Fractional Cable Model for Signal Conduction in Spiny Neuronal Dendrites

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Abstract

The cable model is widely used in several fields of science to describe the propagation of signals. A relevant medical and biological example is the anomalous subdiffusion in spiny neuronal dendrites observed in several studies of the last decade. Anomalous subdiffusion can be modelled in several ways introducing some fractional component into the classical cable model. The Cauchy problem associated to these kind of models has been investigated by many authors, but up to our knowledge an explicit solution for the signalling problem has not yet been published. Here we propose how this solution can be derived applying the generalized convolution theorem (known as Efros theorem) for Laplace transforms.

The fractional cable model considered in this paper is defined by replacing the first order time derivative with a fractional derivative of order \( \alpha \in (0, 1) \) of Caputo type. The signalling problem is solved for any input function applied to the accessible end of a semi-infinite cable, which satisfies the requirements of the Efros theorem. The solutions corresponding to the simple cases of impulsive and step inputs are explicitly calculated in integral form containing Wright functions. Thanks to the variability of the parameter \( \alpha \), the corresponding solutions are expected to adapt to the qualitative behaviour of the membrane potential observed in experiments better than in the standard case \( \alpha = 1 \).

Keywords: Fractional cable equation, Sub-diffusion, Wright functions
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Introduction

The one dimensional cable equation has been used from a long time to describe the spatial and the temporal dependence of trans-membrane potential \( V_m(x, t) \) along the axial \( x \) direction of a cylindrical nerve cell segment. It can be derived directly from the Nernst-Planck equation for electro-diffusive motion of ions. The resulting differential equation for the trans-membrane potential takes the form of a standard diffusion equation with a shift:

\[
\lambda^2 \frac{\partial^2 V_m(x, t)}{\partial x^2} - \gamma \frac{\partial V_m(x, t)}{\partial t} - V_m(x, t) = 0, \quad (1)
\]
where $\lambda$ and $\gamma$ are space and time constants related to the membrane resistance and capacitance per unit length, see e.g. [10]. For simplicity in the rest of this work, following [10], we will use the dimensionless scaled variables $X = x/\lambda$ and $T = t/\gamma$, so that we consider the equation

$$\frac{\partial^2 V_m(X,T)}{\partial X^2} - \frac{\partial V_m(X,T)}{\partial T} - V_m(X,T) = 0.$$ (2)

In signalling problems the cable is considered of semi-infinite length ($0 \leq X < \infty$, initially quiescent for $T < 0$ and excited for $T \geq 0$ at the accessible end ($X = 0$) with a given input in membrane potential $V_m(0,T) = g(t)$. Fundamental problems are the cases of an impulsive input $g(t) = \delta(t)$ and of a unit step input $g(t) = \theta(t)$ where $\delta(t)$ and $\theta(t)$ denote the Dirac and the Heaviside functions, respectively. The solutions corresponding to these inputs read in our notation

$$G_s(X,T) = \frac{X}{\sqrt{4\pi T}} e^{-\left(\frac{X^2}{4T}+T\right)},$$ (3)

and

$$H_s(X,T) = \int_0^T G_s(X,T') dT'.$$ (4)

We refer to $G_s$ to as the fundamental solution or the Green function for the signalling problem of the (standard) cable equation (2), whereas to $H_s$ to as the step response. As known, the Green function is used in the time convolution integral to represent the solution corresponding to any given input $g(T)$ as follows

$$V_m(X,T) = \int_0^T g(T-T') G_s(X,T') dT'.$$ (5)

The spatial variance associated to this model is known to evolve linearly in time, while it has been observed that the spatial variance of an inert tracer in spiny Purkinje cell dendrites evolves as a sub-linear power law of time, as spines may trap and release diffusing molecules, and the diffusion with smaller values of the power exponent is associated to higher spine density [20].

To model anomalous sub-diffusion we substitute the first-order time derivative in Eq.(2) with a fractional time derivative of Caputo type [3], [17] of order $\alpha \in (0,1)$:

$$\frac{\partial^2 V_m(X,T)}{\partial X^2} - \frac{\partial^\alpha V_m(X,T)}{\partial T^\alpha} - V_m(X,T) = 0.$$ (6)

This kind of model is a simple extension to fractional behaviour of the Neuronal Cable Model from a mathematical point of view and it turns to be in some way equivalent to the equation developed in a relevant study [3], which has been derived from a modified Nernst-Planck equation, with diffusion constant replaced by fractional derivatives of Riemann-Liouville type. Other studies consider similar approaches [3], [7], [8], [9], [14]. We will see that beside the apparent simplicity our approach allows to reproduce at least qualitatively the main characteristics observed in experiments [15], [6], [2], [18]. Further generalizations of this model introducing a second fractional time derivative to the shift term could be analysed in future, to refine the biological relevance of the model.
Solution of the signalling problem

Applying the Laplace transform to Eq. (6) with the boundary conditions required by the signalling problem, that is $V_m(X,0^+) = 0$, $V_m(0,T) = g(T)$, we have:

$$(s^\alpha + 1)\bar{V}_m(X,s) - \frac{\partial^2 \bar{V}_m(X,s)}{\partial X^2} = 0,$$

which is a second order equation in the variable $X$ with solution:

$$\bar{V}_m(X,s) = \tilde{g}(s)e^{-\sqrt{(s^\alpha+1)}X}. \quad (8)$$

The inversion of the Laplace transform now requires special effort with respect to the case where the term $V_m(X,T)$ is not present in Eq. (6), that is for

$$\frac{\partial^2 V_m^*(X,T)}{\partial X^2} - \frac{\partial^\alpha V_m^*(X,T)}{\partial T^\alpha} = 0. \quad (9)$$

Indeed for Eq. (9), known as the time-fractional diffusion equation, the solutions of the corresponding Cauchy and signalling problems have been found in the 1990’s by Mainardi in terms of 2 auxiliary Wright functions \([11, 12]\). Specifically for the signalling problem the general solution provided by Mainardi in integral convolution form reads

$$V_m^*(X,T) = \int_0^T g(T-T') \mathcal{G}_{\alpha,s}^*(X,T') dT', \quad \mathcal{G}_{\alpha,s}^*(X,T) = \frac{1}{T} W_{-\alpha/2,0} \left(-X/T^{\alpha/2}\right), \quad (10)$$

where $\mathcal{G}_{\alpha,s}^*(X,T)$ denotes the Green function of the signalling problem of the fractional time diffusion equation (9) and $W_{-\alpha/2,0}(\cdot)$ is a particular case of the transcendental function known as Wright function

$$W_{\lambda,\mu}(z) := \sum_{n=0}^{\infty} \frac{z^n}{n! \Gamma[\lambda n + \mu]}, \quad \lambda > -1, \quad \mu \geq 0. \quad (11)$$

This function, entire in the complex plane, is extensively discussed in the Appendix F of Mainardi’s book \([13]\) where the interested reader can find the following relevant Laplace transform pairs, rigorously derived by Stanković \([19]\):

$$t^{\mu-1} W_{-\nu,\mu}(x/t^\nu) \div s^{-\mu} \exp(-xs^\nu), \quad 0 \leq \nu < 1, \quad \mu > 0. \quad (12)$$

Here we have adopted an obvious notation to denote the juxtaposition of a locally integrable function of time $t$ with its Laplace transform in $s$ with $x$ a positive parameter. It is worth to recall the distinction of the Wright functions in first type ($\lambda \geq 0$) and second type ($-1 < \lambda \leq 0$) and, among the latter ones, the relevance of the two auxiliary functions introduced in \([11]\):

$$F_\nu(z) = W_{-\nu,0}(-z), \quad M_\nu(z) = W_{-\nu,1-\nu}(-z), \quad 0 < \nu < 1, \quad (13)$$

inter-related as $F_\nu(z) = \nu z M_\nu(z)$. Indeed the relevance of both the Wright functions has been outlined by several authors in diffusion and stochastic processes. Particular attention is due to the $M$-Wright function (also referred to as the Mainardi function in \([17]\)) that, since for $\nu = 1/2$ reduces to $\exp(-z^2/4)/\sqrt{\pi},$
is considered a suitable generalization of the Gaussian density, see [16] and references therein.

Then the Green function for the signalling problem of the time fractional diffusion equation (9) can be written in the original form provided in [11] as

$$G_{\alpha,s}(X,T) = \frac{1}{T} F_{\alpha/2} \left( \frac{X}{T^{\alpha/2}} \right) = \frac{\alpha}{2} \frac{X}{T^{\alpha/2+1}} M_{\alpha/2} \left( \frac{X}{T^{\alpha/2}} \right),$$

(14)

where the superscript * is added to distinguish the time fractional diffusion equation from our fractional cable equation, both depending on the order $\alpha \in (0,1)$.

Because of the shift constant in the square root of the Laplace transform in Eq.(8), the inversion is no longer straightforward with the Wright functions as it is in the time fractional diffusion equation (9). Consequently, we have overcome this difficulty recurring to the application of the Efros theorem that generalizes the well known convolution theorem for Laplace transforms. For sake of convenience let us hereafter recall this theorem, usually not so well-known in the literature.

The Efros theorem [4] states that if we can write a Laplace transform $\tilde{f}(s)$ as:

$$\tilde{f}(s) = \phi(s) \cdot \tilde{F}(\psi(s)),$$

(15)

where the function $\tilde{F}(s)$ has a known inverse Laplace transform $F(T)$, the inverse Laplace transform is:

$$f(T) = \int_0^\infty F(\tau) G(\tau, T) d\tau$$

(16)

where:

$$G(\tau; T) = \tilde{G}(\tau, s) = \phi(s) e^{-\tau \psi(s)}$$

(17)

For the solution (8) of our signalling problem we thus have:

$$\phi(s) = \tilde{g}(s), \quad \psi(s) = s^\alpha,$$

(18)

and

$$\tilde{F}(s)|_{X} = e^{-X \sqrt{s + T}}.$$  

(19)

Then, having $\tilde{G}(\tau, s) = \tilde{g}(s) e^{-\tau s^\alpha}$, thanks to the standard convolution theorem of Laplace transforms, we obtain:

$$G(\tau, T) = \int_0^T \frac{g(T - T')}{T'} W_{-\alpha,0}(-\tau/T'^\alpha) dT'$$

(20)

where $W_{-\alpha,0}$ is the F-Wright function, and

$$F(T)|_{X} = \frac{X}{\sqrt{4\pi T^3}} e^{-\frac{x^2}{4T} + T}$$

(21)

is the solution (3) of the standard cable equation (2).

Then, the general solution of our signalling problem can be written in terms of known functions:

$$V_m(X, T) = \int_0^\infty \frac{X}{\sqrt{4\pi T^3}} e^{-\frac{X^2}{4T} + T} \left[ \int_0^T \frac{g(T - T')}{T'} W_{-\alpha,0}(-\tau/T'^\alpha) dT' \right] d\tau$$

$$= \int_0^T g(T - T') \left[ \int_0^\infty \frac{X}{\sqrt{4\pi T^3}} e^{-\frac{X^2}{4T'} + T'} \frac{1}{T'} W_{-\alpha,0}(-\tau/T'^\alpha) d\tau \right] dT'$$

(22)
Example 1: \( g(T) = \delta(T) \)

Substituting \( g(T) = \delta(T) \) in the general solution \(^{[2]}\) we obtain the Green function for the fractional model \(^{[6]}\):

\[
V_m(X,T) := G_{\alpha,s}(X,T) = \int_0^{\infty} G_s(X,\tau) \frac{1}{T} W_{-\alpha,0}(-\tau/T^\alpha) d\tau = \int_0^{\infty} G_s(X,\tau) \frac{1}{T} F_\alpha(\tau/T^\alpha) d\tau
\]

This solution is plotted versus \( X \) for \( T = 0.1 \) and \( T = 100 \) and versus \( T \) for \( X = 1 \) in Fig. 1.

Example 2: \( g(T) = \theta(T) \)

When \( g(T) = \theta(T) \) we obtain the step response of our fractional cable equation:

\[
V_m(X,T) := H_{\alpha,s}(X,T) = \int_0^{\infty} H_s(X,\tau) \cdot 1/T \cdot M_{\alpha}(\tau/T^\alpha) d\tau
\]

After some manipulations including the change of variable \( z = \tau/T^\alpha \) and integrating by parts after using the recurrence relation of Wright functions:

\[
\frac{dW_{\lambda,\mu}(z)}{dz} = W_{\lambda,\lambda+\mu}(z)
\]

and the relation between the auxiliary functions: \( F_\nu(z) = \nu z M_\nu(z) \) we may rewrite the step-response solution as:

\[
V_m(X,T) := H_{\alpha,s}(X,T) = \int_0^{\infty} H_s(X,\tau) \cdot 1/T \cdot M_{\alpha}(\tau/T^\alpha) d\tau
\]

This solution is plotted versus \( X \) for \( T = 1 \) and versus \( T \) for \( X = 1 \) in Fig. 2.
The plotted solutions were computed without any particular difficulty except the careful truncation of the series defining the auxiliary $F$ and $M$ functions in our routines.

**Biological interpretation**

Fractional cable models are used to describe subthreshold potentials, or passive potentials, associated to dendritic processes in neurons. The travelling potential is summed up at the soma and the cell produces an action potential when a threshold is exceeded.

It has been observed in [20] that diffusion results more anomalous, i.e. the fractional exponent $\alpha$ decreases, with increasing spine density. Decreasing spine density is characteristic of aging [6], [2], pathologies as neurological disorders [15] and Down's syndrome [18]. It has been suggested that increasing spine density should serve to compensate time delay of postsynaptic potentials along dendrites and to reduce their long time temporal attenuation [5].

Looking at our plotted solutions for the fractional cable equation short and long space and time behaviour can be distinguished about the evolution of the sub-diffusion process.

When an impulsive potential is applied at the accessible end it can be noted from Fig.1 that peak high decreases more rapidly with decreasing $\alpha$ at early times, vice versa is less suppressed at longer times, and the cross over time increases with decreasing $\alpha$. Looking at the potential versus time it can also be noted that potential functions associated to lower $\alpha$ last for longer time at appreciable intensity and arrive faster at early times with respect to the normal diffusion case.

By the way, when a constant potential is applied at the accessible end we note from Fig.2 that the exponential suppression of the potential along the dendrite is reduced for high $X$ values with respect to normal diffusion. Instead for small $X$ the potential results just slightly more suppressed in the sub-diffusion process.
Conclusions

The presented fractional cable model satisfies the main biological features of the dendritic cell signalling problem. With respect to models solved as Cauchy problem, our approach could include specific time dependent boundary conditions, which will allow to reconstruct with accuracy the expected signal at the soma if the model will result capable to predict real data behaviour. Furthermore the solutions can be computed directly, i.e., calculating the integral associated, as well as by Laplace transform inversion [1] without any remarkable issue.

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