Dendritic signal transmission induced by intracellular charge inhomogeneities

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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 obtained a modified cable equation. We show that the charge inhomogeneities acting on the 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 signalling.

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 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].

The cable equation can be derived by constructing an equivalent electrical circuit with elements describing the electrical properties of neurites [2]. However, it does not take into account inhomogeneous distributions of ion concentrations within dendrites. To overcome this, Qian and Sejnowski [6] modified the cable equation by 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 [7-9] as well as active wave propagation [10,11]. Several authors used the Maxwell’s equations to generalise the cable equation and account for the charge accumulation nearby endogenous structures of the dendrites [12,13]. Bédard and Destexhe [14] considered the non-ideal properties of the membrane as a capacitor arising from the non-instantaneous motion of ions within the dendrites.

In neuroscience, many recent findings suggested that signal propagation in the dendritic tree may implement simple information processing functions at the level of a single neuron [15]. Interestingly, that together with the summation of local inputs attenuated in propagation from periphery to the active zones in soma resonant and oscillatory properties of the dendrites were reported [16,17]. These resonances were typically associated with the presence of active channels in the dendrites sustaining the propagation.

In this Letter, we show how charge inhomogeneities within 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 travelling waves propagating over larger distances than solutions predicted by classical cable theory. The model apparently predicts the appearance of resonant zones in the frequency band of 25-35 Hz (for the membrane time constant \( \tau_m = 5 \) ms) what is in agreement with recent experimental findings in neuroscience [18-22].

First, let us consider how charge inhomogeneities can be accounted in cable theory. When charge carriers move in and out of the 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 [23]. The 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 lateral relaxation current:

\[
\frac{dQ_e}{dt} = I_e - I_{ch}.
\] (1)

Because the number of ion channels is high and they are evenly distributed over the membrane’s surface, the overpotential near the channel end is described by a smooth function \( V_e(x,t) \). The total potential over the channel is \( V_{tot} = V_m + V_e \). The transchannel current is linearly related to the transchannel potential \( I_{ch} = G_{ch}V_{tot} \), where \( G_{ch} \) is the conductivity of the single channel. We suppose that the excess charge relaxates with characteristic time \( \tau_p \) if \( I_e = -Q_e/\tau_p \). This time constant \( \tau_p \) (sometimes called the Maxwell-Wagner time constant [14]) may be estimated by applying the Gauss’ law to the surface \( E \). The lateral current density is determined by \( J = \sigma E + \partial D/\partial t \) (where \( E \) is the electric field, \( D \) is the displacement field, \( \sigma \) is the conductivity of the solution). Then, the value of \( \tau_p \) is given by \( \tau_p = 2\varepsilon/\sigma \), where \( \varepsilon \) is the permittivity of the solution. One can estimate \( \tau_p \leq 1 \) ms, therefore the excess charge within passive cable relaxates at the millisecond or sub-millisecond time scale. It is the fastest time scale of the membrane potential dynamics in neuronal
dendrites [24]. For the extracellular medium (physiological saline) this time constant is approximately $10^{-10} \text{ s}$, which is much smaller than the same time-constant on the inner surface of the membrane. Obviously, 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. $V_e = C_m K_e Q_e$, where $K_e$ is the so-called channel density factor, $C_m$ is the membrane capacitance. It follows from numerical solution of the Nernst-Planck-Poisson problem for cylindrical channel geometry that $K_e$ can be expressed as follows [23]:

$$K_e = \frac{r_e^2}{\tau_{m}} \frac{4d + r_e}{2r_m - r_e}.$$

where $d$ is the Debye length, $r_e$ is the channel radius, $r_m$ is the size of the membrane patch containing one ion channel. Under the assumptions that $r_m \gg r_e$ (low channel density) and $r_e \approx d$ this expression can be simplified to $K_e = 10d^2 \pi \xi \sim 10^3$, where $\xi = 1/\pi r_m^2$ is the ion channel density per unit area of the membrane. Combining these assumptions we get the equation for overpotential dynamics:

$$\frac{\partial V_e(x,t)}{\partial t} = -\frac{V_e}{\tau_p} - \frac{G_{ch}}{C_m K_e}(V_m + V_e). \quad (2)$$

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 $E(x,t) = E(x,t)\hat{x}$. Rosenfalk [25] and Pickard [26] 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 isotopical 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:

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

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 capacitive current density per unit length. The total area of the channels within the cable segment is negligible compared to the segments’ area ($r_m \gg r_e$). Defining $r_i = \sigma/\pi r^2$ and $i_{cap} = 2\pi r I_{cap}$ we find:

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

Combining equations (2) and (3), neglecting the terms divided by $K_e \gg 1$ and noticing that $d_{ch} G_{ch} = g_{ch}$ is the membrane conductivity per unit length we get

$$\frac{1}{r_i} \frac{\partial^2 V_m}{\partial x^2} = c_m \frac{\partial V_m}{\partial t} + g_{ch} V_m - \frac{\tau_p}{\tau_i} \frac{\partial^2 V_m}{\partial x^2} + \frac{\tau_p c_m}{\tau_i} \frac{\partial^2 V_m}{\partial t^2}.$$  

Let us introduce membrane time constant, $\tau_m = c_m/g_{ch}$, and membrane length constant, $\lambda = \sqrt{g_{ch}\tau_i}$. In terms of dimensionless variables $X = x/\lambda$ and $T = t/\tau_m$ we can write the generalized cable equation in the following form:

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

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

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

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

Substituting it into equation (4) we can express the dispersion relation in the following form:

$$1 + i\omega = -k^2 - i\gamma k^2 \omega + \gamma \omega^2 \quad (5)$$

An estimate from the Maxwell’s equations for typical biophysical parameters of dendrites gives the value of $\gamma$ of about $10^{-3}$. Note, however, that larger values of $\gamma$ can be also considered when finite velocity of charge carriers is taken into account. Bédard and Destexhe [14] phenomenologically modified the cable equation to account for calorific dissipation caused by the charge movement. If we assume that the excess charge evenly covers the neural membrane our model will turn into the one obtained

\[ \text{FIG. 1: Formation of excess charge regions in the vicinity of ion channels (not to scale). Modified from } \text{http://www.neusentis.com/IonChannels.php} \]
In [14], following this work, we consider the value of $\gamma = 0.3$. Solutions of equation (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 new solutions with $\text{Re}\omega \neq 0$. This means that for a certain range of frequencies there exist travelling waves which decay with characteristic time given by $1/\text{Im}\omega$. Note that for the value of $\gamma = 0.3$ the real part of $\omega$ is non-zero 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 wavenumbers where $\omega' \neq 0$ is given by

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

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

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

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

which implies that in the oscillatory zone the frequency $\omega'$ varies from 0 to $\omega'_{\text{max}} = 1/\sqrt{\gamma}$. Outside the oscillatory zone 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 such travelling waves the effective propagation distance, e.g. the distance at which the signal amplitude decreases by a factor $1/e$, is $L_{\text{prop}} = (1/k)\text{Re}\omega/\text{Im}\omega$. The dependence of $L_{\text{prop}}$ on the signal frequency is presented in Fig. 3. It illustrates that there exist a range of frequencies defining the resonant zone ($25-35$ Hz for $\tau_m = 5$ ms), where the travelling 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 $f_{cr} = \sqrt{4\gamma - 1}/4\pi\gamma\tau_m \approx 25$ Hz for which the propagation distance theoretically tends to infinity as

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

Our formalism can be also applied to a boundary-condition problem. 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 $\omega'$. It is formulated by the following boundary conditions:

$$V|_{X=0} = V_0 \exp(i\omega'T), \ \ \left. \frac{\partial V}{\partial X} \right|_{X=L} = I^L(T)$$

![FIG. 2: Dispersion curves of the modified cable equation. Shown are the (a) real and (b) imaginary parts of $\omega$ (in units of $1/\tau_m$) for real $k$ (in units of $1/L$) and $\gamma = 0.3$. There is apparently a frequency band for which travelling waves exist.](image)

where the frequency $\omega'$ is taken so that the travelling wave solutions may exist, and $I^L(T)$ is an arbitrary function. The travelling wave solutions have the following form

$$V_\sim(X,T) = A \exp(-\omega''T) \exp(i\omega'T - ikX)$$

Any solution of the standard cable equation $V_0(X,T)$ will also be an approximate solution to the generalized cable equation:

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

Consider the superposition of the solutions $V(X,T) = V_\sim + V_0$ which will also be a solution to the Eq. (4) as long as Eq. (4) is linear. Rewriting the boundary conditions in terms of the unknown function $V_0(X,T)$, we get

$$V_0|_{X=0} = -V_\sim|_{X=0} + V_0 \exp(i\omega'T), \ \ \left. \frac{\partial V_0}{\partial X} \right|_{X=L} = -\left. \frac{\partial V_\sim}{\partial X} \right|_{X=L} + I^L(T)$$
The quantity \( I_{\text{eff}} \) is a transcendental equation determining the possible wavenumbers \( k(L) \).

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. A mathematical derivation of the equation governing voltage in a one-dimensional cable with an intrinsic inhomogeneous charge distribution is presented. 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. Our model predicts the existence of a resonance frequency band for which electrical oscillations observed in dendrites may propagate as travelling 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. 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.

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