

Spatiotemporal Ca^{2+} dynamics in neuronal dendrites: responses and support of travelling waves

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Abstract

Since the onset of intracellular voltage recording techniques, additional methods have been developed and improved upon, such as using voltage-activated dyes, sodium indicators, fluorescent proteins (namely Green fluorescent protein (GFP)), synthetic and genetically encoded indicators, in conjunction with calcium imaging. These techniques have shown that dendrites are not just simple transmission lines, but are sophisticated cellular systems with nonlinear multiscale dynamics that evolve over different timescales and are involved in neural signalling, information processing, along with any underlying computations. Calcium imaging has been important in this regard, having highlighted how reaction-diffusion processes between calcium, buffers and other proteins shape neuronal activity, through dynamical interaction and synaptic plasticity, over different timescales compared to the evolution of electrical signals. To this end, experiments have shown the involvement of calcium and calcium dependent buffers in the response dynamics of neurons. A novel participant during morphological studies, using electron microscopy, fluorescence and immunostaining have illustrated that the Endoplasmic Reticulum (ER) (present in the soma and extends into the distal dendrites) is also a calcium store that can release calcium as puffs through the activation ryanodine receptors into the cytosol of neuronal dendrites. This is called Ca^{2+} -induced Ca^{2+} release (CICR), which have been implicated in a number of processes, including the occurrence of calcium waves in the presence of an unsaturated buffer. In this situation, one can observe local changes to the Ca^{2+} and buffer concentrations in response to some stimuli, such as the presentation of orientated stationary or moving bars or gratings, in a selective fashion through the manifestation of a bias in the resulting calcium concentration in space along the dendrite, that underpins some computation. Studies have shown that Ca^{2+} plays many important roles in neuronal function and information processing. To better understand the role of Ca^{2+} , we constructed a computational model of a dendrite with a mechanism that describes CICR in the presence of an unsaturated buffer and study the conditions permitting the occurrence calcium waves and the underlying requirements of timed inputs from CICR. Modeling the heterogeneity of CICR from the endoplasmic reticulum by using a formulation that permits essential dynamics to be analyzed. Using a two-pool model calcium dynamics, we present an analysis of how CICR impacts calcium activity in space in the presence of a calcium buffer and study the potential conditions supporting the propagation of CICR induced Ca^{2+} waves.

Keywords: Endoplasmic reticulum, Calcium ions, Calcium-Induced-Calcium Release mechanism, Two-pool calcium model.

1. Introduction

Selective neural responses, such as orientation and direction selectivity, have been demonstrated in many published papers that have used different mammals, such as cat, monkey, and ferret. Upon

presentation of some preferred stimuli, neurons show vigorous responses while to non preferred stimuli, the responses are markedly weaker or lacking. The first demonstrated example of selective neural responses was orientation selectivity

where cortical neurons responded strongly to the presentation of visual stimuli composed of bars at some preferred orientation (Blasdel, 1992; Heggelund & Moors, 1983; Martinez et al., 2002; Merkulyeva et al., 2025; Murphy & Sillito, 1986; Scholl et al., 2013; Volgushev et al., 1993), which was followed by illustrating direction selectivity in cortical neurons of the early visual cortex (Barlow et al., 1964; Barlow & Levick, 1965; Bonhoeffer & Grinvald, 1993; Gizzi et al., 1990; Movshon, 1975).

To this end, the strong selective responses of retinal ganglion cells were shown to be *direction-selective*, responding maximally to stimuli moving in the cells' preferred direction (Barlow et al., 1964; Barlow & Levick, 1965), and can be attributed to the spatial extent of the dendrite and the timing and patterning of input, as an underlying mechanism. For starburst amacrine cells (SAC) Euler et al. (2002) has further demonstrated that they are also directional-selective with respect to their Ca^{2+} response, highlighting that there are other signals, timescales, and ions that important for the input selectivity.

The role of Ca^{2+} in neural signalling has been investigated experimentally and theoretically, for its involvement in shaping neural responses, uses as a selective marker/secondary messenger, and its involvement during learning and memory. To obtain a better understanding of the impact of Ca^{2+} dynamics on these neural processes and the role of propagating calcium waves in dendrites (Coombes, 2001; Keizer et al., 1998; Thul et al., 2008) and the generation of direction-selective responses in SAC (Bootman et al., 2012; Koizumi & Poznanski, 2015).

Influx of Ca^{2+} into the cytosol of neuronal dendrites, including those of SACs, occurs through calcium-dependent ion channels in the membrane, like the L-Type calcium channel, and by the calcium-induced activation of ryanodine receptor (RyRs) in the ER, which leads to the efflux of Ca^{2+} from the ER to the cytosol. This process of CICR will consequently induces more RyRs to open more Ca^{2+} channels in the membrane of the dendrite. This leads to a near continuous release of Ca^{2+} resulting in an increase the Ca^{2+} concentration level until it becomes too high, leading to

the activation of Ca^{2+} pumps to remove Ca^{2+} from the cytosol back into the ER or extruded out of the cell. This underlying mechanism for CICR leads to Ca^{2+} wave propagation in neuronal dendrites while subject to a Ca^{2+} buffer. In order to support this calcium wave along the dendrite, the timing between CICR events require to be precisely timed or else the wave will fail to propagate. To analyse this mechanism and the underlying dynamics resulting from CICR, a mathematical model of Ca^{2+} dynamics is presented that is subject to the effects of a Ca^{2+} buffer. This model is analysed with a focus on the conditions for supporting the resultant travelling Ca^{2+} wave in the presence of a buffer.

2. Methods

This paper presents a mathematical model for a two-pool CICR mechanism, and solves it using advanced Green's function techniques. This is the crucial step before progressing to the next step, which is the simulation. In the first step, the construction of an algorithm and mathematical model for the CICR mechanism will employ a mix of numerical and analytical approaches. First, we adopt a simple model that captures the nature of the CICR mechanism, yet is amenable to analytical techniques, before progressing to the next step, which is the analysis of underlying the support of a calcium wave in the presence of an unsaturated buffer.

2.1. The two-pool model equations for CICR

We consider a section of dendrite to be a cable of finite length (ℓ) and extend the CICR two-pool model of Kuba & Takeshita (1981) and Goldbeter & Berridge (1990) to involve spatial effects of Ca^{2+} signalling via diffusion. We assume a model of calcium induced calcium release (CICR) where upon increases in $[Ca^{2+}]_i$ then so does the likelihood of release of free Ca^{2+} from the ER, and therefore Ca^{2+} stimulates its own release.

Fig. 1 illustrates a schematic of the two-pool model of the CICR mechanism incorporating spatial aspects of Ca^{2+} signalling along a section of dendrite, which includes as a calcium buffer dynamics and Ca^{2+} release from the ER via RyR receptor activation. The (extended) model sets out to explore spatial aspects of Ca^{2+} signalling along a cable representing a neuronal dendrite in the presence of a buffer.

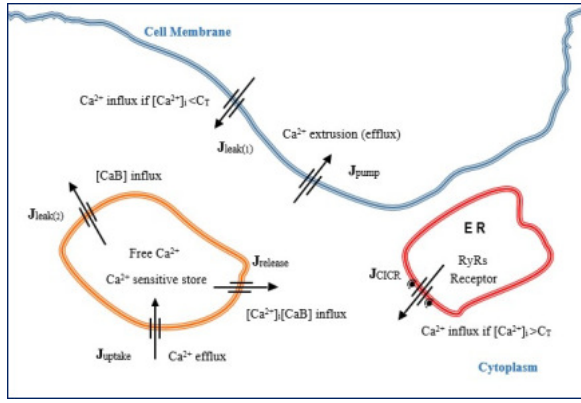


Figure 1: CICR mechanism operation in a two-pool model of a section of the dendritic cytoplasm.

Formally, **Fig.1** describes important processes and dynamics used to describe the two pool model of CICR, where $[Ca^{2+}]_i$ represents the free intracellular calcium concentration; $[CaB]$ is the concentration of bound buffer to Ca^{2+} ; RyR are the Ryanodine receptors which are essentially calcium-gated ion channels located along the ER that take part in releasing Ca^{2+} into the cytoplasm of the dendrite; J_{pump} denotes Ca^{2+} pump responsible for calcium efflux out of the cytoplasm via a molecular energy based process involving Adenosine Triphosphate (ATP); J_{CICR} represents the calcium puffs/sparks released into the cytoplasm through the activation of RyRs along the ER when $[Ca^{2+}]_i > C_T$ where C_T is some threshold Ca^{2+} level for calcium puffs to occur; J_{uptake} denotes Ca^{2+} efflux from cytoplasm into the Ca^{2+} sensitive pool; $J_{release}$ is influx of free Ca^{2+} and Ca^{2+} bound to the buffer from the Ca^{2+} sensitive pool into the cytoplasm; $J_{leak(1)}$ is Ca^{2+} influx into the cytoplasm through Ca^{2+} -dependent ionic channels; $J_{leak(2)}$ is influx of Ca^{2+} bound from the Ca^{2+} sensitive pool into the cytoplasm.

From **Fig. 1**, there are two pools inside the cytoplasm. The first pool (orange circle) represents the calcium buffer and the second (red circle) is the pool representing the endoplasmic reticulum (ER). As the dendrites intracellular $[Ca^{2+}]_i$ increases, so does release of free Ca^{2+} from the ER, a nonlinear calcium-dependent process where Ca^{2+} induces its own further release; this autocatalytic amplification is called calcium-induced calcium release (CICR).

By taking into consideration the processes presented in **Fig. 1**, we begin to formulate our model system by considering the release of Ca^{2+} from intracellular sources, in particular the ER via CICR mechanism. The dynamics involve interactions with an internal buffer and Ca^{2+} extrusion processes. The starting point of the model is to allow one to investigate dynamic changes to Ca^{2+} -dependent excitability, the spatial diffusion dynamics of Ca^{2+} -signalling, and the impact of a buffer on Ca^{2+} spatial dynamics. For simplicity, we will assume the diffusion of both calcium and a single buffer species where Fick's law applies to a 1D cable structure where the dynamics of Ca^{2+} diffusion is given by

$$\frac{\partial [Ca^{2+}]_i}{\partial t} = D_{Ca} \frac{\partial^2 [Ca^{2+}]_i}{\partial x^2} - \text{Buffer} + J_{leak} - P([Ca^{2+}]_i) + \sum_{j=1}^N v_{CICR}^j H([Ca^{2+}]_i - C_T) \delta(x - x_j)$$

where x is the physical position along the cable of (cm), t is the time in (sec), D_{Ca} is the diffusion constant of free calcium ($\mu m^2/sec$), "Buffer" represents the calcium buffer, J_{leak} is the leak Ca^{2+} influx, $P([Ca^{2+}]_i)$ represents a calcium pump that describes the removal of calcium ions (in order to maintain Ca^{2+} homeostasis) through an ATP-driven Ca^{2+} extrusion system, v_{CICR} denotes the calcium current density through RyR channels ($\mu M/sec$), H is the Heaviside step-function, C_T is the RyR activation threshold (μM) required to generate a calcium puff/spark, and δ is the Dirac delta function (whose dimensions are the inverse of its argument). The final term describes the Ca^{2+} -dependent activation of RyR in the ER which lead to an increase in cytosolic calcium via CICR release from the ER, when the calcium concentration exceeds a threshold C_T . Note that this process is nonlinear where the shape of the Ca^{2+} input in time describes by what is called a spark/puff, whose duration can vary depending on the local dynamics of Ca^{2+} , individually modelled as square pulse whose time duration can vary between release events in a Ca^{2+} -dependent manner.

For the buffer, the rate which it binds to calcium is proportional to the $[Ca^{2+}]_i$ and the free buffer concentrations. The buffer also dissociates from Ca^{2+} at a rate proportional to the concentration of

the complex. This allows one to write down the corresponding buffer dynamics as:

$$\frac{\partial[CaM]}{\partial t} = D_{CaM} \frac{\partial^2[CaM]}{\partial x^2} - b[CaM] + f([B]_{TOTAL} - [CaM])[Ca^{2+}]_i,$$

where f and b are the forward and backward reaction rates with units $\mu M^{-1} msec^{-1}$ and $msec^{-1}$, respectively, D_{CaM} is the diffusion constant for the calcium bound buffer with units $\mu m^2/sec$, and $[B]_{TOTAL} = [CaM] + [M]$ is the total concentration of calcium bound $[CaM]$ and unbound $[M]$ buffer, respectively.

The extrusion of calcium occurs through high affinity and low capacity ATP-operated Ca^{2+} pumps, which are assumed to be homogeneously distributed over the dendritic membrane, and whose dynamics follows the following Hill-type expression:

$$P([Ca^{2+}]_i) = \frac{4P_m}{d} K_P \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_P},$$

where P_m is the membrane pump parameter (m/sec), K_P (μM) is the pump dissociation constant and the $4/d$ is the area-to-volume ratio for a cable of diameter d (cm). Now assuming Ca^{2+} concentration is much lower than the pump dissociation constant K_P , this is a reasonable approximation. If a high mobile buffer concentration is present, permitting these homogeneously distributed pumps over the dendrite membrane to extrude endogenous Ca^{2+} in a linear manner. This linear behaviour can be deduced and follows the following Hill-type expression:

$$\lim_{[Ca^{2+}]_i \ll K_P} P([Ca^{2+}]_i) \rightarrow \gamma[Ca^{2+}]_i.$$

This has become known as the excess buffer approximation (EBA), where the assumption of unsaturability of the Ca^{2+} buffer is likely to be valid for low Ca^{2+} concentrations or when there is an excess of available buffer.

Under these conditions, the spatiotemporal dynamics of calcium diffusion within dendrites can be

rewritten as

$$\begin{aligned} \frac{\partial[Ca^{2+}]_i}{\partial t} &= D_{Ca} \frac{\partial^2[Ca^{2+}]_i}{\partial x^2} - (\gamma + f[B]_{TOTAL})[Ca^{2+}]_i \\ &\quad + \frac{f[B]_{TOTAL}}{k_0}[CaM] \\ &\quad + \sum_{j=1}^N v_{CICR}^j H([Ca^{2+}]_i - C_T) \delta(x - x_j) \\ \frac{\partial[CaM]}{\partial t} &= D_{CaM} \frac{\partial^2[CaM]}{\partial x^2} - \frac{f[B]_{TOTAL}}{k_0}[CaM] \\ &\quad + f[B]_{TOTAL}[Ca^{2+}]_i. \end{aligned} \quad (1)$$

A solution to the above reaction-diffusion system can be expressed as an integral equation involving the Green's function:

$$\begin{aligned} [Ca^{2+}]_i(x, t) &= \int_0^L \int_0^t \sum_{j=1}^N v_{CICR}^j G_{Ca}(x, \zeta, t - s) \\ &\quad \times H([Ca^{2+}]_i(\zeta, s) - C_T) \delta(\zeta - x_j) ds d\zeta, \end{aligned}$$

where integrating over the spatial variable ζ leads to the following integral equation:

$$\begin{aligned} [Ca^{2+}]_i(x, t) &= \sum_{j=1}^N v_{CICR}^j \int_0^t G_{Ca}(x, x_j, t - s) \\ &\quad \times H([Ca^{2+}]_i(x_j, s) - C_T) ds \end{aligned} \quad (2)$$

The Green's function satisfies the following system of reaction-diffusion equations,

$$\begin{aligned} \frac{\partial[Ca^{2+}]_i}{\partial t} &= D_{Ca} \frac{\partial^2[Ca^{2+}]_i}{\partial x^2} - (\gamma + f[B]_{TOTAL})[Ca^{2+}]_i \\ &\quad + \frac{f[B]_{TOTAL}}{k_0}[CaM] \\ \frac{\partial[CaM]}{\partial t} &= D_{CaM} \frac{\partial^2[CaM]}{\partial x^2} - \frac{f[B]_{TOTAL}}{k_0}[CaM] \\ &\quad + f[B]_{TOTAL}[Ca^{2+}]_i. \end{aligned} \quad (3)$$

The Green's function for our coupled system of reaction-diffusion Eqn (3) are difficult to find, but can be obtained via the formal solutions presented in Hill (1981). These formal solutions have been obtained by uncoupling the system Eqn (3) using an affine mapping technique that involves a Green's function solution to a non-linear integro-partial differential equation of the Riccati type (see section 4, pages 132-157, Lions

(1971)). Hill presented a general procedure to obtain closed form representations to the solutions of a coupled linear reaction-diffusion system including the corresponding boundary conditions. The coupled system is formally reduced to two boundary value problems involving the classical heat equation, whose solutions are given in terms of integrals involving the Green's function of the heat equation. Note that Hill (1981) illustrated that this method can also be applied to systems of non-homogeneous reaction-diffusion systems.

The formal solutions for the Green's functions for the system of reaction-diffusion equations given by Eqn (3) are

$$G_{Ca}(x, x_j, t) = e^{-at} \mathcal{G}_{Ca}(x, x_j, D_{Ca}t) + \frac{e^{\lambda t}}{D_{Ca} - D_{CaM}} \int_{D_{CaM}t}^{D_{Ca}t} e^{-\mu\xi} \times \left\{ \sqrt{bc} \left(\frac{\xi - D_{CaM}t}{D_{Ca}t - \xi} \right)^{\frac{1}{2}} I_1(\eta) \mathcal{G}_{Ca}(x, x_j, \xi) + bI_0(\eta) \mathcal{G}_{CaM}(x, x_j, \xi) \right\} d\xi, \quad (4)$$

$$G_{CaM}(x, x_j, t) = e^{-dt} \mathcal{G}_{CaM}(x, x_j, D_{CaM}t) + \frac{e^{\lambda t}}{D_{Ca} - D_{CaM}} \int_{D_{CaM}t}^{D_{Ca}t} e^{-\mu\xi} \times \left\{ \sqrt{bc} \left(\frac{D_{Ca}t - \xi}{\xi - D_{CaM}t} \right)^{\frac{1}{2}} I_1(\eta) \mathcal{G}_{CaM}(x, x_j, \xi) + cI_0(\eta) \mathcal{G}_{Ca}(x, x_j, \xi) \right\} d\xi, \quad (5)$$

where the constants are given by

$$a = (\gamma + f[B]_{TOTAL}), \quad b = \frac{f[B]_{TOTAL}}{k_0} \\ c = f[B]_{TOTAL}, \quad d = \frac{f[B]_{TOTAL}}{k_0} \\ \lambda = \left(\frac{aD_{CaM} - dD_{Ca}}{D_{Ca} - D_{CaM}} \right), \quad \mu = \left(\frac{a - d}{D_{Ca} - D_{CaM}} \right), \\ \eta = \frac{2\sqrt{bc}}{D_{Ca} - D_{CaM}} [(D_{Ca}t - \xi)(\xi - D_{CaM}t)]^{\frac{1}{2}},$$

and I_0 and I_1 are the modified Bessel functions. Note the $\mathcal{G}_{Ca}$ and $\mathcal{G}_{CaM}$ are the Green's function

solutions to their corresponding heat equations

$$\frac{\partial \mathcal{G}_{Ca}}{\partial t}(x, x_j, t) = \frac{\partial^2 \mathcal{G}_{Ca}}{\partial x^2}(x, x_j, t) \quad (6)$$

and

$$\frac{\partial \mathcal{G}_{CaM}}{\partial t}(x, x_1, t) = \frac{\partial^2 \mathcal{G}_{CaM}}{\partial x^2}(x, x_1, t). \quad (7)$$

One can calculate the corresponding solutions for Eqns (6) and (7) via Laplace transform techniques to arrive at the following expressions for $\mathcal{G}_{Ca}$ and $\mathcal{G}_{CaM}$ (see Appendix).

Having determined $\mathcal{G}_{Ca}(x, x_j, t)$ and $\mathcal{G}_{CaM}(x, x_1, t)$, one can now focus on developing an efficient solution for the formal solutions of $G_{Ca}(x, x_j, t)$ and $G_{CaM}(x, x_1, t)$, respectively. Closer inspection of the formal solutions given by Eqns (4) & (5), one notices that it involves a mathematical form with some similarity to a convolution integral. This can be better seen by applying the following transformation of variables,

$$\xi = D_{CaM}t + (D_{Ca} - D_{CaM})\tau$$

This allows Eqns (4) and (5) to be rewritten as

$$G_{Ca}(x, x_j, t) = e^{-at} \mathcal{G}_{Ca}(x, x_j, D_{Ca}t) + e^{(\lambda - \mu b_1)t} \int_0^t e^{-\mu b_2 \tau} \times \left\{ \sqrt{bc} \left(\frac{\tau}{t - \tau} \right)^{\frac{1}{2}} I_1(\eta) \mathcal{G}_{Ca}(x, x_j, b_1t + b_2\tau) + bI_0(\eta) \mathcal{G}_{CaM}(x, x_j, b_1t + b_2\tau) \right\} d\tau, \quad (8)$$

$$G_{CaM}(x, x_j, t) = e^{-dt} \mathcal{G}_{CaM}(x, x_j, D_{CaM}t) + e^{(\lambda - \mu b_1)t} \int_0^t e^{-\mu b_2 \tau} \times \left\{ \sqrt{bc} \left(\frac{t - \tau}{\tau} \right)^{\frac{1}{2}} I_1(\eta) \mathcal{G}_{CaM}(x, x_j, b_1t + b_2\tau) + cI_0(\eta) \mathcal{G}_{Ca}(x, x_j, b_1t + b_2\tau) \right\} d\tau, \quad (9)$$

where $b_1 = D_{CaM}$, $b_2 = D_{Ca} - D_{CaM}$, and $\eta = 2\sqrt{bc}[\tau(t - \tau)]^{\frac{1}{2}}$

Observation of Eqns (8) and (9) highlights that the integral parts represent a generalized convolution

and show some similarity to the traditional convolution integral and to some extent are also dependent on non-euclidean/deformed warping involving two time variables. Furthermore, the reader should not that the argument appearing in the modified Bessel functions strictly does not resemble convolution, but a higher-order nonlinear temporal dependence. Unfortunately, there are no closed-form solutions to the aforementioned equations thus these integrals need to be calculated numerically. Given this fact, there is a potential approximation which can be employed that may permit a obtaining a closed-form expression for the corresponding approximation. Note that in both Eqns (8) and (9) one can perform a Taylor expansion of the corresponding Green's functions $\mathcal{G}_{CaM}(x, x_j, b_1 t + b_2 \tau)$ and $\mathcal{G}_{CaM}(x, x_j, b_1 t + b_2 \tau)$. This leads to the integral component of Eqn (8) to be expressed as,

$$\int_0^t e^{-\mu b_2 \tau} \times \left\{ \sqrt{bc} \left(\frac{\tau}{t-\tau} \right)^{\frac{1}{2}} I_1(\eta) \times \sum_{n=0}^{\infty} \frac{(b_1 t)^n}{n!} \frac{\partial^n \mathcal{G}_{Ca}}{\partial \tau^n}(x, x_j, b_2 \tau) + b I_0(\eta) \sum_{n=0}^{\infty} \frac{(b_1 t)^n}{n!} \frac{\partial^n \mathcal{G}_{CaM}}{\partial \tau^n}(x, x_j, b_2 \tau) \right\} d\tau,$$

noting that the expression for the integral component of Eqn (9) takes the following similar form

$$\int_0^t e^{-\mu b_2 \tau} \times \left\{ \sqrt{bc} \left(\frac{t-\tau}{\tau} \right)^{\frac{1}{2}} I_1(\eta) \times \sum_{n=0}^{\infty} \frac{(b_1 t)^n}{n!} \frac{\partial^n \mathcal{G}_{CaM}}{\partial \tau^n}(x, x_j, b_2 \tau) + b I_0(\eta) \sum_{n=0}^{\infty} \frac{(b_1 t)^n}{n!} \frac{\partial^n \mathcal{G}_{Ca}}{\partial \tau^n}(x, x_j, b_2 \tau) \right\} d\tau,$$

Now keeping the first terms in both Eqns (8) and (9),

$$\int_0^t e^{-\mu b_2 \tau} \times \left\{ \sqrt{bc} \left(\frac{\tau}{t-\tau} \right)^{\frac{1}{2}} I_1(\eta) \mathcal{G}_{Ca}(x, x_j, b_2 \tau) + b I_0(\eta) \mathcal{G}_{CaM}(x, x_j, b_2 \tau) \right\} d\tau,$$

and

$$\int_0^t e^{-\mu b_2 \tau} \left\{ \sqrt{bc} \left(\frac{t-\tau}{\tau} \right)^{\frac{1}{2}} I_1(\eta) \mathcal{G}_{CaM}(x, x_j, b_2 \tau) + b I_0(\eta) \mathcal{G}_{Ca}(x, x_j, b_2 \tau) \right\} d\tau.$$

then from this truncated series, a closed-form expression could be obtained for $\mathcal{G}_{CaM}(x, x_j, t)$ by using the following identity,

$$\mathcal{L} \left[\int_0^t \left(\frac{t-\tau}{\tau} \right)^{\frac{\nu}{2}} I_{\nu} \left(a \sqrt{\tau(t-\tau)} \right) f(\tau) d\tau \right] = \left(\frac{a}{2} \right)^{\nu} s^{-(\nu+1)} F \left(s - \frac{a^2}{4s} \right),$$

where $f(\tau) = e^{-\mu(D_{Ca}-D_{CaM})\tau} \mathcal{G}_{CaM}(x, x_j, b_2 \tau)$ or $f(\tau) = e^{-\mu(D_{Ca}-D_{CaM})\tau} \mathcal{G}_{Ca}(x, x_j, b_2 \tau)$ where appropriate, however a closed form expression for the truncated series for $\mathcal{G}_{Ca}(x, x_j, t)$

$$\int_0^t \left(\frac{t-\tau}{\tau} \right)^{\frac{\nu}{2}} I_{\nu} \left(a \sqrt{\tau(t-\tau)} \right) f(\tau) d\tau$$

could be calculated analytically, involving a series representation of the I_{ν} resulting in an infinite series that may not be represented by a closed-form expression, and thus leads to serious concerns about computation and accuracy. In this case it is preferable to apply numerical techniques to calculate the generalized integral directly.

3. Results

In order to proceed, the resulting Green's functions, $\mathcal{G}_{Ca}(x, x_j, t)$ and $\mathcal{G}_{CaM}(x, x_j, t)$ are calculated using MATLAB's inbuilt integral function. In **Fig. 2**, some examples of these Green's functions are presented at various locations, keeping in mind that these represent the zeroth order for the calcium $[Ca^{2+}]_i$ and buffer $[CaM]$ concentrations, respectively.

3.1. Support for saltatory calcium waves

To explore the properties of saltatory waves and the conditions that support this, one needs to observe how the spacing between RyR and their respective activation times impacts wave propagation. Here, our calcium system presented in Eqn (1) describes the evolution of calcium through the assumption that $[Ca^{2+}]_i$ is continuously removed while being

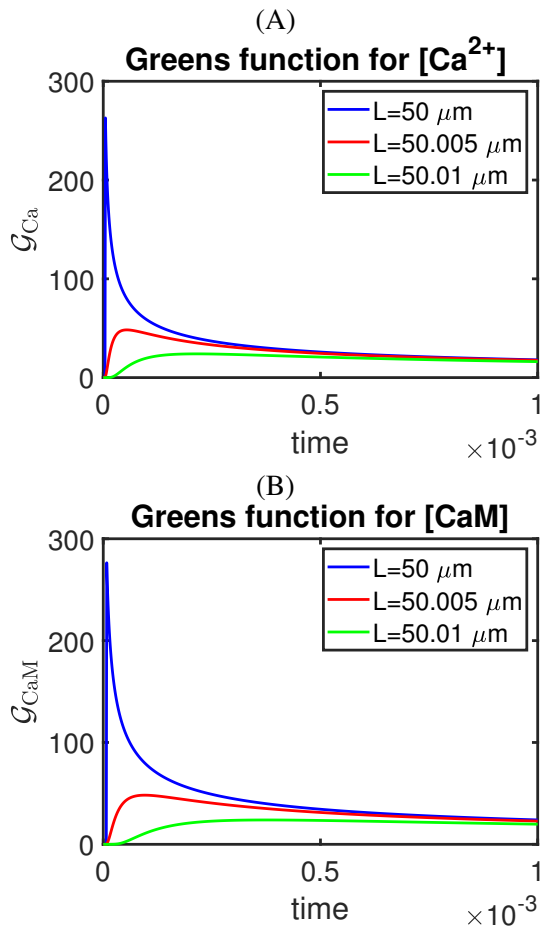


Figure 2: Example plots of the Green's function associated with (A) calcium $\mathcal{G}_{Ca}(x, x_j, t)$ and the (B) calcium buffer $\mathcal{G}_{CaM}(x, x_j, t)$ taken at three different distances from a specific source location $x_j = 0.5l$

released from discrete sites where the RyR in the presence of a buffer. Noting that calcium release from the RyRs are calcium dependent and occurs when $[Ca^{2+}]_i$ reaches some threshold value C_T at some release site and instantaneously releases a discrete amount of $[Ca^{2+}]$ into the cytosol of the dendrite. This mechanism permits the propagation of a $[Ca^{2+}]$ wave through the sequential puffs coming from the firing of RyR release sites, each responding to $[Ca^{2+}]$ diffusing from nearby RyR release sites, along the direction of the travelling wave, that can support saltatory propagation and hence the timing of these events is important for its propagation, resembling a *fire-diffuse-fire* process.

Noting that the integral equation, represented by Eqn (2), describes $[Ca^{2+}]$ evolution through the action of the system's Green's function and the discrete, yet $[Ca^{2+}]$ -dependent CICR via the RyRs at

specific times t_j . One can apply a useful approximation to Eqn (2) by assuming these puff release events can be modelled by delta functions, Eqn (2) can be expressed as

$$[Ca^{2+}]_i(x, t) = \int_0^t \sum_{j=1}^N v_{CICR}^j G_{Ca}(x, x_j, t-s) \times H([Ca^{2+}]_i(x_j, s) - C_T) \delta(s - t_j) ds,$$

Now let's consider that the location of RyR are equally spaced along the ER with a distance between these release sites of Δx , thus

$$[Ca^{2+}]_i(x, t) = \sum_{j=1}^N v_{CICR}^j G_{Ca}(x, x_j, t - t_j) \times H([Ca^{2+}]_i(x_j, t_j) - C_T).$$

Here, t_j is the time where $[Ca^{2+}]$ at position x_j first reaches the threshold value of C_T at the j^{th} RyR release site. When this occurs, the j^{th} site releases a calcium puff of size v_{CICR}^j , where the dependence of the j^{th} depends on the evolution of $[Ca^{2+}]$ concentration, and for a single puff from site j the calcium profile is given by the Green's function $\mathcal{G}_{Ca}(x, x_j, t)$,

$$[Ca^{2+}]_i^j(x, t) = v_{CICR}^j G_{Ca}(x, x_j, t - t_j) H(t - t_j),$$

where H is the Heaviside step function and noting that $G_{Ca}(x, x_j, t - t_j) H(t - t_j)$ is the solution to our reaction-diffusion system for an impulse input at $x = x_j$ at $t = t_j$ (Hill, 1981). Superimposing the contribution from each site, we arrive at

$$[Ca^{2+}]_i(x, t) = \sum_{j=1}^N v_{CICR}^j G_{Ca}(x, x_j, t - t_j) H(t - t_j),$$

noting that calcium concentration $[Ca^{2+}]_i$ is not a continuous function of time t at any release site x_j . Let's consider that the amount of $[Ca^{2+}]$ released at sites $j = M, M-1, \dots$ was identical and small, namely $v_{CICR}^j = v_{CICR}$ and whose activation times were known and consistent $t_M > t_{M-1} > \dots$. Now the next release event at time t_{M+1} at x_{M+1} occurs when $[Ca^{2+}]_i$ at x_{M+1} first reaches threshold C_T , that is,

$$[Ca^{2+}]_i((M+1)\Delta x, t_{M+1}^-) = C_T, \\ \frac{\partial}{\partial t} [Ca^{2+}]_i((M+1)\Delta x, t_{M+1}^-) > 0.$$

Now, t_{M+1} must satisfies

$$C_T = \sum_{j \leq M} \nu_{\text{CICR}} G_{\text{Ca}}(x_{M+1}, x_M, t_{M+1} - t_M).$$

Now for a wave to propagate corresponds to the situation of having $t_j - t_{j-1} = \tau$, where τ is a constant for all release sites j , that is, each site releases a $[Ca^{2+}]$ puff at a fixed time after the preceding release site had released a puff. Therefore a propagating solution exist when $t_{M+1} - t_j = \tau(M+1-j)$, and τ is a solution to the following equation satisfying,

$$\begin{aligned} \frac{C_T}{\nu_{\text{CICR}}} &= \sum_{j \leq M} G_{\text{Ca}}((M+1)\Delta x, j\Delta x, \tau(M+1-j)), \\ &\equiv \sum_{m=1}^N \bar{G}_{\text{Ca}}(\Delta x, m, \tau) \equiv \bar{\mathcal{G}}(m, \Delta x, \tau, N), \end{aligned}$$

where $\bar{G}_{\text{Ca}}(\Delta x, m, \tau)$ is given by

$$\begin{aligned} \bar{G}_{\text{Ca}}(\Delta x, m, \tau) &= e^{-a\tau m} \mathcal{G}_{\text{Ca}}((M+1)\Delta x, j\Delta x, D_{\text{Ca}}\tau m) \\ &+ e^{(\lambda - \mu b_1)\tau m} \int_0^{\tau m} e^{-\mu b_2 \rho} \\ &\times \left\{ \sqrt{bc} \left(\frac{\rho}{\tau m - \rho} \right)^{\frac{1}{2}} I_1(\eta) \right. \\ &\times \mathcal{G}_{\text{Ca}}((M+1)\Delta x, j\Delta x, b_1\tau m + b_2\rho) \\ &\left. + bI_0(\eta) \mathcal{G}_{\text{CaM}}((M+1)\Delta x, j\Delta x, b_1\tau m + b_2\rho) \right\} d\rho, \end{aligned}$$

$$\begin{aligned} \bar{G}_{\text{Ca}}(\Delta x, m, \tau) &= e^{-a\tau m} \mathcal{G}^*_{\text{Ca}}(m\Delta x, D_{\text{Ca}}\tau m) \\ &+ e^{(\lambda - \mu b_1)\tau m} \int_0^{\tau m} e^{-\mu b_2 \rho} \\ &\times \left\{ \sqrt{bc} \left(\frac{\rho}{\tau m - \rho} \right)^{\frac{1}{2}} I_1(\eta) \right. \\ &\times \mathcal{G}^*_{\text{Ca}}(m\Delta x, b_1\tau m + b_2\rho) \\ &\left. + bI_0(\eta) \mathcal{G}^*_{\text{CaM}}(m\Delta x, b_1\tau m + b_2\rho) \right\} d\rho, \end{aligned}$$

where $\eta = 2\sqrt{bc}[\rho(\tau m - \rho)]^{1/2}$, $m = (M+1) - j$

$$\begin{aligned} \mathcal{G}_{\text{Ca}}((M+1)\Delta x, j\Delta x, b_1\tau m + b_2\rho) \\ &= \mathcal{G}^*_{\text{Ca}}((M+1) - j)\Delta x, b_1\tau m + b_2\rho \\ &= \mathcal{G}^*_{\text{Ca}}(m\Delta x, b_1\tau m + b_2\rho), \end{aligned}$$

where $\mathcal{G}^*_{\text{Ca}}(m\Delta x, b_1\tau m + b_2\rho)$ is expressed in terms of the form

$$\begin{aligned} \mathcal{G}^*_{\text{Ca}}(m\Delta x, \tau m) \\ &= \frac{1}{\sqrt{4\pi\tau m}} \left[e^{(m-2nN)^2\Delta x^2/(4\tau m)} + \text{similar terms} \right] \end{aligned}$$

Fig. 2 is a plot of $\bar{\mathcal{G}}(m, \Delta x, \tau, N)$, where we have used the parameters listed in Table 1 (see Appendix).

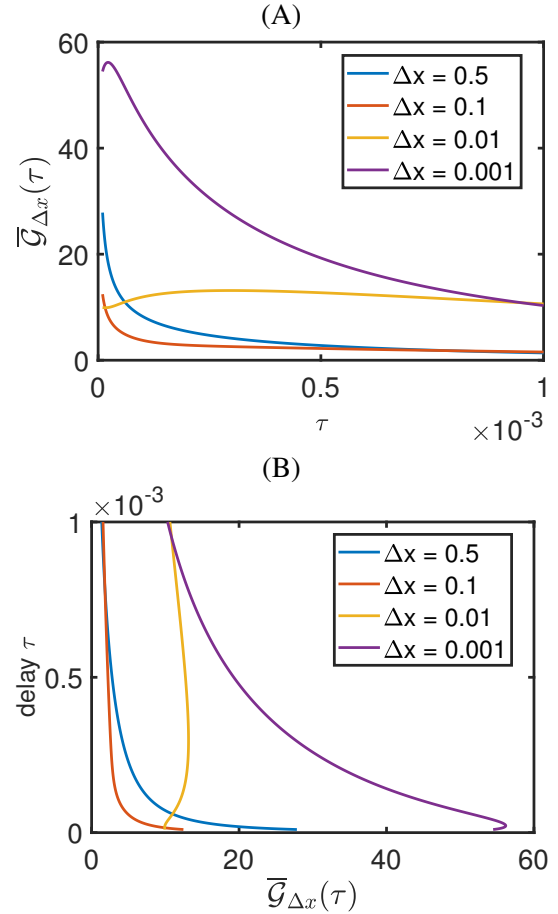


Figure 3: Plots of (A) $\bar{\mathcal{G}}_{\Delta x}(\tau)$ and the delay (B) τ for several values of Δx . Note that some of profiles in (A) are monotonically decreasing but the others have maximal values.

The plots of **Fig. 3A** are presented for several values of Δx , in particular, for some values of Δx , the function $\bar{\mathcal{G}}_{\Delta x}(\tau)$ is not monotone increasing, but has a maximal $\bar{\mathcal{G}}_{\Delta x}$ value, say $\bar{\mathcal{G}}_{\text{max}}(\Delta x)$, which is a concave function of Δx (data not shown). Note that, $\bar{\mathcal{G}}_{\Delta x}(\tau) \rightarrow \beta$, where β has some finite value as $\tau \rightarrow 0$, but $\bar{\mathcal{G}}_{\Delta x}(\tau) \rightarrow 0$ as $\tau \rightarrow \infty$. Now for the condition that $C_T/\nu_{\text{CICR}} > \bar{\mathcal{G}}_{\text{max}}(\Delta x)$ then propagation failure

is expected, but if $C_T/\nu_{\text{CICR}} < \bar{\mathcal{G}}_{\text{max}}(\Delta x)$, then a physical solution is expected, corresponding to the time when $[Ca^{2+}]$ first crosses the threshold C_T .

For larger values of τ , the function $\bar{\mathcal{G}}_{\text{max}}(\Delta x)$ has a concave profile (data not shown) and potentially agrees with the function $\exp(-\Delta x)$. This gives us an approximate criterion for propagation failure, that is when $C_T/\nu_{\text{CICR}} > \exp(-\Delta x)$, the saltatory wave fails to propagate, but keeping in mind that both calcium and buffer diffusion constants influence this criterion.

For **Fig. (3B)**, we have plotted the delay τ as a function of C_T/ν_{CICR} ($\bar{\mathcal{G}}_{\Delta x}(\tau)$) by reversing the axes in **Fig. 3A**. Note that with $\tau \neq 0$ one expects the propagation of the wave to fail at some positive velocity. Thus, when the distance between release sites, or the threshold is too large, or the amount of ν_{CICR} calcium released is not sufficient, then propagation fails.

In **Fig. 4**, we have plotted the buffer function $\bar{\mathcal{H}}_{\Delta x}(\tau)$ and its corresponding delay τ in a similar manner as $\bar{\mathcal{G}}_{\Delta x}(\tau)$ using the constants presented in Table1 (see Appendix). Here, in **Fig. 4A** presents curves that monotonically increasing, where each tend towards some maximum or finite asymptotic value. The plots from **Fig. 3-4**, are also indicating the potential for saltatory buffer waves could be present while calcium waves have failed.

4. Discussion

Analytical solutions of reaction-diffusion systems have not attracted as much attention due to the difficulty in solving such systems, especially when there are nonlinearities present; in favour of numerical approaches based on sacrificing continuity with a chain of discrete isopotential compartments connected to each other like a chain (D'Angelo & Jirsa, 2022; Neymotin et al., 2015). These compartments are a consequence of the discretization process applied to reaction-diffusion systems resulting in an approximation based on connected isopotential compartments, that facilitates the reaction-diffusion system to be recast into a system of ordinary differential equations, permitting numerical solutions to be calculated. Over the preceding decades, this has been the tool of choice, where biological realism is typically associated with morphologically detailed

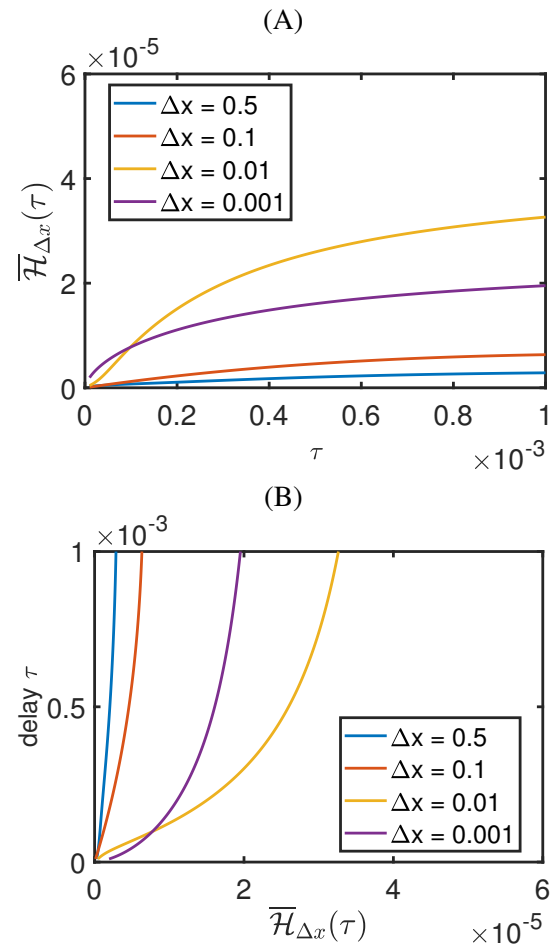


Figure 4: Plots of (A) $\bar{\mathcal{H}}_{\Delta x}(\tau)$ and the delay (B) τ for several values of Δx . Note that some of profiles in (A) are monotonically decreasing but the others have maximal values.

compartmental models (Bhalla, 2012; Bower & Beeman, 1998; Hines & Carnevale, 1997; Holmes & Rall, 1992; Kobayashi et al., 2021; Lindsay et al., 2007).

Here, we have returned to investigate the question of finding analytical solutions of reaction-diffusion systems and its importance for the underlying reaction-diffusion dynamics of the calcium system. Hill's solution (Hill, 1981) is a notable example to explore, although derived as a formal solution we have developed simulations using Hill's equation, but this required numerical integration to evaluate the generalized convolution appearing the Eqns (8) and (9). Unfortunately, an analytical solution was currently not possible to derive, although we have provided some interesting avenues that need to be studied. We have also taken the first steps to investigate the conditions for

supporting the propagation of saltatory waves. We adapted the method presented in Keener (2000); Keener & Sneyd (1998); Keizer et al. (1998) to use Hill's solution Hill (1981) and observed the same qualitative trends compared to these older studies where the distance between RyR release sites decreases supports the propagation of the saltatory wave.

In future, various analysis techniques, including homogenization and analysis of travelling waves need to be applied in a way that explicitly includes buffer dynamics, in order to better understand how the reaction-diffusion dynamics of calcium and buffers influence each other in general and when waves have been generated. This provides insights into the general behaviour and dynamics of such (reaction-diffusion) systems when describing the dynamics and processes involved with the introduction of proteins to the intracellular domain of dendrites and how these can be used to understand experimental procedures and the observed results, as well as how the spatiotemporal nature of these injected proteins impacts neural responses, including their influence on relevant cellular processes such as synaptic plasticity.

Conflicts of interest:

The authors declare no conflict of interest.

Appendix

Here, the solutions to the corresponding heat equations for both calcium and the calcium buffer are presented, where the Green's function for calcium $\mathcal{G}_{Ca}(x, x_j, t)$ and the calcium buffer $\mathcal{G}_{CaM}(x, x_j, t)$ are given by the solution to the following boundary value problem:

$$\begin{aligned} \frac{\partial \mathcal{G}_{Ca}}{\partial t}(x, x_j, t) &= \\ \frac{\partial^2 \mathcal{G}_{Ca}}{\partial x^2}(x, x_j, t) + \delta(x - x_j)\delta(t - t_i) & \quad \text{for } t \geq t_i \\ \frac{\partial \mathcal{G}_{Ca}}{\partial x}(0, 0, t) = \frac{\partial \mathcal{G}_{Ca}}{\partial x}(\ell, \ell, t) &= 0 \\ \text{and} \\ \frac{\partial \mathcal{G}_{CaM}}{\partial t}(x, x_1, t) &= \\ \frac{\partial^2 \mathcal{G}_{CaM}}{\partial x^2}(x, x_1, t) + \delta(x - x_1)\delta(t - t_k) & \quad \text{for } t \geq t_k \end{aligned}$$

$$\frac{\partial \mathcal{G}_{CaM}}{\partial x}(0, 0, t) = \frac{\partial \mathcal{G}_{CaM}}{\partial x}(\ell, \ell, t) = 0,$$

where the length of the cable is ℓ , with sealed-end boundary conditions at both ends subject to impulse inputs at point x_j along the cable. One can solve these equations using either separation of variables (whose solution converges rapidly for large t) or Laplace transform methods whose solutions converge rapidly for all t .

There are two sort after solutions, one where there is an unit impulse at the boundary $x = 0$ and $t = 0$ and the other is where the impulse occurs at any position along the cable at $x = x_j$ at time $t = t_i$. The solution corresponding to the response to a unit impulse at $x = 0$ and $t = 0$. In the case for calcium $\mathcal{G}_{Ca}(x, 0, t)$ for a finite cable with a sealed-end boundary condition, $\frac{\partial \mathcal{G}_{Ca}}{\partial x}(0, 0, t) = -\delta(t)$ at $x = 0$ and a sealed-end condition $\frac{\partial \mathcal{G}_{Ca}}{\partial x}(\ell, 0, t) = 0$ at $x = \ell$, several representations for the Green's function converges for small t (Tuckwell, 1988) for this case, solving the case when the impulse occurs at the boundary $x = 0$ and the above mentioned boundary value for $x = 0$, the corresponding Green's functions $\mathcal{G}_{Ca}(x, 0, t)$ is

$$\begin{aligned} \mathcal{G}_{Ca}(x, 0; t) &= \frac{1}{\sqrt{4\pi t^3}} \sum_{n=0}^{\infty} (-1)^n \left\{ \right. \\ & [2(n+1)\ell - x] \exp\left(-\frac{[2(n+1)\ell - x]^2}{4t}\right) \\ & \left. + [2n\ell + x] \exp\left(-\frac{[2n\ell + x]^2}{4t}\right) \right\}, \\ & t > 0. \quad 0 < x < \ell \end{aligned}$$

Analogously, the corresponding Green's function for the buffer heat equation is $\mathcal{G}_{CaM}$ is given by

$$\begin{aligned} \mathcal{G}_{CaM}(x, 0; t) &= \frac{1}{\sqrt{4\pi t^3}} \sum_{n=0}^{\infty} (-1)^n \left\{ \right. \\ & [2(n+1)\ell - x] \exp\left(-\frac{[2(n+1)\ell - x]^2}{4t}\right) \\ & \left. + [2n\ell + x] \exp\left(-\frac{[2n\ell + x]^2}{4t}\right) \right\}, \\ & t > 0. \quad 0 < x < \ell. \end{aligned}$$

Now the Green's function for unit impulses occurring along the cable $\mathcal{G}_{Ca}(x, x_i; t - t_i)$ is the solution

to the following,

$$\begin{aligned} \frac{\partial \mathcal{G}_{Ca}}{\partial t}(x, x_i; t) = \\ \frac{\partial^2 \mathcal{G}_{Ca}}{\partial x^2}(x, x_i; t) + \delta(x - x_i)\delta(t - t_i), \quad t > t_i, \end{aligned}$$

with the following sealed-end boundary conditions at $x = 0$, $\frac{\partial \mathcal{G}_{Ca}}{\partial x}(0, x_i; t) = 0$ and at $x = \ell$ $\frac{\partial \mathcal{G}_{Ca}}{\partial x}(\ell, x_i, t) = 0$. Using these initial and boundary conditions and applying both Laplace and inverse Laplace transforms, and series expansions leads to

$$\begin{aligned} \mathcal{F}_{Ca}(x, x_i; t - t_i) = \\ \frac{1}{\sqrt{4\pi(t - t_i)}} \sum_{n=0}^{\infty} (-1)^n \left\{ \right. \\ \exp\left(-\frac{(x - x_i - 2n\ell)^2}{4(t - t_i)}\right) \\ + \exp\left(-\frac{(x + x_i + 2n\ell)^2}{4(t - t_i)}\right) \\ + \exp\left(-\frac{(x + x_i - 2(n+1)\ell)^2}{4(t - t_i)}\right) \\ \left. + \exp\left(-\frac{(x - x_i + 2(n+1)\ell)^2}{4(t - t_i)}\right) \right\} \\ \text{for } x < x_i \text{ and } t > t_i \end{aligned}$$

and

$$\begin{aligned} \mathcal{H}_{Ca}(x, x_i; t - t_i) = \\ \frac{1}{\sqrt{4\pi(t - t_i)}} \sum_{n=0}^{\infty} (-1)^n \left\{ \right. \\ \exp\left(-\frac{(x - x_i - 2n\ell)^2}{4(t - t_i)}\right) \\ + \exp\left(-\frac{(x + x_i + 2n\ell)^2}{4(t - t_i)}\right) \\ + \exp\left(-\frac{(x - x_i + 2n\ell)^2}{4(t - t_i)}\right) \\ - \exp\left(-\frac{(x - x_i - 2n\ell)^2}{4(t - t_i)}\right), \\ + \exp\left(-\frac{(x + x_i - 2(n+1)\ell)^2}{4(t - t_i)}\right) \\ + \exp\left(-\frac{(x - x_i + 2(n+1)\ell)^2}{4(t - t_i)}\right) \\ \left. + \exp\left(-\frac{(x - x_i + 2(n+1)\ell)^2}{4(t - t_i)}\right) \right\} \end{aligned}$$

$$\begin{aligned} - \exp\left(-\frac{(x - x_i - 2(n+1)\ell)^2}{4(t - t_i)}\right) \Bigg\}, \\ \text{for } x \geq x_i \text{ and } t > t_i. \end{aligned}$$

Combining the cases for $x < x_i$ and $x \geq x_i$ leads to the following Green's function,

$$\begin{aligned} \mathcal{G}_{Ca}(x, x_i; t - t_i) = \\ \left\{ \mathcal{F}_{Ca}(x, x_i; t - t_i)H(x_i - x) \right. \\ \left. + \mathcal{H}_{Ca}(x, x_i; t - t_i)H(x - x_i) \right\} H(t - t_i), \\ t > t_i, \quad 0 < x, x_i < \ell. \end{aligned}$$

Similarly for the calcium buffer, the corresponding Green's function is given by

$$\begin{aligned} \mathcal{G}_{CaM}(x, x_i; t - t_i) = \\ \left\{ \mathcal{F}_{CaM}(x, x_i; t - t_i)H(x_i - x) \right. \\ \left. + \mathcal{H}_{CaM}(x, x_i; t - t_i)H(x - x_i) \right\} H(t - t_i), \\ t > t_i, \quad 0 < x, x_i < \ell, \end{aligned}$$

where

$$\begin{aligned} \mathcal{F}_{CaM}(x, x_i; t - t_i) = \\ \frac{1}{\sqrt{4\pi(t - t_i)}} \sum_{n=0}^{\infty} (-1)^n \left\{ \right. \\ \exp\left(-\frac{(x - x_i - 2n\ell)^2}{4(t - t_i)}\right) \\ + \exp\left(-\frac{(x + x_i + 2n\ell)^2}{4(t - t_i)}\right) \\ + \exp\left(-\frac{(x + x_i - 2(n+1)\ell)^2}{4(t - t_i)}\right) \\ \left. + \exp\left(-\frac{(x - x_i + 2(n+1)\ell)^2}{4(t - t_i)}\right) \right\} \\ \text{for } x < x_i \text{ and } t > t_i \end{aligned}$$

and

$$\begin{aligned} \mathcal{H}_{CaM}(x, x_i; t - t_i) = \\ \frac{1}{\sqrt{4\pi(t - t_i)}} \sum_{n=0}^{\infty} (-1)^n \left\{ \right. \\ \exp\left(-\frac{(x - x_i - 2n\ell)^2}{4(t - t_i)}\right) \\ \left. \right\} \end{aligned}$$

Table 1: Table of constants

Notation	Description	Quantity
$[Ca^{2+}]_i$	Intracellular calcium concentration (μM) where $M = mol/L$	
$[Ca^{2+}]_o$	Extracellular calcium concentration at rest (μM)	$2000\mu M$
t	Time (msec)	
x	Physical distance along dendrite (μm)	
D_{Ca}	Diffusion constant of free calcium ($\mu m^2/msec$)	$0.23 \mu m^2/msec$
C_T	Channel activation threshold (μM)	$0.5 \mu M$
ν_{CICR}	Calcium source current density ($\mu M/msec$)	$0.0027 \mu M/msec$
P_m	Pump rate ($\mu m/msec$)	$0.2 \mu m/msec$
d	Diameter of dendrite (μm)	$2 \mu m$
$[B]_{TOTAL} = [CaM] + [M]$	Total concentration of calcium binding (μM)	$100 \mu M$
$[CaM]$	Concentration of bound buffer (μM)	
$[M]$	Concentration of unbound buffer (μM)	
f	Forward reaction rate ($\mu Mmsec$) ⁻¹	$0.320 (\mu M)^{-1}(msec)^{-1}$
b	Backward reaction rate ($msec$) ⁻¹	$0.06 (msec)^{-1}$
$K_D = b/f$	Dissociation constant (μM)	$0.20 (\mu M)$
D_{CaM}	Diffusion constant of buffered calcium ($\mu m^2/msec$)	$0.13 \mu m^2/msec$
$k_o = [B]_{TOTAL}/K_D$	Buffer capacity (dimensionless)	500
$\gamma = \frac{4P_m}{d}$	Constant parameter ($msec$) ⁻¹	$0.4 (msec)^{-1}$
ℓ	Physical length along the dendrite (μm)	$100 \mu m$
$\delta[\cdot]$	Dirac delta function (inverse dimension of its argument)	
$H[\cdot]$	Heaviside step-function (dimensionless)	
x_j	Position of calcium sources (μm)	
N	Number of calcium RyR hotspots (dimensionless)	$0-20$

$$\begin{aligned}
& + \exp\left(-\frac{(x + x_i + 2n\ell)^2}{4(t - t_i)}\right) \\
& + \exp\left(-\frac{(x - x_i + 2n\ell)^2}{4(t - t_i)}\right) \\
& - \exp\left(-\frac{(x - x_i - 2n\ell)^2}{4(t - t_i)}\right), \\
& + \exp\left(-\frac{(x + x_i - 2(n+1)\ell)^2}{4(t - t_i)}\right) \\
& + \exp\left(-\frac{(x - x_i + 2(n+1)\ell)^2}{4(t - t_i)}\right) \\
& + \exp\left(-\frac{(x - x_i + 2(n+1)\ell)^2}{4(t - t_i)}\right) \\
& - \exp\left(-\frac{(x - x_i - 2(n+1)\ell)^2}{4(t - t_i)}\right)\Bigg\},
\end{aligned}$$

for $x \geq x_i$ and $t > t_i$.

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