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## A MINIMAL MODEL OF ENERGY MANAGEMENT IN THE BRAIN

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#### ABSTRACT

Models of cerebral blood flow and metabolism have been very successful in reproducing the shape and timing of the haemodynamic response to neural activity. On the other hand, as these models are mechanical or phenomenological in nature, they do not allow for judging the efficiency of the underlying allocation of energy. Here, we describe a complementary approach, suggesting that optimality with respect to resource constraints contributes to the characteristics of the haemodynamic response.

#### **KEY WORDS**

haemodynamic response, metabolism, energy storage, optimality

#### **1** Introduction

When investigating how the brain works, it is natural to look at the different kinds of activity it produces. The electrical activity displayed by single neurons, local networks, and entire brain regions has been studied for many decades. More recently, the brain's haemodynamic activity has additionally attracted attention. It is often being considered as merely an indirect way of measuring neural activity, and theoretical investigations of the phenomenon are usually limited to investigating the link between the two. It is commonly accepted that an increase in neural activity will induce a haemodynamic response carrying with it additional metabolic resources.

While there is no doubt about the virtues of using such haemodynamics as an indirect, often non-invasive measure of electrical activity, we believe it is worth wondering why there is such a signal in the first place. Different ways of allocating resources both spacially and temporally are conceivable, and it is not obvious what the constraints are with respect to which the common haemodynamic response might be optimal.

Current models of cerebral blood flow focus on predicting the shape of the haemodynamic response to an increase in local activity, i.e. to a local signal triggering an increase in blood flow [1]. Therefore, there is a number of questions which cannot be answered by any of these models. For instance, it is unclear how the brain manages to allocate its limited energy resources to a particular cortical region, how this allocation evolves over time, and how closely it reflects metabolic demand at a specific moment.

We suspect that, in addition to the factors suggested by other authors, the shape and timing of the haemodynamic response may arise from resource limitations. We suggest that this response balances the need to efficiently spend these limited resources, thereby seeking to minimize overall consumption, and the need to safeguard against prolonged undersupply of individual regions. To investigate this hypothesis, we propose a minimal model of energy management inside a single cortical area, featuring local energy storage in particular. We introduce these concepts in general terms, and subsequent communications will then investigate their actual biological implementations in more detail.

#### 2 Linear model of energy storage

Here, we propose a simple model for energy management within a single cortical area. By energy management, we mean a set of rules describing how the system reacts to a disparity between local energy demand and energy supply. We do so by introducing three time-dependent variables: the influx of energy into that region, the metabolic energy demand within it, and the amount of energy stored locally. The basic concept of our model is illustrated in figure (1).

Biologically, this kind of energy storage may be implemented in the form of glycogen stores [2][3]. For the purpose of our model, though, the precise nature of these stores is secondary. Furthermore, we are consciously referring to the flow of "energy" in the broad sense, changes of which may or may not be directly related to changes in parameters of blood flow such as total blood volume or desoxyhaemoglobin concentration.



Figure 1: Flux of energy, as described by our model. Energy demand is satisfied by both external energy influx into the region and from local energy stores. On the other hand, energy influx is used to meet current energy demand and to restore depleted energy stores.



Figure 2: Circuit diagram of our model: locally stored energy E, external energy influx x, current energy demand y, control function u.

Naturally, the level of energy storage E(t) will evolve according to the balance of energy influx x(t) and energy demand y(t) following local neural activity:

$$\tau \dot{E}(t) = x(t) - y(t) \tag{1}$$

We assume that in the absence of energy demand, the influx will die out exponentially by diffusing into the surrounding tissue and out of the region we consider.  $\tau$  is the time constant of the system. We assume ongoing activity to give rise to a constant background demand, and therefore a constant background influx. We set the mean of these to zero and consider excess demand and influx only. We furthermore postulate a control function u(t) which relates the current level of energy influx to the current energy demand, and adjusts the influx accordingly:

$$\tau \dot{x}(t) = -x(t) + u(t) \tag{2}$$

The first term on the right hand side of this equation ensures the exponential decay we desire. In fact, the metabolic processes involved in shaping the response are significantly more complex than this [10][11], but for the sake of simplicity, we shall neglect this for now.

We assume that the control function u(t) will depend not only on the amplitude of energy demand, but also on how much energy is available in local energy stores. If we denote the default level of stored energy

the cells seek to maintain by  $E_0$  and introduce a nonnegative parameter  $\alpha$  weighting the influence of energy storage, a simple control function is given by

$$u(t) = \alpha (E_0 - E(t)) + y(t)$$
 (3)

This control function will not only adapt the influx of energy to match energy demand at a given time, but also make sure that local stores are refilled in a timely fashion. Figure (2) shows a circuit diagram of this control system. In matrix notation, we can combine equations (1), (2) and (3) to obtain:

$$\tau \begin{pmatrix} \dot{x} \\ \dot{E} \end{pmatrix} = \begin{pmatrix} -1 & -\alpha \\ 1 & 0 \end{pmatrix} \begin{pmatrix} x \\ E \end{pmatrix} + \begin{pmatrix} \alpha E_0 + y \\ -y \end{pmatrix} \quad (4)$$

From this, we can see that the eigenvalues of the system are given by:

$$\lambda = -\frac{1}{2} \pm \sqrt{\frac{1}{4} - \alpha} \tag{5}$$

Because  $\alpha$  is non-negative, there is a stable fixed point, the location of which is determined by the nullclines of the system. These can be identified by setting

$$\dot{E} = 0 , \quad \dot{x} = 0 \tag{6}$$

in equations (1) and (2), respectively. For an energy demand y which slowly varies over time, the nullclines with respect to E and x are hence defined by

$$E = E_0 + \frac{y}{\alpha} - \frac{x}{\alpha} \tag{7}$$

$$x = y \tag{8}$$

Note that these nullclines are time-dependent as the energy demand y may change over time. As illustrated in figure (3), the fixed point of the system is located at the intersection of these two nullclines at

$$\begin{pmatrix} E\\x \end{pmatrix} = \begin{pmatrix} E_0\\y \end{pmatrix} \tag{9}$$

The vector field in that same figure illustrates that, from any given initial condition, the system will oscillatorily converge towards this fixed point if  $\alpha > 1/4$ . For smaller values of  $\alpha$ , it will converge exponentially, as in the case of an overdamped oscillator. Eventually, the influx of energy will precisely match energy demand, and local energy stores will stabilize at their default value. This is true as long as we consider energy demand to vary slowly compared to the other parameters of the system.



Figure 3: Null isoclines of this minimal system with respect to E (dashed line) and x (solid line), as a function of the time-dependent energy demand y. Vector field indicates  $(\dot{E}, \dot{x})^T$ .

The impulse response of the system for  $\alpha > 1/4$  is shown in figure (4). Following a transient rise in demand, influx and stored energy evolve according to equations (1) and (2). After the sudden displacement by the impulse, they oscillatingly return to their equilibrium value. The precise shape of this falling edge is determined by the parameters  $\alpha$  and  $\tau$ . Note that, although the shape of this relaxation may roughly resemble the falling edge of haemodynamic responses known from neuroimaging experiments, we are not directly modelling variables describing blood flow. Nonetheless, it is conceivable that our model may be combined with existing models of cerebral blood flow to reproduce this haemodynamic response.

#### **3** Discussion

In the last two decades, functional magnetic resonance imaging (fMRI) has arguably been the most prominent technique in neuroimaging. The blood oxygen level dependent (BOLD) signal used in fMRI depends on the concentration of deoxyhaemoglobin (dHb) within a given voxel. This concentration per volume of tissue depends both on the dHb concentration inside local blood vessels and the relative volume of these blood vessels within the voxel. In order to account for the nonlinearities in BOLD signals, several models of cerebral blood flow featuring such nonlinearities have been proposed in recent years.

Among the most noted contributions was the socalled balloon model initially proposed by Buxton and Frank [4][5] and extended by Friston et al. [1]. In its more recent shape, this model can be split



Figure 4: Impulse response of the system. Time course of stored energy E (dashed line) and influx x (solid line) before and after a brief impulse in y (arrows). Model parameters were set to  $\alpha = 1$  and  $\tau = 1$ .

in two parts. First, there is a mechanistic model linking the local inflow of blood into a voxel to the change in BOLD signal which ensues: increased inflow inflates a passive venous balloon, from which blood can then flow out gradually once the influx declines. The resulting changes in blood volume and dHb concentration give rise to the BOLD signal. The mechanical properties of the venous balloon are assumed to be nonlinear [6], and so is the signal. Second, the authors propose a purely linear model to describe how the increase in inflow comes about in the first place; i.e., how this inflow is evoked by precedent neural activity. In summary, the purpose of these models is to reliably predict the shape of the BOLD response to an increase in local activity, i.e. to a local signal triggering an increase in blood flow.

As argued before, such models are not sufficient to answer questions regarding the optimality of energy allocation. However, they provide a versatile framework into which energy-based models like the one we propose can be integrated if desired. With respect to the work by Friston et al., it could potentially replace the phenomenological second part of the model, linking neural activity to the inflow of blood. Still, our emphasis is not on deriving alternative ways of reproducing the haemodynamic response, but on exploring why there is such a response at all.

As to the biological feasibility of local energy storage, it is worth considering just how energy is supplied to brain tissue: Increased metabolic activity in neurons and glial cells leads to higher extraction rates of metabolites, such as oxygen and glucose, from local blood vessels. Whenever the body is at rest, the brain consumes about 20% of its total energy budget. Notably, glial cells such as astrocytes contribute significantly to this energy demand, although their exact share is still under debate [7][8]. This is particularly interesting as the metabolisms of astrocytes and neurons are tightly linked: e.g., the recycling of neurotransmitters released by neurons is accomplished by astrocytes.

Additionally, there is significant experimental evidence of stores of metabolites such as glycogen within these astrocytes. Glycogen can be converted into glucose, which is the main fuel for ATP synthesis. As it has been proposed that lactate, a derivative of glucose, might be shuttled between astrocytes and neurons [9][10], such glycogen stores within astrocytes could serve as local energy reserves for neighbouring neurons [2][3]. Considering that these stores have been found to contain three to four times as much glucose as is freely available within the cell [11], such processes may be crucial for determining the time scales on which increased metabolic activity within tissue requires its perfusion with fresh blood.

Hence, and despite the large variety of hypotheses on cerebral metabolism, we can identify metabolites corresponding to elements of our model: glucose and oxygen released from local capillaries certainly contribute to *energy influx*, while glycogen stores may participate in *energy storage*. Amongst other factors, the consumption of ATP within the cell is a certain cause of *energy demand*.

#### 4 Concluding remarks

The model described here represents a minimal control system for energy management in brain tissue. Although its limitations are obvious, it will serve as a basis on which to construct more elaborate models more closely mapping experimental data. As part of the system presented here, we assume a simple control function which instantaneously reflects changes in energy demand. This, in turn, gives rise to the steep initial increase in the impulse response (see figure (4)). The metabolic processes actually involved in shaping the response are significantly more complex. In subsequent communications, we shall thus investigate higher-order control functions to account for this. Available knowledge on neurovascular coupling and the time constants involved may be incorporated to enhance our model.

Beyond providing just another tool for improving the reproduction of the shape and timing of the haemodynamic function, the true potential of models like the one presented here lies in approaching the question of optimality. Building on the simple concept laid out in this article, we shall develop an optimal control model of energy management in the brain.

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