Analysis of cortical spreading depression in brain with multiscale mathematical models

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Analysis of Cortical Spreading Depression in Brain with Multiscale Mathematical Models

Hina Shaheen, Roderick Melnik, and Sundeep Singh

Abstract The present study aims at modeling the cortical spreading depression (CSD) propagation in brain considering two different approaches available in the literature: (a) a simplified model consisting of six coupled equations of the reaction-diffusion type in two space dimensions and (b) a one-dimensional, more complex neuronal model comprising of ionic currents and ionic pumps. A study has been conducted to quantify the effects of varying extracellular potassium concentrations on the propagation of CSD in the multiscale reaction-diffusion model by monitoring the respective changes in the extracellular and intracellular concentrations of sodium, chlorine and calcium ions, in addition to evaluating the changes in the generated membrane potentials. In the multiscale neuronal model, the influence of gated conductance on the intracellular and extracellular potassium concentrations of the sodium and potassium and the membrane potential has been reported. The study revealed that the variation in gated conductance results in an increase of the pump currents that leads to the spatio-temporal variations of extracellular potassium.

Keywords ■■■

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1 Introduction

Cortical spreading depression (CSD), first discovered by Leão [1] in 1944, is a wave that propagates slowly across the cerebral cortex of the brain. This wave can cause a drastic failure of the brain homeostasis leading to temporary impairment in the normal functioning of neurons. The clinical disorders related to CSD can also lead to pathophysiology of various diseases including migraine, ischemic stroke, transient global amnesia, epilepsy and traumatic brain injury [2, 3]. The main property of neural cells is to produce an action potential comprising a rapid increase of the transmembrane potential, called spike, supported by a recovering of the resting condition through a refractory period, where the cell cannot be excited during this period [4]. CSD is a wave of electrophysiological hyperactivity, whereby neurons are first highly excited. That is being followed by a silent phase of membrane hyper-polarization and later the triggered neurons are slowly recovered to their normal frequencies. This neurophysiological phenomenon of CSD results in abrupt changes in the intracellular ion gradients, i.e. an increase in extracellular K^+ and glutamate, along with rise in intracellular Na^+ and Ca^{+2}, followed by sustained depolarization of neurons [5]. Importantly, there are several biophysical, electrophysiological, neurochemical and anatomical elements involved in the propagation of CSD, such as glia, neurons, synapses, cell swelling, many ion channels, ion and transmitter concentrations, pumps, blood vessels, degree of hypoxia, gap junctions, etc. [6].

The mathematical models of CSD have also been explored in the past decades for a better understanding of CSD instigation, propagation and depolarization in the human cortex (e.g.. [7–10] and references therein). In the present studies, two continuum-based multiscale mathematical models of CSD have been analyzed numerically: (a) a simplified two-dimensional model consisting of six coupled equations of the reaction-diffusion type derived from the Tuckwell model [5] in two space dimensions and (b) a one-dimensional multiscale neuronal model comprising of ionic currents and ionic pumps derived from [9]. The mathematical structure of the two-dimensional model considers diffusion in extracellular (ECS) and intracellular (ICS) spaces while the neuronal model considers diffusion in extracellular space only. We demonstrate that the developed models reproduce many important characteristics of CSD over multiple spatio-temporal scales such as instigation, propagation and depolarization of CSD wave. In addition, the effect of change in concentration of high extracellular potassium on the propagation of CSD of the model in two space dimensions has also been evaluated. Finally, one of the main motivations and novelty of this study has been to quantify the effects of varying strength of gated conductances of sodium and potassium on the instigation and propagation of CSD in the one-dimensional neuronal model along with highlighting the effects of higher extracellular potassium in two spatial dimensions.

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2 Mathematical Modeling of CSD

In this section the mathematical modeling approaches for the analysis of CSD wave instigation and propagation are discussed in the one- and two-dimensional spaces.

2.1 Reaction-Diffusion Model of CSD in Two-Space Dimensions

A mathematical model is developed for the movements of four basic ions, viz., K^+, Ca^{+2}, Na^+, Cl^-, and two neurotransmitter substances, one excitatory (T_E) and the other inhibitory (T_I) in the two-dimensional space (x,y) for simulating the movements of these substance during CSD [5]. Our model assumes that the brain-cell microenvironment can be treated as a porous medium consisting of extra- and intracellular (ECS, ICS) compartments whereby the ions and transmitters are free to diffuse in the extracellular space. The present model is based on reaction-diffusion of ions and neurotransmitters. "Reaction" refers to the ion exchange between ICS and ECS which is the microscopic part of the model at a cellular level and "Diffusion" refers to the ionic propagation between neurons and ECS in the macroscopic part of the model. Thus, the developed model consists of six coupled equations of the reaction-diffusion type which update the extracellular concentrations of ions as follows:

$$\frac{\partial v_i^{ext}}{\partial t} = D_i \nabla^2 v_i^{ext} + F_i(v) \qquad i = 1, 2, \ldots, 6, \tag{1}$$

where v_1, v_2, v_3, v_4, v_5, v_6 are the concentrations of K^+, Ca^{+2}, Na^+, Cl^-, T_E and T_I, respectively, at time t, D_i is the diffusion coefficient for the ith component and $F_i(v)$ is the reaction term associated to each ion. Further, it is presumed that the CSD wave results in intense neuronal activity that leads to the abrupt rise in the potassium or calcium ion concentrations of the extracellular compartment. Thus, in the present analysis, the instigation of CSD has been done by specifying the initial condition of K^{ext} as a "supra threshold" Gaussian elevation of potassium chloride concentration with a peak value of 20 mM that is given by:

$$K^{ext}(x, y, 0) = K^{ext,R} + 20 \exp\left[-\left[\left(\frac{x - 1.25}{0.05} \right)^2 + \left(\frac{y - 1.25}{0.05} \right)^2 \right] \right]. \tag{2}$$

We consider two intracellular compartments, one pertaining to synapses and the other pertaining to nonsynaptic processes accounting for contributions from glia. These processes are assigned different ratios of extracellular to intracellular volumes represented by α_1 and α_2, respectively. Moreover, intracellular ions can only diffuse within a limited region of space or must first become extracellular before becoming free to diffuse over the significant region. The internal ion concentrations (v_i^{int}, i =

1, 2, 3, 4) are assumed to be given by the local conservation equations, which for K^+, Na^+, Cl^- are (with R being a resting equilibrium):

$$v_i^{int}(x, y, t) = v_i^{int,R} + \alpha_1[v_i^{ext,R} - v_i^{ext}(x, y, t)] \qquad i = 1, 3, 4, \tag{3}$$

whereas for Ca^{+2}, we have:

$$v_2^{int}(x, y, t) = v_2^{int,R} + \alpha_2[v_2^{ext,R} - v_2^{ext}(x, y, t)]. \tag{4}$$

The other phenomenological relations for computing the membrane potential, Nernst potential, source and sink terms, pump terms, gated conductance, etc., have been adopted from [5]. In this model, the CSD is initiated based on the potassium hypothesis, whereby the high extracellular potassium concentrations will lead to an increase in the excitability of neurons and promote the further release of potassium. Normally, ion pumps present in the neuron membrane and glia comprehend a set of buffering mechanisms responsible for clearing these extracellular excesses. However, if the concentration exceeds a certain threshold then the process buffers too fast and the resulting mechanism will rise to cope. This reaction-diffusion process depends on both the diffusion of potassium across the extracellular concentrations and the reaction triggered in neighbouring tissue which results in further release of potassium [5]. In what follows, the effect of high extracellular potassium concentration on the propagation of CSD has been quantified utilizing this two-dimensional model ($0 < x < 2.5$ mm, $0 < y < 2.5$ mm) comprising of six coupled reaction-diffusion equation (1).

2.2 One-Dimensional Neuronal Model of CSD

In this section, we will construct a neuronal model that consists of the main characteristics of the more complicated model derived from [9]. The model consists of two ions (sodium and potassium) and two compartments (extracellular and intracellular spaces). According to Kirchhoffs current law [10], the membrane potential V_M (mV) is defined by the ordinary differential equation as:

$$C_m \frac{\partial V_M}{\partial t} = -I, \tag{5}$$

where C_m is the membrane capacitance per unit surface area and I is the total cross membrane ionic current per unit surface area given by the sum of the sodium (I_{Na}), potassium (I_K) and leak currents (I_{Leak}) given by:

$$I_{Na} = I_{Na,T} + I_{Na,P} + I_{Na,Leak} + I_{Na,Pump}; \;\; I_K = I_{K,DR} + I_{K,A} + I_{K,Leak} + I_{K,Pump}. \tag{6}$$

In this model, the cross-membrane currents are developed by using Goldman-Hodgkin-Katz (GHK) formulas for the active membrane currents, such as the fast transient sodium current ($I_{Na,T}$), persistent sodium current ($I_{Na,P}$), potassium delayed rectifier current ($I_{K,DR}$) and transient potassium current ($I_{K,A}$). Further, the sodium leak current ($I_{Na,Leak}$), potassium leak current ($I_{K,Leak}$), fixed leak current (I_{Leak}) and sodium-potassium exchange pump currents ($I_{Na,Pump}$ and $I_{K,Pump}$) are computed using the Hodgkin-Huxley (HH) model. The general expressions for the GHK for sodium and potassium currents is given by [11]:

$$I_{ion,GHK} = g_{ion,GHK} m^p h^q \frac{F V_M \left(ion^{int} - \exp\left(\frac{-V_M}{\phi}\right) ion^{ext} \right)}{\phi \left(1 - \exp\left(\frac{-V_M}{\phi}\right) \right)}, \tag{7}$$

where $g_{ion,GHK}$ is the product of the conductance amplitude and membrane permeability for the active currents, m and h are the ion-specific activation and inactivation gating variables and $\phi = RT/F$ is a parameter where R is the universal gas constant, T is the absolute temperature and F is the Faraday's constant. In the HH model, we assumed that the conductances $g_{ion,HH}$, i.e. the conductance amplitude for the passive currents, are constant. Further, the general expression of HH types of currents is given by:

$$I_{ion,HH} = g_{ion,HH}(V_M - V_{ion}), \tag{8}$$

where V_{ion} is the Nernst potential for Na and K ions. The leak currents of all ions in the HH model are summarized in one specific leak current given by:

$$I_{Leak} = g_{HH}(V_M + 70), \tag{9}$$

where g_{HH} is a conductance constant. The rate equations give the dynamic of the gating variables for the potassium activator (m) and sodium inactivator (h) as $dm/dt = \alpha_m(1-m) - \beta_m m$; $dh/dt = \alpha_h(1-h) - \beta_h h$. The values of α_i and β_i ($i = m, h$) have been adopted from [9].

The pump currents are given as $I_{Na,Pump} = 3I_{Pump}$ and $I_{K,Pump} = -2I_{Pump}$, where $I_{Pump} = I_{max}/(1 + 2.0[K_{ext}^{-1}])^2(1 + 7.7[Na_{int}^{-1}])^3$. The model equations in terms of internal and external concentrations coupled with nonlinear diffusion are given as follows:

$$\frac{\partial Na^{ext}}{\partial t} = \frac{A}{F V_{int} f} I_{Na} + D_{Na} \frac{\partial^2 Na^{ext}}{\partial x^2}; \quad \frac{\partial Na^{int}}{\partial t} = -\frac{A}{F V_{int} f} I_{Na}, \tag{10}$$

$$\frac{\partial K^{ext}}{\partial t} = \frac{A}{F V_{int} f} I_K + D_K \frac{\partial^2 K^{ext}}{\partial x^2}; \quad \frac{\partial K^{int}}{\partial t} = -\frac{A}{F V_{int} f} I_K, \tag{11}$$

where A is the cell surface area, V_{int} and V_{ext} are the intracellular and extracellular volumes, respectively, and $f = V_{ext}/V_{int} = 0.15$. The values of other relevant parameters used in this model have been adopted from [5, 9]. In what follows, the effect of gated conductances of sodium and potassium has been evaluated on the CSD wave propagation based on the one-dimensional neuronal model described here.

Throughout this section, CSD was triggered by initiating the Gaussian potassium chloride (KCl) wave, i.e. by changing the initial condition of external potassium as:

$$K^{ext}(x, 0) = K^{ext,R} + K^{max} \exp\left(\frac{-x^2}{2\tau^2}\right), \tag{12}$$

where $\tau = 0.5 \times 10^{-2}$ mm. Motivated by [9], the domain selected for this one-dimensional model was $0 < x < 6$ mm. A finite element method implemented via [12] has been used to solve the set of coupled ordinary and partial differential equations of the multiscale neuronal model and a simplified two-dimensional model.

3 Results and Discussion

In the present paper, a study has been performed for quantifying the effects of different parameters on the CSD wave propagation. In what follows, the effects of sudden changes in KCl stimulus have been quantified on the membrane potential and extracellular concentrations using the model of CSD in two space dimensions. Whereas, the effects of gated conductance on the extracellular potassium concentration have been investigated utilizing the one-dimensional model. This section is split into two parts. Firstly, we will discuss the results obtained with the two-dimensional model, and then with the one-dimensional model, following the description of theses models given in the previous section.

3.1 Reaction-Diffusion Model of CSD in Two-Space Dimensions

The temporal response of the extracellular concentrations of Na^+, K^+, Ca^{+2}, Cl^{-1}, excitatory and inhibitory transmitters subjected to the initial KCl stimulation applied at the centre of the two-dimensional domain is presented in Fig. 1. As seen from Fig. 1, the KCl stimulus will result in a corresponding increase in the concentration of K^+ and excitatory and inhibitory transmitters, along with a decrease in the Na^+, Ca^{+2} and Cl^{-1} concentrations. One of our main motivations for the present mathematical study is to evaluate the effects of high extracellular potassium concentration on the propagation of CSD. Primarily, two peak values of K^{ext} in a "supra threshold" Gaussian elevation of KCl concentrations have been selected (a) 40 mM and (b) 60

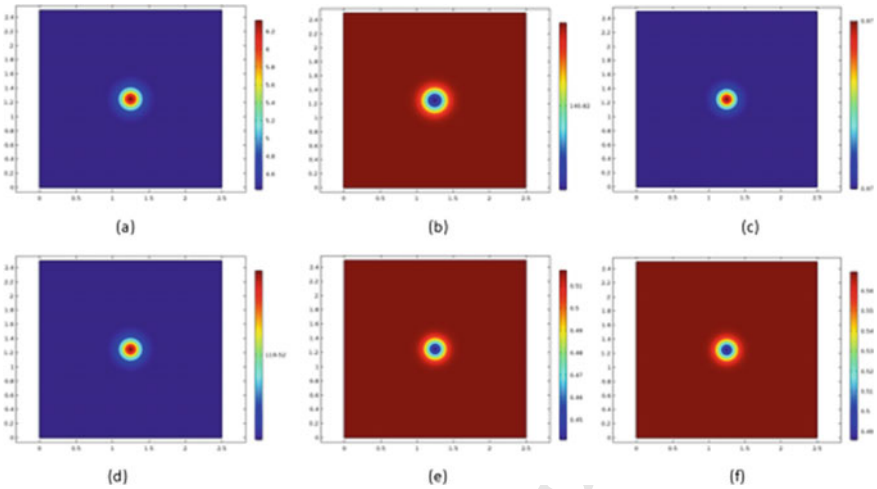

Fig. 1 (Color online) Temporal variation of: **a** Potassium, **b** Chloride, **c** Calcium, **d** Sodium, **e** Inhibitory transmitter and **f** Excitory transmitter at $t = 2$ s subjected to a KCl stimulus

mM. The variation of the peak value of extracellular potassium concentration on the propagation of CSD with time for the two considered cases has been presented in Fig. 2. As evident from Fig. 2, there prevails a significant variation in the predicted membrane potential while the effect on the external potassium concentration is quite negligible. The membrane potential increases as the peak value of the extracellular concentration increases from 20 to 60 mM and vice versa.

3.2 One-Dimensional Neuronal Model of CSD

Here we focus on the analysis of the effects of gated conductance on the extracellular potassium concentration. Based on the model equations (5)–(11) with x $\in (0, 6)$ mm, the spatio-temporal variations in the external potassium concentrations and membrane potential obtained by triggering the CSD with the application of "supra threshold" Gaussian elevation of KCl at the left leading edge ($x = 0$), for a peak value of 50 mM at different time steps, are presented in Fig. 3. As evident from Fig. 3, the extracellular potassium concentration increases tremendously due to the instigation of CSD and the depolarization of membrane potential. Importantly, the influence of the CSD is felt more on the left side where the KCl stimulation was applied. Similar trends were observed for the membrane potentials as depicted in Fig. 3. The effects of the dynamics gated currents in a neuronal model of CSD by increasing the values of g_{Na} and g_K are presented in Fig. 4. Recall that the variations in the gated currents of the CSD model considered in the present study are the fast inward sodium current and the slower outward potassium current. In a physiological

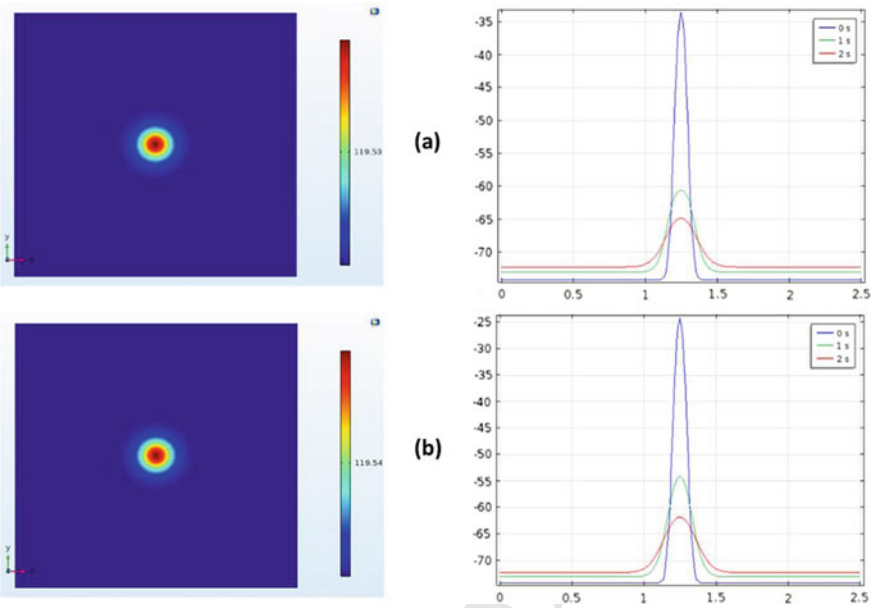

Fig. 2 (Color online) Temporal variation of extracellular potassium concentration ($left$) and membrane potential ($right$) for different values of preset peak value of K^{ext}: **a** 40 mM and **b** 60 mM (on the insert, blue: 0 s, green: 1 s, red: 2 s)

steady state, the gated currents are almost zero and become very strong during the spread of CSD. Even the ionic pump currents are not sufficient to recover the system and alter the CSD to the physiological steady state as presented in Fig. 4. Above all, if the strength of both gated currents is increased by the same factor, a larger pump current will be required to compensate for the gated currents as evident from Fig. 4.

Finally, we note that neural and other electrophysiological activities across the cerebral cortex are stochastic in nature [5], so many sources and sinks of ions and transmitters should be modelled with random processes. A simple way to include these random emissions in the mathematical model of CSD would be by means of a counting process $N(x,t), x_1 \leq x \leq x_2, t > 0$ which gives random numbers of action potentials in the time interval $(0, t]$. In this case, the corresponding differential equation for the extracellular potassium ion concentration becomes:

$$\frac{\partial K^{ext}}{\partial t} = \frac{A}{F V_{int} f} I_K + D_K \frac{\partial^2 K^{ext}}{\partial x^2} + \alpha \frac{\partial^2 N(x,t)}{\partial x \partial t}, \tag{13}$$

where α represents the local increase in potassium. Further details in this direction will be reported in our future studies.

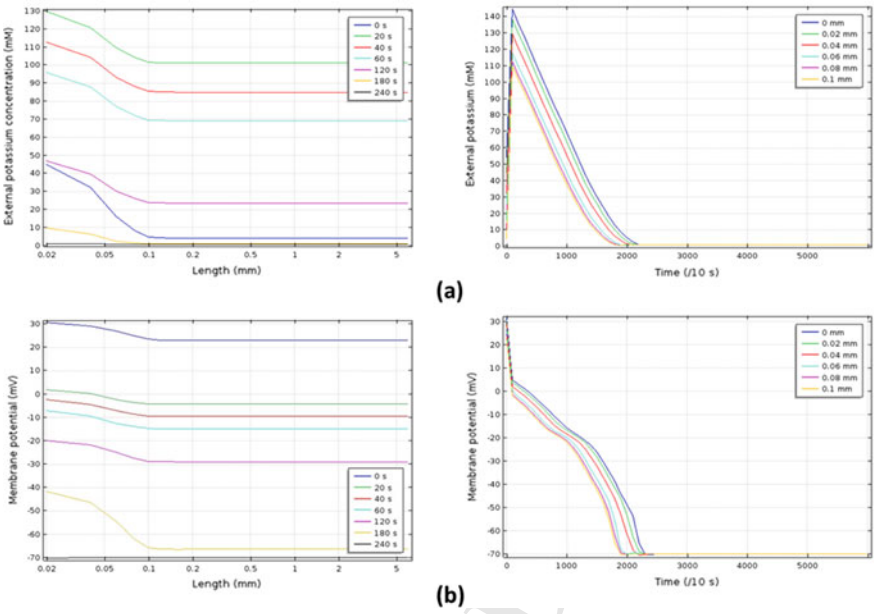

Fig. 3 (Color online) Spatial (*left*) and temporal (*right*) variations of **a** extracellular potassium concentration and **b** membrane potential subjected to initial KCl stimulation at $x = 0$ mm (on the insert left, blue: 0 s, green: 20 s, red: 40 s, light blue: 60 s, pink: 120 s, yellow: 180 s, black: 240 s; on the insert right, blue: 0 mm, green: 0.02 mm, red: 0.04 mm, light blue: 0.06 mm, pink: 0.08 mm, yellow: 0.1 mm)

4 Conclusions

In the present study, mathematical models have been developed for quantifying the effects of CSD propagation instigated by sudden changes in the KCl stimulus. Two different models have been considered: a multicomponent reaction-diffusion model and a single neuronal model with sodium and potassium currents. We instigated CSD by adding a KCl stimulus that leads to an initial condition on extracellular potassium concentration. Adding KCl stimulus results in a large increase in the extracellular concentrations of K^+ and a small increase in excitatory and inhibitory transmitters, along with a large decrease in the Cl^- and small decrease in Na^+, Ca^{+2} extracellular concentrations for the six component model. This behaviour of extracellular concentration of ions is responsible for the propagation of CSD in the brain. The effects of changes in the extracellular potassium concentrations and the gated conductances have also been investigated on the propagation of CSD waves. The results reported in this study could assist in our better understanding of the impact of sudden alterations of the sub-cellular properties on the propagation and instigation of CSD. Future studies will be focused on the inclusion of other compartments, in addition to extracellular and intracellular spaces, such as vascular, glial, neural cell

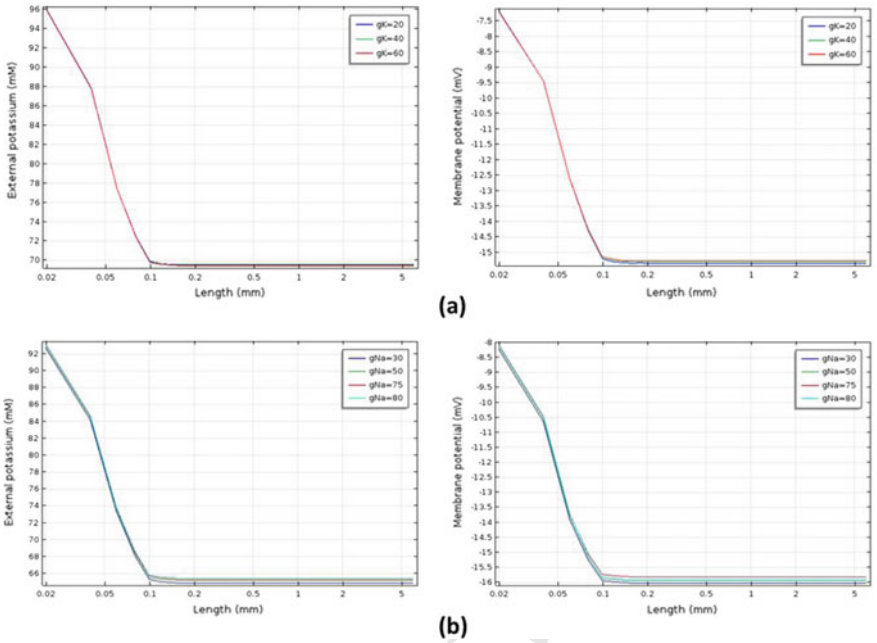

Fig. 4 (Color online) Spatial (*left*) and temporal (*right*) variations of extracellular potassium concentration for different values of potassium and sodium gated conductances: **a** g_k = 20, 40 and 60; and **b** g_{Na} = 30, 50, 75 and 80 (on the insert top, blue: g_k = 20, green: g_k = 40, red: g_k = 60; on the insert bottom, blue: g_{Na} = 30, green: g_{Na} = 50, red: g_{Na} = 75, light blue: g_{Na} = 80)

bodies and dendrites, as well as on the development of a new stochastic model based on the ideas highlighted here. This will lead to further clarification of the key mechanisms underlying the dynamics of CSD propagating within the pathological brain.

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