Analytic modeling of conductively anisotropic neural tissue

Benjamin L. Schwartz, Munish Chauhan, and Rosalind J. Sadleir

School of Biological and Health Systems Engineering, Arizona State University, Tempe, Arizona 85287-9709, USA

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The abdominal ganglion of the *Aplysia californica* is an established *in vitro* model for studying neuroelectric behavior in the presence of an applied electrical current and recently used in studies of magnetic resonance electrical impedance tomography (MREIT) which allows for quantitative visualization of spatially distributed current and magnetic flux densities. Understanding the impact the *Aplysia* geometry and anisotropic conductivity have on applied electromagnetic fields is central to interpreting and refining MREIT data and protocols, respectively. Here we present a simplified bidomain model of an *in vitro* experimental preparation of the *Aplysia* abdominal ganglion, describing the tissue as a radially anisotropic sphere with equal anisotropy ratios, i.e., where radial conductivities in both intra- and extra-cellular regions are ten times that of their polar and azimuthal conductivities. The fully three dimensional problem is validated through comparisons with limiting examples of 2D isotropic analyses. Results may be useful in validating finite element models of MREIT experiments and have broader relevance to analysis of MREIT data obtained from complex neural architecture in the human brain. Published by AIP Publishing.

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I. INTRODUCTION

Magnetic resonance electrical impedance tomography (MREIT) has emerged as an imaging technique to measure non-invasively and quantitatively the electric conductivity of tissue.² MREIT measurements consist of MRI phase data gathered as electric current is injected in an object in synchrony with an imaging pulse sequence. The electric current $\vec{J}$ will induce a magnetic flux density $\vec{B}$ whose strength is governed by Ampere's law $\vec{J} = \mu_0^{-1} \nabla \times \vec{B}$,³ where μ_0 is the permeability of free space. The z component of the induced magnetic field that is parallel to the main magnetic field in an MRI scanner $B_z(x, y, z)$ is spatially encoded in the phase component of the MR images from which electrical conductivity σ maps may be constructed^{4,5} after their relation from the Biot-Savart law⁶

$$B_z(x, y, z) = \frac{\mu_0}{4\pi} \int_{\Omega} \frac{\sigma(\hat{r}) \left[(x - x') \frac{\partial u}{\partial y}(\hat{r}') - (y - y') \frac{\partial u}{\partial x}(\hat{r}') \right]}{|\hat{r} - \hat{r}'|} d\hat{r}',$$

$$\hat{r} = (x, y, z) \in \Omega, \quad (1)$$

where Ω is the object into which the current is injected and u is the electrical potential thus induced.

While many MREIT reconstruction techniques involving B_z data alone are typically isotropic,⁴ it is possible to combine B_z data with information from diffusion tensor imaging to reconstruct conductivity tensors.^{1,26}

In the bioengineering context of MREIT, we are concerned with electrical conductivity as, e.g., a biomarker for pathologies⁷ or even an indicator of neural activity.^{8,9} Therefore, it is crucially important to understand how applied electric fields, akin to those in an MREIT scan, are distributed in complex living tissue. Therefore, in this study we have made a first principles analytic model of spherical anisotropic

bidomain tissue asymmetrically stimulated by injection currents. This description of basic tissue electrical phenomena can serve to verify numeric simulations such as those obtained using finite element models (FEMs).⁸ This work can also be combined with active membrane bidomain models to estimate time-dependent signal changes.¹⁰

The bidomain approach¹¹ to modeling tissue assumes that the tissue is a continuum of two regions, inside and outside a cell boundary, with the two spaces communicating via a membrane. Mathematically, they occupy the same volume because each is an average of all its components. In other words, the inside of every individual cell is averaged over one continuous space uninterrupted by the interstitium, rather than discrete volumes encased in their own individual membranes. This tissue-level approach allows one to model action potential propagation¹² through whole organs, e.g., the heart.¹³

The two curvilinear coordinate systems most commonly used for bidomain tissue modeling are cylindrical (ρ, φ, z) and spherical (ρ, θ, φ),¹⁴ chosen for their close resemblance to heart and head tissue geometries, respectively. Circular cylindrical coordinates are often used to model a nerve bundle. For example, Henriquez *et al.*^{15–17} and Trayanova *et al.*¹⁸ compared models of a single fiber to a bundle of fibers that were excited by a disk or a line source, finding that a single fiber core conductor model can reasonably approximate the central region of a fiber bundle if the bundle's radius is much larger than the core conductor region. Since they were investigating propagation along the nerve axis, they assumed axial symmetry, neglecting any azimuthal dependence. Johnston considered an infinite cylindrical strand of cardiac tissue in a bath with a uniform electric field, perpendicular to the z axis.¹⁹ That paper also considered a two dimensional problem but was parameterized in ρ and φ . However, earlier Altman and Plonsey constructed fully three

dimensional models in cylindrical coordinates, modeling the stimulation emanating from a point source external to the tissue.^{20,21}

Trayanova *et al.*²² and Patel and Roth²³ devised models of the entire heart in a uniform field using spherical coordinates. They described the tissue as a sphere containing a concentric sphere of blood. As in Ref. 19, the tissue was contained in a uniformly conductive bath subject to a uniform electric field. They defined the azimuthal plane to be perpendicular to the field, achieving axial symmetry. To our knowledge, no work has modeled a three dimensional problem in spherical coordinates.

This work relates to the behavior of excitable tissue immersed in a conducting bath and stimulated by currents applied to the bath. Our specific motivation is from MREIT experiments on the abdominal ganglion of (*Aplysia californica*).⁸ This brings us to the other major key difference between our spherical problem and those mentioned earlier, namely, the direction of longitudinal conductivity. In long cylindrical tissue fibers, it has been shown that the conductivity along the length of the fiber is greater than across it,²⁵ i.e., ions are more free to move parallel to the fibers' longitudinal direction than perpendicular to it. This information is also reflected in water diffusion properties.²⁶ In a three dimensional orthogonal coordinate system, the fiber direction is denoted the longitudinal conductivity, σ^l , with the other two directions having identical transverse conductivities, σ^t . Trayanova *et al.*²² and Patel *et al.*²³ modeled cardiac tissue fibers as running in the polar direction, like lines of longitude on a globe. In this work, because of the approximately star like pattern of the radial neural bundles around the tissue, we assume the radial direction, r , to be the direction of σ^l . This architecture may also be encountered in structures of the brain such as the optic chiasm or the centrum semiovale.²⁴ As with all modeling, this is of course a simplified depiction of a real MREIT experiment. Nevertheless, it is a useful exercise both for its mathematic novelty and its electrophysiologic insight.

In this work, we describe the *Aplysia* abdominal ganglion (AG) as a sphere of bidomain tissue submerged in artificial sea water which has an isotropic electrical conductivity and extends infinitely. External to the sphere of tissue, current source and sink points model the injection currents. We assumed the unmyelinated AG fibers were anisotropic, with the ratio σ^l/σ^t being the same in both intra- and extracellular domains.

II. PROBLEM FORMULATION

A. Geometry

Let there be given a sphere of radius $r = a$ whose center is at the origin and current source and sink points in close proximity thereto all in an infinite conducting bath. Hereafter, the current source and sink will be denoted by the subscripts $+$ and $-$, respectively. Using spherical coordinates, the position vectors of the source and sink points are $\vec{r}_{+, -} = (r_{+, -}, \theta_{+, -}, \varphi_{+, -})$ and $a < r_{+, -}$, as shown in Fig. 1. Here, $R_{+, -}$ are the distances and $\gamma_{+, -}$ are the angles between the current points and any point in the domain at $\vec{r} = (r, \theta, \varphi)$.

FIG. 1. Sphere with radius $r = a$ in an infinite conducting medium with current source $\oplus$ and sink $\ominus$ points at $\vec{r}_+ = (r_+, \theta_+, \varphi_+)$ and $\vec{r}_- = (r_-, \theta_-, \varphi_-)$, respectively. The dotted-dashed curves labeled as γ are the angles between the points' position vectors and that of a field point $\vec{r} = (r, \theta, \varphi)$.

B. Bidomain tissue

We model the tissue as a bidomain, holding the intracellular and extracellular regions—indicated with subscripts i and o , respectively—to be volumetrically uniform though electrically distinct, separated by the cellular membrane. The transmembrane current is thus $i_m = \nabla \cdot \vec{J}_i = -\nabla \cdot \vec{J}_o$.¹¹ From Ohm's law, $\vec{J} = \sigma \vec{E}$, where $\vec{E}$ is the electric field strength and σ is the conductivity tensor.³ Since we have assumed the conductivity to be anisotropic, let us define longitudinal σ^l and transverse σ^t components of σ corresponding to conduction along and across the tissue fiber direction, respectively. Further, assume the radial direction to be aligned with σ^l leaving the polar and azimuthal directions having σ^t . Writing σ out in full, we have

$$\sigma = \begin{bmatrix} \sigma^r = \sigma^l & 0 & 0 \\ 0 & \sigma^\theta = \sigma^t & 0 \\ 0 & 0 & \sigma^\varphi = \sigma^t \end{bmatrix}. \quad (2)$$

It is important to note that because $\sigma^r = \sigma^l$ and we hold the fiber direction to be constant, σ is a diagonal tensor. Finally, since we assume quasi-stationarity for $\vec{E}$,²⁷ we may write it in terms of a scalar potential, ϕ , i.e., $\vec{E} = -\nabla \phi$. Thus, we arrive at the bidomain equations

$$\nabla \cdot (\sigma_i \nabla \phi_i) = i_m, \quad (3a)$$

$$\nabla \cdot (\sigma_o \nabla \phi_o) = -i_m. \quad (3b)$$

In this study, we assume a passive membrane giving i_m a linear dependence on the difference between ϕ_i and ϕ_o , i.e.,

$$i_m = (\phi_i - \phi_o) \sigma_m, \quad (4)$$

where $\sigma_m = \beta/R_m$ is the passive membrane conductance per unit volume. Here, β is the membrane surface area to volume ratio and R_m is the membrane resistance times unit area. To uncouple Eq. (3), let us define transmembrane, V_m , and monodomain, ψ , potentials through $\phi_{i,o}$ ²⁸

$$V_m = \phi_i - \phi_o, \quad (5a)$$

$$\psi = \frac{\alpha}{1+\alpha} \left(\phi_i + \frac{1}{\alpha} \phi_o \right), \quad (5b)$$

whose inverse transformations are

$$\phi_i = \psi + \frac{1}{1+\alpha} V_m, \quad (6a)$$

$$\phi_o = \psi - \frac{\alpha}{1+\alpha} V_m, \quad (6b)$$

where $\alpha = \sigma_i^t / \sigma_o^t$. Let us put Eq. (6) into the sum of Eq. (3) to get

$$\nabla \cdot (\sigma_i + \sigma_o) \nabla \psi + \frac{1}{1+\alpha} \nabla \cdot (\sigma_i - \alpha \sigma_o) \nabla V_m = 0. \quad (7)$$

Since we have assumed that the anisotropy ratios of the two domains are equal, i.e.,

$$\frac{\sigma_i^l}{\sigma_i^t} = \frac{\sigma_o^l}{\sigma_o^t} = q, \quad (8)$$

the conductivity tensors are proportional

$$\sigma_i = \alpha \sigma_o; \quad (9)$$

therefore, the addend of Eq. (7) is zero, leaving us with the directional Laplace equation through ψ

$$\nabla \cdot (\sigma_\psi \nabla \psi) = 0, \quad (10)$$

where

$$\sigma_\psi = \begin{bmatrix} \sigma_i^l + \sigma_o^l & 0 & 0 \\ 0 & \sigma_i^t + \sigma_o^t & 0 \\ 0 & 0 & \sigma_i^t + \sigma_o^t \end{bmatrix}. \quad (11)$$

To obtain an expression in V_m alone after inserting Eq. (6) into Eq. (3), Eq. (3b) is multiplied by α and subtracted from Eq. (3a) to get

$$\begin{aligned} \nabla \cdot ((\sigma_i + \alpha^2 \sigma_o) \nabla V_m) - \sigma_m V_m (1 + \alpha)^2 \\ = -(1 + \alpha) \nabla \cdot ((\sigma_i - \alpha \sigma_o) \nabla \psi). \end{aligned} \quad (12)$$

The right side of Eq. (12) is zero, due to our assumption of equal anisotropy ratios, demonstrating that V_m satisfies the directional scalar Helmholtz equation

$$\nabla \cdot (\sigma_V \nabla V_m) - \chi V_m = 0, \quad (13)$$

where

$$\sigma_V = \begin{bmatrix} \sigma_i^l + \left(\frac{\sigma_i^t}{\sigma_o^t} \right)^2 \sigma_o^l & 0 & 0 \\ 0 & \sigma_i^t \left(1 + \frac{\sigma_i^t}{\sigma_o^t} \right) & 0 \\ 0 & 0 & \sigma_i^t \left(1 + \frac{\sigma_i^t}{\sigma_o^t} \right) \end{bmatrix} \quad (14)$$

and

$$\chi = \sigma_m \left(1 + \frac{\sigma_i^t}{\sigma_o^t} \right)^2. \quad (15)$$

C. Infinite medium

The potential, ϕ_e , in the part of the domain external to the tissue may be expressed as

$$\phi_e = \phi_{bath} + \phi_+ + \phi_-, \quad (16)$$

where $\phi_{+,-}$ are the electric potentials due to the current points and ϕ_{bath} is a secondary potential²⁹ satisfying the Laplace equation,

$$\nabla^2 \phi_{bath} = 0. \quad (17)$$

III. SOLUTIONS

A. Transmembrane potential

The divergence of the product of a diagonal tensor and the gradient of a function f is given as¹⁴

$$\nabla \cdot \sigma \nabla f = \sqrt{\xi} \sum_{j=1}^3 \sigma_j \frac{\partial}{\partial u_j} \left(\frac{\sqrt{\xi}}{\xi_j} \frac{\partial f}{\partial u_j} \right), \quad (18)$$

where $\sigma_1 = \sigma^r, \sigma_2 = \sigma^\theta, \sigma_3 = \sigma^\phi$, and, in spherical coordinates, $u_1 = r, u_2 = \theta, u_3 = \phi, \xi_1 = 1, \xi_2 = r^2, \xi_3 = r^2 \sin^2(\theta)$, and $\sqrt{\xi} = r^2 \sin(\theta)$, whence we achieve

$$\begin{aligned} \nabla \cdot \sigma \nabla f = \frac{\sigma_r}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial f}{\partial r} \right) + \frac{\sigma_\theta}{r^2 \sin(\theta)} \frac{\partial}{\partial \theta} \left(\sin(\theta) \frac{\partial f}{\partial \theta} \right) \\ + \frac{\sigma_\phi}{r^2 \sin^2(\theta)} \frac{\partial^2 f}{\partial \phi^2}, \end{aligned} \quad (19)$$

after whose application, and assuming $V_m = R(r)\Theta(\theta)\Phi(\phi)$, Eq. (13) separates to give¹⁴

$$q_V \frac{\partial}{\partial r} r^2 \frac{\partial R(r)}{\partial r} - \left(\frac{\xi}{\sigma_V^t} r^2 + \mu(\mu+1) \right) R(r) = 0, \quad (20a)$$

$$\frac{1}{\sin(\theta)} \frac{\partial}{\partial \theta} \left(\sin(\theta) \frac{\partial \Theta(\theta)}{\partial \theta} \right) + \left(\mu(\mu+1) - \frac{\nu^2}{\sin^2(\theta)} \right) \Theta(\theta) = 0, \quad (20b)$$

$$\frac{\partial^2 \Phi(\phi)}{\partial \phi^2} + \nu^2 \Phi(\phi) = 0, \quad (20c)$$

where $q_V = \sigma_V^l / \sigma_V^t$. We remark that q_V and, to a lesser extent, $q_\psi = \sigma_\psi^l / \sigma_\psi^t$ are cumbersome expressions but our assumption of equal anisotropy ratios allow us, after considerable algebra, to find that $q_V = q_\psi = q$. Thus, hereafter we shall only use q , neglecting any subscript. The solutions to (20a) are the modified spherical Bessel functions of the first i_η and second k_η kind of order η ,³⁰ but V_m is finite at the

origin which precludes our use of the latter as it is singular there. So, V_m is given as

$$V_m(r, \theta, \varphi) = \sum_{\mu=0}^{\infty} \sum_{\nu=-\mu}^{\mu} a_{\mu\nu} i_{\eta} \left(\frac{r}{\lambda} \right) Y_{\mu}^{\nu}(\theta, \varphi), \quad (21)$$

with order $\eta = -\frac{1}{2} - \zeta$ where

$$\zeta = \frac{1}{2} \sqrt{\frac{4\mu(\mu+1)}{q} + 1}, \quad (22)$$

space constant

$$\lambda = \sqrt{\frac{\sigma_o^t \sigma_i^l}{(\sigma_o^t + \sigma_i^l) \sigma_m}} = \sqrt{\frac{\sigma_i^t \sigma_o^l}{(\sigma_o^t + \sigma_i^l) \sigma_m}}. \quad (23)$$

Y_{μ}^{ν} is the tesseral spherical harmonic³¹ of degree μ and order ν , and $a_{\mu\nu}$ is the coefficient determined from the boundary conditions.

B. Monodomain potential

After the application of Eq. (19), separating the product solution of the monodomain $\psi(r, \theta, \varphi) = \mathcal{R}(r)\Theta(\theta)\Phi(\varphi)$ yields three equations, the angular of which is the same as Eqs. (20b) and (20c). The equation through $\mathcal{R}(r)$ is given as¹⁴

$$\frac{\partial^2 \mathcal{R}(r)}{\partial r^2} + \frac{2}{r} \frac{\partial \mathcal{R}(r)}{\partial r} - \frac{\alpha}{q^2 r^2} \mathcal{R}(r) = 0, \quad (24)$$

whose solutions are $r^{-\frac{1}{2}+\zeta}$ and $r^{-\frac{1}{2}-\zeta}$. Since it is always true that $\zeta \geq \frac{1}{2}$, we neglect the solution in which ζ is a subtrahend; so, $\psi(r, \theta, \varphi)$ is then given as

$$\psi(r, \theta, \varphi) = \sum_{\mu=0}^{\infty} \sum_{\nu=-\mu}^{\mu} b_{\mu\nu} r^{-\frac{1}{2}+\zeta} Y_{\mu}^{\nu}(\theta, \varphi), \quad (25)$$

where $b_{\mu\nu}$ is the a coefficient to be determined by the boundary conditions.

C. External potential

We assume the external bath to be isotropic. The potential satisfies the Laplace equation and is well known;¹⁴ therefore, we do not show its derivation here. The radial equation, like Eqs. (20a) and (24), admits two solutions r^{μ} and $r^{-\mu-1}$. Whereas the tissue potentials could not include singular solutions at $r=0$, ϕ_{bath} must remain finite at $r=\infty$, eliminating r^{μ} . The solution then is

$$\phi_{bath}(r, \theta, \varphi) = \sum_{\mu=0}^{\infty} \sum_{\nu=-\mu}^{\mu} c_{\mu\nu} r^{-\mu-1} Y_{\mu}^{\nu}(\theta, \varphi), \quad (26)$$

where $c_{\mu\nu}$ is determined by the boundary conditions. The potentials due to the current points source and sink with magnitude I_o may be expressed as¹¹

$$\phi_+ = \frac{I_o}{4\pi\sigma_e R_+}, \quad (27a)$$

$$\phi_- = -\frac{I_o}{4\pi\sigma_e R_-}, \quad (27b)$$

where σ_e is the conductivity of the external bath. Here $R_{+,-}$ are given as²⁰

$$R_{+,-}^{-1} = 4\pi \sum_{\mu=0}^{\infty} \sum_{\nu=-\mu}^{\mu} \frac{(g_{+,-}^<)^{\mu}}{(g_{+,-}^>)^{\mu+1}} \frac{1}{2\mu+1} Y_{\mu}^{\nu}(\theta, \varphi) Y_{\mu}^{-\nu}(\theta_{+,-}, \varphi_{+,-}), \quad (28)$$

where $g_{+,-}^< = \min(r, r_{+,-})$, $g_{+,-}^> = \max(r, r_{+,-})$.

IV. BOUNDARY CONDITIONS AND COEFFICIENTS

At $r=a$, we enforce Cauchy boundary conditions, equality of potential and normal current between the bath and interstitium³²

$$\phi_o(a, \theta, \varphi) = \phi_e(a, \theta, \varphi), \quad (29a)$$

$$\sigma_o^l \frac{\partial \phi_o(r, \theta, \varphi)}{\partial r} \Big|_{r=a} = \sigma_e \frac{\partial \phi_e(r, \theta, \varphi)}{\partial r} \Big|_{r=a}, \quad (29b)$$

and a Neumann condition, no current flow normal to the intracellular region³²

$$\sigma_i^l \frac{\partial \phi_i(r, \theta, \varphi)}{\partial r} \Big|_{r=a} = 0. \quad (30)$$

The expressions of the biodomain potentials, given in Eq. (6), are weighted sums of the transmembrane and monodomain potentials. Putting our solutions, Eqs. (21), (25), and (26), into our three boundary conditions gives us three equations through three unknowns

$$b_{\mu\nu} a^{\zeta-\frac{1}{2}} - \frac{\alpha}{1+\alpha} a_{\mu\nu} i_{\eta} \left(\frac{a}{\eta} \right) = c_{\mu\nu} a^{-\mu-1} + I_o \rho_e 2(\mu+1)^{-1} (d_+ - d_-), \quad (31a)$$

$$\sigma_o^l \left(a^{-\frac{3}{2}+\zeta} b_{\mu\nu} \left(\zeta - \frac{1}{2} \right) - a_{\mu\nu} \frac{\alpha}{1+\alpha} \left(\frac{\lambda}{a} \eta i_{\eta} \left(\frac{a}{\eta} \right) - i_{\eta+1} \left(\frac{a}{\eta} \right) \right) \right) = (-\mu-1) a^{-\mu-2} c_{\mu\nu} \rho_e^{-1} + \mu a^{-1} I_o 2(\mu+1)^{-1} (d_+ - d_-), \quad (31b)$$

$$a^{-\frac{3}{2}+\zeta} b_{\mu\nu} \left(\zeta - \frac{1}{2} \right) + a_{\mu\nu} \frac{1}{1+\alpha} \left(\frac{\lambda}{a} \eta i_{\eta} \left(\frac{a}{\eta} \right) - i_{\eta+1} \left(\frac{a}{\eta} \right) \right) = 0, \quad (31c)$$

where

$$d_{+(-)} = \frac{a^{\mu}}{r_{+(-)}^{\mu+1}} Y_{\mu}^{\nu}(\theta_{+(-)}, \varphi_{+(-)}), \quad (32)$$

whose solutions yield

$$a_{\mu\nu} = 2(\alpha+1)(2\zeta+1)(d_- + d_+)(2\mu+1)\rho_e I_o s^{-1}(\mu+1)^{-1}, \quad (33a)$$

$$b_{\mu\nu} = 4(d_- + d_+)(2\mu + 1)a^{\frac{1}{2}-\zeta}\rho_e I_0 \left(ai_{\eta+1} \left(\frac{a}{\lambda} \right) - \eta \lambda i_\eta \left(\frac{a}{\lambda} \right) \right) s^{-1} (\mu + 1)^{-1}, \quad (33b)$$

$$c_{\mu\nu} = 2(d_- - d_+) I_0 a^{\mu+1} \rho_e s^{-1} (\mu + 1)^{-1} \times \left(\left(ai_{\eta+1} \left(\frac{a}{\lambda} \right) - \eta \lambda i_\eta \left(\frac{a}{\lambda} \right) \right) (2\mu - (\alpha + 1)(2\zeta - 1)\rho_e \sigma_o^l) + \alpha(2\zeta - 1)\mu i_\eta \left(\frac{a}{\lambda} \right) \right), \quad (33c)$$

where

$$s = \left(\eta \lambda i_\eta \left(\frac{a}{\lambda} \right) - ai_{\eta+1} \left(\frac{a}{\lambda} \right) \right) ((\alpha + 1)(2\zeta - 1)\rho_e \sigma_o^l + 2(\mu + 1)) + \alpha(2\zeta - 1)(\mu + 1)i_\eta \left(\frac{a}{\lambda} \right), \quad (34)$$

completely determining all potential fields.

V. CURRENT DENSITY AND MAGNETIC FIELD

A. Current density $\vec{J}$

Current density is given as $\vec{J} = -\sigma \nabla \phi$, where, in orthogonal coordinate systems, the gradient of a function f is given as³³

$$\nabla f = \sum_{i=1}^3 \frac{1}{\sqrt{g_i}} \frac{\partial f}{\partial u_i} \hat{a}_i. \quad (35)$$

The unit vectors are $\hat{a}_1 = \hat{r}$, $\hat{a}_2 = \hat{\theta}$, and $\hat{a}_3 = \hat{\phi}$ and u_i and g_i are the same as in Eq. (18), thus

$$\nabla f = \frac{\partial f}{\partial r} \hat{r} + \frac{1}{r} \frac{\partial f}{\partial \theta} \hat{\theta} + \frac{1}{r \sin(\theta)} \frac{\partial f}{\partial \phi} \hat{\phi}. \quad (36)$$

Applying Eq. (36) to our expressions for electric potential, and multiplying by their respective σ then yields expressions for $\vec{J}$, i.e.,

$$\begin{aligned} \vec{J}_i(r, \theta, \phi) = & -\sigma_i^l \left(\frac{a_{\mu\nu}}{1+\alpha} \left(\eta \frac{\lambda}{r} i_\eta \left(\frac{r}{\lambda} \right) + i_{\eta+1} \left(\frac{r}{\lambda} \right) \right) + \left(\zeta - \frac{1}{2} \right) b_{\mu\nu} r^{\zeta-\frac{3}{2}} \right) Y_\mu^\nu(\theta, \phi) \hat{r} \\ & - \sigma_i^t \left(\left(\frac{1}{1+\alpha} \frac{a_{\mu\nu}}{r} i_\eta \left(\frac{r}{\lambda} \right) + b_{\mu\nu} r^{\zeta-\frac{1}{2}} \right) \left(\nu \cot(\theta) Y_\mu^\nu(\theta, \phi) + \tau e^{-i\phi} Y_\mu^{\nu+1}(\theta, \phi) \right) \right) \hat{\theta} \\ & - \sigma_i^t \csc(\theta) \left(\frac{1}{1+\alpha} \frac{a_{\mu\nu}}{r} i_\eta \left(\frac{r}{\lambda} \right) + b_{\mu\nu} r^{\zeta-\frac{1}{2}} \right) i_\mu Y_\mu^\nu(\theta, \phi) \hat{\phi}, \end{aligned} \quad (37)$$

$$\begin{aligned} \vec{J}_o(r, \theta, \phi) = & \sigma_o^l \left(a_{\mu\nu} \frac{\alpha}{1+\alpha} \left(\eta \frac{\lambda}{r} i_\eta \left(\frac{r}{\lambda} \right) + i_{\eta+1} \left(\frac{r}{\lambda} \right) \right) - \left(\zeta - \frac{1}{2} \right) b_{\mu\nu} r^{\zeta-\frac{3}{2}} \right) Y_\mu^\nu(\theta, \phi) \hat{r} \sigma_o^t \left(\left(\frac{\alpha}{1+\alpha} \frac{a_{\mu\nu}}{r} i_\eta \left(\frac{r}{\lambda} \right) - b_{\mu\nu} r^{\zeta-\frac{1}{2}} \right) \right. \\ & \times \left. \left(\nu \cot(\theta) Y_\mu^\nu(\theta, \phi) + \tau e^{-i\phi} Y_\mu^{\nu+1}(\theta, \phi) \right) \right) \hat{\theta} \sigma_o^t \csc(\theta) \left(\frac{\alpha}{1+\alpha} \frac{a_{\mu\nu}}{r} i_\eta \left(\frac{r}{\lambda} \right) - b_{\mu\nu} r^{\zeta-\frac{1}{2}} \right) i_\mu Y_\mu^\nu(\theta, \phi) \hat{\phi}, \end{aligned} \quad (38)$$

$$\begin{aligned} \vec{J}_e(r, \theta, \phi) = & \left(\frac{c_{\mu\nu}}{\rho_e r^{2+\mu}} + \frac{I_0}{2\mu+1} (f_-(r) Y_\mu^{-\nu}(\theta_-, \phi_-) - f_+(r) Y_\mu^{-\nu}(\theta_+, \phi_+)) \right) Y_\mu^\nu(\theta, \phi) \hat{r} \\ & - \left(\frac{c_{\mu\nu}}{\rho_e r^{2+\mu}} + \frac{s}{r} \right) \left(\nu \cot(\theta) Y_\mu^\nu(\theta, \phi) + \tau e^{-i\phi} Y_\mu^{\nu+1}(\theta, \phi) \right) \hat{\theta} - \left(\frac{c_{\mu\nu}}{\rho_e r^{2+\mu}} + \frac{s}{r} \right) i_\nu \csc(\theta) Y_\mu^\nu(\theta, \phi) \hat{\phi}, \end{aligned} \quad (39)$$

where

$$f_{+,-}(r) = \begin{cases} \mu \frac{r^{\mu-1}}{r_{+,-}^{\mu+1}}, & \text{if } r < r_{+,-} \\ -(\mu+1) \frac{r_{+,-}^\mu}{r^{\mu+2}}, & \text{if } r > r_{+,-} \end{cases}, \quad (40)$$

$$s = \frac{I_0}{2\mu+1} \left(\frac{(g_+^<)^{\mu}}{(g_+^>)^{\mu+1}} Y_\mu^{-\nu}(\theta_+, \phi_+) - \frac{(g_-^<)^{\mu}}{(g_-^>)^{\mu+1}} Y_\mu^{-\nu}(\theta_-, \phi_-) \right), \quad (41)$$

and

$$\tau = \frac{\sqrt{\Gamma(\mu - \nu + 1)}\sqrt{\Gamma(\mu + \nu + 2)}}{\sqrt{\Gamma(\mu - \nu)}\sqrt{\Gamma(\mu + \nu + 1)}}. \quad (42)$$

Here, Γ is the gamma function.³⁴

B. Magnetic flux density B_z

We numerically calculate the magnetic flux density due to $\vec{J}$ from the Biot–Savart law³⁵

$$\vec{B}(\vec{r}) = \frac{\mu_0}{4\pi} \int_V \frac{\vec{J}(\vec{r}') \times |\vec{r} - \vec{r}'|}{|\vec{r} - \vec{r}'|^3} dV'. \quad (43)$$

Since this technique is done to a volume of simulated data, we are no longer bound to spherical coordinates; so, we use Cartesian coordinates for computational convenience and imaging relevance. An MREIT scan measures the magnetic field component parallel to the MRI scanner bore, i.e., the z component of $\vec{B}(\vec{r})$ given as

$$B_z = \frac{\mu_0}{4\pi} \int_V \frac{J_x(y - y')}{\left((x - x')^2 + (y - y')^2 + (z - z')^2\right)^{\frac{3}{2}}} dx' dy' dz' - \frac{\mu_0}{4\pi} \int_V \frac{J_y(x - x')}{\left((x - x')^2 + (y - y')^2 + (z - z')^2\right)^{\frac{3}{2}}} dx' dy' dz', \quad (44)$$

which is defined through the convolution operation as³⁶

$$B_z = \frac{\mu_0}{4\pi} (J_x * G_y) - \frac{\mu_0}{4\pi} (J_y * G_x), \quad (45)$$

where

$$G_x = \frac{x}{(x^2 + y^2 + z^2)^{\frac{3}{2}}} \text{ and } G_y = \frac{y}{(x^2 + y^2 + z^2)^{\frac{3}{2}}}. \quad (46)$$

Applying the Fourier transform $\mathcal{F}\{\cdot\}$ turns convolution into multiplication;³⁶ thus, B_z finally is calculated as

$$B_z = \frac{\mu_0}{4\pi} \mathcal{F}^{-1} \{ \mathcal{F}\{J_x G_y\} - \mathcal{F}\{J_y G_x\} \}. \quad (47)$$

VI. NUMERIC EXAMPLES AND DISCUSSION

A. Varying conductivity

We now demonstrate our model via some simple examples in which we show the effect of varying σ_o^l . But for calculating B_z , all computations in this paper have been done on Mathematica 10 (Wolfram Research, Champaign, Illinois). We wrote an algorithm in MATLAB (The MathWorks, Inc., Natick, MA) that uses the fast Fourier and inverse Fourier transforms to obtain B_z . We place the cathode 3 mm below and the anode 3 mm left of the sphere of tissue whose radius is $a = 2$ mm. The tissue and stimulating points are in a uniform bath of artificial sea water that extends infinitely in all directions. We choose tissue parameters in a range known to be biologically realistic,¹¹ specifically $\sigma_e = 5.07$ S/m, $\sigma_i^l = 3.36$ S/m, $R_m = 0.15 \Omega \text{ m}^2$, and $\beta = 2 \times 10^4 \text{ m}^{-1}$. The source and sink

are positive and negative, respectively, with equal magnitude $I_0 = 1$ mA. All of these inputs are summarized in Table I. In our first three examples, we hold $\sigma_o^l = 0.1\sigma_e$, $\sigma_o^l = \sigma_e$, $\sigma_o^l = 10\sigma_e$, shown in Fig. 2, from left to right, whose space constants λ are calculated to be 1.81 mm, 3.88 mm, and 4.85 mm, respectively. We assume that in actual AG tissue it is likely that $\sigma_o^l \sim \sigma_e$. Each image in the top row of Fig. 2 shows ϕ_o and ϕ_e distributions in the xy plane that includes the origin. The solid black lines are equipotentials, with the background shade indicating magnitude. The images are squares of 3 mm so as not to include the source and sink which would obscure the behavior in and immediately surrounding the sphere. In the middle row figures show the stream density plots of the current densities, $\vec{J}_e$ outside the sphere and $\vec{J}_i + \vec{J}_o$ within the sphere. The arrows give the direction of $\vec{J}$ while the color gives its magnitude. Since this plane includes the center of the sphere of tissue as well as the source and sink points, a large fraction of the current flow is reflected in the image. The bottom row shows B_z images. We computed B_z from the simulated current density data throughout the volume of a cube with a side length of 3 mm with the sphere at the center. We generated 13 slices along the z axis, each containing 128×128 data points.

As expected, the sphere was distinguishable from the conducting bath in all three graphs of ϕ , even when the longitudinal conductivity of the tissue was the same as the bath. This is because the bath was assumed to be isotropic. The assumption of radial anisotropy created a clear focus at the center of the sphere when $\sigma_o^l = 10\sigma_e$ and to a lesser extent when $\sigma_o^l = \sigma_e$. Since $\sigma^l = 10\sigma^t$ in the tissue, all the current that entered the sphere was funneled toward the center, increasing in magnitude as the cross sectional area gets smaller. Not enough current enters the sphere to make this phenomenon apparent when $\sigma_o^l = 0.1\sigma_e$.

B. Limiting example

As a validating step, let us simplify our system by placing the cathode at $\vec{p}_+ = (5, \frac{\pi}{2}, 0)$ and setting $q = 1$. This is geometrically and electrically equivalent to the two dimensional problem we solved in Ref. 37 wherein the axial symmetry means that the potentials V_m , ψ , and ϕ_e are functions of r and θ , not ϕ . With our cathode now 3 mm to the right of

TABLE I. Modeling inputs.

Parameter	Value
Bath conductivity, σ_e	5.07 S/m
Intracellular longitudinal conductivity, σ_i^l	3.36 S/m
Anisotropy ratio, q	10
Ratio of surface area to volume, β	$2 \times 10^4 \text{ m}^{-1}$
Membrane resistance times unit area, R_m	$0.15 \Omega \text{ m}^2$
Source and sink magnitude, I_0	1 mA
Tissue radius, a	2 mm
Point source position, $\vec{p}_+$	$(5, \pi, 0)$
Point sink position, $\vec{p}_-$	$(5, \frac{\pi}{2}, \pi)$
Space constants:	
$\lambda _{\sigma_o^l=0.1\sigma_e}$	1.81 mm
$\lambda _{\sigma_o^l=\sigma_e}$	3.88 mm
$\lambda _{\sigma_o^l=10\sigma_e}$	4.85 mm

FIG. 2. The top, middle, and bottom rows are plots of the electric potential, current density, and magnetic flux density, respectively, in the plane $z=0$. The dashed white line indicates the circumference of the sphere. In the Cartesian coordinates on this graph, the current point source is at $(0, -5)$ and the current point sink is at $(-5, 0)$. In the columns, from left to right, the ratio of σ_o^l to σ_e is 1, 10, and 0.1, respectively. In the top graph, we show the extracellular potential of the sphere of tissue amid the external potential in the conducting bath. There the black lines are equipotentials, and the shade of color corresponds to the magnitude. In the middle graph, we show the external current density in the bath and the sum of the intracellular and extracellular current densities in the sphere. The magnetic flux density shown in the bottom graph was calculated from the current density field.

FIG. 3. (a) A contour plot of the extracellular potential of the sphere of tissue amid the external potential in the conducting bath. The dashed gray line indicates the circumference of the sphere. The black lines are equipotentials, and the shade of color corresponds to the magnitude. In the Cartesian coordinates on this graph, the current point source is at $(5, 0)$ and the current point sink is at $(-5, 0)$. The ratio $\rho_e/\rho_o = 1$. (b) The intracellular (dotted-dashed), extracellular (solid), transmembrane (dotted), and bath (dashed) potentials are shown as a function of x , along the white line where $y=0$ in (a). The vertical lines at $x = -2$ and 2 correspond to the radius of the sphere, $r = a$, where are also plotted the lines tangent to the curves of the potentials in the boundary conditions.

the tissue, we get the same results, shown in Fig. 3, as those from our earlier work. Figure 3(b) plots the potentials ϕ_o , ϕ_i , and V_m inside the tissue ($-2 \leq x \leq 2$) and ϕ_e outside the tissue ($-3 < x < -2$ and $2 < x < 3$) along the white line at $y = 0$ in Fig. 3(a). The tissue boundaries are indicated by vertical lines at $y = -2, 2$. There ϕ_o (solid line) and ϕ_e (dashed line) are continuous as are their slopes, and ϕ_i (dotted-dashed line) has a slope of zero. Also, by inspection it is clear that Eq. 5(a) is satisfied, i.e., $\phi_i - \phi_o = V_m$ (dotted line).

C. Modeling and insights

Let us now consider this work's relevance in a broader context. Our goal was to model the electromagnetic environment of an MREIT scan of an AG in an artificial sea water medium. We have made several assumptions about the geometry that must be addressed. First, we have simplified the injection current ports to be infinitesimal points out of or into which current flows uniformly in the radial direction. Further, we assume these points, along with the AG, are in an infinite conducting medium, i.e., not contained in a cylinder. Obviously, the experimental reality is more complicated. MREIT scans of an AG are in a finite circular cylindrical volume and current is injected through ports in the wall of the cylinder.⁸ Such simplifying assumptions are not unreasonable approximations of the physical reality, particularly in this study whose focus is the tissue being stimulated. While AG axons are unmyelinated, the assumption of equal anisotropy is overly simplistic and, in future work, unequal anisotropy expressions should be derived.

We have also made geometric assumptions about the AG that require attention. The AG has fibers extending radially outward from a small hub. We have assumed that the intra- and interstitia have the same ratio of longitudinal to transverse conductivities and that all conductivities are constant throughout the spherical volume. These two assumptions imply that the fibers extend from an infinitesimally small hub and that they are continually branching such that their spatial density does not change with radius. Trayanova *et al.* made an analogous assumption about fibers in their spherical model of a heart,²² but in the $\hat{\theta}$ rather than the $\hat{r}$ direction. Despite these simplifying abstractions, this model is useful by giving a general scale of the data one would expect to find in MREIT scans of an AG in a bath of artificial sea water. More physically realistic problems can be formulated by relaxing these mathematic constraints, e.g., not assuming a perfect sphere, but that would undermine the analytic tractability of the problem, requiring then more approximate approaches, e.g., FEM. The work in this paper can therefore be used to validate numeric methods via observation of correspondences found using simple geometries.

D. Going forward

A next step from this first study concerns the boundary where current is injected, here modeled as a point source and sink. The abstraction of an infinite bath is quite appropriate in an analytic solution but would slow computation speed in a finite element approach. Therefore, it would be appropriate to perform an analysis closer to the actual physical setting of

an MREIT scan: a sphere of tissue immersed in a conducting liquid filling a container of finite volume. That is a mixed boundary value problem where the injection current is defined on part of the container surface. Another appropriate modification would be to solve the equations with unequal anisotropy ratios to accommodate more realistically neuron properties.

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