Physics Letters A 383 (2019) 125976

Contents lists available at ScienceDirect

Physics Letters A

www.elsevier.com/locate/pla

Neuron model with conductance-resistance symmetry

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ARTICLE INFO

Article history:
Received 12 December 2018
Received in revised form 4 September 2019
Accepted 6 September 2019
Available online 12 September 2019
Communicated by M.G.A. Paris

Keywords:
Conductance-resistance symmetry
Opening probability for ion transport channel
Opening probability for protein gating channel
Spontaneous firing
Hodgkin-Huxley equations
FitzHugh-Nagumo equations

ABSTRACT

This paper is to derive a mathematical model for neuron by imposing only a principle of symmetry that two modelers must obtain the same model when one models the conductances of ion channels and the other models the channels' resistances. Conductance-voltage characteristics for ion transport channels and protein gating channels are both derived. They are expressed as products of maximal conductances and opening probabilities for both types of channel. It gives an explanation to the role of spontaneous firing of individual channel pores and to the origin of leak current. The model has a better fit to a classical data than the Hodgkin-Huxley model does. It can also be reduced to a 2-dimensional model qualitatively similar to the FitzHugh-Nagumo equation and be expanded to a model of three ion channels capable of spike bursts.

1. Introduction

Because of its complexities no one thought it possible to derive neuron models by logic alone. This paper is to show that perhaps is the case. The place to start is to assume that an ion current across a neuron's membrane to be a nonlinear resister with $I = g(V - E) = \frac{1}{r}(V - E)$ and to ask if a modeler can derive the same model regardless whether he or she prefers to model the conductance g or to model the resistance r. Here, V is the intracellular membrane voltage, E is called the Nernst or reversal potential of the ion channel and is specific to the ion considered, and I is the ion species's cross-membrane current.

2. Theory and calculation

These two approaches are constrained only by the conductance-resistance reciprocal symmetry:

$$gr = 1. \tag{1}$$

As functions of the time, the conductance and resistance must satisfy by the product rule that $r\frac{dg}{dt} + g\frac{dr}{dt} = 0$. The simplest assumption we can make about this relation is to assume the separation of variables equals a constant

$$\frac{1}{g}\frac{dg}{dt} = -\frac{1}{r}\frac{dr}{dt} \equiv a. \tag{2}$$

For $a = 0$, it leads to the linear Ohmic channel $g \equiv$ constant, to which neural ion channels do not belong ([5]). For $a \neq 0$, either $g(t) = g_0 e^{at}$ or $r(t) = r_0 e^{-at}$ grows in time without bound. But this is not consistent with what we know about neurons or any natural process since at clamped voltages both potassium and sodium channels' conductances saturate at finite values ([8]) after a long time. We then assume instead that the righthand side of (2) be a function of the conductance (or equivalently the resistance)

$$\frac{1}{g}\frac{dg}{dt} = A(g), \text{ equivalently }, \frac{1}{r}\frac{dr}{dt} = -A(g). \tag{3}$$

We further ask if there is a function $A(g)$ so that regardless a modeler's preference the two models look the same? That is, if there is a function $A(g)$ so that

$$\frac{1}{g}\frac{dg}{dt} = A(g) \text{ and } \frac{1}{r}\frac{dr}{dt} = -A(g) = A(r)? \tag{4}$$

If true, it imposes the following condition

$$-A(g) = A(r), \text{ equivalently }, A(g) + A(r) = 0. \tag{5}$$

This relation can be extended more generally. In fact, we anticipate a family of functions with parameters to satisfy the sought-after conductance-resistance symmetry. First, we only restrict our

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https://doi.org/10.1016/j.physleta.2019.125976
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attention to those parameters having the same dimensions as the conductance g and the resistance r. That is, if γ is a parameter of the same dimension as g, then $\rho = 1/\gamma$ is the corresponding parameter to $r = 1/g$, satisfying the same CR-reciprocal symmetry (1). As a result, the problem above can be generalized to find a solution $A(g,\gamma)$ to equation (5) above with $A(r)$ replaced by $A(r,\rho)$. Next, for any parameter not having the same dimension as g or r, say α, because the CR-reciprocal symmetry does not apply to α, the problem becomes to find a solution $A(g,\gamma,\alpha)$ to (5) as in below:

$$A(g,\gamma,\alpha) + A(r,\rho,\alpha) = 0, \text{ equivalently},$$
$$A(g,\gamma,\alpha) + A(\frac{1}{g}, \frac{1}{\gamma}, \alpha) = 0. \tag{6}$$

It turns out a simple nontrivial solution to the equation above is of the form

$$A(g,\gamma,\alpha) = \alpha \frac{1}{\sqrt{g\gamma}}(\gamma - g) \tag{7}$$

which is a two-parameter family of functions. Here, parameter γ has the same dimension as g and α has the dimension of A which is $1/[T]$. Parameters such as α are called rate parameters. It is straightforward to check

$$-A(g,\gamma,\alpha) = -\alpha \frac{1}{\sqrt{g\gamma}}(\gamma - g) = \alpha \frac{1}{\sqrt{r\rho}}(\rho - r) = A(r,\rho,\alpha), \tag{8}$$

and thus equation (6) holds. The functional form (7) is said to satisfy the *conductance-resistance symmetry*.

To see how far this line of reasoning can go, we first solve the conductance kinetic equation

$$\frac{dg}{dt} = gA(g,\gamma,\alpha) = \alpha\sqrt{\frac{g}{\gamma}}(\gamma - g) \tag{9}$$

by some undergraduate textbook techniques for ordinary differential equations. The solution is

$$g(t) = \gamma\left[\frac{ke^{\alpha t} - 1}{ke^{\alpha t} + 1}\right]^2, \text{ with } k = \frac{1 + \sqrt{g_0/\gamma}}{1 - \sqrt{g_0/\gamma}} \tag{10}$$

with $g(0) = g_0$ being the initial value. The solution is very illuminating. For $\alpha \neq 0$, $g(t)$ converges to γ as $t \to +\infty$. For $\alpha > 0$ and $0 < g_0 < \gamma$, $g(t)$ is always increasing. This seems to suggest that if the voltage is clamped at a given value, the ion channel's conductance must saturate toward γ. In addition, the rate of convergence is of $e^{-\alpha t}$, implying that α is exactly the rate constant for the conductance kinetics. Because $r(t) = 1/g(t)$ is the solution to the resistance equation $dr/dt = rA(r,\rho,\alpha)$ we have the symmetric form for the solution

$$r(t) = \rho\left[\frac{ke^{\alpha t} + 1}{ke^{\alpha t} - 1}\right]^2, \text{ with } k = \frac{\sqrt{r_0/\rho} + 1}{\sqrt{r_0/\rho} - 1}. \tag{11}$$

Equation (9) and its resistance equivalence are referred to satisfy the *conductance-resistance kinetic symmetry* (CRKS). For a reason to be explained later, we will call it the *switch equation*.

Since γ, ρ are the voltage-clamped conductance and resistance respectively, they are functions of the cross-membrane voltage V satisfying $\gamma(V)\rho(V) = 1$, the same CR-reciprocal symmetry. Differentiating the identity in V we obtain similarly by separating the variables

$$\frac{1}{\gamma}\frac{d\gamma}{dV} + \frac{1}{\rho}\frac{d\rho}{dV} = 0. \tag{12}$$

We assume also these voltage-dependent γ and ρ satisfy a similar conductance-resistance symmetry with respect to the cross-membrane voltage instead. Then,

$$\frac{1}{\gamma}\frac{d\gamma}{dV} = A(\gamma,\bar{g},\eta) \text{ and } \frac{1}{\rho}\frac{d\rho}{dV} = A(\rho,\bar{r},\eta) \tag{13}$$

equivalent to

$$A(\gamma,\bar{g},\eta) + A(\rho,\bar{r},\eta) = 0 \tag{14}$$

for a CR-symmetric functional A. Here parameters $\bar{g}$ and $\bar{r}$ satisfy the CR-reciprocal symmetry (1), having the same dimensions as γ and ρ, respectively, and η is a rate parameter having the dimension of $1/[V]$.

Two types of channels are treated separately: voltage-activation ion channel and voltage-gating protein channel. For the first type, we assume that the CR-symmetric $A(\gamma,\bar{g},\eta)$ has a positive V-rate parameter $\eta > 0$. Specifically we have

$$\frac{d\gamma}{dV} = \gamma A(\gamma,\bar{g},\eta) = \eta\sqrt{\frac{\gamma}{\bar{g}}}(\bar{g} - \gamma). \tag{15}$$

Namely, for the ion channel, the channel conductance γ increases with depolarization in increasing V because $A > 0$ for $0 < \gamma < \bar{g}$. Similarly, γ decreases with hyperpolarization in decreasing V. Again, γ can be solved explicitly as

$$\gamma(V) = \bar{g}\left[\frac{ke^{\eta V} - 1}{ke^{\eta V} + 1}\right]^2, \text{ with } k = \frac{1 + \sqrt{\gamma_0/\bar{g}}}{1 - \sqrt{\gamma_0/\bar{g}}} \tag{16}$$

with parameter γ_0 the 'initial' conductance when $V = 0$, and the property that $\lim_{V\to\infty}\gamma(V) = \bar{g}$, i.e., $\bar{g}$ is the maximal conductance as V increases to infinity. The solution exists at least for $V \geq 0$.

To extend the solution below $V = 0$, we need to note a few facts about Eq. (15). First, it has the trivial solution $\gamma(V) \equiv 0$. Second, a solution is increasing (or non-decreasing) in V if it is below $\bar{g}$ at some value of V. Most important of all, because the right hand is not differentiable at $\gamma = 0$, the solution may not be unique when originated from $\gamma = 0$. In fact, we can explicitly construct another solution which is zero for V below some value, Q, and strictly increasing above Q. More specifically, we can re-parameterize and rewrite the solution above as

$$\gamma(V) = \bar{g}\left[\frac{ke^{\eta V} - 1}{ke^{\eta V} + 1}\right]^2 = \bar{g}\left[\frac{e^{\eta(V-Q)} - 1}{e^{\eta(V-Q)} + 1}\right]^2 \tag{17}$$

with $Q = -\ln k/\eta$. Then $\gamma(V)$ exists for $V \geq Q$ and $\gamma(Q) = 0$. This form can be expressed alternatively as

$$\gamma(V) = \bar{g}\tanh^2\left(\frac{\eta}{2}(V - Q)\right). \tag{18}$$

By further extending this solution below Q to be $\gamma(V) = 0$ we obtain the solution we need

$$\gamma = \bar{g}\tanh^2\left(\frac{\eta}{2}(V - Q)\right)H(V - Q) := \bar{g}\phi(V,\eta,Q) \tag{19}$$

where $H(x)$ is the Heaviside function with $H(x) = 0,\ x < 0$ and $H(x) = 1,\ x \geq 0$. Notice more importantly that the function $\phi(V,\eta,Q) = \tanh^2\left(\frac{\eta}{2}(V - Q)\right)H(V - Q)$ whose range is $[0,1)$ can be interpreted as the probability of opening pores for the ion species. For the sodium and potassium ion channels, we have their corresponding limiting conductances as

$$\gamma_{\mathrm{K}} = \bar{g}_{\mathrm{K}}\phi_{\mathrm{K}}(V,\eta_{\mathrm{K}},Q_{\mathrm{K}}), \text{ and } \gamma_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}}\phi_{\mathrm{Na}}(V,\eta_{\mathrm{Na}},Q_{\mathrm{Na}}) \tag{20}$$

which are referred to as the GV-characteristics for the ion channels with the probability functions ϕ given as in (19).

The phenomenon of voltage-gating ([3]) occurs when a small pulse-like outward current is generated due to the movement of charged molecules from the sodium channel pores in responding to some conformational changes of the pores to depolarizing voltage. Its effect is opposite to voltage-activated ion channels. That is, unlike ion channels, gating conductance decreases with depolarizing voltage and increases with hyperpolarization. Again, we assume the gating channel is Ohmic-like whose time-dependent conductance satisfies CRKS for which the voltage-dependent limiting conductance, i.e., its GV-characteristic, is also CR-symmetric satisfying (15) but with a negative V-rate constant. Specifically we have

$$\frac{d\gamma}{dV} = \gamma A(\gamma, \bar{g}, -\eta) = -\eta\sqrt{\frac{\gamma}{\bar{g}}}(\bar{g} - \gamma). \tag{21}$$

For the conductance equation, we can derive or check by exactly the same arguments above that it has a solution $\gamma_{\mathrm{G}} = \bar{g}_{\mathrm{G}}\phi_{\mathrm{G}}(V, \eta_{\mathrm{G}}, Q_{\mathrm{G}})$ with ϕ_{G} defined as follows

$$\phi_{\mathrm{G}}(V, \eta_{\mathrm{G}}, Q_{\mathrm{G}}) = H(Q_{\mathrm{G}} - V)\tanh^2\left(\frac{\eta_{\mathrm{G}}}{2}(Q_{\mathrm{G}} - V)\right), \tag{22}$$

which is a decreasing function for $V \le Q_{\mathrm{G}}$ and zero for $V \ge Q_{\mathrm{G}}$. Equation (15) and its solutions (19) are said to satisfy the *conductance-resistance characteristic symmetry* (CRCS). The same is said for (21) and (22), because both ion and gating characteristics satisfy the same type of equations and their solutions can be unified as

$$\phi(V, \eta, Q) = H(\mathrm{sign}(\eta)(V - Q))\tanh^2\left(\frac{|\eta|}{2}(V - Q)\right), \tag{23}$$

since (21) can be changed to (15) under the reversal transformation $V \to -V$.

Expectedly, the conductance models satisfying the kinetic symmetry and the characteristic symmetry are unit free or scale-invariant. For example, for the potassium channel we can rescale $g_{\mathrm{K}} = \bar{g}_{\mathrm{K}}n$ to simplify the kinetic equation $dg_{\mathrm{K}}/dt = g_{\mathrm{K}}A(g_{\mathrm{K}}, \gamma_{\mathrm{K}}, \alpha_{\mathrm{K}})$ to its dimensionless form

$$n' = \frac{dn}{dt} = nA(n, \phi_{\mathrm{K}}, \alpha_{\mathrm{K}}). \tag{24}$$

Similarly, for the sodium and gating currents the rescaling $g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}}m$, $g_{\mathrm{G}} = \bar{g}_{\mathrm{G}}h$ transform their dimensional equations to dimensionless ones:

$$m' = mA(m, \phi_{\mathrm{Na}}, \alpha_{\mathrm{Na}}), \quad h' = hA(h, \phi_{\mathrm{G}}, \alpha_{\mathrm{G}}). \tag{25}$$

As a result when we couple the conductance kinetics together with the voltage kinetics by the Kirchhoff current law we obtain the following equations if we prefer to model the neuron by its channel conductances:

$$\left\{\begin{aligned} CV' &= -[\bar{g}_{\mathrm{K}}n(V - E_{\mathrm{K}}) + \bar{g}_{\mathrm{Na}}m(V - E_{\mathrm{Na}}) \\ &\qquad + \bar{g}_{\mathrm{G}}h(V - E_{\mathrm{G}})] \\ n' &= \alpha_{\mathrm{K}}\sqrt{n/\phi_{\mathrm{K}}(V)}(\phi_{\mathrm{K}}(V) - n) \\ m' &= \alpha_{\mathrm{Na}}\sqrt{m/\phi_{\mathrm{Na}}(V)}(\phi_{\mathrm{Na}}(V) - m) \\ h' &= \alpha_{\mathrm{G}}\sqrt{h/\phi_{\mathrm{G}}(V)}(\phi_{\mathrm{G}}(V) - h) \end{aligned}\right. \tag{26}$$

with $\phi_{\mathrm{K}}, \phi_{\mathrm{Na}}, \phi_{\mathrm{G}}$ being the voltage-dependent probabilities given by (23). This model looks exactly the same if we choose to model the channels by their resistances with $\bar{r}_{\mathrm{X}} = 1/\bar{g}_{\mathrm{X}}$, $\psi_{\mathrm{X}} = 1/\phi_{\mathrm{X}}$, $x = 1/n$, $y = 1/m$, $z = 1/h$,

$$\left\{\begin{aligned} CV' &= -[(V - E_{\mathrm{K}})/(\bar{r}_{\mathrm{K}}x) + (V - E_{\mathrm{Na}})/(\bar{r}_{\mathrm{Na}}y) \\ &\qquad + (V - E_{\mathrm{G}})/(\bar{r}_{\mathrm{G}}z)] \\ x' &= \alpha_{\mathrm{K}}\sqrt{x/\psi_{\mathrm{K}}(V)}(\psi_{\mathrm{K}}(V) - x) \\ y' &= \alpha_{\mathrm{Na}}\sqrt{y/\psi_{\mathrm{Na}}(V)}(\psi_{\mathrm{Na}}(V) - y) \\ z' &= \alpha_{\mathrm{G}}\sqrt{z/\psi_{\mathrm{G}}(V)}(\psi_{\mathrm{G}}(V) - z). \end{aligned}\right. \tag{27}$$

The question that remains is will this model work? To this end, we will use the conductance model for a detailed analysis. It turns out for numerical simulations, two issues need be dealt with further, one is computational on ODE solvers and the other is about modeling on excitable membrane. Notice from the last three equations of the model that when one or more of the probability functions become zero $\phi_{\mathrm{X}} = 0$, any numerical solver will fail to converge, a so-called stiff equation problem. Adding a sufficiently small number, $\epsilon > 0$, to each denominator inside the square-roots is one solution to the problem. Even if we can remove this algorithmic problem by moving the denominators to the left side of the equations without such small ϵ-addition, there is a more serious problem. Specifically, if variable n, or m, or h is zero at sometime $\bar{t}$, any numerical solver for the equations will leave it zero for all $t \ge \bar{t}$ rather than tracking the channel opening probability function ϕ_{X}. This is because all standard solvers are build to track only one solution of an initial condition by the uniqueness theorem on differential equations whereas the uniqueness theorem does not apply to our equations. To keep the conductances from being stuck in zero forever because of this inability of all solvers, we need to add a sufficiently small number to each numerator inside the square-roots. Coincidentally, these inclusions of small perturbations can be viewed to model the stochastic phenomenon of spontaneous opening of ion channels. In fact, these two problems only require one modeling treatment to (26): replacing the variables n, m, h by $n + \epsilon_{\mathrm{K}}, m + \epsilon_{\mathrm{Na}}, h + \epsilon_{\mathrm{G}}$, respectively, and the GV-characteristics $\phi_{\mathrm{K}}(V), \phi_{\mathrm{Na}}(V), \phi_{\mathrm{G}}(V)$ by $\phi_{\mathrm{K}}(V) + \epsilon_{\mathrm{K}}, \phi_{\mathrm{Na}}(V) + \epsilon_{\mathrm{Na}}, \phi_{\mathrm{G}}(V) + \epsilon_{\mathrm{G}}$, respectively. Such substitutions into equation (26) create another current term in the first equation after collecting all the ϵ-terms:

$$\begin{aligned} I_L &= \epsilon_{\mathrm{K}}\bar{g}_{\mathrm{K}}(V - E_{\mathrm{K}}) + \epsilon_{\mathrm{Na}}\bar{g}_{\mathrm{Na}}(V - E_{\mathrm{Na}}) + \epsilon_{\mathrm{G}}\bar{g}_{\mathrm{G}}(V - E_{\mathrm{G}}) \\ &:= g_{\mathrm{L}}(V - E_{\mathrm{L}}) \end{aligned} \tag{28}$$

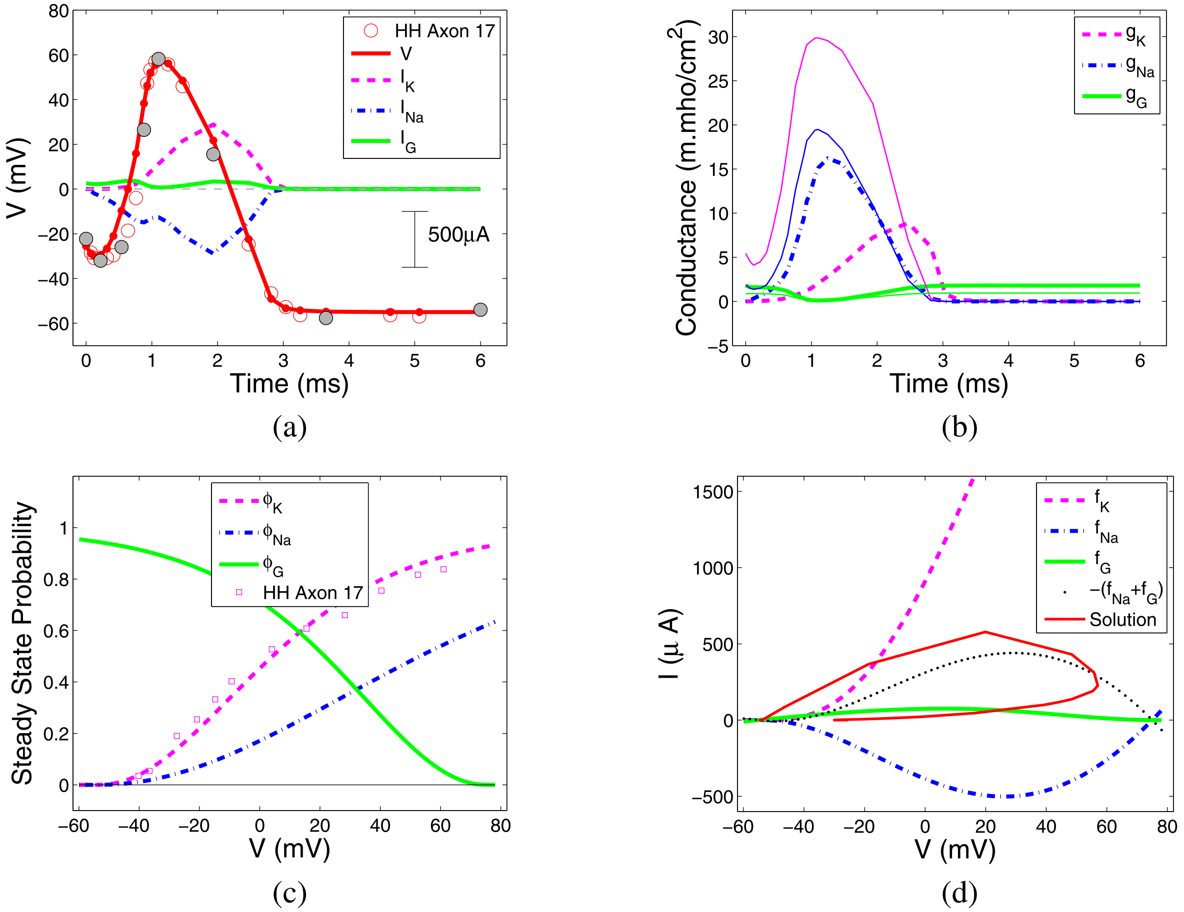
with

$$\begin{aligned} g_{\mathrm{L}} &= \epsilon_{\mathrm{K}}\bar{g}_{\mathrm{K}} + \epsilon_{\mathrm{Na}}\bar{g}_{\mathrm{Na}} + \epsilon_{\mathrm{G}}\bar{g}_{\mathrm{G}}, \text{ and} \\ E_{\mathrm{L}} &= \frac{1}{g_{\mathrm{L}}}(\epsilon_{\mathrm{K}}\bar{g}_{\mathrm{K}}E_{\mathrm{K}} + \epsilon_{\mathrm{Na}}\bar{g}_{\mathrm{Na}}E_{\mathrm{Na}} + \epsilon_{\mathrm{G}}\bar{g}_{\mathrm{G}}E_{\mathrm{G}}). \end{aligned} \tag{29}$$

Notice that, the incorporation of spontaneous firing of neuron channels forces the appearance of the I_L-term which can be interpreted as the leak current discovered by Hodgkin-Huxley ([8]). This leads to the following 4-dimensional model:

$$\left\{\begin{aligned} CV' &= -[\bar{g}_{\mathrm{K}}n(V - E_{\mathrm{K}}) + \bar{g}_{\mathrm{Na}}m(V - E_{\mathrm{Na}}) \\ &\qquad + \bar{g}_{\mathrm{G}}h(V - E_{\mathrm{G}}) + I_L] \\ n' &= \alpha_{\mathrm{K}}\sqrt{(n + \epsilon_{\mathrm{K}})/(\phi_{\mathrm{K}}(V) + \epsilon_{\mathrm{K}})}(\phi_{\mathrm{K}}(V) - n) \\ m' &= \alpha_{\mathrm{Na}}\sqrt{(m + \epsilon_{\mathrm{Na}})/(\phi_{\mathrm{Na}}(V) + \epsilon_{\mathrm{Na}})}(\phi_{\mathrm{Na}}(V) - m) \\ h' &= \alpha_{\mathrm{G}}\sqrt{(h + \epsilon_{\mathrm{G}})/(\phi_{\mathrm{G}}(V) + \epsilon_{\mathrm{G}})}(\phi_{\mathrm{G}}(V) - h) \end{aligned}\right. \tag{30}$$

This basic model can be simplified further in two ways. First, our model can afford to drop the small leak current I_L without altering the qualitative behaviors of the equations. Second, because of the gating protein current is created by deformations of the sodium pores, caused by depolarizing or hyperpolarizing voltages, we can assume the rate-constant α_{G} to be infinity, i.e., the time-evolution of h to its characteristic ϕ_{G} to be instantaneous. As a



(a) (b) (c) (d)

Fig. 1. (a) Best-fit parameter values for (31) are: $E_K = -60.0$ mV, $\bar{g}_K = 35.0$ m.mho/cm^2, $Q_K = -53.0$ mV, $\eta_K = 0.03$/mV, $E_{Na} = 75.0$ mV, $\bar{g}_{Na} = 37.0$ m.mho/cm^2, $Q_{Na} = -53.0$ mV, $\eta_{Na} = 0.015$/mV, $E_G = -55.0$ mV, $\bar{g}_G = 2.0$ m.mho/cm^2, $Q_G = 75$ mV, $\eta_G = 0.03$/mV, $C = 1\mu$F/cm^2, $\alpha_K = 0.7$/ms, $\alpha_{Na} = 8.0$/ms, and $\epsilon_K = \epsilon_{Na} = \epsilon_G = 10^{-4}$. The initial values are $V_0 = -25.5$, a depolarized value from the resting potential, and $n_0 = \phi_K(V_m)$, $m_0 = \phi_{Na}(V_m)$, $h_0 = \phi_G(V_m)$, where $V_m = E_G$ is the resting membrane potential. Filled disks are the data points used for the best fit. (b) The conductances g_X as functions of the time for the action potential. Thin lines are the corresponding GV-characteristics, namely $\bar{g}_X \phi_X$. (c) The opening probabilities ϕ_X are functions of V. In fact, parameters Q_K, η_K are best-fitted to the experiment data of Fig. 5 of [8], and the rest parameter values of (a) are best-fitted to the experiment data of Fig. 12 of [8]. In particular, parameter values $E_K, E_{Na}, \bar{g}_K$ are taken from [8] and the rest are best-fitted by our gradient search algorithm. (d) IV-characteristics for ion currents, e.g., $I = f_K(V)$ is given by $f_K(V) = \bar{g}_K \phi_K(V)(V - E_K)$ etc. Dotted line is the negative of the combined sodium and gating characteristics, $I = -(f_{Na}(V) + f_G(V))$. The resting membrane potential equilibrium is the intersection of this curve with the potassium characteristic curve $I = f_K(V)$.

result, the final conductance model is the following 3-dimensional system of equations:

$$\left\{\begin{array}{l} CV' = -[\bar{g}_K n(V - E_K) + \bar{g}_{Na} m(V - E_{Na}) \\ \qquad + \bar{g}_G \phi_G(V)(V - E_G)] \\ n' = \alpha_K \sqrt{(n + \epsilon_K)/(\phi_K(V) + \epsilon_K)}(\phi_K(V) - n) \\ m' = \alpha_{Na} \sqrt{(m + \epsilon_{Na})/(\phi_{Na}(V) + \epsilon_{Na})}(\phi_{Na}(V) - m) \end{array}\right. \tag{31}$$

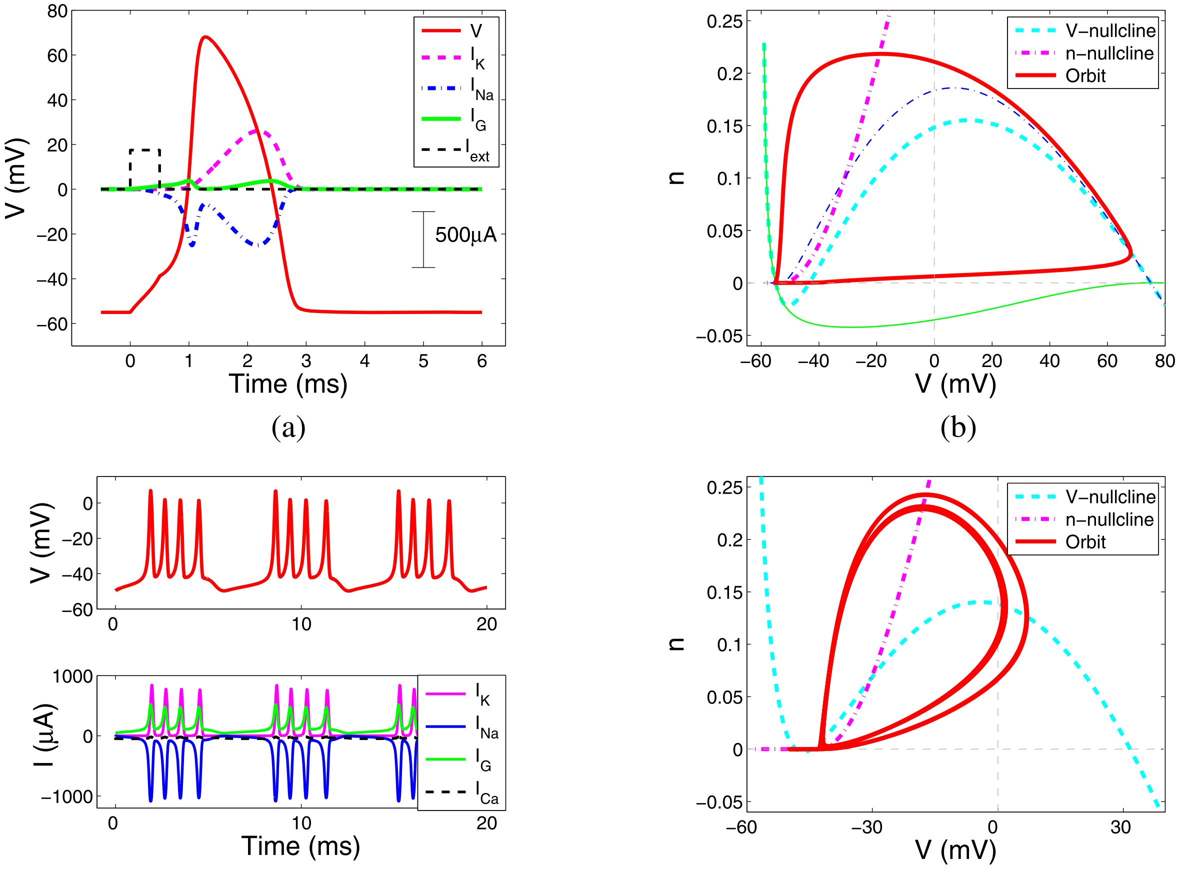
with $\phi_K, \phi_{Na}, \phi_G$ given in (19), (20), (22).

For the resistance model, the issues are somewhat translatable. Although there is no stiffness of the model to deal with, we have to deal with the flip side of the problem, namely, very large values for resistance characteristics ψ_Xs and variables x, y, z, which can slow down or crash an ODE solver. Therefore, we need to cap the characteristics and the variables by large numbers as their upper bounds to count for spontaneous opening of ion channels. This approach should also lead to the derivation of the leak current. However, the required mathematical manipulations may not be as direct as for the conductance model above. Here actually lies a symmetry breaking to the CR-symmetry of equations (26), (27) as a consequence to spontaneous firing.

3. Results

Fig. 1 shows some numerical simulations of the conductance model Eq. (31) after it is fitted to some classical experimental data of [8]. It shows for a set of parameter values, how the solution fits to the experimental data of Hodgkin-Huxley's Axon 17. (The gradient search method used to find this best-fit is the same as described in [4].) By comparing to Hodgkin-Huxley equations' fit to the same data as shown in Fig. 4(d) and Fig. 6(d) of [4], one can conclude that our model does no worse. One can even argue that given its mechanistic derivation our model does better. In particular, as shown in Fig. 1(d), the parallel combination of the sodium and the gating characteristic curves shapes like the letter N, automatically giving rise to the negative conductance branch in the middle. How such N-nonlinearity arises in neuroscience has always been a puzzle ([9,7]). But for our model it is a simple consequence to the underlining bias-free symmetries.

We also used the same parameter values and various large α_Gs greater than 100/ms for the 4-dimensional model (30). The results are virtually the same, giving support to the hypothesis that the temporal dynamics for gating is near instantaneous. It also supports the idea that the leak current can be neglected without problems. All parameter values are very robust. As a result we simply fixed all Q_X values as well as all reversal potential E_X values



(a) (b) (c) (d)

Fig. 2. (a) The parameter values as in Fig. 1 are used for the reduced 2-dimensional model (32) with an intracellular current of $30\mu A$ applied over the time interval $[0, 0.5]$. An action potential is generated from the resting state with a profile and duration comparable to the 3-dimensional model. The intracellular current I_{ext} is magnified 10 times for a better view. It only needs to be greater than the gating current long enough to excite the neuron to fire an action potential. (b) The phase-plane plot for the 2-dimensional model. The V-nullcline is given by $n = -(f_{\text{Na}}(V) + f_{\text{G}}(V))/(V - E_{\text{K}})/\bar{g}_{\text{K}}$ with $f_{\text{Na}}(V)$, $f_{\text{G}}(V)$ the same as in Fig. 1(d). The dot-dash curve in blue and the curve in green are from the sodium ion characteristic and the gating characteristic respectively. (c) A burst of spikes is for the 3-dimensional model (33) with parameter values as $E_{\text{K}} = -60.0$ mV, $\bar{g}_{\text{K}} = 70$ m.mho/cm^2, $Q_{\text{K}} = -43.0$ mV, $\eta_{\text{K}} = 0.04$/mV, $E_{\text{Na}} = 45.0$ mV, $\bar{g}_{\text{Na}} = 332.0$ m.mho/cm^2, $Q_{\text{Na}} = -52.0$ mV, $\eta_{\text{Na}} = 0.01$/mV, $E_{\text{Ca}} = 40.0$ mV, $\bar{g}_{\text{Ca}} = 20.0$ m.mho/cm^2, $Q_{\text{Ca}} = -50.0$ mV, $\eta_{\text{Ca}} = 0.06$/mV, $E_{\text{G}} = -55.0$ mV, $\bar{g}_{\text{G}} = 8.0$ m.mho/cm^2, $Q_{\text{G}} = 75$ mV, $\eta_{\text{G}} = 0.03$/mV, $C = 1\mu$F/cm^2, $\alpha_{\text{K}} = 7.0$/ms, and $\alpha_{\text{Ca}} = -0.04$/ms, and $\epsilon_{\text{K}} = \epsilon_{\text{Na}} = \epsilon_{\text{Ca}} = \epsilon_{\text{G}} = 10^{-5}$. (d) Projections of the intersections of the V and n nullcline surfaces with $c = 0$ and the spike burst orbit onto the Vn-plane. (For interpretation of the colors in the figure(s), the reader is referred to the web version of this article.)

in whole numbers in their ballpark ranges. Small variations to the listed values do not alter the result in any qualitative way.

But between the rate parameter α_{K} and α_{Na}, the former needs to be at least one order of magnitude smaller than the latter. This shows the sodium dynamics is faster than the potassium dynamics. In fact, by assuming the sodium dynamics to be instantaneous with $\alpha_{\text{Na}} = \infty$, the model retains most qualitative properties except for the phenomenon of absolute refraction which is the initial drop in voltage before depolarization develops. With this assumption the 3-dimensional model (31) is reduced to the following 2-dimensional system

$$\begin{cases} CV' = -[\bar{g}_{\text{K}} n (V - E_{\text{K}}) + \bar{g}_{\text{Na}} \phi_{\text{Na}}(V)(V - E_{\text{Na}}) \\ \qquad + \bar{g}_{\text{G}} \phi_{\text{G}}(V)(V - E_{\text{G}})] \\ n' = \alpha_{\text{K}} \sqrt{(n + \epsilon_{\text{K}})/(\phi_{\text{K}}(V) + \epsilon_{\text{K}})}(\phi_{\text{K}}(V) - n). \end{cases} \tag{32}$$

As shown in Fig. 2, it retains similar range and time profiles for the action potentials as (31). Fig. 2(b) clearly shows that for the N-nonlinearity for the combined sodium and gating GV-characteristics, the lower knee is due to the gating characteristic and the upper knee is due to the sodium ion characteristic. This gives a mechanistic derivation for FitzHugh-Nagumo type of models ([8]).

Spike-burst can also be easily generated by introducing a third ion channel, say the calcium ion (Ca^{2+}). Specifically, by assuming the same CR symmetry in time and in GV-characteristic, we have the following 3-dimensional system of equations,

$$\begin{cases} CV' = -[\bar{g}_{\text{K}} n (V - E_{\text{K}}) + \bar{g}_{\text{Na}} \phi_{\text{Na}}(V)(V - E_{\text{Na}}) \\ \qquad + \bar{g}_{\text{G}} \phi_{\text{G}}(V)(V - E_{\text{G}}) + \bar{g}_{\text{Ca}} c (V - E_{\text{Ca}})] \\ n' = \alpha_{\text{K}} \sqrt{(n + \epsilon_{\text{K}})/(\phi_{\text{K}}(V) + \epsilon_{\text{K}})}(\phi_{\text{K}}(V) - n) \\ c' = \alpha_{\text{Ca}} \sqrt{(c + \epsilon_{\text{Ca}})/(\phi_{\text{Ca}}(V) + \epsilon_{\text{Ca}})}(\phi_{\text{Ca}}(V) - c) \end{cases} \tag{33}$$

This model is not fitted to any experimental data but is used to serve as a basic template for spike-burst generations which require three equations minimal to work. The GV-characteristic ϕ_{Ca} is voltage-activated just like ϕ_{K} and ϕ_{Na}, that is, $\eta_{\text{Ca}} > 0$. Spike-bursts can be generated for both positive and negative time rate α_{Ca}. Fig. 2 shows the case for negative α_{Ca}. Spike bursts are also found (not shown) for (33) with the same parameter values as in Fig. 2 except for $Q_{\text{Ca}} = -42.0$ mV, $\eta_{\text{Ca}} = 1.0$/mV, and $\alpha_{\text{Ca}} = 0.002$/ms.

4. Discussion

There are other functions satisfying the CR-symmetric equations (6), (13). Specifically, any function of the form $(\gamma - g)^k/(g\gamma)^{k/2}$

with k being an odd integer is a solution, and any linear combination of two or more of such functions with different γs and odd ks is also a solution. That is, the CR-symmetric equation (6) in its more general form is:

$$A(g,\gamma,\alpha,k)+A(r,\rho,\alpha,k)=0 \tag{34}$$

where $gr=1$, and $\gamma=(\gamma_1,\dots,\gamma_n)$, $\rho=(\rho_1,\ \dots,\rho_n)$, $\alpha=(\alpha_1,\dots,\alpha_n)$, $k=(k_1,\dots,k_n)$, for any integer $n\geq 1$, $\gamma_i>0$, $\rho_i=1/\gamma_i$, and odd integers k_i. CR-symmetric solutions to the equation are:

$$A(g,\gamma,\alpha,k)=\sum_{i=1}^{n}\alpha_i(\gamma_i-g)^{k_i}/(g\gamma_i)^{k_i/2}. \tag{35}$$

In other words, the set of all CR-symmetric functions form a vector space of functions, which can be expressed as

$$S_{\mathrm{CR}}:=\mathrm{Span}\{(\gamma-g)^k/(\gamma g)^{k/2}:\gamma\in\mathbb{R}^+,\ k=2j+1,\ j\in\mathbb{Z}\}, \tag{36}$$

with a spanning set of infinitely many basis functions. The zero vector $A=0$ gives rise to the linear Ohmic GV-characteristic $g\equiv$ constant. The rest give rise to nonlinear GV-characteristics. We only used the simplest vector with $n=1, k=1$ of (35). Notice that for this function, given by (7), it satisfies $A(g,\gamma,\alpha)=A(g/\gamma,1,\alpha)$, which in turn implies that equation (5) can be interpreted as two special cases of (6) that either the parameter γ is equal 1 or g and r are already scaled dimensionless from the CR-reciprocal identity (1). On the other hand, if we treat (g,γ,α,k) in (34), (35) as a vector $\mathbf{g}:=(g,\gamma,\alpha,k)$ of which one type entries satisfy the CR-reciprocal identity (1), such as g and γ, and the others do not, such as α and k, then equation (5) can be treated as the most general CR-symmetric equation in vector form with g replaced by $\mathbf{g}$ and r replaced by $\mathbf{r}:=(r,\rho,\alpha,k)$, respectively. Specifically, only the variable entry of the vector equation for g and r is listed as (5), which is exactly (34) in components, and all parameter parts of the vector equation are omitted for corresponding to the trivial solutions $A\equiv 0$. As another comment, future CR-symmetric neuron models can be constructed from S_{CR}. However, we don't know if S_{CR} is the only CR-symmetric class.

Notice that for our model the conductances of all ion channels increase ($d\gamma/dV>0$) whereas the conductance of the gating protein channel decreases ($d\gamma/dV<0$) when the voltage is depolarizing from rest. This indicates the theoretical possibility that an ion channel can behave like a gating protein channel in theory. That is, such ion channels are not forbidden by our theory.

We call the generic CR-symmetric equation

$$\frac{dx}{dt}=\alpha\sqrt{\frac{x}{\beta}}(\beta-x) \tag{37}$$

the switch equation because of a key feature of its solution $x=\beta\phi(t,\alpha,T)=\beta H(t-T)\tanh^2(\alpha(t-T)/2)$. Specifically, for $t<T$, the state is off, and for $t>T$, the state is on in ascending degrees. In fact, the larger the rate parameter α is the more the solution behaves like an ideal switch $y=\beta H(t-T)$. In particular, it models the off-state extremely well. Specifically, suppose the variable x is not trained to a constant β but rather to a function $\beta(t)$ and $\beta(t)$ falls off to zero as t approach some value t_0. Then it must happen that $x(t)$ tends to zero concurrently as $\beta(t)$ does. Because if it has not happened yet, the increasingly small $\beta(t)$ as t approaches t_0 creates a fast time scale for the equation as the coefficient of $(\beta(t)-x)$ tends to infinity, and as a consequence $x(t)$ must quickly catch up with $\beta(t)$. This can be seen in Fig. 2(b) where the dimensionless potassium conductance n quickly drops down to the off-state of its GV-characteristic $\phi_{\mathrm{K}}(V)$ when the voltage approaches its deactivation potential Q_{K}.

As shown in Fig. 1(d), the IV-characteristic curve for the potassium channel behaves like a semi-conductor, below E_{K} it is mostly nonconducting and above E_{K} it is almost a linear conductor. Notice also that the combined sodium and gating IV-characteristic curve behaves like a tunnel diode. Our results suggest a mathematical theory for nonlinear conductors, or semi-conductors used in modern electronics. This suggests that one can explore the huge parameter space of our model to best fit such devices, and to model them.

The switch equation (37) is very interesting on its own right. For example, for the dimensionless form (with $\beta=1$), the equation can be viewed as a probability pdf equation when t is treated as a random variable, and the solution $x=\phi(t,\alpha,T)$, (23), is the corresponding probability distribution with parameter α defining its sigmoid shape and T its non-vanishing range. One can further explore its applications in probability theory.

The switch equation may also be explored as a population model similar to the logistic equation. Unlike the latter, solution to our model can stay zero until sometime and then start to rise up. That is, it requires a spontaneous or random introduction of non-zero initial conditions for nontrivial solutions. In particular, it may be explored as a population genetic model for the introduction and spreading of genes, or the origin of life in general because it allows something to spring out from nothing. In the context of our neuron model (31), it gives an explanation to random opening of ion channels, without which action potentials cannot be generated. Spontaneous channel opening is believed to be quantum by nature. For our model the small perturbation parameters ϵ_{X}s can be replaced by small random noises, both serving the function to animate the neuron and for it to compute.

The switch equation may also be used as an alternative to Newton's heating-and-cooling model, $\frac{dT}{dt}=s(M-T)$. In our case, instead of the constant heat-conductance rate parameter s, it is scaled by the square-root ratio of the body temperature T and the ambient temperature M as in $\frac{dT}{dt}=s\sqrt{\frac{T}{M}}(M-T)$. Because of this factor, the temperature is always above zero and can reach the absolute zero temperature $T=0$ backward in a finite time $t=q<0$ if the solution is $T(t)=M\phi(t,s,q)$ with initial $T(0)<M$, or an infinity singularity if the solution is $T(t)=M\psi(t,s,q)=M/\phi(t,s,q)$ with $T(0)>M$. In comparison, for Newton's heating-and-cooling model, the temperature, $T(t)=M+(T_0-M)e^{-st}$, goes to $-\infty$ if $T_0<M$ and ∞ if $T_0>M$ when time is traced backward indefinitely.

The switch equation (37) and its solution $x=\beta\phi(t,\alpha,T)$ should find applications in the field of Artificial Intelligence (AI). For example, it can be used as a rectified linear unit for Convolutional Neural Networks (CNN) in place of the step function $f(x)=\max(0,x)$, or the hyperbolic tangent $\tanh(x)$, or the sigmoid function $1/(1+\exp(-x))$ which is a solution to the logistic equation. One advantage lies in the fact that our rectifier has a true inactivation region. Another advantage is because its derivatives are functions of itself. It may also find use in modeling single ion channel because the superposition of multiple individual pore currents will preserve the property that below the minimum of their conductances activation parameters the total sum still remains zero. That is, single channel currents are additive with a common inactive region.

Since Hodgkin and Huxley published their landmark work on the giant squid axon, many researchers believed that their mathematical model is only phenomenological ([1,6,2]). For more than 60 years however, finding mechanistic alternatives to their equations proved to be elusive. A semi-mechanistic model was proposed recently in [4] (Eq. (8)), whose conductance kinetics can be viewed as an approximation of our model by dropping the square-root factors in the conductance equations for n, m, h in Eq. (26) as we expect them to be near their limiting values $\phi_{\mathrm{K,Na,G}}$ or the square-root factors are near 1. Alternatively, this linear kinetic model can be thought as being derived from the separation of variable condition (2) with $A(g) = \alpha(\gamma - g)/g$ whose equivalent form for the resistance kinetics is $dr/dt = \alpha r(\rho - r)/\rho$, the logistic equation, implying that it is not kinetically symmetric. This means if a modeler chooses to model the resistance by a linear kinetics $dr/dt = \alpha(\rho - r)$, then he or she will not get the same linear conductance model. Likewise, if we choose to model the resistances by following Hodgkin-Huxley's approach, a different model from theirs is sure to arise. Our model removes this equivocation. This finding suggests that neurons perhaps can be the consequence to pure mathematics alone which is quite shocking even if it is only possible. Our model also suggests how evolution may have played its essential roles by selecting the right combinations in configuration for the reversal potential parameters E_{X}s, the activation range parameters Q_{X}s, and the rest. Perhaps the evolution of neuron is an unfolding of some elegant symmetries.

5. Conclusions

We have found a neuron model by a first-principle that the model remains invariant under conductance and resistance transformation. As a result we have obtained voltage-dependent opening probabilities for both ion transport channels and protein gating channel. Our model also implies the necessity for the phenomenon of spontaneous activation of ion channels and an origin for the leak current. We also demonstrated that experimental data can be easily fitted to the model. Our model may prove to be the basic building block for neuron models in particular and for nonlinear conductors in general.

Acknowledgement

The author acknowledges a generous summer visitors fellowship of 2017 from the Mathematics and Science College, Shanghai Normal University, Shanghai, China.

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