Dendritic signal transmission induced by intracellular charge inhomogeneities

Ivan A. Lazarevich and Victor B. Kazantsev
Institute of Applied Physics of Russian Academy of Science, 46 Uljanov street, 603950 Nizhny Novgorod, Russia and N.I. Lobachevsky State University of Nizhni Novgorod, 23 Gagarin avenue, 603950 Nizhny Novgorod, Russia
(Received 6 August 2013; published 19 December 2013)

Signal propagation in neuronal dendrites represents the basis for interneuron communication and information processing in the brain. Here we take into account charge inhomogeneities arising in the vicinity of ion channels in cytoplasm and obtain a modified cable equation. We show that charge inhomogeneities acting on a millisecond time scale can lead to the appearance of propagating waves with wavelengths of hundreds of micrometers. They correspond to a certain frequency band predicting the appearance of resonant properties in brain neuron signaling. We also show that membrane potential in spiny dendrites obeys the modified cable equation suggesting a crucial role of the spines in dendritic subthreshold resonance.

DOI: 10.1103/PhysRevE.88.062718 PACS number(s): 87.10.−e, 87.19.ll

I. INTRODUCTION

Cable theory is one of the foundations of bioelectrical signal transmission in nerve tissues [1–4]. It describes the propagation of membrane potential in passive neurites, particularly, in the dendrites where the concentration of active ion channels is not sufficient enough to enable stable action potential propagation. One of the earliest predictions of the cable theory was exponential attenuation of postsynaptic potentials with distance [2]. However, recent experimental findings have suggested that distally located synaptic inputs can also influence the somatic membrane potential [5].

In neuroscience, many findings have suggested that signal propagation in the dendritic tree may implement simple information processing functions at the level of a single neuron [6]. Recently, it has been pointed out that dendrites may play a significant role in neuronal computation beyond the summation of attenuating local inputs. Specifically, Remme *et al*. [7] have theoretically shown that ongoing dendritic oscillations may effectively control the somatic firing rate. The reported resonant and oscillatory properties of the dendrites were typically associated with the presence of active channels in the dendrites sustaining the propagation [7,8].

The cable equation can be derived by constructing an equivalent electrical circuit with elements describing the electrical properties of dendrites [2]. However, it does not take into account inhomogeneous distributions of ion concentrations within dendrites. To overcome this, Qian and Sejnowski [9] modified the cable equation using the Nernst-Planck equation describing electrodiffusive motion of ions. For spiny dendrites, several modifications of the cable model were introduced to account for the influence of the spines on the electrical characteristics of the cable and anomalously slow diffusion of ions [10–12] as well as active wave propagation [13,14]. Several authors used the Maxwell's equations to generalize the cable equation and account for the (linear as well as nonlinear) charge accumulation nearby endogenous structures of the dendrites [15–17]. Bédard and Destexhe [18] considered nonideal properties of the membrane as a capacitor arising from the noninstantaneous motion of ions within the dendrites.

In this paper, we show how charge inhomogeneities in the intracellular space can influence passive signal propagation in dendrites. In particular, we show that the existence of excess charge areas in the vicinity of ion channels can lead to formation of traveling waves propagating over distances larger than diffusion lengths of nontraveling solutions predicted by the classical cable theory. We also show that the same effects arise in the model of a passive spiny dendrite, which may also influence the initiation of active saltatory waves in dendrites [13]. The existence of traveling wave solutions ensures frequency selectivity and resonances in dendrites. Resonant properties represent an important feature of neural systems associated with information processing [19,20]. Neural resonances and oscillations have been typically associated with active voltage-gated ion channels [21–25]. We show that in addition to that charge inhomogeneities as well as dendritic spines may lead to resonant properties in passive dendrites.

II. MODIFIED CABLE EQUATION

First, let us consider how charge inhomogeneities can be accounted in cable theory. When charge carriers move in and out of the ion channel they create regions of *excess charge* in the vicinity of the channel. In this area the potential is higher than in the surrounding medium [26]. Existence of the overpotential near the channel pore leads to the increase of the total local potential over the channel. The area of excess charge can be described as a volume within some closed surface E covering the channel pore (Fig. 1). Therefore, the rate of change of the excess charge is defined by the difference between the transchannel current and the relaxation current:

$$\frac{dQ_e}{dt} = I_e - I_{ch}. \tag{1}$$

The overpotential near the channel end is described by a smooth function $V_e(x,t)$. The total potential over the channel is thus $V_{\text{tot}} = V_m + V_e$. The transchannel current is linearly related to the transchannel potential $I_{ch} = G_{ch}V_{\text{tot}} \approx G_{ch}V_m$, where G_{ch} is the conductivity of the single channel. We suppose that the excess charge relaxes with characteristic time τ_ρ: $I_e = -Q_e/\tau_\rho$. This time constant τ_ρ (often called the Maxwell-Wagner time constant [18]) may be estimated by applying the Gauss' law to the surface E. The lateral current density is determined by $\mathbf{J} = \sigma\mathbf{E} + \partial\mathbf{D}/\partial t$ (where $\mathbf{E}$ is the electric field, $\mathbf{D}$ is the displacement field, σ is the conductivity of the solution). Then, the value of τ_ρ is given by $\tau_\rho = 2\varepsilon/\sigma$,

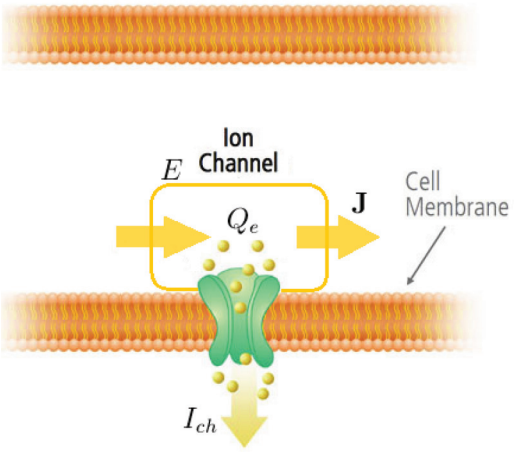

FIG. 1. (Color online) Formation of excess charge regions in the vicinity of ion channels (not to scale). Modified from [28].

where ε is the permittivity of the solution. One can estimate $\tau_\rho \lesssim 1$ ms, therefore the excess charge within a passive cable relaxes at the millisecond or submillisecond time scale. It is faster than time scales typically associated with membrane dynamics [27]. For the extracellular medium (physiological saline) this time constant is approximately 10^{-10} s, which is much smaller than the same time constant on the inner surface of the membrane. Therefore, the effects of the charge inhomogeneities in the extracellular medium can be neglected.

In the first approximation, the excess charge is linearly related to the overpotential, e.g., $Q_e = C_m K_e V_e$, where K_e is the so-called channel density factor, C_m is the membrane capacitance.

Combining these assumptions we get the equation for overpotential dynamics:

$$\frac{\partial V_e(x,t)}{\partial t} = -\frac{V_e}{\tau_\rho} - \frac{G_{ch}}{C_m K_e} V_m. \tag{2}$$

Next we apply a set of common assumptions typically used in cable theory. In particular, we suppose the electric field to be polarized only in the longitudinal direction $\mathbf{E}(\mathbf{r},t) = E(x,t)\mathbf{x_0}$. Pickard [29] showed that the magnetic field is negligible compared to the electric field in neurons due to the slow motion of charges in the intracellular medium. Hence, the electric field can be described by a scalar potential $V_m(x,t)$, and $E(x,t) = -\partial V_m(x,t)/\partial x$. It is assumed that the extracellular medium can be lumped into a single isopotential compartment. The intracellular medium is treated as homogeneous with constant conductivity and the dendritic segment as being a cylinder with radius r. To get the equation for the membrane voltage, the continuity equation is applied:

$$\pi r^2 \frac{\partial J(x,t)}{\partial x} + 2\pi r I_{\text{cap}}(x,t) + d_{ch} I_e(x,t) = 0.$$

Here $I_e(x,t)$ is the current flowing through each excess charge area with coordinate x at time t, d_{ch} is the ion channel density per unit length, I_{cap} is the capacitive current density per unit length. The total area of the channels within the cable segment is negligible compared to the segments' area ($r_m \gg r_c$). Defining $r_i = \sigma/\pi r^2$ and $i_{\text{cap}} = 2\pi r I_{\text{cap}}$ we find

$$\frac{1}{r_i}\frac{\partial^2 V_m(x,t)}{\partial x^2} = c_m \frac{\partial V_m}{\partial t} - \frac{d_{ch} C_m K_e}{\tau_\rho} V_e. \tag{3}$$

Combining Eqs. (2) and (3) and noticing that $d_{ch} G_{ch} = g_{ch}$ is the membrane conductivity per unit length, we may introduce the membrane time constant, $\tau_m = c_m/g_{ch}$, and the membrane length constant, $\lambda = (\sqrt{g_{ch} r_i})^{-1}$. In terms of dimensionless variables $X = x/\lambda$ and $T = t/\tau_m$ we can write the generalized cable equation in the following form:

$$\frac{\partial V}{\partial T} + V = \frac{\partial^2 V}{\partial X^2} + \gamma\left(\frac{\partial^3 V}{\partial T \partial X^2} - \frac{\partial^2 V}{\partial T^2}\right), \tag{4}$$

where $\gamma = \tau_\rho/\tau_m \ll 1$ is a small parameter. Note that Eq. (4) explicitly contains the wave operator $\Box = \gamma\partial^2/\partial T^2 - \partial^2/\partial X^2$.

A similar equation arises if one considers a model of a passive spiny dendrite [13]. Assume that spines are evenly distributed across the dendrite's length and let $U(x,t)$ denote the membrane potential of the spine head. The current from the spines to the dendrite is included by adding the term $(U - V)\lambda^2 r_i \rho/r$ to the classical cable equation (where ρ is the spine density per unit length, r is the spine stem resistance). The spine head potential evolves according to

$$\hat{C}\frac{\partial U}{\partial t} = -\frac{U}{\hat{r}} + \frac{V - U}{r},$$

where $\hat{C}$ and $\hat{r}$ are the capacitance and resistance of the spine head. Combining the equation for U and the cable equation we get Eq. (4) where $\gamma = \tau_{sp}/\tau_m$ is the ratio of the time constants of dendritic and spine head membranes, and the terms proportional to V and $\partial_T V$ are multiplied by factors $1 + \lambda^2 r_i \rho/r(1 + \hat{r}r)$ and $1 + \gamma\lambda^2 r_i \rho/r$, respectively. In this model, γ is no longer a small parameter (for instance, $\gamma = 1$ when the dendritic and spine head membranes have the same properties). This model qualitatively produces the same effects as the model given by Eq. (4), so we will focus on the analysis of Eq. (4).

III. DISPERTION RELATION IN DENDRITES

Performing the Laplace transform of $V(X,T)$ in both space and time we can write

$$\hat{V}(k,\omega) = \int_{-\infty}^{+\infty}\int_{0}^{+\infty} V(X,T)\exp(i\omega T - ikX)dXdT.$$

Substituting it into Eq. (4) we can express the dispertion relation in the following form:

$$1 + i\omega = -k^2 - i\gamma k^2\omega + \gamma\omega^2. \tag{5}$$

For the case of charge relaxation, an estimate from the Maxwell's equations for typical biophysical parameters of dendrites gives the value of γ of about 10^{-3}. Note, however, that larger values of γ can be also considered when finite velocity of charge carriers is taken into account. Bédard and Destexhe [18] phenomenologically modified the cable equation to account for additional factors giving rise to inertia in ion movement, such as friction due to complex molecular structures attached to the membrane. If we consider these effects of charge rearrangement with finite velocity for the charge layer evenly covering the membrane, our model will

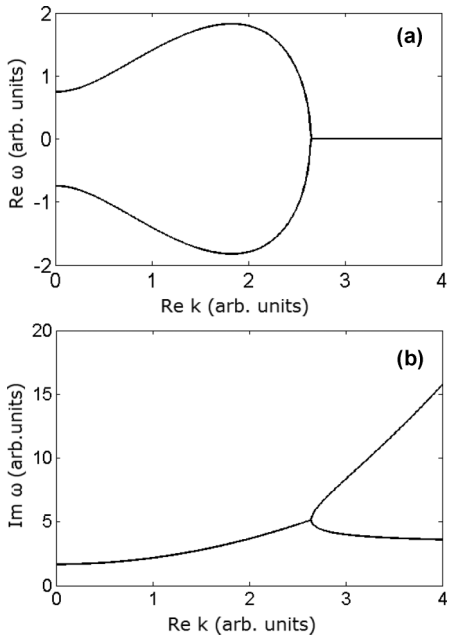

FIG. 2. Dispertion curves of the modified cable equation. Shown are the (a) real and (b) imaginary parts of ω (in units of $1/\tau_m$) for real k (in units of $1/\lambda$) and $\gamma = 0.3$. Traveling waves exist in a specific frequency range due to nonlinear dispertion in dendrites.

turn into the one obtained in [18]. Bédard and Destexhe have shown that the value of $\gamma = 0.3$ gave the best fitting to the power spectral density of intracellular recordings of background synaptic activity. These results suggest to consider larger values of charge relaxation times up to the millisecond range. We thus take $\gamma = 0.3$ in a numerical illustration.

Solutions of Eq. (5) for real wave numbers k and $\gamma = 0.3$ are presented in Fig. 2. The main difference from the classical cable model is the emergence of interesting solutions with $\mathrm{Re}\omega \neq 0$. This means that for a certain range of frequencies there exist traveling waves which decay with characteristic time given by $1/\mathrm{Im}\omega$. Note that for the value of $\gamma = 0.3$ the real part of ω is nonzero as $k \to 0$, which means that the phase velocity of the wave tends to infinity. Let $\omega = \omega' + i\omega''$ ($\omega', \omega'' \in \mathbb{R}$). The interval of wave numbers where $\omega' \neq 0$ is given by

$$k_* = \frac{\sqrt{1-2\sqrt{\gamma}}}{\sqrt{\gamma}} < k < k^* = \frac{\sqrt{1+2\sqrt{\gamma}}}{\sqrt{\gamma}}, \quad \gamma < 0.25,$$

$$k_* = 0 < k < k^* = \frac{\sqrt{1+2\sqrt{\gamma}}}{\sqrt{\gamma}}, \quad \gamma > 0.25.$$

These conditions define the *oscillatory zone*, the size of which is equal to $\Delta k = k^* - k_* = 2 + \mathcal{O}(\sqrt{\gamma})$. If k belongs to the oscillatory zone, the frequency ω is given by

$$\omega'' = \frac{1}{2\gamma} + \frac{k^2}{2}, \quad \gamma\omega'^2 = -\frac{1}{4\gamma}(1-\gamma k^2)^2 + 1,$$

which implies that in the oscillatory zone the frequency ω' varies from 0 to $\omega'_{\max} = 1/\sqrt{\gamma}$. Outside the oscillatory zone

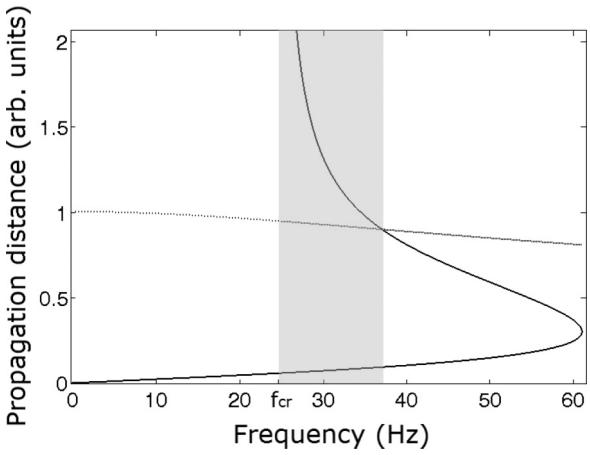

FIG. 3. Comparison of propagation distances for the standard and modified cable models. Shown are the propagation distances L_{prop} of traveling wave solutions (solid line) and standard cable model solutions (dotted line) in length constants λ vs signal frequency (in Hz). The grey area shows the resonant zone, in which the traveling waves propagate over larger distances than cable model solutions. Propagation distance of cable model solutions is given by $L_{\mathrm{cab}} = (\mathrm{Im}\sqrt{-1-i\omega'})^{-1}$. The membrane time constant is set to $\tau_m = 5$ ms.

we have the following two solutions:

$$\omega''_{\pm} = \frac{1}{2\gamma}\left((1+\gamma k^2) \pm \sqrt{(1-\gamma k^2)^2 - 4\gamma}\right).$$

For traveling wave solutions the effective propagation distance, e.g., the distance at which the signal amplitude decreases by a factor $1/e$, is $L_{\mathrm{prop}} = (1/k)\mathrm{Re}\omega/\mathrm{Im}\omega$. The dependence of L_{prop} on the signal frequency is presented in Fig. 3. It illustrates that for $\gamma > 0.25$ there exist a range of frequencies defining the *resonant zone* (25–35 Hz for $\tau_m = 5$ ms and $\gamma = 0.3$, 4–6 Hz for $\tau_m = 30$ ms and $\gamma = 0.3$), where the traveling waves propagate over larger distances than the "diffusing" solutions of the classical cable model (dotted curve in Fig. 3). Moreover, there is a resonant frequency given by $f_{cr} = \sqrt{4\gamma - 1}/4\pi\gamma\tau_m$ (Fig. 4) for which the propagation distance theoretically tends to infinity as

$$L_{\mathrm{prop}} \sim \frac{\omega'\sqrt{\gamma}}{\sqrt{\omega_{cr}(\omega' - \omega_{cr})}}.$$

IV. FINITE DENDRITE CASE

Next, we consider a finite dendrite of electrotonic length L. Suppose that on the left end of the dendrite ($X = 0$) there is a voltage oscillation with the frequency ω'. It is formulated by the following boundary conditions:

$$V|_{X=0} = V_\omega \exp(i\omega' T), \quad \left.\frac{\partial V}{\partial X}\right|_{X=L} = I^L(T),$$

where the frequency ω' is taken so that the traveling wave solutions may exist, and $I^L(T)$ is an arbitrary function. Let $V_\sim(X,T)$ denote a traveling wave solution of Eq. (4). Any solution of the standard cable equation $V_0(X,T)$ will also be an approximate solution to the generalized cable equation for

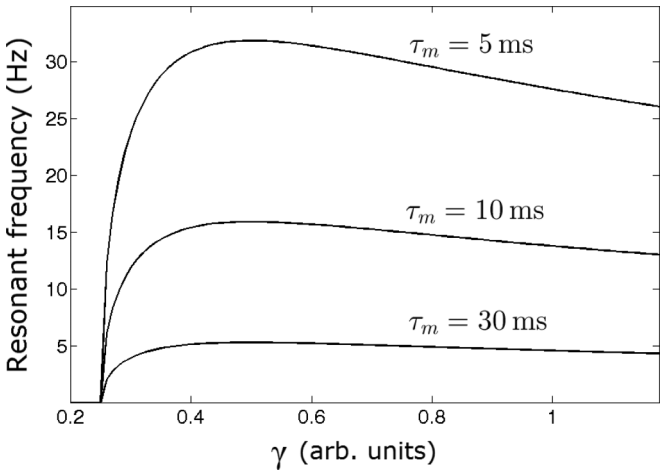

FIG. 4. Resonant frequency f_{cr} (in Hz) vs dimensionless parameter γ for three different values of the membrane time constant $\tau_m = 5$ ms (top), 10 ms, and 30 ms.

small γ:

$$\gamma \left| \left(\frac{\partial^3 V_0}{\partial T \partial X^2} - \frac{\partial^2 V_0}{\partial T^2} \right) \right| = \gamma \left| \frac{\partial V_0}{\partial T} \right| \ll \left| \frac{\partial V_0}{\partial T} \right|.$$

Consider the superposition of the solutions $V(X,T) = V_\sim + V_0$ which will also be a solution to Eq. (4) as long as Eq. (4) is linear. We may then write the boundary conditions for the unknown function $V_0(X,T)$ and also set $V_0(X,0) = -V_\sim(X,0)$. Thus, the function $V_0(X,T)$ is now uniquely defined by one initial and two boundary conditions. Rewriting the cable equation for $V_0(X,T)$ in terms of $V(X,T)$ we find

$$V + \frac{\partial V}{\partial T} = \frac{\partial^2 V}{\partial X^2} + \varphi(\omega) V_\sim, \tag{6}$$

where $\varphi(\omega') = k^2 + i(\omega' + i\omega'') + 1$. Thus, for a set of solutions with particular initial conditions, Eq. (4) is reduced to the standard cable equation with a definite source term. The quantity $I_{\text{eff}} = -\varphi g_{ch} V_\sim$ can be interpreted as an effective membrane current density arising due to oscillatory properties of the dendritic tissue. Let us consider the zero initial condition, $V(X,0) = 0$. Matching the initial condition for V_T with the boundary conditions we find $A = i\omega' V_\omega/\varphi$ and $-ik\varphi A \exp(-ikL) = I_T^L(T=0)$, which for small $k \ll 1$ implies $|I_T^L(T=0)| \ll 1$. In case of a sealed end [$I^L(T) = 0$, and assuming $A \in \mathbb{R}$] one can obtain the following constraint on k to satisfy $\text{Re} I_T^L(0) = 0$:

$$kL = \text{Arg}\varphi(k) + \pi n, \quad n \in \mathbb{Z}, \tag{7}$$

which is a transcendental characteristic equation determining the possible wave numbers $k(L)$. Depending on the length of the dendrite, L, solutions of (7) ensure the existence of several wave modes with wavelengths $\lambda_i, i = 1,2,\ldots,M(L)$ (Fig. 5).

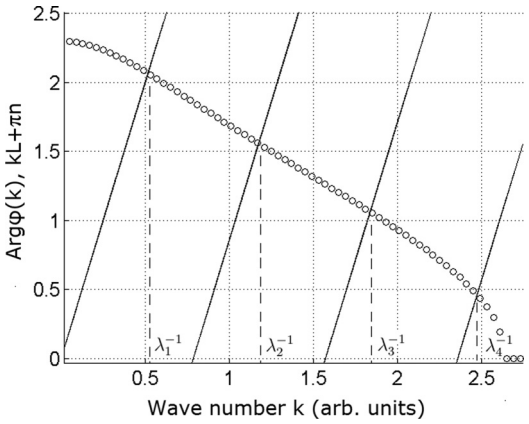

FIG. 5. Solutions, k (in $1/\lambda$), of the characteristic equation (7) for $L = 4$, $\gamma = 0.3$. The function $\text{Arg}\varphi(k)$ is plotted in circles and $kL + \pi n$ is plotted in solid lines.

V. CONCLUSION

To summarize our results, we have derived a modified cable equation taking into account the finite velocity of charge carriers within the intracellular dendritic space. The model accounts for the excess charge regions in the vicinity of intracellular structures such as ion channels of the neuron membrane. The modified equation represents a linear cable equation with additional terms arising due to the overpotential induced by the inhomogeneous distribution of charge carriers in the dendrites. If the time of charge relaxation or the spine head time constant exceeds a certain threshold, our model predicts the existence of a resonance frequency band for which electrical oscillations observed in dendrites may propagate as traveling waves with relatively large wavelengths (several length constants, i.e., hundreds of micrometers). The critical resonant frequency depends only on the membrane time constant and on the characteristic time of charge relaxation (or the spine head time constant). In particular, it does not depend on the radius of the dendritic segment. Our results also suggest that purely passive dendrites may exhibit resonant properties typically associated with the presence of active ion channels.

ACKNOWLEDGMENTS

The work was supported in part by the Ministry of Education and Science of Russia (Project No. 11.G34.31.0012), by the MCB Program of Russian Academy of Sciences, and by the Russian Foundation for Basic Research (Project No. 13-02-01223 A).

[1] I. Segev and M. London, Science **290**, 744 (2000).
[2] W. Rall, *The Theoretical Foundation of Dendritic Function* (MIT Press, Cambridge, MA, 1995).
[3] W. Rall, Exp. Neurol. **1**, 491 (1959).
[4] D. Jonston and S. M. Wu, *Foundations of Cellular Neurophysiology* (MIT Press, Cambridge, MA, 1995).

[5] M. Häusser, Curr. Biol. **11**, R10 (2001).
[6] R. D. Caze, M. Humphries, and B. S. Gutkin, PLoS Comput. Biol. **9**, e1002867 (2013).
[7] M. W. H. Remme, M. Lengyel, and B. S. Gutkin, PLoS Comput. Biol. **5**, e1000493 (2009).
[8] R. S. Kasevich and D. LaBerge, PLoS ONE **6**, e23412 (2011).
[9] N. Qian and T. J. Sejnowki, Biol. Cybern. **62**, 1 (1989).
[10] B. I. Henry, T. A. M. Langlands, and S. L. Wearne, Phys. Rev. Lett. **100**, 128103 (2008).
[11] C. Koch, *Biophysics of Computation, Information Processing in Single Neurons, Computational Neuroscience* (Oxford University, New York, 1999).
[12] S. M. Baer and J. Rinzel, J. Neurophysiol. **65**, 874 (1991).
[13] S. Coombes and P. C. Bressloff, Phys. Rev. Lett. **91**, 028102 (2003).
[14] Y. Timofeeva, S. J. Cox, S. Coombes, and K. Josic, J. Comput. Neurosci. **25**, 228 (2008).
[15] K. A. Lindsay, J. R. Rosenberg, and G. Tucker, Prog. Biophys. Mol. Biol. **85**, 71 (2004).
[16] R. R. Poznanski, Phys. Rev. E **81**, 021902 (2010).
[17] R. R. Poznanski and L. A. Cacha, J. Integr. Neurosci. **11**, 417 (2012).
[18] C. Bédard and A. Destexhe, Biophys. J. **94**, 1133 (2008).
[19] A. C. Crawford and R. Fettiplace, J. Physiol. **306**, 79 (1980).
[20] V. Torre and W. G. Owen, Biophys. J. **41**, 305 (1983).
[21] Y. Gutfreund, Y. Yarom, and I. Segev, J. Physiol. **483**, 621 (1995).
[22] M. Sanhueza and J. Bacigalupo, Eur. J. Neurosci. **22**, 1618 (2005).
[23] H.-C. Pape, D. Paré, and R. B. Driesang, J. Neurophysiol. **79**, 205 (1998).
[24] L. W. Leung and C. Y. Yim, Brain Res. **553**, 261 (1991).
[25] C. A. Chapman and J.-C. Lacaille, J. Neurophysiol. **81**, 1296 (1999).
[26] P. M. Bulai, P. G. Molchanov, A. A. Denisov, T. N. Pitlik, and S. N. Cherenkevich, Eur. Biophys. J. **41**, 319 (2012).
[27] W. Softky, Neurosci. **58**, 15 (1994).
[28] http://www.neusentis.com/IonChannels.php.
[29] W. F. Pickard, Math. Biosci. **5**, 471 (1969).