Biomathematics: What is it and how does it work?

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General Questions

1. How can math be used in biology?
2. What does a biomathematician do?
3. Why do we create mathematical models in biology?
4. How much detail should go into a model? Is more detail always better?
5. How should one calibrate a biological model?

How can math be used in biology?

Population Biology

An early model for population growth was developed by **Thomas Malthus**, who lived from 1766 to 1834. This is based on the observation that a species can increase in numbers according to a geometric series:

$$N_1 = N_0 R \tag{1}$$

$$N_2 = N_1 R \tag{2}$$

$$= N_0 R^2 \tag{3}$$

$$N_3 = N_0 R^3 \tag{4}$$

$$\vdots \tag{5}$$

$$N_j = N_0 R^j \tag{6}$$

This is a **linear discrete dynamical system** that is simple to solve. It also yields a testable pre-

diction, that

$$N_j \to \begin{cases} 0, & \text{if } R < 1 \\ \infty, & \text{if } R > 1 \end{cases} \tag{7}$$

Pierre Verhulst (1838) developed a model that better reflects the biology. His **logistic model** assumes that the growth rate R declines as the population increases:

$$R = \overline{R}\left(1 - \frac{N}{\kappa}\right) \tag{8}$$

Then,

$$N_1 = N_0 R = N_0 \overline{R}\left(1 - \frac{N_0}{\kappa}\right) \tag{9}$$

or

$$N_1 = \overline{R} N_0 - \frac{\overline{R}}{\kappa} N_0^2 \tag{10}$$

and in general

$$N_j = \overline{R} N_{j-1} - \frac{\overline{R}}{\kappa} N_{j-1}^2 \quad . \tag{11}$$

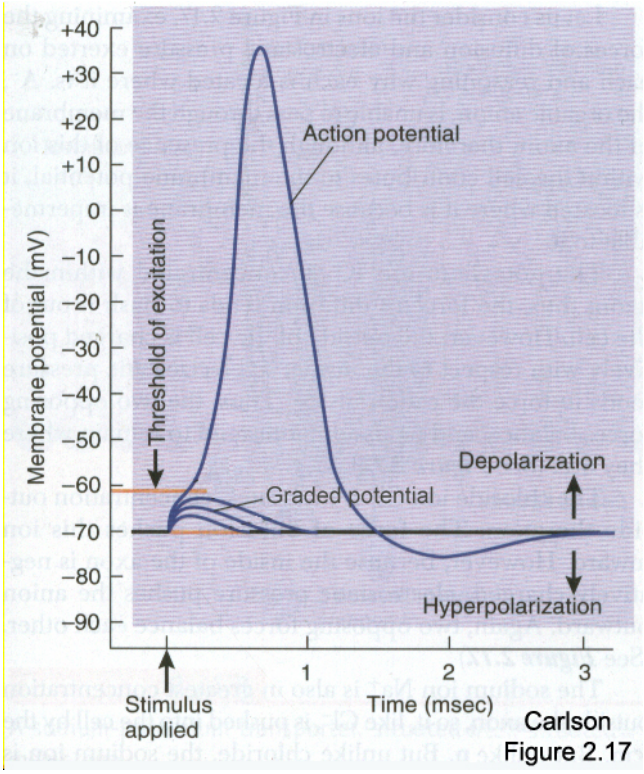
For this **nonlinear difference equation** the asymptotic behavior is bounded when $\overline{R} > 1$:

$$N_j \to \frac{\kappa(\overline{R} - 1)}{\overline{R}} \tag{12}$$

Moral of the story: linear models can provide insight and can typically be solved analytically. However, the most informative and realistic biological models are nonlinear.

Neuroscience

The fundamental unit of information in nerve cells or **neurons** is the **electrical impulse** or **action potential**. Information about the intensity of external input and communication among neurons is all encoded in the frequency or the **firing rate** of electrical impulses.



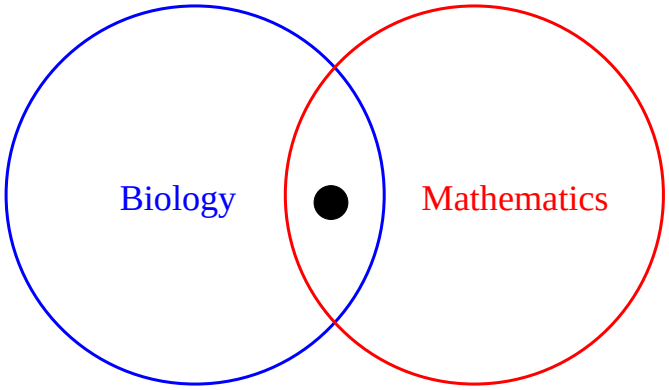
In 1952 **Alan Hodgkin** and **Andrew Hux-**

ley used their own experimental data to develop a mathematical model of the electrical activity of the squid giant axon. This validated their proposed mechanism for impulse generation and its propagation down the axon. Won the Nobel Prize in 1963.

The Hodgkin-Huxley model consists of 4 nonlinear ordinary differential equations (ODEs). As with most useful biological models, the nonlinearity is essential. For impulse propagation a diffusive term is added to one of the equations, yielding a partial differential equation.

What does a biomathematician do?

A biomathematician lives in two worlds:



Things to do to survive in the intersection:

- Read biology papers
- Learn the language of biology
- Talk to experimental biologists
- Work on problems that are interesting to biologists
- Build models that give predictions that can be

tested in the lab

- Form a strong collaboration with one or more experimental labs

Why do we create mathematical models in biology?

- Integrate biological data
- Writing down equations often identifies holes in biological knowledge
- Make testable predictions that can help in experimental design
- Models are inevitably simplifications of the biological system. With these simplifications it is easier to understand the essential elements of the system.

How much detail should go into a model?

A related question: Is a more detailed or accurate model better than a simpler, less accurate model?

There is an example from calculus that can shed light on this.

Reasons that a more detailed model may be less useful than a simpler model:

1. Adding more detail introduces more parameters, whose value probably can't be determined.

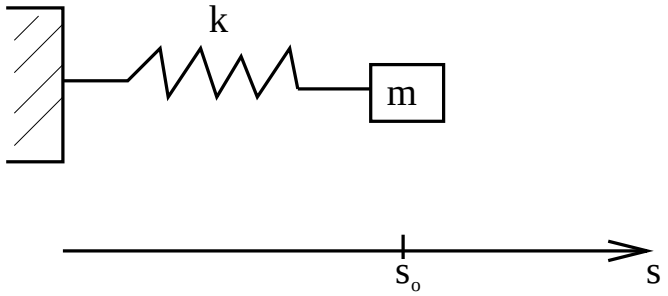
2. With more equations it is harder to understand the mechanism producing the behavior of the model. That is, the added complexity obscures the main elements of the model.

3. The added detail can give the user the false impression that all the components are necessary for the model to reproduce the biological behavior.

How should one calibrate a biological model?

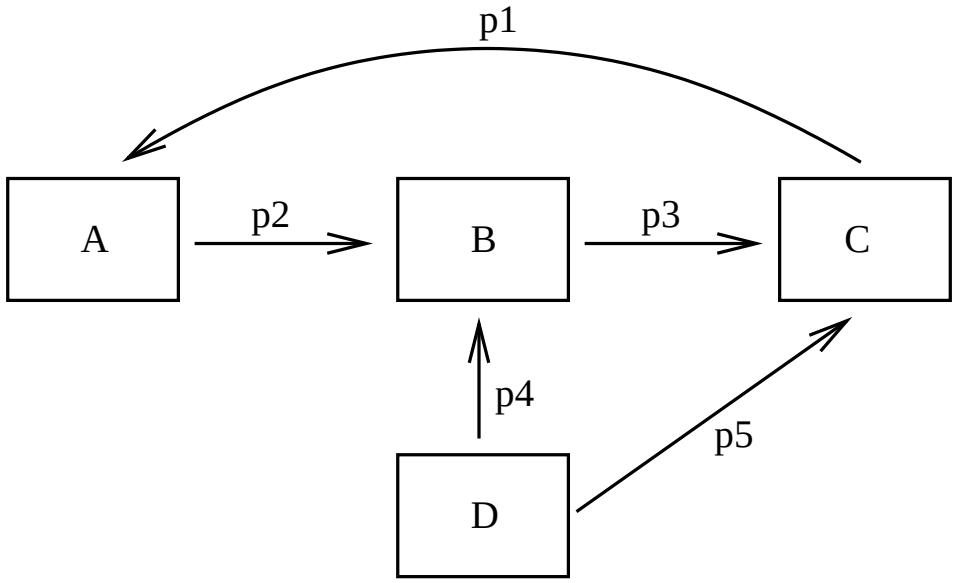
In physics or engineering, one calibrates a model by measuring the parameters. For example, the motion of a spring for small displacements from its unstretched length can be described by Hooke's law in combination with Newton's 2nd Law of Motion:

$$m\frac{d^2s}{dt^2} = -k(s - s_o) \tag{13}$$



The mass parameter m and the spring constant k can both be measured, and in this way the model is calibrated.

For biological models it is rare to be able to measure all or most of the parameters.



If even one of these interaction parameters is unknown, then variation of this parameter could lead to a wide range of model behaviors.

Another problem is that biological systems are often **heterogeneous**, so even if you can get the values of all parameters in one cell, say, they may be very different in another cell of the same type.

Moral: Biological models usually can't be cali-

brated the same way that physics or engineering models can be. Probably the best way to calibrate a biological model is to make model predictions, then test them in the lab, and based on this modify the model (perhaps this simply requires changing parameter values, or perhaps modifying the equations themselves).

Single-Cell and Mean Field Neural Models

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The **neuron** is the basic unit of the nervous system. It is a normal cell that has been adapted morphologically and in terms of protein expression for direct communication with other neurons, with various receptors (e.g., photoreceptors), and with muscle tissue.

Dendrites: input pathways, from **afferent neurons**

Soma or cell body: integration center

Axon: output pathway

Synapses: structures where electrical signals are converted to chemical signals and transmitted to **efferent neurons**

Myelin: insulating cells on vertebrate axons

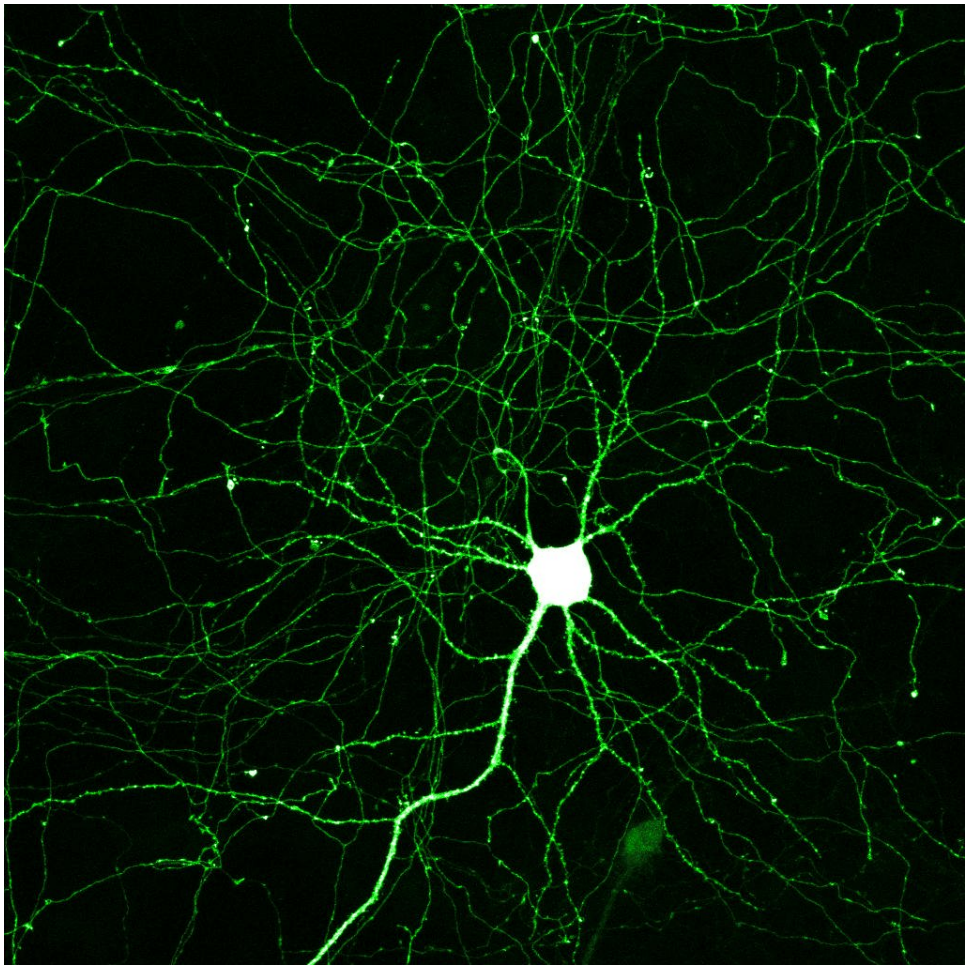

Figure 1: Stained single neuron

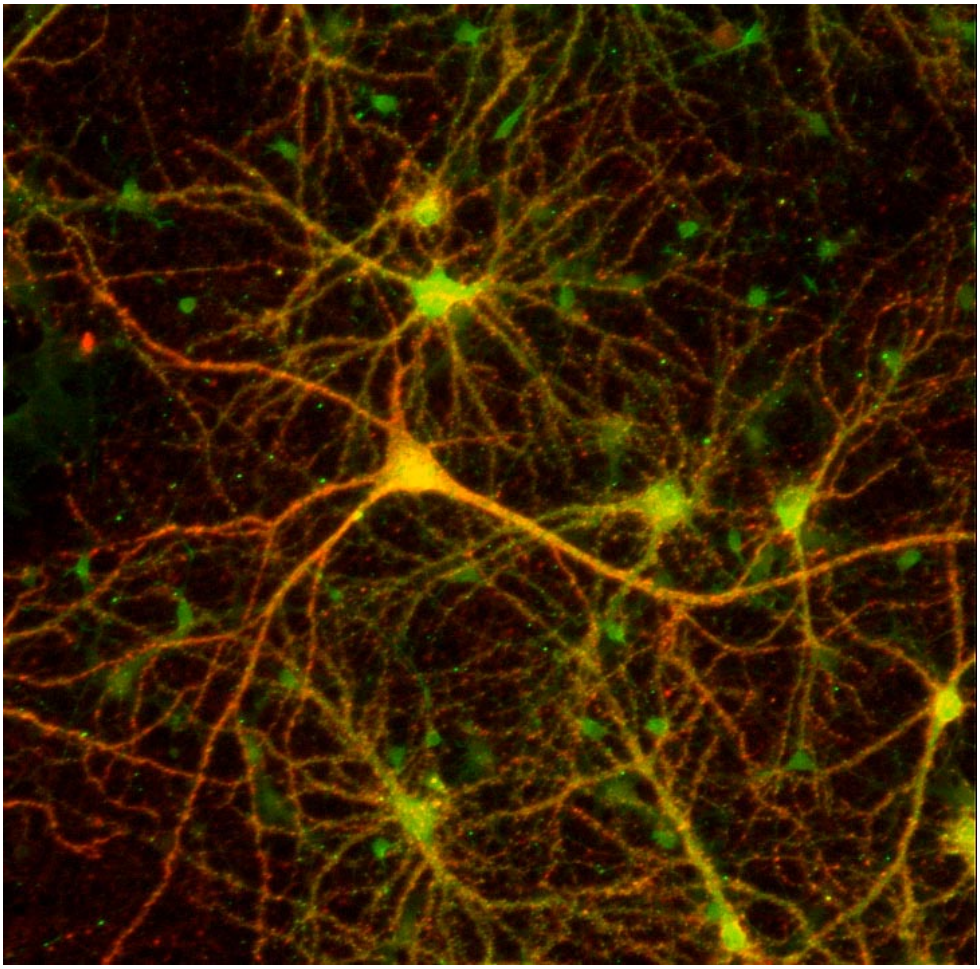

Figure 2: Population of interconnected stained neurons

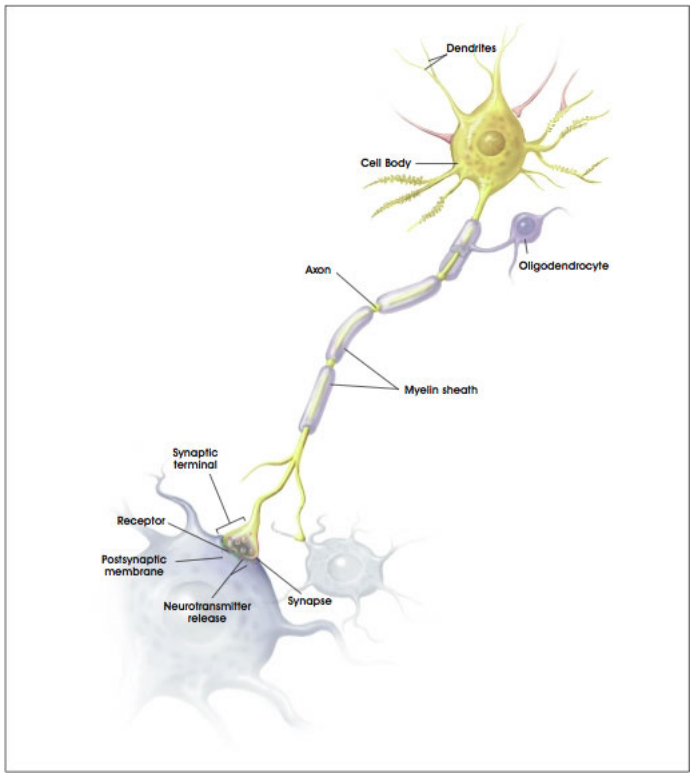

Figure 3: Structure of a neuron

Neurons encode information in the frequency of spiking, or electrical impulse **firing rate**. How are electricity and the neuron related? Answer: ion channels.

An ion concentration gradient is maintained across the plasma membrane by **ion pumps**. An ion

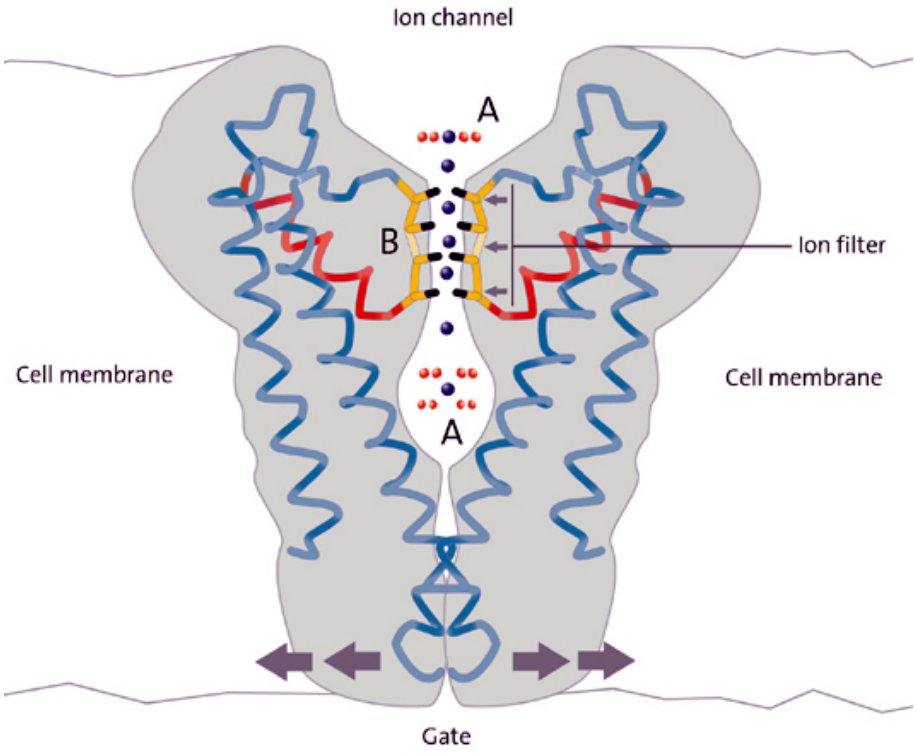

Figure 4: Illustration of an ion channel in a membrane

channel is a portal that allows ions of a specific type (e.g., potassium ions, K^+) to cross the membrane.

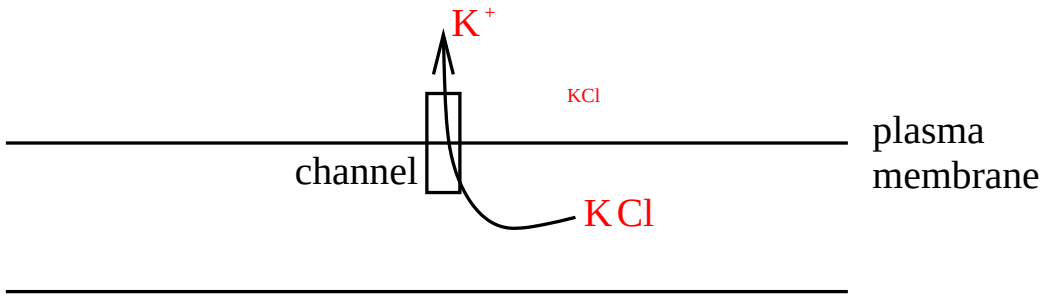

Figure 5: An ion channel allows specific types of ions to flow through

As ions move through the channels an electrical potential develops, which opposes the concentration gradient. The total ion flux across the membrane is described by the Nernst-Planck equation:

$$J = -D\left(\frac{dC}{dx} + \frac{zCF}{RT}\frac{d\Phi}{dx}\right) \tag{14}$$

where C is ion concentration and Φ is the electrical potential. Eventually an equlibrium is reached ($J = 0$). The equilibrium potential is called the Nernst potential:

$$V_{ion} = \frac{RT}{zF} \ln \frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}} \tag{15}$$

where $V_{ion} = \Phi_{in} - \Phi_{out}$. Typically,

$$[K^+]_{in} > [K^+]_{out} \tag{16}$$

so $V_K < 0$,

$$[Na^+]_{in} < [Na^+]_{out} \tag{17}$$

and

$$[Ca^{2+}]_{in} < [Ca^{2+}]_{out} \tag{18}$$

so V_{Na}, $V_{Ca} > 0$. In fact, typical values are:

$$V_K \approx -70 \text{ mV} \tag{19}$$

$$V_{Na} \approx 50 \text{ mV} \tag{20}$$

$$V_{Ca} \approx 100 \text{ mV} \tag{21}$$

The **resting potential** is the weighted average of the Nernst potentials, with the weights being the

macroscopic conductance (g) of the channels in the membrane:

$$V_{rest} = \frac{g_{Na}V_{Na} + g_{Ca}V_{Ca} + g_K V_K}{g_{Na} + g_{Ca} + g_K} \qquad (22)$$

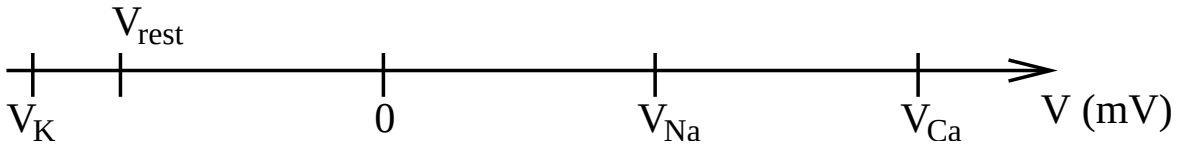

Figure 6: Relative locations of Nernst and resting potential

ELECTRICAL EXCITABILITY

If the conductances were constant, then the neuron would act like a passive resister in parallel with a capacitor. However, the conductances are voltage-dependent; they all increase with voltage, but at different rates and with different time constants. The **depolarizing currents** $I_{Na} = g_{Na}(V - V_{Na})$ and $I_{Ca} = g_{Ca}(V - V_{Ca})$ raise the voltage V and activate first. The **hyperpolarizing current** $I_K = g_K(V - V_K)$ returns the voltage to rest and activates later. This combination of positive feedback and delayed negative feedback produces an electrical impulse or action potential.

A key property of the neuron's electrical dynamics is the presence of a **threshold**. Voltage perturbations above this threshold evoke an impulse.

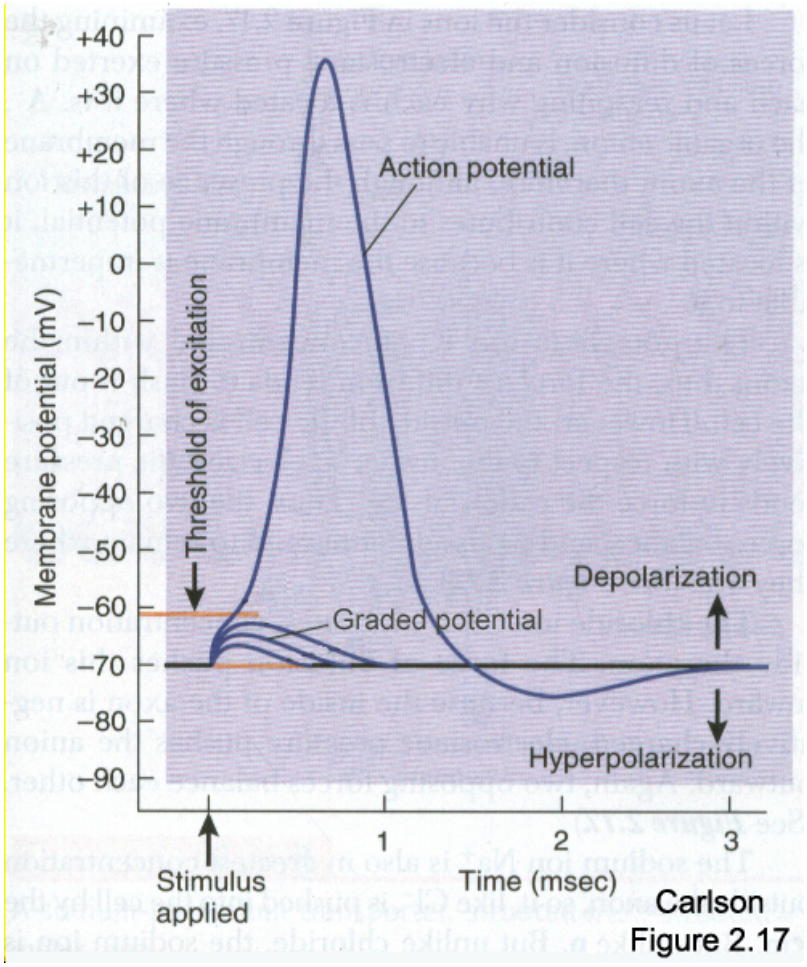

Figure 7: An action potential along with some subthreshold responses

The first mathematical model to describe impulse generation in neurons was developed by Hodgkin and Huxley in 1952. This consists of 4 nonlinear ODEs. Later models were developed that capture the essential dynamics of impulse generation, but that are **planar**. One well-known example was developed by Morris and Lecar in 1981 as a description of a barnacle muscle fiber (muscle also operates by producing electrical impulses).

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^{-1}, where $\tau = \tau(V)$ is the **time constant** (not really a

constant...):

$$\frac{dw}{dt} = [w_\infty(V) - w]\,/\tau(V) \quad . \qquad (23)$$

- 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.

By Kirchoff's Current Law (conservation of charge), the sum of these current must be 0:

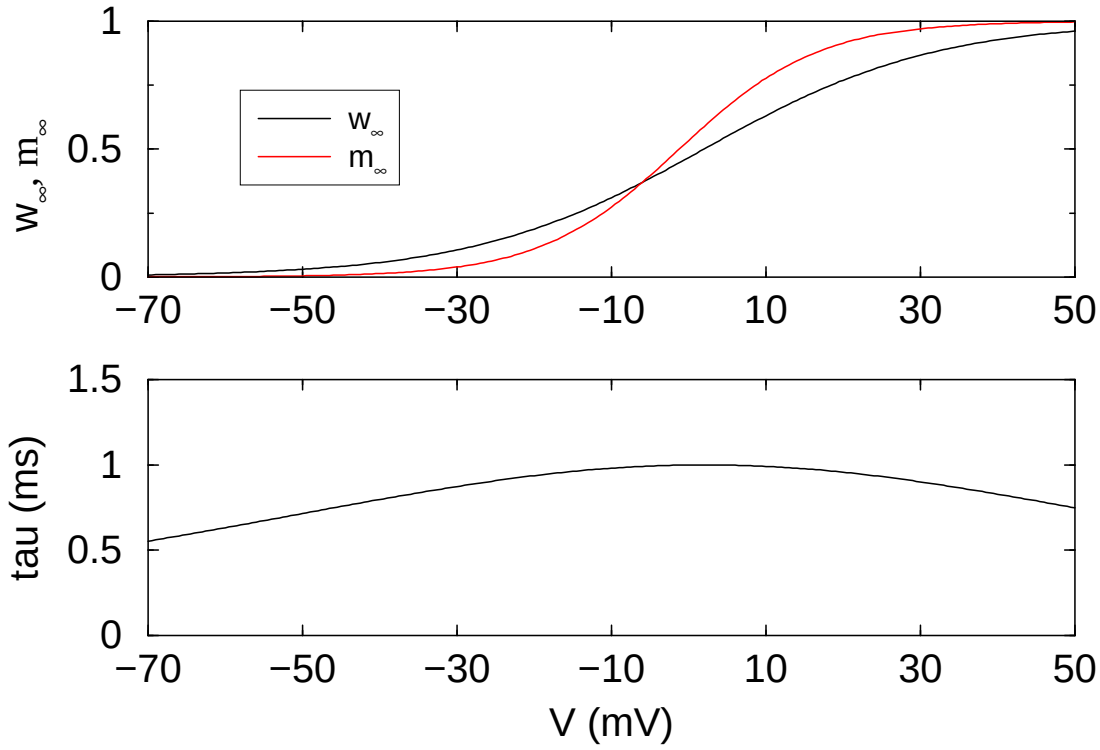

Figure 8: Calcium and potassium equilibrium and time constant functions

$$I_C + I_{Ca} + I_K + I_L - I_{ap} = 0 \qquad (24)$$

or

$$\frac{dV}{dt} = -(I_{Ca} + I_K + I_L - I_{ap})/C. \qquad (25)$$

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

$$\begin{aligned} \frac{dV}{dt} &= -(I_{Ca} + I_K + I_L - I_{ap})/C \\ \frac{dw}{dt} &= [w_\infty(V) - w]/\tau(V) \quad . \end{aligned}$$

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

V-nullcline:

$$w = \frac{I_{ap} - \bar{g}_{Ca} m_\infty(V)(V - V_{Ca}) - \bar{g}_L(V - V_L)}{g_K(V - V_K)} \qquad (26)$$

w-nullcline:

$$w = w_\infty(V) \tag{27}$$

$$= \frac{1}{2[1+\tanh(\frac{V-V_3}{V_4})]} \quad . \tag{28}$$

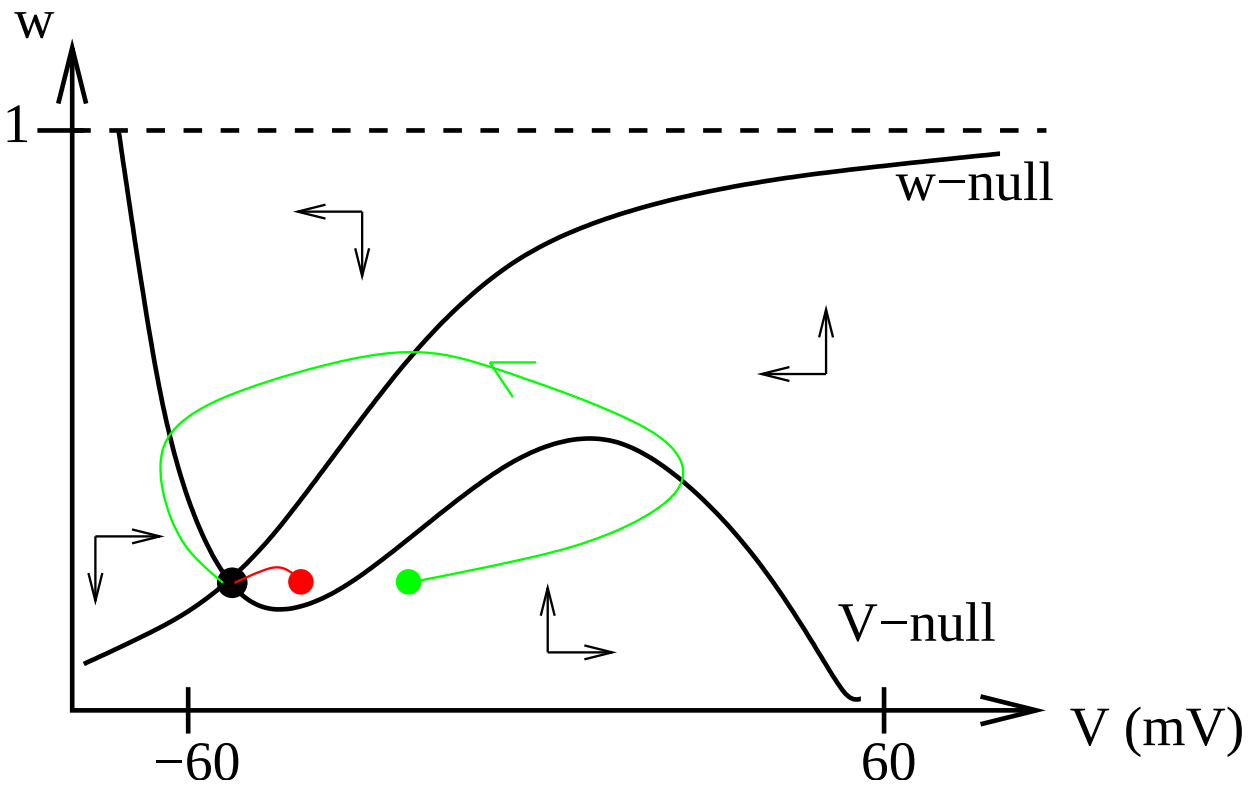

Figure 9: Phase plane analysis of the Morris-Lecar model. Red: subthreshold response, Green: impulse. $I_{ap} = 0$.

The middle branch of the cubic-shaped V-nullcline is the impulse **threshold**. Other planar models for impulse generation have been developed. Most have

cubic-like V-nullclines.

Increasing the applied current translates the V-nullcline upward. The steady state can become **unstable** when the intersection is on the middle branch, through a **Hopf bifurcation**. The stable steady state is replaced with a stable limit cycle, i.e., periodic impulses:

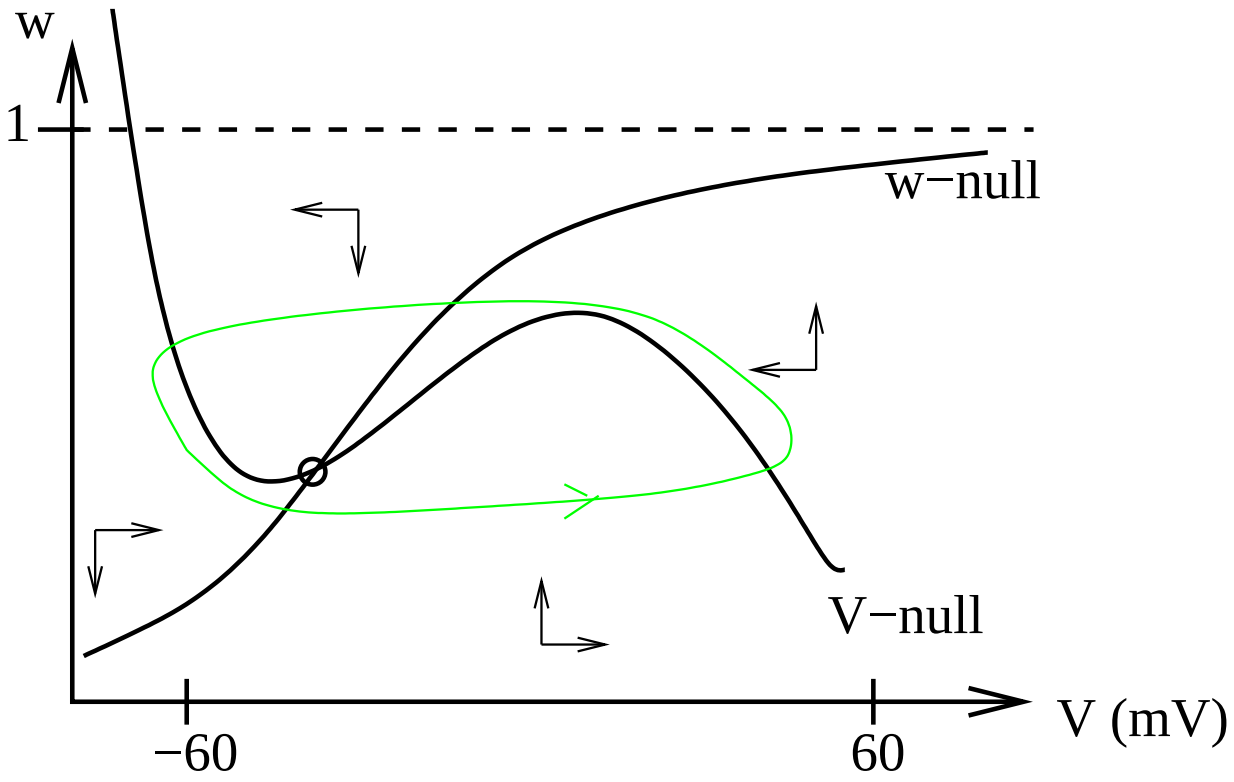

Figure 10: Phase plane analysis of the Morris-Lecar model. Green: Limit cycle. $I_{ap} = 100$ pA.

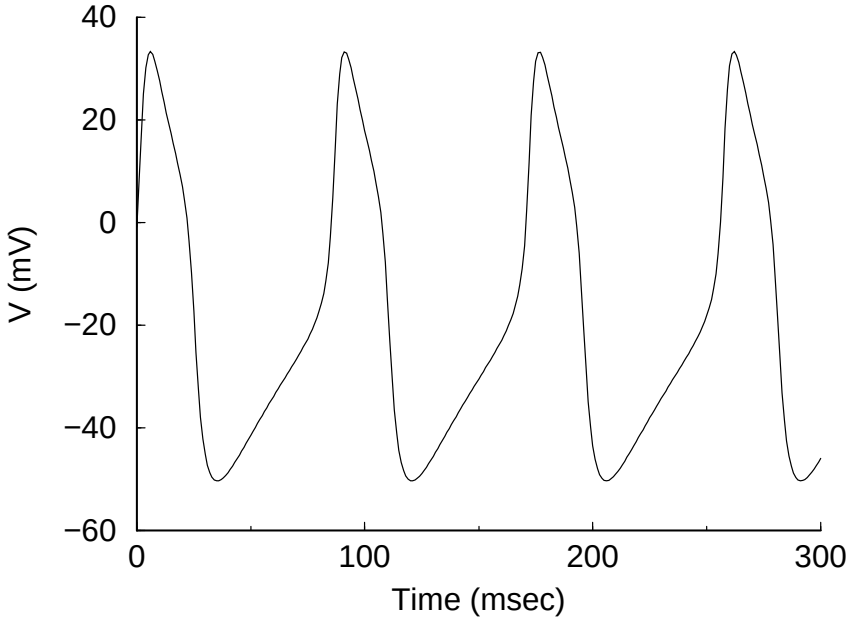

Figure 11: A periodic train of action potentials, when $I_{ap} = 100$ pA.

Increasing the applied current even more can translate the V nullcline high enough so that the intersection is on the right branch. In this case the steady state is **stable** and periodic motion is terminated.

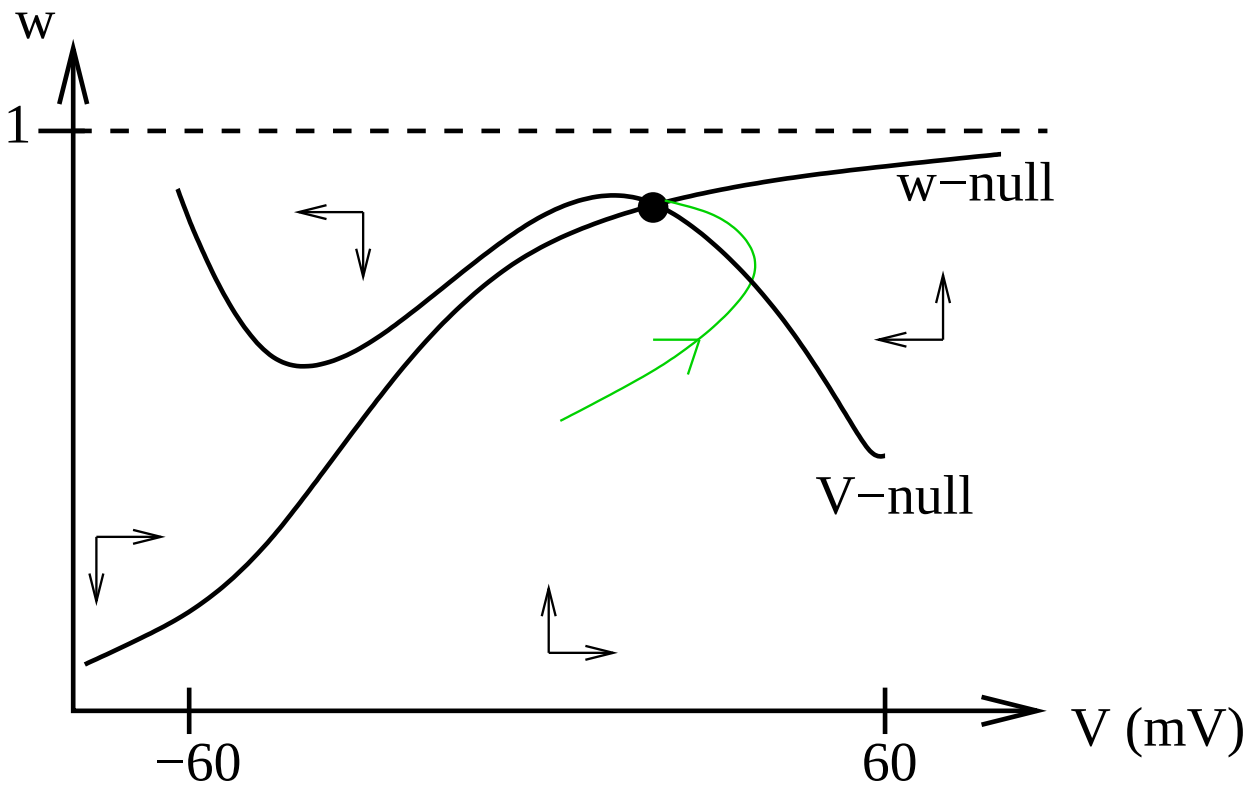

Figure 12: Depolarized resting state, when $I_{ap} = 250$ pA.

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}.

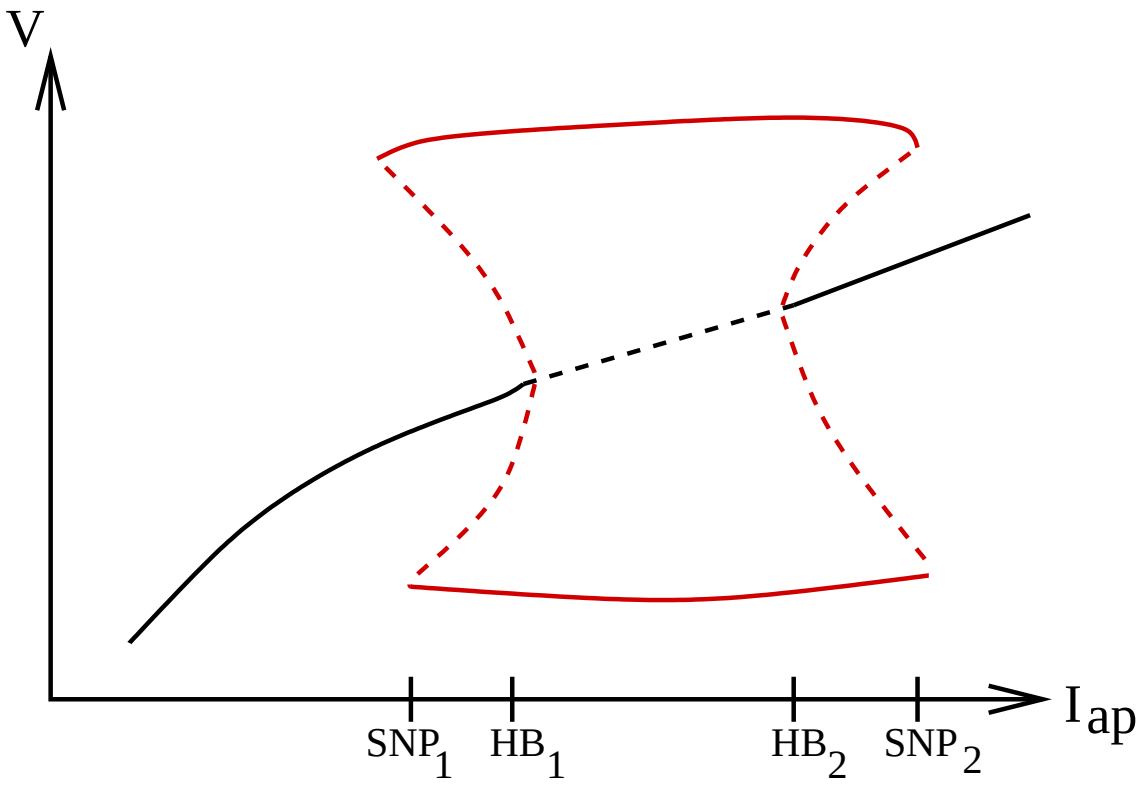

Figure 13: Morris-Lecar bifurcation diagram. Black: stationary branch, Red: periodic branch

One can also view the period vs. parameter, rather than amplitude vs. parameter:

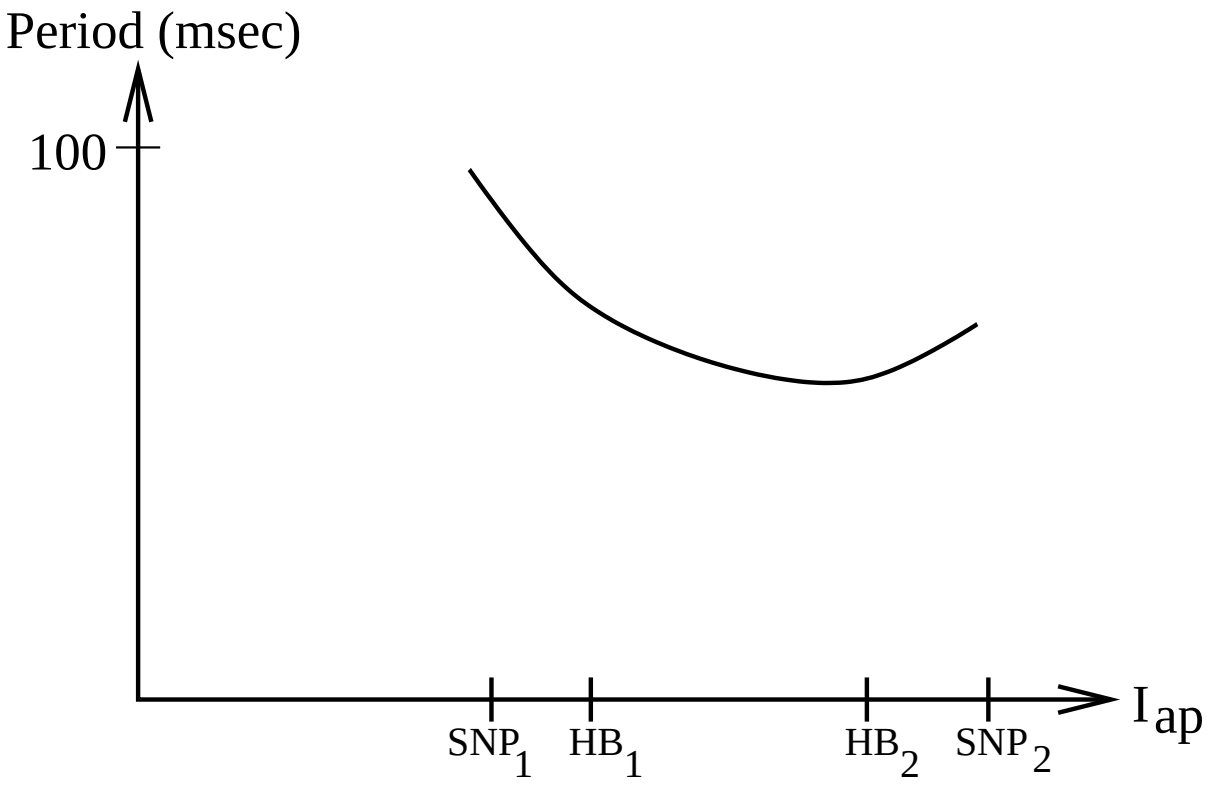

Figure 14: Morris-Lecar bifurcation diagram. Period of stable oscillatory solution

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, called a **homoclinic bifurcation**.

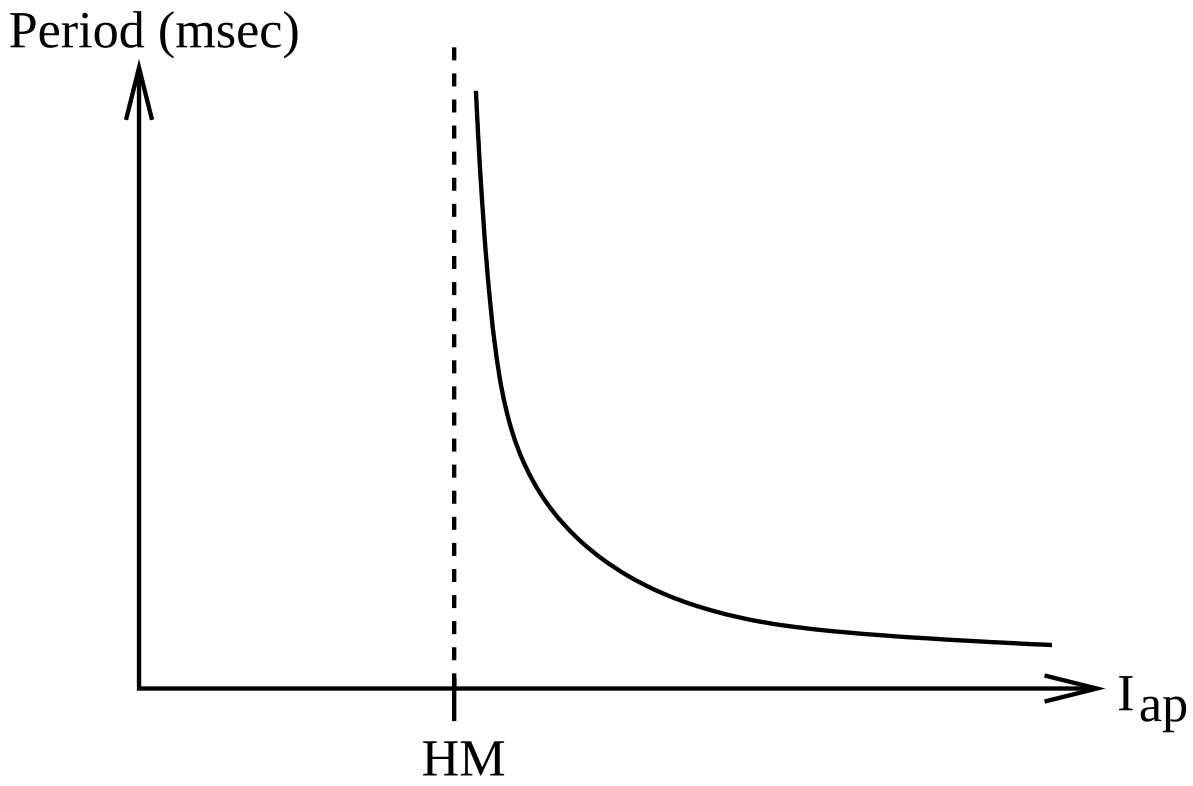

Figure 15: Period bifurcation diagram for a type 1 oscillator. Period approaches infinity at the homoclinic bifurcation (HM).

At a homoclinic bifurcation, the limit cycle connects with a saddle point. In this case, one branch of the saddle's unstable manifold connects to a branch of its stable manifold.

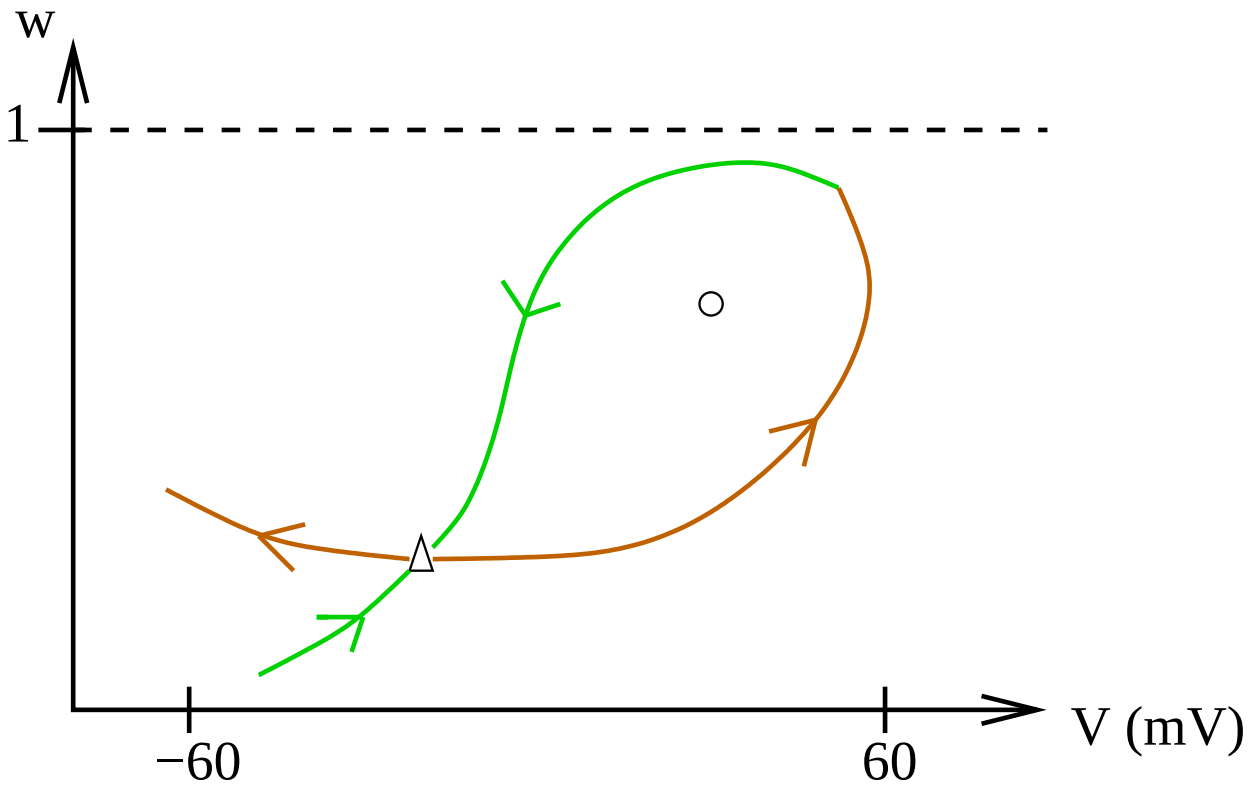

Figure 16: Homoclinic orbit in the phase plane. (blue) stable manifold, (brown) unstable manifold of the saddle point (triangle). The homoclinic orbit surrounds an unstable spiral (open circle).

From this diagram, we can see immediately why the period of the homoclinic orbit is inifinite. (why?)

A generic amplitude vs. applied current bifurcation diagram for a type 1 oscillator looks like:

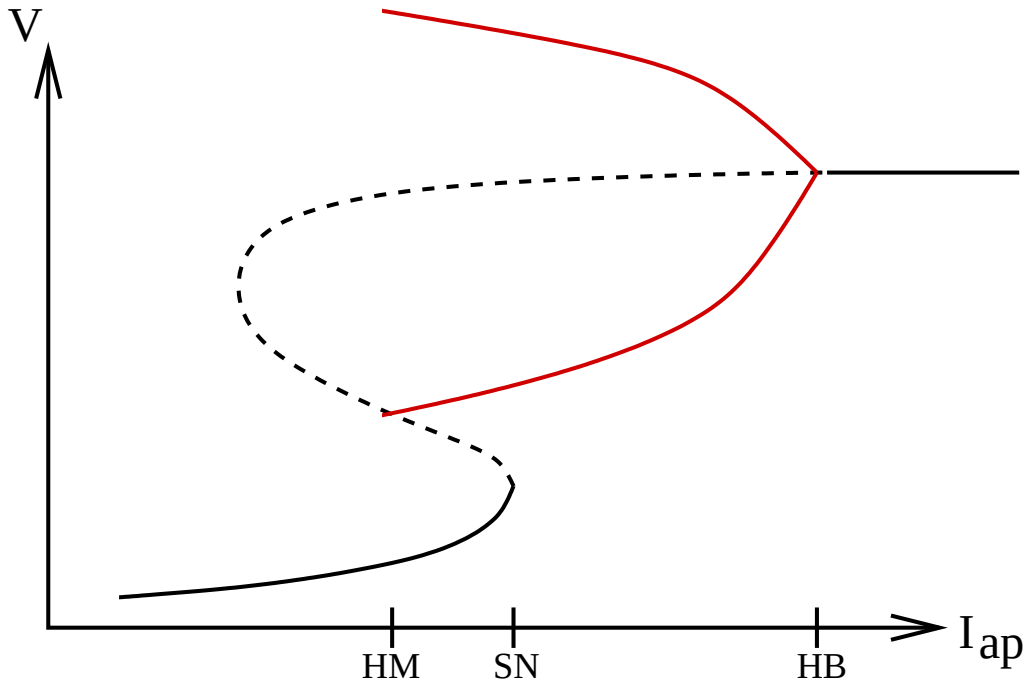

Figure 17: Bifurcation diagram of a type 1 oscillator. (black) stationary branch, (red) periodic branc. HB=supercritical Hopf bifurcation, SN=saddle node bifurcation, HM=homoclinic bifurcation.

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.

The Wilson-Cowan Model

Question: How many equations does it take to describe a population of many thousands of interconnected neurons?

Answer: 2–if you use the Wilson-Cowan model.

The Wilson-Cowan model, developed in 1972 as a model for olfaction, is an example of a **mean field model**. It uses a single variable to describe the mean firing rate of a population of excitatory neurons, and a single variable for a population of inhibitory neurons.

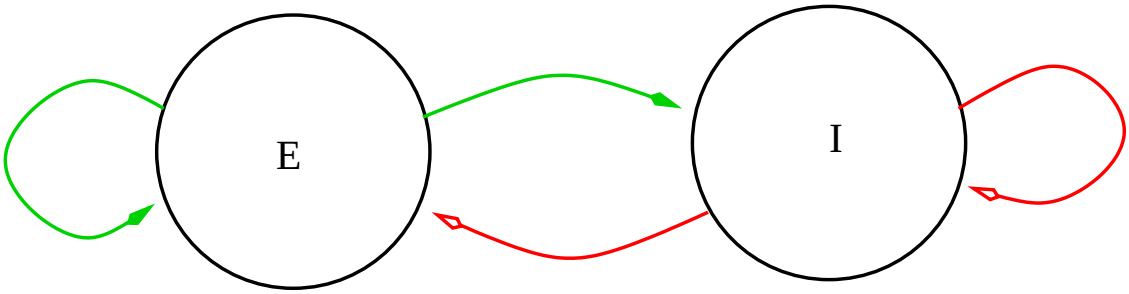

Figure 18: Two neural populations in the Wilson-Cowan model. One (E) is excitatory, the other (I) is inhibitory.

Such a model can be used profitably if there is no special spatial or temporal structure within a subpopulation. For example, it is useful if the E neurons

are randomly connected, but would not be useful if the E neurons are clustered into interconnected layers.

Consider first only the excitatory population, with no I neurons. Then

$$\frac{dE}{dt} = [-E + f_E]/\tau_E \tag{29}$$

where τ_E is a time constant, $-E$ describes the first-order decay of E towards 0, and f_E describes the input into E. If one used a linear function for f_E, then the system could experience uncontrolled growth. Therefore, a saturating function is used:

$$f_E = \frac{1}{1 + e^{-x}} \tag{30}$$

The argument x of the input function includes both the **autofeedback** of E onto itself, and a constant term (p_E) representing extrinsic input:

$$x = aE + p_E \quad . \tag{31}$$

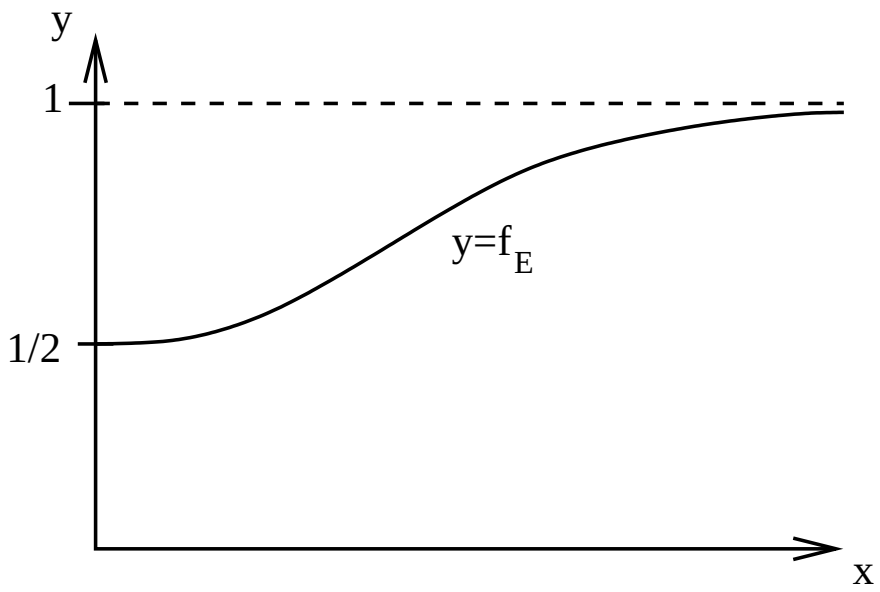

Figure 19: The input function in the Wilson-Cowan model.

Together,

$$\frac{dE}{dt} = [-E + f_E(aE + p_E)]/\tau_E \quad . \tag{32}$$

This is a 1-dimensional system, with equilibria satisfying

$$E^* = f_E = \frac{1}{1 + e^{-(aE^* + p_E)}} \quad . \tag{33}$$

A nice graphical method to solve this nonlinear algebraic equation is to plot $y = E$ and $y = f_E$ and look for intersections.

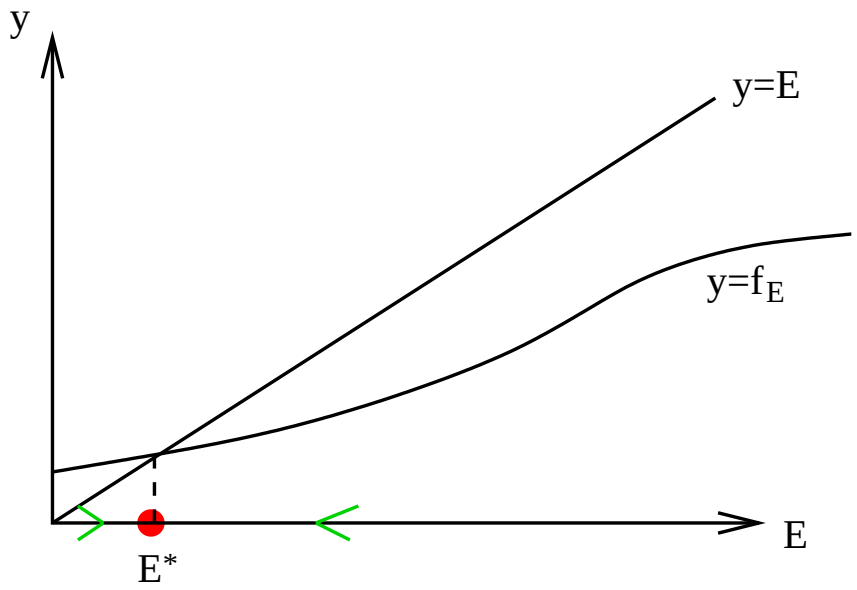

Figure 20: Single steady state when $a = 6$.

The single steady state is **stable** since $E > f_E$ when $E > E^*$, so $\frac{dE}{dt} < 0$ in this case. Also, $E < f_E$ when $E < E^*$, so $\frac{dE}{dt} > 0$. Together, these prove that the steady state is stable.

If the strength of the autofeedback, a, is increased, then the $y = f_E$ curve is deformed and two new steady states are born:

The system is now **bistable**; the outer steady states are stable, the inner one is unstable. The

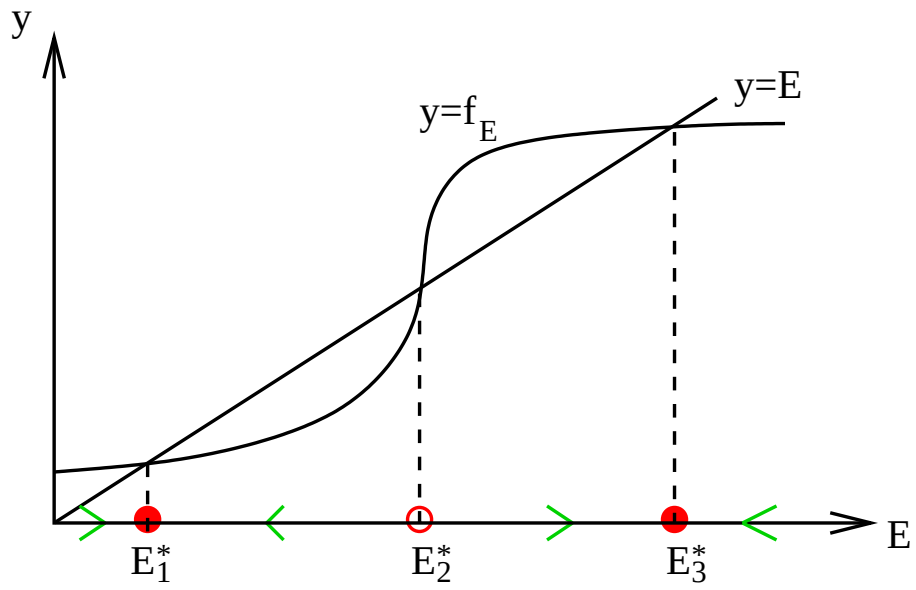

Figure 21: The system is bistable when $a = 10$.

existence of the larger stable steady state E_3^* reflects the regenerative nature of this system due to the presence of positive feedback.

Now we add the inhibitory neurons into the system. These are just like the excitatory neurons, except that their output has the opposite polarity. The I neurons provide input to both the E and I neu-

rons, so the equations for the two types are:

$$\frac{dE}{dt} = [-E + f_E(aE - bI + p_E)]/\tau_E \quad (34)$$

$$\frac{dI}{dt} = [-I + f_I(cE - dI + p_I)]/\tau_I \quad (35)$$

where f_I has the same form as f_E. This is the Wilson-Cowan model.

The E**-nullcline** is $E = f_E(aE - bI + p_E)$. The I**-nullcline** is $I = f_I(cE - dI + p_I)$. For parameter value $p_E = -5$ the phase portrait is:

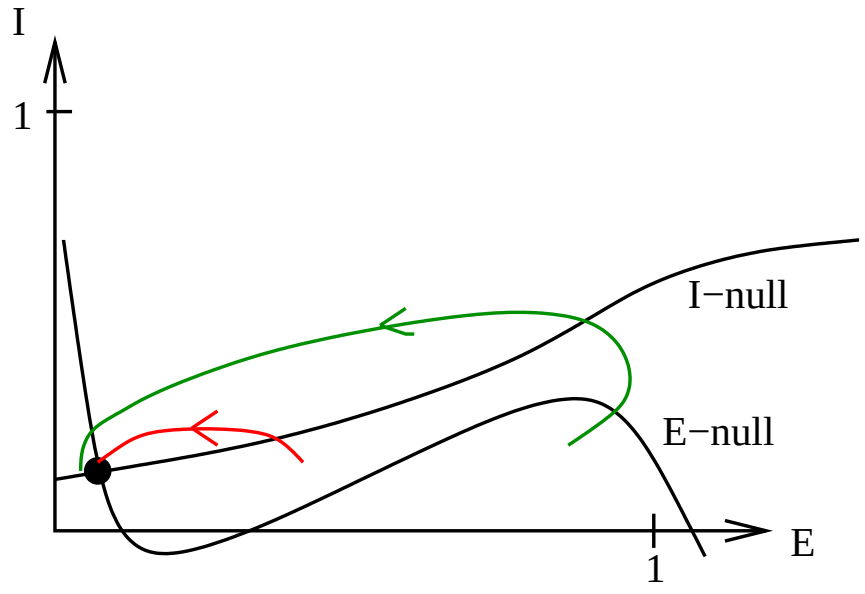

Figure 22: Wilson-Cowan phase portrait, excitable regime ($p_E = -5$).

There is a single stable steady state, but if the phase point is perturbed past the middle branch of the E-nullcline, then there is a regenerative response, with E first increasing further before it begins to decrease back towards the steady state. This is very similar to an **impulse** produced by the Morris-Lecar model. In the context of Wilson-Cowan, this would correspond to a population spike. That is, a spike of activity in the population of E neurons followed by an I spike.

The dynamics of Wilson-Cowan are in fact very similar to the dynamics of Morris-Lecar:

$$E \Longleftrightarrow V$$

$$I \Longleftrightarrow w.$$

These are both prototypical models of an **excitable system**.

Like Morris-Lecar, Wilson-Cowan can produce limit cycle behavior. Increase the p_E parameter, translating the E-nullcline upward so that the intersection is on the middle branch.

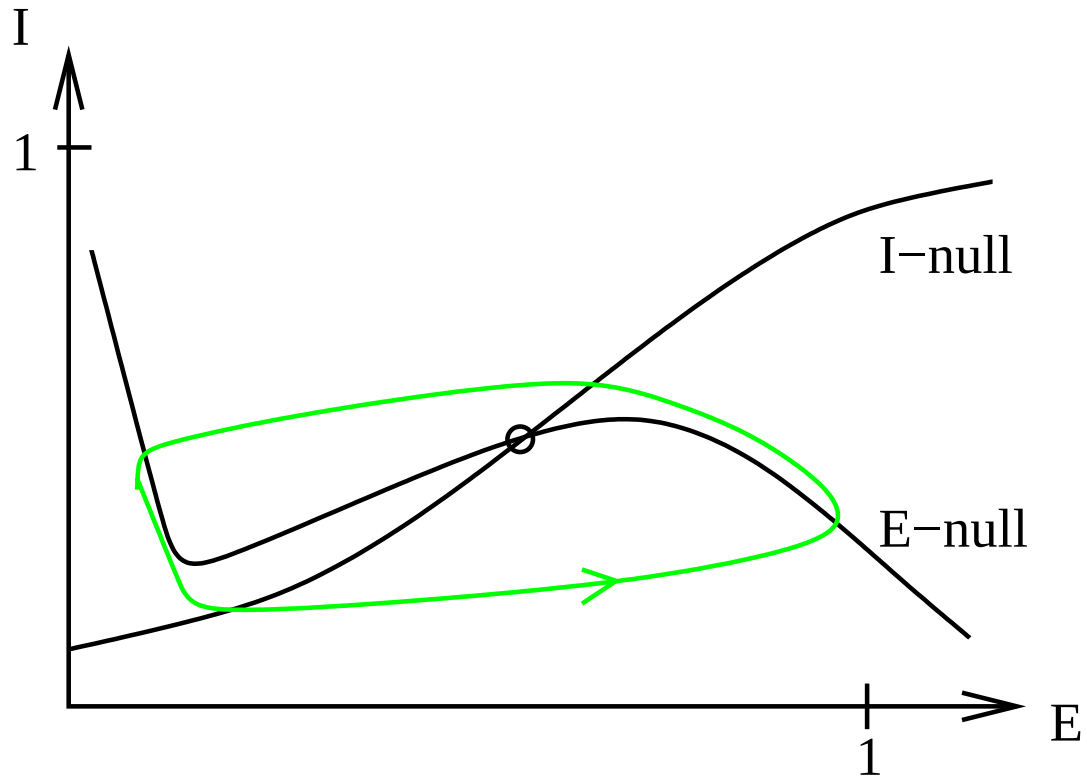

Figure 23: Limit cycle behavior, when $p_E = -1$.

This produces a periodic train of population spikes.

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