

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.

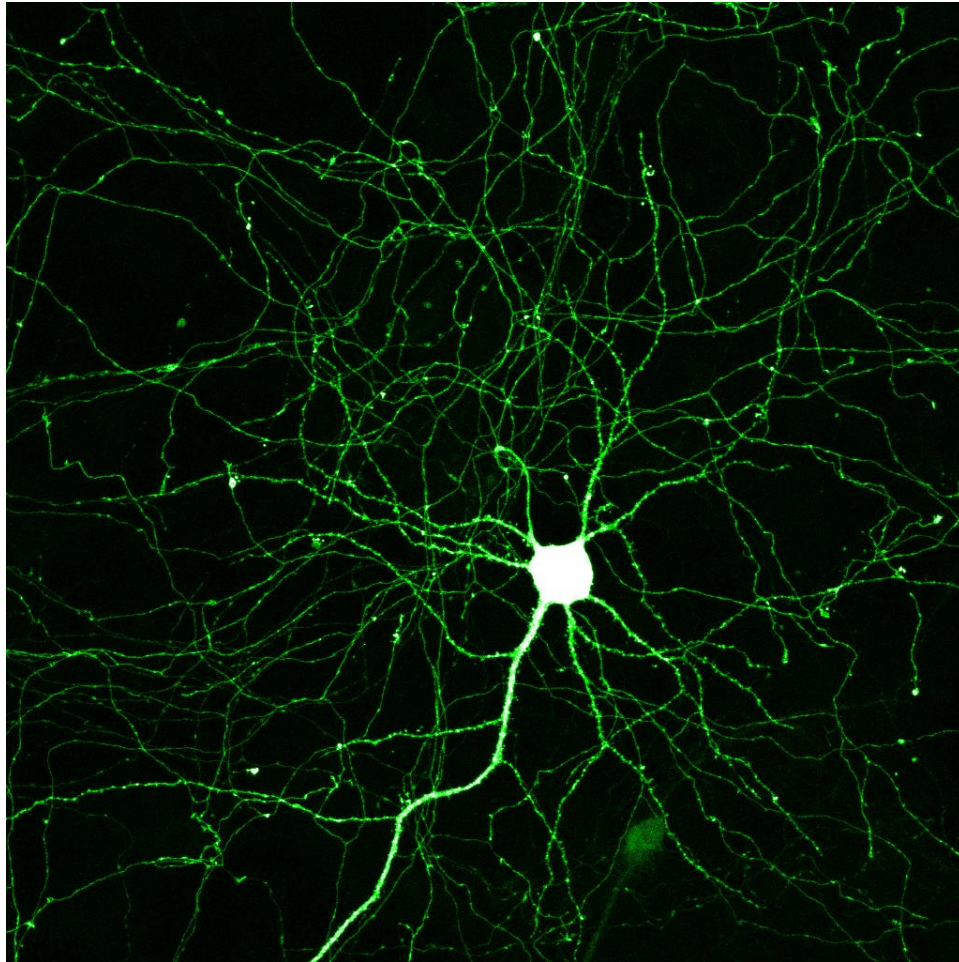


Figure 1: Stained single neuron

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

Soma or **cell body:** integration center

Axon: output pathway

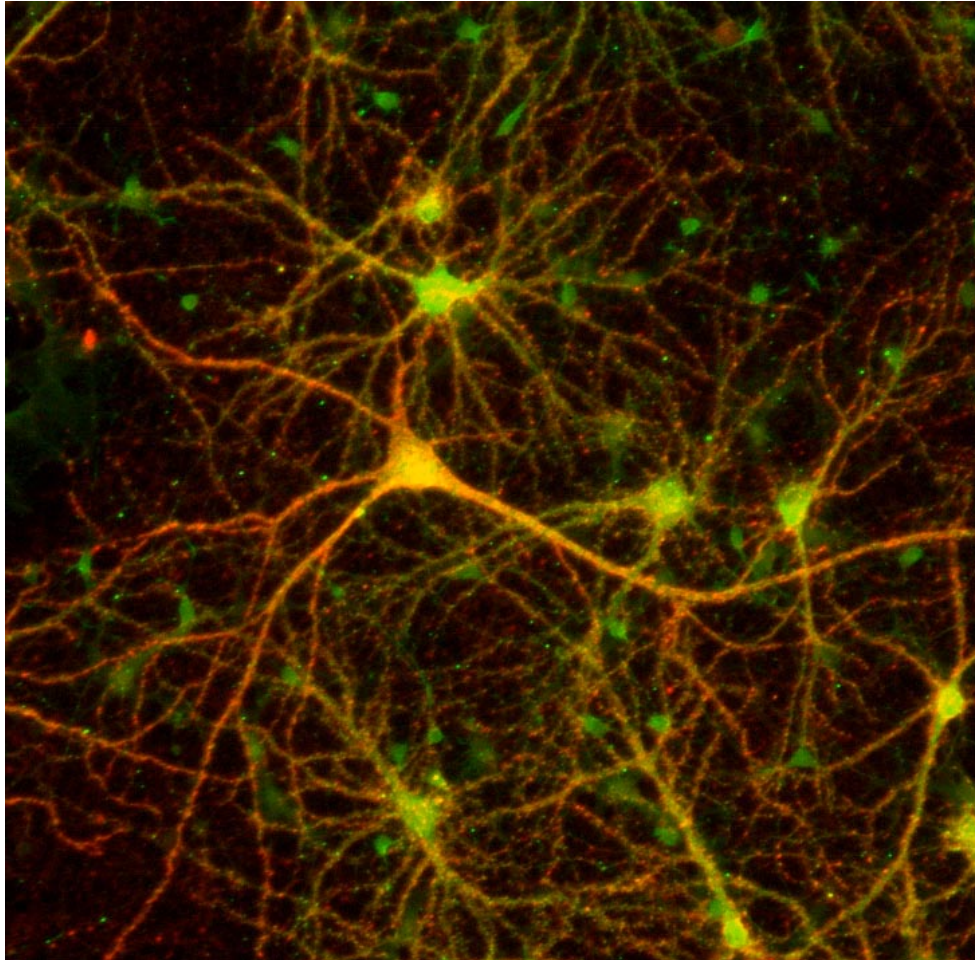


Figure 2: Population of interconnected stained neurons

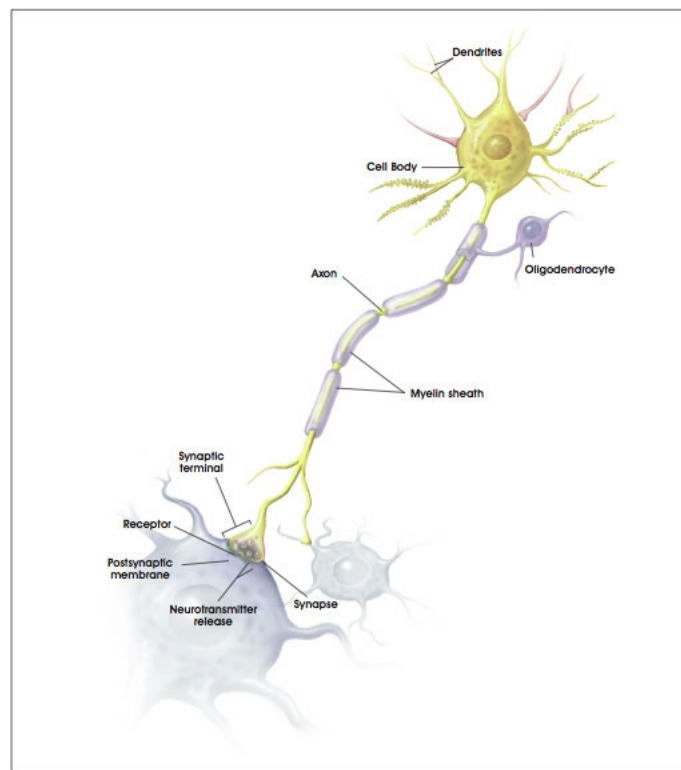


Figure 3: Structure of a neuron

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

Myelin: insulating cells on vertebrate axons

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

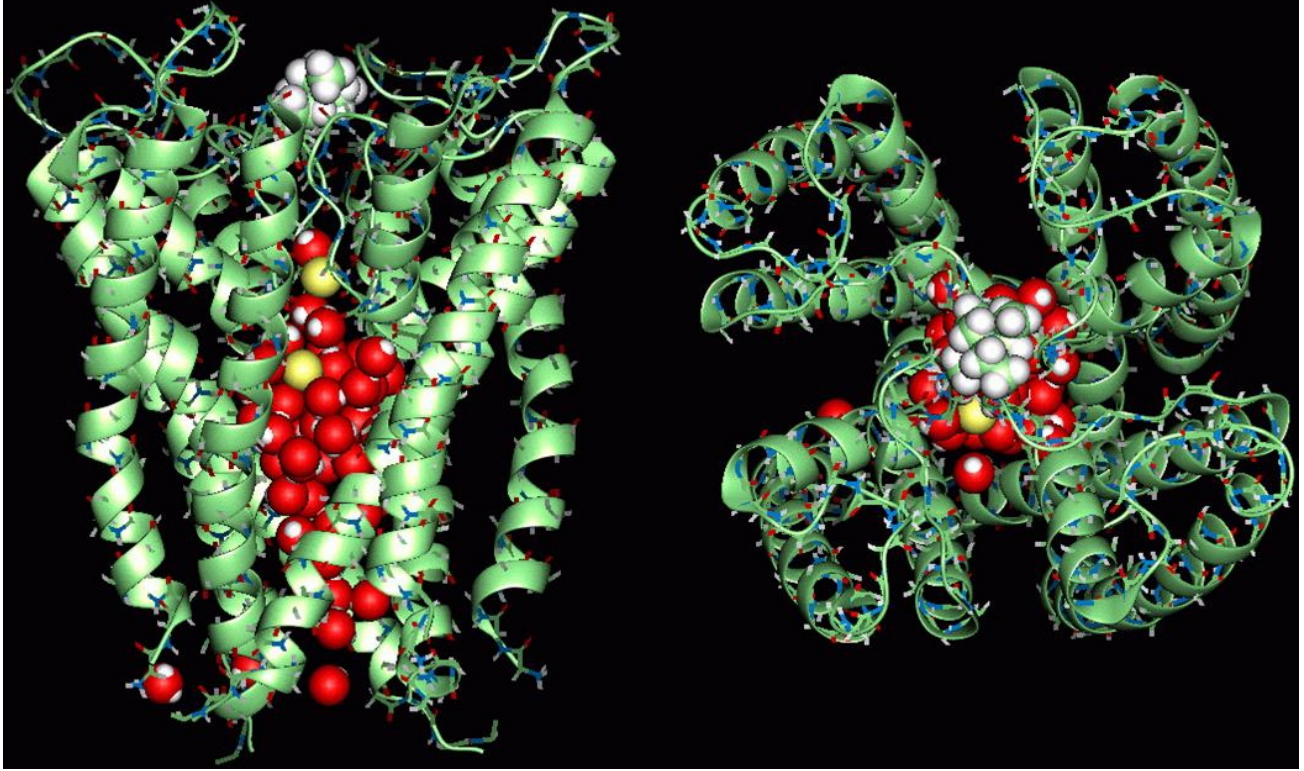


Figure 4: Atomic model of the bacterial KcsA K^+ channel

A concentration gradient is maintained across the plasma membrane by **ion pumps**, which hydrolyze ATP to provide the energy to pump ions upstream. An **ion channel** is a portal that allows ions of a specific type (e.g., potassium ions, K^+) to move through the membrane. The channel is like a gate; when it is open the ions move through it in a downstream fashion, powered by the concentration gradient.

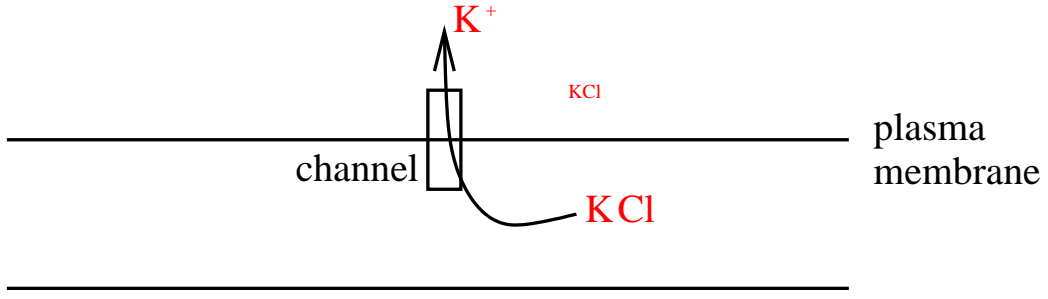


Figure 5: An ion channel allows specific types of ions to flow through

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](#):

$$J = -D \left(\frac{dC}{dx} + \frac{zCF}{RT} \frac{d\Phi}{dx} \right) \quad (1)$$

where C is ion concentration and Φ is the electrical potential. (D is the diffusion coefficient, R is the gas constant, T is temperature, and F is the Faraday constant.) The first term describes the concentration gradient, while the second describes the electrical potential gradient. Eventually an equilibrium is reached ($J = 0$). The equilibrium potential is called the [Nernst potential](#):

$$\boxed{V_{Nernst} = \frac{RT}{zF} \ln \frac{C_{out}}{C_{in}}} \quad (2)$$

where $V_{Nernst} = \Phi_{in} - \Phi_{out}$ and z is the ion valence. Typically,

$$[K^+]_{in} > [K^+]_{out} \quad (3)$$

so $V_K < 0$,

$$[Na^+]_{in} < [Na^+]_{out} \quad (4)$$

and

$$[Ca^{2+}]_{in} < [Ca^{2+}]_{out} \quad (5)$$

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

$$V_K \approx -70 \text{ mV} \quad (6)$$

$$V_{Na} \approx 50 \text{ mV} \quad (7)$$

$$V_{Ca} \approx 100 \text{ mV} \quad (8)$$

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:

$$V_{rest} = \frac{g_{Na}V_{Na} + g_{Ca}V_{Ca} + g_KV_K}{g_{Na} + g_{Ca} + g_K} \quad (9)$$

Here, [macroscopic conductance](#) reflects the permeability of an ion type through all open channels permeable to that ion type. For example, g_{Ca} is the total permeability of Ca^{2+} through all open Ca^{2+} channels.

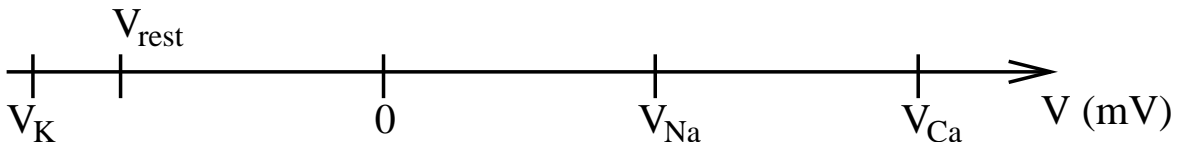


Figure 6: Relative locations of Nernst and resting potentials

THE VOLTAGE EQUATION

The **plasma membrane** of a cell consists of **phospholipids** with proteins like ion channels and ion pumps inserted.

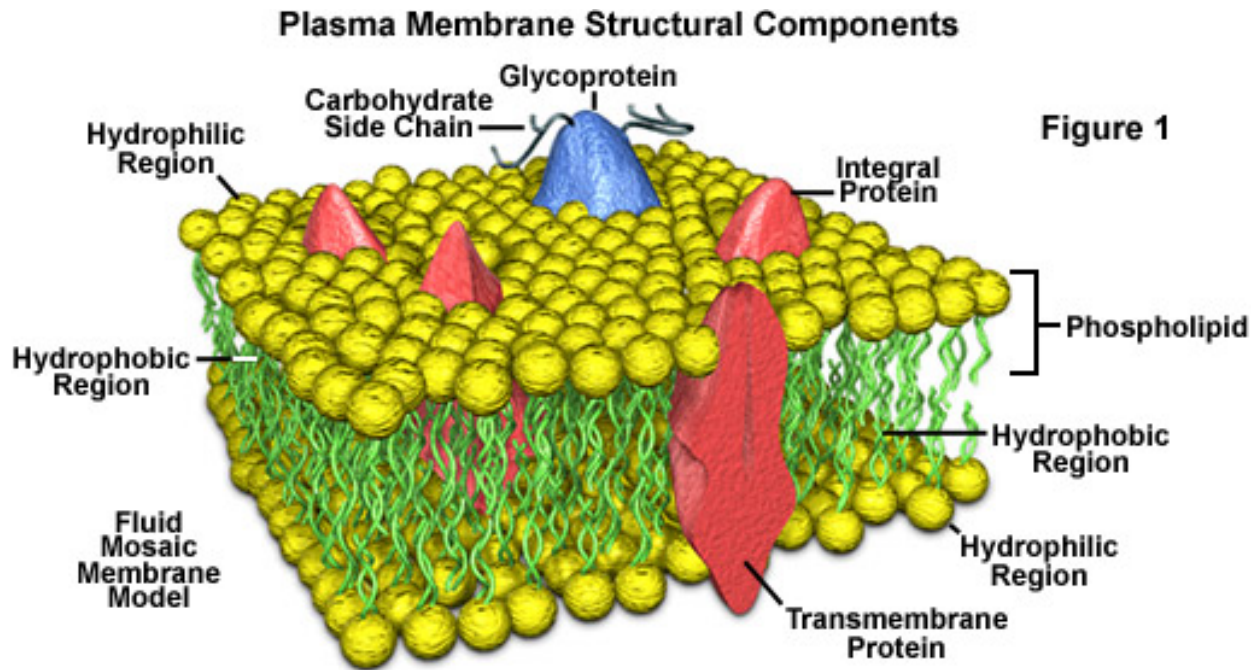
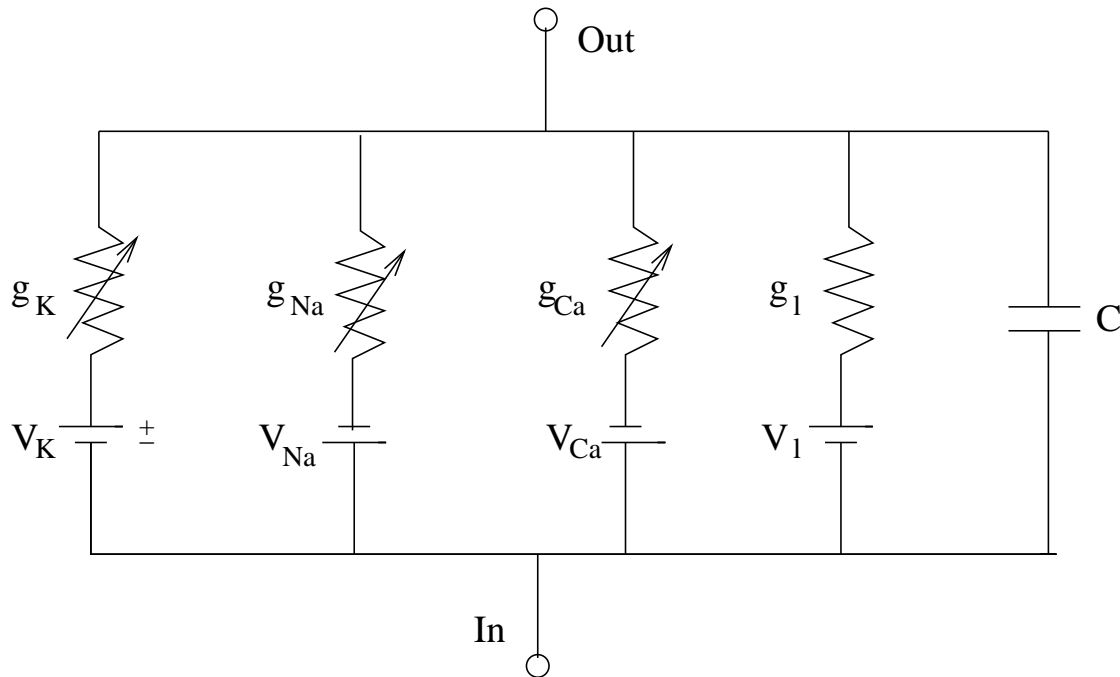


Figure 7: Illustration of the plasma membrane of a cell

The phospholipid bilayer acts as a parallel-plate capacitor, separating charges (inside and outside of cell). The **dielectric** of the capacitor is low, since it is hard for charged particles to get through the electrically neutral lipids. The ion channels that span the bilayer act as electrical conductors, allowing ions to pass through the membrane without crossing through the electrically neutral lipids.

In 1968 K.S. Cole suggested that the electrical properties of a patch of neural membrane are similar to an electrical circuit. This **equivalent**

circuit description allows one to immediately derive equations, based on circuit theory.



The **capacitance** is $C = 1 \mu\text{F}/\text{cm}^2$, and is the same for all neural membranes since it reflects the properties of the lipid bilayer. Each type of channel acts as a **conductor** (conductance= g), while the Nernst potentials provide ionic driving forces. Each conductor, with the exception of the leak, changes with the membrane potential. That is, each is **rectifying**.

The leak conductance is largely due to Cl^- leaking through the various channels. (Most neurons don't have Cl^- channels, although some do.) Typically, the Cl^- concentration is highest on the outside, and since the valence is -1 , $V_l < 0$.

We now use several laws from physics to derive the voltage equation.

First, by **Ohm's law**,

$$V = IR \quad (10)$$

where V is the voltage (membrane potential in the case of neurons), I is the current, and R is resistance. But conductance = 1/resistance, so

$$I = gV \quad (11)$$

We modify this by noting that the current through, say, a K^+ channel is 0 when $V = V_K$, not when $V = 0$. Hence, in general,

$$I = g(V - V_{\text{Nernst}}) \quad (12)$$

Thus,

$$I_K = g_K(V - V_K) \quad (13)$$

$$I_{Na} = g_{Na}(V - V_{Na}) \quad (14)$$

$$I_{Ca} = g_{Ca}(V - V_{Ca}) \quad (15)$$

$$I_l = g_l(V - V_l) \quad (16)$$

These describe the currents through the ion channels. There is also a current through the capacitor, I_c . This **capacitive current** depends on the rate of change of voltage,

$$I_c = C \frac{dV}{dt} \quad (17)$$

We combine the currents through the different branches of the [parallel circuit](#) using **Kirchoff's current law**. This states that the total charge

through a circuit must be conserved, and in the case of a parallel circuit the sum of the currents through the different branches must equal 0. Thus,

$$I_c + I_K + I_{Na} + I_{Ca} + I_l = 0 \quad . \quad (18)$$

Rewriting,

$$I_c = -(I_K + I_{Na} + I_{Ca} + I_l) \quad (19)$$

or

$$\boxed{\frac{dV}{dt} = -(I_K + I_{Na} + I_{Ca} + I_l)/C} \quad (20)$$

This is the **Voltage Equation**.

Since each ionic current is linear in V when the conductances are constant, this is a *linear* ODE. In this case,

$$\frac{dV}{dt} = (-aV + b)/C \quad (21)$$

and the solution is exponential in time. That is, the voltage relaxes to its steady state in an exponential manner if the conductances are constant.

ELECTRICAL EXCITABILITY

If the conductances were constant, then the neuron would act like a passive resistor 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.

The conductance of an ionic current is the product of the **single-channel conductance** and the number of open channels. The single-channel conductance is roughly constant, while the number of open channels depends on the membrane potential. Let \bar{g} denote the **maximum conductance**, i.e., the single-channel conductance times the total number of channels of a single type. Then

$$g = \bar{g} \text{Prob}[\text{channel open}] \quad . \quad (22)$$

To determine this probability function (which depends on V), **Alan**

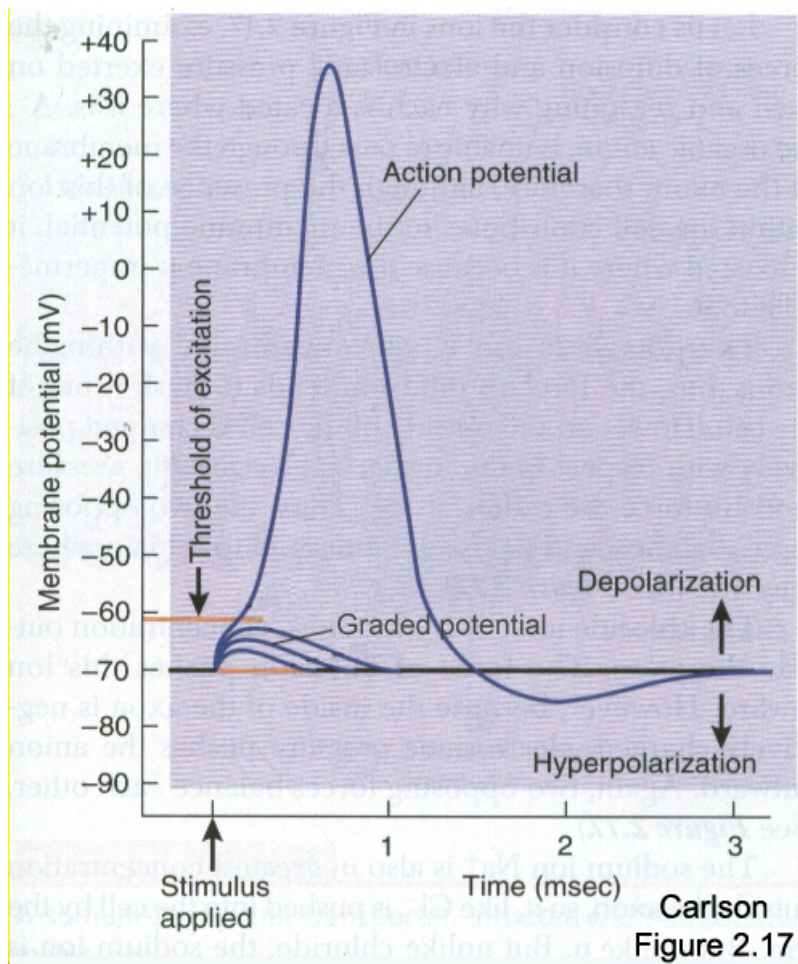


Figure 8: An action potential along with some subthreshold responses

Hodgkin and **Andrew Huxley** used the [squid giant axon](#) as a model system. This is a large axon (up to 1 mm in diameter) that controls part of the squid's water jet propulsion system. Because it is large, it is fairly easy to work with.

The technique that Hodgkin-Huxley used to determine Prob[channel open] is the **voltage clamp**. This acts like a thermostat, injecting the right amount of current to hold the potential at any value of V desired. The injected current is the negative of the current generated by the axon at this voltage. If all currents other than, say, K^+ current, are blocked pharmacologically, then

$$I_{cmp} = -g(V_{cmp})(V_{cmp} - V_K) \quad (23)$$

so that

$$g(V_{cmp}) = \frac{-I_{cmp}}{V_{cmp} - V_K} \quad (24)$$

This can be done for a range of clamping voltages to obtain the $g(V)$ function. The \bar{g} parameter is just $g(V)$ at a high (saturating) voltage. Then

$$\text{Prob[channel open]} = g(V)/\bar{g} \quad (25)$$

Using this approach, H-H found that the best fit is

$$\text{Prob[channel open]} = n_\infty^4(V) \quad (26)$$

where $n_\infty(V)$ is a *sigmoid function*:

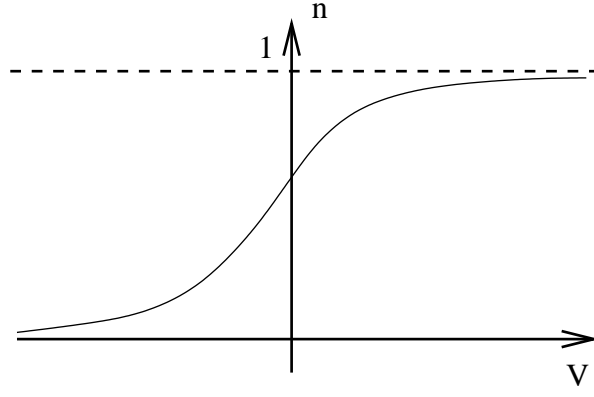


Figure 9: Sigmoidal n_∞ function.

The equation for this is

$$n_\infty(V) = 0.5[1 + \tanh(\frac{V - V_1}{s_1})] \quad (27)$$

where V_1 and $s_1 > 0$ are parameters. By raising n_∞ to the fourth power, the curve is sharpened:

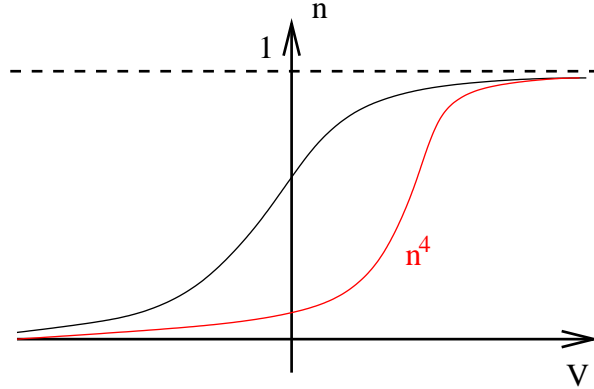


Figure 10: Curve is sharpened by raising n_∞ to an integer power.

This is a steady state description of the channel open probability, but this probability (or channel open fraction) changes over time as it approaches its steady state. Thus,

$$\boxed{\text{Prob}[\text{potassium channel open}] = n^4} \quad (28)$$

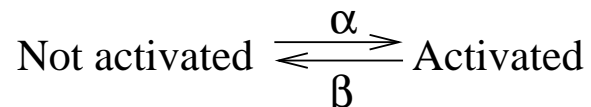
where n is described by a *differential equation*. This variable, which satisfies $n \in [0, 1]$, is called an **activation variable**. Then,

$$g_K = \bar{g}_K n^4 \quad (29)$$

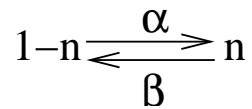
is the time-dependent conductance of the K^+ current. Finally, the K^+ current is

$$\boxed{I_K = \bar{g}_K n^4 (V - V_K)} \quad (30)$$

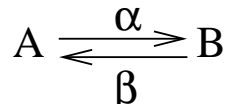
What is n physically? H-H thought of the K^+ channel as composed of 4 independent gates, each of which must be open for the channel to be open. Then n represents the probability that one of the gates is open. This is not an accurate description (as we know today), but intuitively it is very helpful. With this description, we can treat each gate as a 2-state **Markov process**. That is, its opening/closing is a probabilistic event and the transition probability depends only on the current state of the system (open or closed). This process can be depicted using a **reaction scheme**:



where “Activated” has probability of n . What is probability of “Not activated”? $1 - n$. Thus, we can write



We can now use the **Law of Mass Action** to convert the reaction scheme into a differential equation. In general, suppose that we have the following reaction scheme:



By the Law of Mass Action, the rates of change of the concentrations of A and B are *linearly* related to the concentrations of A and B as follows:

$$\frac{dA}{dt} = \beta B - \alpha A \quad (31)$$

$$\frac{dB}{dt} = \alpha A - \beta B \quad (32)$$

Thus, for our activation gate,

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (33)$$

and we simply calculate the fraction of deactivated gates as $1 - n$. The key to the dynamics of this gate is that the transition rates are V -dependent: α_n is an increasing function of V and β_n is a decreasing function of V . Thus, when V is depolarized, the net effect is that the activation variable n increases (so K^+ channels open).

At steady state, the probability that a K^+ gate is open is given by the

equilibrium function:

$$\boxed{n_{\infty}(V) = \frac{\alpha_n}{\alpha_n + \beta_n}} . \quad (34)$$

Since α_n and β_n both depend on V , so too does n_{∞} . The time required to move to the new steady state is determined by the **time constant** τ_n , which is also V -dependent. The formula for this can be found by rewriting Eq. 33 as

$$\boxed{\frac{dn}{dt} = \frac{n_{\infty}(V) - n}{\tau_n(V)}} . \quad (35)$$

and solving for $\tau_n(V)$. This yields

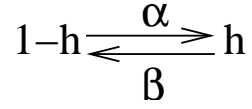
$$\boxed{\tau_n(V) = \frac{1}{\alpha_n + \beta_n}} . \quad (36)$$

The n ODE written in Eq. 35 reveals more about the dynamics of n than does Eq. 33. The voltage clamp technique was used to compute $n_{\infty}(V)$ (Eq. 27) and $\tau_n(V)$. One can then equate the measurements with the formulas above to obtain $\alpha_n(V)$ and $\beta_n(V)$.

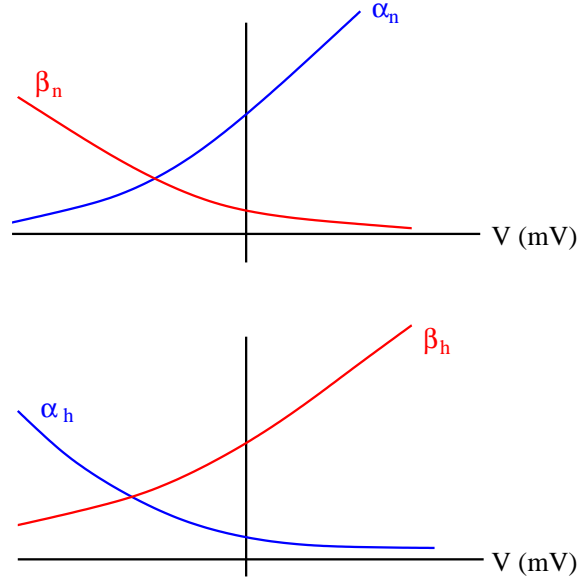
The Na^+ channel is more complicated, since now there is an **inactivation gate** as well as activation gates. This gate is the opposite of an activation gate, it closes when V is depolarized. Let

$$h = \text{Prob}[\text{inactivation gate open}] . \quad (37)$$

Then the reaction scheme is



Note that the transition rates for h , α_h and β_h , are the opposite of those of an activation gate. Here α_h is a decreasing function of V while β_h is an increasing function.



There is also an activation gate, denoted by m , which is qualitatively similar to n :

$$m = \text{Prob}[\text{activation gate open}] \quad . \quad (38)$$

We can use the Law of Mass Action to write ODEs for m and h ,

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \quad (39)$$

$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)} \quad (40)$$

where

$$m_{\infty}(V) = \frac{\alpha_m}{\alpha_m + \beta_m} \quad (41)$$

$$h_{\infty}(V) = \frac{\alpha_h}{\alpha_h + \beta_h} \quad (42)$$

and

$$\tau_m(V) = \frac{1}{\alpha_m + \beta_m} \quad (43)$$

$$\tau_h(V) = \frac{1}{\alpha_h + \beta_h} . \quad (44)$$

According to the H-H data fitting,

$$g_{Na} = \bar{g}_{Na} m^3 h \quad (45)$$

which intuitively means that 3 activation gates and 1 inactivation gate must be open for the channel to be open. Then,

$$\boxed{I_{Na} = \bar{g}_{Na} m^3 h (V - V_{Na})} \quad (46)$$

is the Na^+ current.

An important property of the two types of gate in the Na^+ current is that the activation time constant is smaller than the inactivation time constant, so that when the membrane is depolarized the activation gates open first. This turns on the Na^+ current, causing voltage to rise further. It is only later that the inactivation gates close. So the current provides rapid **positive feedback** followed by a delayed **negative feedback**. The K^+ current provides only delayed **negative feedback**.

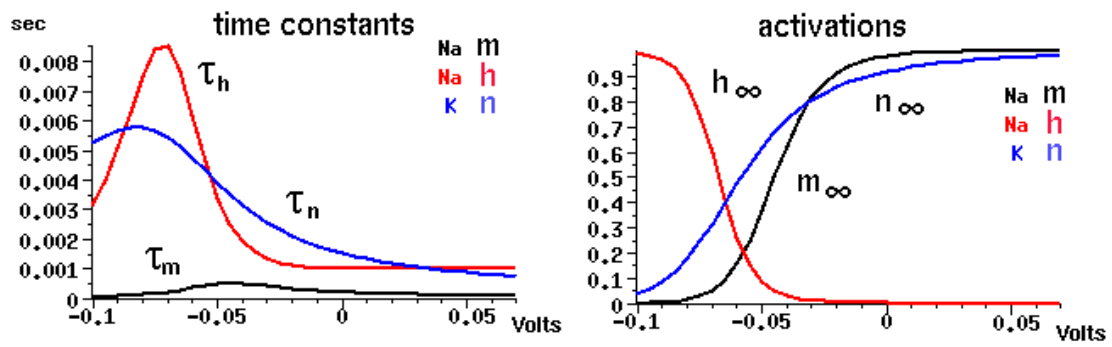


Figure 11: Infinity and time constant functions. The “volts” should be converted to “millivolts” and “sec” converted to “msec”.

The last current in the Hodgkin-Huxley model is a constant-conductance **leak current**. This is due largely to non-specific flow of ions across the membrane through various channel types. The important feature here is that the conductance is not a function of V . The leak Nernst potential is usually about $V_L = -40$ mV, so the current is mildly **depolarizing**. Then

$$\boxed{I_L = g_L(V - V_L)} \quad (47)$$

Combining previous equations, we get the full **Hodgkin-Huxley model**:

$$\frac{dV}{dt} = -[\bar{g}_{Na}m^3h(V - V_{Na}) + \bar{g}_Kn^4(V - V_K) + g_L(V - V_L)]/C \quad (48)$$

$$\frac{dn}{dt} = [n_\infty(V) - n]/\tau_n(V) \quad (49)$$

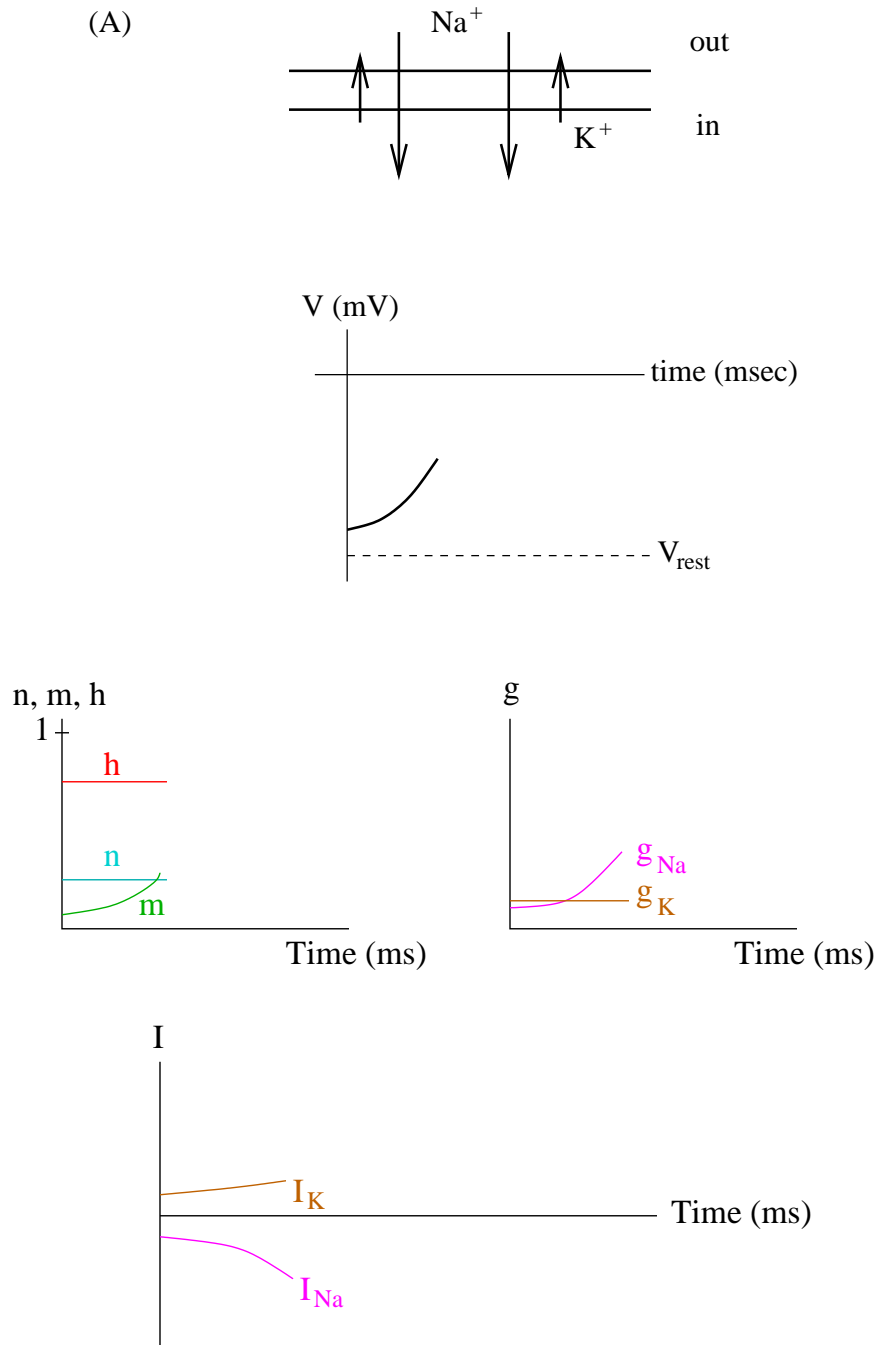
$$\frac{dm}{dt} = [m_\infty(V) - m]/\tau_m(V) \quad (50)$$

$$\frac{dh}{dt} = [h_\infty(V) - h]/\tau_h(V) \quad (51)$$

The Hodgkin-Huxley model was developed to explain how action potentials are produced. The biophysical concept, implemented mathematically in the model, is described below.

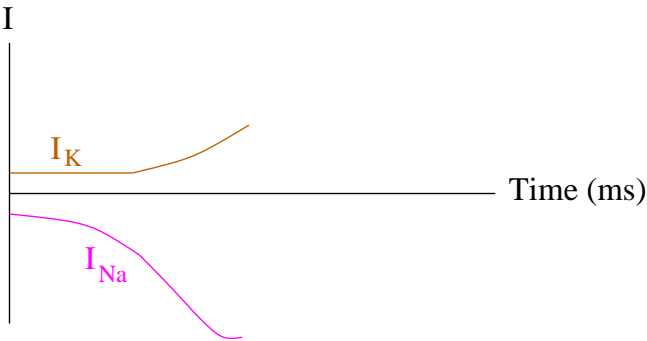
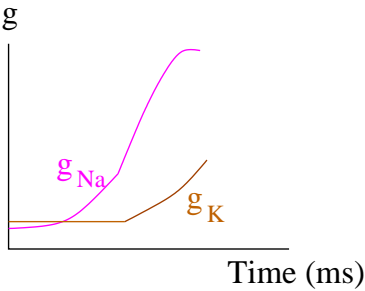
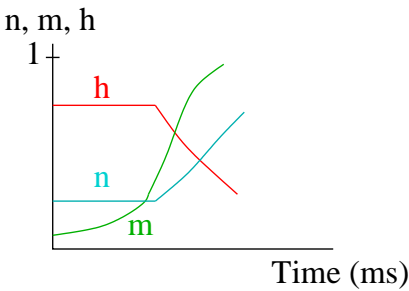
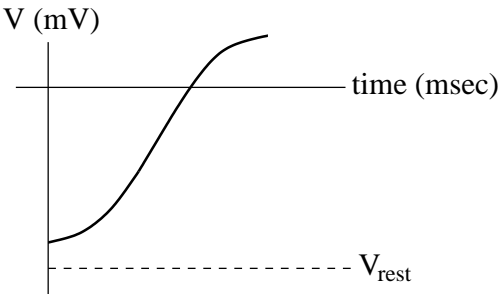
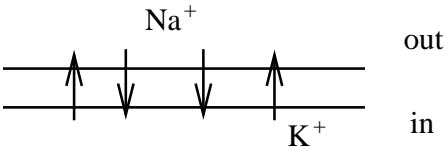
Initially V is **polarized** at a resting potential of ≈ -60 mV. If input from the soma increases V sufficiently, to about -40 mV, then some of the Na^+ channels will open. This produces a negative or inward current (**A**), causing V to increase further. This increase in V is called **depolarization**. The depolarization induces more Na^+ channels to open, providing **positive feedback** and depolarizing the cell even more. Eventually the Na^+ channels

start to inactivate, slowing the rise in V (**B**).

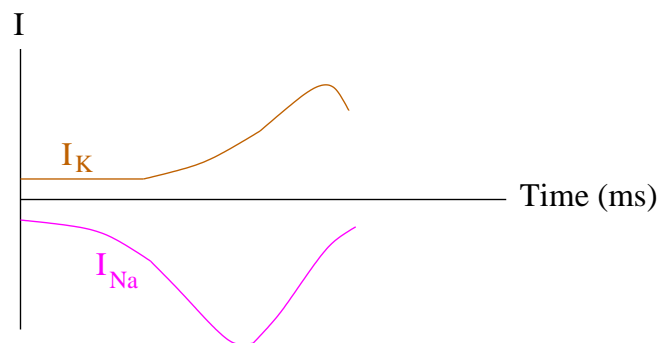
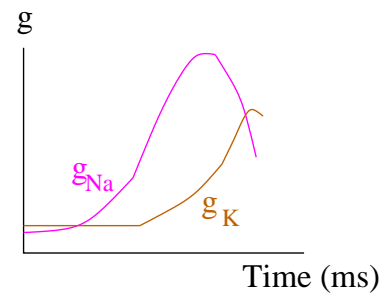
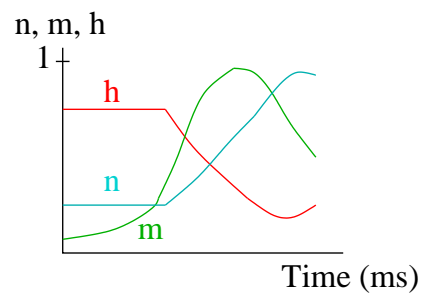
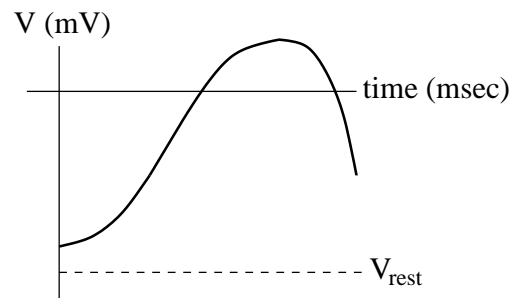
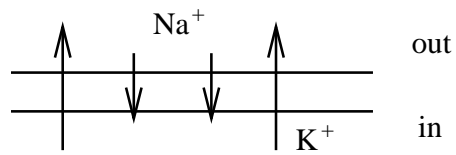


At about the same time, K^+ channels start to open. The delay in opening of these channels is due to the relatively large time constant ($\tau_n > \tau_m$). The resulting I_K current acts to **repolarize** the membrane (since V_K is below V_{rest}). Thus, V begins to decline toward V_{rest} (**C**). The inactivation

(B)



(C)

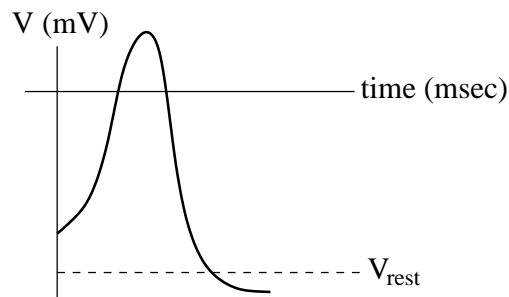
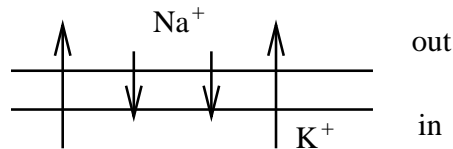


of I_{Na} and the activation of I_K together provide **delayed negative feedback** to the system.

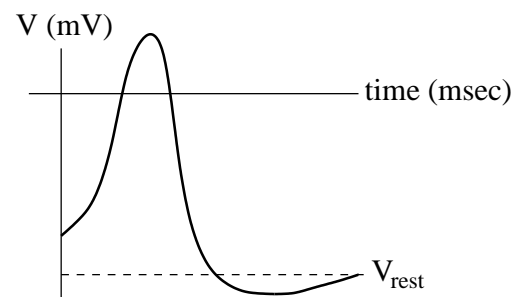
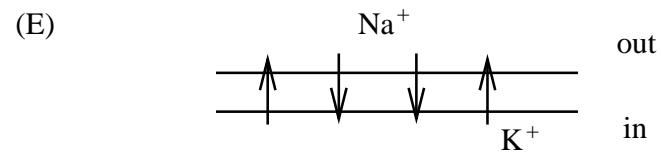
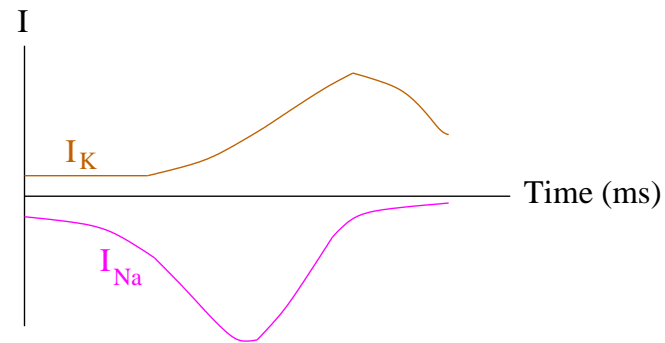
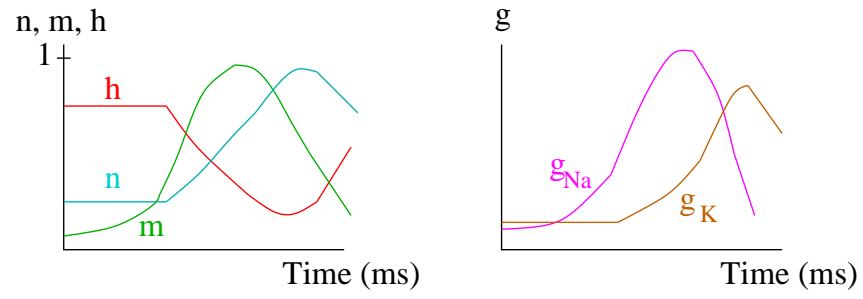
Even as V approaches V_{rest} there is net outward ion flux, since the K^+ channels are slow to close. This drives V below the resting potential. The membrane is now **hyperpolarized (D)**. Thus, I_K is called a **hyperpolarizing current**, while I_{Na} is called a **depolarizing current**.

Finally, the K^+ channels **deactivate**, reducing I_K and returning the system to rest **(E)**.

(D)



The key features of the action potential are: (1) V -dependent conductances, and (2) fast positive feedback (m) and delayed negative feedback (n and h).



Response to Input

Input to nerve cells comes primarily through synaptic connections that link neurons together. At these **synapses** the electrical signal (electrical impulses) is transduced to a chemical signal through the release or **exocytosis** of neurotransmitter molecules. The neurotransmitter diffuses across the space between presynaptic and postsynaptic neurons, called the **synaptic cleft**, and binds to receptors on the postsynaptic membrane. This induces the opening of ion channels, which could either be the postsynaptic receptor itself or other channels activated by the receptor, allowing ionic current to flow. Thus, the input is ultimately an ionic current.

In the lab one can mimic this by applying current to the cell directly with an electrode. In terms of the equations, one simply modifies the voltage equation by adding a term for the applied current, I_{ap} :

$$\frac{dV}{dt} = -(I_{Na} + I_K + I_L - I_{ap})/C \quad (52)$$

where the minus sign is used for I_{ap} so that a positive applied current results in depolarization.

Threshold effect: The H-H model exhibits a threshold response to applied current. If a square pulse of current is applied and the magnitude and duration of the pulse is too small, then the system will have a passive or subthreshold response. If the input pulse is sufficiently large, then the

system will produce an impulse. So the output is all-or-none (Fig. 12).

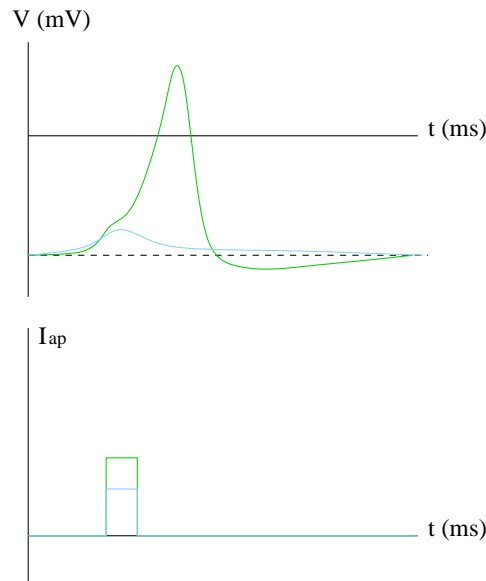


Figure 12: The H-H model produces a passive or subthreshold response if the current pulse is small, or an impulse if the pulse is large enough.

Firing rate and gain function: If applied current is maintained continuously, then the system may either produce a single impulse and then come to rest at a more depolarized voltage, or it may spike continuously if I_{ap} is sufficiently large (in this case, $I_{ap} > 6 \mu\text{A}/\text{cm}^2$). In the H-H model this spike train will be periodic, with some period T . The **firing rate** is then $\nu = \frac{1}{T}$. The **gain function** is ν as a function of I_{ap} . For the H-H model, the spike frequency increases as the applied current increases (Fig. 13). This is not the case in all neurons, or all neuron models.

Notice that there is a discontinuity at $I_{ap} = 6 \mu\text{A}/\text{cm}^2$, where the system goes from a rest state to a continuous spiking state with frequency near 50 Hz. This is an example of a **type II oscillator** since the fre-

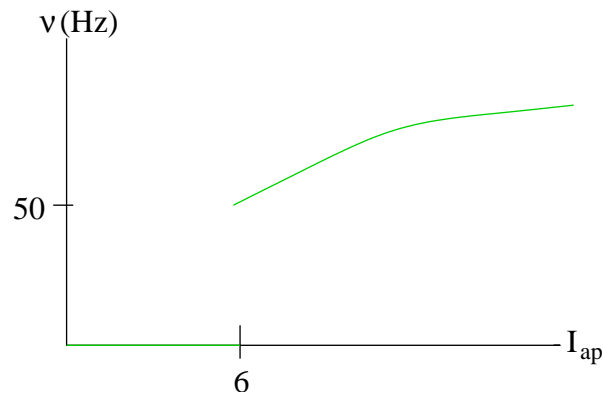


Figure 13: Gain function for the H-H model.

quency did not approach 0. We return to this later.

Refractoriness: If a short superthreshold current pulse is applied to the system, how quickly can a second pulse be applied and still produce an impulse? The H-H model exhibits a **refractory period** during which it is harder for a current pulse to evoke an impulse. That is, during this period the magnitude or duration of the current pulse must be greater for the system to reach spike threshold (Fig. 14). This limits the frequency at which the system can fire action potentials. It is due to the time required for the n and h variables to return to their resting values.

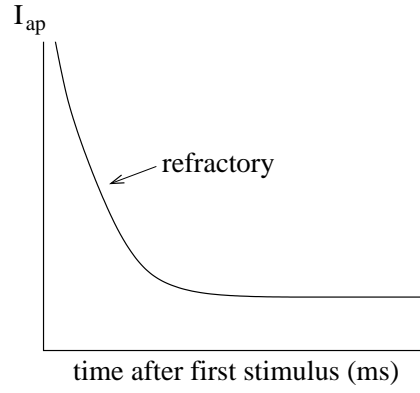


Figure 14: Magnitude of the I_{ap} pulse required to bring the system to threshold following an initial suprathreshold stimulus.

Traveling Pulse

The H-H model describes the electrical activity of a **space clamped** axon, where a wire is run through the center of the axon to maintain uniform potential. Physiologically, an impulse is typically generated in the soma or the **axon hillock** (initial portion of the axon) and travels down the axon by exciting adjacent portions of membrane. It travels down the axon without dissipation, unlike water waves that attenuate as they travel. This is called a **traveling pulse** or a **soliton** and is described mathematically by the **Hodgkin-Huxley cable equation**:

$$\boxed{C \frac{\partial V}{\partial t} = \frac{a}{2R} \frac{\partial^2 V}{\partial x^2} - [I_{Na} + I_K + I_L - I_{ap}]}$$
 (53)

where a is the axon radius and R is the lateral resistivity. There are also the usual ODEs for the activation and inactivation variables. This system of partial and ordinary DEs could be solved numerically using a

finite difference method. Hodgkin and Huxley solved the equations using a shooting method and found that the pulse travels at the same speed as an actual impulse travels in the squid axon, providing more evidence that the mechanism for impulse generation is correct.

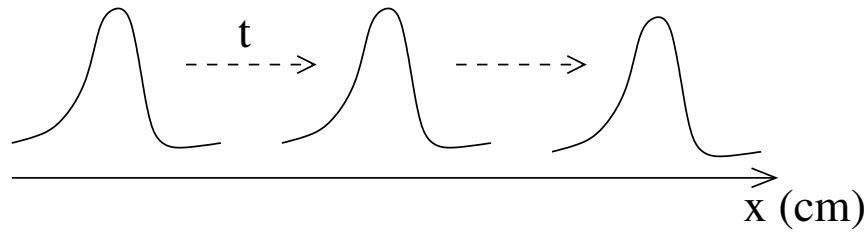


Figure 15: Traveling pulse from the H-H cable equation.

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**. These planar systems are much simpler to analyze since they allow for a phase plane analysis. The first planar model of an excitable system was developed in the early 1960s by Richard FitzHugh and Nagumo, working independently.

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:

$$\frac{dv}{dt} = v - v^3 - w + I_{ap} \tag{54}$$

$$\frac{dw}{dt} = (v - a - bw)/\tau_w \tag{55}$$

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:

$$w = v - v^3 + I_{ap} \quad (56)$$

which is a cubic function in v .

w -nullcline:

$$w = (v - a)/b \quad (57)$$

which is a linear function in v .

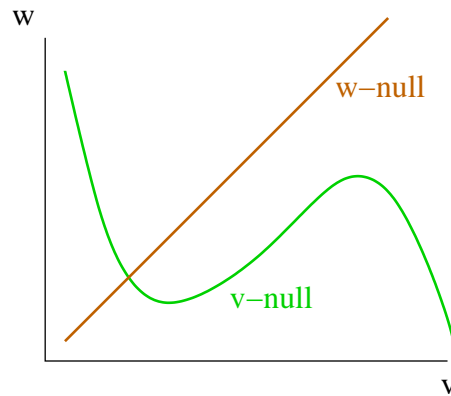


Figure 16: Nullclines of the FitzHugh-Nagumo model.

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:

$$\frac{dw}{dt} = [w_\infty(V) - w] / \tau_w(V) . \quad (58)$$

- 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

$$\frac{dV}{dt} = -(I_{Ca} + I_K + I_L - I_{ap}) / C. \quad (59)$$

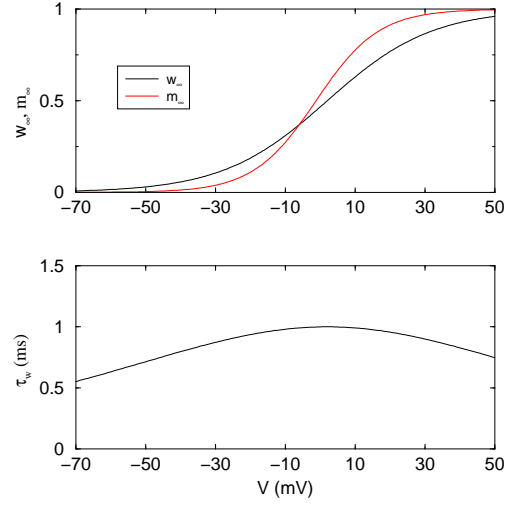


Figure 17: Calcium and potassium equilibrium and time constant functions

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

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

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

V -nullcline:

$$w = \frac{I_{ap} - \bar{g}_{Ca}m_\infty(V)(V - V_{Ca}) - g_L(V - V_L)}{g_K(V - V_K)} \quad (60)$$

w -nullcline:

$$w = w_{\infty}(V) \quad (61)$$

$$= 0.5[1 + \tanh(\frac{V - V_3}{V_4})] \quad (62)$$

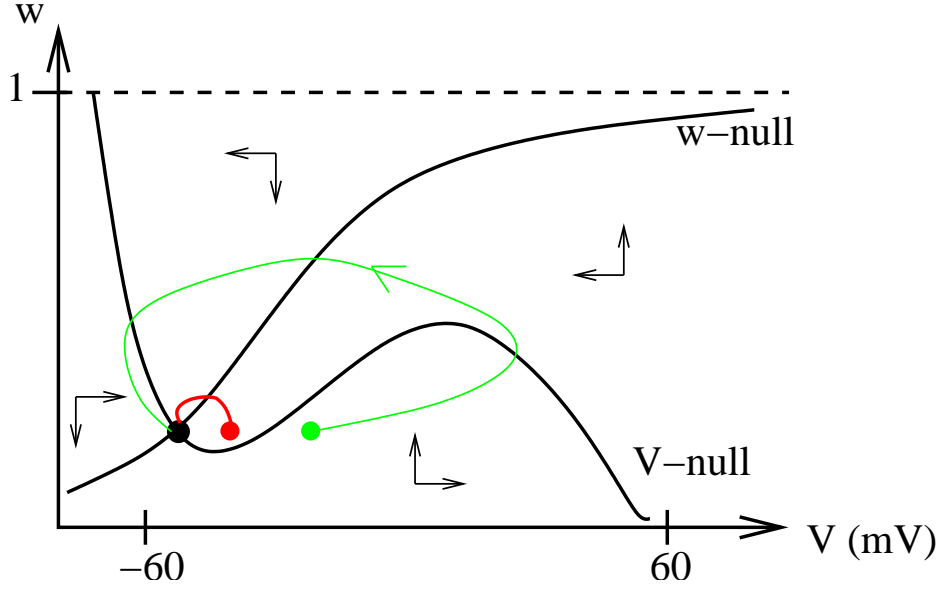


Figure 18: Phase plane analysis of the Morris-Lecar model. Red: subthreshold response, Green: impulse. $I_{ap} = 0$.

The middle branch of the cubic-shaped V -nullcline is the impulse **threshold**. Figure 18 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. 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:

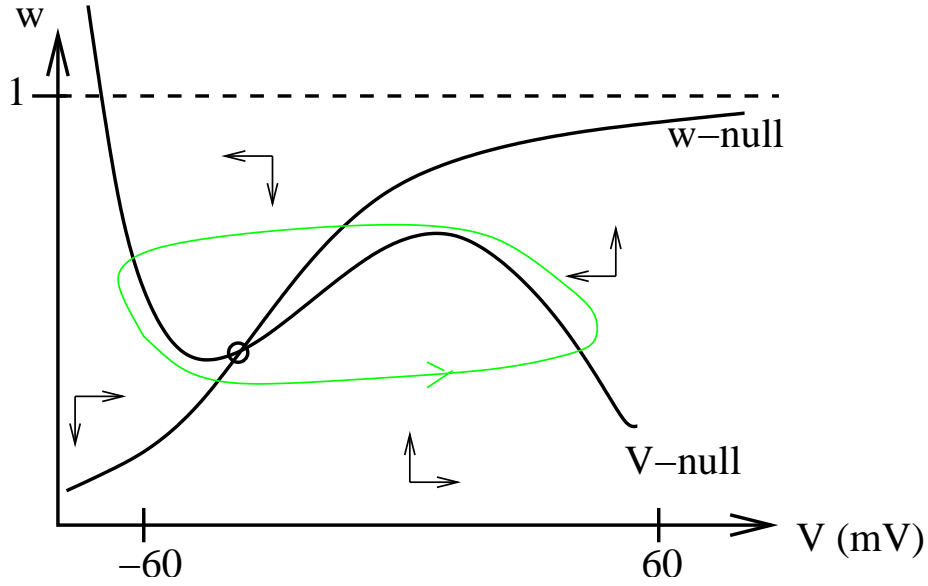


Figure 19: Phase plane analysis of the Morris-Lecar model. Green: Limit cycle. $I_{ap} = 100$ pA.

Why does stability change on the middle branch? Rewrite

$$\frac{dV}{dt} = f(V, w) \quad (63)$$

$$\frac{dw}{dt} = g(V, w) \quad (64)$$

When there is an intersection on the left branch $\frac{\partial f}{\partial V} < 0$ and $\frac{\partial f}{\partial w} < 0$. We see this as follows:

Moving from left to right on the dashed blue line through the steady

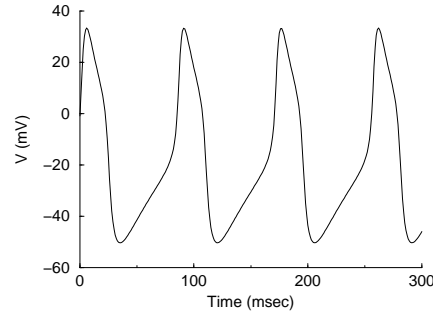


Figure 20: A periodic train of action potentials, when $I_{ap} = 100$ pA.

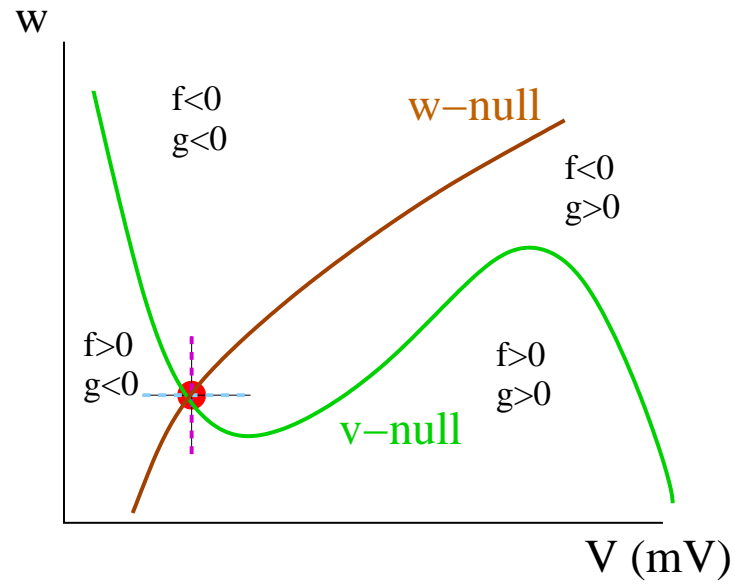


Figure 21: Detecting stability of the Morris-Lecar model.

state, $f > 0 \rightarrow f < 0$, so $\frac{\partial f}{\partial V} < 0$. Moving from down to up on the dashed magenta line, $f > 0 \rightarrow f < 0$, so $\frac{\partial f}{\partial w} < 0$. Similarly, $\frac{\partial g}{\partial V} > 0$ and $\frac{\partial g}{\partial w} < 0$.

As we know, linear stability of the steady state depends on eigenvalues of the **Jacobian matrix** J , where

$$\mathbf{J} = \begin{pmatrix} f_V & f_w \\ g_V & g_w \end{pmatrix} \quad (65)$$

Evaluated at the steady state,

$$\mathbf{J} = \begin{pmatrix} - & - \\ + & - \end{pmatrix} \quad (66)$$

and the trace of the matrix is $(-) + (-) < 0$, so the sum of the eigenvalues is negative. In addition, the determinant is positive $((-)(-) - (-)(+) > 0)$, so the product of the eigenvalues is positive (they have the same sign). Thus, the eigenvalues are both negative and the steady state is stable.

When the intersection is on the middle branch,

$$\mathbf{J} = \begin{pmatrix} + & - \\ + & - \end{pmatrix} \quad (67)$$

so the trace is $(+) + (-)$ which could be positive or negative. Thus, it is possible for the eigenvalues to have positive real part, and the steady state to become unstable.

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,

$$\mathbf{J} = \begin{pmatrix} - & - \\ + & - \end{pmatrix} \quad (68)$$

and the situation is similar to the left branch intersection, so the equilibrium is **stable**. Because this stable equilibrium is at a depolarized V we call this **depolarization block**. The cell is so depolarized that it can't spike.

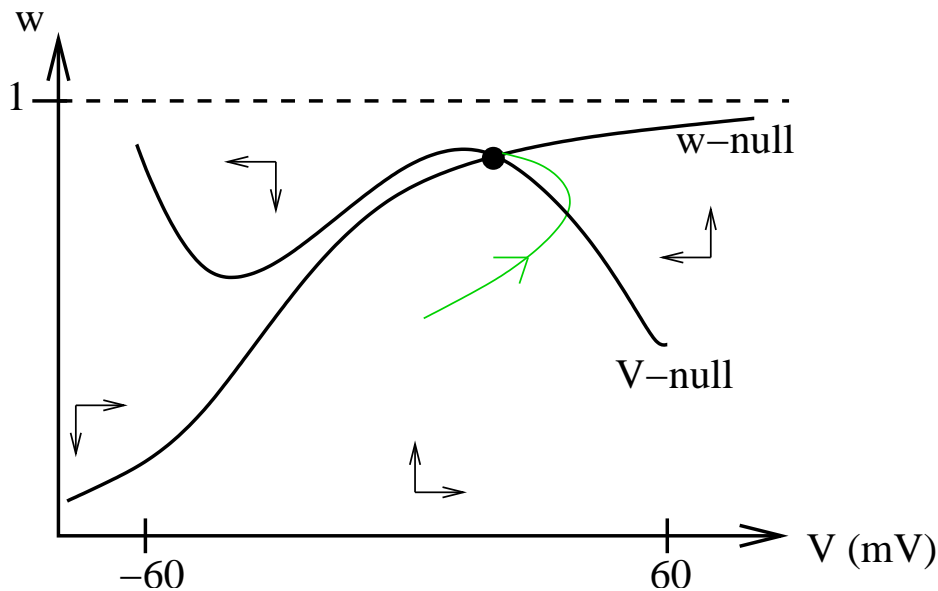


Figure 22: Depolarized resting state, when $I_{ap} = 250$ pA.

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} .

Notice that there are regions of **bistability** between the SNPs and HBs. For values of I_{ap} in these regions the system can either tend to a steady state or a limit cycle, depending on the initial conditions. In terms of the phase plane, the bistable interval $[SNP_1, HB_1]$ corresponds to the nullcline intersection between the lower knee and the occurrence of the Hopf bifurcation. That is, the HB occurs some distance away from the knee, and if the intersection occurs in this interval the system will be bistable. (Similarly, the interval $[SNP_2, HB_2]$ corresponds to nullcline intersection between a second Hopf bifurcation further up the middle branch and the upper knee.)

In addition to a stable steady state and stable limit cycle there is an unstable limit cycle (Fig. 24). Initial conditions starting inside the unstable limit cycle tend

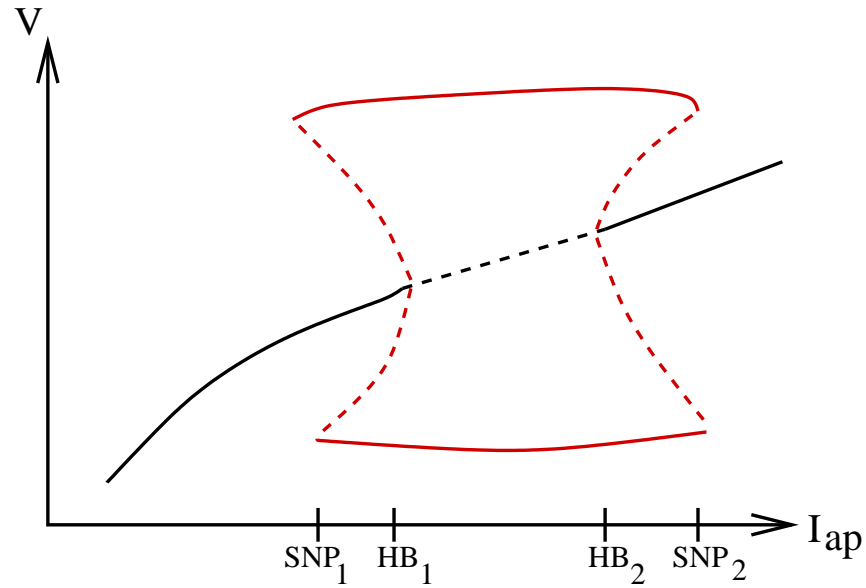


Figure 23: Morris-Lecar bifurcation diagram. Black: stationary branch, Red: periodic branch. SNP=saddle-node of periodics bifurcation, HB=Hopf bifurcation.

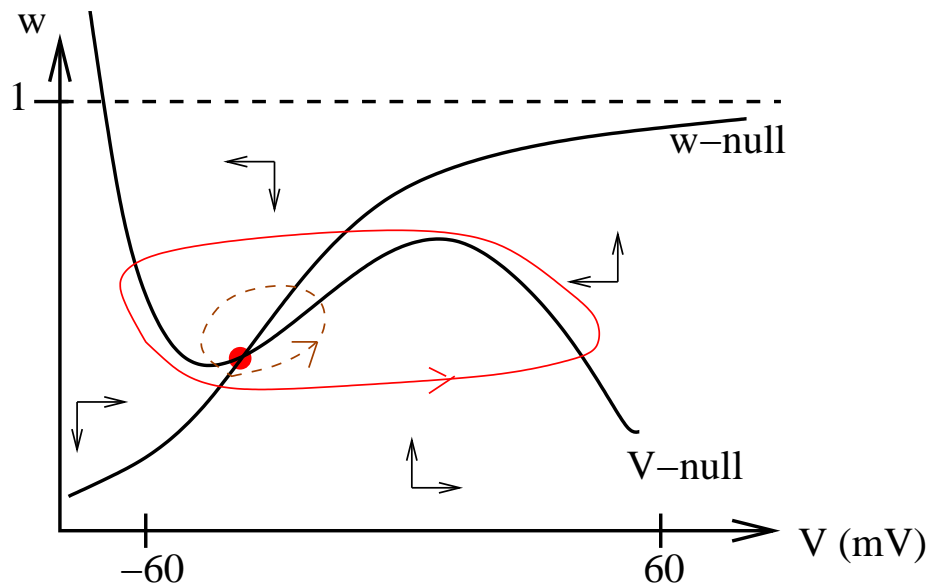


Figure 24: Morris-Lecar phase plane illustrating bistability. red: stable structures, brown: unstable limit cycle acts as separatrix

to the stable steady state. Initial conditions starting outside the unstable limit cycle tend to the stable limit cycle. Thus, the unstable limit cycle is called a **separatrix**, and the points inside the separatrix form the **basin of attraction** of the steady state, while those outside the separatrix form the basin of attraction of the stable limit cycle.

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

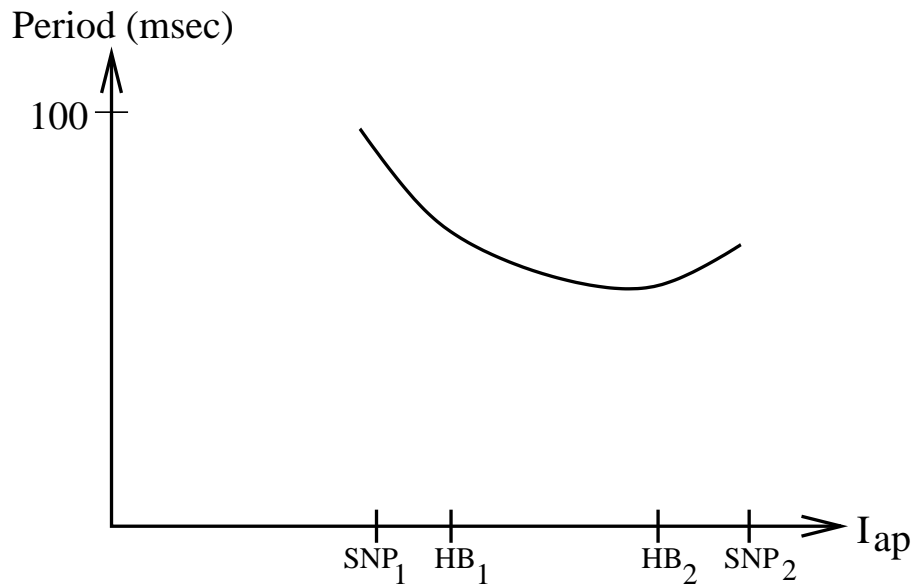


Figure 25: Morris-Lecar bifurcation diagram. Period of stable oscillatory solution

This is an example of a **Type 2 Oscillator**, since the period is bounded (Fig. 25). For a **Type 1 Oscillator** the period is unbounded as I_{ap} approaches a critical value (Fig. 26), called a **homoclinic bifurcation**.

At a homoclinic bifurcation, the limit cycle connects with a saddle point (Fig. 27). In this case, one branch of the saddle's unstable manifold connects to a branch of its stable manifold. From this diagram, we can see immediately why the period of the homoclinic orbit is infinite.

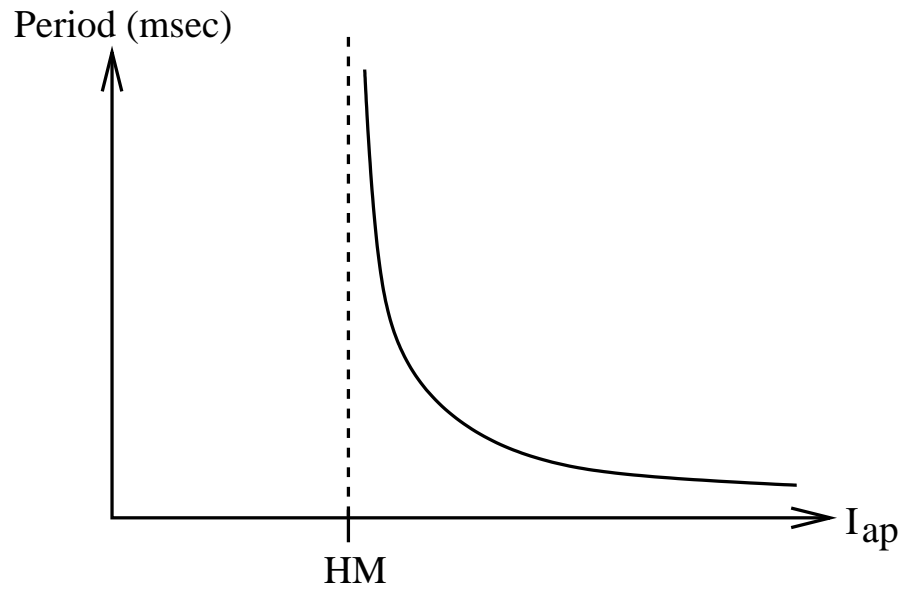


Figure 26: Period bifurcation diagram for a type 1 oscillator. Period approaches infinity at the homoclinic bifurcation (HM).

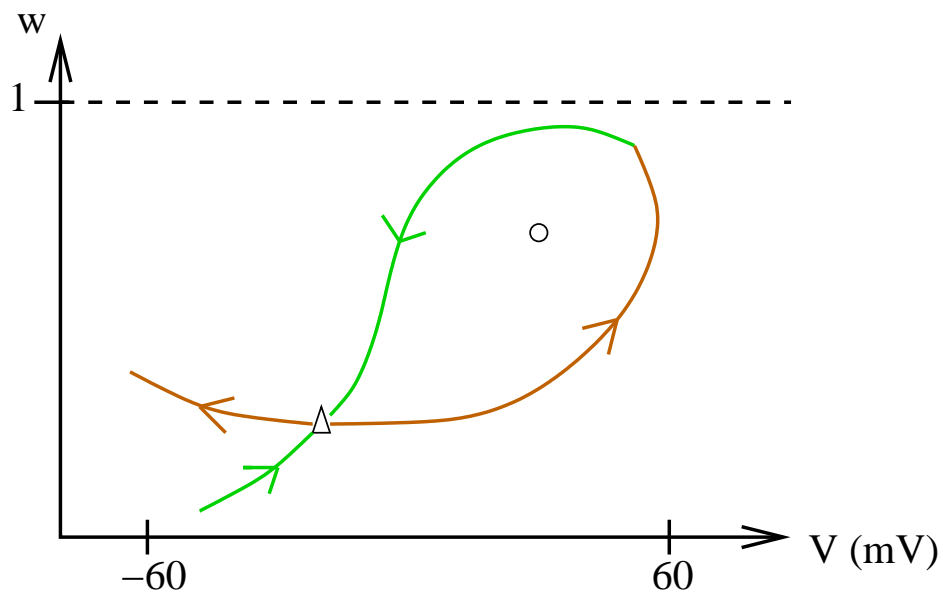


Figure 27: Homoclinic orbit in the phase plane. (blue) stable manifold, (brown) unstable manifold of the saddle point (triangle). The homoclinic orbit surrounds an unstable spiral (open circle).

A generic amplitude vs. applied current bifurcation diagram for a type 1 oscillator is shown in Fig. 28. Notice that in this case the stationary branch is s-shaped. Why does it need to have this shape? How would the two nullclines intersect when there are three equilibria?

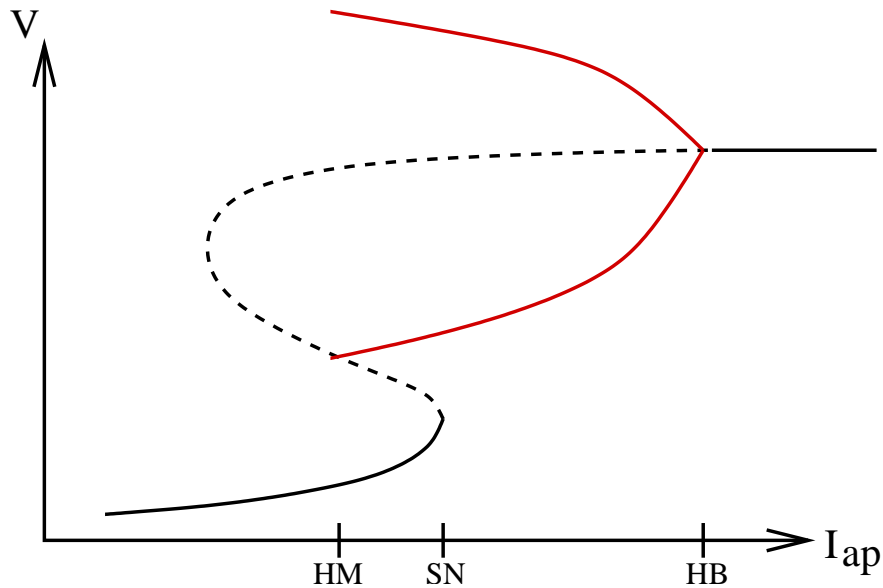


Figure 28: Bifurcation diagram of a type 1 oscillator. (black) stationary branch, (red) periodic branch. HB=supercritical Hopf bifurcation, SN=saddle node bifurcation, HM=homoclinic bifurcation.

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.

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.

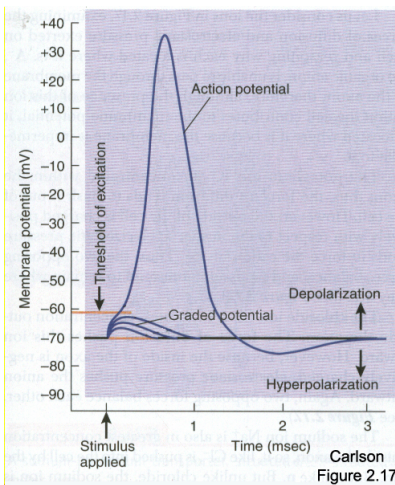


Figure 29: Spike threshold distinguishes sub-threshold from super-threshold responses.

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,

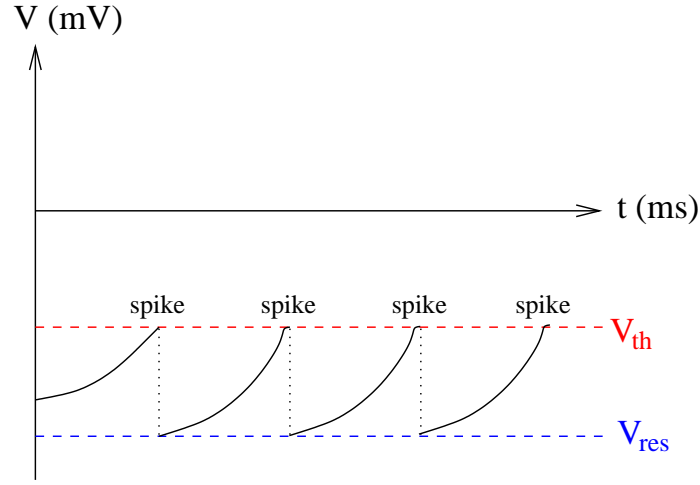


Figure 30: Illustration of time dynamics of an integrate-and-fire model.

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

$$\tau_V \frac{dV}{dt} = V_l - V + I_{ap} \quad (69)$$

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:

$$V(t) = V_l + I_{ap} + [V(0) - V_l - I_{ap}]e^{-t/\tau_V} \quad (70)$$

or

$$V(t) = V_\infty + [V(0) - V_\infty]e^{-t/\tau_V} \quad (71)$$

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} :

$$V_{th} = V_\infty + (V_{res} - V_\infty)e^{-t_{ISI}/\tau_V} \quad (72)$$

solving,

$$\boxed{t_{ISI} = \tau_V \ln \left(\frac{V_\infty - V_{res}}{V_\infty - V_{th}} \right)} . \quad (73)$$

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

$$\frac{V_\infty - V_{res}}{V_\infty - V_{th}} = 1 + z \quad (74)$$

where z is a small number. Thus,

$$z = \frac{V_\infty - V_{res}}{V_\infty - V_{th}} - \frac{V_\infty - V_{th}}{V_\infty - V_{th}} \quad (75)$$

or

$$z = \frac{V_{th} - V_{res}}{V_{\infty} - V_{th}} . \quad (76)$$

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

$$t_{ISI} \approx \tau_V z = \tau_V \left(\frac{V_{th} - V_{res}}{V_{\infty} - V_{th}} \right) \quad (77)$$

when V_{∞} (and I_{ap}) is large.

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

$$\boxed{r \approx \frac{V_{\infty} - V_{th}}{\tau_V(V_{th} - V_{res})} = \frac{V_l + I_{ap} - V_{th}}{\tau_V(V_{th} - V_{res})}} . \quad (78)$$

It is clear from Eq. 78 that the firing rate increases linearly with I_{ap} (when I_{ap} is large). This behavior is observed in some neurons. However, many 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,

$$\tau_V \frac{dV}{dt} = V_l - V - g_a(V - V_K) + I_{ap} \quad (79)$$

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 ,

$$g_a = g_a + \Delta g_a \quad \text{at a spike} \quad (80)$$

and

$$\tau_a \frac{dg_a}{dt} = -g_a \quad \text{between spikes.} \quad (81)$$

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.

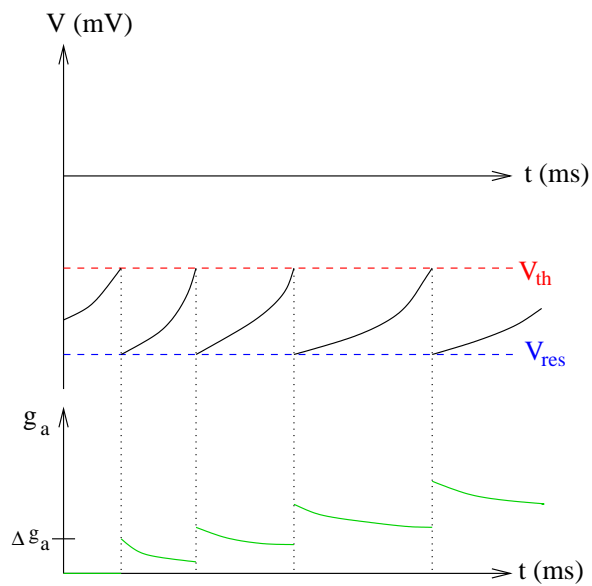


Figure 31: Time dynamics of an integrate-and-fire model with adaptation.

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

The Wilson-Cowan Model

The Wilson-Cowan model, developed in 1972 as model for interacting neural populations, is an example of a **mean field model**. It uses a single variable to describe the fraction of neurons in an excitatory population that are firing at each point in time, and a single variable to describe the fraction of neurons in an inhibitory population that are firing.

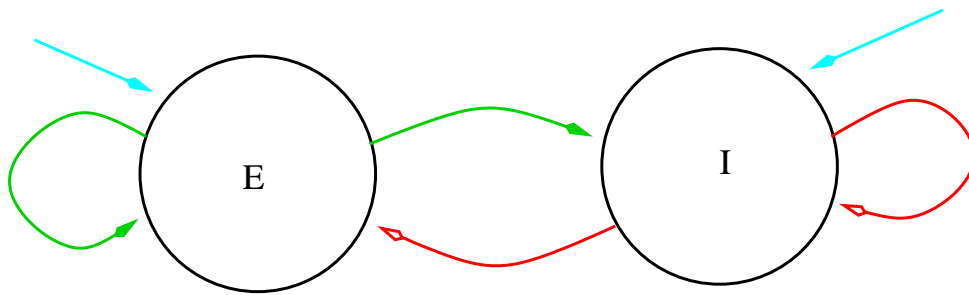


Figure 32: Two neural populations in the Wilson-Cowan model. One (E) is excitatory, the other (I) is inhibitory.

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

$$\frac{dE}{dt} = [-E + f_E]/\tau_E \quad (82)$$

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:

$$f_E = \frac{1}{1 + e^{-x}} \quad (83)$$

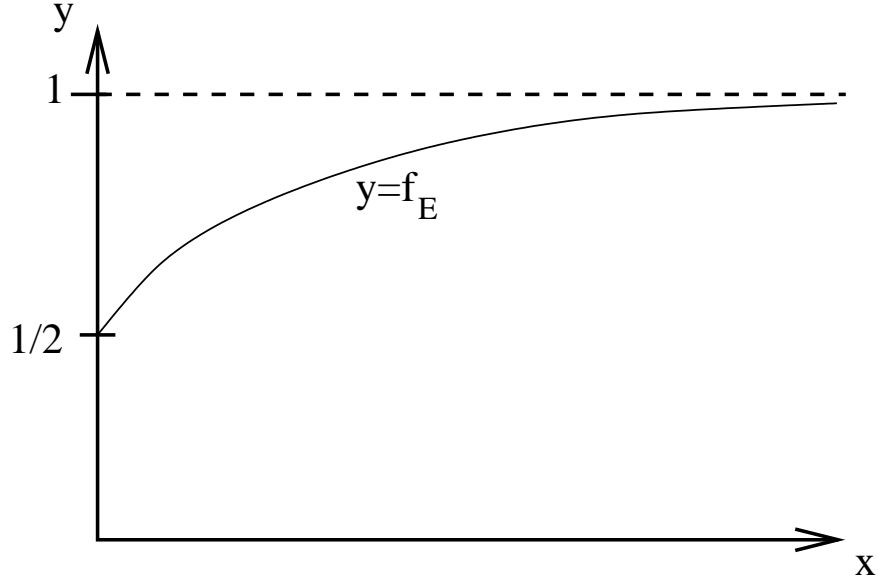


Figure 33: The input function in the Wilson-Cowan model.

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

$$x = aE + p_E \quad . \quad (84)$$

Together,

$$\frac{dE}{dt} = [-E + f_E(aE + p_E)]/\tau_E \quad . \quad (85)$$

This is a 1-dimensional system, with equilibria satisfying

$$E^* = f_E = \frac{1}{1 + e^{-(aE^* + p_E)}} \quad . \quad (86)$$

A nice graphical method to solve this nonlinear algebraic equation is to plot $y = E$ and $y = f_E$ and look for intersections (Fig. 34).

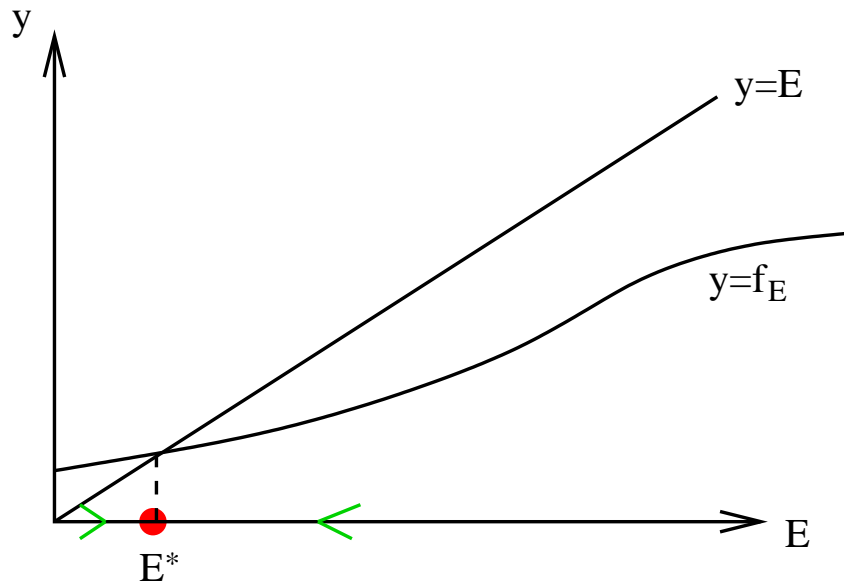


Figure 34: Single steady state when $a = 6$.

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 (Fig. 35). The system is now **bistable**; the outer steady states are stable, the inner one is unstable. The 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.

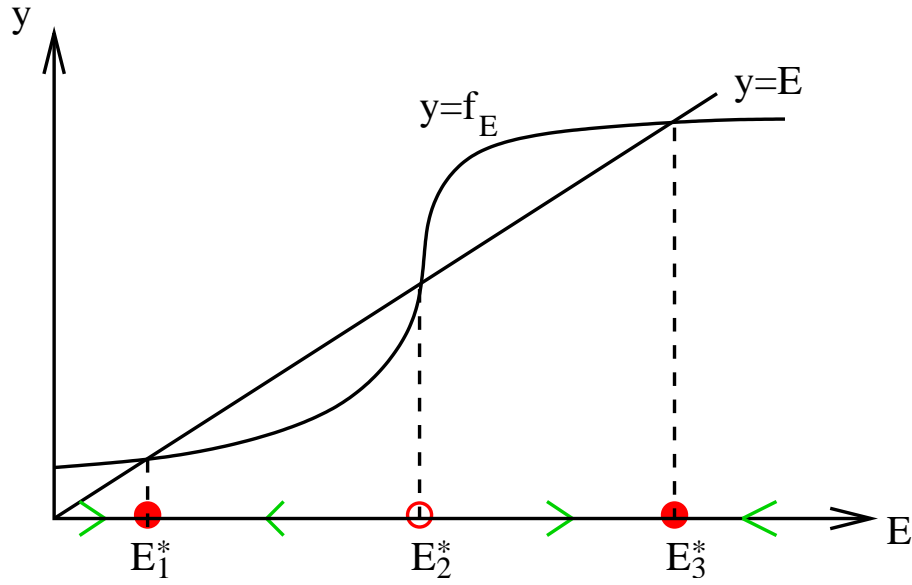


Figure 35: The system is bistable when $a = 10$.

The I neurons provide input to both the E and I neurons, so the equations for the two types are:

$$\frac{dE}{dt} = [-E + f_E(aE - bI + p_E)]/\tau_E \quad (87)$$

$$\frac{dI}{dt} = [-I + f_I(cE - dI + p_I)]/\tau_I \quad (88)$$

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 shown in Fig. 36.

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

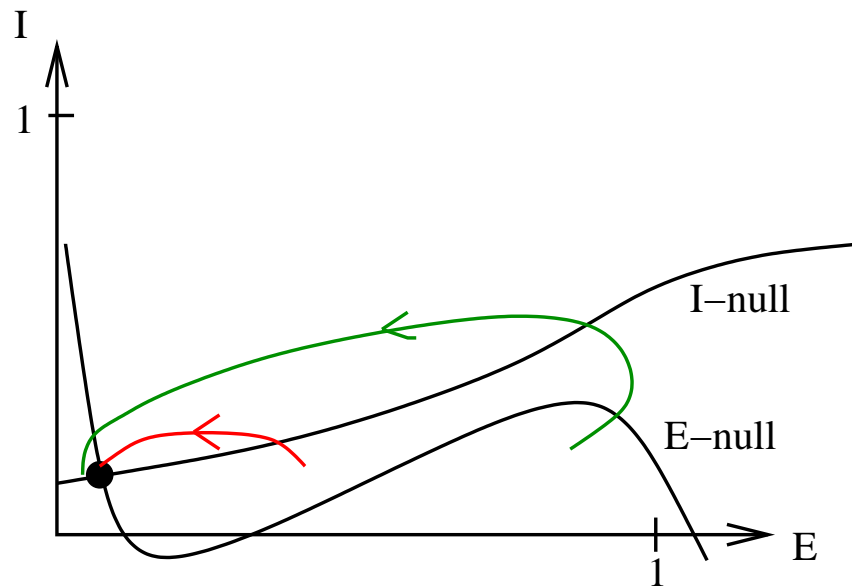


Figure 36: Wilson-Cowan phase portrait, excitable regime ($p_E = -5$).

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:

$$E \iff V$$

$$I \iff w.$$

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.

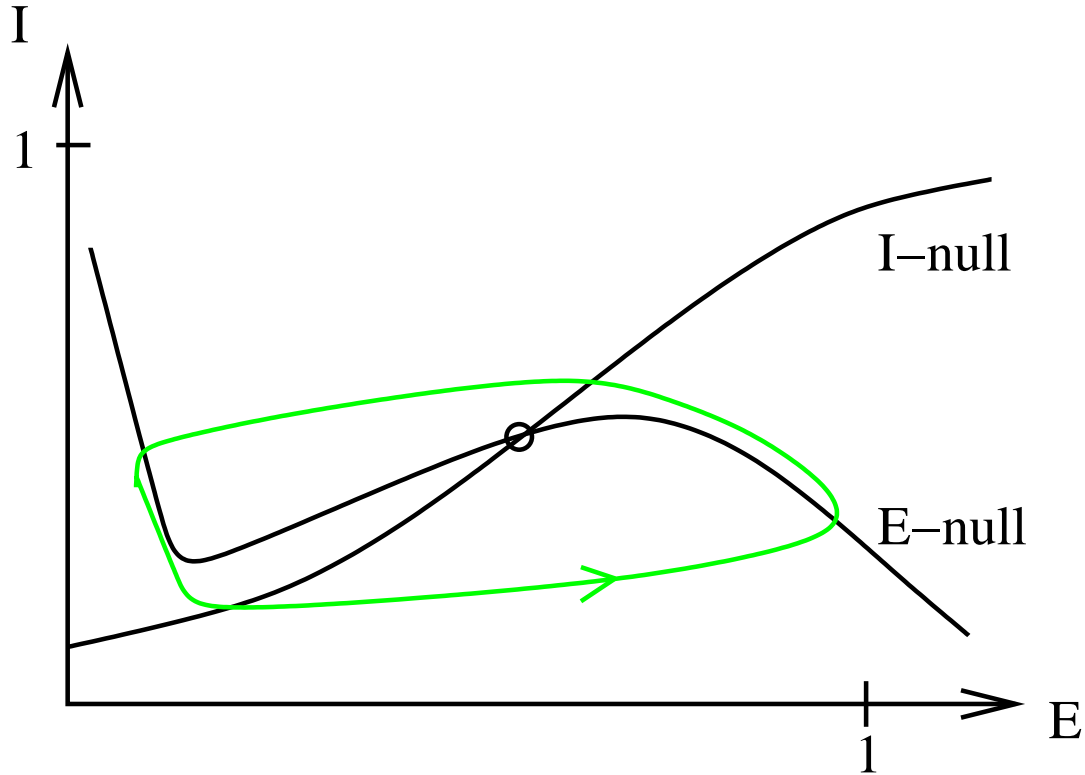


Figure 37: Limit cycle behavior, when $p_E = -1$.

This produces a periodic train of population spikes.

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