Patient-specific solution of the electrocorticography forward problem using biomechanics-based image registration

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Abstract

Invasive intracranial electroencephalography (iEEG) or electrocorticography (ECoG) measures electrical potential directly on the surface of the brain, and, combined with numerical modeling, can be used to inform treatment planning for epilepsy surgery. Accurate solution of the iEEG or ECoG forward problem, which is a crucial prerequisite for solving the inverse problem in epilepsy seizure onset localization, requires accurate representation of the patient’s brain geometry and tissue electrical conductivity after implantation of electrodes. However, implantation of subdural grid electrodes causes the brain to deform, which invalidates preoperatively acquired image data. Moreover, postoperative magnetic resonance imaging (MRI) is incompatible with implanted electrodes and computed tomography (CT) has insufficient range of soft tissue contrast, which precludes both MRI and CT from being used to obtain the deformed postoperative geometry. In this paper, we present a biomechanics-based image warping procedure using preoperative MRI for tissue classification and postoperative CT for locating implanted electrodes to perform non-rigid registration of the preoperative image data to the postoperative configuration. We solve the iEEG forward problem on the predicted postoperative geometry using the finite element method (FEM) which accounts for patient-specific inhomogeneity and anisotropy of tissue conductivity. Results for the simulation of a current source in the brain show large differences in electrical potential (RDM $\geq 0.18$ and MAG $\geq 0.84$) predicted by the models based on the original images and the deformed images corresponding to the brain geometry deformed by placement of invasive electrodes. Computation of the leadfield matrix (useful for solution of the iEEG inverse problem) also showed significant differences between the different models. The results suggest that significant improvements in source localization accuracy may be realized by the application of the proposed modeling methodology.

Keywords: epilepsy, electroencephalography, biomechanics, diffusion tensor imaging, meshless methods, finite element method (FEM)

1. Introduction

Techniques to construct patient-specific models of brain bioelectric activity, and to solve such models accurately and efficiently, form the key enabling technology for neuroscience and neurology. Of particular interest is the application of such modeling and simulation techniques to identification of epileptic seizure onset zones (SOZ) which consider the brain at length scales accessible by medical imaging and electrodes. The spatial resolution of medical images and dimensions of electrodes—as well as the accuracy of surgery—are on the order of 1 mm, but in current practice the SOZ is usually located with much lower accuracy.

Epilepsy is a chronic brain disorder that causes unpredictable and recurrent electrical activity in the brain (seizures). Nowadays, epilepsy is treated with medication. Although drugs do not cure epilepsy, they can efficiently control seizures in up to 70% of patients. In the remaining 30%, drug therapy fails to controls seizures, and surgical resection appears as a feasible alternative (Engel, 2003). However, surgical treatment of epilepsy has been the most underutilized of all proven effective therapeutic interventions in the field of medicine (Engel, 2003). This is because the success of surgical resection depends on the accurate identification of the seizure onset zone (SOZ) and clinicians are often unable to characterize epileptic activity of the brain and identify appropriate resection regions with sufficient accuracy to proceed with surgery.

The SOZ is often identified with the help of intracranial measurement of electrical potential during a seizure. An

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intracranial electroencephalogram (iEEG) or electrocorticography (ECoG) (Jayakar et al., 2016) records electrical activity from the cerebral cortex using electrodes placed directly on the exposed surface of the brain (Fig. 1a), whereas stereoelectroencephalography (SEEG) (Minotti et al., 2018) enables exploration of deeply located structures using needle-like depth electrodes inserted inside the brain (Fig. 1b). Implantation of electrodes is an invasive procedure and therefore applied rarely, as the measurements by these electrodes do not directly yield the location of the seizure onset zone with accuracy comparable to imaging resolutions, but rather form an input to further analysis. To increase the utilization of epilepsy surgery there is a pressing need for new and more effective methods of SOZ localization that will enable clinicians to cure epilepsy in a greater number of patients. As it is estimated that 30 million people on Earth have focal epilepsy that can be permanently cured by precisely targeted surgery, methods for successful identification of the SOZ would be of enormous health benefit. One such promising technology is source localization from invasive measurements. Using a biologic model as the basis for an inverse problem, source localization maps individual electrode measurements to three-dimensional maps of brain activity. These maps have the potential to significantly improve SOZ identification by improved analysis of invasive EEG data.

Accurate and robust patient-specific models of brain bioelectric activity could have applications well beyond guiding surgical treatment of epilepsy. These include the analysis of extracranial measurement data, such as standard electroencephalogram (EEG) and magnetoencephalogram (MEG) often used in neurology, neuroscience and neuropsychiatry (Brette and Destexhe, 2012), as well as generation of high-quality synthetic training data for artificial intelligence (AI) systems based on neural networks. This last possible application is becoming particularly important, as in recent years, deep learning has started to gain popularity for bioelectric signal processing. With a large amount of data, it outperforms traditional feature extraction in terms of classification accuracy (Hu et al., 2019). Deep learning algorithms, especially the convolutional neural network (CNN), are also gradually being adopted in epilepsy management, for example for seizure detection (Gao et al., 2020; Thomas et al., 2018).

Source localization based on ECoG or iEEG can be split into two separate problems: the forward problem that involves calculating the electrical potential within the brain volume given a predefined source; and the inverse problem that involves finding the source location given potential measurements at the sensor electrodes. Accurate source localization requires an accurate representation of the geometry of the patient’s brain and electrical conductivity distribution within the patients head (Castaño-Candamil et al., 2015).

This study is based on the realization that a patient’s brain is significantly deformed by the implantation of the electrodes (Fig. 1) and therefore models built from preoperative images will be geometrically very inaccurate. To remedy this situation, we demonstrate how to construct a model of brain bioelectric activity corresponding to the true deformed brain geometry and how to solve quickly the iEEG forward problem—a prerequisite for the iEEG inverse problem that ultimately needs to be solved to localize sources.

In some previous studies, to account for craniotomy-induced brain shift during placement of grid electrodes, the electrode positions identified from the postoperative CT were projected onto the cortical surface extracted from the preoperative MRI (Dykstra et al., 2012; Yang et al., 2012; Tao et al., 2009; LaViolette et al., 2011; Hermes et al., 2010; Taimouri et al., 2014). Although this approach solves the issue of the electrodes being erroneously located within the brain tissue instead of on the surface of the brain, it does not accurately reflect the actual postoperative configuration of the brain. In the current study, instead of projecting the electrode positions onto the undeformed preoperative cortical surface, we aim to predict the postoperative configuration of the brain such that the cortical surface of the model used for solving the iEEG forward problem corresponds to the actual position of the implanted surface electrode array.

In this paper, we propose a novel modeling pipeline for iEEG source localization that incorporates the tissue deformation caused by the craniotomy and placement of the electrodes. Using preoperative MR and postoperative CT images, our approach employs biomechanics-based image warping to predict the postoperative configuration of the brain (i.e. the configuration deformed by the implantation of intracranial electrodes). The postoperative CT is used to locate the electrode positions and to inform the boundary conditions and loading of the biomechanical model. The approach taken in this study is to register the preoperative anatomical MRI and DTI onto the postoperative CT (with electrodes implanted) using a displacement field computed by a biomechanical model (Miller et al., 2019; Mostayed et al., 2013; Wittke et al., 2007; Wittke and Miller, 2020) to obtain warped MRI and DTI corresponding to the postoperative, deformed configuration of the patient’s brain. Based on these warped images we construct a geometrically correct computational domain on which the partial differential equations of the iEEG forward problem are solved, as well as inhomogeneous and anisotropic patient-specific distribution of conductivity tensor used in the solution procedure.

Continuum models based on partial differential equations are the dominant method for brain bioelectric activity modeling at the spatial and temporal scales accessible via ECoG, iEEG, EEG or MEG. Numerical solution of these equations have attracted considerable attention in the literature. Mainstream numerical methods, such as finite element (FEM) (Drøchler et al., 2009; Marin et al., 1998; Pursiainen et al., 2011; Schimpf et al., 2002), finite volume (FVM) (Cook and Koles, 2006), finite difference (FDM) (Bourantas et al., 2020; Hyde et al., 2012; Saleeheen...
and Ng, 1997; Wendel et al., 2008) and boundary element methods (BEM) (Acar and Makeig, 2010; Mejis et al., 1989; Stenroos and Sarvas, 2012), as well as newer, more sophisticated methods such as meshless methods (Fiétier et al., 2013) that use a point cloud to represent the spatial domain, have been used to numerically solve the governing equations of the EEG forward problem.

Finite element methods achieve high numerical accuracy (Drechsler et al., 2009; Vorwerk et al., 2012) and can be easily used to model complex geometries having anisotropic conductivities (Vorwerk et al., 2014). The FEM uses a tessellation of the computational domain in which the domain is partitioned into a set of elements of simple shape, such as tetrahedrons or hexahedrons (Vorwerk et al., 2018). Tetrahedral meshes are generated by constrained Delaunay tetrahedralization from segmented and reconstructed tissue surface representations. On the other hand, hexahedral models can be easily generated from voxel-based raw image data.

Our methodology is an embodiment of the "image-as-a-model" concept (Zhang et al., 2013) as it is entirely voxel-based and the finite element method with a mesh coinciding with the voxelized structure of the image is used to obtain the solution. The advantage of this voxel-based analysis includes straightforward generation of realistic patient-specific models from three-dimensional image data and a simple data structure that is suitable for storage, handling, numerical solution and visualization.

To demonstrate the application of the proposed methodology and to quantify the effect of geometric accuracy on the model solutions, we solve two example problems using the original preoperative geometry (with both the actual and projected electrode positions) and the geometry after model-based image deformation. In the first example, we apply a current dipole inside the brain and compare the potential computed at the electrodes. In the second example, we compute the leadfield matrices (gain matrices relating the current space with the measurement space which are often used in the solution of the iEEG inverse problem) using the models constructed from the original and deformed image data, and compare the difference between the two sets of results. In both examples, our results suggest that the proposed approach has significant potential in improving the accuracy of source localization.

The paper is organized as follows. In section 2, we describe the mathematical model, patient-specific model construction and the components of the numerical methodology. In section 3, we provide patient-specific numerical results confirming robustness and efficiency of our modeling and simulation pipeline, as well as demonstrating inaccuracies of using models built directly from preoperative, undeformed images. Section 4 contains discussion and conclusions.

2. Methods

2.1. Governing equations of the brain bioelectric activity at scales as measured by EEG and MRI

The electroencephalography (EEG) forward problem involves predicting the electrical potential within the brain and at the implanted electrodes given a predefined source. The relevant frequency spectrum in EEG is typically below 1 kHz, with most studies dealing with frequencies between 0.1 and 100 Hz (Baillet et al., 2001; Brette and Destexhe, 2012). Therefore, the physics of EEG can be approximated...
by Poisson’s equation, which is the quasi-static approximation of Maxwell’s equations. For a spatial domain \( \Omega \in \mathbb{R}^3 \) with boundary \( \partial \Omega = \Gamma_D \cup \Gamma_N \), Poisson’s equation for the EEG forward problem can be written as follows:

\[
\begin{align*}
-\nabla \cdot (C(\nabla u)) &= f \text{ in } \Omega, \quad (1) \\
n \cdot (C(\nabla u)) &= g \text{ on } \Gamma_N, \quad (2) \\
u &= h \text{ on } \Gamma_D, \quad (3)
\end{align*}
\]

where \( u \) is the unknown scalar potential and \( C \) is the (symmetric positive semi-definite) conductivity tensor. The low conductivity of air outside the skull \( (C = 0 \text{ for all } x \notin \Omega) \) implies that a zero-flux Neumann boundary condition \( g = 0 \) can be applied on the surface \( \Gamma_N \). Dirichlet boundary conditions \( h \) on \( \Gamma_D \) are typically applied by setting the potential to zero at a node corresponding to a reference electrode, or by setting the potential at two nodes to create a voltage dipole. Loading can be applied to the model either by prescribing the potential at certain nodes or by applying a current source \( f = \nabla \cdot j \), with \( j \) being a dipole source vector. The epileptic seizure onset source is typically modeled as a current dipole (Hallez et al., 2007). Equivalently, the dipole source may be modeled by setting the potential \( u \) at two points in \( \Omega \) with opposite polarity (Schimpf et al., 2002).

Electromagnetic source localization employs a linear model, known as the leadfield matrix, that relates the measured electrode voltages to the cerebral current sources that generated them (Rush and Driscoll, 1969; Weinstein et al., 2000). Using Helmholtz’s principle of reciprocity, computation of this matrix requires the solution of the forward problem for each sensor and ground electrode pair. To compute the leadfield matrix, one electrode is selected arbitrarily as the reference (ground) electrode. For each row in the leadfield matrix, a unit current is applied to one of the sensor (non-ground) electrodes. The electric field in each element is computed as the gradient of the electrical potential and represents a row in the matrix. The potential at the electrodes for a source located in any element can then be computed as follows:

\[
u = Lj,
\]

where \( L \) is the leadfield matrix and \( j \) is the neural source represented as a current dipole.

Although the iEEG forward problem is linear, it is difficult to solve due to significant difficulties in creating a patient specific domain \( \Omega \) on which the equations (1)–(3) are to be solved and patient-specific spatial distribution of anisotropic conductivity tensor \( C \), addressed below.

2.2. Patient-specific model generation

In this section, we describe the methods used to create a detailed patient-specific model for the EEG forward problem. Accurate solution of the EEG forward problem requires a correspondingly accurate representation of both the computational domain (\( \Omega \) in Eq. (1)) and the tissue conductivity (\( C \) in Eq. (1)) throughout the conducting head volume. The head volume is bounded by the rigid skull and scalp which can be easily extracted from the preoperative images. The brain, however, is a soft tissue that deforms due to the insertion of the electrode grid array. To take into account the brain shift following electrode insertion we apply our biomechanics-based image warping techniques to accurately predict the postoperative brain geometry. A detailed description of each step of the proposed method is provided in the following subsections.

Using the methodology described below, we created the following three models for comparison of the different modeling approaches:

1. \textit{unwarped} model based on preoperative (unwarped) image data with actual electrode positions identified from postoperative CT;
2. \textit{projected} model based on preoperative (unwarped) image data with electrode positions projected from their actual locations identified from postoperative CT onto the cortical surface; and
3. \textit{warped} model based on postoperative (warped) image data predicted by biomechanics-based image registration with actual electrode positions identified from postoperative CT.

2.2.1. Image acquisition and image processing

To create the patient-specific EEG forward model we require preoperative anatomical magnetic resonance image (MRI) to obtain the undeformed brain geometry; preoperative diffusion tensor image (DTI) to classify tissue types at each voxel and to estimate patient-specific tissue conductivity; and postoperative computed tomography (CT) to locate the implanted electrodes.

T1 and T2 structural MRI scans (1 mm isotropic) and diffusion MRI (2 mm isotropic) were collected from an epilepsy patient under evaluation for surgical intervention at Boston Children’s Hospital (BCH ethics approval no. IRB-P00025254, UWA ethics approval no. RA/4/1/9336). All images were coregistered to the T1 scan, and resampled to have matching 1 mm isotropic resolution. Residual motion in the DWI was compensated for by appropriate reorientation of gradient directions, and diffusion tensors were estimated using robust least squares. The dimensions of the images are \( 160 \times 192 \times 192 \) voxels with spacing \( 1 \times 1.09375 \text{ mm} \times 1.09375 \text{ mm} \) (Fig. 2).

An 8×8 grid of platinum-iridium electrode disks (4 mm diameter, 10 mm spacing) was placed on the cortical surface through a craniotomy. Electrode placements were identified from post-surgical CT, coregistered and resampled to the resolution of the presurgical MRI. Intensity thresholding was used to identify individual electrodes, with manual validation of electrode separation. The postoperative electrode positions were projected onto the preoperative brain surface (Taimouri et al., 2014) to obtain the displacement field of the brain surface in the vicinity of
the electrodes, and to correct for the intraoperative brain-shift in the model that was based on undeformed preoperative image data with projected electrode positions.

2.2.2. Patient-specific geometry

**Brain deformation due to intracranial electrode array insertion**

Insertion of intracranial electrodes results in significant brain deformations that need to be accounted for when defining the domain on which the EEG forward problem needs to be solved. The deformed (with respect to the original preoperative MRI and DTI) postoperative configuration of the brain was obtained using biomechanics-based image warping, described in detail in Miller et al. (2019). In this approach, the brain tissue is modeled as a deformable solid and the displacement field is computed using a meshless total Lagrangian explicit dynamics algorithm (Joldes et al., 2019).

The computational grid for the biomechanical model was created as follows. We applied the skull stripping procedure available in FreeSurfer (http://surfer.nmr.mgh.harvard.edu), an open-source software suite for processing and analyzing human brain MRIs (Dale et al., 1999), to the preoperative T1-weighted anatomical MRI to create a mask of the brain. The triangulated surface of the brain mask segment was extracted and remeshed using PyACVD (https://github.com/pyvista/pyacvd) to obtain a high quality uniformly refined surface mesh. A tetrahedral grid was generated from the surface mesh of the brain using Gmsh (https://gmsh.info). The vertices of this grid were used for the meshless approximation while the tetrahedral cells were used for numerical integration. The biomechanical model contained 18,434 nodes (includes rigid skull nodes), 44,821 tetrahedral integration cells, and 179,284 integration points.

The mechanical response of brain tissue was modeled using a neo-Hookean constitutive equation. The material parameters (initial Young’s modulus $E$ and Poisson’s ratio $\nu$) were assigned to each voxel using fuzzy tissue classification (Li et al., 2016; Zhang et al., 2013) conducted on preoperative MRI. As in our previous work (Wittek et al., 2010; Miller et al., 2019), we used $E = 3000$ Pa and $\nu = 0.49$ for brain tissue, and $E = 100$ Pa and $\nu = 0.1$ for cerebrospinal fluid.

As the brain deformations are caused by electrode array insertion, the loading is defined based on the displacement between the brain surface of the preoperative MRI and the location of electrodes in the postoperative CT, rigidly registered to preoperative MRI. The displacement magnitude at each node was obtained by first projecting the electrode centroids from the postoperative CT onto the preoperative brain surface. The displacements of the grid nodes were obtained by interpolating the displacements from the electrode centroids using moving least squares (MLS) approximation (Lancaster and Salkauskas, 1981). The maximum displacement applied was 21.9 mm. The brain deformation problem with displacement loading is a Dirichlet-type problem and therefore the computed displacements are only weakly sensitive to the assumed material model (Wittek et al., 2009; Ma et al., 2011; Miller and Lu, 2013).

The skull was modeled as a rigid surface approximated by the outer surface of the brain mask. Contact between the brain and the skull was modeled using a frictionless finite sliding contact algorithm (Joldes et al., 2008).

The biomechanical model was solved using the meshless total Lagrangian explicit dynamics (MTLED) algorithm (Horton et al., 2010; Miller et al., 2012; Joldes et al., 2019). The MTLED method uses modified moving least squares (MMLS) shape functions (Joldes et al., 2015) and an explicit central difference method with adaptive dynamic relaxation to obtain the static solution (Joldes et al., 2011). Once the discrete solution of the elasticity equations has been obtained, the displacement $u(x)$ at any point $x \in \Omega$ can be evaluated as

$$u(x) = \Phi(x)U_I,$$

where $\Phi$ are the MMLS shape functions and $U$ is the vector of nodal degrees of freedom.

**Image transformations using the computed displacement field**

We projected the displacement vector field onto the image grid using Eq. (5) to obtain the forward displacement field transform. The forward displacement field transform maps each point to its transformed position. However, for image warping the inverse transform that maps each point to its original location is required. The forward displacement field transform was inverted using 3D Slicer, allowing it to be applied directly to scalar, vector or tensor images.

The scalar images (MRIs) were transformed using the ResampleScalarVectorDWIVolume module in 3D Slicer. Fig. 3 shows the electrode positions with respect to the original and deformed image data.

The diffusion tensor image (DTI) was transformed using the ResampleDTIThickness module in 3D Slicer with linear interpolation and the preservation of the principal direction (PPD) tensor transformation method (Alexander et al., 2001). Fig. 4 shows the orientation of the diffusion tensors with respect to the original and deformed image data.

2.2.3. Patient-specific conductivity tensor distribution

**Voxel labeling**

In order to assign conductivity tensors to the image voxels we consider five tissue types in the image: skull, scalp, white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF). Scalar quantities derived from the diffusion tensor, such as mean diffusivity and fractional anisotropy,
Figure 2: Axial, coronal and sagittal slices of the (a,b,c) preoperative MRI and (d,e,f) postoperative CT rigidly aligned with the preoperative MRI.
Figure 3: Original (actual preoperative) and deformed (predicted postoperative) MR images compared with original CT image and electrode positions. Postoperative CT image and electrode positions (white spheres in CT and red points in the slice planes) are overlayed on the (a,b,c) MRI acquired preoperatively and (d,e,f) MRI registered to postoperative configuration of the brain obtained using biomechanics-based image warping.
Figure 4: Original (actual preoperative) and deformed (predicted postoperative) diffusion tensor images (DTI). (a,b,c) DTI acquired preoperatively, and (d,e,f) DTI registered to postoperative configuration of the brain obtained using biomechanics-based image warping.
can be used to classify brain tissue into CSF, gray matter and white matter, based on their diffusion properties (Pierpaoli et al., 1996). For the purpose of this study, we performed the tissue classification of the original and deformed DTIs using fuzzy C-means clustering in two steps. In the first step we used the mean diffusivity to separate the CSF from the brain tissue. In the second step we used the fractional anisotropy to separate the white matter from the gray matter. The method does not have any parameters and does not require any user interaction. Moreover, we do not generate any segmentation surfaces and we do not require that parts of the same tissue class are connected. This simplifies the patient-specific model generation significantly.

To evaluate the accuracy of our automated DTI-based tissue classification procedure we compared our segmentation results with those obtained using the STAPLE method (Warfield et al., 2004). Table 1 lists the number of voxels that belong to white matter, gray matter and CSF using the different segmentation methods. The results are very close as shown in Fig. 5.

More sophisticated methods, some also based on fuzzy C-means clustering (Wen et al., 2013), may be used to improve the labeling accuracy. Segmentation using automated methods that use atlas-based approaches, however, may be difficult to apply because the postoperative configuration of the brain is often very different to a typical healthy brain. The relatively simple automated approach used here demonstrates that the method may be potentially applied in the clinic with minimal manual intervention.

**Fusion of preoperative MRI and DTI, postoperative CT, and deformed MRI and DTI data**

Two label maps, one based on the original preoperative MRI and the other based on the warped MRI corresponding to the postoperative configuration of the brain were created by combining the original preoperative data (skull and scalp) with the original preoperative or predicted postoperative data (original or deformed brain classified as WM, GM or CSF) and actual postoperative CT (electrode grid array). The cavity between the brain and the skull was filled with CSF. Fig 6 shows the label maps for the EEG forward models constructed using the original preoperative and deformed by electrode insertion postoperative MR images. In the preoperative image, the CSF between the actual location of the electrode grid array and the skull is clearly mislabeled as brain tissue. This indicates that using preoperative, undeformed images for patient-specific geometry generation may yield very inaccurate models.

The skull is difficult to segment from the CT image because electrodes and beam hardening artifacts pollute the image with regions of similar intensity as the skull. Many of these regions overlap with bone tissue of the skull which makes it impossible to apply simple thresholding methods to extract the bone tissue. Furthermore, fusion of the deformable soft tissue segments and the rigid but resected and non-conforming skull segment would add significant complications to the imaging pipeline. Therefore, for simplicity, we included the skull and scalp regions in the model by offsetting the brain surface by 4.4 mm (4 voxels). The effect of this simplified skull and scalp geometry on the model results should be negligible. For invasive iEEG or ECoG, as compared to non-invasive scalp EEG, the measurements are taken directly from the brain surface and attenuation by the skull is minimal which suggests that the electrical properties of the skull has little effect on the electrical field within the brain (Hallez et al., 2007). Alternatively, the skull may be segmented from the CT image to provide a more realistic representation of the geometry, but this requires time consuming manual segmentation which is incompatible with a clinical workflow.

The voxels corresponding to the actual and projected locations of the electrode grid array substrate were identified by fitting a surface through the actual electrode centroids visible in the CT image and the electrode centroids projected onto the cortical surface as described in section 2.2.1. The electrode centroids were triangulated to generate a surface representing the electrode grid array substrate. This surface was refined and extruded by the equivalent distance of 2 voxels in the direction away from the brain to create a closed volume. The volume was used to create a segment representing the substrate that is at least one layer thick throughout to ensure that there was no current leakage.

### 2.2.4. Conductivity tensor assignment

The five tissue classes in the EEG forward model were assigned conductivity tensors as follows. Isotropic conductivities (Table 2) were assigned to the scalp, skull, cerebrospinal fluid (CSF), electrode grid array substrate and gray matter regions (Hallez et al., 2007; Vorwerk et al., 2014). The anisotropic conductivity of the white matter was estimated from the diffusion tensors using the fractional method introduced by Tuch et al. (2001). The mean conductivity $\frac{\lambda + \lambda t r C}{2}$ of white matter was in the range from $1 \times 10^{-6}$ to 0.99 S/m which agrees with values reported in the literature (Haueisen et al., 1997; Tuch et al., 2001). Fig 7 shows the mean conductivity for the model based on preoperative images and the model corresponding to the postoperative, deformed configuration of the brain. The unphysical conductivities of the brain tissue between the electrode grid array (represented by the tissue with conductivity close to zero) and the skull are clearly visible, whereas regions further from the implanted electrodes (and therefore further from the deformed brain surface) have similar conductivities in both images.

Patient-specific model of brain bioelectric activity consists therefore of conductivity (tensor $C$ in Eq. (1)–(2)) distribution depicted in the bottom row of Fig. 7 together with the (deformed) geometry ($\Omega$ in Eq. (1)–(2)) depicted in the bottom row of Fig. 3.
Table 1: Number of white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) voxels using the current voxel classification method and STAPLE.

|        | STAPLE         | Our method      |
|--------|----------------|-----------------|
|        | Voxels | Volume (cm$^3$) | Percentage | Voxels | Volume (cm$^3$) | Percentage |
| WM     | 291,185 | 348.3          | 28.4       | 214,381 | 256.5          | 20.3       |
| GM     | 660,152 | 789.7          | 64.5       | 673,756 | 806.0          | 63.7       |
| CSF    | 72,434  | 86.7           | 7.1        | 169,119 | 202.3          | 16.0       |
| Total  | 1,023,771| 1224.7         | 100.0      | 1,057,256| 1264.8         | 100.0      |

Figure 5: Axial slice of the brain showing voxels classified differently as (a) white matter, (b) gray matter or (c) cerebrospinal fluid (CSF) using the STAPLE method (blue) and our approach (red). Voxels that were classified as the same tissue class using both methods are shown in green.

2.3. Solution procedure for the EEG forward problem

Weak form solution methods are preferred as they automatically account for zero-flux (Neumann) out of the scalp surface boundary condition (Eq. 2) (Hughes, 2000). The finite element method using a structured hexahedral grid corresponding to the already available voxelized structure of the image is an obvious choice (Schimpf et al., 2002; Wolters et al., 2007; Rullmann et al., 2009).

The conductivity tensors were assigned directly from voxels to integration points in the elements. We refer to this approach as “image-as-a-model” because the finite element mesh used to solve the problem corresponds directly to the image data. This eliminates time-consuming generation of body-fitted meshes and results in a structured hexahedral mesh with perfect element quality since all elements are cubes. The finite element mesh for the EEG forward problem contained 1,618,745 nodal points and 1,565,095 linear hexahedral elements, compared to 5,898,240 voxels in the original images (the excluded elements correspond to air outside the head).

The EEG forward problem solution method was implemented using the open-source MFEM library (Anderson et al., 2020) (https://mfem.org). A continuous Galerkin formulation with linear hexahedral elements was used for the spatial discretisation of the potential and for computing its gradient, the electric field. The finite element method is based on the weak form of the governing equations which means that the zero-flux boundary condition is naturally satisfied. This is in contrast to strong form methods such as the finite difference method which require more elaborate treatment of the Neumann boundary conditions (Saleheen and Ng, 1997; Bourantas et al., 2020).

The full subtraction approach (Drechsler et al., 2009) was used to model the current dipole source. Other approaches for modeling the dipole, such as the partial integration direct potential approach (Yan et al., 1991; Schimpf et al., 2002), Whitney elements (Tanzer et al., 2005), Raviart–Thomas elements (Pursiainen et al., 2012) or the Venant direct potential approach (Buchner et al., 1997) are also possible but in our experience, supported by previous studies (Schimpf et al., 2002; Drechsler et al., 2009), the subtraction approach gives the most accurate results for realistic 3D problems. The discretised equations were solved using the conjugate gradient (CG) method with an algebraic
Figure 6: Tissue label maps based on (a,b,c) original preoperative and (d,e,f) deformed by insertion of electrodes postoperative image data. Tissue classes are colored as follows: scalp (pink); skull (yellow); GM (gray); WM (white); and CSF (blue). The location of the electrode grid array can be identified by the line of black voxels in the vicinity of the right temporal and parietal lobes.
Figure 7: Mean conductivity ($\frac{1}{4}\text{tr} C$) for models constructed using (a,b,c) original preoperative and (d,e,f) deformed by insertion of electrodes postoperative image data. The location of the electrode grid array can be identified by the black voxels in the vicinity of the right temporal and parietal lobes with conductivity close to zero.
Table 2: Conductive compartments used in the patient-specific EEG forward models.

| Compartment                  | Conductivity (S/m) | References                      |
|------------------------------|--------------------|---------------------------------|
| Scalp                        | 0.33               | Geddes and Baker (1967); Stok (1987) |
| Skull                        | 0.012              | Hallez et al. (2007); Gutierrez et al. (2004) |
| Cerebrospinal fluid (CSF)    | 1.79               | Baumann et al. (1997)           |
| Electrode grid array         | \(10^{-6}\)        |                                 |
| Gray matter                  | 0.33               | Geddes and Baker (1967); Stok (1987) |

multigrid (AMG) preconditioner from the HYPRE library of linear solvers (http://www.llnl.gov/casc/hypre). The computation times for solving the EEG forward problem and constructing the leadfields are discussed in the results section.

2.4. Quantitative measures

We used the following measures to quantify the differences in the topology and magnitude between the predictions made using models based on the original preoperative and the deformed by insertion of electrodes postoperative images. The relative difference metric (RDM) is a measure of the difference in the shape of two data sets and is defined as follows (Meijs et al., 1989):

\[
RDM(y, \hat{y}) = \sqrt{\sum_{i=1}^{n} \left( \frac{\hat{y}_i - y_i}{\sqrt{\sum_{i=1}^{n} \hat{y}_i^2}} \right)^2}.
\]

(6)

The magnitude factor (MAG) is a measure of the difference in magnitude between the two and is defined as follows (Meijs et al., 1988):

\[
MAG(y, \hat{y}) = \sqrt{\sum_{i=1}^{n} \frac{\hat{y}_i^2}{y_i^2}}.
\]

(7)

When comparing leadfields between models we selected \(y\) and \(\hat{y}\) to be stacked vectors of the three columns of the leadfield components at a specific element or voxel to provide a spatially varying map of model similarity. The RDM and MAG metrics measure how the topography and magnitude of the predicted electrode voltages will vary based on model selection. The difference between the models is smallest when RDM is close to 0 and MAG is close to 1 (or, equivalently, \(\log_{10}(\text{MAG})\) is close to 0).

3. Results

3.1. Simulation of electric field originating at seizure onset zone

As a rough approximation of an epileptic seizure we simulated the electric field originating from a dipole in the seizure onset zone (SOZ). We pay particular attention to intracranial electrode recordings. The example serves to demonstrate the application of the proposed methodology, and to assess the effect of the change in model geometry and conductivity on the EEG forward model predictions.

To quantify the effect of the model geometry on the predicted electrical potential within the brain and on the surface electrodes, we solved the iEEG forward problem with a current dipole source using the original image data with both the actual and projected electrode locations (Fig. 7, top row), and the deformed image data with the actual electrode locations (Fig. 7, bottom row). To mimic a current dipole set up by cortical neurons, we placed a dipole, with dipole moment of 100 \(\mu\text{Amm}\), in the gray matter of the brain. The dipole was assumed to be located within the temporal lobe, which is a region that is commonly implicated in epilepsy seizure onset localization (Salami et al., 2020).

Figs. 8 and 9 show the predicted distribution of electrical potential within the brain computed using the models based on the original image data, with actual and projected electrode positions, respectively, and the deformed image data. The difference in the topography and magnitude of the potential predicted by the models appears to be significant. Moreover, there is a large difference in the electrical potential at the electrodes predicted by all three models (Fig. 10). The RDM and MAG between the potential computed using the original image data with the actual electrode positions and the deformed image data for the 64 electrodes is 0.18 and 1.51, respectively. The RDM and MAG between the potential computed using the original image data with the projected electrode positions and the deformed image data for the 64 electrodes is 0.61 and 0.84, respectively. For comparison, previous studies have suggested that an RDM \(\geq 0.2\) can lead to a source localization error of up to 15 mm (Haueisen et al., 2000; Schimpf et al., 2002).

Our results for this example suggest that the modeling error introduced by using incorrect tissue geometry obtained from the original preoperative images (instead of the deformed images that correspond to the postoperative configuration of the brain with implanted electrodes) is significant and we expect this to affect the accuracy of source localization. Conversely, we expect that significant improvements in source localization accuracy may be realized by applying the modeling strategies proposed in this study.
Figure 8: Electrical potential in the brain generated by a current dipole (the current dipole moment vector is denoted by the green arrow) predicted by (left) the model based on original preoperative image data with actual electrode positions and (right) the model based on image data deformed by implantation of electrodes: axial slices of the brain (in a plane coincident with the dipole) showing (a) predicted potential and (c) mean conductivity for the undeformed model, and (b) predicted potential and (d) mean conductivity for the deformed model.
Figure 9: Electrical potential in the brain generated by a current dipole (the current dipole moment vector is denoted by the green arrow) predicted by (left) the model based on original preoperative image data with projected electrode positions and (right) the model based on image data deformed by implantation of electrodes: axial slices of the brain (in a plane coincident with the dipole) showing (a) predicted potential and (c) mean conductivity for the undeformed model, and (b) predicted potential and (d) mean conductivity for the deformed model.
3.2. Towards the solution of the inverse problem: leadfield matrices

One of the most important techniques for measurement of brain activity, especially in the treatment of epilepsy and brain tumors, is source localization using EEG (Grech et al., 2008; Brette and Destexhe, 2012). Source localization requires the solution of the EEG inverse problem which involves locating the current source given sparse data of the electrical potential from electrode recordings. Many inverse solution methods rely on the leadfield matrix which describes the sensitivity patterns of the EEG sensors (Weinstein et al., 2000; Grech et al., 2008; Brette and Destexhe, 2012). The leadfield matrix can be constructed by solving the EEG forward problem for each ground and sensor electrode pair. The leadfield values are computed using reciprocity as the gradient of the computed potential for each ground–sensor electrode pair forward problem, which produces three leadfield columns per spatial location. Once the leadfield matrix has been computed it can be used to calculate the potential at the electrodes produced by a dipole located within any element of the model.

To assess the effect of the geometry and conductivity distribution on the expected source localization accuracy, we compared leadfield matrices computed using the models based on the original (with actual and projected electrode locations) and deformed image data. To construct the leadfields, the first electrode was chosen arbitrarily as the ground electrode, and a unit current source was applied to each of the remaining 63 electrodes.

Computations were performed on a single core of a laptop computer with Intel Core i7-8750H 4.10 GHz CPU and 32 GB RAM. The total computation time for solving 63 forward problems to construct a leadfield matrix for 64 electrodes was less than 15 minutes. Assembly of the stiffness matrix (which can be precomputed and reused for different load cases) took around 1 min, and each row of the leadfield matrix was solved within 13 s (including imposition of boundary conditions, solution of the linear system of equations, and recovery of the gradient of the solution at the element centroids).

To compare the difference between the leadfields we used the relative difference measure (RDM) and magnitude factor (MAG). Figs. 11 and 12 show the differences between the leadfields computed using the original image data, with actual and projected electrode locations, respectively, and the deformed image data. The results show that the difference in the leadfields is greatest in the region close to the electrode grid array. This is to be expected because the region closest to the electrodes corresponds with the greatest amount of tissue deformation. There are also significant differences within the same hemisphere. The electrodes are usually placed close to the expected source location which means that the greatest differences coincide with the region of the brain that is most likely to contain the seizure onset zone. This can be expected to have a detrimental effect on the accuracy of source localization. The histograms of the topographic and magnitude
differences (Figs. 13 and 14) suggest that the difference in leadfields computed by the models is significant in a large number of elements.

The most significant effect on the differences in the leadfield matrices (in both the RDM and MAG) appears to be the misclassification of brain tissue as CSF, and vice versa, in the model that is based on the original preoperative MRI. In these regions the RDM is greater than 0.5, and MAG is less than 1/3 (underestimated by a factor of 3) or greater than 3 (overestimated by a factor of 3). This is in line with studies on model sensitivity to conductivity which reported that while small uncertainties in the CSF conductivity have a negligible effect on the result of dipole reconstruction, outright incorrect tissue classification has strong effects on the forward solutions (Vorwerk et al., 2014, 2019).

The comparison between the leadfields computed using the original (actual preoperative), with both the actual and projected electrode positions, and the deformed (predicted postoperative) image data suggest that accurate source localization based on iEEG or ECoG recordings requires accurate classification of tissue in the postoperative configuration of the brain, after the electrodes have been implanted.

4. Discussion

In this paper, we presented a novel methodology for patient-specific solutions of the intracranial electroencephalography (iEEG) or electrocorticography (ECoG) forward problem that accounts for the brain shift caused by craniotomy and insertion of subdural grid electrodes. The method relies on biomechanics-based image warping to transform the original preoperative image data to the predicted postoperative configuration with implanted intracranial electrodes. Through the analysis of a real, patient-specific case from Boston Children’s Hospital, we have shown that it is possible to apply biomechanical modeling using a meshless approach to compute the deformation field within the brain arising from invasive electrode placement. We used the computed deformation field to warp preoperative MRI and DTI into the postoperative configuration of the brain. This provides a highly detailed map of the electrodes relative to neurological landmarks, and an accurate representation of the postoperative brain geometry which is required as an input to the iEEG forward model.

We generated an efficient pipeline to numerically solve the iEEG forward problem on realistic patient-specific data, that consists of a fast classification algorithm using diffusion tensor images. The automated DTI-based brain tissue classification takes less than a minute. The time required to solve the biomechanical model for image warping was approximately 10 min, and a further hour to process the results and register the deformation field. Once the deformed geometry is made available, the construction of the iEEG forward model can be completed in a few hours. The solution of the iEEG forward problem takes a few minutes, which includes assembly of the system of linear equations and its solution, as well as data input and output.

The generation of the patient-specific computational model for the iEEG forward problem, including skull stripping, segmentation of electrodes, biomechanics-based image warping, brain tissue classification, conductivity tensor estimation, fusion of preoperative and deformed image data and generation of the finite element mesh, took an experienced analyst a total of approximately two days. With further refinement of the modeling pipeline and accumulated experience from additional cases we expect this time to be reduced to about 4 hours per patient. This is acceptable in the research environment and could be considered to be sufficient for clinical applications. As close to real-time processing speeds are not demanded by this application, these simulation and analysis times are compatible with existing clinical workflows. These timeframes would easily fit within the period of 5–7 days of data collection, while the electrodes are in the brain.

Most of the modeling steps have been automated in anticipation of their application in a clinical environment. The complexity of the pre-processing steps was simplified through the use of an image-based approach that circumvents traditional segmentation and meshing. The iEEG forward model is composed of hexahedral elements that match the image geometry with one-to-one correspondence between voxels and elements. This is the highest resolution that can be attained and should provide maximally accurate simulation results as better patient-specific data than the voxelized image is not available. We refer to this as the image-as-a-model approach because the computational grid is created directly from the image data.

To demonstrate the applicability of the proposed approach we applied our methodology to a representative epilepsy case and solved two relevant example problems. The models of the brain with a current dipole showed large differences in the electrical potential predicted using the original (actual preoperative) image data and the deformed (predicted postoperative) image data. The leadfield matrices, typically used for source localization, computed using the different models also showed significant differences. The results show that the tissue geometry and conductivity has a significant influence on the results which suggests that significant improvements in source localization accuracy may be realized by applying the methods described in this study.

Despite the demonstrated efficiency and accuracy of the proposed method there are a few shortcomings that should be addressed in future studies. One of the main difficulties of the proposed approach is the reconstruction of the brain geometry and tissue conductivity maps from the image data. The accuracy of the tissue classification is a limitation that affects the accuracy of the model geometry and the conductivity distribution. Although the method does not require connected segments and surface meshes extracted from these segments, it does require ac-
Figure 11: Difference in leadfields computed using the preoperative model with actual electrode positions and the deformed by insertion of the electrodes postoperative model. Top row: topographic difference (RDM) in (a) axial, (b) coronal and (c) sagittal slices of the brain. Bottom row: magnitude difference ($\log_{10}(MAG)$) in (d) axial, (e) coronal and (f) sagittal slices of the brain.
Figure 12: Difference in leadfields computed using the preoperative model with projected electrode positions and the deformed by insertion of the electrodes postoperative model. Top row: topographic difference (RDM) in (a) axial, (b) coronal and (c) sagittal slices of the brain. Bottom row: magnitude difference ($\log_{10}(\text{MAG})$) in (d) axial, (e) coronal and (f) sagittal slices of the brain.
Figure 13: Histograms of the topographic (RDM) and magnitude ($\log_{10}(MAG)$) differences in the leadfields computed using the original preoperative model with *actual* electrode positions and the deformed by insertion of electrodes postoperative model.

Figure 14: Histograms of the topographic (RDM) and magnitude ($\log_{10}(MAG)$) differences in the leadfields computed using the original preoperative model with *projected* electrode positions and the deformed by insertion of electrodes postoperative model.
Accurate classification of the tissue type of each voxel within the brain. Accurate classification of voxels often requires manual segmentation but this is a difficult and subjective process that does not guarantee repeatability. Automated tissue classification methods appear as the most promising avenue for reducing the effort required to produce accurate label maps of the brain while simultaneously eliminating variability inherent in manual segmentations. The segmentation method based on the DTI that we used in this study is relatively simple but demonstrates the potential to fully automate the tissue classification process. More advanced automated segmentation procedures have been proposed (Wen et al., 2013) and these should be considered if higher accuracy is required. Improvements in the segmentation and tissue classification procedures are expected to improve the solution accuracy of the iEEG forward problem. Finally, we considered only a single patient case in this study. To fully evaluate the methods more patient cases are needed. The patient case analyzed in this study can be considered as a proof-of-concept that demonstrates the accuracy and efficiency of the proposed approach.

A tangential area of interest in the surgical treatment of epilepsy is the modeling of depth electrodes that are inserted stereotactically through openings in the skull. Unlike the grid array electrodes considered in the current study, depth electrodes are long and slender needles that are inserted deep into the brain parenchyma. The electrodes are difficult to control and locate during their insertion, and may cause deformation of the surrounding tissues. Biomechanics-based image registration as described in this paper, combined with a suitable needle insertion model (Witteke et al., 2020), may provide useful guidance for surgeons during these procedures.

Our proposed approach for generating patient-specific iEEG or ECoG forward models for epilepsy patients with implanted subdural electrode grids has significant potential for clinical applications. Results show that the model based on the predicted postoperative image data obtained using biomechanics-based image warping produces leads fields with significant differences from those computed using the original image data, especially in the regions that are close to the electrodes and areas typically implicated in epileptic seizures that are of high interest to the epileptologist. The computation time required to solve the EEG forward problem is short enough to make the solution of the EEG inverse problem feasible. We are currently working on automating more of the modeling tasks to further reduce the time required to construct patient-specific models. Combining the modeling pipeline described in this paper with a suitable method for solving the EEG inverse problem will enable accurate source localization for epilepsy patients who have undergone invasive electrophysiological monitoring and this will be the focus of our future investigations.

Acknowledgments

A. Witteke and K. Miller acknowledge the support by the Australian Government through National Health and Medical Research Project Grant no. APP1162030.

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