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On biomembrane electrodiffusive models

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Abstract. Two models are used in the literature, to study the electric behaviour of cellular membranes such as in protein aggregates, excitable media or ionic currents for examples. The first one is the Electroneutral Model based on Nernst-Planck and Poisson equations with a specific condition of microscopic electroneutrality. The second one is the Cable Model valid for long wavelengths based on an analogy between an electric cable and a cell. Convincing experiments have justified the Cable equation. First, we show that these two models are in contradiction. More precisely the assumption of electroneutrality is not considered in the Cable Model. The main difference between the two models is highlighted by the analysis of the well known voltage instability due to a negative differential conductance. Then, we derive a new semi-microscopic model (the Biomembrane Electrodiffusive Model, called BEM) valid for phenomena at any wavelength. The BEM is based on Nernst-Planck and Poisson equations but, doesn't imply microscopic electroneutrality. It reveals the capacitive behaviour of the membrane. In the limit of long wavelengths, one recovers the behaviour described within the Cable framework, as shown precisely in the study of the negative differential conductance analysis. Finally, we demonstrate the intimate link between the last models: the Cable Model appears as the limit of the BEM for large wavelengths with some prerequisites which are discussed. The effects of geometry and asymmetrical media are introduced.

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1 Introduction

Spatiotemporal pattern formation is ubiquitous in systems driven away from thermal equilibrium [1]. Fascinating patterns occur in biological systems [1,2], such as for example, phyllotaxis [3], banding phenomenon in Characean algae [4], calcium waves [5], spirals in cardiac tissue [6–9] and in discoideum aggregation [10], patterns of protein aggregates (see [11] for experiments and [12–19] for theoretical work) ... They seem to present the same universal character as pattern formation in physics. Examples of ionic currents in Chara corallina and Fucus are provided in the Section 3 because, one part of this work deals with a theoretical mechanism on such a phenomenon.

In this article, we focus on the electric behaviour of cellular membranes. Long ago, the theoretical framework of the studies on electric pattern formation was usually based on a phenomenological equation: the Cable equation [20–22]. It is derived by analogy with the electric behaviour of an electric cable. It provides the temporal evolution of membrane potential along a cylindrical cell (or a flat cell). Its principle is recalled in Section 3.1. This equation has been experimentally checked by several authors [23]. Recent experiments are particularly convincing [24,25]. However, even if this equation provides a powerful means to understand excitable media and protein aggregation, some problems cannot be solved. A first example concerns the electric properties of dendritic spines [26]. The Cable equation ignores diffusive flux. As the characteristic length of spines is small compared to usual cellular size, the diffusion flux of each species can become larger than the ionic flux due to electric fields. A second example is the shape fluctuations of biomembranes coupled to electric activities [27]. Their determination implies the knowledge of the normal stress to the membrane and for instance, the normal electric field gradient. This is not possible with the Cable equation, because it only deals with propagation parallel to the membrane. A fourth example is that the Cable Model is only valid when the characteristic length λ of phenomena is larger than the typical cellular size R: $\lambda \gg R$. This condition is never fulfilled in the study of an isolated flat biomembrane. For such an isolated membrane, with the Cable Model, the theoretical determinations of voltage fluctuations are restricted to temporal correlations but, not spatial [28]. Another important example is the growth physiology of the egg of Fucus, a brown algae, which develops a stationary dipolar ionic circulation through the cell after fertilization [29].

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Wavelength and cellular radius (Fucus is a sphere) are of same order, about 100 μm. Moreover, in this case, the spherical geometry is difficult to take into account. Let us emphasize that even with the above restrictions, the Cable Model is very powerful in many biological interpretations.

However, it is useful to develop a more microscopic model based on the Nernst-Planck and Poisson equations (called the electrodiffusive model in the following). All the difficulty of this approach is the determination of the boundary conditions physically relevant. The main criterion is to be able to derive the Cable equation and to recover the Cable results on well known examples.

To my knowledge, the only electrodiffusive model used in literature, is the Electroneutral Model. It has been notably used to study the membrane protein aggregation [12,13] and ionic currents occurence [30]. Based on a comparison between the Debye time and the characteristic time, the Electroneutral Model assumes that the microscopic electroneutrality is always strictly reached: $\delta\rho_i = \delta\rho_e = 0$ where $\delta\rho_i$ and $\delta\rho_e$ are respectively the variations of charge in intracellular and extracellular media. We recall this model in Section 4.

In the paper, we show that the Electroneutral Model is in contradiction with the Cable Model. On one hand, this is revealed in the study the voltage instability induced by a negative differential conductance (the principle, known long ago, is recalled in Sect. 3.2 [31]). The analysis with the Cable formalism is provided in Section 3.2. On the other hand, in Section 5, we recall the recent results in the literature using the Electroneutral Model. We point out the differences between the two models (final state and characteristic time). We conclude that the Electroneutral Model is not relevant.

In Section 6.1, we propose a new model (the Biomembrane Electrodiffusive Model called BEM) where the stepping stone is to consider new boundary conditions which do not imply microscopic electroneutrality. The evaluation of lipid bilayer and protein (channels and pumps) permeabilities implies small spatial variations of electric field inside the membrane. Then, we deduce that the membrane electric potential is linked to the electric charges in the Debye layer. This confirms the capacitive nature of the membrane potential. We use this model to study the voltage instability due to a negative differential conductance in Section 6.2. The analogy between the results of the BEM and the Cable Model is developed in Section 6.3. We also emphasize geometrical aspects in Section 6.4 and the role of asymmetrical media in Section 6.5.

To our mind, the more convincing criterion of validity of the BEM introduced in this article, is the derivation of the Cable Model given in Section 7.1. The Nernst-Planck and Poisson equations are integrated and it is shown that boundary conditions of the BEM play a crucial role. The capacitive aspect then emerges naturally. In Section 7.2, we briefly discuss possible applications of the BEM and conclude in Section 8.

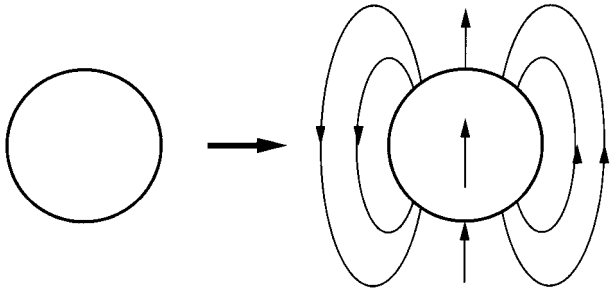

Fig. 1. Symmetry breaking in Fucus, a brown algae. Thirty minutes after fertilization, a dipolar ionic circulation crosses the cell.

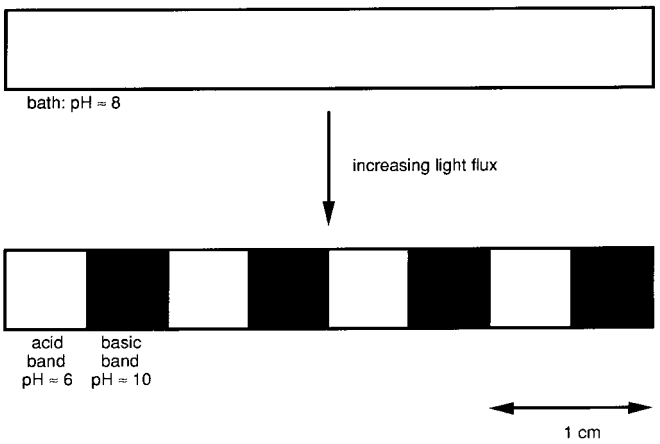

Fig. 2. Symmetry breaking in Chara corallina, a green algae. Above a critical light flux, pH bands develop close to the membrane. The characteristic size is about 1 cm and gradients of pH are usually close to 3 units. The characteristic time is about 30 minutes. The bath pH is close to 8.

2 Ionic currents

A lot of cells develop stationary ionic circulations called ionic currents in biology (potassium, calcium, protons...) [4,32–35]. The characteristic wavelength varies from 10 μm to 1 cm and the time from a few minutes to a few hours. It depends on the type of the cell. Two cells appear as prototypes for the understanding of this phenomenon.

A first example is the generation of ionic currents (notably calcium and potassium) in the spherical egg of Fucus [29], a brown algae. Initially, it has spherical symmetry: the membrane potential is uniform. Thirty minutes after fertilization, a dipolar loop of transcellular currents develops (Fig. 1). It polarizes the cell. Five to ten hours later, the current saturates at about 1 μA cm^{-2} and a protuberance forms at the accurate site of influx. These events could be the first steps of morphogenesis in this type of cells. Dipolar circulation in Fucus breaks the spherical symmetry.

The second typical example is the banding phenomenon in the internodal cell of Chara corallina, a green algae [4]. This cell is a cylinder of radius about 0.5 mm and length about 6 cm. In darkness, the extracellular pH is homogeneous. Above a critical light influx, the pH close to

the membrane becomes periodically modulated (Fig. 2). The usual gradients are about 3 to 4 units of pH over a length about 1 cm! The characteristic time is 30 min. In an acid band there is an efflux of protons, while in a basic band protons enter the cell (probably with another ion). The intensity of ionic currents varies from 10 μA cm^{-2} to 80 μA cm^{-2}. Banding phenomenon breaks the longitudinal symmetry.

Several mechanisms have been proposed in order to explain such symmetry breaking. The first one is due to membrane protein aggregation, either by a coupling between protein electric charges and ionic currents produced by these same proteins (first proposed by Larter and Ortoleva [12,13] using the Electroneutral Model and more recently studied by Fromherz and Zimmermann [14–16] using the Cable Model) or by a coupling between electroosmotic flow and ionic currents produced by membrane proteins [17,18]. The second one proposed by Toko *et al.* [36], is due to a peculiar variation of the current with the concentration of the transfered solute. It has been applied to particular biological problems by others [37,38]. The third one is due to a negative differential conductance. This case of instability is well known in biology [31,39] (for instance, in excitable media [6,7,20]) and also in physical systems [40–42]. However, recent works [30] have also shown that a cell with a negative differential conductance induces a loop of ionic currents through the cell on the time characteristic of diffusion.

3 The cable model

In this section, we summarize briefly the well known theory of Cable. It is based on an analogy between cellular electric behaviour and an electric cable [20–22]. The Cable equation is derived from Kirchhoff's law.

3.1 Cable equation

The basic structure of a biomembrane is a lipid bilayer which is an impermeable barrier to ions. This barrier allows strict control of ionic concentrations in the intracellular medium by specific membrane proteins. The first class of these transport systems is the pump which transfers continuously one or two specific ions from one medium to another, consuming chemical energy by hydrolysis of Adenosine TriPhosphate. It generates an electrochemical gradient across the membrane in the opposite direction. This is an energetic reserve which is used to transfer ions in the other direction by the second class of transport systems: channels, symports and antiports. In this case, I is proportional to the difference of electrochemical potential between media: $\mu = ze\phi + k_B T \ln(C)$ in dilute limit where z is the charge number, ϕ the electric potential and C the solute concentration. Usually, the current I has the following form:

$$I = G(V - E) \tag{1}$$

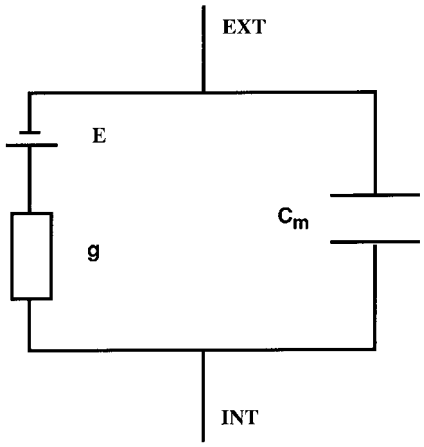

Fig. 3. Equivalent electric circuit of membrane protein activity. Assembly of the bilayer and a protein constitutes a parallel circuit with characteristic parameters: E the electromotive force, G the conductance of the protein and C_m the membrane capacitance.

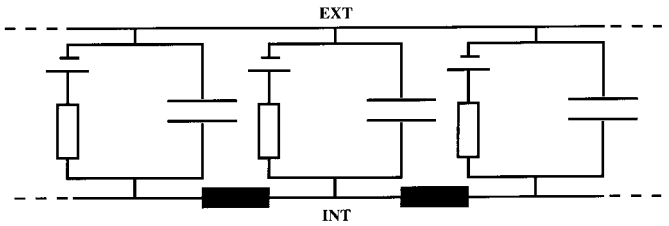

Fig. 4. Equivalent electric circuit of a cylindrical biomembrane. Each previous equivalent circuit of proteins (see Fig. 3) is linked to another by bulk electrical resistivities (in dark in figure). Intracellular resistivity ρ_i is dominant in Cable equation.

where G is the conductance and

$$E = k_B T \ln(C_e/C_i)/ze \tag{2}$$

the electromotive force, with C_e and C_i the external and internal concentrations. Relative variations of concentrations due to I are usually very small. Then, in the Cable formalism, E is assumed to be a constant. Thus, I has the same form as for a battery of conductance G and electromotive force E. However, as the lipid bilayer is a good insulator, current through the protein also induces an electric potential by capacitive effect. It has been proposed that local electric activity of a protein is equivalent to an electric circuit (Fig. 3). Ionic current I passes through internal and external media. The electric cable description is derived by connecting local equivalent circuits by internal electric resistivities ρ_i (Fig. 4). Propagation is unidimensional. The cell is a rigid cylinder of radius R. A simple calculation provides the Kelvin equation or Cable equation [20–22]:

$$C_m \frac{\partial V}{\partial t} = -I + \frac{R}{2\rho_i} \frac{\partial^2 V}{\partial x^2} \tag{3}$$

where C_m is the membrane capacity per unit area and I the current through a unit of cellular surface. Numerous

experiments have checked this equation. Physiologists and physicists have also long ago, developed a two-dimensional model of propagation to deal with pattern formation in excitable media [6,7]. They also introduce anisotropic propagation by replacing the term $\frac{1}{\rho_i}\frac{\partial^2 V}{\partial x^2}$ by $\frac{1}{\rho_{ix}}\frac{\partial^2 V}{\partial x^2}+\frac{1}{\rho_{iy}}\frac{\partial^2 V}{\partial y^2}$ where ρ_{ix} and ρ_{iy} are respectively the x and y resistivities [6]. Other applications of the Cable equation have been performed long ago to parallel fiber interactions, interactions at branching points for excitable cells and more recently, to interactions with a substrate [43]. This list is not exhaustive.

The derivation of equation (3) assumes several prerequisite conditions as Scott notes in his review [20]:

i) the variations of concentrations are negligible during all the phenomenon (in the non linear state as well). It means that the electromotive force is constant, so that diffusion flux is also neglected;
ii) the ionic flux produced by membrane proteins, doesn't depend on concentration. i) and ii) are distinguished because condition ii) doesn't involve i);
iii) the characteristic length of the studied phenomenon must be larger than the cellular radius. Then, electric potential is roughly constant in the section and external variations are expected to be negligible.

These three conditions will be discussed later in Section 7.2. They provide the domain of validity of the Cable Model. Equation (3) can be extended to a flat bidimensional cell if the three conditions are always satisfied. However, let us note the difference between a flat bidimensional cell (two facing biomembranes) and an isolated flat biomembrane.

3.2 Ionic currents with a negative differential conductance

We consider a cylindrical cell and study the linear electric stability of the membrane potential with the formalism of the Cable equation. The pumps and channels are assumed to be fixed. We study the well known instability due to a negative differential conductance.

The stability of the system is studied for normal mode fluctuations $\delta u_i \approx A_i \exp(\omega t + ikx)$ where u_i stands for membrane potential V and electric current I. ω is the growth rate and k the wavenumber. The fluctuation of the membrane potential δV induces an ionic current δI. δI and δV are related by the membrane differential conductance G_d:

$$\delta I = G_d \delta V = \left(\frac{\partial I}{\partial V}\right)_{V=V_{rest}} \delta V \tag{4}$$

where V_{rest} is the membrane potential in the resting state. Let us note that G_d is not equal to the conductance G of the relation (1):

$$G_d = (V-E)\left(\frac{\partial G}{\partial V}\right) + G. \tag{5}$$

Linearization of equation (3) provides the following dispersion relation $\omega = \omega(k)$:

$$\omega = -\frac{R}{2\rho_i C_m}\left(k^2 + \frac{2\rho_i}{R} G_d\right). \tag{6}$$

The necessary condition of instability is a negative differential conductance: $G_d < 0$. Usually, the conductance G_d is a positive quantity. Then, membrane potential is stable. However, negative differential conductance exists in biology [31,39,44–46] and physics [40–42]. Usually, this negative differential conductance is transient for example, in animal excitable media (due to sodium and potassium channels). But, experiments have also brought to the fore, permanent negative differential conductance as Agin notes [39]: see references [44,45]. Beilby has shown clearly that the conductance of potassium channels in Chara corallina is negative in a large range of membrane potential [46] from -200 mV to -100 mV in the potassium state at high pH. One biological characteristic of these channels is that if the membrane depolarizes, the number of open channels increases [47]. So, if $P(V)$ denotes the probability of opening, $(\partial P/\partial V)$ is positive. $1-P(V)$ is the probability of locking. Now, we can explain the origin of this sign. Consider a density N of channels which transfer cations. $i(V)$ is the current produced by such an insulated open channel. For usual membrane potentials (about -100 mV), $i(V)$ through a channel is negative. The macroscopic density I of ionic current due to the collection of these channels is:

$$I = NP(V)i(V). \tag{7}$$

The characteristic of $i(V)$ is usually as equation (1): $i(V) = g(V-E)$. It means that the conductance g of an insulated open channel is positive and constant. The differential conductance G_d satisfies:

$$G_d = (\partial I/\partial V) = N((\partial P/\partial V)i + gP(V)). \tag{8}$$

Thus, the differential conductance G_d can become negative if the probability of opening varies strongly with membrane potential (stronger than $i(V)$ at least) [47]. Now, as an example, we recall a model of probability where the kinetic constants depend on the membrane potential (Boltzmann distribution), which is used to describe such variations [47]:

$$P(V) = 1/(1+\exp(z_c e(V_{open}-V)/k_B T) \tag{9}$$

where z_c is a positive charge number characteristic of the channel, and V_{open} is the characteristic membrane potential of opening. For $V \gg V_{open}$, the channel is open. In Figure 5, the curve $I = NP(V)g(V-E)$ *vs.* membrane potential V reveals a negative differential conductance over a large range of membrane potential.

Now, in the following, we assume that the differential conductance is negative. The principle of instability is that a depolarisation $\delta V > 0$ induces an influx of current $\delta I = G_d \delta V < 0$ which in turn, depolarizes the membrane by capacitive effects.

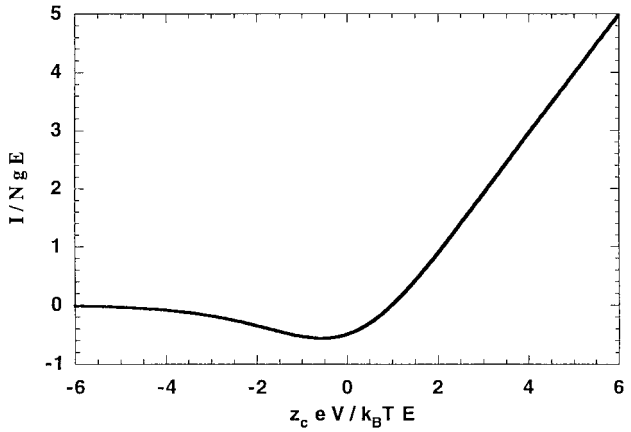

Fig. 5. Typical curve of current I through voltage-gated channels according with the membrane potential V. I is equal to $NP(V)g(V-E)$ where N is the density, $P(V)$ the probability of opening, g the conductance of an insulated channel and E the electromotive force. In a large scale of membrane potential, I has got a negative differential conductance $G_d = (\partial I/\partial V) < 0$. For simplicity, we choose $V_{open} = 0, z_c eE/k_B T = 1$ (see text for details).

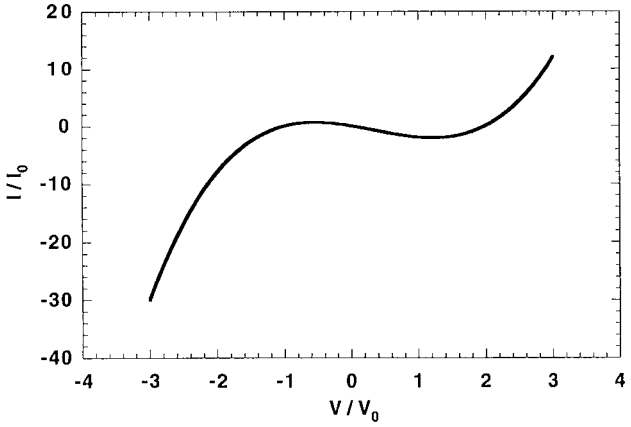

Fig. 6. Typical curve of membrane ionic current I according with the membrane potential V which takes into account different effects (voltage-gated channels, leaks and pumps). Membrane can have three stationary points ($I = 0$): two stable at $V/V_0 = -1$ and $V/V_0 = 2$, and one unstable $V/V_0 = 0$ (see text for details).

Membrane potential is linearly unstable for

$$k < \left(-\frac{2\rho_i}{R} G_d\right)^{1/2}. \tag{10}$$

The dispersion relation is a parabola. The characteristic time of the instability is $T_C = 1/\omega(k=0)$:

$$T_C \approx \lambda_2 \rho_i C_m / R \tag{11}$$

where λ is the characteristic length:

$$\lambda^2 = -\pi R/\rho_i G_d. \tag{12}$$

Another important point is that the most unstable mode (with the larger growth rate) is the homogeneous one *i.e.* $k = 0$. To know the temporal evolution of such an instability, one needs to introduce a relevant nonlinear ionic current I to saturate the process. It is reasonable for several reasons, to think that the cell is dominated by a passive flux (so, stable $G_d > 0$) when the membrane potential is either too depolarized or too hyperpolarized. To my knowledge, it is always the case experimentally if the electrochemical gradient is too high. For example, the flux through proteins due to kinetic conformational changes saturates while the passive flux through the channels and lipid bilayer increases with the electrochemical gradient. Then, an unstable point ($G_d < 0$) is always the neighbour of two stable points (with $G_d > 0$). To show it more mathematically, it is sufficient to add a passive current (proportional to V) due to the leaks and other passive proteins and a positive constant active current due to the pump, to the current $I = NP(V)g(V-E)$ with equation (9) for the probability. In this case, the curve I *vs.* V can have three stationary membrane potentials ($I = 0$) if parameters are conveniently chosen. The simplest current I to model the previous behaviour is a cubic function I of potential V, appearing in Figure 6. An integration or a simple numerical study show that the potential tends always to one of the two stable states. This result is well known in nonlinear studies [48]. For example, a numerical simulation is performed in Figure 7. $I(V)$ is equal to:

$$I(V) = I_0 \frac{V}{V_0}\left(\frac{V}{V_0}+1\right)\left(\frac{V}{V_0}-2\right) \tag{13}$$

where I_0 is a positive current by unit area and V_0 a positive characteristic voltage. $V = 0$, $V = 2V_0$ and $V = -V_0$ are the three stationary states. The former $V = 0$ is unstable and the two following $V = -1$ and $V = 2$ are stable. We study the stationary state $V = 0$ and use the normalized variables $Y = V/V_0$ for the ordinate, $X = x(2\rho_i I_0/RV_0)^{1/2}$ for the abscissa and the time $T = tI_0/V_0 C_m$. Y notes the amplitude of the phenomenon and X the position along the cellular axis. The differential conductance G_d at $V = 0$ is negative and is equal to $G_d = -2I_0/V_0$. A white noise of small amplitude (about 5×10^{-5} compared with the final voltage Y of about 2) is applied around $Y = V/V_0 = 0$ (Fig. 7a). The voltage Y is followed in Figures 7b-d. The voltage changes from an uniform voltage $Y = 0$ to another uniform voltage $Y = 2$.

Finally, the characteristic time is electric and the final state is uniform (not periodically modulated), there are no stationary ionic currents in the final state. However, this result is in contradiction with recent theoretical and numerical works using the Electroneutral Model [30].

4 First electrodiffusive model: the electroneutral model

In this section, we present the Electroneutral Model used in the literature [12,13,30]. It is an electrodiffusive model based of course, on the Nernst-Planck and Poisson equation in the bulk. The important point is the boundary

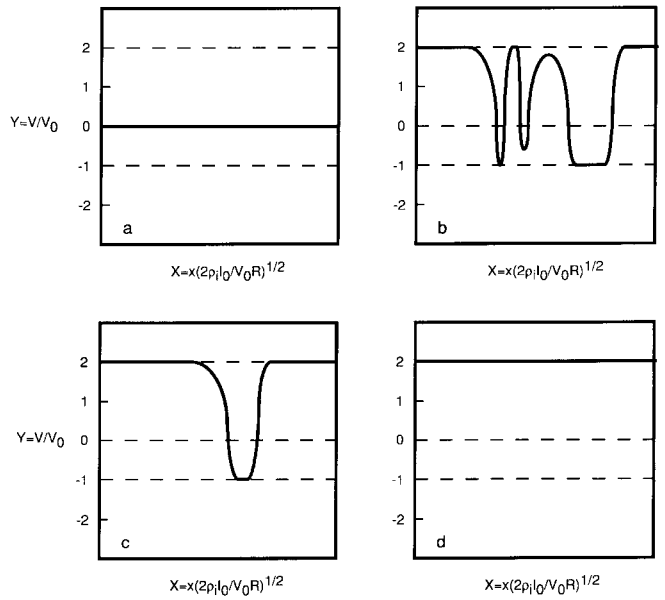

Fig. 7. Numerical simulation of the instability around the voltage $V/V_0 = 0$. The instability comes from a negative differential conductance (Fig. 6). In Figure 7a, a white noise of small amplitude (about 5×10^{-5} compared to 2 the value in the final state) is applied around the stationary value $V/V_0 = 0$. The ordinate (Y-axis) notes the membrane voltage while the abscissa (X-axis) notes the position along the cellular axis. In b, c, d, the temporal evolution of membrane potential is followed. Finally, the membrane potential transits from an uniform voltage $V/V_0 = 0$ (Fig. 7a) to another uniform voltage $V/V_0 = 2$ (Fig. 7d). There are no ionic currents in the final state (see text for details).

conditions. It is notably assumed that microscopic electroneutrality is strictly satisfied.

In intracellular and extracellular media, ionic concentrations C_j of each ion j and electric potential ϕ satisfy Poisson and Nernst-Planck equations:

$$\Delta\phi = -\frac{eN_a}{\varepsilon}\sum z_j C_j \tag{14}$$

$$\frac{\partial C_j}{\partial t} = D_j \Delta C_j + z_j \frac{eD_j}{k_B T}\nabla\cdot(C_j\nabla\phi) \tag{15}$$

where z_j is the charge number and D_j the coefficient of diffusion. In the most general case, internal and external coefficients of diffusion should be distinguished.

The biomembrane is made of a lipid bilayer with embedded proteins. The permeability of potassium through proteins is of order of 10^{-8} m s^{-1} while the one through the lipid bilayer is 10^{-14} m s^{-1} [49]. Then, the internal and external electrodiffusive flux of each species are continuous through the membrane. They are equal to the flux $\mathbf{J}_j$ produced by the specific proteins as pumps, symports, antiports or channels:

$$\mathbf{J}_j = -D_j(\nabla C_j + z_j C_j \nabla(e\phi/k_B T))\mathbf{n} \tag{16}$$

where $\mathbf{n}$ is the normal outward vector. $\mathbf{J}_j$ is a characteristic of the proteins which transfer the species j. It depends on membrane potential $\phi_i - \phi_e$, internal C_{ji} and external C_{je} concentrations and sometimes on divalent cation concentrations, pH, light intensity, ATP [50]... subscripts i and e denote respectively internal and external parameters.

Now, we assume that the media contain N different ions. Let us consider the $2N + 2$ fluctuations δC_{ji}, δC_{je}, $\delta\phi_i$ and $\delta\phi_e$ of concentrations and electric potential which satisfy linear differential equations of the second order. $4N + 4$ boundary conditions are necessary. Fluctuations are equal to zero far from the membrane in the external medium and don't diverge in the intracellular medium (but, are not zero far from the membrane), which provides $2N + 2$ conditions. The continuity of extracellular and intracellular ionic flux (Eq. (16)) gives $2N$ other boundary conditions.

The two lacking conditions are based on the evaluation of the Debye time T_{Deb}. In ionic solutions, charges are screened on the Debye length $\lambda_D = \chi^{-1}$:

$$\lambda_D = \chi^{-1} = \left(\frac{\varepsilon k_B T}{e^2 N_a \sum z_j^2 C_{j0}}\right) \tag{17}$$

where C_{j0} are the concentrations far from the membrane. In physiological experiments, the Debye length is close to 1 nm.

Then, the characteristic time T_{Deb} to reach electroneutrality is about $T_{Deb} \approx \lambda_D^2/D \approx 1$ ns where $D \approx 10^{-5}$ cm^2/s is a typical value of coefficient of ionic diffusion. T_{Deb} is much smaller than all other characteristic times in the problem. Thus, in the Electroneutral Model, variations of ionic charges are neglected. Then, the two last conditions to close the system are:

$$\delta\rho_i = eN_a \sum_j z_j \delta C_{ji} = 0 \tag{18}$$

$$\delta\rho_e = eN_a \sum_j z_j \delta C_{je} = 0 \tag{19}$$

where $\delta\rho_i$ and $\delta\rho_e$ are respectively the intracellular and extracellular fluctuations of charge densities. I emphasize that the works which use this model, apply it to electric phenomena *a priori*, sufficiently slow, such as protein aggregation [12,13] and ionic currents [30] (it is not applied to pattern formation in excitable media [51]).

Applying (18, 19) to the equality between internal and external currents (Eq. (16)) provides the following relation:

$$\mathbf{n}\cdot\nabla\phi_i = \mathbf{n}\cdot\nabla\phi_e. \tag{20}$$

The conditions (18, 19) simplify greatly the linear problem because, the fluctuations of concentrations δC_j and potential $\delta\phi$ satisfy the following equations:

$$\frac{\partial \delta C_j}{\partial t} = D_j \Delta\delta C_j \tag{21}$$

$$\Delta\delta\phi = 0. \tag{22}$$

In this electrodiffusive formalism, it is assumed that the microscopic electroneutrality is satisfied anywhere (even

in the Debye layer). For this reason, we call it the Electroneutral Model. In the following section, we compare it with the Cable Model.

5 First discussion: comparison between the electroneutral model and the Cable Model results

In literature, it has been proposed analytically and numerically using the Electroneutral Model, that a loop of ionic currents could result from a negative differential conductance [30]. We compare the results using the Electroneutral Model and the Cable Model (Sect. 3.2). In Section 5.1, we focus on the physical sense and in Section 5.2, on a more mathematically detailed point of view.

5.1 Discussion of the physical results

In the literature, it has been proposed analytically and numerically [30] that ionic currents could result from a negative differential conductance. The results using the Electroneutral Model, are the following:

i) membrane potential is linearly unstable,
ii) the final state is a loop of stationary ionic currents through the cell,
iii) the characteristic time T of the instability is a diffusion time: $T_D \approx \lambda^2/D$ where λ is the wavelength of the phenomenon and D the coefficient of ionic diffusion.

These predictions are in contradiction with the results deduced from the Cable Model on two main points (see Sect. 3.2). First, the physical nature of characteristic times is different. In the Electroneutral Model, T is a diffusion time $T_D \approx \lambda^2/D$. In the Cable Model, T is the electric time T_C:

$$T_C \approx \lambda^2 \rho_i C_m/R \approx \lambda^2 C_m/\varepsilon D \chi_i^2 R. \tag{23}$$

We have used the identity: $\rho_i = 1/\varepsilon D \chi_i^2$. For that matter, the ratio of these two times is independent from wavelength and can be evaluated for relevant parameters:

$$T_C/T_D \approx C_m/\varepsilon \chi_i^2 R \approx 10^{-6} \tag{24}$$

where $C_m \approx 10^{-2}$ F m^{-2}, $1/\chi_i \approx 1$ nm and $R \approx 10$ μm. This numerical evaluation highlights the difference between the Electroneutral Model and the Cable Model. In fact, a phenomenon with a small characteristic time compared to others, can only be neglected if it's not intimately linked to the characteristic time of the instability.

The second difference concerns the final state. Using the Electroneutral Model, ionic currents are generated and pass through the cell. In the Cable Model, there are no ionic currents. The system is unstable. It transits from an uniform membrane potential to another uniform one, both of them without ionic currents as indicated in the simulation of Section 3.2.

Therefore, the results using the Electroneutral Model are not in agreement with those using the Cable Model. We claim that the origin of the discrepancy comes from the assumption of microscopic electroneutrality. Long ago, Agin noted the impossibility of microscopic electroneutrality in active biomembranes [52] (but, he considered rapid phenomena such as pulse). One means to understand simply this effect is to consider a spherical cell. Let us assume that an external message (a transfer dark-light for a vegetable cell for example) induces an increased pump activity. These expulse uniformly and specifically, cations (protons for a vegetable cell) from the intracellular medium to the extracellular one which is not initially compensated. Thus, this process generates a deficit of cations in the internal medium and an excess in the external medium. After that, the net transfer of charges stops when the passive flux due to the channels and the lipid bilayer compensates the pump flux. The final result is a difference of charges between internal and external media which is the mark of membrane electrical activity. This is known in electrophysiology.

5.2 Discussion of mathematical results

We discuss more accurately the results of the literature using the Electroneutral Model and for instance, the existence of mathematical and physically relevant solutions.

For simplicity, we choose to deal with a flat isolated membrane (it means $kR \gg 1$). The axis x and z are respectively, parallel and orthogonal to the membrane. We want to determine the dispersion relation on the basis of the Electroneutral Model. We consider two concentrations C_1, C_2 and the electric potential ϕ. The fluctuations satisfy equations (21, 22) and are:

$$\begin{aligned} \delta C_{1,2} &= a_{1,2} e^{\pm sz} e^{\omega t + ikx} \\ \delta\phi &= b e^{\pm kz} e^{\omega t + ikx} \end{aligned} \tag{25}$$

where $s^2 = k^2 + \omega/D$, b and $a_{1,2}$ are constants. z is the normal coordinate.

We choose s such that the real part $\mathrm{Re}(s)$ of s is positive: $\mathrm{Re}(s) > 0$. The sign $\pm$ is $+$ for intracellular medium and $-$ for extracellular medium.

Using boundary conditions, extracellular constants are linked to intracellular ones by: $b_e = -b_i$, $a_{1e} = -a_{1i}$ and $a_{2e} = -a_{2i}$. The condition of microscopic electroneutrality provides: $z_1 a_1 + z_2 a_2 = 0$.

Then, we use the boundary conditions on J_1 and $z_1 J_1 + z_2 J_2$:

$$-J_1/D = \left(\frac{\partial C_1}{\partial z}\right) + \frac{e z_1}{k_B T} C_{10} \left(\frac{\partial \phi}{\partial z}\right) \tag{26}$$

$$-(z_1 J_1 + z_2 J_2)/D = \frac{e}{k_B T}(z_1^2 C_{10} + z_2^2 C_{20}) \left(\frac{\partial \phi}{\partial z}\right). \tag{27}$$

We have the following determinant:

$$\left[\frac{eDC_0k}{k_BT}+2\left(z_1\left(\frac{\partial J_1}{\partial\phi}\right)+z_2\left(\frac{\partial J_2}{\partial\phi}\right)\right)\right]b_i + z_1\left[\left(\frac{\partial J_1}{\partial C_{1i}}\right)-\left(\frac{\partial J_2}{\partial C_{2i}}\right)\right]a_{1i}=0 \quad (28)$$

$$\left[2\left(\frac{\partial J_1}{\partial\phi}\right)+\frac{e}{k_BT}z_1C_{10}Dk\right]b_i + \left[\left(\frac{\partial J_1}{\partial C_{1i}}\right)+sD\right]a_{1i}=0 \quad (29)$$

where $C_0=z_1^2C_{10}+z_2^2C_{20}$. We have introduced the variations of J_1 and J_2 respectively, with the intracellular ionic concentrations C_1 and C_2 [53].

As in [30], J_1 only depends on the membrane potential and has a negative differential conductance ($z_1(\partial J_1/\partial\phi)<0$). J_2 depends on membrane potential and intracellular concentration $C2i$ [53]. This last dependance is stable: $(\partial J_2/\partial C_{2i})>0$ [36]. The total differential conductance is still negative: $z_1(\partial J_1/\partial\phi)+z_2(\partial J_2/\partial\phi)<0$.

Let us discuss the marginal mode ($\omega=0$). For simplicity, we now assume that the variations of J_1 and J_2 with the intracellular concentrations are negligible because, the instability comes *a priori*, from the negative differential conductance. Then, equations (28, 29) provide the following equation:

$$\left[k+2\frac{k_BT}{eDC_0}\left(z_1\left(\frac{\partial J_1}{\partial\phi}\right)+z_2\left(\frac{\partial J_2}{\partial\phi}\right)\right)\right]k=0. \quad (30)$$

We deduce easily the two possible solutions:

$$k=0 \text{ and } k=-2\frac{k_BT}{eDC_0}\left(z_1\left(\frac{\partial J_1}{\partial\phi}\right)+z_2\left(\frac{\partial J_2}{\partial\phi}\right)\right). \quad (31)$$

However, the dispersion relation must be studied carefully before a conclusion. If we still neglect the variations of J_1 and J_2 with the intracellular concentrations, (28, 29) provide the following dispersion relation:

$$\left[k+2\frac{k_BT}{eDC_0}\left(z_1\left(\frac{\partial J_1}{\partial\phi}\right)+z_2\left(\frac{\partial J_2}{\partial\phi}\right)\right)\right]s=0. \quad (32)$$

Then, the dispersion relation is $s=0$ or more physically, $\omega=-Dk^2$. So, the relevant marginal mode is $k=0$ (and not the other (31)). The negative differential conductance plays no role. There is no instability in the Electroneutral Model as ω is always negative. This result is in contradiction with the previous ones [30].

However, in the literature, the dependence of J_2 on concentrations is used. An instability is obtained numerically [30]. We must be able to understand such a result before a conclusion. We take the same assumptions. Then, the dispersion relation is:

$$s=\left[\frac{\omega}{D}+k^2\right]^{1/2}=-\frac{z_1^2C_{10}}{C_0D}\left(\frac{\partial J_2}{\partial C_{2i}}\right)\frac{k-p}{k-q} \quad (33)$$

where:

$$p=\frac{-2k_BT}{eDz_1^2C_{10}}z_1\left(\frac{\partial J_1}{\partial\phi}\right) \quad (34)$$

$$q=-2\frac{k_BT}{eDC_0}\left(z_1\left(\frac{\partial J_1}{\partial\phi}\right)+z_2\left(\frac{\partial J_2}{\partial\phi}\right)\right) \quad (35)$$

p and q are positive and $q<p$ as $z_1^2C_{10}<C_0$ and $z_2\left(\frac{\partial J_2}{\partial\phi}\right)>0$.

For $p>k>q$, the growth rate ω exists mathematically. r is the wave vector such that the growth rate is equal to zero. For $p>k>r$, the system is stable ($\omega<0$) while it is unstable ($\omega>0$) for $r>k>q$. We think that the numerical simulation is probably performed in the scale $q<k<p$ [30].

Moreover, for $k<q$ and $k>p$, there is surprinsingly, no mathematical solution as the real part of s must be positive by definition. Moreover, for $k=q$, the right member of (33) diverges. Then, the domain of mathematical validity of the Electroneutral Model is particulary tight: $(p-q)/p\approx 1-z_1^2C_{10}/C_0$.

The study of the Electroneutral Model on this instability provides the following interesting results:

- the Electroneutral Model is in contradiction with the Cable Model on crucial points. From our point of view, this criticism is fundamental because, the Cable equation has been checked experimentally [23–25];
- even when we assume that the Electroneutral Model is correct, we don't recover the results in the literature. For example, $\omega\approx -Dk^2$ when the dependance with concentrations is neglected;
- the Electroneutral Model provides dubious mathematical results in the case of the studied instability. There is no mathematical solution in a large scale of wavenumbers k.

Finally, we think that the Electroneutral Model is not suitable to study electric behaviour of biomembranes. It means notably, if the ionic flux at the membrane depends on membrane electric potential, this model cannot be applied. However, we think that this model could be applied if the ionic flux at membrane doesn't depend on membrane potential in a first approximation [54].

6 The second electrodiffusive model: the Biomembrane Electrodiffusive Model (BEM)

The aim of this part is to propose an electrodiffusive model (based on Nernst-Planck and Poisson equations in the bulk) which is in agreement with the Cable Model. The important point is to derive physically compatible boundary conditions.

Our model (notably, the boundary conditions) will be correct if the following two criteria are fulfilled:

- we must recover the Cable predictions for the instability in the case of a negative differential conductance;

– we must be able to derive the Cable equation on the basis of this new microscopic model.

To our mind, the last criterion will be the most convincing. Notably, it will be interesting to compare the assumptions in the derivation to the limits of validity of the Cable equation [20]. The derivation is provided in Section 7.1.

6.1 The Biomembrane Electrodiffusive Model (BEM)

First, in extracellular and intracellular media, concentrations C_j and electric potential ϕ satisfy Nernst-Planck and Poisson equations. We have recalled these in Section 3: equations (14, 15).

We consider the same physical quantities as in the Electroneutral Model: N ionic concentrations and the electric potential in each medium. As we don't consider the microscopic electroneutrality, we establish two other conditions considering spatial variations of the electric field inside the membrane.

The biomembrane is made of a lipid bilayer with embedded proteins. The lipid bilayer conductance is about 10^{-5} S m^{-2} to compare with 1 S m^{-2}, a usual value in biomembranes. In terms of resistivities, the bilayer one is about 10^{13} Ω m to compare with 10^8 Ω m in a biomembrane and 1 Ω m in ionic solutions [20]. Then, a lipid bilayer should be classified as a very good insulator. It is valid to neglect its permeability compared with that of proteins. Therefore, it is valid to consider a membrane charge equal to zero (at least, for the dynamics). The membrane electric field $\mathbf{E}_m$ satisfies:

$$\nabla \cdot \mathbf{E}_m = 0. \tag{36}$$

The relative variation of the normal electric field $\mathbf{n} \cdot \mathbf{E}_m$ across the biomembrane ($\mathbf{n} \cdot \mathbf{E}_m$(internal) – $\mathbf{n} \cdot \mathbf{E}_m$(external))/mean value of ($\mathbf{n} \cdot \mathbf{E}_m$) is about d/L. d is the membrane thickness about 5 nm. L is either the cellular radius or the characteristic wavelength of the studied phenomenon. Then, it is valid to neglect the normal variations of $\mathbf{n} \cdot \mathbf{E}_m$ in membrane as long as $d/L \ll 1$. Let us emphasize that it is the stepping stone of our model. It is satisfied in all the spatiotemporal phenomena in biological cells to our knowledge.

Tangent electric fields are continuous. Membrane lipids could be charged which induces discontinuities in normal electric field across the membrane:

$$\varepsilon \mathbf{n} \cdot \mathbf{E}_e - \varepsilon_m \mathbf{n} \cdot \mathbf{E}_m = \sigma_e \text{ and } \varepsilon_m \mathbf{n} \cdot \mathbf{E}_m - \varepsilon \mathbf{n} \cdot \mathbf{E}_i = \sigma_i \tag{37}$$

where σ_e and σ_i are the surface charges at the membrane, ε_m the permittivity of lipid bilayer. $\mathbf{E}_e$ and $\mathbf{E}_i$ are respectively electric fields at membrane in external and internal mediums. Adding the two equations (37) provides a first boundary condition:

$$\mathbf{n} \cdot \mathbf{E}_e - \mathbf{n} \cdot \mathbf{E}_i = (\sigma_e + \sigma_i)/\varepsilon. \tag{38}$$

Without surface charges (or for fluctuations), (38) is equal to (20) of the Electroneutral Model. However, the two derivations are physically different. In the BEM, (38) is the classic discontinuity of normal electric field at the passage of a charged surface. In the Electroneutral Model, (20) is due to the microscopic electroneutrality.

Substracting the two equations of (37) gives:

$$2\varepsilon_m \mathbf{n} \cdot \mathbf{E}_m = \varepsilon(\mathbf{n} \cdot \mathbf{E}_i + \varepsilon \mathbf{n} \cdot \mathbf{E}_e) + \sigma_i - \sigma_e. \tag{39}$$

Then, we integrate the two members of this equality over the membrane thickness. The first member provides: $\int \mathbf{n} \cdot \mathbf{E}_m dr = -\int \mathbf{n} \cdot \nabla \phi_m dr = \phi_i - \phi_e$. Therefore, the second boundary condition is:

$$\phi_i - \phi_e = \frac{\varepsilon d}{2\varepsilon_m}(\mathbf{n} \cdot \mathbf{E}_e + \mathbf{n} \cdot \mathbf{E}_i) + \frac{d(\sigma_i - \sigma_e)}{2\varepsilon_m} \cdot \tag{40}$$

We note that another quantity ε_m/d appears in this second model contrary to the Electroneutral Model. Without surface charges and in the resting state $\sum_j z_j J_j = 0$, applying (16), (40) is equal to:

$$(\phi_i - \phi_e) \approx (d/\varepsilon_m)\mathbf{n} \cdot \nabla \rho_i / \chi^2 \tag{41}$$

in the resting state.

$\mathbf{n} \cdot \nabla \rho_i / \chi^2$ is the quantity of charge in the Debye layer close to the membrane. Then, we recover the capacitive behaviour as in the Cable approach:

$$C_m = \varepsilon_m / d. \tag{42}$$

It corresponds to a flat capacitance as we have neglected the effects of cellular curvature ($d/L \ll 1$).

Let us emphasize that in the BEM, the charge is "free" to be zero or not. For instance, if we assume electroneutrality in the resting state, $\mathbf{n} \cdot \nabla \rho_i = 0$ and the membrane potential $\phi_i - \phi_e$ is equal to zero. Then, in this second electrodiffusive model, the membrane potential is correlated with the lack of microscopic electroneutrality. Of course, the charge is limited to the Debye layer. Then, variations of membrane potential are mainly due to a net transfer of charges. We emphasize that we have neglected the spatial variations of charges inside the protein [55].

In the following, we apply the BEM to the negative differential conductance instability and compare the results with those of the Cable Model. However, let us note now that the equations (40, 38) establish a difference between the membrane surface charges and the charges in the Debye layers. It could be possible with BEM to investigate their quantitative role if a chemical binding of ions to the membrane is allowed.

6.2 The negative differential conductance instability

We consider a cylindrical cell of radius R. The following general assumptions are made:

i) the ionic flux J_j of each species j at the membrane only depends on the membrane potential and not on concentrations;

ii) only unidimensional modes are considered;
iii) no ionic binding-release chemical reactions with membrane lipids and proteins or fixed negative charges in volume due to macromolecules;
iv) the gradients of concentrations and electric potential in the Debye layer are neglected in the linear analysis of stability. It means that concentrations and electric potential are assumed to be uniform in the resting state.

For simplicity sake, we consider two ions 1 and 2. The characteristic quantities of the system are the charge numbers z_1 and z_2, concentrations C_{10} and C_{20} in the stationary state and the coefficient of diffusion D. We distinguish the external and internal quantities by subscripts i and e. Fluctuations $\delta\phi$, δC_1 and δC_2 satisfy linearized equations:

$$\frac{\partial \delta C_j}{\partial t} = D\Delta\delta C_j + \frac{eD}{k_BT} z_j C_{j0} \Delta\delta\phi \tag{43}$$

$$\Delta\delta\phi = -\frac{\delta\rho}{\varepsilon}\,. \tag{44}$$

We look for modes of the type $f(r)e^{ikx+\omega t}$ where k is the wavenumber and ω the growth rate. The charge fluctuation $\delta\rho = eN_a(z_1\delta C_1 + z_2\delta C_2)$ satisfies:

$$\frac{\partial \delta\rho}{\delta t} = D\Delta\delta\rho - D\chi^2\delta\rho. \tag{45}$$

If we denote $\delta\rho = f(r)e^{ikx+\omega t}$, one gets:

$$\frac{d^2f}{dr^2} + \frac{2df}{rdr} - s^2 f = 0 \tag{46}$$

where $s^2 = k^2 + \frac{\omega}{D} + \chi^2$. The real part of s is assumed to be positive.

Then, solutions of (46) are Bessel functions of imaginary argument:

$$\delta\rho_i = a_i\varepsilon\chi_i^2 \frac{k_BT}{e} I_0(s_i r)e^{ikx+\omega t} \tag{47}$$

$$\delta\rho_e = a_e\varepsilon\chi_e^2 \frac{k_BT}{e} K_0(s_e r)e^{ikx+\omega t} \tag{48}$$

where a_i and a_e are constants. We have used the fact that fluctuations are equal to zero far from the membrane. The charges are screened on the Debye length as $s \approx \chi$ checked in the following.

We follow the same procedure for the electric potential $\delta\phi$:

$$\delta\phi_i = \frac{k_BT}{e}(b_i I_0(kr) - \frac{\chi_i^2}{s_i^2 - k^2} a_i I_0(s_i r))e^{ikx+\omega t} \tag{49}$$

$$\delta\phi_e = \frac{k_BT}{e}(b_e K_0(kr) - \frac{\chi_e^2}{s_e^2 - k^2} a_e K_0(s_e r))e^{ikx+\omega t} \tag{50}$$

where b_i and b_e are constants.

In the following, we assume that internal and external parameters are equal (see Sect. 6.5 in the contrary case). Thus, the boundary conditions (16, 38) provide the following relations between coefficients:

$$b_e = \frac{I_0'(kR)}{K_0'(kR)} b_i \text{ and } a_e = \frac{I_0'(kR)}{K_0'(sR)} a_i \tag{51}$$

where I_0' and K_0' are respectively the derivatives of I_0 and K_0.

Fluctuations satisfy the boundary conditions (16,40). We do the relevant assumption: $\chi R \gg 1$ which is always satisfied in physiological conditions. Then, the dispersion relation $\omega = \omega(k)$ is:

$$\omega = \frac{2G_d}{s\varepsilon} - \left(\frac{2}{s} + \frac{\varepsilon d}{\varepsilon_m}\right) D\chi^2 \frac{k\frac{I_0'}{I_0}(kR) + \frac{G_d}{\varepsilon D\chi^2}\left(1 - \frac{K_0 I_0'}{K_0' I_0}(kR)\right)}{\left(1 - \frac{K_0 I_0'}{K_0' I_0}(kR)\right) + \frac{\varepsilon d}{\varepsilon_m} k \frac{I_0'}{I_0}(kR)} \tag{52}$$

where G_d is the differential conductance:

$$G_d = eN_a\left(z_1\left(\frac{\partial J_1}{\partial\phi}\right) + z_2\left(\frac{\partial J_2}{\partial\phi}\right)\right). \tag{53}$$

If we consider a perfectly insulating membrane ($G_d = 0$) and the limit d close to zero, the growth rate ω becomes independent of the membrane capacitance. Then, in the short wavelength limit ($kR \gg 1$), ω is of order of

$$-D\chi k \tag{54}$$

which is in agreement with the case of an ionic solution.

The term $\left(\frac{2}{s} + \frac{\varepsilon d}{\varepsilon_m}\right)$ reduces to $\frac{\varepsilon d}{\varepsilon_m}$ as $\frac{\varepsilon d}{\varepsilon_m} s \approx 100 \gg 1$ because $s \approx \chi$ (checked in the following). Moreover, the second term of the right member of (51) is about $\frac{G_d d}{\varepsilon_m}$. Then, the ratio of the second term on the first one of the right member is about $\frac{\varepsilon d}{\varepsilon_m} s \gg 1$.

The dispersion relation (52) reduces to:

$$\omega = -\frac{\varepsilon d}{\varepsilon_m} D\chi^2 \frac{k\frac{I_0'}{I_0}(kR) + \frac{G_d}{\varepsilon D\chi^2}\left(1 - \frac{K_0 I_0'}{K_0' I_0}(kR)\right)}{\left(1 - \frac{K_0 I_0'}{K_0' I_0}(kR)\right) + \frac{\varepsilon d}{\varepsilon_m} k \frac{I_0'}{I_0}(kR)}\,. \tag{55}$$

If $\frac{\varepsilon d}{\varepsilon_m} k \gg 1$, $\omega/D\chi^2 \approx 1$ while $\omega/D\chi^2 \ll 1$ if $\frac{\varepsilon d}{\varepsilon_m} k \ll 1$. Then, in the previous limits, the condition $s \approx \chi$ is checked.

Equation (55) simplifies in the limits of a short wavelength $kR \gg 1$ or a large wavelength $kR \ll 1$:

$$kR \gg 1: \quad \omega = -\frac{\varepsilon d}{2\varepsilon_m} D\chi^2 \frac{\frac{2G_d}{\varepsilon D\chi^2} + k}{1 + \frac{\varepsilon d}{2\varepsilon_m} k} \tag{56}$$

$$kR \ll 1: \quad \omega = -\frac{\varepsilon d}{2\varepsilon_m} D\chi^2 \left(\frac{2G_d}{\varepsilon D\chi^2} + k^2 R\right). \tag{57}$$

At the denominator of (57), there is the term $1 + \frac{\varepsilon d}{\varepsilon_m} k^2 R/2 \approx 1$ as $kR \ll 1$. Two different typical curves are derived depending on the geometry.

6.3 Comparison between cable equation and BEM results

To compare results with the Cable equation, it is useful to take the same notations: $\varepsilon D\chi^2 = 1/\rho_i = 1/\rho_e$.

Firstly, as noted in the previous Section 6.1, the growth rate is proportional to the capacitance $C_m = \varepsilon_m/d$.

Secondly, in the limit of large wavelength, the dispersion relation is the same than the Cable one (Eq. (6) in Sect. 3.2). This result is satisfactory because, large wavelength corresponds to one of the Cable validity's condition (condition iii in Sect. 3.1).

The characteristic time T at $k = 0$ can be recovered simply. Consider an uniform disturbance of charge densities: $\delta\rho_e$ and $\delta\rho_i$. These charges are spatially localized at the membrane, in the Debye layer of width χ^{-1}. As $\chi R \gg 1$ where R is the cellular radius, $\delta\rho_e(r = R) \approx -\delta\rho_i(r = R)$. The equivalent surface charges are respectively $\chi^{-1}\delta\rho_e$ and $\chi^{-1}\delta\rho_i$. The capacitive nature of the membrane potential provides: $\chi^{-1}\delta\rho_i \approx C_m(\delta\phi_i - \delta\phi_e)_{r=R}$. An ionic current is induced: $\delta I \approx G_d(\delta\phi_i - \delta\phi_e)_{r=R} \approx (G_d\chi^{-1}/C_m)\delta\rho_i(r = R)$. The characteristic time T of the process measures the rate of charge accumulation at the membrane: $T\delta I \approx -\chi^{-1}\delta\rho_i(r = R)$. The negative sign means that an influx of charges ($\delta I < 0$) induces an increase of intracellular charges ($\delta\rho_i(r = R) > 0$). Combining the previous equations provides $T \approx -G_d/C_m$ in agreement with the previous result of the dispersion relation (57). It is the characteristic time at $k = 0$. In this evaluation, we emphasize that no diffusive parameters are taken into account.

Finally, we recover the results of the Cable Model (Sect. 3.2) in its domain of validity.

6.4 The effect of geometry

In the limit of a short wavelength $kR > 1$, as in the case of ionic currents in Fucus for example, the variation of the growth rate with k is linear (Eq. (56)) and not parabolic (Eq. (57)) contrary to the cable equation predictions. The dependence on the wavelength has never (to our knowledge) been analysed quantitatively [56] (for instance, the limit $kR \gg 1$). However, we emphasize that the physics in the two limits are the same. It means that the growth rate is still proportional to electric parameters such as membrane capacitance and bulk conductivity. The main physical reason of this effect is the geometrical constraint. For $kR \ll 1$, the intracellular ionic current is limited to flow in a confined medium. Then, the intracellular electric potential becomes larger than the extracellular one as it is shown in the derivation of the Cable Model in 7.1.

We have also recently [18], applied the effect of geometry to protein aggregation in flat isolated cellular membranes for the electro-osmotic and Larter-Ortoleva instabilities. This last instability can also be a test for the BEM because, it has been proposed initially by Larter and Ortoleva using an Electroneutral Model [12,13] and more recently studied by Fromherz using the Cable Model [14–16]. If we only consider the variations of the ionic current with the local concentration of proteins (conductance neglected), the results are different. The results obtained with the BEM are similar to those obtained by Fromherz [57] in the limit of large wavelengths. Then, the BEM compared to the Electroneutral Model, is once again validated.

6.5 The effect of asymmetrical media

In Section 6.2, we have assumed the same electric properties in intracellular and extracellular media while it can be different. The first reason is the difference in ionic concentrations due notably to the activity of pumps, metabolism and Turgor regulation. The second reason is due to the difference in coefficient of diffusion due to the slight difference between the physical properties of the external and internal media. Moreover, coefficients of diffusion (notably, the cations) between internal and external, are also different due to intracellular binding-release chemical reactions with intracellular negative proteins [58].

Then, we distinguish the Debye lengths χ_i^{-1} and χ_e^{-1} and the coefficients of diffusion D_i and D_e. The intracellular and extracellular fluctuations of density of ionic charge and electric potential satisfy equations (47-50). In intracellular medium, $s_i^2 = \chi_i^2 + k^2 + \omega/D_i$ while in extracellular medium, $s_e^2 = \chi_e^2 + k^2 + \omega/D_e$. In asymmetrical media, we cannot determine the constants b_e and a_e according to b_i and a_i respectively, as in the case of symmetric media (Eq. (51)). Then, we must solve a 4×4 determinant. However, the procedure of determination and simplification (however, longer) of the dispersion relation is similar to the symmetric problem.

To simplify the dispersion relation, we restrict the study to $k < -10$ ($G_d/\varepsilon D\chi^2$). Then, the dispersion relation $\omega = \omega(k)$ satisfies $a\omega^2 + b\omega + c = 0$ where coefficients a, b and c are:

$$a = \frac{I_0'}{I_0} - \frac{K_0'}{K_0} - \frac{\varepsilon d}{\varepsilon_m} k \frac{I_0' K_0'}{I_0 K_0} \tag{58}$$

$$\begin{aligned} b = {} & D_i\chi_i^2 \frac{I_0'}{I_0} - D_e\chi_e^2 \frac{K_0'}{K_0} - \frac{\varepsilon d}{2\varepsilon_m} k \frac{I_0' K_0'}{I_0 K_0}(D_i\chi_i^2 + D_e\chi_e^2) \\ & + \frac{\varepsilon d}{\varepsilon_m} D_i D_e \left[\frac{2G_d}{\varepsilon} \left(\frac{I_0'}{I_0} - \frac{K_0'}{K_0} \right) \right. \\ & \left. - k \frac{I_0' K_0'}{I_0 K_0} \left(D_i\chi_i^2 + D_e\chi_e^2 \right) \right] \end{aligned} \tag{59}$$

$$\begin{aligned} c = {} & \frac{\varepsilon d}{\varepsilon_m} \left[\frac{G_d}{\varepsilon} \left(D_i\chi_i^2 \frac{I_0'}{I_0} - D_e\chi_e^2 \frac{K_0'}{K_0} \right) \right. \\ & \left. - k \frac{I_0' K_0'}{I_0 K_0} D_i\chi_i^2 + D_e\chi_e^2 \right] \end{aligned} \tag{60}$$

where I_0, I_0', K_0 and K_0' are determined for the argument kR.

In the general case, we cannot *a priori*, simplify this system. Then, we don't recover the point of view of Scott which sums the internal and external resistivities. However, Scott considers only large wavelengths. Then, this discussion is restricted to the condition $\frac{\varepsilon d}{\varepsilon_m} k \ll 1$. In this

case, the growth rate satisfies the following simple equation with a resistance sum:

$$\omega = -\frac{d}{\varepsilon_m}\frac{k+(\rho_i+\rho_e)G_d}{\rho_i+\rho_e} \tag{61}$$

where

$$\rho_i = \frac{1}{\varepsilon D_i \chi_i^2}\frac{I_0'}{I_0}(kR) \tag{62}$$

and

$$\rho_e = \frac{-1}{\varepsilon D_e \chi_e^2}\frac{K_0'}{K_0}(kR). \tag{63}$$

$\varepsilon D_e\chi_e^2$ and $\varepsilon D_i\chi_i^2$ are the ionic conductivities of extracellular and intracellular media.

Equation (61) provides the same discussion as (55): the uniform perturbation is the most unstable, the characteristic time is electric and not diffusive.

For simplicity, we study only, the marginal mode k_c ($\omega = 0$) which satisfies:

$$k_c = -\frac{G_d}{\varepsilon D_i\chi_i^2}\frac{I_0'}{I_0}\left(1-\frac{D_i\chi_i^2}{D_e\chi_e^2}\frac{I_0K_0'}{I_0'K_0}\right) \tag{64}$$

$$\text{for } k_cR \gg 1: \quad k_c = -\frac{G_d}{\varepsilon}\left(\frac{1}{D_i\chi_i^2}+\frac{1}{D_e\chi_e^2}\right) \tag{65}$$

$$\text{for } k_cR \ll 1: \quad k_c = \left[\frac{-2G_d}{\varepsilon D_i\chi_i^2 R}\right]^{1/2}. \tag{66}$$

We recover that in the large wavelength limit, only the electric contribution is important. If we consider the same conductivities in internal and external media, the effect of geometry appears when the wavelength becomes larger than the cellular radius because, the current must flow in a restricted volume.

As a conclusion, the analysis of the negative differential conductance instability is convincing. We now want to derive the intimate relation between the BEM and the Cable Model. For instance, we show that the Cable Model is the limit of the BEM in the limit of large wavelengths (with some assumptions).

7 Second discussion: derivation of the Cable Model

7.1 Derivation of the Cable Model on that the BEM

The Cable equation is only established phenomenologically in Section 3.1 from Kirchoff's law. In this part, we deduce the Cable Model from Nernst-Planck equations with specific boundary conditions (the Biomembrane Electrodiffusive Model). We consider a cylindrical cell of radius R. However, the forthcoming procedure is general.

The first assumption is to consider a unidimensional mode of propagation. Then, concentrations and electric potential only depend on radial and axis coordinates, respectively r and x (no dependence on the angular one). It corresponds to the condition ii) of the Cable Model validity.

We define the following new quantities where u stands for the concentrations C_1, C_2 and the electric potential ϕ:

$$\langle \delta u_i\rangle = \frac{2}{R^2}\int_0^R r\delta u_i dr \tag{67}$$

$$\langle \delta u_e\rangle = \frac{2}{R^2}\int_R^{+\infty} r\delta u_e dr \tag{68}$$

where δ denotes the fluctuations. Let us note that an implicit assumption is the validity (no divergence) of (67, 68). It is easy to check it with fluctuations provided by Section 6.2.

The second assumption is that the variations of concentration are negligible during all the phenomena (in the non linear state also). It is the condition ii) of the Cable Model validity.

Then, we integrate on intracellular medium, the linearized Nernst-Planck equation (43):

$$\frac{\partial\langle\delta C_{ji}\rangle}{\partial t} = D_{ji}\frac{\partial^2\langle\delta C_{ji}\rangle}{\partial x^2} + \frac{eD_{ji}}{k_BT}z_jC_{j0i}\frac{\partial^2\langle\delta\phi_i\rangle}{\partial x^2} + \frac{2D_{ji}}{R}\left(\left(\frac{\partial\delta C_{ji}}{\partial r}\right)+\frac{e}{k_BT}z_jC_{j0i}\left(\frac{\partial\delta\phi_i}{\partial r}\right)\right)_{r=R}. \tag{69}$$

Using the continuity of the electrodiffusive flux through the membrane (boundary condition (16)) provides:

$$\frac{\partial\langle\delta C_{ji}\rangle}{\partial t} = D_{ji}\frac{\partial^2\langle\delta C_{ji}\rangle}{\partial x^2} + \frac{eD_{ji}}{k_BT}z_jC_{j0i}\frac{\partial^2\langle\delta\phi_i\rangle}{\partial x^2} - \frac{2}{R}J_j. \tag{70}$$

By the same procedure on the extracellular medium, we have:

$$\frac{\partial\langle\delta C_{je}\rangle}{\partial t} = D_{je}\frac{\partial^2\langle\delta C_{je}\rangle}{\partial x^2} + \frac{eD_{je}}{k_BT}z_jC_{j0e}\frac{\partial^2\langle\delta\phi_e\rangle}{\partial x^2} + \frac{2}{R}J_j. \tag{71}$$

The integration of Poisson equation (44) provides:

$$\frac{\partial^2\langle\delta\phi_i\rangle}{\partial x^2} + \frac{2}{R}\left(\frac{\partial\delta\phi_i}{\partial r}\right)_{r=R} = -\frac{\langle\delta\rho_i\rangle}{\varepsilon}\cdot \tag{72}$$

$$\frac{\partial^2\langle\delta\phi_e\rangle}{\partial x^2} + \frac{2}{R}\left(\frac{\partial\delta\phi_e}{\partial r}\right)_{r=R} = -\frac{\langle\delta\rho_e\rangle}{\varepsilon}\cdot \tag{73}$$

The third assumption is that ions diffuse with the same coefficient of diffusion D_i and D_e respectively in the intracellular and extracellular media. It is convenient to introduce the following electric charges $\langle\delta\rho_{i,e}\rangle = eN_a(z_1\langle\delta C_{1i,e}\rangle + z_2\langle\delta C_{2i,e}\rangle)$:

$$\frac{\partial\langle\delta\rho_i\rangle}{\partial t} = D_i\frac{\partial^2\langle\delta\rho_i\rangle}{\partial x^2} + \varepsilon D_i\chi_i^2\frac{\partial^2\langle\delta\phi_i\rangle}{\partial x^2} - \frac{2}{R}I \tag{74}$$

$$\frac{\partial\langle\delta\rho_e\rangle}{\partial t} = D_e\frac{\partial^2\langle\delta\rho_e\rangle}{\partial x^2} + \varepsilon D_e\chi_e^2\frac{\partial^2\langle\delta\phi_e\rangle}{\partial x^2} + \frac{2}{R}I. \tag{75}$$

The fourth assumption is that external and internal Debye lengths and coefficients of diffusion are equal. Now, we set the following quantities:

$$\langle\delta\rho\rangle = \langle\delta\rho_i\rangle - \langle\delta\rho_e\rangle \text{ and } \langle\delta\phi\rangle = \langle\delta\phi_i\rangle - \langle\delta\phi_e\rangle. \quad (76)$$

Subtracting (74,75) in the one hand and (72,73) on the other hand, provides:

$$\frac{\partial\langle\delta\rho\rangle}{\partial t} = D\frac{\partial^2\langle\delta\rho\rangle}{\partial x^2} + \varepsilon D\chi^2\frac{\partial^2\langle\delta\phi\rangle}{\partial x^2} - \frac{4}{R}I \quad (77)$$

$$\frac{\partial^2\langle\delta\phi\rangle}{\partial x^2} + \frac{2}{R}\left(\left(\frac{\partial\delta\phi_i}{\partial r}\right) + \left(\frac{\partial\delta\phi_e}{\partial r}\right)\right)_{r=R} = -\frac{\langle\delta\rho\rangle}{\varepsilon}\cdot \quad (78)$$

Then, we use the BEM introduced in this article and notably the boundary condition (40) on membrane potential:

$$\frac{\partial^2\langle\delta\phi\rangle}{\partial x^2} - \frac{4\varepsilon_m}{R\varepsilon d}(\delta\phi_i - \delta\phi_e)_{r=R} = -\frac{\langle\delta\rho\rangle}{\varepsilon}\cdot \quad (79)$$

It is now useful to link external variations $\langle\delta\phi_e\rangle$ and $\langle\delta\rho_e\rangle$ to internal variations $\langle\delta\phi_i\rangle$ and $\langle\delta\rho_i\rangle$. Due to the Debye screening $\chi R = R/\lambda D \gg 1$, we have:

$$\langle\delta\rho_i\rangle \approx \frac{2}{R^2}\int_{R-\lambda_D}^{R} r\delta\rho_i dr \approx \frac{2}{\chi R}\delta\rho_i(r=R) \quad (80)$$

$$\langle\delta\rho_e\rangle \approx \frac{2}{R^2}\int_{R}^{R+\lambda_D} r\delta\rho_e dr \approx \frac{2}{\chi R}\delta\rho_e(r=R). \quad (81)$$

From the condition $\left(\frac{\partial\delta\rho_i}{\partial r}\right)_{r=R} = \left(\frac{\partial\delta\rho_e}{\partial r}\right)_{r=R}$ deduced from (16, 38). For $\chi R \gg 1$, we deduce:

$$\delta\rho_i(r=R) = -\delta\rho_e(r=R). \quad (82)$$

Then, we have from (80, 81):

$$\langle\delta\rho_i\rangle + \langle\delta\rho_e\rangle = 0. \quad (83)$$

It is the condition of macroscopic electroneutrality (and not microscopic). Let us note that the charge $\delta\rho_{i,e}(r=R)$ close to the surface is much larger that the mean charge $\langle\delta\rho_{i,e}\rangle$ on the section.

So, the sum of equations (72, 73) provides with (83):

$$\frac{\partial^2\langle\delta\phi_i\rangle}{\partial x^2} + \frac{\partial^2\langle\delta\phi_e\rangle}{\partial x^2} + \frac{2}{R}\left(\left(\frac{\partial\delta\phi_i}{\partial r}\right) - \left(\frac{\partial\delta\phi_e}{\partial r}\right)\right)_{r=R} = 0. \quad (84)$$

Using the boundary condition (38), we obtain:

$$\langle\delta\rho_i\rangle + \langle\delta\rho_e\rangle = 0. \quad (85)$$

However, (85) doesn't mean that for $r=R$, $\delta\phi_i = -\delta\phi_e$. This identity is only valid in the limit of a short wavelength ($kR \gg 1$).

The fifth assumption is that the wavelength of the phenomenon $\lambda = 2\pi/k$ is much larger than the cellular radius R: $kR \ll 1$. We now want to show that the variations δV of the membrane potential are dominated by the intracellular one: $\delta V \approx \langle\delta\phi_i\rangle$.

To simplify, we work on the fluctuations of the Section 6.2 and we consider only, the marginal mode ($\omega = 0$) in the following evaluations. We set: $\delta\phi_i = \delta\phi_{i1} + \delta\phi_{i2}$ where $\delta\phi_{i2} = -\delta\rho_i/\varepsilon\chi^2$. In the limit $kR \ll 1$, $\delta\phi_{i1}(r=R)/\delta\phi_{i2}(r=R) \approx \frac{\varepsilon d}{\varepsilon_m}\chi \gg 1$. The conditions (37, 39) of the BEM have been used. So, as $\delta\phi_{i1}$ varies slightly on the cellular radius R, we obtain:

$$\langle\delta\phi_i\rangle \approx \delta\phi_i(r=R) \approx \delta\phi_i(r=0). \quad (86)$$

In extracellular medium, we set $\delta\phi_e = \delta\phi_{e1} + \delta\phi_{e2}$ where $\delta\phi_{e2} = -\delta\rho_e/\varepsilon\chi^2$. The ratio $\delta\phi_{e1}$ on $\delta\phi_{e2}$ is about $\frac{\varepsilon d}{\varepsilon_m}\chi\frac{K_0 I_0'}{K_0' I_0}(kR) \ll 1$ in the limit $kR \ll 1$. We have used the boundary conditions (38, 40). Then, usually (at least, when the Debye length is not too small), $\delta\phi_{e1}(r=R) \ll \delta\phi_{e2}(r=R)$. Let us note that it is the contrary in intracellular medium. Moreover, (82) implies $\delta\phi_{e2}(r=R) \approx -\delta\phi_{i2}(r=R)$. It is now easy to evaluate the ratio between internal and external fluctuations for $r=R$: $\delta\phi_i/\delta\phi_e \approx \delta\phi_{i1}/\delta\phi_{e2} \approx \delta\phi_{i1}/\delta\phi_{i2} \approx \frac{\varepsilon d}{\varepsilon_m} \gg 1$. Finally, the variation of membrane potential $\delta V = (\delta\phi_i - \delta\phi_e)_{r=R}$ is dominated by the variation of intracellular electric potential $\delta\phi_i$ in the limit of large wavelength. Then, considering these evaluations and (85, 86), we have the relation:

$$\delta V = (\delta\phi_i - \delta\phi_e)_{r=R} \approx \delta\phi_i \approx \langle\delta\phi_i\rangle \approx -\langle\delta\phi_e\rangle \approx \langle\delta\phi\rangle/2. \quad (87)$$

The last step is to simplify the equation (79). $\frac{\partial^2\langle\delta\phi\rangle}{\partial x^2} \approx k^2\langle\delta\phi\rangle$. The ratio between the two terms of the left member of (79) provides $\frac{\partial^2\langle\delta\phi\rangle}{\partial x^2}/\frac{4\varepsilon_m}{\varepsilon dR}\delta V \approx \frac{k^2 R\varepsilon d}{4\varepsilon_m} \ll 1$ in the large wavelength limit. Then we recover the capacitive nature of the membrane potential:

$$\frac{4\varepsilon_m}{Rd}\delta V = \langle\delta\rho\rangle. \quad (88)$$

So, using the equations (88, 87, 77) and $C_m = \varepsilon_m/d$, δV satisfies the following equation:

$$C_m\frac{\partial\delta V}{\partial t} = \delta I + \left(DC_m + \frac{\varepsilon D\chi^2 R}{2}\right)\frac{\partial^2\delta V}{\partial x^2}\cdot \quad (89)$$

The ratio between DC_m and $\varepsilon D\chi^2 R$ is about: $DC_m/\varepsilon D\chi^2 R \approx 10^{-11}/R \ll 1$. Thus, the Cable equation is recovered.

Finally, the Cable equation (3) is derived by a complete integration of Nernst-Planck and Poisson equations. The BEM allows us to derive the relation (88) which is the basis of the demonstration. The capacitive current appears without an assumption on the nature of the transmembrane current. For instance, we don't state initially that a capacitive current exists explicitly and we solve fully the electrodiffusive equations (even in the Debye layer). These two points constitute the fundamental differences with the previous work [59]. For another difference, the BEM distinguish clearly the charges in the Debye layers and the surface charges. The Cable Model appears as the limit of the BEM for large wavelengths.

7.2 Discussion about the demonstration and possible applications of the BEM

We present the necessary comments on the derivation in Section 7.1 and we propose some possible applications of the BEM to biological problems.

– A first comment on the derivation of the Cable equation is that it was only valid for $kR \ll 1$. One of the interests of the BEM framework is its validity for any wavelength and its relevance to describe radial variations of the current, the concentrations and the electric potential. For example, Fucus algae generates a dipolar ionic circulation [29]. Thus, $k\ R$ is about 1 in such a system. A second example is the development of pH bands in Chara corallina [4]. When the cytoplasmic streaming is inhibited by Cytochalasine D [60], it seems that pH varies also on the circumference: $kR > 1$. Moreover, to study properly the ionic currents, it is necessary to understand the variations of physical quantities othogonal to the membrane. For example, in Chara corallina, the electric potential varies as $1/r$ in an acidic band and as $1/r^2$ in a basic band. It is impossible to predict such behaviours with the Cable Model because, it considers only the variations parallel to the cell. Then, comparisons between experiments and theory become difficult.

– A second comment is on the comparison between $\delta\phi_e$ and $\delta\phi_i$. The numerical evaluation in large wavelength limit provides $-\delta\phi_e(r = R) \ll \delta\phi_i(r = R)$ for $r = R$ while $\langle\delta\phi_i\rangle = -\langle\delta\phi_e\rangle$. It comes from the definition of $\langle\delta\phi_e\rangle$: equation (68). The small magnitude of $\delta\phi_e$ is balanced by an integration on a larger scale from R to infinity.

– A third comment is on the dynamics of the electric charge. Firstly, equation (88) shows clearly that the membrane potential is mainly produced by a net transfer of charges through the membrane. A numerical evaluation supports such a fact. Let us assume a membrane potential about -100 mV, a radius R about 10 μm and a typical membrane capacitance $C_m = \varepsilon_m/d \approx 0.01\ \mathrm{F\,m^{-2}}$. Then, applying equation (88), the charge is about $-100\ \mathrm{C\,m^{-3}}$ which corresponds to a deficit of monovalent cations about 1 μM. The typical ionic concentrations are easily about 100 mM. Then, a relative variation of only 0.001 per cent of ionic concentration is necessary to produce a typical membrane potential. Thus, the membrane potential in biological cells is dominated by a net transfer of charges. Secondly, the equation (88) (a macroscopic charge) seems to be in contradiction with the equation (47, 48) (no charge in the bulk) deduced from the BEM. It is not the case. $\langle\delta\rho_i\rangle$ is the mean charge in the intracellular medium and is linked to the microscopic charge $\delta\rho_i$ (at the membrane, in the Debye layer) by $\langle\delta\rho_i\rangle \approx \delta\rho_i(r = R)/\chi R$. Thirdly, these evaluations show that the concentration of charge varies greatly, from zero in the bulk to 10 mM close to the membrane. Then, the gradient of some concentrations could be non-negligible: notably, for calcium and proton whose concentrations are regulated to very small levels in the bulk. We expect new interesting non linearities from such strong gradients. Another aspect is the change in the concentrations in the Debye layer which could modify sufficiently the ionic conductivity (this effect could provide another way for pattern formation as shown in [61]). We recall that Agin was first, to point qualitatively, to the lack of microscopic electroneutrality in the dynamics of membrane potentials [52].

– An important application of the BEM could be the correct determination of the role of diffusion in electrical activities of cellular membranes. Qian and Sejnowski have studied the generation and the conduction of action potentials in small structures to understand synaptic events in dendritic spines [26]. The challenge was important because, many vertebrate and invertebrate neurons receive synaptic inputs on spines. They show that in small structures, ionic flux (potassium and sodium in their case) due to diffusion could dominate the electric flux. This behaviour should be also true for the ionic species with very small intracellular concentrations (as calcium and protons for example). Moreover, the Debye layer can contribute to non linearities due to the coupling $C\nabla\phi$ in the electrodiffusive flux. We also expect a change in the threshold of the instability. Hydrodynamic flow is also expected due to electro-osmosis (see the protein aggregation by electro-osmotic instability for example [17,18]).

– A fourth comment is on the necessary assumptions to derive the Cable equation from the BEM. We recover the assumptions of the Cable Model: only propagation parallel to the membrane, negligible variations of concentrations and a characteristic wavelength larger than cellular radius [62]. Let us note that we have implicitely assumed that the bath is infinite (at least, of dimension larger than the radius and the wavelength). These three assumptions are discussed by Scott in his review [20]. To derive the Cable equation, we have set two other assumptions.

We assume that internal and external properties (Debye length and coefficient of diffusion) are the same. This assumption has no importance because external parameters don't play a role. Only internal parameters are relevant due to the assumption $kR \ll 1$ (see Sect. 6.5 and the evaluations in Sect. 7.1). The only interest is to simplify the first steps of the derivation (however, the condition (83) is *a priori*, not verified for asymmetrical media). Another interesting fact is the following. In Section 6.5, we have shown using the BEM, that the dynamics is electrical (and not diffusive) in the limit $kR \gg 1$.

We also assume that the coefficients of ionic diffusion are the same. This condition has never been brought to the fore to my knowledge. However, this assumption is still ambiguous for several reasons. On the one hand, we argue that this point is not important since each ion contributes to the conductivity in a global way. In the Cable Model, such an effect is taken into account by: $1/\rho = \varepsilon \sum_j D_j \chi_j^2$ where $\chi_j^2 = \frac{e^2 N_a z_j^2 C_{j0}}{\varepsilon k_B T}$. On the other hand, we propose two arguments supporting a possible (but, still speculative) role of the difference between the diffusion coefficients. The channels, symports, antiports and pumps are proteins which transfer specifically, one species of ion. Then, if we consider that, only one type of channel is open, the current in the Debye layer is characterized by the conductivity of the transfered ion and not by the bulk conductivity. However, this effect might be restricted to the Debye

layer. The second reason is due to the work of Qian and Sejnowski who have shown that the ionic flux due to the diffusion can be more significant than the ionic flux due to the electric field [26]. In this case, the coefficients of diffusion could have an importance in pattern formation (as in Turing instability [63]). In any case, if there is an effect of the difference between the diffusion coefficients other than a change in the conductivity, we expect an effect appearing in very peculiar circumstances. This point is still unclear and therefore, will be studied in a further article [64].

8 Conclusion

The main aim of this article is to discuss how the dynamic electric behaviour of a cellular membrane could be modeled on the basis of the Nernst-Planck and Poisson equations. All the difficulty is the determination of relevant boundary conditions. Fortunately, we knew long ago, that the Cable Model established by analogy with an electric cable, provides a good approximation widely validated by experimental observations [23–25]. This is the reason we use it to test our model.

We have tested the only model in the literature to our knowledge based on the Nernst-Planck and Poisson equations: the Electroneutral Model. It assumes especially that the microscopic electroneutrality is satisfied everywhere. This model fails for physical (Sect. 5.1) and mathematical (Sect. 5.2) reasons. It doesn't provide the same results as the Cable Model in the instability due to a negative differential conductance. For instance, the capacitance is not taken into account. Moreover, the mathematical approach is not convincing as shown in Section 5.2. However, the Electroneutral Model could provide correct results (in a first approximation) if the flux at the membrane only depends on concentrations and not on membrane potential. We emphasize that this point has not been checked.

Then, we propose a new model (the BEM) taking into account the dynamic variations of membrane voltage as a function of the charge in the Debye layer. This point would not appear if the assumption of electroneutrality was made. A good description of the negative differential conductance instability is obtained with the BEM. One convincing point of our approach is the derivation of the Cable equation, which appears as the limit of the BEM for large wavelengths.

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