Analysing High-Dimensional Neuroscience Models: Neurovascular Coupling.

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Abstract

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1 INTRODUCTION

During the last two decades functional magnetic resonance imaging (fMRI) has proven to be an established tool in studying the human brain. This is especially true in the case of the blood-oxygen-level dependent (BOLD) signal, where changes in blood oxygen levels can

be detected via the magnetic signal [18]. However due to the constraint on the resolution of BOLD, fMRI methodology has not been used extensively to study the underlying cellular neural architecture and their associated cerebral functions. Complex models that address this important relationship and constructing a detailed compartmental model with the relevant cell types involved will allow simulations relating certain brain functions performed in a region to its fMRI BOLD response. The neurovascular coupling (NVC) mechanism, the cerebral metabolic rate of oxygen consumption, and the cerebral blood volume (CBV) are known to contribute to the fMRI BOLD response [3], however a thorough understanding of these factors has yet to be fully established.

The NVC response, the ability to locally adjust vascular resistance as a function of neuronal activity, is believed to be mediated by a number of different signalling mechanisms. Roy and Sherrington [20] first proposed a mechanism based on a metabolic negative feedback theory. According to this theory, neural activity leads to a drop in oxygen or glucose levels and increases in CO_2, adenosine, and lactate levels. All of these signals could dilate arterioles and hence were believed to be part of the neurovascular response. However, recent experiments illustrated that the NVC response is partially independent of these metabolic signals [10, 11, 17, 19, 13]. An alternative to this theory was proposed where the neuron releases signalling molecules to directly or indirectly affect the blood flow. Many mechanisms such as the potassium (K^+) signalling mechanism [8], the nitric oxide (NO) signalling mechanism or the arachidonic acid to epoxyeicosatrienoic acid (EET) pathway are found to contribute to the neurovascular response [2].

The K^+ signalling mechanism of NVC seems to be supported by significant evidence, although new evidence shows that the endfoot astrocytic calcium (Ca^{2+}) could play a significant role. The K^+ signalling hypothesis mainly utilises the astrocyte, positioned to enable the communication between the neurons and the local perfusing blood vessels. The astrocyte and the endothelial cells (ECs) surrounding the perfusing vessel lumen exhibit a striking similarity in ion channel expression and thus can enable control of the smooth muscle cell (SMC) from both the neuronal and blood vessel components [12]. Whenever there is neuronal activation K^+ ions are released into the extracellular space (ECS) and synaptic cleft (SC). The astrocyte is depolarised by taking up K^+ released by the neuron and releases it into the perivascular space (PVS) via the endfeet through the BK channels [7]. This increase in ECS K^+ concentration ($3 - 10$ mM) near the arteriole hyperpolarises the SMC through the inward rectifying K^+ (KIR) channel, effectively closing the voltage-gated Ca^{2+} channel, reducing smooth muscle cytosolic Ca^{2+} and thereby causing dilation. Higher K^+ concentrations in the PVS cause contraction due to the reverse flux of the KIR channel [6].

Amidst the difficulty in monitoring and measuring the rapid changes in metabolic demands in the highly heterogeneous brain, speculative estimates of the relative demands of the cerebral processes that require energy were given based on different experimental data by Ames [1]. As per the estimate, the vegetative processes that maintain the homeostasis including protein synthesis accounted for $10 - 15\%$ of the total energy consumption. The costliest function seems to be in restoring the ionic gradients during neural activation. The sodium potassium (Na^+/K^+) exchange pump is estimated to consume $40 - 50\%$, while the

Ca^{2+} influx from organelles and extracellular fluid consumes $3-7\%$. The processing of neurotransmitters such as uptake or synthesis consumes $10-20\%$, while the intracellular signalling systems which includes activation and inactivation of proteins consumes $20-30\%$. The rest of the energy is estimated to be consumed by the axonal and dendritic transport in both directions.

Previous work [15] has provided the construction of an experimentally validated numerical (*in silico*) model based on experimental data to simulate the fMRI BOLD signal associated with NVC along with the associated metabolic and blood volume responses. An existing neuron model [16, 14] has been extended to include an additional transient sodium (Na^+) ion channel (NaT) expressed in the neuron, and integrated into a complex NVC model [5, 4, 9]. This present model is based on the hypothesis that the K^+ signalling mechanism of NVC is the primary contributor to the vascular response and the Na^+/K^+ exchange pump in the neuron is the primary consumer of oxygen during neural activation. The model conatins 160 parameters, most of which come from non-human experiments.

Such a complex model constructed with a high-dimensional parameter space is not easily amenable to sensitivity analyses considering the significant computing resource required. Indeed no formal theory exists which allows direct mathematical investigation of the variability of the large dimensional parameter vector and the resulting output. From a purely physiological perspective an understanding of the dominant cellular mechanisms resulting in cerebral tissue perfusion after neuronal stimulation would be of particular interest.

We have used the cerebral blood flow (CBF) change from the experimental data [21] taken from the rat barrel cortex.

2 Methodology

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2.1 Simulated Data

We use a square pulse of 10 seconds duration for stimulation such that the resulting output (after a substantial number of realisations) can be analysed in a formal manner. We assume that stimulation occurs for $t_1 \leq t \leq t_2$.

2.2 QoIs

A number of quatities of interest (QoIs) have been analysed with respect to the 10 second square stimulation pulse and defined as

1. As a representation of the volumetric flow rate in the cerebral tissue

$$\frac{1}{t_2 - t_1} \int_{t_1}^{t_2} R^4(s) ds \tag{2.1}$$

2. ECS potassium has a distinct effect on the flux into the Neuron. Hence we look at the average and the maximum.

$$[K^+]_{max,ECS}$$

$$\frac{1}{t_2 - t_1} \int_{t_1}^{t_2} [K^+]_{ECS}(s) ds \tag{2.2}$$

3. ECS potassium has a distinct effect on the flux into the astrocyte. Hence we look at the average and the maximum.

$$[K^+]_{max,AC}$$
$$\frac{1}{t_2 - t_1} \int_{t_1}^{t_2} [K^+]_{AC}(s) ds \tag{2.3}$$

4. the combined concentration of the actin myosin complex, both phosphorylated and unphosphorylated, determines the effect stress due to the contraction fo teh smooth muscle cell.

   $[AM + AM_p]_{max}$

5. The phase lag between neuronal stimulation and the radius changed effects a number of markers. Notably the BOLD signal, hence we choose to investigate

   the time, τ, to max value of AM_p

2.3 Experimental Data

Using the experimental data set we choose the same set of QoIs as defined above.

1. $[K^+]_{max}$ in the ECS or $\frac{1}{t_2-t_1} \int_{t_1}^{t_2} [K^+]_{ECS}(s) ds$
2. $[K^+]_{max}$ in the AC or $\frac{1}{t_2-t_1} \int_{t_1}^{t_2} [K^+]_{AC}(s) ds$
3. $[AM + AM_p]_{max}$
4. time, τ, to max value of AM_p

5. $\int_{t_1}^{t_2} R^4(s)ds$ since this is proportional to volumetric flow rate, by virtue of Poiseuille flow.

3 Results

4 Discussion

5 Conclusion

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