Entropy production of ion thermo-diffusion in cell membranes

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Abstract. Here, we developed a mathematical model for the ion diffusion in thermo ion-channels. Ion channels modulated by temperature are responsible for several physiological processes, including thermo-sensation. Our model is based on non-equilibrium thermodynamic theory, where the entropy production plays a fundamental role characterizing the thermodynamic of cell and the natural processes associated with ion permeation. We modelled ion channels activity using the conventional electrochemical approach, and we also considered a difference of temperature between the boundaries of the channel. We proposed that this assumption may influence the ion diffusion contributing to the entropy production. By using partial differential equations we attempted to determine the temperature, the ion concentration and the electrostatic potential as function of the position and time within the channel, aiming a characterization of the entropy production of the system.

1. Introduction

One of the fundamental properties of the thermodynamic behaviour of biological systems is its continuous exchanging of energy and matter with the environment. Moreover, living systems are open and actually, dissipative structures. This conclusion is based on the fact that living systems are immersed in an environment that accumulate heat [1]. The main characteristic of these structures is their capacity to reach a steady state, where the entropy production governs the complex chains of events, processes and reactions. All of these are highly coordinated in space and time. It has been established that the minimum entropy production principle for systems close to the equilibrium comprehends a variational principle for this functional [2]. Based on these results, authors [3] proposed a theoretical model for the entropy production in cells, suggesting that the entropy production is a relevant parameter to characterize the metabolism of the biological systems.

Ion channels are models of exchange of matter and energy at cellular level. These proteins, located at cellular membranes, constitutes selective pores permeable to a variety of ions [4]. Interestingly, ion channels respond to different kind of stimulus. Typically, the dynamics of the ion flux is governed by the electrochemical potential. The relation evidences its dependence on the electrostatic potential $V$ and the ion concentration $c$.

$$\tilde{\mu} = \mu_0 + kT \ln c + ezV$$

(1)
Additionally, we can find ion channels whose gating can be triggered by mechanical pressure or even, by thermal fluctuations. From these, the transient receptor potential, TRP, channels family, are widely expressed in different cell types and mediate several physiological processes including thermosensation. TRP channels family are divided in seven subfamilies. From these, TRPA (Ankyrin), TRPV (vanilloid) and TRPM (mucolipin) respond to changes in temperature, ranging from ‘cold sensors’, TRPM8, to heat activated channels (TRPV1 and TRPV3) [5].

In this work we are interested in to develop a theoretical model for the entropy production generated by the ion-diffusion in thermo-TRP channels [6]. Additionally, biophysical models of the physiological gating of these channels built on equilibrium thermodynamic theory can be found in [7], [8] and [9]. In these proteins, the temperature becomes a function that depends on the spatial coordinates and time. Accordingly, we considered that the heat flow driven by the thermal gradient and the coupling of the temperature to the electro-chemical potential, modifies the diffusion behaviour of the ion through the channel.

2. Entropy production of ion thermo-channels in the linear regime

In order to fix parameters, we assume the geometry of the ion-channel as a regular cylinder with constant radius. The flow along the channel will be one dimensional oriented connecting the intracellular and extracellular environments, thus the operator gradient becomes the partial derivative in the coordinate \( x \), \( \nabla = \frac{\partial}{\partial x} \). Also, the origin of the coordinate system, \( x = 0 \), is in the intracellular boundary of the channel, which is assumed of length \( L \).

In our description, the electrochemical potential, as well as the temperature along the channel are functions that depends on the position and time, \( \tilde{\mu} = \tilde{\mu}(x,t) \) and \( T = T(x,t) \). The main goal of this work is to describe the entropy production rate density, \( \sigma(x,t) \equiv \frac{dS}{dt} \), produced by the coupling between the thermodynamic forces, namely, the gradient of the temperature, \( \nabla T(x,t) \) and the electrochemical potential, \( \nabla \tilde{\mu}(x,t) \) and the thermal and electro-diffusion currents respectively [10].

\[
\sigma = \sigma_q + \sigma_{ed} \\
\sigma = J_u \cdot \nabla \left( \frac{1}{T(x,t)} \right) - \sum_{k=1}^{n} J_k \cdot \nabla \left( \frac{\tilde{\mu}(x,t)}{T(x,t)} \right)
\]

From the last equation we observe that the temperature couples to the electrochemical potential, Equation (1), which is also dependent on temperature. De-coupling the contribution that involve the chemical potential coupled to the thermal current and taking in account the definition of molar entropy we find

\[
\sigma = \left( J_u - \sum_{k=1}^{n} J_k h_k \right) \cdot \nabla \left( \frac{1}{T} \right) - \frac{1}{T} \sum_{k=1}^{n} J_k \cdot (\nabla \tilde{\mu})_T
\]

Where \( h_k = \tilde{\mu}_k + Ts_k \) is recognized as the partial molar enthalpy at thermodynamic equilibrium, and \( (\nabla \tilde{\mu})_T \) is the gradient of the electrochemical potential at constant temperature. This feature, that is common for thermal diffusion processes [10], allows us to define the reduced heat current \( J_q = (J_u - \sum_{k=1}^{n} J_k h_k) \)

\[
\sigma = J_q \cdot \nabla \left( \frac{1}{T} \right) - \frac{1}{T} \sum_{k}^{n} J_k \cdot (\nabla \tilde{\mu})_T
\]

Once we have written the entropy production rate in a compact form, we can use the phenomenological laws for the flow of heat and ions. In the simplest case of one ion, the sum is suppressed in the entropy production and the currents of heat and matter are written as
\[ J_q = L_{qq} \nabla \left( \frac{1}{T} \right) - L_{nq} \frac{1}{T} (\nabla \tilde{\mu}) T \]  
\[ J_n = L_{qn} \nabla \left( \frac{1}{T} \right) - L_{nn} \frac{1}{T} (\nabla \tilde{\mu}) T \]

Where the phenomenological coefficients \( L \) associated to the linear description of the involved thermodynamic forces should be related to the Fourier law of heat conduction, the Fick law of diffusion. Note that the equations above can be put in matrix notation,

\[ \begin{pmatrix} J_q \\ J_n \end{pmatrix} = - \frac{1}{T} \begin{pmatrix} L_{qq} & L_{qn} \\ L_{nq} & L_{nn} \end{pmatrix} \begin{pmatrix} \nabla c \\ \nabla \tilde{\mu} \end{pmatrix} \]

Following the Onsager theory [11], we can identify the diagonal elements of the phenomenological matrix (8), \( L_{qq} \) and \( L_{nn} \) with heat conductivity and the electro-diffusion coefficient, the reciprocal relations are given by \( L_{qn} = L_{nq} \).

\[ \kappa = \frac{L_{qq}}{T^2} \quad D_n = \frac{R}{c} L_{nn} \]

the cross heat flow \(-\left( L_{qn}/T^2\right) \nabla T \), written in terms of the coefficient of thermal diffusion as \(-cD_T \nabla T \). Thus, the information about the cross effect of the electro-diffusion due to the thermal gradient is encoded in the Soret coefficient

\[ s_T = \frac{D_T}{D_n} = \frac{L_{qn}}{L_{nq} T^2 c} \]

Finally, as it is apparent from the Equations (4) and (7), it’s necessary to compute an explicit form of the temperature \( T(x, t) \), the ion concentration \( c(x, t) \) and the electric potential \( V(x, t) \). Therefore, to achieve this, we assume that the heat conduction equation, the diffusion equation and the Poisson equation provides a suitable description for the temperature, the ion concentration and the electrostatic potential along the channel,

\[ \frac{\partial^2 T(x, t)}{\partial x^2} = \kappa \frac{\partial T(x, t)}{\partial t} \]  
\[ \frac{\partial^2 c(x, t)}{\partial x^2} = D \frac{\partial c(x, t)}{\partial t} \]  
\[ \frac{\partial^2 V(x, t)}{\partial x^2} = \frac{\rho(x, t)}{\epsilon} \]

Where \( \kappa \), \( D \) and \( \epsilon \) are the heat conductivity coefficient, the diffusion coefficient and the electric permeability coefficient, respectively.

3. Experimental setup, initial and boundary conditions of the system

As a starting point we shall assume that the ion-channel protein is in thermal equilibrium with the intracellular environment,

\[ T(x, 0) = T_0 \]

In turn, due to external heat sources, the exterior edge of the channel changes its temperature so that the boundary conditions become non-homogeneous,

\[ T(0, t) = T_0 \]  
\[ T(L, t) = T_1 \]
Where \( T(0, t) = T(x, 0) \) because of the initial intra-cellular thermal equilibrium.

On the other hand, the experimental setup allow us to hold one of the boundary conditions of the ion concentration at a fixed value. Thus, by construction we shall keep a constant value for the ion concentration in the external side of the membrane, \( c(L, t) = c_0 \). Instead, the intra-cellular ion concentration, \( c(0, t) \), will be a function that only varies with time, \( c(0, t) = g(t) \).

The initial condition for the process, \( c(x, 0) \), encodes the information about the initial distribution of the ion concentration in the interior of the channel and correspond to a function of the position only. In this way, the simplest initial condition compatible with this scenario is a linear distribution of the concentration as a function of the position.

In Figure 1, we display a simple representation of the ion channel located in the cell membrane with the variables involved in the phenomena at the beginning of the diffusion process.

\[
\begin{align*}
T(0, t) &= T(x, 0) \\
n(0, t) &= n(x, 0) \\
L(t) &= L(0)
\end{align*}
\]

**Figure 1.** Simplified representation of the initial conditions of an isolated ion channel in experimental controlled conditions. The temperatures, \( T_1 \) and \( T_2 \), are considered constants; \( C_0 \) is controlled experimentally as constant and \( C(t) \) is the intra-cellular boundary condition. \( V_1 \) and \( V_2 \) are the voltages in each side of the membrane that are determined by the ion concentration. The yellow box is the inner section of the channel and \( F(x) \equiv C_0 \frac{z}{L} \) represents the initial function ion concentration.

Taking in account these considerations, the initial and boundary conditions for the diffusion Equation (13) are defined by

\[
\begin{align*}
    c(x, 0) &= \frac{c_0 x}{L} \\
    c(0, t) &= \frac{c_0 t}{\tau} \\
    c(L, t) &= c_0
\end{align*}
\]
In the latter expression, we have chosen the intra-cellular boundary condition \( c(0, t) \) as a linear function of time just for simplicity. The parameter \( \tau \) correspond to the characteristic time of the process.

As we have already discussed, the electrostatic potential is governed by the Poisson Equation (13),

\[
\epsilon \frac{\partial^2 V(x, t)}{\partial x^2} = z e c(x, t)
\]  

(20)

where the density charge \( \rho(x, t) \) is determined by the ion distribution \( c(x, t) \) times the electron charge \( e \) and valence number \( z \). Therefore, the initial and boundary conditions for the electrostatic potential \( V(x, t) \) are influenced by the conditions on the ion concentration.

4. Towards a complete description of the entropy production functional

Once we have the differential equations and the initial and boundary conditions well defined, we are able to compute the solution of the heat and diffusion equations. Despite the fact that the method of separation of variables [14] cannot be used for non-homogenous boundary conditions, it is possible to find an expression for \( T(x, t) \) as a combination of an stable solution independent of time plus a standard solution with homogeneous boundary conditions. Therefore, the temperature distribution takes the form

\[
T(x, t) = T_0 + \frac{T_1 - T_0}{L} x + 2 (T_0 - T_1) \sum_{n=1}^{\infty} \frac{(-1)^n}{n \pi} \sin \left( \frac{n \pi x}{L} \right) e^{-\left( \frac{n \pi}{L} \right)^2 t}
\]

(21)

On the other hand, the boundary value problem for the ion concentration distribution \( c(x, t) \) may be mapped into an homogeneous initial value problem for an auxiliar variable \( v(x, t) \) with an extra source term in the equation,

\[
\frac{\partial^2 v(x, t)}{\partial x^2} - D \frac{\partial v(x, t)}{\partial t} = \frac{D}{L} (L - x) c_0 \frac{\partial u}{\partial t}
\]

(22)

with homogeneous initial and boundary conditions, where \( v(x, t) \equiv c(x, t) + u(x, t) \) and \( u(x, t) \) is parametrized by \( u(x, t) = \frac{1}{2} [(L - x) g(t) + L f(x)] \), with \( g(t) = c_0 \frac{\tau}{L} \) and \( f(x) = \frac{\tau}{\pi} x \).

Then, we suppose that \( v(x, t) \) can be written as an infinite serie \( v(x, t) = \sum_n X_n(x) T_n(t) \).

Thus, the solution can be found by solving an eingenvaleu problem for \( X_n(x) \) and replacing it in Equation (22)

\[
X_n(x) = \sin \left( \frac{n \pi x}{L} \right) ; \quad n \geq 1
\]

(23)

\[
T_n(t) = \frac{2 D L^2 c_0}{n^2 \pi^3} \left( e^{\frac{2 n^2 x^2}{L^2}} - 1 \right)
\]

(24)

Replacing these both expression in the equation \( c(x, t) = u(x, t) - v(x, t) \), we find

\[
c(x, t) = c_0 + \frac{L - x t}{L} + \frac{2 D L^2 c_0}{n^2 \pi^3} \sum_{n=1}^{\infty} \sin \left( \frac{n \pi x}{L} \right) \left( e^{\frac{2 n^2 x^2}{L^2}} - 1 \right)
\]

(25)

Finally, for the electrostatic potential \( V(x, t) \) is enough to impose a constant boundary condition in the extra-cellular side, according to the ion concentration \( c(L, t) \) and a constant electric potential net flux in the boundaries of the channel, \( \frac{\partial V(0, t)}{\partial x} = 0 \). With this assumptions we integrate Equation (20), obtaining

\[
V(x, t) = \frac{z e}{\epsilon} \left( \frac{c_0 x^2}{2} + \frac{c_0 t}{\tau} \left( \frac{L - x}{L} \right) \right) x^2 + \frac{2 D L^2}{\pi^2} \sum_{n=1}^{\infty} \frac{T_n(t)}{n^2} \sin \left( \frac{n \pi x}{L} \right)
\]

(26)
5. Discussion
In the following points we discuss the future work directions:

- Once we have characterized the quantities $T(x,t)$, $c(x,t)$ and $V(x,t)$ explicitly in terms of the position and time, the next step is to analyze, by numerical methods, the entropy production Eq. (4). As a first approach we can plot the diagonal elements of $\sigma$, as a surface in terms of $(x,t)$, what maybe could be useful to compare thermo-channels with different experimental data of anomalous behaviour such as mutant channels with impaired conduction.

- One of the main goals of the paper is related to the phenomenological matrix Eq. (8). In particular, by determining the non-diagonal coefficient that encodes the cross effect of thermo-diffusion, we sought to classify the thermo-channels by the influence of the thermal current in the ion diffusion.

- Experimental approaches will be performed to test the model using heterologous system expressing TRP channels. Concretely, we are interested into measure the electro-diffusion and currents modulated by temperature in order to determine the phenomenological parameters in (8).

6. Conclusion
In this work we have proposed a biophysical model for the entropy production of ion channels dominated by ion diffusion and modulated by thermal fluctuations. Despite the simplicity of the model, we have shown that non-equilibrium thermodynamic provides a useful framework for the quantitative study of these proteins. Further investigation is needed in order to obtain a detailed description of the thermodynamics of these and others molecular machines.

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