Communication

The Activating Function for Magnetic Stimulation Derived From a Three-Dimensional Volume Conductor Model

Peter J. Basser, Ranjith S. Wijesinghe, and Bradley J. Roth

Abstract—**A three-dimensional volume conductor model of magnetic stimulation is proposed that relates transmembrane potential of an axon to the induced electric field in a uniform volume conductor. This model validates assumptions used to derive a one-dimensional cable model of magnetic stimulation (Roth & Basser, *IEEE Trans. Biomed. Eng.*, vol. 37, pp. 588–597, 1990) of unmyelinated axons. The three-dimensional volume conductor model reduces to this one-dimensional cable equation forced by the activating function, $-\partial E_A^z/\partial z$.**

Introduction

We recently proposed a model of magnetic stimulation of an unmyelinated nerve fiber that predicts where and when excitation occurs [1]. It consists of a one-dimensional cable equation that is forced by a term that is analogous to the activating function for electrical stimulation with extracellular electrodes [2]. While neural stimulation is caused by a three-dimensional electric field distribution, the response of the nerve is generally described by a one-dimensional cable model. The activating function in the one-dimensional cable equation should represent the action of this applied electric field. We show how to reconcile these one- and three-dimensional representations of nerve stimulation and derive an activating function for magnetic stimulation that is consistent with both.

In this communication, we present a three-dimensional volume conductor model of magnetic stimulation in which the induced electric field and its resultant transmembrane potential distribution along an axon are derived analytically. We show that this three-dimensional model of magnetic stimulation reduces to a one-dimensional cable equation [1] whose activating function is identical to one that we proposed previously, $-\partial E_A^z/\partial z$.

We also use the three-dimensional volume conductor model to assess the validity of several simplifying assumptions made in deriving our original cable equation [1]. One is that the electric field within the axon is axial; another is that the field in the membrane is radial. These have been validated for a cable model describing propagating action potentials [3], but not for magnetic stimulation. We also assumed that the electric field in the membrane due to induction is negligible compared to the electric field due to charge separation. Finally, we made the unintuitive assumption that the extracellular potential is negligible, so that transmembrane potential equals intracellular potential.

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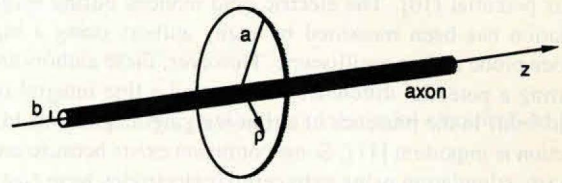

Fig. 1. Schematic diagram of the axon and the filament of magnetic flux.

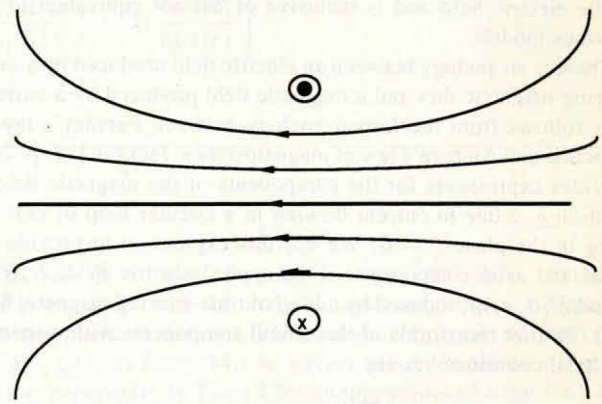

Fig. 2. Schematic diagram of the electric field lines induced by the filament of magnetic flux along a plane through the center of the coil for $d\Psi/dt > 0$.

Model

We consider a single, unmyelinated axon with radius b and intracellular conductivity σ_i, having a membrane of thickness d and conductivity σ_m. It is threaded through a wire-wound toroid of radius a with a high-permeability core (Fig. 1). The axon lies in an unbounded, homogeneous volume conductor of conductivity σ_o. Current passes through the toroid winding creating a time-varying magnetic field confined to the core, inducing an electric field in the volume conductor surrounding both the axon and toroid (Fig. 2). We model the toroidal coil as a filament of magnetic flux, $\Psi(t)$, produced by current in the winding. Also, we assume that the current in the winding changes slowly enough so that skin depth and propagation effects are negligible. Cylindrical coordinates, ρ, θ, and z, are used. The axon lies along the z-axis, which coincides with the axis of the coil; ρ measures the radial distance from the axon's center. The assumption of symmetry with respect to the azimuthal angle θ simplifies the description of this three-dimensional volume conductor problem to a two-dimensional one.

The configuration of the nerve and filament of magnetic flux shown in Fig. 1 is similar to experimental preparations used by Maass and Asa [4], Ueno *et al.* [5], [6], Riecken [7], and McCarthy and Haradem [8] to stimulate axons; it is also used to measure action currents by detecting their associated magnetic field [9]. This coil geometry is different than that used in clinical applications of magnetic stimulation. In this note, however, we are primarily interested in the mechanism of stimulation, which should be the same for various applications.

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The electric fields in the bath and axon have two sources: a time-varying magnetic field and charge. We first consider the inductive contribution. In our example, the electric field produced by electromagnetic induction is the "applied electric field" because it is the electric field that would exist in the bath if the axon were not present. This electric field cannot be expressed as the gradient of a scalar potential [10]. The electric field induced during magnetic stimulation has been measured by many authors using a bipolar electrode probe and an oscilliscope. However, these authors are not measuring a potential difference, but instead a line integral of the electric field. In the presence of a time-varying magnetic field, this distinction is important [11]. Some confusion exists because models of electric stimulation using extracellular electrodes were cast only in terms of the potential [2], [12]. Our model of magnetic stimulation, and the activating function that we derive, is cast in terms of the electric field and is inclusive of but not equivalent to the previous models.

There is an analogy between an electric field produced by a time-varying magnetic flux and a magnetic field produced by a current. This follows from the formal analogy between Faraday's law of induction and Ampere's law of magnetostatics. Jackson [13, p. 206] provides expressions for the components of the magnetic field at position ρ, z due to current flowing in a circular loop of radius a lying in the plane $z = 0$. We use this expression to provide the radial and axial components of the applied electric field, $E_A^\rho(t, \rho, z)$ and $E_A^z(t, \rho, z)$, induced by a loop of time-varying magnetic flux, $\Psi(t)$. Fourier transforms of these field components with respect to the axial coordinate, z, are

$$e_A^\rho(t, \rho, k) = -a \frac{d\Psi(t)}{dt} ikI_1(|k|\rho)K_1(|k|a) \tag{1}$$

$$e_A^z(t, \rho, k) = -a \frac{d\Psi(t)}{dt} |k| I_0(|k|\rho)K_1(|k|a) \qquad \rho < a \tag{2}$$

where k is the spatial frequency and I_0, I_1, K_0, and K_1 are modified Bessel functions.

The second contribution to the electric field arises from charge separation across the axon membrane. An electric field caused by charge can be expressed as the gradient of a scalar potential. The potentials inside, $\Phi_i(t, \rho, z)$, and outside, $\Phi_o(t, \rho, z)$, the axon obey Laplace's equation, so that their Fourier transforms (with respect to z), ϕ_i and ϕ_o, can be written in terms of Bessel functions in ρ [13, p. 107]:

$$\phi_i(t, \rho, k) = \alpha(t, k)I_0(|k|\rho) \qquad \rho \le b \tag{3}$$

$$\phi_o(t, \rho, k) = \beta(t, k)K_0(|k|\rho) \qquad \rho \ge b \tag{4}$$

where we have used the facts that $\lim_{\rho \to 0} \phi_i$ and $\lim_{\rho \to \infty} \phi_o$ are finite. We define the transmembrane potential at $\rho = b$ as the difference between intra- and extracellular potential:

$$\phi_m(t, k) = \phi_i(t, b, k) - \phi_o(t, b, k). \tag{5}$$

The functions $\alpha(t, k)$ and $\beta(t, k)$ above must be determined from the boundary conditions at the membrane, i.e., the normal component of the current is continuous at the interfaces between the intracellular space and the membrane, and between the extracellular space and the membrane:

$$\sigma_i \left(e_A^\rho(t, b, k) - \frac{\partial \phi_i(t, \rho, k)}{\partial \rho}\bigg|_{\rho = b} \right) = \sigma_m \left(e_A^\rho(t, b, k) + \frac{\phi_m(t, k)}{d} \right), \tag{6}$$

$$\sigma_o \left(e_A^\rho(t, b, k) - \frac{\partial \phi_o(t, \rho, k)}{\partial \rho}\bigg|_{\rho = b} \right) = \sigma_m \left(e_A^\rho(t, b, k) + \frac{\phi_m(t, k)}{d} \right). \tag{7}$$

Zhang [14] considered the case in which the membrane has finite thickness, but we take the membrane thickness, d, to be so small that we can treat it as a high resistance surface separating the intracellular and extracellular volumes. We also neglect membrane capacitance (steady state simulation), although it can easily be included above by using Fourier transforms in time and a complex membrane conductivity.

If we solve (3)–(7) for the two unknown functions, $\alpha(t, k)$ and $\beta(t, k)$ we find that

$$\alpha(t, k) = \frac{e_A^\rho(t, b, k)}{I_0(|k|b)} \frac{\dfrac{\sigma_m}{\sigma_i |k| d} \dfrac{K_0(|k|b)}{K_1(|k|b)} \left(\dfrac{\sigma_i}{\sigma_o} - 1 \right) + \left(1 - \dfrac{\sigma_m}{\sigma_i} \right)}{\dfrac{\sigma_m}{\sigma_i d} \left(1 + \dfrac{\sigma_i I_1(|k|b) K_0(|k|b)}{\sigma_o I_o(|k|b) K_1(|k|b)} \right) + |k| \dfrac{I_1(|k|b)}{I_0(|k|b)}} \tag{8}$$

and

$$\beta(t, k) = \frac{e_A^\rho(t, b, k)}{K_0(|k|b)} \frac{\left(\dfrac{\sigma_m}{\sigma_i |k| d} \dfrac{K_0(|k|b)}{K_1(|k|b)} \right) \left(\dfrac{\sigma_i}{\sigma_o} - 1 \right) - \left(1 - \dfrac{\sigma_m}{\sigma_i} \right) \left(\dfrac{\sigma_i I_1(|k|b) K_0(|k|b)}{\sigma_o I_0(|k|b) K_1(|k|b)} \right)}{\dfrac{\sigma_m}{\sigma_i d} \left(1 + \dfrac{\sigma_i I_1(|k|b) K_0(|k|b)}{\sigma_o I_0(|k|b) K_1(|k|b)} \right) + |k| \dfrac{I_1(|k|b)}{I_0(|k|b)}}. \tag{9}$$

These expressions for α and β can be used in (3), (4) to determine ϕ_m,

$$\phi_m(t, k) = \frac{e_A^\rho(t, b, k) \left(1 - \dfrac{\sigma_m}{\sigma_i} \right) \left(1 - \dfrac{\sigma_i I_1(|k|b) K_0(|k|b)}{\sigma_o I_0(|k|b) K_1(|k|b)} \right)}{\dfrac{\sigma_m}{\sigma_i d} \left(1 + \dfrac{\sigma_i I_1(|k|b) K_0(|k|b)}{\sigma_o I_0(|k|b) K_1(|k|b)} \right) + |k| \dfrac{I_1(|k|b)}{I_0(|k|b)}}. \tag{10}$$

Next we use (1) and (2) to express the Fourier transform of the applied radial electric field in (10) in terms of the Fourier transform of the applied axial electric field,

$$e_A^\rho(t, b, k) = \frac{ikI_1(|k|b)}{|k| I_0(|k|b)} e_A^z(t, b, k). \tag{11}$$

TABLE I
UNMYELINATED AXON

d	0.006	μm
b	5	μm
σ_i	2	S/m
σ_o	2	S/m
σ_m	$62.5\ 10^{-9}$	S/m
λ	0.67	mm

The transmembrane potential is now written as the product of a "transfer function," $H_{\text{analytic}}(k, b)$, and the axial electric field

$$\phi_m(t, k) = \left[\frac{ikI_1(|k|b)}{|k|I_0(|k|b)} \frac{\left(1 - \frac{\sigma_m}{\sigma_i}\right)\left(1 - \frac{\sigma_i I_1(|k|b)K_0(|k|b)}{\sigma_o I_0(|k|b)K_1(|k|b)}\right)}{\frac{\sigma_m}{\sigma_i d}\left(1 + \frac{\sigma_i I_1(|k|b)K_0(|k|b)}{\sigma_o I_0(|k|b)K_1(|k|b)}\right) + |k|\frac{I_1(|k|b)}{I_0(|k|b)}} \right] e_A^z(t, b, k)$$

$$= H_{\text{analytic}}(k, b)\, e_A^z(t, b, k). \tag{12}$$

We can draw several general conclusions by examining the form of the transfer function in (12). First, σ_m is much smaller than σ_i (by a factor of about 10^7, Table I). Thus, $(1 - \sigma_m/\sigma_i) \approx 1$. This is tantamount to assuming that the electric field in the membrane due to magnetic induction is negligible compared to the electric field in the membrane due to charge, justifying one of our assumptions. Second, Kleinpenning and van Oosterom [15] interpreted the fractor $\sigma_i I_1(|k|b)K_0(|k|b)/\sigma_o I_0(|k|b)K_1(|k|b)$ as the ratio of extracellular to intracellular resistance along the axon. Because the Fourier transform of the applied electric field, $e_A(k)$, contains negligible power at spatial frequencies near to and above the inverse axon radius, i.e., $|k|b \ll 1$, and σ_i/σ_o is generally not too large, the ratio of extracellular to intracellular resistance is on the order of $(|k|b)^2$, which is much less than one. This supports another assumption that the extracellular potential is negligible during magnetic stimulation. Note that this assumption does not imply that the extracellular electric field is negligible. Instead, it means that the extracellular electric field is approximately equal to the applied electric field, and that only that part of the extracellular electric field produced by charge separation on the cell membrane can be ignored.

We can further simplify (12) by substituting the length constant, λ,

$$\lambda = \sqrt{\frac{\sigma_i d b}{2\sigma_m}} \tag{13}$$

for factors containing the membrane conductivity. Using all the simplifying assumptions discussed above, expanding the transfer function in (12) in a power series in $|k|b$, and retaining the lowest order term, we find that

$$\phi_m(t, k) \cong \frac{ik\lambda^2}{(k\lambda)^2 + 1} e_A^z(t, b, k) = H_{\text{approx}}(k, b)\, e_A^z(t, b, k). \tag{14}$$

Equation (14) is the spatial frequency domain (k space) representation of the steady-state, forced cable equation that we previously derived [1] to describe magnetic stimulation of an axon. This is seen by taking the inverse Fourier transform of (14), obtaining

$$-\lambda^2 \frac{\partial^2 \Phi_m}{\partial z^2} + \Phi_m \cong -\lambda^2 \frac{\partial E_A^z}{\partial z}. \tag{15}$$

It is easy to show that if the membrane had capacitance, then the left-hand side of (15) also would contain the term $\tau\, \partial\Phi_m/\partial t$ where τ is the membrane time constant.

RESULTS

To see how well the approximate activating function, $-\partial E_A^z/\partial z$, agrees with the analytical one, we compare the magnitude and phase of the transfer functions, $H_{\text{analytic}}(k, b)$ from (12) and $H_{\text{approx}}(k, b)$ from (14), which are plotted together in Fig. 3. We use parameters in Table I for an unmyelinated axon [16] with a length constant of 0.67 mm. The toroid's radius is 2 mm. The flux changes from 0 to 1 T mm^2 in 100 μs, so that the peak rate of change of flux is 0.01 T m^2/s. Agreement between analytical and approximate transfer functions is excellent. Maximum deviations appear to increase with k^2 but remain less than 0.8% at $k = 16$ mm^{-1}. Therefore the exact and approximate curves are virtually indistinguishable in Figs. 3–5.

The resulting analytical and approximate transforms of the transmembrane potential are plotted as a function of k in Fig. 4.

The real part of the inverse Fourier transform of $\phi_m(k)$ is the transmembrane potential distribution, $\Phi_m(z)$. The approximate and exact transmembrane potential distributions, computed from (12) and (14) using an IFFT algorithm, are shown in Fig. 5.

DISCUSSION

This derivation of the activating function is also valid for myelinated axons with the proviso that λ is interpreted as the effective space constant, given by the space weighted average of the nodal and internodal impedances [17], [18]. There also must be negligible power in $e_A^z(k)$ for $|k| < 1/\lambda$ in addition to the requirement that $|k| \ll 1/b$.

Magnetic and electrical stimulation depolarize the axon in the same way. Our description of magnetic stimulation would be exactly analagous to the description of electric stimulation presented by Rattay if he had cast his activating function in terms of the applied electric field instead of the extracellular potential. If E_A were produced by distant electrodes instead of a time-varying magnetic field this derivation would be unchanged. Thus, this analysis verifies the one-dimensional cable model of electrical stimulation proposed by Rattay [2]. Also, any contribution of charge accumulation on distant tissue surfaces [19] can be included easily in the activating function for magnetic stimulation when it is cast in terms of the applied electric field.

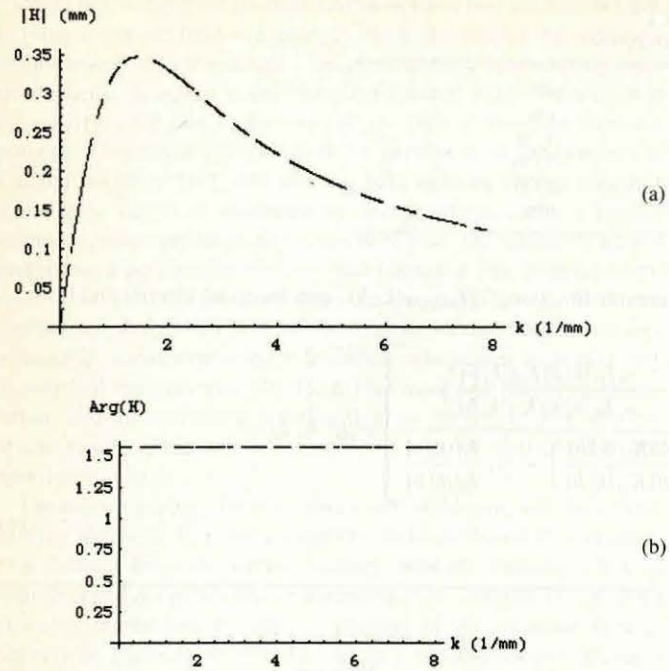

Fig. 3. The (a) magnitude and (b) phase of the transfer function between the axial electric field and the transmembrane potential as a function of k with the exact and approximate solutions, (12) and (14), superimposed. Parameters in Table I for an unmyelinated axon are used to construct this figure.

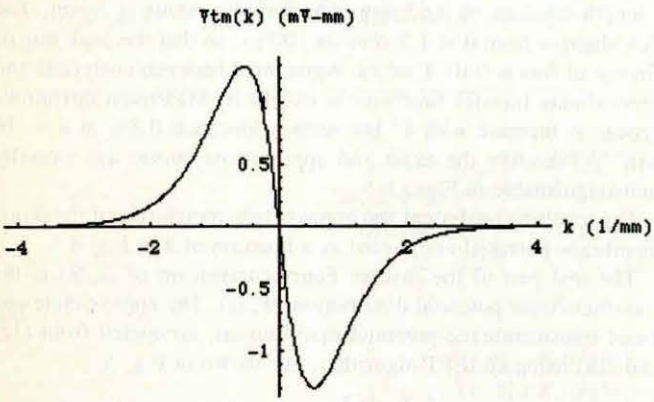

Fig. 4. The real part of the Fourier transform of transmembrane potential as a function of k with the exact and approximate solutions, (10) and (14), superimposed. Parameters in Table I for an unmyelinated axon are used to construct this figure.

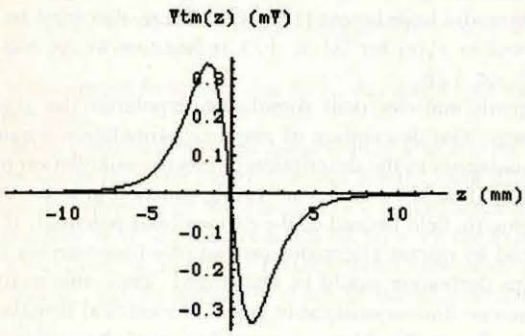

Fig. 5. The transmembrane potential, $V_{tm} = \Phi_m(z)$, as a function of the axial coordinate, z, with the exact and approximate solutions superimposed. These are obtained by taking the real parts of the inverse Fourier transforms (IFFT) of (12) and (14) using the parameters in Table I.

The magnitude of the transmembrane potential is more than a factor of ten below rheobase threshold potential of both myelinated and unmyelinated axons. The induced transmembrane potential depends on parameters of the nerve and the toroid that we selected in Table I. For example, increasing the axon diameter will increase transmembrane potential. Also, the peak magnetic flux of 1 T m^2 was obtained by assuming a 1 T magnetic field in a core whose cross-sectional area is 1 mm^2. If the cross-section were larger, the flux would also increase, and so would the induced transmembrane potential; however, cross-sectional area cannot be increased too much without violating our assumption that the electric field in the nerve is caused by a filament of flux. These considerations suggest that electromagnetic induction alone may be responsible for stimulating larger axons using an appropriate toroidal geometry. It is also possible that stimulation of the nerve in the bath may be caused or enhanced by another mechanism. One reasonable proposal offered by McCarthy and Haradem is that capacitive currents flowing between an unshielded coil and the ground electrode contribute to stimulation [8].

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Correction to "A Model of the Stimulation of a Nerve Fiber by Electromagnetic Induction"

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There is an error in the above paper [1] and its subsequent correction [2]. The capacitor voltage, V_0, was improperly scaled; the quoted capacitor voltages in [1] and [2] should all be multiplied by a factor of 120. None of the other results or conclusions, qualitative or quantitative, is affected. This error was corrected in a subsequent publication [3].

We thank Frank Evans (Department of Biomedical Engineering, Duke University, Durham, NC) for pointing out this problem.

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