Modeling the Dynamics of Cardiac Action Potentials

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The nonlinear dynamics of cardiac action potentials is explained via simple model equations describing the membrane potential and the inward and outward currents through the membrane. The equations approximate ionic models, yet are expressed as polynomial functions, and robustly capture the phase-space dynamics of action potentials.

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Action potentials are the characteristic time series observed in the electrical potential across the membrane of a cardiac or nerve cell following depolarization (firing). While action potentials vary significantly from cell type to cell type [1,2], a typical example for a cardiac cell, obtained from an ionic model [3,4], is shown in Fig. 1(a), together with the associated inward and outward currents through the cell membrane [Fig. 1(b)]. The dynamics of the membrane potential and associated currents are extremely important because these dictate wave propagation in extended physiological media, and in the case of cardiac tissue, these waves are believed responsible for certain arrhythmias, often leading to death [5].

Detailed ionic models are immensely complicated, making analytical treatment impossible and simulations costly (and currently impossible in three dimensions). For this reason, the FitzHugh-Nagumo model [6] has been popular in theoretical and computational studies, e.g., Ref. [7]. The model has just two variables and a cubic nonlinearity. It nevertheless captures the most basic features of action potentials and its simple phase portrait with N-shaped nullcline explains key aspects of excitability. However, the standard FitzHugh-Nagumo model fails to capture the form of fast response action potentials in real cardiac tissue where the time scales of depolarization and repolarization are significantly different, and where early partial repolarization generally follows the upstroke [Fig. 1(a)]. Furthermore, the propagation of wave trains in the FitzHugh-Nagumo model is qualitatively at odds with what is found in cardiac tissue (Fig. 2) where restitution is strong, promoting instability at small diastolic interval [8–10], and dispersion is weak, with wave speed insensitive to the postrepolarization state of the medium.

Models have been proposed to improve the fidelity of the FitzHugh-Nagumo equations while not resorting to full physiological modeling. Of particular importance are models that attempt to capture the restitution and dispersion of cardiac tissue, either through modification of the FitzHugh-Nagumo equations [11,12] or through characterizing basic ionic mechanisms [13]. However, as far as we are aware, there is no published simple model that accurately captures the characteristic action potential and currents shown in Figs. 1(a) and 1(b), and provides explanation for these dynamics.

Here we propose a surprisingly simple approach to understanding and modeling action potentials. Analysis is based on the currents through the cell membrane rather than on the gating mechanisms responsible for these currents. This allows model differential equations to be constructed in terms of low-order polynomials that correctly account for all of the important phase-space features found in ionic models and thus reproduce in detail the dynamics of these complex equations.

Noble’s modification [3] of the Hodgkin-Huxley equations [14] produces action potentials and membrane currents (shown in Fig. 1) close to those observed experimentally, and yet for an ionic model it contains few variables. Thus we shall use it as the starting point for developing simple polynomial approximations. The Noble model is

\[ \dot{V} = -(I_i + I_o)/C_m, \]
\[ I_i = (400m^3h + \bar{g}_{Na})(V - 40), \]
\[ I_o = [g_K(V) + 1.2n^4](V + 100), \]
\[ \dot{y} = [\gamma_o(V) - y]/\tau_y(V) \quad \text{where} \quad y = m, h, n, \]

with dynamical variables \( \dot{V} \) (membrane potential), and \( m, h, \) and \( n \) (gate variables). \( C_m \) is the membrane capacitance.

![FIG. 1. (a) Typical action potential and (b) corresponding inward (solid) and outward (dotted) membrane currents from the Noble model.](image-url)
where we have defined nondimensional currents $I_i$ and $C_m$ the complicated functions Eqs. (2), the dynamics of action potentials can be understood, and, in fact, almost exactly reproduced, by replacing the complicated functions $f_i$, $g_i$ derived from the Noble model by relatively simple polynomials. Specifically, $f_2$ can be approximated by zero (a significant reduction in the nonlinearity of the equations), $f_0$, $f_1$, and $f_4$ can be replaced by constants, $g_0$ can be taken to be a linear function of $V$ only, and $f_5$ is proportional to $V$. While these approximations are generally consistent with the forms obtained from Eqs. (1), the source and justification for the approximations are an analysis of their role in governing dynamics.

We consider two model systems. The first is a qualitative model, with at most cubic nonlinearity, capturing the essential fast or slow dynamics of physiological media:

$$\dot{V} = I_1 - I_2, \quad \dot{I}_1 = -(VI_1 + 1)I_1 - I_2, \quad \dot{I}_2 = \epsilon [(I_1 - I_2)(I_2 - V) + \alpha + V].$$

where $\alpha$ and $\epsilon$ are parameters. A phase portrait and time series from these equations are shown in Fig. 3. The dynamics is oscillatory with periodic action potentials.

From Eq. (3a), the extrema of $V$ occur at points where the currents are equal. The cubic term $-VI_1^2$ in Eq. (3b) is the essential nonlinearity in the model, and modulo constants, this approximates well $f_2I_1^2$: the dominant term in Eq. (2b) for large $I_1$. The role of the nonlinear term can be seen in the $I_1$ nullclines (curves on which $I_1 = 0$). For $I_2 = 0$ these are $I_1 = 0$ and $I_1 = -1/V$ (Fig. 3 inset). For nonzero $I_2$ the nullclines change qualitatively near $I_1 = 0$ and the symmetry $(V, I_1) \rightarrow (-V, -I_1)$ in Fig. 3 is broken, but the curve $I_1 = -1/V$ is persistent for large

![Figure 2](image_url)

**FIG. 2.** (a) Restitution and (b) dispersion for the Noble model (squares), the FitzHugh-Nagumo model (circles), model (3) (crosses), and model (4) (triangles). Plotted are the normalized action potential duration APD and wave speed $C$ versus the normalized diastolic interval $D$. APD$_0$ and $C_0$ are the action potential duration and speed of an isolated pulse ($D \rightarrow \infty$).

All functions of $\tilde{V}$, e.g., $m_\infty(\tilde{V})$, are rational functions of exponentials. We use $I_1$ and $I_2$ to denote the inward and outward currents to emphasize that, while originally assumed to be due to sodium and potassium ions only, in reality many other ions participate [15] and only the total inward and outward currents are captured by this model [1]. In particular, the total inward current is primarily due to sodium and calcium currents. In the following we shall indicate parenthetically the roles of the sodium, calcium, and potassium currents.

We write Eqs. (1) in a form useful for subsequent analysis. We adiabatically eliminate the variable $m$ in terms of the voltage-dependent equilibrium $m_\infty(\tilde{V})$, which is a monotonic function of $\tilde{V}$. This is possible since the time scale of the (sodium activation) gate $m$ is at least an order of magnitude faster than any other time scale in the system [1,2]. Simulations show that only small quantitative effects result from the elimination of $m$ [9,16]. We then perform a straightforward change of variables from $V$, $h$, and $n$ to $V$, $\tilde{I}_1$, and $\tilde{I}_2$, and obtain

$$\dot{V} = I_1 - I_2, \quad \dot{\tilde{I}}_1 = (f_sI_1 + f_3)(I_1 + f_3) + f_2I_1I_2 + f_1I_2 + f_0, \quad \dot{\tilde{I}}_2 = (I_1 - I_2)g_1(V, I_2) + g_0(V, I_2),$$

where we have defined nondimensional currents $I_1 = -\tilde{I}_1/I^* + I_2 = \tilde{I}_2/I^*$, where $I^* = 125 \mu A/cm^2$ for $C_m = 12 \mu F/cm^2$. We have also made the voltage nondimensional by $V^* = 16.3 \text{ mV}$ and time by $t^* = 1.57 \text{ msec}$. The $f_i$ are functions of $V$ only.

Following a detailed analysis [16] of the phase space of Eqs. (2), the dynamics of action potentials can be understood, and, in fact, almost exactly reproduced, by replacing the complicated functions $f_i$, $g_i$ derived from the Noble

![Figure 3](image_url)

**FIG. 3.** Dynamics from Eqs. (3) with $\alpha = 3$ and $\epsilon = 0.09$. (a) Phase portrait showing inward current $I_1$ (solid) and outward current $I_2$ (dotted) vs $V$. Inset shows the $I_1$ nullclines for $I_2 = 0$. Arrows indicate the sign of $\tilde{I}_1$. (b) Action potential and (c) currents.
$I_1$. Approximating $g_1(I_2, V)$ by $\epsilon(I_2 - V)$ in Eq. (3c) is the simplest choice giving correct behavior for $I_2$ and a reasonable form for the action potentials [17].

Starting from the potential minimum at $t = 0$ (Fig. 3), the dynamics are as follows. The currents balance with $I_1$ increasing and $I_2$ decreasing. $I_1$ is above but near the hyperbolic portion of the nullcline. $I_2$ reaches a minimum and then increases so that the two currents remain close until $t = 4$, during which time $V$ is small. At $t = 4$, $I_1$ begins to deviate significantly from the nullcline and the term $-V I_1^2 > 0$ leads to explosive nonlinear growth of the inward (sodium) current. This produces the large voltage derivative ($V = I_1 - I_2 \gg 1$) of the upstroke. $V$ very quickly becomes positive driving $I_1$ across its nullcline at a large value ($I_1 = 56$). Then $I_1$ changes sign and $I_1$ rapidly falls. The fast dynamics of the upstroke abruptly ends when $I_1 = I_2$ and $V$ obtains its maximum.

The time scale of repolarization is vastly slower than that of depolarization because the two currents remain close in magnitude. The outward current agrees qualitatively with the outward (potassium) current in physiological media where it plays a dominant role in repolarization. In Eqs. (3) the inward current is not correctly modeled during repolarization (roughly, the effect of the calcium current in cardiac tissue is neglected), and as a result there is no voltage plateau prior to repolarization and the system does not recover to an excitable fixed point. Otherwise, the essential fast (sodium) and slow (potassium) dynamics of physiological media are well captured with a cubic nonlinear model, significantly different from those with N-shaped nullclines as in Fig. 1.

Consider now the quantitative model given by

$$\dot{V} = I_1 - I_2,$$
$$\dot{I}_1 = -V(I_1 - h_f(V)) + \delta(\beta - I_2),$$
$$\dot{I}_2 = \epsilon(I_1 - I_2)(I_2 - h_g(V)) + \gamma(\alpha + V),$$

where $\beta$, $\gamma$, and $\delta$ are additional parameters and $h_f(V)$ and $h_g(V)$ are quartic and quadratic polynomials, respectively. The coefficients in $h_f(V)$ and $h_g(V)$ are easily determined by fitting to the nullclines in the Nobel equations. For $I_2 = \beta$, the $I_1$ nullclines are $I_1 = -1/V$ and $I_1 = h_f(V)$ as shown in Fig. 4.

Figure 5 shows time series from this model, and Fig. 6 shows phase portraits for both Eqs. (1) and (4). The dynamics of the two systems are almost identical. For comparison with the Nobel model, and physiological media in general, in Figs. 5 and 6 we plot dimensional variables, $\tilde{V} = V V^*$, $\tilde{I}_1 = I_1 I^*$, $\tilde{I}_2 = I_2 I^*$, and time $\tilde{t} t^*$.

The nonlinear mechanism of fast depolarization [region 1 of Fig. 6(b)] is as in Eqs. (3). Following the voltage maximum, $I_1$ falls to nearly zero, and $V$ briefly becomes moderately large and negative (region 2). This generates the partial repolarization from the outward (potassium) current generally observed in fast response action potentials [1,2]. There is then a second rise of the inward (calcium [1,2]) current as $I_1$ follows the quartic branch of the nullcline (region 3). [Heuristically, the dynamics of the calcium component of the inward current results from the nullcline $I_1 = h_f(V)$.] The voltage plateau occurs because a near balance of current is established. Both currents increase slowly ($I_2$ is small because $I_1 - I_2$ is small, and hence $\gamma$ dictates the length of the plateau). Once $I_1$ reaches the local maximum of its nullcline it again decreases, increasing $|V|$ and leading to repolarization (region 4).

The final recovery of the system and establishment of a voltage threshold for reexcitation is shown in Figs. 4(b) and 4(c). With $I_2 > \beta$ the nullclines form a channel for the $I_1$ trajectory. The system is absolutely refractory because no voltage perturbation can put the system above the upper nullcline in Fig. 4(b) and reexcite the system. (Note that $I_2 > \beta = 0.3$ corresponds to $I_2 > \beta t^* = 37.5 \mu A/cm^2$.) After $I_2$ falls below the value $\beta$, the nullclines change qualitatively establishing a voltage threshold for excitation.

We have simulated wave trains in one dimension and spiral waves in two dimensions using both current models.

FIG. 5. (a) Action potential and (b) membrane currents from Eqs. (4) shown in dimensional variables. Parameters are $a = 4.9$, $\beta = 0.3$, $\gamma = 8 \times 10^{-4}$, $\delta = 0.12$, $\epsilon = 0.33$; $h_f(V) = -0.0333(V + 1.23)^2 + 0.365$ and $h_g(V) = 4.65 \times 10^{-3}V^4 + 0.0205V^3 - 0.0384V^2 - 0.188V + 0.288$. 

FIG. 4. (a) $I_1$ nullclines with $I_2 = \beta$ for Eqs. (4). (b) $I_2 > \beta$: nullcline crossing in (a) breaks to form channel for $I_1$ trajectory (bold). (c) $I_2 < \beta$: nullcline crossing breaks in other direction generating an excitation threshold for fixed point (dot).
nullcline models such as the FitzHugh-Nagumo model. On potentials and have significant advantages over N-shaped nonlinearity of all fast response action can be used to reproduce and understand detailed for explanation of the four regions in (b).

Both systems are excitable: trajectories start from $V = -76$ and eventually return to fixed points with $V = -80$. See text for explanation of the four regions in (b).

FIG. 6. Trajectories of inward (solid) and outward (dotted) currents vs voltage for (a) the Noble model and (b) Eqs. (4). By varying the parameter values and functions $h_f$ and $h_g$ in Eqs. (4), it is possible to capture, at least qualitatively, many types of action potentials observed in physiological media [16]. Finally, work is ongoing using four-dimensional models with independent sodium and calcium currents. While desirable from a physiological perspective, this extension diminishes the simplicity of phase-space analysis reported here and will be presented elsewhere.

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[5] The most recent review can be found in Chaos 8 (1998).


[16] G. Duckett (to be published).

[17] The simpler approximation $g_1 = \epsilon$ results in a model with a single nonlinear term, but gives poorer approximation to action potentials.

[18] Including spatial variation introduces the Laplacian of voltage into both the $V$ and also the current equations. See [16] for details.