Focussed Research Group on Spreading Cortical Depression and Related Phenomena (10frg116)

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August 1-8, 2010

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1 Introduction

The brain is a complex organ composed largely of neurons, glial cells, and blood vessels. There exists an enormous experimental and theoretical literature on the mechanisms involved in the functioning of the brain, but we still do not have a good understanding of how it works. The brain maintains a homeostatic state with relatively small ion concentration changes. The major ions are sodium, potassium, and chloride with a lower concentration of calcium ions, which plays an important role in many phenomena.

Cortical spreading depression (CSD for short) was discovered over 65 years ago by A.A.P. Leão, a Brazilian physiologist doing his doctoral research on epilepsy at Harvard University [9]. Cortical spreading depression, which occurs in the cortex of different brain structures in various experimental animals, is characterized by depression of cellular electrical activity and pathological shifts in ion concentrations, e.g., extracellular potassium concentration can reach values as high as 50 mM, and is manifest as slow nonlinear chemical waves, with speeds on the order of mm/min. CSD is associated with migraine with aura, see [5], where a scintillation in the visual field propagates, then disappears, and is followed by a sustained headache. This connection with migraine with aura strongly motivates our research on understanding CSD mechanisms.

A number of mechanisms have been hypothesized to be important for CSD wave instigation and propagation. These mechanisms involve ion diffusion, membrane ionic currents, osmotic effects, spatial buffering, neurotransmitter substances, gap junctions, metabolic pumps, synaptic connections, and the vascular system. Many of these are discussed in Miura et al. [11]. In spite of knowing many of the basic mechanisms involved in CSD, we still do not understand the relative importance of these mechanisms and details of how they conspire to produce the observed wave phenomena. To date, CSD remains an enigma, and further theoretical investigations are needed to develop a comprehensive picture of the diverse mechanisms involved in producing CSD.

In this FRG, we brought together a group of applied mathematicians involved in biological modelling, mathematical analysis, and scientific computing of fundamental problems in neuroscience (Huang, Miura, Mori, Tao, Wilson, Wylie) and mechanical engineers involved in physiological modeling and fluid dynamics experiments (Sugiyama, Takagi) to address fundamental issues related to CSD. The main objectives of the FRG were to discuss recent issues arising in the context of understanding CSD, which included: 1) the propagation of dilation and constriction waves along blood vessels as a result of electrical and blood pressure waves, 2) the effects of the vascular system on the propagation of CSD waves, 3) the effects of electrodiffusion and chemical diffusion of ions, and in particular the boundary-layer effects along a cell membrane due to

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unequal charge distributions when embedded in an ionic fluid, and 4) the putative connection between a CSD wave in the visual cortex and the aura in the visual field that precedes migraine.

Blood vessels account for a significant portion of the brain volume. Dilation and constriction of blood vessels during the propagation of CSD waves are important and relevant phenomena affecting the supply of oxygen to the tissue. The exact mechanisms for these are not well understood, and we investigated some of these during the FRG.

To better understand the actual mechanisms involved in CSD (and develop some clues into how the brain is organized to perform its normal functions), it is necessary to start from basic principles and build models based on fundamental biochemical and biophysical principles. Below, we describe some of the problems that we studied during the FRG.

2 Modelling the Dilation and Constriction of a Blood Vessel

In order to understand the mechanism of blood vessel dilation and constriction, and to gain useful insights into the biochemical and biophysical processes involved in CSD and in normal physiological conditions, we began to explore the role played by the ion concentrations and their relations to the blood perfusion rate, under normal and CSD conditions. It has been shown in the literature that blood vessel radius is correlated with blood pressure as well as the shear stress experienced by the vessel, which are affected by the concentrations of the ions such as calcium [3]. CSD provides an interesting case to test the coupling of neuronal and blood prefusion models.

A variety of hypotheses for the observed vasodilation were developed and examined. For example, it is possible that during CSD, in an effort to restore the depolarized cell membrane potential, it is the increased energy demand (as measured for example by ATP) which leads to the increased blood flow. However, such an hypothesis does not explain the constriction of the vessel. Takano et al. [15] review evidence that hyperpolarisation is key to spreading vasodilation, and examine various hypotheses for mechanisms underlying this spreading hyperpolarisation.

Flow induced: Wall shear-stress releases NO which dilates vessels. However, we identified other experimental studies which indicated that it is possible to disable NO synthesis and still observe vasodilatation.

Perivascular nerves: These may be important in vasoconstriction but not in vasodilatation, since one can use TTX to abolish vasoconstriction but not vasodilatation.

Endothelial Ca^{2+}: Ca^{2+} and IP_3 can pass across gap junctions to adjacent cells. But while Ca^{2+} is observed to rise locally with hyperpolarisation, it has yet to measurably reach a distance of 0.5 mm from the initial application of ACh when hyperpolarisation had travelled to at least 2 mm.

Based broadly on the above, the hypothesis that we spent the most time discussing in this FRG was the possibility of a calcium wave generating the "signal" to cause the blood vessel to dilate or constrict upstream and downstream of the CSD location. A model which we have discussed for investigating this hypothesis involved two compartments: a smooth muscle cell compartment (SMC or MC) and an endothelial cell compartment (EC), following some of the ideas in Kapela et al. [7].

The EC is hypothesised to be the main location for the calcium wave. However, maintaining such a wave requires a positive feedback loop. One possibility for such a loop involves the IP_3 receptors (IP_3R). It is possible that as the membrane depolarizes, the inwardly-rectifying potassium channel opens (further depolarizing the membrane), leading to an increase in extracellular calcium which opens the potassium-calcium channels, creating positive feedback to the membrane depolarization.

3 Effects of the Vascular System on CSD

The metabolic demand associated with repolarizing cell membranes and re-establishing resting ion concentrations in the wake of the CSD wave requires an increased supply of oxygen-carrying blood from the cerebral arterial network. Recalling that the CSD wave propagates with speeds on the order of mm/min, the question

of local arterial responses is dealt with in line with the work in §2. However, on lateral cortical lengthscales on the order of millimeters or centimeters, we must probe the response of a larger branching network of cerebral arterioles. In fact, we must do this if we wish to consider the communicated effects of CSD at deeper levels within the brain.

In general, this linking of neurons and blood vessels is known as *neurovascular coupling*, and as seen in §2, involves a multitude of pathways connecting blood flow to neuronal activity, and vice versa. Here, we are also interested in how the topology and geometry of the cortical architecture and the cerebral arteriolar network are interrelated. A major challenge in creating an accurate mathematical model of these interdigitating trees is that experimental techniques to determine their topology and geometry are usually mutually exclusive.

Nevertheless, during this FRG, we were able to discuss linking existing models of the arteriolar network, such as that presented in [4], with models of CSD instigation and propagation [6], and the work discussed in §2. In particular, the model in [4], building on [3], features a physiologically-realistic cerebral arterial tree that is able to autoregulate in response to changes in metabolism in the surrounding tissue, such as those caused by the passing of a CSD wave. Our discussion focused on (a) updating the autoregulation model in line with the detailed local study and considerations of §2, and (b) linking a detailed arterial tree model with the compartmental model of CSD instigation and propagation of [6]. As we take this work forward, we expect to also build upon the model developed in [1]. There, we can construct a more detailed coupled model, consisting of both neuronal and vascular components, and carry out numerical simulations on the model.

4 Electrodiffusion and CSD

Since there are large fluctuations in ionic concentrations in CSD, we discussed the merits of using an electrodiffusion model instead of the more conventional chemical diffusion approach in treating ion concentration dynamics in CSD [14]. One interesting complication that arises in such an effort is the treatment of membrane boundary conditions. The basic equations that govern electrodiffusion in the dilute regime are the Poisson-Nernst-Planck equations, but the smallness of the Debye length makes it attractive to take the electroneutral limit [12, 13]. In this singular perturbation limit, however, a boundary layer of electrical charges forms at the membrane interfaces. The presence of such boundary layers lead to capacitive (or cable) effects, the inclusion of which may be particularly important in studying the initiation of CSD. We worked to clarify the mathematical and physical structure of this boundary layer by revisiting the formal asymptotic computations performed in [13].

Another question we tackled was the validity of using the diffusion approximation in place of ionic electrodiffusion in certain contexts. We were able to show, through formal asymptotic computations, that this is indeed possible when the concentration of the ion of interest has a considerably lower concentration than the other co-ions in the electrolyte solution. This justifies the use of simple diffusion to track calcium concentration inside the cell, which has a 10^4-fold lower concentration than the major co-ions (sodium, potassium, chloride) in the cell. This is an important observation given the widespread use of simple diffusion in modeling intracellular calcium dynamics, a major area of cell biology [8].

5 Mapping of CSD in the Visual Cortex to the Visual Field

Our study is concerned with a visual experience that accompanies some of the migraine headaches associated with CSD. Among the patients who have migraine headaches, 20% of them have so-called migraine with aura [5]. In these patients, the onset of a migraine is preceded with visual auras. These visual patterns often take the form of expanding arcs in the visual field and can last up to half an hour. It has been conjectured that CSD waves in the occipital lobe in these patients may be responsible for these auras. That is, these visual auras in the visual field do not correspond to exogenous visual stimulus, but are instead perceptions directly related to the neuronal activity patterns of CSD waves in one or more areas of the visual pathway.

During our FRG, we examined how a CSD wave in the primary visual cortex (V1) would appear in the visual field. V1 is the first part of the visual pathway in the neocortex and is thought to be responsible for the processing of simple geometric features in the visual scene (for instance, local orientation, spatial frequency, and other features that presumably would aid in the detection of lines, edges, and contours). The coordinate

transformation mapping the locations in the visual field to locations in V1 is well known [2]. We use this retinotopic-V1 map to examine how various wave fronts (modeled as moving lines) in V1 could correspond to objects in the visual field. The conjecture that visual auras could be perceptions of CSD waves in V1 is corroborated, as certain wave fronts that propagate correspond to arcs expanding away from the fovea in the visual field, and thus may be perceived as such.

How spatio-temporal neuronal activity in V1 could be perceived is a much more general problem and is of great interest to the visual neuroscience community. The forward problem of how a visual stimulus is coded as neuronal activity in V1 is well studied (especially for simple geometric patterns, see, for example, [10] and references therein), but the inverse problem of determining which visual stimulus could lead to a given spatio-temporal pattern of neuronal activity is not well understood. During our week at BIRS, we examined a few toy models of small neuronal networks to gain intuition for this problem. For a first problem, we examined a network of two neurons driven by independent inputs. So a natural question is: by observing the two neurons in the network, can we determine the inputs that each neuron is receiving.

We used the so-called linear integrate-and-fire point neuron to model each neuron. Each action potential is modeled as decaying exponentials in the synaptic conductances of individual neurons. This is one of the simplest models that could take a generalized input and produce detailed spike times (i.e., timing of action potentials). Within the framework of this highly idealized model, and assuming that we know the strength of coupling between these neurons, we showed that given the detailed neuronal spiking times, we may be able to reconstruct the input into each neuron that is responsible for the activity. We plan to extend this approach to larger networks of networks with more generalized inputs which may contain correlations in the visual scene and to cases where we have partial information (e.g., all of the couplings between the neurons may not be known) or only have statistical information (e.g., statistics of the neuronal activity, instead of detailed spike timings of each neuron).

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