6 Action Potentials - Reduction to Phase Space

The Hodgkin-Huxley equations for the behavior of the action potential in squid, and similar equations for action potentials in other cells, are "exact" but impossibly complicated. We now consider the use of phase plane techniques a means to get insight into regenerative neuronal events, such as those exhibited by the Hodgkin Huxley equations.

The Hodgkin-Huxley equations were functions of 4 variables.

- $V(x,t) \leftarrow$ transmembrane potential
- $m(V,t) \leftarrow$ activation parameter for Na^+ current
- $h(V,t) \leftarrow$ inactivation parameter for Na^+ current
- $n(V,t) \leftarrow$ activation parameter for K^+ current

The goal is to reduce the Hodgkin Huxley equations from a dependence on 4 variables to a dependence on 2 variables. Why two? We can graph the dynamics. There is no chaos in 2-D.

FIGURE - chapt-8-hh-currents.eps

6.1 Dimensional Reduction of the Hodgkin-Huxley Model

We ignore space so that we have as the voltage equation

$$\begin{aligned}\tau\frac{\partial V(t)}{\partial t} &= -\frac{r_m}{2\pi a}I_o(t) - \frac{r_m\overline{g}_{Na^+}m^3(V,t)h(V,t)}{2\pi a}\cdot V(t)\frac{1-e^{-\frac{e[V(t)-V_{Na^+}]}{k_BT}}}{1-e^{-\frac{eV}{k_BT}}} \qquad (6.1)\\ &- \frac{r_m\overline{g}_{K^+}n^4(V,t)}{2\pi a}\cdot V(t)\frac{1-e^{-\frac{e[V(t)-V_{K^+}]}{k_BT}}}{1-e^{-\frac{eV}{k_BT}}} - \frac{r_m g_{leak}}{2\pi a}(V(t)-V_{leak})\end{aligned}$$

which has 10 independent biophysical parameters, i.e., a, τ, λ, r_m, $\overline{g}_{Na^+}$, $\overline{g}_{K^+}$, g_{leak}, V_{Na^+}, V_{K^+}, and V_{leak} as well as 3 (or more in principle) fitting parameters as exponents on the activation and inactivation functions.

$$\frac{dh(V,t)}{dt} = \frac{h_\infty(V) - h(V,t)}{\tau_h(V)} \qquad (6.2)$$

$$\frac{dm(V,t)}{dt} = \frac{m_\infty(V) - m(V,t)}{\tau_m(V)} \qquad (6.3)$$

$$\frac{dn(V,t)}{dt} = \frac{n_\infty(V) - n(V,t)}{\tau_n(V)} \tag{6.4}$$

where $n_\infty(V) \equiv n(V, t \to \infty)$ and the parameterization for each rate expression has three fitting parameters, i.e., z', V_{th}, $\tau_{obs}(0)$, for a total of 9 parameters.

Four equations and 18 parameters is too much!. More so, we know that the I-V relation during the rising phase of the action potential has a region of negative conductance, i.e., "N"-shaped. To get there, we methodically brutalize the dynamical equation as as follows:

1. The response time for the activation of the sodium current is fast time. We approximate this as infinitely fast and replace $m(V,t)$ by its steady state value, i.e., by $m_\infty(V)$. This implies that the action turns-on instantaneously.

FIGURE - chapt-10-mhn.eps

This leaves us with a single "fast" variable, that we continue to denote $V(t)$.

2. The equation for $V(t)$ will contain an essential nonlinearity to allow regenerative behavior. This is found by looking at the I-V relation for the squid axon at short times, when the Na^+ current is fully activated. Roughly, there are three zero-crossings. Two are "stable", correcting to the rest-date and the top of the action potential. The third is unstable and corresponds to the threshold potential. The form will be approximated as a cubic, although this is smoother than the real function. We denote the nonlinearity by $f(V)$, for which

$$f(V) = (V - V_{rest})\,(V - V_{thresh})\,(V - V_{peak}) \tag{6.5}$$

FIGURE - chapt-10-volt-clamp-summary.eps

3. Both the inactivation of the Na^+ current and the activation of the K^+ current are slow. It was noted by Fitzhugh that an increase in $n(V,t)$ corresponds to a decrease in $h(V,t)$ so that the functions $n(V,t)$ and $1 - h(V,t)$ (almost) linearly covary. This effect is near perfect for the squid axon, approximate for mammalian neurons.

SKETCH - "n" VERSUS "1-h"

Rinzel showed that this can take the form

$$W(V,t) = \frac{S_o}{1 + S_o^2}\left\{S_o\,[1 - h(V,t)] + n(V,t)\right\} \tag{6.6}$$

where S_o is defined at rest, i.e.

$$S_o \equiv \frac{1 - h(V_o, t_o)}{n(V_o, t_o)}. \tag{6.7}$$

This leaves us with a single "slow" variable, that we denote $W(t)$

4. The membrane time-constant can be ignored, that is, taken as zero. Thus the rise of the action potential can be arbitrarily fast. The relaxation of the neuronal dynamics will occurs on the time-scale of the slow recovery variable $W(t)$. Thus a single parameter, that we denote ϕ, is essentially the ratio of fast to short time-constants. Thus ϕ is a small number and $\frac{1}{\phi}$ sets the time scale for the slow variable.

5. All of the above motivates the simplified form credited to Fitzhugh and Nagumo, which in it's most basic form contains two equations to describe fast and slow (recovery) variables

$$\frac{dV}{dt} = f(V) - W + I \tag{6.8}$$

where $f(V)$ is a cubic polynomial, similar in form to the instantaneous Hodgkin-Huxley Na^+ current, and given above, and

$$\frac{dW}{dt} = \phi\,(V + a - bW)\,. \tag{6.9}$$

Note that there are no product terms, i.e., terms of the form "WV", to complicate the mathematics.

Our goal is to use this brutalized from to derive the properties of the spike by viewing the action potential as a limit cycle, etc.

6.2 A Quick Review of the Phase Plane

Before we get knee deep in the phase plane, let's back up and recall what is meant by graphical analysis.

Consider $\frac{dx}{dt} = f(x)$

- When $\frac{dx}{dt} > 0$, x is increasing and the flow is the right along x, i.e., $\rightarrow$
- When $\frac{dx}{dt} < 0$, x is decreasing and the flow is the left along x, i.e., $\leftarrow$

This is illustrated for the case of $\frac{dx}{dt} = \sin x$

FIGURE - chapt-10-phase-plane-sinx.eps

Another way to look at this is to consider a potential, $U(x)$, where $f(x) = \frac{-\partial U(x)}{\partial x}$ so that $U(x) = \cos x$.

The power of this method comes with sets of equations with 2 dependent variables, i.e., of the form

$$\begin{aligned}
\frac{dV}{dt} &= function(V, W, I, constants) \;\equiv\; F(V, W, I, constants) \qquad (6.10)\\
\frac{dW}{dt} &= another\ function(V, W, constants) \;\equiv\; G(V, W, constants)
\end{aligned}$$

Then we can observe the possible trajectories of the system graphically, and get insight into certain perturbations.

6.3 The Fitzhugh-Nagumo Model

6.3.1 Formulation

For simplicity, we will take $V_{rest} = 0$, so that

$$\begin{aligned} f(V) &= V\left(V - V_{thresh}\right)\left(V - V_{peak}\right) \\ &= \left(V_{thresh} + V_{peak}\right)V^2 - (V_{thresh}V_{peak})V - V^3 \end{aligned} \tag{6.11}$$

we will later find it useful to consider the derivative of this function

$$f'(V) \equiv \frac{df(V)}{dV} = 2\left(V_{thesh} + V_{peak}\right)V - \left(V_{thresh}V_{peak}\right) - 3V^2 \tag{6.12}$$

The fast variable, $V(t)$, captures the features of the instantaneous I-V relation at the height of the action potential. It obeys

$$\begin{aligned} \frac{dV}{dt} &= f(V) - W + I \\ &= \left(V_{thresh} + V_{peak}\right)V^2 - \left(V_{thresh}V_{peak}V\right) - V^3 - W + I \end{aligned} \tag{6.13}$$

FIGURE - chapt-10-FN-nullclines.eps

The slow variable, $W(t)$, obeys

$$\frac{dW}{dt} = \phi\left(V + a - bW\right) \tag{6.14}$$

where, we recall, $\phi << 1$.

6.3.2 Analysis

1. In steady state these must satisfy

$$\frac{dV}{dt} = \frac{dW}{dt} = 0 \tag{6.15}$$

so that

$$\begin{aligned} W &= f(V) + I \\ &= \left(V_{thresh} + V_{peak}\right)V^2 - (V_{thresh}V_{peak})V - V^3 + I \end{aligned} \tag{6.16}$$

which has a local minimum at $dW/dV = 0$ and $d^2W/dV^2 > 0$, and for the case $I = 0$ is given by

$$V_{-} = \frac{1}{3}\left(V_{thresh} + V_{peak} - \sqrt{V_{peak}(V_{peak} - V_{thresh}) + V_{thresh}^2}\right) \tag{6.17}$$

and a local maximum given by

$$V_{+} = \frac{1}{3}\left(V_{thresh} + V_{peak} + \sqrt{V_{peak}(V_{peak} - V_{thresh}) + V_{thresh}^{2}}\right) \tag{6.18}$$

Lastly, the corresponding values of W are found from

$$W_{\pm} = \frac{1}{b}\left(V_{\pm} + a\right) \tag{6.19}$$

The parameter b sets the scale of growth versus decay. The idea is that a train of pulses will be produced when $dW/dt \approx 0$ when V is near rest and $dW/dt > 0$ when V is near it's peak value.

This immediately implies that $b > 0$, so that the slow parameter turns on at high potentials.

FIGURE - chapt-10-flow.eps

2. We want only a single fixed point near the lcal maximum of $f(V)$. Rather than try to solve a cubic, we note that slopes are equal when the curves just touch in the upper right-hand plane and two solutions just form, i.e.,

$$\frac{dW}{dV} = 2(V_{thresh} + V_{peak})V - (V_{thresh}V_{peak}) - 3V^{2} \tag{6.20}$$

and

$$\frac{dW}{dV} = \frac{1}{b} \tag{6.21}$$

or

$$\frac{1}{b} > 2(V_{thresh} + V_{peak})V - (V_{thresh}V_{peak}) - 3V^{2}. \tag{6.22}$$

We can get a worst case estimating bt selecting V to the above inequality to be the point with the largest slope. This occurs at the inflection point, or when

$$\frac{d^{2}W}{dV^{2}} = 2(V_{thresh} + V_{peak}) - 6V = 0 \tag{6.23}$$

or at $V = (1/3)(V_{thresh} + V_{peak})$. Thus

$$\frac{1}{b} > V_{peak}(V_{peak} - V_{thresh}) + V_{thresh}^{2}. \tag{6.24}$$

$$0 < b < \frac{1}{V_{peak}(V_{peak} - V_{thresh}) + V_{thresh}^{2}} \tag{6.25}$$

This is a statement that the relative density of the slow current cannot exceed an upper limit.

3. Additional constraints appear by considering the stability of the system. We expand around an equilibrium point (V_o, W_o). Then we can expand the original equations to obtain an expression for $(V(t), W(t))$ in the vicinity of (V_o, W_o). We write

$$F(V,W) \approx F(V_o, W_o) + \frac{\partial F}{\partial V}\bigg|_{(V_o,W_o)} \delta V + \frac{\partial F}{\partial W}\bigg|_{(V_o,W_o)} \delta W \tag{6.26}$$

etc., so that with $F_1(V,W) = f(V) - W + I$ and $F_2(V,W) = \phi\,(V + a - bW)$ we have

$$\frac{d\delta V}{dt} = f'(V_0)\delta V - \delta W \tag{6.27}$$

$$\frac{d\delta W}{dt} = \phi\,\delta V - b\phi\,\delta W \tag{6.28}$$

where $\delta V \equiv V - V_o$ and $\delta W \equiv W - W_o$, so that

$$\begin{pmatrix} \frac{d\delta V}{dt} \\ \\ \frac{d\delta W}{dt} \end{pmatrix} = \begin{pmatrix} f'(V_0) & -1 \\ \\ \phi & -b\phi \end{pmatrix} \begin{pmatrix} \delta V \\ \\ \delta W \end{pmatrix} \tag{6.29}$$

We do the usual thing of assuming that the solutions are of the form $\delta V(t) \cong V_1 e^{\alpha_1 t}$ and $\delta W(t) \cong W_1 e^{\alpha_1 t}$, etc.,with the constraints that the real parts of both α's must be negative for a solution to be stable, and the α's must be purely imaginary for a stable limit cycle , i.e., oscillatory solution.

Noting that

$$\begin{pmatrix} \frac{d\delta V}{dt} \\ \\ \frac{d\delta W}{dt} \end{pmatrix} = \alpha \begin{pmatrix} \delta V \\ \\ \delta W \end{pmatrix} \tag{6.30}$$

we evaluate

$$\begin{pmatrix} f'(V_0) - \alpha & -1 \\ \\ \phi & -b\phi - \alpha \end{pmatrix} \begin{pmatrix} \delta V & \\ & = 0 \\ \delta W & \end{pmatrix} \tag{6.31}$$

or

$$\begin{vmatrix} f'(V_0) - \alpha & -1 \\ \phi & -b\phi - \alpha \end{vmatrix} = 0 \tag{6.32}$$

for which

$$\alpha_{1,2} = \frac{(f'(V_0) - b\phi) \pm \sqrt{(f'(V_0) + b\phi)^2 - 4\phi}}{2} \tag{6.33}$$

The first term on the RHS is always negative only for $b\phi > f'(V_0)$. This is the statement of stability. For the cell to fire repetitively, we must have instability, or satisfy

$$f'(V_0) > b\phi \tag{6.34}$$

Since both b and ϕ are positive, this means that the slope of $f(V_0)$ must be positive. This only happens only between the minimum and maximum values of $f(V)$. The details of $f(V)$ are seen to be unimportant.

As a means to look at the onset of firing, we expand just about the point of stability/instability. We let

$$1 + \epsilon \equiv \frac{f'(V_0)}{b\phi} \tag{6.35}$$

so that

$$\alpha_{1,2} = \epsilon\frac{b\phi}{2} \pm i\sqrt{\phi - b^2\phi^2} \tag{6.36}$$

As ϵ goes from negative to positive the system goes from stable to unstable, yet the value of the imaginary past, which sets the frequency, is unchanged. This is why the frequency jumps from zero (stable solution, with no oscillation) to a finite value of

$$\begin{aligned} f &\approx \frac{1}{2\pi}\sqrt{\phi}\,\sqrt{1 - b^2\phi} \qquad (6.37) \\ &\sim \frac{1}{2\pi}\sqrt{\phi} \end{aligned}$$

where the final step holds if $b^2\phi << 1$ consistent with b of order 1 and $\phi << 1$. It is of interest that the frequency depends only on ϕ, which is the scale of the difference in time scales between the fast and slow variables. Thus, as the system changes from stability to unstable, the frequency remains the same, i.e., the oscillations start from a nonzero value.

SHOW ANIMATION

The choice of the parameter b such that the system is unstable will lead to a limit cycle ($\epsilon > 0$). This corresponds to a neuron that oscillates in the absence of external input.

SHOW ANIMATION

3. The presence of a small value of ϕ implies that the trajectories are simple. In particular, the slope of the trajectory is

$$\frac{dW}{dV} = \frac{\frac{dW}{dt}}{\frac{dV}{dt}} = \phi\frac{V + a - bW}{f(V) - W + I} \tag{6.38}$$

so that $dW/dV \approx \phi \approx 0$, i.e., the trajectories are nearly horizontal, unless we are close to the nullcline for dV/dt. Further, the speed along the horizontal nullcline is small compared to that on the vertical nullclines.

FIGURE - chapt-10-FN-trajectories-1.eps

6.3.3 Examples

It is now useful to examine the behavior to perturbed values of V and W. We see that the response is stable so long as we are on the left side of the cubic curve, otherwise a spike is initiated.

FIGURE - chapt-10-FN-trajectories-2-eps

Interesting cases occur when the value of b is chosen to insure stability in the absence of input, but transient current injection leads to a shift in V. In particular:

- Spike initiation by a depolarizing current pulses (point C).
- Absolute refractory period in response to a depolarizing current pulse(point A).
- Relative refractory period in response to a depolarizing current pulse(point B).
- Abolition of a spike by a hyperpolarizing pulse (point D).

SHOW ANIMATIONS

Our final and perhaps most important example is to consider the effect of injecting steady current, I, which causes the nullcline for dV/dt to shift up or down. This leads to a current threshold. As mentioned above, the firing rate jumps discontinuously from 0 to a nonzero value. This happens when I is increased so that $b\phi = f'(V_o)$ or $\epsilon = 0$ in the above analysis, and the α's are imaginary with value

$$\alpha_{1,2} \approx \pm i\sqrt{\phi}. \tag{6.39}$$

Thus the frequency at the onset of oscillations starts away from zero.

FIGURE - chapt-10-f-vs-I.eps

6.3.4 Saddle Node versus Hoft Bifurcations

Our final point concerns the onset of oscillations from zero frequency. Unlike the case of digital logic, when strongly nonlinear circuitry is the order of the day, sensory systems and motor plants tend to require the use of graded system (although one can build this from an ensemble of binary systems with a spectrum of thresholds).

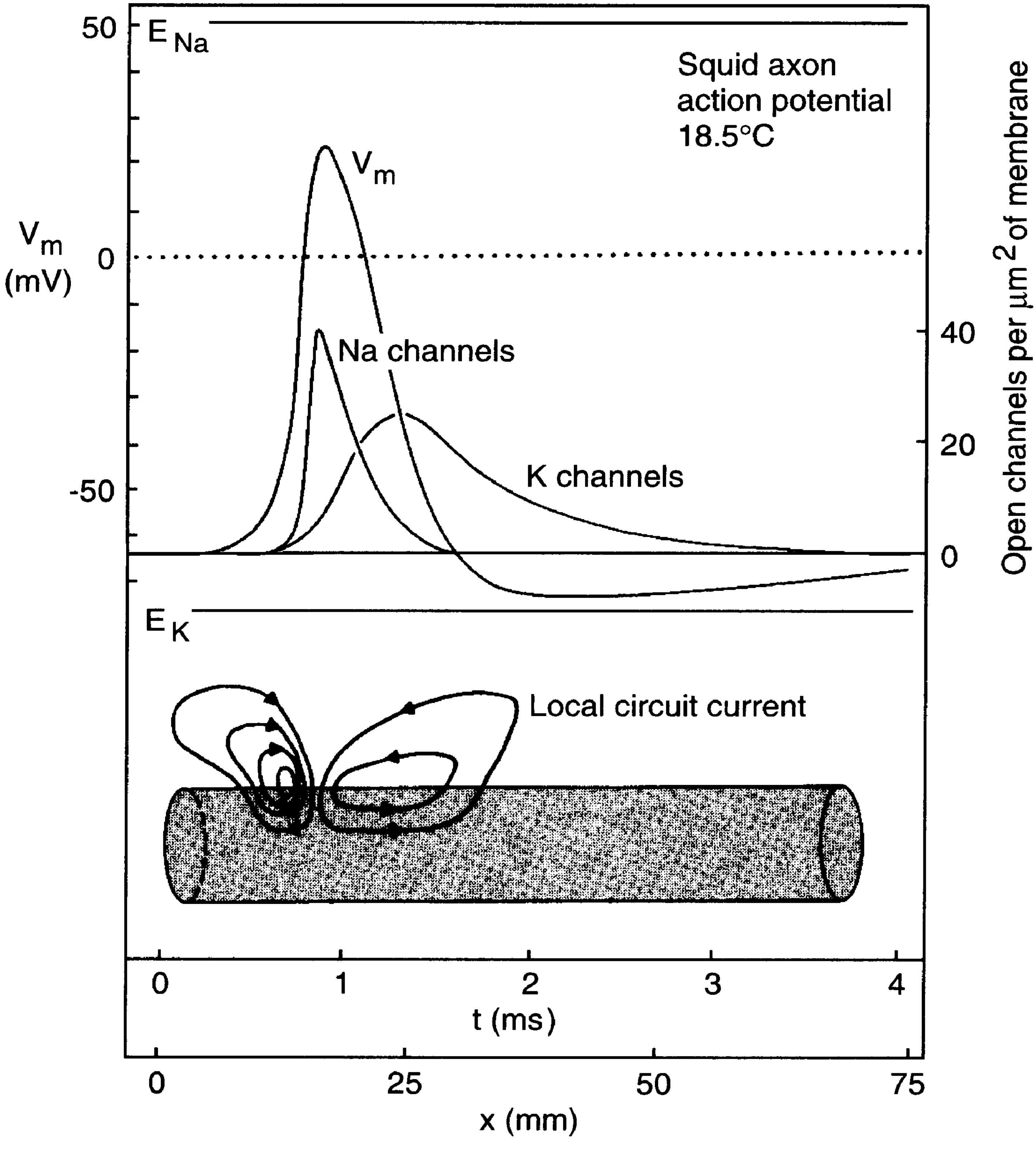
Oscillations can start at zero frequency for the case $b > 1$ (strong inhibition), so that $4b^2\phi \sim 1$. This is accompanied by three rather than a single crossing of the

$dV/dt = 0$ and $dW/dt = 0$ nullclines. The initial frequency can obtain any value as the real part of α becomes positive (unstable), i.e.,

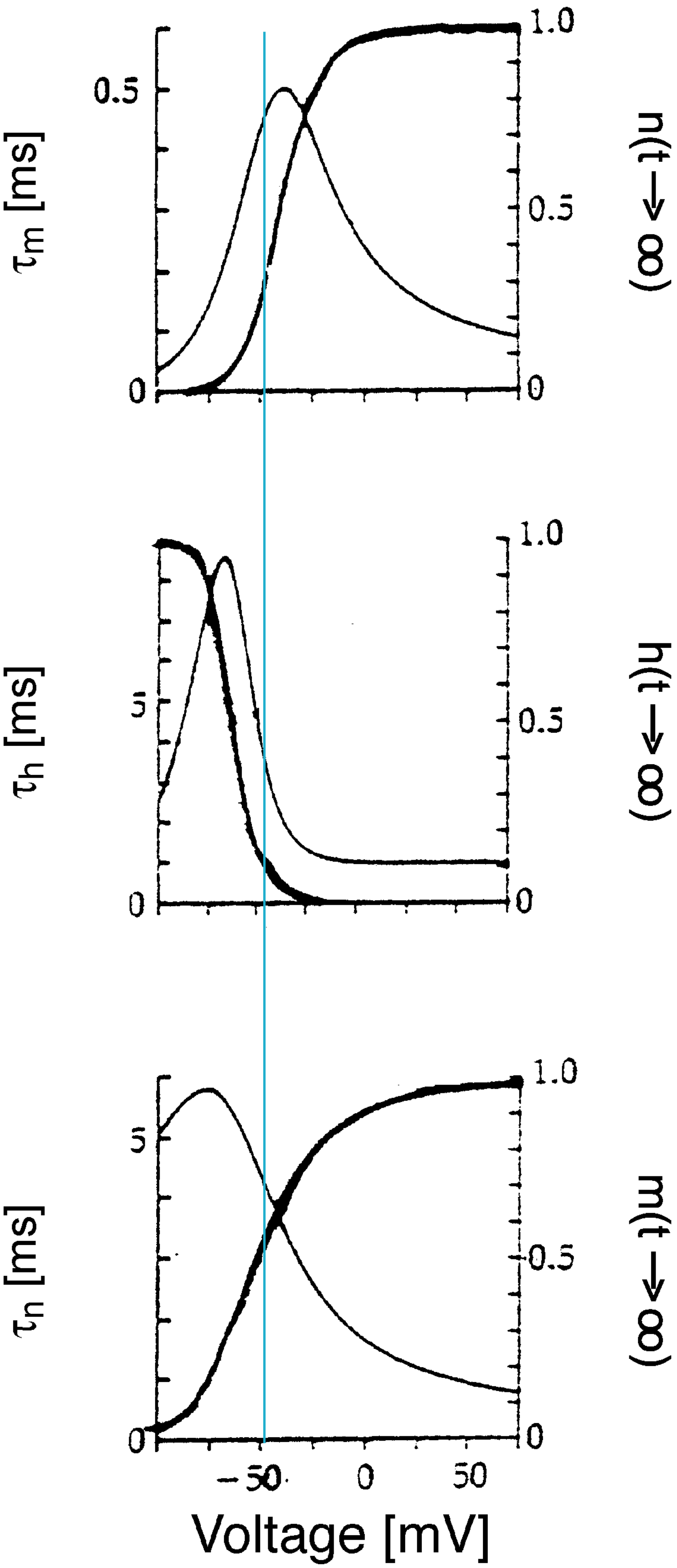
$$f \approx \frac{1}{2\pi}\sqrt{\phi}\,\sqrt{1-b^2\phi} \tag{6.40}$$

The intermediate crossing serves as a saddle point, that is, paths along a particular trajectory lead to the point while all other paths lead away. As the current I increases, the stable resting point and the unstable threshold point begin to merge and oscillations start. An example of this occurs with A-type K^+ currents

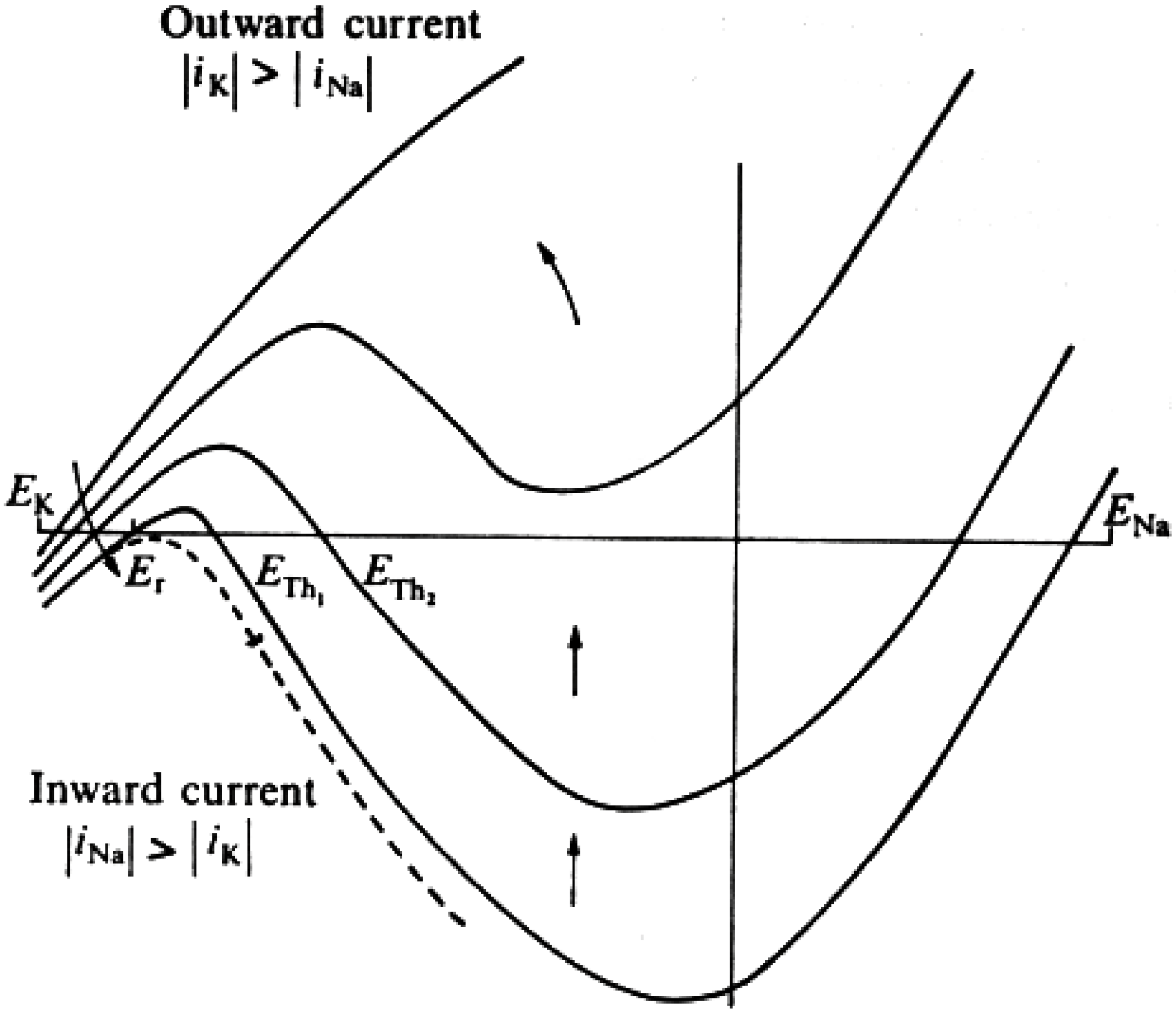
FIGURE - chapt-10-saddle-node.eps



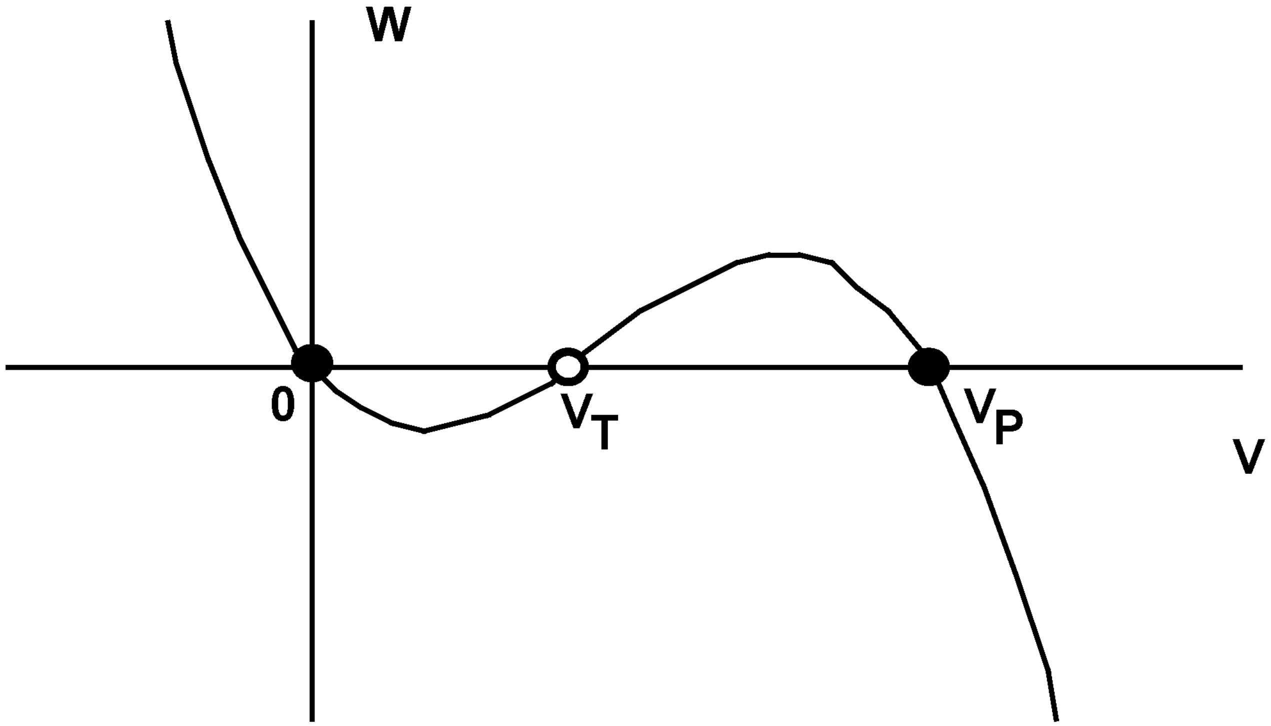
chapt_8_hh_currents.eps



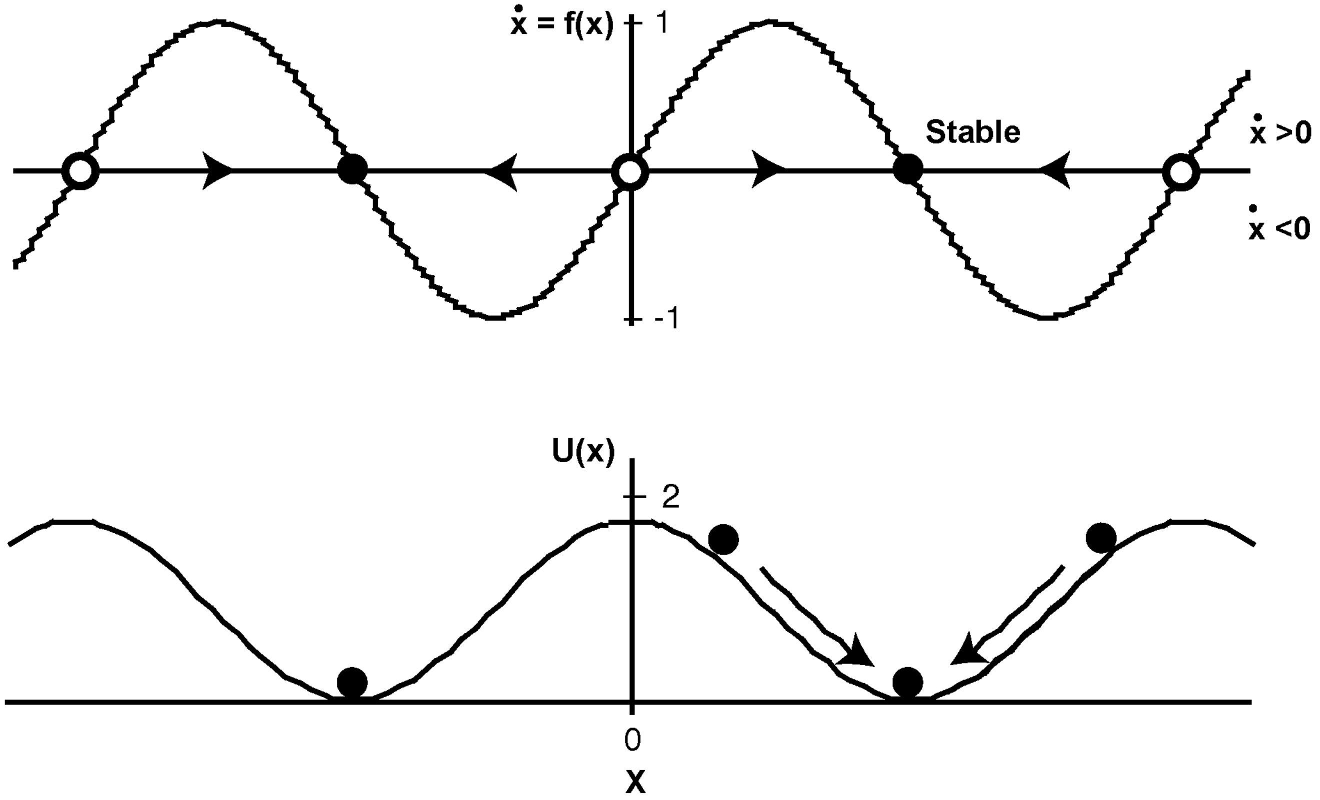
chapt_10_mhn.eps



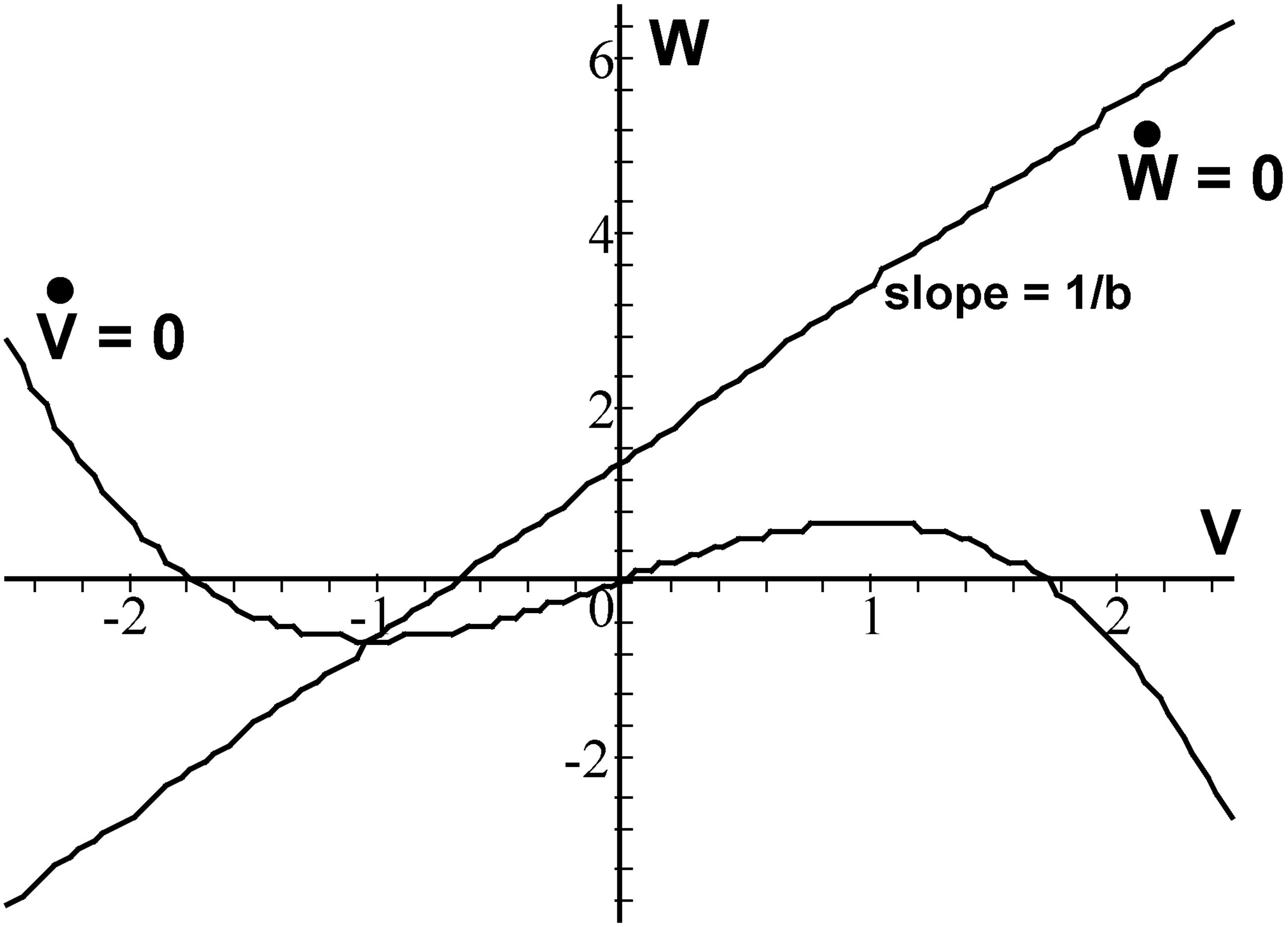
chapt_10_volt_clamp_summary.eps



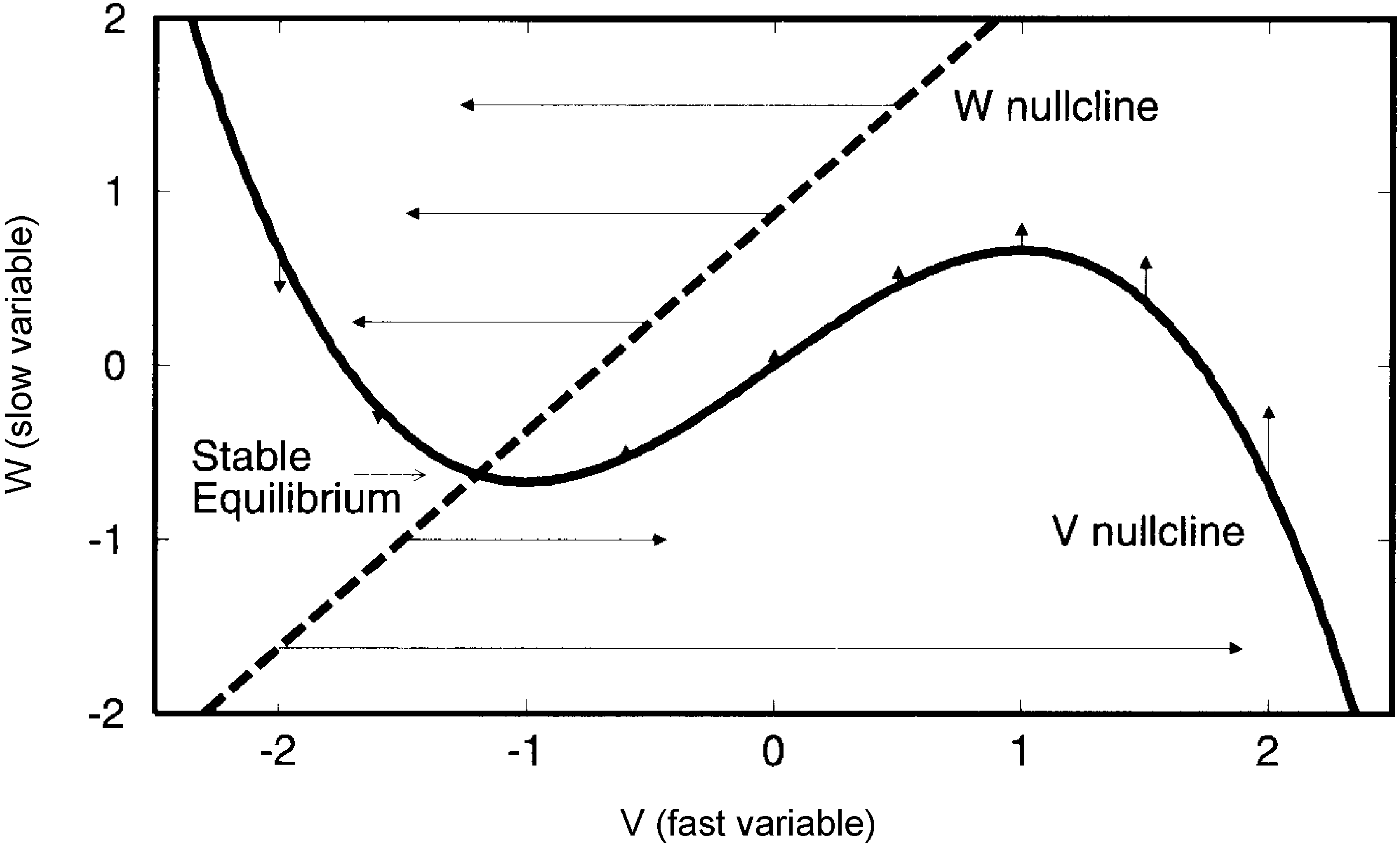
chapt_10_F(V).eps



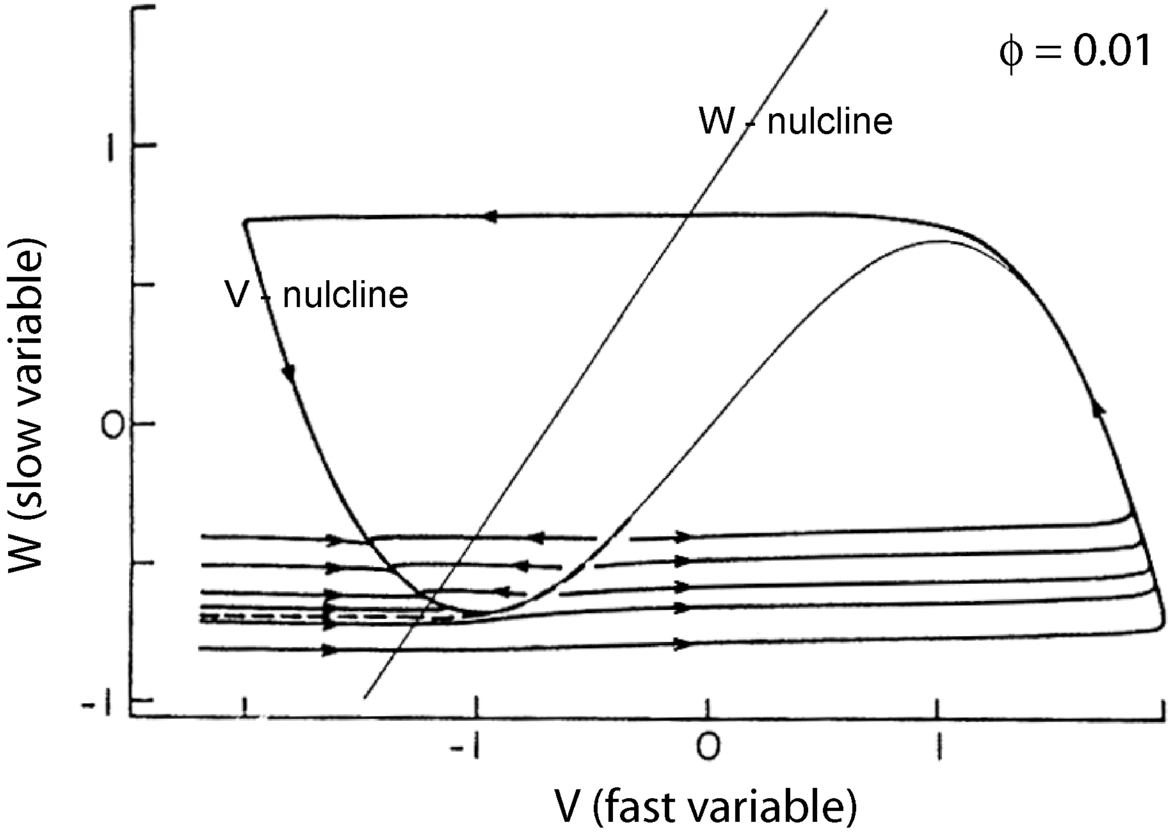
chapt_10_phase_plane_sinx.eps

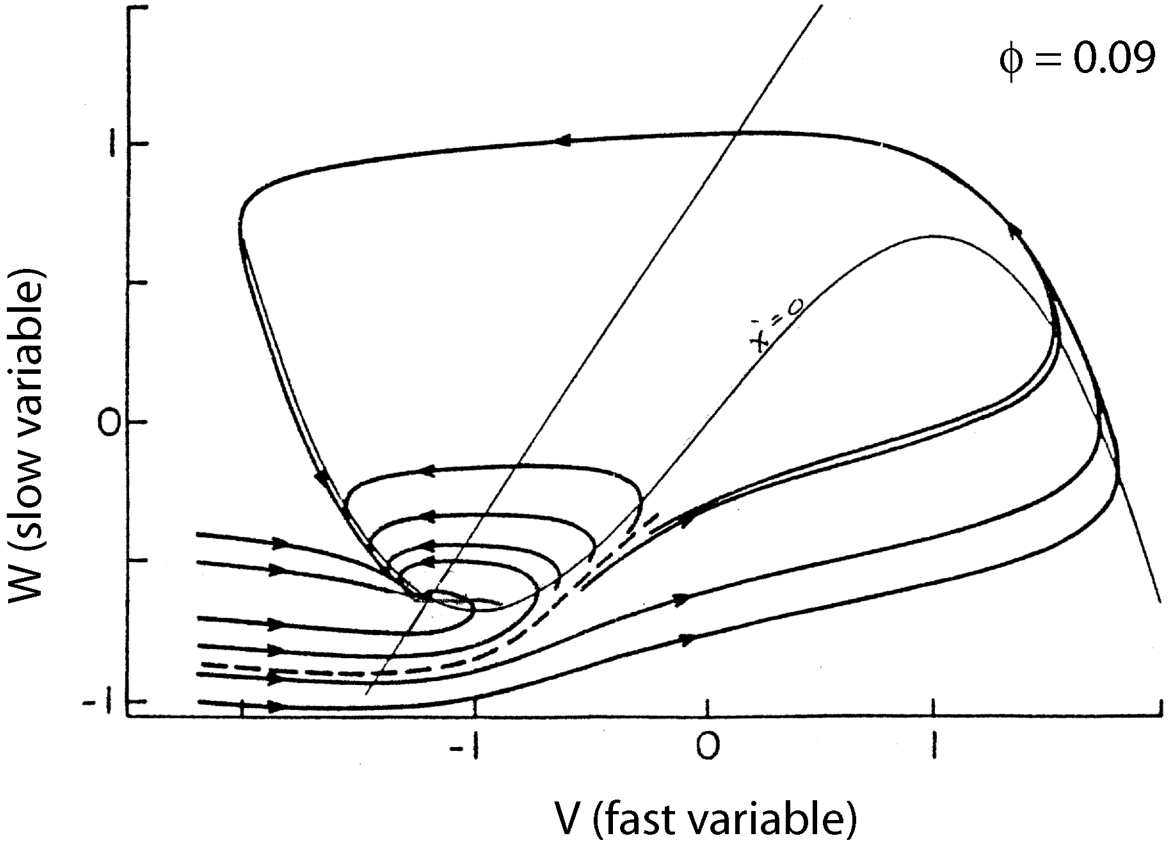


chapt_10_FN_nulclines.eps

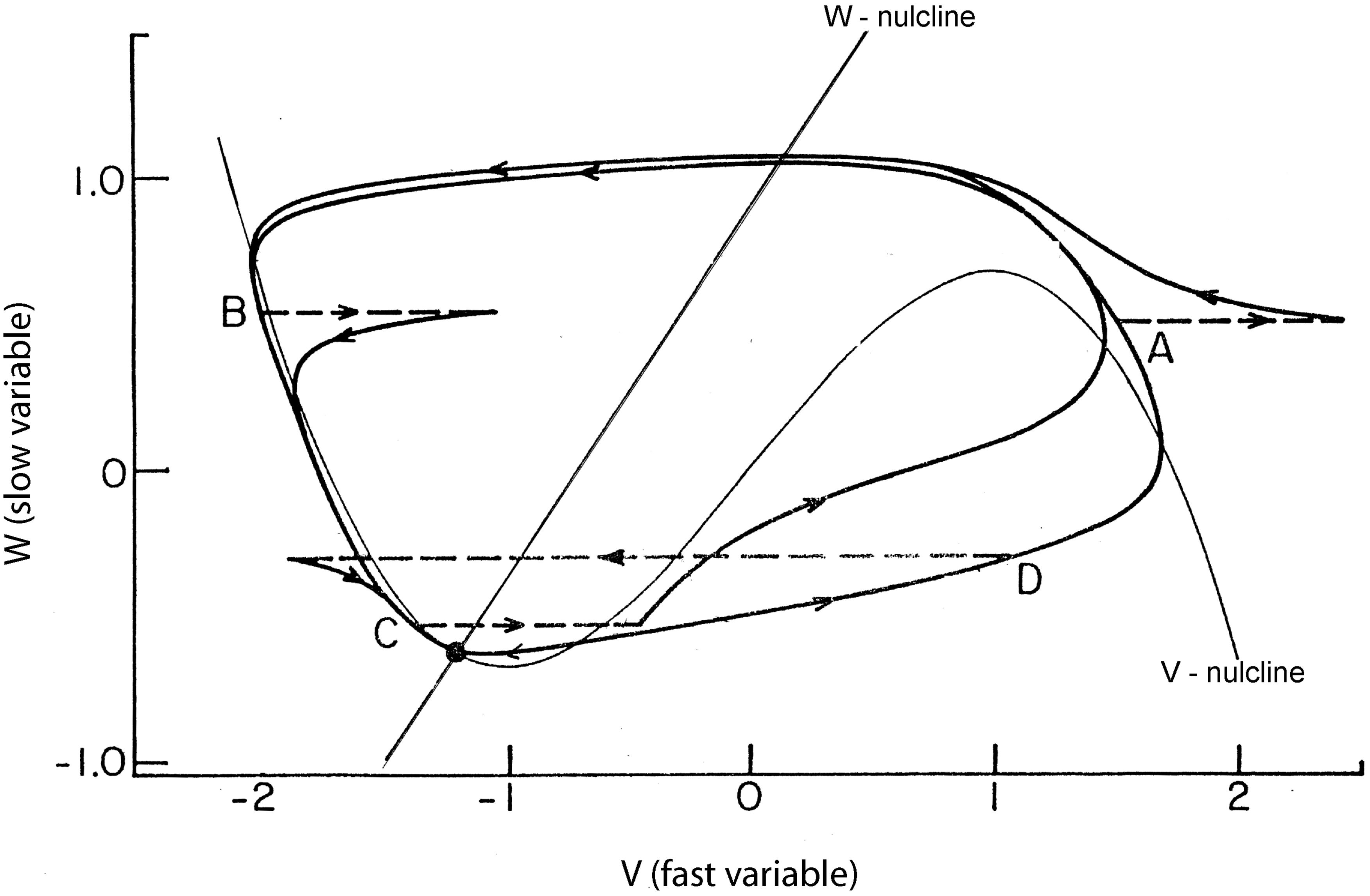


chapt_10_flow.eps

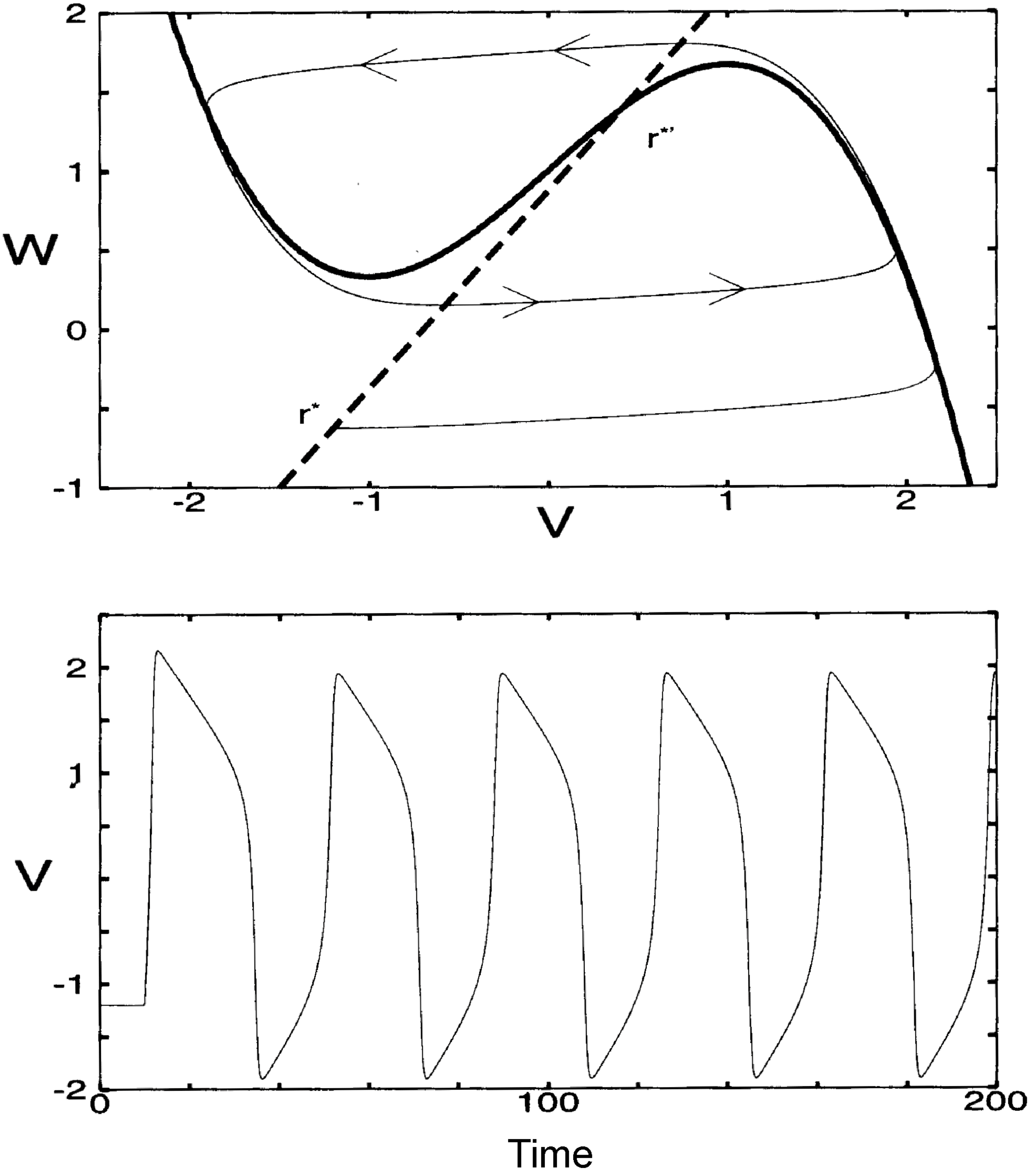




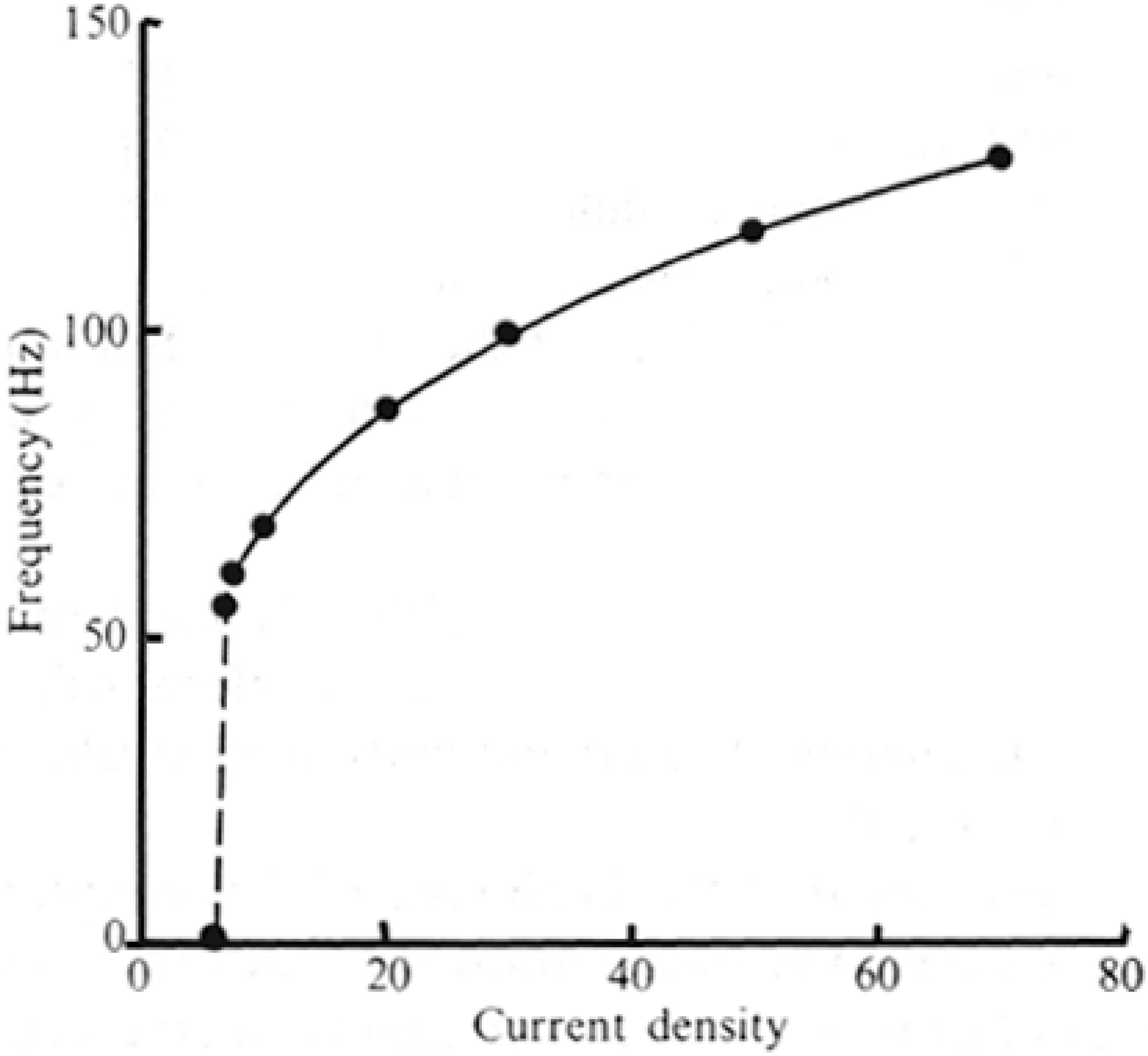
chapt_10_FN_trajectories_1.eps



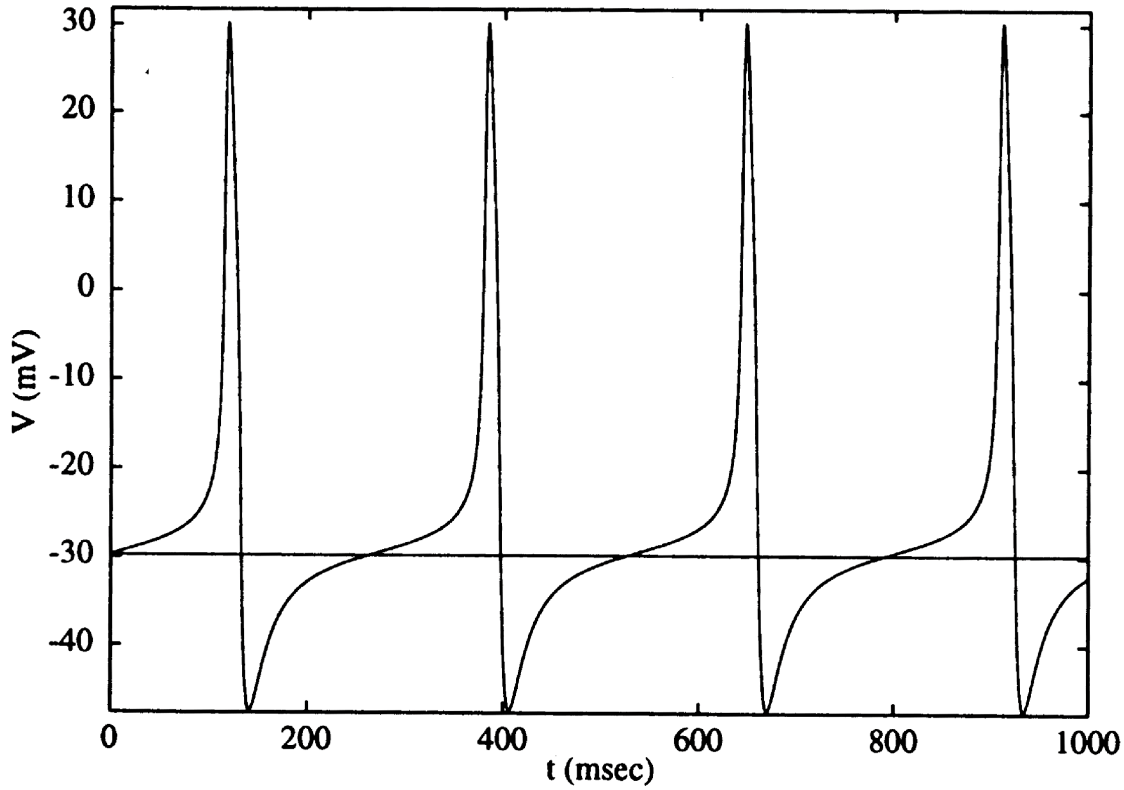
chapt_10_FN_trajectories_2.eps

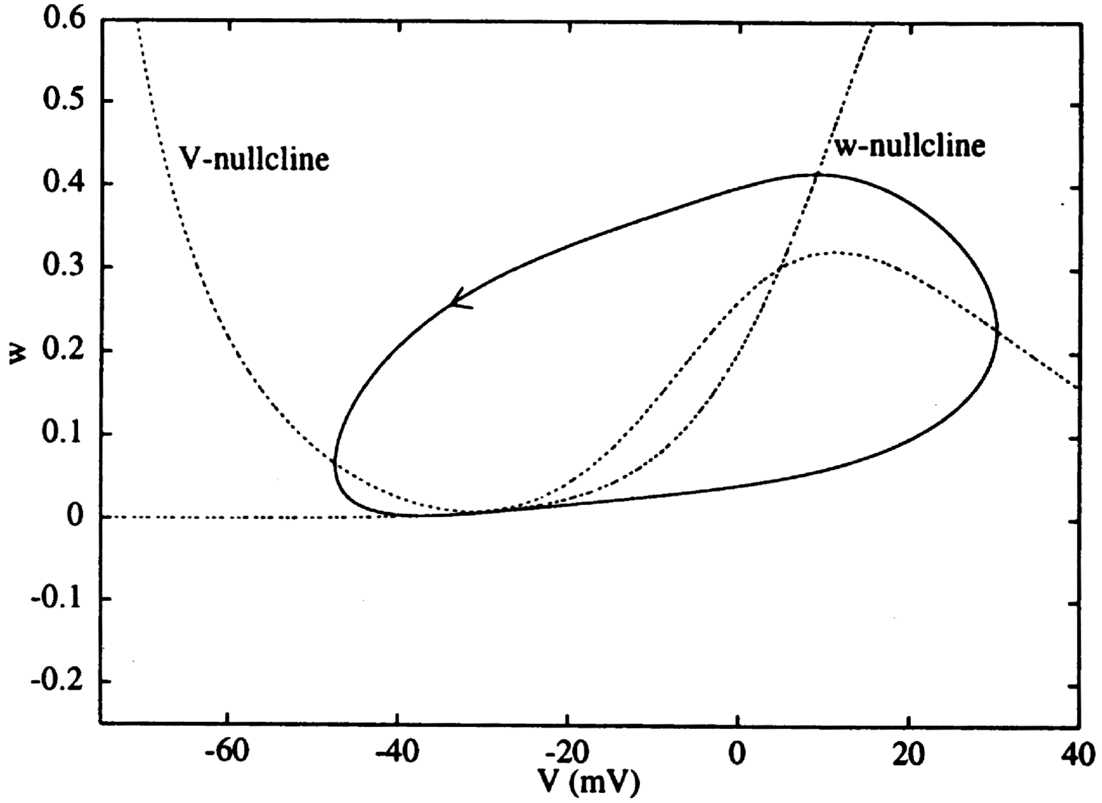


chapt_10_repetitive_firing.eps



chapt_10_f_vs_I.eps





chapt_10_saddle_node.eps