22 High-Resolution Source Imaging From EEG

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22.1 Introduction

As described in the introduction to the proposed DBPs (Section 14), there are three DBPs concerned with bioelectricity and the brain. Two DBPs, this one and our collaboration with Dr. Warfield (Section 21), have the goal of reconstructing neuroelectric brain sources measured passively by sensors on or outside the head. The third, with Dr. Butson (Section 20), has the goal of changing physiological function by applying electrical energy (stimulation) with electrodes placed in or on the head. Through key scientific and computational contributions at several points of intersection, the CIBC’s integrative approach will allow us to make unique contributions to this community of researchers studying head electromagnetics for neurophysiological analysis and stimulation.

In collaboration with Dr. Don Tucker, this DBP is specifically concerned with improving our ability to reconstruct neuroelectric sources in the brain from EEG measurements. For both research and clinical practice, EEG is a cost-effective tool for understanding brain activity. Although functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) provide high spatial resolution, their temporal resolution is limited and they are based on indirect measures of neurophysiological activity, i.e. hemodynamic and metabolic changes. EEG, on the other hand, is directly sensitive to the underlying neural sources. Its temporal resolution is limited only by the sampling rate; however, its spatial resolution is generally assumed to be poor, even in comparison to PET. In fact, the true intrinsic spatial resolution of the human EEG remains unknown because the limits of electrical source reconstruction have not been tested with adequate measurement technology. Advances in EEG technology now include fast, robust, dense (256-channel) sensor arrays, exact sensor position measurement (such as with photogrammetry), and EEG source localization methods that take advantage of carefully regularized linear inverse estimations and precise specification of head tissue geometry from MRI. These advances have significantly improved the spatial resolution of source estimates with EEG and offer the promise of accurate monitoring of cortical activity in both space and time. By itself, high-resolution EEG would be affordable even for small hospitals in remote locations and could be easily managed by technicians in the field.

Our collaborator Dr. Tucker and his co-workers at University of Oregon and Electrical Geodesics, Inc. (EGI) are pioneers in the development of dense array EEG technology (which they refer to as “dEEG”). Their systems are in use in over 400 locations around the world. A diverse array of scientific and clinical applications are being examined in those 400+ laboratories using EGI technology. Many of these development efforts would directly benefit from the advances we propose. As an example of immediate clinical application, we focus here on the improvement of neurosurgical planning for resection of the epileptic focus using dEEG constrained by accurate head conductivity estimates. We do want to note that there are many other clinical applications that would be supported by improved source estimation. One example is in emergency and intensive care settings, where it is often important to differentiate coma due to metabolic encephalopathy, which is diffuse and non-local, from that due to stroke, hematoma, or other structural lesion, which often has a focal localization of the EEG pathology. However, there are a number of on-going limitations of EEG-based neural source localization that are topics of current and planned research for Dr. Tucker and his group, which span the interests of all of CIBC’s TRDs.
The current and planned research topics stem from Dr. Tucker and his co-workers' scientific and clinical high-priority objectives, which are:

**Scientific/Clinical Objectives:**

**Scientific Aim 1:** Improve our ability to accurately and robustly estimate neural sources from EEG in clinical settings by improving the accuracy of the associated forward models.

**Scientific Aim 2:** Specifically, improve our ability to estimate individualized skull conductivity distributions by constructing an appropriate electrical impedance tomography (EIT) system and instrumenting it with effective forward and inverse solution algorithms and software.

**Scientific Aim 3:** Improve our ability to evaluate the source localization methodologies and apply them in clinical settings through accelerated forward model and inverse solution computation, improved multimodal visualization, and an extensible software platform that includes alternative forward and inverse solution strategies for comparison and cross-validation.

**Collaboration Objectives:** In accordance with the match between these objectives and the interests and strengths of CIBC, we propose the following specific collaborative aims for this DBP (noting for each Aim the associated CIBC TRD):

**Collaboration Aim 1:** Compare structured and unstructured meshing / PDE-solving strategies, including the use of GPU acceleration, for the EEG forward problem (Image-based Modeling, Simulation, Estimation).

**Collaboration Aim 2:** Improve the accuracy of our EEG inverse solutions through the development of algorithms for subject-specific estimation of conductivity parameters, especially the skull, using electrical impedance tomography, tailored for the EIT measurement systems being developed by Dr. Tucker (Estimation).

**Collaboration Aim 3:** Implement multi-modal visualization software of the component imaging modalities (including at least MRI, DT-MRI, and EIT) which are used to build geometries for forward models (Visualization).

**Collaboration Aim 4:** Develop an enhanced platform for reproducible comparisons of forward and inverse methods for EEG source localization by leveraging our collaborators’ GeoSource system as well as CIBC software (Simulation, Estimation).

**22.2 Background**

**Introduction:** Dr. Tucker is the CEO and Chief Scientist at Electrical Geodesics, Inc. He is also Professor of Psychology and Associate Director of the NeuroInformatics Institute at the University of Oregon. He has published over 140 articles and book chapters on normal and abnormal psychology, brain function, and the electrophysiological methods for investigating brain activity. His 2007 book for Oxford University Press, *Mind From Body*, has been received as a major contribution to theoretical neuropsychology. His basic research examines self-regulatory mechanisms of the human brain. These mechanisms include motivational and emotional control of cognition, as well as neurophysiological control of arousal, sleep, and seizures. His applied research focuses on high-performance computing for analyzing human brain activity with dense arrays of scalp sensors, including electroencephalography, electrical impedance tomography, and near-infrared spectroscopy. Based on the Geodesic Sensor Net, which Tucker invented, the dense array (64 to 256 channel) EEG systems made by Electrical Geodesics Inc. are now used in over 400 laboratories world-wide; over 400 publications with this technology are now in the scientific literature.

Dr. Tucker’s group’s work on source localization is one effort in a tremendously diverse and active field of neuroscience and clinical research. Current efforts range from development of neural mass models to a large number of methods for forward modeling and regularization of inverse solutions (for a relatively recent survey, see), to perhaps an even larger number of papers on clinical applications. There even exist a number of established software packages, some of which are described below.

As an illustration, we briefly describe an important clinical application for EEG source analysis, the localization of seizure onset prior to neurosurgical resection of the epileptic focus, which has been a recent area of activity for Dr. Tucker and EGI. (We note that this application, specifically in the pediatric setting, is the main
focus of our DBP project with Dr. Warfield, as described in Section 21). The current standard of care for epilepsy involves long-term in-patient EEG recordings at low channel counts (typically 19 channels). However, recent research with source localization of epileptic foci\textsuperscript{905} has shown that dense-array EEG provides substantial improvements in source estimation. Partial epilepsy syndromes affect about 0.5\% percent of the population.\textsuperscript{910} A significant percentage cannot achieve satisfactory control of their seizures with medication alone. Patients in this group may be considered for surgical treatment of their epilepsy. Of these candidates, many are excluded because they have obvious multifocal or generalized forms of epilepsy that are not amenable to surgery.\textsuperscript{911} The remaining candidates are usually recommended for additional evaluation at a tertiary comprehensive epilepsy center. There, they participate in a battery of tests and procedures in order to clarify exactly a) what type of epilepsy syndrome they have,\textsuperscript{912} b) where the epileptogenic zones may be located, and c) whether they are an appropriate candidate for surgical resection of the epileptic focus. A specific case study of Dr. Tucker’s efforts in this area is described under Preliminary Work.

**Background on accurate forward modeling (Collaboration Aims 1 and 2):** The general task for electrical source localization is finding the electrical source generators for the potentials that are measured by EEG sensors on the scalp. In this situation, the inverse procedure estimates the amplitudes to be attributed to sources in the cortex, such that the forward solution most accurately describes the electrical potentials observed, subject to constraints on what constitutes a valid or desirable set of cortical sources. Perhaps the key problem with EEG source localization is, at least to date, the forward problem: because the volume conduction of current through head tissues (from brain source to scalp) is known only in gross approximation, an accurate inverse (from scalp to brain source) cannot be estimated with precision. When the physical model is three-dimensional and geometrically complex, like the human cortex within the head, an accurate forward solution can be difficult to construct and compute. The computational formulation of the source localization problem assumes the forward calculation is without error. However, this assumption in turn implies that the geometry and the conductivity values of the modeled head tissues are known. In general, for any individual, they are not known. Until recently, most practical research in this field has opted for analytical or semi-analytical spherical models of the human head in the forward calculations.\textsuperscript{913,914}

However, to reach the true resolution limits of EEG source localization, we believe it is necessary to attempt to construct as accurate a forward model as it is practical to achieve. Perhaps the most straightforward solution is to use dense structured grids, which are easy to create using the voxel resolution of the underlying anatomical imaging modality (MRI). In turn, they lead to either finite difference method (FDM) or finite element method (FEM) solutions to the underlying Poisson’s equation PDE. However, it can be difficult with such meshes to accurately capture the boundaries of important internal structures where there may be large conductivity interfaces. Moreover, merging multiple imaging modalities with different resolutions can be difficult. Finally, they tend to lead to a large number of nodes and, thus, high computational complexity. On the other hand, unstructured meshes can capture anatomical complexity more accurately and efficiently and still be solved effectively using the FEM. In settings where conductivity isotropy is a reasonable assumption, the number of degrees of mesh freedom can be even further reduced through the use of surface meshes only in Boundary Element Method (BEM) computations. Computationally unstructured meshes trade-off greater complexity in mesh construction against more efficient solutions to the forward and inverse problems once the mesh is constructed. The effective, accurate, and efficient use of FEM and BEM methods requires a significant degree of highly specialized expertise in mesh construction and optimization, appropriate trade-offs between mesh density and basis polynomial degree, and iterative, or even GPU-based, solutions to large, often sparse, sets of equations. The full range of approaches to PDE construction is well reflected in the E/MEG reconstruction community, with adherents of all these approaches being present.

Even when realistically shaped finite-element or finite-difference models based on MRI scans are employed, the conductivity values of tissues are taken from assumptions in the literature because no routine in vivo methods for measuring conductivity are available.\textsuperscript{915} Dead or animal tissues may have electrical properties that vary considerably from those of live human tissues.\textsuperscript{916–918} Furthermore, there may be substantial individual differences in head tissue conductivity, such as suggested by invasive measures with brain tumor patients.\textsuperscript{919} A method for measuring head tissue conductivity with good accuracy in each patient is required.

Magnetoencephalography (MEG) has been touted as a superior method to EEG because it is relatively insensitive to variations in head tissue conductivity. However, MEG requires measurements to be made with expensive, superconductive magnetometers in a magnetically shielded room. The traditional comparisons of MEG with EEG have been made with the assumption that the skull is 80 times more resistive than the brain, as estimated by Rush and Driscoll.\textsuperscript{920} However, a number of recent studies have questioned this assumption and
have suggested that the skull is relatively transparent to electrical volume conduction.

Several other imaging modalities have been proposed for measuring head tissue conductivity, but all have limitations. Magnetoacoustic Hall effect imaging relies on propagation of ultrasound into the tissue and is not quantitative. Magnetic resonance current density imaging requires applying a high level of external currents to produce a magnetic field contrast visible by MRI and has not been found to be practical for human subjects. The electrical conductivity tensor of tissue can be quantitatively inferred from the water self-diffusion tensor as measured by diffusion tensor magnetic resonance imaging (DT-MRI). It can be successful in extracting anisotropic conductivities of brain tissue, but it is not helpful for the major problem of estimating conductivity of the skull, where the water content is limited.\(^1\)

Another approach is to attempt to directly measure the required conductivities through the use of electrical impedance tomography (EIT). The principle of EIT is to inject known currents and measure the induced voltage, or alternatively, apply known voltages and measure the induced currents, using arrays of electrodes on the surface. This measurement is repeated using an appropriate set of distinctly applied current or voltage patterns and the collected results are fed into an inverse calculation to estimate the distribution of conductivity in the interior. Both simulations and experimental estimates with EIT in recent studies (Oostendorp et al., 927 Goncalves et al., 928, 929 Clerc et al., Hoekeme et al., 931 and Zhang et al. 932) have suggested that the skull’s resistivity may be only 15 times more resistive (less conductive) than brain rather than 80 times. To return to the EEG / MEG comparison, these findings would cause a revision of previous efforts at electrical source localization, previous EEG versus MEG comparisons, and they have been strongly disputed by both EEG and MEG researchers (e.g., Michael Scherg, personal communication to Dr. Tucker). Recent simulations (Ryynanen et al., 933 Ryynanen et al., 934 Malmivuo and Suihko935) indicate that, if the new information on the conductivity of the skull is correct, the spatial resolution of EEG would be better than that of MEG. One limitation of these simulations is that they were carried out with a spherical model of head tissue conductivities, which fails to account for the major conductive pathways through skull orifices, including the optical canals and basal foramina.

Traditional electrical impedance tomography attempts to image the structure of body tissues. It is generally assumed to exhibit poor spatial resolution in the presence of resistive interfaces like skull tissues, particularly at the low frequencies of physiological interest (i.e., matching those of the EEG). In an approach developed by Dr. Tucker and his co-workers, the problem of skull conductivity was addressed in vivo within the framework of what they refer to as “bounded” EIT (bEIT). In bEIT, the geometry or structure of head tissues is specified from the MR and CT data and the unknowns are restricted to the conductivity values of the major head tissues. For some spaces, such as that occupied by cerebral spinal fluid, the value does not vary and can be set. Thus in bEIT the parameters to be estimated can be limited, such that reasonable degrees of precision can be achieved by reasonable computational resources. Indeed, bEIT may become a routine adjunct to EEG measurements.

Mathematically, bounded EIT is more reliable, stable, and solvable than traditional EIT. Determining the realistic geometries of the human head can be accomplished by segmenting MRI/CT scans into several tissues and through anatomical parcellation of the skull, such as into the major bones. Once this is done, the whole-head conductivity map can be represented by compartments with unknown piecewise constant conductivities and known boundaries. Several previous studies have been reported by other authors who parameterized the problem to solve for a small number of conductivity parameters using nonlinear inverse methods, assuming that the internal geometry of the head was already known. This approach was suggested by Eriksen based upon the three-sphere model of Rush and Driscoll. Eyuboglu et al.\(^939\) and Olmi et al.\(^940\) used similar approaches, although not in the human head. Glidewell and Kwong\(^941, 942\) implemented a similar technique for use in the field of electrocardiography (ECG). They performed 2D and 3D simulations using FEM and obtained some promising results using only 16 electrodes. Oostendorp et al.\(^943\) and Van Burik and Peters\(^944\) showed in a three-layer BEM head model that it is possible to determine the scalp/brain ratio. Goncalves et al.\(^928, 929, 945\) also applied spherical and three-layer boundary element models (BEM) to fit their EIT measurements for six subjects. In fact, the CIBC has also recently published several reports on what we referred to as “known-geometry” EIT,\(^475, 478, 482\) which is similar in spirit to the bEIT approach. We proposed specific algorithms for known-geometry EIT for both BEM

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\(^1\)We note that the use of diffusion tensor MRI for conductivity estimation for brain source localization is a significant component of our DBP collaboration with Dr. Warfield (Section 2). Of course any advances made in that collaboration in terms of this use of DT-MRI will be fed back into this DBP. Moreover, whatever means are used to determine skull conductivity, basic science advances are now being made in the neurophysiology of cognition that require dEEG source localization constrained not only by the cortical surface, but by tractography information on the connectivity of the cortex and subcortical circuits. For example, recent insights into specific circuits in thalamocortical networks suggest a specific analysis for understanding the anatomy of oscillatory mechanisms in the cortex. This analysis is just an example of a range of theoretical advances that will be made through combining detailed brain connectivity information with accurate electrical source localization of cortical activity.
and FEM forward models and validated our results by simulations and measurements made in a cylindrically-shaped tank at the Impedance Imaging Lab at RPI. This work was done in the context of torso imaging, similar to the work of Goncalves et al. just cited, but can be applicable to brain imaging as well. It is described in more detail in the Estimation TRD, Section 12. However, since skull thickness and conductivity are interchangeable to some extent in sphere and boundary element models, more accurate geometry representation is needed. Furthermore, BEM models are unable to deal with skull inhomogeneities and anisotropies and, in fact, are topologically equivalent to the spherical models.

Background on multimodal visualization (Collaboration aim 3): Accurate solutions to the EEG source localization problem requires integration of data from a number of sources, including anatomical MRI, likely diffusion-weighted MRI, EIT, photogrammetry, and the EEG sensor data itself. Moreover, invasive validation measurements are likely to be important during the development and even during routine deployment (see Preliminary Results, Figure 22.2, for an example) and compared to reconstructed source activity images. Each of these data sources has not only its own characteristics and importance, but also its own level of noise and other types of geometric uncertainty. An effective tool to visualize these data together becomes an essential component for their successful integration. Visualization is important as a means of validation for the scientific investigator. It is also critical to eventual acceptance of the tools by potential clinical users. Thus, there is a need for flexible, interactive, visualization tools which are a) integrated with the model-building, simulation, and reconstruction software, b) able to handle multiple large data-sets, and c) able to visualize uncertainties inherent in each type of data as well as growing out of their joint use to produce derived results. Finally, provenance of the original data, the derived results based on the data, and the various visualizations themselves will be critical to reproducibility and transferability of results, and must be integrated with the visualization capabilities.

Background on EEG inverse solutions (Collaboration Aim 4): Standard inverse solutions to localize sources either assume the existence of a known number of dipole-like sources and solve for their position, orientation (both non-linearly related to the measurements), and amplitude (or, in time, waveform), or they apply a linear inverse solution in which the unknowns are the source amplitude at all voxels in the appropriate subvolume of the head model (referred to as an “imaging approach” in the appropriate literature). Both problems are ill-posed and require regularization constraints. One standard example of the linear approach is to constrain the sources by the LAURA (Local AUtoRegressive Average) assumption. The LORETA (LOw REsolution Electrical Tomographic Analysis) regularization is another standard method which gives generally similar results. However, both of these approaches have significant limitations in terms of both accuracy and robustness; the development of better constraints and associated algorithms is a topic of significant current research.

22.3 Significance of the collaboration

Each of the collaboration aims outlined above will provide a testbed for CIBC TRDs, which will guide, and even drive, our technical research and software development, and, at the same time, provide resources to Dr. Tucker and his group that can be expected to significantly accelerate their ability to achieve their own scientific and clinical goals.

Collaboration Aim 1: Dr. Tucker's group has concentrated in the past on the FDM method, primarily because of its ease and adaptability. However, they are very motivated to work together with CIBC to compare unstructured mesh-based methods in the context of their data, modeling, and application scenarios. This is in line with their drive towards exploring the actual limits of EEG resolution while at the same time providing practical clinical solutions to their collaborators and, in the case of EGI, customers. Thus, we will use our collaboration with Dr. Tucker as a prime focus of our mesh construction and optimization work as described in the Image-based modeling TRD (Section 9), our forward solution work on bioelectric field problems as described in the Simulation TRD (Section 11), and our mesh quality estimation and model optimization as described in the Estimation TRD (Section 12). Our plans to develop efficient tools for meshing multi-material volumes and for hybrid meshes involving prisms for thin structures (which we anticipate will be of particular use in the skull) are of particular relevance in CIBC’s collaboration with Dr. Tucker. Hybrid meshes also are a key component in our work on optimizing meshes for our inverse solution accuracy and robustness, as described in Section 12. This DBP will be an ideal test case for approaches to hybrid multi-material meshing and, at the same time, will provide Dr. Tucker with technology that should be of great use in their drive to maximize the clinical applicability of EEG source localization.

Moreover, as model complexity grows, in particular through fusing information from multiple modalities (MR, DT-MR, EIT, EEG), and as we move to ever more detailed subject-specific models, the computational burden
of solving the “forward” problem (computing estimated EEG measurements based on a hypothesized set of neural sources), grows accordingly. At the same time, as we move to more sophisticated regularized solutions, especially for non-linear problems like EIT or dipole-based source localization, the complexity growth of inverse solutions is further increased, both in its own right and as a consequence of the need to repeatedly perform forward solves. Thus, in the effort to obtain clinically meaningful source localization, computational bottlenecks become significant obstacles. As described in the Simulation TRD section, GPU-based acceleration of FEM solutions to PDEs such as Laplace’s equation is a significant goal of our renewal proposal. Again, we will use the clinically-driven focus of our collaboration with Dr. Tucker as a prime arena to motivate, evaluate, and improve our GPU acceleration work.

**Collaboration Aim 2:** Dr. Tucker has been developing both the hardware and algorithms for EIT, specifically bEIT. However CIBC’s previous work on EIT has been highly complementary to that of EGI and Dr. Tucker; we anticipate a highly synergistic relationship. Specifically, the history and literature of EIT development have shown that practical decisions on imaging hardware strategies can significantly affect the achievable reconstruction accuracy. For instance, there are practical cost versus accuracy trade-offs between current injection and voltage application. There are similar trade-offs with regards to maximizing electrode coverage of the outer surface while determining the number and size of electrodes used. One particular practical design decision is whether current (or voltage) is measured with the same electrodes used to apply voltage (or inject current). As an example, there are a large suite of EIT imaging strategies that inject current with a pair of electrodes and measure voltage with the remaining electrodes. However, a whole series of theoretical and practical studies have indicated that this is significantly suboptimal for two reasons. First, using only two electrodes to apply energy dramatically restricts the possible spatial patterns of current or voltage that can be applied. From a theoretical point of view, the optimal patterns are the eigenvectors of the forward operator. For example, for a sphere or cylinder the ideal patterns are sinusoids over the outer surface. The closer one approximates those patterns, the higher the resulting signal-to-noise ratio, and thus, the higher the potential reconstruction accuracy and resolution. Approximating the ideal patterns almost always requires using many, perhaps all, of the electrodes to apply energy at the same time. Secondly, perhaps the most valuable information available (because of the high local gradients) can be obtained by measuring with the electrodes that apply the current or voltage. In our own previous work on EIT, for example, we found that sensitivity to error in our knowledge of the exact locations of the electrodes is significantly reduced if measurements are also made with the current-injecting electrodes, even in the setting where only two electrodes are used to inject the current.

However, both of these design elements—multiple electrode energy application patterns and measurement with energy application electrodes—as well as some of the other considerations previously mentioned, have significant implications regarding hardware expense and complexity in order to enact them.

The interests of Dr. Tucker’s group in practical application of EIT will guide our EIT research as described in Section 12, especially for known geometries. At the same time, our background and future developments in EIT will help guide EGI’s application of this technology to head conductivity estimation in the context of brain source localization.

**Collaboration Aim 3:** Dr. Tucker’s group has already been working on their own multi-modal visualization, as can be seen in Figure 22.1. CIBC and the SCI Institute have world-renown expertise in the very areas of visualization need outlined above and there is great opportunity for synergy. Moreover, many of the visualization needs of this DPB are similar to those of the DBP with Dr. Warfield (Section 21).

**Collaboration Aim 4:** As described in the section on estimation (Section 12), CIBC has, in the most recent grant period, performed research in the area of EEG and MEG inverse solutions. We continue to pursue a number of bioelectric field inverse solution aims, again as described in that section. However, our primary interaction with Dr. Tucker’s group in this Aim will surround integration between their existing techniques and our current and proposed inverse methods, mostly at the level of software interoperability. There are a number of existing software packages available for solving various aspects of the EEG (and MEG) source localization problem. Each has its own areas to which it gives special attention; each makes certain assumptions about the solutions to be used for the various aspects of the complete problem (i.e. model building, forward solution method, inverse solution method, visualization); and, each has its advantages and limitations. Some of these packages are commercial and proprietary, while others are open source or at least free. Some require proprietary software infrastructure such as MatLAB, while others do not. Examples include NeuroFEM, IP, ASA (Advanced Source Analysis, http://www.ant-software.nl, 2002) and CAUCHY, CURRY, Brainstorm, MNE (http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/sofMNE.php), and EEGLab. As already noted, EGI...
Figure 22.1: Finite difference current modeling with the atlas typical brain data, showing the skull orifices (red, left) and the complex current paths in the inferior head regions (middle, right).

has its own proprietary package, GeoSource. In this context, our goal will be to leverage existing products to the maximum extent possible, to increase both our ability to test CIBC efforts and Dr. Tucker’s capability to evaluate their development efforts for GeoSource. For instance, we have a long-standing collaboration with Dr. Carsten Wolters around interoperability between SCIRun and NeuroFEM.

22.4 Rationale and preliminary results

Preliminary work and existing software

The proposed collaboration with Dr. Tucker is new for CIBC. Therefore, we do not have explicit collaborative preliminary results. We do have considerable past expertise in the area of inverse EEG and MEG imaging, EIT, and other technologies relevant to this DPB—our work in this area in the past grant period is described in the TRD sections on simulation (Section 11) and estimation (Section 12). As is clear from the description of Dr. Tucker’s background, his group has a very strong track record of preliminary results in translational research in this area, as most clearly exemplified by their commercial experience with both hardware (Geodesic Sensor Net) and software (GeoSource) products.

However, to give some specificity to this success, we here describe an example of the utility of dense-array EEG in epilepsy, in the form of a brief case report (Holmes et al., submitted). A 13-year old girl was evaluated for possible surgical resection of drug-resistant epilepsy at the University of Washington’s Harborview Hospital. She had complex partial seizures an average of once daily, during which her head would droop, turn to the left, and her right arm would extend. She was evaluated at the Long Term Monitoring (LTM) unit with 128-channel EEG using EGI’s HydroCel Geodesic Sensor Net (Figure 22.2(a)) during which time a typical seizure was recorded. The corresponding recorded EEG’s at the initial onset are shown in Figure 22.2(b). Source localization of the initial EEG pathology (slow wave prior to polyspikes) during seizure onset was examined with EGI’s GeoSource electrical source estimation software. This software (now submitted for FDA 510k certification) is based on the source analysis methods and findings in epilepsy by the Geneva group. The patient’s sensor positions were registered with a head model constructed from the Montreal Average MRI, using EGI’s FDM conductivity model, with the 1:15 skull to brain conductivity ratio. In GeoSource, the cortex is parcelated into 2400 voxels, each with a triple (3 orthogonal dipoles) source model. The linear inverse of the 128 (or 256) scalp recordings to reconstruct the source amplitudes across these sources is constrained by the LAURA (Local AUtoRegressive Average) assumption. The LORETA (LOw REsolution Electrical Tomographic Analysis) regularization is also available in GeoSource and gives generally similar results.

The initial slow wave of seizure onset localized to the left occipitotemporal area (Figure 22.3(a), 0 ms), after which the apparent focus rapidly shifted to the homologous region of the right hemisphere (70 ms). From 200 to 500 ms (selections at 235 and 411 ms), the focus shifted to the left superior parietal area, describing
the wave-polyspike pattern in the EEG which was typical for this patient’s interictal activity. Finally, as the large synchronous discharges of the seizure developed, the primary focus of the seizure was in the medial occipital cortex (not shown). Intracranial electrodes were then surgically placed and two additional seizures were recorded. A 6x8 grid was placed over the left parietal region (the focus of the polyspike activity and suspected epileptogenic zone). Based on the 128 scalp EEG findings, strips were also placed over the inferior and lateral occipital and temporal lobes on both sides. The recording of seizure onset showed that the initial, high-frequency activity of seizure onset was observed in the left inferior occipital region (Figure 22.3(b), red dots), as predicted by the scalp EEG results. The high frequency oscillations spread to the lateral left temporal area and to homologous regions of the right hemisphere within 100 ms or so, again as predicted by the scalp EEG, before engaging more widespread regions including the left parietal polyspike focus. Surgical intervention involved resection of both the left occipitotemporal region and the polyspike focus of the left parietal region (which appeared to involve a focal cortical dysplasia). The patient has remained seizure free 24 months after the operation.

At this time, EGI has upgraded the dense-array system to 256 channels at Harborview Hospital and has recorded EEG on over 70 patients. Ten of the LTM patients have had intracranial placements and, in eight of these, the prediction from the scalp recording was confirmed by the intracranial data.\textsuperscript{960–962} Although the atlas-based head model used in the GeoSource software modeling for these studies has proven useful for a first estimation of seizure onset, it is clear that neurosurgical planning should be guided by a head model constructed from the patient’s own MRI, with empirical measurement of head tissue conductivity.

Dr. Tucker’s interest in the proposed collaboration with CIBC is motivated precisely by meeting the type of clinically-relevant challenges illustrated by this case.

### 22.5 Methods

We organize our description of the proposed work in this DBP according to the collaboration aims as described above.

#### 22.5.1 Collaboration Aim 1: PDE solution enhancements

**Structured vs unstructured grids:** On-going and proposed work on construction of meshes for multi-material volumes, construction of meshes with hybrid elements, evaluation of the importance of various model components (organs, anisotropy, etc.), and estimation of mesh quality, are described in the Simulation and Estimation TRD sections. As noted above, we will use data and geometry from Dr. Tucker as test cases for all of this work and use feedback from Dr. Tucker’s group on the results to guide this on-going research.

In addition, in Section 12 we describe our recent efforts to optimize FEM meshes from an inverse solution point of view. This work has been carried out in the context of inverse electrocardiography. However, we believe...
there is no reason it will not have the potential for significant impact on the inverse EEG problem as well. As part of our collaboration with Dr. Tucker, we propose to explore mesh density improvement without deterioration of ill-conditioning, in particular, through the use of hybrid elements and truncated higher-order elements, closely following on and leveraging the results we anticipate achieving in the inverse electrocardiography work carried out in that TRD.

**GPU-based acceleration:** Similarly, there is a synergistic fit between the needs of this DBP and the work planned on GPU acceleration of forward solutions described in Section 11. Here again the main task will be to coordinate acquisition of appropriate test data from EGI and to use their feedback to guide our own work.

### 22.5.2 Collaboration Aim 2: Estimation of conductivities with EIT

Just as the needs of this DBP will drive our research into meshing and geometric and anatomical modeling for forward and inverse solutions, it will be a primary platform for our research in EIT, as described in Section 12. In this Aim, we will need to go beyond the work already planned in the TRD. In particular, we will expand our known-geometry methods in collaboration with Dr. Tucker to incorporate the bEIT concept of tight bounds on conductivities in certain compartments. We will also apply the methods we describe in the TRD for anisotropic conductivity estimation in this same context. Perhaps more importantly, Dr. Tucker is actively developing the measurement technology for EIT in the brain imaging context. We propose to work closely with his team to help ensure that synergistic design decisions are made with respect to the required accuracy of conductivity estimation.

We see our role in working with Dr. Tucker's team as they design and build their own EIT systems as a simulation resource. As they consider design decisions, we will ensure that our forward model and inverse solution software gives them the capability of testing those designs *in silico* in realistic head models. If their design search requires simulation capabilities not currently planned, or not existing at the time their need is anticipated, we will modify our own EIT software to include them.

In parallel with this effort, as noted above, we plan to work with DBP collaborator Dr. Warfield on the use of DT-MRI for brain conductivity estimation. The CIBC organizational structure will help to ensure that the current DBP effort will benefit from developments in algorithms, results, and software in addressing this critically important component of effective EEG-based source localization.

**Collaboration Aim 3: Multi-modal visualization**
We will implement multi-modal visualization software of the component imaging modalities (including at least MRI, DT-MRI, and EIT), which are used to build geometries for forward models (visualization) as test cases for the planned work described in Section 10. Specific techniques that will be tested in the context of this DBP include large data visualization on unstructured grids, scalar/vector/tensor visualization techniques, quantitative visualization, and error and uncertainty visualization. In this same time period, under separate ARRA funding, we will be developing the provenance capabilities of SCIRun and other CIBC software, which we expect to be of great use to Dr. Tucker's work, especially in the clinical context.

Collaboration Aim 4: Platforms for inverse solutions:

The direction of CIBC software development over the past few years has been towards greater flexibility in our architecture and greater interoperability with other platforms. We envisage that our segmentation software Seg3D, our meshing pipeline BioMesh3D, our simulation and estimation modules in SCIRun, and our visualization package, ImageVis3d, will all be of interest to Dr. Tucker in the context of comparing different approaches in terms of inverse solution accuracy. Our efforts in this aim will generally be developmental rather than research-oriented. This software development will be coordinated through the CIBC management structure and implemented by our core software developers, who will be in frequent communication with their counterparts at EGI who are working on GeoSource development. The goal will be to maximize the ability of GeoSource developers to leverage the algorithms available from CIBC all along the image-to-reconstruction pipeline.

22.5.3 DBP interaction and management

We anticipate that the interactions with Dr. Tucker and his group in this DBP will involve a number of different CIBC personnel since the technical efforts are spread across all four TRDs. In particular, Prof. Brooks will bear primary responsibility for Collaboration Aim 2 and Prof. Johnson for Aim 3, while management of Aims 1 and 4 will be the responsibility of the CIBC Technical Manager. As is standard with all CIBC DBPs, progress is reviewed regularly in our weekly Executive Committee and Management meetings. In addition we plan to hold monthly progress meetings via electronic conferencing with Dr. Tucker and his staff which will include, from the CIBC side, at least Profs. Brooks and Johnson, our Technical Manager, as well as post-doctoral fellows, graduate students, and software developers as appropriate at each given stage of the project.

22.5.4 Impact

Within the broad scope of research activity in the field of neural source imaging, Dr. Tucker and CIBC have chosen a selected subset of potential projects with the goal of maximizing the potential impact of our collaborative work in terms of:

1. Improving near-term translational uses of EEG-based source localization (appropriate with the involvement of the commercial entity EGI Inc. in this collaboration),

2. Moving closer to determining the true resolution possible with EEG, as described above, and

3. Improving the capabilities of our other neuroscience collaborators (in particular the DBP projects with Dr. Warfield as described in Section 21 and Dr. Butson (Section 20).

The algorithms and tools developed in this project will be of immediate use to EGI and Dr. Tucker, and we expect to be able to achieve immediate and broad-based dissemination through their base of more than 400 users of their technology. In addition we believe that our ability to collaboratively begin to assert the true potential resolution of EEG in source imaging could make a very positive contribution to the adoption of this relatively low-cost technology in many research and clinical laboratories.