Cortical Spreading Depression: An Enigma

Robert M. Miura[(1)], **Huaxiong Huang**[(2)], **and Jonathan J. Wylie**[(3)]

[(1)] Department of Mathematical Sciences
New Jersey Institute of Technology
Newark, NJ 07102

[(2)] Department of Mathematics and Statistics
York University
Toronto, Ontario, Canada M3J 1P3

[(3)] Department of Mathematics
City University of Hong Kong
Hong Kong

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Abstract

The brain is a complex organ with active components 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 on a gross mechanistic level. In general, the brain maintains a homeostatic state with relatively small ion concentration changes, the major ions being sodium, potassium, and chloride, as well as a very important ion, calcium.

Cortical spreading depression (CSD for short) was discovered over 60 years ago by A.A.P. Leão, a Brazilian physiologist doing his doctoral research on epilepsy at Harvard University, "Spreading depression of activity in the cerebral cortex," J. Neurophysiol., 7 (1944), pp. 359-390. Cortical spreading depression is characterized by massive changes in ionic concentrations and slow nonlinear chemical waves, with speeds on the order of mm/min, in the cortex of different brain structures in various experimental animals. In humans, CSD is associated with migraine with aura, where a light scintillation in the visual field propagates, then disappears, and is followed by a sustained headache.

To date, CSD remains an enigma, and further detailed experimental and theoretical investigations are needed to develop a comprehensive picture of the diverse mechanisms involved in producing CSD. A number of mechanisms have been hypothesized to be important for CSD wave propagation. In this paper, we briefly describe several characteristics of CSD wave propagation, and examine some of the mechanisms that are believed to be important, including ion diffusion, membrane ionic currents, osmotic effects, spatial buffering, neurotransmitter substances, gap junctions, metabolic pumps, and synaptic connections. Continuum models of CSD, consisting of coupled nonlinear diffusion equations for the ion concentrations, and a discrete lattice-Boltzmann method approach will be described. Also, we will describe some open problems and remaining challenges.

1 Introduction

Understanding the brain, which consists of neurons, glial cells, and blood vessels, is one of the remaining major frontiers in human knowledge. There is an enormous published literature on the detailed mechanisms operative in the brain, but our knowledge of how the combination of these mechanisms leads to the functioning mammalian brain remains very incomplete. This literature on electrical and chemical effects at the subcellular level and at the single neuronal and glial cell levels shape our view of how the brain works. Recent studies on neuronal networks, where neurons communicate via synaptic connections, have been important for understanding how collections of neurons lead to observed electrical behavior. In addition, the microenvironment of brain cells provides nonsynaptic mechanisms to integrate some of the activity between cells, called "volume transmission" [1]. Such integration is mediated by ion diffusion [65] and concomitant membrane electrical effects. These effects influence brain function because they affect neurons and glial cells as well as the interactions between them. In particular, the electrical excitability of neurons depends crucially on the local milieu of ionic concentrations. The

[1]Department of Mathematics, New Jersey Institute of Technology, Newark, New Jersey 07102 USA, miura@njit.edu

[2]Department of Mathematics and Statistics, York University, Toronto, Ontario, Canada M3J 1P3, hhuang@yorku.ca

[3]Department of Mathematics, City University of Hong Kong, Kowloon, Hong Kong, wylie@math.cityu.edu.hk

diffusion of ions through the extracellular and intracellular spaces, and ionic movements across cell membranes constitute ubiquitous mechanisms for various cell behaviors, including electrical activity, resting membrane potentials, and maintaining homeostasis of the brain microenvironment. The coupling of these basic mechanisms with other effects, such as osmosis (resulting in cell swelling or shrinking from the flow of water across the membranes) and spatial buffering (due to electrotonic spread of electrical potential along extended membranes of cellular syncytia, e.g., along glial syncytia) produce normal brain function, but are not well understood despite extensive experimental studies. Note that cell coupling in this context combines (fast) electrical coupling with (slow) processes associated with ion and water diffusion.

The normal brain functions with relatively large changes in electrical potentials across cell membranes, but maintains ionic homeostasis at all levels via small changes in ionic concentrations. All of the mechanisms mentioned above operate in concert to achieve homeostasis of the brain-cell microenvironment. Our understanding of how these mechanisms interact to maintain this condition comes from results using a variety of experimental techniques on quiescent brain tissue. These techniques include applications of drugs and dyes, measurements of extracellular ionic concentrations by inserting ion-selective microelectrodes into tissue, and measurement of cell membrane potentials by inserting microelectrodes into cells. A different approach to determine how ionic fluxes and diffusion affect normal brain function is to observe extreme phenomena that cause major ionic concentration changes. Such studies can tell us a lot about how different mechanisms influence brain function and interact with each other.

In this paper, we will describe one such extreme brain phenomenon called cortical spreading depression (CSD for short), which is a slowly propagating wave in the cortex of the brain. In Section 2, we briefly describe CSD. In Section 3, we give sketches of different mathematical models that have been proposed for CSD. Open problems associated with CSD and some challenges will be discussed in Section 4.

2 Cortical Spreading Depression

Cortical spreading depression was first described over 60 years ago by A.A.P. Leão [49] in his doctoral studies on epilepsy in the rabbit. The name 'spreading depression' comes from the massive synchronized depression of normal electrical activity as observed in the electroencephalogram (EEG), resulting in depolarization and then repolarization of all cell types in the affected region. Spreading depression consists of slow chemical waves and fast electrical waves, and these are associated with large ionic concentration changes in the cortices of many different brain structures in different animals [8, 52, 81]. These ions consist of the three major ions, $Na^+, K^+,$ and Cl^-, and Ca^{2+}, which is very important in many different neuronal subcellular processes.

Waves of cortical spreading depression can be instigated using a variety of stimuli, including applications of potassium chloride (KCl) on the cortical surface, mechanical impact, electrical stimulation, as well as other means [8, 81]. Note that the precise mechanisms of instigation of CSD and of CSD wave propagation appear to be different. Spreading depression suppresses neuronal electrical activity and is associated with a redistribution of ions, shrinkage of the extracellular space, and increased metabolism. Most studies of CSD have focussed on the propagation of CSD waves, which are extremely slow with speeds of 1-15 mm/min. Since diffusion coefficients of the various ions are fixed, an explanation of the variability in the speed of CSD involves tissue cell types and structures, volume fraction of the extracellular space, and membrane ionic channel distributions and currents, as well as other possible mechanisms.

These waves of CSD have many properties in common with action potential propagation in nerve axons. They appear to be solitary waves, although multiple waves are seen experimentally. These waves are all or none, i.e., either a wave is generated or no wave is generated. They exhibit refractoriness, i.e., a point stimulus at a location following a CSD wave may not generate a second

wave if it is too close to the refractory part of the wave. On the other hand, experiments have been carried out whereby a stimulus following a wave is located essentially where the tissue is refractory on one side of the stimulus and no longer refractory on the other side. This can result in a single wave front propagating in a direction opposite to the first wave. Finally, two CSD waves will annihilate each other when they collide head on. What distinguishes CSD waves from action potentials, however, is the difference in time scales, namely CSD evolves on a time scale of minutes whereas action potentials propagate on a millisecond scale.

The literature on spreading depression is large, and a number of excellent reviews have been written [8, 24, 52, 64, 80, 81]. There have been numerous studies on ionic and chemical correlates of the phenomenon. Furthermore, the complexity of CSD waves elevates the role of mathematical modelling, through which one can alter, control, and focus on specific mechanisms.

There are numerous references in the literature to putative relationships between CSD and a variety of pathological states of the brain, including migraine with aura [3, 13, 24, 28, 47, 69, 70], cerebral ischemia-infarction [24], and transient global amnesia [24]. The relationship between CSD and migraine with aura has been established [29]. There also are suggestions of the protective role that CSD could play to reduce ischemic brain injury [40]. These are important biomedical correlates of CSD, and each one deserves further study from the modeling point-of-view. Our focus here and in this research is to identify the relevant mechanisms that appear involved in cortical spreading depression and to include them in a comprehensive model of CSD.

In spite of knowing many of the basic mechanisms involved in CSD, we still do not understand the relative importance of these mechanisms and how they conspire to produce the observed wave phenomena. We can greatly extend our basic knowledge of how the brain functions by understanding what happens and causes the "massive failure of ion homeostasis" during CSD [38]. It is extremely difficult to perform detailed experiments that record the multifarious variables that are changing during CSD. Therefore, a good understanding of the complex interactions between these mechanisms can come only from a detailed mathematical modeling viewpoint where one can turn mechanisms on and off. Furthermore, CSD serves as a paradigm for our understanding of the basic mechanisms that are important in neuroscience. Charles Nicholson, who has been at the forefront of research for many years on ion diffusion in the brain and in spreading depression, states [63]:

> **No matter how many channel proteins we sequence, how many neuromodulators we identify and how many neural networks we construct, if we cannot explain spreading depression, we do not understand how the brain works.**

Cortical spreading depression remains an enigma today, and identification of how the precise mechanisms involved lead to the instigation and propagation of CSD waves has remained elusive. Cortical spreading depression is a wonderful research tool to help us understand basic neurophysiological mechanisms for the normal functioning brain. The study of CSD continues to challenge experimental and mathematical neuroscientists in the 21^{st} century.

3 Mathematical Modeling and Mathematical Models

3.1 Early models

It was suggested early on by B. Grafstein [26] that K^+ was an important ion for CSD. The first (simple) mathematical model of CSD was proposed by A. Hodgkin and published in a paper by Grafstein [27]. The importance of K^+ in CSD phenomena remains valid today [87]. One of the tenants of Grafstein's theory was that neuronal action potentials play an important role in CSD propagation. However, critical experiments by Sugaya et al. [86] showed that CSD could even

propagate through tissue treated with tetrodotoxin (TTX), which prevents neurons from firing action potentials. A simple kinematic model of a wavefront in cardiac muscle tissue by Wiener and Rosenblueth [96] had been proposed as a model for CSD. A cellular automata model of CSD was proposed by Reshodko and Bures [74].

As noted above, there are clear similarities between CSD waves and neuronal action potentials. Since action potentials have received extensive study, there have been many different models proposed, from detailed ionic models of action potentials in squid axon by Hodgkin and Huxley (HH) [32] to a caricature of the HH model by FitzHugh [19, 20] and Nagumo et al. [60]. Note that if the dependent variable in these equations is interpreted as an ionic concentration rather than the membrane potential of cells, then their solutions would mimic the ionic concentration changes observed in CSD. For example, the FitzHugh-Nagumo equations look like

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + F(C, A), \tag{1}$$

$$\frac{\partial A}{\partial t} = G(C, A) \tag{2}$$

where C is the ionic concentration at (x, t), A is the recovery variable, in the interpretation of the FHN equations, D is the diffusion coefficient, F is a cubic equation in C and linear in A, and G is linear in both C and A. Any of these models are capable of reproducing the general characteristics of a solitary CSD wave and even multiple CSD waves by appropriate alterations in the values of the relevant parameters and slight modifications of the model equations. However, these simplified models would not give detailed biophysical features of CSD waves and would give little insight into the physiological mechanisms involved in instigating CSD waves and their propagation. In particular, the application of such simple models to understand and devise treatments for medical diseases would be severely limited by the lack of incorporating detailed mechanisms into the models.

3.2 Mathematical models of CSD

3.2.1 Tuckwell-Miura model

The first mathematical model for CSD wave propagation that incorporated physiological mechanisms was proposed in 1978 by Tuckwell and Miura (TM model) [91]. The TM model did not contain action potentials, as shown by Sugaya et al. [86]. The TM model postulated that an initial large increase in the potassium concentration in the extracellular space (ECS) would depolarize presynaptic terminals, resulting in neurotransmitter release from intracellular stores. The neurotransmitter released would open K^+ channels in post-synaptic neurons, leading to increased release of potassium from the intracellular space (ICS). (Note that van Harreveld postulated that the neurotransmitter glutamate was the excitatory mechanism causing release of K^+ [92, 93].) This process is regenerative and would lead to the propagation of the CSD wave. This idea is similar to that proposed by Grafstein except the mechanism for K^+ release was different. Recovery of the ionic concentrations to their normal levels in the ECS and the ICS are accomplished by metabolic pumps, which consume energy.

An important contribution of the TM model was the idea that since CSD occurs in multicompartmental brain tissue, i.e., ECS and ICS of neurons and glial cells, then these compartments each could be treated as continuum regions in space, but overlapping everywhere. This approximation is valid provided the space scale of CSD is large compared to cell size, which it is. Whereas ECS and ICS would be overlapping everywhere, the connection to the experimental situation is that the concentration of an ion in the ECS (or ICS) would be correlated to that in the nearest ECS (or ICS) position.

The TM model was a minimal continuum model for ionic concentrations in one space dimension that included only potassium and calcium, and only two compartments, the ECS and the

ICS of neurons. The model equations do account for mechanisms at the cellular level, including diffusion of ions, ionic membrane currents, and electrogenic pumps. These basic mechanisms are expected to be important in CSD wave propagation. The TM model takes the form

$$\frac{\partial K^o}{\partial t} = D_K \frac{\partial^2 K^o}{\partial x^2} + \rho_1 (I_K + P_K), \tag{3}$$

$$\frac{\partial K^i}{\partial t} = -\frac{\alpha}{1-\alpha} \rho_1 (I_K + P_K), \tag{4}$$

$$\frac{\partial C^o}{\partial t} = D_C \frac{\partial^2 C^o}{\partial x^2} + \rho_2 (I_C + P_C), \tag{5}$$

$$\frac{\partial C^i}{\partial t} = -\frac{\alpha}{1-\alpha} \rho_2 (I_C + P_C) \tag{6}$$

where K^o, C^o and K^i, C^i are the ionic concentrations of potassium and calcium in the ECS and ICS, respectively, D_K and D_C are the ion diffusion coefficients for potassium and calcium, respectively, ρ_1 and ρ_2 are constant coefficients that reflect channel distributions and cell membrane area, and I_K, P_K and I_C, P_C correspond to the membrane ionic currents and the pumps for potassium and calcium, respectively, and α is the fraction of the total volume occupied by the ECS.

The TM model produces a wave speed of approximately 1 mm/min, after compensating for the effect of tortuosity (the scale factor to account for the effective increase in path length for diffusion of ions around cells - approximately 1.5). In addition to the complexity of the TM equations due to highly nonlinear functions, to generalize the model, one has to increase the number of equations by two for each additional ion to be added to the model.

Wylie and Miura [97] have examined the TM model equations more closely from a mathematical point of view. Note that the TM model equations do not possess isolated rest states, i.e., these equations are characterized by having degenerate source terms. Using general forms of physically relevant source terms, they derived conditions that are required to trigger traveling waves when a stable uniform steady-state solution is perturbed by a highly localized disturbance. They showed that the degeneracy in the source terms implies that traveling waves have a number of surprising properties that are not present for systems with nondegenerate source terms.

Ikeda and Miura [33] have carried out a singular perturbation analysis for the solitary wave solution of the dimensionless TM model. They have proved existence of the leading-order solution.

3.2.2 Generalized TM model

The TM model equations account for two major mechanisms, namely ion diffusion and ion movements across the cell membranes due to ion channel flow and to energy-consuming pumps that can drive ion flow against the electro-diffusion gradient. As such, the TM equations can be generalized in several different ways, including increasing the number of spatial dimensions to two or three, increasing the number of ionic species to include all major ions, and increasing the number of ICS compartments to include both neurons and glial cells. If we increase the number of ionic species to n and the number of space dimensions, then the system of model equations for the j^{th} ion would be given by

$$\frac{\partial C_j^o}{\partial t} = D_j \nabla^2 C_j^o + I_j(Cl^o, \ldots, C_n^0, C_1^i \ldots C_n^i) + P_j(C_j^o, C_j^i), \tag{7}$$

$$\frac{\partial C_j^i}{\partial t} = -\frac{\alpha}{1-\alpha} \left[I_j(C_1^o, \ldots, C_n^o, C_1^i, \ldots, C_n^i) + P_j(C_j^o, C_j^i) \right] \tag{8}$$

where t corresponds to time, C_j^o and C_j^i are the extracellular and intracellular concentrations of ion $j, j = 1, \ldots, n,\ D_j$ is the diffusion coefficient for ion j, ∇^2 is the Laplacian operator in two or three dimensions, I_j consists of the membrane ionic currents for ion j, P_j is the pump term for the j^{th} ion, which is an energy consuming mechanism, and $0 < \alpha < 1$ is the extracellular volume fraction (the fraction of the total tissue volume that is extracellular space - approximately 0.2).

The first term on the right-hand side of (7) corresponds to the diffusion of ion j in the extracellular space. We are assuming that diffusion is isotropic for this model. However, if the diffusion is not isotropic, as in the new technique called diffusion tensor imaging, then the diffusion coefficient becomes a tensor instead. Both I_j and P_j are highly nonlinear functions of their arguments. In this model, the effects of action potentials are ignored since they occur on a much shorter time scale than the time scale for CSD, and recalling Sugaya and his colleagues finding that action potentials are not an important mechanism for CSD propagation. However, the membrane potential, V, undergoes slow changes and can be expressed as an algebraic function of the ionic concentrations, e.g., using the Goldman-Hodgkin-Katz equation [37]. These equations form a complex system of coupled highly nonlinear ordinary differential equations (ODEs) and partial differential equations (PDEs).

3.2.3 Shapiro model

Recently, a completely different biophysical model of CSD was proposed by Shapiro [78, 79]. Experiments have suggested that there is a need for gap junctions for CSD propagation [43, 53, 61] and that glial poisons do not block CSD waves but rather enhance their speeds [43, 44, 45]. Shapiro hypothesized that the gap junctions are neuronal, and so he formulated a continuum model is in one space dimension with two compartments representing the ECS and ICS. Specifically, the ICS consists of gap junctionally connected neurons. There are three main assumptions in his model. The first assumption is that as CSD propagates, the ECS contracts from the expansion of neurons due to osmotic effects following ion movements across the cellular membranes. He finds that without the physical expansion of the neurons, an CSD wave cannot propagate. A second assumption is that ICS ion movements must be modelled electrodiffusively, which can produce a precursor ICS K^+ pulse. This leads to additional ion movements leading to additional osmotic effects. The third assumption is that in the neuronal tissue, there are enough open interneuronal gap junctions that permit CSD wave propagation through the ICS. One surprising consequence of this model is that ion diffusion in the ECS is not necessary for CSD propagation.

3.2.4 Somjen model

Somjen and his colleagues [35, 36, 80] have approached CSD from a different point of view and have focused on the instigation of the phenomenon. They have studied a single hippocampal pyramidal neuron model using the software program NEURON, a simulation environment, developed by Hines, Carnevale, and Moore [31]. By incorporating a restricted interstitial space around the neuron, they were able to simulate the effects of rising and falling ion concentrations, partially as a result of osmotic cell volume changes. They found that with adequate control of extracellular K^+ by the $Na - K$ exchange pump and an imposed glial uptake function, stimulated tonic firing of the neuron ceased as soon as the stimulating current in the soma was shut off. However, without adequate control on K^+, stimulated firings did not cease after removal of the stimulus and the resulting burst firing continued, resembling what one would expect from a seizure. A CSD-like depolarization occurred when NMDA-currents and persistent Na-currents in the apical dendrites were activated by depolarization spreading from the soma.

3.2.5 Other models

Models of CSD have been formulated to study pathological situations. Reggia and Montgomery [73] formulated a two-dimensional computational model of visual hallucinations during migraine. A fairly detailed mathematical model of CSD in focal ischemia was proposed by Revett et al. [75], which built on the Reggia and Montgomery model and included many different ionic currents, as well as ion diffusion.

3.3 Mathematical models of related phenomena and mechanisms

3.3.1 Volume fraction and tortuosity

Nicholson and Phillips [66] used porous media theory to mimic ion diffusion in the extracellular space. (Reviews of diffusion in brain tissue have been given by Nicholson and Sykova [68] and by Nicholson [64].) They used this theory to determine the extracellular volume fraction and the tortuosity of the brain tissue as a porous medium. The tortuosity is a measure of the increased path lengths required by ion as a result of the tortuous path that has to be taken by the ions to go from one location in the ECS to another location. Also, they confirmed that the diffusion coefficients for ions in the brain were the same as in aqueous solution.

In the early 1990s, Doolen and his colleagues [16, 17] developed an alternative method, called the lattice gas algorithm, to study fluid flow in porous media. This method was applied to the problem of oil recovery in porous media. This method seems ideally suited for the study of ion movements in the brain since the brain is effectively a porous medium [66], except the cell membranes allow the movements of ions and water through them. The lattice Boltzmann method (LBM) is more suitable for calculations involving real numbers. Dai and Miura [14, 15] used the lattice Boltzmann method to study the same problem as Nicholson, i.e., to determine tortuosity and diffusion coefficients in artificial brain tissue. The lattice Boltzmann method requires a detailed knowledge of tissue structure, i.e., cell membrane locations.However, compared to the changes in ECS ion concentrations observed in CSD, the changes in ECS ion concentrations needed for these calculations were small.

Further work using the LBM has been carried out by Wang and Miura [95] and applied to more realistic brain tissue geometry.

3.3.2 Glial cells and spatial buffering in the brain-cell microenvironment

In brain tissue, glial cells are ubiquitous between neurons. However, they do not generate action potentials nor do they form synapses. The functional roles of glial cells are not well understood, although the regulation of ECS potassium is one of the best examples of glial-neuronal interactions [89]. Glial cell membranes are highly selective for potassium ions. Potassium is the principal intracellular cation, and stable neuronal electrical activity requires regulation of the spatial K^+ concentration gradient. For example, increases in extracellular K^+ concentration ($[K^+]_o$) from 3 mM to 5 mM can lead to hyperexcitability of the surrounding neurons [50], and further increases may affect the efficiency of synaptic transmitter release [5]. Normally, $[K^+]_o$ never exceeds about 12 mM. During CSD, $[K^+]_o$ can reach as high as 40-50 mM. Thus, buffering of K^+ may play an important role in CSD propagation.

Temporary $[K^+]_o$ accumulation can be caused by prolonged neuronal activity [87, 88], iontophoretic K^+ injection [51, 66], application of drugs, or pathological conditions such as hypoxia and ischemia [67, 72]. Resting K^+ levels are restored by mechanisms that dissipate $[K^+]_o$ gradients more rapidly than does simple passive diffusion. Three primary glial mechanisms have been emphasized for removal of extracellular K^+ [12]: 1) enhanced K^+ transport by the Na^+/K^+-ATPase; 2) passive KCl co-transport; and 3) current-mediated K^+ entry by means of K^+ channels. The latter mechanism, termed spatial buffering (SB) by K^+ channels, was

the primary focus of the paper by Chen and Nicholson [12]. Their study included SB, ECS diffusion, and passive KCl uptake with only the ECS and glial cells. Also, their focus was on small perturbations from homeostatic conditions, so CSD wave propagation is not covered by their analysis.

Spatial buffering of ECS potassium by glial cells first was described by Kuffler and his colleagues [41, 71]. This mechanism for potassium clearance was further elaborated by Gardner-Medwin [21, 22], Gardner-Medwin and Nicholson [23], Chen and Nicholson [12], and Steinberg et al. [85]. From experimental observations, we know that CSD wave speeds are in the range of 1-15 mm/min. Spatial buffering is a mechanism that would allow variation of CSD wave speeds. However, this has not been investigated thoroughly in the context of CSD wave propagation. The simplified one-dimensional version of SB has been treated both numerically [22] and analytically [12].

To describe spatial buffering, consider glial cells in a syncytium that are connected by gap junctions, so the membranes of neighboring cells tend to remain isopotential. However, a local increase in $[K^+]_o$ will cause a local depolarization of the glial cell membrane, which then spreads electrotonically along the membrane to remote regions of the syncytium. Glial cell membranes have resting membrane potentials at about 20 mV lower than neuronal membrane potentials. This represents the predominance of K^+ channels in the resting state. Thus there is an influx of extracellular K^+ at the site of local depolarization and an efflux of K^+ into the ECS at distal regions where the $[K^+]_o$ is near resting levels. Note that thus effectively, K^+ ions are transported rapidly from an ECS location of high $[K^+]_o$ ions to regions with low $[K^+]_o$. The circuit current loop is closed by intracellular and extracellular ionic current flows, primarily those of Na^+ and Cl^- [94]. This passive buffering mechanism has been shown to be energy-independent and more efficient than passive ECS diffusion [21, 23].

At rest, the glial membrane is selectively permeable to K^+ ions, so the membrane potential equals the Nernst equation for K^+ [11]. Several different voltage dependent K^+ channels contribute to the K^+ conductance, including the inward rectifier, Kir; delayed rectifier, Kd; transient A-type, K_A; and Ca^{2+} -activated channel, K_{Ca} [84]. For SB, the Kir channel is important since it maintains an open configuration at rest and can be activated at more negative potentials. Also, the inward rectifier channel has different responses to hyperpolarization and to depolarization. The Kir channels enhance the efficiency of SB by increasing the influx of K^+ in regions of high $[K^+]_o$ [62] and by allowing the membrane depolarization to spread along the glial cell and syncytium [2].

Also, Steinberg et al. [85] have applied the LBM to the spatial buffering mechanism, which is important to buffer ECS potassium in the brain-cell microenvironment, see the description and discussion below. This study elaborates on previous theoretical work by Chen and Nicholson [12], but incorporates a more realistic structure of the brain cell microenvironment, which was not feasible earlier.

3.3.3 Cell swelling

In view of the recent theories of CSD from Shapiro [79] and from Somjen and his colleagues [35, 36, 80], the TM postulate [91] that neurotransmitter release resulting from depolarization of synapses may not be the only mechanism involved in the propagation of CSD waves. While neurotransmitter release is undoubtedly still occurring, the new theories focus on a major role played by cell swelling that results from ions crossing neuronal membranes leading to osmotic stresses. With cell swelling being an important component in both the Shapiro and Somjen models, the importance and relevance of spatial buffering in glial cells to CSD wave propagation become questionable. In addition, it has been shown that although calcium dynamics accompany CSD, increases in ICS calcium are not essential for CSD initiation or propagation [6] nor for (molluscan) neuronal swelling [30]. However, recent evidence shows that voltage-gated calcium

channels are important for repetitive CSD waves [76]. Thus, the simple view of CSD from 10 years ago is no longer valid, and the recent modelling efforts will help guide future studies.

4 Assessment of the Models

Having described a number of different mechanisms that are believed to be important for CSD wave propagation, it remains open as to how these mechanisms interact and are manifest as CSD waves.

To put the models of CSD described above in perspective, we summarize the basic pros and cons of the three main approaches to modeling CSD, namely the continuum models by Tuckwell and Miura [91] and by Shapiro [78, 79] and the single neuron model by Kager et al. [35, 36]. The TM model only contains diffusion, membrane ion currents, and electrogenic pumps. From that point of view, this model is simple and captures the crucial characteristics for CSD propagation, namely shape and speed. Furthermore, it is much more amenable to mathematical analysis. Its main deficiency at this time is that it does not include the new mechanisms which have been suggested by more recent experiments. The Shapiro model takes a similar continuum approach, but includes more detailed ionic currents, incorporates swelling, neuronal gap junctions, and also produces some of the crucial characteristics of the CSD waves. This model is a good simulation model that includes details of the various mechanisms. Its disadvantage is that it is a very complex model and would be difficult to analyze mathematically and to isolate the crucial physiological mechanisms.

The work done by Kager et al. [35, 36] is based on simulations of CSD using NEURON for a single neuron. This gives a very well-modeled system at the cellular level that includes detailed currents and geometry. However, restriction to a single neuron setting does not permit simulating CSD wave propagation.

5 Open Problems and Challenges

Some of the open problems and outstanding challenges that remain to be addressed are described below.

1. Observed CSD waves have a range of speeds. The continuum models consist of nonlinear diffusion equations, which are diffusion controlled. (Shapiro states that diffusion is not required in his model, but there is an effective diffusion term in his equations, which is interpreted differently.) The variability in speeds cannot come from variations in the diffusion coefficients because it has been shown that their values equal those for diffusion in aqueous solution. It remains to resolve this issue by determining a mechanism that controls the speed, whether it be the strength of the nonlinear terms in the models, the specific structures in the tissue, or by some other etiology. One proposal is that spatial buffering can alter the speed of the CSD wave as a result of altering the effective diffusion speed of ECS potassium.

2. One of the essential differences between the TM model and the Shapiro model with respect to CSD wave propagation is that the TM model's main mechanism is diffusion of ions in the ECS whereas that for Shapiro's model is the internal gap junctions between neurons. A possible way to resolve this issue is the use of gap junction blockers in experiments to distinguish between these two models. A significant change in the CSD behavior with and without the blockers would mean that gap junctions do play a significant role in CSD wave propagation. However, a negative result does not validate the TM model. Detailed modeling at the cellular level could distinguish between the validity of a mechanism using the Kager et al. approach on a network of neurons instead of a single neuron.

3. In Kager et al. [36], the authors report limitations in their approach to a study of CSD. In particular, their simulations produced CSD-like depolarization of the single neuron;

however, they note a discrepancy in the repolarization phase of the single cell model compared to CSD. Thus there remains the question, to what extent is this discrepancy a consequence of the restriction to one computational neuron?

In the descriptions above, there were two major objectives: 1) develop and study mathematical models incorporating physiological mechanisms believed to be important in experimental CSD, e.g., in addition to ionic diffusion and ionic currents across cell membranes, the effects of osmosis on cell volume, and the effect of spatial buffering on fast transport of extracellular potassium ions, and 2) develop, study, and analyze simplified mathematical models that retain some of the essential mathematical features present in these CSD models, e.g., influence of degenerate sources in the model equations on asymptotic states of the ionic concentrations. Below, we flesh out some of these problems to see how one might make progress towards reaching these objectives.

It will be interesting to study how the various ionic mechanisms known to be operative in the brain conspire to produce different changes in neuronal and glial behavior. By using mathematical modeling and computer simulations as the main analytical tools, there are two different approaches to achieve this goal. The first approach is to use continuum modeling, in the same spirit as that which went into the derivations of the TM model [91] and the more detailed Shapiro model [79]. The main objective of the continuum modeling approach is to develop an approximate mathematical description of CSD which accounts for the overall behavior of CSD waves and takes into account physiological details at the cellular level, but not to reproduce the exact nature of CSD waves in all its detail. Comparisons with experimental observations could be made whenever it is appropriate. This approach is in the spirit of physics modeling where individual mechanisms can be separated out and examined more closely. Such separation of mechanisms generally is not possible in live biological systems, but mathematical modeling provides us with the opportunity to examine each mechanism in detail and possibly in isolation.

One can study aspects of CSD using a continuum approach on a scale much larger than the individual cells, which accounts for ion diffusion, ionic currents through membranes, spatial buffering in glial and neuronal syncytia, and osmotic effects leading to local volume fraction changes. There are two phenomena to consider: 1) instigation of CSD waves and 2) propagation of CSD waves. One can modify the original TM model in two ways. One can use ion transport due to gap-junctions as the main mechanism instead of neuron-transmitters, as suggested by recent experimental findings. We will also incorporate osmotic cell volume changes. Unlike Shapiro, however, the basic model can be kept simple and the number of variables and parameters can be kept to a minimum. The primary reason for favoring a simple model at this level of modeling is to avoid unnecessary complications typically associated with a complex model that has a large number of variables and parameters. Another reason for this preference for a simpler model is that mathematically, it will be easier to manage. Since the set of equations consists mainly of electro-diffusion equations for Na^+ and K^+ in the ICS and ECS, the system is similar to the coupled reaction diffusion equations analyzed by Wylie and Miura [97]. The stability analysis can be extended to the modified TM model consisting of four coupled reaction diffusion equations with degenerate source terms (ion currents and pumps). This type of analysis can reveal much more than direct computer simulations and provide a more complete pictures of the main mechanism of the instigation and propagation of CSD waves.

The macroscopic continuum model can provide general information on how CSD is affected by certain parameter values when a simplified mathematical model has been constructed. To identify more fundamental physiological mechanisms, a more detailed microscopic model is desirable.

A different approach to study CSD waves consists of using a system composed of a finite number of neurons by extending the single neuron simulations carried out by Somjen and his colleagues. As demonstrated in Kager et al., simulations based on a single neuron can reveal a number of interesting insights. However, there are limitations in the single neuron setting due

to restricted ion diffusion. As a result, there exist notable differences between the simulation results and the experimental observations. Also, the single neuron model cannot simulate the propagation of CSD waves. In such a limited version of the microscopic model, one can allow ECS electro-diffusion, which is missing from the single neuron simulations.

For formulating the models proposed here, important information comes from the modelling efforts of Nicholson and his colleagues [9, 10, 11, 12, 64, 68], Miura and his colleagues [14, 15, 85, 91, 95], Shapiro [78, 79], and Somjen and his collaborators [35, 36, 59, 80, 83].

5.1 Continuum modelling

The continuum modelling approach [91] is applicable for the study of CSD waves provided the assumptions of slow spatial and temporal variations of ion concentrations and membrane potentials on the scale of many cells remain valid. These restrictions require a space scale which is much larger than that looked at by Kager et al. [35, 36], who considered events that occurred on the scale of a single hippocampal neuron. The basic idea is that the extracellular space is treated as one continuum and the intracellular spaces of the neurons and of the glial cells are treated as separate continua. Therefore, the continuum intracellular space of the neurons and the continuum intracellular space of the glial cells interact directly through their membranes with the continuum extracellular space, but do not interact directly with each other. Each ion species has a concentration in each of the three continuous spaces and would be governed by a nonlinear diffusion equation and additional equations needed for the auxiliary variables. Ions move between the extracellular and intracellular spaces through the corresponding membrane channels according to the Hodgkin-Huxley model or Goldman-Hodgkin-Katz model for ion membrane currents.

A continuum model for CSD waves can be formulated in vector notation to account for one-, two-, or three-dimensions with the three overlapping "spaces", the extracellular space denoted by o, the neuronal intracellular space denoted by n, and the glial intracellular space denoted by g. The concentrations of ion j in the ECS and in the ICS of the neurons and the glial cells are given by C_j^i, and the volume fractions for these spaces are denoted by α^i with $\alpha^o+\alpha^n+\alpha^g = 1$. The diffusion coefficients, denoted by $\hat{D}_j$, are not scalars because the ECS and ICS spaces are anisotropic with respect to ion diffusion. Furthermore, the diffusion coefficients are scaled for tortuosity in a fixed way depending on the initial cortical structure. It is known that extracellular tortuosity and volume fraction are independent when volume changes occur as a result of osmotic changes [42]. The many membrane ionic currents are denoted by I_j^i where $j = Na^+, K^+, Cl^-$, and Ca^{2+}, and some of these ion-specific currents may have different components. For example, the sodium current has transient and persistent components. Also, the cell microenvironment maintains homeostasis with the use of ions pumps located in the cell membranes, which are denoted by p_j^i where $i = n$ or g for neuronal and glial membranes, respectively. Combining these ideas, the general form of the concentration equations is given by

$$\frac{\partial}{\partial t}\left(C_j^o\alpha^o\right) = \nabla\cdot\left(\hat{D}_j\alpha^o\nabla C_j^o\right) + \beta_n\left(I_j^n + P_j^n\right) + \beta_g\left(I_j^g + P_j^g\right), \tag{9}$$

$$\frac{\partial}{\partial t}\left(C_j^n\alpha^n\right) = \nabla\cdot\left(\hat{D}_j\alpha^n\nabla C_j^n\right) - \beta_n\left(I_j^n + P_j^n\right), \tag{10}$$

$$\frac{\partial}{\partial t}\left(C_j^g\alpha^g\right) = \nabla\cdot\left(\hat{D}_j\alpha^g\nabla C_j^g\right) - \beta_g\left(I_j^g + P_j^g\right) \tag{11}$$

where the $\beta_i = S/V^tF,\ i = n, g$, where S is cell surface area in a local volume V^t of tissue and F is the Faraday constant. This variable coefficient β_i is needed to account for the change in ion concentrations as a result of crossing the membrane.

For simplicity, Hodgkin-Huxley-type models for the ionic currents [32] are used in the form

$$I_j = g_j(V - V_j)$$

where g_j is the membrane conductance for ion j, V is the membrane potential, and V_j is the Nernst potential for ion j. Because of the extremely low ICS concentration of Ca^{2+}, when these currents are included, they will be modelled using the Goldman-Hodgkin-Katz current equation [18]. The relative importance of calcium ions in CSD, especially its involvement in neurotransmitter release and neuronal swelling, is unclear [4, 6, 30, 39, 76]. The ion pumps will include an electrogenic $Na^+ - K^+$ exchange pump for both neurons and glia [35, 46], as well as additional pumps and co-transporters for Na^+, K^+, Cl^-, and Ca^{2+} [79].

There are some specific problems that need to be investigated and challenges that need to be explored, which are listed below.

1. The spatial buffer is an important mechanism for buffering ECS potassium in the brain-cell environment. This mechanism, associated with glial cells, has been treated theoretically both numerically [22, 85] and analytically [12]. Both the numerical and analytical works have addressed a simplified one-dimensional description, mainly in the linear regime. With the continuum model, one can study spatial buffering using all of the additional membrane ion fluxes and following the return of the system to homeostasis. From the perspective of nonlinear ODEs and PDEs, it remains to determine the effects of nonlinearity on potassium clearance when the potassium perturbations are no longer sufficiently small to consider linearized approximations. Furthermore, the results can be extended at least to two space dimensions.

2. Neuronal cell swelling can have effects in the normal brain near homeostasis after significant neuronal electrical activity [57, 58]. Glial cells also can undergo swelling [55, 56, 90]. It is expected that the effect of cell swelling will be to prolong the relaxation time to homeostasis. Following Jakobsson [34] and Shapiro [79], the ECS and ICS are locally in isotonic conditions, e.g.,

$$S^o = \sum_j C_j^n + \frac{A^n}{\alpha^n} \tag{12}$$

where A^n is the amount of ICS that is impermeant to anions inside the neurons and S^o is the total local concentration of ECS solute. The cell volume change, using the neuron volume fraction, is given by

$$\frac{\partial \alpha^n}{\partial t} = \frac{1}{S^o} \sum_j \frac{\partial (\alpha^n C_j^n)}{\partial t}. \tag{13}$$

Because the neurons and glial cells are packed tightly in the ECS with limited space available, an addition constraint can be imposed, namely,

$$\alpha^n_{\min} \leq \alpha^n \leq \alpha^n_{\max}. \tag{14}$$

A similar equation can be written for the change of volume fraction of glial cells.

3. For cortical spreading depression, there are two distinct problems to study. One problem is that of instigation of CSD, and the second problem is that of CSD wave propagation. Kager et al. [35, 36] examined CSD instigation at the single cell level. The continuum model can be used to determine what mechanisms may be responsible for instigation of a single outward propagating annulus of depressed electrical activity when either KCl is injected at the center or there is an electrical stimulus. This problem involves spatial dependence and will not be spatially homogenous as in the case of Kager et al. However, it is expected that these results will mimic the observations of Kager et al. In particular, it is not clear how important cell swelling is in terms of initiating CSD and in forming a blockade to K^+ diffusion. The problem

of CSD initiation was not addressed by Shapiro. Furthermore, both Shapiro and Kager et al. put in an artificial glial uptake mechanism for excess K^+. In the continuum model described here, this mechanism is included explicitly since the glial cells are to be treated as a separate compartment.

4. For CSD wave propagation, the objective will be to reproduce the results obtained by Shapiro [78, 79] but with a much simpler set of equations. A major premise in the work of Shapiro is that osmosis and cell swelling are essential for CSD propagation [54]. One can examine the effects of osmosis in the continuum model as well as cell swelling to determine their influences on CSD waves and on changing the extracellular volume. Furthermore, explicit glial uptake of excess K^+, as well as glial swelling, are included to see what effects they will have on the level of ion concentration changes and on the time course and spatial extent of the CSD waves. Also, in the continuum model, ECS and ICS volume fraction variations under osmolarity changes in the bathing solution [64] can be incorporated. It also will be important to compare the results of two different mechanisms, namely, neurotransmitters and gap-junctions.

5. With a continuum model for CSD wave speeds, the effect of spatial buffering on CSD wave speeds can be determined. As noted earlier, some experimental evidence indicates that glial cells are not essential for CSD wave propagation [43, 44, 45]. However, Shapiro [79] indicates that glial cells slow down CSD waves. Although spatial buffering has been thought of as a phenomenon that occurs primarily in glial cells, neurons with gap junctions may form neuronal syncytia [53] through which spatial buffering also can occur. Therefore, a major question to be answered is whether spatial buffering speeds up or slows down CSD waves. Since neurons have active membranes, it also would be of interest to determine if there are differences in the effects of spatial buffering when occurring in neuronal syncytia or in glial syncytia.

5.2 Dimensionality and numerical methods

Experimental CSD is a three-dimensional phenomenon. However, it appears that some of the basic associated phenomena can be investigated in one and two spatial dimensions using the continuum model. For example, in the study of spatial buffering by Steinberg et al. [85], it is concluded that using the LBM for two-dimensional realistic cell geometries basically gives the same results as for the one-dimensional continuum model. Waves of CSD, however, exhibit much larger ion concentration changes, and it is unclear whether the same conclusion about dimensionality can be made for these waves.

CSD waves can be generated by a localized application of KCl to the cerebral cortex, and one observes an annulus of depressed EEG activity propagating outward from the stimulus center parallel to the cortex. There is a spatial structure to the CSD wave in the direction perpendicular to the cortex surface [77], so the basic phenomenon is three dimensional. However, it appears that one can gain a lot of insight into CSD mechanisms and phenomena from two-dimensional models. In particular, looking down on the cortex surface, it has been observed that multiple waves of depressed EEG activity propagate outwards, producing a target pattern of waves [25, 82]. If the depth variation in the CSD wavefront can be ignored, then this is a two-dimensional problem that involves both the instigation and propagation of CSD waves. The "clonic" bursting found by Kager et al. [35, 36] may provide a mechanism by which K^+ rises and falls repeatedly to produce multiple CSD waves. However, it is unclear whether the timing of these bursts and the level of increased ECS K^+ concentration would be sufficient to trigger additional CSD waves.

Alternatively, there is the issue of neuronal swelling. Is cell swelling near the stimulus source sufficient to form a blockade for K^+ diffusion [90]? If so, can cell swelling reduce sufficiently quickly for a time course commensurate with the temporal spacing between CSD waves? While it is known that CSD waves have a refractory period, analogous to that for action potentials, the exact relationship of the refractory period to the temporal spacing between successive CSD

waves is unknown. A second two-dimensional view of CSD is what could be called "plane waves". From a planar view of the cortex, these waves could be viewed as one dimensional, i.e., varying in one direction and not in a direction parallel to the wavefront. The second dimension would be the depth, in which there is some variation. The continuum model used consists of a complicated system of nonlinear diffusion equations for the various local ionic concentrations in the extracellular and intracellular spaces and the volume fractions of the extracellular space, neurons, and glial cells. Additional equations may be included for the conductances.

The numerical methods for continuum models are standard. The method of lines can be used to solve this system in time and one, two, or three space dimensions. The spatial derivatives can be finite differenced and the resulting system of ODEs in time could be solved using a linear multi-step method or Runge-Kutta method in Matlab for the 1-D case, or custom written codes in two- and three-dimensions.

5.3 Continuum models with degenerate sources

The systems of coupled nonlinear diffusion equations of the form (9)–(11) are generalizations of the systems of equations that have been studied in detail by Wylie and Miura [97]. Mathematically, these equations with degenerate source terms do not have isolated rest states, and it has been shown that a global conservation law implies that the system could only evolve to a discrete set of points [97]. If a large initial disturbance is introduced and certain technical conditions are satisfied, then the system will rapidly evolve to the vicinity of the one-dimensional manifold and then slowly evolve, remaining in the vicinity of the one-dimensional manifold, to one of the discrete points. Travelling waves correspond to trajectories that move along the one-dimensional manifold from one of the discrete points to another one. Since the slow dynamics is essentially confined to a one-dimensional manifold, solitary waves in which the trajectories must leave a discrete point and return to the same discrete point along a homoclinic orbit cannot occur.

Note that CSD waves differ from travelling wavefronts in that the ionic concentrations return to the original values after the wavefront has passed, i.e., they are solitary waves. The above theoretical arguments therefore suggest that solitary waves cannot exist in systems of two degenerate coupled diffusion equations. However, if one considers systems of four degenerate diffusion equations of the form (7)–(8), then steady states are given by a two-dimensional manifold. There now are two global conservation laws that again imply that the system can only evolve to a discrete set of points. Therefore, the slow dynamics is confined to a two-dimensional manifold and homoclinic trajectories, i.e., solitary waves, can exist. The conditions that are required for the existence of such homoclinic trajectories therefore place constraints on models that can produce CSD waves.

There also is a very broad range of phenomena that can occur on a two-dimensional manifold that cannot occur on a one-dimensional manifold, such as homoclinic and heteroclinic bifurcations. The generic behavior of systems of four degenerate coupled diffusion equations needs to be investigated. This will be achieved by first determining the conditions for the stability of spatially homogeneous states. If such states correspond to the undisturbed state of the brain, they must necessarily be stable. One can apply asymptotic methods to determine the way in which large disturbances in ionic concentrations initially propagate. For source terms with sufficiently strong nonlinearities, this will imply that trajectories will rapidly evolve towards the vicinity of a two-dimensional manifold. The existence of solitary and traveling waves can be determined by studying the equations in a frame of reference propagating with a fixed wave speed. By analyzing the resulting ordinary differential equations, one can determine the possibility of homoclinic and heteroclinic orbits that correspond to solitary waves and traveling waves, respectively. The previous experience with systems of two equations indicates that the degenerate nature of the source terms can lead to a number of interesting results that are not present when the source terms are non-degenerate. The synergy of this theoretical work with numerical simulations of

model equations can identify and isolate concrete examples of solitary waves and confirm the theoretical predictions.

5.4 Microscopic modeling

In Kager et al. [36], a single neuron is divided into many computational segments using the NEURON modeling and computational simulation environment. A simulation of CSD waves would require the study of a system of inter-connected neurons, as an extension of the work done in Kager et al. A basic outline of an approach to this problem is given below.

Consider a three-dimensional domain that is part of the grey matter region in the cortex. The neuronal axes are assumed to line up perpendicular to the cortical surface, with its dendritic branches closer to the surface than the cell body (soma). Individual neurons then are connected via axons and synapses to neighboring neurons. In addition to the neurons, there are smaller glial cells that occupy roughly half of the total cellular volume. The problem can be simplified by studying a two-dimensional system.

As pointed out by Kager et al. [36], simulations using a "complete" cell model, even for a single neuron, can become computationally intensive. Therefore, one could use the "simplified" cell model proposed in Kager et al. [36], since it produces results that are qualitatively similar to those from using the "complete" cell model. Thus, the simulations would be computationally less expansive to run. The neurons could be connected via synapses as well as by gap-junctions, which was proposed by Shapiro [79] as the pathway for ICS ions to diffuse from one neuron to its neighbors.

There are two main objectives in using this system of inter-connected neurons. The first objective is to investigate if neurons behave in a different way when they are isolated or belong to a network of interconnected neurons. The second objective is to study the effect of connectivity between the neurons among themselves as well as to the environment (ECS and glial cells). There are a number of interesting issues which can be explored by this system of neurons. For example, using simulation as a tool, one can investigate the importance of extracellular diffusion of ions and the intracellular transport of ions via gap-junctions. One also could examine the effects of spatial variations in ionic concentrations on the dynamics of neurons under CSD conditions.

5.5 Vascular changes

Although cortical spreading depression and vascular changes have been linked for some time [48], the relationship between them is not well understood. Recent experimental studies by Charles and his colleagues at UCLA [7] have focused on this relationship using optical intrinsic signal imaging and electrophysiology. They have observed both CSD and vascular changes simultaneously. Their experimental findings lead to the conclusion that vascular changes during CSD are a distinct component of the CSD wave complex. Therefore, a new challenge is to develop an extension to the continuum model that incorporates this vascular component of CSD waves.

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