Commun Nonlinear Sci Numer Simulat 000 (2020) 105066

Contents lists available at ScienceDirect

Commun Nonlinear Sci Numer Simulat

journal homepage: www.elsevier.com/locate/cnsns

Research paper

Single-variable delay-differential equation approximations of the Fitzhugh-Nagumo and Hodgkin-Huxley models

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Hodgkin-Huxley
Fitzhugh-Nagumo
Delay-differential equation

ABSTRACT

In this work, we revisit two traditional models of action potential generation in excitable cells, the Hodgkin-Huxley (HH) and the FitzHugh-Nagumo (FHN) models. The main goal is to evaluate the possibility of modeling the generation of the action potential via a single delay-differential equation (DDE). Delay-differential equations are important mathematical tools and can reproduce a great diversity of biological phenomena. However, their use in modeling of action potentials is still incipient. In this paper, we present new models based on single delay-differential equation. The solutions of the new models are similar to those of the original HH and FHN models. Based on these results, we claim that delay-differential equations can also be used as building blocks in the development of models of cell electrophysiology.

1. Introduction

In a series of articles published in the Journal of Physiology, Alan Lloyd Hodgkin and Andrew Fielding Huxley proposed models [1,2] for the dynamics of ion channels and for the generation of action potentials (APs) in neurons. From the experimental data captured in their studies, the authors proposed a system of four ordinary differential equations (ODEs) to describe the phenomenon. The researchers received the Nobel Prize in Physiology and Medicine for their work. Today their model is still considered a seminal reference in the neuronal and cardiac electrophysiology community.

Among the works inspired by Hodgkin and Huxley (HH) is the FitzHugh-Nagumo model (FHN) [3,4], which is a reduced system composed of only two ODEs. The FHN model allows relevant analytical analyses in studies of action potentials [5, p. 136]. Recent studies revealed that significant delays could take place between voltage changes and ion channel activation/inactivation dynamics [6]. Formulations based on Markov-chains are often used to model these delayed processes in the cell membrane [7]. Markov-chain models represent delayed responses of channel conductivity to changes in voltage via a discrete sequence of states. An alternative mathematical formulation to represent this delayed response is a delay-differential equation (DDE).

Delay-differential equations are important mathematical tools and can reproduce a great diversity of biological phenomena. However, their use in modeling of action potentials is still novel. Whereas the right-hand side of first-order ODEs can be written as $f(u(t), t)$, delay-differential equations (DDEs) use expressions that can depend on the present time t and on

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https://doi.org/10.1016/j.cnsns.2019.105066
1007-5704/

the past at time $t-\delta$, where δ is called the delay. General expressions have the form $f(u(t-\delta_1), u(t-\delta_2), \dots, u(t-\delta_n), t)$. As an example, we can cite the Hutchinson equation, which is a delayed logistic equation defined as follows:

$$\frac{dx}{dt} = rx(t)\left(1 - \frac{x(t-\delta)}{K}\right).$$

New behaviors and bifurcations arise for the logistic modeling equation when it is transformed into a DDE. In [8, p. 5], a variety of solutions can be observed only with the variation of the parameter δ. In general, the incorporation of delays provides a great diversity of solutions and consequently different information and characteristics for the phenomena under study.

The main contribution of the work is to show that it is possible to replace ordinary differential equations, such as those originally proposed by Hodgkin and Huxley, by DDEs. We propose new models based on a single DDE that can reproduce action potentials that are similar to those obtained with the original Hodgkin-Huxley and FitzHugh-Nagumo models.

2. Methods

The new models proposed in this work were generated following two basic steps. First, we seek an integro-differential equation that can approximate the results of the system of ODEs of the FitzHugh-Nagumo and Hodgkin-Huxley models. Second, we approximate the integral part of the equations using standard numerical methods, i.e., we approximate the integral using few discretized points, which converts the integro-differential equation into a DDE.

The next section gives a brief presentation of the HH and FHN models, an overview of the new proposed models, and the mathematical notation adopted.

2.1. Original FitzHugh-Nagumo and Hodgkin-Huxley models and overview of new models

Consider the following FHN model:

$$\begin{cases} \epsilon u' = u(u-a)(1-u) - w + I(t), \\ w' = \dfrac{\beta u - w}{\tau}, \end{cases} \tag{1}$$

where $\epsilon = 0.01,\ \beta = 2,\ \tau = 2,\ I(t)$ is a current stimulus, and a is a parameter that controls the oscillatory behaviour of the model. Note that we use a concise notation, where $u = u(t)$ and $u' = \dfrac{du(t)}{dt}$.

The second equation can be interpreted as setting $w = \beta u$ after some delay that is continuously represented by τ in the differential equation for w. As a first step, we will look for an integral differential equation that is an approximation of the original system of ODEs:

$$\epsilon u' = u(u-a)(1-u) + I(t) - \int_{-\infty}^{t} g(u(s), t, s) ds.$$

To simplify the notation we may use $g(u) = g(u(s), t, s)$. Note that the integral term of the equation takes into account past values of u and should be an approximation for w.

As a second step, we approximate the integral term using classical numerical methods, such as the trapezoidal rule, to arrive at a single DDE:

$$\epsilon u' = u(u-a)(1-u) + I(t) - \sum_{i=0}^{2} k_i g(t - i\delta),$$

where k_i are weighting functions that depend on the method used for numerical integration, δ is a discrete delay that may also depend on time, and $g(t-\delta)$ is a concise notation for $g(u(t), u(t-\delta), t, t-\delta)$. Note that although we could propose DDE models based on an arbitrary numbers of delays, for simplicity, all the models presented here use only two past values of u, $u(t-\delta)$ and $u(t-2\delta)$.

In the original Hodgkin-Huxley model, the membrane potential is described by the following equation:

$$C_m v' = I(t) - g_{Na} m^3\ h(v - E_{Na}) - g_K n^4 (v - E_K) - g_l (v - E_L).$$

Each gate variable m, n, and h is described by an ODE of the following form (here a general gate variable w is used) :

$$w' = \alpha_w (1 - w) + \beta_w w,$$

where in this paper we used the original voltage-dependent rate constants, α_n, β_n, α_m, β_m, α_h, β_h, maximum conductance values, g_{Na}, g_K, g_l, and corresponding Nernst potentials as described in [1]. As before, we first seek an approximation for each gate variable in the form $w \approx w_g = \int_{-\infty}^{t} g(u(s), t, s) ds$. Then, we approximate each integral numerically. In this way, the DDE approximation for the HH models is in the following form:

$$C_m v' = I(t) - g_{Na} w_m^3 w_h (v - E_{Na}) - g_K w_n^4 (v - E_K) - g_l (v - E_L),$$

with $w_m = \sum_{i=0}^{2} k_i g_m(t - i\delta),\ w_h = \sum_{i=0}^{2} k_i g_h(t - i\delta),\ w_n = \sum_{i=0}^{2} k_i g_n(t - i\delta)$.

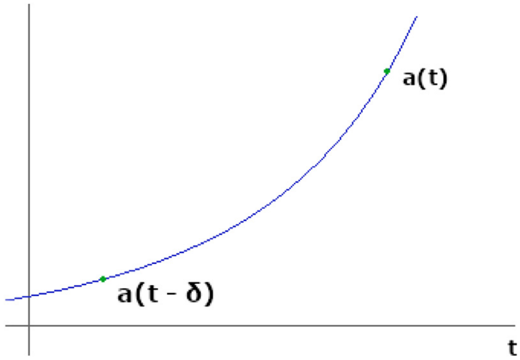

Fig. 1. Present and past events properly weighted by an exponential kernel.

2.2. From a system of ODEs to a single integro-differential equation

2.2.1. The FHN case

Let us write the FitzHugh-Nagumo model as follows.

$$\begin{aligned} u' &= f(u) - w \\ w' &= \frac{\beta u - w}{\tau} \end{aligned} \tag{2}$$

Consider the variable w given by

$$w = \int_{-\infty}^{t} \gamma e^{-\gamma(t-s)} \beta u(s) ds,$$

with $\gamma = \frac{1}{\tau}$. The function w is chosen so that it also accounts for values of the past, but with an appropriate weighting. In this way, the more remote an event is, the less it influences w. We can visualize this in Fig. 1. If we differentiate w and use Leibniz's rule, we have:

$$\begin{aligned} w' &= \int_{-\infty}^{t} \frac{d}{dt}\left(\gamma e^{-\gamma(t-s)} \beta u(s)\right) ds + \gamma e^{-\gamma(t-s)} \beta u(s) \Big|_{-\infty}^{t} \\ &= \int_{-\infty}^{t} (-\gamma) \gamma e^{-\gamma(t-s)} \beta u(s) ds + \gamma \beta u(t) \\ &= -\gamma w + \gamma \beta u \\ &= \frac{\beta u - w}{\tau}. \end{aligned}$$

Therefore the system of ODEs (2) is equivalent to the following:

$$u' = f(u) - \int_{-\infty}^{t} \gamma e^{-\gamma(t-s)} \beta u(s) ds.$$

2.2.2. The Hodgkin-Huxley case

Let us perform a similar analysis for the Hodgkin-Huxley equations, in particular, for the activation m and inactivation h gate variables for the sodium ion channel and for the activation n gate variable for the potassium ion channel. Let us represent an arbitrary gate variable as w, associated with the following differential equations:

$$\begin{aligned} u' &= f(u) + w\bar{g}(u - \bar{u}), \\ w' &= \frac{w_\infty(u) - w}{\tau_w(u)}, \end{aligned} \tag{3}$$

where $\bar{g}$ and $\bar{u}$ are the maximum conductance and Nernst potential of the ions passing through the channel associated with w, respectively, and

$$\tau_w(t) = \frac{1}{\alpha_w(t) + \beta_w(t)}$$

and

$$w_\infty(t) = \frac{\alpha_w(t)}{\alpha_w(t) + \beta_w(t)} \tag{4}$$

are the original functions from the HH model. Note that we use a concise notation and $\alpha_w(t) = \alpha_w(u(t))$.

Define a new variable w_g as follows:

$$w_g(t) = \int_{-\infty}^{t} \gamma(s) e^{-\gamma(t)(t-s)} w_\infty(s) ds, \tag{5}$$

where

$$\gamma(t) = \frac{1}{\tau_w(t)} = \alpha_w(t) + \beta_w(t).$$

Note that in this case γ is a function of time. Using Eq. (4), we can rewrite Eq. (5) as

$$w_g(t) = \int_{-\infty}^{t} \alpha_w(s) e^{-\gamma(t)(t-s)} ds. \tag{6}$$

Note that we use a concise notation and $w_g(t) = w_g(u(t), t)$.

If we differentiate w_g and use Leibniz's rule, we have

$$\begin{aligned} w_g'(t) &= \frac{d}{dt} \int_{-\infty}^{t} \alpha_w(s) e^{-\gamma(t)(t-s)} ds \\ &= \gamma(t) w_\infty(t) + \int_{-\infty}^{t} \alpha_w(s) e^{-\gamma(t)(t-s)} [(s-t)\gamma'(t) - \gamma(t)] ds \\ &= \gamma(t) w_\infty(t) - \gamma(t) \int_{-\infty}^{t} \alpha_w(s) e^{-\gamma(t)(t-s)} ds + \gamma'(t) \int_{-\infty}^{t} \alpha_w(s) e^{-\gamma(t)(t-s)} (s-t) ds. \end{aligned}$$

Therefore, using Eq. (6), we can rewrite the derivative above as

$$w_g'(t) = \gamma(t) w_\infty(t) - \gamma(t) w_g(t) + \gamma'(t) \int_{-\infty}^{t} \alpha_g(s) e^{-\gamma(t)(t-s)} (s-t) ds$$

or as

$$w_g' = \frac{w_\infty(u) - w_g}{\tau_w(u)}, +\epsilon.$$

When compared to the original equation for w (see Eq. (3)), ϵ can be taken as an approximation error and is equal to $\gamma'(t) \int_{-\infty}^{t} \alpha_w(s) e^{-\gamma(t)(t-s)} (s-t)$. Since the approximation error is proportional to $\gamma(u(t))' = \frac{d\gamma}{du} u'(t)$, we anticipate non-negligible approximation errors during depolarization (high values of $u'(t)$) and whenever γ changes too much with respect to a small change in u ($\frac{d\gamma}{du}$). Note that when $\gamma'(t) = 0$, the time constant does not vary and the error is zero, which was exactly the case for the FHN model. Therefore, the following integro-differential equation is an approximation of the ODE system given in Eq. (3):

$$u' = f(u) + \bar{g}(u - \bar{u}) \int_{-\infty}^{t} \alpha_w(s) e^{-\gamma(t)(t-s)} ds.$$

2.3. From integro-differential equation to DDE

Consider a generic integro-differential equation:

$$u'(t) = f(t) - \int_{t_{int}}^{t} g(u, s) ds. \tag{7}$$

Note that we use a concise notation and $g(u, s)$ or $g(t, s)$ may stand for $g(u(t), u(s), t, s)$. Following the trapezoidal rule, to compute the value of a definite integral, we divide the area under the curve $g(u, s)$ into two trapezoids of width δ and heights $g(t, t)$, $g(t, t-\delta)$, and $g(t, t-2\delta)$. Next, we add the areas of each trapezoid to obtain the approximate value for the proposed integral. As shown in Fig. 2, using two trapezoids we have $\delta = \frac{t - t_{int}}{2}$ and the area equivalent to the proposed integral is calculated by the following expression:

$$\int_{t_{int}}^{t} g(t, s) ds \approx A + B = \frac{(g(t,t) + g(t, t-\delta))\delta}{2} + \frac{(g(t, t-\delta) + g(t, t_{int}))\delta}{2} = \frac{\delta}{2}(g(t,t) + 2g(t, t-\delta) + g(t, t_{int})). \tag{8}$$

In our scenario, we evaluate the integral from t_{int} to t as an approximation of the integral from $-\infty$ to t. Substituting approximation (8) into Eq. (7), we obtain the following DDE:

$$u'(t) = f(t) - \frac{\delta}{2}(g(t,t) + 2g(t, t-\delta) + g(t, t_{int})).$$

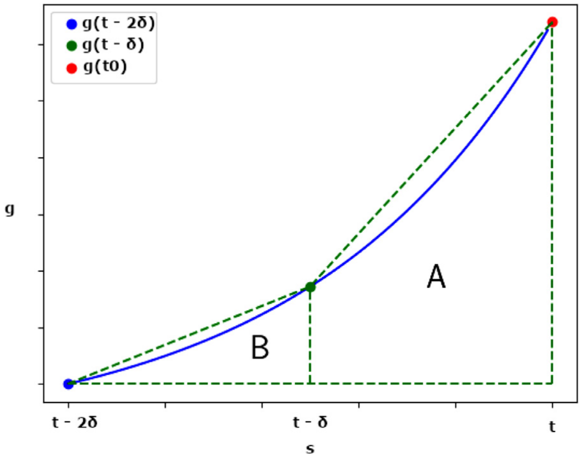

Fig. 2. Calculating the integral of g by adding the areas A and B.

2.4. Implementations

All the models presented in this work were discretized using the explicit Euler method with time steps equal to 0.01 and implemented in Python 2.7. The integrals were approximated using the trapezoidal rule, as discussed earlier. The Python source codes can be made available upon request to the authors.

3. Results

3.1. Fitzhugh-Nagumo model

Consider the FHN model given by Eq. (1), with stimulus given by:

$$I(t) = \begin{cases} 0.1, & \text{if } 2k \leq t \leq 2k + 0.05, \ k = 0, 1 \ldots, N, \\ 0.0, & \text{otherwise.} \end{cases}$$

Comparing systems (2) and (1), we have $\beta = 2$ and $\tau = 2$, so that $\gamma = \frac{1}{2}$. With these values we can formulate the equivalent integro-differential equation:

$$\epsilon u' = u(u - a)(1 - u) + I(t) - \int_{-\infty}^{t} \frac{1}{2} e^{-\frac{(t-s)}{2}} 2u(s)ds.$$

We first take $a = 0.1$ and compare the solutions from the original system of ODEs and from the integro-differential equation. The integral was evaluated using the trapezoidal rule with a discretization of $\delta = 0.01$. For the integro-differential equation we have also included the existence of an initial history (before $t = 0$) of two time units rather than an infinite past; therefore, we are actually solving:

$$\epsilon u' = u(u - 0.1)(1 - u) + I(t) - \int_{-2}^{t} e^{-\frac{(t-s)}{2}} u(s)ds.$$

Fig. 3 compares the results, which are equivalent. To support conversion of the integro-differential equation to a delay-differential equation, we next evaluate a sliding window for integration where the inferior limit varies with time. The integral then becomes

$$w(t) = \int_{t_{int}}^{t} e^{-\frac{(t-s)}{2}} u(s)ds,$$

where the lower integration limit t_{int} is 0 for the first time step but is updated based on the values of u and u'. Here, we define t_{int} as follows:

$$t_{int}(t) = t_m(t) - \rho_t,$$

where $t_m(t) = \max\{0, t\}$, such that $u'(t_m) > 0$ and $0 < u(t_m) < \rho_u$. In other words, $t_m(t)$ is the most recent time where u is increasing but is still smaller than some threshold value (ρ_u), and we set the lower integration limit $t_{int}(t)$ to be slightly lower than this value (by ρ_t). In this work, we use $\rho_u = 0.15$ and $\rho_t = 0.22$. The resulting equation is

$$\epsilon u' = u(u - 0.1)(1 - u) + I(t) - \int_{t_{int}(t)}^{t} e^{-\frac{(t-s)}{2}} u(s)ds.$$

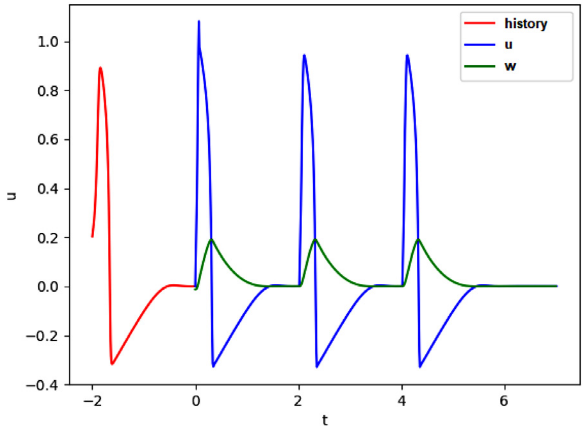

Fig. 3. Action potentials and refractory variable traces obtained from the original and integro-differential equation for the FHN model, along with the history data used for the integro-differential version. Note that the results of the two models are indistinguishable.

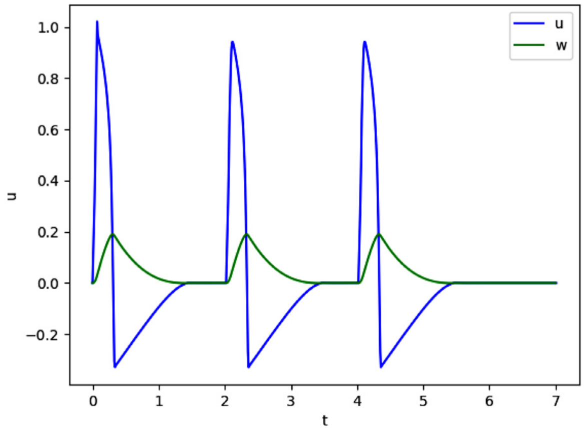

Fig. 4. Results from using the integro-differential equation with the sliding-window method to evaluate the integral.

Fig. 4 shows that the results obtained with the sliding-window version are again the same as those of the original FHN model. Therefore, throughout the remainder of this work all the integro-differential equations will be evaluated using the sliding-window method.

Next, we will approximate the integral using a few points to derive a delay-differential equation. The interval of the integral is $[t_{int}, t]$ and we will use only two trapezoids that involve the points t, $t-\delta$ and $t_{int}=t-2\delta$. Since we are integrating something similar to $g(t)=e^{\frac{-(t-s)}{2}}u(s)$, by definition of t_{int} we have $g(t_{int})$ near zero and we will approximate it by setting $g(t_{int})=0$. In addition, $g(t)=e^{\frac{-(t-t)}{2}}u(t)=e^0u(t)=u(t)$. In this way we have only one delay given by $g(t-\delta)$. For simplicity, we choose two trapezoids with equal bases, i.e., $\delta=(t-t_{int})/2$. Putting it all together, we have the following approximation for the FHN variable w:

$$w(t)\approx\frac{\delta}{2}(u(t)+2e^{-\frac{\delta}{2}}u(t-\delta))=\frac{t-t_{int}}{4}(u(t)+2e^{\frac{t_{int}-t}{4}}u(\frac{t+t_{int}}{2}).$$

Therefore, we arrive at the following single DDE that approximates the two equations of the FHN model:

$$\epsilon u'=u(u-a)(1-u)+I(t)-\frac{t-t_{int}}{4}\left(u(t)+2e^{\frac{t_{int}-t}{4}}u(\frac{t+t_{int}}{2})\right). \tag{9}$$

Fig. 5 presents the solution of the DDE-based model given by Eq. (9). We observe that the approximations we performed affected the shape of the AP. For instance, the time the AP is in the hyperpolarization phase is decreased in the DDE-based model as compared to the original FHN action potential.

For comparison, we also analyzed the case where we use only one trapezoid defined by the points t_{int} and t to approximate the integral. Doing so, we find a single non-autonomous differential equation, i.e., there is no longer a delay involved in the formulation:

$$\epsilon u'=u(u-0.1)(1-u)+I(t)-u(t)\frac{t-t_{int}}{2}$$

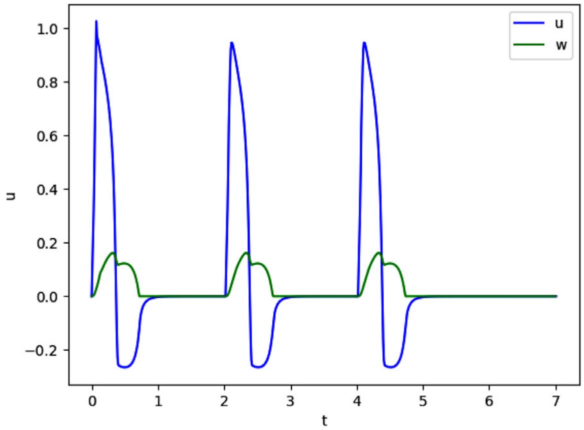

Fig. 5. Results of the DDE-based model to approximate the FHN model. Action potentials have shapes similar to those of the original model and include a hyperpolarization phase.

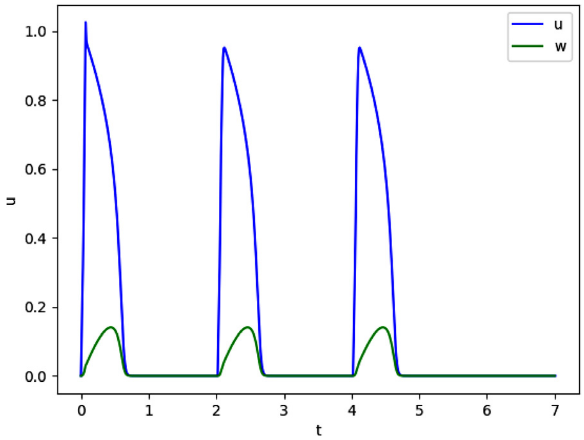

Fig. 6. Approximating the FHN model with a single non-autonomous differential equation. The hyperpolarization phase no longer is reproduced.

The results obtained are presented in Fig. 6. Although this model represents the states of depolarization, repolarization, and rest, it does not capture hyperpolarization. However, it might be an interesting starting point for the modeling of excitable cardiac myocytes, which repolarize directly to a resting potential. Because our focus in the present work is on reproducing the FHN and HH models, we will not further pursue this particular approach here.

Fig. 7 summarizes the results we obtained for the different FHN representations. The integro-differential equation matches exactly the original FitzHugh-Nagumo model, whereas the approximation via a single DDE reproduces all the phases of the action potential, but hyperpolarization is shorter. The single non-autonomous differential equation does not reproduce the hyperpolarization phase.

As a final experiment for the FHN model, we tested our approximations in an auto-oscillatory scenario by making $a = -0.1$ in Eq. (1), which destabilizes the fixed point corresponding to the rest state. Fig. 8 presents the results for the original FHN and the integro-differential equation. Once again, the results match and reproduce oscillations with a period of 1.36s. When using the DDE, the results are very close to those of the original model, but the period is equal to 1.05s, which is shorter than the period of the original model, as shown in Fig. 9.

3.2. Hodgkin-Huxley model

Consider the HH model given by Eq. (2), with stimulus given by:

$$I(t) = \begin{cases} 500, & \text{if } 15k \leq t \leq 15k + 0.2, \; k = 0, 1 \ldots, N, \\ 0.0, & \text{otherwise.} \end{cases}$$

Fig. 10 shows the reference solution obtained with the original HH model.

As with the FHN model, as a first step we generated an integro-differential equation that approximates the original system of ODEs by replacing the m, n, and h gates with their respective approximations using integrals as in Eq. (6) to

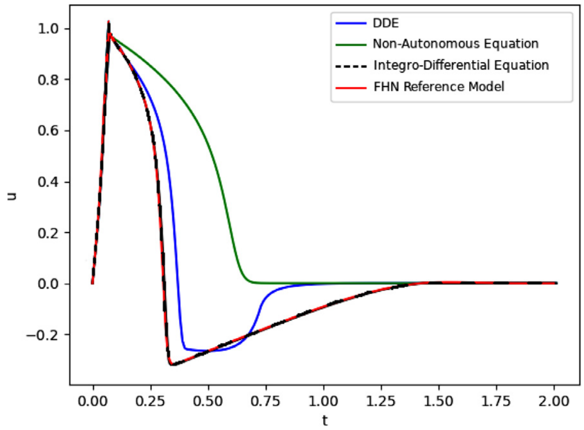

Fig. 7. Comparison of action potential shapes obtained using the original, integro-differential, single DDE, and non-autonomous differential equation representations of the FitzHugh-Nagumo model.

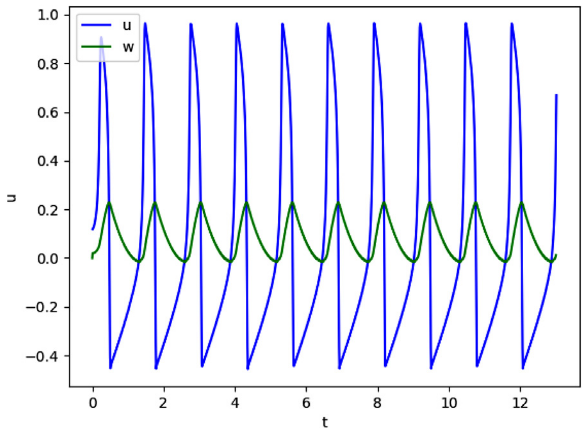

Fig. 8. Auto-oscillatory behavior in the integro-differential equation formulation of the FHN model. The action potentials match those obtained using the original FHN model under the same conditions.

obtain w_m, w_n, and w_h, respectively. The following integrals were used to approximate the original gate variables:

$$w_h(t) = 1 - \int_{-\infty}^{t} \beta_h(v(s))e^{-\alpha_h(v(t))+\beta_h(v(t))(t-s)}ds,$$

$$w_n(t) = \int_{-\infty}^{t} \alpha_n(v(s))e^{-\alpha_n(v(t))+\beta_n(v(t))(t-s)}ds,$$

$$w_m(t) = \int_{-\infty}^{t} \alpha_m(v(s))e^{-\alpha_m(v(t))+\beta_m(v(t))(t-s)}ds.$$

From the above, we see that the approximations favor one of the constant rates, usually α. However, for the sodium inactivation gate, h, better results were obtaining using the rate β. In addition, these approximations generated values that were not always between 0 and 1. Therefore, Heaviside functions were used to ensure that $w_h \geq 0$ and $w_n \leq 1$. Fig. 11 shows the results of the single integro-differential equation that approximates the HH model. Although for the FitzHugh-Nagumo case we obtained exact agreement for this step, the use of multiple gates in the HH model as well as the more complicated derivative expressions prevented the same level of agreement here, especially for the m gate. However, the results remain qualitatively similar overall: action potentials are generated, although they are shorter in duration.

Next, we generated a DDE-based model by (1) considering a sliding window where the interval of the integral is $[t_{int}(t), t]$ and (2) numerically integrating w_n, w_m and w_h using the trapezoidal rule. Therefore, we use the same approximations and techniques as used before for the FHN model. Consider the integrand

$$F_g(t,s) = \alpha_g(u(s))e^{-(\alpha_g(u(t))+\beta_g(u(t)))(t-s)},$$

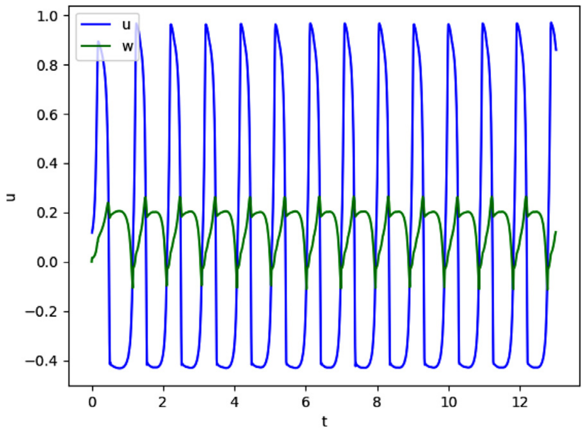

Fig. 9. Action potentials using the DDE formulation of the HH model for the same parameters as in Fig. 8. Qualitatively similar results are obtained, although the period is shorter for the DDE version.

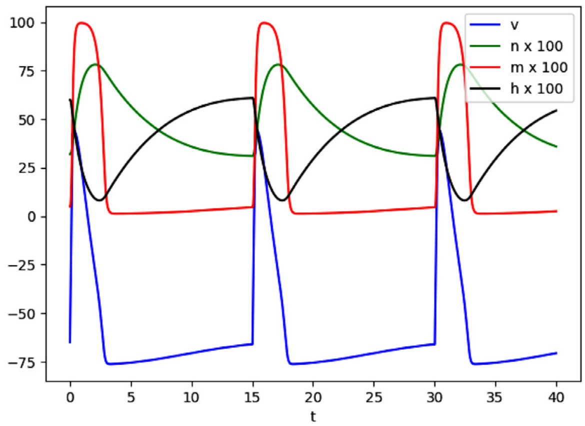

Fig. 10. Reference solution for the original Hodgkin-Huxley model. Note that the gating variables have been multiplied by 100.

where g represents n, m, or h. As before, we used only two trapezoids involving the points t, $t-\delta$ and $t_{int}=t-2\delta$, with $\delta=(t-t_{int})/2$. In this way, we arrive at the following approximations for w_n, w_m and w_h:

$$w_n(t,s) = \delta\frac{F_n(t,t)+F_n(t,t-\delta)}{2} + \delta\frac{F_n(t,t-\delta)+F_n(t,t_{int})}{2},$$
$$w_m(t,s) = \delta\frac{F_m(t,t)+F_m(t,t-\delta)}{2} + \delta\frac{F_m(t,t-\delta)+F_m(t,t_{int})}{2},$$
$$w_h(t,s) = \delta\frac{F_h(t,t)+F_h(t,t-\delta)}{2} + \delta\frac{F_h(t,t-\delta)+F_h(t,t_{int})}{2}.$$

Unfortunately, the DDE model obtained using these approximations did not provide good solutions. The problem is related to the m gate. Since it changes so fast, the approximation of w_m using only two trapezoids was very poor. One option would be to increase the number of trapezoids, which is equivalent to adding more delays. In pursuing this approach, we observed that w_m needed a minimum of six delays to generate a good approximation of the AP of the original HH model. Instead, to keep our DDE model as simple as possible, we assumed here that m instantaneously reached its equilibrium; i.e., we assumed $w_m = m_\infty$. The results of this DDE formulation of the HH model are shown in Fig. 12, where they are compared with the results of the original model and the integro-differential model. Both the integro-differential and DDE versions result in shorter action potentials than the original HH model. Despite these quantitative differences, the three models produce qualitatively similar results. In addition, our new DDE model includes other important properties. For example, like the original HH model, it has a qualitatively similar refractory period, as shown in Fig. 13.

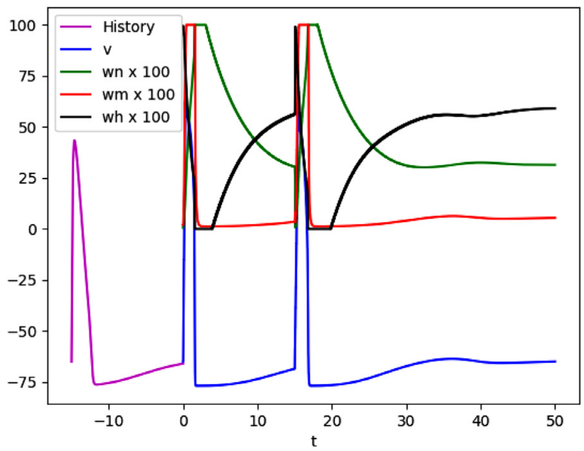

Fig. 11. Results of the single integro-differential equation that approximates Hodgkin-Huxley model. Although good qualitative agreement is obtained, the match with the original model is not as close as for the FHN model.

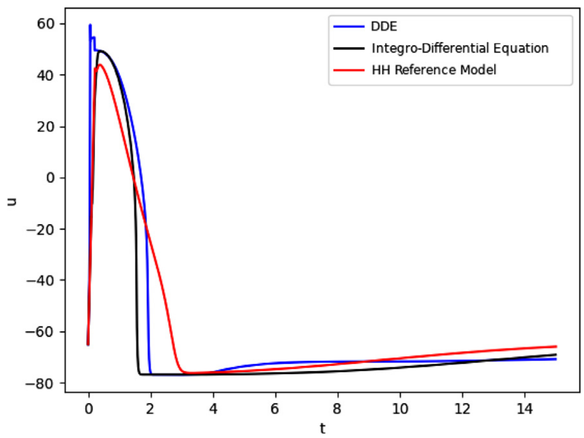

Fig. 12. Comparison of action potentials produced using the integro-differential equation, the single DDE, and the original HH models.

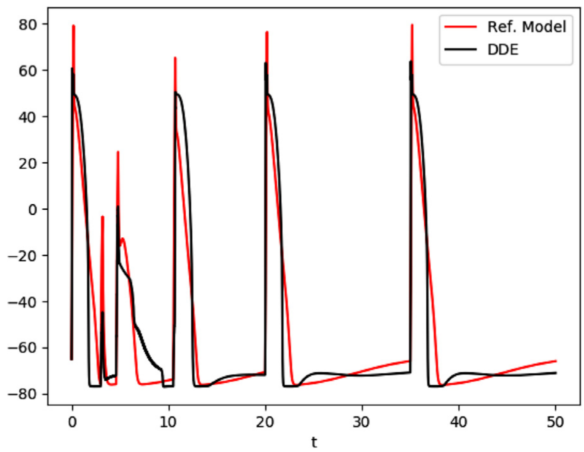

Fig. 13. Response to a series of stimuli during different times within the refractory period using the DDE-based approximation to the HH model and the reference HH model. The single DDE-based model can qualitatively reproduce the refractory period mechanism of the original HH model.

4. Discussion

4.1. Conclusion

We have presented, for the first time, alternative versions of two well-known models of neural action potentials (and excitable systems more broadly) using single delay-differential equations. The two-variable FitzHugh-Nagumo and the four-variable Hodgkin-Huxley models were each reduced to a single variable delay-differential equation. We described in detail our methodology. We first searched for a model based on an integro-differential equation and then converted it to a single delay-differential equation using classical numerical integration. We also compared simulation results obtained using the original, integro-differential, and delay-differential models. For the FHN case, our new model was in good agreement to the original one and could reproduce essential properties, such as automaticity and refractory period. For the HH model, we also were able to represent the model using a single variable with delays. However, to obtain good results with a reduced number of delays (up to two delays), we chose to approximate the m gate with its steady-state value. Doing so allowed us to obtain qualitatively similar action potentials. Without this simplification, the single variable delay-differential equation needed to use six delays to generate a good approximation of the m gate.

4.2. Relation to prior DDE modeling for neural and cardiac cells and tissue

Delay-differential equations have been used previously to describe dynamics in neural and cardiac settings. For example, previous studies have been performed to analyze the effects of delays in neural networks based on the FHN model [9,10]. Among these effects, it is possible to cite mixed-mode oscillations [11], which consist of oscillatory alternations of different amplitudes in a dynamical system. Delayed equations are also capable of representing bursting and chaotic behavior [12]. Other studies have used DDEs to represent spatial AP propagation in ring-shaped geometries [13–15]. Fewer studies have considered using delays in models of action potentials themselves; two of the authors have done so previously in [16] and [17], where DDEs were used in electrophysiological models of the heart to study the phenomenon of alternans in cardiac cells.

4.3. Limitations and future work

The goal of this paper was to demonstrate the possibility of achieving dynamics similar to the original two-variable FHN and four-variable HH models using a single DDE formulation in each case. Because the FHN model includes only one refractory variable, it was relatively straightforward to transform it into an integro-differential formulation and then to a single DDE. For the HH model, even though it includes more variables, we again were able to qualitatively reproduce the solutions of the original model using only a single-variable DDE. Therefore, it was possible to successfully incorporate the dynamics of all the HH gating variables into a single variable DDE.

In this first attempt, we did not try to optimize our DDE models for the best quantitative match with the original models. Instead, we focused on demonstrating that it was possible to generate action potential models with a single DDE. Nevertheless, there is plenty of room for further improvements. For instance, here we chose to retain all the original functions and parameter values of the FHN and HH models. In future studies, we aim to improve the quantitative agreement between the solutions of the models by adjusting the parameter values and possibly the functions of the new models. In addition, there is also room for further tuning the methods and numerical parameters chosen for the DDE implementations, including thresholds, discretization values, and integration rules, among others.

We have focused on the evaluation of basic action potential properties of the new models, such as AP waveform, oscillatory behavior, and refractory period. A more detailed study of the dynamics of the new models is still pending. For instance, in the near future, we plan to study the existence and stability of fixed points and limit cycles, particular parameter regimes, and the full range of dynamics of the new DDE-based models. Finally, we plan to evaluate if this new approach could be applied to other excitable systems, such as cardiac myocytes.

In summary, we have shown that it is possible to use delay-differential equations as building blocks for the modeling of cellular action potentials. We believe our results open a new path for the development of models of cell electrophysiology. The precise details of how these new models based on delay-differential equations compare to traditional HH equations or more recent formulations based on Markov-chains is a topic that deserves further attention.

Acknowledgments

This work was supported in part by UFJF, Universidade Federal de Juiz de Fora Grant: Programa de Pós-graduação em Modelagem Computacional, CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico Grant: Bolsa de Produtividade em Pesquisa, CAPES, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Grant: Programa de Pós-graduação em Modelagem Computacional, FAPEMIG, Fundação de Amparo à Pesquisa do Estado de Minas Gerais Grant number: APQ-03213-17 and the National Science Foundation CNS-1446312 (EMC).

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