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, \(-\partial E_z/\partial t\).

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, \(-\partial E_z/\partial t\).

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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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 oscilloscope. 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 \(p, z\) 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, \(E_r(t, p, z)\) and \(E_z(t, p, z)\), 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

\[
e^\alpha_r(t, \rho, k) = -a \frac{d\Psi(t)}{dt} i k I_1(k_{\rho}) K_0(k_{\rho} a) \tag{1}
\]

\[
e^\beta_r(t, \rho, k) = -a \frac{d\Psi(t)}{dt} |k| I_0(k_{\rho}) K_0(k_{\rho} a) \tag{2}
\]

where we have used the facts that \(\lim_{\rho \to 0} \phi_i, \phi_o, \phi_m\) 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:

\[
\sigma_0 \left( e^\alpha_r(t, b, k) \left( -\frac{\partial \phi_i}{\partial \rho} \right)_{\rho=b} \right) = \sigma_m \left( e^\alpha_r(t, b, k) + \frac{\phi_m(t, k)}{d} \right), \tag{6}
\]

\[
\sigma_0 \left( e^\alpha_r(t, b, k) \left( -\frac{\partial \phi_o}{\partial \rho} \right)_{\rho=b} \right) = \sigma_m \left( e^\alpha_r(t, b, k) + \frac{\phi_m(t, k)}{d} \right). \tag{7}
\]

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

\[
\begin{align*}
\phi_i(t, b, k) & = \frac{\sigma_0}{\sigma_1} K_0(k_{\rho}) \left( \frac{\sigma_1}{\sigma_0} - \frac{1}{\sigma_0} \right) + \left( 1 - \frac{\sigma_m}{\sigma_0} \right) K_1(k_{\rho}) I_0(k_{\rho}) L_0(k_{\rho} a) \\
\phi_o(t, b, k) & = \frac{\sigma_0}{\sigma_1} K_0(k_{\rho}) \left( \frac{\sigma_1}{\sigma_0} - \frac{1}{\sigma_0} \right) - \left( 1 - \frac{\sigma_m}{\sigma_0} \right) \frac{\sigma_1 I_1(k_{\rho} |k| b) K_0(k_{\rho} |k| b)}{\sigma_0 I_1(k_{\rho} |k| b) K_0(k_{\rho} |k| b)}
\end{align*}
\]

These expressions for \(\alpha\) and \(\beta\) can be used in (3), (4) to determine \(\phi_m\):

\[
\begin{align*}
e^\alpha_r(t, b, k) & = \frac{\sigma_m}{\sigma_1} \frac{\sigma_0}{\sigma_1} \left( 1 - \frac{\sigma_m}{\sigma_0} \right) \frac{\sigma_1 I_1(k_{\rho} |k| b) K_0(k_{\rho} |k| b)}{\sigma_0 I_1(k_{\rho} |k| b) K_0(k_{\rho} |k| b)} \tag{8}
\end{align*}
\]

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,

\[
\frac{\sigma_0}{\sigma_1} \frac{\sigma_0}{\sigma_1} \left( 1 - \frac{\sigma_m}{\sigma_0} \right) \frac{\sigma_1 I_1(k_{\rho} |k| b) K_0(k_{\rho} |k| b)}{\sigma_0 I_1(k_{\rho} |k| b) K_0(k_{\rho} |k| b)} \frac{\sigma_1 I_1(k_{\rho} |k| b) K_0(k_{\rho} |k| b)}{\sigma_0 I_1(k_{\rho} |k| b) K_0(k_{\rho} |k| b)}
\]
The transmembrane potential is now written as the product of a "transfer function," $H_{\text{analytic}}(k, b)$, and the axial electric field 

$$
\phi_n(t, k) = 
\begin{bmatrix}
\frac{i k l_1(|k| b)}{|k| l_0(|k| b)} \\
\frac{\sigma_m}{\sigma_i} \\
\frac{1 + \frac{\sigma_i l_1(|k| b) K_0(|k| b)}{\sigma_m l_0(|k| b) K_1(|k| b)}} \\
\frac{|k| l_0(|k| b) K_0(|k| b)}{\sigma_m l_0(|k| b) K_1(|k| b)} \\
\end{bmatrix} 
\begin{bmatrix}
\frac{1}{|k| l_0(|k| b)} \\
\frac{\sigma_m}{\sigma_i} \\
\frac{1}{\sigma_m} \\
\frac{|k| l_0(|k| b)}{\sigma_m l_0(|k| b)} \\
\end{bmatrix} 
\begin{bmatrix}
\frac{1 - \sigma_m}{\sigma_i} \\
\frac{\sigma_i l_1(|k| b) K_0(|k| b)}{\sigma_m l_0(|k| b) K_1(|k| b)} \\
\end{bmatrix} 
e A(t, b, k) e^\alpha(t, b, k).
$$

We can draw several general conclusions by examining the form of the transfer function in (12). First, $\sigma_m$ is much smaller than $\sigma_i$ (by a factor of about $10^2$, 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 factor $\sigma_i l_1(|k| b) K_0(|k| b)/\sigma_m l_0(|k| b) K_1(|k| b)$ as the ratio of extracellular to intracellular resistance along the axon. Because the Fourier transform of the applied electric field, $e_\alpha(k)$, contains negligible power at spatial frequencies near to and above the inverse axon radius, i.e., $|k| b \ll 1$, and $\sigma_i/\sigma_m$ 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, $\lambda$,

$$
\lambda = \sqrt{\frac{\sigma_i \sigma_b}{2 \sigma_m}},
$$

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

$$
\phi_n(t, k) \equiv \frac{i k l_1(|k| b)}{(k^2 + 1) e_\alpha(t, b, k) = H_{\text{approx}}(k, b) e_\alpha(t, b, k).}
$$

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

$$
-\lambda^2 \frac{\delta^2 \Phi_n}{\delta z^2} + \Phi_n \equiv -\lambda^2 \frac{\delta E_\alpha}{\delta z}.
$$

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

<table>
<thead>
<tr>
<th>TABLE I</th>
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<tbody>
<tr>
<td>UNMYELINATED AXON</td>
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<tr>
<td>---------</td>
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<tr>
<td>$d$</td>
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<tr>
<td>$b$</td>
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<tr>
<td>$\sigma$</td>
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<td>$\lambda$</td>
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RESULTS

To see how well the approximate activating function, $-\delta E_\alpha/\delta z$, 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 m$^2$ in 100 $\mu$s, 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 $\phi_n(k)$ is the transmembrane potential distribution, $\Phi_n(z)$. 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 $\lambda$ 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 $e_\alpha(k)$ for $|k| < 1/\lambda$ in addition to the requirement that $|k| >> 1/b$.

Magnetic and electrical stimulation depolarize the axon in the same way. Our description of magnetic stimulation would be exactly analogous 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.
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 $1 \text{T m}^2$ 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].

REFERENCES

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].

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