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BIOLUMINESCENCE TOMOGRAPHY: BIOMEDICAL BACKGROUND, MATHEMATICAL THEORY, AND NUMERICAL APPROXIMATION*

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Dedicated to Professor Junzhi Cui on the occasion of his 70th birthday

Abstract

Over the last couple of years molecular imaging has been rapidly developed to study physiological and pathological processes *in vivo* at the cellular and molecular levels. Among molecular imaging modalities, optical imaging stands out for its unique advantages, especially performance and cost-effectiveness. Bioluminescence tomography (BLT) is an emerging optical imaging mode with promising biomedical advantages. In this survey paper, we explain the biomedical significance of BLT, summarize theoretical results on the analysis and numerical solution of a diffusion based BLT model, and comment on a few extensions for the study of BLT.

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1. Introduction

Tomography is an important branch of imaging science and technology which targets image reconstruction from indirect measurement of an object under consideration. Among its numerous applications, tomography has been the driving force in biomedical imaging. As cornerstones of modern hospitals and clinics, x-ray computed tomography (CT), magnetic resonance imaging (MRI), nuclear and ultrasound imaging are widely applied for spatial and temporal reconstructions of anatomical and functional features, generated tremendous healthcare benefits over the past decades.

Guided by the so-called NIH Roadmap, molecular imaging has been rapidly developed to study biological processes in vivo at the cellular and molecular levels [27, 29]. While some classic microscopic and spectroscopic techniques do reveal information on micro-structures of the tissues, only recently have molecular probes been utilized along with imaging technologies to detect and image molecular targets sensitively, specifically, and non-invasively. Among molecular imaging modalities, optical imaging is most attractive because of its unique advantages, especially performance and cost-effectiveness [8, 20, 30]. Fluorescent and bioluminescent probes

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are commonly used for optical molecular imaging in preclinical studies of mice and rats as models of various human diseases, as well as to a limited extent in clinical research. In this context, fluorescence molecular tomography (FMT) [21] and bioluminescence tomography (BLT) [26,28] are emerging as complementary optical molecular tomography modes.

Given the fast pace of the development in the BLT area and the major needs for more mathematical work, we present this survey as a reference for those mathematicians who are interested in solving cutting edge inverse problems for biomedical applications. In the following, first we explain the biomedical significance of BLT in Section 2. Then, we summarize theoretical results on the analysis and numerical solution of a diffusion-approximation based BLT model in Section 3. Finally, we discuss a few extensions of BLT in Section 4.

2. Biomedical Background

In the post-genomic era, great efforts are being made to associate genes to phenotypes for development of systems medicine that are predictive, preventive and personalized. An important aspect of this perspective is small animal imaging that allows *in vivo* studies at anatomical, functional, cellular and molecular levels. In molecular/cellular imaging, small animal features of interest are labeled with molecular probes [18,30]. A molecular probe has a high affinity for attaching itself to a target molecule and a tagging ability with a marker molecule that can be tracked outside a living body. Optical imaging methods include florescence molecular tomography (FMT) [21] and bioluminescent imaging (BLI) [22], which are most promising because of their performance and cost-effectiveness, and already successfully used to investigate tumorigenesis, cancer metastasis, cardiac diseases, cystic fibrosis, gene therapies, drug designs and so on. Particularly, bioluminescent imaging has unique capabilities in probing molecular and cellular processes, and produces superior signal-to-noise ratios with little background auto-fluorescence. In the March 2005 issue of the Molecular Imaging Outlook[1)] , Contag mentioned that BLI arose out of the frustration with sampling limitations of the standard assay techniques. Also, since the genes are duplicated with the cell division, BLI is more sensitive than other techniques such as nuclear imaging in which the radioactive signal is reduced with the cell division. Piwnica-Worms underlined in the same report that BLI could be applied to study almost all diseases in every small animal model.

Dr. Wang's group conceptualized and developed the first bioluminescence tomography (BLT) prototype which compensates for heterogeneous scattering properties of a mouse and performs quantitative 3D reconstruction of internal sources from bioluminescent views measured on the external surface of the mouse [7, 26, 28]. BLT has now become a rapidly developing area for optical molecular imaging. The introduction of BLT relative to planar bioluminescent imaging (BLI) can be in a substantial sense compared to the development of x-ray CT based on radiography. Without BLT, bioluminescent imaging is primarily qualitative. With BLT, quantitative and localized analysis on a bioluminescent source distribution become feasible inside a living mouse

The pre-requisites for BLT are bioluminescent probes, corresponding substrates, and subsequent signal collection. Naturally-occurring luciferases exhibit emission maxima between 480 nm and 635 nm. In principle, we may use luciferases with different spectral properties to sense various biological events. Recent results in the luciferase technology have confirmed spectrally-shifted signals from luciferases in various species and/or by mutagenesis. Among

[1)] http://www.diagnosticimaging.com/molecularimagingoutlook/2005mar/02.jhtml