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MODELING THE NON-HOMOGENEOUS NERVE FIBERS LOCATED INSIDE THE HUMAN SPINAL CORD

BY

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Abstract. The research is based on some previously performed preliminary experiments of the authors and tries to find out the necessary characteristics of a magnetic stimulator (the proper value for the initial voltage on the circuit capacitor) that can trigger the activation of the spinal cord. The effect of the induced electric field upon the nerve fiber located inside the spine is determined using an active cable model. The possible non-homogeneities of the fiber are also considered, and we assess their influence on the activation of the spinal cord.

Key words: cable model; magnetic stimulation; nerve fiber; spinal cord.

1. Introduction

The medical recovery of certain injuries, such as stroke, paraplegia or other sources of paralysis is often accompanied by physical therapy with neuromuscular stimulation (Kobayashi *et al.*, 2003). In recent years, magnetic stimulation became an important method of stimulation (Krause *et al.*, 2004;

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Rossini *et al.*, 2015) and compared to electrical stimulation (Minassian *et al.*, 2004) could lead directly to the activation of the spinal cord (the electromagnetic field can pass high resistive layers) with a lower level of pain perception (Tazoe *et al.*, 2015; Awad *et al.*, 2015). Preliminary experiments and computer simulations (Dărăbant *et al.*, 2013; Crețu *et al.*, 2015) aimed to evaluate if transcutaneous magnetic stimulation is able to directly stimulate the spinal cord.

The previously performed experiments involved the magnetic stimulation of the rostro-caudal area of seven healthy subjects (aged 20-35, 5 males, 2 females) with intact nervous system, using a Magstim Rapid² (The Magstim Company Ltd, Whitland, UK) magnetic stimulator. The stimulation was applied at several levels (from T12 to L4 vertebrae) at the maximum intensity tolerated by the subject. The compound muscle action potentials (CMAP) were recorded from the lower limbs' muscles using an eight channels EMG device.

The experimental protocol started by positioning the stimulating coil (we used the "eight"-shaped, supplied by the manufacturer) above the subject's back Fig. 1. This position is known in theory to create, below the edge of the coil, an appropriate derivative of the induced electric field (activation function), that would lead to the activation of the nerve fibers located here.

At a certain point of our researches (Dărăbant *et al.*, 2013), based on the latency of the recorded signals, we concluded that the responses elicited in the lower limbs muscles could be identified as M-wave responses of the muscles (activation of the moto-neurons afferent to the spine), and no direct stimulation of the cortical-spinal tract was achieved.

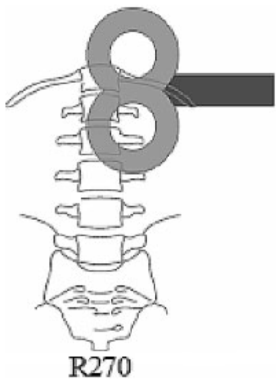


Fig. 1 – Stimulation coil and its position with respect to the spine. (The coil is placed in the right part above the vertebrae and the angle between its handle and spine is 270º).

Since the existent commercial devices (Aciu *et al.*, 2011) were unable to trigger the activation of the spinal cord (Dărăbant *et al.*, 2013), this paper starts by emphasizing the necessary characteristics of magnetic stimulators able to deliver enough energy to the spine in order to activate it.

Then, we assess the influence of the variation of the electrical parameters of the nerve fiber (the non-homogeneities of the nerve fiber located inside the spinal cord) on its activation and important conclusions are drawn.

2. Theoretical Background

Our simulations aimed in resuming real stimulation conditions from the experimental protocol: the human lumbar area is modeled by a parallelepiped, inside the parallelepiped is the spinal cord, shaped as a continuous cylinder, while the vertebral bone is represented by a cylinder - concentric with the first one - but interrupted. The entire model used is described in (Dărăbant *et al.*, 2013).

We first compute the induced electric field and its derivative (the activation function), along the length of the nerve fiber embedded within the spinal cord and then calculate the response of a nerve fiber to the stimulation applied, using a virtual stimulator with variable coil and drive voltage.

According to the electromagnetic field theory, the electric field inside the tissue can be computed by means of the vector magnetic potential and the scalar electric potential, which depend on the geometry of the tissue-air interface (Roth *et al.*, 1990; Nagarajan *et al.*, 1993; Mills, 1999):

$$\overline{\mathrm{E}} = \underbrace{-\frac{\partial \overline{\mathrm{A}}}{\partial t}}_{\overline{\mathrm{E}}_A} \underbrace{-\mathrm{grad} V}_{\overline{\mathrm{E}}_V}. \tag{1}$$

The first term of the electric field is due directly to the electromagnetic induction phenomenon (Roth et al., 1990; Essele *et al.*, 1992; Weber *et al.*, 2002). The magnetic vector potential, for coils of non-traditional shapes (Păcurar *et al.*, 2013; Răcăşan *et al*., 2014), is computed using an approximation method in which the contour of the coil is first divided into a variable number of equal segments (Roth *et al.*, 1990), and the magnetic vector potential in the calculus point is obtained by adding the contribution of each segment to the final value.

The second term from (1) is due to charge accumulation on the tissue-air boundary (Roth *et al.*, 1990; Stet *et al*., 2013; Weber *et al.*, 2002). The electric potential, *V*, inside the domains (*i*) with different electrical properties is numerically evaluated by solving Laplace equation ($\Delta V^{(1)} = 0$) inside each domain. The computations were performed using a Matlab (The Math Works Inc., Natick, Massachusetts, USA) routine, based on the Finite Difference Method. The created system of equations was solved using Gauss elimination algorithm.

To evaluate the characteristics of the applied stimulus, we compute the circuit parameters of the magnetic stimulator, which is approximated by an RLC series circuit working in transient regime (Roth *et al.*, 1990; Nagarajan *et al.*, 1993). The current pulse is generated when a capacitor *C* initially charged with a voltage U_0 is discharged through a coil whose inductance is L and resistance R. In this paper we studied both transient regimes that can be established in the circuit: overdamped and underdamped.

For the overdamped transient regime, usually used for single pulse magnetic stimulation, the parameters of the circuit need to respect the following condition: $(R/2L)^2 > 1/LC$. 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 cancelled for $t \to \infty$. If the above inequality is reversed, the circuit works in an underdamped transient regime. Now, the current intensity has a damped oscillatory variation and its amplitude decreases exponentially in time: $\mathrm{e}^{-\frac{R}{2L}t}$. The oscillation frequency is: $f = 1/2\pi\sqrt{LC}$. The oscillatory pulse is often used in repetitive magnetic stimulation, because such a signal allows easy recovery of energy to the capacitor.

In the last step of the algorithm that describes the mechanism of magnetic stimulation, we evaluate the response of the neuronal structures to the stimulus applied. The neuronal structures are 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. The relation between the transmembrane potential along an infinitely long nerve fiber (placed along the z axis) in the presence of induced electric fields is given by (Nagarajan *et al.*, 1993; Roth *et al.*, 1990):

$$\frac{a}{2\rho_i}\frac{\partial^2 V_m}{\partial z^2} - \left[g_{Na}\mathrm{m}^3\mathrm{h}\left(V_m - E_{Na}\right) + g_K n^4\left(V_m - E_K\right) + g_S\left(V_m - E_S\right)\right] = \\ = C_m\frac{\partial V_m}{\partial t} + \underbrace{\frac{a}{2\rho_i}\cdot\frac{\partial E_z}{\partial z}(z,t)}_{f(z)}, \tag{2}$$

where: a is the radius of the fiber (a = 0.0238 cm), ρ_i – the axoplasma resistivity (ρ_i = 0.0354 kΩ.cm), V_m – the transmembrane potential, E_z – the axial component of the induced electric field, g_{Na}, g_K and g_S are the peak sodium, potassium and leakage membrane conductances per unit area, E_{Na}, E_K and E_S are the sodium, potassium and leakage Nerst potentials and C_m is the membrane capacitance (C_m =1 .0 μF/cm^2). The term on the right hand side of (2) – $f(z)$ – represents the activation function.

The gating variables m, n, h dimensionless functions of time and voltage which vary between zero and one.

Then, we solve numerically the system of equations that describes the active behaviour of the nervous fiber, using also a Matlab routine. The transmembrane potential V_m and the three gating parameters $m(z,t)$, $n(z,t)$ and

$h(z,t)$ 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:

$$\frac{\partial V_m}{\partial t} = \frac{\partial m}{\partial t} = \frac{\partial h}{\partial t} = \frac{\partial n}{\partial t} = 0 \text{ for } t = 0. \qquad (3)$$

The transmembrane voltage is taken to be its resting value and the initially m, n and h each are evaluated at the resting potential of –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:

$$\frac{\partial V_m}{\partial z} = \frac{\partial m}{\partial z} = \frac{\partial h}{\partial z} = \frac{\partial n}{\partial z} = 0. \qquad (4)$$

The other electrical parameters involved in the active model of the cellular membrane are taken from (Roth *et al.*, 1990).

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.

3. Results and Discussions

The magnetic coil considered in our simulation has the same characteristics as the commercial one used in experiments: it is a "figure of eight" coil with 18 turns, an outer radius of 35 mm, the wire radius of 1 mm and the insulation gap between turns of 1 mm. The inductivity of this coil is specified by the manufacturer of the magnetic stimulator and is L = 16.35 μH. The coil is part of a magnetic stimulator that also comprises a capacitance, C = = 200 μF and a resistance. The coil resistance is evaluated using the analytical formula:

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

where: ρ_{Cu} is the copper resistivity; r – radius of the coil; N – number of turns; r_w – radius of the wire conductor. The total resistance of the circuit (including the coil and wires resistances) is considered to be $R_{\text{overdamped}}$ = 3 Ω, for the overdamped transient regime and $R_{\text{underdamped}}$ = 0.565 Ω, for the underdamped regime, respectively.

In our experiments, to use the magnetic stimulator to 100% of its total power, the initial voltage on the stimulator's capacitor was set to U_0 = 50 V. The maximum value of the stimulator current derivative is dI = dU_0 A/μs. Using this value for the initial voltage on the capacitor, we concluded in (Dărăbant *et al.*, 2013) that the magnetic stimulator, used in our preliminary experiments, as described above, was unable to stimulate structures within the spinal cord, but only adjacent spinal nerves. Therefore, we gradually increased the value of the capacitor initial voltage until stimulation of the spinal cord tracts is achieved (an action potential is evoked). We found out that that the activation would occur at U_0 = 750 V, for the overdamped transient regime and U_0 = 850 V, for the underdamped regime, respectively.

Further on, we tried to lower the value of this initial voltage on the capacitor by magnetic coil design. Since our research team previously had some good results in this field (Crețu *et al.*, 2015), we investigated new configurations for the "figure of eight" coil, with a different turn distribution inside the coil, in order to determine direct activation of the nerve fiber inside the spinal cord.

On designing the new configurations of coil, we kept all the constructive parameters of the commercial coil that could remain unchanged: the value of the coil outer radius, the total number of turns, the wire diameter and the insulation gap between turns (all the values are specified above). Beside the commercial coil, we designed 4 additional configurations of magnetic coil. The turn distribution for each configuration is given in Table 1.

Depending on the turn distribution in space, the coil can be a disc when turns are placed concentrically in a planar configuration – this is the commercial coil C5 – Fig. 2 *a* – or a solenoid, consisting of coaxial turns displaced on *S* layers in the axial direction, each of them having N_i turns – Fig. 2 *b* – C3 and *c* – C1.

Table 1
Coil Configurations

Configuration	4,3,2-2,3,4 **C1**	5,3,1-1,3,5 **C2**	3,3,3-3,3,3 **C3**	Solenoid **C4**	Disc **C5**
L, [μH]	32.8	29.6	33	30.8	16.35
U_0, [V] Underdamped	1,550	1,400	1,600	1,550	850
U_0, [V] Overdamped	1,300	1,200	1,350	1,300	750

The inductances for the other considered configurations are evaluated by taking the line integral of the vector potential around the coil for unit current: $L = \int \overline{A} \cdot \mathrm{d}\overline{l}$; this formula permits the computation of inductances of coils with special shapes. For all the coils configurations tested, we computed the inductivities and the values of the capacitor initial voltage required to trigger the stimulation of the spinal cord tracts, for every type of transient regime and coil designs. Results are shown in Table 1.

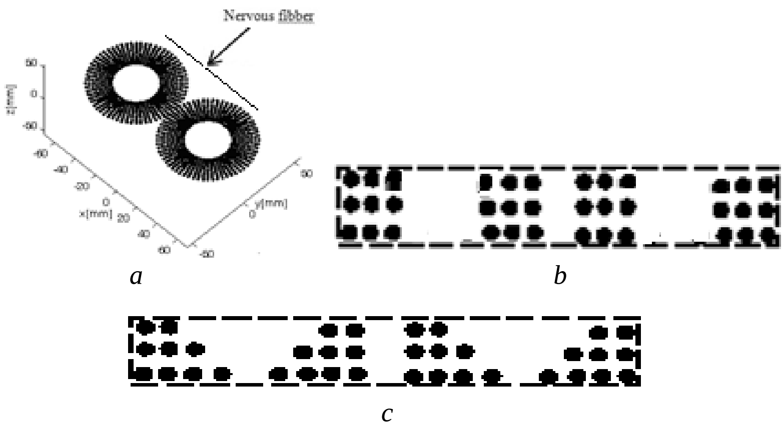


Fig. 2 – Distribution of turns inside the "eight" shape coil: *a* – commercial coil, disc shape, 9 turns/leaf in one plane; *b* – solenoid shape distributed on three layers (3 turns on each layer, for both leafs); *c* – solenoid shape distributed on three layers (4,3,2 turns on the three layers, for each leaf).

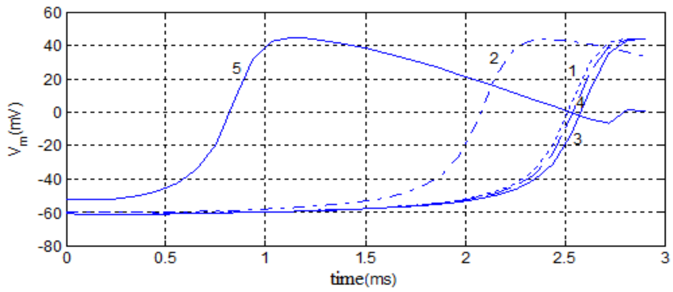
From the table, one can see that, for both regimes, the lowest value is achieved for disc configuration and the highest is for the C3 configuration. Also, we may conclude that using the underdamped transient regime, the values of U_0, where the stimulation appears are increased with over 13% compared to the overdamped one.

The first sets of simulations were performed to investigate the latency period, which is different for each of the configurations considered. One can see in Fig. 3 that we achieve activation of the nerve fiber with all the considered coils – the number on the curve represents the configuration of the coil. In both transient regimes, the latency period is much shorter for the disc configuration – C5 – (about 0.75 ms) than for the other configurations. The longest latency is for the third geometry, about 2.6 ms.

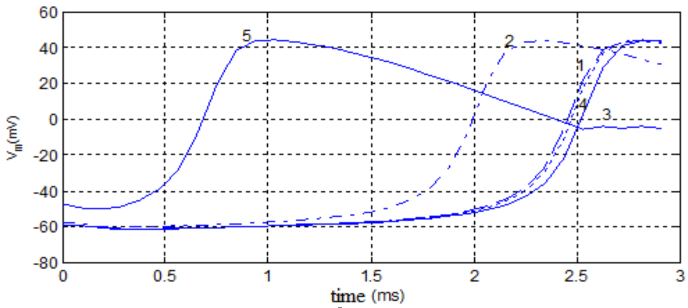
Next, we included a model of possible non-homogeneities of the nerve fiber on the existing cable model for neural structures, and assess their influence on the fiber response to the stimulus applied. Nerve fiber models with parameter variability within the fiber were investigated in Struijk *et al.* (2000), resulting in a change of the excitation threshold up to 20% compared to the standard model, when varying only a parameter. It is known that the nerve fiber is a non-homogeneous medium, so we suppose 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:

$$\begin{cases} g_{Na} = 120 + 12\sin(\mathrm{j}2\pi / x)\,\mathrm{m}\Omega / \mathrm{cm}^2, \\ g_K = 36 + 3.6\sin(\mathrm{j}2\pi / x)\,\mathrm{m}\Omega / \mathrm{cm}^2, \\ C_m = 1 + 0.1\sin(\mathrm{j}2\pi / x)\,\mu\mathrm{F} / \mathrm{cm}^2, \end{cases} \tag{6}$$

where: *j* represents a parameter that follows the length of the nerve and *x* is modified to show the frequency of variation of the electric parameters of the nervous cell's membrane (Fig. 4).



a



b

Fig. 3 – Time variation of the transmembrane potential, highlighting the latency period for each configuration: *a* – overdamped regime (for all the coils, the value of the circuit's capacitor is considered to be U_0 = 1,350 V); *b* – underdamped regime (for all the coils, the value of the circuit's capacitor is considered to be U_0 = 1,600 V).

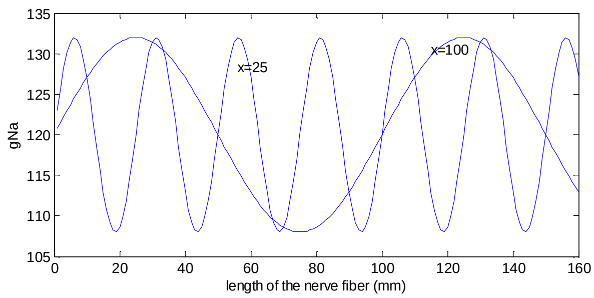


Fig. 4 – The variation of the electrical parameter g_{Na} along the nerve fiber for different values of the *x* parameter.

Further on, we assess the influence of this variation of the electrical parameters on the nerve fiber activation threshold (Fig. 5). One can observe that for the same value of the initial voltage U_0 = 1,600 V, the value of the latency of nerve activation varies slightly when these parameters vary compared with the model with constant parameters. When the conductance of the sodium channels changes, this latency is smaller than for constant parameters. When we change any of the other parameters, or all of them simultaneously, this latency is larger than for constant parameters.

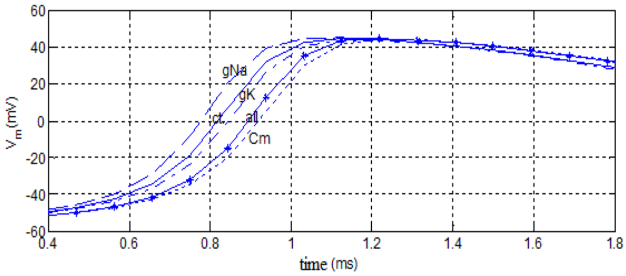


Fig. 5 – Variation of the transmembrane potential in time, for an over-damped transient regime, considering the variations of the electric parameters of the nervous cell membrane. (Simulations are performed for the disc configuration coil, with the capacitor of the magnetic stimulator initially charged with the voltage U_0 = 1,600 V. The x parameter from (6) is x = 50).

Considering the same disc configuration coil, since this one proved to require the lowest value of the initial voltage on the circuit's capacitor to trigger spinal cord activation, we find out that the variation of the x parameter from (6) also influences the response of the non-homogeneous nerve fiber to magnetic stimulation.

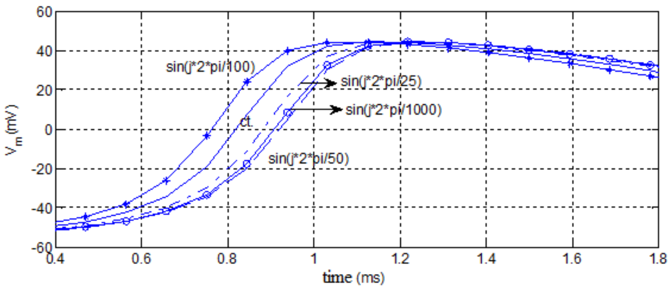


Fig. 6 – Nervous fiber response for an initial voltage U_0 = 1,600 V at the variations of the capacitance of the cell's membrane, with different values of the parameter x from (6).

One can notice that the frequency of variation of the electrical parameters is also a factor that influences the nerve fiber response. We cannot state that the increase or decrease of this frequency will determine a similar response of the nerve. What we can say is that if the value of the electrical parameters of the nervous cell's membrane in the nodes of the nerve, where the gating parameters and the transmembrane potential are computed, changes with respect to the constant value, this will lead to a visible influence on the nerve response. A very high frequency of variation could lead to a smaller influence, while a very small frequency is also more likely to lead to a very small change of the electrical parameters in the above mentioned nodes. This is why the most visible influence is achieved for medium frequencies.

In the end, we try to prove that the variation of the electric parameters of the nervous fiber influences the value of the required initial voltage on the circuit's capacitor. The simulation is made for the underdamped regime considering the same disc configuration.

For constant parameters, the value of U_0 was set to 850 V – the lowest value that triggers the activation of a spinal cord nerve fiber. When we considered that only the parameter g_{Na} varies, we can still achieve spinal cord stimulation at the same initial voltage, and even with a lower latency period (Fig. 7).

When we consider the variation of C_m only or g_K only, we could not achieve the activation of the nerve fiber for U_0 = 850 V, and therefore we needed to raise U_0 to 900 V. The same phenomena occurred when all the electrical parameters of the nervous cell's membrane varied simultaneously.

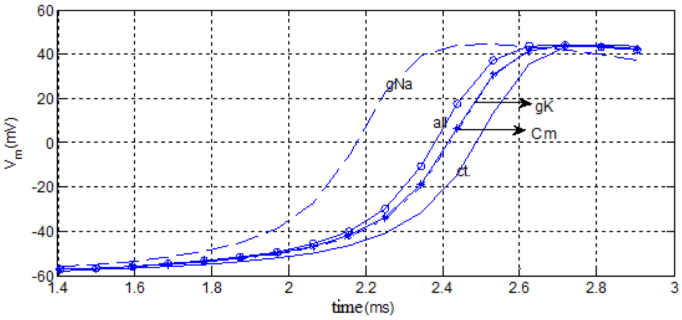


Fig. 7 – Variation of the transmembrane potential in time, for an underdamped transient regime, considering the variation of the electric parameters of the nervous cell membrane. (Simulations are performed for the disc configuration coil, where the *x* parameter from (6) is *x* = 50).

Another study aimed to assess how the variation of g_{Na} influences the latency of activation of the nerve fiber, considering both the overdamped and underdamped transient regime. The simulation is performed for the disc configuration coil (C5), and the *x* parameter in formula (6) is 100; also, the initial voltage on the capacitor is U_0 = 1,000 V for both cases. The latency for the over-damped regime is of 1.45 ms and the one for under-damped regime is 1.75 ms (see Fig. 8). This shows that the latency of activation increases in both cases compared to the situation when g_{Na} does not change (1.6 ms for overdamped and 1.9 ms for underdamped regimes).

The three-dimensional plot in Fig. 9, shows the nerve fiber response to magnetic stimulation. One can also notice the speed of the wave, the latency period and the site of stimulation.

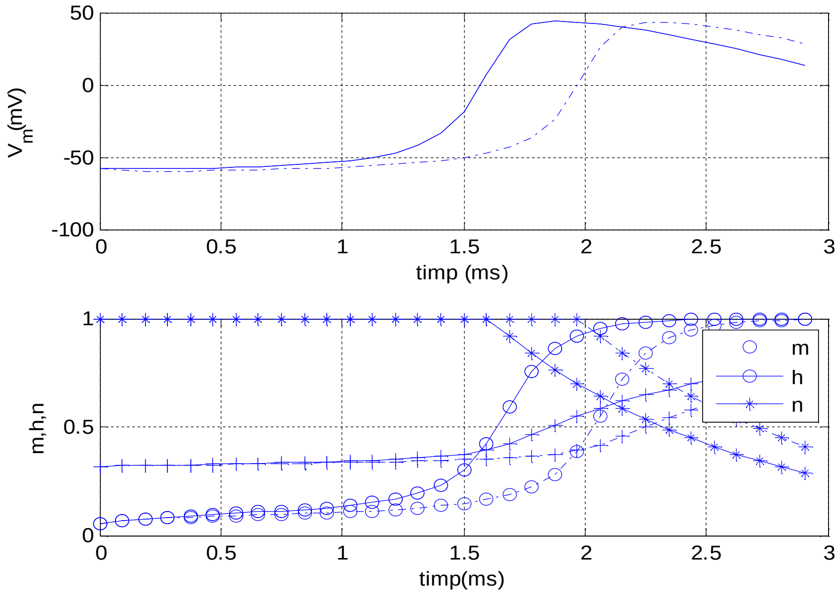


Fig. 8 – Variation of the transmembrane potential in time, for an over-damped (full line) and underdamped (dotted line) transient regime, considering the variations of the sodium channels of the nervous cell membrane. Variation of the three gating parameters (m, n, h).

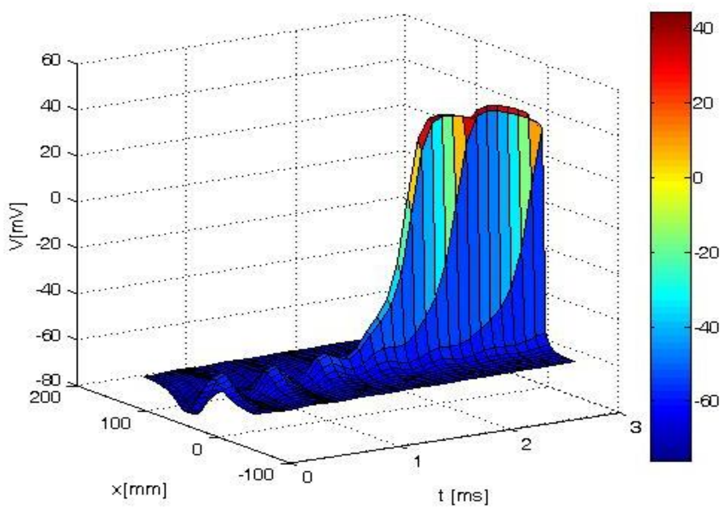


Fig. 9 – Nerve fiber response to magnetic stimulation: The vertical axis represents the action potential, while the horizontal ones represent the distance along the fiber and the necessary time for the discharge of the capacitor in the stimulator's equivalent circuit (underdamped regime).

4. Conclusions

This paper investigates the necessary characteristics of magnetic stimulators able to deliver enough energy to the spine in order to activate it. Several configurations of magnetic coils are considered, but finally the commercial "figure of eight" coil (disc configurations) proves to be the most effective one.

The influence of the variation of the electrical parameters of the nerve fiber located inside the spinal cord (the non-homogeneities of the nerve fiber) on its activation is also investigated, for two possible functioning regimes of the magnetic stimulator. We first conclude that the overdamped regime requires less electrical energy stored in the circuit's capacitor than the underdamped regime in order to trigger the activation of the spinal cord. Next, we see that the frequency of variation of the electrical parameters along the nerve fiber influences its response more intensely for medium frequencies. Finally, we conclude that the variation of the conductivity of the sodium channels can lead to a smaller value of the activation threshold for the nerve fiber, while the variation of the conductivity of the potassium channels or the membrane capacitance or of all these parameters simultaneously would lead to an increase of this threshold by 6%.

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MODELAREA FIBRELOR NERVOASE NEOMOGENE SITUATE ÎN INTERIORUL MĂDUVEI SPINĂRII

(Rezumat)

Pe baza unor experimente anterioare efectuate de către autori, obiectivul principal al acestei lucrări este de a determina caracteristicile constructive necesare ale unui stimulator magnetic (valoarea corespunzătoare a tensiunii iniţiale pe condensatorul din circuitul de stimulare), care pot produce activarea măduvei spinării. Efectul câmpului electric indus asupra fibrei nervoase situate în interiorul coloanei vertebrale se determină cu ajutorul modelului activ al membranei celulare. De asemenea, sunt luate în considerare posibilele neomogenităţi ale fibrei nervoase, evaluându-se şi influenţa acestora asupra activării măduvei spinării.