From Wilson's Book

9 *Action potentials and limit cycles*

In the previous chapter we developed criteria for the existence of limit cycles in nonlinear dynamical systems, namely the Poincaré–Bendixon theorem and the Hopf bifurcation theorem. As one example, we examined the FitzHugh–Nagumo equations, the simplest approximation to the dynamics of action potentials. However, these equations are not closely related to physiology, as they fail to include ionic currents and equilibrium potentials.

We are now poised to study the dynamics of ionic currents underlying the generation of action potentials in the Hodgkin–Huxley equations, where it will be shown that a periodic spike train is in fact a limit cycle. Following a brief review of the concepts behind the Hodgkin–Huxley equations, we shall study a set of equations that are simple to analyze mathematically but that provide a remarkably accurate description of action potentials. Subsequent topics examine hysteresis in spike generation, a dynamical categorization of neuron types, and various nonlinear resonance phenomena, including stochastic resonance.

9.1 Hodgkin–Huxley equations

The Hodgkin–Huxley (1952) equations describe the change in membrane potential or voltage V as a function of the sodium (I_{Na}), potassium (I_K), leakage (I_{leak}), and stimulating (I_{input}) currents across the membrane as well as membrane capacitance C. The most general form of the Hodgkin–Huxley equations is:

$$C\frac{dV}{dt} = -I_{Na} - I_K - I_{leak} + I_{input} \tag{9.1}$$

As each current obeys Ohm's law, the current $I = g(V - E)$, where g is the electrical conductance (reciprocal of the resistance), V is the voltage across the membrane, and E is the equilibrium potential of the ion in question computed from the Nernst equation (2.16). The capacitance C (in micro-Farads/cm^2, μF/cm^2) arises from the fact that the lipid bilayer of the axon membrane forms a thin insulating sheet that serves to store electrical charge in the same way as an electrical capacitor (cf. Hille, 1992; Johnston and Wu, 1995; Delcomyn, 1998). Hodgkin and Huxley discovered empirically that the conductances were not constant but rather were functions of the membrane potential V, and this voltage dependence is the key to understanding action potentials. Therefore, (9.1) was

rewritten as:

$$C\frac{dV}{dt} = -g_{Na}m^3$$

$$\frac{dm}{dt} = \frac{1}{\tau_m(V)}($$

$$\frac{dh}{dt} = \frac{1}{\tau_h(V)}(-$$

$$\frac{dn}{dt} = \frac{1}{\tau_n(V)}(-$$

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\begin{aligned}
C\frac{dV}{dt} &= -g_{Na}m^3h(V-E_{Na}) - g_K n^4(V-E_K) - g_{leak}(V-E_{leak}) + I_{input} \\
\frac{dm}{dt} &= \frac{1}{\tau_m(V)}(-m + M(V)) \\
\frac{dh}{dt} &= \frac{1}{\tau_h(V)}(-h + H(V)) \\
\frac{dn}{dt} &= \frac{1}{\tau_n(V)}(-n + N(V))
\end{aligned}
\tag{9.2}
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In the first equation, E_{NA}, E_K, and E_{leak} are the equilibrium potentials at which each of the three currents is balanced by ionic concentration differences across the membrane. Evidently, the Hodgkin–Huxley equations are a fourth order system of nonlinear differential equations. The additional variables m, h, and n represent the rates of Na conductance channel activation, Na channel inactivation, and K channel activation respectively. Nonlinearity results from the fact that the equilibrium values of these variables, $M(V)$, $H(V)$, and $N(V)$ are all functions of the membrane potential V, as are the time constants τ_m, τ_h, and τ_n. Explicit mathematical forms for all these functions may be found in Hodgkin and Huxley (1952), Cronin (1987), and Johnston and Wu (1995).

The scientific content of the Hodgkin–Huxley equations comes from two sources. First is the observance of Ohm's law for the individual currents. The second is the hypothesis that the Na, K and leakage currents are all independent and therefore sum in (9.1). This hypothesis was tested by solving the mathematical model (9.2) that resulted (on a mechanical desk calculator!) and showing that it reproduced the experimentally observed shape and duration of the action potential in the squid giant axon. The mathematical forms chosen for the functions τ_m, τ_h, τ_n, $M(V)$, $H(V)$, and $N(V)$, were biologically motivated curve fits to the data. Hodgkin and Huxley's (1952) work represents the first and perhaps most dramatic success of nonlinear dynamics in predicting neurophysiological data.

The mathematical forms chosen by Hodgkin and Huxley for functions τ_m, τ_h, τ_n, $M(V)$, $H(V)$, and $N(V)$ are all transcendental functions. Both this and the presence of four equations in (9.2) make the Hodgkin–Huxley equations difficult to analyze mathematically. Fortunately, detailed study of these equations has led to several insightful simplifications. Rinzel (1985) noticed that τ_m is so small for all values of V that the variable m rapidly approaches its equilibrium value, $M(V)$. As a good approximation, therefore, the second equation in (9.2) can be eliminated and $m = M(V)$ substituted into the equation for dV/dt. Second, Rinzel noted that the equations for h and n were similar in time course and in their equilibrium values $H(V)$ and $N(V)$. In fact, an accurate approximation is obtained by setting $h = 1 - n$. What this means in ionic terms is that Na^+ channel closing, h, occurs at the same rate but in the opposite direction to K^+ channel opening, n. This relationship permits one to eliminate the equation for h, thereby reducing (9.2) to a

two-dimension dynamical system. Under these assumptions, (9.2) assumes the form (Rinzel, 1985):

$$\begin{aligned} C\frac{dV}{dt} &= -g_{Na}M(V)^3(1-R)(V-E_{Na}) - g_K R^4(V-E_K) - g_{leak}(V-E_{leak}) + I \\ \frac{dR}{dt} &= \frac{1}{\tau_R(V)}(-R+G(V)) \\ \tau_R(V) &= 1 + 5\exp\left(\frac{-(V+60)^2}{55^2}\right) \end{aligned} \tag{9.3}$$

To emphasize the simplifications and changes of variables, R has been used to describe the K^+ channel opening and Na^+ channel closing, which together constitute the recovery variable (hence the appellation R). The explicit expression for $\tau_R(V)$, the recovery time constant, has been included to indicate the general transcendental nature of these functions.

Using the forms of $H(V)$ and $G(V)$ derived from the original Hodgkin–Huxley equations as described above, let us examine the action potentials and the state space of the system. (Mathematical forms for $M(V)$ and $G(V)$ are contained in the MatLab scripts **MM.m** and **GG.m**, but they are too complex to provide much analytical insight.) The script **RinzelHH.m** implements (9.3), and action potentials are plotted in Fig. 9.1 for $I_{input} = 10\,\mu A$. The state space for (9.3) is plotted on the left of Fig. 9.2. Note in particular that the $dR/dt = 0$ isocline is straight over most of its range, while the dV/dt isocline is approximately cubic, although it does not agree with the exact cubic shape assumed in the FitzHugh–Nagumo equations (8.8). Changes in the spike rate and isocline shapes can be explored by running **RinzelHH.m** for different values of the input current. You can also estimate the threshold current necessary for spike generation: it lies in the range $0 < I_{input} < 10$.

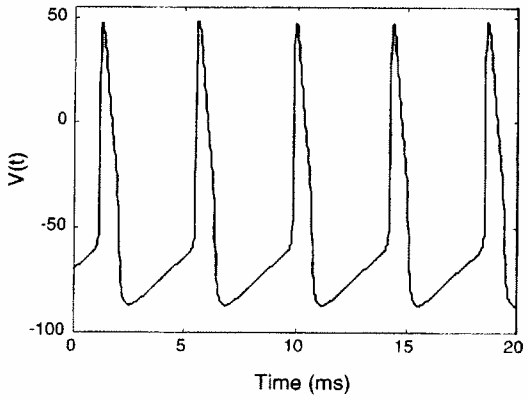
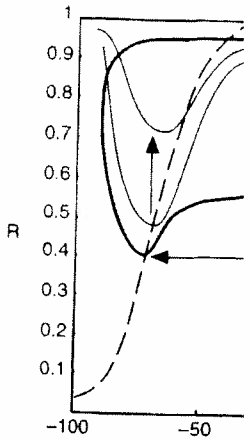


Fig. 9.1 Action potentials generated by (9.3), the Rinzel (1985) approximation to the Hodgkin–Huxley (1952) equations. In this instance $I_{input} = 10\,\mu A$, and the resultant spike rate is 250 Hz.



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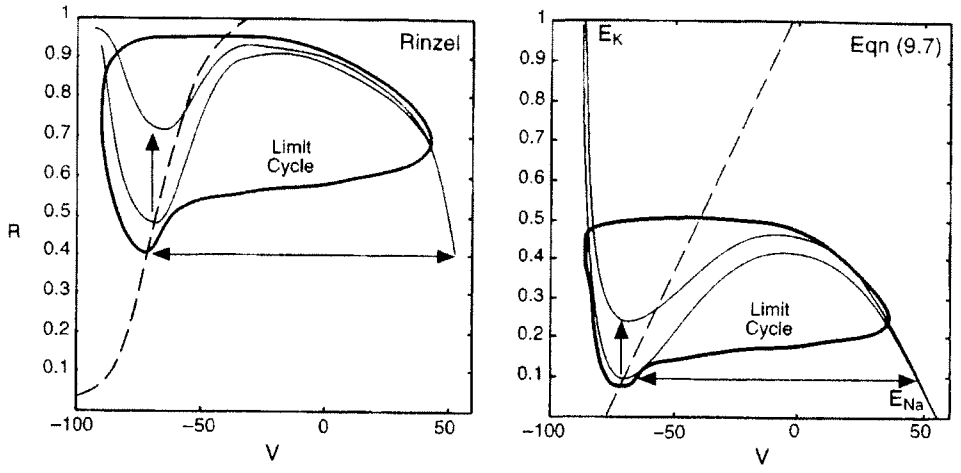

Fig. 9.2 Phase planes for (9.3) on left and (9.7) on right. For both equations the primary effect of increasing I_{input} is to shift the lower left lobe of the dV/dt isocline (solid curves) upwards as shown by the vertical arrows. Spike height (horizontal double-headed arrows) is primarily determined by the distance between the equilibrium point on the dR/dt isocline (dashed) and the right branch of the dV/dt isocline.

9.2 Essential dynamics of the Hodgkin–Huxley equations

The two-dimensional Rinzel approximation to the Hodgkin–Huxley equations in (9.3) can be simplified still further to reveal the essential dynamical principles underlying action potential generation. It is evident from the phase plane diagram in Fig. 9.2 (left) that the dV/dt isocline is roughly cubic in shape, while the dR/dt isocline is linear over most of its range. These observations were exploited by FitzHugh (1961) in developing the simplified FitzHugh–Nagumo equations discussed in the previous chapter. In the interests of mathematical simplicity, however, the FitzHugh–Nagumo equations ignored most physiological aspects of the Hodgkin-Huxley equations, such as adherence to Ohm's law and explicit reference to the Na^+ and K^+ equilibrium potentials. Let us develop a more accurate approximation to the Hodgkin–Huxley equations that rectifies the shortcomings of the FitzHugh–Nagumo equations while retaining their mathematical tractability. To maintain biophysical significance, Ohm's law and the dependence on Na^+ and K^+ equilibrium potentials must be made explicit. This approach, which exposes the biological significance of the isoclines, leads to equations of the form:

$$\begin{aligned} C\frac{dV}{dt} &= -g_{Na}(V)(V - E_{Na}) - R(V - E_K) + I \\ \frac{dR}{dt} &= \frac{1}{\tau_R}(-R + G(V)) \end{aligned} \tag{9.4}$$

These equations have the same form as (9.3), namely an equation for dV/dt that is the sum of Na^+ and K^+ currents plus the stimulating current I, and a second equation for the recovery variable R. (The passive leakage current in (9.3), which plays no role in spike

generation, has been absorbed into the Na^+ current for convenience.) For mathematical tractability, the first equation can be restricted to a cubic in V (based on isocline shapes discussed above), so $g_{Na}(V)$ must be restricted to a quadratic polynomial. Similarly, $G(V)$ can only be quadratic if the term $R(V - E_K)$ in the first equation is to remain no higher than cubic. Given these constraints, let us examine the isoclines of (9.4), which are:

$$\begin{aligned} R &= \frac{-g_{Na}(V)(V - E_{Na}) + I}{(V - E_K)} \quad \text{for} \quad \frac{dV}{dt} = 0 \\ R &= G(V) \quad \text{for} \quad \frac{dR}{dt} = 0 \end{aligned} \tag{9.5}$$

Setting $I = 0$ for the moment, it is evident from the first isocline equation that:

$$\begin{aligned} R &= 0 \quad \text{when} \quad V = E_{Na} \\ R &= \infty \quad \text{when} \quad V = E_K \end{aligned} \tag{9.6}$$

These points are marked on the right-hand phase plane in Fig. 9.2. Thus, simply writing the dynamics in a form obeying Ohm's law leads to a $dV/dt = 0$ isocline with a natural biophysical interpretation in terms of E_{Na} and E_K!

A fit of (9.5) to the isoclines on the left of Fig. 9.2 leads to the following differential equations:

$$\begin{aligned} C\frac{dV}{dt} &= -(17.81 + 47.71V + 32.63V^2)(V - 0.55) - 26.0R(V + 0.92) + I \\ \frac{dR}{dt} &= \frac{1}{\tau}(-R + 1.35V + 1.03) \end{aligned} \tag{9.7}$$

where the capacitance $C = 0.8\,\mu F/cm^2$ and $\tau_R = 1.9$ ms. In generating these equations, the voltages were divided by 100 to keep the parameter values near unity. Thus, the equilibrium potentials are $E_{Na} = 0.55$ (or + 55 mV), and $E_K = -0.92$ (or −92 mV), which are the same values that were used in (9.3). Thus, (9.7) expresses potential in deci-volts, and the input current I is in $\mu A/100$. For all comparisons with Hodgkin–Huxley results the solutions of (9.7) will therefore be multiplied by 100.

Having derived these equations, let us first determine whether they produce spikes that are accurate reflections of the Hodgkin–Huxley solutions. Figure 9.3 compares spike shapes at two different spike frequencies and also plots spike rates for both (9.7) and the full Hodgkin–Huxley formulation over the entire physiological range of input currents I. Equation (9.7) produces a good approximation to action potential shape, the correlation between the two spike shapes being > 0.96, and it also reproduces the reduction in spike amplitude with increasing spike rate observed in the Hodgkin–Huxley equations. The reader can explore the dependence of spike rate and spike height on input current I by running MatLab script **HHWeqn.m** and varying input current over the range $0 < I < 2.0$. Note that the numerical values of I are also 100 times smaller than those for the Hodgkin–Huxley equations, so the threshold value is in the range $0.0 < I < 0.090$. Figure 9.2 also shows that the dV/dt isocline in (9.5) deforms primarily on the lower left side as I is

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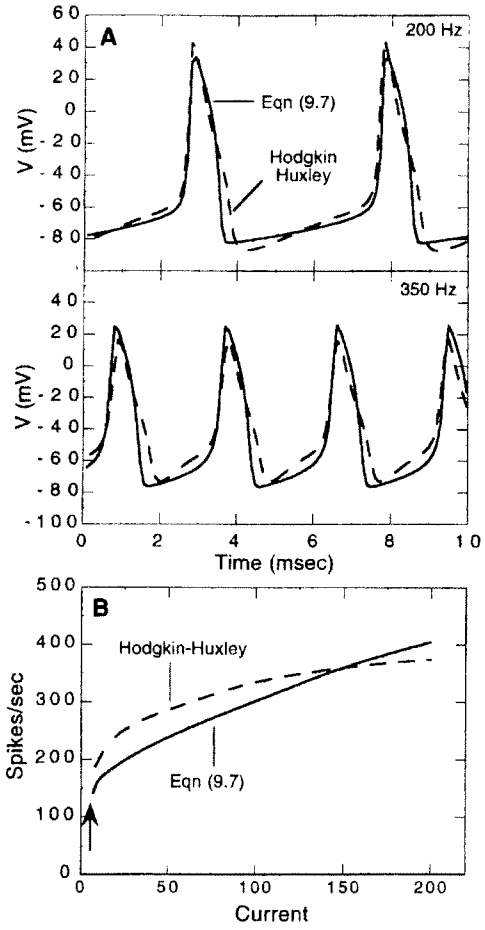


Fig. 9.3 Comparison of spike trains generated by (9.7) and the Hodgkin–Huxley equations (9.2). (A) Spike trains at 200 and 350 Hz for (9.7) (solid lines) and Hodgkin–Huxley (dashed lines). In addition to the similarity in shape, both equations produce a reduction in spike amplitude with increasing frequency. (B) Spike rate as a function of input current for Hodgkin–Huxley (dashed line) and (9.7) (solid line). Spike threshold is indicated by the arrow.

changed from threshold to 10 times threshold. Finally, Fig. 9.2 also shows that the limit cycles for (9.3) and (9.7) are quite similar in shape when plotted in state space. Thus, (9.7) provides a reasonably accurate approximation to the Hodgkin–Huxley equations given the simplifying assumptions made by Rinzel (1985) to obtain (9.3).

Let us now see how easy the analysis of (9.7) can be. The equilibrium state is given by the simultaneous solution of (9.5), which becomes, with parameters from (9.7):

$$-40.788V^3 - 81.079V^2 - 63.302V + 1.25I - 18.553 = 0 \qquad (9.8)$$

This can either be solved for specific values of I using the **roots** function in MatLab. For example, $I = 0$ yields only one real root: $V = -0.70$, or -70 mV, the same as for the Hodgkin–Huxley simulations in Fig. 9.3, and $R = 0.088$ at rest. The Jacobian matrix for (9.7) is:

$$A = \begin{pmatrix} -122.36V^2 - 118.28V - 22.937 & -32.5V - 29.9 \\ 0.71053 & -0.52632 \end{pmatrix} \tag{9.9}$$

where the equilibrium equation for R has been used to eliminate it from the matrix. Equations (9.8) and (9.9) can now be used to determine the stability of the equilibrium point for any value of I in the usual way. For example, if $I = 0.25$, $V = -0.67$ from (9.8), and the eigenvalues of the A matrix are $\lambda = 0.53 \pm 2.18i$, so the steady state is an unstable spiral point. The Poincaré–Bendixon Theorem can now be used to prove the existence of a limit cycle using a construction similar to that employed for the FitzHugh–Nagumo equation (see Exercise 1).

9.3 Hysteresis in the squid axon

One of the most striking aspects of dynamical modeling in neuroscience is the fact that nonlinear equations frequently predict novel phenomena that the creators of the equations had never imagined. As a case in point, Hodgkin and Huxley created their equations in 1952, yet many years elapsed before it was shown that the equations predicted a novel hysteresis effect that had never been observed (Cooley *et al.*, 1965; Rinzel, 1978; Best, 1979). Subsequently, Guttman, Lewis, and Rinzel (1980) tested this prediction and showed that hysteresis actually occurred in the squid axon. Figure 9.4 shows the results of their experiment. A squid axon was stimulated with a current I that began at 0 and

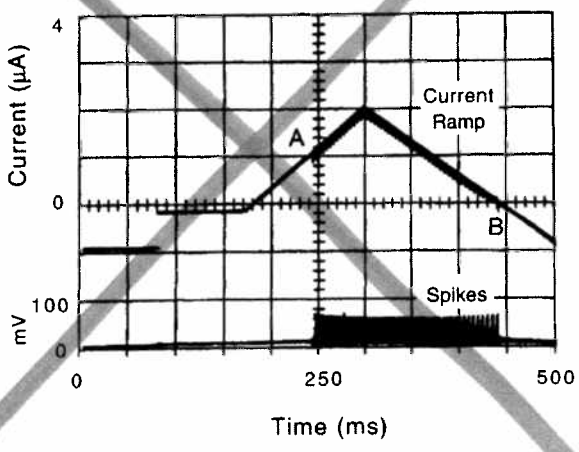
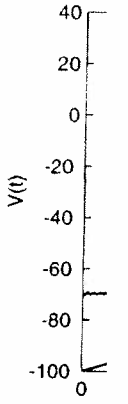


Fig. 9.4 Hysteresis in the giant axon of the squid (reproduced with permission, Guttman *et al.*, 1980). In response to a triangular current ramp, spiking activity begins at a high current at A but then continues to the much lower current at B, thus demonstrating hysteresis.



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