In Vivo Diffuse Optical Tomography and Fluorescence Molecular Tomography

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ABSTRACT
Diffuse optical tomography (DOT) and fluorescence molecular tomography (FMT) are two attractive imaging techniques for *in vivo* physiological and psychological research. They have distinct advantages such as non-invasiveness, non-ionizing radiation, high sensitivity and longitudinal monitoring. This paper reviews the key components of DOT and FMT. Light propagation model, mathematical reconstruction algorithm, imaging instrumentation and medical applications are included. Future challenges and perspective on optical tomography are discussed.

Keywords: Diffuse Optical Tomography; Fluorescence Molecular Tomography; clinical and preclinical application

1. INTRODUCTION
Optical imaging depends on the interaction between light and biological tissue. It uses multiple physical parameters to produce contrast mechanism. Compared with other functional and physiological imaging, optical approaches have distinct advantages such as non-invasiveness, non-ionizing radiation, high sensitivity and longitudinal monitoring. Visualization with light is among the most common practices in today's academic and clinical research [1].

The ability of light to penetrate tissue was first exploited by Bright as early as 1831 [2]. For light in the visible spectrum, penetration depth is limited by strong absorption of hemoglobin and other molecules. In 1977, Jobsis found the 'near-infrared window' between 700 nm and 1000 nm [3]. At these wavelengths, absorption by haemoglobin, lipid, and water is minimum. Near-infrared light can penetrate up to several centimeters in biological tissue [4].

Oxy-haemoglobin and deoxy-haemoglobin are two main absorption molecules in the near-infrared spectrum [5]. They are indicators of tissue's blood volume and oxygenation. To monitor these physiological signatures, near-infrared spectroscopy (NIRS) was

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developed [6–8]. This technique uses wavelength scanning at a single site. In order to get spatial information, scientists combined multiple NIRS measurements and made the first images of brain [9]. Up to now, many imaging techniques have been developed to produce spatially resolved information. Generally speaking, there are two kinds of techniques, i.e., topography and tomography. The former refers to methods that produce two-dimensional (2D) or planar images of subjects. It has intrinsic inability to quantify or detect deep targets due to the non-linear dependence of light on depth [10]. Diffuse optical tomography (DOT), a three-dimensional (3D) tomographic technique, was developed to overcome the limitation [11].

DOT models the light propagation in tissue by taking the highly scattered photons into account [12]. It illuminates the tissue with near-infrared light from an array of sources and observes the multiply-scattered light using an array of detectors. By means of an inversion scheme, DOT reconstructs the tissue properties (absorption and scattering coefficients) that have close correlation with oxy- and deoxy-haemoglobin concentration blood saturation. Since carcinogenesis features like angiogenesis and hypoxia are often associated with blood saturation, DOT can reveal functional or pathological disorders of living subjects [13].

Traditional DOT is based on absorption and scattering coefficients. The intrinsic contrast mechanism suffers from low sensitivity and lacks specificity to targeted cells. Extrinsically administered molecules are employed to enhance the contrast [14]. These reagents often aggregate in the tumor region while washed out in the normal ones. Among them, Indocyanine Green (ICG) is the only NIR agent approved by the US Food and Drug Administration (FDA) for human use [15].

Fluorescence molecular tomography (FMT) is another strategy to improve the contrast and detection specificity. It was first put forward by Vasilis *et al*. in 2002 [16]. It shares tomographic principles of DOT, but simultaneously uses optical properties and fluorescence measurements for accurate 3D reconstruction of exogenous probes, such as green fluorescent protein (GFP), red fluorescent protein (RFP), cyanine dyes (Cy5.5, Cy7) and nano-particles [17]. These injected fluorophores accumulate preferentially in diseased tissue. This specificity distribution as well as their different decay properties could be useful to localize tumors [18].

FMT has unique features such as repeatable excitation and emission, *in vivo* multi-target labeling and visualization of specific physiological activity [19]. In addition, the use of fluorophore can also have access to information like pO_2, pH and intracellular calcium concentration [20]. In recent years, FMT has aroused increasing interest among scientists and clinicians [19, 21–23].

This work reviews the key components of DOT and FMT. First, we describe the fundamental principle of DOT, including light propagation model, mathematical algorithm and imaging instrumentation. The current clinical application in optical mammography, infant brain imaging and detection of other tissues are followed. Unlike DOT, most of *in vivo* studies using FMT are conducted on small animals. We present basic theories of FMT in a separate section with the emphasis on its distinctive features and preclinical application. In the end of this article, future challenges and perspective on optical tomography are discussed.

2. FUNDAMENTAL PRINCIPLE OF DOT

2.1. Light Propagation Model

When near-infrared light travels through biological tissue, it will undergo reflection, diffraction, absorption, scattering, etc [24]. Modeling light propagation through tissues is critical for making quantitative optical imaging a feasible endeavor [25, 26].

There are many different models to describe light propagation within tissue [27–30]. Generally, they can be classified into two categories: deterministic and stochastic.

Deterministic models use Maxwell equation to well interpret the interaction between light and medium taking into account scattering, absorption and reflection. But it is too complex to get its analytic solution in practice. In most biological tissues, the effect of scattering dominates. Radiative transfer equation (RTE) is usually chosen to treat photons as elastic particles after ignoring any wave effects [31]. RTE is a conservation formulation describing the change of energy radiance due to changes in energy flow. Its analytical solution is usually scarce and exists only in certain simple and homogeneous cases [32]. When geometries of tissue and the distribution of optical properties are complicated, diffusion equation is favorable. Diffusion approximation is based on the assumption that scattering dominates over absorption and regions of interest are far from sources and detectors [30]. This is generally the case in bulk tissues, but it breaks down in regions near the source, the surface, internal boundaries, as well as in anisotropic and high absorbing or low scattering tissues. In these situations, the higher-order spherical harmonics approximation [33] or RTE-based models [34, 35] may be required.

Stochastic models simulate the trajectories of individual photon that either escapes from the boundary or is absorbed by the tissue. By tracking a sufficient number of photons, physical quantities such as diffuse reflectance can be estimated [36]. The procedures are conceptually simpler to implement and rely on fewer assumptions, but at the expense of computational time. Among them, Monte Carlo (MC) is the most commonly used method [28]. It incorporates Poisson error into the model naturally and simulates the photon migration in both the diffusive and non-diffusive domains [37–39]. In fact, MC is often regarded as the 'golden standard' in diffuse optics [40]. Another statistical approach is the Random walk theory, where photon transport is modeled as a series of steps on a discrete cubic lattice. It is particularly suited to time-domain measurements, and has been used, for example, to quantify the optical properties of a breast tumor [41] and to simulate diffusion in brain extracellular space [42]. More details can be found in [12].

2.2. Reconstruction Algorithm

Photons do not follow straight paths as X-ray does, so the standard back projection in computer tomography (CT) is no longer accurate for image reconstruction. Instead, the model is dictated by the above-mentioned Maxwell equation, radiative transport equation, or the diffusion approximation. Two problems are involved: the forward problem and the inverse problem [43].

The forward problem uses the light transport model to predict the distribution of light in the object under examination. This stage generates a sensitivity matrix (the

Jacobian) that relates the measurements to the internal optical properties. Since scatter is dominant, the forward problem becomes a series of integrals over the entire volume. Arridge first derived the analytical solution using Green's function for different geometries [44] and various modification such as Kirchhoff approximation [45] and regularization theories[46] were proposed. Finite element method (FEM) [12, 47], finite difference method (FDM) [48–50], finite volume method (FVM) [49, 51, 52] and boundary element method (BEM) [53–55] are employed to discrete the continuous partial differential equations (PDE). Among them, FEM is most widely used, because it can represent the inhomogeneous distribution of optical properties in an arbitrary geometry [30, 56].

In the inverse problem, the sensitivity matrix is inverted and the spatial distribution of optical parameters is reconstructed according to the boundary measurements. Since each measurement is sensitive to the whole volume, the inverse problem is often ill-posed. Up to now, many reconstructive techniques have been proposed [30, 57]. For example, Hielscher and Klose proposed an iterative image reconstruction model (MOBIIR) based on the equation of radiative transfer [58, 59]. Davis *et al*. compared the Tikhonov approach with a modified Levenberg-Marquardt formulation [60]. Schweiger *et al*. attempted Gauss-Newton method [61], and Konovalov *et al*. used algebraic reconstruction with post-processing [62]. Generally, these approaches can be categorized into linear reconstruction and non-linear reconstruction [63]. Linear problems use difference data between two neighboring states to quantify images of measured changes, rather than absolute quantitative ones [30]. Nonlinear reconstruction establishes an objective function and repeatedly narrows the gap between predicted data and measurements to update the reconstructed variables [64]. More details of reconstruction algorithm can be found in reference [65].

2.3. Imaging Instrumentation

With regard to excitation-detection manner, there are three types of optical imaging systems: continuous-wave (CW), time-domain (TD), and frequency-domain (FD).

CW mode requires a source that either emits at a constant intensity or is modulated at a low (a few kHz) frequency [63]. The transmitted light is collected to resolve the attenuation. The major advantages of CW system include its compactness and economical hardware as well as optimum signal-to-noise performance. Philips Research Laboratories evaluated a breast tomography system based on CW measurements[66]. Schmitz *et al*. used a CW DOT system, named DYNOT (NIRx Medical technologies, NY) to reveal cyclic hemodynamic changes[67]. Other companies like Imaging Diagnostic Systems Inc. and Advanced Research Technologies Inc. once developed diffuse optical imagers. Nowadays, CW systems have been intensively used in optical tomography [68–71].

TD technology uses a short pulse of light (100 fs~100 ps) to illuminate the medium. The time-of-flight and amplitude of photons are recorded by high-speed electronic instrumentation, such as streak cameras, fast avalanche photodiodes and gated optical image intensifiers [24]. Temporal distribution of photons can be described with

temporal point spread function (TPSF), which extends over several nanoseconds after travelling through several centimeters. For instance, a 32-channel time-resolved system was developed based on time-correlated single-photon counting (TCSPC) technology [67]. Some research was conducted on a custom-made dual-wavelength (670 nm, 785 nm) time-domain optical mammogram instrument [72]. Eda *et al*. built a 64-channel time-resolved optical tomographic imaging system [73]. Other studies using TD systems can be found in [74–76].

FD technology uses modulated light of a modulated intensity at 100 MHz to 1 GHz frequency. Amplitude attenuation and phase shift of diffuse photon density wave (DPDW) are measured by sensitive detectors such as a gain-modulated ICCD [77]. Data obtained at multiple frequencies improve its performance over CW mode and is equivalent to TD data via the inverse Fourier Transform. During the mid-1990s, two companies, Carl Zeiss and Siemens have developed two breast imaging systems based on FD measurements [40]. In 2001, McBride *et al*. reported a FD system for breast imaging using five optical wavelengths and 16 photomultiplier tubes [78]. Recently, Orlova *et al*. have invented an experimental multicolor FD DOT system to visualize neoplastic of breast tissue [79].

It is noted that each mode has its pros and cons. CW system is compact and inexpensive. But it is somewhat difficult to distinguish absorption with scatter. TD and FD setups suffer from low signal-to-noise ratio and complex structures, though their contrast and resolution are higher than CW mode. For more details refer to [40].

3. MEDICAL APPLICATION OF DOT

3.1. Optical Mammography

Breast cancer is among the leading causes of death for women all over the world [80]. The survival chance of breast cancer drops from a rate of about 95% when the lesion is about 0.5 cm in size to a rate of 75% when the cancer is treated at a size of about 2.5 cm [81]. Early detection and treatment is of vital importance for decreasing mortality.

X-ray mammography is the routine method for mass screening of the population. However, relatively large lesion is required to produce detectable contrast. X-ray also causes ionizing radiation and its diagnosis is not satisfactory in premenopausal women. On the other hand, magnetic resonance imaging (MRI) and ultrasound techniques are technically demanding and not suitable for routine inspection [82].

Optical mammography utilizes non-ionizing, low-power near-infrared light to scan the female breast [83]. It measures wavelength-dependent tissue optical absorption coefficient, which in turn provides the access to blood dynamics, total hemoglobin concentration (THC) and tissue blood oxygen saturation (StO_2) [84]. Since tumors are often associated with increased vascularization [85], the contrast in growing tumors is physiologically plausible for optical imaging. The noninvasive nature of NIR and its potential of high specificity are also attractive for human breast imaging.

Optical techniques for imaging the breast can be traced back to the late 1920's [86]. Cutler presented the first clinical results using transillumination as an aid in the diagnosis of breast lesions. In the past two decades, optical techniques received

renewed attention owing to the development of accurate mathematic models and reconstruction strategies [87]. Especially in recent years, diffuse optical tomography has been intensively applied in 3D breast imaging [82, 88–90].

Generally, optical mammography features either a compressed or an uncompressed system, as shown in Figure 1. The former measures optical properties using parallel plate geometry. The breast is compressed either between two parallel arrays of sources and detectors, or between two plates over which individual sources and detectors are scanned in a rectilinear manner. Vasilis and his colleagues at the Massachusetts General Hospital and Harvard Medical School first used this configuration to obtain images of a 70-year-old patient with a 0.8 cm infiltrating ductal carcinoma [93]. ICG was used as the contrast agent and optical results were validated by simultaneous MRI images. Later, they integrated optical tomography into a breast X-ray tomosynthesis system and measured 18 patients, aged 49 to 79, all of whom were scheduled for biopsy for suspicious findings [91]. Optical images were reconstructed for both benign and malignant lesions, revealing optical contrast close to the location of the lesions shown in the corresponding X-ray images. They also studied the spatio-temporal imaging of hemoglobin in the compressed breast with this setup and observed the global return of blood following compression [94].

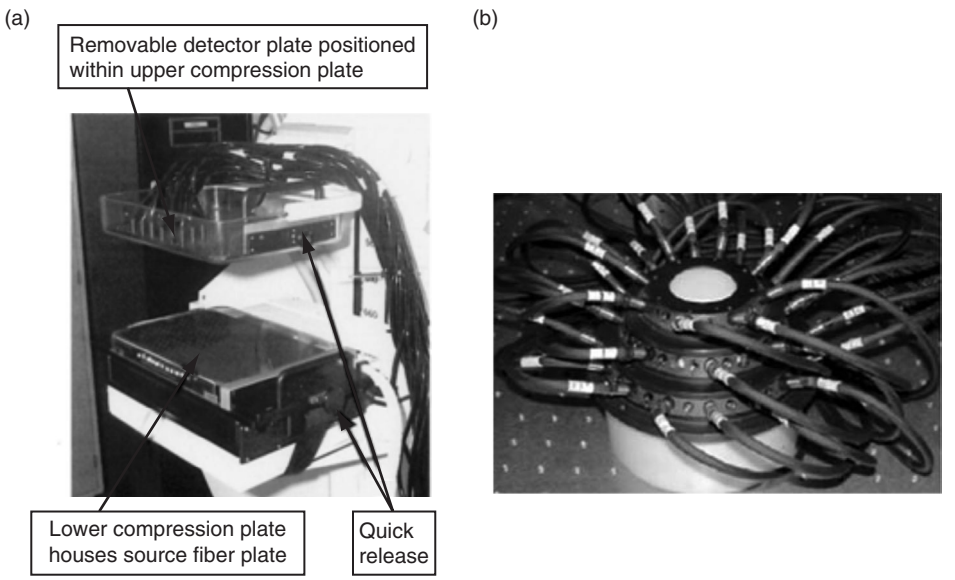

Figure 1. (a) Structure of compression plates designed for coregistered X-ray and optical breast imager [91].
(b) Arrangement of source-detector fiber bundles attached to three interconnecting rings [92].

Researchers have also developed a three-dimensional diffuse optical tomography system in the parallel-plate compression geometry. They studied three cases of invasive ductal carcinoma, ductal and lobular carcinoma in situ and fibro adenoma. The data demonstrated that malignant lesions had a twofold average increase in optical parameters, while the benign tumors did not exhibit significance in the tumor-to-normal ratios of any parameter. Figure 2 shows the DOT result of a 53-year-old woman with a 2.2-cm invasive ductal carcinoma in her right breast comparing with MRI images [83].

It is considered that compression may cause some physiological changes or potential reduction in the blood volume [95, 96]. Uncompressed geometry was explored and developed fast in recent years. As early as 1997, Pogue *et al*. built a frequency domain optical imaging device for breast cancer detection [97]. The imaging chamber was composed of 16 source and 16 detectors located around a two-dimensional ring with the pendulous breast stabilized naturally within it. With this system, the distribution of absorption and reduced scattering coefficients of a patient with a 3.4 cm fibro adenoma in the upper central region of her breast was displayed [98]. They also quantified typical values of hemoglobin concentration, oxygen saturation, water fraction, scattering power, and scattering amplitude within the breast tissue, and conducted a systematic study of the menstrual variations in these parameters [99]. Later, they integrated MRI into the system and imaged the breast tissue of 11 normal female subjects. Higher water and blood signals were found in fibro-glandular fraction than that in adipose tissue [100].

Using a DOT system to image uncompressed breast, Jiang *et al*. conducted a study to differentiate cysts from solid tumors. The pilot results showed that solid breast tumors demonstrated higher absorption and scattering related to the normal tissue while cysts had lower absorption and scattering coefficients compared with the surrounding normal tissue [101]. Yates *et al*. imaged uncompressed breast using 32-channel time-resolved system composed of a conical fiber holder in the form of three connecting rings. The breast was placed in a hemispherical cup surrounded by sources and detectors, and the remaining space was filled with a fluid with tissue-like optical properties [102]. One of their experiments was conducted with three healthy volunteers and twenty-one patients. Seventeen cases of lesion were successfully detected [92]. They also used this system to monitor the changes of optical properties after laser treatment of a fibro adenoma in breast tissue. Images of the absorbing and scattering coefficients revealed the expected response consistent with corresponding ultrasound examinations [103]. A series of clinical three-dimensional optical images have been presented, showing that hypervascularization associated with tumors provides high contrast due to the increased absorption by hemoglobin [104].

Some commercial systems are currently available for breast imaging such as DYNOT (NIRX Inc., NY, USA) [105], CTLM (Imaging Diagnostic Systems Inc., FL, USA) [106], and SoftScan (ART Inc., Quebec, Canada) [107–109] . The first two work in CW mode while the SoftScan is based on time-resolved measurements. SoftScan uses two plates to perform compression, while CTLM uses uncompressed

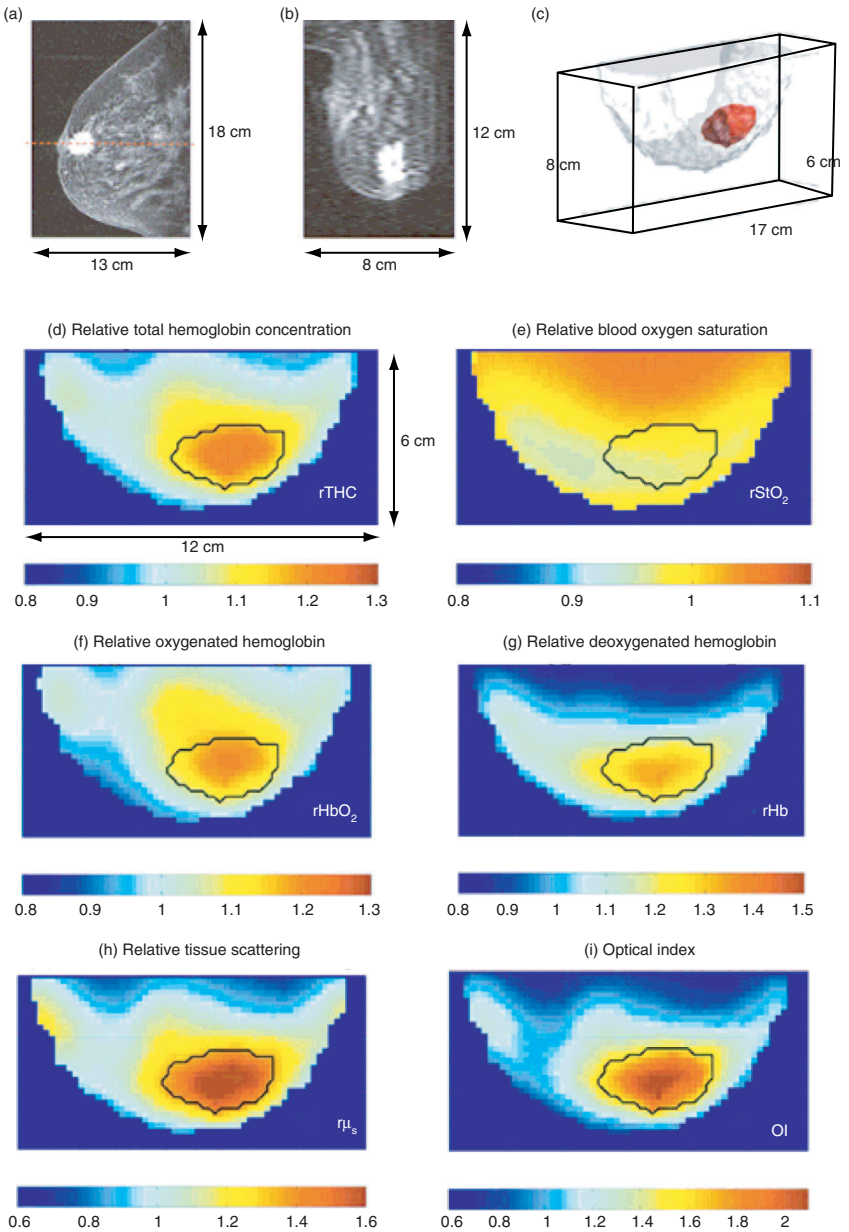

Figure 2. MRI and DOT images of a 53-year-old woman with a 2.2-cm invasive ductal carcinoma in her right breast [83]. (a) The sagittal dynamic-contrast-enhanced (DCE) -MRI showing the tumor center. (b) The axial DCE MRI slice along the red horizontal line in (a), oriented in caudal-cranial view.

chamber. DYNOT system has exchangeable heads with various geometries including circular geometry for the limbs, folding hemisphere for the breast, helmet-like device for the head, and various two-dimensional fiber array designs for nearly planar geometries [110].

3.2. Infant Brain Imaging

Optical brain imaging has undergone 30 years of intense development [111]. It is portable and less sensitive to motion artifact (compared with functional MRI). It can obtain repeated quantitative regional information and longitudinal monitoring of brain function (unfeasible for CT). Furthermore, it avoids the radioactive exposure that may cause injury in the neonate or premature infant (superior to PET) [112]. Therefore, it is particularly suitable for infant brain.

Optical diagnosis includes spectroscopy, 2D topography and 3D tomography. In the beginning, NIRS was used to study infant cerebral hemodynamic and neural activation [113]. Later, optical topography was employed to produce 2D images of activated regions on the surface of the brain [114–118]. To identify changes occurring in deeper tissues, tomographic methods have been studied to produce 3D volumetric images of the whole neonatal brain [119–123].

As early as 1985, Arridge *et al*. pointed out that NIR trans-illumination could be used to visualize and measure the oxygenation state of brain and muscle in newborn infants [124]. In 2000, Benaron *et al*. demonstrated the first tomographic images of infant brain [125]. They measured the flight times of photons between points on the head circumference with a headband of 34 source-detector pairs. Images of an infant undergoing heart-lung bypass and another infant with hypoxic-ischemic injury were successively showcased and compared with CT, ultrasound and MRI images [125, 126].

Hebden *et al*. used a 32-channel time-resolved instrument (named MONSTIR) as a continuous bedside monitor to obtain functional images of premature infants' brains [127]. Sources and detectors are coupled to the infant head by a custom-made foam-lined plastic helmet [128]. Although the positions of the bundles on the helmet are recorded using a 3D digitizing arm immediately before or after the clinical

Figure 2. (*Continued*)

Enhancement of gadolinium uptake in MRI indicates the malignancy. (c) The tumor region (in red) determined based on optical data with the guidance of MRI and the breast outline in 3D space. DOT images of (d) relative total hemoglobin concentration rTHC, (e) relative blood oxygen saturation rStO2, (f) relative oxygenated hemoglobin concentration rHbO2, (g) relative deoxygenated hemoglobin concentration rHb, (h) relative tissue scattering $r\mu_s'$ at 786 nm and (i) optical index are shown in caudal-cranial view with a black solid line indicating the region identified as tumor using a region-growing algorithm. High tumor-to-normal contrast in rTHC, rHbO2, rHb, $r\mu_s'$ and OI are visible within the region.

measurement, these are not always sufficiently accurate for absolute imaging given the natural displacement during the scan. To overcome this problem, scientists inserted a 'reference' subject (fluid-filled balloon, fluid-filled latex shell or compressible head phantom) into the helmet for a difference imaging [119, 129, 130]. They compared the acquired data with those obtained from the homogenous reference and found that regional cerebral blood volume (rCBV) and regional tissue oxygen saturation ($rSTO_2$) from healthy infants were symmetrical, while those from intraventricular hemorrhage (IVH) were asymmetrical with a much greater light absorption on the side of hemorrhage [131].

Optical tomography can detect not only static brain injury, but also changes in brain oxygenation due to changes in inspired oxygen and carbon dioxide in ventilated infants. Imaging by MONSTIR system was reported on a severely brain-injured 38-week-old female infant who had suffered a global hypoxia-ischemic insult following uterine rupture [132]. Three dimensional absorption images of brain in response to the increase in ventilated CO_2 were reconstructed. Gao *et al*. also studied hemodynamic changes in response to the alterations of the ventilation settings on two preterm infant brains [75].

DOT has also been applied in imaging passive motor-evoked responses in premature babies. Gibson *et al*. conducted optical tomography during raising and lowering an infant's arm. Their reconstructed results showed good agreement of changes in optical property with the expected anatomical position of the contra lateral motor cortex, as shown in Figure 3 [131].

DOT has not been used as widely in infant brain as optical topography and spectroscopy [132–134]. This is partly due to the complexity of instrumentation and difficulties in taking measurements from premature babies. Moreover, light transmission across the whole head is challenging due to its serious attenuation with depth [135].

3.3. Other Tissues

In addition to the above typical clinical applications, optical tomography has been employed in the 3D imaging of high scattering media such as human forearm and low scattering region like finger joint.

The forearm muscle has been studied by optical imaging since 1994 [136]. In 2000, Graber *et al*. used a CW optical tomography system to explore the real-time response of the forearm vasculature to rhythmic contraction of antagonistic striated muscle groups [137]. Hillman *et al*. also evaluated adult forearm using their 32-channel TD system [138]. Zhao *et al*. used an NIR DOT system composed of time-correlated single-photon-counting channels to obtain *in vivo* images of human lower legs and forearm. Their images showed increases in blood volume and oxyhemoglobin concentration in the arteries and hypoxia in the corresponding muscles [139].

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory disease that primarily attacks peripheral joints and surrounding tendons and ligaments. As early as 1998, Klose *et al*. developed an NIR scanning system to collect amplitude and phase delay of photon density waves in frequency domain [140]. Xu *et al*. investigated the

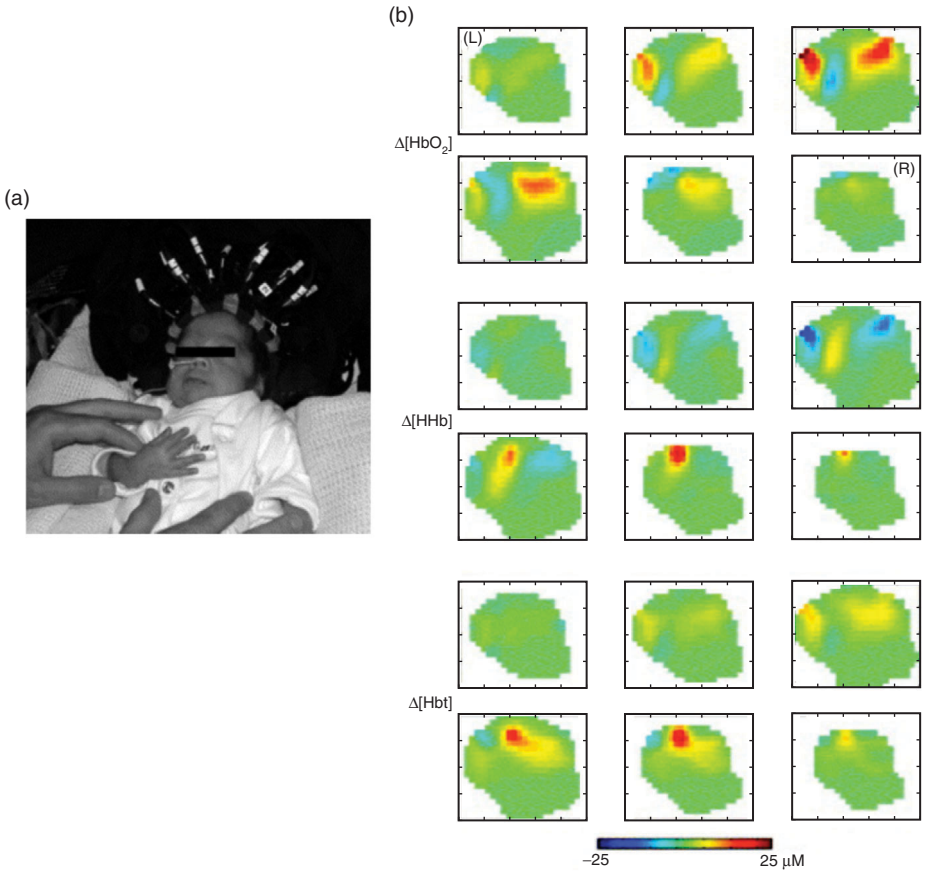

Figure 3. (a) Activating the right arm of a neonate wearing a helmet with optical tomography connectors. (b) Images of Δ[HbO2], Δ[HHb], and Δ[HbT] during left motor activity, showing increases in Δ[HHb] and Δ[HbT] near the estimated position of the motor cortex [131].

in vitro and *in vivo* bones and joints with a Clemson multi-channel diffuse optical imager based on CW measurements [70]. In 2005, Hielscher reported a sagittal laser optical tomography for rheumatoid finger joints [141] and was clinically evaluated by Scheel *et al*. a year later [142]. Using dual-wavelength tomography and MOBIIR software, Hielscher *et al*. proposed a dynamic optical tomography system and observed differences of hemodynamic effect in finger joints between healthy volunteers and RA patients [143]. Recently, new diagnostic strategies such as photoacoustic tomography [144] and X-ray guided optical tomography [145] have been explored for RA detection.

4. FUNDAMENTAL PRINCIPLE OF FMT

4.1. Theoretical Models

The interaction of light with tissue in FMT is similar to that in DOT. The main difference falls in the number of equations. Fluorescence involves the following two processes: (1) fluorescent probes absorb excitation energy and change from the ground to the excited state, and (2) the excited fluorophore returns to the ground state with a characteristic time constant as well as the emission of photons with a longer wavelength. Two parameters are commonly used to describe the fluorescence phenomena: the fluorescence lifetime and Stoke shift.

Predicting photon paths in real high scattering and anisotropic tissues is extremely complex. Statistical methods based on Monte Carlo are valid to model fluorescent photon trajectories [146–149]. However, in most cases, two coupled RTE or DE approximations are preferable [81, 150–158]. One of the equations describes the excitation plane wave from the external light source to the medium while the other refers to the fluorescence emission from the fluorophore marker to the detector. Other mathematical formulations such as Monte Carlo with diffusion model [159, 160], hybrid transport and diffusion model [35, 161, 162] and telegrapher equation (TE) based model [163] have also been reported.

4.2. Reconstruction Algorithm

The inverse problem in FMT is to reconstruct the concentration distribution or lifetime of fluorescent probes. Many effective algorithms have been proposed, including the gradient-based optimization technique [164–168], penalty/modified barrier function (PMBF) method [169–171], Born-type approximation techniques [172, 173], Landweber iteration [174], Newton's or Newton-type optimization methods [175], Bayesian nonlinear least squares approaches [176], adaptive finite-element-based method [177], Tikhonov regularization method [178], the matrix-free algorithm [179], to name just a few.

FMT features an ill-posed inverse problem with certain challenges. One challenge is the optical heterogeneity of biological tissue [180–183]. The fluorescence intensity recorded at tissue boundary is a comprehensive effect of the fluorescence distribution and the tissue absorption and scattering distribution. However, it is difficult to determine tissue's optical properties. Most of the current approaches assume a homogeneous background with known absorption and scattering parameters. On the other hand, normalized Born ratios [172], video reflectometry measurements [25] and DOT guided FMT [150, 184] are proposed to deal with the heterogeneity.

FMT is also greatly affected by the excitation leakage [185–187], system noise [188] as well as the nonspecific background autofluorescence [189]. Strategies such as using interference filters[186] or gradient index (GRIN) lenses [187], data pre-processing with subtraction [190, 191] or pre-filtration schemes [192, 193], as well as multispectral imaging [194] have been attempted to remove these influences.

FMT suffers from a large number of unknowns and a relatively limited number of measurements, which essentially causes under-determined equations. A promising solution is to use a priori information to guide the reconstruction [195, 196]. Typically, two types of prior information are available. One type is the localization information of

a certain fluorophore based on its chemical and physical properties. The other is the internal edge structure information from another imaging modality such as CT [197] , MRI [198], PET [199], and ultrasound [200].

4.3. Imaging Systems

There are three types of FMT instrumentation: CW, TD and FD. FMT prototype for small animal was first developed by Ntziachristos *et al*. [16]. In 2003, Graves *et al*. developed a constant-wave sub-millimeter resolution imaging system that enabled planar imaging as well as fluorescence tomography [173]. Fluorescence measurement of referenced ac intensity and phase shift in response to point illumination measurement geometry was conducted using a homodyned intensified charge-coupled device system [201]. In 2005, Patwardhan *et al*. reported a TD FMT system for imaging the kinetics of probe distributions through the whole body of small animals [202]. Other researches on TD system can be found in [203–207].

The past two decades have witnessed the great structural improvement in the FMT system. For example, the earlier systems were mainly based on fiber coupling and imaging chambers with matching fluids [172]. Later, the cumbersome system was replaced with the flying spot illumination and charge coupled device (CCD)-based detection for multi-view boundary measurements [173, 208]. In 2007, a non-contact free-space fluorescence tomography system of full angle geometry was reported [209]. Such imaging strategies eliminate the need for individual fibers in contact with the highly scattering volume. In addition, noncontact measurements from diffuse media could facilitate the use of large detector arrays at multiple angles that are well-suited for tomography applications. Recently, real-time continuous detection becomes a new trend, and is expected to realize full-angle dynamic observation superior to the traditional step-by-step mode [210]. Figure 4 shows the schematic rendering of such a system.

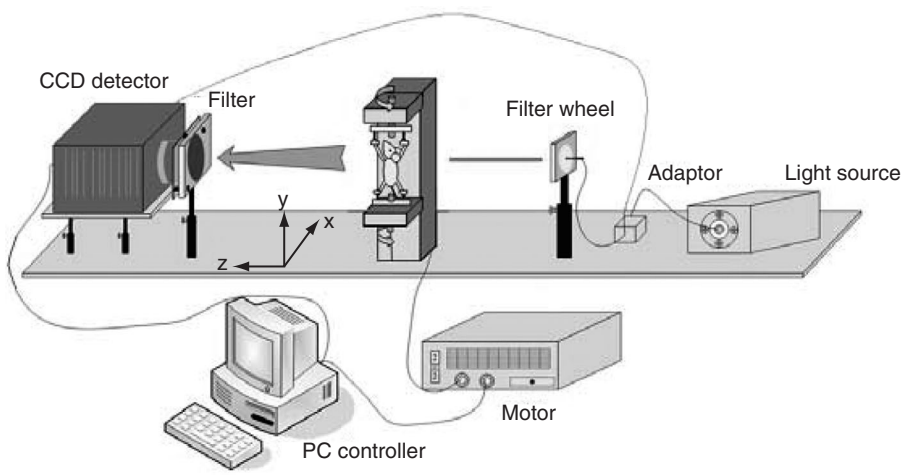

Figure 4. Non-contact full-angle continuous FMT system.

Currently, there are some commercial systems for *in vivo* small animal fluorescence imaging, such as IVIS® Spectrum (Xenogen Corporation), FMT 2500LX (VisEn Medical Corporation), Maestro™ (Cambridge Research & Instrumentation Incorporation), Pearl™ Imager (Li-COR Biosciences), eXplore Optix® Series (General Electric Healthcare Corporation), etc. Among them, IVIS® Spectrum and FMT 2500LX can perform three-dimensional tomography in some applications. For more details see reference [211].

4.4. Preclinical Application

Unlike DOT, FMT has not reached a state of maturity which allows routine clinical practice in human. Most of preclinical studies have been conducted on small animals or tissue phantoms.

As early as 2002, Vasilis *et al*. used a prototype FMT imager to obtain three-dimensional *in vivo* images of a protease in orthopic gliomas [16]. They found a correlation between matrix metalloproteinase, cathepsinsB and the HT-1080 tumor burden [212]. In terms of tumor responses to treatment, they studied antitumor treatment with an annexin V-Cy5.5 conjugate [213]. With the same system they quantified tumor therapeutic modulation with an anti–vascular endothelial growth factor (anti-VEGF) antibody drug [214]. After the appearance of non-contact configuration, 3D *in-vivo* images of GFP-expressing T-cells in mice were reported [215]. FMT has been so far successfully applied in pulmonary inflammation [216], lung cancer [217], neurological disorders [218], cardiovascular diseases [219, 220], immunologic diseases [221], etc. Human breast phantom has been extensively studied using fluorescence-enhanced optical tomography [77, 171, 192, 201, 222–227].

Combination of FMT with other modalities is another growing application. For example, Davis *et al*. implanted U-251 human gliomas into nude mice and completed MRI and FMT acquisition after administration of a VEGF-targeted NIR fluorophore. Tissue structural information obtained from standard and contrast enhanced T1-weighted images was used to spatially constrain the FMT reconstruction [228]. Gliomas response to chemotherapy was also explored by combined FMT-MRI system in the living mouse brain [229]. Hybrid FMT-CT imaging is another example which has been applied to detect inflammation in murine atherosclerotic plaques [230], and amyloid-β plaques in a murine Alzheimer's disease model [218]. Figure 5 compares the *ex vivo* results with *in vivo* FMT imaging for a 13-month-old C57B/6 control mouse (first row), a 17-month-old APP23 tg mouse (Second row), and a 26-month-old APP23 tg mouse (third row) [218].

The process of drug development is a long, high-risky and costly endeavor with an average of 10~15 years and $1.9 billion for a new approved drug [231]. Imaging methods, such as positron emission tomography (PET) [232], MRI [233] and bioluminescence [234], have been employed to enhance the speed of preclinical study for novel anti-cancer agents. In 2007, three-dimensional FMT was adopted to explore the effect of a vascular endothelial growth factor (VEGF) blockade on angiogenesis [235]. Scientists have designed experiments to evaluate the treatment of

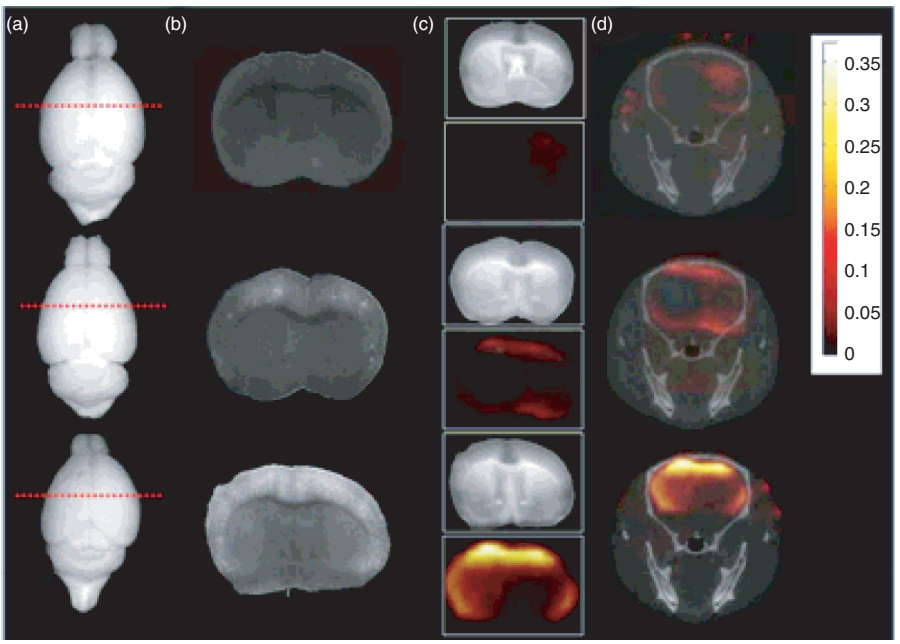

Figure 5. (a) Full brain images in the excitation channel using a planar reflectance imaging system. The red dotted line denotes the approximate location corresponding to the slice shown in subsequent columns. (b) Planar reflectance images of normalized fluorescence from a single slice. (c) Planar images at the excitation wavelength (top) and FMT reconstructions overlaid on normalized planar fluorescence images (bottom). (d) *In vivo* multi-modal FMT reconstructions for a slice corresponding to the same location as the *ex vivo* images, overlaid on a representative CT slice. All FMT reconstructions are scaled to the same colorbar.

the anti–VEGF antibody. Fifty-eight CT26 colon tumor–bearing mice were imaged after intravenous administration of long-circulating near-infrared fluorescent blood-pool agents. Figure 6 shows FMT imaging in three cohorts of mice: animals receiving no treatment (normal), animals receiving saline (PBS), and animals receiving treatment (Avastin) [235].

As mentioned earlier, specific fluorophores are vital for the application of FMT. To optimize the parameters in labeling NIR fluorescent dye, Qian *et al*. inspected the stability of cypate-protein conjugate in blood serum and its distribution in small animals under various labeling conditions [236]. Preclinical application of FMT is now rapidly growing [211, 237–239].

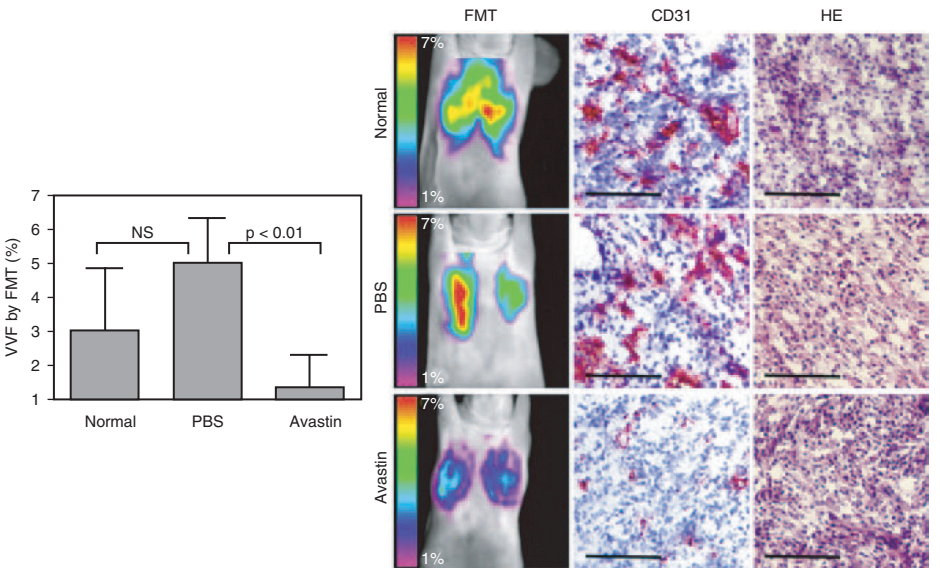

Figure 6. *In vivo* angiogenic data. Scale bar = 100 μm. NS = not significant. Error bars = standard deviation. Vascular volume fraction (VVF) for treatment group was lower than control and baseline groups. Fluorescence tomographic images were validated with immunohistochemical staining including CD31 and hematoxylineosin (HE).

5. CONCLUSION

After decades of development, DOT has emerged from a research concept to a practical, working clinical tool [240]. Though FMT is not as mature as DOT, it is an evolving field that has already achieved major advances in human breast phantom and small animal imaging. Currently, the major difficulties may be in the improvement of quantitation, spatial resolution, as well as the identification of more target-specific biomarkers [135]. Most of the light propagation models are based on simplified assumptions which may lead to inaccuracies in the imaging. Advances in theory and reconstruction algorithms are needed to facilitate the development of more sophisticated models. Additionally, more efficient computational technology and imaging instrumentation are in demand to collect large data sets. It is hoped that optical tomography may become a promising alternative to the existing imaging technologies.

Multi-modality imaging, which combines two or more different imaging techniques into one context, is an emerging field in both clinical research and small animal imaging [241–244]. As modern medical and diagnostic technology develops, comprehensive information provided by different imaging modalities may be needed. In the past several years, DOT-ultrasound [245], DOT-MRI [246], DOT-CT [247], FMT-MRI

[248], FMT-CT [249, 250], FMT-PET [251] and FMT-ultrasound [252] have been extensively studied. Although few multimodality systems have been clinically applied to date, there are encouraging signs that a new generation of multi-modality imaging will emerge and find wider application in the near future.

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