A dendritic cable model for the amplification of synaptic potentials by an ensemble average of persistent sodium channels

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Abstract

The persistent sodium current density ($I_{NaP}$) at the soma measured with the ‘whole-cell’ patch-clamp recording method is linearized about the resting state and used as a current source along the dendritic cable (depicting the spatial distribution of voltage-dependent persistent sodium ionic channels). This procedure allows time-dependent analytical solutions to be obtained for the membrane depolarization. Computer simulated response to a dendritic current injection in the form of synaptically-induced voltage change located at a distance from the recording site in a cable with unequally distributed persistent sodium ion channel densities per unit length of cable (the so-called ‘hot-spots’) is used to obtain conclusions on the density and distribution of persistent sodium ion channels. It is shown that the excitatory postsynaptic potentials (EPSPs) are amplified if hot-spots of persistent sodium ion channels are spatially distributed along the dendritic cable, with the local density of $I_{NaP}$ with respect to the recording site shown to specifically increase the peak amplitude of the EPSP for a proximally placed synaptic input, while the spatial distribution of $I_{NaP}$ serves to broaden the time course of the amplified EPSP. However, in the case of a distally positioned synaptic input, both local and nonlocal densities yield an approximately identical enhancement of EPSPs in contradiction to the computer simulations performed by Lipowsky et al. [J. Neurophysiol. 76 (1996) 2181]. The results indicate that persistent sodium channels produce EPSP amplification even when their distribution is relatively sparse (i.e., approximately 1–2% of the transient sodium channels are found in dendrites of CA1 hippocampal pyramidal neurons). This gives a strong impetus for the use of the theory as a novel approach in the investigation of synaptic integration of signals in active dendrites represented as ionic cables. © 2000 Elsevier Science Inc. All rights reserved.

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1. Introduction

The classical Sherrington–Eccles doctrine of how a neuron functions, namely the passive conduction of small graded potentials towards the soma for action potential initiation at the axosomatic region, needs to be revised (see Refs. [1,2]) in view of patch-clamp recordings and imaging studies revealing voltage-dependent Na\(^+\) channels distributed predominantly on the somata and primary trunks of some neurons [3], as well as backpropagation of Na\(^+\) action potentials [4–6] and initiation of Na\(^+\) action potentials in distal dendrites [7–11]. In particular, it has been shown in Refs. [12–17] that voltage-activated channels in neocortical neurons are involved in shaping the time course of subthreshold depolarizations. Similar findings have been observed in spinal motoneurons [18], hippocampal pyramidal neurons [19], and retinal neurons [20,21].

The persistent or sustained-type current (\(I_{NaP}\)) activated in the subthreshold voltage range of the membrane potential [12,22] was shown to be responsible for the voltage-dependent amplification of EPSPs. Stuart and Sakmann [17] suggested a persistent sodium current in the axosomatic region per se to be the amplification mechanism, while Schwindt and Crill [23] predicted enhancement EPSPs by both dendritic \(I_{NaP}\) and synaptically-activated NMDA receptors. Indeed the persistent Na\(^+\) current appears to be the major mechanism (see Ref. [24]), but not the only mechanism for the voltage-dependent amplification of EPSPs in dendrites (see Refs. [25,26] for reviews); other possibilities, such as the low-threshold Ca\(^{2+}\) current, have also been associated with the amplifying mechanism (see Refs. [27,28]).

Cable theory originally applied to neurons at the turn of this century from the earlier work on trans-Atlantic telegraph cables by Lord Kelvin around 1855 is not ionic, but electrotonic. Although Rall [29] pioneered the application of electronic cable theory to dendrites, no attempt to further ionic cable theory by incorporating discrete loci of voltage-dependent ionic channels into cable models with particular reference to the persistent sodium ion channels has been undertaken to the best of our knowledge. Earlier theoretical work dealing with graded potential amplification in dendrites was mostly numerical [30,31] or based on compartmental models [32–39], which approximates the distributed, continuous membrane of the neuron by a set of discrete interconnected compartments.

Mozrzymas and Bartoszkiewicz [40] presented an alternative approach by discretely juxtaposing values of membrane resistivity to allow for the inclusion of ionic channels. However, they considered only the discrete nature of the membrane resistivity in the absence of voltage-dependent ion channels (see also Ref. [41]). Furthermore, they assumed an infinite membrane resistance that ignored the ‘leaky’ nature of the cable at rest, or small voltage excursion from rest. They did show that the assumption of leaky cable holds since the difference between a segmented cable (cf. Ref. [42]) and a continuous leaky cable was negligibly small. Baer and Tier [43] modeled a cable with a non-linear boundary condition, representing voltage-dependent ionic channels at one end point along the cable. This is mathematically equivalent to a single loci of ionic channels, but did not take into consideration a multiple loci of ionic channels.

A ‘new’ cable theory was proposed by Baer and Rinzel [44] to gain new insights into synaptic amplification mediated by active dendritic spines. In a limiting case, they assume the stem resistance of each spine is zero, so the spine heads are contracted onto the membrane, thus reducing their cable model to one with density-dependent capacitance and an extra leakage term. However, their asymptotic approach still assumed a continuous dependence on channel density. Similarly, a
paper by Bell and Holmes [45] considered a passive cylindrical cable with active filopodia continuously distributed along the dendrite and characterized by a density (i.e., the number of filopodia per unit length). Based on the Baer–Rinzel theory, they assumed the distribution of filopodia and channel densities on a Pacinian corpuscle to be a continuum with about one or two active channels per filopodia. Toth and Crunelli [46] considered a continuously inhomogeneous ion channel distribution with exponentially decaying densities of voltage-activated channels.

Although such models are satisfactory for large densities of channel distributions, for less dense distributions it is better to consider the cable as a ‘leaky’ (i.e., an RC cable) with densities of voltage-dependent ionic channels discretely imposed at specific locations along the cable and referred to as hot-spots (see Fig. 1). The non-linearities occur only at discrete points along the linear cable rather than continuously along the entire cable structure, this is valid provided the cable at rest is mostly passive (i.e., voltage-independent channels are opened along the entire cable).

An a priori assumption of the theory is that persistent sodium ion channels along the somadendritic axis occur in discrete patches resembling hot-spots, but this assumption can be made as general as we like by reducing the distance between hot-spots in order to approximate a continuous layer of ionic channels. As yet there is no experimental verification of the validity of this assumption because determination of the spatial distribution of persistent sodium channels in dendrites is a difficult if not an impossible task, and in most cases an average estimate is found based on recording from only a few dendritic patches. However, single-channel recordings from rat hippocampal neurons show a possible homogeneous distribution throughout the neuron [47]. It is stressed, however, that a homogenous distribution may not imply a continuous distribution since recordings using patch-pipettes are always measured discretely along the dendrite, and hence the advantage of the present model over the classical Sabah and Leibovic [48] model is that the latter assumes voltage-dependent conductances are distributed continuously along the entire length of the axonal cable, leaving the problem difficult to solve analytically.

The notion that active propagation in dendrites might occur by saltatory conduction between patches of excitable membrane or hot-spots is not new (see Ref. [49]). The cable model for saltatory conduction in myelinated axons as described by FitzHugh [50] consists of segments of passive (RC-leaky) cable interrupted by isopotential patches of excitable membrane described by Hodgkin and Huxley [51]. However, the FitzHugh cable model is segmented because the nodes are intrinsically imbedded in the membrane (cf. Ref. [42]), and therefore it should not be seen as identical to the present cable model where patches of voltage-dependent ion channels or hot-spots constitute active point sources of current on a homogeneous (nonsegmented) leaky cable structure. This is justified if each hot-spot is assumed to occupy an infinitesimal region represented explicitly by a Dirac-delta function.

MacGregor [52] was the first to introduce the Dirac-delta function into neuroscience modeling in order to represent synaptic input at a specific point along a passive cable; FitzHugh [50] did not consider the advantage of using the Dirac-delta function in his saltatory conduction model. Madsen [53] proposed a cable model for saltatory conduction in a myelinated fiber, with the nodes of Ranvier to be of zero length comparable to the Dirac-delta function assumption. A more recent approach by Basser [54] assumes a Heaviside-step function instead of the Dirac-delta function for the node of Ranvier in a model of a myelinated axon, which to some extent is a more realistic assumption.
Recently, in order to explain saltatory-like wave propagation in cardiac myocytes and skeletal muscle, a model has been formulated based on a non-linear diffusion equation with regularly spaced sources called ‘sparks’ comparable to the instantaneous release of Ca\textsuperscript{2+}. This numerical approach is similar to an earlier model [56] implementing the sources at a single grid point. However, only limited analytical solutions were obtained in [55] consisting of a simpler ‘fire-diffuse-fire’ model or a linear diffusion equation (i.e., a passive RC cable) with an infinite number of source terms represented by Dirac-delta functions, and referred to as ‘Dirac-delta function spikes’. Their work can also be related to that found in [52].
The present theory deals with amplification of non-regenerative potentials (i.e., EPSPs) as a result of linearized ensemble average or macroscopic $I_{\text{NaP}}$ current sources, and, in a companion paper, a whole range of synaptic potential amplifications produced by persistent sodium channels is investigated in order to include the non-linear properties of clusters of small numbers of ionic channels (see Ref. [57]).

2. Formulation of the model

2.1. The cable equation for discretely imposed persistent sodium channels

Let $V$ be the depolarization (i.e., membrane potential less the resting potential) in mV, and let $I_{\text{NaP}}$ be the transmembrane sodium current density per unit membrane surface of cable in (A/cm). The voltage response or depolarization in a leaky cable representation of a cylindrical passive dendritic segment with $I_{\text{NaP}}$ occurring at discrete points along the cable (see Fig. 1) satisfies the following cable equation:

$$C_m V_t = \frac{d}{4R_i} V_{xx} - V/R_m + \sum_{i=1}^{N} I_{\text{NaP}}(x, t; V) \delta(x - x_i) + I(t) \delta(x - x_0) + \sum_{z=1}^{N} P \delta(x - x_z), \quad t > 0,$$

where $I(t)$ is the time course of the applied current density per unit membrane surface of cable in A/cm, $x$ the distance in cm, $t$ the time in seconds, $d$ the diameter of the cable in cm, $C_m = c_m/\pi d$ the membrane capacitance (F/cm²), $R_m = r_m \pi d$ the membrane resistivity (Ω cm²), $R_i = r_i \pi d^2 / 4$ the cytoplasmic resistivity (Ω cm), $N$ the number of hot-spots (dimensionless), $P$ the sodium-pump current density which contains ion fluxes due to active transport per unit membrane surface of cable in A/cm, and $\delta$ is the Dirac-delta function reflecting the axial position along the cable where the ionic current is positioned in cm⁻¹ (see Ref. [58]) with the synaptic (current) injection at location $x = x_0$, the pump location at $x = x_z$, and the hot-spot locations at $x = x_i$. Note subscripts $x$ and $t$ indicate partial derivatives with respect to these variables.

Eq. (1) describes the membrane depolarization in a single cable or dendrite, but a possible extension to multiple cables or $M$ dendrites emanating from a common soma can be shown to satisfy

$$C_m V_{jt} = \frac{d_j}{4R_{jm}} V_{jxx} - V_j/R_{jm} + \sum_{i=1}^{N_j} I_{\text{NaP}}(x_j, t; V_j) \delta(x_j - x_{ji}) + I_j(t) \delta(x_j - x_{j0}) + \sum_{z=1}^{N_j} P_j \delta(x_j - x_{jz}), \quad t > 0,$$

for $j = 1, 2, \ldots M$ with all other parameters being modified accordingly. Eqs. (1) and (2) can be further modified to include tapering geometries as discussed in [59,60], respectively.

2.2. Linearization of the persistent sodium current

It is still widely accepted that near the resting potential the $I-V$ relationship is linear and the electrotonic structure of neurons can be seen as the scaffolding upon which the active conductances come into action (see Fig. 2). Thus graded responses may be treated analytically by
linearizing the voltage-dependent ionic currents. This approach was first advocated in [51] and was further developed in [48] who obtained solutions for graded responses in an infinite cable by applying linearization theory to the voltage-dependent ionic currents (see also Refs. [61,62]).

The application of linearization theory is particularly suited to the analysis of EPSPs not exceeding a few millivolts from rest, but this depends on the particular neuron in question. A better criterion, therefore, should be the voltage range around the resting state before the non-linearity comes into play, which in some mammalian CA1 hippocampal neurons could reach values of up to 30 mV from the resting state (see Fig. 2). However, in Refs. [48,62] linearization theory was applied to the ionic current densities expressed in the Hodgkin–Huxley equations on the assumption that the membrane potential did not exceed a few millivolts from the resting potential. A recent paper [63] provides experimental evidence for localized dendritic spike-like potentials not exceeding about 30 mV and for active dendritic conductances linearizing synaptic potentials. Thus dendritic spike-like potentials can be modeled based on the linearization procedure.

The persistent Na\(^+\) transmembrane current density per membrane surface of cable (\(\mu A/cm\)) described in [35] based on the experimental data of French et al. [64] can be represented by

\[
I_{NaP}(x, t; V) = g_{NaP}m(V)[V - V_{NaP}], \quad t > 0
\]

with \(V_{NaP} = E_{NaP} - E_r\), \(E_r = -70\) mV is the resting membrane potential, and \(E_{NaP} = 65\) mV is the persistent sodium equilibrium potential (mV). The strength (conductance) of persistent sodium ion channel densities is given by (cf. Ref. [65])

\[
g_{NaP} = g_{NaP}^* N^*,
\]

where \(N^* / \pi d\) is the number of persistent sodium channels per unit membrane surface of cable in cm\(^{-1}\), and \(g_{NaP}^* = 18pS\) is the maximum attainable conductance of a single sodium channel [66,67]. The dimensionless activation variable \(m(V)\) is governed by the first-order reaction equations [51]:
\[
\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,
\]

where the rate-constants (sec\(^{-1}\)) are taken from [64]

\[
\alpha_m = -1.74(V + E_r - 11)/\{\exp[-(V + E_r - 11)/12.94] - 1\},
\]

\[
\beta_m = 0.06(V + E_r - 5.9)/\{\exp[(V + E_r - 5.9)/4.47] - 1\}.
\]

If the rates of change of \((m)\) with respect to time are altered by a dimensionless factor \(\varphi\) [68], then Eq. (5) becomes

\[
\varphi \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,
\]

which takes into consideration the slow activation time of persistent sodium current (see [69]). Consequently, it can be shown by linearizing the \(I_{NaP}\) current in the vicinity of the resting membrane potential along the same lines as in [48] that a linearized version of Eq. (3) becomes

\[
I_{NaP} = g_{NaP} m_t (V - V_{NaP}) + (\tau_{mr}/\varphi)g_{NaP} V_{NaP} \exp(-t/\tau_{mr})\{m_t[(dx_m/dV)_t] + (d\beta_m/dV)_t\}V, \quad t > 0,
\]

where \(m_t = \alpha_{mr}/(\alpha_{mr} + \beta_{mr})\), \(\tau_{mr} = 1/(\alpha_{mr} + \beta_{mr})\), and \(\alpha_{mr}\) and \(\beta_{mr}\) are Eqs. (6) and (7) with voltages set equal to zero, respectively. It should be noted that Eq. (9) is strictly applicable to small excursions from a resting state (i.e., \(V = 0\)) of a few millivolts and not greater than about 5 mV (see Fig. 2), but it remains a relatively good approximation before the \(I-V\) relationship bends upwards. Thus, linearization is appropriate for membrane potentials typically under 30 mV, as depicted in Fig. 2.

The inclusion of an outward current would effectively remove the \(g_{NaP} m_t V_{NaP}\) term in Eq. (9) by conservation of current that corresponds to the non-decaying (persistent) level, thus causing the membrane potential to decay over time to its resting state. One interesting candidate for the outward current is a slowly inactivating (calcium-independent) A-type \(K^+\) current (\(I_{AS}\)) recently found to have a critical role in the subthreshold depolarization of neostriatal neurons [39,70]. Another is the hyperpolarization-activated current (\(I_h\)) known to decrease EPSP amplitude and duration as well as the time window over which temporal summation of EPSPs takes place [71]. In fact, both \(I_{AS}\) and \(I_h\) may act in concert to reduce the excitability in the dendrites caused by \(I_{NaP}\).

In the present theory the maintenance of zero ionic current at rest (i.e., when \(I = 0\)) is accomplished with a sodium pump, which counters the resting ionic fluxes in order to maintain equilibrium so that ionic conductances are at their resting values and the membrane potential returns to the resting state. Consequently, the current balance equation at the site of the hot-spot reads: \(I_{NaP} - P = 0\), where \(P\) is the outward sodium pump current density.

2.3. Analytical time-dependent solutions

If the outward sodium pump current density is positive (by convention) then \(P = g_{NaP} m_t V_{NaP}\). Taking advantage of linearity and applying the Green’s function method of solution (see Ref. [72, p. 191]) to Eq. (1), we obtain the following result upon substitution of Eq. (9):
\[ V(x, t) = \int_{0}^{t} \left[ I(s)G(x, x_0; t - s) + g_{NaP} \sum_{i=1}^{N} \rho(s)V(x_i, s)G(x, x_i; t - s) \right] ds, \quad t > 0, \]  
\( (10) \)

where

\[ \rho(t) = m_t - \left( \frac{\tau_m}{\varphi} \right) V_{NaP}\{(d\varphi_m/dV)_t - m_t[(d\varphi_m/dV)_t + (d\beta_m/dV)_t]\} \exp(-t/\tau_m), \]

and

\[ I(t) = \beta x t \exp(1 - \alpha t) \]

is the synaptic current per unit surface (\( \mu A/cm \)). Here \( \alpha \) and \( \beta \) are taken to be constants; \( \beta \) is the charge carried by the synaptic current through the unit membrane surface per unit time. Later we use \( \beta \) (in dimension of \( \beta \) per unit time) to be the input charge corresponding to the area found by integrating \( I(t) \). \( G \) is the Green’s function corresponding to the solution of the standard linear cable equation (see Appendix A). Here the hot-spot points \( i \) and sodium pump points \( z \) are juxtaposed on the cable. Techniques for obtaining analytical solutions to such linear problems have been derived for single cables \([73, 74]\), for multiple equivalent cylinders \([75, 76]\), and for arbitrarily branching cables \([77]\).

The system of Volterra integral equations (10) can be solved numerically or analytically by the method of successive substitutions \([78, pp. 182, 183]\). Both methods have advantages and disadvantages, but we feel the analytic approach in contrast to a numerical solution provides a better theoretical insight into the problem, especially when faced with network modeling. Adopting the latter approach, Eq. (10) is re-written in the form corresponding to the voltage response at location \( x = x_p \) to a synaptic (current) injection at location \( x = x_0 \), and hot-spot locations at \( x = x_i \):

\[ V_p(t) = f_p(t) + g_{NaP} \int_{0}^{t} \sum_{i=1}^{N} M_{pi}(t, s)V_i(s) ds, \quad t > 0, \]  
\( (11) \)

where

\[ f_p(t) = \int_{0}^{t} I(s)G(t - s) ds \]

and

\[ M_{pi}(t, s) = G_{pi}(t - s) \rho(s). \]

We formally present the solution to Eq. (11), but readers interested in a more mathematically meticulous treatment should consult \([78]\) for the existence and uniqueness of solutions, the radius of convergence and the speed of convergence.

The Liouville–Neumann series or Neumann series solution of the system of Volterra integral equations (11) is given as a series of integrals:

\[ V_p(t) = f_p(t) + g_{NaP} \int_{0}^{t} \sum_{i=1}^{N} R_{pi}(t, s, g_{NaP})f_i(s) ds, \quad t > 0, \]  
\( (12) \)

where the resolvent kernels \( R_{pi} \) are the sums of the uniformly convergent series.
\[ R_{pt}(t, s, g_{NaP}) = M_{pt}(t, s) + \sum_{j=1}^{\infty} (g_{NaP})^j M_{pt}^{(j)}(t, s) \]

and the \( j \)-fold iterated kernels \( M_{pt}^{(j)} \) are defined inductively by the relations

\[
M_{pt}^{(1)}(t, s) = \sum_{k=1}^{N} \int_{s}^{t} M_{pk}(t, \xi) M_{k1}(\xi, s) \, d\xi
\]

and

\[
M_{pt}^{(j)}(t, s) = \sum_{k=1}^{N} \int_{s}^{t} M_{pk}(t, \xi) M_{k1}(\xi, s) \prod_{h=2}^{j} \left( \int_{s}^{\xi_{h-1}} M_{pk}(\xi_{h-1}, \xi_{h}) \, d\xi_{h} \right) \, d\xi_{1}.
\]

By writing Eq. (12) in terms of the Green’s functions explicitly, it can be shown that

\[
V_{pt}(t) = \int_{0}^{t} I(s) G_{p0}(t-s) \, ds + g_{NaP} \int_{0}^{t} \sum_{i=1}^{N} \left( \int_{0}^{s} I(\bar{\xi}_0) G_{i0}(s-\bar{\xi}_0) \, d\bar{\xi}_0 \right) \times \left[ G_{pt}(t-s) \rho(s) + g_{NaP} \sum_{k=1}^{N} \int_{s}^{t} G_{pk}(t-\xi_1) G_{k1}(\xi_1-s) \rho(s) \rho(\xi_1) \, d\xi_1 \right] \, ds + R_j, \quad t > 0,
\]

where \( R_j \), which is the remainder of the series, is

\[
R_j = g_{NaP}^{(j+1)} \int_{0}^{t} \sum_{i=1}^{N} \left( \int_{0}^{s} I(\bar{\xi}_0) G_{i0}(s-\bar{\xi}_0) \, d\bar{\xi}_0 \right) \times \sum_{k=1}^{N} \int_{s}^{t} G_{pk}(t-\xi_1) \rho(\xi_1) \, d\xi_1 \prod_{j=2}^{j-1} \int_{s}^{\xi_{j-1}} G_{pk}(\xi_{j-1}-\xi_j) G_{k1}(\xi_j-s) \rho(s) \rho(\xi_j) \, d\xi_j \, ds, \quad j = 2, 3 \ldots
\]

(14)

It can be shown from the theory of linear integral equations (e.g., Ref. [78]) that the Neumann series solution given by Eq. (13) converges uniformly provided \( \|g_{NaP}G_{ij}\| < 1 \) is satisfied, and that the remainder (14) tends to zero as \( j \) increases (see Ref. [78, pp. 10,11]). To prove this it suffices to show that \( \tau^j \rho G_{ij} \) is bounded on \( (0, t] \) for \( 0 < \theta < 1 \), which can be shown by calculating the remainder of the Green’s function (see Ref. [79]).

In evaluating Eq. (13), terms containing integrals with respect to time greater than two multiples can be neglected because the per unit time scaling factor of 0.001 from sec to msec renders such terms negligible. Eq. (13) is numerically solved using *Mathematica* (version 3) software. The computation required under 10 min on a Hitachi Flora 370 PC workstation with a 400 MHz processor and a 384-MB memory if only the first three terms in the Green’s function with sealed ends are used. The first term dominates with other terms decreasing exponentially with time. No significant difference in results occurred by truncating the Green’s function with sealed ends, but at small times \( (t < 0.01) \) an alternative Green’s function should be used that converges more rapidly (see Appendix A).
3. Results

3.1. How hot-spot location with identical number and strength of persistent sodium ion channels affects the membrane potential

Lipowsky et al. [35] used a reduced compartmental model to simulate the effect of various densities and distributions of persistent Na\(^+\) channels on EPSP enhancement. They showed that somatic placement of \(I_{NaP}\) alone did not significantly elevate the amplitude of EPSPs. They showed dendritic \(I_{NaP}\) produced a large ‘plateau’ potential with extreme slowing of the somatic membrane potential decay. They introduced a transient potassium current \(I_A\) [80] in the dendrites so that the simulated wave form matched the experimental data. They concluded that the most important parameter determining the role of dendritic \(I_{NaP}\) in synaptic integration is its distribution rather than its local density.

However, since they did not consider unequal distributions of dendritic persistent Na\(^+\) channels in their simulations, we investigated this problem by considering a cable of length \(L = 1.6\) mm that has a diameter of 4 \(\mu\)m, and two variations in the spatial distribution of hot-spots. The first variation is an equal distribution of hot-spots from \(x = 0\) to \(x = 0.1L\) located at length intervals of \(0.1jL/N\), where \(j = 1, 2, \ldots N\), on the path between the soma \((x = 0)\). The second variation is a uniform distribution of hot-spots along the entire length of cable at length intervals of \(jL/N\), where \(j = 1, 2, \ldots N\), for an identical number of hot-spots \((N = 5)\) and an identical number of persistent sodium channels per hot-spot \((N^* = 10/\pi d)\).

In Fig. 3, we show EPSPs affected by the presence of an outward current or sodium pump for two different sites of the synaptic input located at: (i) \(x_0 = 0.1L\) (i.e., 160 \(\mu\)m from the end \(x = 0\)), and (ii) \(x_0 = 0.9L\) (i.e., 1440 \(\mu\)m from the end \(x = 0\)). It is possible to compare a discrete or sparse distribution of persistent sodium channels as shown in Fig. 3(c) and (d), and a more dense or continuous distribution of persistent sodium channels as shown in Fig. 3(a) and (b) by keeping the total number of persistent sodium channels fixed in both cases (i.e., \(N^* N = 50\)).

It is evident from Fig. 3 that a continuous distribution appears to produce a greater amplification of EPSPs in comparison with the discrete distribution. Indeed, this difference can be especially apparent when the synaptic input is located close to the recording point and is in close vicinity to the hot-spots. Even for a very distal synaptic input (i.e., at \(0.9L\)) it can be seen from Fig. 3 that the continuous distribution yields a slightly greater amplification in comparison with the discrete distribution of hot-spots along the cable. These results are compatible with the concept that a higher density of persistent sodium channels per hot-spot, should produce a greater amplification in the voltage response in comparison to a sparser density distribution of persistent sodium channels.

In the case of proximally placed synaptic input as shown in Fig. 3(a), the spatial location proximal to the recording point \(x = 0\) is more advantageous over the discretely placed distribution of hot-spots as shown in Fig. 3(c). However, in the case of distally placed synaptic input, the spatial location of the hot-spots yields almost the same enhancement of EPSPs (cf. Figs. 3(b) and (d)). Therefore, it seems that the ‘local density’, defined as the density of persistent sodium channels positioned in close proximity to the recording site, has a significantly greater amplifying effect in comparison to nonlocal densities for proximally placed synapses and an identical amplifying effect for distally placed synapses. This contradicts the conclusions made in [35] on the
importance of the local density of $I_{NaP}$ for distally placed synapses from the soma or recording site.

3.2. How the number of hot-spots ($N$) with identical location and strength of persistent sodium ion channel densities affects the EPSP

The next problem was to investigate how the hot-spot number ($N$) affects the EPSP, assuming identical location and strength of persistent sodium ion channel densities along the dendritic cable. This was done by considering a cable of length $L = 1.6$ mm that has a diameter of $4 \mu m$, and a uniform distribution of hot-spots from $x = 0$ to $x = L$ located at length intervals of $jL/N$, where $j = 1, 2, \ldots N$. The current input is assumed to be located at: (i) $x_0 = 0.1L$ (i.e., $160 \mu m$ from the end $x = 0$) and (ii) $x_0 = 0.9L$ (i.e., $1440 \mu m$ from the end $x = 0$) for two $N$ values: (a), (b) $N = 10$, }

Fig. 3. The amplification of electrotonic potentials mediated by persistent sodium hot-spots distributed: (a) and (b) near the $x = 0$ region and (c) and (d) uniformly. In each case the location of synaptic input is at: $x_0 = 0.1L$ and $x_0 = 0.9/L$, respectively. The number of hot-spots is assumed to be $N = 5$ in each case, together with the following parameters as used in [35]: $R_i = 200 \Omega \ cm$, $C_m = 1 \mu F/cm^2$ and $R_m = 50,000 \Omega \ cm^2$, $d = 4 \mu m$, $\lambda = 0.158 \ cm$, $\beta = 0.438 \mu A/(cm \ ms)$, $z = 0.25/\mu s$, $g_{NaP} = 0.143 \mu S/cm$ and $\phi = 0.2073$. The values of $\beta$ and $z$ were selected arbitrarily to yield a response at $x = 0$ of approximately 1 mV (in the absence of hot-spots) for a synaptic input current located at $x_0 = 0.6L$, and the value of $g_{NaP}$ was based on the number of persistent sodium channels per hot-spot of $N^* = 10/\pi d$. The total membrane capacitance per unit area $C_m = c_m/\pi d$, where $c_m = c_0 + N^* c_m^*$ (cf. Ref. [65]) is the total capacitance of membrane per unit length ($\mu F/cm$), $c_m^* = 8 \times 10^{-18} \ F$ is the capacitance associated with a single sodium channel [65], and $c_0 = 1 \mu F/cm^2$ is the capacitance of membrane per unit length without any channels. Hence, in theory the total membrane capacity needs to be increased, but such an increase is negligibly small. The dashed curve corresponds to the amplification in the EPSP, and the continuous curve represents the EPSP without any persistent sodium ion channels present. Inset shows schematically the position of hot-spots along the cable of length $L = 1.6$ mm as well as the position of the synaptic current injection.

importance of the local density of $I_{NaP}$ for distally placed synapses from the soma or recording site.
and (c), (d) $N = 20$. In Fig. 4, all EPSPs are measured at the point $x = 0$ in the presence of an outward current or sodium pump. The results in Fig. 4 clearly show that a greater number of hot-spots results in greater amplification of the distal synaptic signal. What is particularly interesting from Fig. 4 is that for a greater number of persistent sodium channels distributed along the cable, the peak amplitude of the EPSP is not significantly increased, but rather the time-course of the EPSP is broadened. Furthermore, the spatial distribution of $I_{NaP}$ need not be along the entire length of the cable to produce significant broadening of the response.

The amplification of small graded potentials like EPSPs produces a much slower time course of decay, which was initially believed to be caused by NMDA receptor activation in dendrites [14,81], but the broadening was not as great as seen here. Furthermore, prolonged broadening of the EPSP time-course is not observed in some neurons (see Ref. [35]), which may indicate the presence of other rapidly gating channels in the nerve cell membrane. However, we believe that the process of linearization of the somatic $I_{NaP}$ introduces an inductive element that, if in large numbers, could be the major cause behind such intense broadening of the EPSP time-course. Thus the linearization of $I_{NaP}$ appears insufficient to explain most results related to EPSP modulation. Only full treatment of the non-linear effects of the $I–V$ relationship could better explain our full understanding of these phenomena (see Ref. [57]).

The question of concern is whether there is a saturation point where further increases to the number of hot-spots distributed in the proximal dendrites results in no amplification to the EPSP. It was found that there is no such optimal number for greatest amplification to EPSP; i.e., a larger

![Fig. 4](image_url)

Fig. 4. The amplification of EPSPs mediated by persistent sodium hot-spots distributed uniformly for two different numbers of hot-spots: (a) and (b) $N = 10$, and (c) and (d) $N = 20$. The same parameters as those in Fig. 3 are used. The continuous curve represents the membrane potential without any persistent sodium ion channels present. Inset shows schematically the number (denoted by value of $N$) of hot-spots along the cable of length $L$. 
number of hot-spots results in a more enhanced amplification of EPSP (see Table 1). This is not surprising as it simply reflects a consequence of linearity in modeling the persistent sodium $I-V$ relation. However, it is thought that an optimal density could be found if the $I_{\text{NaP}}$ relation is left non-linear (see Ref. [57]). It is clear from Table 1 that only 10 hot-spots distributed uniformly along the cable produce a 43% amplification of the signal, while 20 hot-spots uniformly distributed result in a 100% amplification of the signal. An amplification of 300% results if 50 hot-spots are uniformly distributed along the cable. These results are dependent on both the location of the synaptic input and the density distribution of hot-spots. The data in Table 1 only consider a single location of the synaptic input.

Alzheimer et al. [82] estimated about 17,000–23,000 transient sodium channels on isolated pyramidal neurons (excluding the axon). Given that only a small fraction of the transient channels are persistent sodium channels (1–2%), a rough estimate yields between 170 and 460 persistent sodium channels, which is in the ballpark observed here for moderate amplifications of the synaptic potentials (see Table 1). Poznanski and Bell [57], using a different approach, have shown similar estimates of persistent sodium channel densities represented as non-linear current sources.

### 3.3. How the strength (conductance) of persistent sodium ion channel densities with identical location and number of hot-spots affects the EPSP

It is also important to know the exact number of persistent sodium channels per hot-spot (assuming each hot-spot has an equal number of such channels). One way to proceed is to examine the strength (i.e., conductance) of a single hot-spot (i.e., $N=1$) or density of persistent sodium channels. In the case of a somatically placed $I_{\text{NaP}}$ it has been shown that a 12% amplification of distal synaptic input at the soma is observed from the experimental data [35]. In the Green’s function representation of the neuron, the soma is assumed to be space-clamped, so the distribution of hot-spots is only permissible at a single point (i.e., $x_p = 0$), which theoretically implies $N=1$. This value is used in the simulation with varying $N^*$ values to see what conductance value would bring an amplification in the EPSPs to 12%.

The simulations based on the space-clamped soma approximation used in the present model indicate that a maximum attainable conductance of $g_{\text{NaP}} = 0.2860 \, \mu\text{S/cm}$ or $N^* = 20/\pi d$ is required.
to produce a 12% amplification in the peak of an EPSP (see Fig. 5). These results also indicate that a single hot-spot, regardless of the density, does not produce the broadening effect seen in Figs. 3 and 4, although greater density indicates a slightly higher peak amplitude. If the density is given by \( \frac{20}{D} \), then this is equivalent to approximately 16 channels per 10 \( \mu \text{m}^2 \) where \( D \) is the uniform spacing between successive hot-spots in microns. For example, if there is one persistent sodium channel per 10 \( \mu \text{m}^2 \), then the spacing between hot-spots will be 16 \( \mu \text{m} \) or approximately 0.01 \( L \) (see Fig. 6).

Consequently, the maximum attainable specific conductance \( g_{\text{max}} = g_{\text{NaP}} / \Delta = 1.7875 \text{ pS/\mu m}^2 \) is very close to the average specific conductance of \( 1.7 \pm 0.6 \text{ pS/\mu m}^2 \) for the persistent sodium current, but it is only a small fraction (1.5%) of the specific conductance of 113 \( \pm 11.6 \text{ pS/\mu m}^2 \) for the transient sodium current [64]. Indeed, the estimate of one persistent sodium channel per 10 \( \mu \text{m}^2 \) is also a small fraction (1.25%) of the density distribution of transient Na\(^+\) channels to be about 80 channels per 10 \( \mu \text{m}^2 \) in dendrites of CA1 hippocampal neurons [47]. These results suggest that \( I_{\text{NaP}} \) may flow through noninactivating Na\(^+\) channels that are distinct from the transient Na\(^+\) channels, or through the same channels with different gating mechanisms [82], with the density distribution of the activated channels being very sparse, in the vicinity of 1–2% in comparison to the transient sodium channels.
4. Discussion and conclusions

Elements of an ionic cable theory were developed by incorporating the density distribution of ion channels into cable models of neurons with time and voltage-dependent ionic current imposed discretely rather than continuously as assumed in classical non-linear cable theory. This was accomplished by superimposing a finite number of sodium current sources at discrete loci along the dendritic cable. The protocol differs from the segmented cable modeling used to investigate the saltatory conduction in axons (see Ref. [50]).

The rationale behind the modeling is the belief that a continuous distribution of voltage-dependent ion-channels in dendrites may be inappropriate because such channels occur more sparsely in dendrites as compared with axons, and so the continuum approximation used in cable theory needs to be modified to include the discreteness of ion-channel density distribution. Experimental evidence for a relatively sparse density distribution of voltage-dependent sodium channels comes indirectly from the observed decrement in the amplitude of back-propagating sodium spikes [5,6].
In this paper, we introduced various discrete density distributions of dendritic persistent sodium channels (hot-spots) to study the effects of varying the distributions of persistent sodium channels on the enhancement of EPSPs, and to look at how different strengths of persistent sodium densities affect processing of synaptic signals. Given that the contribution of such voltage-dependent ionic channels to dendritic information processing is at present not well understood, our results can elucidate the role of amplified EPSPs in the initiation of sodium spike-like potentials in the dendrites.

The following conclusions emerged from the analysis: (i) Local density defined as the number of persistent sodium channels in close vicinity to the recording site, and not the spatial distribution of Na\(+\)P channels, produces a greater increase in the peak amplitude of the EPSP. That is, peak EPSPs will be amplified the most if a high density of Na\(+\)P channels are in close vicinity to the activating synapses. (ii) Local density together with the spatial distribution of Na\(+\)P channels produces broadening in the time-course of the amplified EPSP. That is, the distribution of Na\(+\)P channels along the entire ionic cable with a higher density near the synaptic region may result in a greater probability of action potential initiation. (iii) An increase in the number of Na\(+\)P channels without any local density or spatial distribution will only slightly increase the peak amplitude of the amplified EPSP. That is, the notion of Na\(+\)P channels concentrated at high densities at the axosomatic region of the neuron will have a minimum effect on the dendritic integration of synaptic signals.

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Appendix A. Green’s function for some linear cable structures

The Green’s function $G(x,x_0;\tau)$ corresponds to the response at time $\tau$ at location $x$ to a unit impulse at location $x_0$ at time $\tau=0$, and is given by the solution of the following initial-value problem:

$$C_m G_t(x,x_0;\tau) = (d/4R_m) G_{xx}(x,x_0;\tau) - G(x,x_0;\tau)/R_m,$$

$$G(x,x_0;0) = \delta(x-x_0).$$

For a multiple cable, the Green’s function is defined in notation $G_k^j(x_j,x_{k0};\tau)$ to represent the response at a point $x = x_j$ in the $j$th cable to a unit impulse input at a location $x = x_0$ along the $k$th cable with the above initial-value problem changed to:

$$C_m \partial_t G_k^j(x_j,x_{k0};\tau)/\partial \tau = (d/4R_{jm}) \partial^2 G_k^j(x_j,x_{k0};\tau)/\partial x^2 - G_k^j(x_j,x_{k0};\tau)/R_{jm},$$

$$G_k^j(x_j,x_{k0};0) = \delta(x_k-x_{k0}).$$
A.1. Single cable with sealed ends

This case represents a single finite cable of length \( L \) in cm with both ends sealed (i.e., \( G_s(0,x_0;t) = G_s(L,x_0;t) = 0 \)). A representation which converges fast for large \( t \) is [72]

\[
G(x,x_0;t) = \left( R_m / L \right) \exp(-t/\tau_m) \left[ \exp(-t/\tau_m) + 2 \sum_{n=1}^{\infty} \cos(n\pi x/L) \cos(n\pi x_0/L) \right] \\
\times \exp\left[ -\left\{ 1 + (n\lambda^2/L^2) \right\} (t/\tau_m) \right], \quad t > 0, \tag{A.1}
\]

where

\[
\tau_m = R_mC_m \quad \text{and} \quad \lambda = (R_md/4R_i)^{1/2}.
\]

An alternative representation which converges more rapidly at small times is given by [59]

\[
G(x,x_0;t) = \left( R_m / \lambda \right) \exp(-t/\tau_m) \sqrt{(\tau_m/4\pi)}(H(x_0 - x) \{ \exp[-\tau_m(x - x_0)^2/4\lambda^2 t] \\
+ \exp[-\tau_m(x + x_0)^2/4\lambda^2 t] + \exp[-\tau_m(x + 2L - x_0)^2/4\lambda^2 t] \}
+ \exp[-\tau_m(x + 2L + x_0)^2/4\lambda^2 t] + \exp[-\tau_m(x + 2nL - x_0)^2/4\lambda^2 t] \\
+ \exp[-\tau_m(x - 2nL - 2L + x_0)^2/4\lambda^2 t] + H(x - x_0) \{ \exp[-\tau_m(x - x_0)^2/4\lambda^2 t] \\
+ \exp[-\tau_m(x + x_0)^2/4\lambda^2 t] + \exp[-\tau_m(x + 2L - x_0)^2/4\lambda^2 t] \}
+ \exp[-\tau_m(x + 2L + x_0)^2/4\lambda^2 t] + \exp[-\tau_m(x + 2nL - x_0)^2/4\lambda^2 t] \\
+ \exp[-\tau_m(x - 2nL - 2L + x_0)^2/4\lambda^2 t] + \exp[-\tau_m(x - x_0)^2/4\lambda^2 t] \\
+ \exp[-\tau_m(x + x_0)^2/4\lambda^2 t] + \exp[-\tau_m(x + 2L - x_0)^2/4\lambda^2 t] \}, \quad t > 0, \tag{A.2}
\]

where \( H(.) \) represents the Heaviside step function.

A.2. Single cable with lumped-soma

This case represents a single finite cable of length \( L \) with a lumped-soma attached to the end \( x = 0 \) (i.e., \( G(0,x_0,t) + G_r(0,x_0,t) - \gamma G_s(0,x_0,t) = 0 \), where \( \gamma \) is the dendritic-to-somatic conductance ratio) and a sealed end at \( x = L \) (i.e., \( G_s(L,x_0,t) = 0 \)). A representation which converges fast for large \( t \) is [72]

\[
G(x,x_0;t) = \left( R_m / \lambda \right) \exp(-t/\tau_m) \sum_{n=0}^{\infty} \varphi_n(x)A_n(x_0) \exp[-(\psi_n^2 t/\tau_m)], \quad t > 0, \tag{A.3}
\]

where \( \varphi_n(x) = \cos(\psi_n x/\lambda) - (\psi_n/\gamma) \sin(\psi_n x/\lambda) \). The eigenvalues \( \psi_n \) are the roots of \( \gamma \tan(\psi_n L/\lambda) + \psi_n = 0 \) and the coefficients are...
\[ A_n(x_0) = 2\gamma \cos \theta_n / \left[ \sin \psi_n L / \lambda \{ (\gamma / \psi_n - \psi_n L / \lambda) + (\gamma / \lambda)(x_0 - L) \tan \theta_n \} + \cos \psi_n L / \lambda \{ (2 + \gamma L / \lambda) + \theta_n \tan \theta_n \} \right], \]

and

\[ A_0(x_0) = \gamma / (1 + \gamma L / \lambda), \]

where \( \theta_n = (x_0 - L) / \lambda \psi_n \) and \( n = 1, 2, \ldots \)

### A.3. Multiple cable with lumped-soma

This case represents a multiple number \( (P) \) of finite cables of length \( (L_j) \) with a lumped-soma attached to the end \( x_j = 0 \) (i.e., \( G(0, x_j; t) + G_i(0, x_j; t) - \gamma G(0, x_j; t) = 0, \) where \( \gamma = \sum \gamma_j, \ j = 1, 2, \ldots, P \) is the dendritic-to-somatic conductance ratio) and a sealed end at \( x_j = L_j \) (i.e., \( G_i(L_j, x_j; t) = 0). \) A representation of the Green’s function for recording at \( x = x_j \) in the \( j \)th cable to a current input (i.e., a unit impulse) at \( x = x_0 \) along the \( k \)th cable is [76]

\[
G_j^s(x_j, x_{k0}; t) = (R_{jm} / \lambda_j) \sum_{n=0}^{\infty} E_{kn} \Psi_{jn}(x_j) \Psi_{kn}(x_{k0}) \exp \left[ -(1 + \omega_n^2) t / \tau_\infty \right], \quad t > 0, \quad (A.4)
\]

where the spatial eigenfunctions are given by \( \Psi_{jn}(x_j) = \cos[\omega_n(L_j - x_j) / \lambda_j] / \cos[\omega_n L_j / \lambda_j] \) and \( \Psi_{kn}(x_{k0}) = \cos[\omega_n(L_k - x_{k0}) / \lambda_k] / \cos[\omega_n L_k / \lambda_k] \), and the eigenvalues \( \omega_n, \ n = 0, 1, 2 \ldots \) are the positive roots of the equation:

\[-\omega_n^2 = \omega_n \sum_{j=1}^{P} \gamma_j \tan(\omega_n L_j / \lambda_j) \]

and the coefficients \( E_{kn} \) are defined as

\[
E_{kn} = 2\gamma_k \sqrt{\left\{ 2 + \sum_{j=1}^{P} \gamma_j (L_j / \lambda_j) \left[ \tan(\omega_n L_j / \lambda_j) / (\omega_n L_j / \lambda_j) + \sec^2(\omega_n L_j / \lambda_j) \right] \right\}}.
\]

The coefficients \( E_{k0} \) need particular care since the first root is \( \omega_0 = 0 \) with the corresponding coefficient

\[
E_{k0} = 2\gamma_k \sqrt{\left\{ 1 + \sum_{j=1}^{P} \gamma_j L_j / \lambda_j \right\}}, \quad \text{where} \quad \lambda_j = \sqrt{(d_j R_{jm} / 4R_{ij})}.
\]

### References


