Focussed Research Group

Cerebral Blood Flow, Neurovascular Coupling, and Cortical Spreading Depression

Organizers: H. Huang*and R.M. Miura†

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1 Participants

Due to the complexity of the multiple topics discussed at this workshop, the group of participants possess diverse and complementary expertise. Here is a brief description of the participants.

K.C. Brennan (Utah, Neuroscience) Brennan is a neurologist with interests in headache. His research explores the effects of CSD on blood vessels and vice versa.

J.C. Chang (Ohio State, Math. Biosciences Institute, Neuroscience) Chang has expertise in biomathematics and experience on experimental CSD in the context of contraction and dilation of blood vessels and modeling of CSD related to blood flow.

T. David (Canterbury, NZ, Biomedical Engineering) David leads a group in bioengineering and has done work on modeling and numerical computations of complex vascular trees.

X. Gong (Shanghai Jiaotong University, Biofluids) Gong has expertise in biofluids and developed multiphase models to study mass transport in capillaries.

H. Huang (York, Fluids, Modelling and Scientific Computing) Huang has expertise in modeling and computation and developed models of ion transport in the brain as well as numerical algorithms for solving the model equations.

R.M. Miura (NJIT, Physiology, Fluids, Ions) Miura is a mathematical biologist. He has broad knowledge of CSD phenomena and modeling and will guide the group's efforts on related issues.

S. Takagi (Tokyo, Fluids, Biofluids) Takagi has expertise in bioengineering. He works on biofluids related to cells and cell membranes, and on important issues concerning mass transport in the brain.

J.J. Wylie (City U, HK, Fluids) Wylie is an applied mathematician with a broad knowledge of physics and mechanics, and has worked on problems related to fluid mechanics and to CSD.

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2 Overview of the Field

Although the brain represents only 2% of the body weight, it receives 15% of the cardiac output, 20% of total body oxygen consumption, and 25% of total body glucose utilization. In an active brain, the local cerebral blood flow (CBF) is not static. Neuronal activity can induce localized changes in blood flow, known as neurovascular coupling, which is widely used to monitor human brain function and diagnose pathology. While the correlation between the alterations in neural activity (and metabolism) and changes in CBF is well established, the mechanisms linking these processes are subject to debate. Previously, it was believed that CBF is directly controlled by the energy needs via a feedback sensing mechanism. However, recent experimental evidence support a feedforward mechanism involving neuronal signaling via astrocytes or smooth muscle cells [1].

Neurovascular coupling fails under certain pathological conditions, including during cortical spreading depression (CSD for short). Beyond the acute perfusion changes accompanying the CSD wave, there is a long lasting hypoperfusion and concomitant alteration in neurovascular coupling that follows the spreading wave for at least an hour [5]. Beyond this time scale, CSD causes changes in the neurovascular response that can last days. Known as ischemic preconditioning, the occurrence of CSD up to several days before an ischemic insult reduces the size of injury. On the other hand, changes in perfusion can induce CSD. The most prominent example is a stroke causing peri-infarct depolarizations (PID), which are electrophysiologically indistinguishable from CSD [17]. Conditions that mimic the effects of hypoperfusion, such as oxygen glucose deprivation (OGD) and perfusion with ouabain (an inhibitor of the sodium potassium ATPase), also generate spreading depolarizations. Finally, perfusion changes can modulate the characteristics of CSD. Depending on the underlying oxygenation or blood pressure, the amplitude and duration of depolarization, and velocity of propagation of CSD can be altered.

Regulation of cerebral arterial blood flow, neurovascular responses, and cortical spreading depression have been extensively studied, but little has been done to link these aspects in a unified way. Research on neurovascular coupling is mostly experimental and descriptive, but, existing work in the biomedical literature is mostly based on observations of superficial capillaries and microvessels up to 250 μm and often ignores the biochemical mechanisms that control CBF. Quantitative studies usually focus on simplified models that ignore the fine structure of the capillary network. Finally, most of the theoretical studies of CSD have neglected the effects of arterial blood flow [14, 15, 16, 17].

The main objective of the workshop is to address some of the fundamental issues related to CBF, neurovascular coupling and CSD and incorporate recent advances in experimental studies into mathematical models. Fundamental laws of biochemistry and biophysics that can reproduce observed phenomenon are incorporated into the models to make predictions that can be verified by further experimental studies.

Clinically, CSD has been implicated in migraine with aura [8]. Migraine, a neurological disorder, is characterized by mild to severe headaches, and three times more common in women than in men [2]. Furthermore, approximately a third of these people see an associated visual aura that precedes the migraine. This is a world-wide disease, and affects more than 10% of the world's population, which includes young and old. This FRG is a Mathematics of Planet Earth project and falls under the topic of quantitative studies of the medical arts.

3 Extension of the Neurovascular Coupling Model

CSD provides ideal conditions for studying neurovascular coupling and our initial modeling of this coupling with CSD is given in [4]. First of all, CSD is relatively easy to instigate. In the original experiments when CSD was first observed [11, 12], Leão induced CSD in laboratory animals using electrical, mechanical, and chemical stimuli of the cerebral cortex. Second, CSD induces a large pathological elevation of extracellular K^+ concentration ($[K^+]_e$), which results in depolarization of presynaptic terminals, release of neurotransmitters, and then further release of intracellular space (ICS) potassium into the extracellular space (ECS), to continue to drive the wave of CSD [9, 18]. In addition, CSD is a relatively slow phenomenon. A stimulus to the cortex generates an outward propagating CSD wave with a speed of about 3 mm/min that stops cellular electrical activity almost completely. It takes approximately 2-5 minutes after passage of the CSD wavefront for the normal cortical electrical activity to resume. Finally, CSD is repeatable and a second CSD wave can

be instigated after a refractory period of about 3 minutes [3, 13, 16].

The relevant phenomena during the propagation of a CSD wave, as demonstrated by K.C. Brennan and his collaborators [5], are the dilation and contraction of blood vessels that change local CBF and distributions of blood in the cortex. The exact mechanisms are not yet well understood. One possible explanation for the dilation is that during CSD, there is an increased energy demand to restore the ionic concentrations, which leads to an increased blood flow rate. Clearly, a better understanding of the connection between CSD and changes in the blood vessels would shed light on our understanding of neurovascular coupling.

In order to help us understand the actual mechanisms involved in CSD (and subsequently some clues into how the brain is organized to perform its normal functions), it is necessary to build models based on fundamental biochemical and biophysical principles. Below, we describe some of the relevant problems that we considered during the workshop.

3.1 Coupling of conductive constriction and dilation with CSD

In [10, 19], neuronal models for instigating CSD have been developed. These models serve as the starting point for building a comprehensive model that couples CSD and brain energy metabolism. In particular, we will incorporate the effects of astrocytes and energy metabolism on CSD and test various mechanisms for neurovascular coupling.

Chang et al. [4] was the first modeling effort towards this end, as it was able to causally link oxygen delivery to metabolic activity during the CSD phenomenon. This model coupled vasculature to external potassium concentrations in a phenomenological manner, reproducing the local constrictive behavior of the vascular system during CSD. Blood flow was then modeled using the assumption of Poiseuille flow combined with a lumped circuit model, from which the oxygen flux into the tissue was determined.

While the model of Chang et al. [4] was largely able to reproduce the vascular activity seen during CSD, it is unable to capture the behavior of the vascular tree under normal circumstances or in the wake of the CSD wave where ionic concentrations have returned to normal yet pathological vasoconstriction is present. In order to better understand neurovascular coupling and CSD in these circumstances, one needs to consider the detailed physiology and biochemistry behind the regulation of vascular tone.

3.2 Physiological modeling of vasculature

It was the immediate goal of this focused research group to marry the physiological neuronal CSD model of Chang et al. [4] with prior physiological models of vascular regulation in the literature. In particular, the study of Farr and David [7] provided a starting point for such a task as it incorporated neurons, astrocytes, vascular smooth muscle, endothelial cells, and the important messenger molecules involved in signaling of vasoconstriction and vasodilation. The primary links between the two models are extracellular potassium, and extracellular glutamate. Our group made progress in taking the cellular model of Farr and David and translating it into a continuum representation that fit naturally into the simulation framework of Chang et al. [4]. The next step in implementing this framework is to work on parallelization of the codebase, so that it can run on the IBM supercomputer clusters that are available to Tim David, a participant of our research group. The use of this type of computation will also allow us to use more realistic models for blood flow, in particular we will be able to observe the network effects of the vascular tree. The new combined model will allow us to explore many aspects of CSD, as well as the normal link between brain activity and blood flow.

4 Electrodiffusion Model using Homogenization

As CSD and related vascular regulation occur on the scale much greater than the individual cells and capillaries, we have used homogenized models for ion and oxygen transport. One of our previous assumptions is that diffusion is the main mechanism for ion transport in the extracellular space. In this FRG, we have started to develop an electrodiffusion model using a well-established homogenization approach. Our preliminary results show that the basic structure of the micro-scale model remains intact in the homogenized model. However, there are important issues related to membrane currents that need to be addressed.

5 Long–Term Recovery of Homeostasis

One primary theoretical focus in the study of CSD is to explain the vasoconstriction that follows for an hour after the passage of the initial CSD wave [5]. This constriction is on the same timescale as the effects of migraine, so it may have important clinical implications. There are several possible hypotheses for the cause of this second phase which we will be able to evaluate with our modeling efforts.

In particular, there is good reason to believe that aberrant calcium dynamics plays a role in the etiology of this phase, as abnormally high amounts of calcium enter into neurons, glia, and vascular cells as the depolarizing wave of CSD travels through tissue. Calcium is normally at extremely low levels inside cells, and normal buffering mechanisms for calcium may not be adequate during CSD, leading to long–term aberrant calcium oscillations. In vascular smooth muscle cells, these oscillations can cause vasoconstriction.

A second hypothesis that we will be able to explore is the role of nitric oxide deficiency [6]. Nitric oxide is a messenger that is used as a signal to dilate blood vessels. During CSD, there is a large depletion of oxygen. Since oxygen is needed for the synthesis of nitric oxide, this depletion may cause inadequate nitric oxide production. Furthermore, there is a feed-forward interaction involved as decreased nitric oxide production leads to decreased blood flow and decreased oxygen availability.

6 Scientific Progress Made

The natural instigation and direct causes of propagation of cortical spreading depression remain a mystery after almost 70 years since Leáo's initial discovery of CSD. Persistent detailed studies over the years of the mechanisms believed to be instrumental in the manifestation of this phenomenon are beginning to bear fruit. The Focussed Research Group workshop was very successful in generating new insights and conjectures about how CSD works. These come from including more details about the effects of cerebral blood flow in supplying oxygen to the brain during CSD and the concomitant neurovascular coupling needed to fully explain the phenomenon.

New mechanisms including astrocytes, vascular smooth muscle, endothelial cells, and the important messenger molecules involved in signaling of vasoconstriction and vasodilation proposed earlier by Farr and David [7] have been merged with those postulated in [4] to create a more versatile model to study numerically. The merged code has been written and implementation studies are being pursued.

Earlier modeling of CSD utilized continuum evolution equations that were based on assumed homogeneity of the neural tissue with interactions between the different components, neurons, glia, extracellular space, and vascular space. At this FRG, we have made initial attempts to put these equations on a more rigorous mathematical footing by incorporating electrodiffusion effects and introducing a multiple scales approach to derive the governing equations from more detailed interactions between the cells. This homogenization of the neural tissue immediately become complicated beyond the leading order because of nonlinearity, existence of Debye layers, and biological constraints, such as electroneutrality in the bulk media. Work continues on this problem.

Finally, discussions were held on the long-term recovery of homeostasis after the passage of a CSD wave. The time scale of this recovery is on the order of an hour, much longer than the time for an active CSD wave. The accompanying long-term vasoconstriction may have two explanations: 1) aberrant calcium oscillations or 2) nitric oxide deficiency, which normally would lead to vasodilation.

7 Outcome of the Meeting

This FRG has been successful in bringing together eight mathematical scientists, bioengineers, and a neurological research scientist/clinician to collaborate on an important neurological phenomenon, cortical spreading depression. There remain many unanswered questions and the need for further collaboration. Progress on this research problem can benefit from further intensive workshops, such as the FRG.

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