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A spatially distributed computational model of brain cellular metabolism

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HIGHLIGHTS

- A new spatially distributed model for brain energy metabolism is developed.
- A standard lumped model is recovered by spatial averaging.
- The sensitivity of parameter estimation to scale change is demonstrated by computed examples.
- The question of glucose vs. lactate as metabolites is revisited.

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ABSTRACT

This paper develops a three-dimensional spatially distributed model of brain cellular metabolism and investigates how the locus of the synaptic activity in reference to the capillaries and diffusion affects the behavior of the model, a type of analysis which is impossible to carry out in spatially lumped models, which are shown to be consistent spatially averaged approximations of the distributed model. To avoid a geometrically detailed modeling of the complex structure of the tissue consisting of different cell types and the extracellular space, the distributed model is based on a novel multi-domain formulation of reaction–diffusion equations, accounting also for separate mitochondria. The model reduction relating the spatially distributed model and lower dimensional reduced models, including the well-mixed spatially lumped compartment model, is carefully explained. We illustrate the effects of losing the spatial resolution with a computed example which is based on a reduced one-dimensional distributed radial model, and look into how the model behaves when the locus of the synaptic activity in reference to the capillaries is changed. By averaging the fluxes and concentrations in the distributed radial model to correspond to quantities in a lumped model, and further by estimating the parameters in the lumped, we conclude that varying the locus of the synaptic activity in reference to the capillaries alters significantly the lumped model parameters. This observation seems to be consequential for parameter estimation procedures from data when the spatial resolution is insufficient to determine the locus of the activity, indicating that the model uncertainty is an inherent feature of lumped models.

1. Introduction

Brain energy metabolism continues to be an active research topic, providing the key to understanding the neurovascular connection, and playing a central role in the interpretation of data arising from different imaging modalities. The complexity of the brain biochemistry, and the difficulty in performing direct measurements of the relevant quantities without disrupting its activity are some of the factors that make direct observations of the metabolic state almost impossible and therefore, to interpret the scarce indirect observations and to assimilate them into a coherent picture, mathematical metabolism models need to be employed. Mathematical models of increasing complexity and sophistication have been proposed in the past two decades to provide a narrative context in which to interpret the experimental results, and to test the feasibility of proposed mechanistic interpretation of brain metabolism. Over the years, mathematical models of brain energy metabolism have gradually evolved into complex systems with fine compartmentation and detailed metabolic pathways (Aubert and Costalat, 2005; Gruetter

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et al., 2001; Calvetti and Somersalo, 2011; Occhipinti et al., 2008, 2010; Calvetti and Somersalo, 2012, 2013; Cloutier et al., 2009; DiNuzzo et al., 2010; Simpson et al., 2007). The evolution of the modeling paradigm, and the rationale for the differences in the published brain metabolism models are discussed in a recent overview (Somersalo et al., 2012).

The existing mathematical models of brain energy metabolism can be broadly divided into those which look at the various reaction fluxes and cross membrane exchange rates supporting a given steady state, and kinetic models which track the changes of the metabolites and intermediates over time. A feature common to all mathematical models of brain energy metabolism is the spatially lumped framework, in which a physical region of interest is represented in terms of well-mixed compartments representing, e.g., different cell types, extracellular space, and capillary blood (Aubert and Costalat, 2002; Gruetter et al., 2001; Calvetti and Somersalo, 2011; Cloutier et al., 2009; DiNuzzo et al., 2010; Simpson et al., 2007). While these models shed some light on details of the brain metabolism, they overlook some potentially important factors, including the effect of the locus of the synaptic activity in reference to capillaries, the effect of diffusion, the different roles of pre- and postsynaptic neurons, and possible variations of mitochondrial density within the cells. In principle, the different availability of glucose and oxygen in particular could affect the role of aerobic and anaerobic metabolism and use of lactate, pointing towards an important role of the diffusion. In this work, we develop a spatially distributed metabolism model that better takes into account the aforementioned factors.

This paper proposes the first compartmentalized, spatially distributed mathematical model of brain energy metabolism. The compartmentation as well as the description of the reaction rates and cross-membrane exchange rates is locally in agreement with the paradigms followed by the spatially lumped models proposed in the literature, which makes it possible to reduce the distributed model into a lumped model by integrating out the spatial dimension. The new, spatially distributed model that we propose is based on a multi-domain reaction–diffusion system of partial differential equations, akin to the bi-domain models of myocardium (Henriquez, 1993; Colli Franzone et al., 2005; Roth, 1994). The mathematical framework, which allows a finer or coarser space resolution that can accommodate a more or less detailed local compartmentation at the metabolic level, is naturally suited to model regions where, for example, the density of mitochondria may change in space. Furthermore, the model allows geometric model reduction in particular geometries, making it possible to investigate the effects of spatial distribution without the need to implement the computationally challenging full three-dimensional model.

To illustrate the features of the model we present results of computed examples in a cylindrical geometry modeling a Krogh cylinder around a single blood vessel (Krogh, 1919), showing that the predictions about oxygen concentrations as a function of the distance from the blood vessel are in agreement with experimental findings (Kasischke et al., 2011). Moreover, our model suggests that the different oxygen availability in the watershed of the Krogh cylinder may cause a change in glycolytic activity at different spatial locations. To understand how the lack of fine-scale spatial details may affect the interpretation of metabolic processes when a lumped model is used, we derive the latter as a spatial mean model of the fine-scale distributed model, and investigate the effect of different activation scenarios on the parameter distribution of the lumped model. One of the main findings of this analysis is that the lack of resolution in spatially lumped models seems to induce significant uncertainties to model parameter estimates. The metabolic network in the computed example is strongly simplified; however, this simplification is not a limitation of our general approach, and the example is intended only to demonstrate the effect of the spatial distribution of the model as compared to a lumped model with the same biochemical complexity. In particular, the model demonstrates that ignoring the effect of diffusion may lead to parameter estimates that disagree with the underlying microscopic parameters, underlining the multi-scale nature of the metabolic models.

2. Multi-domain reaction–diffusion model

Consider a bounded three dimensional domain $D \subset \mathbb{R}^3$ representing a sample of the brain, with brain tissue occupying a subset $\Omega \subset D$, and L capillaries running through the sample. Brain tissue consists of various neurons and glial cells, surrounded by a diffusive extracellular space. To avoid having to deal with the complex details of the underlying geometry, we define a multi-domain structure as follows: let Ω^k be a copy of the domain Ω with a corresponding volume fraction η^k, $0 \le k \le K$. We assume that

$$\eta^0 + \ldots + \eta^K = 1.$$

The domain Ω^k represents a homogenized compartment that occupies a fraction η^k of the domain; a point $x \in \Omega$ belongs simultaneously to all subdomains, each one of them contributing according to a weight reflecting the corresponding volume fraction. We formalize this idea by defining the kth compartment as

$$\Omega^k = \left(\Omega, \eta^k\, dx\right),$$

with Ω^k being an identical copy of the physical domain Ω equipped with the Lebesgue measure weighted by η^k, i.e., for any integrable function $f : \Omega \to \mathbb{R}$, we define the integral over Ω^k by

$$\int_{\Omega^k} f(x)\, dx = \eta^k \int_{\Omega} f(x)\, dx.$$

Hence, we may interpret the volume fractions as

$$\eta^k = \frac{|\Omega^k|}{|\Omega|},$$

with $|\cdot|$ denoting the volume of the set. The multi-domain is then defined as

$$\overline{\Omega} = \Omega^0 \times \Omega^1 \times \ldots \times \Omega^K,$$

where the notation indicates that an element of $\overline{\Omega}$ has $K+1$ components, one for each subdomain. The construction bears some similarity with the bi-domain theory in a different context, see Henriquez (1993), Colli Franzone et al. (2005), and Roth (1994).

The model problem with $K=2$ consists of three subdomains, the extracellular space (ECS), ($k=0$), neuron ($k=1$), and astrocyte ($k=2$). However, the formalism extends to more detailed models by further subdividing these subdomains to comprise, e.g., pre- and postsynaptic neurons, and glutamatergic and GABAergic neurons.

In general, the tissue domain Ω and the blood in the capillaries exchange certain metabolites, which diffuse within each subdomain. In turn, the subdomains within the tissue may exchange some of the metabolites: these processes are described in terms of a reaction–diffusion model.

Consider a single metabolite A, for example oxygen, glucose, or lactate. Suppressing the reference to the particular metabolite, we denote by $C^k(t,x)$ the concentration in the subdomain Ω^k at time t at $x \in \Omega$. The metabolite may diffuse within the subdomain Ω^k with a diffusion constant D^k which is characteristic to the subdomain and to the metabolite. In the general model the diffusion coefficient D^k can be space and time dependent, and anisotropic. If there were no exchanges between subdomains and no biochemical reactions involving the metabolite took place, the process which changes the concentration of C^k over time could be described by a diffusion