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A computational multiscale model of cortical spreading depression propagation

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ABSTRACT

Cortical Spreading Depression (CSD) is a disruption of the brain homeostasis that, originating in the visual cortex and traveling towards the frontal lobe, temporarily impairs the normal functioning of neurons. Although, as of today, little is known about the mechanisms that can trigger or stop such phenomenon, CSD is commonly accepted as a correlate of migraine visual aura. In this paper, we introduce a multiscale PDE-ODE model that couples the propagation of the depolarization wave associated to CSD with a detailed electrophysiological model for the neuronal activity to capture both macroscopic and microscopic dynamics.

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1. Introduction

Migraine is a prevailing disease in contemporary society, commonly associated to a number of impairing effects from unilateral severe headache and nausea to photophobia [1]. About one third of migraine patients also experience a migraine aura preceding the typical headache [2,3]. Several experiments suggest that a propagating depolarization wave on the cerebral cortex is underlying migraine, see [2–4] and references therein. This wave, named Cortical Spreading Depression (CSD), causes a drastic failure of the brain homeostasis that temporarily impairs the normal functioning of neurons [5,6]. A key property of neural cells is to produce an action potential (AP), consisting in a sudden increase of the transmembrane potential, called spike, followed by a recovering of the resting condition through a refractory period, during which the cell cannot be excited. The neuronal activity is measured in terms of number of AP produced in one second and is called firing rate (Hz). In the wake of the CSD propagation wavefront, complex dynamics are triggered: neurons undergo a brief period of intense firing, followed by a membrane hyperpolarization which silences the spiking activity for a variable period (between 1 and 3 min), after which the neurons slowly recover their firing activity and eventually get back to normal frequency (see e.g. [7]). CSD is characterized by relevant increases in both extracellular K^+ and glutamate, as well as rises in intracellular Na^+ and Ca^{2+}, and the two most accepted hypotheses suggest that its propagation is due to diffusion of potassium or glutamate in the extracellular space [8].

Several mathematical tools have been proposed in the past to model CSD, from macroscopic reaction-diffusion equations [9] to microscopic biophysical models accounting for specific physiological quantities, such as cells' metabolism [10] or electrodiffusion and osmotic water flow at the tissue level [11]. For a general overview of those models we refer the reader to [8,12–14]. Recently, an increasing attention has been paid to the effects of the cortical geometry on CSD propagation, as fissures and sulci of the cortex are expected to influence the propagation of depolarization waves. Pocci and collaborators studied the effect of the cortical bending by using a reaction diffusion equation in a simplified geometry consisting of a 2D duct containing a bend [15], showing how sharp bends naturally block the wave propagation. Dahlem and his collaborators

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proposed in [16] to use the Gaussian curvature of the cortex, computable from Magnetic Resonance Imaging (MRI) data, to identify potential targets for neuromodulation (see also [17]). The authors of this paper, together with their collaborators, proposed in [18] a computational neural firing rate model distributed throughout a realistic cortical mesh reconstructed from MRI, as well as, in [19], a more personalized model where the propagation of a potassium wave in the extracellular space was modeled by taking into account diffusion coefficients recovered from Diffusion Tensor Imaging (DTI) data.

As a common trait of the existing literature, biophysical models provide insights about interactions and dynamics at a cellular level, while phenomenological models are more suited for analyzing the general CSD propagation. The aim of this paper is to create the first (to the best of our knowledge) bridge between the biophysical and phenomenological modeling approach, in order to provide a deeper understanding of the complex dynamics that are triggered by the passage of the depolarization wave.

Following the potassium assumption for the CSD, we introduce a multiscale coupled PDE-ODE model to deal with both the macroscopic propagation of the depolarization wave and the microscopic neuronal dynamics. The coupled problem is inherently multiscale in time, as CSD propagates very slowly across the cortex (around 20 min from back to front), while the electrophysiological dynamics features a way faster temporal scale (in the order of the millisecond). At the macroscopic level, we model the extracellular potassium bath concentration with a modification of the distributed FitzHugh–Nagumo type model proposed by the authors and their collaborators in [19]. The dynamics of the extracellular potassium bath concentration is then used as a driver for the activity of a detailed microscopic electrophysiological model for the neurons. Among the various neuronal models available in literature (see, e.g., [20–22]), the microscopic electrophysiological model we build our model upon is the one introduced by Wei et al. [23]. Like all the electrophysiological models available in literature, this model aims at representing the behavior of a single cell in a compartment setting: lacking a spatial component, it is not suitable to describe a propagative dynamics such as the one of CSD. Nevertheless, its microscopic variables in a given point $x \in \Omega$ can be used, as part of a distributed ensemble model, to represent the average values of the corresponding quantities for the bundle of neurons physically present in the spatial location at hand (a few thousands). Moreover, the use of an ensemble model in space allows, once applied on a geometry reconstructed from medical imaging, to use a computational grid whose characteristic size is of the order of millimeters, the standard resolution of common MRI scanners, without the need of resorting to the micron scale of the neuron.

The paper is organized as follows. In Section 2 we describe the microscopic and macroscopic components of the model, as well as their multiscale coupling. Section 3 is devoted to the numerical approximation of the coupled model. Finally, in Section 4 we present some numerical experiments to illustrate the features of our model, for both simple geometries in one and two dimensions, and a cortical geometry reconstructed from MRI.

2. A multiscale distributed model of Cortical Spreading Depression

Cortical Spreading Depression is a disruption of the brain homeostasis that temporarily impairs the normal functioning of neurons and propagates across the cerebral cortex. In the wake of the propagation wavefront a complex dynamics is triggered. At first neurons undergo a brief period of intense activity, exhibiting a firing rate 10–20 times higher than the one at rest (between 8 and 12 Hz, see [24,25]). This brief period of intense excitation is followed by a membrane hyperpolarization which silences the spiking activity for a variable period (between 1 and 3 min), after which the neurons slowly recover their spiking activity and eventually get back to normal spiking frequency (see e.g. [7]). Four hypotheses to explain the CSD propagation on the cortex have been proposed, and the two most accepted ones suggest that CSD propagates due to diffusion of potassium or glutamate in the extracellular space, which is presumed to follow ordinary diffusion laws [8]. Differently from what happens in modeling cardiac electrophysiology (see, among others, [26,27] for an overview of the topic), setting up a distributed model for the membrane potential would not be effective in the description of CSD. Distributed models in cardiac electrophysiology describe the propagation of AP along a cardiac fiber. In the CSD case, we aim at describing the changes in the neuronal activity that are driven by the depolarization wave, and not the synaptic signaling. In this paper we follow the potassium assumption in describing the propagation of the homeostatic disturbance at the cortical level, and we couple it with a detailed microscopic description of the neuronal dynamics. The microscopic electrophysiological model we build our model upon is the one introduced by Wei et al. [23]. At the macroscopic level, we model the extracellular potassium wave with a modification of the FitzHugh–Nagumo type model proposed by the authors and their collaborators in [19]. In the rest of this section we present in detail the Wei model and we highlight its limitations in properly describing realistic features of CSD induced dynamics. We then introduce a modification allowing the Wei model to overcome such limitation, and finally present a multiscale coupled model, able to properly represent the neuronal activity patterns triggered by the passage of CSD.

2.1. Wei's neuronal model

The model introduced by Wei et al. [23] is an extension of the neural model proposed in [21], accounting for a wider range of neuronal activities than the original one. The Wei model supports various behaviors from seizure to spreading depression, tonic firing and a steady state, whose occurrence depends on the values of potassium and oxygen bath concentrations, denoted by k_{bath} and O_{bath}, respectively. A detailed analysis of the bifurcation parameters can be found in [23]. For the sake of completeness, we give here a brief summary of the model, whose parameters are collected in Table 2.

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