Bioluminescence Tomography Imaging *In Vivo*: Recent Advances

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***Abstract*—We review the current state-of-the-art of bioluminescence tomography (BLT) imaging, which is an emerging technique for monitoring and assessment of biological processes *in vivo*. The aim of BLT is to reconstruct 3-D distribution of the internal bioluminescent source using boundary measurements acquired by a BLT imaging system. Thus, BLT becomes a task of solving an inverse problem with an appropriate photon propagation model. In this paper, we discuss recent advances in models of photon transport, and review in detail the current techniques for BLT reconstructions. Specifically, we consider the reconstruction algorithms based on the permissible source region strategy, and multispectral and regularization techniques. The progress in the BLT imaging system is also briefly introduced. Finally, future challenges are also discussed.**

***Index Terms*—Bioluminescence tomography (BLT), light propagation, molecular imaging, multimodality fusion, optical tomography.**

I. Introduction

BIOLUMINESCENCE imaging (BLI) is a newly noninvasive and cost-effective optical molecular imaging technique that uses luminescent imaging probes as imaging contrast to visual monitoring and assessment of biological events in small living animals at cellular and molecular levels prior to the appearance of macroscopic tissue changes [1]–[7]. Over the past several years, the use of BLI for the applications in cancer research and drug development has been steadily growing [5], [6], [8]. Since bioluminescence, the action of luciferases on their substrates, releases light continually, which precludes the use of time-resolved methods, but the absence of autoluminescence in mammalian tissues results in very high signal-to-noise ratio (SNR), yielding very sensitive measurements as compared with another imaging technique, fluorescence molecular imaging (FMI) [9], [10].

However, 2-D bioluminescent images are incapable of providing depth information of the bioluminescent source inside tissue due to strong light scattering [2], [11]. In contrast, the aim of bioluminescence tomography (BLT) is to recover the spatial distribution of the bioluminescent source based on the photons detected on the surface of the body by a highly sensitive charged-coupled device (CCD) camera coupled with an image reconstruction algorithm [11]. Due to the strong absorption and scattering of the biological tissues, bioluminescent photons can travel only a few millimeters, which limits this application mainly to preclinical imaging [12], [13]. However, on the preclinical level, the high sensitivity has made BLT even more popular than positron emission tomography (PET) in oncology, gene expression, and *in vivo* stem cell tracking [1], [14], [15]. The process of BLT mainly contains the following four steps [16], [17]:

1) Acquire 2-D bioluminescent images in single- or mutispectral bands by the BLT imaging system.
2) Map the previously acquired images onto the surface of the small animal.
3) Solve the forward problem and establish the relation between the unknown source and the boundary measurements.
4) Solve the inverse problem to reconstruct the source distribution by minimizing the difference between the simulated and measured data.

In step 1, highly sensitive imaging systems are required because the power of bioluminescent photons which escape the tissues and reach the mouse body surface is weak. For example, for a bioluminescent source with 1 mm^3 cells, the power of the bioluminescent source is between nW and pW [18]. In addition, the noncontact detection scheme is usually employed to obtain the large boundary datasets to improve the spatial resolution [19]–[24]. Therefore, in step 2, the acquired 2-D images need to be mapped on the surface of the small animal based on free-space theory before BLT reconstructions [19]. To recover the bioluminescent source, step 3 is the core technique because the inverse problem is dependent on the accuracy and efficiency

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to solve the forward problem that describes the light propagation in tissues [25]. The forward problem can be mathematically formulated as the radiative transport equation (RTE) [26]. However, the RTE is computationally expensive [26]; therefore, a computationally feasible forward model is required. The inverse problem associated with the reconstruction of the source distribution is a very challenging ill-posedness problem [11]. There are no direct methods for the solution of this problem, and thus it is typically formulated as a minimization problem such as the regularized output least squares [16]. Large efforts should be devoted to step 4, which determines the potential of BLT in practical applications [4].

Wang's group published the first journal paper about BLT [11]. In the paper, the uniqueness of the solution for BLT was proven under practical constraints and a theoretical basis for BLT was also established [11]. Since the publication of the paper, the number of publications on BLT has greatly increased and many research groups have been devoted to developing BLT imaging systems and BLT reconstruction algorithms. Therefore, the development of the technique has been significantly motivated.

Recent developments of BLT have followed four major aspects:

1) Develop an accurate and computationally effective light propagation model to describe photon scattering and absorption in tissues.
2) Develop fast, robust, and quantitative BLT reconstruction algorithms with promising results.
3) Combine various individual modalities such as computed tomography (CT), magnetic resonance imaging (MRI), or diffuse optical tomography (DOT) to build multimodality imaging systems.
4) Apply BLT systems and reconstruction algorithms for biological processes.

Considering that it is not possible to cover the entire BLT field in one article, this paper will mainly focus on the progress which has been made in the first three aspects. The rest of the paper is organized as follows. In Sections II and III, we introduce the models of light propagation in tissue and computational methods in BLT, respectively. In Section IV, recent advances in BLT reconstruction algorithms are reviewed. Section V presents multimodality fusion algorithms and Section VI introduces some of BLT systems developed in academia and in industry. Finally, the future challenges are discussed and conclusions are made.

II. Modeling Light Propagation in Tissues

Before BLT reconstructions are performed, a model of photon transport in biological tissues is required. The photon propagation in biological tissues can be accurately modeled by the RTE [25]–[30]:

$$\left(\frac{1}{c}\frac{\partial}{\partial t} + \hat{s}\cdot\nabla + \mu_a(r) + \mu_s(r)\right)\phi(r,\hat{s},t) = q(r,\hat{s},t) + \mu_s(r)\oint_{s^2}\Theta(\hat{s},\hat{s}')\phi(r,\hat{s},t)d\hat{s}' \quad (1)$$

where $\phi(r,\hat{s},t)$ is the radiance at the point r in the direction $\hat{s}$ at time t. μ_a and μ_s are the absorption and scattering coefficients respectively, c is the speed of light in the tissues. $\Theta(\hat{s},\hat{s}')$ is the scattering phase function, which gives the probability of photon scattering from direction $\hat{s}$ to $\hat{s}'$. $q(r,\hat{s},t)$ is the light source at r at time t travelling in direction $\hat{s}$. Since the bioluminescent source intensity is generally assumed to be stable when photons are collected, the time term t can be omitted [11].

However, a steady-RTE is a complicated integro-differential equation for the radiance ϕ dependent on five variables in the 3-D case, and exact analytical solutions of the RTE are difficult to be obtained because the biological tissues are of irregular shapes [11]. Even though analytical solutions of the RTE exist for simple tissue geometries with uniform optical tissue parameters [26], [28], it requires large computational time and memory cost. Therefore, the development of computationally efficient light propagation models but with higher accurate solutions is essential [30].

High-order approximations to the RTE have been proposed to yield an exact solution and are more easily solved and less computationally expensive for such complex problems compared with the RTE [31]. These approximations include the discrete ordinates (S_N) method [32]–[34], the spherical harmonics (P_N) method [25], [33], [34], and the simplified spherical harmonics (SP_N) method [31]. With these approximations, the RTE equation can be transformed into algebraic systems of coupled differential equations. For the S_N method, $N(N+2)$ coupled equations are obtained, where N is the number of direction cosines [26], [29]. The P_N approximation requires $(N+1)^2$ equations to be solved, where N is the number of Legendre polynomials [26], [29], [35]. For the SP_N approximation, only $(N+1)/2$ equations are required and the SP_N solution is obtained faster than the solution using the S_N or P_N methods by several orders of magnitude [31]. Therefore, the SP_N approximation has attracted particular interest for BLT recently [36]–[40].

In practice, due to the computational burden for solving the high-order approximations, diffusion approximation (DA), a lower-order P_N approximation, is the most popular light propagation model in BLT [16], [17], [41]–[50]. The steady-state DA can be expressed as

$$-\nabla\cdot D(r)\nabla\Phi(r) + \mu_a\Phi(r) = q(r) \quad (2)$$

where $D(r)$ is the diffusion coefficient and $\Phi(r)$ is the photon fluence rate. Nevertheless, the DA model is only valid in the region where light scattering dominates light absorption ($\mu_a \ll \mu_s'$), where μ_s' is the reduced scattering coefficient. Moreover, the DA model could not be modeled accurately in the proximity of the light sources and close to the boundaries of the inspected region [51].

Recently, the hybrid model which combines the Monte Carlo (MC) simulation with the DA approximation has been reported [52]. However, it has the disadvantage of requiring a long computation time. A coupled RTE-DA model has also been developed to describe light propagation in tissues [53]–[56]. For the coupled RTE-DA model, the RTE is used to describe light propagation in subdomains where the assumptions of the DA are

not valid, and the DA is used elsewhere. Results demonstrated that the coupled RTE-DA model could obtain almost the same accuracy as the RTE but with a lower computational burden.

III. Computational Methods

The light propagation model can be solved through stochastic, analytical and numerical methods. One of the most common stochastic methods is the MC approach [57]. The MC method can accurately describe light propagation and thus can be taken as the gold standard [57]–[62]. However, the MC method has a long computational time due to the calculations of a large number of photon propagation. Recent research illustrated that parallel implementation based on graphic processing units (GPU) can dramatically speed up the process of the MC simulation [61], [63]. Despite these advances, the MC method is not practical even on a current high-end desktop workstation and is usually used as a reference method for other methods.

The analytical solutions of the RTE and the DA have the advantage of being computationally faster but suffer from the disadvantage of being limited to certain specific geometries with nearly homogeneous interior values [32], [64], [65]. Therefore, numerical methods are usually used to solve the RTE and the DA models. One merit of numerical methods is able to deal with complex heterogeneous small animals, which can facilitate the combination of BLT with practical applications [29].

Because the finite element method (FEM) can be applied to any geometry, FEM is the natural choice for optical tomography including BLT [27], [66]–[69]. Besides the FEM, the finite difference method (FDM) [70]–[72], the finite volume method (FVM) [73], the boundary element method (BEM) [74]–[76], and the meshless method (MM) [77] are also applied to solve the RTE and the DA equations. Due to the heavy computational and memory requirements of meshes, adaptive and multigrid techniques have been developed within the FEM [44], [45], [78]–[83] and the FVM approaches [84].

In conclusion, with the numerical methods, the forward problem is generally posed as a vector value function $f(q)$, which represents the exact value of the outgoing flux for the assumed value of the source density q.

IV. BLT Reconstruction Algorithm

The BLT reconstruction problem is to determine the bioluminescent source distribution from measured light intensities on the surface of small animals, which is a typically inverse problem. Unlike X-ray CT which deals only with nonscattered or single-scattered photons, multiple scattering of photons that propagate through biological tissues needs to be taken into account in BLT [11]. As a result, a major difficulty in determining the bioluminescent source distribution is imposed by multiple scattering of photons, which leads to the ill-posedness of the BLT problem [11]. Meanwhile, the limited number of boundary measurements compared to the number of unknown bioluminescent sources makes the BLT problem ill-conditioned.

To reduce the ill-posedness of BLT, it is necessary to incorporate multiple types of *a priori* information into the reconstruction process [11]. The commonly used *a priori* information is the permissible source region, which constrains the region where the unknown sources possibly exist [17]. Cong *et al.* first proposed *a priori* permissible source region to reduce the ill-posedness of BLT [17], and promising results were obtained [17], [44]. However, the *a priori* permissible source region is inferred according to the surface light power distribution and the heterogeneous structure of the small animal, and it is not always reliable to infer such a region especially when deeper and/or multiple sources exist [45]. Lv *et al.* developed *a posteriori* permissible source region, and its feasibility to reduce the ill-posedness was validated using a virtual mouse phantom [45]. Feng *et al.* proposed an optimal permissible source region and results demonstrated that not only could the ill-posedness be reduced but also the computational efficiency could also be improved [47]. In addition, adaptive modifications of the permissible source region were also performed to improve the BLT reconstructions [85], [86].

An available method to reduce the ill-posedness is multispectral measurements, which increase the measured data for BLT [36], [41], [42], [45]–[49], [72], [87], [88]. The firefly luciferase emission spectrum ranges from 500 nm to 800 nm [89], [90]. In general, 2–6 wavelengths are adequate for BLT reconstructions. For example, a sphere-like source was accurately localized with two wavelength data (650 nm and 700 nm) [91]. Five different wavelengths (580–660 nm; 20 nm separation) were used to reconstruct a luciferase reporter system [72]. Reconstructed results using six wavelengths (600–650 nm; 10 nm separation) were also reported [42]. To date, the importance of multispectral measurements has been realized and a general consensus is made that nonspectrally resolved BLT results in a nonunique problem [42]. Han *et al.* have analyzed the theoretical properties of the multispectral BLT including the solution existence, uniqueness, and continuous dependence on the data and established a mathematical framework for studies of multispectral BLT [92]. Numerical simulation, phantom, and *in vivo* studies show that multispectral approaches can significantly improve the accuracy and stability of BLT reconstructions [41], [42], [45]–[47], [72], [87]. However, the use of multispectral data increases the problem size by the number of spectral bins, which seriously affects the computational efficiency of BLT reconstructions [45], [46]. Ahn *et al.* investigated fast iteration algorithms for multispectral BLT and concluded that the on-the-fly approach could lead to substantial reductions in total cost when combined with a rapidly converging iterative algorithm [46].

Note that the BLT reconstruction is underdetermined and very sensitive to noise in the measurement; therefore, the BLT reconstruction is generally converted into a least-square problem with a regularization term after incorporating the permissible source region information and multispectral information [11], [16], [93]–[95]

$$\min\Theta(q) = \|\Phi^{meas} - f(q)\|^2 + \lambda J(q) \tag{3}$$

where Φ^{meas} is the boundary measured data, $J(q)$ represents the regularization term, and λ denotes the regularization parameter. When $J(\cdot) = \|s\|_2^2$, the above regularized problem becomes the popular Tikhonov regularization, which inherently provides smoothed solutions and therefore offers compromised

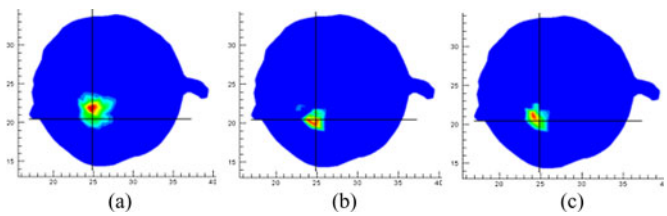

Fig. 1. (a)–(c) *In vivo* reconstruction results with l_2, l_1, and TV regularizaitons, respectively [103].

accuracy in localizing bioluminescent sources [49]. When we use bioluminescence probes to observe the specified biological events of interest, the domain of the light source is relatively small and sparse compared with the entire small animal. Consequently, the sparse prior information can be used to recover the source distribution. When $J(s) = \|s\|_1$, equation (3) becomes a sparsity-inducing regularized problem, i.e., l_1 regularization, which has received an increasing amount of attention in BLT [39], [40], [49], [96], [97]. Numerical simulation, phantom and *in vivo* examples demonstrated that l_1 regularization allows high quality images to be reconstructed from a small amount of measurements [39], [49], [97]. However, l_1 regularized problems can sparsify the bioluminescent source distribution [40]. For BLT experiments, the bioluminescent source density is generally assumed to be stable when photons are collected [72]; therefore, the source distribution can be taken as a nearly piecewise-constant. As a result, total variation (TV) regularization is a particularly attractive and natural choice for piecewise-constant source distribution in BLT. However, TV regularization is one of the most difficult optimizations to be solved computationally due to its nondifferentiability, which prevents TV methods from the application in practice. Recently, Osher and his collaborators developed a split Bregman method [98]–[102], which provides a new avenue to solve TV regularization. *In vivo* results demonstrated that TV regularization solved by the split Bregman method can provide better regularization quality over l_2 and l_1 regularizations (Fig. 1) [103].

In fact, for regularization-based BLT reconstructions, the regularization parameter controls the regularized solution, therefore plays an important role in BLT reconstructions. However, selecting a reasonably good regularization parameter is very difficult and time-consuming with a high computational cost. To avoid this, several strategies for choosing regularization parameters have suggested, for instance, the L-curve method [104], [105], the cross-validation method [106], [107], and the discrepancy principle [108], [109]. The L-curve method has been extensively analyzed and applied in different areas. However, due to the high ill-posedness of BLT, the corner corresponding to maximum curvature on the L-curve is difficult to determine [91]. The generalized cross-validation method is based on *a priori* knowledge of a structure of the input error, which means the errors in the measurement data can be considered to be white noise [110]. However, the noise is unknown for BLT experiments. The discrepancy principle is an *a posteriori* strategy for choosing a regularization parameter which requires an accurate estimate

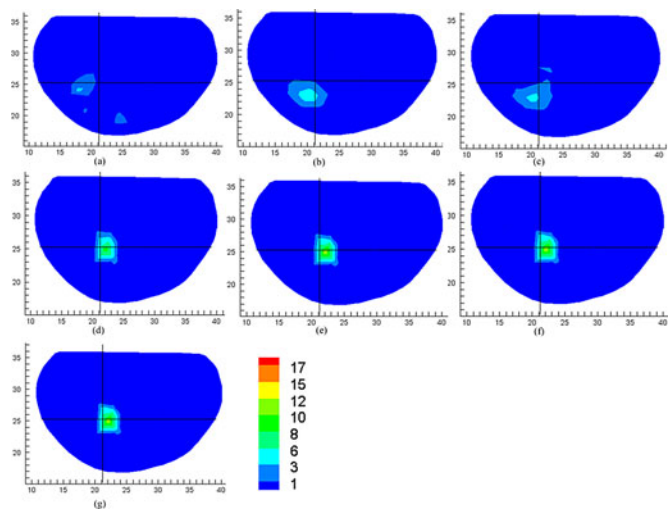

Fig. 2. Evolution results of iteratively estimating the regularization parameter. (a)–(g) The results at the kth iteration. The point where the two lines intersect denotes the central position of the actual source [91].

of the noise level. However, the noise level is unavailable in practical BLT experiments [111]. Recently, Camorro-Servent *et al.* studied the feasibility and effectiveness of the U-curve to choose the regularization parameter for fluorescence diffuse optical tomography (FDOT) [112], which needs to be further analyzed when applied to BLT. Feng *et al.* investigated a model function method to automatically choose the regularization parameter for BLT and promising results were obtained [91]. The basic idea is to approximate the minimum of the regularized function by a model function with a regularization parameter as a variable. Actually, the algorithm is an iterative algorithm. Fig. 2 shows an example of the algorithm to iteratively estimate the regularization parameter [91].

In addition to regularized-based BLT reconstructions, iterative reconstruction algorithms are attractive due to their regularization property [113], [114]. These algorithms impose regularization to the BLT problem by setting iteration numbers without choosing the regularization parameter. Jiang *et al.* used an expectation maximization (EM) algorithm to reconstruct the bioluminescent source; however, the convergence of EM has not been established [113]. The Bayesian approach applied to BLT was also reported [114]. The Bayesian approach provides a natural framework to incorporate multiple types of *a priori* information and localizes the source accurately (Fig. 3).

Furthermore, stochastic methodology was also introduced to perform the BLT reconstruction [115]. In this algorithm, stochastic and evolution mechanisms play important roles, where the initial source distribution pool is generated randomly, and the alteration is randomly selected (with bias) [115]. 2-D numerical phantom results were used to demonstrate the feasibility. Nevertheless, more testing with 3-D *in vivo* examples is needed to verify the performance of this algorithm.

V. Multimodality Fusion

Each imaging modality has its own advantages and limitations, and BLT is no exception. Strictly speaking, BLT is a mode

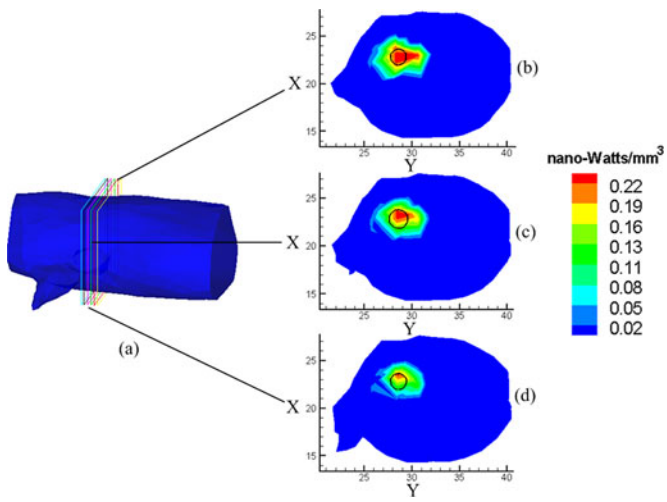

Fig. 3. BLT reconstruction with the Bayesian approach. (a) The 3-D rendering of the reconstructed results. (b)–(d) Three different slices of the reconstruction which are selected to illustrate the result in more detail [114].

of functional imaging, and does not provide structural information [29]. However, for *in vivo* small animal imaging, the internal organs are different. Therefore, photon scattering and attenuation varies according to the organs and tissues through which they penetrate [2], [9]. The highly optically heterogeneous tissues aggravate the ill-posedness of BLT [11]. Alexandrakis *et al.* [89] pointed out that the localization of the bioluminescent source was not accurate with the assumption that the whole small animal was homogeneous. The effects of homogeneous tissue on localization and quantification of BLT were further evaluated [37], [116], [117].

Meanwhile, highly curving boundary characteristics of the internal organs further make BLT reconstructions to be particularly challenging [11]. To overcome the problem, the use of anatomical information from CT or MRI has been demonstrated as *a priori* information to greatly improve BLT [43], [72], [114], [118]. These methods make assumptions on the relationship between tissue structures and optical properties for a given wavelength. Each of the tissues is assigned appropriate optical properties calculated using classic formulations [89] or using a database of the optical properties compiled for this purpose [11]. Note that the inaccuracy of optical parameters could lead to poor reconstructions even if the heterogeneous characteristic was considered [43], [45]. For example, in the case of 20% errors of the optical parameters, the difference in the reconstructed light source position is over 3 mm, and the errors in the estimated source power are over 100% [43]. Therefore, it is critically important to determine *in vivo* optical properties as accurately as possible. Fortunately, the accurate optical parameters can be obtained by DOT. Experimental evidence shows that the quantitative accuracy of BLT could be significantly improved by combining DOT [119].

Wang *et al.* [18] showed a trimodality fusion sketch map for BLT, including CT, DOT, and BLT. In such a multimodality approach, CT provides the structural information of the internal organs, DOT reveals functional information about the tissues (i.e., optical parameters), and BLT indicates the quantitative molecular information of specific molecules. Since each of the different image modalities has a unique advantage, the combination of multiple modalities can provide complementary information and improved results should be obtained.

The fusion of BLT and nuclide imaging, such as PET and SPECT, is exciting because of the opportunity to obtain complementary data from both contrast mechanisms [121]. Compared with nuclide imaging, BLT is easy to operate, and it has much better temporal resolution. For instance, a PET scanning often takes several tens of minutes, while a few minutes for BLT. Therefore, the combination of nuclide imaging and BLT can overcome the drawback of nuclide imaging in temporal resolution, and it benefits to dynamically monitor the interesting tracers or markers [120]. In addition, nuclide imaging can be used to cross-validate BLT results [121]. For example, Lu *et al.* used PET imaging to validate the effectiveness of BLT [122].

VI. BLT Imaging System

The task of BLT system is to acquire 2-D bioluminescent images used for BLT reconstructions. For a BLT system, it mainly includes a CCD camera, a lens, a rotation mouse stage, and a light enclosure box. In such a system, the CCD camera is the main ingredient. For selection of the CCD camera, high sensitivity is essential because the escaping light is very weak. Meanwhile, the quantum efficiency is top in the wavelength range of bioluminescence. In the section, some of BLT systems developed in academia and in industry are briefly introduced.

The first BLT prototype system in academia was conceived and built by Wang's group [123]. The system uses the noncontact detection scheme to obtain a large amount of boundary measurements to improve the resolution of BLT reconstructions. When acquiring bioluminescent images, the small animal is fixed on a rotation mouse stage in the front of the CCD camera and multiple planar views are acquired by rotating the rotation mouse stage, which is controlled by a computer. Furthermore, they developed a system which was capable of simultaneous multispectral and multiview acquisition of bioluminescent images [124]. The motivation behind this system is that multispectral imaging is particularly attractive for BLT [41], [42], [87], and it will take a long time if multiple views are acquired for each wavelength [123]. The system makes full use of the reflection theory of the planar mirror to realize the simultaneous acquisition of four views. Similarly, a schematic of the mirror set-up for gathering data was also discussed in [41].

The commercial imaging systems are mainly Caliper IVIS series. We will be looking at two systems, IVIS 200 series and 3D series. IVIS 200 series is a single-view dual-modality system, which can be used for fluorescence and bioluminescence imaging [90]. The system uses a group of filters at different wavelengths to gather spectral images and a laser scanning device to provide 3-D surface topography used in the localization of internal sources. However, the system does not reconstruct the source distribution. In contrast, 3D series is a 3-D commercial system, which can acquire eight views without rotating the animal or the CCD camera [125]. In this system, the small

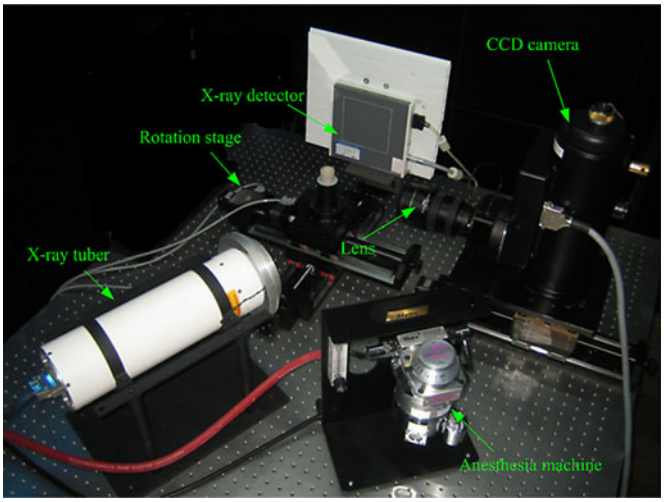

Fig. 4. Prototype BLT/CT dual modality imaging system [127].

animal is placed on a flat transparent glass plate, and a mirror system rotates around the animal to capture eight views without adjusting the posture of the specimen and rotating the CCD camera. Multispectral capability is also possible for 3D series, but it needs to capture bioluminescent images and spectral channels one by one. In addition, the system does not consider the heterogeneous structure of internal organs of the small animal.

Recent studies show that the quantitative accuracy of BLT benefits from the multimodality fusion methods, which facilitate the development of multimodality system. Fig. 4 is a dual modality prototype system constructed by our group [120], [126], [127], which fuses the BLT and CT systems. It can provide multiview multispectral bioluminescent images and high resolution anatomical images of the internal organs. In addition, Chatzioannou's group developed a hardware fusion system (Optical-PET) [89]. In the system, a single detector is able to detect bioluminescent photons and high-energy gamma-rays. This unique advantage of the Optical-PET system will enable direct comparison of how well the BLT and PET modalities can localize and how sensitively they can detect emission sources existing at different tissue depths [89]. Currently, the multimodality fusion system is evolving at a fast pace.

VII. Future Challenges and Conclusion

The field of BLT has made significant advances in the imaging system, light propagation model and reconstruction algorithm; however, the potential of BLT has not been fully explored. Improvements are still required in qualitative and quantitative accuracy.

Numerical accuracy and computational speed will determine the success of BLT in preclinical applications. However, developing fast and robust numerical solution techniques is a mathematically and computationally challenging task. The ill-posedness of BLT is an open question which will require continued effort. Although the use of high-order approximations of the RTE improves the accuracy of BLT reconstructions, the memory requirement for the numerical solutions is much larger. As a result, a bulk of the computation time is consumed. In addition, the computational burden is increased remarkably due to the use of the multiview multispectral noncontact detection mode. Thus, it is highly desirable to develop computationally efficient reconstruction algorithms for the RTE and multiview multispectral detection scheme. For regularized-based BLT reconstructions, the choice of the regularization parameter has a profound effect on the reconstructed images. Automatic methods for selecting the regularization parameter with the fast global convergence need to be developed further.

It was recognized that the stand-alone BLT imaging system could not provide a complete picture of the function and structure of tissues [128], [129]. In contrast, multimodality combines the advantages of each modality; therefore, it is essential to fuse other imaging modalities to develop BLT system. Note that the current multimodality fusion techniques are mostly based on reconstruction algorithm fusion, or named software fusion. Reconstruction algorithm fusion approach provides greater flexibility than physically integrated multimodality systems, thereby removing the requirements of the other imaging modality. However, data fusion that utilizes the high-quality data and versatility of the stand-alone imaging systems needs to be developed further.

In conclusion, our intention here is to present an overview of the recent advances in methods and systems developed for BLT. BLT is a complex and fast-moving field and has a promising future in biological applications.

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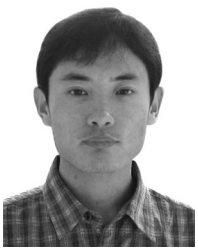

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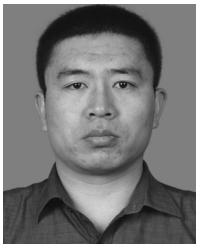

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