Single-Neuron Dynamics

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References: Chapters 5 and 8 of *Mathematical Models in Biology*, by Leah Edelstein-Keshet. Chapter 6 of the Strogatz text.

The FitzHugh-Nagumo Model

This model retains an ODE for voltage and an ODE for a single recovery variable w, which plays the role of n in the Hodgkin-Huxley model. The voltage is now really a voltage-like variable, and the model is usually written in dimensionless form:

$$\frac{dv}{dt} = v - v^3 - w + I_{ap} \tag{1}$$

$$\frac{dw}{dt} = (v - a - bw)/\tau_w \tag{2}$$

where a, b, τ_w and I_{ap} are parameters. The right hand sides of these equations are both polynomials, which makes them easier to work with than the exponential functions in the Hodgkin-Huxley model. This model has only one negative feedback variable (w) rather than the two of Hodgkin-Huxley, and the positive feedback is direct through the linear term in the v ODE rather than through a separate variable.

To start a phase plane analysis one first finds the nullclines, where individual derivatives are zero.

v-nullcline:

$$w = v - v^3 + I_{ap} \tag{3}$$

which is a cubic function in v.

w-nullcline:

$$w = (v - a)/b \tag{4}$$

which is a linear function in v.

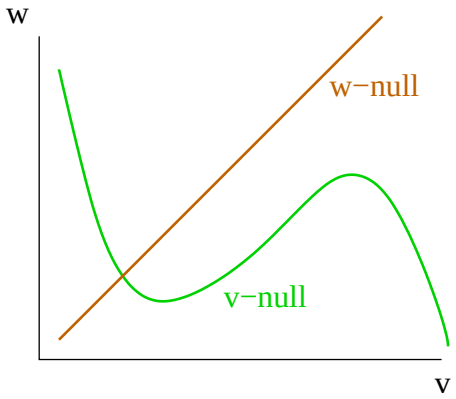

Figure 1: Nullclines of the FitzHugh-Nagumo model.

As we will see, the cubic v-nullcline is an essential feature for an excitable system model. The polynomial right hand sides are convenient mathematically, but they are a turn off for neuroscientists, who expect to see ionic currents. In 1981 Morris and Lecar developed a model of the barnacle muscle fiber that was planar and had ionic currents. This is now the standard model used by mathematical neuroscientists.

The Morris-Lecar Model

- One hyperpolarizing current: $I_K = \bar{g}_K w(V - V_K)$, where $\bar{g}_K$ is maximum conductance and w is an activation variable, the fraction of open

K^+ channels. w approaches its equilibrium value, $w_\infty(V)$, with a rate of τ_w^{-1}, where $\tau_w = \tau_w(V)$ is the so-called time constant:

$$\frac{dw}{dt} = [w_\infty(V) - w]/\tau_w(V) \quad . \tag{5}$$

- One depolarizing current: $I_{Ca} = \bar{g}_{Ca} m_\infty(V)(V - V_{Ca})$, which is assumed to activate instantaneously.
- One leakage current: $I_L = g_L(V - V_L)$, which is depolarizing and has a V-independent conductance.
- One capacitance current: $I_C = C\frac{dV}{dt}$, where C is the membrane capacitance.
- One applied current: I_{ap}, the current applied through an electrode.

The voltage equation is then

$$\frac{dV}{dt} = -(I_{Ca} + I_K + I_L - I_{ap})/C. \tag{6}$$

The ODEs for the **Morris-Lecar model** are then:

$$\frac{dV}{dt} = -(I_{Ca} + I_K + I_L - I_{ap})/C \tag{7}$$

$$\frac{dw}{dt} = [w_\infty(V) - w]/\tau_w(V) \quad . \tag{8}$$

This can be analyzed in the $w - V$ phase plane.

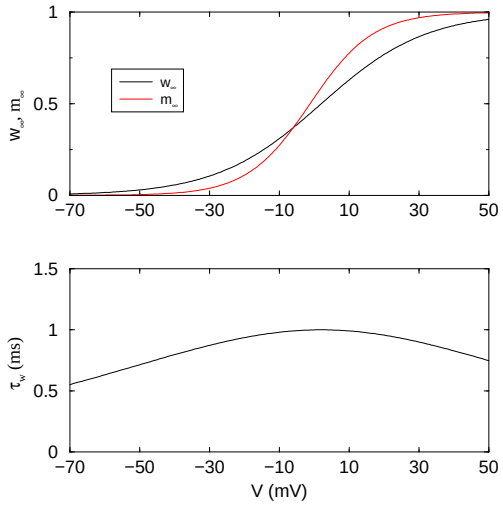

Figure 2: Calcium and potassium equilibrium and time constant functions

V-nullcline:

$$w = \frac{I_{ap} - \bar{g}_{Ca} m_\infty(V)(V - V_{Ca}) - g_L(V - V_L)}{g_K(V - V_K)} \tag{9}$$

w-nullcline:

$$\begin{aligned} w &= w_\infty(V) && (10)\\ &= 0.5[1 + \tanh(\frac{V - V_1}{s_1})] && (11)\\ &= \frac{\mathrm{e}^u}{\mathrm{e}^u + \mathrm{e}^{-u}} && (12) \end{aligned}$$

where $u = \frac{V - V_1}{s_1}$ with parameters V_1 and $s_1 > 0$ that modify the shape of the function.

The middle branch of the cubic-shaped V-nullcline is the impulse **thresh-**

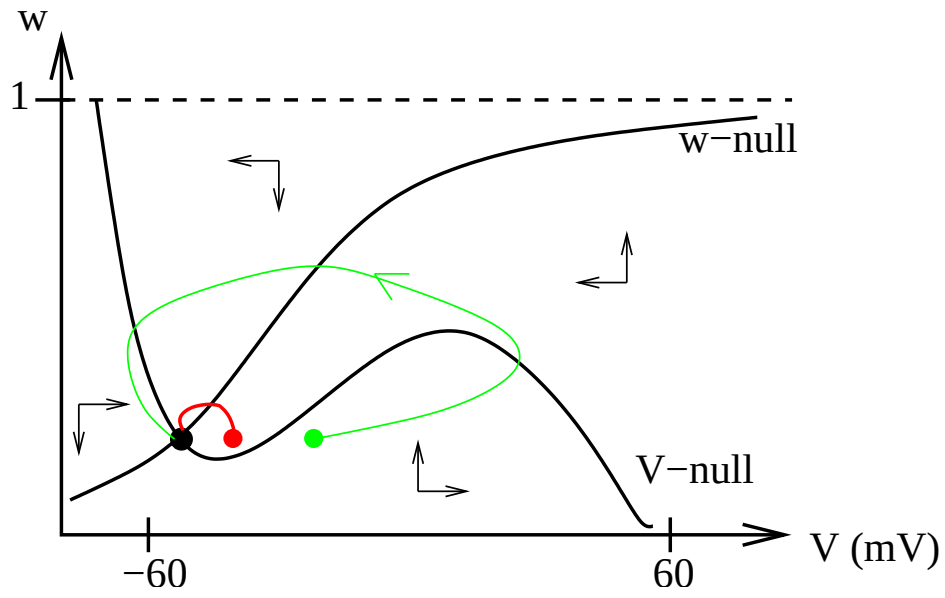

Figure 3: Phase plane analysis of the Morris-Lecar model. Red: subthreshold response, Green: impulse. $I_{ap} = 0$.

old. Figure 3 shows the response to a small voltage perturbation from the resting state. In one case the perturbation is not large enough to push the system past the spike threshold, so a passive or subthreshold response occurs (red). In the other case the perturbation is sufficiently large to activate a regenerative response; the trajectory moves far away from rest before finally returning. This is an impulse, or action potential. A cubic-like V nullcline is important for this excitable behavior with a threshold, and most other planar models for impulse generation have cubic-like V-nullclines.

Increasing the applied current translates the V-nullcline upward. With enough current the system starts to spike continuously. That is, periodic impulses are produced. This is called **tonic spiking**, and it is often seen

in neurons when external current is injected, and sometimes even when it's not. This is clearly a big change in behavior compared with a single-spike response. A qualitative change in behavior is called a bifurcation, and this particular bifurcation is called a Hopf bifurcation. This is probably the most important type of bifurcation in neuroscience, and we will discuss it in detail. But first we should set the mathematical foundation.

Linear Stability Analysis

An equilibrium or steady state is considered locally stable if the phase point returns to the equilibrium if perturbed away by a small amount. This is regardless of the exact perturbation (i.e., the direction of perturbation in the phase space), as long as it is not a large perturbation. A good example is a pendulum, which has a stable steady state in which the bob is straight down; following a tap it will swing back and forth, but the amplitude of the swing will decline and eventually it will return to the straight-down position. Can you think of an example of an unstable equilibrium?

Mathematically, we can determine the stability of an equilibrium by performing a linear stability analysis. We will go through the steps of doing this with the Morris-Lecar model, which can be written as:

$$\frac{dV}{dt} = F(V, w) \tag{13}$$

$$\frac{dw}{dt} = G(V, w) \tag{14}$$

where F (the sum of the currents) and G (the first-order kinetic terms) can be thought of as velocities. That is, F describes the rate at which V is changing and G is the rate at which w is changing. Suppose (V^*, w^*) is an equilibrium, then $F(V^*, w^*) = 0$ and $G(V^*, w^*) = 0$ since there is no motion at equilibrium. In fact, this is how we can find the equilibria, by setting the velocities to 0!

The velocity functions in the M-L model are nonlinear, which makes it impossible to solve the differential equations without the aid of a computer. However, there is a theorem called the Hartman-Grobman Theorem that says that in the neighborhood of an equilibrium (technically this only applies to hyperbolic equilibria, but ignore this for now) the flow of the nonlinear system can be approximated accurately using a linear system. The good news is that we can solve the linear system by hand! Consider what happens when you perturb voltage a distance x from its equilibrium value, and w a distance y from its equilibrium value, so $V = V^* + x$ and $w = w^* + y$. Then the subsequent dynamics of x and y can be approximated by the linearized system, which is

$$\frac{dx}{dt} = F_v^* x + F_w^* y \tag{15}$$

$$\frac{dy}{dt} = G_v^* x + G_w^* y \tag{16}$$

where the coefficients are partial derivatives of the velocity functions, eval-

uated at the equilbrium:

$$F_v^* = \frac{\partial F}{\partial v}(V^*, w^*) \tag{17}$$

$$F_w^* = \frac{\partial F}{\partial w}(V^*, w^*) \tag{18}$$

$$G_v^* = \frac{\partial G}{\partial v}(V^*, w^*) \tag{19}$$

$$G_w^* = \frac{\partial G}{\partial w}(V^*, w^*) \quad . \tag{20}$$

This comes directly from Taylor's theorem. The linearized system can be written in terms of a matrix and vectors:

$$\frac{d\vec{x}}{dt} = \mathbf{J}\vec{x} \tag{21}$$

where

$$\vec{x} = \begin{pmatrix} x \\ y \end{pmatrix} \tag{22}$$

and $\mathbf{J}$ is the 2×2 **Jacobian matrix** evaluated at the equilibrium:

$$\mathbf{J} = \begin{pmatrix} F_v^* & F_w^* \\ G_v^* & G_w^* \end{pmatrix} \quad . \tag{23}$$

The solution to this linear matrix differential equation is very similar to that of a linear scalar differential equation, involving the exponential function. It is sometimes called the spectral solution,

$$\vec{x}(t) = c_1 \mathrm{e}^{\lambda_1 t}\vec{v_1} + c_2 \mathrm{e}^{\lambda_2 t}\vec{v_2} \tag{24}$$

where c_1 and c_2 are constants that depend on the initial conditions, λ_1 and λ_2 are called eigenvalues and $\vec{v_1}$ and $\vec{v_2}$ are called eigenvectors of matrix

J. These things are very important in the field of dynamics, but we won't go into their mathematical meening except to say that an eigenvector of a matrix is special in that when it multiplies the matrix the only effect is to shrink or stretch the vector (and perhaps reverse its orientation). No other changes in orientation of the vector occur. The amount that the vector is shrunk/stretched is equal to the corresponding eigenvalue (and if the vector orientation is reversed then the eigenvalue is negative).

The spectral solution makes it easy to see what happens over time to the perturbation $\vec{x}(t)$. Suppose that both eigenvalues are negative, then both components of $\vec{x}$ tend to 0 over time. Since the perturbation therefore disappears over time, the equilibrium (V^*, w^*) is stable when $\lambda_1 < 0$ and $\lambda_2 < 0$. Otherwise, (V^*, w^*) is unstable, and (most) perturbations away from equilibrium will grow over time.

Tonic Spiking

We have seen that when $I_{ap} = 0$ a large enough perturbation can produce a spike, but after that spike the system returns to rest. This is because the equilibrium is stable. When depolarizing current is added ($I_{ap} > 0$) the V-nullcline is shifted upward, so that the location of the equilibrium gets closer to the lower knee or fold of the V-nullcline. The strength of attraction of the equilibrium gets weaker as this occurs. With even more depolarizing current the intersection of the nullclines moves to the middle

branch of the cubic V-nullcline. At such an intersection the equilibrium becomes unstable, no longer attracting the phase point. When this happens the system will spike continuously, which neuroscientists often call tonic spiking.

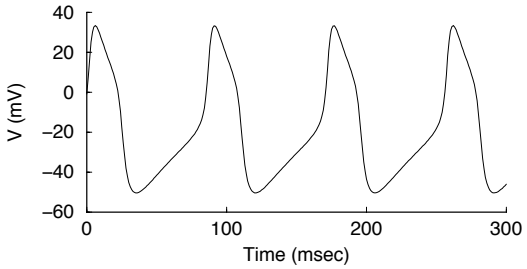

Figure 4: Tonic spiking with the Morris-Lecar model, when $I_{ap} = 100$ pA.

Mathematically speaking, tonic spiking is an example of a periodic solution to the differential equations. When viewed in the phase plane, as in Fig. 5, the trajectory of the periodic solution is called a limit cycle. Since initial conditions that start near the limit cycle are attracted to it, we have a stable limit cycle. This qualitative change in behavior, from a system at rest (stable equilibrium) to a system exhibiting tonic spiking (stable limit cycle) is an example of a bifurcation. There are several types of bifurca-

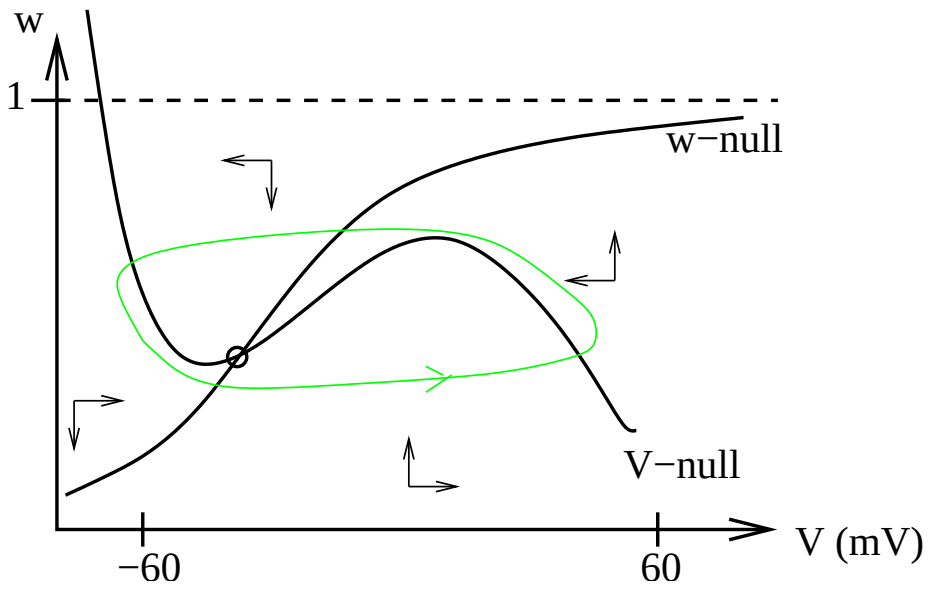

Figure 5: Phase plane analysis of the Morris-Lecar model. Green: Limit cycle. $I_{ap} = 100$ pA.

tion that can occur in dynamical systems, and they play a central role in understanding how changes in the values of parameters affect the behavior of the system. The particular bifurcation that we have encountered in the M-L model is a Hopf bifurcation. This is one way that periodic behavior can be initiated. You can even determine the value of the parameter I_{ap} where this bifurcation occurs by looking at the eigenvalues. At a Hopf bifurcation the eigenvalues are purely imaginary: $\lambda_{1,2} = \pm\gamma \mathrm{i}$ for some non-zero number γ.

What happens if I_{ap} is increased even more? This continues to move the V-nullcline upward, shifting the intersection (i.e., the equilibrium) closer and closer to the right knee or fold. With enough applied current the equilibrium will be on the right branch and it will regain stability.

It does this be going through a second Hopf bifurcation. The new stable equilibrium has a high or depolarized voltage and is very different from the equilibrium that occurred when the intersection was on the left branch. This depolarized equilibrium is called depolarization block since when the voltage is this high it is no longer possible to produce action potentials.

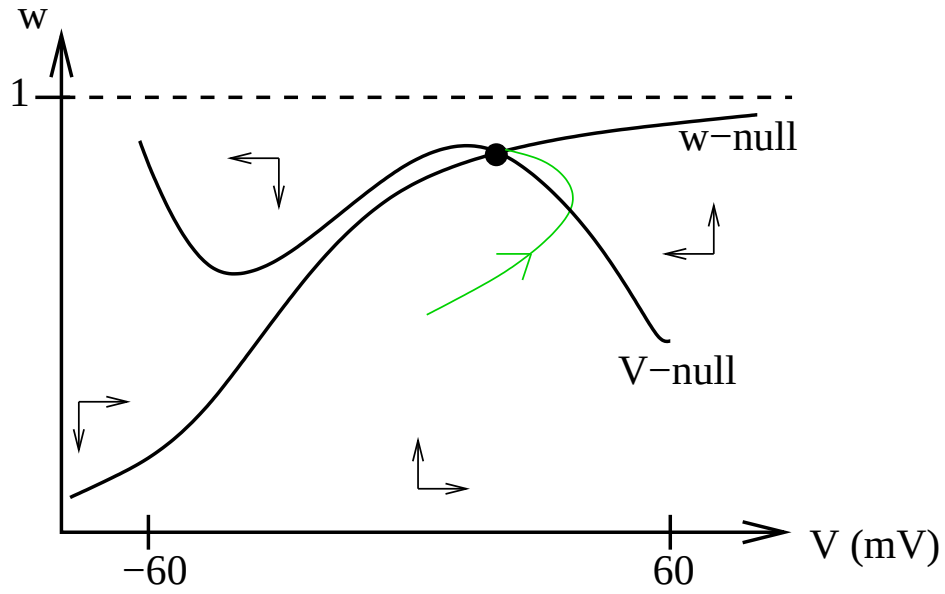

Figure 6: Depolarized resting state produces depolarization block, when $I_{ap} = 250$ pA.

Bifurcation Analysis

The dynamics of the Morris-Lecar model as I_{ap} is varied can be summarized with a bifurcation diagram. Such a diagram describes the asymptotic state of the system over a range of values of a bifurcation parameter, in this case I_{ap}. Points on the diagram at which the number or nature of the asymptotic dynamics exhibit qualitative changes (like changes in the number of equilibria or their stability) are called bifurcations. These are

the organizing centers of the system dynamics.

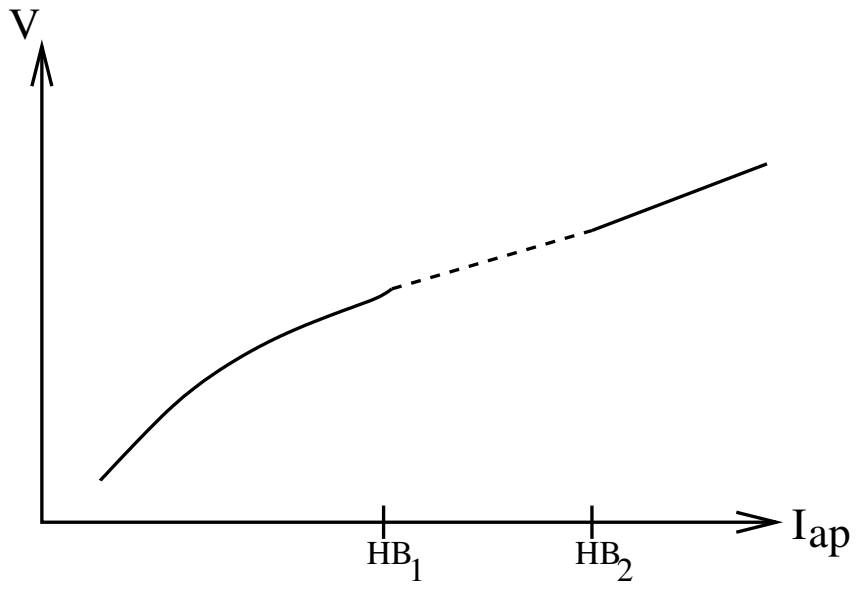

Figure 7: Stationary bifurcation diagram for the Morris-Lecar model. Dashed portion of curve represents unstable equilibria. HB=Hopf bifurcation.

Figure 7 shows a stationary bifurcation diagram for the Morris-Lecar model. This focuses entirely on the equilibria (also called **stationary points**). As I_{ap} is increased the equilibrium voltage increases. That is, the cell's resting equilibrium depolarizes. At the Hopf bifurcation, labelled as HB_1, the equilibrium becomes unstable, even as it continues to become more depolarized. There is a second Hopf bifurcation, at HB_2, where the equilibrium regains stability. The stable and very depolarized equilibria for I_{ap} beyond this are in the depolarization block state.

Where do the tonic spiking solutions fit in? We should expect them to be present between the Hopf bifurcations, since the equilibrium is unstable in this interval. But it turns out that the tonic spiking solutions exist even

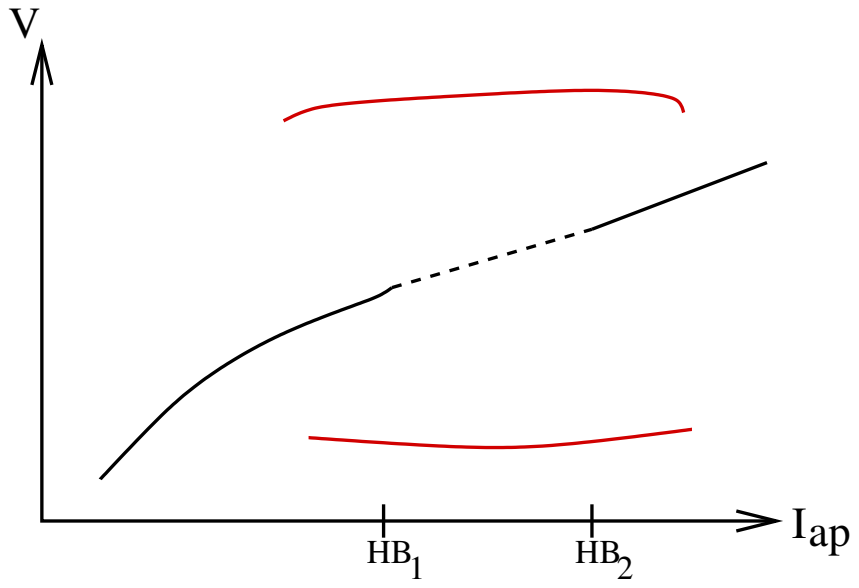

Figure 8: Bifurcation diagram for the Morris-Lecar model, showing asymptotic stationary and tonic spiking solutions (minumum and maximum voltage are shown). HB=Hopf bifurcation.

beyond the Hopf bifurcations, i.e., to the left of HB_1 and to the right of HB_2. Since a periodic solution is not just a point, as equilibria are, it's not obvious how to represent a branch of periodic solutions. One approach, which we will use, is to plot the minimum and the maximum value of V during the oscillation. Thus, for each I_{ap} where periodic solutions exist, we'll plot two points. If we connect all the minimum points and all the maximum points we get two curves, as in Fig 8. You can see from this that the spike amplitude, the distance between the two tonic spiking branches, does not change much when I_{ap} is varied. This reflects the typical all-or-none behavior of action potentials.

What happens in the overlap interval? For each I_{ap} in this interval there is a stable rest state and a stable tonic spiking state. How does the

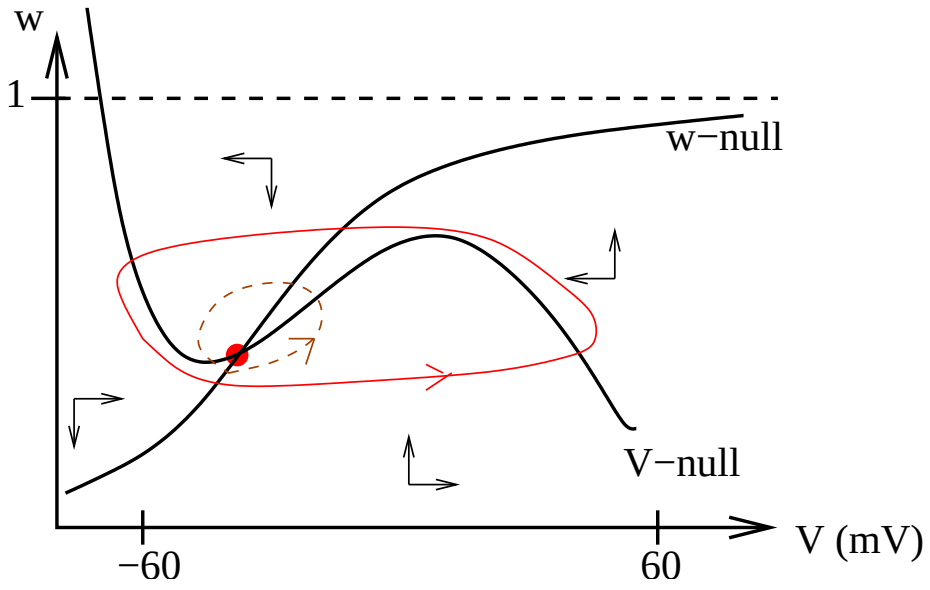

Figure 9: Phase portrait of the Morris-Lecar model for I_{ap} in the overlap interval, where the system is bistable. The dashed brown curve, an unstable limit cycle, is the separatrix.

cell know which one to get attracted to? There must be something that separates them. In fact there is, and it's called the separatrix. This is best visualized in the phase plane. In Fig. 9 we see the phase portrait for a value of I_{ap} in the overlap region. Both the stable equilibrium (red point) and the stable periodic solution or limit cycle (red curve) are present, and there is a circular dashed curve that lies between. This is the separatrix. But what is it? It's actually another limit cycle, but it's unstable! If the system starts on this curve, then it stays on it. But if it starts inside the separatrix the phase point is attracted to the equilibrium. We say that the basin of attraction of the equilibrium is the region inside the separatrix. If the initial conditions are outside of the separatrix, then the phase point is attracted to the stable limit cycle. The basin of attraction of the stable

limit cycle is thus all the points in the phase plane that lie outside of the separatrix.

This is an example of a **bistable system**, where two stable structures co-exist for the same value of the parameters. Such systems are important to recognize, since the state that a bistable system is in depends on it's starting state. In a neuron, this means that you may record a silent cell, and then come back later and the cell is tonically spiking. This transition could be the result of noise in the system that pushes the cell from the basin of attraction of the rest state across the separatrix and into the basin of attraction of the tonic spiking state. Later on, noise could push it back into the basin of attraction of the rest state and the cell can be silent again!

For each I_{ap} in the overlap region of the bifurcation diagram there is an unstable limit cycle. We can plot the minimum and maximum values of these limit cycles and we'll get two curves in the bifurcation diagram. They should both be dashed to reflect the fact that the limit cycles are unstable. It turns out that the same behavior occurs in the vicinity of the second Hopf bifurcation. When we put it all together we get the complete bifurcation diagram of the Morris-Lecar model, treating I_{ap} as the bifurcation parameter (Fig. 10).

A Hopf bifurcation can be thought of as one of the ways in which peri-

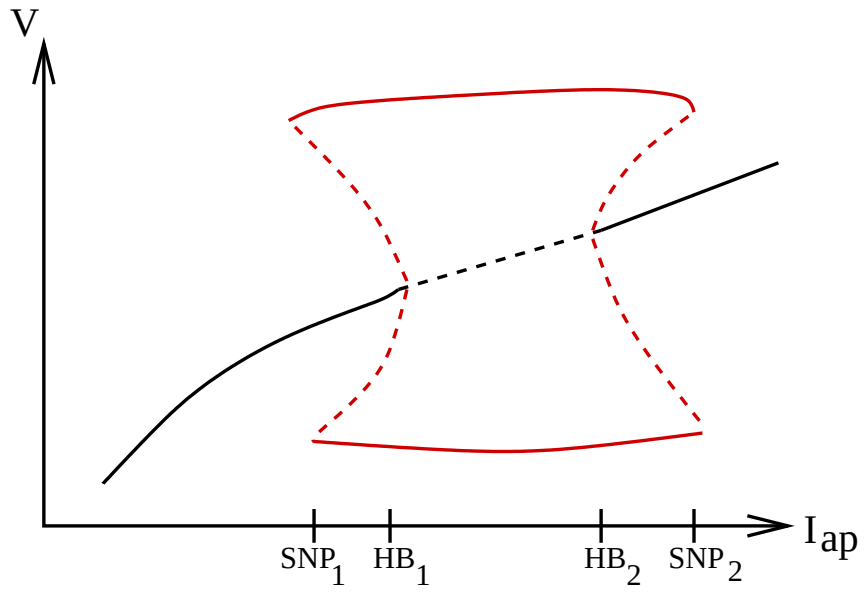

Figure 10: Complete Morris-Lecar bifurcation diagram. Black: stationary branch, Red: periodic branch. Dashed=unstable. SNP=saddle-node of periodics bifurcation, HB=Hopf bifurcation.

odic solutions are born. In this case, the periodics are born unstable, and the periodic branch emerging from the HB bends backwards. When this happens the bifurcation is called a subcritical Hopf bifurcation, abbreviated as subHB. So both HB_1 and HB_2 in Fig. 10 are subHB's.

There is another type of bifurcation shown in the figure. This occurs when the branch of unstable periodic solutions coalesces with the branch of stable periodic solution. It is called a saddle-node of periodics bifurcation, abbreviated as SNP. There are two of these in Fig. 10; it is very common for an SNP bifurcation to be present when there is a subHB bifurcation. Looking in the phase plane at a value of I_{ap} near the SNP bifurcation, what we see is that the two limit cycles are very close together (Fig. 11). The unstable one is on the inside, surrounded by the stable one. When

they coalesce, at the value of I_{ap} corresponding to the SNP, the resulting structure is half-stable. It attracts from the outside and repels from the inside. For I_{ap} beyond the SNP the whole structure disappears; the SNP is the death of the limit cycles (or the birth, if you come from the other direction).

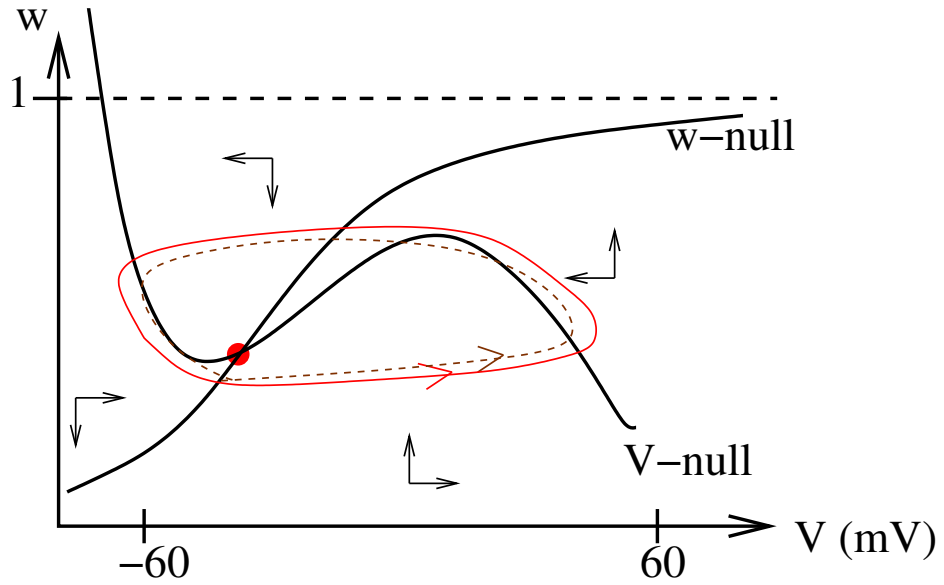

Figure 11: Near an SNP bifurcation the stable and unstable limit cycles are very close together. At the SNP they coalesce, creating a half-stable limit cycle that attracts from the outside and repels from the inside.

One can also view the period vs. parameter, as in Fig. 12. This is an example of a Type 2 Oscillator, since the period is bounded. For a Type 1 Oscillator the period is unbounded as I_{ap} approaches a critical value (Fig. 13), called a **homoclinic bifurcation**.

At a homoclinic bifurcation, the time required for the trajectory to go all the way around the limit cycle is infinite. This strange limit cycle is

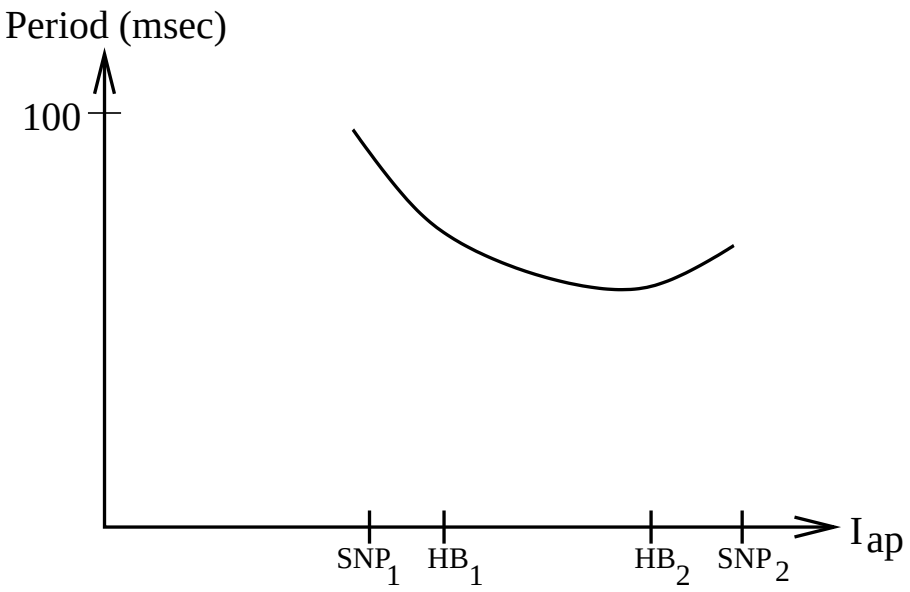

Figure 12: Periodic bifurcation diagram for a type II oscillator. The period of the stable oscillatory solution remains bounded.

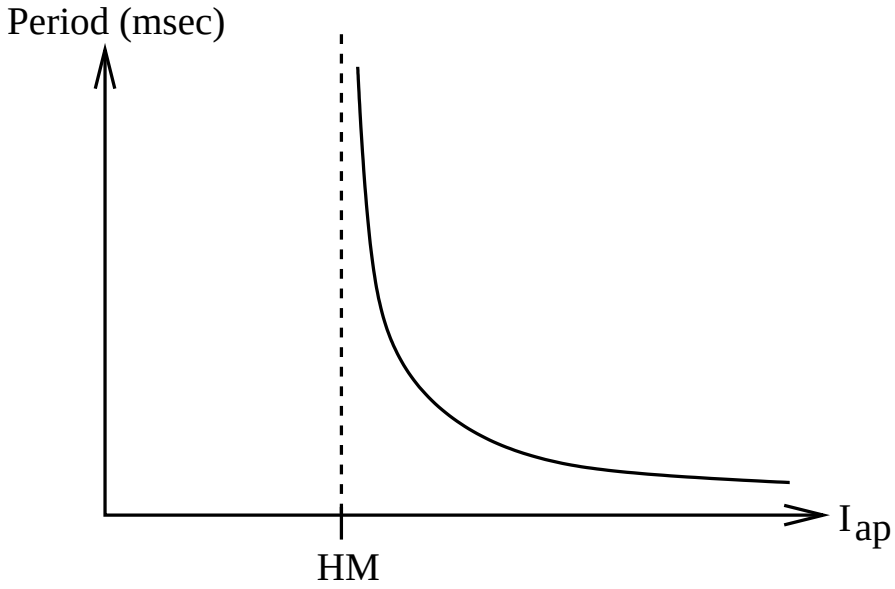

Figure 13: Periodic bifurcation diagram for a type 1 oscillator. The period approaches infinity at the homoclinic bifurcation (HM).

called a homoclinic orbit. The reason it takes so long to traverse the homoclinic orbit is because it actually contains an equlibrium point. This is an equilibrium point, called a saddle point, that attracts from one direction and repels from the other. There is a curve that contains the saddle point on which all trajectories are attracted to the saddle point as $t \to \infty$. This is called the stable manifold of the saddle point. It actually consists of two branches, one branch that comes into the saddle point in one direction and another branch that comes in at a direction 180^o opposite. There is also a curve, again with two branches, on which all trajectories are attracted to the saddle point in reverse time, that is, as $t \to -\infty$. This is called the unstable manifold. A homoclinic orbit occurs when one branch of the stable manifold connects with a branch of the unstable manifold. From the diagram in Fig. 14 we can see immediately why the period of the homoclinic orbit is infinite (right?).

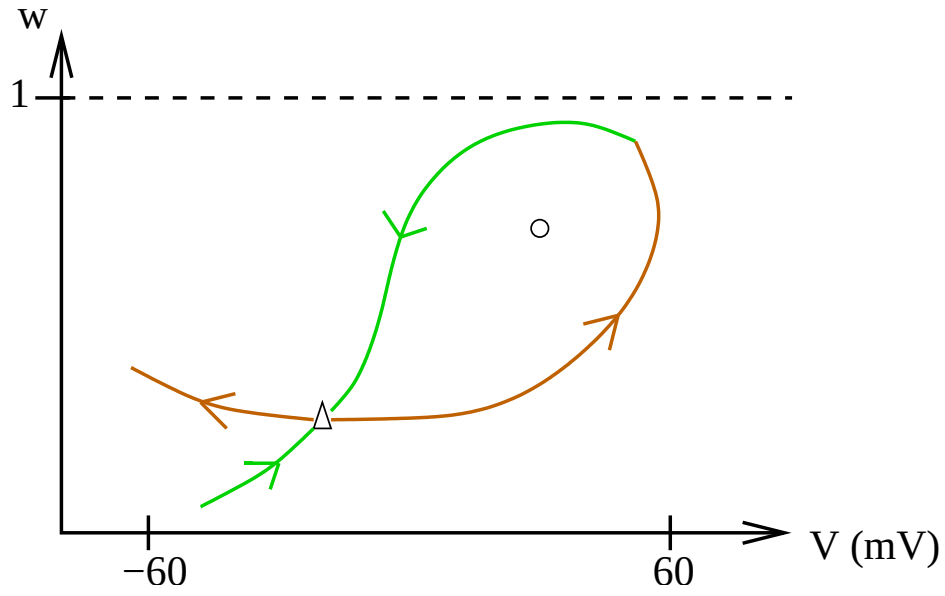

Figure 14: Homoclinic orbit in the phase plane. (green) stable manifold, (brown) unstable manifold of the saddle point (triangle). The homoclinic orbit surrounds an unstable equilibrium (open circle).

Some neurons exhibit type 1 dynamics, so the firing rate declines to near 0 as the applied current is decreased. Other neurons exhibit type 2 dynamics, so the system makes an abrupt transition from continuous spiking to rest as the applied current is decreased. Knowing which behavior occurs allows one to develop an appropriate model for the neuron.

Integrate-and-Fire Models

The Morris-Lecar model is a simplification of the Hodgkin-Huxley model, reducing the dimension from 4 to 2. One can further reduce the dimensionality to 1 by using an **integrate-and-fire model**. The principle behind this is simple: An action potential is an all-or-none event (approximately) in which a spike occurs if a threshold (V_{th}) is reached.

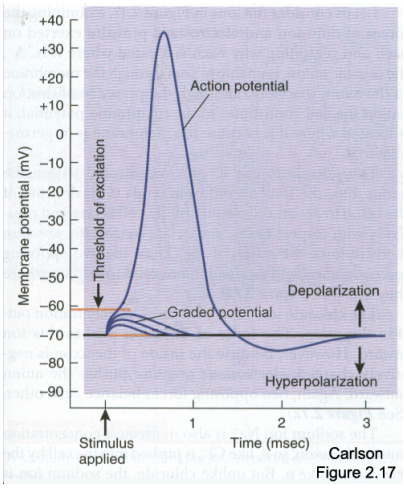

Figure 15: Spike threshold distinguishes sub-threshold from super-threshold responses.

In models discussed so far, this threshold behavior is part of the nonlinear dynamics of the equations. In integrate-and-fire models the equations themselves are linear (and thus easily solved), but when $V > V_{th}$ a spike is recorded and the voltage is reset to a value (V_{res}) that would occur *after* the spike is over. The spike itself is not produced by the single differential equation for the voltage.

In this simplest integrate-and-fire model the conductances are constant,

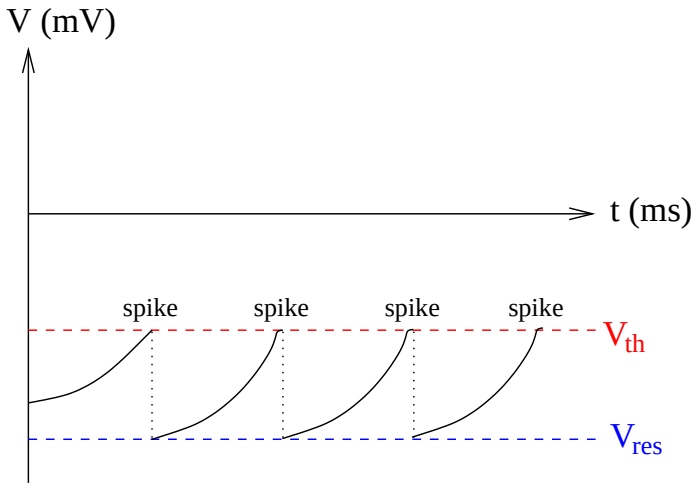

Figure 16: Illustration of time dynamics of an integrate-and-fire model.

so dynamics are linear between spikes. This is often called a **passive** or **leaky integrate-and-fire model**. The voltage equation is

$$\tau_V \frac{dV}{dt} = V_l - V + I_{ap} \tag{25}$$

where τ_V is the membrane time constant, which would be $\frac{C}{g_{tot}}$ in biophysical models (where g_{tot} is the total conductance).

The model also contains a conditional statement, which introduces the nonlinearity:

"If $V \geq V_{th}$ then a spike is implied, so (1) record the spike time, and (2) reset V to V_{res}."

The time required to reach the threshold can be adjusted by varying V_{th} or V_{res}. Also, τ_V determines the rate at which V rises. If I_{ap} is kept constant, then the V ODE is linear with constant forcing, so it can be

solved:

$$V(t) = V_l + I_{ap} + [V(0) - V_l - I_{ap}]e^{-t/\tau_V} \tag{26}$$

or

$$V(t) = V_\infty + [V(0) - V_\infty]e^{-t/\tau_V} \tag{27}$$

where $V_\infty \equiv V_l + I_{ap}$. If the applied current is sufficiently large, then the model neuron will produce a periodic train of impulses. Because the system is piecewise linear one can derive an expression for the period of spiking, called the interspike interval. Suppose that at $t = 0$ the neuron has just fired an impulse, so that $V(0) = V_{res}$. The next impulse will occur when V reaches the threshold, at time t_{ISI}:

$$V_{th} = V_\infty + (V_{res} - V_\infty)e^{-t_{ISI}/\tau_V} \tag{28}$$

solving, solving,

$$\boxed{t_{ISI} = \tau_V \ln\left(\frac{V_\infty - V_{res}}{V_\infty - V_{th}}\right)} \ . \tag{29}$$

We can derive a simpler expression for this by making use of approximations. Suppose that I_{ap} is large, then V_∞ is large and we can write

$$\frac{V_\infty - V_{res}}{V_\infty - V_{th}} = 1 + z \tag{30}$$

where z is a small number. Thus,

$$z = \frac{V_\infty - V_{res}}{V_\infty - V_{th}} - \frac{V_\infty - V_{th}}{V_\infty - V_{th}} \tag{31}$$

or

$$z = \frac{V_{th} - V_{res}}{V_\infty - V_{th}} \quad . \tag{32}$$

Since $t_{ISI} = \tau_V \ln(1+z)$ where z is small we can use a linear Taylor approximation, centered at $z = 0$, $\ln(1+z) \approx z$, so

$$t_{ISI} \approx \tau_V z = \tau_V \left(\frac{V_{th} - V_{res}}{V_\infty - V_{th}} \right) \tag{33}$$

when V_∞ (and I_{ap}) is large.

The firing rate r is $r = \frac{1}{t_{ISI}}$, so for large I_{ap},

$$\boxed{r \approx \frac{V_\infty - V_{th}}{\tau_V (V_{th} - V_{res})} = \frac{V_l + I_{ap} - V_{th}}{\tau_V (V_{th} - V_{res})}} \quad . \tag{34}$$

It is clear from Eq. 34 that the firing rate increases linearly with I_{ap} (when I_{ap} is large). This behavior is observed in some neurons. However, many neurons exhibit spike-frequency adaptation under current injection. That is, the spiking starts out fast and then slows down. To simulate this, we can add another current to the V ODE,

$$\tau_V \frac{dV}{dt} = V_l - V - g_a(V - V_K) + I_{ap} \tag{35}$$

where $g_a(V - V_K)$ is an adapting current. We assume that g_a is increased by Δg_a with each spike and between spikes it relaxes to 0 exponentially with time constant τ_a,

$$g_a = g_a + \Delta g_a \quad \text{at a spike} \tag{36}$$

and

$$\tau_a \frac{dg_a}{dt} = -g_a \quad \text{between spikes.} \tag{37}$$

During repetitive firing g_a builds up. Since $g_a(V - V_K)$ is a hyperpolarizing current, the effect of the buildup in g_a is to slow down the approach to spike threshold, and thus to reduce the firing rate. This yields a spike train that starts out fast and then slows down.

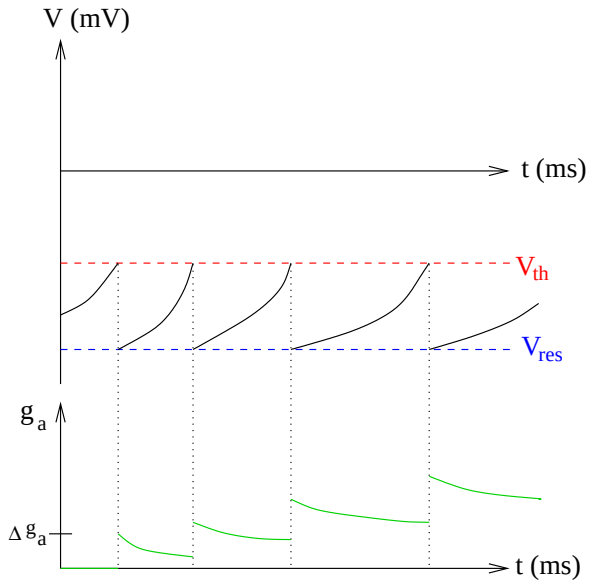

Figure 17: Time dynamics of an integrate-and-fire model with adaptation.

Other variations to the leaky integrate-and-fire model can be made, reflecting properties of the neuron under investigation.