Chapter 11

Excitable systems and the FitzHugh–Nagumo equations

In this chapter we will describe a simple caricature of an excitable system, the FitzHugh–Nagumo model. While the original motivation for this chapter resides in neuronal excitation, its usefulness as a paradigm extends far beyond that realm. A good reference for much of this material is the chapter by Rinzel and Ermentrout in the book [80]. See also [68] for another modern treatment of phase plane behavior applied to neuronal systems. Here, we will use the example to practice and interpret a phase plane analysis. An important concept will be that of excitability, where a significant response only occurs in response to large enough stimuli. We will also encounter **limit cycle** dynamics. What was the historical origin of the FitzHugh–Nagumo model? Recall that the Hodgkin–Huxley equations (10.27)–(10.30) of Chapter 10 are relatively complicated and too numerous to understand directly by phase plane methods. For that reason, they have been explored and analyzed by simulations. Hoping to gain greater analytical insight into these equations prompted the simplification that eventually culminated in the FitzHugh–Nagumo model. We first describe this elegant model in a general setting, analyze its behavior, and only later link it to neuronal dynamics.

11.1 A simple excitable system

It is helpful to know a little about the qualitative behaviors that we wish to explain, especially because such behaviors are widespread in many biological contexts. One such behavior is **excitability**. If a system at rest is subjected to a small stimulus, then the resulting perturbation to the system rapidly returns to rest. But if the stimulus is above a certain threshold, then the perturbation grows rapidly and extensively for a certain period of time, but even here the perturbation eventually dies out. During the period when the perturbation grows, the system is **absolutely refractory** to further stimulus, in the sense that such a stimulus is essentially without effect. But later, during the period of perturbation decay, a sufficiently large stimulus can excite the system a second time before it returns to rest.

To capture these ideas, we consider a two-variable model due to FitzHugh, with excitation and a refractory component. First, let us define the variable x as the level of excitation (such as "voltage," or depolarization in a neuronal context). We assume that

x satisfies the ODE

$$\frac{dx}{dt} = c\left(x - \frac{1}{3}x^3\right). \tag{11.1}$$

In (11.1), we take the parameter c to be large so that dx/dt is large and hence x will be a "fast variable" (in the sense that it changes rapidly).

Equation (11.1) should be familiar. As we have already seen in Section 5.3.1, there are three steady states of (11.1), one at $x = 0$ and the others at $x = \pm\sqrt{3}$. The steady state at $x = 0$ is unstable, while both the "rest state" $x = -\sqrt{3}$ and the "excited state" $x = \sqrt{3}$ are stable (Exercise 5.8 or Exercise 11.1). The phase line in Fig. 11.1 is repeated here for convenience. In the model equation (11.1), the threshold is $x = 0$; a positive initial value of x induces further growth of x.

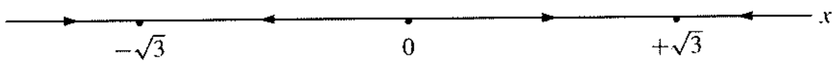


Figure 11.1. *The "phase line" for* (11.1). *Steady states are indicated by dots, and trajectories with arrows show the direction of "flow" as t increases.*

To (11.1) we add a slow recovery variable,[55] here denoted by y. As y increases, it "damps out" the excitation x (recovery neutralizes excitation). We choose the equation for the rate of change of y to be as simple as possible: linear kinetics. The FitzHugh–Nagumo model we study is

$$\frac{dx}{dt} = c\left[x - \frac{1}{3}x^3 - y + j\right], \tag{11.2a}$$

$$\frac{dy}{dt} = \frac{1}{c}[x + a - by]. \tag{11.2b}$$

In Eqn. (11.2b) the factor $1/c$ has been included so that when c is large, dy/dt is relatively small. Introducing both a parameter c in (11.2a) and $1/c$ in (11.2b) does not seem strictly necessary, but this way of doing things provides a certain symmetry to rendering x faster and y slower by increasing c. In (11.2), the parameters a, b, and c are all positive. Later it turns out that desirable ranges of these parameters are $1 - \frac{2b}{3} < a < 1$ and $0 < b < 1$. The parameter j represents a stimulus (that could be excitatory or inhibitory, and so can have either sign). In the neuronal caricature, j would represent the effect of an applied current, with positive j (current injection) increasing the "depolarization" x.

While x represents **excitation**, y represents **recovery**. In the absence of y, Eqn. (11.2a) takes the form

$$\frac{dx}{dt} = c\left[\left(1 - \frac{1}{3}x^2\right)x + j\right].$$

Note that the quantity j in this equation plays the same role dynamically as the parameter A in the "revised" cubic kinetics we investigated in Eqn. (5.16). Recall that varying A in (5.16) resulted in changes in the number of steady states of the system (revisit Fig. 5.5). This type of effect will play a role in what follows.

[55] y is sometimes called a "refractory variable."

If x^2 is small and $j = 0$, then x is self-exciting, for the equation is now

$$dx/dt = cx$$

and (since c is positive) the excitation x increases exponentially with growth rate c. As x grows, the growth rate has the diminished value $c\left(1 - \frac{1}{3}x^2\right)$. Thus x is self-exciting but with a magnitude of self-excitation that decreases as the excitation x grows: the variable x is a **self-limited self-exciter**. There is also a constant **source of excitation**, represented by a nonzero value of the parameter j. (If j is negative, the "excitation source" is in fact an inhibiting sink.) When excitation diminishes, we will say that recovery (from excitation) is taking place. We see from Eqn. (11.2a) that the **recovery variable** y diminishes excitation.[56]

Equation (11.2b) shows that in the absence of excitation ($x = 0$), the self-limiting recovery variable y tends to a steady state $y = a/b$. But *an increase in the excitation x promotes recovery*. We wish to consider a case where excitation is rapid and recovery is slow. We thus take

$$c \gg 1 \tag{11.2c}$$

so that dx/dt will generally be large compared to dy/dt. With these preliminary remarks, we next turn to the analysis of Eqs. (11.2).

11.2 Phase plane analysis of the model

Here we use detailed phase plane analysis to understand the FitzHugh–Nagumo equations (11.2). This approach is relevant not only to the discussion in this chapter, but also more broadly, to other excitable systems.[57] We first consider the shapes of the nullclines and the steady states at their points of intersection. We construct a phase portrait, complete with a direction field, and then discuss the stability properties of the steady states. These analyses, together, allow us to understand many aspects of the dynamics. Simulations will then furnish further details and confirmation to complete the picture.

11.2.1 Nullclines

In this chapter we use interchangeably the synonymous notation $\dot{y}$ and dy/dt. The **y nullcline** (also "horizontal nullcline") of the system (11.2) is given by

$$dy/dt = 0, \quad \Rightarrow \quad y = \frac{1}{b}x + \frac{a}{b}\,. \tag{11.3a}$$

This is a straight line with slope $1/b$ and x intercept $-a$.

[56] In neurobiology, the "excitation variable" x is the voltage and positive x corresponds to "depolarization." The excitation source j is the current. With our sign conventions, a positive current is associated with depolarization (by Eqn. (11.2a), positive j tends to provide positive dx/dt and hence to increase x) and a negative current with hyperpolarization ($x < 0$). L.A.S.

[57] An example of the use of the FitzHugh equation in other biological contexts occurs in connection with the behavior of cellular slime mold amoebae, where "excitable...dynamics can be described reasonably well in a quantitative way by the two-variable FitzHugh–Nagumo equations..." [92]. See Exercise 15.9 for discussion of some of the issues involved (not employing the FitzHugh equations). L.A.S.

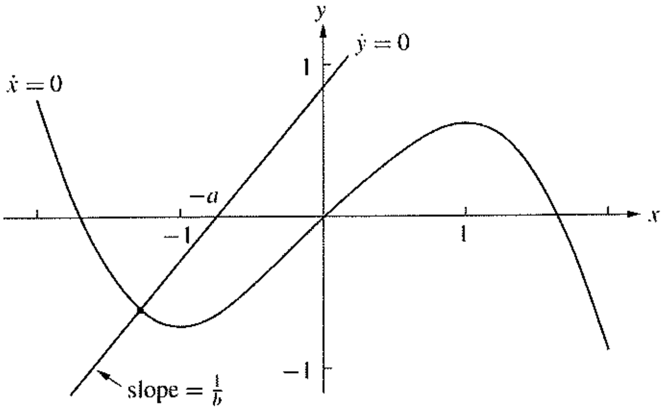


Figure 11.2. *Nullclines for FitzHugh equations* (11.2) *with* $j=0$, $a=0.7$, $b=0.8$, $c=10$. *These parameters are also used for succeeding figures unless indicated otherwise.*

The x **nullcline** (also "vertical nullcline")[58] is given by

$$dx/dt=0, \quad \Rightarrow \quad y=x-\frac{1}{3}x^3+j\,. \tag{11.3b}$$

We observe that the parameter c does not appear in either nullcline equation, and hence will not affect the shape of those curves. (As we will see later, c affects the speed of motion in the phase plane.) The slope of the cubic curve described by (11.3b)[59] is

$$M(x)\equiv\frac{dy}{dx}=1-x^2. \tag{11.4}$$

Hence the cubic has extrema (also called "critical points") when

$$M(x)=0\,, \qquad \text{i.e.,} \qquad 1-x^2=0\,, \qquad x=\pm1 \tag{11.5}$$

(see Exercise 11.2). Since $d^2y/dx^2=-2x$, the second derivative is positive (negative) when $x=-1$ ($x=1$) and the corresponding extremum is a minimum (maximum). None of the model parameters affects this conclusion. We later use y_{max} to denote the y coordinate of the local maximum point.

The case $j=0$ is shown in Fig. 11.2. For reasons that will become clear, it is desirable that the nullclines are configured as in Fig. 11.2. In particular we impose the following requirements:

(i) The horizontal nullcline ($dy/dt=0$, given by (11.3a)) has a positive slope ($b>0$).

(ii) There is precisely one intersection of the two nullclines.

(iii) The intersection is at or just to the left of the minimum point ($x=-1$) of the x nullcline (11.3b).

[58] Because of the shape of this curve, it will be denoted as an "N-shaped" nullcline or "the cubic curve." Later on we will refer to similar (rotated) curves as "S-shaped."

[59] This is true since differentiating the nullcline equation (11.3b) with respect to x leads to $dy/dx=1-x^2$.

11.2.2 How many intersections (steady states)?

To ensure condition (ii) we first ask when nullclines would intersect more than once, and then we prevent this. This can be made to occur if b increases to cause the slope of the y nullcline to diminish so that this line first becomes tangent to the x nullcline and then, as b increases further, intersects the x nullcline twice more. When the two nullclines are tangential, their slopes are equal, which requires (Exercise 11.4) that

$$1-x^2=\frac{1}{b} \qquad \text{or} \qquad x^2=1-\frac{1}{b}. \tag{11.6}$$

When $b<1$, the second equation in (11.6) has no (real) solution. We see this from

$$1-\frac{1}{b}<0 \qquad \Longleftrightarrow \qquad b<1. \tag{11.7}$$

Thus the condition $b<1$ is sufficient to guarantee that the nullclines cannot be tangent nor intersect more than once.

We turn now to condition (iii). Given b, $0<b<1$, what are the conditions on a that will yield a steady state precisely at the minimum of the cubic? When $j=0$, the minimum is at $x=-1$, $y=-2/3$. This point lies on the straight line (11.3a) if

$$-\frac{2}{3}=-\frac{1}{b}+\frac{a}{b} \qquad \text{or} \qquad a=1-\frac{2}{3}b. \tag{11.8}$$

Note from the second part of (11.8) that since $0<b<1$,

$$\frac{1}{3}<a<1. \tag{11.9}$$

The straight line (11.3a) will intersect the cubic to the left of the minimum point if a is larger than the value given in (11.8), thereby raising the line (11.3a). The requirement is

$$a>1-\frac{2}{3}b. \tag{11.10}$$

In summary, conditions (i)–(iii) will be satisfied if (11.7), (11.9), and (11.10) are satisfied. The reader is asked to confirm these deductions in Exercise 11.5.

11.2.3 Directions

We now know that the nullclines intersect in a unique steady state. We next determine the directions of the flow arrows on the nullclines (Exercise 11.6). Recall that if dy/dt changes sign, then it does so when the curve $dy/dt=0$ is crossed (or when the curve $dy/dt=\infty$ is crossed, if there is such a curve). We see from Eqn. (11.2b) that, since $c>0$, for fixed y, $dy/dt>0$ when $x\to\infty$ (that is, when x is positive and sufficiently large) and $dy/dt<0$ when $x\to-\infty$. As we saw in Chapter 7, checking extreme values of x is an efficient way of determining the signs of derivatives ($dy/dt>0$ to the right and $dy/dt<0$ to the left of $dy/dt=0$) and thus the directions of the arrows. Figure 11.3a depicts how the line $dy/dt=0$ divides regions where $dy/dt<0$ (trajectories head downward) from regions where $dy/dt>0$ (trajectories head upward).

For any fixed x, examination of Eqn. (11.2a) shows that (since $c>0$) $dx/dt<0$ (trajectories head left) when $y\to+\infty$ and $dx/dt>0$ (trajectories head right)

(a)

(b)

(c)

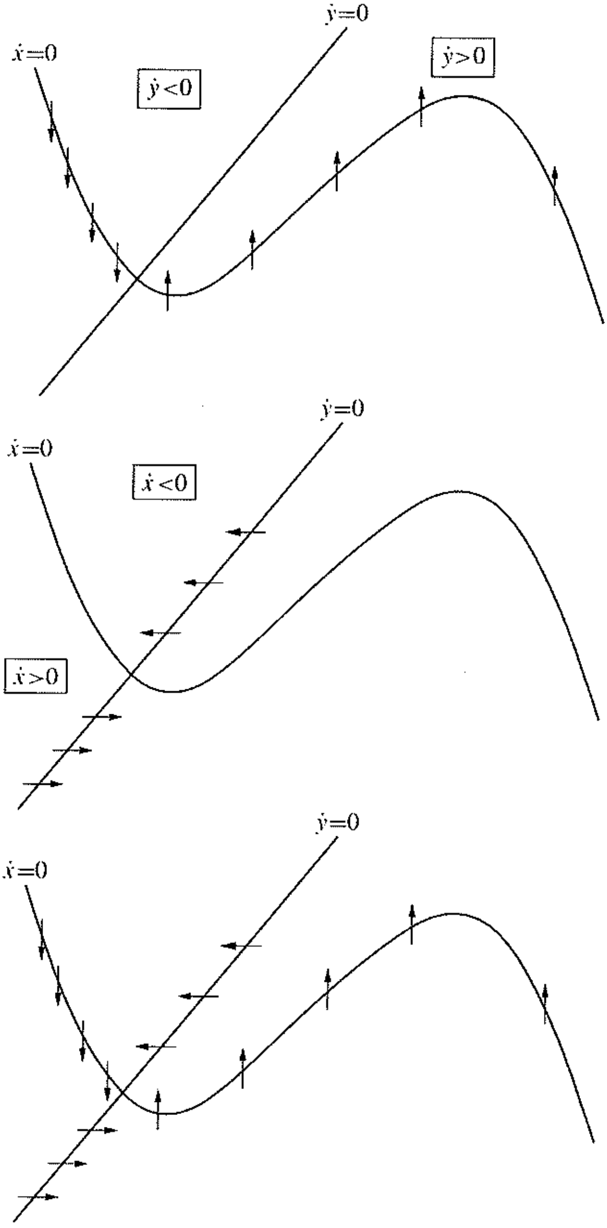


Figure 11.3. (a) *Regions in the xy phase plane for* (11.2) *where y increases* ($dy/dt > 0$) *and decreases* ($dy/dt < 0$), *which yields the directions of trajectories on the y nullcline.* (b) *Regions in the phase plane where x increases or decreases, which yields the directions of trajectories on the x nullcline.* (c) *Combining information from* (a) *and* (b).

when $y \to -\infty$. This leads to Fig. 11.3b. Combining Figs. 11.3a and 11.3b, we obtain Fig. 11.3c.

11.2.4 Stability of the steady state

The next step is to determine the nature of the steady state point at the intersection of the nullclines in Fig. 11.3. We use the usual tool of linear stability analysis from Section 7.4. This requires calculating the coefficients (7.18) and evaluating them at the steady state.[60] We denote these coefficients[61] by A, B, C, D to avoid confusion with the coefficients a, b, c of (11.2). As the reader should verify (Exercise 11.7),

$$A = -c\frac{\partial}{\partial x}\left[y - x + \frac{1}{3}x^3 - j\right] = c(1-x^2) = cM \text{ , where } M(x) \equiv 1 - x^2, \quad (11.11a)$$

$$B = -c\frac{\partial}{\partial y}\left[y - x + \frac{1}{3}x^3 - j\right] = -c \, , \quad (11.11b)$$

$$C = \frac{1}{c}\frac{\partial}{\partial x}[x + a - by] = \frac{1}{c} \, , \quad (11.11c)$$

$$D = \frac{1}{c}\frac{\partial}{\partial y}[x + a - by] = -\frac{b}{c} \, . \quad (11.11d)$$

Note that the coefficients in (11.11) are unaffected by the magnitude of the constant j. In writing A we have used the abbreviation $M(x) = 1 - x^2$ for the slope of the $dx/dt = 0$ nullcline at the various values of x as defined previously.

We now determine the coefficients $\beta = \text{Tr}(J)$ and $\gamma = \det(J)$ of the characteristic equation (7.19) in Chapter 7, and find them to be

$$\beta \equiv (A + D) = cM - (b/c) \, , \qquad \gamma \equiv AD - BC = -bM + 1 \, . \quad (11.12)$$

Note that, since we assume that $b < 1$,

$$\gamma \equiv 1 - bM = 1 - b(1-x^2) = 1 - b + bx^2 > 0 \, .$$

Since $\gamma > 0$, the steady state point will be stable if and only if $\beta < 0$, that is, if and only if

$$-cM + (b/c) > 0 \, . \quad (11.13)$$

If $M < 0$, then $\beta < 0$, $\gamma > 0$ so that the steady state is stable. In particular the steady state in Fig. 11.3 is stable, since it lies on a portion of the N-shaped nullcline $dx/dt = 0$ that has a negative slope ($M < 0$). The steady state point will be *un*stable if

$$-cM + (b/c) < 0 \, , \qquad \text{i.e.,} \qquad \text{if } (b/c^2) < M \, . \quad (11.14)$$

Suppose that $M > 0$. Since c is large by assumption, inequality (11.14) will hold unless the positive number M is small. Thus, a steady state point on the middle portion of the N-shaped nullcline $dx/dt = 0$ (the part with a positive slope) will be unstable except

[60] It is often difficult to solve for those steady states explicitly, but we can use properties of those states, such as the slope M to rewrite the coefficients in more convenient forms. L.E.K.

[61] Recall that these are entries in the **Jacobian matrix**, though this terminology is not absolutely needed. See Section 7.4. L.E.K.

near the top and bottom of this part. There it will be stable. (Compare Exercise 11.8a.) In Exercise 11.9, we discuss the Hopf bifurcation at this steady state.

11.3 Piecing together the qualitative behavior

So far, we have carried out the traditional phase plane analysis. We can summarize our results as follows. There is a single steady state point, which is stable if and only if (11.13) holds. If the sole steady state is stable, we might conjecture that this steady state point is approached from all initial conditions, but this is not necessarily true (Exercise 11.8).

We now go further and use properties of the model equations to probe several additional questions. (1) What is the overall direction and speed of flow in various parts of the phase plane, and how does this inform us about the way that the two variables change? (Recall that one variable, x, is "fast" while the other, y, is "slow"; but what does this imply?) (2) In what sense is there a threshold for excitation to occur? (Recall that this is a determining property of an excitable system.) (3) Other than convergence to a stable steady state, what other dynamics do we expect? What if the sole steady state is unstable? Solutions must then continue to vary with time. Indeed, examination of the phase plane shows that solutions continually oscillate (as we shall see). That such oscillations can occur for ranges of parameter values in the FitzHugh–Nagumo model is an interesting result, which will be investigated further.

11.3.1 Limiting behavior for fast dynamics, $c \gg 1$

Suppose that $c \gg 1$ is large. We can use this to further describe the qualitative properties of the flow in the xy plane, and make statements about the directions and speed of that flow. The slope of the trajectory passing through a point (x, y) of the phase plane is given by

$$\frac{dy}{dx} = \frac{dy/dt}{dx/dt} . \qquad (11.15)$$

In the present case, from (11.2a,b)

$$\frac{dy}{dx} = \frac{1}{c^2} \frac{x + a - by}{x - (1/3)x^3 - y + j} . \qquad (11.16a)$$

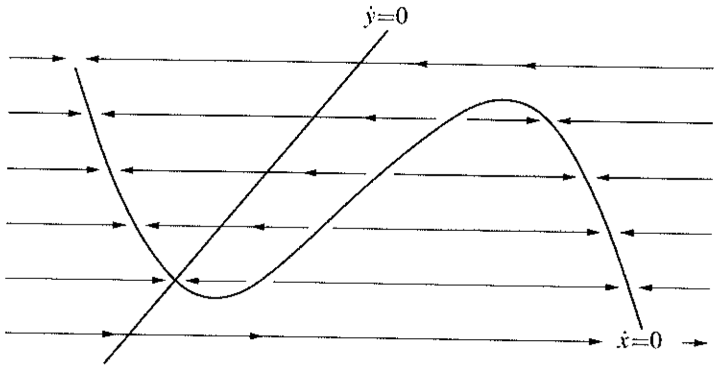
Since c is large compared to unity, from (11.16a) we can deduce the important fact that

$$dy/dx \text{ is small unless } y \approx x - (1/3)x^3 + j . \qquad (11.16b)$$

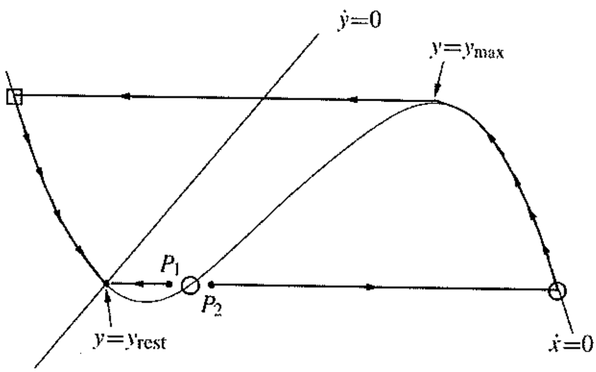
In deducing (11.16b) we use the fact that the product of the small factor $1/c^2$ and the fraction it multiplies need not be small if the fraction is large. From (11.16b) it follows that when c is large,

Trajectories are nearly horizontal except near the dx/dt nullcline . (11.17)

If we add result (11.17) to the information contained in Fig. 11.3b, then we obtain Fig. 11.4a. It appears that once they approach the dx/dt nullcline, trajectories have no choice but to move close to that nullcline.



(a)



(b)

Figure 11.4. (a) *Combining the fact* (11.17) *and Fig.* 11.3c *leads to the conclusion that motion is fast and horizontal as the state point* $(x(t), y(t))$ *approaches the* x *nullcline in the segments shown above.* (b) *Applying the information given in* (a), *for two different initial conditions: trajectories beginning at* P_1 *(subthreshold excitation) and* P_2 *(superthreshold excitation). Arrowheads can be imagined as placed at equal units of time on this graph, so that a relatively high density of arrowheads indicates relatively slow traversal of the corresponding part of the trajectory.*

When a state point moves on a horizontal trajectory, its velocity is given by $\dot{x} = dx/dt$. We see from (11.2a) that the magnitude of dx/dt, the speed $|dx/dt|$, is relatively large, since c is large. When the trajectory moves close to the dx/dt nullcline, its speed v is given by the general formula

$$v = [(\dot{x})^2 + (\dot{y})^2]^{1/2} = \left[\left(\frac{dx}{dt}\right)^2 + \left(\frac{dy}{dt}\right)^2\right]^{1/2}. \qquad (11.18)$$

Equation (11.18), often used in elementary physics, follows from Pythagoras' theorem. In (11.18), dx/dt is relatively small because the state point is near the x nullcline (on which $\dot{x} = dx/dt = 0$). Also $\dot{y} = dy/dt$ is relatively small, from (11.2b), since c is large. We conclude that

$$\text{The state point moves relatively rapidly along horizontal trajectories and relatively slowly near the } x \text{ nullcline} . \tag{11.19}$$

11.3.2 Threshold for excitation

Let us now consider how the phase plane portrait constructed in Fig. 11.4a implies the presence of a threshold for excitation. Let us take initial conditions that are slightly displaced from steady state, shown as P_1 and P_2 in Fig. 11.4b. From P_1 the state point returns directly and horizontally to the steady state. From P_2, by contrast, which is only a slightly larger displacement from the steady state, the state point rapidly moves horizontally in the opposite direction, until it approaches the x-nullcline.

In other words, a large enough stimulus leads to a large excursion in the phase plane that returns to the steady state only after some time. Figure 11.4a shows that the state point is forced to remain near the right branch of that nullcline ($\dot{x} = 0$). But the state point must also move upwards while remaining near this branch (since $dy/dt > 0$, see Fig. 11.3a). When the y-coordinate of the state point barely exceeds y_{max}, then conformity with Fig. 11.4a is attained only by a rapid leftward and horizontal movement to approach the left branch of $\dot{x} = 0$. Here $dy/dt < 0$ (Fig. 11.3a). Hence the state point will move slowly down the left branch of $\dot{x} = 0$, approaching closer and closer to the steady state.

What Fig. 11.4b depicts, in simplified form, is a **threshold phenomenon**. When such a superthreshold excitatory stimulus can evoke a large response, we say that the model describes an **excitable system**.

11.4 Simulations of the FitzHugh–Nagumo model

$$\text{Trajectories are nearly horizontal and approach the } dx/dt \text{ nullcline (which they must cross vertically)} . \tag{11.20}$$

So far, we have analyzed the model equations qualitatively. We now compare our insights with the results of numerical simulations. We first examine numerical simulations when c is large ($c = 10$) and also when c is moderate ($c = 3$). Figure 11.5a shows the computed phase plane behavior when $c = 10$. We examine two initial states, close to P_1 and a little farther away from the rest state, at P_2. We observe that indeed our deductions as to the nature of the trajectories when $c \gg 1$ are fully borne out. Standard graphs of the excitation variable x and the recovery variable y for the larger loop trajectory are shown in Fig. 11.5b. Illustrated are the characteristic rapid rise of the **excitation spike** $x(t)$ and its slower recovery.

Figure 11.5c shows computed phase plane behavior when $c = 3$. The predicted behavior is still mainly borne out by the simulations. In particular, the threshold effect remains. The excitation spike can still be subdivided into alternating slow and fast portions, but not in the distinct manner that is possible when $c \gg 1$. See also Fig. 11.5d for the time profiles of each variable.

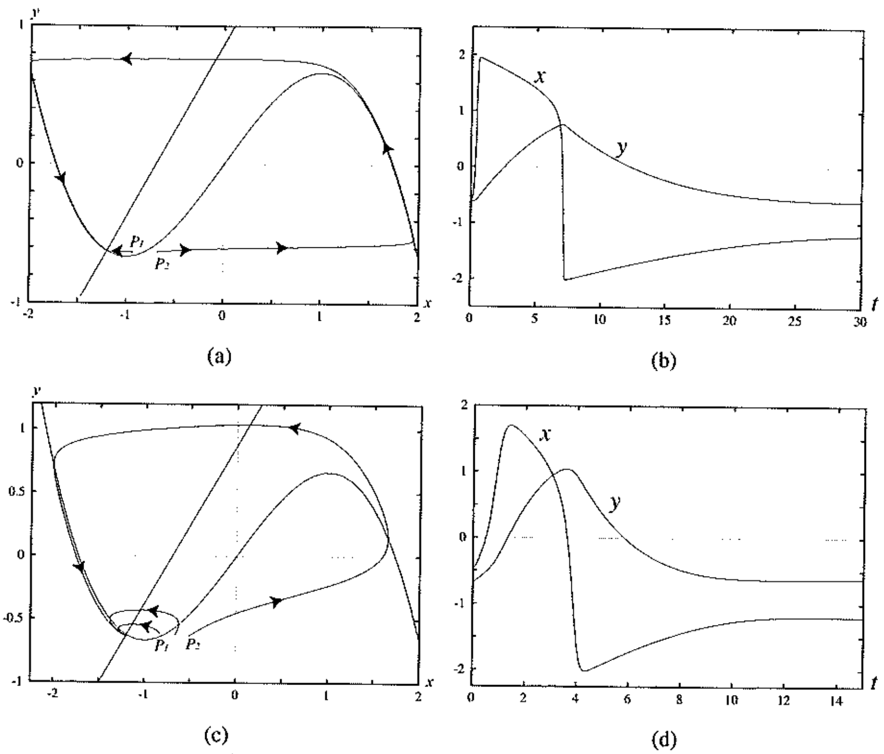


Figure 11.5. (a) *Simulated phase plane behavior for the FitzHugh-model equation for* $c = 10$. *Sub- and superthreshold stimuli,* P_1 *and* P_2. *(Arrows here indicate directions only, not equal time steps.)* (b) *The time behavior of the variables* $x(t)$ *and* $y(t)$ *corresponding to the large trajectory shown in* (a). *See XPP file in Appendix* E.7.2. (c),(d) *As in* (a),(b) *but for* $c = 3$.

We now consider several additional qualitative phenomena, observed experimentally, all of which are common in the neurophysiology that motivated this model, and clearly exemplified by a phase plane analysis of the FitzHugh model equations.[62]

11.4.1 Refractory period, postinhibitory rebound, and limit cycles

We have seen that extensive rapid excitation can be ignited by relatively moderate superthreshold excitations (state point moved sufficiently far rightward). Suppose that a second instantaneous excitation is given later, when the state point is at point A of Fig. 11.6. Recovery commences immediately, as is shown in the figure. If a shock of the same magnitude is applied when conditions correspond to point B, again recovery occurs at once. But if the identical shock is applied at C (or a considerably larger shock is applied at B), then further spontaneous excitation occurs. At B, the stimulus shown in Fig. 11.6 does not result in a new excursion around a loop in the phase plane, but if that stimulus was two or

[62] These phenomena are also properties of the full Hodgkin–Huxley system. L.A.S.

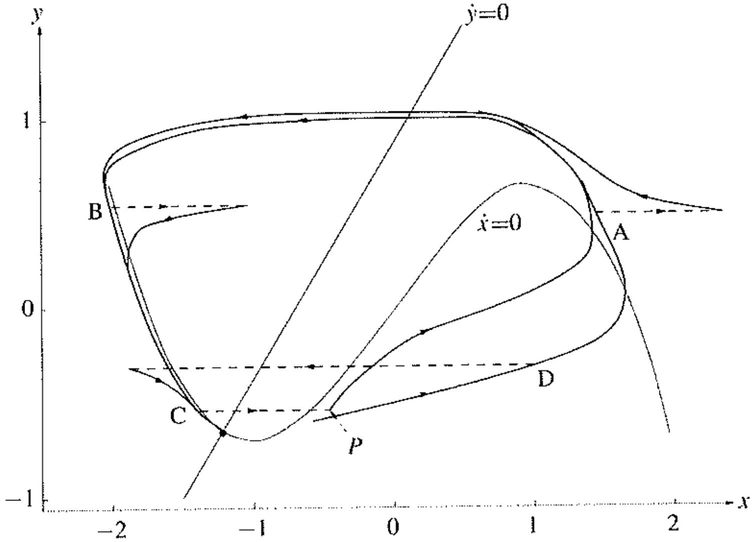


Figure 11.6. *Further study of the model of Fig.* 11.5c. *Shown is the membrane impulse generated when instantaneous excitation shifts the state of the system to P. The dashed lines emanating from A, B, and C depict identical depolarization shocks. The consequent reaction of the system is depicted: only at C is there further excitation. Also depicted is the observation that a sufficiently large instantaneous inhibition at D can abolish the excitation spike.*

three times larger in magnitude, it could put the state point beyond the y nullcline. This would result in a new strong response (circuit around a somewhat smaller loop in Fig. 11.6). Conditions at A are called **absolutely refractory**, while those at B are called **relatively refractory**. Note also that **abolition** of an impulse can occur during the initial stages of excitation potential if a sufficiently strong inhibitory shock is applied (Fig. 11.6, point D).

With a view toward illustrating additional interesting phenomena, let us consider in further detail the behavior of the trajectories near the steady state point. A schematic illustration of the expected trajectories is given in Fig. 11.7a, when $c \gg 1$. A dashed excitation threshold line divides trajectories that directly approach the steady state from those that detour via an extensive excitation. Figures 11.7b and 11.7c show that actual computations verify the sketch very well when $c = 10$, and adequately when $c = 3$, where the threshold is not so sharp.[63]

Let us now examine the consequences of applying a step source of excitation. In terms of our model, this means instantaneously shifting the parameter j in (11.2a) to a positive value and keeping it there. Then each point of the x nullcline $y = x - \frac{1}{3}x^3 + j$ is instantaneously raised a constant distance. Consequently, as shown in Fig. 11.8a, the steady state point alters its position to P'. The point P, previously a steady state, is now an initial point below and to the left of the new steady state. The excitation threshold is given by the

[63]Closer inspection of the trajectories for the case $c = 3$ reveals that the threshold is "fuzzy." See [14] for a careful mathematical study of blurred thresholds. L.A.S.

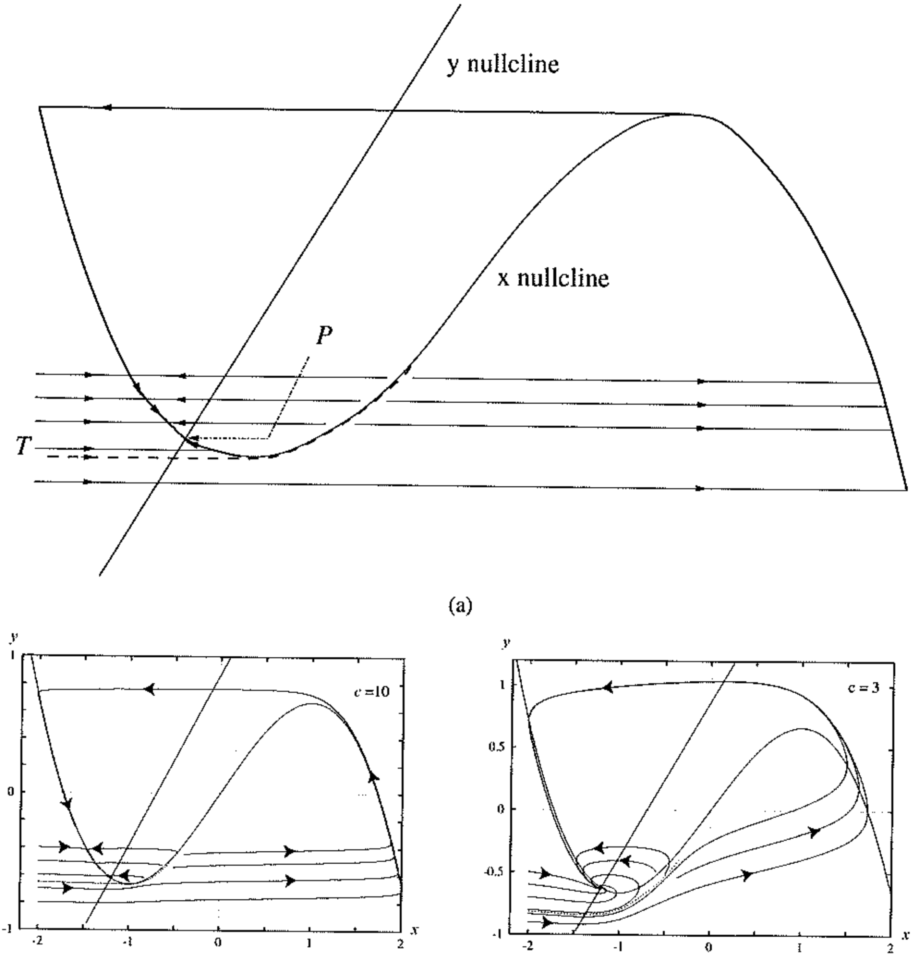
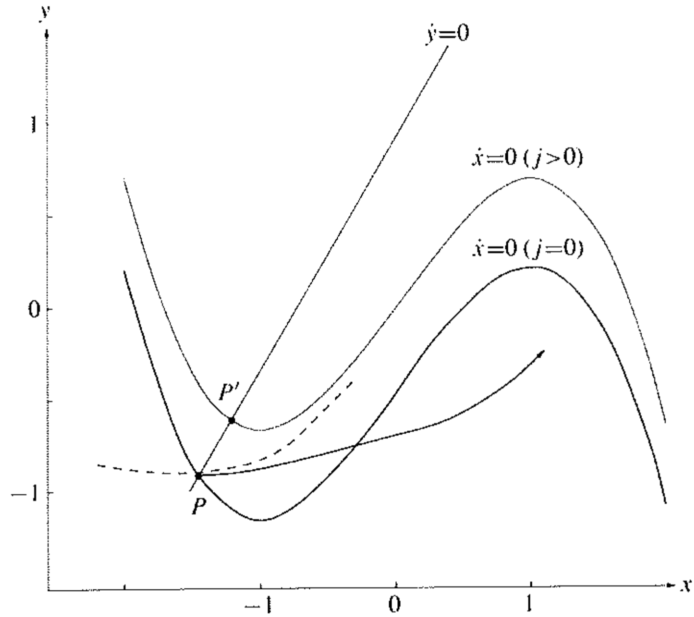


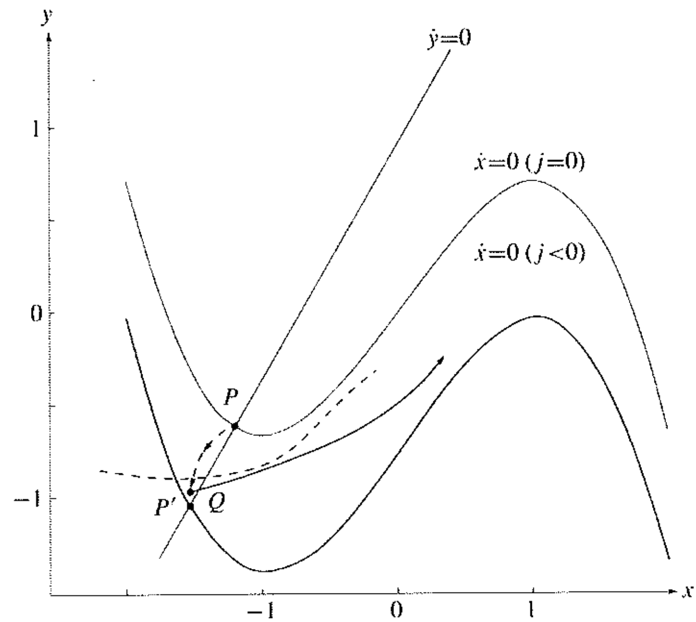
Figure 11.7. *Details of trajectories that start near the steady state point P.* (a) *Schematic predictions for* $c \gg 1$. *Trajectory T, which lies just below the minimum of the x nullcline, divides trajectories that directly approach P from those that do so only after an extensive "detour" of excitation.* (b) *Calculations for* $c = 10$. (c) *Calculations for* $c = 3$. *Panels* (b), (c) *made with XPP file in Appendix* E.7.2.

dashed line in Fig. 11.8a. If the magnitude of the excitation source is sufficiently large, then P is on the "far side" of the threshold and an excitation spike commences.

It is not surprising that sufficient excitation can generate a spike, but we now show that sufficient inhibition can also generate a spike. To be more precise, consider the effect of applying an inhibitory source ($j < 0$) for a considerable period, after which this source is shut off. Figure 11.8b depicts the nullclines in standard position (solid light lines), together with the corresponding threshold.



(a)



(b)

Figure 11.8. (a) *Application of an excitatory source ($j > 0$) raises the x nullcline. It can thereby generate an impulse.* (b) *Phase plane explanation of postinhibitory rebound.*

When an inhibitory source is applied, the x nullcline is lowered (heavy line, Fig. 11.8a). The former steady state point P moves toward the new steady state point P'.

Suppose that the inhibitory source is sufficiently large and that sufficient time has elapsed, so that the state point has reached the point labeled Q in Fig. 11.8b. If the inhibition now ceases, the original nullclines and threshold locus again apply. Point Q is on the far side of the threshold, so that a spike of excitation will ensue. This is **postinhibitory rebound.** The last major phenomenon that we wish to consider occurs when a sufficiently strong excitation source is applied so that the steady state point moves *past* the minimum point to the rising portion of the N-shaped $\dot{x}$ nullcline (away from its ends).

As we have seen, such a steady state is unstable. In the absence of a stable steady state, the system is fated to change its state continually. Analysis of the situation when $c \gg 1$ suggests that this will occur by means of periodic oscillations (Exercise 11.8b). After transients die out, the system is expected to repeatedly traverse a closed curve in the phase plane, a **limit cycle**. (The limit cycle is **stable**, since nearby trajectories always approach it.) Simulations bear out the analysis. Figure 11.9a, calculated for $c = 10$, depicts a trajectory that initially moves horizontally and to the right (dashed line) before perpetually circulating on a limit cycle (solid line). This figure virtually coincides with what would be predicted for $c \gg 1$. Figure 11.9b shows that the major features are retained when $c = 3$. We also show this oscillation behavior in the time plots of Fig. 11.10. In Exercise 11.11, we ask the reader to construct a bifurcation diagram for the FitzHugh–Nagumo model with the applied current j as the bifurcation parameter.

11.5 Connection to neuronal excitation

In this section, we return to the original motivation that led to the simple model that we have studied in this chapter. FitzHugh [45] made a major step forward in the analysis of the Hodgkin–Huxley equations using two main tools. The first was superior computer facilities[64] that allowed a much more extensive analysis of various possible cases than was possible for Hodgkin and Huxley in the early 1950s. In addition, FitzHugh was one of the pioneers in coopting for theoretical biology the mathematical methods of nonlinear mechanics, particularly the use of the phase plane approach, to discern qualitative properties of the solutions to differential equations.

11.5.1 FitzHugh's simulations of the Hodgkin–Huxley equations

Figure 11.11 shows FitzHugh's [45] calculations of solutions to the Hodgkin–Huxley equations (10.27)–(10.30) that we considered in Chapter 10. Displayed are membrane potential and gating variables. Observe that the voltage V and the sodium gating variable m change rapidly, compared to the changes in the gating variables n and h. Also, deviations of n and h

[64] Historical note: In carrying out his calculations, such as those of Fig. 11.11, FitzHugh employed an analog computer. Such analog computers embodied differential equations in electronic circuits whose dynamics were described by the equations in question. Measurements of currents and voltages thus provided approximate solutions of the equations. In their time, analog computers provided a relatively rapid way to solve systems of ODEs, albeit with limited accuracy. They were particularly efficient in exploring the effects of changing parameters, for such a change could be reproduced merely by turning a knob on the machine. Modern digital computers have made analog machines virtually obsolete, although certain electrical analogues of biological circuits have proved of considerable value (Hoppensteadt [64]). L.A.S.

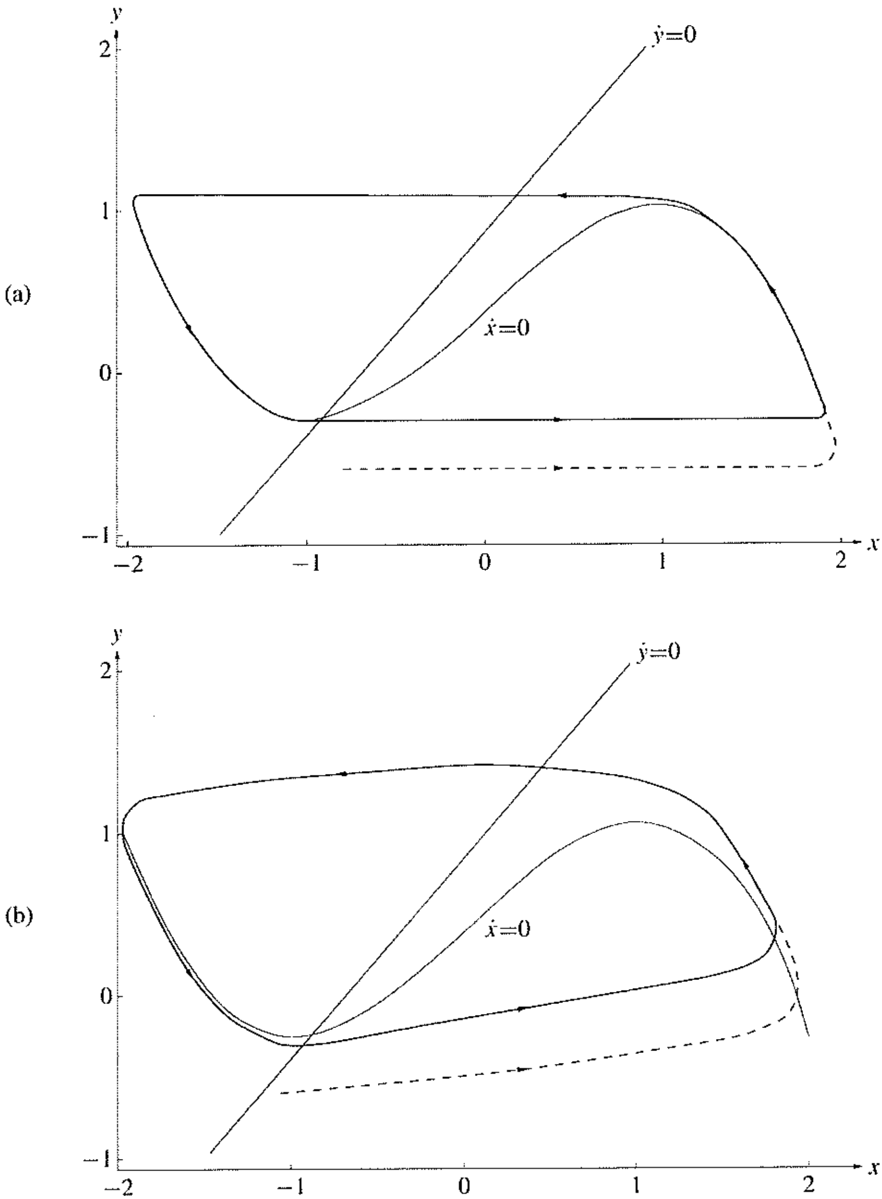


Figure 11.9. *A sufficiently strong source of excitation leads to a limit cycle (periodic solution).* (a) $c = 10$. (b) $c = 3$. *Other parameters as in Fig.* 11.2 *except* $j = 0.35$.

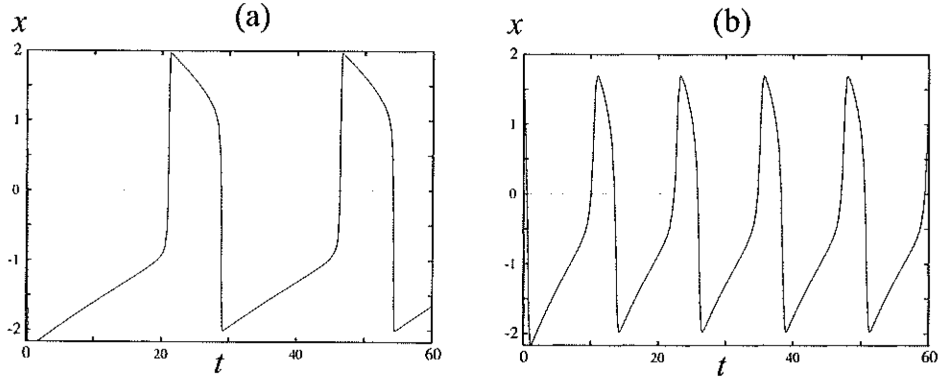


Figure 11.10. *Standard graph of the "voltage" x for the periodic solution.* (a) $c = 10$. (b) $c = 3$. *Graphs produced with XPP file in Appendix* E.7.2 *with parameters* $j = 0.35, a = 0.7, b = 0.8$.

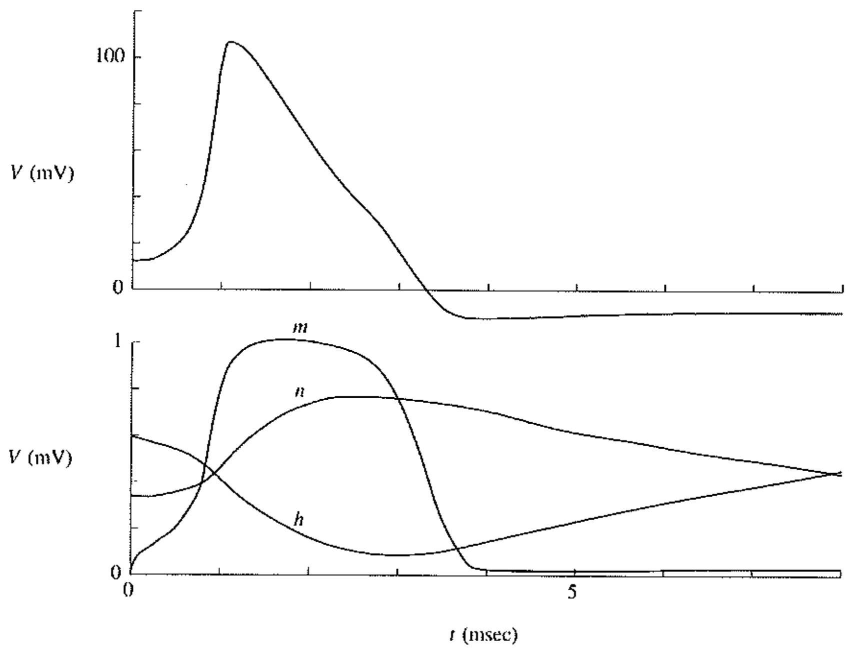


Figure 11.11. *FitzHugh's solutions to the Hodgkin–Huxley equations, for a membrane action potential,* (10.27)–(10.30), *discussed in Chapter* 10. *Top: Voltage. Bottom: Fractions of open channel subunits. Redrawn from FitzHugh* [45, Fig. 1].

from their average values are relatively small compared to variations of m and V. This suggests that a meaningful approximation to the dynamics might be obtained by replacing n and h by constants (Exercise 10.11), keeping only V and m as dynamic variables.

Doing so leads to the following equation system:

$$C\frac{dV}{dt} = -[\bar{g}_{Na} m^3 \bar{h}(V - V_{Na}) + \bar{g}_K \bar{n}^4 (V - V_K) + \bar{g}_L (V - V_L)] + I\,, \quad (11.21a)$$

$$\frac{dm}{dt} = -k_-^{(m)}(V)m + k_+^{(m)}(V)(1-m)\,. \quad (11.21b)$$

Here $\bar{n}$ and $\bar{h}$ are taken to be constants whose values are held at their rest values when $V = 0$.

Some of FitzHugh's solutions $m(t)$, $V(t)$ of (11.21) are shown in the Vm phase plane of Fig. 11.12a. Also shown in Fig. 11.12a are the m (horizontal) and V (vertical) nullclines, the curves in the Vm plane where, respectively, $dm/dt = 0$ and $dV/dt = 0$. These intersect in three points, A, B, and C, the steady states of the system (11.21). Point C corresponds to an excited state. (Note that the trajectories should be, but are not quite, vertical when they pass through the V nullcline. This is due to small errors in the analog computations.)

The nullclines in Fig. 11.12a are almost tangent in the vicinity of B and A, so that details are hard to discern. Figure 11.12b shows a magnification of the region near B and A. A corresponds to the rest state ($V = 0$, with m at its corresponding rest value of about 0.05). As indicated in Fig. 11.13a (a further magnification of the region near the point labeled A in Fig. 11.12), A is a stable node and B is a saddle point. An initial point P in Fig. 11.13b asymptotically approaches the slightly excited steady state B. But any deviation, however tiny, results in an entirely different outcome. A deviation to the left of P would result in an approach to A, while a deviation to the right would result in an approach to C. Thus the two trajectories of Fig. 11.13b with arrows pointing into B provide a **sharp threshold** for excitation or, equivalently, a **separatrix** in the sense of Section 7.7.

FitzHugh used this reduced model to reason heuristically and obtain some qualitative insights about the Hodgkin–Huxley equations. For brevity, we omit that analysis here. One might expect that the reasoning is accurate in the limit where the n and h variables have an intrinsic rate of change that is infinitesimally small compared to the corresponding rates for m and V. But this limit cannot be expected to describe faithfully the actual state of affairs, where n and h change rather more slowly, but certainly not "infinitesimally" slowly compared to m and V. In particular, the exact threshold picture of Fig. 11.12b, with its *two* nearby steady state points A and B, does not give a precise picture even near the rest point A.[65] Eventually abandoning the above reduction, FitzHugh took another major step forward by proposing and analyzing the caricature model, Eqs. (11.2) that we have explored in this chapter. Motivation for the FitzHugh [46] model was as follows:[66]

(i) For maximum simplification one variable should lump together the relatively rapidly changing quantities V (voltage or, more precisely, depolarization) and m (the rapidly changing Na^+ gating variable—whose "activation" promotes depolarization). The other variable should represent the relatively slowly changing quantities n and h, both of which act to promote recovery from depolarization. This yields a two-dimensional problem, far simpler to analyze than a four-dimensional problem.

[65] Recall that the nullclines are almost tangent in the region of A and B. As a consequence, small errors in this region might lead to large effects. It is thus not surprising that there are defects in the approximation that the results for fixed n and h remain valid when n and h are slowly varying. L.A.S.

[66] Some of the motivation is explicit in FitzHugh's paper, some implicit. L.A.S.

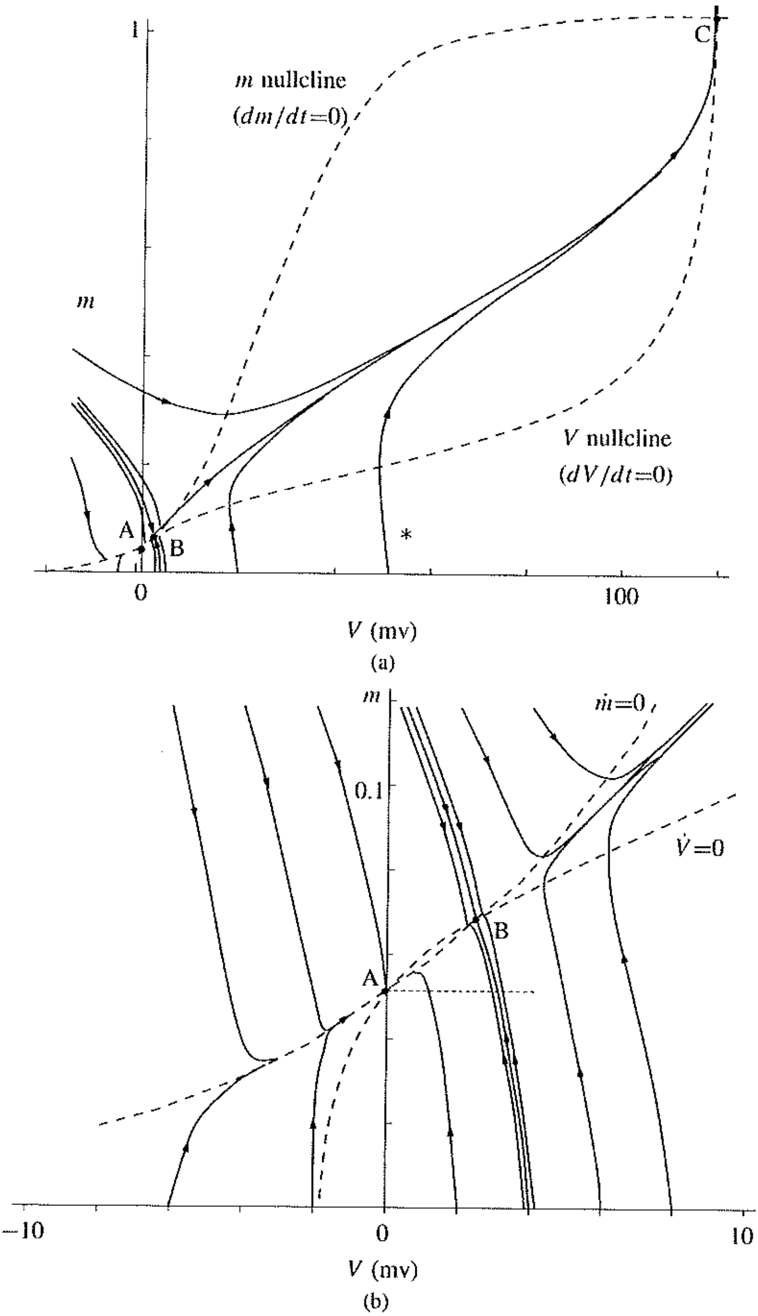


Figure 11.12. *Top: Nullclines (dashed lines) and trajectories (solid lines) for the phase plane of* (11.21). *The intersections of nullclines are the steady state points A, B, and C. Bottom: Detail of part of the phase plane, in the neighborhood of the steady state points A and B. Redrawn from FitzHugh* [45, Figs. 2 and 3].

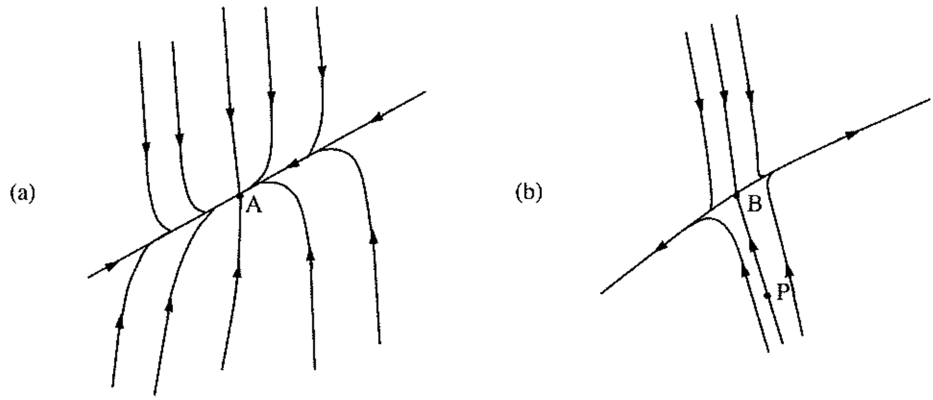


Figure 11.13. *Zooming in on the steady state points of Fig.* 11.12a. (a) *The stable node A. Some trajectories in addition to those calculated by FitzHugh have been sketched and are only qualitatively correct.* (b) *The saddle point B. Point P lies on one of the two special trajectories that approach the saddle point B. Recall that these special trajectories act as a separatrix.*

(ii) As for the full Hodgkin–Huxley equations of Chapter 10, the model should depict a threshold phenomenon in the fast variable in the absence of any recovery effects.

As we have seen, the model (11.2) has precisely these features. The phase plane analysis of the FitzHugh "model" equations in Section 11.2 explains a remarkable variety of phenomena that are observed in experiments such as thresholds of several different kinds, absolute and relative refractoriness, and periodic oscillations. The phase plane description further reveals that only certain features of the mathematical model are responsible for this wide range of qualitative behaviors. Thus, the key features responsible for the phenomena that we have discussed here are an N-shaped nullcline intersected just once by the second nullcline. Further investigation makes clearer the need for an additional feature that we have tacitly assumed, i.e., that the steady state point should be fairly close to the minimum (or the maximum) of the "N."

At the same time, the caricature model is not an accurate quantitative description of neuronal action potential and has some properties that depart from those of the full Hodgkin–Huxley model. A disadvantage of the phase plane explanation is that it is expressed in mathematical rather than biophysical terms. The theoretician should ultimately present both mathematical and biophysical explanations for every important phenomenon. An advantage is that it is mathematically tractable and has motivated advanced analysis techniques, as well as applications to a host of other systems that display excitability.

11.6 Other systems with excitable behavior

Excitability and oscillation occur in other biological systems. One of Lee Segel's favorite examples is the excitability and oscillation in cyclic AMP secretion. These play a major role in a classical model system studied in developmental biology, the cellular slime mold amoebae [54]. The structure of the relevant mathematical model is very similar to that of the FitzHugh model studied here. Characteristically, there is another approach to cyclic AMP oscillations in slime mold, rather different in biochemical detail than that chronicled in [130]. (See Othmer and coworkers [113, 122].) In the latter theory, calcium played a major role. It turns out that the two competing theories have highly similar phase plane structure.

Calcium is the major regulatory molecule in the Odell–Oster–Murray "mechanical" theory for morphogenesis that is discussed in [130, Chapter 9]. Thresholds for excitability play a central role in this theory. Once again, the phase planes contain N-shaped nullclines, with qualitative behavior that is very similar to the excitability found in the FitzHugh equations.

Exercises

11.1. (Review of Section 5.3.1.) Analyze the stability of the steady states of (11.1), and thereby verify the correctness of Fig. 11.1.

11.2. Consider $y = f(x) = c(x - \frac{1}{3}x^3 + A)$ as in Eqn.(5.16). Compute the first and second derivatives of this function. Find the extrema (critical points) by solving $f'(x) = 0$. Then classify those extrema as local maxima and local minima using the second derivative test. (Recall that $f''(p) < 0 \Rightarrow$ local maximum, $f''(p) > 0 \Rightarrow$ local minimum, and $f''(p) = 0 \Rightarrow$ test inconclusive.) This analysis is useful for material in Section 11.2.1.

11.3. Show that if y is fixed at its rest value, the equation (11.2a) for dx/dt has three steady state points, just as in Fig. 11.4a.

11.4. Consider the y nullcline, given by (11.3a), and x nullcline, given by (11.3b). Determine the slopes (dy/dx) for each of these curves. Show that for the curves to be tangent to each other at some point of intersection (so that their slopes are precisely equal), (11.6) has to hold. Then explain why this is not possible so long as $b < 1$.

11.5. Suppose $j = 0$ and $0 < b < 1$. What are the conditions on a that will yield a steady state precisely at the minimum of the cubic nullcline (11.3b)? Show that this implies (11.8). Use your results and reasoning in the text to confirm the inequalities in Section 11.2.2 that are required for conditions (i)–(iii) in Section 11.2.1.

11.6. Verify the directions on the x and y nullclines as described in Section 11.2.3.

11.7. Verify the stability calculations in Section 11.2.4 as follows:

(a) Compute the coefficients for the Jacobian matrix. Show that you obtain the expressions in (11.11).

(b) Calculate the values of the coefficients β and γ of the characteristic equation (Section 7.4 of Chapter 7) in terms of the slope M at the steady state.

(c) Show that stability conditions are as given in (11.13).

11.8. Consider the FitzHugh–Nagumo model (11.2) for $c \gg 1$. Suppose that there is a single steady state on the middle part of the N-shaped nullcline $dx/dt = \dot{x} = 0$.

(a) Demonstrate pictorially that such a steady state is unstable.

(b) Show pictorially that a typical trajectory ends up at a limit cycle.

11.9. Use the results of Section 11.2.4 to explore the bifurcation properties of the steady state of the FitzHugh–Nagumo model. In particular, show that as the slope M of the $dx/dt = 0$ nullcline varies, you expect to see a Hopf bifurcation. (To do so, argue that the eigenvalues are complex, and that there is a value of M for which their real parts vanish.)

11.10. This exercise guides the student in simulating the FitzHugh–Nagumo equations. Use the XPP file in Appendix E.7.2 (or your favorite ODE solver) to simulate the equations of the model.

(a) Use XPP to graph the nullclines.

(b) Show trajectories that start close to the steady state. You should find that some of these return to the steady state directly, and others produce a large loop trajectory that eventually returns to the steady state.

You can use this program to draw the panels shown in Fig. 11.5.

11.11. (a) Use the XPP file in Appendix E.7.2 to produce a bifurcation diagram for the FitzHugh–Nagumo model with the current j as bifurcation parameter (as shown in Fig. 11.14). (Follow the instructions in Appendix E.7.2.)

(b) Interpret what this figure implies. With the parameters in the XPP file, you should find a Hopf bifurcation at $j = 0.3465$ (and a second one at $j = 1.401$, not shown in the figure).

(c) What type of Hopf bifurcation is this? To answer this question, zoom in on the bifurcation point by changing the horizontal axis. Now compare with Figs. 7.16 and 7.17.

(d) To show the second Hopf bifurcation point, extend the horizontal axis and continue to see where the limit cycle disappears.

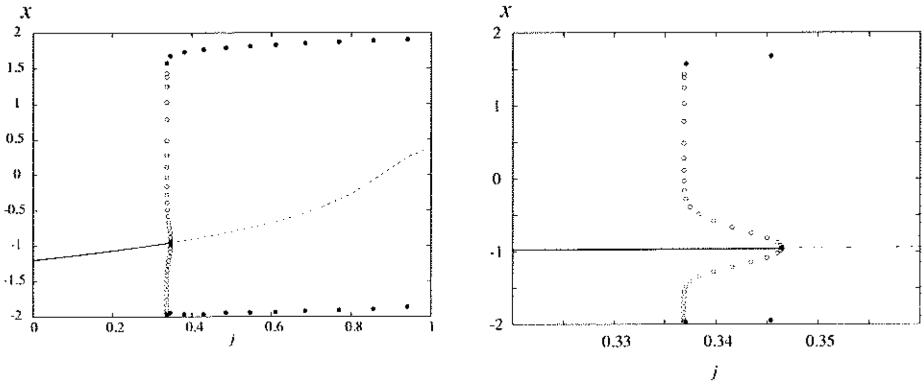


Figure 11.14. *A bifurcation diagram for the FitzHugh–Nagumo model showing one of the Hopf bifurcation points. See Exercise* 11.11. *The right panel shows a zoomed in view of the diagram close to a Hopf bifurcation point.*

(e) Now go back to the xy phase plane and simulate the model for values of j just below, at, and just above each of the bifurcation values to see how the limit cycle is formed and how it disappears.

11.12. This exercise continues the exploration of Exercise 11.11 of the limit cycles in the FitzHugh–Nagumo model.

(a) Use the XPP file in Appendix E.7.2 with the parameter j set to $j = 0.34$ to produce a phase plane diagram in the xy plane, as shown in Fig. 11.15. You will easily find a (large) stable limit cycle.

(b) Now change the time step to $dt = -0.01$ to integrate in the negative time direction. (This makes stable attractors unstable, and vice versa.) Find the (small) limit cycle.

(c) Interpret your findings in the context of the bifurcations discussed in Exercise 11.11.

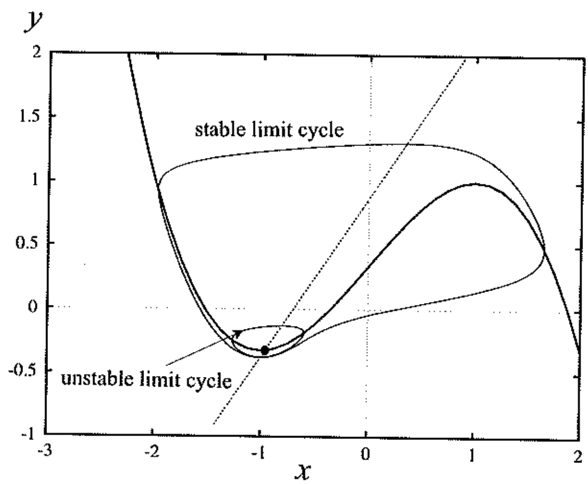


Figure 11.15. *Two limit cycles in the FitzHugh–Nagumo model. $j = 0.34$, all other parameters at their default values ($a = 0.7, b = 0.8, c = 3$). See Exercise* 11.12.

11.13. In this exercise, we examine FitzHugh's original "reduction" of the Hodgkin–Huxley model.

(a) Determine the equation satisfied by the m nullcline using Eqn. (11.21b). Identify this curve as one of the dashed lines in Fig. 11.12a.

(b) Determine the equation for the V nullcline using Eqn. (11.21a). Identify this curve as another of the dashed lines in Fig. 11.12a. Note that steady states are at intersections of these curves, marked by heavy dots in Figs. 11.12a and 11.12b; such steady states cannot be determined analytically in this case.

(c) Show that at any fixed V, changes in n to a higher value and h to a lower value lead to an elevation of the V nullcline.

(d) Using the shapes of the nullclines shown in Fig. 11.12a, verify that in response to such changes, eventually B and C merge and disappear, leaving only the point A.

11.14. See Exercise 15.9 for an extension showing that many of the ideas discussed in connection with neurophysiology in Chapters 10 and 11 find application in other examples of excitable systems such as the aggregation of the amoeba *Dictyostelium discoideum*.

A Primer on MATHEMATICAL MODELS IN BIOLOGY

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