual system CT-FMT results in an improvement over the low resolution conventional FMT. In our simulations, we incorporate the anatomical information in the image formation at two levels: guiding the diffusion of the light and spatially constraining the reconstructed volume. We achieve an increase of the accuracy and a better correlation between probable tumoral sites and FMT reconstruction results. Moreover, we add a constrained \( L_1 \)-regularization to the standard least-squares reconstruction that contributes to the sparsity of the solution.

As future work, we plan to substitute the finite differences approach by a finite element method, which allows more flexibility in the light diffusion model. We also plan to incorporate an explicit probabilistic model of the object boundaries to better handle the difference in resolution between both modalities.

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