Published in final edited form as:

Magn Reson Med. 2019 January ; 81(1): 602–614. doi:10.1002/mrm.27351.

FUNCTIONAL MAGNETIC RESONANCE ELECTRICAL IMPEDANCE TOMOGRAPHY (fMREIT) SENSITIVITY ANALYSIS USING AN ACTIVE BIDOMAIN FINITE ELEMENT MODEL OF NEURAL TISSUE

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Abstract

Purpose—A direct method of imaging neural activity was simulated to determine typical signal sizes.

Methods—An active bidomain finite element model was used to estimate approximate perturbations in MR phase data as a result of neural tissue activity, and when an external magnetic resonance electrical impedance tomography (MREIT) imaging current was added to the region containing neural current sources.

Results—Modeling predicted activity-related conductivity changes should produce measurable differential phase signals in practical MREIT experiments conducted at moderate resolution at noise levels typical of high field systems. The primary dependence of MREIT phase contrast on membrane conductivity changes, and not source strength, was demonstrated.

Conclusion—Because the injected imaging current may also affect the level of activity in the tissue of interest, this technique can be used synergistically with neuromodulation techniques such as Deep Brain Stimulation, to examine mechanisms of action.

Keywords

functional magnetic resonance imaging; electrical conductivity; electrophysiology; deep brain stimulation; brain imaging

Introduction

Improved methods for imaging neural activity sources will allow a better understanding of brain structures and function, and more rapid and sensitive analyses of disease states. Many existing methods of imaging neural sources, though direct, have poor spatial resolution, for example, inverse EEG (1). BOLD fMRI (2) is sensitive to differential blood flow associated with activity, and therefore indirect, but has higher spatial resolution. Despite the relative slowness of MRI compared to EEG, and time lags between activity and blood-flow

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responses, the non-invasive nature of BOLD fMRI techniques has made moderately high temporal resolution investigations of whole brain activity and connectivity feasible.

This work demonstrates properties of a *direct* MR contrast for neural source detection that can potentially be used over a range of scales. It is known that MR magnitude and phase data are slightly sensitive to electromagnetically generated contrasts caused by internal neural sources (3). This approach is termed neural current MRI (ncMRI). ncMRI contrasts have been described in a handful of papers (4,5) using *in-vitro* preparations. However, ncMRI contrasts have not been sustained *in-vivo* (6–9), or found in simulations of large neuron populations (10–12), most likely because of the low intrinsic contrast caused by these sources and, more importantly, the effects of destructive cancellation caused by superposition of magnetic fields from multiple neurons. Magnetic Resonance Electrical Impedance Tomography (MREIT) (13), is a method of using MR phase data to reconstruct tissue conductivity. Related techniques can be used to image electrical current density distributions (14). MREIT has an advantage over related current density imaging (CDI (15,16)) because it is not necessary to rotate the imaged object to acquire data. An earlier work observed (17) that MREIT-based phase measurements might be used to detect and monitor changes in membrane conductance during neural activity and the technique has now been demonstrated *in-vitro* at 11.75 T in sea slug (*Aplysia californica*) abdominal ganglia (18). This variation of MREIT is designated functional MREIT (fMREIT). Since the MREIT contrast (conductivity) is principally scalar, it is not prone to cancellation effects. Because MREIT involves current application, synchronous with MR sequences, MREIT imaging potentially disrupts nearby activity. This may be of use in studying neuroplasticity in deep brain stimulation (DBS) contexts, where stimulating current could also be used for fMREIT.

This paper demonstrates a bidomain model of neural activity, and simulates MREIT imaging of a sample chamber containing active neural tissue. This model was constructed based on MREIT experiments on *Aplysia* abdominal ganglia, in order to estimate signal sizes. A bidomain model (19) was used because it is a naturally volumetric approach that is appropriate for comparison with MR data. This work advances on (17) by using a time dependent, active membrane model. It thus presents a more realistic estimate of likely fMREIT signal magnitudes. Estimates of effects of fMREIT imaging geometry on tissue activity are also developed.

The first purpose of this work was to demonstrate and verify the mechanism of action of MREIT-based neural contrast imaging. With the current amplitudes and geometry used here, it is possible that MREIT imaging currents will cause neural stimulation. Rattay and others (20–25) found that the effects of externally applied electric fields on activity are proportional to the Laplacian of external voltage distributions (the ‘activating function’) near active tissue, with actual effect thresholds depending on the distribution, diameter and internodal spacing of myelinated axons subject to the field. To link this modeling work with an initial target application of imaging neural activity caused by DBS, values of an activating function created by the imaging geometry were computed and compared with thresholds for stimulation of myelinated neurons calculated in McIntyre et al. (26) for DBS, as well as examining current density values nearby tissue.

Predicted MREIT signal sizes were compared with those in typical high-field MR imaging environments. MREIT signal sizes predicted at three different imaging current amplitudes, and at four different internal source strengths, were then assessed to determine whether imaging currents had caused additional activity in the bidomain model. Finally, an MREIT reconstruction method (27) was used to calculate Laplacians of conductivity difference images corresponding to active bidomain model predictions.

Methods

Bidomain Model

The bidomain model (19,28) is an approximation to the quasi-static electrical behavior of active tissue. It is so named because models comprise two collocated spaces, intra- and extracellular. The two domains are coupled via a passive or active membrane model that determines the flow of current between them.

The intra and extracellular spaces shared current density $\mathbf{J}_i$ and $\mathbf{J}_e$, respectively, according to

$$\nabla \cdot \mathbf{J}_i = -\nabla \cdot \mathbf{J}_e = i_m \quad [1]$$

where i_m is the current passing through the membrane per unit volume, measured in Am^{-3} .

The current densities $\mathbf{J}_i$ and $\mathbf{J}_e$ were defined as

$$\begin{aligned} \mathbf{J}_i &= -\mathbf{D}_i \nabla V_i \\ \mathbf{J}_e &= -\mathbf{D}_e \nabla V_e \end{aligned} \quad [2]$$

where in general $\mathbf{D}_{i,e}$ is a conductivity tensor. The model assumed that the active neural tissue was isotropic, therefore in this case conductivity tensors were multiples of the identity matrix.

The membrane voltage V_m was defined as

$$V_m = V_i - V_e \quad [3]$$

where V_i and V_e are potential distributions in the intra- and extracellular spaces respectively. The membrane current was defined by a time- and V_m -dependent non-linear membrane Hodgkin-Huxley model (29). The implementation of the Hodgkin-Huxley model used here is described in the Supporting Material.

The bath potential V_o was described by the Laplace equation, i.e.

$$\nabla \cdot (\sigma_o \nabla V_o) = 0, \quad [4]$$

subject to

$$\int_{\partial\Omega_o} I_o = 0 \text{ and } \frac{\sigma_o \partial V_o}{\partial \mathbf{n}} = J_o \text{ on } \partial\Omega_o. \quad [5]$$

where J_o was the current density normal to electrode surfaces, Ω_o was the surface of the medium containing the active tissue, I_o was the current passing through the bath boundary and $\mathbf{n}$ denotes a unit vector normal to its surface. At the extracellular-bath boundary it was specified that $V_o = V_e$.

Because membrane currents depend upon membrane voltage, stable solutions for membrane voltage may be obtained by rearranging the equations [1–3] to solve for V_e and V_m only (30).

$$\begin{aligned} \nabla \cdot (\sigma_i \nabla V_m) + \nabla \cdot (\sigma_i \nabla V_e) &= i_m \pm i_{source} \quad [6] \\ \nabla \cdot ((\sigma_i + \sigma_o) \nabla V_e) + \nabla \cdot (\sigma_i \nabla V_m) &= 0 \end{aligned}$$

where i_{source} is an internal source. The boundary equations applied to the equations in V_m and V_e were

$$\begin{aligned} -\mathbf{n} \cdot (\sigma_i \nabla V_m + \sigma_e \nabla V_e) &= 0 \quad [7] \\ \text{and } V_e &= V_o \end{aligned}$$

respectively.

Finite Element Model Description

The modeled sample chamber (Fig. 1) contained a small disc representing the *Aplysia* abdominal ganglion (AAG) body. This disc of active tissue was 2.25 mm in diameter and 0.75 mm thick (Fig. 1(a)). The AAG was enclosed in a saline-filled sample chamber with eight current injection ports. The model was formulated in COMSOL (Comsol Inc. Burlington, MA) using six differential equations: three ordinary differential equations describing the behavior of h , m , and n , comprising the Hodgkin-Huxley like model, and three partial differential equations: one for each of V_m , V_e and V_o . The equations for V_m and V_e described the electromagnetic fields in intra- and extracellular compartments inside the active tissue, and the final equation described the electromagnetic behavior of a bath of conductive fluid surrounding the sample, and into which imaging current was injected.

Supporting Tables S1–3 summarize domains, variable names, equations and all parameters used in the finite element model (FEM).

Tissue conductivity and membrane characteristics were taken from the literature and (17). Intra- and extracellular conductivities, β , tissue channel conductances and membrane capacitances were assigned with reference to basic works in the field (31,32). The extracellular conductivity σ_e and bath conductivity σ_o were chosen to be the conductivity of artificial seawater (σ_{ASW}) 5.8 S/m (18). Axoplasm conductivity (σ_i) was chosen to be $\sigma_{ASW}/1.4$ (3.63 S/m) as suggested in (31).

Internal and MREIT Current Sources

An MREIT-like current sequence was applied to the injection ports. Because the model was symmetric, solutions were only calculated for a single current injection pattern via diametrically opposite ports (electrodes 1 and 5). These currents consisted of two Gaussian pulses (A and B), each with a full width at half maximum (FWHM) of 1.6 ms, separated by 6.34 ms. Gaussian MREIT imaging current waveforms were used to improve FEM convergence speeds. Application of current in pairs of pulses, one after the initial 90° RF pulse, and a second after the refocusing pulse, is characteristic of MREIT acquisitions based on spin-echo pulse sequences (13), as described below.

The monopolar active tissue source current i_{source} was specified as

$$i_{source}(r, t) = W(r)i_{spike}(t), \text{ such that } W(r) = \begin{cases} 1 & r < 35 \mu m \\ 0 & r \geq 35 \mu m \end{cases} \quad [8]$$

The time course of the internal source, $i_{spike}(t)$, was also Gaussian, each pulse having a FWHM of 1.9 ms. The relative timing of spikes and MREIT imaging currents is illustrated in Fig. 2. Membrane conductivity and voltages shown in Fig. 2 were derived directly from finite-element data interpolated at the model origin (within the source). At all amplitudes, the internal source propagated spikes throughout active tissue. MREIT imaging currents may also affect active tissue spiking, depending on their amplitude and the current density developed nearby active tissue.

A typical MREIT spin-echo based pulse sequence is shown in Fig. 3. In a simple spin-echo sequence, there will be a total of NS x NAV X PE imaging pulse pairs delivered to the sample, where NS is the number of slices, NAV is the number of averages, and PE is the number of phase encode steps. Pulses A/A' and B/B' in Fig. 3 correspond to pulses A and B in Fig. 2. The difference occurs because in experiments pulse polarity is reversed following the 180° RF pulse to preserve signal, since the refocusing pulse reverses phase sign. Each MREIT recording involves acquisition of two images, one with a positive-going initial pulse (A) and the other with a negative-going initial pulse (A'). These images are subtracted to remove background phase artifact and double signal size.

Because actual MREIT phase data are accumulated during a given pulse sequence echo time (TE), all simulated B_z values (whether MREIT current was injected or not) were integrated

and divided by a candidate TE of 18.3 ms. This value was chosen because it was similar to TE values used in experiments on AAG specimens (18).

Meshing and Solution of Finite Element Models

The finite element mesh contained 268 256 tetrahedral elements, their distribution concentrated in the simulated AAG. The fully coupled set of equations (Supporting Table S1), was solved simultaneously and as a function of time to produce a voltage distribution within the sample chamber at time steps of 0.1 ms, between 0 and 28.6 ms. The coupled model was solved using a backward differentiation formula (BDF) time-dependent solver, with a multifrontal massively parallel sparse (MUMPS) direct solver invoked at each time step. Voltage, J_x and J_y data over the entire domain for each time point were then extracted using COMSOL LiveLink for MATLAB. In contrast to the earlier study (17) B_z values within the model were calculated by a Fourier Transform formulation of the Biot-Savart Law (33). Each solution of the 28.6 ms-long simulation required approximately 50 minutes to solve. Current density norm data from the model was also plotted and magnitudes compared with limits determined for tissue activation.

Conversion of model current density data to MR phase images

A stencil with the same dimensions as experimental voxels was overlaid on the COMSOL model. MREIT images were simulated for three slices, centered on the electrode plane, each having a resolution of 128 x 128. Each voxel had a size of 70 x 70 x 500 μm . The COMSOL command mphinterp was used to extract J_x and J_y values from the model on a fine regular stencil such that there were 1331 points sampled per voxel (an 11 x 11 x 11 grid). The J_x and J_y data were converted to B_z data on this grid. Resulting B_z data were averaged over each voxel to provide a single value representative of volume-averaged MR data.

Activating Function Analysis

Following McIntyre et al (26) the activating function (denoted by them $\Delta^2 V_e$) specific to 5.8 μm diameter myelinated neurons with 500 μm internodal spacing was computed. This was implemented by interpolating exported voltage values onto a 500 μm grid and calculating activating function distribution values at a series of nodes n along linear profiles using (26)

$$\Delta^2 V_e(n) = V_e(n - 500\mu\text{m}) + V_e(n + 500\mu\text{m}) - 2V_e(n). \quad [9]$$

While measured in Volts, the measure is a discrete approximation to the Laplacian of the voltage distribution. Because the applied field was diagonal to the coordinate system, only the x -direction activating function was computed because x - and y - direction distributions were almost identical in this case. $\Delta^2 V_e$ was also computed in directions parallel and orthogonal to the main current flow direction using the same grid.

Model Settings

The conditions below were used to solve nineteen simulations:

PASSIVE: MREIT External imaging current of 1, 2 or 5 mA applied across ports, no internal source

FULL: MREIT External imaging current of 1, 2 or 5 mA applied across ports, internal source amplitude of 500 pA, 1000, 1500 or 2500 pA

NOMREIT: No imaging current applied to model, internal source amplitude of 500 pA, 1000 pA, 1500 pA or 2500 pA.

Differences between FULL and PASSIVE B_z data (B_z data) were analyzed and compared to corresponding data from NOMREIT conditions. This allowed clear comparisons of enhanced signals caused by combining current injection with activity. B_z values (and B_z values predicted in NOMREIT cases) were compared to phase sensitivities reported in the literature (12).

Reconstruction of Conductivity Laplacian

Laplacians of B_z (NOMREIT) and B_z data (FULL-PASSIVE) were computed. For B_z data, Laplacians of apparent conductivity changes (σ) were reconstructed using the Harmonic B_z algorithm (27). Noise with a standard deviation of 0.1 pT (3×10^{-5} ° degrees) was added to individual B_z data sets before computing B_z values. This was much smaller than typical noise levels, but served to highlight effects of noise on reconstruction integrity. Conductivity reconstructions were performed to confirm the existence of conductivity changes resulting from internal source activity, and highlight the underlying structures affecting internal and imaging current flows. Note that in real experiments, statistical analysis of B_z images may be a preferred method of assessing the influence of conductivity changes (18).

The B_z data and σ are related via

$$\frac{1}{\mu_0} \nabla^2 (\Delta B_z) = \left[\frac{\partial \Delta \sigma}{\partial x} \quad \frac{\partial \Delta \sigma}{\partial y} \right] \begin{bmatrix} \frac{\partial u}{\partial y} \\ -\frac{\partial u}{\partial x} \end{bmatrix} = \nabla \times \Delta \mathbf{J} \quad [10]$$

which follows from $\mu_0 \nabla \times \mathbf{J} = \nabla \times \nabla \times \mathbf{B} = -\nabla^2 \mathbf{B} + \nabla(\nabla \cdot \mathbf{B}) = -\nabla^2 \mathbf{B}$, as noted in (27) and (15). In [10], u is the voltage distribution within the object. If data are gathered from two independently applied currents, it is possible to uniquely reconstruct the conductivity gradients (27). Because the model was symmetric, data from a second current direction was synthesized by rotating B_z images 90 degrees.

Monte Carlo Analysis

Initial calculations of differential B_z accumulations assumed that the relative timing of imaging and internal source pulses were as shown in Fig. 2. However, the actual differential signal created depends upon the integral of the product of imaging current and tissue conductance values (17). Therefore, Monte Carlo calculations were used to estimate averaged relative phase accumulations caused by spontaneous spiking occurring relative to

the imaging sequence, including the effect of variability in the interspike interval. Results were compared to relative phase accumulations in the bidomain model. For simplicity, one slice was used (NS=1), at a resolution of 128 x 128 (PE=128) and NAV=8.

Spiking events were modeled as Gaussian pulses with a standard deviation of 800 μ s (FWHM 1.9 ms) with average interspike interval (ISI) of 5 ms, and a fixed ISI variability of 1.25 ms. Membrane conductance spikes were approximated as normal functions with a width of 1.9 ms. The integral of the envelope created by multiplying the conductance waveform by the current injection waveform was then computed. In each Monte Carlo iteration, a spike train with spike placements varying by the standard deviation in the spiking ISI was created. Results were averaged over $1 \times 10^7 \times \text{NS} \times \text{NAV} \times \text{PE}$ iterations. These values were compared with model results to give a better representation of expected averaged signals during spontaneous activity.

Results

Simulated B_z values were similar to those obtained in experiments (18), with maximal values around 10^{-7} T. Fig. 4 (a) shows a 128 x 128 B_z image of the central slice obtained at the maximum amplitude of MREIT pulse A. The simulated ganglion outline is shown in the center. Current flow was from top right (electrode 5) to bottom left (electrode 1).

Fig. 4 (b) shows the current density distribution created within the sample chamber by 1 mA MREIT imaging current. Current density values in the active tissue periphery were around 40 A/m². Three profiles of activating function ($^{-2}V_e$) distributions in the tissue neighborhood in the horizontal direction are plotted in Fig. 4 (c). Profile line locations are overlaid on Fig. 4 (b). Maximal $^{-2}V_e$ values near simulated tissue were about 3.4 mV. With 2 mA imaging current, maximal values were less than 7 mV, as expected. When $^{-2}V_e$ values were computed parallel and perpendicular to the diagonally applied 1 mA imaging currents, maximal absolute $^{-2}V_e$ values were 3.3 mV and 1.4 mV respectively.

Demonstration of MREIT contrast mechanism

No Current—When no MREIT current was applied to a model with an active internal source (Fig. 2), there was still an accumulation of phase, as expected from (10–12,34,35). Maximum B_z values accumulated over the nominal TE were around 21 pT or 4×10^{-3} degrees at 500 pA source amplitude. Resulting B_z distributions in a central (500 μ m thick) slice are shown in Fig. 5 (a). When source strength increased by a factor of 5, maximal B_z values increased to 107 pT/0.025°, approximately scaling with source strength (Fig. 5 (d)). Fig. 6 (a and d) show histograms of B_z values within the active bidomain tissue compartment caused at these two activity levels.

B_z MREIT data were then evaluated. The results are described in the two sections below.

Effect of increasing internal source strength—For an external injection current of 1 mA and an internal source strength of 500 pA, maximal (absolute) B_z values were found to be about 0.12 nT or 0.03°. Note that current paths in images, as shown in B_z data, deviate both inside and outside the active tissue (3,35). This occurs because of current conservation

requirements and counterflows in the contrasting-conductivity bath surrounding the active tissue region. Fig. 6 (b and c), shows another view of these B_z data in histogram form. When source strength increased by a factor of 5 at 1 mA imaging current (Fig. 5 (e), Fig. 6 (e)) maximal B_z values increased only slightly, to 0.14 nT or 0.032 °.

Effect of increasing imaging current—When imaging current increased to 2 mA, accumulated phase and B_z approximately doubled, as shown by comparing Fig. 5 (c and f) and the histograms of Fig. 6 (c and f). Injection of 2 mA increased maximal B_z values at 500 pA source strength to about 0.27 nT/0.06° (from 0.12 nT). The increase was not linear because the larger injected current caused additional conductivity changes throughout the active compartment. Images gathered at 2 mA imaging current and 2.5 nA source strength contained maximal B_z difference values of around 0.37 nT/0.08°.

Comparison with candidate noise levels

Fig. 6 summarizes Fig. 5 data in histogram form. Histograms include data from bidomain (active) tissue voxels only, within all three slices centered on the electrode plane, for 1 and 2 mA imaging currents and 500 and 2500 pA internal source strengths. Histogram bins towards the edges of each plot therefore contain the largest and most detectable B_z values. Noise estimations are overlaid on the histogram B_z data. Noise levels in three different size voxels were estimated using typical signal to noise (SNR) ratios found in directly comparable experiments using the 800 MHz MRI scanner at the Magnetic Resonance Research Center at Arizona State University. Note that since phase noise depends upon magnitude SNR (36), noise levels may differ at other TR or TE values. Numbers above the lines in each plot of Fig. 6 show the number of averages required to achieve a baseline noise level of about 0.1 nT using the same scan parameters and voxels of 70 x 70 x 500 μm^3 (black), 140 x 140 x 500 μm^3 (red) and 280 x 280 x 500 μm^3 (green). Voxel sizes used here reflect the small sizes of the sample and magnet bore. The two simulated spikes that created the B_z distributions, if coherent, would therefore be detectable at this third relatively coarse resolution, using 8 averages and 2 mA MREIT imaging current amplitude.

Reconstruction of conductivity change data

Figs 7 and 8 show Laplacians of B_z data and reconstructions of conductivity changes in the central bidomain region of the model, respectively, using B_z data shown in Fig. 6 with noise added. Laplacian data and reconstructions show changes at tissue compartment boundaries (where there is a conductivity discontinuity) and changes around the source location. This view of distributions and conductivity reconstructions clarifies locations of activity and separates them from B_z information, which has a more diffuse signature.

Conductivity change reconstructions shown in Fig. 8 (b, e) showed 1 mA MREIT data were more prone to noise contamination than with 2 mA current Fig. 8 (c, f). It was also clear that conductivity change extents near source locations were smaller for 500 pA internal source strength (Fig. 8 (b, c)) than 2.5 nA strength (Fig. 8 (e, f)).

Estimation of approximate signal sizes from model data

Monte Carlo calculations predicted that with an average ISI of 5 ms, and ISI standard deviation of 1.25 ms, accumulated phase change caused by spontaneous activity was 725 arbitrary units. Accumulated phase change in the same units for relative placements of imaging current and spikes shown in Fig. 2 was 642. Therefore, if truly spontaneous activity occurring at this rate was imaged, maximal B_z values were predicted to be around 12% larger.

Results from all models are summarized in terms of median B_z changes in Fig. 9. Median activity-related B_z values increased overall with MREIT imaging current amplitude, as expected. However, the dependence on internal source strength was non-linear, which would also be expected because of the interaction between the imaging current and tissue activity states over the TE. Similar parameter dependencies were found for both maximal and median values.

Discussion

The main finding of this study was to demonstrate the mechanism by which external imaging currents can be used to amplify the phase changes caused by neural activity. When MREIT imaging current was introduced to models containing an internal source, larger B_z values were measured, due to membrane conductance changes caused by the source influencing externally applied current paths. This effect was generally enhanced with larger imaging current. Confirmation of the effect's origins and nonlinearity can be observed by comparing median B_z values found when source strength was increased by up to a factor of 5 (Fig. 9). While intrinsic (0 mA) B_z values amplified 5 times when internal source strength increased from 500 to 2500 pA, maximal B_z values found for the 2500 pA internal source and a 1 mA imaging current were only slightly larger (ca. 16%) those found with 1 mA imaging current and 500 pA internal source, and median values decreased. Similarly, when imaging current was set at 2 mA and internal source strength increased to 2500 pA, B_z values increased by around 40%, but differences saturated at around 1500 pA. At 5 mA imaging currents, there was a clear increase in B_z values as source strength increased, but the gradient of effect also decreased with source amplitude. This was because the majority of predicted MREIT signal change was due to membrane conductivity change, and not intrinsic current flow effects. Effects of imaging current magnitude on activity is discussed further below.

Conductivity contrast, typically a scalar, is potentially a more robust contrast than those caused by neural currents alone. This is because magnetic fields created by neural current flows alone are generally likely to cancel, as demonstrated in (10,12). If conductivity is scalar, it is not possible for cancellation to occur, and further, signal size can be controlled with imaging current magnitude. This potentially allows the method to be scaled to image much larger structures than shown here, including the brain. In this study, it was observed that increases in both source and imaging currents produced non-linear effects on maximum signal sizes. Therefore, fMREIT may be a serendipitous adjunct strategy in understanding the effects and mechanisms of electrical stimulation methods such as transcranial DC stimulation (tDCS) and DBS. Use of a DBS current source may be the best prospect for

detection of fMREIT signals *in-vivo*, as this would allow measurement of relatively large signals immediately near active tissue. High-field strategies would also be preferred, since smaller voxel size (and therefore more precise location of sources) or better SNR could be attained (18,37).

It was found that with within the range of source strengths used, which were similar to those used in earlier papers ((12) used a source strength of 400 pA) it should be possible to detect MREIT signals at a resolution of $280 \times 280 \times 500 \mu\text{m}^3$ using 16 averages and an MREIT imaging current amplitude of 2 mA. This was for the specific temporally coherent spiking activity shown in Fig. 2. Monte Carlo simulations showed that for random spiking activity about a fixed frequency, signal sizes may be up to 12% larger.

Comparison with previous work

Maximal B_z values caused by intrinsic source strengths of 500 and 2500 pA in the NOMREIT models were 21 and 107 pT respectively. The maximum phase change predicted in comparable papers, for example in (12), was 0.2° . In the framework used here, this corresponded to a change of 87 pT. Examining Fig. 6, if NAV=8 imaging were to be performed at 800 MHz at $280 \mu\text{m}$ in-plane resolution, signals produced by these sources would not be detected in phase images.

MREIT simulations shown here may be directly compared with those in (17). The models were constructed with many common parameters, so similar results were expected. However, (17) used a passive bidomain model, with differences considered between maximally conducting (membrane conductance 320 S/m^2) tissue compartment and all tissue membrane at rest (conductance of 6.7 S/m^2) conditions. Therefore, predictions in (17) were about 40 times the size of those found here. This scale-change is directly related to the difference between the time varying conductivity pattern shown in Fig. 2 and a condition where membrane conductivity was a constant 320 S/m^2 over each TR.

Assessment of imaging current stimulation

As shown in Fig. 9, increases in intrinsic source strength and imaging current both caused different levels of tissue depolarization, evidenced by the non-linearity of differential phase accumulation when imaging current or source strength was multiplied by factors up to 5. This non-linearity resulted from tissue outside the source region identified in Fig. 1 being depolarized by the source or imaging currents present in under different model settings. In some cases (1 mA imaging current amplitude and 2500 pA source strength) the net effect was to slightly decrease median B_z values. As imaging currents increased, however, larger differential B_z resulted.

Current densities on the tissue periphery in the central plane (Fig. 4 (b)) were around 40 A/m^2 . Mammalian cortical polarization studies indicate that activity modulation may occur at these intensities (38). In nerves, this current density level and effective frequency may be likely to result in spiking activity (39).

While the tissue modeled here was not human brain, it was informative to compare the model results with those predicted using the method of McIntyre et al. (26). In their tests

using a NEURON model (40) McIntyre et al. (26) found that 2V_e values of at least 8 mV were necessary to stimulate activity in 5.8 μm diameter, 500 μm internodal spacing myelinated neurons that were randomly positioned parallel to and over 3 mm away from a DBS electrode. While the isotropic bidomain model and field geometry used here was not directly comparable to this model, it is noted that at 2 mA imaging currents, maximal 2V_e values within the sample chamber were of this order (7 mV). This suggests that the imaging geometry would likely affect activity in a randomly distributed population of such myelinated neurons at this current amplitude. Therefore, while it is unlikely that MREIT can be used to image activity without affecting it, it is possible the technique could be used without stimulating activity in some tissue types, yet still generate detectable B_z signals.

Strategies for future modeling and experimental work

While simulations performed here gave useful indications of measurement scales, actual spike current amplitudes, frequencies, locations and therefore B_z signal sizes and temporal dependence may differ. Larger and more variable changes in spiking frequency, as well as the presence of multiple and dipole sources, would increase model realism.

Recent work (18) has demonstrated that it was possible to identify AAG tissue with potassium-induced increased activity relative to matched controls, using 1 mA imaging currents and a resolution of $70 \times 70 \times 500 \mu\text{m}^3$. Results with 100 μA imaging currents were suggestive of an effect, but were not significant. Analysis in (18) was performed by statistically comparing phase standard deviations in tissue compartments in pre- and post-treatment conditions. In (18) it was not possible to differentiate regions within the AAG with different activity levels. Reconstruction of MREIT conductivity change images during spontaneous behavior will likely not enable a discrete identification of active areas, because of the variable MREIT response expected over the multiple phase encoding steps in a spin-echo sequence. An fMRI-like experimental protocol (37) involving evoked responses and echo planar imaging would be both a faster and more coherent method of generating images, and allow clear spatial differentiation of active and inactive tissue.

Conclusions

An active bidomain framework was implemented to evaluate the feasibility of functional MREIT imaging. The model predicted intrinsic neural activity-related signal sizes consistent with ncMRI models. It was demonstrated that addition of MREIT imaging current to typical ncMRI protocols should result in activity detection at moderate resolutions with currents over 1 mA. Addition of imaging current to the active bidomain model resulted in an increase in activity over that produced by the internal source alone, showing that MREIT imaging currents affected intrinsic neural activity in these cases. Future explorations of this technique in models and experiments will better illuminate the method's potential for direct detection of neural activity during neuromodulatory interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number R01NS077004 to RJS.

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Figure 1.

Model composition showing (a) cross-sectional and (b) oblique views and dimensions of the sample chamber, current injection ports and modeled tissue. The tissue portion of the model was 2.25 mm in diameter and 0.75 mm thick. Each electrode port was a 1.25 mm cube. The octagonal sample chamber was 6.25 mm high. Distances between opposing faces were also 6.25 mm. Voltages in the sample chamber and current injection ports were solved for using the bath (V_o) equation, while all other variables (V_e , V_m , m , h and n) were solved on the tissue compartment. The cylindrical isotropic current source had 70 μm diameter. Source location and scale is indicated in both panels.

Figure 2.

Schematic showing (black) MREIT current source waveforms (A and B), (green) internal source waveform, (red) resulting membrane conductance (G_m) at active tissue center and (blue) membrane voltage V_m at active tissue center. Relative scales and timings of for internal source and MREIT imaging current waveforms are shown above. Main scale applies to membrane conductance and voltage. G_m and V_m values were calculated directly from finite element data at the center of the bidomain tissue (within the internal current source). The echo time TE typically used in imaging is marked on the scale for comparison with other figures.

Figure 3.

Spin-echo-based MREIT pulse sequence. MREIT imaging currents are applied after each RF pulse, with the second pulse reversed to preserve phase. The echo time TE, and repetition time TR, are marked on the sequence. Typical MREIT images are acquired first with positive current (A) after the first RF pulse of each TR ('Positive Current Injection'), and negative current after the refocusing pulse (B). The sequence is repeated with reversed polarity (A' and B') after the first RF pulse ('Negative Current Injection'). The two images are then complex divided to remove background phase and double signal.

Figure 4.

Distributions created by MREIT imaging fields. (a) Example of B_z distribution formed by MREIT current flow from electrode 5 to electrode 1 shown in a slice centered on the electrode plane. Maximal B_z values were of the order of 100 nT. (b) Current density distribution formed in center plane at 1 mA current amplitude. The tissue portion of the model was removed to maintain continuity in the current density data. Profile lines shown in this image are used in the graph of (c). Colored dots on the profile lines delineate the boundary of the tissue model shown in (a). (c) Value of activating function ($\Delta^2 V_e$), within the sample chamber, plotted along the profile lines shown in (b), calculated for a 5.6 μm diameter myelinated nerve model with 500 μm internodal spacing, as per (26). The distribution shown is for a 1 mA imaging current amplitude.

Figure 5.

B_z distributions found in slice centered on electrode plane for six model cases. (a) B_z distribution formed for a source strength of 500 pA and no imaging current. (b) B_z distribution when PASSIVE image was subtracted from FULL B_z data gathered with 1 mA MREIT imaging current, 500 pA source current. (c) as for (b) but with 2 mA MREIT imaging current. (d) B_z distribution formed for a source strength of 2.5 nA and no imaging current. (e) B_z distribution when PASSIVE image was subtracted from FULL B_z data gathered with 1 mA MREIT imaging current, 2.5 nA source current (f) as for (e) but with 2 mA MREIT imaging current. All data were averaged over a TE of 18.3 ms. Each voxel was $70 \mu\text{m} \times 70 \mu\text{m} \times 500 \mu\text{m}^3$.

Figure 6.

Histograms of B_z distributions within active tissue voxels only, for cases shown in Fig. 5. Histogram data were compiled from all three modeled slices. Values are plotted as a fraction of the total active tissue volume. Numbers above the lines in each plot show the number of averages required to achieve a baseline noise level of about 0.1 nT using voxels of $70 \times 70 \times 500 \mu\text{m}^3$ (black), $140 \times 140 \times 500 \mu\text{m}^3$ (red) and $280 \times 280 \times 500 \mu\text{m}^3$ (green).

Figure 7.
Laplacians of B_z data in Fig. 6. Data from the active tissue are highlighted only.

Figure 8.

Reconstructed Laplacians of conductivity difference distributions formed using the Harmonic B_z algorithm, based on the data shown in Fig. 7 with added noise. Data from the active tissue are highlighted only. No data are shown in Fig. 8 (a, b) because these cases do not correspond to MREIT experiments.

Figure 9. Plot of median B_z values found for all imaging cases as a function of internal source strength, for each imaging current amplitude.