MATHEMATICAL MODELING OF THE COUPLING BETWEEN BRAIN ELECTRICAL ACTIVITY, METABOLISM AND HEMODYNAMICS

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Abstract. The coupling between neuronal electrical activity, metabolism and hemodynamics involves diverse physiological mechanisms and biochemists, as neuronal activation, energy metabolism, the Na^+/K^+-ATPase pump activity, mitochondrial respiration, conversion of the phosphocreatine in creatine and exchanges of oxygen, glucose and lactate through the blood-brain barrier. These mechanisms are activated when the cell receives signal that the metabolic processes inside it are excited or sped up, in order to activate the reactions system that produce ATP and, consequently, to induce an increase in the capillaries blood flow. The kinetic models of consume and formation of ATP and ADP play basic role in the mathematical modeling of the coupling, so they bind cellular ionic processes to the energetic metabolism. The considered mathematical model adds to the existing models in literature the kinetic equations for ATP and ADP enclosing the reaction of conversion of the phosphocreatine in creatine, the glycolytic reactions of which they participate, the consume of ATP and the consequent production of ADP for the activity of the Na^+/K^+-ATPase pump and for other enzymatic processes. An equation for the reversible reaction catalyzed by the adenylate kinase enzyme is proposed in this work. The resultant mathematical model is composed for 14 ordinary differential equations, and is numerically solved using the Euler Method. The model predicts appropriately the *in vivo* metabolic concentrations and, therefore, is validated for comparison with data contained in literature.

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Keywords: Mathematical model, Metabolism, Hemodynamics

1. Introduction

The human brain is extremely dependent of the metabolism to keep its functional and structural integrity and requires a continuous and adequate oxygen and glucose supply, which are sent to the brain for the blood circulation. The blood circulation is regulated so that the cerebral blood flow is kept constant in diverse situations. Diverse studies affirm that the cerebral blood flow (CBF), the cerebral metabolic rate of oxygen ($CMRO_2$) and the cerebral metabolic rate of glucose use (CMRglc) are firmly connected in the rest and during neural activations (Kastrup et al., 2002). The regulation of the oxygen and glucose supply for the CBF is adjusted in accordance with the necessities of the tissue and is essential for ATP production.

When a cell receives a signal that metabolic processes inside of it are excited or sped up, the system of reactions that produce ATP also must, directly or indirectly, be activated to satisfy the increase of the ATP consume rate. In excitable tissues, the extracellular signals that stimulate the metabolism are produced by neural stimulations. In function of the increase of the ATP consume rate, the local blood flow will have to increase in order to supply energy substrates to the cell. Initially the ATP is produced by the conversion of the PCr in Cr in the reaction catalyzed for the creatine kinase, but the main source of ATP is the oxidative metabolism (Korzeniewski, 2000).

Bradford (1986) emphasizes that the correlation between neural activity and the increase of the glucose oxidation is notable, indicating that variations in the energy metabolism occur during the functional reply, what comes followed, consequently, of equivalents increases in the CBF. In this direction, Zigmond et al. (1999) affirm that the neuronal activity is firmly connected to the blood flow and the metabolism.

Modern techniques of functional cerebral image make possible the *in vivo* observation of the blood flow, the glucose use and the consume of oxygen associated with neuronal activity. Although the development of these techniques, the physiological mechanisms and involved biochemists in the coupling between CBF and $CMRO_2$, in cerebral states physiologically activated, are not totally understood (Bradford, 1986 and Zigmond et al., 1999). Zigmond et al. (1999) stand out that the search for the

identification of the chemical mediators and the main mechanisms that can bind the neural activity to the local increases in the blood flow and to the metabolism is intense.

Aubert et al. (2001) and Aubert and Costalat (2002) present a mathematical model of the coupling that includes the main involved processes in the cerebral activation. These studies enclose electrophysiological aspects, activity of the Na^+/K^+-ATPase pump, energetic metabolism, glucose, oxygen and lactate transport through blood brain barrier and cerebral hemodynamics.

Most of mathematical models possess a high degree of simplicity in order to diminish the number of equations, parameters and variables to be analyzed and to facilitate the numerical solution of the same ones. This work has the objective to develop a mathematical model that describe the concentration variations of the diverse involved metabolites in the process of coupling between cerebral electrical activity, metabolism and hemodynamics with time. The considered mathematical model adds to the existing models in literature the kinetic equations for ATP and ADP based on the conversion reaction of the fosfocreatine in creatine, in the diverse glycolytic reactions of which these composites participate, in the ATP consume and consequent production of ADP for the activity of the Na^+/K^+-ATPase pump and other enzymatic processes. An equation for the reversible reaction catalyzed by the adenylate kinase enzyme is proposed. This equation was enclosed in the ordinary differential equations of ATP and ADP.

2. Mathematical modeling

The transport of oxygen and glucose to the cell, as well as of the residues of the metabolism, occurs in the interior of capillaries. When the cell is stimulated, due to pre or post-synaptic electrical activity, the opening of the cell sodium channels occurs, increasing the intracellular concentration of this ion. As consequence, the Na^+/K^+-ATPase pump is activated in order to restore the intracellular ionic concentration. This pump carries through the active transport of three sodium ions for the outside of the cell and two potassium ions for inside of the cell. Therefore, the own pump tends to create a potential difference through the cellular membrane. Since this pump must carry Na^+ against both concentration as electrostatic gradients, its operation demands consume of metabolic energy (Berne and Levy, 1996). In this direction, Aubert et al. (2001) emphasize that, to describe the course of the main involved variables in the exchanges

between capillaries and cells, it is necessary to assume the hypothesis that the coupling between cerebral electrical activity and metabolism must, mainly, to the ATP consume by the Na^+/K^+-ATPase pump.

To regenerate the ATP consumed by the Na^+/K^+-ATPase pump one of the mechanisms used for the cell is glycolysis. In accordance with Figure 1, the glucose enters in the cell and by means of many glycolytic reactions is transformed into pyruvate. Under anaerobic conditions, the pyruvate is converted into lactate having allowed the NAD^+ generation, that is essential to keep a continuous glycolytic flow (Zigmond et al., 1999). Figure 1 shows, beyond glycolysis, other mechanisms for ATP regeneration that, according to Aubert and Costalat (2002), are the mitochondrial respiration, that consume intracellular oxygen and pyruvate by means of the tricarboxylic acid cycle, and the conversion of the phosphocreatine in creatine.

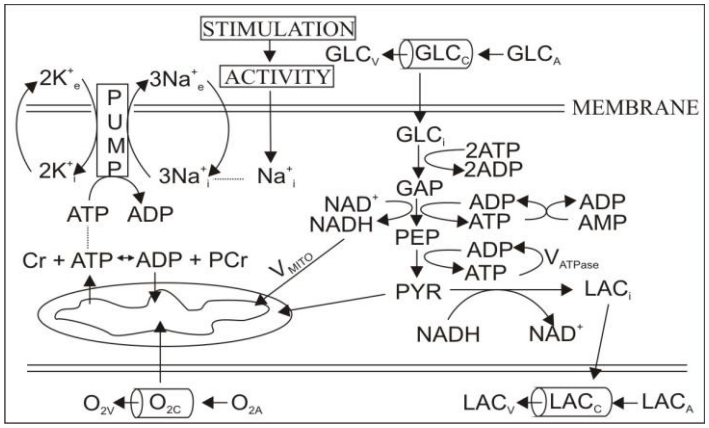

Fig. 1: Mechanisms of ATP regeneration with the conventional reactions orientations.
Source: Aubert et al. (2001).

Table 1 presents the main involved kinetic reactions in the glycolytic process, the reactions that describe the consume of ATP by the Na^+/K^+-ATPase pump and other enzymatic processes, as well as the kinetic reaction of ATP production by the phosphocreatine (PCr). In this table, the GLC_i, ATP, GAP, ADP, NAD^+, PEP, NADH, AMP, PYR, LAC_i, PCr and Cr expressions, represent the intracellular glucose, adenosine triphosphate, the glyceraldehyde-3-phosphate, adenosine diphosphate, the oxidized form of nicotinamide adenine dinucleotide, the phosphoenolpyruvate, the reduced form of nicotinamide adenine dinucleotide, adenosine monophosphate, intracellular lactate, the phosphocreatine and the creatine respectively. The $K_{HK\text{-}PFK}$,

K_{PGK}, K_{PK}, K_{LDH}, K_{CK}, K_{AK}, K_{pump} and K_{ATPase} terms are, in turn, the kinetic constants of the reactions.

Table 1: Considered kinetic reactions in this mathematical model.

Responsible enzymes	**Kinetics reactions**
Hexokinase - phosphofructokinase system (HK-PFK)	$GLC_i + 2ATP \xrightarrow{k_{HR\text{-}PFK}} GAP + 2ADP$
Phosphoglycerate Kinase (PGK)	$GAP + NAD^+ + ADP \xrightarrow{k_{PGK}} ATP + PEP + NADH$
Adenylate Kinase (AK)	$ATP + AMP \xleftrightarrow{K_{AK}} 2ADP$
Pyruvate kinase (PK)	$PEP + ADP \xrightarrow{k_{PK}} PYR + ATP$
Lactate dehydrogenase (LDH)	$PYR + NADH \xrightarrow{k_{LDH}} NAD^+ + LAC_i$
Conversion of phosphocreatine	$PCr + ADP \xleftrightarrow{k_{CK}} ATP + Cr$
Consume of ATP for Na^+/K^+-ATPase pump	$ATP \xrightarrow{k_{Pump}} ADP$
Hydrolysis of ATP for other enzymes	$ATP \xrightarrow{k_{ATPase}} ADP$

The stimulation induces the sodium entrance for the intracellular medium. The equation that describes this stimulation was proposed for Aubert and Costalat (2002). According to them, for the case of sustained activations, it is assumed that the stimulation rate is constant during the stimulation, that is, from t = 0 to t = t_{end}. In turn, if this rate varies during the sustained activation, these authors affirms that $v_{stim}(t)$ is gotten by means of the addition between a constant value (v_1) and an alpha function, the Eq. (1). Considering that t_{end} represents the duration time of the stimulation. The Eq. (1) is used for $0 \leq t \leq t_{end}$ and the terms v_1 and v_2 represent the rates of speed for the stimulation, t indicates time and τ_{stim} represents the time of the stimulation.

$$v_{stim}(t) = v_1 + v_2 \frac{t}{\tau_{stim}} \exp\left(\frac{t}{\tau_{stim}}\right) \quad (1)$$

Table 2 presents the distinguishing equations that mathematically describe the main involved physiological mechanisms in the coupling between cerebral electrical activity, metabolism and hemodynamics that are summarized in Figure 1. Table 3 contains the rates of the diverse reactions considered in this work.

Table 2: Ordinary differential equations of the complete mathematical model.

Variable	Balance Equations
Intracellular sodium (Na_i^+)	$\frac{dNa_i^+}{dt} = (v_{leak-Na^+} + v_{stim}) - 3v_{pump}$ [a]
Capillary oxygen (O_{2c})	$\frac{dO_{2c}}{dt} = v_{O_{2c}} - \frac{1}{r_c} v_{O_{2m}}$ [a]
Capillary glucose (GLC_c)	$\frac{dGLC_c}{dt} = v_{GLC_c} - \frac{1}{r_c} v_{GLCm}$ [a]
Capillary lactate (LAC_c)	$\frac{dLAC_c}{dt} = v_{LAC_c} + \frac{1}{r_c} v_{LACm}$ [a]
Intracellular glucose (GLC_i)	$\frac{dGLC_i}{dt} = v_{GLCm} - v_{HK-PRK}$ [b]
Glyceraldehyde-3-phosphate (GAP)	$\frac{dGAP}{dt} = 2 * v_{HK-PFK} - v_{PGK}$ [a]
Phosphoenolpyruvate (PEP)	$\frac{dPEP}{dt} = v_{PGK} - v_{PK}$ [a]
Pyruvate (PYR)	$\frac{dPYR}{dt} = v_{PK} - v_{LDH} - v_{mito}$ [a]
Intracellular lactate (LAC_i)	$\frac{dLAC_i}{dt} = v_{LDH} - v_{LACm}$ [a]
NADH	$\frac{dNADH}{dt} = v_{PGK} - (v_{LDH} + v_{mito})$ [a]
Intracellular oxygen (O_{2i})	$\frac{dO_{2i}}{dt} = v_{O_{2m}} - n_{Aero} v_{mito}$ [a]
Phosphocreatine (PCr)	$\frac{dPCr}{dt} = -v_{CK}$ [a]
ATP	$\frac{d(ATP)}{dt} = \left[\begin{array}{l} \left(v_{PGK} + v_{PK} + v_{CK} + n_{op} v_{mito} \right) - \\ \left(2v_{HK-PFK} + v_{pump} + v_{ATPase} + v_{AK} \right) \end{array} \right]$ [c]
ADP	$\frac{d(ADP)}{dt} = \left[\begin{array}{l} \left(2v_{HK-PFK} + v_{pump} + v_{ATPase} + 2v_{AK} \right) - \\ \left(v_{PGK} + v_{PK} + v_{CK} \right) \end{array} \right]$ [c]
AMP	$ATP + ADP + AMP = A$ [a]

Note: Rates proposed by the following authors: [a] Aubert et al. (2001), [b] Rapoport e Heinrich (1975a), [c] this work.

Table 3: Rates equations of the complete mathematical model.

Reaction or transport	Rates Equations
Sodium leak current	$v_{leak-Na^+} = \frac{S_m}{Vi}\frac{gNa}{F}\left(\frac{RT}{F}\ln\frac{Na_e^+}{Na_i^+} - Vm\right)$ [a]
Na^+/K^+-ATPase pump	$v_{pump} = 3K_{pump}.ATP.Na_i^+\left(1+\frac{ATP}{K_{m,pump}}\right)^{-1}\frac{S_m}{Vi}$ [b]
Blood-brain transport of oxygen	$v_{O_{2m}} = \frac{PS_{cap}}{V_i}\left(k_{O2}\left(\frac{HbOP}{O_{2c}}-1\right)^{-1/n_h} - O_{2i}\right)$ [c]
Blood-brain transport of glucose	$v_{GLCm} = T_{\max_{GLCm}}\left[\frac{GLC_c}{GLC_c+K_{t,GLC}} - \frac{GLC_i}{GLC_i+K_{t,GLC}}\right]$ [c]
Blood-brain transport of lactate	$v_{LACm} = T_{\max,LAC}\left[\frac{LAC_i}{LAC_i+K_{t,LAC}} - \frac{LAC_c}{LAC_c+K_{t,LAC}}\right]$ [c]
Concentration of oxygen in capillary	$v_{O_{2c}} = \frac{2F_{in}(t)}{V_{cap}}(O_{2a}-O_{2c})$ [d] with: $O_{2c} = \frac{(O_{2a}+O_{2\dot{c}})}{2}$ [d]
Concentration of glucose in capillary	$v_{GLC_c} = \frac{2F_{in}(t)}{V_{cap}}(GLC_a - GLC_c)$ [d]
Concentration of lactate in capillary	$v_{LAC_c} = \frac{2F_{in}(t)}{V_{cap}}(LAC_a - LAC_c)$ [d]
Hexokinase-phosphofructokinase system	$v_{HK\text{-}PFK} = K_{HK-PFK}\cdot\frac{GLC_i}{GLC_i+K_g}.ATP\left[1+\left(\frac{ATP}{K_{i,ATP}}\right)^{nH}\right]^{-1}$ [c]
Phosphoglycerate kinase	$v_{PGK} = K_{PGK}.ADP.GAP\left(\frac{N-NADH}{NADH}\right)$ [c] with: $NADH + NAD^+ = N$ [c]
Pyruvate kinase	$v_{PK} = K_{PK}.PEP.ADP$ [b]

Lactate desidrogenase	$v_{LDH} = K^{+}_{LDH}.PYR.NADH - K^{-}_{LDH}.NAD^{+}.LAC_i$ [c]
Creatine kinase	$v_{CK} = K^{+}_{CK}.PCr.ADP - (K^{-}_{CK}.(C - PCr).ATP)$ [c] with: $PCr + Cr = C$ [c]
Adenylate kinase	$v_{AK} = K^{+}_{AK}.ATP.AMP - K^{-}_{AK}.(ADP)^2$ [e]
Global reaction rate	$v_{ATPase} = 0{,}149\ mMs^{-1}$ [c]
Mitochondrial respiration	$v_{mito} = V_{max,mito} \cdot \frac{PYR}{K_{m,mito} + PYR} \cdot \frac{O_{2i}}{K_{O_{2i}} + O_{2i}} \cdot \frac{1}{1 + \left(\frac{ATP}{ADP.K_{i,mito}} \right)^n}$

Note: Rates proposed by the following authors: [a] Hodgkin and Horowicz (1959), [b] Heinrich and Schuster (1996), [c] Aubert et al. (2001), [d] Aubert and Costalat (2002), [e] this work.

The cerebral activation induces to an increase in the regional blood flow through the capillaries, $F_{in}(t)$. This increase in the blood flow directly modifies the concentrations of GLC_c, LAC_c and of O_{2c} in the capillary and, for the case of sustained activations, it is proposed by Aubert and Costalat (2002) by means of the shown trapezoidal function in the Eq. 2.

$$\begin{aligned} F_{in}(t) &= (1+\alpha_F) * F_0 \qquad \text{for} \quad t_1 \le t \le t_{end} \\ F_{in}(t) &= F_0 \qquad \text{for} \quad t = 0 \text{ ou } t \ge t_{end} + t_1 \end{aligned} \tag{2}$$

In this equation, t_{end} is the duration time of the stimulation, F_0 is the value of the cerebral blood flow in the rest and α_F means the increase fraction of the cerebral blood flow. $F_{in}(t)$ linearly increases of $0 \le t \le t_1$ and decreases to $t_{end} \le t \le t_{end} + t_1$. In the case of repetitive activations the Eq. 2 is applied for each cycle of stimulation.

In this manner, the coupling phenomenon between cerebral electrical activity, metabolism and hemodynamics encloses kinetic mechanisms that group diverse chemical reactions that occur simultaneously in the cell. These reactions present a complex system of ordinary differential equations and of a difficult analytical solution. Ahead of this, the Euler Method is used to solve the mathematical model considered. The numerical resolution of the ordinary differential equations of this model is carried through a computational program written in language FORTRAN, whose compiler is

the Visual Fortran 5.0. The definitions, values and units of the parameters, kinetic constants, concentration data and initial data of the variables necessary to solve the mathematical model complete are presented in Aubert and Costalat (2002).

3. Results and validation of the mathematical model

To solve the mathematical model is necessary, beyond the diverse parameters, kinetic constants, data of concentration and initial data of the model variables present in literature, to consider the constants of the reversible reaction catalyzed by the adenylate kinase enzyme (K^+_{Ak} and K^-_{Ak}) and the maximum rate of lactate transport through the blood-brain barrier ($T_{max,\ LAC}$). In this work, K^+_{Ak}, K^-_{Ak} and $T_{max,\ LAC}$ are the free parameters for adjustment of the model and went through an optimization process. The values found for K^+_{Ak}, K^-_{Ak} and $T_{max,\ LAC}$, are 100 $mM^{-1}\ s^{-1}$, 800 $mM^{-1}\ s^{-1}$ and 0,08 mM s^{-1}, respectively.

In the absence of own experimental data, the concentration curves for the 14 involved variables in the coupling are compared with the work of Aubert and Costalat (2002), whose results were validated by comparison with experimental data. These authors, as well as in this work, had considered a mathematical model of the coupling between cerebral electrical activity, cerebral blood flow and metabolism and used sustained activations in the simulation. The differences between the two models are in the equations for ATP and ADP, since the rate of reversible metabolic reaction catalyzed by the enzyme adenylate kinase (AK) has been considered here.

The comparison among the concentration curves for the intracellular sodium ion presented by Aubert and Costalat (2002) and the one obtained in the solution of the considered mathematical model of this work, shows that the concentration profile is similar and both the curves reach the stability around 300 seconds (Figure 2). These curves differ in terms of maximum concentration reached by the ion during the stimulation probably as a result from the Na_i^+ differential equation include the activity of the Na^+/K^+-ATPase pump, which takes in account the ATP concentration, that is calculated in different ways for the two models.

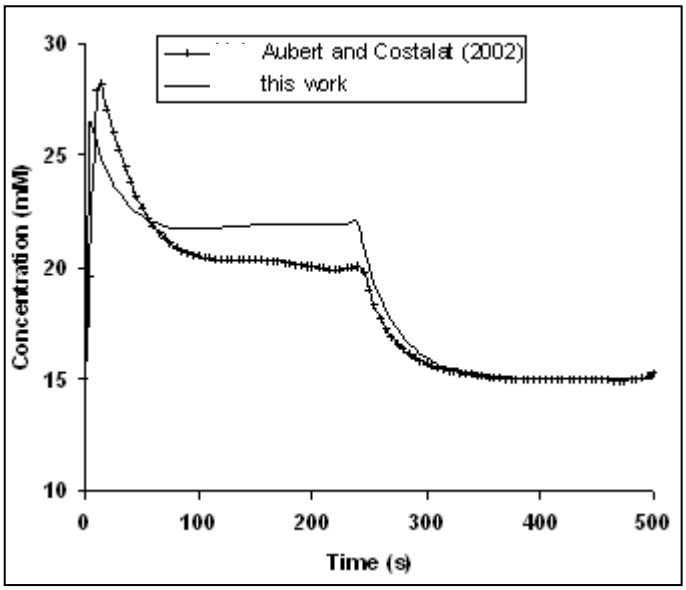

Fig. 2: Behavior of the Na_i^+ presented in the two models.

Figure 3 shows that, for the comparison of the concentration profiles for ATP and PCr, the behavior of these composites are similar in the two models, even when a distinct equation for ATP was used in this work. On the other hand, the ATP concentration presents a more significant reduction of what in the model of those authors, because of the fact that in this work it was included the reaction of ATP consume by the adenylate kinase enzyme.

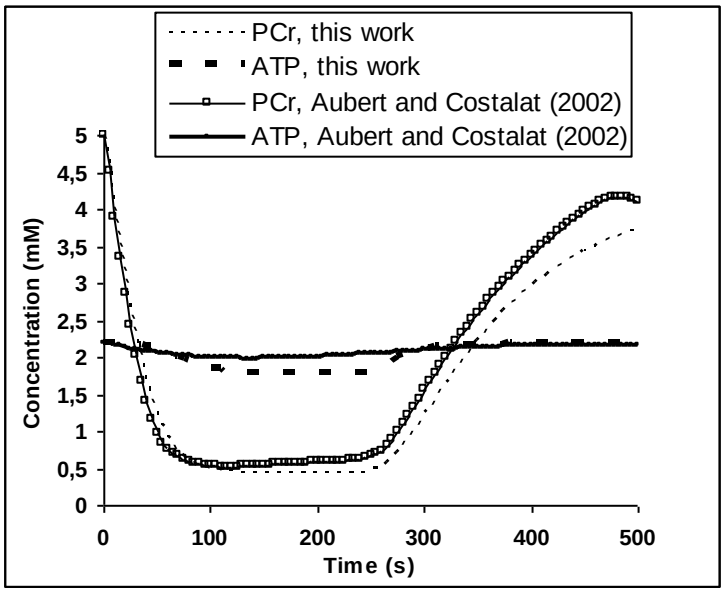

Fig. 3: Behavior of the PCr and ATP presented in the two models.

The initial value for the concentration of ATP is of 2,2 mM. The final concentration for this metabolic composition is of 2,167 mM in Aubert and Costalat (2002) and of 2,191 mM in this work. In this manner, the curve of concentration for ATP of this work presents a bigger approach in relation to its initial value of what the one obtained by the authors. This demonstrates that the equations for the reaction catalyzed by the adenylate kinase enzyme, for ATP and ADP proposed here are valid and describe satisfactorily the diverse mechanisms involved in the coupling between cerebral electrical activity, metabolism and hemodynamics. The comparison was repeated for all metabolic composites and showed that the results gotten in this model are in accordance with the ones found in Aubert and Costalat (2002).

Figure 4 shows the behavior of the stimulation rate (v_{stim}) and the capillary blood flow ($F_{in}(t)$) with the time. The rate v_{stim} increases at the beginning of the stimulation, in the period between 0 and 5 seconds. From 5 seconds, the stimulation rate remains constant up to 240 seconds with value of 0,23 mM s^{-1}, arriving the zero immediately afterwards.

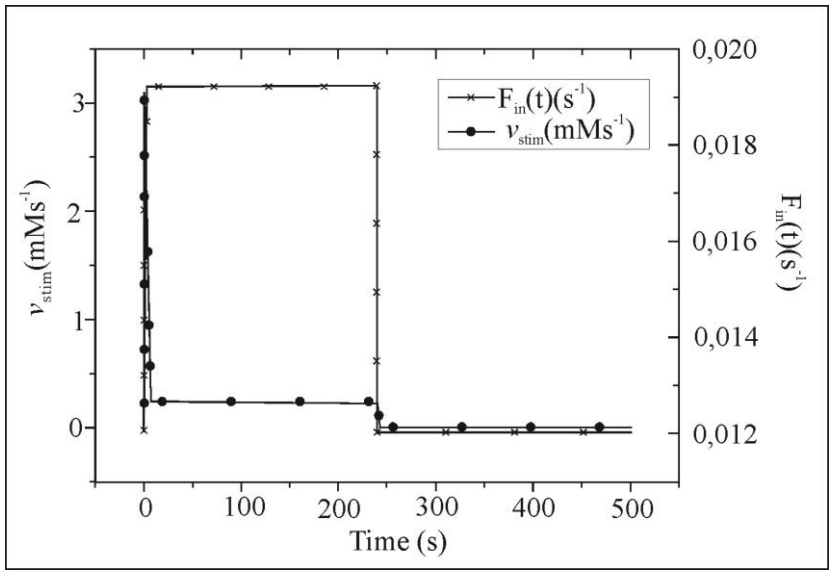

Fig. 4: Stimulation rate and capillary blood flow.

When the cell receives a stimulus, a significant increase in the permeability to ions sodium in the cellular membrane occurs, increasing the intracellular concentration of this ion. This actives the Na^+/K^+-ATPase pump that carry Na_i^+ against concentration gradients, resulting in energy expense. As the ATP is also regenerated by the reaction between PCr and ADP, the second stimulation after has a concentration fall of PCr. In accordance with Aubert and Costalat (2002), the ATP concentration suffers less

expressive reduction than the PCr, what preserves the cellular homeostasis. After the stimulation, as much the concentration of PCr how much the ATP concentration tends to come back to its initial values. The concentrations of oxygen and glucose in the capillary do not suffer significant variation during the activation. Figure 5 presents the curves of concentration of the intracellular sodium ion, the phosphocreatine, the oxygen in the capillary, the glucose in the capillary and ATP.

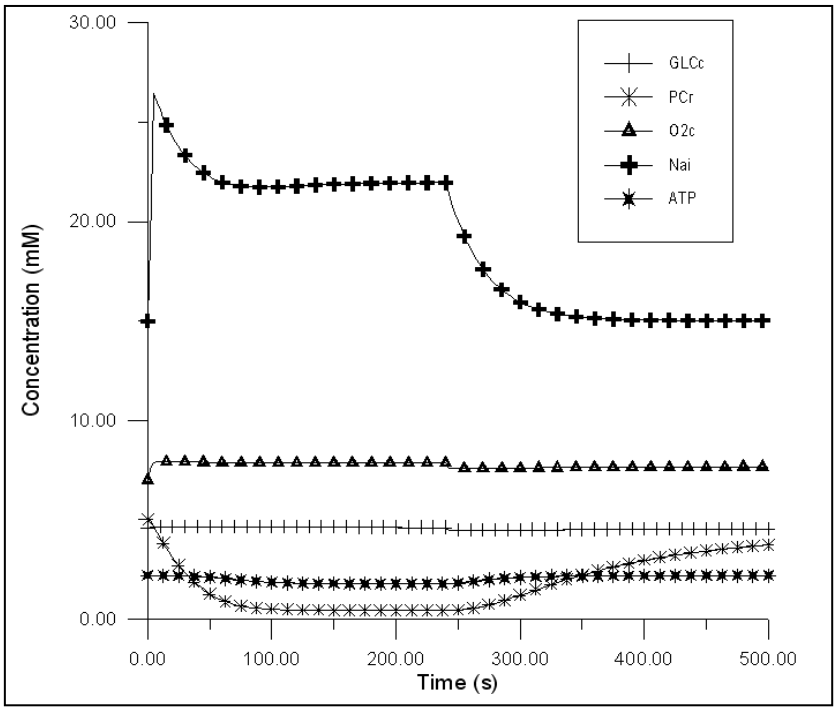

Fig. 5: Profile of concentration for intracellular sodium ion, phosphocreatine, oxygen in capillary, glucose in capillary and ATP.

Figure 6 presents the concentration profile of GAP, PEP, O_{2i} and NADH for the case of sustained activations. The concentration of intracellular oxygen and NADH increases during the period of stimulation. The biggest increase in the concentration of O_{2i} occurs seconds after the stimulation, as resulted of the increase in the oxygen supply for the cerebral blood flow. After that the concentration of O_{2i} presents a reduction due to the increase in the rate of oxygen consumes. These variations in the concentration of O_{2i} had also been observed in Aubert and Costalat (2002). Already the concentrations of GAP and PEP decrease during the activation, but they tend to come back to the initial values after the stimulation.

During the sustained activation, the concentrations of LAC_i and LAC_c increase, and the concentration of the GLC_i decrease (Figure 7). As the cell was stimulated, the

mechanisms of ATP production are activated e, therefore, have an increase in the glucose consume for the cell, causing increase in the intracellular lactate concentration that is then sent for the capillary. Figure 7 shows that the pyruvate concentration presents little variation, indicating probably that all formed pyruvate is transformed into lactate and participates of the mitochondrial respiration.

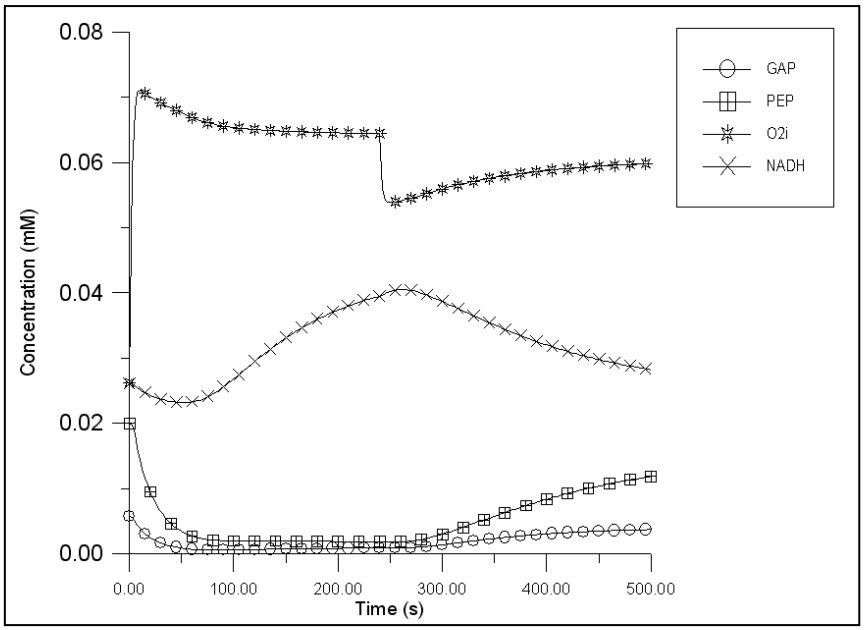

Fig. 6: Curves of concentration for glyceraldehyde-3-phosphate, phosphoenolpyruvate, intracellular oxygen and NADH.

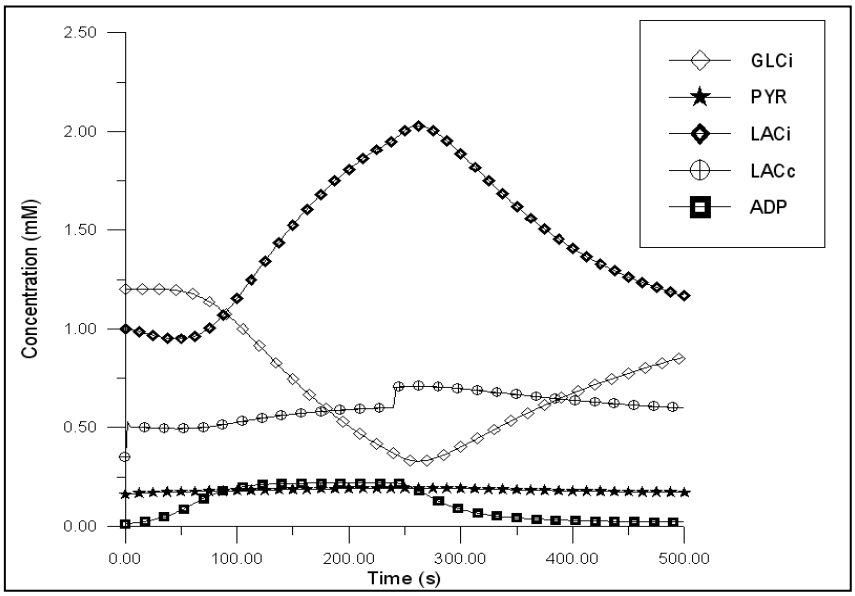

Fig. 7: Curves of concentration of GLC_i, PYR, LAC_i, LAC_c e ADP.

The validation of this mathematical model makes possible the evaluation of repetitive activations in the behavior of the involved variables in the coupling. The repetitive activation refers to the application of stimulations in the brain in regular time intervals (Comfort et al., 2003). The results obtained in this work had been compared with the results of Aubert and Costalat (2002). Similar to that work, is used a repetitive activation consisting of six cycles of 20 seconds of stimulation in intervals of 40 seconds. The stimulation rate (v_{stim}) begins to be constant and equal to 0,53 mM s^{-1} and the initial cerebral blood flow is increased in 50%. The remaining parameters are identical to those used for the case of sustained activation.

For Figure 8, it is observed that the concentration of the intracellular sodium ion increase and decrease in each cycle of activation. In turn, the concentration of PCr, GLC_c, O_{2c} and ATP does not suffer significant variations and the behavior presented for these metabolic composites are similar to the results gotten with the sustained activation.

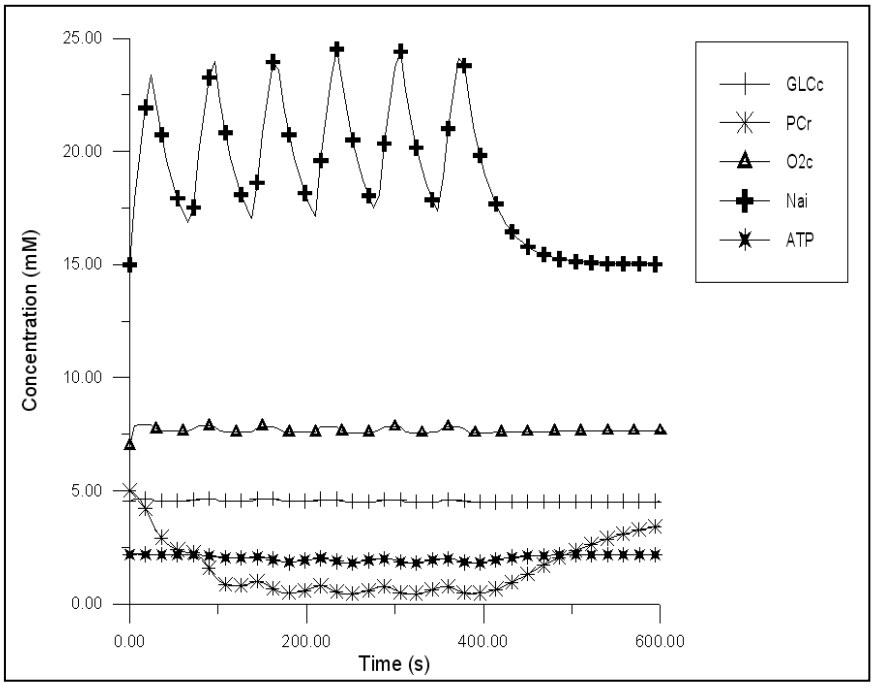

Fig. 8: Profiles of concentration of the repetitive activations case.

It is observed that the concentration variation of intracellular lactate and the intracellular glucose in the repetitive activation is less sharp than in the sustained activation. The PYR concentration practically is kept constant during all the stimulation. The concentration profiles of lactate in the capillary and of ADP increase and decreases in each cycle of the stimulation (Figure 9).

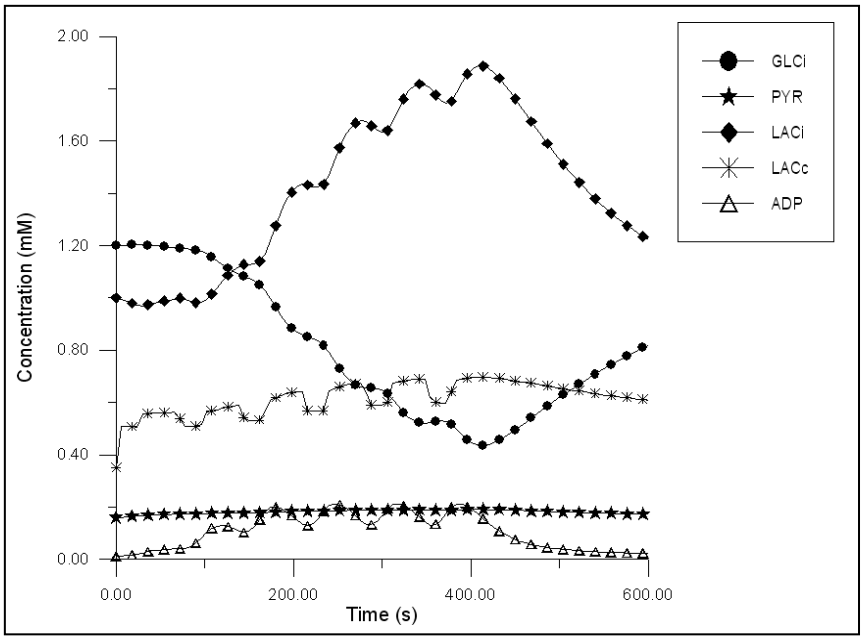

Fig. 9: Profiles of concentration of LAC_i, GLC_i, LAC_c, PYR e ADP.

Figure 10 presents the concentration profile of GAP, PEP, O_{2i} and NADH in the cyclical activation. After each cycle, the concentration of intracellular oxygen decreases, due to the increase in the oxygen demand by the cell. The concentrations of NADH, GAP and PEP, in turn, present a similar behavior to the presented in the sustained activation.

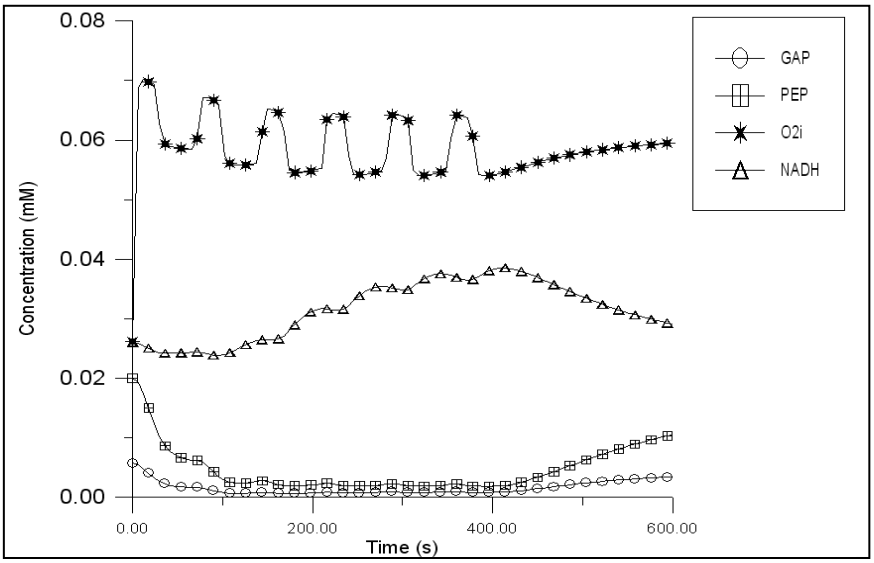

Fig. 10: Profiles of concentration of O_{2i}, NADH, PEP e GAP.

The case of study presented shows that from the 14 considered variables, the accented alterations that had been more observed in the concentration profiles of the intracellular sodium ion and the intracellular oxygen.

4. Conclusions

In this work a mathematical model of the cerebral tissue was considered, presenting ordinary differential equations for ATP and ADP that enclose the conversion reaction of the phosphocreatine in creatine, the diverse glycolytic reactions of which these metabolic composites participate, the consume of ATP and consequent production of ADP by the activity of the Na^+/K^+-ATPase pump and by other enzymatic processes. An equation for the reversible reaction catalyzed by the adenylate kinase enzyme was proposed. This equation was incorporated in the ordinary differential equations of ATP and ADP.

The data obtained in the simulation of Aubert and Costalat (2002) had been used for the validation of our mathematical model. The comparison between the concentration curves of metabolic composites demonstrates that the considered mathematical model adequately describes the diverse mechanisms involved in the coupling between cerebral electrical activity, metabolism and hemodynamics during the sustained activation. The validation of the mathematical model allows the use of it for the analysis of the effect of the repetitive activations in the behavior of the 14 involved variables in the coupling. The results gotten with this type of activation also present great similarity with the literature data.

Acknowledgments

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