Excitation dynamics: insights from simplified membrane models[1]

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ABSTRACT

Excitable nerve membranes and models for their electrical activity exhibit a broad repertoire of dynamic behavior. To reveal these behaviors the theoretician seeks a model that is simple enough to analyze yet one that retains adequate biophysical realism. Here we strike such a balance by describing a two-variable simplification of the Hodgkin-Huxley (HH) model, which exhibits many membrane phenomena and reproduces, with good agreement, many HH responses. Comparisons and illustrations are presented for the single spike response, repetitive firing (and its cessation by a brief current pulse), and bistable behavior for increased extracellular K^+ concentrations.—**Rinzel, J.** Excitation dynamics: insights from simplified membrane models. *Federation Proc.* 44: 2944–2946; 1985.

As a starting point, I recall FitzHugh's (3, 4) landmark geometric treatment of the Hodgkin-Huxley (HH) dynamics (7) and development of a two-variable, simplified model. By first identifying and combining variables that have similar time scales and biophysical roles (e.g., the inhibitory and somewhat slower processes of h, Na^+ inactivation, and n, K^+ activation), he showed that trajectories of the four-variable HH model may be viewed insightfully in two dimensions by examination of appropriate phase plane projections. Then by recognizing the phase plane dynamics as qualitatively similar to that of the van der Pol oscillator (from a quite different physical context), he introduced and utilized a modified two-variable system (Bonhoeffer-van der Pol) to discuss and illustrate geometrically the qualitative phenomena of threshold, refractoriness, repetitive firing, anodal break excitation, etc. The model was not intended to be quantitative, and it did not explicitly contain biophysical quantities such as Na^+ and K^+ conductances and reversal potentials. It did, however, correspond to a nonlinear electronic circuit being studied simultaneously by Nagumo et al. (11) as a nerve analog. Such models are called FitzHugh-Nagumo (FHN) models.

Here I derive an alternative, more biophysical, FHN-type model by reviewing and interpreting more literally FitzHugh's treatment of the HH variables. He observed that the projection of the spike trajectory in the n-h plane follows a nearly linear path. A decent fit is provided by the line L: $h + Sn = 1$ (where the slope $S = (1 - h_0)/n_0$ and h_0, n_0 are the resting values of h and n); L passes through the points (n_0, h_0) and (0, 1). Motion along L is described by a single inhibitory, or recovery, variable W, which is defined precisely by the linear combination $W = S[n + S(1 - h)]/(1 + S^2)$; note that $W = 0$ and $W = 1$ where L intersects the h and n axes, respectively. Thus by solving these two linear equations for h and n in terms of W, two variables are replaced by one: $n = W/S$ and $h = 1 - W$. As a further simplification we neglect the delay in Na^+ activation, i.e., m is so fast (especially at higher temperatures) that we may set $m = m_\infty(V)$. With these two basic approximations, we obtain a two-variable FHN-HH model:

$$C\dot{V} = I_{app} - \bar{g}_{Na} m_\infty^3(V)(1 - W) \times (V - V_{Na}) - \bar{g}_K (W/S)^4 (V - V_K) - g_L(V - V_L) \quad (1)$$

$$\dot{W} = \phi[W_\infty(V) - W]/\tau(V) \quad (2)$$

Here, *Eq. 1* is in standard HH form with the substitutions described above, I_{app} is applied current, $W_\infty(V) = S\{n_\infty(V) + S[1 - h_\infty(V)]\}/(1 + S^2)$, $\tau(V)$ is a compromise between $\tau_h(V)$ and $\tau_n(V)$: $\tau(V) = 5\exp[-(V + 10)^2/55^2] + 1$, and ϕ is the HH temperature correction factor (here, for 18.5 C). For this model, h is defined to be 0 if W should exceed 1.

In Fig. 1 the response to a brief current pulse for the full HH and for the FHN-HH models is compared. Consider first the V-W plots. The nullclines $\dot{V} = 0$ and $\dot{W} = 0$ for the FHN-HH model are shown dashed; their intersection determines the rest state. The V nullcline has a broad hump corresponding to the inward Na^+ current. The V-W spike trajectories of the two models look alike; they start from rest and proceed rightward (upstroke) until the V nullcline is crossed. Recovery increases relatively more slowly, causing upward movement until the W

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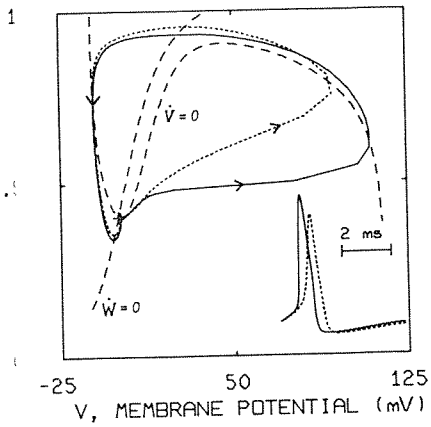


Fig e 1. Response to brief current pulse (15 μA, m² for 1 ms) shown in *V-W* phase plane and s voltage vs. time (lower right). The HH resp nse is dotted, the FHN-HH response, solid. Nul lines (curves where $\dot{V} = 0$, $\dot{W} = 0$) for FHN-HH *Eqs. 1* and *2* are dashed.

nu cline is crossed (during the spike do nstroke). This diagram aids an interpretation of relative refractoriness. During the hyperpolarizing phase (downward movement at left), another spike could be triggered by a brief stimulus that displaces voltage horizontally across the middle branch of the *V* nullcline; the separation between the trajectory and the middle branch decreases the relative size of the just-adequate stimulus throughout this phase. In Fig. 1 both models also exhibit a phase of superexcitability late in their return to rest when recovery

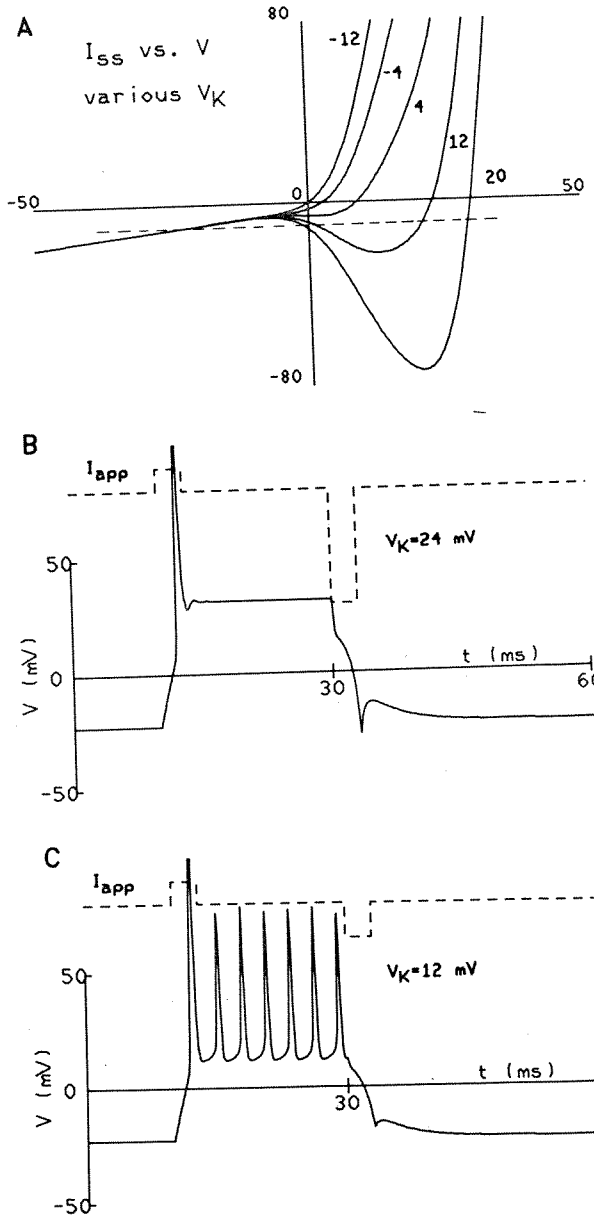
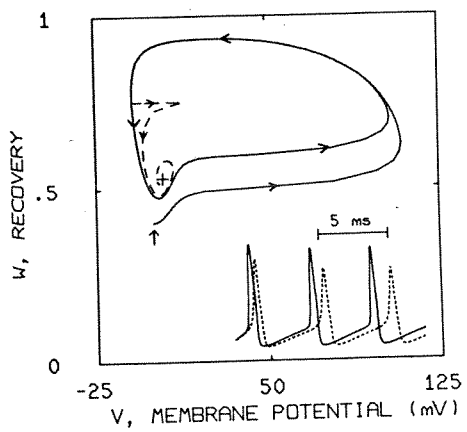


Figure 3. Bistable behavior of FHN-HH model for increased extracellular K^+. V_K is K^+ Nernst potential, relative to −60 mV. Steady-state *I-V* relation becomes N shaped for increased V_K in *A* (units: millivolts and microamperes per square centimeter). Brief current pulse superposed on steady bias of -10 μA/cm² (dashed in *A*) leads to switching between two stable steady potentials in *B*(V_K = 24 mV) or between stable oscillation and steady state in *C* (V_K = 12 mV).

Figure 2. Repetitive response to current step of 12 μA/cm². Upper part of figure: *V-W* trajectory for FHN-HH *Eqs. 1* and *2* winds onto closed curve (solid); appropriately timed current pulse terminates repetitive firing and causes damped oscillation to steady state (dashed trajectory). Lower: voltage time course for FHN-HH (solid) and HH (dotted) repetitive responses.



(e.g., K^+ activation) falls below its rest value. The two voltage time courses are quite similar (lower right); the HH spike has a slower upstroke and smaller peak owing to the activation delay of Na^+.

Both models fire repetitively for steady current in similar ranges. The voltage time courses in Fig. 2 (lower right) illustrate the comparison for I_{app} = 12 μA/cm². The *V-W* trajectories are similar, but to avoid clutter, Fig. 2 shows only that for FHN-HH. The response begins from rest (up arrow) and after one spike it cycles onto a closed curve, which represents repetitive firing. The curve surrounds the now slightly depolarized steady state (cross). The rest state in these models is unstable (physically unrealizable) for most of the I_{app} range for repetitive firing. However, for I_{app} just above rheobase the rest state is still stable and the membrane can either fire repetitively or be quiescent, depending on the stimulus delivery (see ref 14 and

its references for HH results). Figure 2 shows how such a repetitively firing membrane may be kicked off course by a brief perturbing current pulse; the *V-W* trajectory (dashed) leaves the closed curve and winds down onto the stable steady state of quiescence. Theoretical predictions that an oscillating membrane may, in some cases, be switched to quiescence have been verified for squid axon (5) and for cardiac pacemaking tissue (8).

The FHN-HH simplified model can be used to explore variations with respect to other physiological parameters. For increased extracellular K^+ concentration (modeled as an increase in V_K), the steady-state *I-V* relation becomes N shaped (Fig. 3*A*). This is because the K^+ current is activated for $V < V_K$ and is therefore inward in this range. Hence, for some steady I_{app} values the membrane exhibits three steady-state potentials. The lower potential is stable and, for V_K that are large enough, so is the upper one. Brief current pulses switch the membrane from one stable state to the other (Fig. 3*B*). For some ranges of V_K, however, the upper potential is not stable but is surrounded by a stable oscillation; switching between these states is shown in Fig. 3*C*. This latter type of bistable behavior is the mechanism for bursting activity in some membrane models (2) (J. Rinzel, unpublished observations). Responses similar to those in Fig. 3 are exhibited by the HH model for these same parameters (see also ref 1). Correspondingly, squid axon in high external K^+ exhibits an N-shaped *I-V* relation and bistable steady states (9).

Simple yet physiologically reasonable models can reproduce many excitable membrane phenomena. Often they can be analyzed geometrically; numerical and analytic calculations are usually facilitated. Hence by judiciously employing reduced models one can more easily reveal the biophysical/mathematical essence of membrane excitation and oscillation. To formulate reduced models one should recognize and exploit time-scale differences among variables as well as similarities in functional roles. For examples of other FHN-type models and biophysical applications, see refs 6, 10, 12, 13.

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