An analytical solution for the ionic flux in an axonial membrane model

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Abstract

The knowledge of the nerve impulse in medicine is of particular relevance to the improvement of medical diagnostic and therapeutic methods. The electrochemical behaviour of the axon membrane plays an important and key role in the resulting nerve impulse, which can be related to the movement of ions between the extra and intracellular regions due to the active and the passive transports. We present a new contribution for the understanding of the diffusion process in a biological membrane of an axon. The problem is formulated for the sodium current from the electromagnetic theory. Indeed from the Maxwell equations we state a mathematical model considering the Fick-Ohm law for the total electrical current density. An analytical solution is proposed under different physiological parameters.

KEYWORDS: Maxwell and diffusion equations, biological membrane, sodium current, jump condition.

1 Introduction

In the last decades, several works have been appearing that are concerned with the study of cell membranes in unidirectional [20] and two dimensional [14] domains, as well as the of electrical stimulation in functional neural structures [5], [21],[18] and [15]. The above models are formulated using the parabolic difference equations.

In the recent past years, the membrane problem is analyzed by a differential approach. The total flux related with the concentration distribution of some chemical species prescribed in a hole of an arbitrary shape for a thin membrane as well as the total flux under the influence of the pore length are studied in the steady-state case [7]. Indeed, an exact solution to the problem of steady-state diffusion mechanism of biological membranes through an isolated circular hole was found first by Rayleigh (1948) along with a very good approximate solution for the case of a thick membrane.

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In [2], the authors investigate the cell membrane as a dielectric interface, consider the medium as a periodic microstructure, and solve the problem by the homogenization theory. A quasi-static model for the transmembrane potential in electrocardiology considers a bidomain with a dynamic boundary jump condition in [6]. An alternative approach is introduced in [13] via the Clausius-Duhem inequality. However it involves the controversy entropy production in the continuum thermodynamics [12].

The Hodgkin–Huxley model [11], a four–dimensional system of ordinary differential equations, has been a great success on the description of the electrophysiological properties of the (squid) axon. The several discrepancies between experiment and model have led to update versions [4]. The one-dimensional feature of Hodgkin–Huxley model and fine details associated to the ionic fluxes through the cellular membrane, which are often disregarded in the literature, motivated the present work. We present a mathematical model that mimics the sodium concentration in different regions (the intra and extracellular spaces) separated by the cell membrane consisted in a coupled system of partial differential equations of parabolic/elliptic type prescribed in each phase, and complemented with jump boundary conditions at the membrane interface which can be reduced to a system of two parabolic equations (for the intra and the extracellular sodium concentrations). Three factors exist (the mechanical, the chemical and the electrical) that can initiate the activation process through the diffusional interaction in the axon structure.

A nerve cell is constituted, basically, by three parts, the soma (the cellular body that includes the nucleus and the cellular organelles), the dentrite (a branching arbor), and the axon, that connects the previous two. It can be described as an axoplasm cylinder (an electrolytic interior) surrounded by a bilayer lipidic membrane. Some axons, named myelinated axons, are covered with an insulating layer, discontinuous (with Ranvier nodes), called the myelin sheath. These axons belong to central nervous system. The unmyelinated axons are conducting fibres that belong as to the autonomic system (innervating viscera) as to the group of peripheral sensory fibres subserving sensations like pain and temperature, where a rapid response is not required [20, pp33]. There exists, always, a membrane voltage, due to the several types of ions on opposite sites of the membrane, defined as the inside potential minus the outside. The concentration of sodium is about ten times higher outside the membrane than inside, whereas the concentration of the potassium ions is about 30 times higher inside as compared to outside. In a squid axon the sodium intracellular concentration is 50 mol/m^3 and the exterior is 440 mol/m^3. When the membrane is stimulated the ionic permeabilities of the channels change. Indeed, the sodium ion permeability increases very rapidly at first, allowing sodium ions to flow from outside to inside. Since these ions carry a positive charge, the inside becomes more positive related to the outside. If a threshold is reached (about -50 mV in a squid axon, when at the resting state the membrane voltage is -70 mV), an excitation occurs and the active transport propagates itself onto the longitudinal direction leading the desired action potential. After that, the more slowly increasing potassium ion permeability allows potassium ions to flow

from inside to outside, thus returning the intracellular potential to its resting value. If not, then a subthreshold is obtained and the ions movements are in passive transport. Thus the action potential is an electrochemical current that travels along the membrane of a nerve cell caused by the flow of ions through the several types of ionic channels of the membrane (see [10]).

Our research is concerned with unmyelinated axons. Some demyelinated diseases, such as multiple sclerosis, do not constituted a motivation for the study of unmyelinated axons, since the nerve fibre is destroyed or damaged and the conduction becomes blocked. It should be remarked that in some cases axons with a totally lost of the myelin sheath are not unmyelinated axons, since its membrane has different constitution. On the other hand, mammalian axons, which have been chronically demyelinated by diphtheria toxin, can develop the ability on the conduction of electrical impulses through a demyelinated region, since sodium channels appear in the exposed region of the membrane (see [20] and their references.) Cases like the last one constituted a motivation for the study of unmyelinated axons.

The present work aims at understanding the role of the sodium in a normal membrane of an unmyelinated nerve axon and to present an analytical solution, because the analytical solutions improve the models ability to simulate *in vivo* phenomena and consequently to improve the medical diagnostic and therapeutic methods. The interaction of sodium, potassium and other species needs further investigation.

The paper is organized as follows. Next section is devoted to derive an initial and boundary value problem with one parabolic partial differential equation from the phenomena under study. Indeed, it is based on physical and chemical laws and also on an interpretation of the physiological phenomena. Section 3 presents an analytical solution. Section 4 contains a discussion of our model showing that our investigation is consistent with physical principles and our conclusions are presented. In Section 5 we provide a detailed formal derivation. We remark that we have delicate and long computations in the last section, which can not and should not be avoided. Dealing with biological processes we can not expect simple ways to give an effective development on the modelling of the subject.

2 Statement of the problem

An axon can be described as a cylinder of length ℓ and radius h, surrounded by a membrane of negligible thickness (the cylinder surface). Mammalian axons are usually about 1-20 μm in diameter. Squid axon diameter is 500 μm and crayfish one is 30 μm [14]. Some axons in larger animals may be several meters in length [20]. It should be mentioned that some axons may exhibit a length lesser than 1 μm. In this work we keep the physiological sizes abstract. This procedure allows us to use the model in each particular case dealing with the corresponding parameters. As it is described in the introduction the action potential is a membrane potential change caused by the flow ions through ionic

channels in the membrane. From experiments, only a neighbourhood of the membrane contributes in the nerve impulse process. Consequently we focus our attention in a neighbourhood of the axon's membrane.

Let $\mathcal{A}$ be the axon

$$\mathcal{A} := \{(x, y, z) \in \mathbb{R}^3 : \ 0 < x < \ell, \ y^2 + z^2 < h^2\}$$

and, for $0 < \varepsilon < h$, $\mathcal{A}_\varepsilon$ a neighbourhood of the $\mathcal{A}$-membrane

$$\mathcal{A}_\varepsilon := \{(x, y, z) \in \mathbb{R}^3 : \ 0 < x < \ell, \ (h - \varepsilon)^2 < y^2 + z^2 < h^2\}.$$

$\mathcal{A}$ is embedded in an extracellular medium defined as an open solid cylinder without a cylindrical core of radius $(h - \varepsilon)$, that is $\Omega :=]0; \ell[\times \{(y, z) \in \mathbb{R}^2 : (h - \varepsilon)^2 < y^2 + z^2 < r^2\}$ of $\mathbb{R}^3$, where ℓ, h, r are positive real constants such that $h < r << 1$. Thus $\Omega_i := \mathcal{A}_\varepsilon$, $\Omega_e := \Omega \setminus \overline{\Omega}_i$ and $\Gamma_m := \Omega \setminus (\Omega_i \cup \Omega_e)$ denote the intracellular, the extracellular spaces, and the membrane surface, respectively.

The electric current density $\mathbf{J}$ is defined by the Fick-Ohm law [14]:

$$\mathbf{J} = \mathbf{J}_I + \sigma \mathbf{E} = -FDz_{Na^+} \nabla c - \sigma \nabla \phi, \tag{1}$$

where $\mathbf{J}_I$ denotes the ionic current (A/m^2), σ is the electrical conductivity measured in S/m, $\mathbf{E}$ is the electrical intensity field (V/m), F is the Faraday constant ($F = 9.649 \times 10^4$ C/mol, [14]), D is the sodium diffusion coefficient ($D = 0.267 \times 10^{-9} m^2/s$, [10]), c is the sodium concentration, measured in mol/m^3, z_{Na^+} is the valence ($z_{Na^+} = +1$) and ϕ is the electrical potential, measured in V.

The electromagnetic field is described by the Maxwell equations ([23]):

$$\frac{\partial \mathbf{B}}{\partial t} + \nabla \times \mathbf{E} = 0, \quad \nabla \cdot \mathbf{B} = 0 \tag{2}$$

$$\frac{\partial \mathbf{D}}{\partial t} + \mathbf{J} = \nabla \times \mathbf{H}; \tag{3}$$

$$\nabla \cdot \mathbf{D} = F z_{Na^+} c, \tag{4}$$

where $\mathbf{E}$ and $\mathbf{H}$ are, respectively, the electric and magnetic intensity fields, $\mathbf{D}$ and $\mathbf{B}$ are, respectively, the electric and magnetic induction fields, and the right hand side of Equation (4) is the charge. Using, in (4), the constitutive law $\mathbf{D} = \varepsilon \mathbf{E}$, where ε is the sodium permittivity ($\varepsilon = 6.4 \times 10^{-10}$ F/m), we obtain

$$F z_{Na^+} c = \nabla \cdot \mathbf{D} = \nabla \cdot (\varepsilon \mathbf{E}) = -\nabla \cdot (\varepsilon \nabla \phi) = -\varepsilon \nabla^2 \phi. \tag{5}$$

From (1), (3) and (4) we obtain

$$F z_{Na^+} \frac{\partial c}{\partial t} - F z_{Na^+} \nabla \cdot (D \nabla c) = \nabla \cdot (\sigma \nabla \phi). \tag{6}$$

Electrical conductivity is considered homogeneous and constant at each subdomain (extra and intracellular domains). From [15] we have

$$\sigma_e = \frac{1}{30000} \, S/m, \quad \text{in} \quad \Omega_e \quad \text{and} \qquad \sigma_i = \frac{1}{6000} \, S/m, \quad \text{in} \quad \Omega_i. \tag{7}$$

Then we are able to formulate the problem

$$\frac{\partial c_s}{\partial t} - D\nabla^2 c_s + \frac{\sigma_s}{\varepsilon} c_s = 0 \text{ in } \Omega_s, \;\; s \in \{i, e\}, \tag{8}$$

where c_e and c_i denote the sodium concentration, respectively, in Ω_e and in Ω_i.

We assume that $\Gamma :=]0, \ell[\times \{(y, z) : \; y^2 + z^2 = r^2\}$ is an insulating boundary, that is, there is no outflow. Then

$$\nabla c_e \cdot \mathbf{n} = 0, \qquad \text{on } \Gamma, \tag{9}$$

where $\mathbf{n}$ denotes the outward normal to Γ.

Due to many conducting channels the lipid axon membrane exhibits a capacitive/conductive behaviour. It separates internal and external conducting solutions. Such gap between two conductors forms a significant electrical capacitor. In living cells, the ions lost via ionic channels by diffusion are returned by ionic pumps in order to overcome the electrochemical gradient (see [10]). We can distinguish three main states of the channel: open, closed, and inactivated. The opening of those channels requires several gating events. The probability information in the active position is provided by two gating functions $\alpha(t)$ and $\beta(t)$ [20]. Following [2] we assume that $\alpha(t) = \alpha$ and $\beta(t) = \beta$, where α, β are positive real constants. We believe that our model can be applied for general functions $\alpha(t)$ and $\beta(t)$. However, new experimental work should be developed to achieve the understanding of ionic channel gating kinetics. We define $[c] := c_e - c_i$. The concentration jumps across the membrane satisfy a dynamical condition [2]. Thus we assume it on $\Gamma_m \times]0, T[$:

$$\alpha \frac{\partial}{\partial t}[c] + \beta[c] = D\nabla c_e \cdot \mathbf{n}, \tag{10}$$

where $\mathbf{n}$ denotes the unit outward normal vector to Γ_m.

The nerve cell is a three dimensional structure. When a stimulus current pulse is arranged by the insertation of an electrode, a local current is developed. The membrane potential of the cell is not uniform at all points. The depolarization spreading passively from an excited region of the membrane (near the inserting region of the electrode) to a neighbouring unexcited region occurs in three dimensions until uniformity is reached. This means that there is an interval of time, where the flow has an angular dependence.

We assume that a stimulus current pulse was arranged to depolarize the resting membrane and we analyse two situations.

In the first one (Case I), we assume an angular dependent concentration. At the instant $t = 0$, there exists a point $(r, 0)$ in the two-dimensional boundary $\{x = 0\}$ where is applied an external stimulus Φ which could be electrical, mechanical or chemical, that is:

$$\nabla c_e \cdot \mathbf{n}(0, y, z, 0) = \Phi(y, z) \tag{11}$$

where $\mathbf{n} = (1, 0, 0)$. Precisely, in cylindrical coordinates, we consider:

$$\Phi(\rho, \theta) = (\kappa_1 \rho^{-1/2} \exp(\tau\rho) + \kappa_2 \rho^{1/2}) \cos\left(\frac{\theta}{2}\right) \tag{12}$$

with $\kappa_1, \kappa_2, \tau \in \mathbb{R}$.

On the second one (Case II) we assume that the concentration has angular uniformity distribution at instance $t = 0$ and on Γ_m we have

$$\left(\frac{c_e}{c_i}\right)_{x=0,t=0} > \mathcal{N} := \exp\left[\frac{FzV_d}{RT_r}\right] \tag{13}$$

where V_d represents the depolarization voltage, R denotes the universal gas constant ($R = 8.314$ J/(mol·K), [14]) and T_r denotes the reference absolute temperature, measured in Kelvin. Note that the threshold $\mathcal{N}$ corresponds to the Nernst potential.

The initial condition is assumed constituted by an averaged condition:

$$\int_{\Omega_i} c_i(\cdot, 0) = C_i, \qquad \int_{\Omega_e} c_e(\cdot, 0) = C_e, \tag{14}$$

the values of C_i and C_e depending on the physiological data. For instance, in a squid axon of length $\ell\,\mu$m and radius h μm embedded in a cylinder of radius r μm we have $C_e = 460 \times \ell(r^2 - h^2)10^{-18}\pi$ meaning that at $t = 0$ the extracellular concentration of sodium is 460 mol/m^3.

3 Analytical solution

In this section we present an analytical solution for (8), for $s = i, e$. For the sake of simplicity in notations, we will omit the index s in the first step (when we look only the equation). When we also take into account the boundary and the initial conditions, we will denote with an index s, the solution and all the constants involved, for $s = i, e$.

In cylindrical coordinates, equation (8) reads as follow:

$$\frac{\partial c}{\partial t} - D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial \rho^2} + \frac{1}{\rho}\frac{\partial c}{\partial \rho} + \frac{1}{\rho^2}\frac{\partial^2 c}{\partial \theta^2}\right) + \frac{\sigma}{\varepsilon}c = 0, \tag{15}$$

with $(x, \rho, \theta, t) \in]0, \ell[\times]h - \varepsilon, r[\times] - \pi, \pi[\times]0, T[$. In order to get a solution to the previous equation, we proceed in two approaches corresponding to the two cases introduced in section 2.

Case I

A useful method of finding a solution of a partial differential equation with several variables is the Fourier method of separation of variables. We define:

$$c(x, \rho, \theta, t) = Y(x, \rho, t)Z(\theta).$$

Consequently, from (15) we obtain

$$-\frac{1}{D}\frac{\partial_t Y}{Y} + \frac{\partial_{xx} Y}{Y} + \frac{\partial_{\rho\rho} Y}{Y} + \frac{1}{\rho}\frac{\partial_\rho Y}{Y} + \frac{1}{\rho^2}\frac{Z''}{Z} - \frac{\sigma}{D\varepsilon} = 0, \tag{16}$$

where $\partial_\varkappa Y := \partial Y/\partial\varkappa$ and $\partial_{\varkappa\varkappa} = \partial^2 Y/\partial\varkappa^2$, for $\varkappa \in \{t, x, \rho\}$. Thus we get a solution (see Section 5 - Case I for details):

$$c_e(x,\rho,\theta,t) = \frac{1}{\xi}\Big(\kappa_1\rho^{-\frac{1}{2}}\exp[\tau\rho]+ \\ +\kappa_2\rho^{\frac{1}{2}}\Big)\exp\Big[\xi x + (\xi^2 D - \frac{\sigma_e}{\varepsilon})t\Big]\cos(\theta/2), \quad (17)$$

with ξ given by (51), and

$$c_i(x,\rho,\theta,t) := \Big(\delta_{1,i}\rho^{-\frac{1}{2}}\exp[\xi x + (\xi+\iota)\rho + (\xi^2 D - \frac{\sigma_e}{\varepsilon})t]+ \\ + \Big(\delta_{2,i}\rho^{-\frac{1}{2}}\exp[(\eta+\iota)\rho] + \delta_{0,i}\rho^{\frac{1}{2}}\Big)\exp[\eta x + (\eta^2 D - \frac{\sigma_i}{\varepsilon})t]\Big)\cos(\theta/2), \quad (18)$$

with $\delta_{1,i}$, $\delta_{2,i}$, ι and η are correlated such that (60), (61) and (62) hold, and $\delta_{0,i} \in \mathbb{R}$. The validation of the initial and the boundary conditions can be achieved by the choice of the several constants.

Case II

In the present case the concentration does not have angular dependence. The uniformity around the membrane is reached at $x = 0$ and $t = 0$. So we rewrite (15) as

$$\frac{\partial c}{\partial t} - D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial \rho^2} + \frac{1}{\rho}\frac{\partial c}{\partial \rho}\right) + \frac{\sigma}{\varepsilon}c = 0, \quad (19)$$

with $(x,\rho,t) \in]0,\ell[\times]h-\varepsilon, r[\times]0,T[$. Let us define:

$$c(x,\rho,t) = X(x,t)W(\rho). \quad (20)$$

Consequently, from (19) we obtain

$$-\frac{1}{D}\frac{\partial_t X}{X} + \frac{\partial_{xx}X}{X} + \frac{W''}{W} + \frac{1}{\rho}\frac{W'}{W} - \frac{\sigma}{D\varepsilon} = 0. \quad (21)$$

Thus we get a solution (see Section 5 - Case II for details):

$$c_e(x,\rho,t) = (G_{1,e}\cos\left(\nu_e x - 2D\nu_e^2 t\right)\exp[-\nu_e x + \lambda_{2,e}t]+ \\ + G_{2,e}\exp[\lambda_{2,e}t])W_e(\rho) \quad (22)$$

$$c_i(x,\rho,t) = (G_{1,i}\sin(\nu_i x - 2D\nu_i^2 t)\exp[-\nu_i x + \lambda_{2,i}t]+ \\ + G_{2,i}\exp\left[\lambda_{2,i}t\right])W_i(\rho) \quad (23)$$

with

$$W_s(\rho) = (F_{1,s} + F_{2,s}(\gamma + \log\left(\lambda_{1,s}^{1/2}\rho/2\right)))B_{1,s}(\rho) + F_{2,s}B_{2,s}(\rho), \quad (24)$$

$$B_{1,s}(\rho) = 1 + \sum_{n=1}^{\infty} \frac{(-1)^n}{4^n (n!)^2} (\lambda_{1,s}^{1/2} \rho)^{2n},\ B_{2,s}(\rho) = \sum_{n=1}^{\infty} \frac{(-1)^{n+1} H_n}{4^n (n!)^2} (\lambda_{1,s}^{1/2} \rho)^{2n}, \quad (25)$$

for $s \in \{i, e\}$ and

$$H_n := \sum_{k=0}^{n} \frac{1}{k} \quad (26)$$

and γ is the so called *Euler-Mascheroni* constant, which value is

$$\gamma := \lim_{n \to \infty} (H_n - \log n) = 0,577215664901532860606512090 08 \ldots. \quad (27)$$

The constants involved in the definition of c_s satisfy a list of conditions with hard computations, some of them depending on experimental data. The reader is pleased invited to check section 5 where they are listed and justified. We gave the solution as abstract as possible in order to be applied to any experiment. We kept abstract the values of the biological functions.

4 Discussion and conclusions

The most striking difference between myelinated and unmyelinated axons is the gating mechanism which causes different behaviours on the membrane voltage. The relative long internodal distance in the case of myelinated axons implies a firing behaviour dependence on the distance to the stimulating electrode and also on the x-distance to a node ([20, pp. 145]).

We strongly believe that our model can be adapted to myelinated axons, since it obeys to laws of physics and chemistry in consonance with the physiological phenomena. To be faithful to the physiologic context further research should be done. For instance, the geometry of the Schawnn cells constituted a delicate point which needs to be worked out. The nerve impulse is a phenomenon full of biological functions. As far as it was possible we kept their values abstract (axon's length, etc).

We develop our model, as so many authors, in assuming the homogeneity of the conductivity, of the permeability and of the diffusion coefficient. However improvements on the model should take into account that these parameters are biological nonconstant functions. For instance, if we consider the Nernst-Einstein relation [14] then the conductivity satisfies $\sigma = \frac{z_\varsigma^2}{|z_\varsigma|} uFc$, where $u = |z_\varsigma| DF/(RT)$ represents the constant mobility in the radial direction of an ionic specie ς. Following the steps that lead us to equation (8), we obtain a new model

$$\frac{\partial c}{\partial t} - D\nabla^2 c - \frac{z_\varsigma}{|z_\varsigma|} u \nabla\phi \cdot \nabla c = -\frac{z_\varsigma^2}{|z_\varsigma|} \frac{Fu}{\varepsilon} c^2. \quad (28)$$

We observe the similarity between the obtained equation (28) and the advection-reaction-diffusion equations in [8] and in [17]. The electroconvective term corresponds to $u\nabla\phi$, the advective term with the velocity $\mathbf{v} = -\frac{z_\varsigma}{|z_\varsigma|} u\nabla\phi$ and the nonlinear term on the right hand side of the equation (28) corresponds to the

reactive term due to the consummation of the species now at the following form $f(c) = -\frac{z_\varsigma^2}{|z_\varsigma|}\frac{Fu}{\varepsilon}c^2 = -z_\varsigma^2\frac{F^2D}{\varepsilon RT}c^2$. We emphasize that our model which is derived from the Maxwell equations is consistent with the principle of conservation of electricity:

$$\frac{\partial \varrho}{\partial t} + \nabla \cdot \mathbf{J} = 0, \tag{29}$$

where ϱ is the charge, coupled with the Poisson equation

$$-\nabla \cdot (\varepsilon \nabla \phi) = \varrho. \tag{30}$$

We refer for instance to [3] and [19] where the authors consider the electrodiffusion equation by the Nernst-Planck theory (we use our notations)

$$\frac{\partial c}{\partial t} + \frac{1}{Fz_\varsigma}\nabla \cdot \mathbf{J} = 0 \tag{31}$$

together with the Poisson equation (30). Considering only one specie, the principle of conservation of electricity (29) is coherent with the electrodiffusion equation (31) by the Nernst-Planck theory, and the accurate Poisson equation:

$$-\nabla(\varepsilon \cdot \nabla \phi) = Fz_\varsigma c \tag{32}$$

is still consistent to (30).

The principal feature of our model is the two/three-dimensional characterization of the space-domain and the time dependence. Other feature includes the natural appearance of the membrane as an interface between the extra and intracellular spaces, avoiding the membrane structure characterization, its specificity or frictional interaction [9] and [22], as well as the random motion description.

The choice in formulating our model for sodium current is based on the importance that sodium ions have among all ions presented in the axoplasm. Actually, our model may also be applied to other ion species, if we deal with the corresponding electro-physiological parameters (diffusion coefficient, permittivity, electrical conductivity).

A further remark is imposed by the fact that we present analytical solutions (see Section 5).

We remark that the nonlinearity of the logarithmic function, which invalids the application of the Nernst potential to the coupled diffusion was the cause of some incorrect models in the literature. Analogously to the passage to the Goldman–Hodgkin–Katz potential as a nonlinear extension to the Nernst potential only valid for one specie, the passage from one to several species seems not to be a system constituted of the electrodiffusion equation from Nernst-Planck theory for each specie. This still is an open problem and it is the prior concern for a future work. Indeed, further experimental work should be done to confirm the theoretical findings and to raise new questions on the structure of the solutions of the system.

5 Appendix - A Formal Derivation

In this section we show an analytical solution for (8).

Case I

Precisely we are going to study the differential equation (16), that is

$$-\frac{1}{D}\frac{\partial_t Y}{Y}+\frac{\partial_{xx}Y}{Y}+\frac{\partial_{\rho\rho}Y}{Y}+\frac{1}{\rho}\frac{\partial_\rho Y}{Y}+\frac{1}{\rho^2}\frac{Z''}{Z}-\frac{\sigma}{D\varepsilon}=0.$$

Then there exists $\lambda\in\mathbb{R}$ such that

$$\begin{cases} Z''(\theta)=\lambda Z(\theta) \\ \lambda=\left[\frac{1}{D}\left(\frac{\partial_t Y}{Y}(x,\rho,t)+\frac{\sigma}{\varepsilon}\right)-\frac{\partial_{xx}Y}{Y}(x,\rho,t)-\frac{\partial_{\rho\rho}Y}{Y}(x,\rho,t)-\frac{1}{\rho}\frac{\partial_\rho Y}{Y}(x,\rho,t)\right]\rho^2. \end{cases}$$

From now on we take $\lambda=-\frac{1}{4}$. Thus the second order ordinary differential equation for Z has the following solution:

$$Z(\theta)=d_1\cos\left(\frac{\theta}{2}\right)+d_2\sin\left(\frac{\theta}{2}\right), \tag{33}$$

where d_1, d_2 are real constants. Since we are interested in nonnegative valued solution for (8), we assume that Y and Z are both nonnegative functions, thus from (33) we get

$$Z(\theta)=d\cos(\theta/2), \tag{34}$$

with d nonnegative real constant. We will now analyse the remaining equation, that is:

$$\rho^2\left[\partial_{xx}Y+\partial_{\rho\rho}Y-\frac{1}{D}\partial_t Y-\frac{\sigma}{D\varepsilon}Y\right]+\rho\partial_\rho Y-\frac{1}{4}Y=0. \tag{35}$$

Arguing as in the theory for the confluent hypergeometric equation (see [16]), we look for a function in the form:

$$Y(x,\rho,t)=\rho^{-\frac{1}{2}}u(x,\rho,t)+\rho^{\frac{1}{2}}v(x,t) \tag{36}$$

that satisfies the equation (35), where

$$u(x,\rho,t)=\sum_{j=0}^{\infty}f_j\left(x+\rho+pDt\right)^j\exp\left[ax+b\rho+qDt\right] \tag{37}$$

and a, b, p, q are real constants to be chosen later. Solving (35) for $\rho^{\frac{1}{2}}v$, we get

$$\partial_{xx}v-\frac{1}{D}\partial_t v-\frac{\sigma}{D\varepsilon}v=0, \tag{38}$$

thus we choose (see [1])

$$v(x,t)=v_0\exp\left[\xi x+(\xi^2 D-\frac{\sigma}{\varepsilon})t\right], \tag{39}$$

with $\xi \in \mathbb{R}$, and $v_0 > 0$ in order to get positive solutions. We remark that the statement $\lambda = -1/4$ was essential in the calculation (38) and it will be in the following one. Solving (35) for $\rho^{-\frac{1}{2}}u$, we obtain

$$\sum_{j=0}^{+\infty}[2(j+1)(j+2)f_{j+2} + (2(a+b)-p)(j+1)f_{j+1} + \\ +(a^2+b^2-q-\frac{\sigma}{\varepsilon D})f_j\Big]\cdot(x+\rho+pDt)^j = 0. \quad (40)$$

In order to find the extracellular concentration c_e, we use (9) in cylindrical coordinates. For simplicity, we will keep the unknown constants d, f_j, p, a, b, q, v_0 and η without the extracellular subscripts.Thus from (37) we get

$$\sum_{j=0}^{\infty}[(j+1)f_{j+1} + (b-\frac{1}{2r})f_j](x+r+pDt)^j = \\ = -\frac{v_0}{2}\exp\Big[(\xi-a)x - br + (\xi^2 - q - \frac{\sigma_e}{\varepsilon D})Dt)\Big]. \quad (41)$$

Applying the Taylor formula in $(x-x_0)$, with $x_0 = -(r+pDt)$, and denoting $U_j = j!f_j$, we have

$$U_{j+1} + (b-\frac{1}{2r})U_j = -\frac{1}{2}v_0(\xi-a)^j\times \\ \times\exp\Big[(a-\xi-b)r + ((a-\xi)p + \xi^2 - q - \frac{\sigma_e}{\varepsilon D})Dt\Big]. \quad (42)$$

Since there is no dependence in time, we get

$$(\xi-a)p + q = \xi^2 - \sigma_e/(\varepsilon D). \quad (43)$$

Denoting by $M := b - 1/(2r)$ and $N := -v_0\exp[(a-\xi-b)r]/2$ it follows

$$U_{j+1} = -MU_j + N(\xi-a)^j; \quad (44)$$
$$U_{j+2} = M^2U_j + N(-M+\xi-a)(\xi-a)^j. \quad (45)$$

From (40) it results

$$2U_{j+2} + (2(a+b)-p)U_{j+1} + (a^2+b^2-q-\frac{\sigma_e}{\varepsilon D})U_j = 0. \quad (46)$$

Thus, introducing (44)-(45) into (46) and using (43), after some calculations we obtain $U_j = (\xi-a)^j f_0$, with

$$f_0 = v_0\exp\left[(a-\xi-b)r\right]\cdot\frac{\xi + \frac{1}{2r} - \frac{p}{2}}{(a-b)^2 + \frac{a-b}{r} + \frac{1}{2r^2} + p(b+\xi-a-\frac{1}{2r}) - \xi^2}. \quad (47)$$

Thus

$$u_e(x,\rho,t) = f_0\exp[\xi x + (\xi-a+b)\rho + (\xi^2 - \frac{\sigma_e}{\varepsilon D})Dt)] \quad (48)$$

and consequently

$$Y_e(x,\rho,t) = (f_0\rho^{-\frac{1}{2}}\exp\,[(\xi-a+b)\rho] + \\ + v_0\,\rho^{\frac{1}{2}})\cdot\exp\left[\xi x + (\xi^2 D - \frac{\sigma_e}{\varepsilon})t\right]. \quad (49)$$

Thus from (11) we obtain:

$$c_e(x,\rho,\theta,t) = \frac{1}{\xi}\left(\kappa_1\rho^{-\frac{1}{2}}\exp[\tau\rho] + \right. \\ \left. +\kappa_2\rho^{\frac{1}{2}}\right)\exp\left[\xi x + (\xi^2 D - \frac{\sigma_e}{\varepsilon})t\right]\cos\frac{\theta}{2}. \quad (50)$$

Finally, the initial condition (14) yields:

$$\frac{\exp[\xi\ell]-1}{\xi}\left(\kappa_1\int_h^r \rho^{\frac{1}{2}}\exp[\tau\rho]\,d\rho + \frac{2}{5}\kappa_2(r^{5/2}-h^{5/2})\right) \qquad = \qquad \frac{C_e}{4}. \quad (51)$$

Next we are interested in finding the intracellular concentration c_i using the form (37) and (39):

$$c_i(x,\rho,\theta,t) = \left(d\rho^{-\frac{1}{2}}u(x,\rho,t) + \delta_{0,i}\rho^{\frac{1}{2}}\exp[\eta x + (\eta^2 D - \frac{\sigma_i}{\varepsilon})t]\right)\cos\frac{\theta}{2}\,, \quad (52)$$

with $\delta_{0,i} = dv_0$. Here we consider new unknown constants d, f_j, p, a, b, q, $\delta_{0,i}$ and η (some of them relabelled to avoid the use of the intracellular subscripts) in order to verify (10). Introducing (50) and (52) in (10) we obtain

$$\sum_{j=0}^{\infty} d(\alpha p D f_{j+1}(j+1) + (\alpha q D + \beta)f_j)(x+h+pDt)^j = \\ -\delta_{0,i}h\exp[-bh + (\eta-a)x + (\eta^2 D - \sigma_i/\varepsilon - qD)t](\alpha(\eta^2 D - \frac{\sigma_i}{\varepsilon}) + \beta) \\ + \frac{\exp[-bh + (\xi-a)x + (\xi^2 D - \sigma_e/\varepsilon - qD)t]}{\xi} \\ \left(\kappa_1(\alpha(\xi^2 D - \sigma_e/\varepsilon) + \beta + D(\frac{1}{2} - h\tau))\exp(\tau h)\right. \\ \left. +\kappa_2 h(\alpha(\xi^2 D - \sigma_e/\varepsilon) + \beta - \frac{D}{2})\right). \quad (53)$$

Arguing as in the exterior case we can apply the Taylor formula in $(x-x_0)$ with $x_0 = -(h+pDt)$ resulting, for each time level,

$$U_{j+1} = -MU_j + N(\xi-a)^j + P(\eta-a)^j; \quad (54)$$
$$U_{j+2} = M^2 U_j + N(-M+\xi-a)(\xi-a)^j + P(-M+\eta-a)(\eta-a)^j, \quad (55)$$

where $M := q/p + \beta/(\alpha p D)$ and

$$P(t) := -\frac{\delta_{0,i} h}{d\alpha p D} \exp[(a-\eta-b)h + ((a-\eta)p + \eta^2 - \frac{\sigma_i}{\varepsilon D} - q)Dt] \times(\alpha(\eta^2 D - \frac{\sigma_i}{\varepsilon}) + \beta); \tag{56}$$

$$N(t) := \frac{1}{d\alpha p D\xi} \exp[(a-\xi-b)h + ((a-\xi)p + \xi^2 - \frac{\sigma_e}{\varepsilon D} - q)Dt] \times \left(\kappa_1(\alpha(\xi^2 D - \sigma_e/\varepsilon) + \beta + D(\frac{1}{2} - h\tau))\exp(\tau h) + \kappa_2 h(\alpha(\xi^2 D - \sigma_e/\varepsilon) + \beta - \frac{D}{2})\right). \tag{57}$$

Now the independence in time to (56)-(57) implies

$$(\eta - a)p + q = \eta^2 - \sigma_i/(\varepsilon D), \tag{58}$$

$$(\xi - a)p + q = \xi^2 - \sigma_e/(\varepsilon D). \tag{59}$$

Thus $N(t) \equiv N$ and $M(t) \equiv M$, for all t. Again (40) implies (46) with σ_e replaced by σ_i. Introducing (54)-(55) into this new version of (46) and using (58) we conclude that $j! df_j = (\xi - a)^j \delta_{1,i} + (\eta - a)^j \delta_{2,i}$, where

$$\frac{\delta_{1,i}}{d} = -2N \frac{M + \xi + b - p/2}{2M^2 - M(2(a+b) - p) + a^2 + b^2 + (\eta - a)p - \eta^2}; \tag{60}$$

$$\frac{\delta_{2,i}}{d} = -2P \frac{M + \eta + b - p/2}{2M^2 - M(2(a+b) - p) + a^2 + b^2 + (\eta - a)p - \eta^2}. \tag{61}$$

For the sake of simplicity if we take $\iota = b - a$, then (52) leads us to (18), and condition (14) reads

$$\frac{C_i}{4} = \frac{\exp[\xi\ell] - 1}{\xi}\delta_{1,i}\int_{h-\varepsilon}^{h} \rho^{\frac{1}{2}} \exp[(\xi + \iota)\rho]\, d\rho + \frac{\exp[\eta\ell] - 1}{\eta}\left(\delta_{2,i}\int_{h-\varepsilon}^{h} \rho^{\frac{1}{2}} \exp[(\eta + \iota)\rho]\, d\rho + \frac{2\delta_{0,i}}{5}(h^{\frac{5}{2}} - (h-\varepsilon)^{\frac{5}{2}})\right). \tag{62}$$

Then the validation of the conditions yields the choice for our constants.

Case II

From (21) there exists $\lambda_1 \in \mathbb{R}$ such that

$$W'' + \frac{1}{\rho}W' + \lambda_1 W = 0 \tag{63}$$

and

$$\partial_t X = D\partial_{xx} X + \lambda_2 X, \tag{64}$$

with

$$\lambda_2 := -(\lambda_1 D + \frac{\sigma}{\varepsilon}). \tag{65}$$

Equation (63), by a change of variable, is the so called *Bessel Equation* of zero order (see [24]). Using the *Bessel function of the first kind* we obtain a solution $B_1(\rho)$ (see (25)) of (63). Another solution, linearly independent of B_1 is obtained from the *Bessel function of the second kind* ($Y_0(\rho)$)

$$Y_0(\lambda_1^{1/2}\rho) := (\gamma + \log\,(\lambda_1^{1/2}\rho/2))B_1(\rho) + \sum_{n=1}^{\infty} \frac{(-1)^{n+1}H_n}{4^n(n!)^2}(\lambda_1^{1/2}\rho)^{2n} \tag{66}$$

where H_n and γ are defined in (26) and (27), respectively. From the theory of differential equations, for all F_1, $F_2 \in \mathbb{R}$, $W(\rho) = F_1 B_1(\rho) + F_2 Y_0(\lambda_1^{1/2}\rho)$ is a solution of (63) and we can write it as follows

$$W(\rho) = (F_1 + F_2(\gamma + \log\,(\lambda_1^{1/2}\rho/2)))B_1(\rho) + F_2 B_2(\rho), \tag{67}$$

with B_2 defined in (25). For $\lambda_1 > 0$, $W(\rho)$ is a real valued function. Since we are interested on nonnegative valued solutions we also consider

$$\lambda_1 < \min\left\{ \left(\frac{\max\{\rho > 0 :\ B_1(\lambda_1^{-1/2}\rho) \geq 0\}}{r}\right)^2, \right.$$
$$\left. \left(\frac{\max\{\rho > 0 :\ Y_0(\rho) \leq 0\}}{r}\right)^2 \right\} \tag{68}$$

and we choose F_1 and F_2 such that:

$$F_2 > 0 \quad \text{and} \quad F_1 + F_2(\gamma + \log(\lambda_1^{1/2} r/2)) > 0. \tag{69}$$

Now we focus our attention in equation (64). It is well known that $\exp[\lambda_2 t]$ is a solution of equation (64). Since we have a second order differential equation, we look for a second linearly independent solution of the form

$$\varphi(x,t) = \sum_{n=0}^{\infty} a_n (x - 2D\nu t)^n \exp[-\nu x + \lambda_2 t], \tag{70}$$

with $a_n, \nu \in \mathbb{R}$, for all $n = 0, 1, 2, 3, \ldots$. Solving (64) for φ, we get

$$\sum_{n\geq 0} D(\nu^2 a_n + (n+2)(n+1)a_{n+2})(x - 2D\nu t)^n = 0. \tag{71}$$

Consequently, $a_{n+2} = -\frac{\nu^2 a_n}{(n+2)(n+1)}$, for $n = 0, 1, 2, \ldots$, that implies

$$a_{2n} = a_0 \frac{(-1)^n \nu^{2n}}{(2n)!} \quad \text{and} \quad a_{2n+1} = a_1 \frac{(-1)^n \nu^{2n}}{(2n+1)!}. \tag{72}$$

Thus, with $\nu \neq 0$,

$$\varphi(x,t) = [a_0 \cos(\nu x - 2D\nu^2 t) + \frac{a_1}{\nu} \sin(\nu x - 2D\nu^2 t)] \exp[-\nu x + \lambda_2 t]. \quad (73)$$

Finally we obtain a solution for (64)

$$X(x,t) = G_1 \varphi(x,t) + G_2 \text{exp } (\lambda_2 t), \quad G_1, G_2 \in \mathbb{R}. \quad (74)$$

Taking into account (20), (67) and (74), we can now write a solution for each equation in (8)

$$c_s(x,\rho,t) = (G_{1,s}\varphi_s(x,t) + G_{2,s}\text{exp } (\lambda_{2,s}t))\, W_s(\rho). \quad (75)$$

Condition (13) means that the ionic gradient, at $x = 0$ and $t = 0$, is larger that the one in the resting state. Consequently there will be an influx of sodium which implies a diminution on the exterior concentration and an increasing on the interior one. Linking the physiological interpretation with the knowledge of the behaviour of the involved functions (from its mathematical study), we can proceed, choosing, in Ω_e, $a_0 = 1$, $a_1 = 0$, in Ω_i, $a_0 = 0$ and $a_1 = \nu_i$, and $\nu_s > 0$, for $s \in \{i, e\}$.

We first analyse the solution in Ω_e. From the previous analysis (73)-(74), X_e becomes:

$$X_e(x,t) = G_{1,e} \cos\left(\nu_e x - 2D\nu_e^2 t\right) \exp[-\nu_e x + \lambda_{2,e} t] + G_{2,e} \exp[\lambda_{2,e} t]. \quad (76)$$

We look for nonnegative functions, so we take

$$G_{1,e},\, G_{2,e} > 0 \quad \text{and} \quad 1 < \nu_e^2 \leq \min\{\frac{\pi}{2\ell}, \frac{\pi}{4DT}\}, \quad (77)$$

observing that $-\pi/2 \leq -2D\nu_e^2 T < \nu_e x - 2D\nu_e^2 t < \nu_e \ell \leq \pi/2$, for all $(x,t) \in]0,\ell[\times]0,T[$. From (9), we get $W_e'(r) = 0$, thus

$$F_{1,e} = -F_{2,e} \frac{B_{1,e}(r)/r + B_{2,e}'(r) + (\gamma + \log(\lambda_{1,e}^{1/2} r/2)) B_{1,e}'(r)}{B_{1,e}'(r)}. \quad (78)$$

Introducing (78) into (69), (69) and (78) become compatible providing that $\lambda_{1,e} > \left(\frac{2}{r \exp(1-\gamma)}\right)^2$.

From (14) we get

$$\int_0^\ell \int_h^r \rho\, (G_{1,2}\varphi_e(x,0) + G_{2,e})\, W_e(\rho)\, dx d\rho = C_e. \quad (79)$$

We can compute the integrals related to each variable, so

$$\int_0^\ell X_e(x,0)\, dx = \frac{G_{1,e}}{2\nu_e} \left(1 + (\sin(\nu_e \ell) - \cos(\nu_e \ell)) \exp[-\nu_e \ell]\right) + G_{2,e}\ell \quad (80)$$

and the integral related to ρ gives the long computation

$$\int_h^r \rho W_e(\rho)\,d\rho = (F_{1,e}+\gamma F_{2,e})\left(\sum_{n=0}^{\infty}\frac{(-1)^n\lambda_{1,e}^n}{4^n(n!)^2}\frac{r^{2n+2}-h^{2n+2}}{2n+2}\right)+$$
$$F_{2,e}\sum_{n=1}^{\infty}\frac{(-1)^n H_n\lambda_{1,e}^n}{4^n(n!)^2}\frac{r^{2n+2}-h^{2n+2}}{2n+2}+$$
$$F_{2,e}\sum_{n=0}^{\infty}\frac{(-1)^n\lambda_{1,e}^n}{4^n(n!)^2}r^{2n+2}\left(\frac{\log\,(\lambda_{1,e}^{1/2}r/2)}{2n+2}-\frac{1}{(2n+2)^2}\right)-$$
$$F_{2,e}\sum_{n=0}^{\infty}\frac{(-1)^n\lambda_{1,e}^n}{4^n(n!)^2}h^{2n+2}\left(\frac{\log\,(\lambda_{1,e}^{1/2}h/2)}{2n+2}-\frac{1}{(2n+2)^2}\right). \tag{81}$$

So the product of the values in (80) and (81) gives C_e. We proceed with the analysis in Ω_i. From (73)-(74) and the above considerations we have

$$X_i(x,t) = G_{1,i}\sin(\nu_i x - 2D\nu_i^2 t)\exp[-\nu_i x+\lambda_{2,i}t] + G_{2,i}\exp[\lambda_{2,i}t]. \tag{82}$$

Since we are interested on nonnegative solutions we choose

$$G_{2,i}\geq G_{1,i}\geq 0, \tag{83}$$

observing that $\sin(\nu_i x - 2D\nu_i^2 t)\exp[-\nu_i x]\geq -1$ for all $(x,t)\in]0,\ell[\times]0,T[$. From (14) we get

$$\int_0^{\ell}\int_{h-\varepsilon}^{h}\rho\left(G_{1,i}\varphi_i(x,0)+G_{2,i}\right)W_i(\rho)\,dx d\rho = C_i. \tag{84}$$

We can compute the integrals related to each variable, so

$$\int_0^{\ell} X_i(x,0)\,dx = \frac{G_{1,i}}{2\nu_i}(1-(\sin(\nu_i\ell)+\cos(\nu_i\ell))\exp[-\nu_i\ell])+G_{2,i}\ell \tag{85}$$

and the integral related to ρ gives the long computation, similar to (81),

$$\int_{(h-\varepsilon)}^{h}\rho W_i(\rho)\,d\rho = (F_{1,i}+\gamma F_{2,i})\left(\sum_{n=0}^{\infty}\frac{(-1)^n\lambda_{1,i}^n}{4^n(n!)^2}\frac{h^{2n+2}-(h-\varepsilon)^{2n+2}}{2n+2}\right)+$$
$$F_{2,i}\sum_{n=1}^{\infty}\frac{(-1)^n H_n\lambda_{1,i}^n}{4^n(n!)^2}\frac{h^{2n+2}-(h-\varepsilon)^{2n+2}}{2n+2}+$$
$$F_{2,i}\sum_{n=0}^{\infty}\frac{(-1)^n\lambda_{1,i}^n}{4^n(n!)^2}h^{2n+2}\left(\frac{\log\,(\lambda_{1,i}^{1/2}h/2)}{2n+2}-\frac{1}{(2n+2)^2}\right)-$$
$$F_{2,i}\sum_{n=0}^{\infty}\frac{(-1)^n\lambda_{1,i}^n}{4^n(n!)^2}(h-\varepsilon)^{2n+2}\left(\frac{\log\,(\lambda_{1,i}^{1/2}(h-\varepsilon)/2)}{2n+2}-\frac{1}{(2n+2)^2}\right). \tag{86}$$

So the product of the values in (85) and (86) gives C_i. From (13) we obtain

$$\frac{G_{1,e}+G_{2,e}}{G_{2,i}} > \mathcal{N}\frac{W_i(h)}{W_e(h)}. \tag{87}$$

From (10) we get a very long computation. For our purposes, it is enough to write it in the next form:

$$\left(\alpha\frac{\partial X_e}{\partial t}+\beta X_e\right)W_e(h) - X_e W_e'(h)h = \left(\alpha\frac{\partial X_i}{\partial t}+\beta X_i\right)W_i(h). \tag{88}$$

We observe that the validation of the several conditions yields the choice for our several constants, this implies the existence of a solution. From the mathematical point of view the uniqueness of a solution is not guaranteed since there exists no boundary condition at $\{x=\ell\}$. However without data experiments we can not go further. We point out that the qualitative behaviour of the solutions are described in our study.

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