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The Excitation Functional for Magnetic Stimulation of Fibers

D. Suárez-Bagnasco, R. Armentano-Feijoo and R. Suárez-Ántola

Abstract—**Threshold problems in electric stimulation of nerve and muscle fibers have been studied from a theoretical standpoint using the excitation functional. Here the excitation functional is extended to magnetic stimulation of excitable nerve and muscle fibers. A unified derivation of the functional is done, for (*non myelinated*) nerve and muscle fibers, by means of the nonlinear cable equation with a Fitzhugh-Nagumo membrane model and a generalized Rattay's activating function. The identification problem of the excitation functional for magnetic stimulation, from strength-duration experimental data, is briefly considered.**

I. Introduction

THE goal of electric and magnetic stimulation of excitable cells is to produce (or to block) action potentials in suitable locations. From the standpoint of a black box approach, the stimulation process may be described by a correspondence between each applied electric current history and a binary variable Λ that takes the value 0 if stimulation fails and 1 if it succeeds (Fig.1).

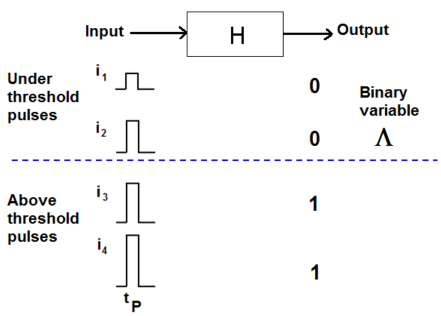

Fig.1. Black box approach to electric and magnetic stimulation

From the standpoint of the stimulation equipment, the black box comprises the electrodes (and their leads) or the magnetic coils, the volume conductor of the tissues and the target elements (nerve or muscle fibers, etc.). So, this black box may be considered as an electric load seen by the stimulating equipment. The binary variable may be obtained through an electric measurement (detection of action potential by recording electrodes) or by external manifestations (like muscle twitches, function inhibitions, etc).

For the electrical stimulation, there is already a theoretical tool, the *excitation functional*, introduced by R. Suárez-Antola [1], [2]. It allows both a *description* and a *prediction* of the output given by the binary variable in the black box approach. As each system composed by the electrodes, the tissues and the target elements is unique (due to different spatial, temporal, electrical and in general, physiological properties), the black box must be duly identified from suitable experimental data.

The experimental strength-duration curves for a given system can be used to obtain the excitation functional for the electrical stimulation of the just mentioned system [3].

The excitation functional opens a third way between a pure experimental approach and a pure computational approach (working with nonlinear cable equation for electrical stimulation). As an analytical tool (which parameters can be adjusted from real experimental data) it allows a mathematical formulation of threshold related problems of interest for biomedical engineering. For example, to find optimal pulse shapes given an optimization criterion [2]. So, it could be of certain interest to try to extend the excitation functional to magnetic stimulation.

The purpose of this paper is threefold: (a) to extend the excitation functional to magnetic stimulation produced by external coils, (b) to present a unified derivation of the functional both for electric and magnetic stimulation, and (c) to briefly discuss the identification problem of the functional from experimental data (from strength-duration curves).

A unified derivation is possible because (from the non linear cable equation with a generalized activating function [4] [5]) it is the external electric field parallel to the fibers the responsible of both magnetic and electric stimulation. One of the consequences of this extension is to have a tool that allows to characterize the system and to predict the outcome of the binary variable given a certain current history in the stimulating coil.

This tool can be used also to pose and solve certain engineering problems related to the system, like how to shape an input current pulse in the stimulating coil that is both threshold and optimum from the standpoint of minimizing the energy dissipated per pulse in the tissues [6].

For the purposes of the present work, a suitable background in electric and magnetic stimulation may be found in [7]. Further information about electric stimulation can be found in [8] to [10], and in [11] to [16] for magnetic stimulation.

D. Suárez-Bagnasco is with the School of Medicine, CLAEH, Punta del Este, Uruguay (corresponding author, phone/fax: +598 2 3096456; e-mail: dsuarezb@adinet.com.uy).

R. Armentano-Feijoo is the Dean of the Engineering School of Favaloro University, Buenos Aires, Argentina.

R Suárez-Ántola is with the School of Engineering of the Catholic University of Uruguay, Montevideo, Uruguay

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II. EXTENSION OF THE EXCITATION FUNCTIONAL TO THE MAGNETIC CASE

A. *Formulation for the electrode case*

The simplest formulation of the excitation functional corresponds to a single active electrode or a bipolar electrode and may be applied both to cathodic make excitation and to anodic break excitation [2]. The excitation functional when the excitable membrane is at rest prior to t=0 can be written in two steps. First we obtain a function $q_E(t)$, making the convolution of a history of injected current $i_E(t)$ with a *non dimensional* impulse response function $G_E(t)$ characteristic of the system (black box).

$$q_E(t)=\int_0^t G_E(t-u)\cdot i_E(u)\cdot du\,. \qquad (1)$$

In this case, by definition $G_E(0)=1$. The injected current appears in (1) related to the fact that the electric field in a given point of the tissues is the product of $i_E(t)$ and a vector function of the position of the considered point in the volume conductor [4].

In a second step, the maximum of $q_E(t)$ is taken from t=0 onwards and compared with a threshold charge $Q_{Th,0}$. This threshold charge is not the charge injected by the electrode neither the charge that crosses the excitable membrane of the target fiber.

A history of applied current is just threshold if and only if

$$\underset{t\geq 0}{máx}\ \{q_E(t)\}=Q_{Th,0}\,. \qquad (2)$$

Fig.2 shows three possible outcomes of the convolution

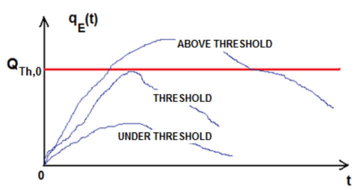

Fig.2. Under threshold, just threshold and above threshold time evolution of $q_E(t)$

$Q_{Th,0}$, which is a characteristic parameter of the system, allows the definition of the digital variable Λ_E that was presented in the introduction. As will be seen in section *D*, in this case $Q_{Th,0}$ coincides with the well known limit threshold charge that can be obtained from strength-duration curves.

B. *Formulation for the coil case*

In the magnetic case, assuming that the membrane is at rest prior to t=0, we propose to convolve time derivative of the electric current in the coil $\frac{di_C(t)}{dt}$ with a **non dimensional** impulse response function $G_M(t)$ in order to obtain the time function $i_M(t)$. Here, by definition, $G_M(0)=1$.

$$i_M(t)=\int_0^t G_M(t-u)\cdot \frac{di_C(u)}{du}\cdot du\,. \qquad (3)$$

The derivative of the coil current appears in (3) related to the fact that the electric field in a given point of the tissues is the product of $\frac{di_C(t)}{dt}$ and a vector function of the position of the considered point in the volume conductor [4], [5], [6], [16].

In a second step, the maximum of $i_M(t)$ is taken from t=0 onwards and compared with a threshold current $I_{Th,0}$ (Fig. 3).

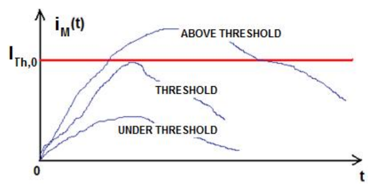

Fig.3. Under threshold, just threshold and above threshold time evolution of $i_M(t)$

A history of current in the coil is just threshold when:

$$\underset{t\geq 0}{máx}\ \{i_M(t)\}=I_{Th,0}\,. \qquad (4)$$

$I_{Th,0}$ (a characteristic parameter of the system) allows again the definition of a digital variable, in this case Λ_M. It can be obtained from experimental strength-duration curves, as shown in section IV.

III. A UNIFIED DERIVATION OF THE EXCITATION FUNCTIONAL

The construction of the impulse response function and the threshold charge for electric stimulation, and the impulse response function and the threshold current for the magnetic stimulation of a (non myelinated) fiber will follow a common procedure. This allows an easier grasp of the similarities and differences between the two situations.

Let us begin with the nonlinear cable equation with Rattay's activating function generalized to take into account both electric and magnetic stimulation [4], [5], [6], [16]. To simplify the derivation we use the well known Fitzhugh-Nagumo model for the unit membrane [17]. If the (*possibly bended*) target fiber is represented by a curve of directed arc length s measured from a suitable fixed point of the fiber, $v(t,s)$ is membrane voltage field and $w(t,s)$ is the recovery variable field, both relative to their rest values, we obtain the following set of equations [6]:

$$\tau_m\frac{\partial v}{\partial t}=\left(-v+b\cdot v^2-c\cdot v^3-\alpha\cdot w\right)+\lambda_m^2\frac{\partial^2 v}{\partial s^2}-\lambda_m^2\frac{\partial E_e(t,s)}{\partial s}\,. \qquad (5a)$$

$$\tau_w\frac{\partial w}{\partial t}=(v-\gamma w)\,. \qquad (5b)$$

The time constant of the membrane is τ_m , and τ_w is the time constant of the recovery variable (under physiological conditions at least an order of magnitude greater than τ_m).

The fiber's space constant is λ_m . The parameters of the unit membrane model b,c,α,γ are positive.

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Rattay's generalized activating function is given by [4], [5], [6], [12], [16]:

$$-\lambda_m^2 \frac{\partial E_e(t,s)}{\partial s} = \begin{cases} \lambda_m^2 \cdot F_E(s) \cdot i_E(t) \rightarrow \text{electric} \\ \lambda_m^2 \cdot F_M(s) \cdot \frac{d}{dt} i_C(t) \rightarrow \text{magnetic} \end{cases} . \quad (6)$$

The functions $F_E(s)$ and $F_M(s)$ give the spatial distribution of the perturbation produced on the excitable membrane by the electric field due to the electrodes or induced by the time varying magnetic flux due to the coil, and may be called geometric form factors for electric and magnetic stimulation, respectively. Now, the stimulation is always a localized phenomenon. As a consequence, outside a certain *interval of influence* along the fiber, of length ℓ, the form factors may be neglected [6], [18], [19], [20]. If we assume that until the fiber reaches a threshold state, the fields of membrane voltage and recovery variable take their rest values at the end points of this interval of influence, it is possible to make a nonlinear modal analysis of the cable equations. The value of ℓ depends of the form factor. If s is measured from the mid-point of the interval of influence, we may use the Fourier development:

$$\begin{aligned} v(t,s) &= A_1(t) \cdot \sqrt{\frac{2}{\ell}} \cos\left(\frac{\pi \cdot s}{\ell}\right) + A_2(t) \cdot \sqrt{\frac{2}{\ell}} \sin\left(\frac{2\pi \cdot s}{\ell}\right) + \ldots \\ w(t,s) &= B_1(t) \cdot \sqrt{\frac{2}{\ell}} \cos\left(\frac{\pi \cdot s}{\ell}\right) + B_2(t) \cdot \sqrt{\frac{2}{\ell}} \sin\left(\frac{2\pi \cdot s}{\ell}\right) + \ldots . \quad (7) \\ F_M(s) &= F_{M,1} \cdot \sqrt{\frac{2}{\ell}} \cos\left(\frac{\pi \cdot s}{\ell}\right) + F_{M,2} \cdot \sqrt{\frac{2}{\ell}} \sin\left(\frac{2\pi \cdot s}{\ell}\right) + \ldots \end{aligned}$$

Substituting (7) in the nonlinear cable equation and eliminating the spatial dependence, we obtain a system of first order nonlinear ordinary differential equations in the unknown mode amplitudes $A_j(t)$ and $B_k(t)$. Solving this system with suitable initial conditions, we obtain the mode amplitudes. The procedure is the same as already developed for stimulation by electrodes [18], [19]. The only difference between electric and magnetic stimulation in this approach is the forcing term. So the dynamics of the unforced fiber, after the end of the stimulating pulse, is the same if the length of the interval of influence is the same.

Digital simulation of both cathodic make and anodic break electrical stimulation using up to seventeen mode amplitudes suggest that the first mode is the most relevant in determining threshold behavior of the fiber [20].

Truncation to the first mode, uncoupled, gives in both cases, a set of nonlinear ordinary differential equations in the mode amplitudes corresponding to membrane voltage and the recovery variable [19].

The study of threshold dynamics done with the aforementioned equations, with parameter's values within the physiological ranges, shows that a threshold barrier may be defined in phase space (A_1, B_1) such that when the phase point reaches the barrier, an action potential emerges [6], [19].

The under threshold behavior can be described with enough accuracy, up to the threshold barrier, by the linear system:

$$\begin{aligned} \tau_m \frac{dA_1}{dt} &= -(1+\pi^2 \frac{\lambda_m^{\ 2}}{\ell^2}) A_1 - \alpha B_1 + \lambda_m^{\ 2} \cdot F_{M,1} \cdot \frac{d}{dt} i_C(t) . \\ \tau_w \frac{dB_1}{dt} &= (A_1 - \gamma \cdot B_1) . \end{aligned} \quad (8)$$

This approach is the equivalent, for a fiber with a non-uniformly polarized membrane, to the classical discussion of Fitz-Hugh for a unit membrane [19]. Fig 4 shows the simplified dynamics in the (A_1, B_1) state space. The results of the digital simulation suggest the introduction of a decaying and an amplifying set, separated by a threshold curve [19].

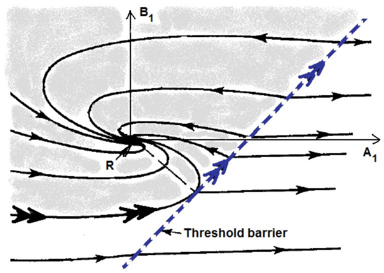

Fig 4. Sketch of the dynamics of the system, simplified by the threshold barrier. R is the rest state. The decaying set is shown as a shaded area bounded by the double arrowed threshold curve.

The threshold curve is composed by: half-straight line taken from the threshold barrier and an orbit in the decaying set that is just tangent to the threshold barrier. The construction of the threshold barrier can be seen in [17].

The linear dynamic system (8) can be recast in a matrix form:

$$\frac{d}{dt} \vec{x}(t) = A \cdot \vec{x}(t) + \lambda_m^{\ 2} \cdot F_{M,1} \cdot \frac{d}{dt} i_C(t) \cdot \vec{e}_1 . \quad (9)$$

$$\vec{x} = \begin{bmatrix} A_1 \\ B_1 \end{bmatrix} \quad A = \begin{bmatrix} \frac{-1}{\tau_m}\left(1+\pi^2 \frac{\lambda_m^{\ 2}}{\ell^2}\right) & \frac{-\alpha}{\tau_m} \\ \frac{1}{\tau_w} & \frac{-\gamma}{\tau_w} \end{bmatrix} \quad \vec{e}_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix} . \quad (10)$$

In the matrix A, the spatial properties appear in the element $\frac{-1}{\tau_m}\left(1+\pi^2 \frac{\lambda_m^{\ 2}}{\ell^2}\right)$ through the non-dimensional number $\frac{\lambda_m}{\ell}$. The other elements of the matrix A depend only on unit membrane properties through the parameters $\alpha, \gamma, \tau_m, \tau_w$.

The solution, beginning from the rest state, and until the first arrival to the threshold barrier, is:

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$$\vec{x}(t) = \lambda_m{}^2 \cdot F_{M,1} \cdot \int_0^t \frac{d}{du} i_C(u) \cdot \left(e^{(t-u)A} \vec{e}_1\right) \cdot du \, . \qquad (11)$$

From the results of digital simulation (summarized in Fig 4) the condition that characterizes a just threshold magnetic stimulation is (Fig.5):

$$\max_{t \in [0,+\infty)} \left\{ \vec{n}^T \vec{x}(t) \right\} = p \, . \qquad (12)$$

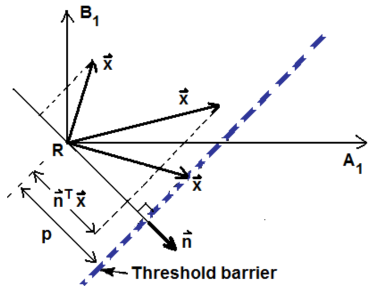

Fig.5. Graphical interpretation of Eq.(12). The unit vector $\vec{n}$ is normal to the threshold barrier.

There are analytical formulae for the unit vector $\vec{n}$ and the distance p as functions of system's parameters [19], [20]. We put $\vec{x}(t)$ from (11) into (12) and define:

(a) The impulse response function

$$G_M(t) = \frac{\vec{n}^T e^{t \cdot A} \vec{e}_1}{\vec{n}^T \vec{e}_1} \quad . \qquad (13)$$

(b) The threshold current

$$I_{Th,0} = \frac{p}{\lambda_m^2 \cdot F_{M,1} \cdot \vec{n}^T \vec{e}_1} \quad . \qquad (14)$$

Then *we obtain the just threshold condition for magnetic stimulation in terms of the excitation functional* (equivalent to (3) and (4) combined)

$$\max_{t \in [0,+\infty)} \left\{ \int_0^t G_M(t-u) \frac{d_C i(u)}{du} du \right\} = I_{Th,0} \, . \qquad (15)$$

The same procedure applied to electric stimulation gives

$$Q_{Th,0} = \frac{p}{\lambda_m^2 \cdot F_{E,1} \cdot \vec{n}^T \vec{e}_1} \qquad G_E(t) = \frac{\vec{n}^T e^{t \cdot A} \vec{e}_1}{\vec{n}^T \vec{e}_1}$$

So, if the parameters of the unit membrane are the same, the only difference in the impulse response function (in the framework of this mathematical model) is due to different values of ℓ related with differences in the form factor.

The activation of peripheral nerves can be studied under the following modeling conditions: the medium can be considered as homogeneous, the fiber can be considered as straight and unbounded but the external electric field varies in a region along the fiber [12].

In the framework of the present mathematical model, the degree of spatial localization of the perturbation of the peripheral nerve membrane due to the external field is given by the length of the *interval of influence* ℓ .

It is possible to show that an approximate formula for the time constant of the cathodal strength-duration curve for a nerve fiber is given by [21]

$$t_S \approx \frac{\tau_m}{\left(1 + \pi^2 \frac{\lambda_m{}^2}{\ell^2}\right)} \, . \qquad (16)$$

The chronaxy is proportional to t_S. For a given peripheral nerve, in the electric stimulation ℓ is smaller than in the magnetic stimulation case. From (16) it follows that chronaxies for electric stimulation should be smaller than chronaxies for magnetic stimulation. This explains the experimental findings [13].

Equation (16) is obtained from the simplest model for the impulse response function. A more realistic model of G_M (given by (13)) is sketched in Fig.6.

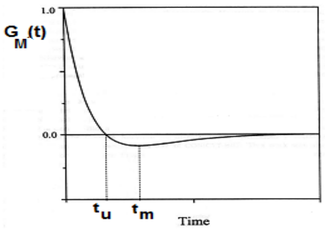

Fig.6. Schematic representation of an impulse response function taken from [19].

It allows the calculation of the chronaxies both for cathodic and anodic stimulations. However, despite the analytical formulae are different, the same theoretical predictions about the behavior of chronaxies for electric and magnetic stimulation of peripheral nerves are derived from this more complete model.

IV. THE IDENTIFICATION OF THE IMPULSE RESPONSE FUNCTIONS

For electric stimulation, the identification problem of the excitation functional is already studied in [2], [3], [6].

For magnetic stimulation, let us consider a linear ramp of electric current in the coil. From the excitation functional (15) it follows that for a ramp of duration t_P, that produces a suitable depolarization of the fiber membrane in the interval of influence, the threshold slope $\frac{di_{C,Th}}{dt}(t_P)$ is given by:

$$\frac{di_{C,Th}}{dt}(t_P) = \frac{I_{Th,0}}{\int_0^{t_P} G_M(u) \cdot du} \, . \qquad (17)$$

From (15) when the ramp duration tends to zero, we derive

$$I_{Th,0} = \lim \left(t_p \cdot \frac{d}{dt_p} i_{C,Th}(t_P) \right) . \qquad (18)$$

Once $I_{Th,0}$ is known, from (16) and (17) it follows

$$G_M(t_P) = \frac{\partial}{\partial t_P} \left(\frac{I_{Th,0}}{\frac{di_{C,Th}}{dt}(t_P)} \right) . \qquad (19)$$

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This means that *the impulse response functions may be obtained from experimental strength-duration curves for magnetic stimulation*. These experimental curves can be done using equipment similar to the one described in [22]. However the derivative makes it an ill posed problem. A way out of this difficulty is to use analytical formulae (13) and (14) derived in this paper and adjust the parameters of (15) to the experimental data.

V. FINAL COMMENTS

The excitation functional is a systemic property. From the standpoint of attaining the threshold in a given target fiber in an external electric field, an action potential can emerge under four *modeling circumstances*: (a) the external field is uniform and the fiber crosses a region of fast variation of the electrical conductivity of the medium, (b) the external field is uniform and the medium can be considered as homogeneous but the fiber bends, (c) the external field is uniform and the medium can be considered as homogeneous but the fiber originates or terminates (short circuit or open circuit conditions), (d) the medium can be considered as homogeneous, the fiber can be considered as straight and unbounded but the external electric field varies in a region along the fiber. The model of the present paper applies to circumstances (b) and (d), because what matters is the spatial variation of the projection of the electric field tangential to the fiber and its time variation. This time variation is proportional to: time variation of the current in the electrode case, and the time derivative of the current circulating in the working coils. An extension to cases (a) and (c) could be done.

In the magnetic case the determination of the form factor is a difficult problem that deserves further study.

However, once determined $G_M(t)$ and $I_{Th,0}$, the binary output response of a given target fiber to different pulse shapes in the coil *could be predicted and contrasted with experiments*, assuming that the system composed by the coil, volume conductor and target fiber remains unchanged.

An extension of the present derivation of the excitation functional for magnetic excitation, to take into account *lag effects* in the activation of the excitation channels in fiber's membrane, and *myelinated* fibers, both neglected in this paper, remains to be done.

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