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ATP Consumption and Neural Electrical Activity: A Physiological Model for Brain Imaging

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Abstract— **The relation between neural electrical activity and oxygen consumption is the key issue in almost all brain image modalities based on perfusion. Despite the large amount of physiological information available in the literature about the processes involved in neural activation, a practical, tractable and simultaneously accurate mathematical model to describe this relation is needed.**

The *sodium-potassium pump* (Na,K-ATPase) and its *adenosine triphosphate* (ATP) consumption seems to play a central role in this process. The Na,K-ATPase activity is deeply related with the spike density and this pump is the main consumer of the energy used in the brain, particularly, within the neuron.

In this paper we present a mathematical model relating the temporal spike density across the neuron, which reflects the electrical activity, with the corresponding ATP consumption rate. The expenditure of ATP stimulate the metabolic pathways responsible for the ATP synthesis, for instance, the aerobic pathway via the *Krebs cycle*. The main motivation to derive this model is its inclusion in a larger model of the *Haemodynamic Response Function* (HRF) for *functional Magnetic Resonance Imaging* (fMRI) analysis.

The model, depending on several parameters, is linear and was tunned with physiological information obtained from the literature.

I. Introduction

fMRI is becoming a widely used tool for brain mapping and studying the neural basis of human cognition. The *blood-oxygen-level dependent* (BOLD) signal measures local changes in the *haemodynamic response* that indirectly reflects the neural activity [1], [2]. Although knowledge is expanding rapidly, the physiological basis underlying this coupling remains unclear, since the biological and neurophysiological processes occurring within the brain cells and their microvasculature are complex [3].

In the last years, the contribution of both spike and synaptic activity to the BOLD signal has been studied. Currently, it is admitted that functional activation is associated to both processes [1], since they are strongly correlated in many cases, specially in sensory cortices [2]. Neuronal signaling, which concerns spike and synaptic activity, involves ionic flow through specific channels present in the neuronal membrane. These ionic currents are restored by the Na,K-ATPase [4]. It was shown that blocking this enzyme reduces the energy consumption for less than half, for the whole brain, leaving a residual energy expenditure which likely sustains basic cellular activities that are not deeply correlated with signaling [5]. Thus, the ATP metabolism is due mainly, if not entirely, to the Na,K-ATPase activity [1].

In this paper, it is proposed a linear mathematical model to describe the coupling between the electrical activity and the energy consumption in a single neuron. Further, this model can be easily extended to a neuron mass model. The aim is to describe the dynamics of the ionic intracellular concentration and its effects on the Na,K-ATPase activity, particularly, its ATP expenditure. ATP is regenerated mainly via the *Krebs cycle*, that occurs within the neuron, leading to a localized increase of the cerebral metabolic rate of oxygen, which is measured by the BOLD signal. This metabolic process will be incorporated, in future work, as well as the features related to the regional increase of the blood flow, to build a mathematical model linking the *haemodynamic response* to the correspondent *neural electrical activity*.

A. Physiological background

The neuron is the basic structural unit of the nervous system. It is highly specialized for the processing and transmission of signals since its membrane is capable to produce electrochemical impulses and conduct them along the membrane [6]. This cell has a characteristic negative resting voltage with respect to its outer surface, which results from the differences in ion concentration (namely Na^+, K^+, Cl^-) on opposite sides of the membrane [4]. Under normal resting conditions, the ion flow, by means of *leakage channels*, is permanent and determined by the isostatic balance between the electrostatic force and ion diffusion [6].

The action potential is used for long-distance information transmission. It has been shown that it is generated by ionic current through nonlinear ionic channels [7]. Once a nerve cell is activated, the sodium conductance increases sharply and there is an influx of Na^+, causing membrane depolarization. Afterward, the rapid increase of potassium conductance allows the efflux of K^+, reestablishing the intracellular potential. The open-close mechanism of the *voltage-gated channels* happens in a fraction of a millisecond and the duration of the nerve impulse is around 1ms [4]. Once activation occurs, the membrane is insensitive to new stimuli. This phase, called the *absolute refractory period*, has a duration that nearly matches with the entire time course of the action potential [6].

The ions uptake and extrusion constantly modifies the ionic concentrations of the intracellular and extracellular space. The ionic composition is maintained by the Na,K-ATPase, which transfers, against the concentration gradient, the Na^+ back outside the membrane and K^+ back inside the

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membrane with a stoichiometric ratio of $3Na^+$:$2K^+$:1ATP [4]. The ionic flow associated with action potentials are here considered instantaneous events, since their time constants are much smaller than the long-term Na,K-ATPase activity, which is the key issue of this paper.

II. Model Description

The proposed mathematical model considers the significant ionic currents (Na^+ and K^+) flowing through the membrane channels by means of both passive and active transport. The following balance equations governs the rate of change of intracellular ionic concentration of sodium, Na, and potassium, K

$$\frac{dNa}{dt} = \alpha\nabla Na + \beta\nabla V - 3\nu_{pump} + \epsilon_N r(t), \quad (1)$$

$$\frac{dK}{dt} = \gamma\nabla K + \delta\nabla V + 2\nu_{pump} + \epsilon_K r(t), \quad (2)$$

where $\nabla Na = (Na_e - Na)/x$ and $\nabla K = (K_e - K)/x$ denote the concentration gradients of Na^+ and K^+, respectively. Na_e and K_e are the extracellular concentrations of Na^+ and K^+, x is the membrane thickness and ν_{pump} describes the Na,K-ATPase activity. The neuronal activity is given by $r(t)$. Furthermore, by multiplying $r(t)$ by the parameters ϵ_N or ϵ_K, it is obtained the rate, per volume unit, of Na^+ inflow or K^+ outflow, respectively, in response to the neuron stimulation. Therefore, this represents the ionic exchanges between the intracellular and extracellular spaces that occurs either during action potential firing or when excitatory synapses are activated.

This model describes the ion passive transport across the membrane similarly to the *Nernst-Planck Equation* [6]. The first term in the right hand side of equations (1) and (2) represents the ion diffusion led by the concentration gradient, while the second terms takes into account the influence of the electric field in its diffusion. This term depends linearly on the differences of ionic concentrations at each side of the neuronal membrane

$$\nabla V = \frac{V_e - V_i}{x} = -\xi\frac{(Na_e - Na + K_e - K)}{x}, \quad (3)$$

where V_e is the extracellular potential and is assumed the reference ($V_e = 0V$), V_i is the intracellular potential and ξ is the constant of proportionality.

According to the literature [4], [8], the Na,K-ATPase activity rate, ν_{pump}, is proportional to Na,

$$\nu_{pump} = \rho Na \quad (4)$$

where ρ is the constant of proportionality. In equations (1) and (2), the Na,K-ATPase stoichiometry is considered: each ATP molecule is used to pump in $2K^+$ and pump out $3Na^+$.

The Na,K-ATPase needs energy to transport the ions against their concentration gradient. However, under normal conditions, it is expected that the ATP synthesis is adapted to the cell energy demands. Thus, it is assumed enough ATP concentration within the neuron for a properly working of the Na,K-ATPase, which means, the pump activity only depends on the Na and not on the ATP availability.

Table I lists the physiological constants, obtained from the literature, used to calculate some parameters of the model. The parameters α and γ are proportional to the diffusion coefficients of Na, D_{Na}, and K, D_K, whereas β and δ are proportional to the ion mobility of Na, μ_{Na}, and K, μ_K. Na_e and K_e are assumed to be constant. S_m denotes the cell membrane area and V_{in} is the intracellular volume, k_P is the kinetic constant of Na,K-ATPase, $K_{m,P}$ denotes the *Michaelis* constant of Na,K-ATPase for ATP uptake and ATP_c is the concentration of ATP that is constantly available in the neuron.

TABLE I
Physiological parameters values [4], [6] [9], [8].

Parameter	Values
$\alpha' = \frac{\alpha}{x} = \frac{D_{Na}}{x}.\chi_1$	Na_e = 150 mM
	K_e = 5.5 mM
$\gamma' = \frac{\gamma}{x} = \frac{D_K}{x}.\chi_1$	$x = 5\times10^{-7} cm$
	D_{Na} = $1.33\times10^{-5} cm^2 s^{-1}$
$\beta' = \frac{\beta}{x}.\xi = \frac{\mu_{Na}}{x}.\xi.\chi_2$	D_K = $1.96\times10^{-5} cm^2 s^{-1}$
	μ_{Na}=$5.19\times10^{-4} cm^2 V^{-1} s^{-1}$
$\delta' = \frac{\delta}{x}.\xi = \frac{\mu_K}{x}.\xi.\chi_2$	μ_K=$7.62\times10^{-4} cm^2 V^{-1} s^{-1}$
	S_m/V_{in}= $9\times10^4 cm^{-1}$
$\rho = S_m/V_{in}.k_P.\lambda$	k_P= $0.29\times10^{-6} cm\ mM^{-1} s^{-1}$
$\lambda = ATP_c(1 + \frac{ATP_c}{K_{m,P}})^{-1}$	ATP_c = 2.2 mM
	$K_{m,P}$ = 0.5 mM

The parameters ξ, χ_1 and χ_2 are calculated assuming the following stationary conditions, $d/dt = 0$, of equations (1) and (2): i) the membrane potential is $V_i = -0.080$ V and ii) the intracellular ionic concentrations are $Na = 15$ mM and $K = 140$ mM [4], [6].

The parameter ξ converts the differences of concentration on potential and is calculated using equation (3):

$$\xi = \frac{V_i}{Na_e - Na + K_e - K} = -0.16V.mM^{-1}. \quad (5)$$

Regarding the parameters χ_1 and χ_2, they are used to adjust the unities of the first and second terms on equations (1) and (2), respectively (see Table I). Considering the steady-state, χ_1 and χ_2 rest the only unknowns of equations (1) and (2) and they are calculated with the following system of two equations, written in the matrix form:

$$\begin{bmatrix} \frac{D_{Na}}{x}(Na_e - Na) & -\frac{\mu_{Na}}{x}V_i \\ \frac{D_K}{x}(K_e - K) & -\frac{\mu_K}{x}V_i \end{bmatrix} \cdot \begin{bmatrix} \chi_1 \\ \chi_2 \end{bmatrix} = \begin{bmatrix} 3\rho Na \\ -2\rho Na \end{bmatrix}. \quad (6)$$

The solution of the system (6) is $\chi_1 = 9.5 \times 10^{-5} cm^{-1}$ and $\chi_2 = 1.5 \times 10^{-3} cm^{-1}.mM^2$.

An action potential sequence can be characterized by a list of spike occurrence times. In a continuous time model, each spike is represented by ideal *Dirac* pulses [10]. Therefore, $r(t)$, is modeled as a train of pulses with frequency f (period $T = 1/f$) and magnitude A. Since the magnitude of the pulses for a given neuron is assumed constant, $r(t)$ (see Fig. 1 (a)) is characterized by the pulse density, or equivalently, by its frequency. As referred before, the sudden variation in Na and K, associated with action potentials, is fast enough (about 1 ms) to be approximated by a step function. Consequently, the train of pulses are converted into ideal step

ionic entrances or extrusions by integration, as shown in Fig. 1 (b) for the case of Na^+ ions.

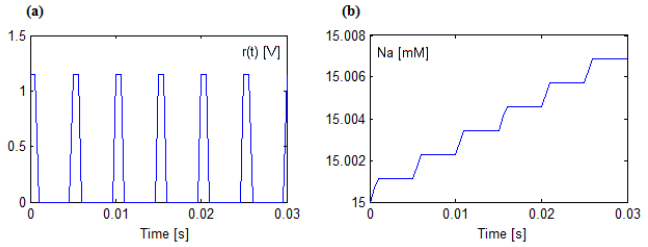

Fig. 1. (a) Sequence of pulses with a time pulse $\tau = 1$ms, frequency $f = 200$Hz and amplitude $A = 1.15$V, to stimulate the neuronal membrane. (b) Change in Na after the stimulus. The initial value for Na is 15mM. The positive direction is that from extracellular fluid to the intracellular one. Each spike is associated with the increase of Na, which is followed by a slightly decrease in Na. This is due to the Na,K-ATPase activity, whose time constant is not sufficient to reestablish ion concentration to its resting value, before the next spike.

The parameters ϵ_N and ϵ_K, are equal to 1 $\text{mMs}^{-1}\text{V}^{-1}$, since it is considered [5] that action potential involve an equal influx and efflux of Na^+ and K^+, respectively, to bring the membrane potential essentially back to its resting value.

The transfer function of this MIMO (multi-input, multi-output) system can be obtained by applying the Laplace transform to both equations (1) and (2). After some straightforward simplifications and arrangements the following second-order Transfer Functions is obtained,

$$Na(s) = G_{Na_e}(s)Na_e + G_{K_e}(s)K_e + G_{r(t)}(s)R(s) \quad (7)$$

$$K(s) = H_{Na_e}(s)Na_e + H_{K_e}(s)K_e + H_{r(t)}(s)R(s) \quad (8)$$

where the functions $G_{Na_e}(s)$, $G_{K_e}(s)$, $G_{r(t)}(s)$, $H_{Na_e}(s)$, $H_{K_e}(s)$ and $H_{r(t)}(s)$ are second order systems (two poles) with a zero.

As stated above, the Na,K-ATPase is the major consumer of ATP within the neuron. Further, given the stoichiometry of the pump, its ATP consumption rate (ATP_r) is given by the Na,K-ATPase activity rate, ν_{pump}. Consequently it is proportional to Na, $APT_r(t) = \rho Na(t)$. Therefore the relation between ATP_r with the neuronal electrical activity can be derived directly from equation (7), being a second order system (two poles) with a zero

$$ATP_r(s) = \rho \frac{\eta_1 s + \eta_2}{s^2 + \psi_1 s + \psi_2} R(s), \quad (9)$$

where

$$\eta_1 = \epsilon_N, \quad (10)$$

$$\eta_2 = \epsilon_K \beta' + \epsilon_N(\gamma' + \delta'), \quad (11)$$

$$\psi_1 = \alpha' + \beta' + \gamma' + \delta' + 3\rho, \quad (12)$$

$$\psi_2 = (\alpha' + 3\rho)(\gamma' + \delta') + \beta'\gamma' + 2\rho\beta'. \quad (13)$$

III. Results and Discussion

A MatLab/Simulink model, displayed in Fig. 2, is used to simulate the equations (1) and (2) and compare the results with real ones obtained from the literature. In a

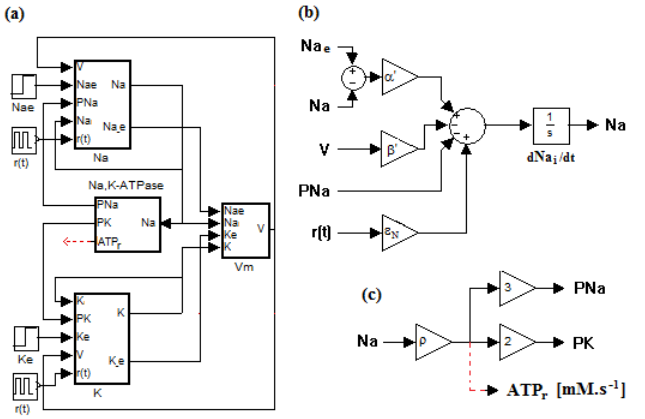

Fig. 2. **(a)** The proposed model divided into different blocks: **Na** and **K** compute Na and K; **Na,K-ATPase** represents the pump; **Vm** computes the sum of the concentration gradients of Na^+ and K^+ that, multiplied by ξ (see equation (3) and Table I), represents the intracellular potential. **(b)** The **Na** block. **(c)** The **Na,K-ATPase** block.

first experiment the dynamics of Na, K and ATP_r was computed when the neuronal membrane is stimulated by a *spike train* (see Fig. 4.a)). In a second experiment it is shown that the same response is obtained if the input is a *sustained activation* (square pulse) with magnitude equal to the mean value of the previous applied pulse train, (see Fig. 4.b)), which confirms that the metabolic dynamics mainly depends on the spike density [5]. Finally, the neuronal membrane is stimulated by a *repetitive activation* (see Fig. 4.c)). These last two experiments have a good agreement with the results published in [8] (see Fig. 3) that are consistent with experimental results, namely in human primary visual cortex.

In all experiments a 360 sec period of stimulations is followed by a 360 sec period without simulation, as shown in Fig.4.

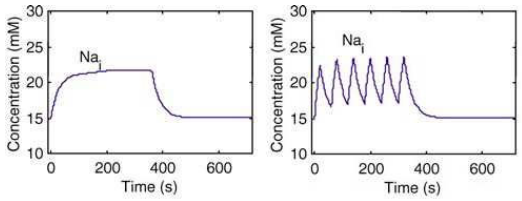

Fig. 3. Na_i (intracellular concentration of sodium) dynamics when the neuronal membrane is stimulated by a *sustained activation* (left) and a *repetitive activation* (right) for 0s<t<360s, followed by a control period of the same duration. The initial value for Na_i is 15mM. The positive direction is that from extracellular fluid to the intracellular one (in [8]).

In Fig. 4 (a) the neuronal membrane is stimulated with a train of pulses, each one with a typical time width of $\tau = 1$ms, frequency $f = 200$Hz and magnitude $A = 1.15$V with a mean value at the input of 0.23V [8].

The second-order system described in (9) presents a typical response of a first order systems. The analysis of the pole-zero map, displayed in Fig. 5 supports this observation. In fact, by using the parameters with physiological meaning

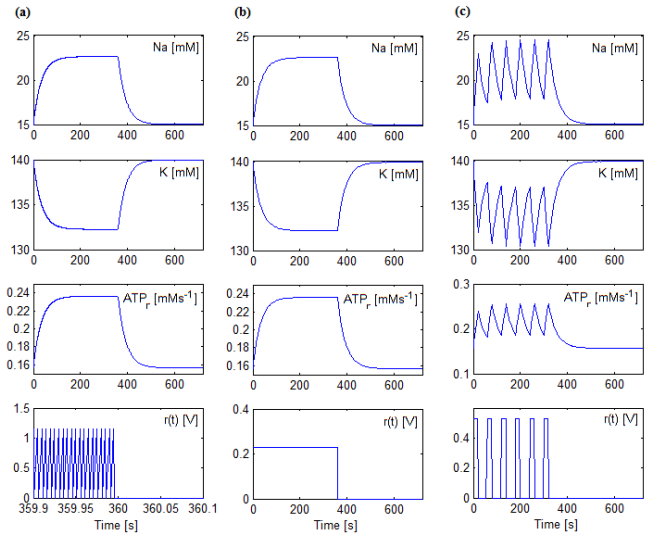

Fig. 4. Dynamics of Na, K and ATP_r in the case of **(a)** a *spike train activation* (sequence of *Dirac* pulses) for $0s < t < 360s$. $f = 200$Hz, $\tau = 1$ms and $A = 1.15$V; **(b)** a *sustained activation* for $0s < t < 360s$ with $A = 0.23$V; and **(c)** a *repetitive activation* for $0s < t < 360s$: 6 cycles of 60s time period, time pulse of 20s and $A = 0.53$V.

the zero almost cancel one of the poles, leading to a configuration of dominant pole, $p = -0.029\ rad.s^{-1}$, corresponding to a time constant of $1/0.029 \simeq 35\ s$ which is consistent with the values published in the literature for the time constant of Na for mammalian CNS neurons [8]. Since the Na,K-ATPase activity depends on the Na [4], [8] and the pump is the main ATP consumer [1], the computed time constant for Na is also a consistent time constant value for ATP_r dynamics.

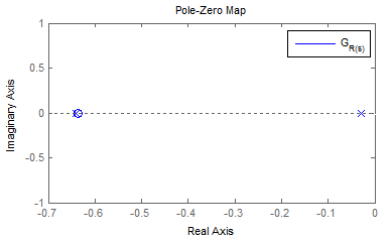

Fig. 5. Pole-Zero Map of the Transfer Functions of equation (9). The zero is $z \simeq -0.637 rads^{-1}$ and the poles are $p_1 \simeq -0.029 rads^{-1}$, $p_2 \simeq -0.641 rads^{-1}$.

Figure 4 (b) presents the evolution of Na, K and ATP_r for a sustained activation of the neuron, when $r(t) = 0.23$ V. The results are similar to those obtained in the first experiment, when stimulating with a train of pulses with a mean value $< r(t) >= 0.23$ V. Hence, the dynamic of the variables is actually dependent on the spike density.

In figure 4 (c) the input consists in a *repetitive activation*. The stimulus, $r(t) = 0.53$ V, is given within 20 sec in 6 cycles with a period of 60 sec. During the 40 sec of control the ionic concentrations approaches their resting values, due to the Na,K-ATPase activity. However, its time rate is not sufficient to reestablish these values.

The aim of experiments (b) and (c) is to reproduce the same simulations found in the literature [8]. The results obtained for Na with the proposed linear model are consistent with those obtained by these authors (compare Fig.3 with the Na dynamics of Fig.4 (b) and (c)). Regarding the results for ATP_r, it is not possible to compare them directly, nevertheless, the physiological-based assumption regarding the dependence on Na of the Na,K-ATPase activity, as well as knowing its stoichiometry, suggest the goodness of the model to describe the relation of the electrical activity with the ATP consumption rate.

IV. Conclusions

In this paper a physiological-based model to describe the relation between the neural electrical activity with the corresponding ATP consumption rate is presented. The linear model, tunned with parameters with physiological meaning extracted from the literature, shows considerable agreement with data obtained from in vivo specimens.

The overall *transfer function* (TF) relating the ATP consumption rate with the electrical activity, mainly described by the spike density, is a second order system with a zero. However, the zero cancels the effect of one of the poles, leading to a dominant pole condition. Therefore, the resulting TF is equivalent to a first order linear system with a time constant of $1/0.029 \simeq 35\ s$ which is consistent with the values published in the literature for the time constant of Na for mammalian CNS neurons.

This model will be included in a more general parametric one, aiming at describe the *Haemodynamic Response Function* (HRF) used in *functional Resonance Magnetic Imaging* (fMRI).

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