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Abstract: Recently, the role of thermal resonance has been highlighted in living cells. As a consequence of this approach, the electrochemical potential was obtained in a partial differential equation concerning the cell membrane depth and its external temperature surface. In this paper, this last equation is studied and its solution's consequences are discussed concerning the cells' ion fluxes and their related entropy variation and power generation. Moreover, the metabolic power of the whole body is evaluated by using these previous numerical results.

Keywords: transport in living cells; cancer; membrane electrochemical potential

MSC: 80A17; 80A20

1. Introduction

The wave model approach to heat transfer in solids pointed out the finite speed propagation [1,2], analytically expressed by the relaxation time [3]. Experimental evidence supports the wave model approach [4,5], with a particular interest in the thermal wave speed and relaxation time for media with non-homogeneous inner structures [3]. Moreover, the wave model resulted in being very effective for temperature ripples propagating in solids under abrupt boundary heating [6] and thermal shock formation [7], for fast-propagating crack tips [8], in transient stages of material damage due to thermal cracking [9], and in solids subjected to periodic surface irradiations of heat flux [10]. In analysing the interaction between waves and systems, the resonant effect plays a fundamental role in physics. Any system has a proper oscillation frequency. Let us consider a wave (mechanical or electromagnetic) with the resonant frequency of a system, which affects the system itself. This wave forces the system to enter into vibration [11]. The resonant approach was also introduced in a biophysical study of cancer cell behaviour [12–14] based on the thermodynamic experimental analysis of heat flux [15–17]. Indeed, cells are open systems that convert their metabolic energy into mechanical and chemical processes. A thermodynamic approach models the cell as a thermodynamic engine able to convert inflow energy into work [18]. Healthy and tumour cells have two different metabolisms [19]:

- Healthy cells use the Krebs cycle, based on the oxidation of acetyl-CoA, derived from carbohydrates, fats, and proteins;
- Cancer cells use the Warburg cycle, which is a modified cell metabolism that favours a specialised fermentation over the aerobic respiration pathway.

Independently of the metabolic cycle used, any cell must outflow heat into its environment [18,20,21] through the cell membrane. However, different heat outflows occur for

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different cycles. Heat transfer through the cell membrane was studied using the thermo-kinetic lumped model [12–14], obtaining a characteristic resonant time. The theoretical results were experimentally confirmed [15–17], too.

This paper develops the analytical consequences of this approach to propose some considerations on cell membrane interactions with the cell environment, which could represent the analytical basis for experimental investigation with the aim of improving our knowledge on the role of heat and mass transfer through living cell membranes.

2. Materials and Methods

The non-equilibrium thermodynamic approach was introduced [22] to study the heat and mass transfer through the living cell membrane concerning cancer [14,23,24] and glaucoma [25], obtaining a physical–mathematical model in agreement with the experimental results reported in the literature [26–33]. To do so, the Onsager general phenomenological relations were used [21,23,34,35]:

$$\begin{cases} \mathbf{J}_e = -L_{11}\,\dfrac{\nabla \mu_e}{T} - L_{12}\,\dfrac{\nabla T}{T^2} \\ \mathbf{J}_Q = -L_{21}\,\dfrac{\nabla \mu_e}{T} - L_{22}\,\dfrac{\nabla T}{T^2} \end{cases} \tag{1}$$

where $\mathbf{J}_e$ is the net current density [A m^{-2}], related to ion fluxes through the membrane; $\mathbf{J}_Q$ denotes the heat flux [W m^{-2}]; $\mu_e = \mu + Ze\phi$ [18,35] is the electrochemical potential [J mol^{-1}], with μ the chemical potential [J mol^{-1}], ze the electric charge [A s mol^{-1}], and ϕ the membrane potential [V]; T is the living cell temperature; and L_{ij} represents the phenomenological coefficients, such that [18] $L_{12}(\mathbf{B}) = L_{21}(-\mathbf{B})$ (Onsager–Casimir relation [36]), $L_{11} \geq 0$ and $L_{22} \geq 0$, and [18] $L_{11}L_{22} - L_{12}L_{21} > 0$. Starting from these phenomenological relations, the following equation was deduced [22]:

$$\frac{\partial \mu_e}{\partial r} = \frac{\partial \mu_e}{\partial T}\,\frac{\alpha}{\lambda}\,(T_{surf} - T_0) \tag{2}$$

where α and λ are the convection and conduction coefficients, respectively, T_{surf} is the temperature of the membrane's external surface, and T_0 is the temperature of the cell's environment.

In this paper, we develop the analytical solution of this last equation and the consequences on cell behaviour. To do so, we consider splitting the electrochemical potential into its spatial and thermal components:

$$\mu_e = \vartheta(r)\,\varphi(T) \tag{3}$$

where $r = -\ell$ is the internal cell membrane surface, while $r = 0$ is the external cell's membrane surface with temperature $T(0) = T_{surf}$. Consequently, if we consider the temperature gradient through the membrane, and introduce the dimensionless variable $x = r/\ell$, it follows that

$$\frac{1}{\vartheta}\,\frac{d\vartheta}{dx} = \frac{1}{\varphi}\,\frac{d\varphi}{dT}\,\frac{\ell\,\alpha}{\lambda}\,(T_{surf} - T_0) \tag{4}$$

The integration [37] of this differential equation results in

$$\mu_e(r,T) = \gamma\,\exp\left(\frac{\lambda}{\alpha\,\ell\,(T_{surf} - T_0)}\,T + \frac{r}{\ell}\right) \tag{5}$$

where γ is the integration constant.

In Equation (5), the coefficient of convection can be evaluated as [12]

$$\alpha \approx \frac{0.023\,Re^{0.8}\,Pr^{0.35}\,\lambda}{\langle R \rangle} \tag{6}$$

where $\lambda \approx 0.6\,\mathrm{W\,m^{-1}K^{-1}}$ is the conductivity of water, used also for the biological tissue [14], $Re \approx 0.2$ is the Reynolds number, and $Pr \approx 6.9$ is the Prandtl number. The mean value of the cell radius $\langle R \rangle$ is considered of the order of 10^{-5} m. Consequently, the coefficient of convection results to be around $7.49 \times 10^{-8}\,\mathrm{W\,m^{-2}\,K^{-1}}$.

The surface temperature changes in relation to the metabolic and biochemical activity of the cell, but in stationary conditions it can be assumed that $T_{surf} - T_0 \approx 0.4\,^{\circ}\mathrm{C}$.

The constant γ can be obtained considering that the electrochemical potential on the external surface of the cell membrane is $\mu_e(0, T_{surf}) = \mu_{e,out}(T_{surf})$, so Equation (5) results in

$$\gamma = \mu_{e,out}(T_{surf})\,\exp\left(-\frac{\lambda}{\alpha\,\ell\,(T_{surf} - T_0)}\,T_{surf}\right) \tag{7}$$

When $r = -\ell$, with $\ell \approx 0.004\,\mu\mathrm{m}$ as the mean value of the cell membrane depth, then $\mu_e(\ell, T_{surf}) = \mu_{e,in}(T_{surf})$. Equation (5) results in

$$\mu_e(r, T) = \mu_{e,out}(T_{surf})\,\exp\left(\frac{\lambda\,(T - T_{surf})}{\alpha\,\ell\,(T_{surf} - T_0)} + \frac{r}{\ell}\right) \tag{8}$$

remembering that $\mu_e(0, T_{surf}) = \mu_{e,out}(T_{surf})$, $\mu_e(\ell, T_{surf}) = \mu_{e,in}(T_{surf})$.

3. Results

These results are in agreement with the present knowledge on the physiological behaviour of cells [38]. The result obtained is interesting because it represents the analytical approach to the living cell membrane electrochemical potential gradient. Indeed, it allows us to explain some experimental evidence that represents open problems in biophysics. In this paper, we have suggested a new viewpoint in relation to these biophysical aspects of cell behaviour, as deeply discussed in the next section.

Now, we consider the second law of thermodynamics [39]:

$$T\,\frac{ds}{dt} = \nabla \cdot \left(\mathbf{J}_Q - \sum_{i=1}^{N} \mu_i\,\mathbf{J}_i\right) - \sum_{i=1}^{N} \mathbf{J}_i \cdot \nabla \mu_i \tag{9}$$

where s is the specific entropy, T is the temperature, and μ is the chemical potential. $\mathbf{J}_S = \mathbf{J}_Q - \sum_{i=1}^{N} \mu_i\,\mathbf{J}_i$ is the contribution of the inflows and outflows, and $T\sigma = -\sum_{i=1}^{N} \mathbf{J}_i \cdot \nabla \mu_i$ is the dissipation function [34]. This law allows us to evaluate the effect of the ion fluxes. To do so, we consider the better condition for life ($T\sigma \approx 0$) such that Equation (9) becomes

$$T\,\frac{ds}{dt} = -\nabla \cdot \left(\mathbf{J}_Q - \sum_{i=1}^{N} \mu_i\,\mathbf{J}_i\right) \tag{10}$$

Following the Prigogine approach ($ds/dt = 0$) [39], with T constant, Equation (10) becomes

$$\nabla \cdot \left(\mathbf{J}_Q - \sum_{i=1}^{N} \mu_i\,\mathbf{J}_i\right) = 0 \tag{11}$$

Now, we consider the first law of thermodynamics for the cell membrane [23]

$$\frac{du}{dt}\,dV = \rho\,c\,\frac{dT}{dt}\,dV = \delta\dot{Q} = -\alpha\,(T - T_0)\,dA \tag{12}$$

where $\rho \approx 10^3\,\mathrm{kg\,m^{-3}}$ is the cell density, $c \approx 4186\,\mathrm{J\,kg^{-1}\,K^{-1}}$ is the specific heat of the cell, $\alpha \approx 7.49 \times 10^{-8}\,\mathrm{W\,m^{-2}\,K^{-1}}$, as previously evaluated, A is the area of the cell membrane, V is the cell volume, and $\beta = \alpha\,dA/dV$ is constant [23]. Thus, it follows that

$$\nabla \cdot \mathbf{J}_Q = \alpha\,\frac{dA}{dV}\,(T - T_0) \tag{13}$$

and

$$\sum_{i=1}^{N} \nabla \cdot \mu_i \mathbf{J}_i = \frac{\delta \dot{Q}}{dV} = \alpha \frac{dA}{dV} (T - T_0) \tag{14}$$

$$\sum_{i=1}^{N} \mu_i \mathbf{J}_i \approx \frac{\ell \cdot \alpha}{\langle R \rangle} (T - T_0) \tag{15}$$

where $\ell \approx 0.004$ µm is the depth of the cell membrane [40] and $\langle R \rangle$ is the mean radius of the cell, considered, in the first approximation, as a sphere of mean radius of the order of 10^{-6}–10^{-5} m, and $T - T_0 \approx 0.4$ °C [41]. To develop the physical analysis of the mathematical results, we can evaluate the power generated by the cell by means of these fundamental fluxes for its life. Considering that the electric potential at the membrane is of the order of 10–100 mV and its electric field is of the order of 10^7–10^8 V m^{-1}, we can evaluate the basal metabolism as the power generated by the fluxes of the fundamental ions (Na^+, K^+, Cl^-, Ca^{2+})

$$\begin{aligned} \dot{W} &= \sum_i \frac{\ell \cdot \alpha}{\mu_i \cdot \langle R \rangle} (T - T_0) \cdot \mathcal{N} \cdot Z_i e \cdot E_i \cdot 4\pi \langle R \rangle^2 \\ &= \sum_i \frac{\ell \cdot 0.023 Re^{0.8} Pr^{0.35} \lambda}{\mu_i \cdot \langle R \rangle^2} (T - T_0) \cdot \mathcal{N} \cdot Z_i e \cdot E_i \cdot 4\pi \langle R \rangle^2 = \\ &= 4\pi \cdot \mathcal{N} e \cdot (T - T_0) \cdot \ell \cdot 0.023 Re^{0.8} Pr^{0.35} \lambda \cdot \sum_i \frac{Z_i \cdot E_i}{\mu_i} \end{aligned} \tag{16}$$

where $\mathcal{N} = 6.022 \times 10^{23}$ mol^{-1}, $e = 1.6 \times 10^{-19}$. Concerning the value of the elementary electric charge, $Z_i = 1$ for $i = Na^+$, K^+, $Z_i = -1$ for $i = Cl^+$, $Z_i = 2$ for $i = Ca^{2+}$, and E is the electric field. The metabolic power of a cell is 5.79×10^{-12} W. Considering the total number of cells in a body (30.0×10^{12} [40]), the metabolic power of a human body is 174 W. Considering an efficiency of around 40% (around 60% is outflown as heat) [40], the available power for the human body is around 70 W, of which around 75% is used to perform essential body functions, while 25% is used to maintain the electrical potential of the nerve cells in agreement with the accepted value in medicine [40].

4. Discussion and Conslusions

All living cells maintain a potential difference through their membrane. This results from different concentrations and permeabilities of ions across the living cell membrane. The transport of ions, nutrients, molecules, and water (active and passive) is achieved by channels and pumps within the cell membrane. This transport changes the internal and external ionic concentrations. Any change in membrane potential allows the cell to communicate and obtain information due to the electrical signals related to any potential variation. Active and passive ion transports across the cellular membrane contribute to the change in membrane potentials [42]. So, cells must continuously balance mass transport to maintain their electric membrane potential to regulate normal cell functions [43], for example

- Mitogen-stimulated cell proliferation, mediated by K^+ channel [44];
- K^+ channel inhibitors can block the activation of murine B lymphocytes and murine noncytolytic T lymphocytes [45];
- Ca^{2+} inflow drives G1/S transition [46];
- Mice teratocarcinoma cells express L-type Ca^{2+} and outward channels, and Na^+ and inward rectifier channels during differentiation.

The transport of some molecules, such as water, can occur due to concentration gradients, while for macromolecules, such as glucose or nucleotides, channels are needed [38]. For some ions, ATPase pumps are present as ion transporters and voltage-gated channels. Moreover, transport proteins can pump ions against their concentration gradient. An example is the transport of Sodium (Na^+) and Potassium (K^+). Table 1 represents their concentration and respective electric potentials.

Table 1. Concentration, chemical potential (in water solution), and electric membrane potential of some ions in normal cells [42].

Ion Species	Extracellular Concentration	Intracellular Concentration	Chemical Potential μ_i	Membrane Potential E_i
	[mM]	[mM]	[kJ mol^{-1}]	[mV]
Na^+	18	150	−261.89	+56
K^+	140	5	−283.26	−89
Cl^-	120	7	−131.26	−76
Ca^{2+}	1.2	0.1	−553.04	+125

Concerning the Na^+/K^+ pump, we can highlight that Na^+ presents a higher concentration outside of the cell while K^+ presents a high concentration inside the cell. Consequently, an active outflow transport of Na^+ and an active inflow of K^+ follows. Moreover, for the Ca^{2+} ion inflow, concerning cancer, this induces a growth decrease.

In summary, this paper is an improvement of the previous one on thermal resonance [13,14]. In that paper, a differential equation concerning the electrochemical potential was obtained. Here, the analytical solution of that equation is obtained and its biophysical consequences are discussed. The result obtained here allows us to evaluate the power generation of the living cells obtained by ion fluxes through the cells' membranes.

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