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Traumatic brain injuries (TBI) are among the leading causes of death and permanent disability worldwide. Recent experimental observations suggest that damage in brain tissue involves complex local as well as nonlocal chemomechanical interactions that happen on multiple spatiotemporal scales. Biomechanical models of TBI existing in the literature do not incorporate either electrochemical or multiscaling features. Given that neurons are the brain cells responsible for electrochemical signaling on multiplexed temporal scales we propose a novel mathematical model of neuronal electromechanics that uses a constrained Lagrangian formulation and Hamilton's principle to couple Newton's law of motion for a linear viscoelastic Kelvin–Voigt solid-state neuron and the classic Hodgkin–Huxley equations of the electronic neuron. We will use fractional order derivatives of variable order to model multiple temporal scales. Numerical simulations of possible damage dynamics in neurons due to mechanical trauma will be presented and discussed.

A list of symbols can be found on page 53.

1. Introduction

Traumatic brain injuries (TBI) are among the main causes of death and disability worldwide, contributing to approximately 30% of all injury deaths in the United States in 2010 [CDC 2016]. The data collected in the United States during the period 2001-2010 [CDC 2016] show a dramatic increase of 70% in TBI-related visits to emergency rooms, while the death rates decreased only by 7%. This prompted an unprecedented unified effort from various US organizations (government, health and social services) to come up with a public health approach for TBI in [Bell et al. 2015]. The authors of that article concluded it by emphasizing the need for continued progress in brain science that can "inform and suggest solutions for a problem that is of significant concern to the public". In particular, mathematical models and corresponding computer simulations can increase our comprehension of brain responses to TBI and help us design better experiments for measurements and hypothesis testing that ultimately will lead to improved medical diagnostic and therapeutic protocols. In the last few decades a multitude of mathematical models have been proposed to study brain biomechanics and, independently, brain biochemistry at cell and tissue levels (see [Goldsmith 2001; Goriely et al. 2015] for comprehensive reviews of these models). However, most of these models have many physical parameters which are hard, if not impossible, to find experimentally and the high complexity of the corresponding computations makes these models hard to use in today's clinical applications. In addition, these biomechanical models were built at the tissue level and thus they cannot predict the mechanochemical responses of brain cells to mechanical and/or electrochemical events that happen at the tissue and organ scales.

Keywords: fractional derivatives of variable order, entangled scales, Hamilton's principle, fractional calculus, Hodgkin–Huxley model, neuronal electromechanics, TBI.

Following the recommendation of Goriely et al. [2015] for the development of *bottom-up* mathematical models that link brain mechanics and electrochemistry at each relevant length scale as well as across scales, we recently proposed a lower-dimensional electromechanical model of a neuron which is simple enough so that its predictions may be experimentally verified, and could be used as a foundation model for more advanced multiscaling mathematical models [Drapaca 2015]. By assuming that the electrochemical activity of a neuron is described by the classic Hodgkin–Huxley [1952] equations and that the neuron behaves mechanically like a linear viscoelastic Kelvin–Voigt solid, we showed through numerical simulations that very fast initially applied speeds (jabbing) inhibit the action potentials and thus might cause neuronal damage.

In this paper we generalize the model from [Drapaca 2015] by incorporating multiple time scales using fractional order temporal derivatives of variable orders. In the last few decades fractional calculus has been successfully used in a wide range of applications to model stochastic, multiscaling and nonlocal phenomena in various physical systems (some relevant books on fractional calculus and its applications are [Podlubny 1999; Samko et al. 1993; Oldham and Spanier 2006; Hilfer 2000; Baleanu et al. 2012; Milici and Draganescu 2015; West 2015; Tarasov 2010]). Given that neuronal electrochemical dynamics are stochastic [Schiff 2012] and fractional calculus is a natural mathematical representation of stochasticity [West 2015], Sherief et al [2012] generalized the classic Hodgkin–Huxley model by replacing the first order temporal derivatives with fractional order ones. The use of fractional order derivatives in mathematical models of neuronal dynamics is supported by the experimental observations made in [Lundstrom et al. 2008], and only last year Grevesse et al. [2015] showed empirically that mechanical creep of neurons follow a power law of fractional order. Thus we propose to replace the first order time derivatives in the model from [Drapaca 2015] with fractional temporal derivatives with variable orders. The time-dependency of the fractional orders represents the biological variability of neurons as well as the intrinsic entanglement of states existing in the complex mixture of physical components that makes up a neuron. We call this inseparability of time scales *entangled scales*.

In this paper we use the respective left and right Riemann–Liouville fractional derivatives of variable order which were introduced in [Atanackovic and Pilipovic 2011] as

$$ {}_0D_t^{\alpha(t)} f(t) = \frac{f(0)}{\Gamma(1-\alpha(t))t^{\alpha(t)}} + \int_0^t \frac{\mathrm{d}f(\tau)/\mathrm{d}\tau}{\Gamma(1-\alpha(t-\tau))(t-\tau)^{\alpha(t-\tau)}}\,\mathrm{d}\tau, \tag{1-1} $$

$$ {}_tD_T^{\alpha(t)} f(t) = \frac{f(T)}{\Gamma(1-\alpha(T-t))(T-t)^{\alpha(T-t)}} - \int_t^T \frac{\mathrm{d}f(\tau)/\mathrm{d}\tau}{\Gamma(1-\alpha(\tau-t))(\tau-t)^{\alpha(\tau-t)}}\,\mathrm{d}\tau, \tag{1-2} $$

where f is an absolutely continuous[1] function on $[0, T]$ with $f(t) = 0$, $\forall t \in \mathbb{R} - [0, T]$, and the variable order $\alpha(t)$ is a continuous function on $[0, T)$ and $0 \le \alpha(t) < 1$. Definitions (1-1) and (1-2) allow us to use a nonconservative form of Hamilton's principle proposed in [Atanackovic and Pilipovic 2011] and obtain the generalized integro-differential Euler–Lagrange equations corresponding to our electromechanical model.

Although Definitions (1-1) and (1-2) can model the fading memory of materials with variable viscoelasticity [Lorenzo and Hartley 2002], it was shown in [Chicone and Mashhoon 2002] that in the case of

[1]The absolute continuity of a real-valued function f on an interval $[0, T]$ is equivalent to the existence almost everywhere of the derivative $\mathrm{d}f/\mathrm{d}t$ which is Lebesgue integrable and $f(t) = f(0) + \int_0^t (\mathrm{d}f/\mathrm{d}s)\mathrm{d}s$, $\forall t \in [0, T]$.

piecewise uniform accelerated (linear and circular) motions these derivatives introduce additional memory effects that infringe causality. On the other hand, the respective left and right Marchaud fractional derivatives of variable order

$$ {}_0\tilde{D}_t^{\alpha(t)} f(t) = \frac{f(0)}{\Gamma(1-\alpha(t))t^{\alpha(t)}} + \frac{1}{\Gamma(1-\alpha(t))} \int_0^t \frac{\mathrm{d}f(\tau)/\mathrm{d}\tau}{(t-\tau)^{\alpha(t)}}\,\mathrm{d}\tau, \tag{1-3} $$

$$ {}_t\tilde{D}_T^{\alpha(t)} f(t) = \frac{f(T)}{\Gamma(1-\alpha(t))(T-t)^{\alpha(t)}} - \frac{1}{\Gamma(1-\alpha(t))} \int_t^T \frac{\mathrm{d}f(\tau)/\mathrm{d}\tau}{(\tau-t)^{\alpha(t)}}\,\mathrm{d}\tau, \tag{1-4} $$

satisfy the causality law [Chicone and Mashhoon 2002] and therefore their mathematical properties and applications have been increasingly studied [Coimbra and Kobayashi 2002; Coimbra 2003; Soon et al. 2005; Sun et al. 2012; Almeida and Torres 2013]. However, it is easy to check (using power series expansions) that for variable order functions $\alpha : [0, T] \to [0, 1)$ which are differentiable with continuous derivatives and $|\mathrm{d}\alpha/\mathrm{d}t(t)| \ll 1,\ t \in (0, T)$, the approximations

$$ {}_0D_t^{\alpha(t)} f(t) \approx {}_0\tilde{D}_t^{\alpha(t)} f(t) \quad \text{and} \quad {}_tD_T^{\alpha(t)} f(t) \approx {}_t\tilde{D}_T^{\alpha(t)} f(t) \tag{1-5} $$

hold, which are identically satisfied for $\alpha(t) = \text{constant} \in [0, 1)$. Thus, in this paper we will use the left and right Riemann–Liouville fractional derivatives (1-1) and (1-2) with variable orders belonging to the following class of functions: $\mathscr{C} = \{\alpha : [0, T] \to [0, 1)/(\mathrm{d}\alpha/\mathrm{d}t)$ exists and is continuous $|(\mathrm{d}\alpha/\mathrm{d}t)| \ll 1\}$ such that, thanks to the approximations (1-5), the causality and nonlocality criteria introduced in [Chicone and Mashhoon 2002] are satisfied and the expansion formulas with higher-order derivatives proposed in [Almeida and Torres 2013] can be applied.

We model a neuron as a linear viscoelastic Kelvin–Voigt solid with variable viscoelasticity whose electrochemical activity is described by fractional order Hodgkin–Huxley equations with variable order. In addition, we introduce three linear viscoelastic Maxwell fluid elements with variable viscoelasticity that provide a physical representation for the three ionic gates with gating variables m,n, and h introduced by the Hodgkin–Huxley model. The physical analogy of the ionic gates is that of door closers. We use a Lagrangian formulation and Hamilton's principle to obtain the equations of motion that couple macroscopic (cell level) and microscopic (ionic level) mechanical and electrical information and therefore they can describe neuronal mechanotransduction. As in [Drapaca 2015], we assume that at the macroscopic level the membrane's capacitance depends on the mechanical displacement of the neuron and that the Young's modulus of the neuron depends on the gated variables m,n, and h. Our numerical simulations solve a simplified version of the proposed equations using Matlab. Our results are comparable to those in [Drapaca 2015]: when a constant external electric current is applied and the initial displacement and speed are of orders of magnitude comparable to the size of the membrane, the action potentials look similar to the ones seen in healthy neurons, while at very fast initial speeds (which could model a serious traumatic event) and in the presence of a constant applied external current, high persisting oscillations in the volume of the neuron are observed and the action potentials do not happen. Some points of note: these results were obtained for a variable fractional order of the macroscopic Kelvin–Voigt element, which was chosen based on mathematical simplicity rather than physical inspiration; and the classic Hodgkin–Huxley equations were used instead of those of the microscopic Maxwell elements. The classic Hodgkin–Huxley model has very finely adjusted equations and parameters which might have hidden the possible effects of the variable viscoelasticity modeled with fractional order time derivatives of variable

order. It is also possible that there exist other variable fractional orders that enclose physical information that complements the Hodgkin–Huxley model. The lack of experimentally supported information on neuronal mechanics and mechanotransduction limits our ability to explore the full capabilities of the proposed model. However, the model is general enough and can be adapted to practical applications. For instance, the model is independent of the Hodgkin–Huxley equations and thus simpler equations could be used together with fractional order time derivatives of variable orders (and possibly the corresponding evolution equations of the variable order functions) to observe action potentials and neuronal mechanics. In this case the model might have fewer parameters with better prospects of finding experimental proof. Therefore the work presented here can be seen as a first step towards a simpler chemomechanical model of a neuron and its membrane.

In short, the main contributions of this paper are:

(1) Providing the physical structure of door closers to the ionic gates m,n, and h.

(2) Introducing the concept of entangled temporal scales for the stochastic nature of the action potential and for the inseparability of the multiple time scales involved in the neuronal mechanochemical processes.

(3) Use of fractional temporal derivatives of variable orders to model the entangled temporal scales.

(4) Showing through numerical simulations that after a serious traumatic event the elastic behavior of a neuron dominates over its viscoelastic response, which appears to be in agreement with the experimental observations reported in [Grevesse et al. 2015].

In the next section we present our mathematical model, followed by our results. The paper ends with a section of conclusions and future directions which contains a first attempt at modeling entanglement using an area law and level sets.

2. Mathematical model

We model the neuron as an axisymmetric circular cylindrical annulus whose inner core is filled with the intracellular space and the outer core is the cell's membrane (Figure 1). We assume that the intracellular space and the membrane are homogeneous and thus reduce the study of neuronal electromechanics to the study of a simple electromechanical element that we introduce here. Our low-dimensional electromechanical model couples spring-dashpot-mass mechanical elements for the intracellular space and for the ionic gates located in the cell's membrane to an electric circuit model of the cell's membrane (Figure 1). Motivated by the experimental findings in [Lu et al. 2006; Grevesse et al. 2015], we model the intracellular space as a linear viscoelastic Kelvin–Voigt solid. We use the Hodgkin–Huxley [1952] electric circuit to model the macroscopic electric dynamics of neuron's membrane. Besides providing a mathematical representation for neuronal electric dynamics, the Hodgkin–Huxley model introduces three ion gates, m,n, and h, that produce action potentials by controlling the ionic flow into and out of the neuron. Although m,n, and h are seen as nondimensional gate positions whose open or close state is determined by phenomenologically established first order ordinary differential equations, no physical structure has been given to them so far. In this paper we propose to model the m,n, and h gates as linear viscoelastic Maxwell fluid elements located in the cell's membrane (Figure 1). The physical analogy for these ionic gates is a door closer. It is important to notice here that the electric circuit and Maxwell

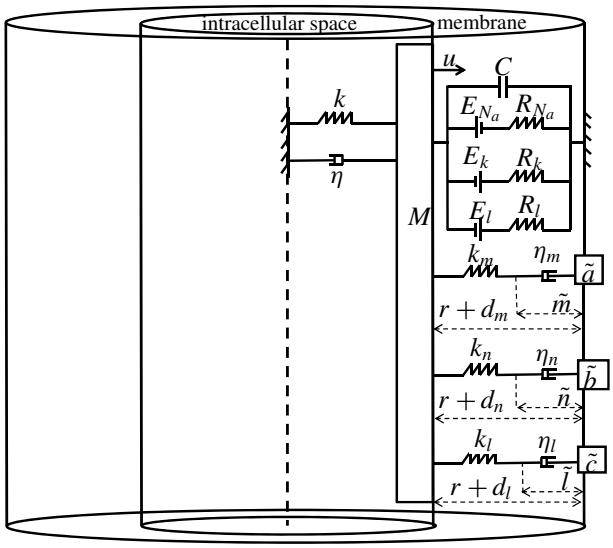

Figure 1. Schematic of the proposed model: the neuron is an axisymmetric homogeneous circular cylinder whose inner core is the intracellular space, and the outer layer is the membrane. Due to the symmetry (dashpot line) and material homogeneity, it is enough to study half of the neuron whose properties are encapsulated into a spring-dashpot-mass mechanical system with the spring and dashpot connected in parallel (Kelvin–Voigt model), and the membrane is represented as an electric circuit governed by the classic Hodgkin–Huxley equations.

elements shown in Figure 1 might not actually be independent and this could be further investigated using the method of mechanoelectric analogy, which is commonly employed in systems engineering [Koenig and Blackwell 1961] (a few insightful comments on the mechanoelectric analogy are stated after formula (2-32)). However, given the empirical nature of the Hodgkin–Huxley model and the current lack of knowledge of neuronal mechanotransduction, in this paper we will treat the electric circuit and the Maxwell elements as independent. The coupling of the Kelvin–Voigt and Maxwell mechanical elements to the Hodgkin–Huxley electric circuit is achieved by using a Lagrangian formulation and Hamilton's principle. We introduce a Lagrangian of the form [Drapaca 2015; Galley et al. 2014]

$$\begin{aligned}\mathcal{L}(q_{\mathrm{Na}}, q_{\mathrm{K}}, q_l, u, d_m, d_n, d_h, \tilde{m}, \tilde{n}, \tilde{h}) = {} & \tfrac{1}{2}M({}_0D_t^{\alpha(t)}u)^2 + \tfrac{1}{2}\tilde{a}({}_0D_t^{\beta(t)}(r+d_m))^2 \\ & + \tfrac{1}{2}\tilde{b}({}_0D_t^{\beta(t)}(r+d_n))^2 + \tfrac{1}{2}\tilde{c}({}_0D_t^{\beta(t)}(r+d_h))^2 \\ & - \frac{1}{2C(u)}q_C^2 - \tfrac{1}{2}k(\tilde{m},\tilde{n},\tilde{h})u^2 - \tfrac{1}{2}k_m(q_C,u)(r+d_m-\tilde{m})^2 \\ & - \tfrac{1}{2}k_n(q_C,u)(r+d_n-\tilde{n})^2 - \tfrac{1}{2}k_h(q_C,u)(r+d_h-\tilde{h})^2, \quad (2\text{-}1)\end{aligned}$$

where M is half of the constant mass of the neuron with constant cross-sectional area A; $u(t)$ is the macroscopic (cell scale) displacement of mass M that depends on time t; $\tilde{a}$, $\tilde{b}$, and $\tilde{c}$ are the masses of the gates m, n, and h, respectively; $r + d_m$, $r + d_n$, and $r + d_h$ are the relative displacements between

mass M and each of the masses $\tilde{a}$, $\tilde{b}$, and $\tilde{c}$, respectively; r is the constant thickness of the membrane; and $\tilde{m}$, $\tilde{n}$, and $\tilde{h}$ are the microscopic (ionic scale) displacements of the dashpots in the Maxwell elements corresponding to the m, n, h gates, respectively. In addition, $C(u)$ is the macroscopic capacitance of membrane's lipid bilayer modeled as a capacitor of electric charge q_C, $k(\tilde{m}, \tilde{n}, \tilde{h})$ is the spring constant of the Kelvin–Voigt element, while k_m, k_n, and k_h are the spring constants of the corresponding Maxwell elements. Lastly, q_{Na}, q_{K}, and q_l are the electric charges of Na^+, K^+, and leakage channels, respectively. For simplicity, we assume that the relative displacements d_m, d_n, and d_h are independent of displacement u. The fractional derivative in formula (2-1) is given by (1-1) for a variable order $\alpha \in \mathbb{C}$. In formula (2-1) we identify the first term of the Lagrangian $\mathcal{L}$ with a macrokinetic mechanical energy, and the second, third and fourth terms with microkinetic mechanical energies. The fifth term in formula (2-1) represents a macropotential electric energy, the sixth term is a macropotential mechanical energy, and the last three terms are micropotential mechanical energies.

The conservation law of electric charges provides the constraint

$$q_C + q_{\mathrm{Na}} + q_{\mathrm{K}} + q_l = 0. \tag{2-2}$$

We take q_{Na}, q_{K}, q_l, u, d_m, d_n, d_h, $\tilde{m}$, $\tilde{n}$, and $\tilde{h}$ to be generalized coordinates and introduce corresponding independent variations δq_{Na}, δq_{K}, δq_l, δu, δd_m, δd_n, δd_h, $\delta\tilde{m}$, $\delta\tilde{n}$, and $\delta\tilde{h}$ that vanish at times $t = 0$ and $t = T$. Using formula (2-2) we calculate the first variation of the Lagrangian $\mathcal{L}$ as

$$\begin{aligned}
\delta\mathcal{L} &= \lim_{\epsilon\to 0}\frac{\mathrm{d}\mathcal{L}}{\mathrm{d}\epsilon}(q_{\mathrm{Na}}+\epsilon\delta q_{\mathrm{Na}}, q_{\mathrm{K}}+\epsilon\delta q_{\mathrm{K}}, q_l+\epsilon\delta q_l, u+\epsilon\delta u, d_m+\epsilon\delta d_m, d_n+\epsilon\delta d_n,\\
&\qquad\qquad d_h+\epsilon\delta d_h, \tilde{m}+\epsilon\delta\tilde{m}, \tilde{n}+\epsilon\tilde{n}, \tilde{h}+\epsilon\tilde{h})\\
&= \Bigg[M_0 D_t^{\alpha(t)} u_0 D_t^{\alpha(t)}(\delta u) - ku - \frac{1}{2}\frac{\partial k_m}{\partial u}(r+d_m-\tilde{m})^2\\
&\qquad\qquad -\frac{1}{2}\frac{\partial k_n}{\partial u}(r+d_n-\tilde{n})^2 - \frac{1}{2}\frac{\partial k_h}{\partial u}(r+d_h-\tilde{h})^2 + \frac{1}{2C^2}q_C^2\Bigg]\delta u\\
&\quad + \left[\tilde{a}_0 D_t^{\beta(t)}(r+d_m)_0 D_t^{\beta(t)}(\delta d_m) - k_m(r+d_m-\tilde{m})\right]\delta d_m\\
&\quad + \left[\tilde{b}_0 D_t^{\beta(t)}(r+d_n)_0 D_t^{\beta(t)}(\delta d_n) - k_n(r+d_n-\tilde{n})\right]\delta d_n\\
&\quad + \left[\tilde{c}_0 D_t^{\beta(t)}(r+d_h)_0 D_t^{\beta(t)}(\delta d_h) - k_h(r+d_h-\tilde{h})\right]\delta d_h + \left[-\frac{1}{2}\frac{\partial k}{\partial\tilde{m}}u^2 + k_m(r+d_m-\tilde{m})i\right]\delta\tilde{m}\\
&\quad + \left[-\frac{1}{2}\frac{\partial k}{\partial\tilde{n}}u^2 + k_n(r+d_n-\tilde{n})\right]\delta\tilde{n} + \left[-\frac{1}{2}\frac{\partial k}{\partial\tilde{h}}u^2 + k_h(r+d_h-\tilde{h})\right]\delta\tilde{h}\\
&\quad + \Bigg[-\frac{1}{C}q_C - \frac{1}{2}\frac{\partial k_m}{\partial q_C}(r+d_m-\tilde{m})^2 - \frac{1}{2}\frac{\partial k_n}{\partial q_C}(r+d_n-\tilde{n})^2\\
&\qquad\qquad -\frac{1}{2}\frac{\partial k_h}{\partial q_C}(r+d_h-\tilde{h})^2\Bigg](-\delta q_{\mathrm{Na}} - \delta q_{\mathrm{K}} - \delta q_l).
\end{aligned} \tag{2-3}$$

We define the virtual work done by nonconservative forces by [Drapaca 2015]

$$\begin{aligned}\delta\mathcal{W} = &-\big[R_{\mathrm{Na}}({}_0D_t^{\gamma(t)}q_{\mathrm{Na}})\delta q_{\mathrm{Na}} + R_{\mathrm{K}}({}_0D_t^{\gamma(t)}q_{\mathrm{K}})\delta q_{\mathrm{K}} + R_l({}_0D_t^{\gamma(t)}q_l)\delta q_l\big]\\ &-\big[\eta({}_0D_t^{\alpha(t)}u)\delta u + \eta_m({}_0D_t^{\beta(t)}\tilde{m})\delta\tilde{m} + \eta_n({}_0D_t^{\beta(t)}\tilde{n})\delta\tilde{n} + \eta_h({}_0D_t^{\beta(t)}\tilde{h})\delta\tilde{h}\big]\\ &+\big[-E_{\mathrm{Na}}\delta q_{\mathrm{Na}} - E_{\mathrm{K}}\delta q_{\mathrm{K}} - E_l\delta q_l + F_m\delta d_m + F_n\delta d_n + F_h\delta d_h + F\delta u\big]. \quad (2\text{-}4)\end{aligned}$$

In formula (2-4), the terms inside the first two sets of parentheses represent dissipative forces: the first is due to the resistors with resistances R_{Na},R_{K}, and R_l in the Hodgkin–Huxley electric circuit, and the second is due to the linear dashpots in the Kelvin–Voigt and Maxwell elements whose damping coefficients are η,η_m,η_n, and η_h. The last set of parentheses in (2-4) contain the reverse potentials E_{Na},E_{K}, and E_l of the Hodgkin–Huxley model and the forces F_m, F_n, F_h, and F which are work conjugates for the Maxwell elements and the Kelvin–Voigt element, respectively. Again, the fractional derivatives in formula (2-4) are given by (1-1) with variable orders $\beta, \gamma \in \mathscr{C}$. The choice of signs in formula (2-4) guarantees that $\delta\mathcal{W}$ is thermodynamically consistent. The nomenclature of the physical and structural quantities used throughout the paper is given on page 53.

We use now the nonconservative form of Hamilton's principle

$$\int_0^T \delta\mathcal{L} + \delta\mathcal{W}\,\mathrm{d}t = 0. \quad (2\text{-}5)$$

We assume that the generalized coordinates and their variations are absolutely continuous functions on $[0, T]$ so that the following integration by parts formula can be applied [Atanackovic and Pilipovic 2011]:

$$\int_0^T \big({}_0D_t^{\alpha(t)}f(t)\big)\big({}_0D_t^{\alpha(t)}\delta f(t)\big)\,\mathrm{d}t = \int_0^T {}_tD_T^{\alpha(t)}({}_0D_t^{\alpha(t)}f(t))\delta f(t)\,\mathrm{d}t. \quad (2\text{-}6)$$

Thus, by replacing formulas (2-3) and (2-4) into (2-5), using the integration by parts formula (2-6), the independence of the variations of generalized coordinates and the fact that these are zero at 0 and T, we obtain the generalized Euler–Lagrange equations[2]

$$\begin{aligned}&M_tD_T^{\alpha(t)}({}_0D_t^{\alpha(t)}u) - \eta_0D_t^{\alpha(t)}u - ku + \frac{1}{2}\frac{\mathrm{d}C}{\mathrm{d}u}V^2\\ &\quad -\frac{1}{2}\left[\frac{\partial k_m}{\partial u}(r+d_m-\tilde{m})^2 + \frac{\partial k_n}{\partial u}(r+d_n-\tilde{n})^2 + \frac{\partial k_h}{\partial u}(r+d_h-\tilde{h})^2\right] + F = 0, \quad (2\text{-}7)\\ &\tilde{a}_tD_T^{\beta(t)}({}_0D_t^{\beta(t)}(r+d_m)) - k_m(r+d_m-\tilde{m}) + F_m = 0, \quad (2\text{-}8)\\ &\tilde{b}_tD_T^{\beta(t)}({}_0D_t^{\beta(t)}(r+d_n)) - k_n(r+d_n-\tilde{n}) + F_n = 0, \quad (2\text{-}9)\\ &\tilde{c}_tD_T^{\beta(t)}({}_0D_t^{\beta(t)}(r+d_h)) - k_h(r+d_h-\tilde{h}) + F_h = 0, \quad (2\text{-}10)\\ &-\eta_{m0}D_t^{\beta(t)}\tilde{m} + k_m(r+d_m-\tilde{m}) - \frac{1}{2}\frac{\partial k}{\partial\tilde{m}}u^2 = 0, \quad (2\text{-}11)\\ &-\eta_{n0}D_t^{\beta(t)}\tilde{n} + k_n(r+d_n-\tilde{n}) - \frac{1}{2}\frac{\partial k}{\partial\tilde{n}}u^2 = 0, \quad (2\text{-}12)\\ &-\eta_{h0}D_t^{\beta(t)}\tilde{h} + k_h(r+d_h-\tilde{h}) - \frac{1}{2}\frac{\partial k}{\partial\tilde{h}}u^2 = 0, \quad (2\text{-}13)\end{aligned}$$

[2]These equations can also be obtained directly from [Atanackovic and Pilipovic 2011, Equation (35)].

$$-R_{\mathrm{Na}}({}_0D_t^{\gamma(t)}q_{\mathrm{Na}}) + V - E_{\mathrm{Na}} + \frac{1}{2C}\left[\frac{\partial k_m}{\partial V}(r+d_m-\tilde{m})^2 + \frac{\partial k_n}{\partial V}(r+d_n-\tilde{n})^2 + \frac{\partial k_h}{\partial V}(r+d_h-\tilde{h})^2\right] = 0, \tag{2-14}$$

$$-R_{\mathrm{K}}({}_0D_t^{\gamma(t)}q_{\mathrm{K}}) + V - E_{\mathrm{K}} + \frac{1}{2C}\left[\frac{\partial k_m}{\partial V}(r+d_m-\tilde{m})^2 + \frac{\partial k_n}{\partial V}(r+d_n-\tilde{n})^2 + \frac{\partial k_h}{\partial V}(r+d_h-\tilde{h})^2\right] = 0, \tag{2-15}$$

$$-R_l({}_0D_t^{\gamma(t)}q_l) + V - E_l + \frac{1}{2C}\left[\frac{\partial k_m}{\partial V}(r+d_m-\tilde{m})^2 + \frac{\partial k_n}{\partial V}(r+d_n-\tilde{n})^2 + \frac{\partial k_h}{\partial V}(r+d_h-\tilde{h})^2\right] = 0, \tag{2-16}$$

where $V = q_C/C$ is the electric potential of the capacitor.

As in [Sherief et al. 2012], we introduce a generalized Kirchhoff's current law of the form

$${}_0D_t^{\gamma(t)}\,(CV + q_{\mathrm{Na}} + q_{\mathrm{K}} + q_l) = I, \tag{2-17}$$

where I is a known external current applied on the membrane. By replacing Equations (2-14), (2-15), and (2-16) into (2-17) we obtain an equation for the membrane potential given as

$${}_0D_t^{\gamma(t)}(CV) = I - \frac{1}{R_{\mathrm{Na}}}(V-E_{\mathrm{Na}}) - \frac{1}{R_{\mathrm{K}}}(V-E_{\mathrm{K}}) - \frac{1}{R_l}(V-E_l) - \frac{1}{2C}\left(\frac{1}{R_{\mathrm{Na}}}+\frac{1}{R_{\mathrm{K}}}+\frac{1}{R_l}\right)\left[\frac{\partial k_m}{\partial V}(r+d_m-\tilde{m})^2 + \frac{\partial k_n}{\partial V}(r+d_n-\tilde{n})^2 + \frac{\partial k_h}{\partial V}(r+d_h-\tilde{h})^2\right]. \tag{2-18}$$

The unknown functions u, d_m, d_n, d_h, $\tilde{m}$, $\tilde{n}$, $\tilde{h}$, and V can be found by solving the coupled Equations (2-7), (2-8)–(2-13) and (2-18) with appropriate initial conditions. Given the insufficient knowledge of neuronal mechanotransduction processes, it is very difficult to provide expressions for $\tilde{a}$, $\tilde{b}$, $\tilde{c}$, k, k_m, k_n, k_h, η_m, η_n, η_h, C, F_m, F_n, and F_h which are needed in order to solve these equations. Therefore, we now make some simplifying assumptions. We start by observing that the equations are not only coupling neuronal mechanical and electrical behaviors but also microscopic (ionic level) and macroscopic (cell level) length scales. This mixture of length scales will cause the system of differential equations to be stiff numerically. Considering how little is known about most of the parameters in our model, a proper analysis of the system and separation of the length scales using perturbation theory is not feasible at this time. Thus we will give a qualitative rather than quantitative analysis of the terms of the equations. We assume that the microscopic masses $\tilde{a}$, $\tilde{b}$, and $\tilde{c}$ are negligible with respect to the cell's mass M and thus we remove Equations (2-8)–(2-10) from the system of equations and also remove d_m, d_n, and d_h from the set of unknowns. We further assume that the first variations of the spring constants k_m, k_n, and k_h of the microscopic Maxwell elements with the macroscopic functions V and u are very small and thus we neglect these terms from Equations (2-7) and (2-18). For simplicity, we take $F = 0$. Lastly, we introduce the nondimensional displacements

$$m = \tilde{m}/r, \quad n = \tilde{n}/r, \quad h = \tilde{h}/r. \tag{2-19}$$

With these assumptions, the system of equations reduces to

$$M_t D_T^{\alpha(t)}({}_0D_t^{\alpha(t)}u) - \eta {}_0D_t^{\alpha(t)}u - ku + \frac{1}{2}\frac{dC}{du}V^2 = 0, \tag{2-20}$$

$${}_0D_t^{\beta(t)}m = -\frac{k_m}{\eta_m}m + \left[\frac{k_m}{\eta_m}(1+d_m/r) - \frac{1}{2r^2\eta_m}\frac{\partial k}{\partial m}u^2\right], \tag{2-21}$$

$${}_0D_t^{\beta(t)}n = -\frac{k_n}{\eta_n}n + \left[\frac{k_n}{\eta_n}(1+d_n/r) - \frac{1}{2r^2\eta_n}\frac{\partial k}{\partial n}u^2\right], \tag{2-22}$$

$${}_0D_t^{\beta(t)}h = -\frac{k_h}{\eta_h}h + \left[\frac{k_h}{\eta_h}(1+d_h/r) - \frac{1}{2r^2\eta_h}\frac{\partial k}{\partial h}u^2\right], \tag{2-23}$$

$${}_0D_t^{\gamma(t)}(CV) = I - \frac{1}{R_{\mathrm{Na}}}(V-E_{\mathrm{Na}}) - \frac{1}{R_{\mathrm{K}}}(V-E_{\mathrm{K}}) - \frac{1}{R_l}(V-E_l). \tag{2-24}$$

We notice now that when $\beta(t)=1$, Equations (2-21)–(2-23) have the same forms as the classic Hodgkin–Huxley equations for the gating variables m, n, and h and thus we identify our nondimensional displacements m, n, and h with the variables representing the activations of the Na^+ and K^+ channels and the inactivation of Na^+ channel, respectively. Consequently, we have provided a physical meaning for m,n, and h and their evolution equations which was, missing from the original ad hoc derivation of the classic Hodgkin–Huxley [1952] model. Since the physical parameters required by Equations (2-21)–(2-23) are not known we will replace the right-hand sides of these equations and Equation (2-24) by the expressions from the Hodgkin–Huxley model [Dayan and Abbott 2001] and thus obtain the system of equations

$$M_t D_T^{\alpha(t)}({}_0D_t^{\alpha(t)}u) - \eta {}_0D_t^{\alpha(t)}u - ku + \frac{1}{2}\frac{dC}{du}V^2 = 0, \tag{2-25}$$

$${}_0D_t^{\beta(t)}m = \alpha_m(1-m) - \beta_m m, \tag{2-26}$$

$${}_0D_t^{\beta(t)}n = \alpha_n(1-n) - \beta_n n, \tag{2-27}$$

$${}_0D_t^{\beta(t)}h = \alpha_h(1-h) - \beta_h h, \tag{2-28}$$

$${}_0D_t^{\gamma(t)}(CV) = I - g_{\mathrm{Na}}m^3h\tilde{A}(V-E_{\mathrm{Na}}) - g_{\mathrm{K}}n^4\tilde{A}(V-E_{\mathrm{K}}) - g_l\tilde{A}(V-E_l), \tag{2-29}$$

where $\tilde{A}$ is the surface area of the neuron, g_{Na}, g_{K}, and g_l are respectively the maximal conductances of the Na^+, K^+, and leakage currents, and

$$\begin{aligned}
\alpha_m &= \frac{0.1(V+40)}{1-\exp(-0.1(V+40))}, & \beta_m &= 4\exp(-0.0556(V+65)),\\
\alpha_n &= \frac{0.01(V+55)}{1-\exp(-0.1(V+55))}, & \beta_n &= 0.125\exp(-0.0125(V+65)),\\
\alpha_h &= 0.07\exp(-0.05(V+65)), & \beta_h &= \frac{1}{1+\exp(-0.1(V+35))}.
\end{aligned} \tag{2-30}$$

The physical units of the parameters in (2-30) are the same as those of the left-hand sides of the Equations (2-26)–(2-28), since all the constants multiplying potential V are meant to remove its physical units (mV). Lastly, we notice that for a constant C, Equations (2-26)–(2-29) reduce to either the equations proposed in [Sherief et al. 2012] when $\beta(t)$ and $\gamma(t)$ are constants between 0 and 1, or the equations of the classic Hodgkin–Huxley model [Dayan and Abbott 2001] when $\beta(t)=\gamma(t)=1$.

In addition, we need to provide expressions for $C(u)$, $k(m,n,h)$, $\alpha(t)$, $\beta(t)$, and $\gamma(t)$. As in [Drapaca 2015], we assume that the membrane acts like a parallel plate capacitor and introduce

$$C = c_m \tilde{A} = \frac{\epsilon \tilde{A}}{r(1+u/r)} \approx \frac{\epsilon \tilde{A}}{r}(1-u/r), \tag{2-31}$$

where c_m is the specific membrane capacitance and ϵ is membrane's permittivity. For the dynamic spring constant $k(m,n,h)$ we propose the expression [Drapaca 2015]

$$k(m,n,h) = k_0(1+m^3(1-h)n^4), \tag{2-32}$$

where k_0 is the spring constant of the neuron in the inactive state. Equation (2-32) suggests that the cell stiffens during an action potential which appears to be in agreement with the observations made in [Hille 2001; Zou et al. 2013]. Lastly, due to a lack of knowledge of relationships among the multiple time scales on which physical processes in a neuron take place, mathematical simplicity rather than physical inspiration was used to select expressions for $\alpha(t)$, $\beta(t)$, and $\gamma(t)$ and these will be provided in the results section.

The system of Equations (2-25)–(2-29) with parameters given by (2-30), (2-31), and (2-32) can be solved either by direct numerical discretization or, as we will see below, by using higher order expansion formulas that transforms the system into a system of first and second order differential equations which can be solved using existing software such as Matlab. Before proceeding further it is worthwhile to comment on the features of some of these equations. For the sake of argument we take $\beta(t) = \gamma(t) = 1$. Then, Equations (2-26)–(2-29) and (2-30) become the classic Hodgkin–Huxley equations. The amount of combined work, intuition and inspiration needed to obtain these very well tuned equations is obvious from their expressions and this is why we decided to keep these formulas in our model. However, given our interpretation of the gating variables m, n, and h as nondimensional displacements of the dashpots in the microscopic Maxwell elements that model the ionic gates present in the membrane, we could use the mechanoelectric analogy [Koenig and Blackwell 1961] to provide a macroscopic mechanical description of the membrane corresponding to the Hodgkin–Huxley electric circuit. According to the mechanoelectric analogy, the capacitance C is the average mass of the membrane seen as a multicomponent and multiphasic porous medium, the voltage V is the average velocity of the membrane, the external current I is an external force, the reverse potentials E_{Na}, E_{K}, and E_l are flux velocities of Na^+, K^+, and Cl^- (leakage), and the inverses of the resistances $1/R_{\mathrm{Na}}$,$1/R_{\mathrm{K}}$, and $1/R_l$ are viscous damping coefficients describing the friction caused by the transport of ions through the membrane. In this analogy, Equation (2-24) (or (2-29)) is Newton's second law of motion where the only internal forces are the damping forces $(1/R_{\mathrm{Na}})(V-E_{\mathrm{Na}})$, $(1/R_{\mathrm{K}})(V-E_{\mathrm{K}})$, and $(1/R_l)(V-E_l)$ corresponding to the ion fluxes expressed relative to the average velocity of the membrane. One advantage of this mechanical analog is that thermodynamics theory can be used to relate the flux velocities of the considered ionic species to their concentrations via their chemical potentials [Doi and Edwards 1986] and thus recover the Nernst equations, which are commonly used to express the dependency of the reverse potentials on ion concentrations (see for instance [Wei et al. 2014]). Another possible advantage is that as experimentally supported information on the chemomechanical properties of the membrane's components becomes available, the validation of a simpler mechanical model with fewer parameters may become possible. In this context we notice that our model is not only independent of the Hodgkin–Huxley equations but also

could be made to have fewer parameters thanks to the use of fractional order derivatives of variable order. For instance, according to the Hodgkin–Huxley model, the damping coefficients $1/R_{\mathrm{Na}}$, $1/R_{\mathrm{K}}$, and $1/R_l$ in the mechanical analog model depend on m, n, and h and thus vary in time according to (2-26)–(2-29). This means that the mechanical analog model implements already variable viscoelasticity. Alternatively, using a fractional order derivative of variable order $\gamma(V(t)) \in [0, 1)$ in Equation (2-24) to model variable viscoelasticity could drastically simplify Equations (2-26)–(2-28) and (2-30) and reduce the number of parameters needed to be found experimentally. Thus the work presented in this paper can be seen as a first step towards a simpler chemomechanical model of a neuron and its membrane.

We propose to simplify the system of Equations (2-25)–(2-29) even more by using (1-5) and the expansion formulas (written here for a generic function f) [Almeida and Torres 2013]

$$
\begin{aligned}
{}_0D_t^{\alpha(t)} f(t) \approx{}& \frac{1}{\Gamma(1-\alpha(t))}\left[1+\sum_{p=2}^{N}\frac{\Gamma(p-1+\alpha(t))}{\Gamma(\alpha(t))(p-1)!}\right]t^{-\alpha(t)} f(t)\\
&+\frac{1}{\Gamma(2-\alpha(t))}\left[1+\sum_{p=1}^{N}\frac{\Gamma(p-1+\alpha(t))}{\Gamma(\alpha(t)-1)p!}\right]t^{1-\alpha(t)}\frac{\mathrm{d}f}{\mathrm{d}t}(t)\\
&+\sum_{k=2}^{N}\frac{\Gamma(k-1+\alpha(t))}{\Gamma(-\alpha(t))\Gamma(1+\alpha(t))(k-1)!}t^{1-k-\alpha(t)}F_k(t), \qquad (2\text{-}33)
\end{aligned}
$$

$$
\frac{\mathrm{d}F_k}{\mathrm{d}t}(t) = (k-1)t^{k-2}f(t), \quad F_k(0)=0, \quad k=2,3,\ldots,N, \qquad (2\text{-}34)
$$

$$
\begin{aligned}
{}_tD_T^{\alpha(t)} f(t) \approx{}& \frac{1}{\Gamma(1-\alpha(t))}\left[1+\sum_{p=2}^{N}\frac{\Gamma(p-1+\alpha(t))}{\Gamma(\alpha(t))(p-1)!}\right](T-t)^{-\alpha(t)} f(t)\\
&-\frac{1}{\Gamma(2-\alpha(t))}\left[1+\sum_{p=1}^{N}\frac{\Gamma(p-1+\alpha(t))}{\Gamma(\alpha(t)-1)p!}\right](T-t)^{1-\alpha(t)}\frac{\mathrm{d}f}{\mathrm{d}t}(t)\\
&+\sum_{k=2}^{N}\frac{\Gamma(k-1+\alpha(t))}{\Gamma(-\alpha(t))\Gamma(1+\alpha(t))(k-1)!}(T-t)^{1-k-\alpha(t)}G_k(t), \qquad (2\text{-}35)
\end{aligned}
$$

$$
\frac{\mathrm{d}G_k}{\mathrm{d}t}(t) = (1-k)(T-t)^{k-2}f(t), \quad G_k(T)=0, \quad k=2,3,\ldots,N. \qquad (2\text{-}36)
$$

By replacing formula (2-33) into formula (2-35) the expression

$$
\begin{aligned}
{}_tD_T^{\alpha(t)}({}_0D_t^{\alpha(t)} f(t)) \approx{}& -\frac{1}{\Gamma(2-\alpha(t))^2}\left[1+\sum_{p=1}^{N}\frac{\Gamma(p-1+\alpha(t))}{\Gamma(\alpha(t)-1)p!}\right]^2(t(T-t))^{1-\alpha(t)}\frac{\mathrm{d}^2 f}{\mathrm{d}t^2}\\
&+\text{lower order terms} \qquad (2\text{-}37)
\end{aligned}
$$

is obtained, where some of the lower order terms are linear in f and $\mathrm{d}f/\mathrm{d}t$ and the rest of the terms are combinations of the extra functions F_k, G_k, $k = 2, 3, \ldots N$. Formulas (2-33)–(2-36) suggest that the extra terms in (2-37) introduce additional memory effects which could invalidate the causality law.

Thus in Equation (2-20) we take ${}_tD_T^{\alpha(t)}({}_0D_t^{\alpha(t)}u) = -(\mathrm{d}^2u)/(\mathrm{d}t^2)$ and obtain a much simplified form of the equation of motion for displacement u. If we replace formula (2-33) into Equations (2-20)–(2-24) and add the extra $N-1$ equations (2-34) corresponding to each unknown function u, m, n, h, V we obtain a system of integer order differential equations with $5N$ equations. It was shown in [Almeida and Torres 2013] that a value of $N = 3$ gives very accurate results, so we take $N = 3$ and obtain a total of 15 equations: 14 of them are first order and one is a second order differential equation. We notice that these mathematical approximations replace the variable fractional order time derivatives by integer (first or second) order derivatives and the effect of the variable orders is contained in extra memory terms (represented as power functions of time with variable fractional order) which are added to the proposed equations and their corresponding evolution equations.

3. Results

In our numerical simulations we used the following parameters [Dayan and Abbott 2001]:

$$\begin{aligned} E_{\mathrm{Na}} &= 50\,\mathrm{mV}, \\ E_{\mathrm{K}} &= -77\,\mathrm{mV}, \\ E_l &= -54.387\,\mathrm{mV}, \\ g_{\mathrm{Na}} &= 1.2\,\mathrm{mS/mm^2}, \\ g_{\mathrm{K}} &= 0.36\,\mathrm{mS/mm^2}, \\ g_l &= 0.003\,\mathrm{mS/mm^2}, \\ r &= 4\,\mathrm{nm}, \\ r_0 &= 2\,\mu\mathrm{m}, \\ \tilde{A} &= 0.01\,\mathrm{mm^2}, \end{aligned} \tag{3-1}$$

where r_0 is the radius of the neuron. At mechanical equilibrium ($u = 0$), the specific membrane capacitance is $0.01\,\mu\mathrm{F/mm^2}$, which combined with formula (2-31) gives

$$c_m = 0.01(1 - u/r)\,\mu\mathrm{F/mm^2}.$$

We also used $E_0 = 200\,\mathrm{Pa}$ as an average Young's modulus of a neuron [Lu et al. 2006; Zou et al. 2013], $M = 0.1\,\mathrm{ng}$ as half of the neuronal mass [Corbin et al. 2014], and $\mu = 4\,\mathrm{mPa\cdot s}$ as neuronal dynamic viscosity [Park et al. 2010]. From these parameters and the assumption of circular cylindrical shape, the following parameters can be calculated [Drapaca 2015]:

$$k_0 = 0.0013\,\mathrm{mg/ms^2}, \quad \eta = 2.5\cdot 10^{-11}\,\mathrm{mg/ms}, \quad \mathrm{vol}_0 = 9.95\cdot 10^{-6}\,\mathrm{mm^3},$$

where vol_0 is the volume of the neuron at mechanical equilibrium. In all numerical simulations we applied a constant external current per unit surface area $I = 0.1\,\mu\mathrm{A/mm^2}$. Lastly, we used a characteristic time of 25 ms, and $\alpha(t) = 0.001\exp(1 - t/25) \in \mathscr{C}$, $\beta(t) = \gamma(t) = 1$. We chose a simple function $\alpha(t)$ that belongs to the class $\mathscr{C}$, looks similar to the parameters from formulas (2-30), and gives apparently reasonable results when the neuronal electrochemistry is described by the classic Hodgkin–Huxley model ($\beta(t) = \gamma(t) = 1$).

In this case the system of Equations (2-20)–(2-24) with approximations (2-33)–(2-34) become

$$\frac{\mathrm{d}}{\mathrm{d}t}u = v, \tag{3-2}$$

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}v = &-\left[\frac{k}{M}+\frac{\eta}{M}\frac{1}{\Gamma(1-\alpha(t))}\left(1+\sum_{p=2}^{3}\frac{\Gamma(p-1+\alpha(t))}{\Gamma(\alpha(t))(p-1)!}\right)t^{-\alpha(t)}\right]u\\ &-\frac{\eta}{M}\frac{1}{\Gamma(2-\alpha(t))}\left(1+\sum_{p=1}^{3}\frac{\Gamma(p-1+\alpha(t))}{\Gamma(\alpha(t)-1)p!}\right)t^{1-\alpha(t)}v\\ &-\frac{\eta}{M}\sum_{k=2}^{3}\frac{\Gamma(k-1+\alpha(t))}{\Gamma(-\alpha(t))\Gamma(1+\alpha(t))(k-1)!}t^{1-k-\alpha(t)}F_k+\frac{1}{2}\frac{\mathrm{d}C}{\mathrm{d}u}V^2,\end{aligned} \tag{3-3}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}F_k = (k-1)t^{k-2}u, \quad k=2,3, \tag{3-4}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}m = \alpha_m(1-m)-\beta_m m, \tag{3-5}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}n = \alpha_n(1-n)-\beta_n n, \tag{3-6}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}h = \alpha_h(1-h)-\beta_h h, \tag{3-7}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}(V) = \frac{1}{C}\left[I-g_{\mathrm{Na}}m^3h\tilde{A}(V-E_{\mathrm{Na}})-g_{\mathrm{K}}n^4\tilde{A}(V-E_{\mathrm{K}})-g_l\tilde{A}(V-E_l)\right]-\frac{1}{C}v\frac{\mathrm{d}C}{\mathrm{d}u}V. \tag{3-8}$$

We solved the system (3-2)–(3-8) with the initial conditions

$$V(0) = -65\,\mathrm{mV}, \qquad m(0) = \frac{\alpha_m(V(0))}{\alpha_m(V(0))+\beta_m(V(0))}, \tag{3-9}$$

$$n(0) = \frac{\alpha_n(V(0))}{\alpha_n(V(0))+\beta_n(V(0))}, \qquad h(0) = \frac{\alpha_h(V(0))}{\alpha_h(V(0))+\beta_h(V(0))}, \tag{3-10}$$

$$F_k(0) = 0, \quad k=2,3 \tag{3-11}$$

$$\begin{aligned}&\text{Set 1: } u(0) = 1\,\mathrm{nm}, \quad v(0) = 10\,\mathrm{nm/ms},\\ &\text{Set 2: } u(0) = 0, \quad v(0) = 1\,\mathrm{nm}/\mu\mathrm{s},\end{aligned}$$

Some numerical experimentation with physically plausible values for $u(0)$ and $v(0)$ showed the existence of two trends in the behavior of stable solutions and thus the initial conditions given by sets 1 and 2 were chosen such that both of these situations could be presented.

We used Matlab's built-in function ode15s that solves stiff ordinary differential equations using

(1) a modified linear multistep backward difference formula of order up to 5 known to have good stability, and

(2) an adaptive step size that changes according to a numerical scheme that calculates relative and absolute error tolerances [Shampine and Reichelt 1997].

In our simulations we kept the default values of ode15s for the relative error tolerance (10^{-3}) and for the absolute error tolerance (10^{-6}). For the chosen parameters and initial conditions we noticed that the order of magnitude of $\mathrm{d}C/\mathrm{d}uV$ in Equations (3-3) and (3-8) is much bigger than the rest of the terms in

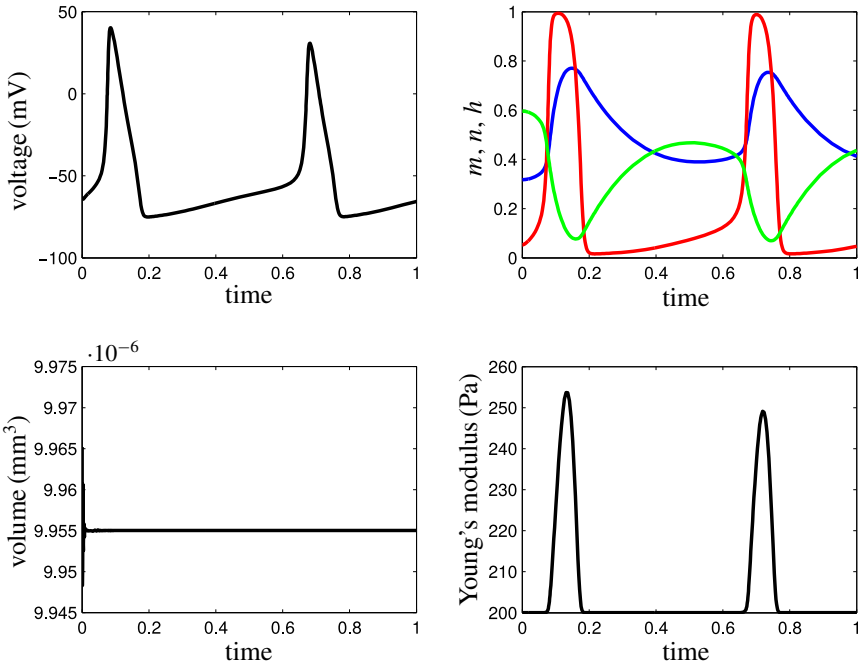

Figure 2. Results for initial displacement of 1 nm and initial speed of 10 nm/ms: voltage; functions n (blue curve), m (red), and h (green); volume; and Young's modulus.

these equations and no action potentials are observed. Thus, as in [Drapaca 2015], we remove this term from Equations (3-3) and (3-8). This simplification preserves a weaker coupling between the mechanical and electrical behaviors of the neuron expressed by (2-31) and (2-32).

In Figures 2 and 3 we show the evolutions of the voltage, gating variables, volume and Young's modulus for the mechanical initial conditions in set 1 and set 2, respectively. For set 1, the action potentials occur and the Young's modulus and the volume variations appear to be physically admissible and possibly within a healthy range. The dynamics of the cell's stiffness (Figure 2, bottom right) seems in agreement with the experimental observations in the normally functioning regime reported in [Zou et al. 2013]. The initial conditions in set 2 mimic a more serious traumatic event and our simulations show that there are no action potentials (Figure 3, top left), and the displacements of the gates m, n, and h (top right) as well as the Young's modulus (bottom right) remain at their corresponding initial values. The solutions obtained in this case might show damaging effects of a very fast initial speed (jabbing) on the material structure and electrochemical activity of a neuron. To better understand the simulated neuronal mechanotransduction, in Figures 4 and 5 we look closer at the voltages and corresponding volumes obtained using the mechanical initial conditions in set 1 and set 2. While oscillations in the cell's volume are quickly attenuated for set 1 of initial conditions (Figure 4, right) such that the action potential can develop soon afterwards (Figure 4, left); for the initial conditions of set 2 the amplitudes of the oscillations in volume are much higher than in the previous case and do not appear to diminish in time (Figure 5, right), and thus the membrane's depolarization does not happen. These results look similar to the ones we reported in [Drapaca 2015], even though here Equation (3-3) has extra, time-dependent terms

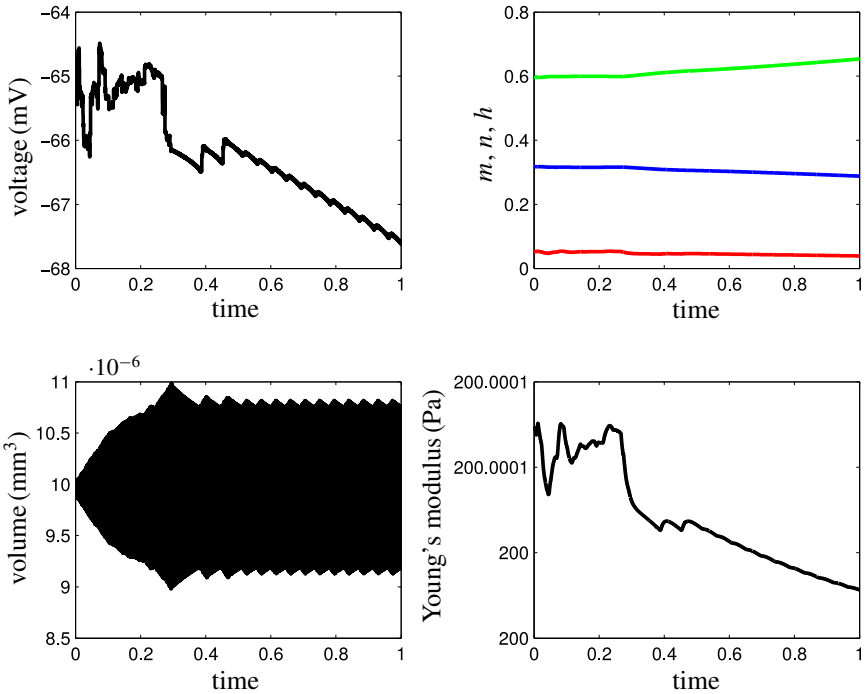

Figure 3. Results for zero initial displacement and initial speed of speed of 10 nm/ms: voltage; functions n (blue curve), m (red), and h (green); volume; and Young's modulus.

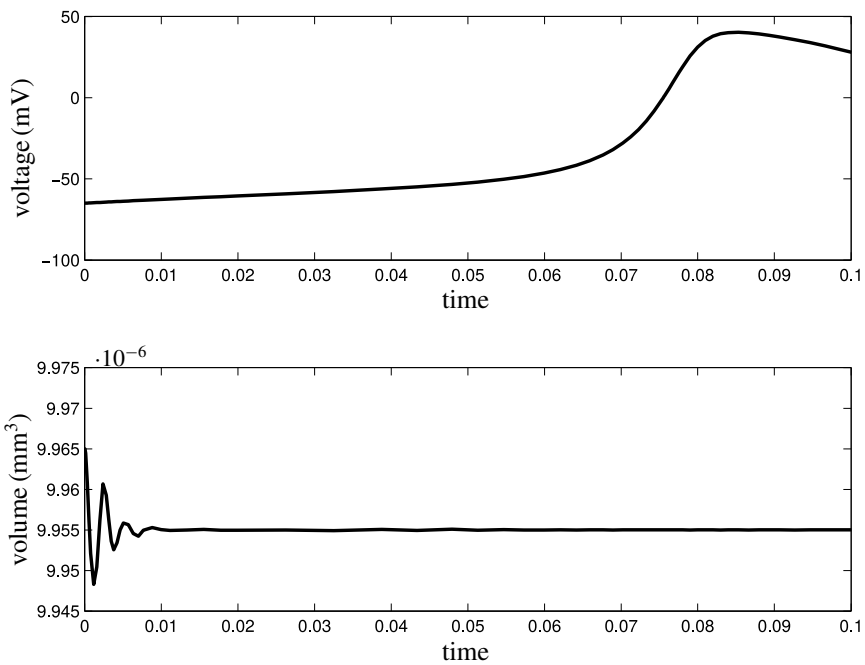

Figure 4. A zoom-in of Figure 2: voltage potential (top) and volume (bottom).

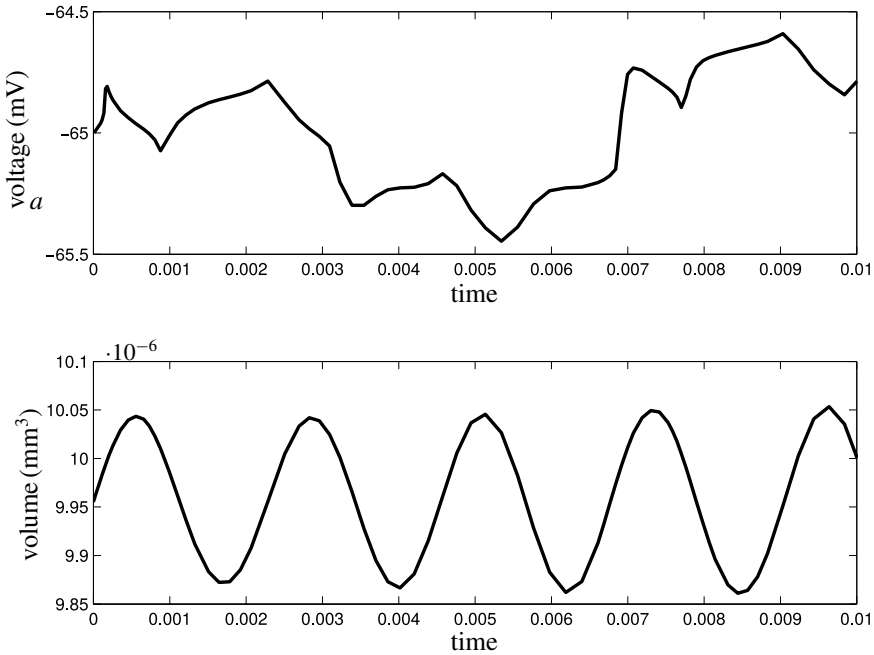

Figure 5. A zoom-in of Figure 3: voltage potential (top) and volume (bottom).

that account for the variable viscoelasticity. This might suggest that — for the chosen initial conditions, parameters and electromechanical couplings — after a serious traumatic event the elastic behavior of a neuron dominates over its viscoelastic response, which agrees with the experimentally supported claims made in [Grevesse et al. 2015].

4. Conclusions and future directions

In this paper we proposed a generalization of our electromechanical model from [Drapaca 2015] in which the temporal variations of the physical fields are represented using Riemann–Liouville fractional derivatives of variable orders. The neuron was modeled as a linear viscoelastic Kelvin–Voigt solid with variable viscoelasticity whose electrochemical activity was described by fractional order Hodgkin–Huxley equations. In addition, we introduced three linear viscoelastic Maxwell fluids with variable viscoelasticity to model the three ionic gates with gating variables m,n, and h. This provides a *physical structure for the ionic gates which can be interpreted as door closers*. The fractional orders of the derivatives model the multiple temporal scales used by a neuron for electrochemical signaling. The time dependency of the fractional orders models the biological variability of neurons as well as the intrinsic entanglement of states existing in the complex mixture that makes up a neuron. For this reason we call these time scales *entangled scales*. We used a Lagrangian formulation and Hamilton's principle to obtain the coupled equations of motion. This approach links macroscopic (cell level) and microscopic (ionic level) mechanical and electrical information and hence it can describe neuronal mechanotransduction [Drapaca 2015]. As in [Drapaca 2015], we assumed that at the macroscopic level the membrane's

capacitance depends on the mechanical displacement of the neuron and the Young's modulus of the neuron depends on the nondimensional displacements of the dashpots in the Maxwell elements. In order to satisfy the physical criterion of causality, we restrict the class of allowable variable order functions to the class of differentiable functions with continuous first order derivatives and of slow variation. For such variable order functions, we can approximate the Riemann–Liouville derivatives to Marchaud fractional derivatives and further use the higher integer order expansions proposed in [Almeida and Torres 2013] to transform the integro-differential Euler–Lagrange equations into classic Euler–Lagrange equations with extra time-dependent terms, some with their own evolution equations. We further performed numerical simulations in Matlab using the built-in function ode15s to solve simplified versions of our differential equations. We used the same initial conditions and physical constants as in [Drapaca 2015] and we obtained results comparable with those in the same paper. Namely, when a constant external electric current was applied and the initial displacement and speed were of orders of magnitude comparable to the size of the membrane, the action potentials occurred and looked similar to the ones seen in healthy neurons. In this case the dynamics of the neuron's stiffness seemed to agree with experimental measurements done on healthy neurons [Zou et al. 2013]. At very fast initial speeds (which could model a serious traumatic event) and in the presence of a constant applied external current, our numerical simulations showed high persisting oscillations in the volume of the neuron and the action potentials did not happen. Also, the Young's modulus of the neuron and the displacements m, n, and h of the dashpots in the Maxwell elements were almost constant, suggesting possible structural and functional damage of the neuron.

Some of the limitations of the proposed model and solution approach are as follows. One limitation is finding physically valid capacitance-displacement and, respectively, stiffness-gating variable relationships because there are no experimental observations that could guide us. Given the simplicity of the proposed model, we hope that our model will inspire future experimental work that will provide empirical relationships among the model's mechanical and electrical parameters. Another limitation of our approach is the use of the Matlab built-in function ode15s to solve the simplified system of stiff differential equations. Shampine and Bogacki [1989] advised caution in drastically reducing the step size in the discretization implemented in ode15s since this action could increase numerical error and cause instabilities in the solutions. In addition, the class of admissible variable order functions is too restrictive. In our future work we plan to develop our own numerical solver for the stiff system of differential equations that uses the Riemann–Liouville fractional derivatives of variable orders. We believe that for living neurons the causality law should not be imposed and therefore by removing this restriction on our model we could use the Riemann–Liouville derivatives with variable order functions belonging to a larger class of admissible (continuous) functions. A numerical solver will allow us to address another limitation of our model: providing a more physically meaningful expression for the variable fractional order $\alpha(t)$. One approach is to use the experimentally found dependence of a power law exponent on the stress reported in [Grevesse et al. 2015] to calculate a corresponding $\alpha(t)$. Another approach is to add the unknown function $\alpha(t)$ to the list of generalized coordinates and use Hamilton's principle to obtain one more Euler–Lagrange equation that presumably could be solved for α [Atanackovic and Pilipovic 2011]. Another possible limitation is the use in our numerical simulations of the classic Hodgkin–Huxley model, whose very well tuned equations and parameters might have hidden the possible effects of the variable viscoelasticity modeled with fractional order time derivatives of variable order. Since the proposed model is not dependent on the Hodgkin–Huxley equations, we could use the mechanoelectric analogy mentioned

in Section 2 to obtain a macroscopic mechanical analog model of the neuronal membrane made of the membrane's mass and three dashpots connected in parallel and located between the neuronal mass M and the membrane's mass. The corresponding equations of motion with classic time derivatives as well as with fractional order derivatives of variable orders will not only have much simpler forms but also may be easier to analyze and solve. In particular, a bifurcation analysis might be possible in this case and the role of variable fractional order derivatives in critical transitions could be investigated.

Lastly, we intend to generalize our model by including spatial variations. Let $\Omega \subset \mathbb{R}^3$ be the domain occupied by the intracellular space, the cell's membrane, and a very small ϵ-neighborhood of the membrane located in the extracellular space that contains the ions exchanged with the neuron through its membrane. This domain is filled with a very complex mixture of solids, fluids, ionic components and other proteins and molecules that interact dynamically with each other on multiple time and space scales and thus there exists a subset $\omega \subset \Omega$ that contains the entangled state. This region ω could be seen as a sort of black hole in the sense that once components enter ω, any information about them is lost (however, unlike black holes, components can "escape" ω). Thus the energies contributing to the Lagrangian form are the kinetic and potential energies as well as an interfacial energy due to the presence of ω. All these energies are in fact part of the total entropy of domain Ω, and the entanglement entropy, which is the entropy of ω, satisfies a so-called *area law* that says that the entanglement entropy is proportional to the surface area of ω [Eisert et al. 2010]. If we introduce the level set function

$$\phi(\mathbf{x}) = \begin{cases} d_x & \text{if } \mathbf{x} \in \Omega - \omega, \\ -d_x & \text{if } \mathbf{x} \in \omega, \\ 0 & \text{if } \mathbf{x} \in \partial\omega, \end{cases}$$

then we can introduce the Lagrangian

$$\begin{aligned} \mathcal{L} = \int_\Omega & \tfrac{1}{2}\rho_M({}_0D_t^{\alpha(t,\boldsymbol{x})}u)^2 H(\phi) + \tfrac{1}{2}\rho_{\tilde{a}}({}_0D_t^{\beta(t,\boldsymbol{x})}(r+d_m))^2 H(\phi) \\ & + \tfrac{1}{2}\rho_{\tilde{b}}({}_0D_t^{\beta(t,\boldsymbol{x})}(r+d_n))^2 H(\phi) + \tfrac{1}{2}\rho_{\tilde{c}}({}_0D_t^{\beta(t,\boldsymbol{x})}(r+d_h))^2 H(\phi) \\ & - \frac{1}{2C(u)}q_C^2 H(\phi) - \sigma_u \cdot \epsilon_u H(\phi) - \sigma_{dm} \cdot \epsilon_{dm} H(\phi) \\ & - \sigma_{dn} \cdot \epsilon_{dn} H(\phi) - \sigma_{dh} \cdot \epsilon_{dh} H(\phi) + \lambda\delta(\phi)||\nabla\phi||\,\mathrm{d}\boldsymbol{x}, \end{aligned} \tag{4-1}$$

where $H(\phi)$ is the Heaviside function; $\delta(\phi)$ is the Dirac distribution; ρ_M, $\rho_{\tilde{a}}$, $\rho_{\tilde{b}}$, and $\rho_{\tilde{c}}$ are the densities of the masses represented as subindices; $\sigma_u, \sigma_{dm}, \sigma_{dn}, \sigma_{dh}$ are the stress tensors for the displacements $u, r + d_m - \tilde{m}, r + d_n - \tilde{n}, r + d_h - \tilde{h}$ with $\epsilon_u, \epsilon_{dm}, \epsilon_{dn}$, and ϵ_{dh} the corresponding strain tensors. We denoted by $||\nabla\phi||$ the Euclidean norm of the Jacobian matrix of ϕ. The last term in formula (4-1) is the surface area of ω. An expression for the corresponding virtual work can be obtained from formula (2-4) in a similar manner. Hamilton's principle will provide again the system of nonlinear integro-differential Euler–Lagrange equations, which will have to be completed with the Kirchhoff current law and an evolution equation for the level set function ϕ. Appropriate initial and boundary conditions will complete this model which we intend to fully describe and study in the near future.

List of Symbols

A	neuronal cross-sectional area
$\tilde{A}$	neuronal surface area
r_0	neuronal radius
r	thickness of neuronal membrane
t	time (independent variable)
$\alpha, \beta, \gamma \in [0, 1)$	time-dependent fractional orders (entangled time scales)
M	half of the neuronal mass
$\tilde{a}, \tilde{b}, \tilde{c}$	masses attached to the Maxwell elements
u	neuronal displacement
$r + d_m, r + d_n, r + d_h$	relative displacements between M and each of $\tilde{a}, \tilde{b}, \tilde{c}$
$\tilde{m}, \tilde{n}, \tilde{h}$	displacements of the dashpots in the Maxwell elements
k	spring constant of the Kelvin–Voigt element
η	damping coefficient of the Kelvin–Voigt element
F	force (work conjugate) for the Kelvin–Voigt element
k_m, k_n, k_h	spring constants of the Maxwell elements
η_m, η_n, η_h	damping coefficients of the Maxwell elements
F_m, F_n, F_h	forces (work conjugates) for the Maxwell elements
C	capacitance of neuronal membrane
c_m	specific membrane capacitance
q_C	electric charge of the capacitor
V	electric potential (voltage) of the capacitor
ϵ	membrane's permittivity
I	external current
q_{Na},q_{K},q_l	electric charges of Na^+,K^+, and leakage channels
$R_{\mathrm{Na}}, R_{\mathrm{K}}, R_l$	resistances of the resistors
$E_{\mathrm{Na}}, E_{\mathrm{K}}, E_l$	reverse potentials
$g_{\mathrm{Na}}, g_{\mathrm{K}}, g_l$	maximal conductances of the Na^+, K^+, and leakage currents
$\alpha_m, \alpha_n, \alpha_h, \beta_m, \beta_n, \beta_h$	voltage-dependent parameters of the Hodgkin–Huxley model
$F_k, G_k, k = 2, 3$	extra memory terms due to mathematical approximations

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