A Finite Element Model for The Axon of Nervous Cells

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Abstract: This paper proposes a FEM model for a segment of a nervous cell axon, which takes into account, through the so called Hodgkin-Huxley equations, the non linear and time varying dynamics of the membrane surrounding it. A combination with Maxwell equations is performed in a numerical procedure implemented in the COMSOL Multiphysics® environment. A thin layer approximated alternative model is presented too, which proves to reduce calculus burden. Results are shown demonstrating a very good agreement with literature data for both the proposed approaches.

Keywords: Axon, Neuron, Hodgkin-Huxley equations, FEM.

1. Introduction

Neural prosthetics can considerably widen the lifespan and health quality of people and thus the mechanisms of neuron firing and transmission of signals are increasingly investigated. In order to study the influence of electrical signals on the nervous cells for setting appropriate stimulation protocols and to design efficient equipment, proper models are needed capable of describing the phenomena occurring at the interface between neural cells and stimulating electrodes [1]-[4]. In this paper an accurate model for a tubular segment of a nervous cell axon (the neuronal structure carrying nervous signals) is presented which takes into account, through the so called Hodgkin-Huxley (HH) equations [5], the non linear and time varying behaviour of the membrane that surrounds it. The lumped-circuit quantities of the HH electrophysiological model are transformed into parameters adapt to a *field solution* study. In fact, the Electro Quasi Static (EQS) formulation of the Maxwell equations describing the relevant phenomena is faced by using the Finite Element Method (FEM). The non linear differential equations describing the membrane behaviour are efficiently and accurately combined with the FEM solution in a numerical procedure performed by using COMSOL Multiphysics®. The proposed procedure is then employed to evaluate the space and time dynamics of the Action Potential (AP) along the axon segment, when excited by current density stimuli of different amplitude and duration and under two different temperature conditions. Due to its simple implementation the proposed model can be easily used to simulate the behaviour of more complex nervous structures. The simulation procedure encompasses three phases: the first, in which the resting (static) solution is calculated, thus ensuring that the correct starting point for dynamic simulations is obtained, the second one, exploited to simulate *non-propagated APs* and the third one to reproduce their propagation along the segment under examination.
The *extrusion* feature of COMSOL Multiphysics proves to be a very helpful tool in projecting variables (voltages) from cell membrane boundaries onto the domain itself, where the calculation of its voltage-dependent electric conductivity needs to be performed.
In addition, the very small dimension of the membrane thickness compared to the other geometrical dimensions of the system is approximated, in an alternative version of the model depicted in Figure 1, as a thin layer thus leading to a sensible reduction of the computation burden.

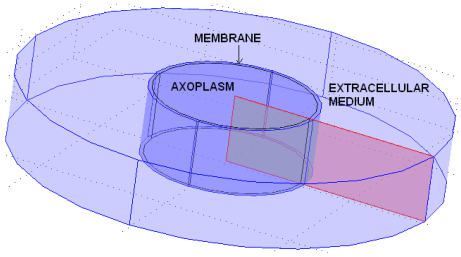

Figure 1. The axon slice under analysis (3D sketch). The section in r-z plane is highlighted in pink.

A comparison between the two model versions has led to very satisfactory results, as far as APs elicitation and propagation are concerned.
The work is structured as follows. The second section describes the model implementation and the settings, used to perform the "translation" of HH circuit equations into those suitable for a field solution, while its subsection explains the particulars of the thin layer approximated alternative model. A detailed comparison between the two proposed modelling solutions, is, instead, carried out in the third section, where different stimulation conditions are employed. The effect of temperature settings on membrane dynamics is, then, investigated within the fourth one, together with the propagation phenomenon. All simulations results are in keeping with theoretical expectations.

2. Use of COMSOL Multiphysics

The schematic structure of an axon segment of nerve cell surrounded by its membrane (or axolemma) is pictured in Figure 1. Due to its axial symmetry, it is possible to consider only the highlighted section by modelling it in a cylindrical coordinate system as shown in Figures 2a and 2b. The 2D axial symmetric transient analysis packet of the Quasi-Static Electric

AC/DC module, the time dependent analysis of the PDE mode packet in general (version A) and weak form (version B), the extrusion tool and the possibility to perform a thin layer approximation (as in [8]) given by COMSOL Multiphysics are exploited, in order to evaluate the behaviour of the considered structure.

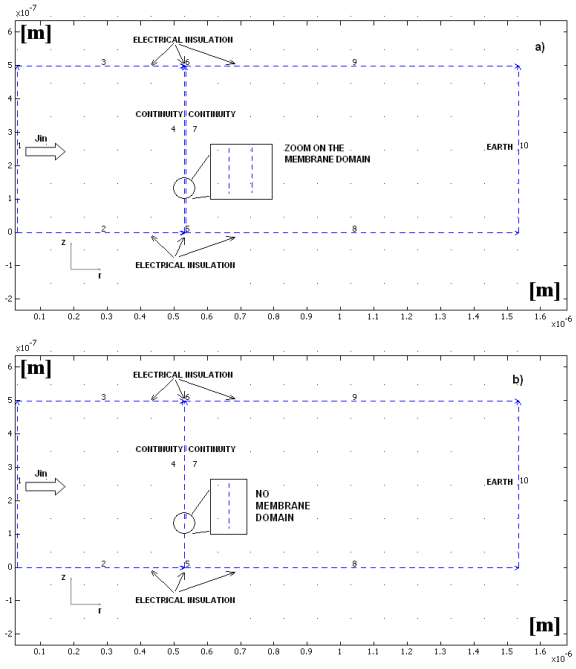

Figure 2 Axisymmetric 2D section in r-z plane, with boundary conditions chosen: model version A (Fig.2a), model version B (Fig. 2b).

In particular, we model a section of 0.5×1.505 μm^2 (0.5μm×0.5μm for the axon domain, D_a, 0.5μm×5nm for the membrane domain, D_m, and 0.5μm×1μm for the external medium represented by D_e). The small size of the system with respect to the characteristic wavelength of the electromagnetic field and the low contribution of the energy associated to the magnetic field compared to that stored in the electric field allow the adoption of the EQS approximation of Maxwell equations. Sub-domains D_a and D_e are considered as linear, homogeneous and isotropic dielectric materials, described by their constant electric conductivity, σ_a and σ_e, and dielectric permeability, ε_a and ε_e respectively. The corresponding values are reported in Table 1. On D_m, besides a linear permittivity ε_m, a non linear equivalent conductivity σ_m defined by (2) and an external current density depending on the voltage across the membrane are used in order to approximate the nonlinear behaviour of the medium with respect to the imposed electric field (according to the HH model of the membrane). In particular, HH circuit-equations must be "converted" to obtain their *field equivalent*.
First of all, since membrane thickness is very small, it can be looked at as a parallel plate capacitor. Therefore its dielectric and equivalent conductivity can be derived from values found in literature [5]. In particular, once defined all the constant parameters as in Table 1 [5], the dielectric constant per unit area is

$$\varepsilon_m = \frac{C_m d_m}{\varepsilon_0} \tag{1}$$

whereas membrane equivalent conductivity σ_m can be derived by HH overall membrane conductance, G_m, defined as a function of the Sodium, Potassium and Leakage conductances, depending on transmembrane voltage (TMV) through the so called channel activation variables. Then, σ_m becomes:

$$\sigma_m = G_m \cdot d_m \tag{2}$$

where

$$G_m = G_{Na} + G_K + G_l \tag{3}$$

Table 1. Parameters appearing in the model.

Parameter	Value	Description
V_{sta}	*-60*[mV]	Static TMV, at which membrane is polarized in the simulation
ε_m	*5.65*	Membrane relative dielectric constant
C_m	*1*[μF/cm^2]	Membrane capacitance per unit area
d_m	*5*[nm]	Membrane thickness
G_{Namax}	*120*[mS/cm^2]	Conductance per unit area of the Na channel
G_{Kmax}	*36*[mS/cm^2]	Conductance per unit area of the K channel
G_l	*0.3*[mS/cm^2]	Conductance per unit area of the leakage channels
E_{Na}	*55* [mV]	Nernst voltage due the Na concentration
E_K	*-72* [mV]	Nernst voltage due the K concentration
E_l	*-49.387*[mV]	Nernst voltage due other ionic concentrations
a_{nsta}	*58.197*	Initial value[1/s]
b_{nsta}	*125*	Initial value [1/s]
a_{msta}	*223.563*	Initial value [1/s]
b_{msta}	*4000*	Initial value [1/s]
a_{hsta}	*70*	Initial value [1/s]
b_{hsta}	*47.425*	Initial value [1/s]
σ_{Ax}	*0.5*	Axoplasm conductivity
ε_{Ax}	*80*	Axoplasm diel. constant
σ_{Ext}	*1*	Ext. Med. conductivity.
ε_{Ext}	*80*	Ext. Med. diel..constant

The expressions of ionic channel conductances, reported in (4.a) and (4.b) show their connection with the activation variables *m*, *n* and *h*, implicitly defined by the differential equations set (5):

$$G_{Na} = G_{Na\max} m^3 h \tag{4.a}$$

$$G_K = G_{K\,max} n^4 \tag{4.b}$$

$$\frac{dx}{dt} = \alpha_x \cdot (1-x) - \beta_x \cdot x \tag{5}$$

where $x \in \{m,n,h\}$.
The transfer rate coefficients α_x, β_x, in (5), are not constant numbers but, as shown in Table 2, depend on the value of the voltage across the axon membrane $V_m(x,y,z,t)$.
The HH trans-membrane current density equation for a unit area patch of membrane can be expressed as:

$$I_m = C_m \frac{dV_m}{dt} + G_m V_m - J_e \tag{6}$$

with

$$J_e = G_{Na} E_{Na} + G_k E_k + G_l E_l \tag{7}$$

Furthermore, the equation of continuity implemented everywhere over the FEM model can be written as (8)

$$\nabla \cdot \frac{\partial(\varepsilon_i \nabla V)}{\partial t} + \nabla \cdot \left(\sigma_i \nabla V - \bar{J}_{ext}\right) = 0 \tag{8}$$

where

$$\bar{J}_{ext} = \begin{cases} 0 & \text{over } D_a \cup D_e \\ Je \cdot \hat{r} & \text{over } D_m \end{cases} \tag{9}$$

The continuity equation (8) must be implemented on the whole model, whereas the HH equations system must be associated only to the membrane domain.
As the three voltage-controlled conductances G_{Na}, G_K and G_l are meaningful *only on membrane domain* and not externally, they require to be *only locally* defined.
The flexibility of COMSOL Multiphysics® proves useful in handling variables, as well as in the post-processing phase.
In the simulation session a *PDE packet in general form* is coupled to the Electrostatic module: the first one is employed in order to solve equation (8) with respect to the so-called dependant variable (in this case *electric potential, V*), whereas the second one is introduced to solve the three differential equations in *m, n, h (dependent variables)*, representing channel activation variables according to the HH model ([1],[3]), as shown in equations (5) and Table 2.
In order to obtain the voltage values along both sides of membrane, point by point along the z coordinate, the "extrusion" feature of COMSOL Multiphysics® is conveniently employed.

Table 2. Expressions of the transfer rate coefficients. $V'=V_m-V_{sta}$ represents the TMV deviation from the resting value [mV].

$\alpha_n = 1000 \frac{0.1 - 0.01V'}{e^{(1-0.1V')} - 1}$	$\beta_n = 1000 \frac{0.125}{e^{0.0125V'}}$
$\alpha_m = 1000 \frac{2.5 - 0.1V'}{e^{(2.5-0.1V')} - 1}$	$\beta_m = 1000 \frac{4}{e^{(V'/18)}}$
$\alpha_h = 1000 \frac{0.07}{e^{0.05V'}}$	$\beta_h = 1000 \frac{1}{e^{(3-0.1V')} + 1}$

In fact, the equations implemented there, explicitly depend on TMV, $V_m(z, t)$:

$$V_m(z,t) = V_i(z,t) - V_o(z,t) \tag{10}$$

where V_i and V_o are the voltage across the boundaries 4 and 6, respectively (Figure 2a). In this way the HH lumped-circuit quantities are "translated" into parameters adapt to a field solution study, as previously highlighted.
It must also be noticed that, while ε_m obtained is a constant, σ_m depends on $V_m(z,t)$.
The simulation is carried out, by fixing all initial conditions from nominal resting values. The iterative procedure is stopped when the numerical variations are *sufficiently* negligible leading to the "equilibrium" steady state conditions.
This condition is adopted as a starting point for studying the membrane dynamical behaviour in the second step of the procedure in which the cellular responses elicitation are evaluated. Square window current density stimuli of different amplitude and duration have been applied to boundary 1 (Figure 2).

2.1. Thin Layer Approximation

The cell membrane is an extremely thin structure that increases the simulation time and memory request in finite element modelling.
This applies for the short axon segment under analysis and it is especially true in the perspective of a generalization of the model to a whole axon.
Indeed, if it were necessary to simulate a very long neuron (i.e. motor neuron) behaviour, this would result in a form factor (length of the axon divided by membrane thickness) that could also be of the order of 10^9.
In order to simplify meshing and to greatly reduce simulation time and memory request it is useful to employ a *thin layer approximation* [8] for the membrane.
In this way it is completely avoided the physical realization of the corresponding thin domain, by substituting it with an interface surface.
This leads to an alternative model, B (Figure 2b), that completely satisfies the hypotheses of applicability of the approximation:

1) there is a substantial difference between membrane domain conductivity and those of the other two domains;
2) lateral boundaries are insulated (null net flux);
3) current density components along φ and z are negligible with respect to that along r-axis.

In particular, it is possible to approximate the potential distribution along the membrane thickness as being linearly varying from V_o to V_i. Thus, by using the continuity equation for the current, it is easy to derive the expression for an equivalent current density J_{eq} [8]:

$$J_{eq} = \sigma_m \frac{(V_2 - V_1)}{d_m} + J_e + \frac{\varepsilon_m \varepsilon_0}{d_m} \frac{\partial (V_2 - V_1)}{\partial t} \qquad (11)$$

where V_1 and V_2 represent the voltage values along the membrane boundaries 4 and 7 of Figure 2, respectively. This equation can be implemented by using two different Electrostatics packets in order to allow the solutor to "see" interface surface (substituting the membrane domain of the model A) once as belonging to axoplasm D_a, once to external medium domain D_e.It is clearly expectable that voltage on that boundary will have a discontinuity (V_2-V_1) almost equal to the value that transmembrane voltage would have reached, if the membrane were really implemented in the model as a 2D domain.
Thus, V_1 is set as an *active* variable only in the axoplasm domain, V_2 only on the external medium domain, while both are defined on their interface. J_{eq} is imposed as an input current density on this boundary.
In addition, an alternative formulation of the three non linear differential equation must be provided on this surface where all expressions are locally defined. The idea is to use a *weak form for boundary* approach, instead of the *COMSOL PDE packet in general form*, as that adopted in version A.
This choice allows to handle all the equations in the integral form, multiplying both sides of each equation by a test function and then integrating.

3. Comparison Between the Two Models

In order to make a fair comparison between the two modelling solutions, some common parameters are adopted (Table 3).

Table 3. Parameters used for comparing the two models

Calculus and mesh parameters	Value
Simulation times	$0{:}10^{-4}{:}0.02$s
Relative tolerance	10^{-4}
Absolute tolerance	10^{-8}
Max. element size scaling factor	1
Element growth rate	1.3
Mesh curvature factor	0.3
Mesh curvature cut off	0.001

The same initial and boundary conditions are fixed everywhere, exception made for the various settings related to membrane domain since it is not present in the second model. This settings induce the meshes pictured in Figure 3. Even before introducing any current density source to elicit membrane response, a clear improvement can be observed when adopting the weak solution for the model B, instead of A, since the Delunay algorithm does not lead to crowd the great amount of triangles next to the thin membrane domain, as Figure 3 demonstrates. The savings in terms of simulation time and amount of memory consumed are summarised in Table 4 to simulate a stationary equilibrium state.

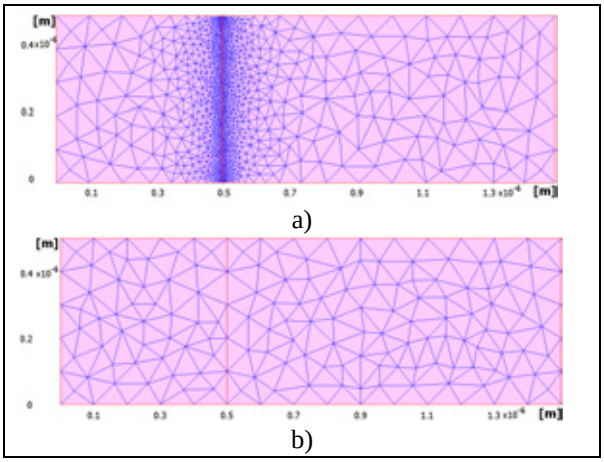

Figure 3 Mesh in the model with membrane, a) and without membrane using thin layer approximation, b).

Table 4. Figures of merit concerning the two models

PARAMETER/MODEL	A	B
Degrees of freedom	7086	685
Number of boundary sides	220	45
Number of elements	2378	300
Minimum quality level	0.5867	0.5666
Simulation duration	13.000 s	2.630 s

In Table 5, instead, the case of 20ms of membrane behaviour simulation is reported when it undergoes a stimulus-induced response.

Table 5. Simulation times in [s]. Stimulus duration: short (d), long (D). Stimulus amplitude: low (a), high (A)

	d/a	d/A	D/a	D/A
Model A	83.64	185.594	119.313	183.719
Model B	19.797	48.968	26.891	42.704

In this case an appropriate current density (J_{in}, the square window shown in the Inset of Figure 4a) is applied at r=r_1=1nm, very close to the symmetry axis, in order to trigger the excitable membrane (if current density stimulus where injected exactly at r=0μm, current density would have been undefined). A great advantage is offered by Model B in the dynamic case too, as far as stimulation length is concerned (Table 5). It is interesting to observe how membrane responses, in the four corresponding cases (Figure 4a) almost coincide in the two modelling approaches and are in accordance with theoretical expectations [4]. In the first case (*da*), the stimulus is not sufficient to elicit any AP (sub-threshold behaviour, whose parameters, rise time and amplitude, are those expected) showing a passive electrotonic nature of the membrane, being it approachable (at least in first approximation) as an R-C circuit. In the second and in the third one, an AP is observed, while in the fourth one, since both strength and duration of the stimulus pulse are high (see [3]), two APs are excited, the second of which is lower than the other, because refractory period is not respected.

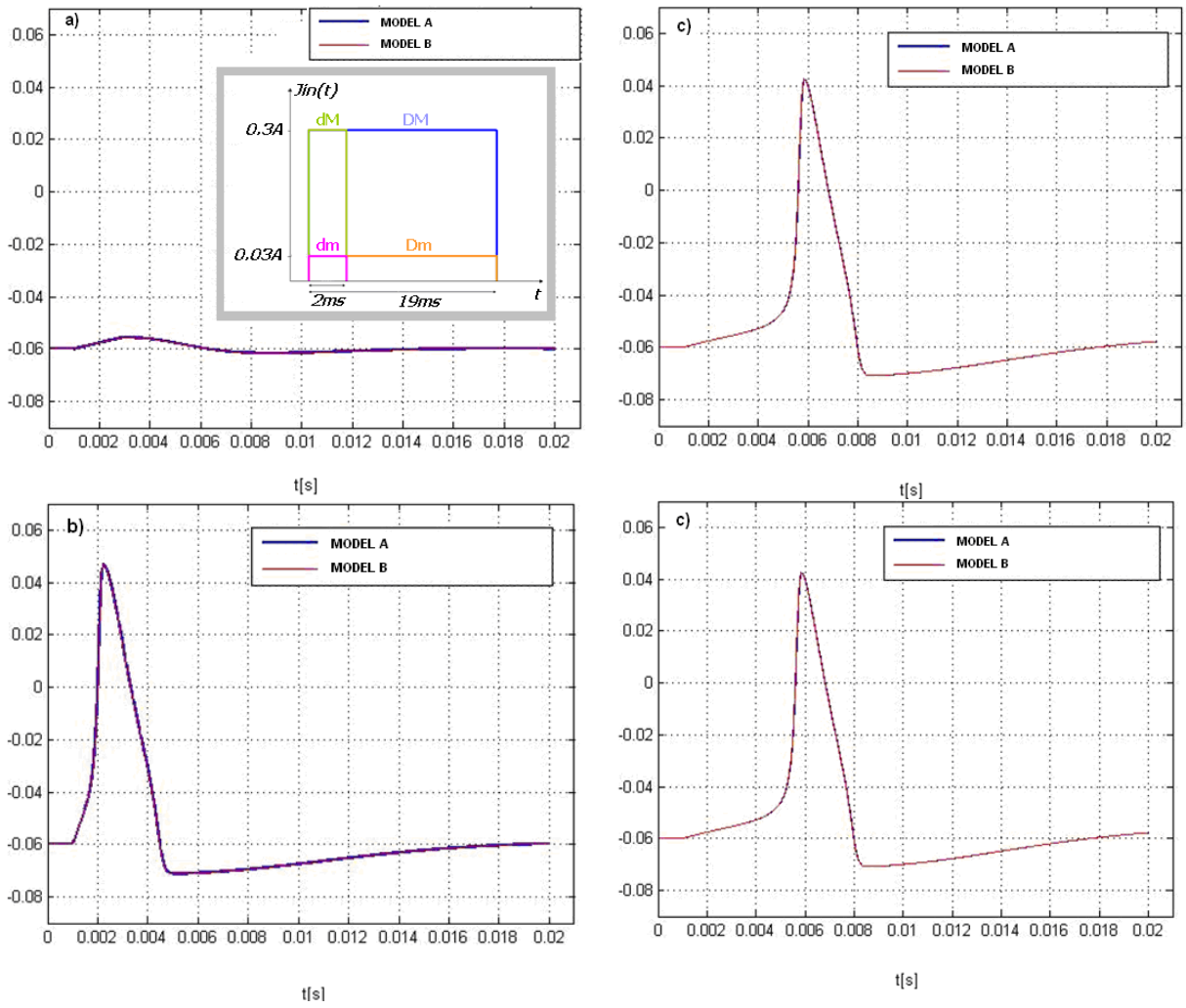

Figure 4 (a),(b),(c),(d) Membrane response (T= 6.3°C) in cases *da*, *dA* ,*Da*, *DA*, respectively. **Inset:** Input stimulus parameters

4. Temperature Dependence and Propagation Effect

The simulations described in the previous section are carried out supposing an operation temperature of 6.3°C. Adding also temperature dependence to the model, it has been possible to obtain the results shown in Figure 5. As theoretically expected, when the temperature is 18.5°C the membrane response results in a sequence of six APs, shorter than the two observed at lower temperature (Figure 4d). Indeed, channel time constants are all scaled by the factor $3^{(0.1T-0.63)}$, see [3], since the new differential equations become:

$$\frac{dx}{dt} = [\alpha_x(1-x) - \beta_x x] \cdot 3^{\frac{T-6.3}{10}} \qquad (12)$$

with $x \in \{m,n,h\}$.This yields to:

$$\frac{dx}{dt} = [\alpha'_x(1-x) - \beta'_x x] \qquad (13)$$

where α'_x and β'_x correspond to the old values times the factor just introduced, modifying the τ_x of the "channel-gating" processes as:

$$\tau'_x = \frac{1}{\alpha'_x + \beta'_x} = \frac{\tau_x}{3^{\frac{T-6.3}{10}}} \qquad (14)$$

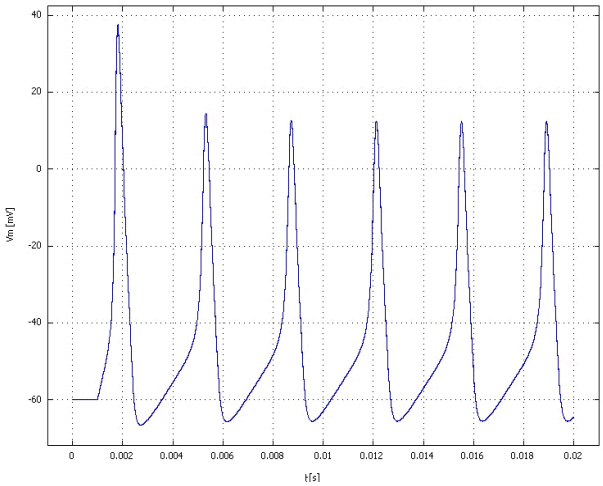

Figure 5. Multiple APs at T=18.3°C.

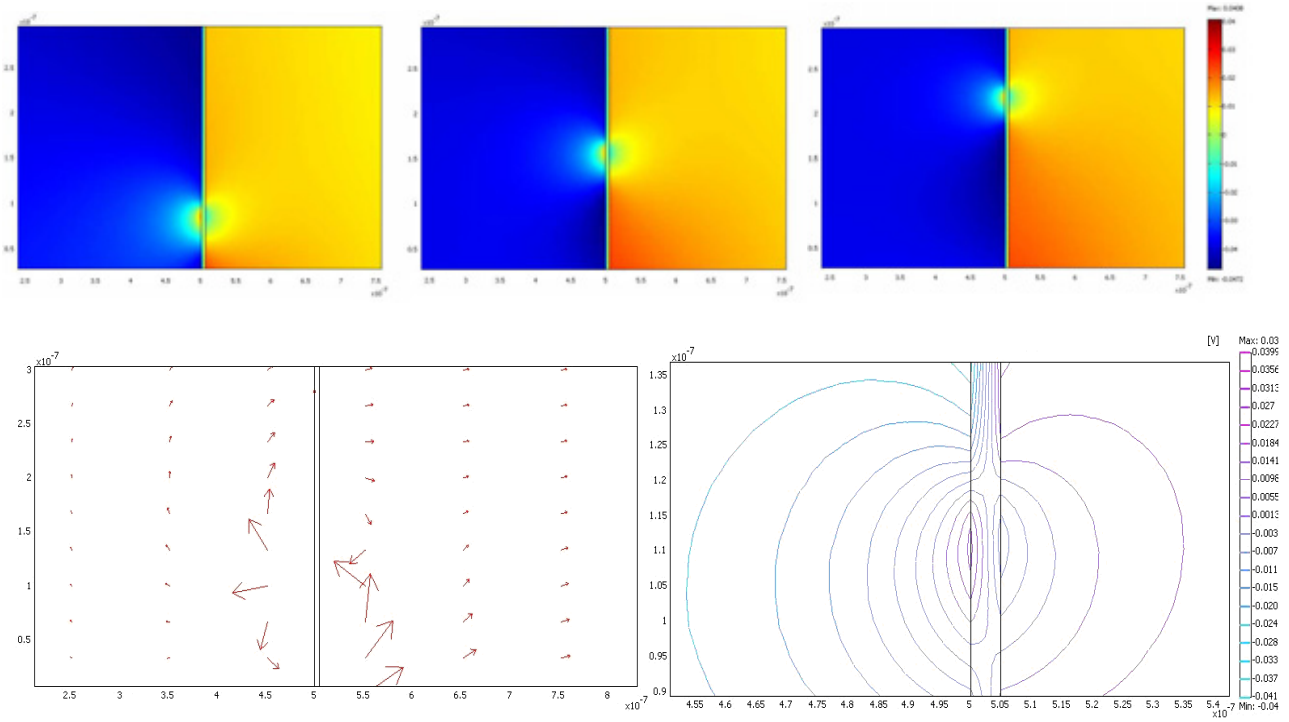

Figure 6. a) Propagation phenomenon: the moving active zone. Potential map at three different times of pulse conduction (Axes [m], Voltage [V]). b) Simulation results for local currents in an activated zone. c) Zoom in an active zone: electric potential lines inside and outside membrane, for model A. (Axes [m], Voltage [V]).

This results in a reduced time constant τ'_x, which induces a faster dynamics in the TMV.

Another particularly meaningful remark concerns the possibility to reproduce nervous stimulus propagation offered by the models. Specifically, in accord to Hodgkin and Huxley experimental setup, once the resting state conditions have been achieved over all the structures, a potential difference, beyond the natural excitement threshold, can be fixed across membrane at any transversal section (in this case at z = 0) of the models to elicit a local action potential. This propagates along the considered axon segment, thanks to the well-known physiological mechanisms proper of non-myelinated fibres, whose reproduction was the objective of this phase of simulation. In particular, in the two model solutions this is achieved by fixing a 15mV voltage difference across axon membrane in the point whose coordinates are r=0.5μm and z=0, thus obtaining the propagation effect shown in Figure 6.

The explanation of these results is the presence in a certain instant of an AP in an area (the *active zone*, emulated constraining TMV). This implies that the inner side of the membrane is "more positive" with respect to the outer one. The charge distribution non-homogeneity, thus created, induces longitudinal potential gradients; these in turn generate electric currents (known as *local currents*) in both intra and extra-cellular media, whose lines merge into the active zone (Figure 6b and 6c). All this process results, as it would have been expected theoretically, in the activation of the other near areas interested by these charge fluxes. Simulation results for model A are reported to show equipotential lines distribution within an activated section of membrane domain (Figure 6c).

The visualization of the propagation effect would not have been easy if actual electric properties of external means and axoplasm domains had been used in the simulation environment: the time an AP needs to pass all along the segment implemented is of the same order of amplitude of a reasonable discretization time step. So, in order to make propagation phenomenon not "instantaneous", but better "visible" at this phase of model testing, a choice has been done to divide the two dielectric constants and electric conductivities of those domains by the appropriate factor 10^6. Indeed, a theoretical approximation of propagation speed is (11):

$$v = \sqrt{\frac{Ka}{2C_m\rho_i}} \qquad (15)$$

where v is propagation speed [m/s], K the constant *10470* [1/s], a axon radius [cm], ρ_i axoplasm resistivity [Ω cm] as those used by Hodgkin and Huxley. It is, thus, possible to understand why the simulated velocity is a thousand times smaller than the real one, since $\rho_{i,simulated}=10^6\rho_{i,real}$..

5. Conclusions

The described FEM models allows to simulate the electrophysiological behaviour of a portion of nervous cell axon, to carry out the simulation of the static, underthreshold and active dynamic behaviour, to reproduce action potentials proposing a less expensive

method to achieve accurate simulation results. It must be noticed that FEM implementation of the weak formulation on discontinuity boundary has required particular attention due to the nonlinear characteristics of the equations for the thin layer approximation. The model thus obtained, validated using literature curves [4], has proved a very useful starting point for a wide range of future works. It is now possible, without dealing with enormous form factors, to simulate a whole non-myelinated fibre, to introduce soma and dendrites, implementing their behaviour simply considering locally differentiated channel densities and translating them into opportune conductances per unit area. It could also be thought to reproduce saltatory conduction of myelinated fibres or to model synaptic receptors reaction to different types of neurotransmitters, synaptic excitatory and inhibitory synaptic potential or their spatial and temporal summation. However, the most interesting application of these modelling efforts is in the field of the Functional Electric (or Magnetic) Stimulation: this medical treatment, used to stimulate peripheral nerves or deep zones in the brain of patients, usually suffers from a certain amount of lack in available data as far as the efficacy of electrodes is concerned. The models realized offer a good chance, especially if improved, by adding complex dependences to it, to realize huge simulation campaigns, aiming to perform a range analysis on the most significant synthesis parameters of Functional Electric Stimulation electrodes.

8. References

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