Generalized cable models of neurons and dendrites

Claude Bedard and Alain Destexhe

Unité de Neuroscience, Information et Complexité (UNIC),
CNRS, Gif-sur-Yvette, France

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Abstract

Cable theory was introduced for neurons by Wilfrid Rall more than half a century ago, and is widely used today for modeling the voltage and current flow in neuronal and dendritic structures. This theory was derived assuming that the extracellular medium is either inexistent, or modeled as a resistor. For modeling neurons in more realistic situations, where the extracellular medium has more complex electric properties, it is necessary to generalize Rall's cable equations. We summarize here such generalized cable equations, and show that the nature of the surrounding extracellular medium can exert non-negligible influences on the cable properties of neurons.

1 Introduction

One of the most significant contribution of theoretical neuroscience is the formulation of cable theory by Rall [1], which was shown to explain a large range of phenomena (reviewed in [2]). Cable theory relies on a fundamental assumption, that the extracellular space around neurons can be modeled by a resistance, or in other words, that the medium around neurons is resistive or ohmic. While some measurements seem to confirm this assumption [3], other measurements revealed a marked frequency dependence of the extracellular resistivity [4, 5], which indicates that the medium is non-resistive. Indirect measurements of the extracellular impedance also show evidence for deviations from resistivity [6, 7, 8, 9], which could be explained by the influence of ionic diffusion [10]. More recent direct measurements *in vivo* and *in vitro* [11, 12, 13] also seem to confirm the non-resistive nature of the extracellular medium.

Unfortunately directly integrating such non-resistive extracellular properties in Rall's cable equations is not possible, it would contradict one of the basic assumption of this formalism. For this reason, a generalization of the cable equations was proposed [14], to obtain a formalism to describe the cable properties of neurons embedded in media with arbitrarily complex electrical properties. This generalized cable formalism reduces to Rall's cable equations when the medium is taken as resistive. Furthermore, integrating non-resistive extracellular properties, such as the effect of ionic diffusion ("Warburg" impedance), can have drastic consequences on basic cable properties such as the attenuation of voltage along dendrites [14], as we illustrate here.

2 Theory

We start by reviewing the traditional Rall's cable equations for neurons. We next show how such cable equations can be generalized to yield a model as general as possible, where the neuronal membrane is embedded within intracellular and extracellular media of arbitrarily complex electrical properties. Finally, we use numerical simulations to illustrate the behavior of the cable equation, comparing the traditional and generalized models.

2.1 Traditional cable equations

We start by deriving the cable equations. Starting from Ohm's law, according to which the axial current i_i and the external current i_e on a differential element of a cylindric cable, can be written as:

$$\begin{aligned} i_i &= \sigma_i \vec{E} \cdot S_i \hat{k} &= -\tfrac{1}{r_i}\tfrac{\partial V_i}{\partial x} \\ i_e &= \sigma_e \vec{E} \cdot S_e \hat{k} &= -\tfrac{1}{r_e}\tfrac{\partial V_e}{\partial x} \end{aligned} \tag{1}$$

where $\hat{k}$ is a unit vector pointing towards the axis of the cylinder, $S_i = \pi a_i^2$ is the section area and a is the radius of the cylinder, S_e is the section area of a cylindric volume of extracellular medium around the cable, r_i is the cytoplasmic resistivity and r_e is the resistivity of the external medium along the length of the cylindric cable. Note that both resistivities are expressed per unit length, with $r_i = 1/S_i\sigma_i$ and $r_e = 1/S_e\sigma_e$. In general, we have $r_e << r_i$ because $S_e >> S_i$ and $\sigma_e \approx \sigma_i$.

Under the return current hypothesis (i_e is of opposite sign as i_i), the membrane current per unit length i_m is given by:

$$i_m = -\frac{\partial(i_i - i_e)}{\partial x} = c_m \frac{\partial(V_e - V_i)}{\partial t} + \frac{(V_e - V_i))}{r_m}\,, \tag{2}$$

where the first term represents the capacitive current, with specific membrane capacitance c_m, and the second term represents the passive "leak" membrane current, with membrane resistance per unit length r_m.

If we write $V_m = V_e - V_i$, combining these equations leads to the *cable equation*:

$$\frac{r_m}{r_i + r_e} \frac{\partial^2 V_m}{\partial x^2} = \tau_m \frac{\partial V_m}{\partial t} + V_m \ . \tag{3}$$

where $\tau_m = r_m c_m$ is the membrane time constant. Note that we have a very good approximation of these equations by neglecting r_e because $r_e << r_i$, which is equivalent to consider that the external medium is a perfect conductor. Indeed, the formulation with $r_e = 0$ was the original Rall's formulation.

This equation can also be written in Fourier frequency space:

$$\lambda^2 \frac{\partial^2 V_m(x,\omega)}{\partial x^2} = \kappa^2(\omega) V_m(x,\omega) \ , \tag{4}$$

where $\kappa^2(\omega) = 1 + i\omega\tau_m$ and $\lambda = \sqrt{\frac{r_m}{(r_i + r_e)}}$ is the electrotonic constant that characterizes the cable, and τ_m is the membrane time constant.

This cable equation will be referred to as the "traditional cable", and considers that the neuron is embedded in an extracellular medium that has ohmic properties and which can be modeled as a resistive medium.

2.2 Generalized cable equations

As mentioned in the Introduction, there is fair evidence that the extracellular medium is more complex than a resistor; there is evidence that the medium accumulates charges (like a capacitor), polarization phenomena, or that the ionic diffusion affects the flow of current. These mechanisms and processes will cause deviations from resistivity, which will be seen as a frequency dependence of the electric parameters such as the medium resistivity.

To model such phenomena, the traditional approach is not adequate and a generalized approach is needed. The reason is that the free charge current, used in the traditional cable, is not conserved anymore if the medium is non-ohmic. One must use the *generalized current*, which density is given by:

$$\vec{j}^{\,g} = \vec{j}^{\,f} + \frac{\partial \vec{D}}{\partial t} \ . \tag{5}$$

Unlike the free-charge current $\vec{j}^{\,f}$, the generalized current $\vec{j}^{\,g}$ is always conserved in any given volume, even if the extracellular medium is non-ohmic or frequency-dependent. One must re-derive the cable equations using the generalized current, which leads the the *generalized cable equation*, as derived earlier [14].

Based on this definition, and considering a one-dimensional cylindric cable of constant radius a, the generalized current at a position x of the cable can be written as:

$$i_i^{\,g}(x,t) = \vec{j}_i^{\,g}(x,t) \cdot (\pi a^2 \, \hat{n}) = -\pi a^2 \gamma_i \frac{\partial V_i}{\partial x}(x,\omega) \tag{6}$$

where $\gamma_i = \sigma_i^e(x,\omega) + i\omega\varepsilon_i(x,\omega)$ is the cytoplasm admittance, and V_i is the intracellular voltage difference with respect to a given reference (which can be far away).

It follows that, using the generalized current, the cable equations can be written in a form similar to the standard cable equation:

$$\lambda^2 \frac{\partial^2 V_m(x,\omega)}{\partial x^2} = \kappa^2 V_m(x,\omega) \tag{7}$$

where

$$\begin{cases} \lambda^2 &= \frac{r_m}{\bar{z}_i} \\ \kappa^2 &= 1 + i\omega\tau_m \end{cases}, \tag{8}$$

for a cylindric compartment. Here, the quantity $\bar{z}_i$ is an equivalent impedance, which depends on the model considered. $\bar{z}_i = r_i + r_e$ for the traditional cable model, $\bar{z}_i = z_i + z_e$ for a cable model embedded in a medium with frequency-dependent extracellular impedance z_e. Other configurations are also possible, such as a cable models within an "open circuit", where the current is allowed to be exchanged between different neurons. In this case, $\bar{z}_i = z_i/[1 + \frac{z_e^{(m)}}{r_m}(1 + i\omega\tau_m)]$, where $z_e^{(m)}$ is the extracellular impedance (see Ref. [14] for details).

The general solution of this equation in Fourier space $\omega \neq 0$ is given by [14]:

$$V_m(x,\omega) = A^+(\omega)e^{\frac{\kappa(l-x)}{\lambda}} + A^-(\omega)e^{\frac{-\kappa(l-x)}{\lambda}} \tag{9}$$

for each cylindric compartment of length l and with constant diameter. For a given frequency, we have a second order differential equation with constant coefficients.

The mathematical form of Eqs. 7 and 9 are identical to that of the standard Rall's cable model, but with different definitions of λ and κ. Thus, we directly see that the nature of the extracellular medium will change the value of these parameters, which may become frequency dependent. This can affect fundamental properties of the dendrite, such as voltage attenuation, as shown previously [14] and as we illustrate in the next section.

3 Numerical simulations of the cable models

To solve the generalized cable equations numerically, we used a different method than that used in used in common simulator programs such as NEURON [15]. In NEURON, each isopotential compartment is connected to intracellular and extracellular resistances or impedances, and these are normally used to solve the cable equations. We used another, equivalent method which consists of a series of continuous cylindric compartments, of constant diameter, and which are not necessarily isopotential (see Appendix A). These continuous compartments are connected to an *auxiliary impedance* [14], which is defined as $Z_a = \frac{V_m}{i_i}$, where V_m and i_i are respectively the transmembrane potential and the axial current per unit length at the point where Z_a is

connected (see Fig. 1A). This auxiliary impedance is important because it allows one to take into account the influence of other compartments, including the soma, over the axial current and transmembrane potential. The connection between these continuous compartments is mathematically equivalent to consider the continuity conditions on axial current and transmembrane potential (see details in Appendix A and in Ref. [14]).

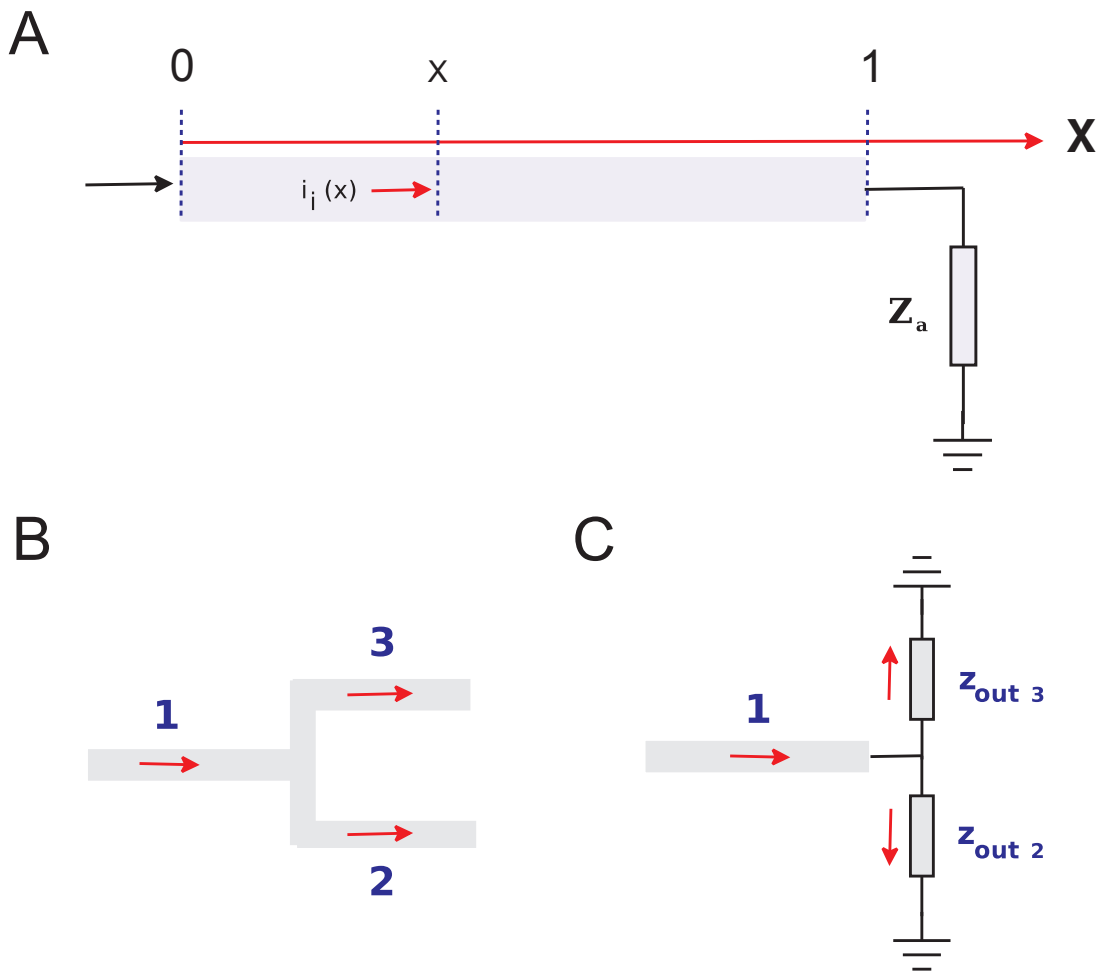

Figure 1: Coordinate convention and impedances involved in solving the generalized cable equations A. Cable segment of unit length, in series with an "auxiliary impedance" Z_a, which takes into account the influence of the other compartments. B. Scheme of branching cables. A mother dendrite (1) separates into two daughter segments (2, 3). C. Equivalent circuit of the configuration shown in B. The auxiliary impedance of segment 1 is equal to the input impedances of segments 2 and 3 ($z_{out\ 2}$ and $z_{out\ 3}$) taken in parallel. Figure modified from Ref. [14].

In what follows, we have used different expressions for the parameters $z_e^{(m)}$ and λ, comparing a resistive model to a diffusive model (see Ref. [14] for details). All computations were made in MATLAB in Fourier space.

Figure 2 shows a simulation of the generalized cable equations in a simple model. A ball-and-stick model was simulated, with a noisy current injection in the middle of the dendrite, as illustrated in Fig. 2A. This paradigm was simulated for two possible configurations of extracellular medium, a resistive model (Fig. 2B, left), in which case

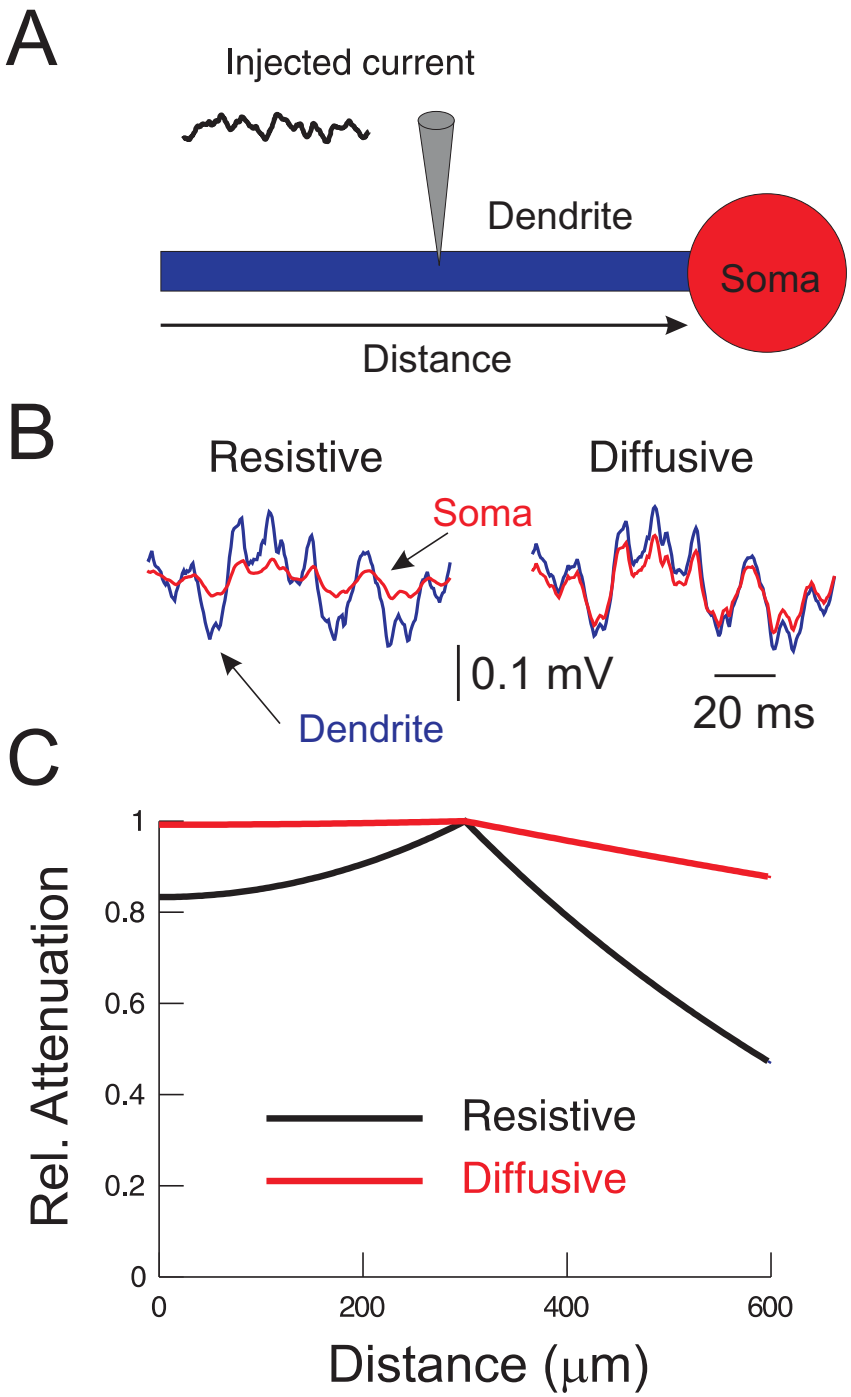

Figure 2: The electric nature of the extracellular medium influences voltage attenuation in dendrites. A. Scheme of a ball-and-stick neuron model where a noisy current waveform was injected in the middle of the dendrite. B. Voltage traces obtained in the dendrite (blue; site of injection) and in the soma (red) for resistive (left) and diffusive (right) media. C. Relative voltage attenuation profile obtained (at 5Hz) when the neuron is simulated in a resistive (black) or diffusive (red) medium. When the medium is diffusive, the voltage attenuation is greatly reduced and the cell is therefore more compact electrotonically. The extracellular impedance was matched to the *in vitro* measurements (modified from Ref. [13]).

the generalized cable is equivalent to the traditional cable. The distance profile of the voltage shows the typical attenuation with distance obtained with this model (Fig. 2C, black). A more complex "diffusive" extracellular impedance was simulated (Fig. 2B,

right). In this case, the extracellular impedance is frequency-dependent and scales as $\sqrt{\omega}$, as found experimentally [13]. Only the generalized cable model can simulate such a situation, and the dendritic attenuation profile obtained is markedly different from the traditional cable (Fig. 2C, red). This shows that the nature of the extracellular medium can influence the propagation and attenuation of the membrane potential in dendritic structures, as found previously [14].

4 Discussion

In this chapter, we have reviewed one of the most fundamental contribution of computational neuroscience to the study of neurons: the cable equations. This formalism was initially introduced by Rall and was later developed by many authors (reviewed in Ref. [2]). The cable equations have been successfully applied to many paradigms are are today widely recognized as an important tool to study dendrites and the spatial integration of inputs by neurons. Indeed, some of the most popular neural simulation tools directly implement Rall's cable equations, as for example for the NEURON simulator [15].

In the present chapter, we also explored one of the (rare) caveats of Rall's cable theory, the fact that it applies only to a simplified model of the extracellular medium. The traditional cable equation was derived assuming that the medium surrounding neurons can be modeled by a resistor, and is therefore ohmic. If the medium is considered with more realistic electric properties, departing from ohmic behavior, then the traditional Rall's cable formalism cannot be used and must be generalized. This generalization was done previously [14] and the generalized cable equations were derived for arbitrarily complex extracellular media. The generalized cable reduces to the traditional cable when the medium is resistive.

One of the main finding of the generalized cable is that the nature of the extracellular medium can have a strong influence on the integrative properties of the neuron. As we illustrated in Fig. 2, the attenuation of voltage with distance on dendrites is dependent on the nature of the medium. Thus, we conclude that the generalized cable constitutes a useful tool to study the behavior of neurons with an unprecedented level of realism, because one can integrate any electrical properties of the extracellular medium.

Finally, on a physical point of view, it is important to realize that the key concept here is the notion of generalized current. In media more complex than a resistor, there can be charge accumulation, and therefore the free-charge current is not necessarily conserved. One must use the generalized current (the sum of the free-charge current and displacement current), which is always conserved for any arbitrarily complex structure. This notion was also used to obtain generalized expressions for the current-source density analysis [10]. Like the traditional cable equation, this method

was based on the free-charge current, and was unable to account for non-resistive situations. Thus, like the generalized cable, the generalized CSD allows one to study neurons in complex extracellular media, and they both constitute powerful tools for future neuroscience applications.

Appendices

A Method to solve the generalized cable

The basis of the method to solve the generalized cable is that Eq. 9 is exact for a continuous cylindric compartment of constant diameter (which is equivalent to an infinite number of membrane RC circuits). In other words, we can use this property to simulate exactly the full cylindric compartment as a continuum with no need of spatial discretization into segments that is usually done in numerical simulators. This exact solution is only possible if the cylindric compartment has a constant diameter. This approach was called the "continuous compartment" method [14], and this leads to an efficient method to simulate the generalized cable formalism in complex cable structures.

To apply this formalism to more complex morphologies than a single cable, one must adjust the specific limit conditions of the different compartments (continuity of V_m and of the current $i_i^{\,g} = -\frac{1}{\bar{z}_i}\frac{\partial V_m}{\partial x}$; see details in Ref. [14]).

We must calculate the input impedances needed to compute the membrane voltage in complex morphologies. We consider the input impedance of the membrane, as well as the impedance of the extracellular medium, both of which are needed to calculate the spatial profile of the V_m in a given cable segment.

In a first step, one separates the cable into a series of continuous compartments of constant diameter, where parameters $2a$, z_i, r_m and $z_e^{(m)}$ are constant and specific to each compartment.

In a second step, one calculates the (transmembrane) input impedance $Z_{in}^{n+1} = \frac{V_m(0)}{i_i(0)}$ at the begin of each compartment by taking into account the auxiliary impedance at the end of this compartment, $Z_a = Z_{out}^{n+1} = \frac{V_m(l_{n+1})}{i_i(l_{n+1})} = Z_{in}^{n}$ (see Fig. 1A) if there is no branching point. At the branching points, the auxiliary impedances are simply equal to the equivalent input impedance of n dendritic branches in parallel (where n is the number of "daughter" branches; see Fig. 1B-C). Thus, because the input impedance at one end is equal to the input impedance of the other compartment connected to this end, one obtains a recursive relation (see details in Ref. [14]):

$$Z_{in}^{n+1}[Z_{in}^{n}] = \frac{\bar{z}_{i_n}}{\kappa_{\lambda_n}} \frac{(\kappa_{\lambda_n} Z_{in}^{n} + \bar{z}_{i_n})\, e^{2\kappa_{\lambda_n} l_n} + (\kappa_{\lambda_n} Z_{in}^{n} - \bar{z}_{i_n})}{(\kappa_{\lambda_n} Z_{in}^{n} + \bar{z}_{i_n})\, e^{2\kappa_{\lambda_n} l_n} - (\kappa_{\lambda_n} Z_{in}^{n} - \bar{z}_{i_n})}\,, \tag{10}$$

where $\kappa_{\lambda_n} = \kappa/\lambda_n$. $\bar{z}_i$ takes its value according to the model considered.

Thus, we can write

$$Z_{in}^{n+1} = F\left[Z_{in}^{n}\ ;\ \bar{z}_{i_n}, \kappa_{\lambda_n}, l_n\right]$$

This leads to the following expression to relate the first to the n^{th} segment:

$$Z_{in}^{n+1} = F\left[...F\left[F\left[Z_{in}^{1}\ ;\ \bar{z}_{i_1}, \kappa_{\lambda_1}, l_1\right];\ \bar{z}_{i_2}, \kappa_{\lambda_2}, l_2\right]...;\ \bar{z}_{i_n}, \kappa_{\lambda_n}, l_n\right] \tag{11}$$

In a third step, to calculate the profile of V_m along the cable, one must use the spatial transfer function $\frac{V_m(P_{n+1},\omega)}{V_m(P_n,\omega)}$ on a continuous cylindric compartment of arbitrary length, and calculate the product of the transfer functions between each connected compartment. This leads to (see details in Ref. [14]):

$$F_T(l,\omega; Z_{out}^{n}) = \frac{\kappa_{\lambda_n} Z_{out}^{n}}{\kappa_{\lambda_n} Z_{out}^{n}\, cosh(\kappa_{\lambda_n} l) + \bar{z}_i sinh(\kappa_{\lambda_n} l)} \tag{12}$$

$$\frac{V_m(P_n,\omega)}{V_m(P_1,\omega)} = \prod_{i=1}^{n-1} \frac{V_m(P_{i+1},\omega)}{V_m(P_i,\omega)} \tag{13}$$

In a fourth step, one evaluates $z_{proximal}$. To do this, one must calculate the first impedance Z_{in}^{1} which enters the recursive relation 12. This impedance corresponds to the impedance of the soma, which is given by:

$$Z_{in}^{1} = Z_s + Z_{cs}, \tag{14}$$

where Z_s is the soma membrane impedance and Z_{cs} is the cytoplasm impedance inside the soma. This relation is obtained under the hypothesis that the soma is isopotential, and the application of the generalized current conservation law implies $i^{\,g} = \frac{V_i - V_e}{Z_s + Z_{cs}} \approx \frac{V_m}{Z_s + Z_{cs}}$ where V_i and V_e are the electric potentials at both sides of the membrane, inside and outside, respectively relative to a reference located far-away.

The impedance of the bilipidic membrane is approximated by a parallel RC circuit where $R = R_m$ is the resistance and $\tau_m = R_m C_m$ is the membrane time constant. Thus, Z_{in}^{1} can be written as:

$$Z_{in}^{1} = Z_s + Z_{cs} = \frac{R_m}{1 + i\omega\tau_m} + Z_{cs} \tag{15}$$

Finally, to evaluate z_{distal}, we use the "sealed end" boundary condition $Z_{in}^{1} = \infty$. In this condition, we have $Z_{in}^{2} = \frac{\bar{z}_{i_1}}{\kappa_{\lambda_1}}\, coth(\kappa_{\lambda_1} l_1)$ (see Eq. 10). In the case of a single dendritic branch, we can write:

$$Z_{in}^{distal} = \frac{\bar{z}_i}{\kappa_\lambda}\, coth(\kappa_\lambda l)\ , \tag{16}$$

where l is the total length of the cable.

Thus, this method allows one to calculate the value of the V_m at any point of the dendritic structure. The method is analytical besides approximating the structure by

a finite set of continuous compartments, because each continuous compartment has an analytic solution. The connection between compartments is calculated by a finite iteration method. Thus, the V_m can be calculated at every coordinate with an excellent approximation, without the need of discretizing the dendritic tree into isopotential segments (like in simulators such as NEURON). It should also be faster, and more accurate because it does not rely on a specific integration method.

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