An electrophysiology model for cells and tissues

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Abstract

We introduce a kinetic model to study the dynamics of ions in aggregates of cells and tissues. Different types of communication channels between adjacent cells and between cells and intracellular space are considered (ion channels, pumps and gap junctions). We shows that stable transmembrane ionic Nernst potentials are due to the coexistence of both specialised ion pumps and channels. Ion pumps or channels alone do not contribute to an equilibrium transmembrane potential drop. The kinetic parameters of the model straightforwardly calibrate with the Nernst potentials and ion concentrations. The model is based on the ATPase enzymatic mechanism for the ions Na^+, K^+, and it can be generalised for other ion pumps. We extend the model to account for electrochemical effects, where transmembrane gating mechanism are introduced. In this framework, axons can be seen as the evolutionary result of the aggregation of cells through gap junctions, which can be identified as the Ranvier nodes. In this kinetic framework, the injection of current in an axon induces the modification of the potassium equilibrium potential along the axon.

Keywords: ATPase, electrophysiology, sodium-potassium gates, gap junctions, axons, diffusion.

1 Introduction

The main goal of this paper is to derive a mathematical model describing the electrophysiology states of cells and tissues, derived from the laws of molecular dynamics and chemical kinetics. This model describes the transport of several types of ions in cells and tissues, including mechanisms of transmembrane transport through channels, pumps or gap junctions.

Cells can be arranged in three-dimensional structures, in two-dimensional layers, or in linear arrays. Several biological functions are done inside the cell, as protein production and regulation. To fulfil these functions nutrients migrate through intracellular spaces and enter into the cell through ion channels, pumps or gap junctions. Ion channels are holes on the cellular membrane, through which nutrients and other substances can flow. Pumps are active proteins that selectively transport specific ions from the inside to the outside of the cell, and vice versa. Gap junctions are intercellular connections between the cytoplasm of adjacent cells. Ion channels, pumps and gap junctions can be opened or closed.

The adenosine triphosphate (ATP) molecule is a nucleotide responsible for the transport of energy to cells in organisms, [2]. It provides the necessary energy for metabolic reactions to occur inside the cell (1 glucose $\rightarrow$ 2 ATP). This process of energy delivery to the cell is controlled by ions, Na^+ and K^+, among others, which mediate the dephosphorylation/phosphorylation of ATP, followed by the hydrolysation of ADP, releasing energy to the cell in an exergonic reaction.

The ATP mechanism is controlled by the fluxes of Na^+ and K^+ ions from outside to the inside of the cell and vice versa. Other ions like Cl^-, H^+ and Ca^{2+} may also be present. These fluxes induce different steady concentrations of ions in the interior and in the exterior of cells, which can be measured by the difference of potential between the inside and the outside the cell. The values of the equilibrium potential drop measured relative to the outside potential are in the range -20 mV to -80 mV (neurones), [19], and characterises the electrophysiological state of cells or tissues.

To describe the electrophysiological state of a cell, Hodgkin and Huxley (HH) made a phenomenological electric model of the cell membrane. This model predictions have been compared with data from patch clump experiments with a squid neurone, [12]. Their results were so remarkably close to the experimental observations that this model become the inspiration for modern electrophysiological models, [13, 14, 15]. The HH model introduces two assumptions. Firstly, the pumping mechanism between the exterior and the interior of cells behave as an electric circuit with a capacitor in parallel with a variable resistance and a battery. Secondly, there is a gating

mechanism responsible for the opening and closing of ion channels in cell membranes. This gating mechanism is based on the premise that the rates between the open and close states of gates depend on the transmembrane potential drop. Other derived mechanisms have been proposed in [3, 5, 15].

More recently, several experiments concentrated on the importance of electrical signalling for the induction and maintenance of several biological functions in organisms, [1, 17, 4]. For example, it has been shown that the ATPase mechanisms, regulating the ion concentrations inside and outside cells and the electrostatic potential drop across cellular membranes, might be important for regeneration of tissues, [1].

Independently of the enormous success of the HH model, both from the experimental and theoretical point of view, it is importante to obtain a derivation of this model from the first principles of molecular dynamics. This is one of the goals of this paper.

This paper is organised as follows. In the next section, we derive the basic linear kinetic model, describing the propagation of ions in aggregates of cells and tissues. In this section, the main biochemical and physical assumptions based on ATPase mechanisms are introduced. The basic model equations reduce to a system of linear reaction-diffusion equations, two equations for each ion type. This basic model contains the effects of ion pumps, channels and gap junctions. In section 3 and following the proposal of Hodgkin and Huxley, [12], we introduction of voltage dependent gates for ion channels. This makes the new model equations dependent of the potential drop across cellular membranes. This general model admits any type of voltage dependent gating mechanism, and, by construction, may also describe the effect of patch clump experiments. Numerical solutions for the sodium-potassium dynamics are analysed in section 4, including the effect of patch clamp type experiments in cells and tissues. In section 5, we summarise and discuss the conclusions of this paper.

2 Derivation of the basic molecular dynamics model

We consider a bidimensional arrangement of cells in the plane. The cells may communicate with each other through gap junctions, or through the fluid that fils the intercellular space. The communication with the intercellular fluid is done through ion channels and pumps, figure 1.

To describe the kinematics of Na^+ and K^+ ions between the intracellular regions and the cytoplasm of cells, we start by modelling the pumping

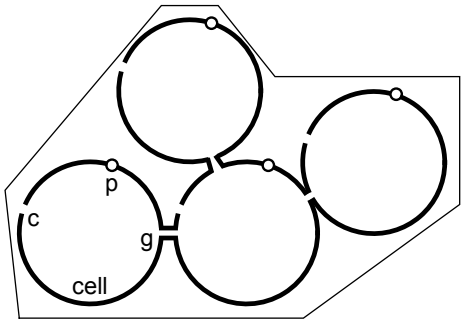

Figure 1: A two-dimensional arrangement of cells in a tissue. Ion channels, pumps and gap junctions are indicated by "c", "p" and "g", respectively.

mechanism of these ions. The model introduced here is based on the ATPase enzymatic mechanism for NaK pumps of Chapman, Johnson and Kootsy, [8], and adapted by Enderle and Bronzino, [11, pp. 483]. This mechanism is described by the system of kinetic diagrams

$$
\begin{aligned}
&\xrightarrow{k_1} \mathrm{ATP}_i \\
&3\mathrm{Na}_i^+ + \mathrm{E}_i \xrightarrow{k_2} (\mathrm{Na}_3^+\mathrm{E})_i \\
&(\mathrm{Na}_3^+\mathrm{E})_i + \mathrm{ATP}_i \xrightarrow{k_3} (\mathrm{Na}_3^+\mathrm{EP})_i + \mathrm{ADP}_i \\
&(\mathrm{Na}_3^+\mathrm{EP})_i \xrightarrow{k_4} (\mathrm{Na}_3^+\mathrm{EP})_o \xrightarrow{k_5} 3\mathrm{Na}_0^+ + (\mathrm{EP})_o \\
&(\mathrm{EP})_o + 2\mathrm{K}_o^+ \xrightarrow{k_6} (\mathrm{K}_2^+\mathrm{EP})_o \xrightarrow{k_7} \mathrm{P}_i + (\mathrm{K}_2^+\mathrm{E})_o \\
&(\mathrm{K}_2^+\mathrm{E})_o \xrightarrow{k_8} 2\mathrm{K}_i^+ + \mathrm{E}_i \\
&\mathrm{ADP}_i \xrightarrow{k_9},
\end{aligned}
\tag{1}
$$

where E represents the transmembrane enzyme ATPase and the subscripts "i" and "o" refer to its localisation, inside or outside the cell. The enzyme E has the index "i" or "o" because it is a transmembrane carrier protein and its action can be from the inside to the outside and vice versa. The first diagram represents the production of ATP, eventually by glucose, and the k_i's are rate constants. The kinetic equations (1) are possible kinetic realisations of the ATPase stoichiometric dephosphorylation mechanism

$$
\mathrm{ATP}_i + 3\mathrm{Na}_i^+ + 2\mathrm{K}_o^+ \longrightarrow \mathrm{ADP}_i + \mathrm{P}_i + 3\mathrm{Na}_o^+ + 2\mathrm{K}_i^+. \tag{2}
$$

The temporal variation of concentrations of all the substances in (1) and (2) can be described by differential equations derived from the mass action law. However, the diagrams (1) and (2) are associated with two very different model approaches, with different parameters and eventually with different

temporal behaviour. In order to maintain the model sufficiently detailed and consistent with the physical and the chemical microscopic mechanisms occurring in tissues and cells, we expand the molecular collisions in (1) evolving three and four molecules to a more realistic bimolecular collisional mechanisms. We substitute the mechanisms in the second and fifth equations in (1) by bimolecular collisional diagrams:

$$3\mathrm{Na}_i^+ + \mathrm{E}_i \xrightarrow{k_2} (\mathrm{Na}_3^+\mathrm{E})_i \;\rightarrow \begin{cases} \mathrm{Na}_i^+ + \mathrm{E}_i \xrightarrow{k_2} c_1 \\ \mathrm{Na}_i^+ + c_1 \xrightarrow{k_2} c_2 \\ \mathrm{Na}_i^+ + c_2 \xrightarrow{k_2} (\mathrm{Na}_3^+\mathrm{E})_i \end{cases} \tag{3}$$

and

$$(\mathrm{EP})_o + 2\mathrm{K}_o^+ \xrightarrow{k_6} (\mathrm{K}_2^+\mathrm{EP})_o \;\rightarrow \begin{cases} (\mathrm{EP})_o + \mathrm{K}_o^+ \xrightarrow{k_6} d_1 \\ \mathrm{K}_o^+ + d_1 \xrightarrow{k_6} (\mathrm{K}_2^+\mathrm{EP})_o, \end{cases} \tag{4}$$

where c_1, c_2 and d_1 are intermediate complex states.

Besides NaK pumps, cells have ion channels. We consider (open) channels for the ions Na^+, K^+ and Cl^-. In these cases, the exchange of ions through channels follows a diffusion type process which can be described by the kinetic mechanisms

$$\begin{aligned} &\mathrm{Na}_o^+ \underset{k_{10}}{\overset{k_{10}}{\rightleftharpoons}} \mathrm{Na}_i^+ \\ &\mathrm{K}_o^+ \underset{k_{11}}{\overset{k_{11}}{\rightleftharpoons}} \mathrm{K}_i^+ \\ &\mathrm{Cl}_o^- \underset{k_{12}}{\overset{k_{12}}{\rightleftharpoons}} \mathrm{Cl}_i^-, \end{aligned} \tag{5}$$

where the the constants k_{10}, k_{11} and k_{12} are the rates of transfer of matter through the channels.

The kinetic mechanism (1), (3), (4) and (5) describe the osmotic/diffusion processes of ions across the cell membrane, mediated by NaK pumps and open ion channels.

To apply the mass action law to the mechanisms (1), (3), (4) and (5), we first introduce the following steady state simplifying assumptions, $c_1' = 0$, $c_2' = 0$, $(\mathrm{Na}_3^+\mathrm{E})_i' = 0$, $(\mathrm{Na}_3^+\mathrm{EP})_i' = 0$, $(\mathrm{Na}_3^+\mathrm{EP})_o' = 0$, $(\mathrm{EP})_o' = 0$, $d_1' = 0$, $(\mathrm{K}_2^+\mathrm{EP})_o' = 0$ and $(\mathrm{K}_2^+\mathrm{E})_o' = 0$, where the apostrophe refers to time derivatives. Under these conditions, and using the Mathematica software package *kinetics* ([10]), the concentrations of the non steady substances evolve in time

according to the system of linear equations

$$\begin{cases} \dfrac{d\mathrm{Na}_o^+}{dt} = -k_{10}(\mathrm{Na}_o^+ - \mathrm{Na}_i^+) + 3k_2\mathrm{E}_i\mathrm{Na}_i^+ \\ \dfrac{d\mathrm{Na}_i^+}{dt} = k_{10}(\mathrm{Na}_o^+ - \mathrm{Na}_i^+) - 3k_2\mathrm{E}_i\mathrm{Na}_i^+ \\ \dfrac{d\mathrm{K}_o^+}{dt} = -k_{11}(\mathrm{K}_o^+ - \mathrm{K}_i^+) - 2k_2\mathrm{E}_i\mathrm{Na}_i^+ \\ \dfrac{d\mathrm{K}_i^+}{dt} = k_{11}(\mathrm{K}_o^+ - \mathrm{K}_i^+) + 2k_2\mathrm{E}_i\mathrm{Na}_i^+ \\ \dfrac{d\mathrm{Cl}_o^-}{dt} = -k_{12}(\mathrm{Cl}_o^- - \mathrm{Cl}_i^-) \\ \dfrac{d\mathrm{Cl}_i^-}{dt} = k_{12}(\mathrm{Cl}_o^- - \mathrm{Cl}_i^-), \end{cases} \tag{6}$$

where $\mathrm{E}_i > 0$ is a constant related with the concentration of ATPase (transmembrane protein). Clearly, the system of equations (6) are not linearly independent and $\mathrm{Na}_o^+(t) + \mathrm{Na}_i^+(t) = \mathrm{Na}_o^+(0) + \mathrm{Na}_i^+(0)$, $\mathrm{K}_o^+(t) + \mathrm{K}_i^+(t) = \mathrm{K}_o^+(0) + \mathrm{K}_i^+(0)$ and $\mathrm{Cl}_o^-(t) + \mathrm{Cl}_i^-(t) = \mathrm{Cl}_o^-(0) + \mathrm{Cl}_i^-(0)$, for every $t \geq 0$.

The system of equations (6) describes the establishment of a steady concentration of ions inside and outside a cell. Equating to zero the right hand-side of equations (6), it follows that the steady state concentration of ions inside and outside of a cell are

$$\begin{aligned} \mathrm{Na}_o^{+*} &= \mathrm{Na0}\frac{k_{10}}{2k_{10} + 3\mathrm{C}_i k_2} + \mathrm{Na0}\frac{3\mathrm{C}_i k_2}{2k_{10} + 3\mathrm{C}_i k_2} \\ \mathrm{Na}_i^{+*} &= \mathrm{Na0}\frac{k_{10}}{2k_{10} + 3\mathrm{C}_i k_2} \\ \mathrm{K}_o^{+*} &= \frac{1}{2}\mathrm{K0} - \mathrm{Na0}\frac{\mathrm{C}_i k_2 k_{10}}{(2k_{10} + 3\mathrm{C}_i k_2)k_{11}} \\ \mathrm{K}_i^{+*} &= \frac{1}{2}\mathrm{K0} + \mathrm{Na0}\frac{\mathrm{C}_i k_2 k_{10}}{(2k_{10} + 3\mathrm{C}_i k_2)k_{11}} \\ \mathrm{Cl}_o^{-*} &= \frac{1}{2}\mathrm{Cl0} \\ \mathrm{Cl}_i^{-*} &= \frac{1}{2}\mathrm{Cl0}, \end{aligned} \tag{7}$$

where $\mathrm{Na0} = \mathrm{Na}_o^+(0) + \mathrm{Na}_i^+(0)$, $\mathrm{K0} = \mathrm{K}_o^+(0) + \mathrm{K}_i^+(0)$ and $\mathrm{Cl0} = \mathrm{Cl}_o^-(0) + \mathrm{Cl}_i^-(0)$. From (7), we have $\mathrm{Na}_o^+ > \mathrm{Na}_i^+$, $\mathrm{K}_o^+ < \mathrm{K}_i^+$ in agreement with experimental data, [19]. Moreover, a simple analysis shows that this steady state is stable, for any positive choice of the rate constants. From this model, we conclude that the NaK pumps are responsible for the establishment of a

difference in the concentrations of the ions Na^+ and K^+ between the inside and the outside of the cell. On the other hand, if a cell has NaK pumps and no channels, at steady state, sodium ions would fully concentrate outside the cell, and potassium ions inside the cell.

At this stage, some remarks are necessary. Firstly, the system of equation (6) is linear, provided the rate constants do not change with time or are function of the transmembrane potential drop. In the case of the Hodgkin-Huxley model, we have a similar situation but the transmembrane conductivities (k_i) can change with the transmembrane potential drop, [15]. Secondly, in cells and in equilibrium situations, it is reported a difference in the chlorine steady state concentration between the inside and the outside of (mammalian) cells ($Cl_o^- > Cl_i^-$), [19], which is not the case for the steady state (7), where a pure diffusive mechanisms for chlorine ions has been considered. Therefore, in real cellular systems, it may exist some active mechanism of chlorine pumping similar to the ATPase mechanism.

We assume further that ions can diffuse along the intercellular spaces and also in the cytoplasm of cells through gap junctions. Due to the low concentrations of ions in tissues, of the order of the millimole per litre, the repulsive or attractive electric field effects between charged ions can be neglected. Therefore, extending the model equations (6), the dynamic of ions in an agglomerate of cells or tissue is described by the linear system of reaction-diffusion equations

$$\begin{cases} \dfrac{\partial \mathrm{Na}_o^+}{\partial t} = -k_{10}(\mathrm{Na}_o^+ - \mathrm{Na}_i^+) + 3k_2 \mathrm{E}_i \mathrm{Na}_i^+ + D_{Na_o} \Delta \mathrm{Na}_o^+ \\ \dfrac{\partial \mathrm{Na}_i^+}{\partial t} = k_{10}(\mathrm{Na}_o^+ - \mathrm{Na}_i^+) - 3k_2 \mathrm{E}_i \mathrm{Na}_i^+ + D_{Na_i} \Delta \mathrm{Na}_i^+ \\ \dfrac{\partial \mathrm{K}_o^+}{\partial t} = -k_{11}(\mathrm{K}_o^+ - \mathrm{K}_i^+) - 2k_2 \mathrm{E}_i \mathrm{Na}_i^+ + D_{K_o} \Delta \mathrm{K}_o^+ \\ \dfrac{\partial \mathrm{K}_i^+}{\partial t} = k_{11}(\mathrm{K}_o^+ - \mathrm{K}_i^+) + 2k_2 \mathrm{E}_i \mathrm{Na}_i^+ + D_{K_i} \Delta \mathrm{K}_i^+ \\ \dfrac{\partial \mathrm{Cl}_o^-}{\partial t} = -k_{12}(\mathrm{Cl}_o^- - \mathrm{Cl}_i^-) + D_{Cl_o} \Delta \mathrm{Cl}_o^- \\ \dfrac{\partial \mathrm{Cl}_i^-}{\partial t} = k_{12}(\mathrm{Cl}_o^- - \mathrm{Cl}_i^-) + D_{Cl_i} \Delta \mathrm{Cl}_i^-, \end{cases} \tag{8}$$

where D_{Na_o}, D_{Na_i}, D_{K_o}, D_{K_i}, D_{Cl_o} and D_{Cl_i} are sodium, potassium and chlorine diffusion coefficients, and Δ is the Laplace operator in one, two or three space variables. The diffusion coefficients D_{Na_o}, D_{K_o} and D_{Cl_o} correspond to diffusion along intercellular spaces, and the diffusion coefficients D_{Na_i}, D_{K_i} and D_{Cl_i} correspond to ion diffusion along gap junctions. In principle, $D_{Na_i} < D_{Na_o}$, $D_{K_i} < D_{K_o}$ and $D_{Cl_i} < D_{Cl_o}$. Although not explicitly

represented, all concentration variables depend on time t, and space variables x, y and eventually z.

For the case of two space variables, we can think of a tissue of cells arranged in a two dimensional plane and with all cells connected by gap junctions to their closest neighbours. If $D_{Na_i} = D_{K_i} = D_{Cl_i} = 0$, there are no gap junctions connecting adjacent cells.

In equations (8), the first terms on the right hand side correspond to the effect of ion channels. The terms with the constant E_i describe the effect of the NaK pump.

In a tissue of cells in steady state, these equations show that concentrations of Na^+ and K^+ are different inside and outside cells, inducing a transmembrane potential drop across cellular membranes. This transmembrane potential drop is determined according to the Goldman law, [18],

$$V_{\mathrm{mem}} = (V_{\mathrm{in}} - V_{\mathrm{out}}) = \frac{kT}{e} \ln \frac{P_K \mathrm{K}_o^+ + P_{Na} \mathrm{Na}_o^+ + P_{Cl} \mathrm{Cl}_i^-}{P_K \mathrm{K}_i^+ + P_{Na} \mathrm{Na}_i^+ + P_{Cl} \mathrm{Cl}_o^-}, \qquad (9)$$

where P_{Na}, P_K and P_{Cl} are electric permeability constants, k is the Boltzmann constant, T is the absolute temperature and e is the electric charge. Moreover, the Nernst potentials of each ion species is defined by the relation $V_N = kT \ln([C]_o^+/[C]_i^+)/e$ or $V_N = kT \ln([C]_i^-/[C]_o^-)/e$, $[C]$ represents ion concentrations.

In figure 2a), we show the time evolution of ion concentrations inside and outside one single cell, as well as the transmembrane potential, calculated from (6) and (9). In figure 2b), we show the time variation of the equilibrium Nernst potential. The parameters have been chosen in order to obtain Nernst potential values of the same order of magnitude of the values observed in the HH squid biological model, for the temperature $T = 6.3$ °C. Theses figures show that the kinetic model just derived here describes well the osmotic and the electrophysiological equilibrium of a single cell.

The equations (8) with (9) define the basic model for the study of bioelectric phenomena in spatial distributions of cells. For this basic model, the potencial drop across cellular membranes does not affect the dynamics of ions.

As the system of equations (8) is linear, simple basic arguments show that, in extended spatial regions with zero flux of ions at the boundaries, the ion concentrations converge to the spatially homogeneous equilibrium values (7). Different choices of the parameter values does not change qualitatively the steady state concentration along arrays, layers or three-dimensional arrangements of cells.

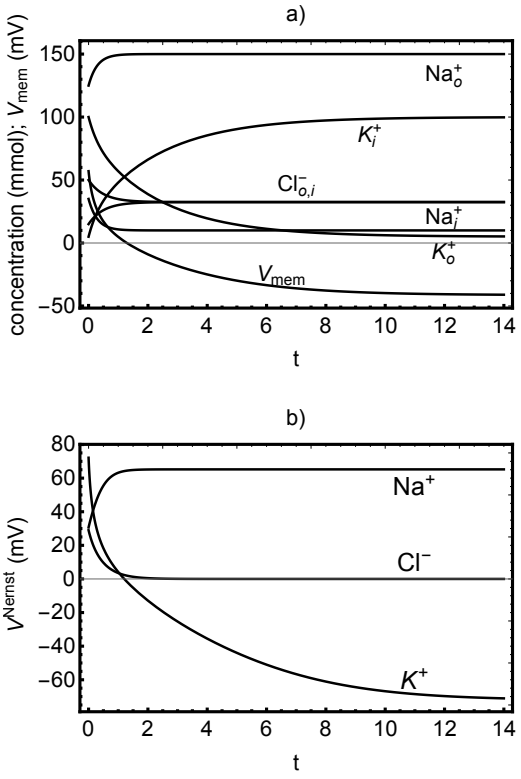

Figure 2: a) Time evolution of concentration of ions inside and outside a cell, and transmembrane potential ($V_{\rm mem}$), calculated from (6) and (9). The parameter values are: $k_2 = 1.0$, $k_{10} = 3/14$, $k_{11} = 4/19$, $k_{12} = 1.0$, $\mathrm{E}_i = 1.0$, $P_{Na} = 0.019$, $P_K = 1.0$ and $P_{Cl} = 0.38$, [**?**]. Initial conditions: $\mathrm{Na}_o^+(0) = 0.125$ mol, $\mathrm{K}_o^+(0) = 0.100$ mol, $\mathrm{Cl}_o^-(0) = 0.015$ mol, $\mathrm{Na}_i^+(0) = 0.035$ mol, $\mathrm{K}_i^+(0) = 0.005$ mol, $\mathrm{Cl}_i^-(0) = 0.05$ mol. Equilibrium ion concentrations are: $\mathrm{Na}_o^{+*} = 150$ mmol, $\mathrm{Na}_i^{+*} = 10$ mmol, $\mathrm{K}_o^{+*} = 5$ mmol, $\mathrm{K}_i^{+*} = 100$ mmol and $\mathrm{Cl}_o^{-*} = \mathrm{Cl}_i^{-*} = 32.5$ mmol. Equilibrium membrane potential $V_{\rm mem}^* = -41.4$ mV. b) Time variation the equilibrium Nernst potentials for each ion. For these parameter values, the Nernst equilibrium membrane potentials are reached in the limit $t \to \infty$, $V_{Na}^* = 65$ mV, $V_K^* = -72$ mV and $V_{Cl}^* = 0$ mV, where $\gamma = KT/e = 24.08$ mV.

3 The electrophysiology model

One of the important discoveries of the electrophysiology of the cell is the dependence of the aperture of ion channels on the potential drop between

the inside and the outside of the cells. This dependence has been successfully explored by Hodgkin and Huxley, [12], and subsequente developments, [15, 14, 13].

ion channels can open or close as a function of the potential difference between the inside and the outside of cells. To be more specific, if k represents any of the rate constant in any of the mechanisms in (5), as in Hodgkin and Huxley, [12], we assume the existence of a (phenomenological) gate variable $g(V)$, with $0 \leq g(V) \leq 1$, such that the opening and the closing mechanisms of channels can be described by new rate constants $\tilde{k}_{ion}$ that are related with the old ones through

$$\tilde{k}_{ion} = 2k_i g_{ion}(V_{\text{mem}}), \tag{10}$$

where, from (5), $i = 10, 11, 12$, V_{mem} is the potential difference across the two sides of the ion channel. As channels can be open or closed, [15], a simple hypothesis is to assume that the gating function has a sigmoidal shape described by a logistic function

$$g_{ion}(V_{\text{mem}}) = \frac{1}{1 + e^{-q_{ion}(V_{\text{mem}} - V^*_{ion})}}, \tag{11}$$

where V^*_{ion} is the equilibrium Nernst potential of the corresponding ion, and q_{ion} is a positive or negative constate measuring the sensitivity of the channel to changes in V_{mem} around V^*_{ion}. From the gating function choice in (11), it follows that $g(V^*_{ion}) = 1/2$ and $g'(V^*) = q_{ion}/4$. The gating functions $g_{ion}(V)$ are similar to the Hodgkin and Huxley $\alpha(V)$ and $\beta(V)$ functions, [12].

We now introduce into equations (8) the gating mechanism just described. For that, we take the system of equations (8) and the equation (9), and we make the generic substitution (10) for the corresponding channel. So, we

obtain

$$\begin{cases} \dfrac{d\mathrm{Na}_o^+}{dt} = -2k_{10}g_{Na}(V)(\mathrm{Na}_o^+ - \mathrm{Na}_i^+) + 3k_2\mathrm{E}_i\mathrm{Na}_i^+ + D_{Na_o}\Delta\mathrm{Na}_o^+ \\ \dfrac{d\mathrm{Na}_i^+}{dt} = 2k_{10}g_{Na}(V)(\mathrm{Na}_o^+ - \mathrm{Na}_i^+) - 3k_2\mathrm{E}_i\mathrm{Na}_i^+ + D_{Na_i}\Delta\mathrm{Na}_i^+ \\ \dfrac{d\mathrm{K}_o^+}{dt} = -2k_{11}g_K(V)(\mathrm{K}_o^+ - \mathrm{K}_i^+) - 2k_2\mathrm{E}_i\mathrm{Na}_i^+ + D_{K_o}\Delta\mathrm{K}_o^+ \\ \dfrac{d\mathrm{K}_i^+}{dt} = 2k_{11}g_K(V)(\mathrm{K}_o^+ - \mathrm{K}_i^+) + 2k_2\mathrm{E}_i\mathrm{Na}_i^+ + D_{K_i}\Delta\mathrm{K}_i^+ \\ \dfrac{d\mathrm{Cl}_o^-}{dt} = -2k_{12}g_{Cl}(V)(\mathrm{Cl}_o^- - \mathrm{Cl}_i^-) + D_{Cl_o}\Delta\mathrm{Cl}_o^- \\ \dfrac{d\mathrm{Cl}_i^-}{dt} = 2k_{12}(V)(\mathrm{Cl}_o^- - \mathrm{Cl}_i^-) + D_{Cl_i}\Delta\mathrm{Cl}_i^- \\ V = \dfrac{kT}{e}\ln\dfrac{P_K\mathrm{K}_o^+ + P_{Na}\mathrm{Na}_o^+ + P_{Cl}\mathrm{Cl}_i^-}{P_K\mathrm{K}_i^+ + P_{Na}\mathrm{Na}_i^+ + P_{Cl}\mathrm{Cl}_o^-} + Ri(x,t), \end{cases} \tag{12}$$

where V is the potential drop calculated across cell membranes, and $g_{ion}(V)$ is given by (11). In the last equation in (12), we added the extra term Ri describing external perturbations. R is a resistance and $i(x,t)$ is a current. This extra term might describe patch clamp experiments, where an electrode is introduce in a tissue at spatial coordinate x. The value of i can be positive or negative, depending if the current is injected extracellularly or intracellularly.

Due to the parameterisation in (10), equation (12) has the steady state solution (7), with V_{mem} given by (9).

If the diffusion coefficients of the different ions inside and outside cells are the same, then adding the pair of equations of each ion, we obtain diffusion equations for the sum of each ion's concentrations. In this case, this implies that the sum of concentration evolve in time along the spatial domain as a pure diffusive process, independently of the gating mechanism.

Equations (12) is the model for the study the time and spatial evolution of ion concentrations and transmembrane potentials in tissues, single cells and also neurones. Equations (12) have been derived from the first principles of chemical kinetics. From the electrophysiology point of view, their results should lead to effects similar to the ones found in the Hodgkin-Huxley model for the propagation of action potentials in axons.

4 The dynamics of ions

We consider the dynamics of the sodium, potassium and chlorine ions. To simplify, we consider the propagation along a one dimensional array of cells. Equations (12) also describe the propagation of an action potential along an axon. For that, we assume that the axon of a neurone can be seen as an array of cells connected through gap junctions, these gap junctions may correspond to the Ranvier nodes, figure 3. In this case, the diffusion coefficients of ions for the propagation in the cytoplasm or in the intercellular space should have the same order of magnitude. So, we have assumed that $D_{Na_o} = D_{Na_i}$, $D_{K_o} = D_{K_i}$ and $D_{Cl_o} = D_{Cl_i}$. As we have seen in the previous section, a non homogenous distribution of ions inside and outside the cell will evolve to the uniforme distribution.

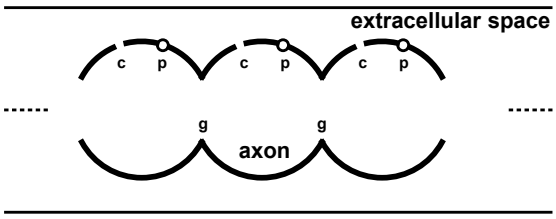

Figure 3: Model of a neurone as an aggregate of cells connected by gap junctions. The location of the gap junctions ("g") may be seen as the localisation of the Ranvier nodes of the axon. Ion channels and pumps are represented by "c" and "p", respectively.

To numerically analyse the solutions of the reaction-diffusion equations (12), with zero flux boundary conditions, we used a calibrated and validated algorithm for the numerical integration of reaction diffusion-equations, minimising numerical errors [9]. We have considered a one-dimensional spatial regions of lengths L, divided into N intervals of length $\Delta x = L/N$, with $N = 100$. To minimize the numerical integration error, we made the choices $dt = \Delta x^2/(6 \max\{D_i\})$, where $\max\{D_i\}$ is the maximum value of all the diffusion coefficients in the model equations (12) (see [9] for details). The Goldman law (9) has been calibrated for $T = 6.3$ °C, with $\gamma = kT/e = 24.08$ mV, and time is measured in milisecond.

To analyse numerically the solutions of the model equation (12) for sodium, potassium and chlorine, we have considered a one dimensional domain of length $L = 10$ cm, with zero flux boundary conditions, and, at time $t = 0$, a random initial distribution of the three ions were chosen, as shown in fig-

ure 4. After some time, the concentrations of ions evolves to the uniform distribution, as well as the membrane potential. For other choices of the diffusion coefficients, the spatial distribution of ions becomes uniform.

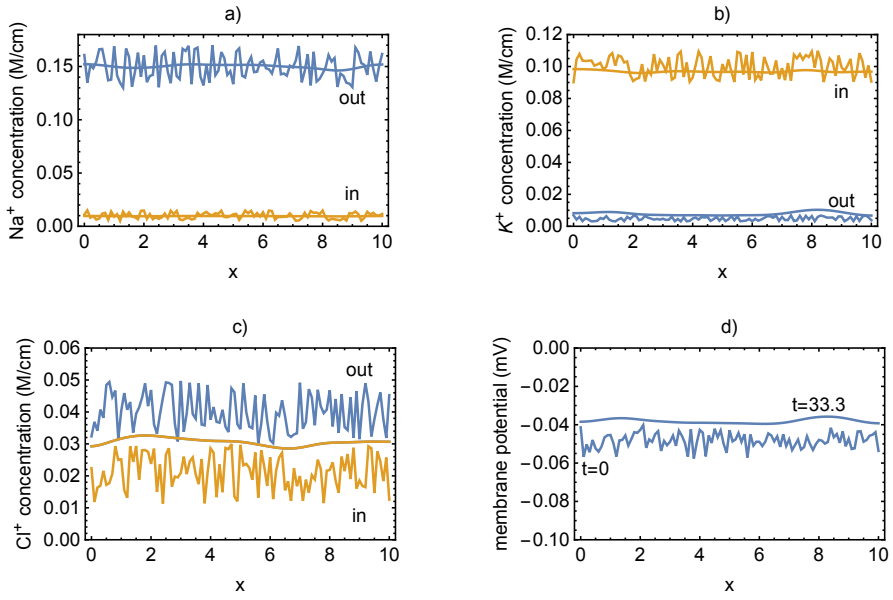

Figure 4: a)-c) Time evolution of the sodium, potassium and chlorine concentrations along a one dimensional domais of length $L = 10$ cm, calculated from (12) and (11), with zero flux boundary conditions. We considered a spatial discretisation divided into $N = 100$ intervals. We show the initial random concentration of ions and their spatial distribution at time $t = 33.3$ ms, inside (in) and outside (out) the cells in the one-dimensional array of cells. In c), the concentrations of chlorine inside and outside the cells have the same distribution. The diffusion coefficients are $D_{Na_o} = D_{K_o} = D_{Cl_o} = 0.01$ and $D_{Na_i} = D_{K_i} = D_{Cl_i} = 0.01$, and the other parameters are $\gamma = 24.08$ mV, $P_K = 1.0$, $P_{Na} = 0.019$, $P_{Cl} = 0.38$, $k_{10} = 3/14$, $k_{11} = 4/19$, $k_{12} = 1.0$, $k_2 = 1.0$, $E_i = 1.0$, $q_{Na} = q_K = q_{Cl} = 1$ and $R = 0$. d) Spatial distribution of the membrane potential along the spatial region, calculated from the last equation in (12), at the indicated instants of time.

To analyse the effect of a localised injected current in the one-dimensional array of cells, simulating the propagation of ion concentrations along the one-dimension axon of length L, we have considered an external source of current with parameters $Ri(x,t) = -100$ mV, for $x \in [L/2-2\Delta x, L/2+2\Delta x]$,

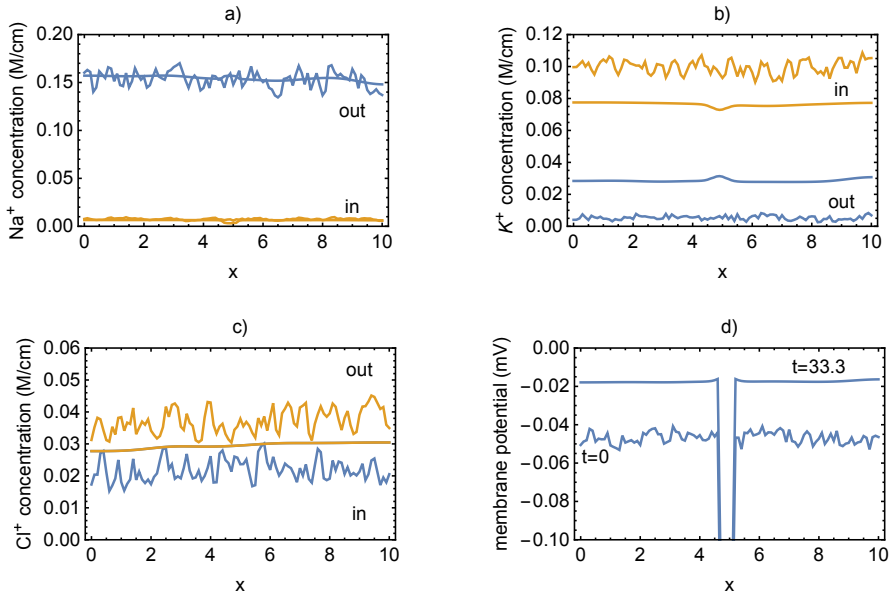

Figure 5: Time evolution of the sodium (a), potassium (b) and chlorine (c) concentrations along a one-dimensional domain of length $L = 10$ cm, calculated from (12) and (11), with zero flux boundary conditions and random initial conditions. We depict the concentrations of ions inside (in) and outside (out) the cells in the tissue. In d), we show the time evolution of the transmembrane potential. In this simulation, we have introduced an external current in the central region of the spatial domain: $Ri(x,t) = -100$ mV, for $x \in [L/2 - 2\Delta x, L/2 + 2\Delta x]$, where $\Delta x = 1$ mm. We show the initial random concentration of ions and their spatial distribution at time $t = 33.3$ ms. The parameters of these simulations are: $D_{Na_o} = D_{K_o} = D_{Cl_o} = 0.01$ and $D_{Na_i} = D_{K_i} = D_{Cl_i} = 0.01$, $\gamma = 24.08$ mV, $k_{Na} = 3/14$, $k_K = 4/19$, $k_2 = 1.0$, $E_i = 1.0$ and $q_{Na} = q_K = q_{Cl} = 10.0$.

superposed to a random initial distribution of ions. For a time $t \geq 30$ ms, the concentrations of sodium and potassium are numerically close to the steady state. The results are depicted in figure 5. The injected current affects the steady state distribution of ions along the one-dimensional domain only if the parameters q_{Na}, q_K and q_{Cl} are large enough. Comparing figure 5a) with figure 5b), the injected current changed the spatial distribution of potassium, but the spatial distribution of sodium is almost unchanged. This is expected, due to the difference of permeabilities between sodium and potassium. On

the other hand, comparing figure 4b) with figure 5b, the only difference observed is on the steady state distribution of potassium. Action potential signals are not observed as in the HH model, [6]. This implies that the model introduced in this paper and the HH model, based essentially on the same assumptions, both lead to different predictions.

5 Conclusions and final remarks

We have derived an electrophysiology kinetic model for the dynamics of ions in cells and tissues, based on the NaK ATPase energy storage mechanism, together with a voltage dependent gating mechanism. However, other pumping mechanisms are also possible and the model can be straightforwardly extended or adapted. One of the important properties of the model is the straightforward calibration of the kinetic parameters with equilibrium Nernst potentials and ion concentrations.

We have considered that cells in tissues may communicate with the surrounding cells through gap junctions, and communicate with the extracellular space through (open) channels and pumps made of transmembrane proteins. The first conclusion derived from the one cell model is that the non-zero equilibrium potential drop across cellular membranes is due to the simultaneous existence of pumps and channels specialised for specific ions. Ions without specialised transmembrane pumps do not contribute to the non-zero transmembrane potential. Moreover, if a cell has a NaK pumps and no channels, at steady state, sodium ions would fully concentrate outside the cell, and potassium ions would fully concentrate inside the cell.

The simple incorporation in the model of open channels for Cl^- ions, shows that, to be consistent with the existence of an equilibrium non-zero transmembrane Cl^- potential ([19]), a chlorine specialised pump should exist.

In the model derivation, we have considered that, for each ion family, there are two diffusion coefficients, one responsible for the extracellular ion dispersion and other for the intracellular dispersion. With this assumption an axons can be seen as the (evolutionary) result of the aggregation of cells through gap junctions. These gap junctions may correspond to the Ranvier nodes.

In a patch clump experiment, this model predicts that ion concentrations reach a steady state. The parameter calibration for sodium and potassium Nernst potentials show that current forcing of axons induce a change on the potassium resting potential, and the transmembrane potential drop along the axon also reaches a steady state.

Despite the similarities between the kinetic model of this paper and the

HH model, based on the basic assumptions used in their derivations, they show different predictions. The discrepancies may be due to different causes: i) to an improper gating mechanism, which can be easily modified in the model equations; ii) to the deficient calibration of diffusion coefficients or gate parameters q; iii) to a new biochemical mechanism responsible for action potential signalling. In fact, several authors have addressed the need of a more detailed derivation to the HH electric analog model, [5] and [3], and a precise calibration of the action potential effects, [16, 20, 7].

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