Multimodality Molecular Imaging

Improving Image Quality

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Molecular imaging is a newly emerging and rapidly developing biomedical imaging field in which the modern technologies and instruments are being merged to study biological and medical processes, as well as diagnosing and managing diseases. In the study of molecular imaging, the three research focuses are the imaging techniques, specific molecular probes, and molecular imaging applications in pathology and pharmacology. Therefore, novel molecular imaging theories and algorithms, new molecular probes, multimodality molecular imaging prototype systems, experiments, and biomedical applications are introduced as a whole project.

Focusing on the core theory of in vivo fluorescent labeling, molecular imaging and related techniques, systems, and deep-seated issues of radionuclide labeling molecular imaging, our work is to develop a research platform for the discipline in China and actively promote the domestic development and manufacturing of related diagnostic facilities.

The work is supposed to offer several new effective means for exploring the pathology, clinical diagnostics, monitoring, and efficacy evaluation in the treatment of cancers or other fatal diseases. The results are expected to dramatically speed up the developing tempo of new drugs by reducing the time for preclinical research, and providing an in vivo quantitative assessment of toxic side effects and efficacy of the drug, and exploring drug-administering routes, stereostructure, pharmacometrics, and the impact of animal species on drug efficacy. In addition, what we achieved may promote the basic research of life sciences, and open a new era of in vivo, dynamic, and continuous probes into a gene's functions, cellular dynamics, and the whole process of life activity. The enforcement of the project will greatly facilitate the realization of a number of key national goals in population and public health [1]–[3].

The work has the following objectives preset for its implementation: propagation theory of light in complicated organisms with strong scattering property and related inverse algorithms; a unified computational framework and algorithmic platform for data analysis and treatment; a framework for demonstration and appraisal of the in vivo molecular imaging; and a prototype system for fluorescence or nuclide-labeling imaging. Based on these objectives, a series of biological experiments were conducted. Furthermore, the experimental results provided the information to optimize algorithms and systems. The work will explore the molecule's impact on the nuclide-tagging process applicable to clinical medicine and the fluorescence-tagging process applicable to the models of small animals [4]–[6].

The following sections demonstrate our work so far in detail. Two types of optical molecular imaging modalities are presented in the "Optical Molecular Imaging" section: fluorescence molecular tomography (FMT) and bioluminescence tomography (BLT). Nuclide medical imaging and probe studies in molecular imaging are studied in the "Nuclide Molecular Imaging" and "Molecular Probe" sections, respectively. We discuss the biological applications related to molecular imaging in the "Biological Application" section and conclusions are drawn in the end.

Optical Molecular Imaging

Fluorescence Molecular Tomography

In the recent years, FMT has developed rapidly as a promising tool for in vivo small animal imaging because of its ability to resolve three-dimensional (3-D) spatial distributions of fluorescence probes associated with molecular and cellular functions [7]. A prototype of FMT is also developed. The progress on imaging system construction, photon migration modeling, and the corresponding reconstruction methods are reported in the following sections.

Development of Imaging Systems

First, a fiber-contact imaging system based on a photomultiplier tube (PMT) was developed, which works within the near-infrared spectral range under continuous-wave mode [8] (Figure 1). In this system, a small animal was dipped into matching fluid in a glass cup, with 16 launch fibers and 16 detector fibers placed alternatively around the boundary of the cup at each horizontal plane. The 16 detector fibers were connected to only one PMT by using an optical multiplexer to alter the detector channels. To get rid of the influence caused by the background light, the laser is modulated by a low-frequency sinusoidal function, and the detected signal of the same frequency is extracted for reconstruction. Compared with the charge-coupled device (CCD)-based imaging system,

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it is relatively simple and considerably inexpensive because it uses only one PMT. Besides, the proposed imaging instrumentation was designed as a highly automated system in which all the components can work harmoniously. Moreover, it could either act as a diffusion optical tomography (DOT) system or work as fluorescence tomography to achieve the location of the embedded fluorescence probes. For the latter, two kinds of experiments, with and without the embedded fluorescence probes, are required, and the difference of the detected values yields the fluorescence photon field. Figure 2 shows phantom experiments based on the proposed imaging system and the corresponding reconstructed results.

Recently, a CCD-based noncontact fluorescence tomography of 360° geometry projections was developed. The 3-D surface of the imaging animal had been reconstructed using a filtered back-projection method, after taking photos of the animal through different projections [9]. The influence of the prospective effects on the accuracy of the derived information and the image quality of noncontact fluorescence tomography was also studied [10], [11].

Monte Carlo Method for Photon Migration Modeling

We began to study the photon propagation models in biological tissue in 1998. First, a controlled Monte Carlo (MC) method was developed to calculate the time-dependent transmittance of light through a thick tissue, especially for the evaluation of the contribution from early-arriving photons [12]. Recently, we proposed a table-based random sampling (TBRS) algorithm to simulate photon propagation in a turbid medium [13] based on the theory of the MC method. It retained the merits of flexibility and accuracy of the

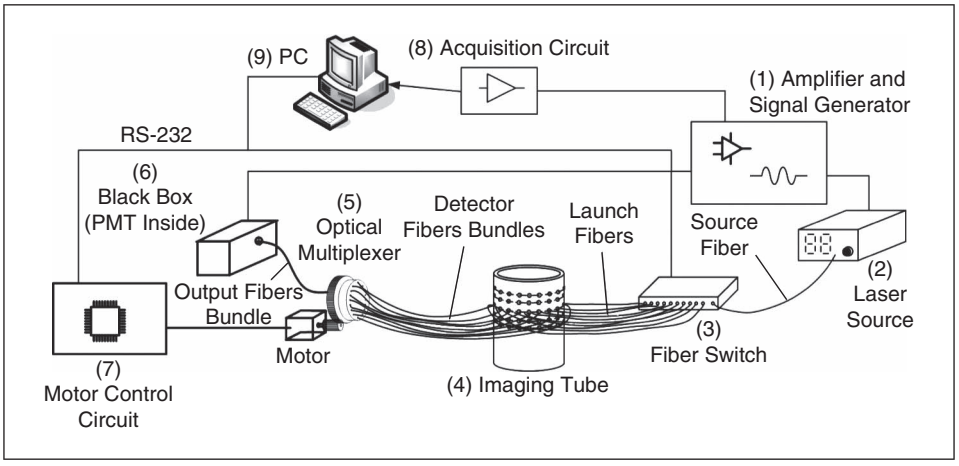

Fig. 1. System scheme of the fiber-contacted PMT-based optical tomography (8).

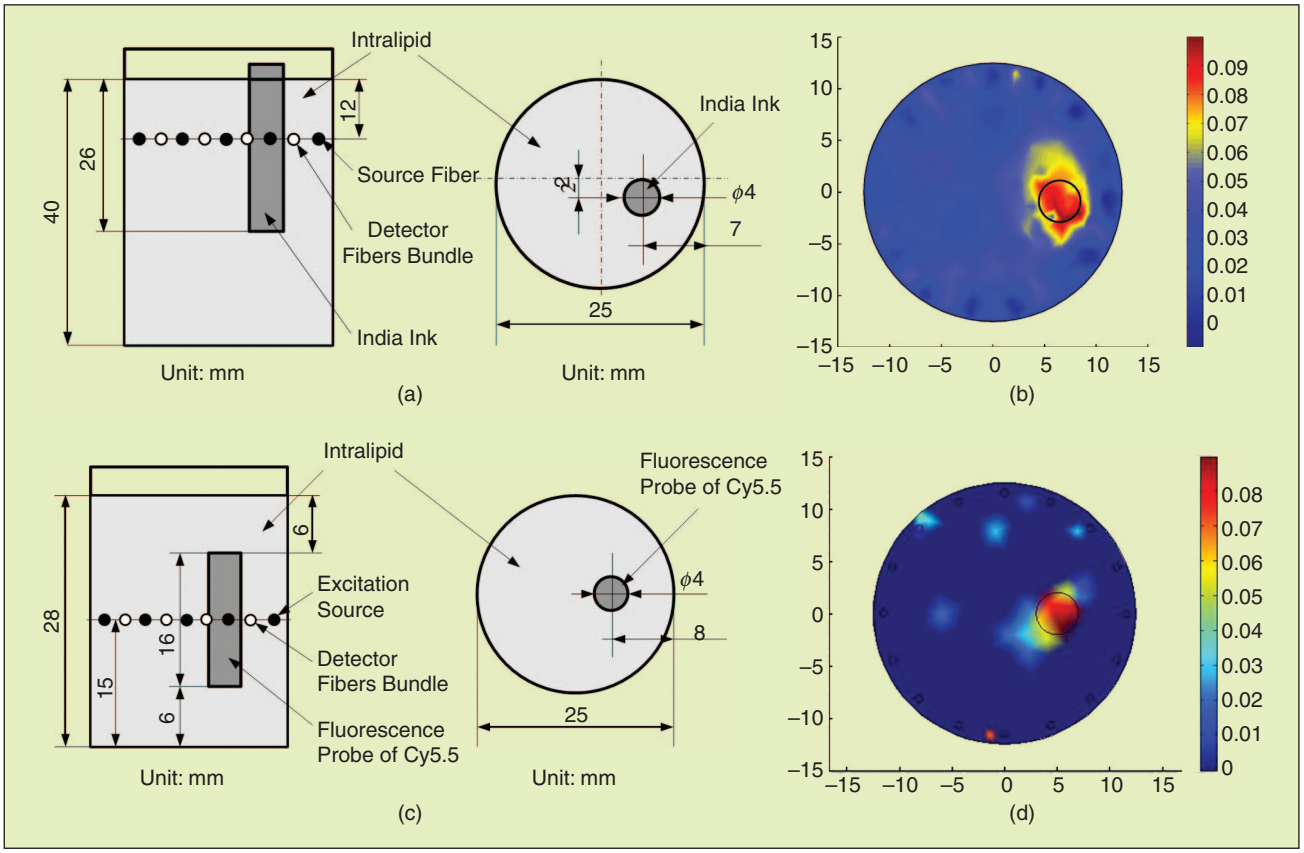

Fig. 2. The experimental setup for DOT and FMT is separately shown in (a) and (c). The corresponding reconstructed distribution of the absorption parameter is plotted in (c), whereas (d) shows the estimated distribution of fluorescence probes (8).

We can achieve high computation efficiency and spatial resolution for models with irregular shape and inhomogeneous distributions of optical parameters.

conventional MC method and adapted well to complex geometric media and various source shapes but significantly reduced the computing time. To verify the feasibility of the TBRS algorithm, we compared its results with the simulation results of the conventional MC method and the finite element method (FEM) and with the results of phantom experiments. Good agreement was found among the results.

New Imaging Reconstruction Method

Along with the development of imaging systems, we have also proposed several inversion methods. For the system shown in Figure 1, a parallel reconstructed scheme for inhomogeneous mediums with unknown absorption properties is proposed, where fluorescence and tissue absorption could be reconstructed at the same time [14].

Based on a linear scheme, a series of inversion skills are developed, with the forward model of diffusion equations solved either by FEM or by analytical method [15]–[18]. For example, preiteration-based fast reconstruction methods are proposed [15], [16], where the time-consuming iterations are executed before data acquisition, and for updated measurements, only a matrix-vector multiplication and simple postprocessing are required. Additionally, in the preiteration step, a two-order iteration expression is employed for the approximation of generalized inverse matrix, which exponentially accelerates the convergence rate when compared with the one-order form. Figure 2(d) is an example of reconstruction using the fast preiteration method for experiment data.

Recently, we reported a new reconstruction algorithm by combining an adaptive mesh refinement technique and the analytical solution of diffusion equations [18]. In the adaptive procedure, the optimization method of an interior point conjugate gradient method with trust region (interior/CG) is employed to determine the distribution of fluorescent targets. Numerical studies have been performed on a parallel plate FMT system with matching fluid. Computational experiment results show that reconstructions of targets embedded in turbid media are accurate and fast using the algorithm proposed, as shown in Figure 3. Because of the combination of the adaptive mesh refinement technique and the analytical solution of diffusion equations, the reconstruction took an

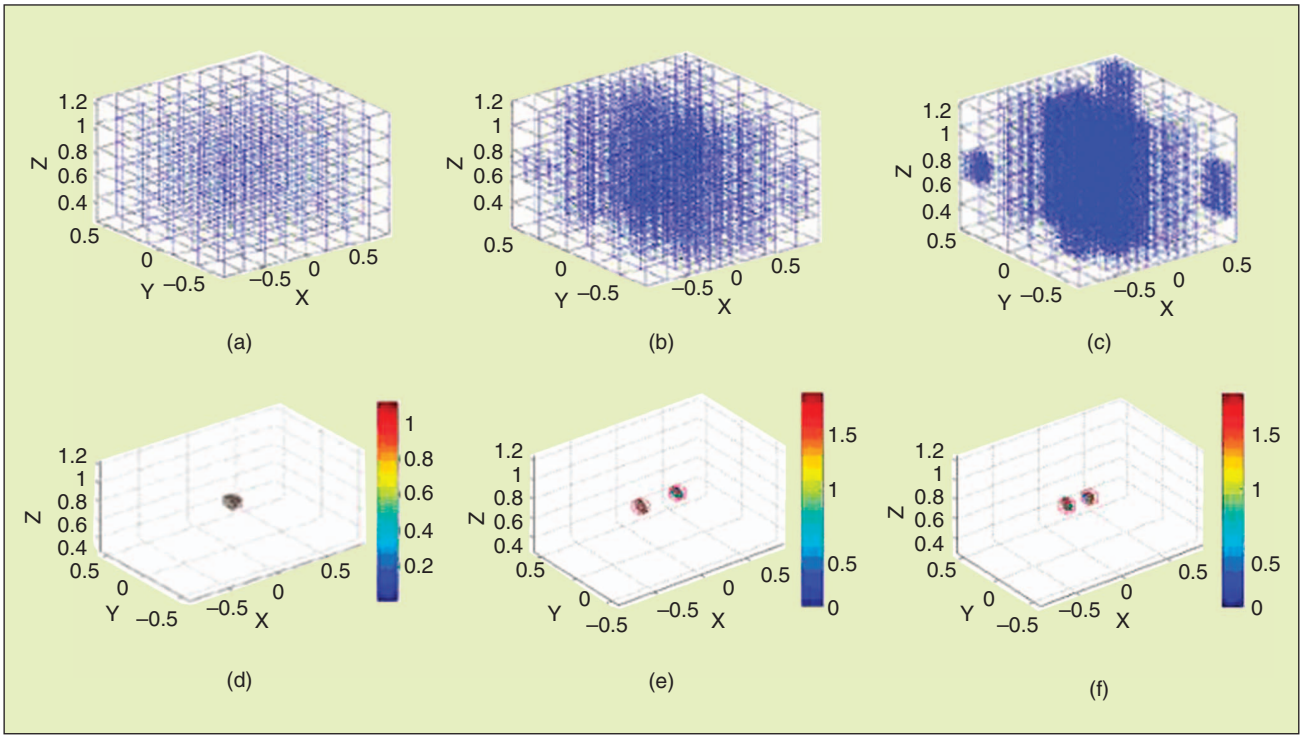

Fig. 3. Discretization evolution in the reconstruction is illustrated sequentially in (a), (b), and (c), from uniformly coarse mesh to selectively refined meshes. Top 70% of the contour levels of reconstructed fluorescence distribution are shown in (d)–(f), in which the red cubes represent the real targets. The edge-to-edge distance for fluorescent targets are 0.3 cm (e) and 0.15 cm (f) (18).

The whole-body optical imaging system is external and noninvasive and affords unprecedented continuous visual monitoring of heart growth.

average computation time of 140 s, which is 20% of the time cost of uniformly coarse mesh using the algebraic reconstruction technique (ART).

With the development of in vivo free-space fluorescence molecular imaging and multimodality imaging for small animals, there is a need for new reconstruction methods for real animal-shape models with large data sets. We proposed a novel hybrid adaptive finite element algorithm for fluorescence tomography reconstruction, where two different inversion strategies (conjugate gradient and Landweber iterations) are applied to the first mesh level and the succeeding levels, respectively [19]. Based on the latest free-space setup of fluorescence tomography with 360° geometry projections, the new algorithm was numerically proved using a 3-D digital mouse model, incorporating the known optical heterogeneity. The results suggest that we are able to achieve high computation efficiency and spatial resolution for models with irregular shape and inhomogeneous distributions of optical parameters.

Bioluminescence Tomography

BLT as an optical imaging modality that enables quantitative reflection of the molecular and cellular information in intact living subjects by precisely localizing bioluminescent sources.

Theoretically, 3-D reconstruction of a bioluminescent source is an inverse source problem, which has not been adequately investigated. In highly heterogeneous biological tissues, scattering and absorption of the photon emitted by a bioluminescent source increases the level of source localization difficulty. Compared with FMT, it complicates the tomographic problem, although the absence of external illumination accords a highly sensitive signal. Therefore, the unique and quantitative reconstruction of a bioluminescent source and the development of a fast and robust tomographic algorithm are the topics for further investigation. To develop the next-generation optical molecular imaging system, sophisticated research needs to be performed at its various aspects, such as photon propagation, source reconstruction, and so on [4], [20]. In terms of imaging theory and algorithm and system verification of BLT, we have made some progress in the research area.

Molecular Optical Simulation Environment

As an important part of bioluminescence imaging, an optical simulation software platform named the molecular optical simulation environment (MOSE) has been developed to simulate the bioluminescent phenomena of a small living animal (e.g., the mouse) and to predict bioluminescent signals detectable outside the animal. With photon transport algorithms based on the MC method [21], bioluminescent signals in CCD detectors and physical quantities (e.g., absorption attribution schematics) can be obtained after their propagations. To significantly improve the precision of bioluminescent imaging simulation, the virtual optical simulation environment has been realized with 3-D image processing algorithms and several graphic editing tools, which have been integrated in the MOSE. Some key techniques and algorithms such as surface rendering, mesh simplification, in-or-out strategy, and superquadric models were proposed [22]. This platform has been downloaded for free since 2005, and more than 300 researchers in research institutes and medical staffs in hospitals have used it as a tool in their study. Two transparent views [Figure 4(a) and (b)] of the 3-D simulated environment with biological tissues of the mouse thorax are seen. The blue ball indicating the light source can be totally modified by certain parameters shown in Figure 4(c) and locally modified by Bezier cubic spline curves.

An Adaptive FEM Appropriate for Photon Propagation in Complex Biological Tissues

To enhance the solution accuracy of the forward problem in BLT, an adaptive finite element algorithm based on the diffusion equation had been introduced. This proposed method utilizes tetrahedron as a basic element suitable for description of complex geometry and performs local mesh refinement based on a posteriori error estimation technique. Considering the intrinsic triangulation sequence obtained by adaptive mesh refinement, multilevel preconditioner with Jacobi-type smoothing (which can be called BPX preconditioner) was also used to significantly accelerate the iterative procedure for solving the linear equation. The use of these strategies makes us not only obtain high numerical precision but also improve the simulation speed. The accuracy and effectiveness of the method is validated in comparison with the analytical method and experimental detection.

A Multilevel Adaptive Finite Element Algorithm for Bioluminescent Source Reconstruction

By combining the developed adaptive FEM and a priori permissible source region strategy, a multilevel adaptive finite element algorithm had been developed to resolve the contradiction between the reconstruction quality and speed and the a priori fixed discretization degree to the given domain in BLT. The permissible region was conferred by using achromatic or monochromatic measurement-based surface light power distribution and anatomical and optical information. The multilevel strategy was also fused into the algorithm, which enhances numerical stability and robustness [23]–[25].

In simulation experiments, the effectiveness and feasibility of this proposed method had been validated with a heterogeneous cylindrical mouse chest phantom and MC simulation data. The phantom comprises five kinds of

simulation tissues—muscle, lungs, heart, bone, and liver [Figure 5(a)]. The final reconstruction results are displayed in Figure 5(b) and (c).

A Multispectral Multiscale Source Reconstruction Algorithm

On the basis of the multilevel adaptive finite element algorithm, a spectrally solved tomographic algorithm with a posteriori permissible source region selection has been proposed for the use of multispectral detection information as a restriction for the possible solution in BLT reconstruction [26], [27]. The proposed method further combines local mesh refinement to realize multiscale source reconstruction. In the numerical simulation experiment, a micro-MRI-based mouse phantom is employed to provide the anatomical information, and the optical parameters of the biological tissues are also determined through a priori experiments. The reconstruction results showed the preferable ability of this developed algorithm for sources at half-radius and center positions as shown in Figure 6(a) and (b).

Experimental Verification of the Necessity of Multimodality Imaging Fusion for BLT

Multimodality imaging fusion is essential for quantitative BLT reconstruction, and it has been presented by us first through the experimental comparison based on the multilevel adaptive finite element algorithm. A heterogeneous mouse-like phantom with two bioluminescent sources is used to validate the necessity of multimodality for BLT as shown in Figure 7(a). If the physical phantom is an anatomical and optical homogeneous object or all a priori information is not considered, the BLT reconstruction [Figure 7(b)] cannot distinguish two light sources, and the reconstructed position is also far from the actual one. The permissible source region can be determined when the anatomical information is fused. Two light sources can be distinguished from the reconstruction results as shown in Figure 7(c). Although there are small relative errors in source density between the reconstructed and actual sources, the preferable source localization cannot be obtained. Finally, Figure 7(d) displays the reconstruction results in terms of the utilization of anatomical and optical

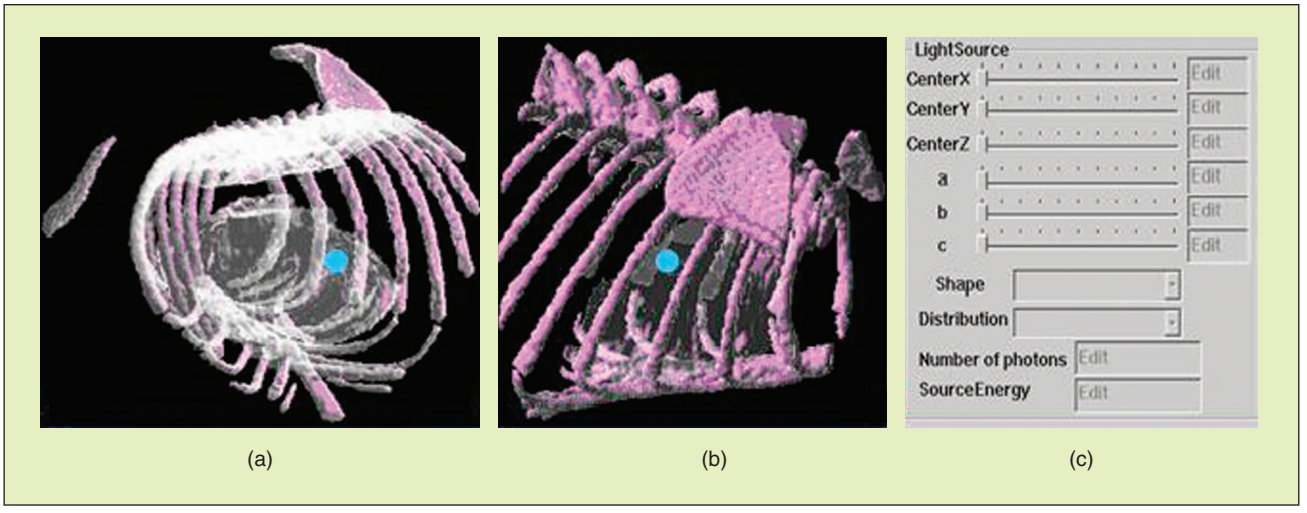

Fig. 4. Real tissue environment simulated by MOSE (22).

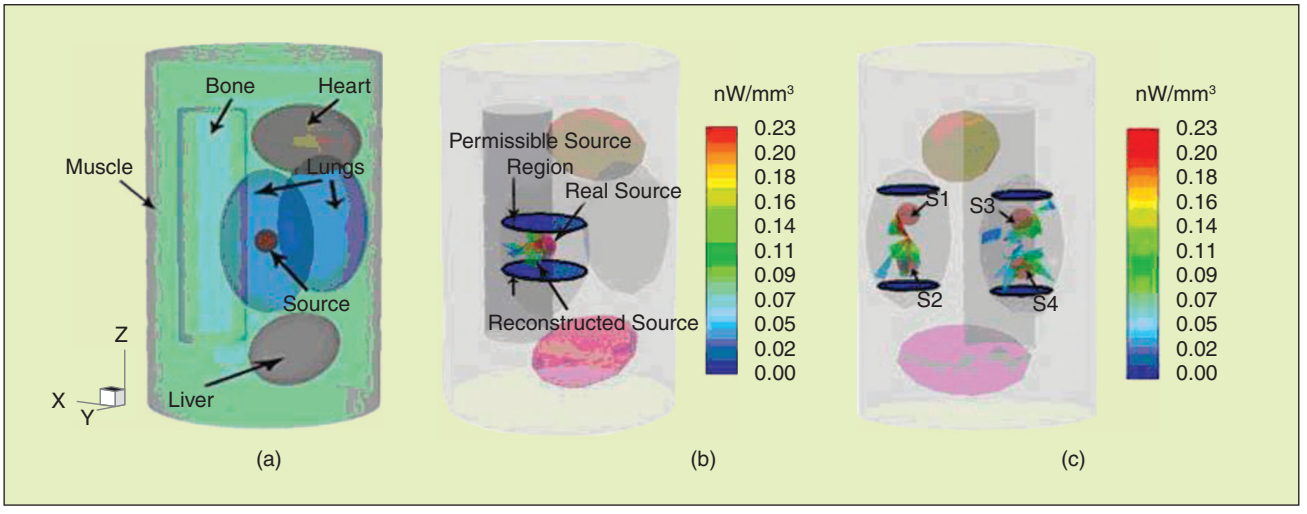

Fig. 5. Comparison between the actual and reconstructed sources. (a) A heterogeneous phantom with a single light source, composed of muscle (green), lungs (blue), heart (carmine), bone (white), liver (pink), and source (red); (b) BLT reconstruction in the case of a single light source; (c) BLT reconstruction in the case of four light sources (25).

Optical imaging can be divided into fluorescence molecular tomography and bioluminescence tomography.

information. The position and density of light sources are better reconstructed. Therefore, the above BLT reconstruction with the multilevel adaptive finite element algorithm demonstrates the necessity of the micro-CT-based anatomical information and optical property based on tomographic measurement, and it also provides a preferable validation for installing the next-generation BLT prototype.

Nuclide Molecular Imaging

This is the mainstream direction in molecular imaging because of its clinical predominance with a high transmission rate of γ-ray emitted from radioisotope-labeled molecules (RLMs), which dynamically move according to their physiological mechanism in vivo. The relatively mature technology has been widely used in gene and protein engineering and clinical applications such as diagnosis and treatment. Tumor imaging in medical physics and radiochemistry and its clinical applications is a major area of research. We focused our efforts on animal molecular imaging equipment and its applications.

Dynamic data analysis for positron emission technology (PET), contrast-enhanced magnetic resonance imaging (CE-MRI), and fMRI or MR spectroscopy used for tumor diagnosis and radiotherapy, the high-resolution imaging facilities of cone bean CT and MRI, and the dose calculation and measurement for radiotherapeutical treatment plan (TP) are the main research directions. We focused to solve the problems of how to use the fluorescence and radioisotope double-labeled molecular probes to get the probe distributions data in vivo for the photodynamic therapy (PDT), which is combined with radiochemistry for probe development. Both theoretical calculation and measurement of these data are challenges because the transmission rate of near infrared light emitted from red fluorescence in tissue is very low. The distribution measurement in vitro by only fluorescence-labeled probes is not easy although these data are very important for making the individual clinical treatment plan.

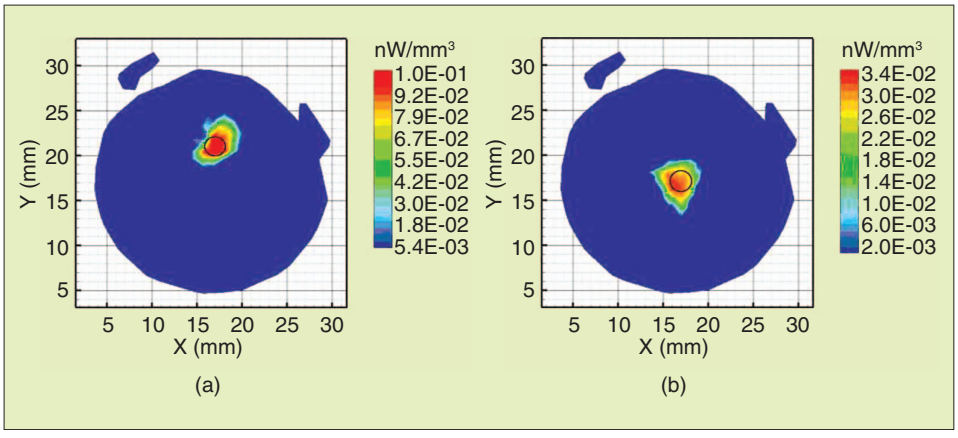

Fig. 6. Spectrally resolved BLT reconstruction with the proposed algorithm. (a) and (b) Transverse views of the reconstructed results with actual sources placed at half-radius and center positions in the mouse phantom, respectively. The cross section perpendicular to the *z*-axis direction is through the actual source's center (27).

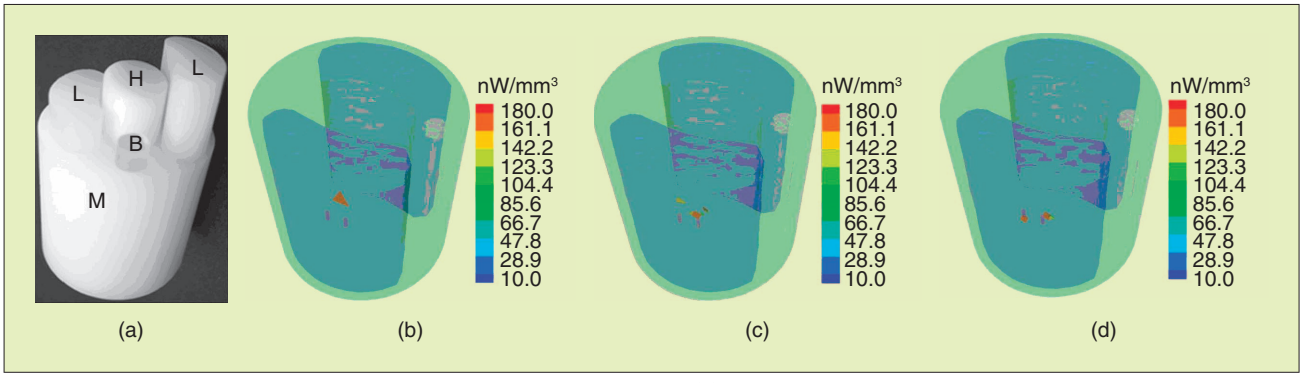

Fig. 7. Comparison between the actual and reconstructed sources: (a) The physical heterogeneous phantom consisting of bone (B), heart (H), lungs (L), and muscle (M); (b) the BLT reconstruction without anatomical and optical information; (c) the counterpart only with anatomical information; and (d) that with anatomical and optical information (28).

Stem cell therapy offers exciting promises for cardiac regeneration.

Therefore, until now, there are almost no existing data in PDT technology. Following are the samples that are more close to nuclide medical imaging.

Parametric images generated from dynamic PET studies are useful for presenting functional/biological information in the 3-D space but usually suffer from their high sensitivity to image noise. To improve the quality of these images, in this study, we proposed a modified linear least square (LLS) fitting method named cLLS that incorporates a clustering-based spatial constraint for the generation of parametric images from dynamic PET data of high noise levels [29]. In this method, the combination of K-means and hierarchical cluster analysis was used to classify dynamic PET data. Compared with conventional LLS, cLLS can achieve high statistical reliability in the generated parametric images without incurring a high computational burden. The effectiveness of the method was demonstrated both with computer simulation and with a human brain dynamic fluorodeoxyglucose (FDG) PET study. The cLLS method is expected to be useful for the generation of parametric images from dynamic FDG PET study.

Dynamic contrast-enhanced (DCE) MRI has been used to investigate the temporal and spatial distribution of contrast agents in different tissues of prostate [30]. In clinical settings, these dynamic images are most commonly analyzed by qualitatively analyzing the time-intensity curve (TIC) of the region of interest (ROI), which is operator dependent and results in intra- or interobserver variation. In our research, a retrospective study was carried out to quantify DCE-MRI by the choice of an appropriate mathematical model for Gd-diethylene triamine pentaacetic acid (DTPA) TIC and constructing a prostate cancerous probability model to predict whether a lesion is cancerous or not. Three mathematical models considered for the enhancement of TIC are as follows: segmented line model, bi-exponential model, and mono-exponential plus line model. The methods were applied to 52 ROIs (ten malignant, 26 benign, and 16 normal) in the peripheral zone (PZ) of the prostate from 18 patients undergoing needle biopsy and eight normal volunteers. By comparing the results from different mathematical models with two sample independent t test and logistic regression, we found that the segmented line model is the best model and its feature parameters are good predictors of prostate disease. The prediction results of the prostate cancer probability model based on the segmented line model were in good agreement with histopathologic results: 90.4% for the total agreement rate, 60% for malignant, and 97.6% for nonmalignant.

Glioma is one of the most toxic tumors due to the special construction of the glial cell and its character of infiltration. The usual procedure for treatment is the surgical resection followed by radiotherapy, with or without chemotherapy. This combined treatment needs the information to precisely define the tumor extension and tumor grading to determine when, where, and what kind of treatment modality should be used. Molecular imaging modalities display advantages in defining the heterogeneous characters and histological grade. We described how the ratios of Cho/NAA and Lac/NAA measured by magnetic resonance spectroscopy imaging (MRSI) could be used to define the cancer cell distribution in tissue, tumor burden, and malignancy, and the results conformed with the histological data; a sample compared with normal subject is shown in Figure 8 [31].

Molecular Probe

Development of Fluorogenic Probes

We have developed two new fluorogenic probes: TaqMan-molecular beacon (TaqMan-MB) and duplex probes. TaqMan-MB is a new oligonucleotide fluorogenic probe, possesses a stem-hairpin structure as seen in conventional molecular beacons, and can be cleaved during polymerized chain reaction (PCR) as conventional TaqMan probes. The presence of a stem-hairpin structure makes the probe have a much lower background level than the conventional TaqMan probes. The cleavage behavior during PCR makes the probe give a much higher fluorescence signal than conventional molecular beacons [32].

In the developed duplex probes, two single-labeled oligonucleotide probes are used instead of conventional dual-labeled probes. In the absence of a target, the two single-labeled probes anneal to each other, the fluorophore labeled at one probe is in proximity to the quencher labeled at the other probe, and fluorescence is quenched. In the presence of a target, one of the two single-labeled probes anneals to the target and causes the fluorophore and quencher to move away from each other, and the fluorescence is switched on. To ensure the disassociation of the duplex formed by the two single-labeled probes, base mismatch is presented between the two probes or the two probes have different lengths. Compared with dual-labeled probes, single-labeled ones have the advantages of lower expense and ease of design, synthesis, and purification.

Detection of Telomerase Activity Using Specific Fluorogenic Probes

Two novel methods have been developed for the specific detection of telomerase activity, in which telomere sequence-specific probes, such as duplex scorpion primers or molecular beacons [33], were used. The use of telomere sequence-specific probes significantly overcame the drawback of low detection specificity in the conventional telomerase activity

detection method, eliminating the effect of nonspecific PCR products, such as primer-dimmer.

Fluorescence Nanoparticles as Molecular Probes

Quantum dots (QDs) (semiconductor nanocrystals) are generally composed of II–VI and III–V elements. They own excellent optical properties, such as broad excitation spectrum, narrow emission spectrum, precise tunability of their emission peak, longer fluorescence lifetime, and negligible photobleaching. Recently, we have prepared several kinds of QDs and evaluated their potential as molecular probes.

The thioglycolic acid-functionalized cadmium telluride (CdTe) QDs in aqueous solution were synthesized using safe and low-cost inorganic salts as precursors and were employed to probe lysozyme by the resonance light-scattering technique. A fluorescence resonance energy transfer (FRET) system was established between CdTe QDs (donor) and butyl-rhodamine B (acceptor) in the presence of cetyltrimethylammonium bromide (CTMAB). CTMAB micelles formed in water reduced the distance between the donor and the acceptor significantly and thus improved the FRET efficiency, which resulted in an obvious fluorescence enhancement of the acceptor.

Water-soluble CdHgTe nanoparticles (NPs) with the emission in the near-infrared regions were prepared in aqueous solution by using safe and low-cost inorganic salts as precursors. A novel method for the determination of proteins with CdHgTe NPs as a near-infrared fluorescence (693 nm) probe was developed based on the quenching of the fluorescence of CdHgTe NPs in the presence of proteins.

CdSe nanoparticles capped by CdS were synthesized in the aqueous solution at room temperature using cysteine (Cys) as the stabilizer. Fluorescence spectra were used to probe the effect of time, pH, quantity of shell, adding rate of shell precursors, and the quantity of Cys on the spectral characterization of CdSe/CdS.

Biological Application

Regulation of Cardiac Growth by the Akt

Molecular imaging, a rapidly emerging and developing discipline, is defined as the visual representation, characterization, and quantification of biological processes at the cellular and molecular levels within intact living organisms such as the cellular and molecular pathway and in vivo mechanism of disease, gene function, and pharmacon selection. Optical imaging, a branch of molecular imaging, can be divided into FMT and BLT. Now, molecular imaging instruments that are developing or have been developed so far need standardized protocols for the evaluation of their efficiency. We have established some cell lines and transgenic mice, which were stably cotransfected with some reporter genes, so the FMT can be implemented simultaneously with BLT. We also constructed two plasmids, which ligated a functional gene to a reporter gene controlled by a tissue-specific gene promoter. The plasmid was transfected into the embryonic stem cells and generated a transgenic mouse.

Akt (also named protein kinase B) plays a critical role in a variety of stimuli and effectors relevant to cardiac function in normal and diseased hearts. Numerous evidence shows that Akt controls the heart size. Several groups have also reported that overexpression of the activated form of Akt1 or Akt3 in the heart under the control of mouse α-myosin heavy chain promoter disarranged the heart growth and induced cardiac hypertrophy [34], [35]. However, Akt3 is required to promote cardiac growth and attenuate contractility in response to pathological growth stimuli (pressure overload) [36]. Akt2 knockout mice exhibit normal cardiac growth in response to pressure overload. Akt2 predominantly regulates cardiac glucose metabolism but has little impact on cardiac growth control. Akt1 regulates the growth and survival of the heart, but the precise role of Akt1 in embryonic heart growth needs to be examined in vivo.

To examine the effects of Akt activation in the heart development, we have developed transgenic mice with cardiac-specific overexpression of constitutively active Akt. The Akt cDNA was subcloned and controlled by murine myosin light chain 2v promoter, and coexpressed with the DsRed reporter gene. The transgenic mouse was developed through oocyte injection. Positive founders were identified by Southern blotting. We can image, in real time, the fluorescent heart growing in live mice. The whole-body optical imaging system is external and noninvasive and affords unprecedented continuous visual monitoring of heart growth with overexpression of Akt1. It will provide a new in vivo

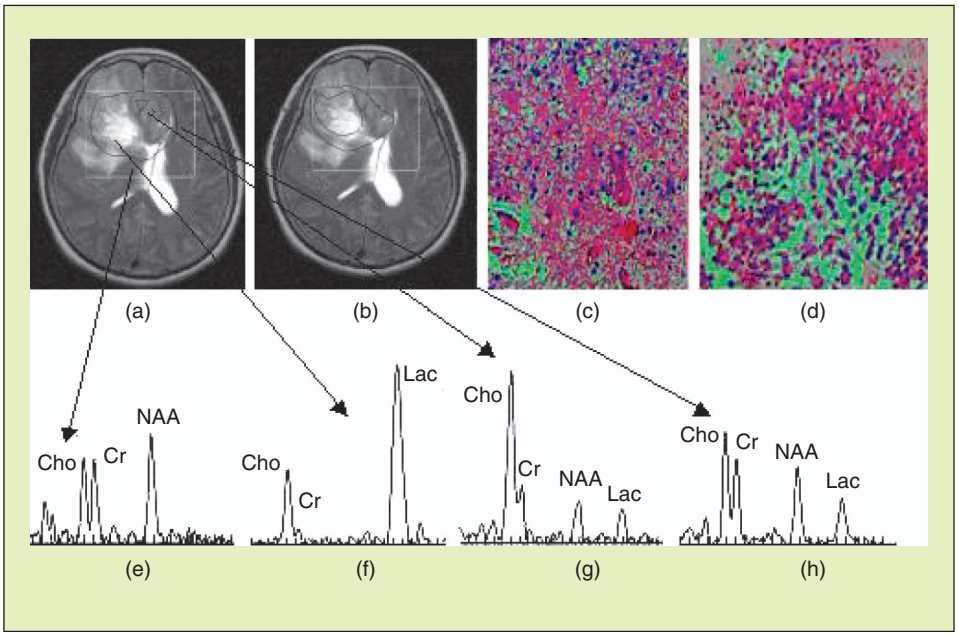

Fig. 8. (a) and (b) Examples of MRIS of a 56-year-old female patient diagnosed as Grade 4 glioma, showing the tumor boundary (indicated by outer black line) and the high metabolism rate area (indicated by inner black line). (c) and (d) The histological results of biopsy samples from the two black line circled areas. (e)–(h) The spectroscopy from different areas indicated by arrows (31).

imaging platform for researching the effect of Akt1 on the heart development.

In Vivo Visualization of Stem Cell Survival, Proliferation, and Migration After Cardiac Delivery

The in vivo cardiac differentiation and functional effects of unmodified adult bone marrow mesenchymal stem cells (BMSCs) after myocardial infarction (MI) is controversial. Our previous results suggest that hypergravity promotes the cardiomyogenic differentiation of BMSCs, and ex vivo pretreatment of BMSCs using hypergravity and 5-Aza will lead to cardiomyogenic specification and result in superior biological and functional effects on cardiac regeneration of infarcted myocardium.

Stem cell therapy offers exciting promises for cardiac regeneration. Yet, currently, we know very little about stem cell behavior in vivo. To understand the fate of stem cells in vivo, imaging techniques have recently been proposed and evaluated in a limited number of cell-delivery models. BMSCs were marked with DsRed reporter gene and specified into a cardiac lineage by adding 5-Aza and hypergravity for three days and then injected into the rat with the MI model, generated by ligation of the coronary artery. We can image the transplanted rat heart noninvasively and accurately monitor cell survival, proliferation, and migration. This imaging platform will have broad applications for basic research and clinical studies on stem cell therapy.

Conclusions

In this article, we reported the progress of our research in molecular imaging. Nevertheless, there are critical challenges in the area that still need to be addressed. Improving the image quality in all modalities is one of the urgent tasks. Developing a high-quality contrast agent is crucial in our further research. Attempts to integrate molecular imaging studies are difficult and time consuming. The field is full of opportunities for us to make significant contributions that will construct the framework in molecular imaging study.

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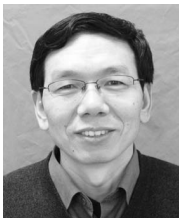

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