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Boundary Integral Formulation for the Electrical Response of a Nerve to an Extracellular Stimulation

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***Abstract*—We present a two-dimensional boundary integral formulation of nerve impulse propagation. A nerve impulse is a potential difference across the cellular membrane that propagates along the nerve fiber. The traveling transmembrane potential is produced by the transfer of ionic species between the intra- and extra-cellular mediums. This current flux across the membrane –composed of conduction, diffusion and capacitive terms– is regulated by passive and active mechanisms that are highly complicated to describe mathematically from a microscopic point of view. Based on the Hodgkin and Huxley axon model, we propose a well-posed integral formulation based on a quasi-static approximation amenable to time-stepping schemes and discuss first results.**

I. Introduction

Since Luigi Galvani discovered that dead frog's legs move when an external electrical stimuli is applied, the scientific community has increased its interest in understanding and modeling the effects of electricity in the human body [1]. Nowadays, we know that the operational bases of several biological structures, such as the heart and the nervous system, are related to electricity, i.e. current flow and voltage differences [2]. More concretely, a nerve is a cable–like bundle of a specific kind of neurons. Each neuron has different structures among which we distinguish the axon. Its main function is to propagate the nerve impulse as a traveling voltage difference across the cellular membrane [3]. Current larger computational power allows for a significant body of research focusing on the mathematical modeling of such processes. Indeed, given the complexity of the phenomena at hand, techniques such as Peripheral Nerve Stimulation (PNS) – used in regional anesthesia [4], [5] and cardiac defibrillation [6]– can greatly benefit from this. However, most of the literature focuses on the propagation of the transmembrane voltage along the axon, only tangentially discussing the chemical connection between neurons. As a means to study the nerve conduction problem, Rattay [7], [8], [9] proposed a formulation called the *cable equation model* in which through a non–linear PDE it is possible to obtain the transmembrane voltage, in a one–dimensional spacial coordinate along the axon, and its temporal evolution. An integral–based formulation combined with a time–difference numerical scheme is proposed by Leon *et al.* [10]. The authors find a solution that takes into account the three–dimensional nature of the nerve, phenomena that Rattay's approach neglects.

Although Leon *et al.* results shown concordance with the ones presented by Rattay, radial symmetry over the voltage difference across the membrane is imposed, and therefore, the transmembrane voltage is a function only of the coordinate situated along the nerve's axis. The way an external excitation is introduced in the mathematical formulation is of great importance. Classically, current point sources located over the nerve surface are used. This formulation does not represent practical ways to perform the stimulus. Yin *et al.* [11] proposed a Finite Element Method (FEM) formulation in which a non zero thickness nerve is considered and the external stimulus is included as a electric field constant in space established in practice, for example, by a pair of external electrodes. Their results shown changes in the transmembrane potential measured over the cellular membrane at different points, revealing that the radial symmetry assumption does not hold.

In a nerve conduction problem, all useful information is defined over the cellular membrane, i.e. the transmembrane voltage and the total current flowing across it. Given the relative sizes involved, the nature of the problem makes the Boundary Element Method (BEM) suitable to formulate the model. Other computational approaches, such as the finite element method (FEM) or finite difference method (FDM), require large amounts of degrees of freedom to calculate the field in the entire domain when, in fact, one is only interested on a precise solution for physical quantities defined over the cellular membrane. In this work, we propose a boundary integral formulation based on the so-called Multiple Trace Formulation (MTF) introduced by Hiptmair and Jerez-Hanckes [12], to study the axon's behavior under an external stimulation, performed with an electrical field produced, for example, through extracellular electrodes. We set up a two dimensional model, although it can be easily extended to three dimensions. One of the model achievements is a suitable decomposition of the extracellular electric potential in order to include the stimulating external electric field. Our results are in agreement with the ones presented by Yin *et al.*, also portraying no radial symmetry of the transmembrane potential.

II. Problem Model

We now set main assumptions and hypotheses of our model coming from mathematical and physiological considerations.

A. The Cellular Membrane and the Hodgkin–Huxley Equations

Nerve impulse propagation along the axon is basically due to the nonlinear electrical behavior of the cellular membrane that delimits the axon. Current passing across the membrane depends on the transmembrane voltage. There are three main effects that contribute to the total current – capacitive, diffusive and conductive effects – regulated by complex active and passive mechanisms that cannot be derived directly from theoretical considerations. Thus, several works based on experimental results aim to describe the dynamics of the cellular membrane, i.e. the non–linear current–voltage relation [9], [13]. Among these, the first and most important model comes from the experiments performed by Hodgkin and Huxley (H–H model) in 1952 [14], [15], and which we use in the following. Under this framework, the total current per unit area passing through a point of the membrane surface, denoted I_m, depends on the transmembrane voltage difference at this point, V_m, defined as the intra-cellular voltage minus the extra-cellular voltage across the cellular membrane. Let us define $V = V_m - V_{\text{rest}}$ with $V_{\text{rest}} = -70\ mV$, the equation that relates I_m and V_m at each point of the cellular membrane is

$$I_m = C_m \frac{\partial V}{\partial t} + I_{\text{ion}}(V, \mathbf{q}), \tag{1}$$

$$\frac{\partial \mathbf{q}}{\partial t} = \mathcal{M}(V, \mathbf{q}). \tag{2}$$

The term I_{ion} (1) represents the contribution to the total transmembrane current produced by the movement of ionic species across the cellular membrane. It depends on the transmembrane voltage V_m and on the state vector $\mathbf{q}$ coming from the chosen cellular membrane model. Equation (2) corresponds to a system of non-linear ODEs that the state vector must satisfy for each value V.

B. Geometry of the Problem

For the sake of simplicity, we consider an infinitely long nerve composed of only one cylindrical axon running along a given direction, for example $\hat{\mathbf{z}}$. Based on this assumption, we can summarize the entire problem to find the voltage and current field in a cut perpendicular to the axon, which yields a two–dimensional problem. The membrane of the axon, which in a our model is reduced to a circunference centered on the axon axis, separates $\mathbb{R}^2$ in two domains, namely, the intra– and extra–cellular domains, Ω_i and Ω_e, respectively. The vector $\hat{\mathbf{n}}$ denotes the outer normal of the intra cellular domain, the cellular membrane is denoted Γ.

C. Extracellular Stimulation

We assume that the nerve is immersed in an external electric field $\mathbf{E}$ perpendicular to the axon's main direction and independent of position and time. In particular, the independence of the electric field $\mathbf{E}$ with respect to the axon's main direction $\hat{\mathbf{z}}$ is needed in order to avoid contradictions with the two–dimensional approach. From an experimental point of view this electric field represents the stimulation performed by extracellular electrodes. It is important to notice that far away from the axon the extra cellular potential has to be equal to $-\mathbf{E}\cdot\mathbf{x}$. The last condition means that the response of the nerve to the electric field $\mathbf{E}$ must decay, but the potential due the extra cellular stimulation does not.

D. Mathematical Formulation

Recalling the models proposed in [11], [10], the intra– and extra–cellular potentials fields satisfy the Laplace equation for each time instant. This is the so called *quasi–static approximation*. Also, current continuity holds over the cellular membrane. Nevertheless, the current across Γ depends on the transmembrane potential through the H–H model, as discussed in Section II, Subsection A. All the considerations and assumptions explained in the previous subsections are included in the model composed by equations (3) – (5), in which we want to find $u \in H^1(\Omega_i \cup \Omega_e)$ such that,

$$-\nabla \cdot (\sigma \nabla u) = 0 \text{ in } \Omega_i \cup \Omega_e \subset \mathbb{R}^2, \tag{3}$$

$$-\mathbf{n} \cdot \sigma_e \nabla u = -\mathbf{n} \cdot \sigma_i \nabla u = I_m \text{ on } \Gamma, \tag{4}$$

$$u = -\mathbf{E} \cdot \mathbf{x}, \text{ as } ||\mathbf{x}|| \to \infty, \tag{5}$$

where σ is equal to σ_i and σ_e in the intra and extracellular domain, respectively. As explained before, the symbol I_m corresponds to the current per area flowing across Γ. This quantity depends on the transmembrane potential V_m through equations (1) and (2).

III. Boundary Integral Formulation of the Problem

A. Notation

Before moving forward, its first necessary to introduce fundamental notation recalled in our mathematical development. Let $\Omega \subset \mathbb{R}^2$ be a bounded and simple connected domain with Lipschitz boundary $\Gamma = \partial\Omega$ and $u \in H^1(\Omega)$, then we define

- γ_D *or Trace operator*: corresponds to the restriction of a function u to the boundary Γ, i.e.

$$\gamma_D u = u|_\Gamma . \tag{6}$$

  When applied to u, it gives the Dirichlet trace $\gamma_D u$.
- γ_N *or Normal trace operator*: evaluation of the normal derivative of the function u over the boundary Γ, i.e.

$$\gamma_N u = \left.\frac{\partial u}{\partial n}\right|_\Gamma , \tag{7}$$

  where n is the outer normal to the boundary Γ. When applied to u, it gives the Neumann trace $\gamma_N u$.

The spaces $H^{1/2}(\Gamma)$ and $H^{-1/2}(\Gamma)$ denote functional spaces for Dirichlet and Neumann traces defined over Γ.

B. Decomposition of u in $\Omega_i \cup \Omega_e$

For $\mathbf{x}_i \in \Omega_i$ and $\mathbf{x}_e \in \Omega_e$, let $u_i \in H^1(\Omega_i)$ and $u_e \in H^1(\Omega_e)$, i.e in the corresponding Sobolev's spaces, such that,

$$u|_{\Omega_i} = u_i \text{ and} \tag{8}$$

$$u|_{\Omega_e} = u_e - \mathbf{E} \cdot \mathbf{x}_e. \tag{9}$$

It is important to notice that in the extracellular domain the function u is decomposed in two terms. The first one, u_e, represents the nerve's response to the external electric field $\mathbf{E}$ and the term $-\mathbf{E}\cdot\mathbf{x}_e$ is the voltage field produced by the extra cellular stimulation. From a physical point of view, we are considering the superposition of two potential fields that satisfy the Laplace equation: one of them representing the external stimulation and the other the voltage field produced by the neural activity.

C. Integral Representation of u in $\Omega_i \cup \Omega_e$

The following integral representation of u in both the intra and extra cellular mediums holds,

$$\begin{aligned} u(\mathbf{x}_i) &= \mathrm{SL}^i\gamma_N u_i(\mathbf{x}_i) - \mathrm{DL}^e\gamma_D u_i(\mathbf{x}_i), \quad (10)\\ u(\mathbf{x}_e) &= \mathrm{SL}^i\gamma_N u_e(\mathbf{x}_e) - \mathrm{DL}^e\gamma_D u_e(\mathbf{x}_e) - \mathbf{E}\cdot\mathbf{x}_e, \quad (11)\end{aligned}$$

for $\mathbf{x}_i \in \Omega_i$ and $\mathbf{x}_e \in \Omega_e$. The symbols SL^α and DL^α with $\alpha = \{e, i\}$ are the single layer and double layer potential, respectively, defined in [16] as

$$\begin{aligned} \mathrm{SL}^\alpha\phi(\mathbf{x}) &= \int_\Gamma \phi(\mathbf{y})G(\mathbf{x},\mathbf{y})ds_\mathbf{y}, \quad (12)\\ \mathrm{DL}^\alpha\phi(\mathbf{x}) &= \int_\Gamma \phi(\mathbf{y})\partial_{n_\alpha}G(\mathbf{x},\mathbf{y})ds_\mathbf{y}, \quad (13)\end{aligned}$$

where n_α is the exterior normal to the corresponding domain, with $\alpha = \{e, i\}$. The expression $G(\mathbf{x},\mathbf{y})$ corresponds to the Green's function or the fundamental solution of the Laplace operator. It can be shown that in $\mathbb{R}^2$ this function is equal to

$$G(\mathbf{x},\mathbf{y}) = -\frac{1}{2\pi}\log||\mathbf{x}-\mathbf{y}||. \quad (14)$$

Taking the limit $\Omega_i \ni \mathbf{x}_i \to \mathbf{x} \in \Gamma$ and $\Omega_e \ni \mathbf{x}_e \to \mathbf{x} \in \Gamma$ along with the application of the normal derivate for both (10) and (11) [16, Chapter 6], yields the following system of boundary integral equations in Γ,

$$\begin{pmatrix} \gamma_D u_\alpha \\ \gamma_N u_\alpha \end{pmatrix} = \underbrace{\begin{pmatrix} \frac{1}{2}\mathbf{I}-\mathbf{K}_\alpha & \mathbf{V}_\alpha \\ \mathbf{D}_\alpha & \frac{1}{2}\mathbf{I}+\mathbf{K}'_\alpha \end{pmatrix}}_{\mathcal{C}_\alpha} \begin{pmatrix} \gamma_D u_\alpha \\ \gamma_N u_\alpha \end{pmatrix}. \quad (15)$$

Where $\alpha = \{e, i\}$. In the system of boundary integral equations (15), the matrix $\mathcal{C}_\alpha : H^{-1/2}(\Gamma)\times H^{1/2}(\Gamma) \to H^{-1/2}(\Gamma)\times H^{1/2}(\Gamma)$ is in fact a projector, i.e., $\mathcal{C} = \mathcal{C}^2$, known as the Calderón projector. The symbols $\mathbf{I}, \mathbf{K}_\alpha, \mathbf{V}_\alpha, \mathbf{D}_\alpha, \mathbf{K}'_\alpha$ are respectively the identity, the double layer, the single layer, the hypersingular and the adjoint double layer operators. For $\alpha = \{e, i\}$, consider the following decomposition of the proyectors $\mathcal{C}_\alpha$,

$$\mathcal{C}_\alpha = \begin{pmatrix} \frac{1}{2}\mathbf{I}-\mathbf{K}_\alpha & \mathbf{V}_\alpha \\ \mathbf{D}_\alpha & \frac{1}{2}\mathbf{I}+\mathbf{K}'_\alpha \end{pmatrix} = \frac{1}{2}\mathbf{Id} + \mathbb{A}_\alpha. \quad (16)$$

From (16) follows $\tilde{\gamma}u_\alpha = 2\mathbb{A}_\alpha\tilde{\gamma}u_\alpha$, where $\tilde{\gamma}u_\alpha = (\gamma_D u_\alpha, \gamma_N u_\alpha)^\top$. From the definition of V_m,

$$V_m = \gamma_D u_i - \gamma_D u_e + \mathbf{E}\cdot\mathbf{x} \text{ for } \mathbf{x}\in\Gamma. \quad (17)$$

Based on (5) and (17), it is possible to write

$$\begin{pmatrix} \gamma_D u_i \\ \gamma_N u_i \end{pmatrix} - \underbrace{\begin{pmatrix} \mathbf{I} & \mathbf{0} \\ \mathbf{0} & -\frac{\sigma_e}{\sigma_i}\mathbf{I} \end{pmatrix}}_{\mathbf{X}_\sigma} \begin{pmatrix} \gamma_D u_e \\ \gamma_N u_e \end{pmatrix} = \begin{pmatrix} V_m - \mathbf{E}\cdot\mathbf{x} \\ \frac{\sigma_e}{\sigma_i}\mathbf{E}\cdot\mathbf{n} \end{pmatrix}. \quad (18)$$

Replacing $\tilde{\gamma}u_i = 2\mathbb{A}_i\tilde{\gamma}u_i$ in (18) and $\tilde{\gamma}u_e = 2\mathbb{A}_e\tilde{\gamma}u_e$ in the same equation, but multiplying by $\mathbf{X}_\sigma^{-1}$ it is possible to obtain a formulation in which all the traces of the problem are involved, as shown in equation (19):

$$\begin{pmatrix} \mathbb{A}_e & -\frac{1}{2}\mathbf{X}_\sigma^{-1} \\ -\frac{1}{2}\mathbf{X}_\sigma & \mathbb{A}_i \end{pmatrix} \begin{pmatrix} \tilde{\gamma}_e u_e \\ \tilde{\gamma}_i u_i \end{pmatrix} = \begin{pmatrix} -\frac{1}{2}(V_m - \mathbf{E}\cdot\mathbf{x}, -\mathbf{E}\cdot\mathbf{n})^\top \\ \frac{1}{2}(V_m - \mathbf{E}\cdot\mathbf{x}, \frac{\sigma_e}{\sigma_i}\mathbf{E}\cdot\mathbf{n})^\top \end{pmatrix}. \quad (19)$$

A variational formulation of the matricial system (19) can be done to solve it by means the Boundary Element Method [16], [17]. The proposed integral representation and the corresponding variational formulation are based in the Multiple Traces Formulation, by Hiptmair & Jerez–Hanckes [12]. It is importat to notice that the normal vector $\mathbf{n}$ is defined as shown in Figure 1, the outer normal to the intra cellular domain.

IV. Numerical Scheme

Using the variational formulation of (19), the temporal evolution equations (1) and (2), a time step Δt and a given initial condition for V_m and $\mathbf{q}$, we adopt the following numerical scheme to solve the problem. For $n \in \mathbb{N}$,
At $t = n\Delta t$

- The transmembrane current I_m at each element of Γ is calculated using the variational formulation of (19). We complete the right hand side of (19) with V_m corresponding to $t = (n-1)\Delta t$.
- Using (1) and (2), for each element and with the transmembrane current I_m, we calculate the new transmembrane voltage.

Repeat until the simulation time is reached.
The existence and uniqueness at each time is ensured in [12]. To solve the time–dependent problem, a suitable algorithm as the Euler scheme or a Runge–Kutta type methods can be chosen.

V. Results

Using a forward Euler scheme and based on the parameters proposed in [11], [9], we are able to reconstruct the behavior of the transmembrane potential when an external electric field of $\mathbf{E} = 5\hat{\mathbf{x}}$ V/cm is applied. We choose a time step $\Delta t = 0.015\mu s$, an intra– and extra–cellular conductivities of $\sigma_i =$ 5 mS/cm and $\sigma_e = 20$ mS/cm, respectively. The diameter of the axon is equal to $d_c = 15\ \mu m$. Figure 2 shows the transmembrane potential V_m for ten equidistant points over the cellular membrane, distributed as shown in Figure 1.

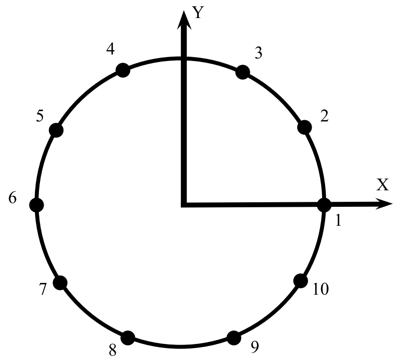

Fig. 1: The figure show the position of ten equidistant points over the membrane surface. The vector field $\mathbf{E}$ is parallel to the $\hat{x}$ direction $\mathbf{E} = 5\mathbf{x}$ V/cm.

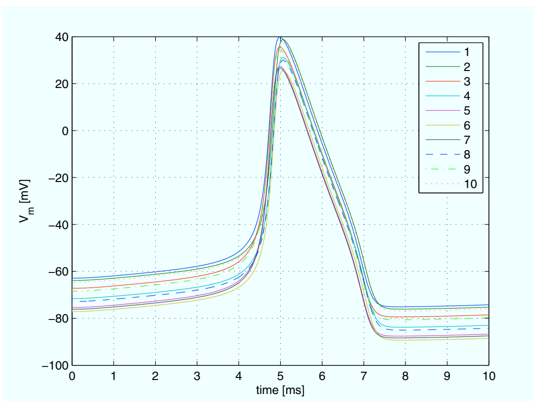

Fig. 2: Results of the simulation. The model proposed is able to recover the non–linear dynamics of the cellular membrane when an external stimulation is applied.

VI. Conclusion

We present an approach based on a boundary integral formulation for the nerve conduction problem. This technique allows us to calculate the transmembrane potential when an extracellular stimulation is performed by means of an electric field. First at all, we can notice the similarity between or results and the ones presented by Ying *et al* [11], therefore validating our results. The first achievement of our mathematical formulation is how the external stimulation is included in the model. Equation (9) reflects the decomposition of the external electric potential between the nerve response to the stimulus and the stimulus by itself. In this work a electric field constant in time and space is applied, but it can easily extended to other situations. Given any electric potential field $\phi(\mathbf{x})$, satisfying the Laplace' s equation, we can change the term $-\mathbf{E}\cdot\mathbf{x}$ (the electric potential field produced by a constant in space electric field) by $\phi(\mathbf{x})$. Then the procedure described in Subsection III-C is still valid and the construction of the formulation follows in the same way. This can be useful when studying the interaction of an arbitrary shape electrode and the nerve, because solving the entire problem in time and space including the electrode and the nerve could be expensive from a computational point of view. Using our approach it is only needed to know the voltage field produced by the external electrode once, coming from a single computation that can be performed using the desired numerical method.

Finally, we can notice in the results that there is no radial symmetry in the voltage. In fact biggest difference between the maxim peaks of the transmembrane potential over the average amplitude of the pulses is equal to 12.31%. Then, the differences between differents points of the transmembrane voltage measured in surface nodes is a considerable fraction of the amplitude of the nerve impulse.

Further improvements of the model are headed by the development of a three dimensional approach to study the propagation of the nerve impulse along the axon.

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