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A model of the Ca^{2+} and Na^{+} waves kinetics in astrocytes and its relevance to functional brain imaging

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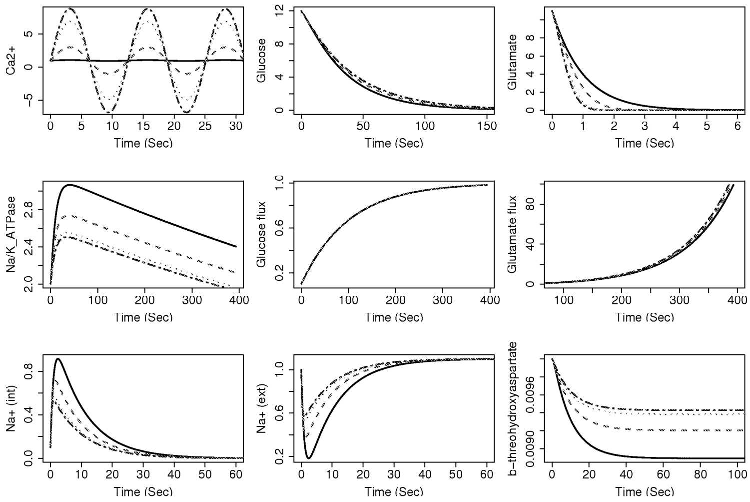
ABSTRACT

Introduction. Although in recent years the functional brain imaging based on ^{18}F-deoxyglucose DG Positron Emission Tomography (^{18}FDG PET) has experienced enormous advances, the cellular and molecular mechanisms generating the signals detected by these techniques are not completely known. In this paper, we present a computational model that attempts to disentangle the intricate nature of the molecular interactions governing the brain energy metabolism. The model describes the glutamate-stimulated glucose uptake and use into astrocytes. In particular our study provides a quantitative modeling of the consequences of the astrocytic generation of intercellular Na^{+} and Ca^{+} waves on the glucose metabolism. As far as we know a mathematical computational model of the brain energy metabolism at molecular level has been never proposed. The authors developed a first simplified model not including sodium and calcium waves in [4]. The significance of the current extended model to the PET brain imaging consists in supporting medical image understanding at cellular and molecular detail. Moreover the model acts as a more comprehensive *in silico* framework in which to experiment the glucose metabolism and elucidate its largely unknown aspects.

The model. Glutamate released in the synaptic cleft during neuronal activity is removed by surrounding astrocytes. One of the roles of the glutamate clearance by astrocytes is triggering a cascade of molecular events that provides metabolic substrates to neurons. Glutamate is cotransported with three Na^{+} ions by amino acid transporters expressed in astrocytes, inducing an intracellular Na^{+} ($[Na^{+}]_i$) elevation. The consequence of the $[Na^{+}]_i$ increase is the activation of the Na^{+}/K^{+}-ATPase, causing an increase of energy demand in astrocytes. This increase in turn enhances glucose utilization and glycolysis. Astrocytes can also release glutamate. Recently it has been shown that glutamate is released in association with Ca^{2+} waves [1] [2], which represent a form of multicellular bidirectional communication with neurons. In particular an increased cytosolic concentration of Ca^{2+} induces a release of astrocytic glutamate in the extracellular space. Astrocytes can also generate Na^{+} waves whose behavior is driven by the Ca^{2+} waves. It has been observed that inhibiting Na^{+}/glutamate transporters blocks the Na^{+} waves without affecting the Ca^{2+} waves [3]. On the contrary each process that inhibits Ca^{2+} also inhibits the Na^{+} waves. Our model describes how the Na^{+} waves depend on the Ca^{2+} waves and quantifies the influence of these oscillations on the rate of glucose consumption. Unlike the model in [4], the present one consists of nine rate equations (Fig. 1) defining the time behavior of the concentration of glucose

$[\mathrm{Gluc}]$, glutamate $[\mathrm{Glut}]$, $[\mathrm{Na/K\_ATPase}]$ and its inhibitor, $[\beta\mathrm{\_threohydroxyaspartate}]$, sodium and calcium ions, respectively $[\mathrm{Na}^{+}]$ and $[\mathrm{Ca}^{2+}]$. The superscript "$'$" denotes the time derivative. We also introduced the rate equations for the glutamate and glucose fluxes in astrocyte ($\mathrm{Gluc_{flux}}$ and $\mathrm{Gluc_{flux}}$), and the number of glucose transporters ($\mathrm{Gluc\_t_{open}}$, for those being open and $\mathrm{Gluc\_t_{total}}$ for the total number), and of glutamate transporters Glt and Glast [4]. The $[\mathrm{Ca}^{2+}]$ oscillations are modeled by a cosine waveform (Eq. (9)). The subscripts "i"' and "e" denote the intracellular and extracellular concentration of a species. The rate constants k's have been inferred from dynamic ^{18}FDG PET data of a normal subject provided by the Neurobiology Research Group of Rigshospitalet of Copenhagen. The amplitude A of the $[\mathrm{Ca}^{2+}]$ wave has been increased from the inferred value of 0.0345 (black solid line) up to 3.91 (dot-dash blue line) to evaluate changes in glucose consumption rate and in the shape of the glutamate and $[\mathrm{Na}^{+}]$ time course. The dependency of the $[\mathrm{Na}^{+}]$ wave from the $[\mathrm{Ca}^{2+}]$ wave has been modeled in the following way: the release of glutamate in Eq. (2) is represented by the negative term proportional to $[\mathrm{Ca}^{2+}]_i$. In Eq. (7), the rate of change of $[\mathrm{Na}^{+}]_i$ contains a term proportional to $[\mathrm{Glut}]_\mathrm{i}$, so that glutamate is the mediator that transfers the $[\mathrm{Ca}^{2+}]$ oscillations to the intracellular sodium. As from experimental observations [3], the simulations show that increasing the amplitude of the calcium wave only slightly affects the glucose flux and the rate of glycolysis, while the rate of glutamate release significantly increases and the amplitude of the $[\mathrm{Na}^{+}]$ wave strongly decreases.



(1) $[\mathrm{Gluc}]'_i = k_1[\mathrm{Glut}]_\mathrm{i} + k_2\ \mathrm{Gluc_{flux}}[\mathrm{Gluc}]_\mathrm{i} +$

$-k_3[\mathrm{Na/K\_ATPase}][\mathrm{Gluc}]_\mathrm{i}$

(2) $[\mathrm{Glut}]'_\mathrm{i} = k_4\ \mathrm{Glut_{flux}}\ [\mathrm{Glut}]_i - [\mathrm{Ca}^{2+}]_i[\mathrm{Glut}]_\mathrm{i}$

(3) $[\mathrm{Na/K\_ATPase}]' = k_5[\mathrm{Na}^{+}]_\mathrm{i} +$

$-k_6[\beta\mathrm{\_threohydroyaspartate}][\mathrm{Na/K\_ATPase}]$

(4) $\mathrm{Gluc'_{flux}} = k_7\mathrm{Glut\_t_{open}} - k_8\mathrm{Glut\_t_{total}}$

(5) $\mathrm{Glut'_{flux}} = (k_9\mathrm{Glt} + k_{10}\mathrm{Glast}) \cdot [\mathrm{Na}]_i^{+}$

(6) $[\beta\mathrm{\_threohydroxyaspartate}]' =$

$-k_{11}[\mathrm{Na}^{+}]_\mathrm{i}[\beta\mathrm{\_threohydroyaspartate}]$

(7) $[\mathrm{Na}^{+}]'_\mathrm{i} = k_{12}[\mathrm{Glut}]_\mathrm{i} - k_{13}[\mathrm{Na}^{+}]_\mathrm{i}$

(8) $[\mathrm{Na}^{+}]'_\mathrm{e} = -[\mathrm{Na}^{+}]'_\mathrm{i}$

(9) $[\mathrm{Ca}^{2+}]'_\mathrm{i} = A\cos(0.5t)$

Figure 1: time course of the species as solution of the equations of the model. The concentrations are expressed in units of Bq/cc. Black solid line refers to A=0.0345, dashed red line refers to A=1, dotted green line refers to A=2.94, and dot-dash blue line to A=3.91.

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