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Modeling the Activation of a Non-Homogenous Nerve Fiber by Magnetic Stimulation

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Abstract— **In this paper we present a model that combines circuit analysis with Maxwell's equations of electromagnetic theory and non-linear cable theory, to explain the action of the induced electric field upon a nerve fiber. The current source and stimulating coil are modeled as a series RLC circuit. The induced electric field distribution within a homogeneous cylindrical volume conductor modeling the arm is calculated for different time courses of the current. The effect of the induced electric field upon the nerve is determined with a cable model which contains active Hodgkin-Huxley elements. The possible non-homogeneities of the nerve's electrical properties are also considered, and we assess their influence on the activation of the nerve.**

Keywords- Magnetic stimulation, stimulating coil, non-homogenous Hodgkin-Huxley model, activation function.

I. INTRODUCTION

The preoccupation for improving the quality of life, for persons with different handicaps, led to extended research in the area of functional stimulation. Due to its advantages compared to electrical stimulation (painless stimulation, magnetic field passes high resistive layers, etc.), magnetic stimulation of the human nervous system is now a common technique in modern medicine.

The paper starts by emphasizing the mechanism of magnetic stimulation (computation of induced electric field, the description of the stimulating circuit and the behavior of the nerve fiber – active cable model). Then, a computer model with all its characteristics is presented. Finally, we assess the influence of the variation of the electrical parameters of the nerve fiber on its activation and important conclusions are drawn.

II. THEORETICAL CONSIDERATIONS

A. Mechanism of magnetic stimulation

The magnetic stimulation is based on Faraday's law and is referred to induce an electric field in nervous tissue by an alternating current flowing through a coil, placed near the fiber to be stimulated. According to the electromagnetic field theory, the electric field inside the tissue can be computed by means of the scalar electric potential and the vector magnetic potential:

$$\overline{E} = \underbrace{-\frac{\partial \overline{A}}{\partial t}}_{\overline{E}_A} \underbrace{- gradV}_{\overline{E}_V} \qquad (1)$$

The first term of the electric field is called "primary electric field", and it is due directly to the electromagnetic induction phenomenon, while the second term represents the "secondary electric field", due to charge accumulation on the tissue-air boundary [1].

According to (1), the computation of the electric field due to electromagnetic induction is done by means of the magnetic vector potential [1]:

$$\overline{A}(\overline{r},t) = \frac{\mu_0 \cdot N \cdot I(t)}{4\pi} \int_{coil} \frac{\overline{dl}}{\left|\overline{r}\right|}. \qquad (2)$$

where the vector $\overline{dl}$ represents the differential element of the coil, the vector $\overline{r}$ is the distance from the coil element to the field point, and N is the number of turns of the coil.

For coils of different shapes, one can compute $\overline{A}$ using the following technique: the contour of the coil is divided into a certain number of equal segments, and the magnetic vector potential in the calculus point is obtained by adding the contribution of each segment to the final value [2], [3].

A common application of magnetic stimulation is to excite peripheral nerves [1]. We assume that the arm can be modeled as a cylindrical volume conductor. The secondary electric field depends on the geometry of the tissue-air interface, considered a cylindrical surface [4]. This term is computed knowing that on the surface, the boundary condition to be fulfilled is: $\overline{n} \cdot \overline{E}_A = -\overline{n} \cdot \overline{E}_V$ (continuity of the normal component of the current density vector, valid considering the fact that the regime of the electromagnetic field is quasistatic (f < 1000 (Hz)) and therefore the time variation of the charge accumulated on the tissue-air boundary is zero). The electric potential inside this domain, V, is numerically evaluated by solving Laplace equation $(\Delta V = 0)$ with Neumann boundary conditions inside the tissue $\left(\frac{\partial V}{\partial \overline{n}} = \overline{n} \cdot \overline{E}_A\right)$. In order to solve this problem we implemented a Matlab routine based on the Finite Difference Method. The system of equations created is solved using Gauss elimination algorithm.

For the operating frequency of magnetic stimulation, the electrical and magnetic properties of the medium are assumed to be σ=1 (S/m) and $\mu=\mu_0$.

B. Stimulating circuit

The coil current *I(t)* ($\overline{A}$ is proportional to *I* – see (2)) is predicted by a series RLC model of the current stimulator. If $\left(\frac{R}{2L}\right)^2 > \frac{1}{LC}$ the circuit works in an overdamped transient state. The current waveform through the discharging of a capacitor, with an initial voltage U_0, to the coil is:

$$I = U_0/\omega L \cdot \sinh(\omega t)\exp(-\alpha t) \qquad (3)$$

where $\alpha = R/(2L)$, $\omega = \sqrt{\alpha^2 - 1/LC}$, *C* is the capacitance, and *R* and *L* are the resistance and inductance of the coil, respectively. In this case, the current intensity increases from zero (for t=0) to its maximum, and then decreases tending to zero, without changing its sense; theoretically the current is canceled for $t \to \infty$.

If the above inequality is reversed, the circuit works in an underdamped transient state, and therefore the current is computed using:

$$I(t) = U_0 C \omega' e^{-\delta t}\left(\left(\frac{\delta}{\omega'}\right)^2 + 1\right)\sin(\omega' t) \qquad (4)$$

Now, the current intensity has a damped oscillatory variation and its amplitude decreases exponentially in time: $e^{-\frac{R}{2L}\cdot t}$. The oscillation frequency is: $f = 1/2\pi \cdot \sqrt{LC}$.

The inductance is evaluated by taking the line integral of the vector potential around the coil for unit current: $L = \oint \overline{A} \cdot \overline{dl}$. This formula permits the computation of inductances of the special coils; these coils are designed to improve focality (the ability of a coil to stimulate a small area of tissue). The resistance is evaluated using the analytical formula:

$$R = \frac{\rho_{Cu} 2\pi r N}{\pi r_w^2} \qquad (5)$$

where ρ_{Cu} - copper resistivity; *r* – radius of the coil; *N* – number of turns; r_w - radius of the wire conductor.

C. Hodgkin-Huxley model

Neuronal structures can be modeled in the form of a cable and the membrane response can be computed by solving the equations describing the transmembrane potential across the membrane of the cable in the presence of induced electric fields [5], [6]. The relation between the transmembrane potential along an infinitely long nerve fiber (placed along the *x* axis) in the presence of induced electric fields is given by the passive cable model:

$$\tau \frac{\partial V_m}{\partial t} + V_m - \lambda^2 \frac{\partial^2 V_m}{\partial x^2} = \underbrace{-\lambda^2 \frac{\partial E_x}{\partial x}}_{=f(x)} \qquad (6)$$

where V_m is the transmembrane voltage, E_x the axial component of the induced electric field, λ the space constant of the cable and τ the time constant.

The term on the right of (6) represents the activation function, equal to the spatial derivative of the electric field induced along the nerve fiber. This term is computed using the method described in paragraph A.

While the passive cable model provides the way of the interaction between the induced electric field and the nerve, it does not completely describe the dynamics of nerve stimulation. In order to study the stimulation and propagation of action potentials, we must consider an active membrane model. We use the Hodgkin-Huxley model to represent the nerve membrane (Fig. 1). To implement this model, we modify the initial passive cable model. The extracellular potential produced by the fiber's own activity is negligible. This assumption is valid because the extracellular potential produced by an action potential propagating along a single nerve axon lying in a large extracellular volume conductor is less than 1 mV [7].

The resistance per unit length of the fiber r_i can be expressed in terms of the fiber radius *a* and the resistivity of the axoplasm R_i, as: $r_i = R_i/\pi a^2$. The membrane current per unit length i_m is related to the membrane current density J_m by the expression: $i_m = 2\pi a J_m$; similarly the membrane capacitance per unit length c_m is related to the capacitance per unit area C_m by: $c_m = 2\pi a C_m$. Finally we replace the membrane resistance per unit length r_m by an active model of time and voltage dependent sodium, potassium and leakage channels. With these changes, the cable equation becomes:

$$\frac{a}{2R_i}\frac{\partial^2 V_m}{\partial x^2} - \left(g_{Na} m^3 h (V_m - E_{Na}) + g_K n^4 (V_m - E_K) + g_S (V_m - E_S)\right) = C_m \frac{\partial V_m}{\partial t} + \frac{a}{2R_i}\frac{\partial E_x}{\partial x}(x,t) \qquad (7)$$

where g_{Na}, g_K and g_S are the peak sodium, potassium and leakage membrane conductances per unit area, and E_{Na}, E_K and E_S are the sodium, potassium and leakage Nerst potentials. The gating variables *m*, *n*, *h* are dimensionless functions of time and voltage which vary between zero and one:

$$\frac{\partial m}{\partial t} = \alpha_m (1-m) - \beta_m m \qquad (8)$$

$$\frac{\partial h}{\partial t} = \alpha_h (1-h) - \beta_h h \qquad (9)$$

$$\frac{\partial n}{\partial t} = \alpha_n (1-n) - \beta_n n \qquad (10)$$

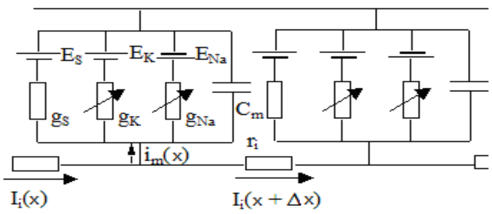


Figure 1. Hodgkin-Huxley model of the active cellular membrane [1]

α and β are voltage dependent rate constants, determined from the voltage clamp measurements:

$$\alpha_m = \frac{0,1(-40 - V_m)}{e^{\left(\frac{-40-V_m}{10}\right)} - 1} \tag{11}$$

$$\beta_m = 4e^{\left(\frac{-65-V_m}{18}\right)} \tag{12}$$

$$\alpha_h = 0,07e^{\left(\frac{-65-V_m}{20}\right)} \tag{13}$$

$$\beta_h = \frac{1}{e^{\left(\frac{-35-V_m}{10}\right)} + 1} \tag{14}$$

$$\alpha_n = \frac{0,01(-55 - V_m)}{e^{\left(\frac{-55-V_m}{10}\right)} - 1} \tag{15}$$

$$\beta_n = 0,125e^{\left(\frac{-65-V_m}{80}\right)} \tag{16}$$

We assumed that the resting potential is -65 (mV), V_m is measured in (mV), α and β in (ms^{-1}). Equations (7) - (16) constitute a system of four, nonlinear, coupled partial differential equations.

The values of model parameters used in our computations are given in Table 1 [1]:

TABLE I.

E_{Na}	Sodium Nerst potential	50 (mV)
E_K	Potassium Nerst potential	-77 (mV)
E_S	Leakage Nerst potential	-54.387 (mV)
g_{Na}	Sodium conductance	120 (mΩ/ cm^2)
g_K	Potassium conductance	36 (mΩ/ cm^2)
g_S	Leakage conductance	0.3 (mΩ/ cm^2)
C_m	Membrane capacitance	1 (μF/ cm^2)
R_i	Resistivity of axoplasm	0.0354 (kΩ⊙cm)
a	Fiber radius	0.0238 (cm)

III. Results

The magnetic coil considered in our simulation has 30 turns, a radius of 25 (mm) and the wire's radius is 1 (mm). The computed inductance of this coil is 0.165 (mH) [8]. The coil is part of a magnetic stimulator that also comprises a capacitance, C=200 (μF). If the total resistance of the circuit (including the coil and wires resistances) is considered to be 1.75 (Ω), the circuit elements respect the following formula $\frac{R^2}{4L^2} < \frac{1}{LC}$, and therefore the transient regime of the circuit is underdamped. For a larger value of the total resistance (R=3 (Ω)), the inequality is reversed and the transient regime is overdamped. In the paper we studied both cases, because the overdamped regime is used for single pulse magnetic stimulation, while the underdamped oscillatory regime is more suitable for repetitive stimulation.

Fig. 2 shows the geometry of the problem, for both cases. One can see that the coil is parallel with the tissue, but with 25 (mm) displacement with respect to the cylinder axis.

In order to obtain the transmembrane potential as a function of distance and time, first we modulate the electric field gradient in time ($\partial E_Z(z,t)/\partial z$). The electric field gradient represents the activation function and is calculated along the cylinder (the arm) – Oz axis, on a line with y=0 (mm) and x= 25–6.25 = 18.75 (mm), that is on a depth of 6.25 (mm) in the tissue, below the edge of the coil.

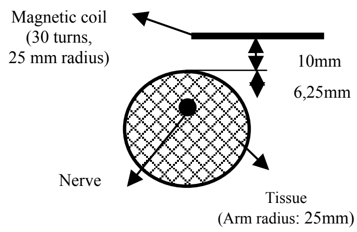


Figure 2. Geometry of the problem

Our simulations start with the overdamped regime. For simulation purposes, the initial voltage on the circuit's capacitor is set to U_0=30 (V), and Fig. 3 shows the induced electric field gradient as a function of time and distance along the fiber.

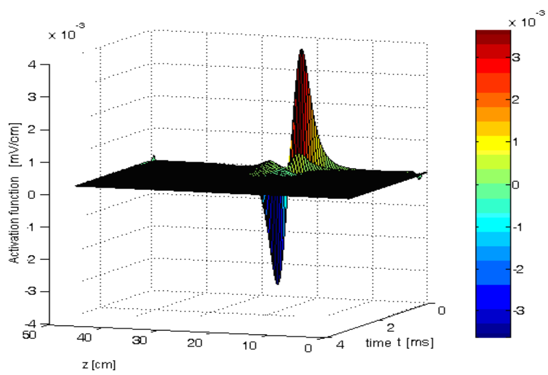


Figure 3. The activation function evaluated along the length of the nerve fiber considering an overdamped transient regime

Then, we solve Eqn. (6) – (15) numerically, using a software medium: Matlab. The transmembrane potential $V_m(x,t)$ and the three gating parameters $m(x,t)$, $n(x,t)$ and $h(x,t)$ are computed using the method of finite differences, implemented with an iterative algorithm (we compute the value of each parameter knowing its value for the previous time step - 0.1 (ms)). The space discretization uses a step of 5 (mm). It is assumed that the membrane is initially at rest:

$$\frac{\partial V_m}{\partial t} = \frac{\partial m}{\partial t} = \frac{\partial h}{\partial t} = \frac{\partial n}{\partial t} = 0 \quad for\; t = 0 \qquad (17)$$

The transmembrane voltage is taken to be its resting value and the initially *m*, *n* and *h* each are evaluated at the resting potential -65 (mV).

The boundary conditions of the problem, applied for $x = \pm L$, far from the region where the stimulus strength is large, are that the axial gradients in the transmembrane potential and the three gating parameters vanish.

$$\frac{\partial V_m}{\partial x} = \frac{\partial m}{\partial x} = \frac{\partial h}{\partial x} = \frac{\partial n}{\partial x} = 0 \qquad (18)$$

The model is used to determine the response of the nerve membrane, the action potential, to the applied electric field, for different values of the initial voltage on the capacitor of the stimulation circuit.

When the circuit works in an over-damped transient regime, the minimum value for the initial voltage on the circuit's capacitor, required to produce fiber activation, is U_0= 37 (V). For U_0= 30 (V) the nerve fiber is not stimulated. Not the same applies for an underdamped transient state, when an action potential is evoked much earlier, at U_0= 10 (V) (Fig. 4 – the second curve).

One can see that, after a latency period, the transmembrane potential rises rapidly to the value of about 50 (V).

The first sets of stimulations were performed to investigate the latency period, which is different for the two types of transient regime. For both cases, we considered the same initial voltage on the capacitor U_0= 50 (V). One can see in fig. 5 that we achieve activation of the nerve fiber in both cases, but the latency period is much shorter for the underdamped case (0.35 (ms)) than for the overdamped one (1.7 (ms)). Also, by comparing the results in fig. 4 and 5, one can notice that the value of the initial voltage on the capacitor does not influence the shape of the nerve response (this one obeys the law of "all or nothing"), but a larger value of this voltage leads to a shorter latency period until an action potential arises.

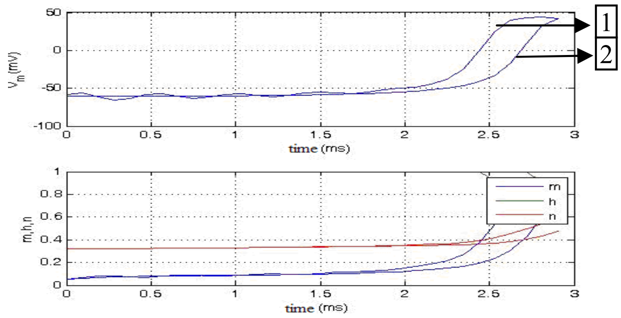


Figure 4. Variation of the transmembrane potential and the three gating parameters in time, 1 – for an underdamped oscillatory regime, U_0= (10 V); 2 – overdamped regime, U_0= 37 (V)

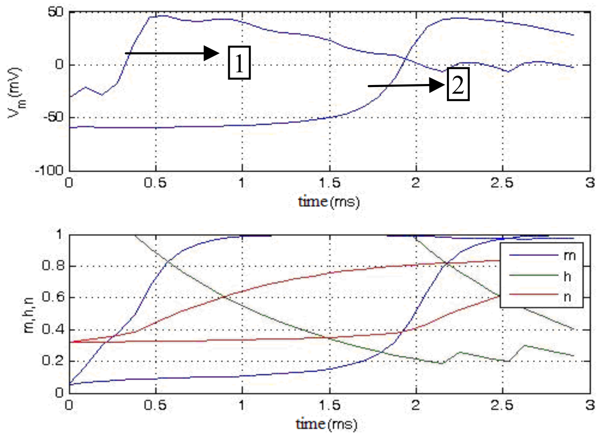
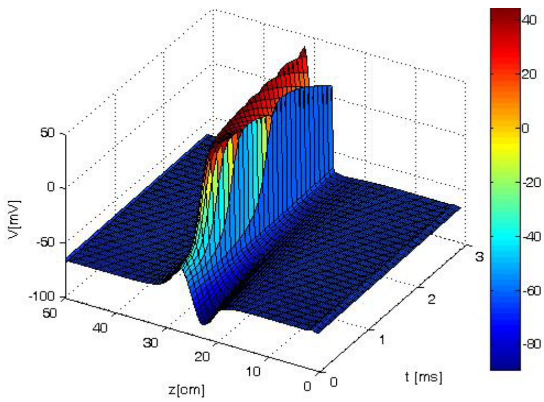
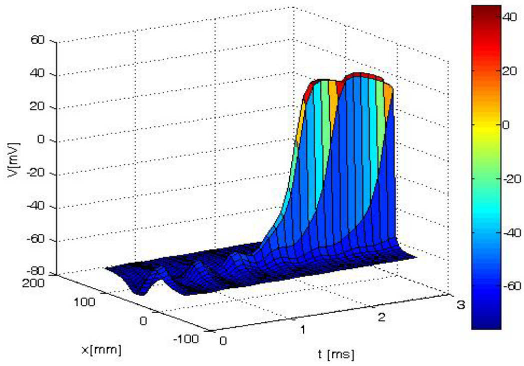


Figure 5. Variation of the transmembrane potential and the three gating parameters in time, for U_0= 50 V. 1 – underdamped and 2 – overdamped regime

The three – dimensional plot in Fig. 6, shows the depolarized portion of the nerve has been stimulated, while the hyperpolarized portion is not. One can also notice the speed of the wave, the latency period and the site of stimulation.



a)



b)

Figure 6. Nerve fiber response to magnetic stimulation – action potential. The vertical axis represents the action potential, while the horizontal axis represent the distance along the fiber and the necessary time for the discharge of the capacitor in the stimulator's equivalent circuit a) over-damped regime and b) underdamped regime

In most of the publications the electrical properties of the membrane are considered uniform along the fiber, even in the original model, elaborated by Hodgkin and Huxley [1], [5], [10]. So far, we considered that the electric parameters in the model are constant along the nerve fiber. This assumption may not always be true, considering the fact that the human tissue is, always, a very non-homogenous area. Nerve fiber models with parameter variability within the fiber were investigated in [11], resulting in a change of the excitation threshold up to 20% compared to the standard model, when varying only a parameter. Compared to our model, they used a compartmentalized nerve fiber model, adopted from McNeal. Other investigations referred to the importance of considering the undulation of the nerve fiber, which significantly influences the excitation threshold [7].

Unlike the existing publications, we assume that the electric parameters of the membrane vary within a range of 10% from the generally assumed value and they have a sinusoidal variation along the nerve fiber [9]. The electrical parameters we changed are: g_{Na} – Sodium conductance; g_K – Potassium conductance and C_m – Membrane capacitance. We assumed that:

$$\begin{cases} g_{Na} = 120 + 12 \cdot \sin(j \cdot 2\pi / 10)\, m\Omega / cm^2 \\ g_K = 36 + 3.6 \cdot \sin(j \cdot 2\pi / 10)\, m\Omega / cm^2 \\ C_m = 1 + 0.1 \cdot \sin(j \cdot 2\pi / 10)\, \mu F / cm^2 \end{cases} \quad (19)$$

where j represents a parameter that follows the length of the nerve.

Next, our work consisted in assessing the influence of this variation of the parameters on the nerve fiber activation threshold. We considered first the overdamped state, and we represented in Fig. 7 the behavior of the fiber for different cases. The first line -1, represents the behavior for constant parameters of the fiber, and an initial voltage on the capacitor below 37 (V). Line 2 is still for constant parameters, but since U_0=37 (V), one can notice that the fiber was now activated. The third line considers a variation of the C_m parameter, and in that case, the activation appears at the same value of U_0, but with a slightly shorter latency. Line 4 is drawn for a variable g_{Na}, but in this case, the activation only occurs for U_0>100 (V)! The last curve - 5 – corresponds to a variable g_K, where an activation can be noticed even for U_0=30 (V)!

So far we considered that only one of the three parameter changes at the time, but next (Fig. 8) we will emphasize what happens if all the parameters change simultaneously. Curve one shows that for constant parameters the nerve fiber is activated when U_0=37 (V). Curve two shows that if all the parameters change, the nerve is no longer activated for the same value of the initial voltage, but the fiber is activated again – 3 - when the voltage applied rises up to U_0=45 (V).

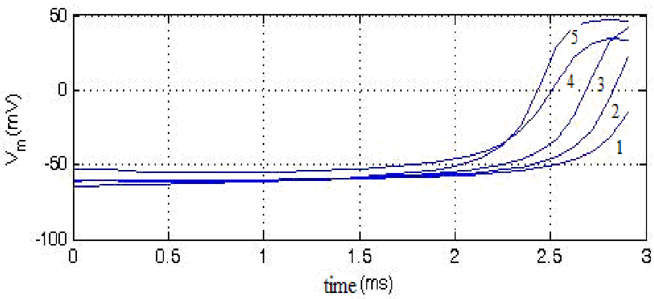


Figure 7. Variation of the transmembrane potential in time, for an over-damped transient regime, considering different variations of the electric components of the nerve membrane

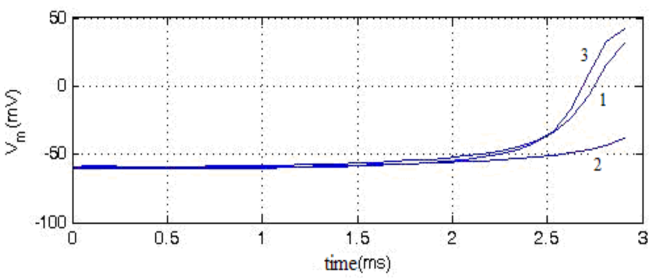


Figure 8. Variation of the transmembrane potential in time, for an over-damped transient regime, considering the variations of all the electric components of the nerve membrane

The same study was resumed for the underdamped transient state, and we represented in Fig. 9 the behavior of the fiber for different cases. The first line -1, represents the behavior for constant parameters of the fiber, and an initial voltage on the capacitor below 10 (V). Line 2 is still for constant parameters, but since U_0=10 (V), one can notice that the fiber was now activated. The third line is drawn for a variable g_{Na}, but in this case, the activation only occurs for U_0=25 (V)! Line 4 considers a variation of the C_m parameter, and in that case, the activation appears at the same value of U_0 as for constant parameters. The last curve - 5 – corresponds to a variable g_K, where an activation can be noticed even for U_0=5 V!

If all the parameters change simultaneously, Fig. 10 shows the nerve fiber behavior for an underdamped state. Curve one shows that for variable parameters the nerve fiber is not activated when U_0=10 (V), even though the nerve is activated for constant electrical parameters along the fiber– 2. For variable parameters – 3 - when the volt-age applied rises up to U_0=20 (V) we can, again, achieve the activation of the nerve.

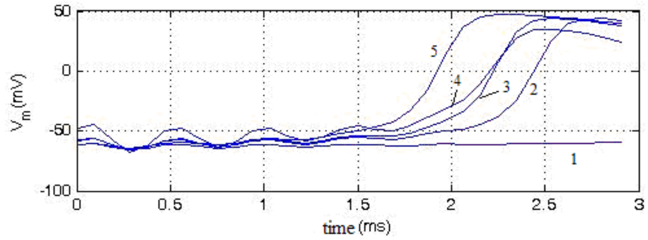


Figure 9. Variation of the transmembrane potential in time, for an underdamped transient regime, considering different variations of the electric components of the nerve membrane

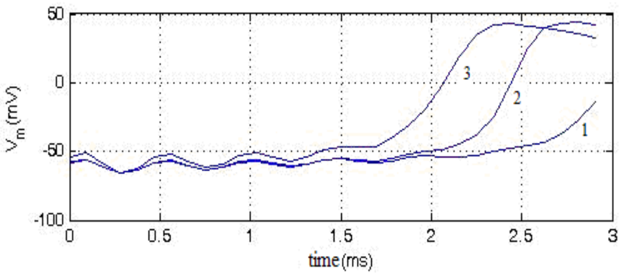


Figure 10. Variation of the transmembrane potential in time, for an under-damped transient regime, considering the variations of all the electric components of the nerve membrane

IV. Discussions and Conclusions

In our paper we have computed the response of the nerve fiber to magnetic stimulation. Three aspects of electromagnetic stimulation are considered together in one model: the current pulse shape (over or under damped), the spatial distribution of the induced electric field and the interaction of the electric field with the nerve.

Depending on the operating mode of the stimulation circuit (overdamped or underdamped state), the action potential is evoked at different values of the voltage on the circuit's capacitor. For the overdamped transient regime, the initial voltage that leads to stimulation must be equal to or larger than 37 (V). For the underdamped regime, this value is U_0 = 10 (V). For the same value of the initial voltage on the capacitor (50(V)), the current pulse corresponding to an underdamped transient state leads to a shorter latency period that the one computed for the overdamped case (0.35 (ms) compared to 1.7 (ms)).

Fibers with different diameters or membrane properties have different stimulus thresholds. In this paper we investigated the influence of the membrane electric parameter variability upon the excitation threshold, for two transient regime of the stimulating circuit. One can notice that the variation of the C_m parameter will not significantly influence the activation threshold of the nerve.

However, a variation of g_{Na} will always lead to a higher threshold. For the overdamped state, the excitation threshold rises up almost three times compared to the standard model, where the electric parameters are constant (U_0=100 (V), while for the standard model U_0=37 (V)). In the underdamped transient state, the variation of g_{Na} determines an increasing of 250% of the excitation threshold compared to the standard model (U_0=25 (V) while for the standard model U_0=10 (V)).

A variation of g_K will lead to a slightly lower threshold compared to the model with constant parameters (U_0=30 V for the overdamped case and U_0=5 V for the underdamped state).

When all parameters vary simultaneously, the value of the threshold is always higher then the one for constant parameters. For overdamped transient state of the circuit, the variability of the parameters leads to a change of the excitation threshold up to 21.6% compared to the standard model. For the underdamped state, the threshold for variable parameters is double compared to the initial one. This is due to the role played by each type of ions in the dynamic of the nerve fiber.

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