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Methodology development for simultaneous diffuse optical tomography and magnetic resonance imaging in functional human brain mapping

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Abstract

We present an integrated methodology for human brain mapping by simultaneous BOLD fMRI and NIR imaging. This methodology consists of three innovative components: the construction of MRI-compatible optical probes that can be affixed to any part of the human head inside a standard MRI head-coil with minimal MR image distortion, the accurate determination of optode positions on the head from MR images, and the application of a perturbation approach and Monte Carlo method to compute the integral kernel of the Born solution to the diffusion equation for baseline optical properties. This integrated approach has been used to demonstrate promising capabilities for studying functional hemodynamic activation in human visual cortex by simultaneous fMRI and NIR tomography.

Keywords

fMRI; near-infrared tomography; diffuse optical tomography; functional imaging; human brain; visual cortex; hemodynamic response

1. INTRODUCTION

The study of cerebral hemodynamic and neuronal responses due to functional stimulation is essential for understanding the mechanism of neuronal activity and hence brain function. Blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) study has become one of the most important methods of investigating neuronal activity in the human brain since it provides high-resolution images associated with multiple physiological parameters closely related to cerebral activity^{1,2}. However, as a secondary measurement of cerebral hemodynamics, the underlying physiological mechanism of the BOLD signal is not yet fully understood. BOLD fMRI also suffers from relatively low temporal resolution dictated by the hemodynamic response and this makes it difficult to study the fast response of neuronal activity. In contrast, near-infrared spectroscopy (NIRS) provides direct measurement of oxy- and deoxyhemoglobin concentrations with a response time on the order of milliseconds, which enables it to study the fast neuronal, as well as the slow hemodynamic, responses.

Previous studies have demonstrated that the integration of the two methods can uncouple the contributions due to blood flow and deoxyhemoglobin concentrations to the BOLD signal^{3–6} in addition to the fast optical neuronal responses⁷. However, the achievable spatial resolution of NIRS is comparable with the source-detector distance, typically 1–3 cm laterally and worse longitudinally⁸, which is relatively low compared with fMRI.

In this paper, we introduce a complete methodology of simultaneous BOLD fMRI and diffuse optical tomography (DOT) with high spatial resolution and chemical specificity for a model functional study of the human visual cortex. The same methodology can be readily applied to other fMRI methods and other cortical areas of the human head as well. The forward problem was formulated in terms of a perturbation approach using the Born approximation. In this approximation, the changes in optical signals are expressed as a linear combination of changes in voxel-by-voxel optical properties with coefficients dependent on the baseline point-spread functions of the light bundles. The novelty of our approach is the use of the Monte Carlo method on MRI-based head models to compute these point-spread functions, i.e., the integral kernel of the Born solution to the diffusion equation. These realistic head models were obtained by segmenting 3-D anatomical MR image into different tissues, such as scalp-skull, cerebral spinal fluid (CSF), gray matter, and white matter. We have developed a technology for building MRI-compatible optical probes that can be used on any part of the human head inside a standard MRI birdcage head-coil with minimal MR image distortion. We have also developed a method for determination of the optode positions on the head. This method enables both functional NIR image reconstruction based on structural MRI and its coregistration with fMRI.

2. METHODS

2.1 Experimental setup

The optical probe is attached to the back the head and aligned with the primary visual cortex of the patient, as shown in Figure 1. Nonmagnetic goggles conducting visual stimulus are fixed in front of the patient's eyes inside the birdcage head coil of the MR scanner. The BOLD fMRI study is performed using a standard echo-planar imaging (EPI) pulse sequence (FOV 240×240 mm², resolution 64×64, voxel size 3.75×3.75×4.00 mm³, gap 0.4 mm, $\theta = 60^\circ$, TE 25 ms, TR 2000 ms). A 3-D MR image of the same imaging volume is taken for co-registration of the fMRI data with the “anatomical” images. A high-resolution 3-D MR image, termed the “probe localizer,” is acquired to assist automatic recovery of the positions of the optical fibers (optodes). Finally, a T_1 -weighted high-resolution 3-D full-head anatomical image (MPRAGE) is acquired for optical image reconstruction and serves as the basis for co-registration of different imaging modalities. The optical signal is recorded by the near infrared spectrometer (Imagent, ISS), which is synchronized with the fMRI study and the visual stimulation by a “trigger” signal from the MRI scanner (3 tesla, Allegra, Siemens). The optical sources are laser diodes (690 and 830 nm) which are amplitude modulated at 150 MHz and time-multiplexed. Photons reaching the optical detectors are amplified by the photomultiplier tubes (PMT) and consequently converted into AC, DC, and phase signals for each of the source-detector combinations, or channels, at each wavelength.

2.2 Optical probe

Constraints imposed by fMRI required rigorous optical probe design and optical fiber preparation. Due to the strong static magnetic (B_0) fields and RF pulses (B_1 field) generated, the design of the optical probe should be completely metal-free. The physical structure of the MRI scanner imposes another important constraint on the design of the optical probe for studying the visual cortex. As illustrated in Figure 1(a), the optical probe has to be positioned within fairly limited space between the back of the head and the inner wall of the head-coil; optical fibers have to be placed in parallel with the long axis of the birdcage head coil, i.e. the B_0 field of the MRI scanner. In order to maintain homogeneity of the B_0 field the optical fibers were “ferruled” using plastic tubing instead of stainless steel. The frame of the optical probe was made of the rubber (polyurethane, 70A durometer, FDA approved, McMaster-Carr) that produced the least amount of visible artifact in MR images among those with appropriate mechanical characteristics, which, from the structural point of view, is robust enough to maintain its structure yet flexible enough to fit the shape of the head and provide good contact. The topology of optodes are designed so that the optical channels are overlapped and the distribution of source-detector distances evenly covers the optimal range⁴ – between approximately 20 and 30 mm, as shown in Figure 2.

The optical probe has 16 pairs of 400- μ m-diameter core plastic clad multimode silica source fibers (FT-400-EMT, Thorlabs) and 4 detector fiber bundles (Fiberoptics Technology). An MRI visible marker is attached adjacent to each of the 16 optical source and detector fibers so that accurate source- and detector-positions can be recovered from MRI images for data processing.

2.3 Data processing procedure

A flowchart describing the network connecting multiple data sources with various data processing methods is shown in Figure 3.

2.4 Recovery of optode positions from MR images

The most commonly used method to digitize the optical source- and detector-positions with respect to the patient's head is by measuring a polarized 3-D electromagnetic field with a specially designed sensor. This method is convenient but suffers from artifacts from multiple sources, even though various correction methods have been developed⁹. In this paper, since the optical and fMRI data are acquired simultaneously inside the MRI scanner, it is convenient to determine the positions of the optodes using MRI, and register both optical and fMRI results onto the anatomical MR image of the brain. By doing this, the accuracy of co-registration is expected to be comparable to the resolution of the MR images and the chance of introducing human error as a result of extra measurement is virtually eliminated.

As described previously, a high-resolution 3-D MR image of the optical probe, termed a “probe localizer”, is acquired *in situ* to determine the deformation of the optical probe based on the marker-positions. The location of the entire optical probe in the coordinate system defined by the 3-D anatomical MR image (MPRAGE) can be determined by identifying several specific markers. The spatial relationship between the positions of the markers and their corresponding sources/detectors can be determined by taking a reference MR image

which covers the optical probe. The reference is a high-resolution 3-D MR image of the optical probe on a layer of oil-containing material – so that the actual positions of optodes appear as dark spots on a bright background.

In our algorithm that recovers the positions of optodes from the MR images, only one assumption is made about the optical probe: the frame of the optical probe is “locally rigid”, i.e. the deformation between a marker and its corresponding source or detector position is negligible. This is an acceptable assumption because the optodes are inserted in a rubber ring to which the markers are firmly attached.

Taking one source-marker pair in the reference probe localizer as an example, subtracting the coordinates of the optical fiber from its marker gives a vector representing the coordinates of the optical fiber in the coordinate system with the marker as the origin. The probe localizer is used to identify the actual positions of the markers, which can be fully automated with the help of image processing routines written in Matlab (Mathworks, Natick, NJ). Because the anatomical image and probe localizer are taken along different axes, the first step is to compute the rotation and translation of the reference coordinate systems so that the marker identified in the probe localizer can be aligned with the one appearing in the anatomical MR image. Up to now, the marker has been considered as a point (centroid of the identified voxels) in 3-D space. However, since the marker is cylindrical, its angular position has to be determined as well. Therefore, the next step is to compute the rotation of the coordinate system due to the rotation of the optical probe. This can be done by identifying and comparing the marker pair in the probe localizer and the reference image. The third step is to correct the misalignment due to the deformation (twisting along the edge of the frame) of the optical probe. This can be done by aligning the two vectors representing the same marker cylinder in the two MR images. Finally, the transformed vector representing the optical fiber with respect to the marker in the reference image is added to the coordinates of the aligned centroid of the marker. This completes the recovery of coordinates of the optodes in the anatomical MR image coordinate system, which is essential for later optical image reconstruction, data processing, and co-registration. If necessary, these points can be converted into the Talairach coordinate system³.

Two methods are used to perform rigid coordinate transformations as mentioned above, i.e. mapping points between two coordinate systems related by rotations and translation. The first is based on the concept of transformation of coordinate system (“moving frame”). The second is based on the concept of rotation and translation of a vector (“moving point”).

The first method is more convenient if the origin and orientation of both coordinate systems are known. If the position of a given point P in two coordinate systems $(A) = (O_A, i_A, j_A, k_A)$ and $(B) = (O_B, i_B, j_B, k_B)$ are denoted as $P^{(A)}$ and $P^{(B)}$, respectively, one has

$$P^{(A)} = R_{(A)}^{(B)} P^{(B)} + {}^{(B)}O_{(A)} \quad (1)$$

where $R_{(A)}^{(B)}$ can be written as a matrix of dot products of the axis vectors of the two coordinate systems

$$R_{(A)}^{(B)} = \begin{bmatrix} i_A \bullet i_B & j_A \bullet i_B & k_A \bullet i_B \\ i_A \bullet j_B & j_A \bullet j_B & k_A \bullet j_B \\ i_A \bullet k_B & j_A \bullet k_B & k_A \bullet k_B \end{bmatrix} \quad (2)$$

and ${}^{(B)}O_{(A)}$ is the translation of the origin from $O^{(B)}$ to $O^{(A)}$.

The second method, rotation and translation of a vector, works best if the coordinates of several reference points are known and one needs to know the new coordinates of different points, for example, track a moving object. The transformation can be expressed as

$$P' = RP + t \quad (3)$$

Although Equations (1) and (3) have identical mathematical format, their rotation matrices R and translation vectors are determined in very different ways. Specifically, if the two frames are known, $R_{(A)}^{(B)}$ is uniquely determined, while

$$R = \prod_m R_m \quad (4)$$

is dependent on the order of rotation, where $m = x, y, \text{ or } z$, each of which represents rotation of an angle θ about the x -, y -, or z -axis and

$$R_x(\theta) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos \theta & \sin \theta \\ 0 & -\sin \theta & \cos \theta \end{bmatrix}, R_y(\theta) = \begin{bmatrix} \cos \theta & 0 & -\sin \theta \\ 0 & 1 & 0 \\ \sin \theta & 0 & \cos \theta \end{bmatrix}, \text{ and } R_z(\theta) = \begin{bmatrix} \cos \theta & \sin \theta & 0 \\ -\sin \theta & \cos \theta & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

2.5 MRI-constrained NIR tomography

Using the Born approximation, the general solution to the first-order perturbative approximation of the heterogeneous diffusion equation in the frequency-domain can be obtained¹⁰. For the preliminary study presented in this paper, only the absorption term will be considered. Note that the frequency parameter ω is dropped from the equations because the modulation frequency of the light sources is fixed

$$\delta\Phi(r_s, r_d) = \Phi(r_s, r_d) - \Phi_0(r_s, r_d) = - \int_V \delta\mu_a(r) \Phi_0(r_s, r) G(r_d, r) d^3r \quad (5)$$

where the integral kernel $\Phi_0(r_s, r)G(r, r_d)$ is the product of the photon density due to the source r_s and the Greens' function due to the detector r_d at position r in the frequency domain. For the purpose of numerical computation, the equation is discretized, and summation is used to approximate integration. As a result, Equation (5) can be converted into the sum of linear equations if the discretized integral kernel is known for each voxel:

$$\Delta\Phi(r_s, r_d) = - \sum_r \Delta\mu_a(r) \Phi_0(r_s, r) G(r_d, r) \Delta V \quad (6)$$

In this paper, computation of the integral kernel is achieved by using a Monte Carlo method, as described in detail later. In practice, the optical signal is recorded as a time-series for each

source-detector combination. The data acquired for each source-detector combination as a function of time is called a measurement. It follows that for M measurements on an imaging volume of N voxels, Equation (6) can be expressed in a generalized matrix form $AX = B$. A is an M -by- N matrix, called the coefficient matrix, where $a_{ij} = -\Phi_0(r_{s,i}, r_j)G(r_{d,i}, r_j)$. B is an M -by-1 vector, called the measurement vector, where $b_i = \Phi(r_{s,i}, r_{d,i})$. The solution X is a 1-by- N vector that contains all voxels where $X_j = \mu_a(r_j)$.

For the usual spatial resolution, $4 \times 4 \times 4 \text{ mm}^3$, of optical image reconstruction used in this work, the number of measurements ($M = 64$) is much less than the number of voxels ($N = 10^3 \sim 10^4$) within the field of interest. Applying physiological and spatial *a priori* constraints is a method that effectively helps solving such underdetermined and ill-conditioned inverse problems¹¹.

The effects of access order on the speed of convergence and the accuracy of image reconstruction have been numerically investigated among so-called systematic (“detector-first”), sequential (“source-first”), and random access orders¹². In this paper, we adapted the sequential access order which was considered optimal in terms of the quality of image reconstruction.

Our numerical simulations and computations of the coefficient matrix a_{ij} , representing the integral kernel in Equation (5), are based on the Monte Carlo method. We evaluated and adapted a relatively mature and well documented software package¹³, which was modified to produces the photon “pathway” in addition to the “history” files. The pathway file contains the exact path of each detected photon in the simulations. By following the pathways of all photons that travel from a given source to a given detector, the probability of photons passing through every voxel for a given source-detector combination is obtained, which is proportional to the magnitude of the integral kernel. The history file records how long every detected photon has traveled in each type of tissues, which can be used to compute the phase of the integral kernel. For the purpose of this preliminary study, the phase of the integral kernel is ignored because its value is relatively uniform over the “sensitive region”. The photon density due to every source at each detector can also be computed from such history files¹³, these serve as the simulated optical signals for our qualitative study.

To explain why the probability of detected photons appearing at a given voxel is proportionally to the integral kernel for that voxel, one needs to review the definition of the integral kernel. It is the product of the photon density $\Phi_0(r_s, r)$ at a given voxel r due to a given source r_s under the baseline condition and the Greens' function $G(r_d, r)$. The Green's function can be regarded as the “impulse-response” of the transfer function of the system. In other words, for the diffusion equation, the Greens' function is the photon density detected by the detector r_d due to an infinitesimal unit source at voxel r . The photon density is defined as the radiant energy of light per unit volume at a given time. Knowing that in the context of diffusion equation, the energy of light is expressed as the number of photons for a given wavelength, the integral kernel is therefore proportional to the number of photons detected by the detector r_d from source r_s passing through voxel r . This is in turn proportional to the probability that a photon migrates from r_s to r_d and passes through r . Overall, for a given channel, the probability of a photon passing through a particular voxel is

proportional to the integral kernel evaluated at that voxel. Note that the integral kernel is a complex function, and so is the “probability” value at each voxel, whose phase is determined by its length of pathway within each type of tissue on its way from the source to the detector.

However, the constant factor connecting the map of the photon pathway and the integral kernel has to be determined for quantitative image reconstruction. The integral kernel is proportional to the number of photons emitted by the optical source during the measurement, as one assumes the system is linear time-invariant (LTI), which is a reasonable assumption because the power of the light sources is fairly small (on the order of milliwatts), and the transit time of photons between corresponding sources and detectors is very short (on the order of nanoseconds). For a particular optical measurement, Equation (6) can be re-written as

$$\Delta\Phi(r_s, r_d) = - \sum_r \Delta\mu_a(r) \frac{N(r) N_{input}}{\sum_{r'} N(r')} \quad (7)$$

where $N(r)$ is the number of photons that can be “seen” at a voxel r of size V during a simulation, and N_{input} is the number of photons injected by the source during the measurement. Note that

$$\frac{N(r)}{\sum_{r'} N(r')}$$

is the probability that a photon passes through a particular voxel r . However, the measured optical signal is a voltage or current which is proportional to the number of photons detected. Therefore, Equation (7) must be normalized by the baseline optical signal, which gives

$$\frac{\Delta V(r_s, r_d)}{V_0(r_s, r_d)} = \frac{\Delta\Phi(r_s, r_d)}{\Phi_0(r_s, r_d)} = - \sum_r \Delta\mu_a(r) \frac{N(r)}{\sum_{r'} N(r')} \frac{N_{input}}{N_{output}} \quad (8)$$

where N_{input} and N_{output} are the numbers of photons injected and detected during the measurement, respectively, which are unknown. However, their ratio was determined from the simulations. Our image reconstruction of changes in the absorption coefficient is based on simulations using realistic head models with solutions constrained to the brain. In addition, the reconstructed activation is limited to the portion of the brain that is illuminated by light sources, i.e. voxels that have probability (the magnitude of the integral kernel) above the threshold for image reconstruction (a value of 0.01 was used in this paper). In other words, scalp and skull, as well as cerebral tissues far away from the optical probe are excluded from the solution space. As a result, the number of unknowns is greatly reduced.

To simulate the hemodynamic activation within the head models, an “activated” sphere with a diameter of 20 mm was “embedded” into the heterogeneous (realistic) head model. The optical properties of the sphere are the same as the gray matter except for a 10% increase in

absorption coefficient. The sphere is positioned directly beneath the surface of the visual cortex of the left hemisphere, approximately half the radius left of the center of the optical probe. Upon simulated activation, the light emitted from sources 12–14 is expected to be affected most, refer to Figure 2 (b). Optical properties used for Monte Carlo simulations are listed in Table 1, where n is the refractive index, g is the average cosine of the scattering angle, and μ_s is the scattering coefficient, which is related to the reduced scattering coefficient μ_s' by $\mu_s' = \mu_s(1-g)$. Note that since no accurate literature values of g are available, we assume $g = 0$, which suggests that the distribution of the scattering angle is almost random.

3. RESULTS AND DISCUSSION

Figure 4(a) shows the reconstructed positions of the optodes, shown as red dots, superimposed on the rendered 3-D anatomical MR image (MPRAGE). The error of localization is estimated to be within 2 mm. This result has been compared with the one obtained using the traditional electromagnetic digitization method, as shown in Figure 4(b)–(e).

Multiple image reconstruction algorithms have been applied to the data, including matrix left division, singular value decomposition (SVD), algebraic reconstruction techniques (ART), and simultaneous iterative reconstruction technique (SIRT). Among the algorithms tested, SIRT gives the best result in terms of the quality of reconstructed images.

For the reconstructed image (with optical properties listed in the case (a) of Table 1) using scalp/skull stripping and threshold, the maximum value in the simulated change in absorption coefficient is $0.82 \times 10^{-3} \text{ mm}^{-1}$, and the minimum is $-0.16 \times 10^{-3} \text{ mm}^{-1}$. The difference of the two is $0.98 \times 10^{-3} \text{ mm}^{-1}$, whereas the simulated activation is $1.0 \times 10^{-3} \text{ mm}^{-1}$. The simulated activation and reconstructed images are shown in Figure 5.

Having shown that image reconstruction of optical properties works reasonably well in ideal cases, where the baseline values of optical properties are known, it is important to determine the robustness of the method by examining its output as response to inaccurate baseline optical properties. This is an important test because determining accurate optical properties of the human head *in vivo* is not a trivial task. Furthermore, such *in vivo* baseline values differ across patients, physical conditions, or even time.

We change the optical properties for Monte Carlo simulations to the values shown in Table 1, case (b)–(d), based on which new integral kernels are computed in order to mimic the error due to biased optical properties. The image reconstruction is conducted using the new integral kernels but with previously simulated standard optical signal. The difference of the new image reconstruction results from the standard one reflects the robustness of the entire image reconstruction method. In addition, the effect of noise (related to the number of detected photons) on image reconstruction is also evaluated. The noise level for each channel is obtained from actual measurement of optical signals.

As summarized in Table 2, the standard result is compared with the ones based on biased optical properties, the one based on limited number of photons, as well as the ones with different noise levels.

When computing the integral kernel, its phase due to scattering has been ignored for simplicity. This approximation should not impose significant error on the results because the magnitude of the phase is relatively small and uniform across the region of interest according to our estimation using Monte Carlo simulations. On the other hand, information provided by the Monte Carlo simulations is sufficient to determine the phase of the integral kernel, which will be implemented in later work. In Monte Carlo simulations, the refractive indices of all tissues are set to be the same typical value ($n = 1.4$) because of the lack of literature values of *in vivo* tissues. The inhomogeneity of refractive indices occurring at the boundaries of different tissues may result in negligible changes in the amplitudes of optical signals but could result in non-negligible changes in the differential pathlength and phase of the optical signals^{14,15}.

In vivo optical properties may need to be measured for more accurate Monte Carlo simulations. However, simulation results suggest that the optical image reconstruction methodology discussed in this paper is fairly robust from inaccurate baseline optical properties (especially the absorption coefficient) of the head model, as shown in Table 2. More accurate baseline optical properties could be determined by incorporating an *in vivo* optical property measurement method⁵ into the procedure of optical data acquisition. On the other hand, if the values of baseline optical properties do not substantially deviate from the correct values, i.e. within the range where the Born approximation is still valid, such biased optical properties can be regarded as constituting a virtual baseline. In other words, such systematic error can be easily eliminated by forcing the actual baseline to be zero.

Structural and physiological *a priori* knowledge is applied to reduce the number of unknowns in image reconstruction. From the anatomical MR image (MPRAGE), the brain tissue can be used as a spatial constraint to the solution. Another spatial constraint to the solution is via the estimation of the optical sensitivity region, which consists of voxels with significant contributions to the optical signal. The method is to find voxels that produce signal with magnitude greater than the noise level of the optical signal of all channels/measurements. In other words, the forward problem is solved one voxel at a time (with maximum possible activation, e.g. 5% from the baseline value was used in this paper); and the result (estimated optical signal due to activation from that particular voxel) is compared with the normalized noise level (obtained from experiment) to determine if this channel/measurement is sensitive to that particular voxel, as shown in Figure 6.

4. CONCLUSIONS

Compared with other algorithms tested, the SIRT algorithm gives the smoothest and the most accurate reconstruction result from simulated optical measurements. In terms of the accuracy of localizing the simulated activation, the reconstructed images typically produce correct positions of activation. Furthermore, in terms of the accuracy of the amplitude of reconstruction, the regions of activation in reconstructed images are slightly larger and less

homogeneous. As shown in Table 2, the position and magnitude of activation are identified fairly close to their original values compared with typical reported near infrared imaging resolution of 1–3 cm.

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Figure 1.
Placement of the optical probe on the head inside the “birdcage” head coil of the MRI scanner.

Figure 2.

Schematic (a) and photos (b) of the optical probe. In (b), the numbers 1–16 are the indices of the optical sources; and A–D are indices of the prisms (detectors).

Figure 3.
The network connecting multiple data sources with various data processing methods.

Figure 4.

(a) shows reconstructed source and detector positions (red dots) of the optical probe superimposed on 3-D head model rendered from anatomical MRI images. The circularly positioned dark dots are the markers attached to the optical probe. (b)–(e) are comparisons of the source-detector positions determined by MRI reconstruction and the traditional EM field method in (b) 3-D view, and (c)–(e) projection views. Note that ELP represents the EM field method. In the figures, the large triangles (red and blue ones overlapping) represents the fiducial points of the subject (nasion, left and right preauriculars).

Figure 5.
(a) simulated and (b) reconstructed image of absorption coefficient.

Figure 6.
The sensitivity region estimated from the signal-to-noise ratio of optical signal.

Table 1

Optical Properties used for Monte Carlo Simulations

Tissue type	μ_a (mm ⁻¹)				μ_s (mm ⁻¹)				g	n
	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)		
Scalp and skull	0.014	0.0154	0.0168	0.012	0.860	0.86	0.86	0.90	0	1.4
Cerebrospinal fluid	0.004	0.0044	0.0040	0.004	0.100	0.10	0.10	0.10	0	1.4
Gray matter	0.010	0.0110	0.0150	0.015	1.110	1.11	1.11	1.10	0	1.4
White matter	0.010	0.0110	0.0100	0.010	1.110	1.11	1.11	1.11	0	1.4
Activation region	0.011	0.0154	0.0168	0.012	1.110	0.86	0.86	0.90	0	1.4

Table 2

Reconstruction Results based on Different Simulation Parameters

Parameter set used for the integral kernel	Max μ_a (mm ⁻¹)	Min μ_a (mm ⁻¹)	Max-value voxel	Num. of voxels > 50% of max μ_a
Phantom (head model)	10.0×10^{-4}	0	(19,0,11,25,33.5)*	48
Case (a) (standard)**	8.20×10^{-4}	-1.59×10^{-4}	(19,10,32)	36
Case (b) (biased)	8.20×10^{-4}	-1.59×10^{-4}	(19,10,32)	36
Case (c) (biased)	8.20×10^{-4}	-1.59×10^{-4}	(19,10,32)	36
Case (d) (biased)	7.63×10^{-4}	-1.49×10^{-4}	(19,10,32)	35
Case (a), but 10^6 photons	8.34×10^{-4}	-1.53×10^{-4}	(19,10,32)	33
Case (a), w. noise SNR = 2	9.30×10^{-4}	-4.63×10^{-4}	(21,10,33)	50
Case (a), w. noise SNR = 1	11.3×10^{-4}	-8.13×10^{-4}	(21,10,33)	52

* Center of the simulated activation, which is a homogeneous sphere with a radius of 2.5 pixels (10 mm).

** 10^7 photons are used in Monte Carlo simulations for all cases unless otherwise specified.