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Validating atlas-guided DOT: A comparison of diffuse optical tomography informed by atlas and subject-specific anatomies

Robert J. Cooper [a,*,1], Matteo Caffini [b,g,1], Jay Dubb [a], Qianqian Fang [a], Anna Custo [c], Daisuke Tsuzuki [d], Bruce Fischl [a], William Wells III [e,f], Ippeita Dan [d], David A. Boas [a]

[a] Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA
[b] Department of Health Sciences, University of L'Aquila, L'Aquila, Italy
[c] Centre Medical Universitaire, Functional Brain Mapping Laboratory University of Geneva, Geneva, Switzerland
[d] Functional Brain Science Laboratory, Center for Development of Advanced Medical Technology, Jichi Medical University, Shimotsuke, Tochigi 329-0498, Japan
[e] Department of Radiology, Harvard Medical School, Boston, MA, USA
[f] Brigham and Women's Hospital, Boston, MA, USA
[g] Dipartimento di Fisica - Politecnico di Milano, Milan, Italy

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ABSTRACT

We describe the validation of an anatomical brain atlas approach to the analysis of diffuse optical tomography (DOT). Using MRI data from 32 subjects, we compare the diffuse optical images of simulated cortical activation reconstructed using a registered atlas with those obtained using a subject's true anatomy. The error in localization of the simulated cortical activations when using a registered atlas is due to a combination of imperfect registration, anatomical differences between atlas and subject anatomies and the localization error associated with diffuse optical image reconstruction. When using a subject-specific MRI, any localization error is due to diffuse optical image reconstruction only. In this study we determine that using a registered anatomical brain atlas results in an average localization error of approximately 18 mm in Euclidean space. The corresponding error when the subject's own MRI is employed is 9.1 mm. In general, the cost of using atlas-guided DOT in place of subject-specific MRI-guided DOT is a doubling of the localization error. Our results show that despite this increase in error, reasonable anatomical localization is achievable even in cases where the subject-specific anatomy is unavailable.

Introduction

Near-infrared spectroscopy (NIRS) provides functional information about the oxygenation status of tissue by measuring optical signals which reflect changes in the concentrations of oxygenated-hemoglobin (HbO) and deoxygenated-hemoglobin (HbR) (Jöbsis, 1977). Diffuse optical tomography (DOT) is a multichannel NIRS approach, whereby numerous near-infrared sources and detectors coupled to the skin enable depth-resolved images of the spatio-temporal variations in hemoglobin concentrations to be reconstructed (Bluestone et al., 2001; Culver et al., 2003; Gibson et al., 2005; Zeff et al., 2007). Both NIRS and DOT have been widely applied to investigate brain function over the last 15 years (Durduran et al., 2010; Gibson et al., 2005; Lloyd-Fox et al., 2010). Recently, DOT has been used to map the visual cortex and investigate functional connectivity and motor–visual coordination with millimeter-order spatial resolution (White et al., 2009; Zeff et al., 2007). Whole-head, three-dimensional image reconstruction of regional blood volume and oxygenation has also been demonstrated in healthy and neurologically damaged infants (Austin et al., 2006; Gibson et al., 2006).

Numerous approaches have been investigated for improving DOT image sensitivity, resolution and accuracy (Boas et al., 2004; Gibson et al., 2005; Zeff et al., 2007). Employing a large number of sources and detectors (optodes), densely packed so as to provide spatially overlapping measurements, is essential for accurate DOT image reconstruction (Culver et al., 2003; Durduran et al., 2010; Zeff et al., 2007). The importance of including source–detector pairs with a relatively short separation (of 10 mm or less) has also been confirmed for both NIRS (Gagnon et al., 2011) and DOT (Gregg et al., 2010). Short-separation channels are sensitive to superficial tissues only. Such measurements not only allow the confounding effects of scalp hemodynamics to be removed from standard-separation signals in NIRS studies, but also improve the separation of superficial and cortical signals inherent to depth-resolved DOT.

Despite these advances, the most significant drawback of traditional DOT approaches is the absence of corresponding images of brain structure. Knowledge of the specific brain anatomy not only allows registration of DOT images to the cerebral cortex, but can also significantly improve the images themselves by restraining the

* Corresponding author.
E-mail address: rcooper@nmr.mgh.harvard.edu (R.J. Cooper).
[1] These authors contributed equally to this paper.

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ill-posed DOT image reconstruction problem. This same approach has been investigated extensively for EEG and MEG techniques; registration to an anatomical MRI image can be used to restrain the source reconstruction problem and has been shown to be of significant benefit (Dale and Sereno, 1993; Huppertz et al., 1998). The same has been achieved for diffuse optical tomography using subject-specific MRI images (Barbour et al., 1995; Boas and Dale, 2005; Ntziachristos et al., 2002). However, the requirement to obtain a subject's MRI undermines one of the fundamental advantages of DOT systems: that they are portable and can be easily applied to vulnerable subjects. A promising alternative is therefore to use a registered 3D atlas head model in place of the subject's MRI, as described by Custo et al. (2010). This MRI-free approach to anatomically guided DOT image reconstruction and interpretation is based on registering a selected atlas to the subject's head surface and solving the photon migration forward problem in the registered atlas space. This approach requires measuring the positions of the optical sources and detectors and the cranial landmarks of the subject's head in 3D space, commonly using an electromagnetic tracking system. This allows the atlas to be transformed into the subject space (or 'registered') using an affine transformation computed using the corresponding cranial landmarks in the two spaces (Singh et al., 2005; Tsuzuki et al., 2007).

Atlas-guided DOT will clearly exhibit errors in the localization of cortical activations. The sources of this error will be: 1) imperfect registration between the subject and atlas spaces, 2) differences between the subject's true anatomy and the atlas anatomy and 3) the localization error associated with diffuse optical image reconstruction. These sources of error have previously been investigated, but not in combination. Studies have shown that by employing the subject-specific MRI, the error associated with DOT localization of simulated brain activation in the cortex is 5–10 mm (Boas and Dale, 2005). The error due to the registration process has also been explicitly investigated and found to be on the order of 4–7 mm (Singh et al., 2005; Tsuzuki et al., 2007). However, it is clearly necessary to explicitly test the entire atlas-based DOT process, and how errors in localization, registration and anatomy will affect the accuracy of the image reconstruction process.

In this paper we seek to validate the atlas-guided DOT methods described in Custo et al. (2010), and quantify the corresponding error in the localization of simulated cortical activations. Using an MRI library of 32 subjects, we simulate DOT measurements of brain activation in the subject space then reconstruct the corresponding DOT images using both an atlas registered to the subject and the subject's true anatomy. This allows us to directly compare the anatomical location of the images reconstructed in the atlas space with those reconstructed in the subject space.

Materials and methods

MRI data, atlas and pre-processing

Anatomical MRI images with a voxel size of $0.94\times0.94\times1.5$ mm were obtained using the multi-echo FLASH pulse sequence described in Fischl et al. (2004) for 32 adult subjects. The atlas MRI volume we employed was the high-resolution 'Colin27' digital brain phantom as described by Collins et al. (1998). The atlas MRI volume and all subject MRI volumes were automatically transformed into a single coordinate system in FreeSurfer, which ensures consistent orientation. Preprocessing of the 32 individual MRI volumes and of the anatomical MRI atlas was performed in order to segment the volumes and extract the pia mater surface as a 3D mesh. The subject-specific MRI volumes were segmented into gray matter, white matter and extra-cerebral tissue, using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) (Dale et al., 1999; Fischl et al., 1999). The anatomical atlas was segmented in the same manner and then registered to each subject space using an affine transformation from the 10/20 scalp positions on the atlas to the 10/20 scalp positions on the real anatomy (Singh et al., 2005). The 10/20 scalp positions were identified on the different head surfaces following the procedure outlined in Jurcak et al. (2007). This pre-processing produced 32 segmented subject brain volumes and 32 registered, segmented atlas volumes.

Virtual DOT probe and sensitivity mapping

In order to simulate DOT measurements it was first necessary to produce a virtual DOT probe and map this probe to our 32 MRI data sets and our 32 registered atlases. We utilized a large virtual probe with 100 detectors and 29 sources arranged in a hexagonal pattern such that the nearest and second-nearest source-detector separations are 20 and 34.6 mm respectively. The virtual probe was created in 2D space, but was designed to be wrapped to the 3D surface of the scalp. The 2D probe was first anchored in each MRI space such that the midline of the probe was aligned to the midline of each head (i.e. the nasion–inion sagittal plane) and a specific optode was positioned at Cz, the apex of the head. The remaining 128 source and detector positions were then wrapped to the head using an iterative, spring-relaxation algorithm. This algorithm introduces a spring constant between nearest neighbor optodes such that a force is applied if the separation between those optodes deviates from the optimal 20 mm. The force exerted on the optodes was then minimized by allowing the optodes to move in 3D space by up to 1 mm per iteration. Between iterations, all optode locations are forced to the surface of the scalp. Iterations continued until optode locations converged. After this process was complete, the average nearest and second-nearest source-detector separations, were 20.1 ($\pm$0.69) and 34.5 ($\pm$0.91) mm. The 2D probe is shown in Fig. 1a, and the virtual probe wrapped to a registered atlas head is shown in Figs. 1b and c. Note that in a real atlas-based DOT study, the 3D coordinates of the optode positions on the subject scalp would be measured and those positions would then be transformed into the registered atlas space. For the current study, we wrapped the virtual probe to the registered atlas directly rather than transforming the subject-space optode positions. The transformation of optode locations usually results in many optodes being placed above or below the scalp, which then necessitates the application of a relaxation algorithm similar to that described above to force the optodes to the scalp and correct source–detector separations.

Once we had obtained each source and detector position for each of the 64 head models, Monte Carlo photon migration simulations were performed using a GPU-based Monte Carlo algorithm (Fang, 2010). Measurement sensitivity profiles were obtained for the nearest and second-nearest neighbor source–detector pairs, providing a total of 284 channels. The absorption and reduced scattering coefficients were 0.0178 mm^{-1} and 1.25 mm^{-1} for white matter and gray matter and 0.0159 mm^{-1} and 0.8 mm^{-1} for extra-cerebral tissues respectively (Boas and Dale, 2005). The resulting measurement sensitivity profiles form rows in the matrix $\boldsymbol{A}$ that transforms from the voxel space of localized changes in the absorption coefficient, $\boldsymbol{x}$, to the measurement space $\boldsymbol{y}$ of optical density changes. That is, $\boldsymbol{y}=\boldsymbol{A}\,\boldsymbol{x}$. Summing along columns of $\boldsymbol{A}$, we obtain the aggregate sensitivity of our probe geometry to absorption changes at each voxel. This aggregate sensitivity to absorption changes within the cortex is exemplified for three subjects in Fig. 2.

Simulating cortical activation

Given the measurement sensitivity matrix, simulated DOT measurements of brain activation can be computed by first simulating a vector which defines a change in the absorption coefficient of selected voxels. Simulating an activation in the subject space allows us to compute the localization errors inherent to the DOT images reconstructed using both the subject's anatomy and the atlas anatomy.