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Course: CIS II Project 15
Assignment: Seminar - Critical Review Report

Note: this critical review report was written as a complement to the presentation slides and includes some response to instructor feedback given during the presentation. Some material may be better illustrated in the slides.

Paper Selection

The article chosen for this review was "Bioluminescence Tomography-Guided Radiation Therapy for Preclinical Research" by Bin Zhang and Ken Wang [1]. This article was chosen because it describes recent work done involving the Small Animal Radiation Research Platform (SARRP), and therefore it describes the context for Project 15, Mouse Segmentation and Optical Properties for Bioluminescence Tomography (BLT). Project 15 aims to incorporate organ-specific optical property information into the existing bioluminescence tomography reconstruction used in the SARRP, which is described and validated in the article reviewed here. All other aims for Project 15 entail facilitating or validating the above-mentioned purpose by attempting to automate mouse segmentation, to produce a look-up table of optical properties, and to test the reconstruction parameters in virtual and implanted light source experiments.

Summary of Problem & Key Results

The problems that this article address are twofold and related: firstly (1) to validate the BLT reconstruction results and secondly (2) to validate guided radiation therapy targeting using the BLT reconstruction results. Three overall categories of experiments were performed: phantom, carcass, and in vivo experiments. In the phantom experiments an average 3D offset of 0.6 +/- 0.1 mm was observed between the center of mass (COM) of a Trigalight source as computed via BLT reconstruction, as opposed to CBCT, which was used as ground truth. In the mouse carcass experiments, average 3D offset was 1.0 +/- 0.6 mm. In vivo experiments using two sources showed that the BLT reconstruction algorithm was able to properly separate two simultaneous light sources in the mouse abdomen and yield COM's within 0.8 and 0.9 mm of position based on CBCT image. The in vivo experiment using a subcutaneous tumor model expressing firefly luciferase enzyme, the BLT reconstructed source distribution was observed to coincide with the mouse surface regions with highest measured emittance. Deviations in field of irradiations from targeting based on BLT and CBCT localization closely followed the observed deviations in reconstruction results.

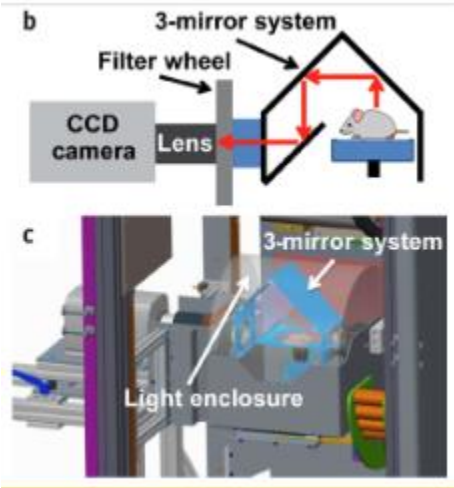
Significance of Key Results

The key results are a promising indicator that BLT reconstruction is a valid strategy of localizing target tissues in mouse models, including cases with multiple simultaneous targets and in vivo subcutaneous tumors. Even with some simplifying assumptions, such as optical homogeneity of the mouse body, the BLT reconstruction yielded overall 1 mm targeting accuracy, when compared to the CBCT targeting results as ground truth. Furthermore, in both phantom and carcass experiments, the largest observed COM deviations between the CBCT and BLT

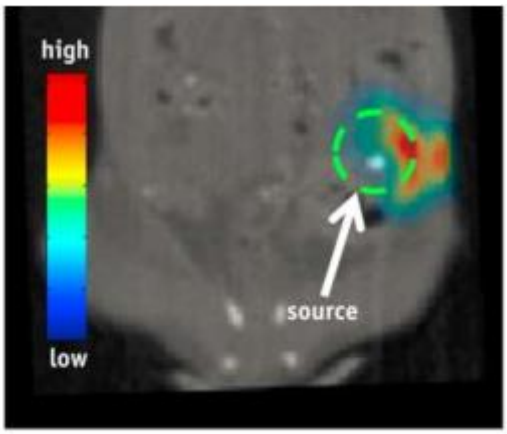
reconstruction results and targeting results were found along the z-axis. In the targeting results, BLT and CBCT deviation on the AP plane were negligible (<0.2 mm), but the largest offsets were 0.6 mm and 0.8 mm along the z-axis for the phantom and carcass studies, respectively. In my assessment, the results seem to indicate firstly that the bottleneck in reconstruction accuracy may be the depth reconstruction, and secondly that the bottleneck in targeting accuracy is the accuracy of the reconstruction. I believe z-axis errors from reconstruction may be propagated into the errors of targeting.

Necessary Background

This article effectively explains the necessary background for understanding the performed experiments, including diagrams of the physical setup for the BLT module docked with the SARRP.



It describes SARRP as a preclinical research platform combining scaled-down CBCT imaging and therapeutic irradiation for use with small animal models. It explains the need for an imaging modality such as BLT for use in targeting studies involving small or low-contrast targets that are not easily localized using CBCT alone. It describes the advantages of BLT compared to alternatives, based on factors such as bulkiness and expense. BLT can be used for soft tissue targeting, provided a genetically engineered bioluminescent tumor model is used. In this study, BLT is performed using information from a single Bioluminescence Image (BLI) view. The reason raw BLI alone is not ideal as the second imaging modality is because it lacks depth information and the available x-y position information, based on the regions of highest surface intensity in the image, do not reflect the truth. The following image shows the deviation between the true source and the position suggested by the BLI taken at face value.



The computation approach employed in the SARRP's BLT reconstruction is discussed with a good amount of detail. The article describes the presents the basic form of the BLT reconstruction problem via an imaging equation $\varphi = \widetilde{G}s$. The vector φ represents the surface emittance measurements. $\widetilde{G}$ is a matrix of Green's functions computed based on wavelength of light and the optical path between each originating source node to the destination surface node. The Green's function relates the source concentration at each internal node to the observed surface measurement. The following equation (2) from the article describes the multispectral approach, since the surface measurements can be taken at specific wavelengths of light, and the Green's function is also specific to the wavelength of light in question. The multispectral approach is used to improve depth reconstruction.

$$\begin{bmatrix} \varphi(\lambda_1) \\ \vdots \\ \varphi(\lambda_k) \end{bmatrix} = \begin{bmatrix} \eta(\lambda_1)G(\lambda_1) \\ \vdots \\ \eta(\lambda_k)G(\lambda_k) \end{bmatrix} [s]$$

The coefficient η accounts for the inherent differences in source emittance of light at each wavelength. Further modification includes normalization of the surface measurements and Green's function values by the magnitude of the maximum surface measurement observed at corresponding wavelengths, since longer wavelength light in this study was less attenuated than the shorter wavelength light and would otherwise bias the reconstruction. The final BLT minimization problem was described.

BLT Minimization Problem

$$\min_s \frac{1}{2} \left\| \overline{G}s - \overline{\varphi} \right\|_2^2 + \tau \|s\|_1$$

Mesh Nodes

During the in-class presentation, a question was asked regarding the selection of an L_1 norm for use in the regularization term, as opposed to the L_2 Euclidian norm. Additional inquiry in the source cited in the article yielded the following statement: "Previous studies in … demonstrated the superiority of L_1-norm regularization to L_2-norm for sparse reconstruction in BLT, thus no such comparisons were presented in this paper" [2].

The article also describes the use of an iterative region-shrinking strategy to improve convergence and computational efficiency. The possible source nodes after each iteration were

reduced by a factor β, defined below. After each iteration, only the nodes with the highest source concentrations, as given from solution to the BLT minimization problem, were retained for the next iteration. The reconstruction results from each iteration were evaluated using an objective function f_i also defined below. The solution producing the smallest objective function value was selected as the final solution.

Iterative Region Shrinking Strategy

Initial Nodes — Iterations = 20

$$\beta = (N_1/N_f)^{1/(N_{it}-1)}$$

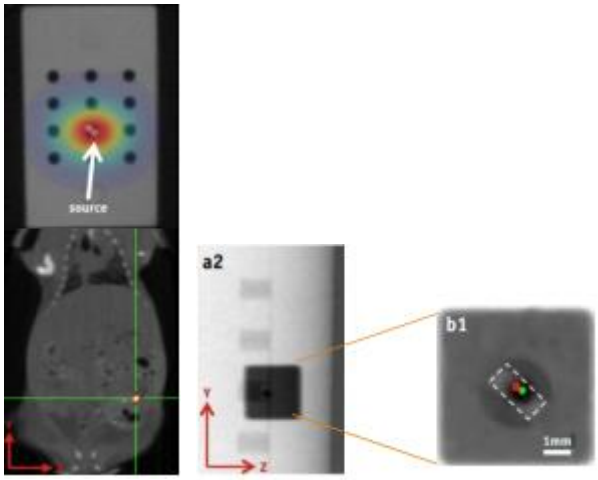
Permissible Region Reduction Factor — Final Nodes = 1

Objective Function to Choose Solution

$$f_i = \sum \left\| \overline{G}s^{(i)} - \overline{\varphi} \right\|_1$$

Description of Experiments

Phantom and carcass experiments had similar procedures. In both cases, Trigalight tritium gas cylinders with good CBCT contrast and size 0.9x2 mm were used as the light source. In the phantom, the Trigalight was deposited into a well, and in the mouse carcass, the Trigalight was implanted into the mouse abdomen (images below, left). In these experiments, after the BLT reconstructed COM of the light source was obtained, it was used to guide vertical and lateral beams of radiation. Film was placed orthogonal to the beam direction, on the exit side of the mouse and phantom. The BLT reconstructed target COM was irradiated with a 5x5 mm irradiation field. The CT reconstructed target COM was irradiated with 0.5 mm diameter beam. Then the COM's of the fields of irradiation in the two targeting schemes were compared (image below, right). During the class presentation, there was a question regarding how the accuracy of the BLT and CT targeting was assessed, which was resolved by establishing that the field of irradiation from the CT targeting was assumed to be ground truth, as was the case in assessment of BLT reconstruction result. Results from these experiments are discussed in above sections: Significance of Key Results, and Summary of Problems & Key Results.



The image on the top left shows an overlay of the BLI image and the AP view of the phantom. The image on the bottom left shows the reconstructed source at the center of the crosshairs, overlaid with AP view of the mouse. The image on the right shows an example of results from a lateral beam used in targeting evaluation. The dark gray square is the field of irradiation from BLT-based targeting, and the darker small circle inside is the field of irradiation from CBCT-based targeting.

Two in vivo experiments were also performed. In the first experiment, two larger Trigalights, with size 2x6 mm, were implanted into the mouse abdomen. The BLI image produced by the two sources was contiguous, but the BLT reconstruction was able to recreate the two sources with accuracy comparable to the carcass experiments involving one source, once again using the source's position in the CT image as ground truth. In a second in vivo experiment, a subcutaneous bioluminescent tumor was imaged with BLI and then BLT reconstructed. In this case the BLI mapped onto the mesh surface was assumed to be ground truth, since the subcutaneous tumor was near enough to the mouse surface. The reconstructed source distribution manifested in a cluster of sources, all coinciding with the regions of highest intensity in the BLI image. The results are also discussed in above sections: Significance of Key Results, and Summary of Problems & Key Results.

Assessment and Conclusions

Some aspects of this article that I thought could be expanded were the use of the COM as the predominant metric for accuracy of reconstruction. I think it would be useful to experiment with different source geometries as a possible next step, but doing so may require a more detailed metric for similarity between the reconstructed source distribution and the ground truth distribution. Originally I had taken some issue with the scarcity of description of the Incomplete Variables Truncated Conjugate Gradient (IVTCG) algorithm used in solving the minimization problem; however, as pointed out during the presentation, the cited source was very detailed on that topic. Some strengths of the articles include analysis of the limitations of the assumptions of optical homogeneity of the mouse, which segues into discussion of possible next steps. The article's suggestion of organ specific optical properties is the motivating idea behind Project 15. The article also mentions the possibility of using diffuse optical tomography to investigate the optical property distribution inside the mouse body to aid in reconstruction. Overall, this article was well-written with good detail, and explained at a level that was effective for understanding, and the studies performed are a good foundation for future work.

Reference

1. Bin Zhang, Ken Kang-Hsin Wang, Jingjing Yu, Sohrab Eslami, Iulian Iordachita, Juvenal Reyes, Reem Malek, Phuoc T. Tran, Michael S. Patterson, and John W. Wong.

"Bioluminescence Tomography-Guided Radiation Therapy for Preclinical Research". International Journal of Radiation Oncology*Biology*Physics.

2. Xiaowei He, Jimin Liang, Xiaorui Wang, Jingjing Yu, Xiaochao Qu, Xiaodong Wang, Yanbin Hou, Duofang Chen, Fang Liu, and Jie Tian, "Sparse reconstruction for quantitative bioluminescence tomography based on the incomplete variables truncated conjugate gradient method," Opt. Express 18, 24825-24841 (2010)