Introduction to Neural Computation

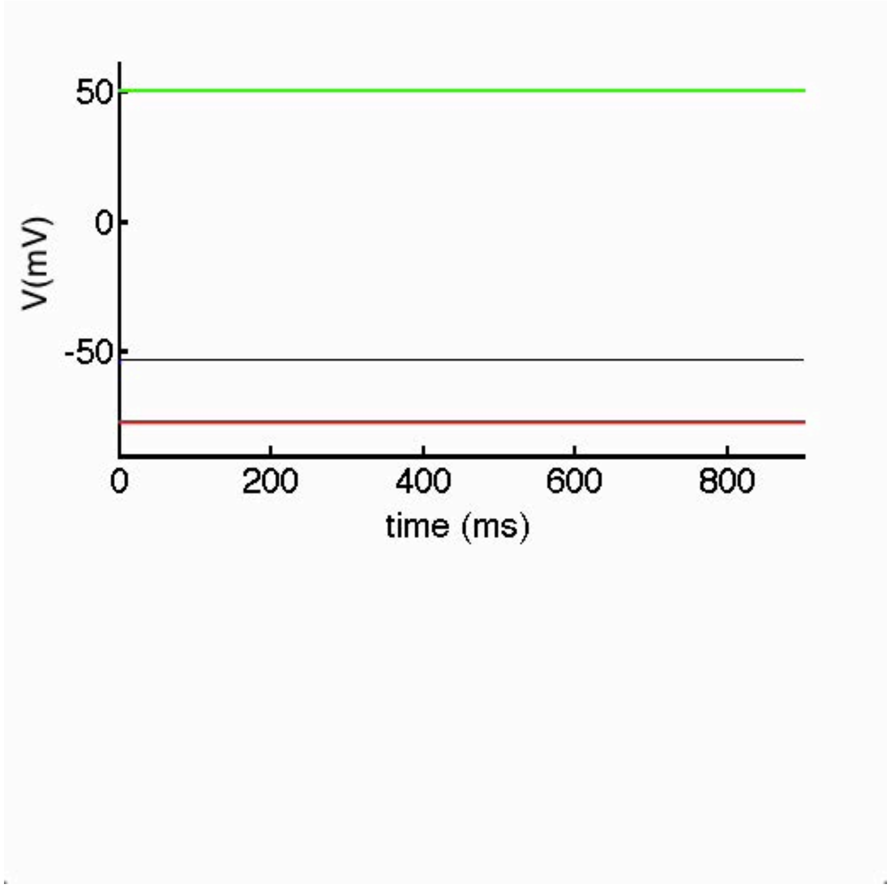
Prof. Michale Fee

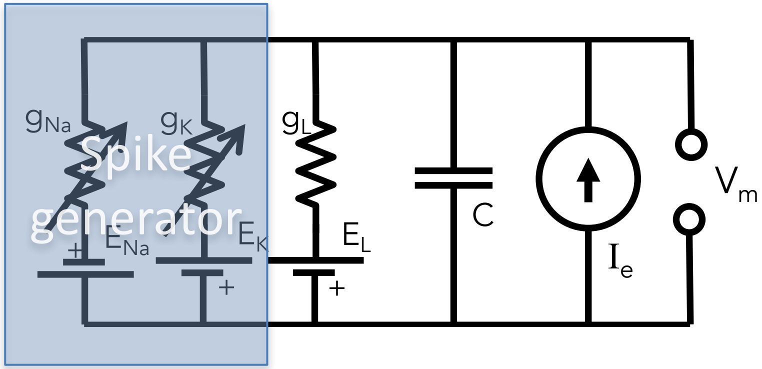
MIT BCS 9.40 — 2018

Lecture 4

Hodgkin-Huxley model of action potential generation

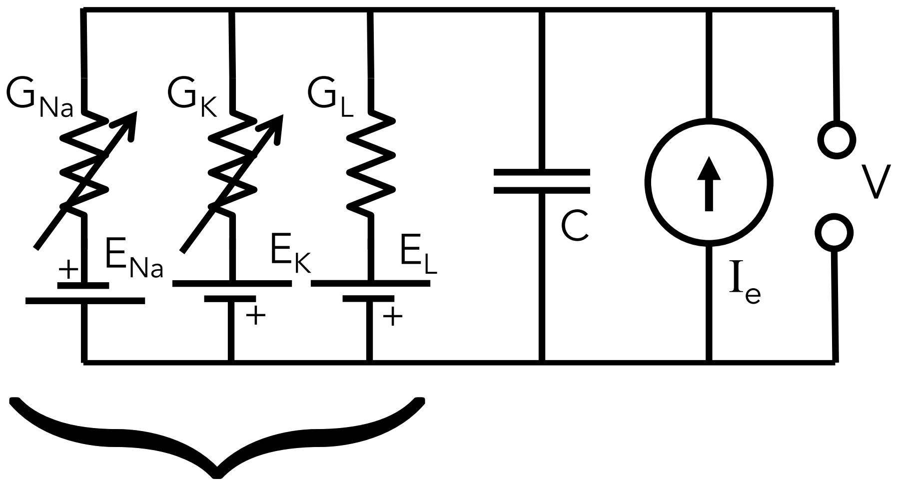
Voltage and time-dependent ion channels are the 'knobs' that control membrane potential.





Removed due to copyright restrictions: Figure 1a: The first intracellular recording of an action potential, from squid axon. Häusser, M. "The Hodgkin-Huxley theory of the action potential." *Nature Neuroscience* 3 (2000).

Hodgkin-Huxley model of action potential generation



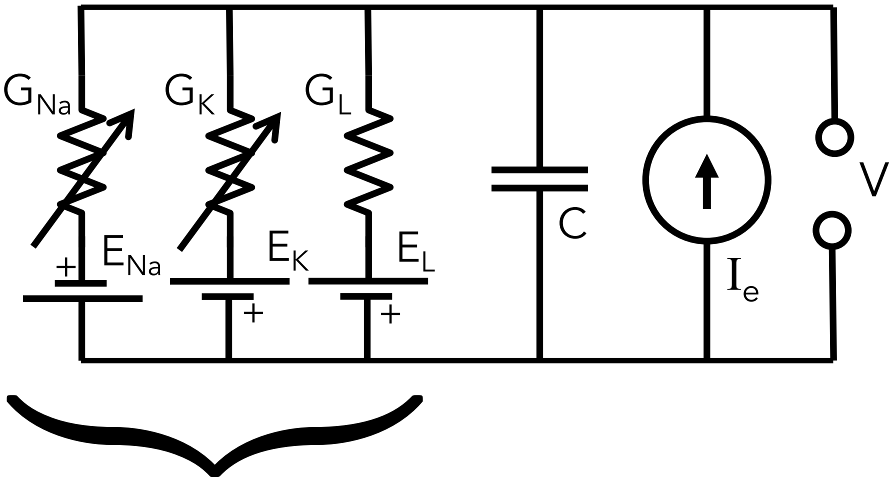
$$I_m = I_{Na} + I_K + I_L$$

This is the total membrane ionic current, and it includes the contribution from —sodium channels, potassium channels and a ‘leak’ conductance.

The equation for our HH model neuron is

$$I_m(t) + C\frac{dV(t)}{dt} = I_e(t)$$

Hodgkin-Huxley model of action potential generation



$$I_m = I_{Na} + I_K + I_L \qquad I_m(t) + C\frac{dV(t)}{dt} = I_e(t)$$

$$I_{Na} = G_{Na}(V,t)\left(V - E_{Na}\right) \qquad I_K = G_K(V,t)(V - E_K) \qquad I_L = G_L(V - E_L)$$

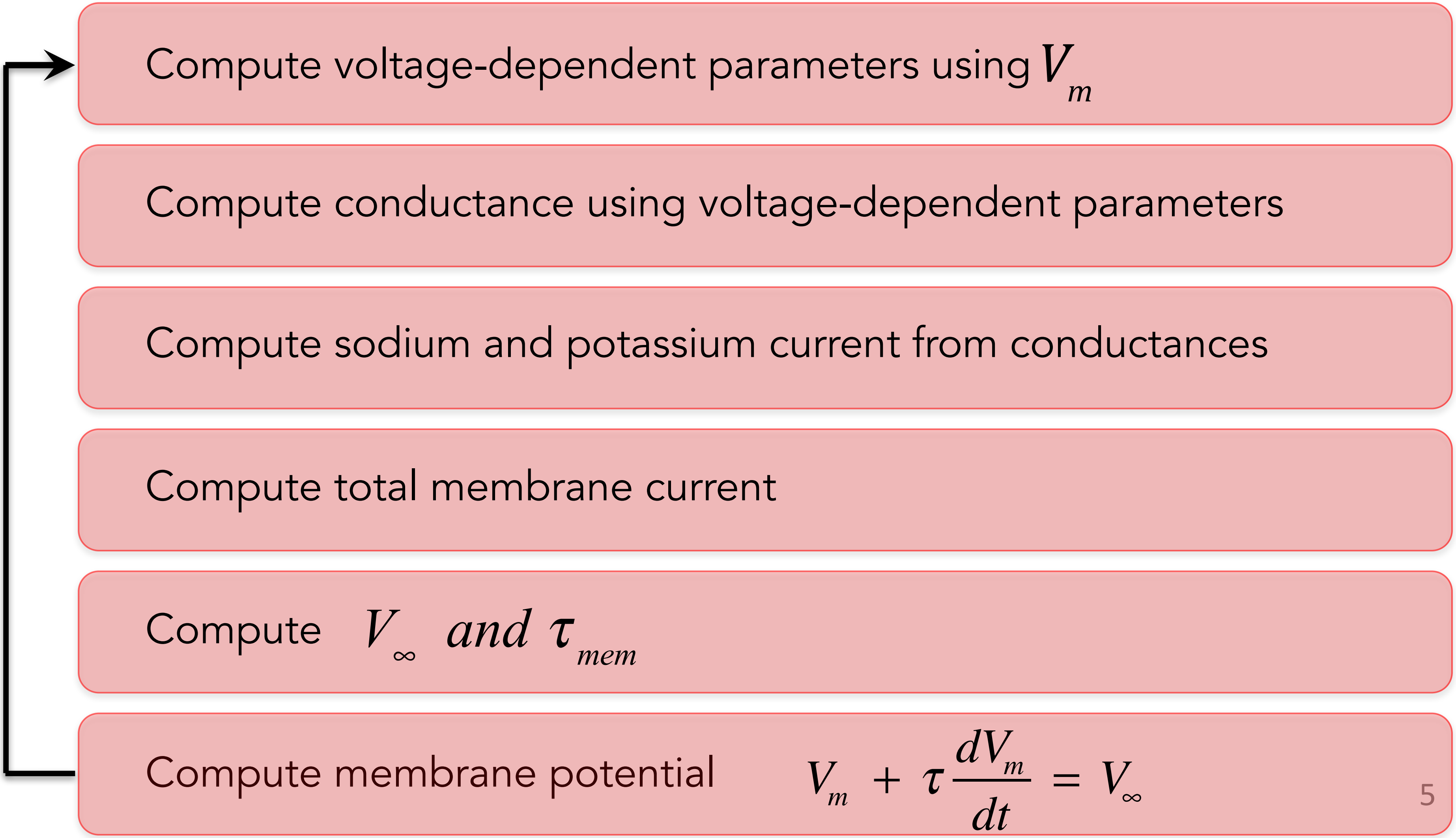
We can see that the membrane potential depends on current

…which depends on all the conductances

…which depend on the membrane potential

We are going to write down an algorithm for how a neuron spikes!

Start with V_m :



Compute voltage-dependent parameters using V_m

Compute conductance using voltage-dependent parameters

Compute sodium and potassium current from conductances

Compute total membrane current

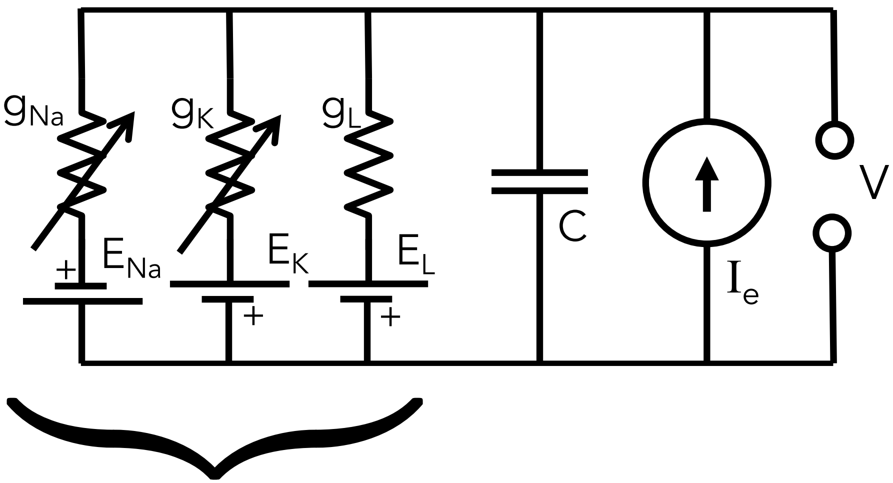
Compute V_∞ *and* τ_{mem}

Compute membrane potential $V_m + \tau \frac{dV_m}{dt} = V_\infty$

Learning objectives for Lecture 2

- To be able to draw the circuit diagram of the HH model
- Understand what a voltage clamp is and how it works
- Be able to plot the voltage and time dependence of the potassium current and conductance
- Be able to explain the time and voltage dependence of the potassium conductance in terms of Hodgkin-Huxley gating variables

Outline of HH model



$$I_m = I_{Na} + I_K + I_L$$

$$I_X = G_X \cdot (V - E_X)$$

$$I_{Na} = G_{Na}(V,t)\left(V - E_{Na}\right)$$

The sodium conductance is time-dependent and voltage-dependent

$$I_K = G_K(V,t)(V - E_K)$$

The potassium conductance is time-dependent and voltage-dependent

$$I_L = G_L(V - E_L)$$

The leak conductance is neither time-dependent nor voltage-dependent

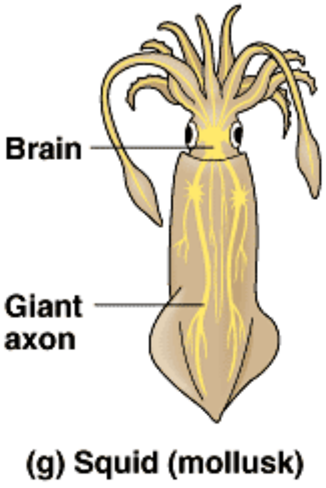
$$E_{Na} = +55mV$$

$$E_K = -75mV$$

$$E_L = -50mV$$

Voltage and Time dependence

- Voltage and time-dependent ion channel conductances are the 'knobs' that control membrane potential.
- H&H studied the properties of K and Na channels in the squid giant axon. In particular they wanted to study the voltage and time dependence of the K and Na channels.



Squid diagram from The CellularScale.
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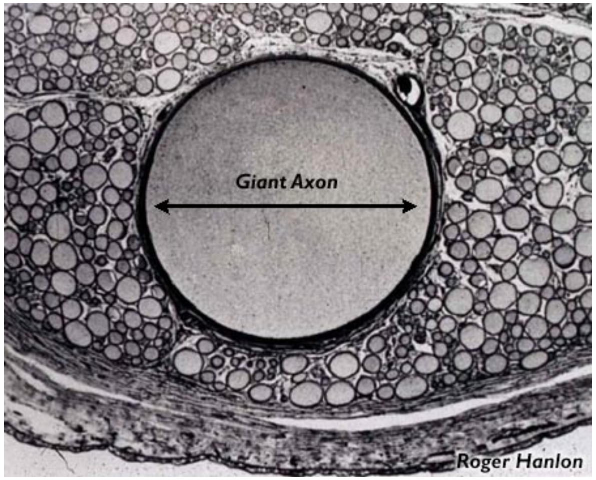


1mm diameter!

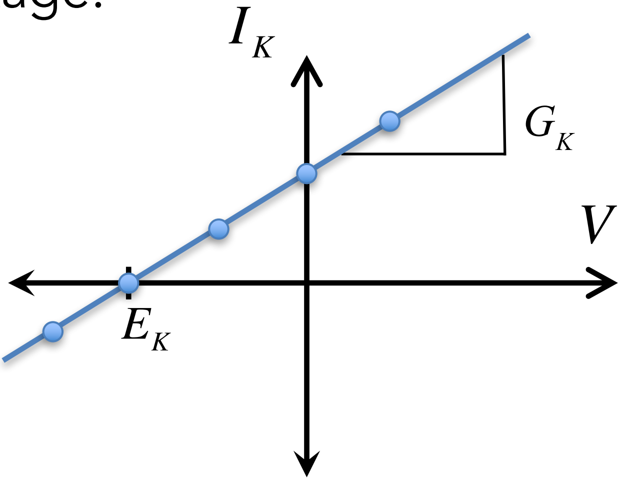
Image of squid giant axon © Kay Cooper and Roger Hanlon. Used with permission.

Most axons in our brain are 1um dia

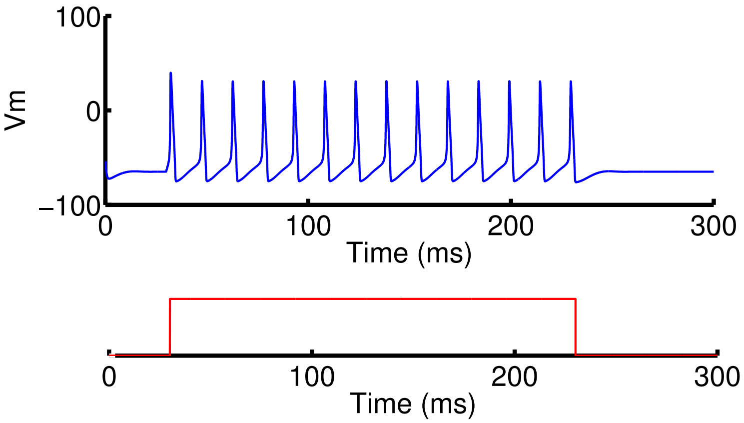
Outline of HH model

The best way study the time and voltage dependent conductance of ionic channels is to suddenly ‘set’ the voltage at different values and measure the current required to hold that voltage.

Then plot the I-V curve.

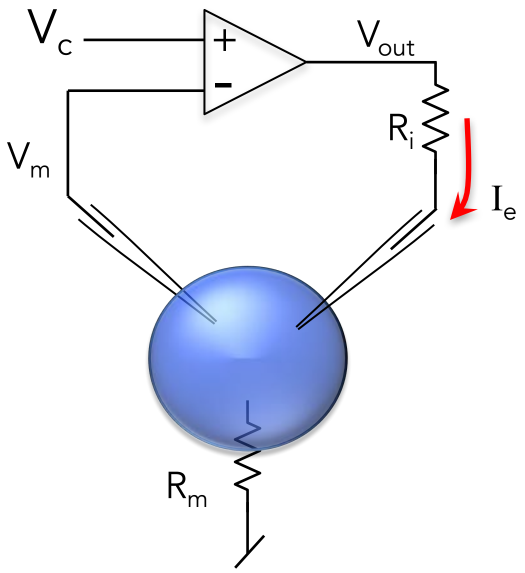


This not easy, because as soon as you depolarize the axon, the axon begins to spike!

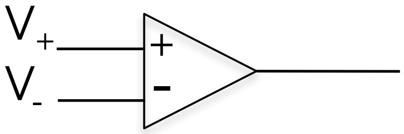


Voltage Clamp

A voltage clamp is a device that holds the membrane potential of a cell to any desired 'command' voltage V_c, and measures the current required to hold that voltage.



The key component is an operational amplifier (op-amp)



The basic equation of an op-amp is:

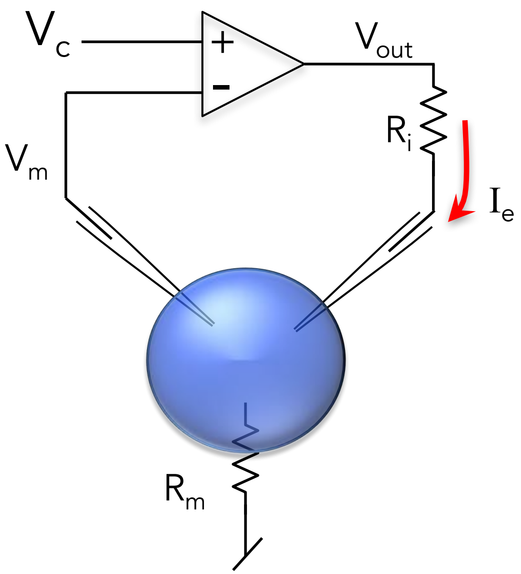
$$V_{out} = G(V_+ - V_-)$$

where G is the gain, typically ~10^5 or 10^6,

Don't get confused here. G is gain, not conductance!

Voltage Clamp

$$V_{out} = G(V_c - V_m)$$



$$\text{If } V_m < V_c \text{ then } V_{out} >> 0$$

- Drives current into neuron
- Increases membrane potential

$$\text{If } V_m > V_c \text{ then } V_{out} << 0$$

- Pulls current out of neuron
- Decreases membrane potential

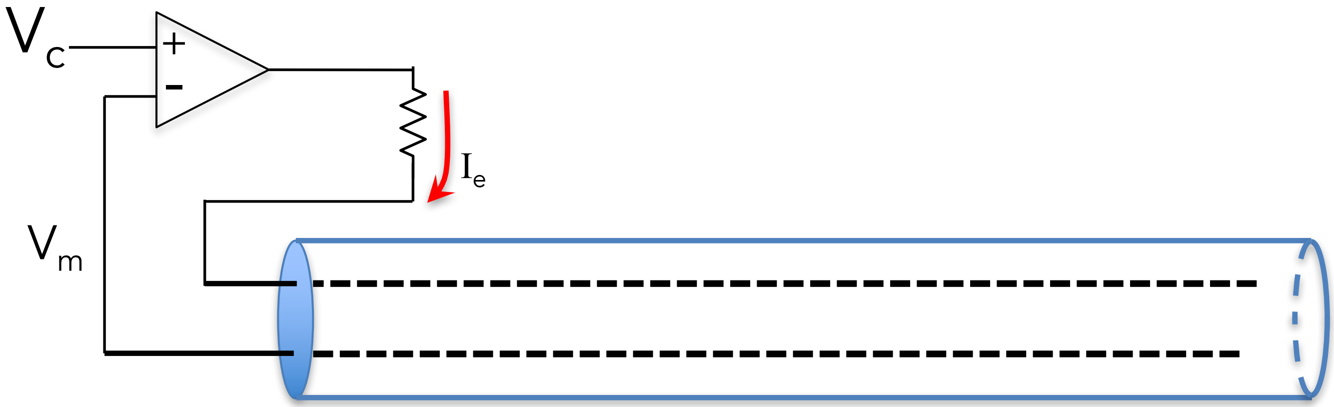
This is called ‘negative feedback’.

- It is easy to show that, for large gain:

$$V_m \simeq V_c$$

- Thus, the voltage clamp circuit drives whatever current (I_e) is necessary to ‘clamp’ the voltage of the neuron to the command voltage.
- During a voltage clamp experiment, we step the V_c around within the voltage range of interest and measure I_e.

Ionic currents

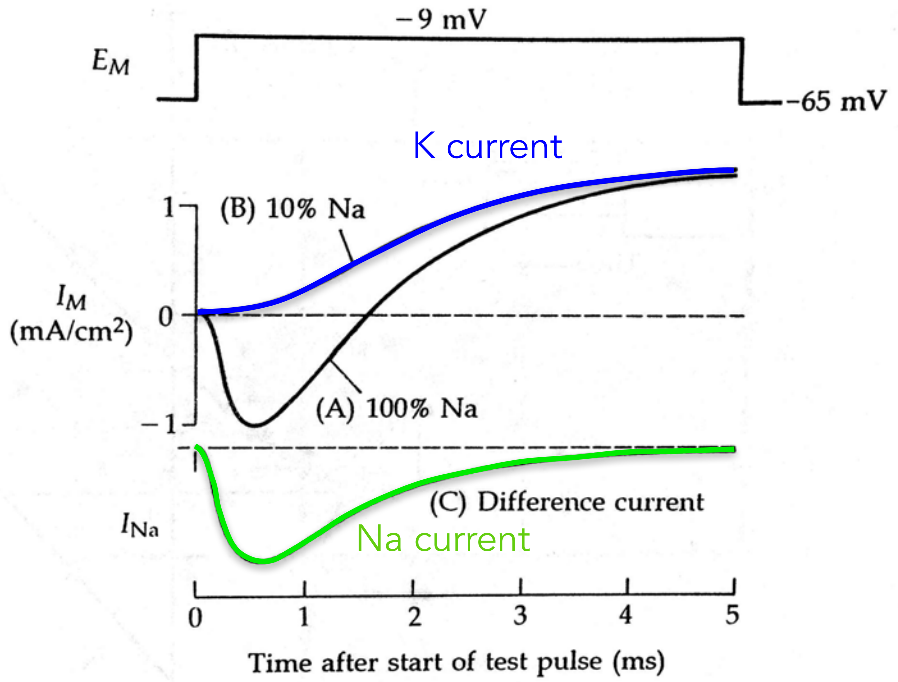


Removed due to copyright restrictions: Figure 2.6 p. 36 *In*: Hille, Bertil. *Ion Channels of Excitable Membranes* (3rd Ed.). 2001, Sinauer / Oxford University Press.

Ionic currents

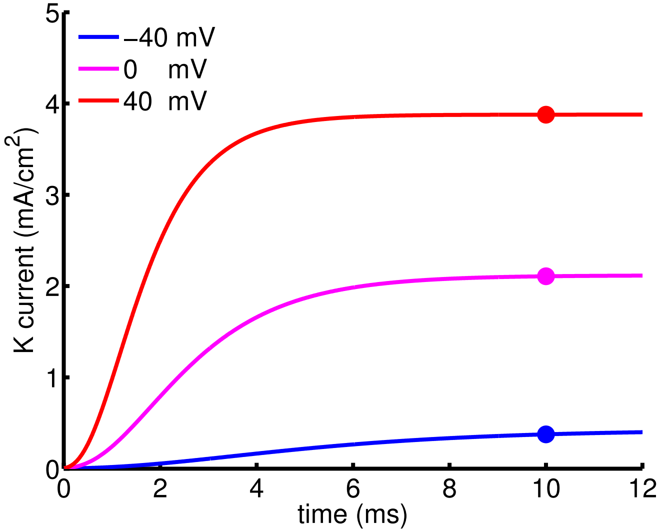
How do we figure out the contribution of Na and the contribution of K?

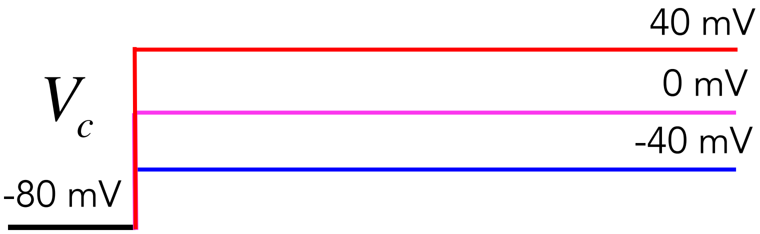
Ionic substitution (e.g. replace NaCl with choline chloride)



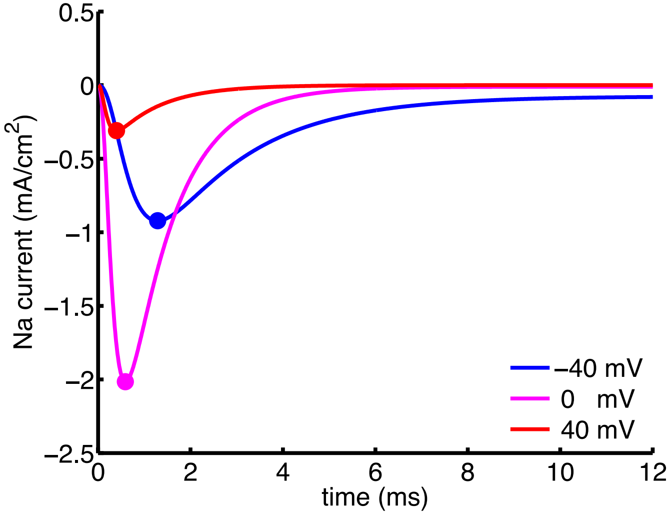
Ionic currents

K current



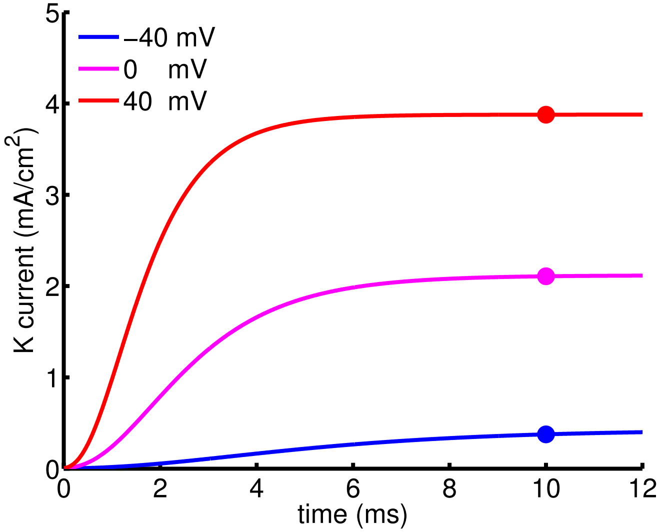


Na current

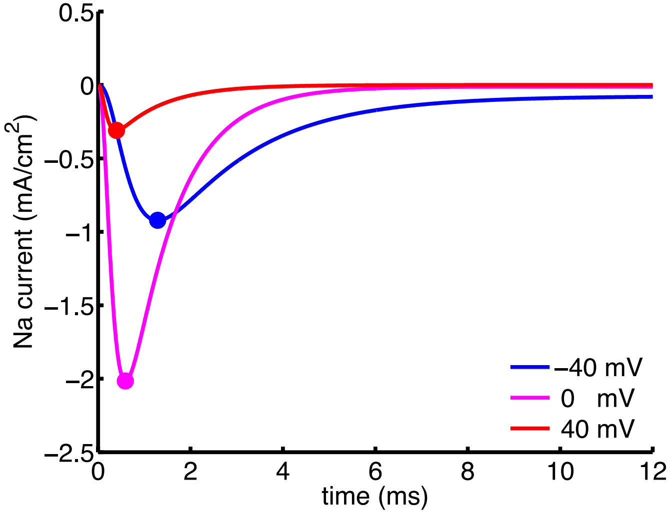


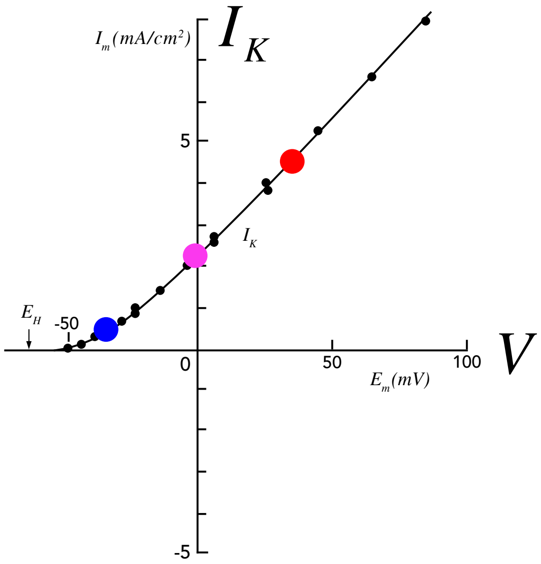
Ionic currents

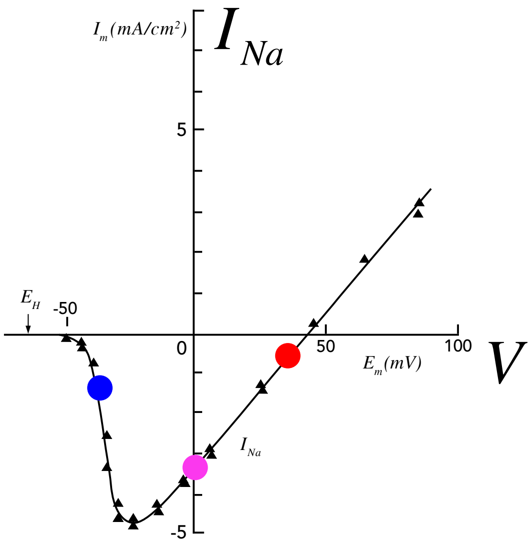
K current



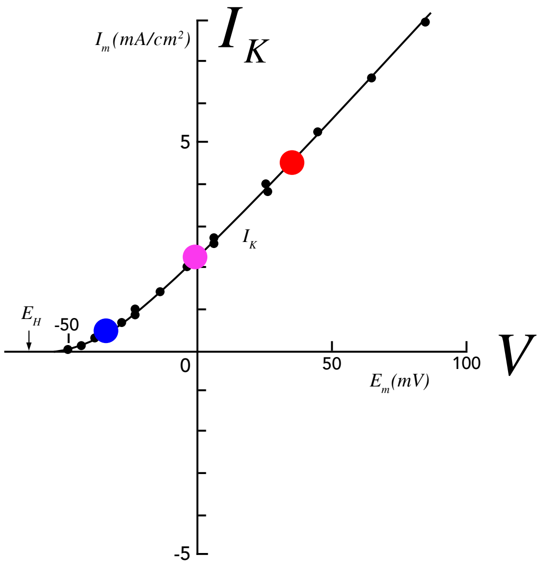
Na current

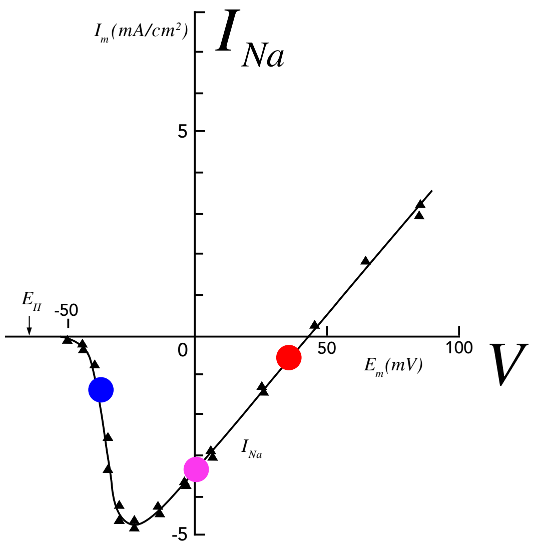






Ionic currents (voltage dependence)





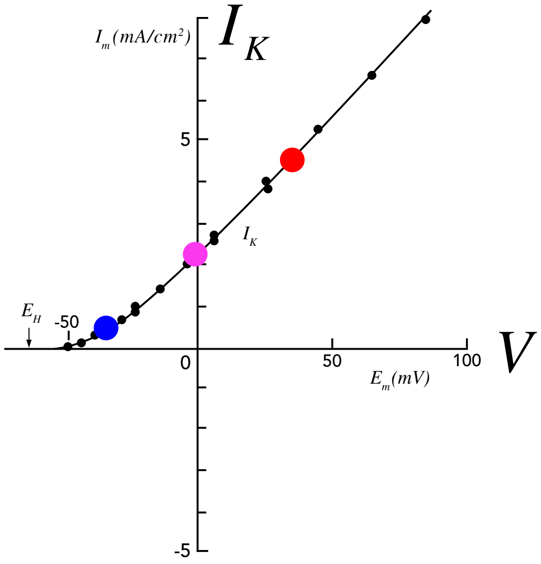
We used the voltage clamp to measure ***current*** as a function of voltage.

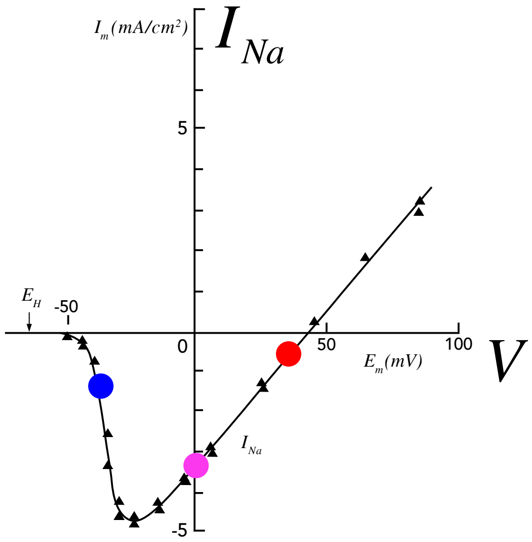
But what we are really trying to extract is ***conductance*** as a function of voltage!

$$I_K(V) = G_K(V)\left(V - E_K\right) \qquad I_{Na}(V) = G_{Na}(V)\left(V - E_{Na}\right)$$

$$G_K(V) \equiv \frac{I_K(V)}{\left(V - E_K\right)} \qquad G_{Na}(V) \equiv \frac{I_{Na}(V)}{\left(V - E_{Na}\right)}$$

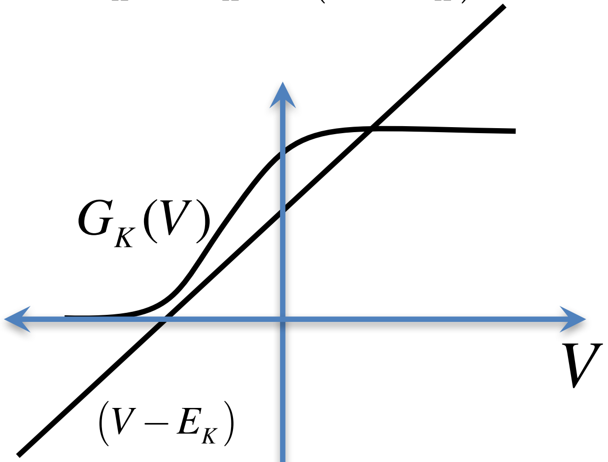
Ionic currents (voltage dependence)

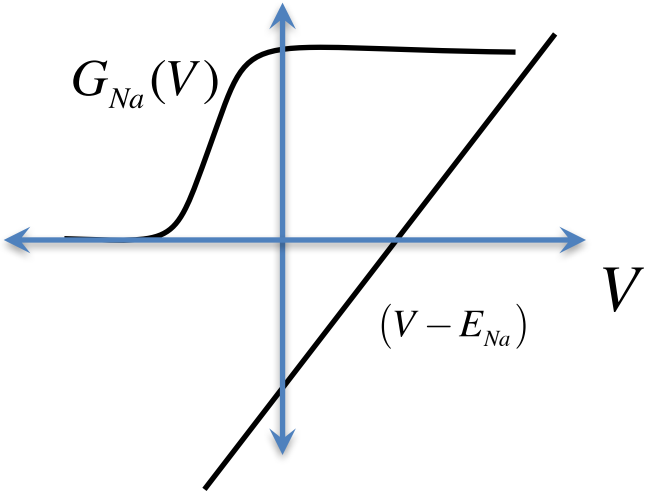




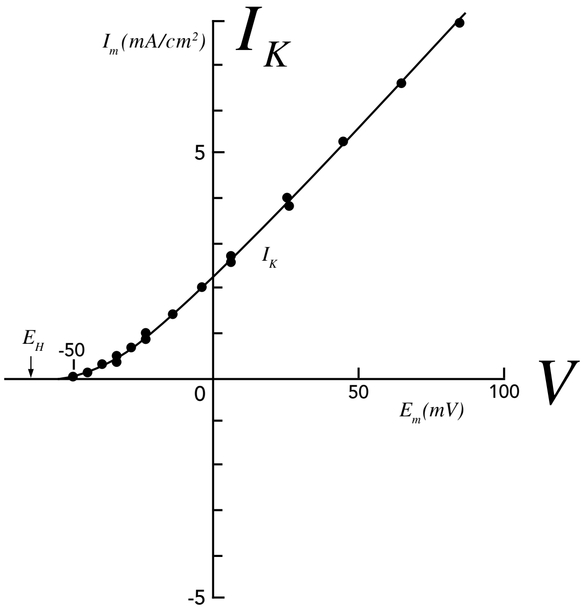
$$I_K = G_K(V)\left(V - E_K\right)$$

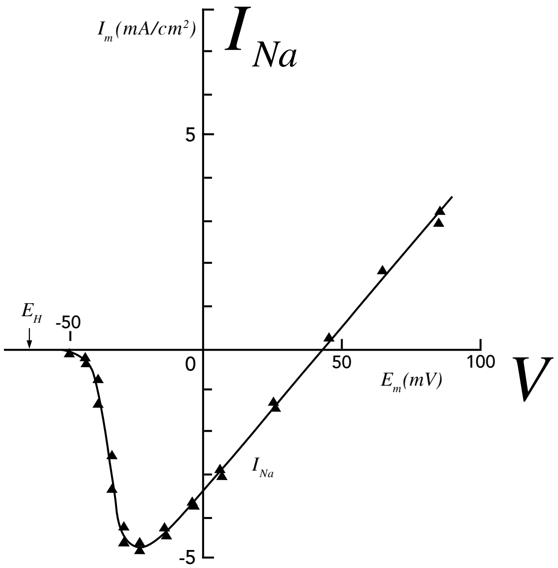
$$I_{Na} = G_{Na}(V)\left(V - E_{Na}\right)$$

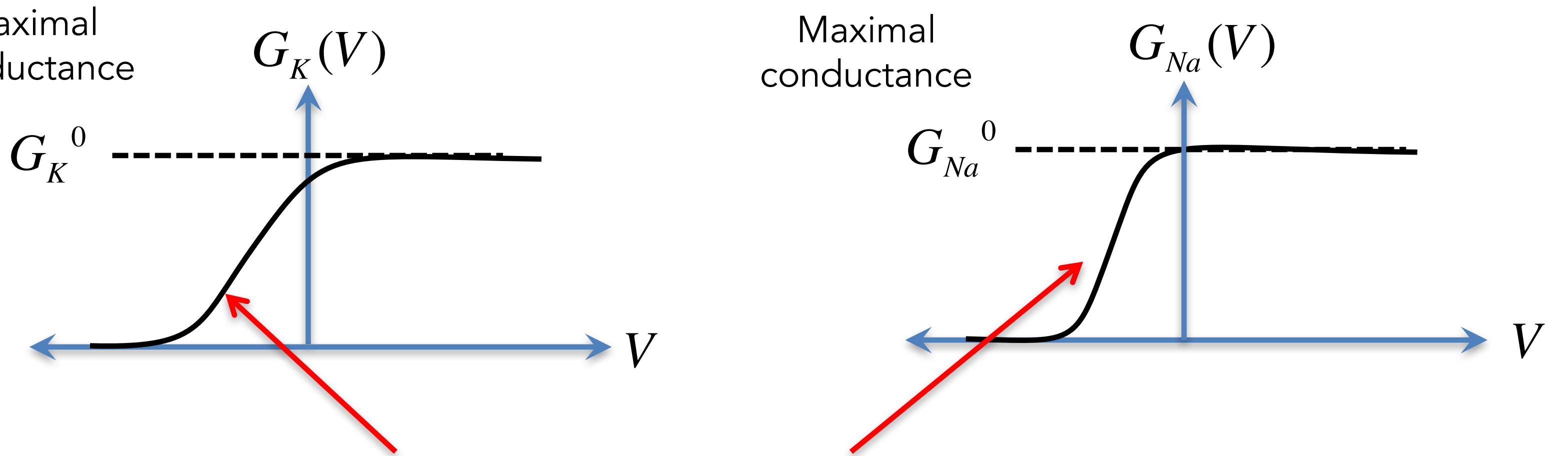




Ionic currents (voltage dependence)

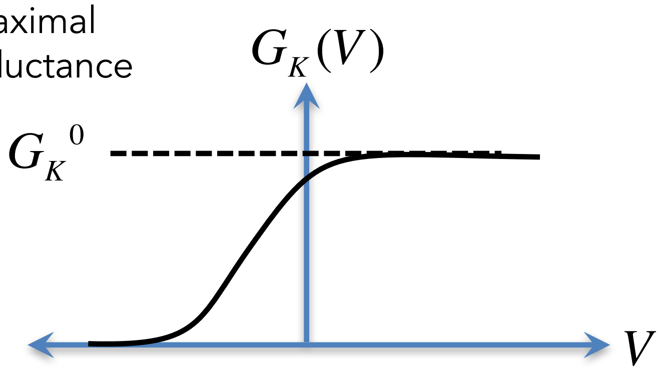






Sigmoidal voltage-dependence of activation

Ionic currents (Voltage dependence)

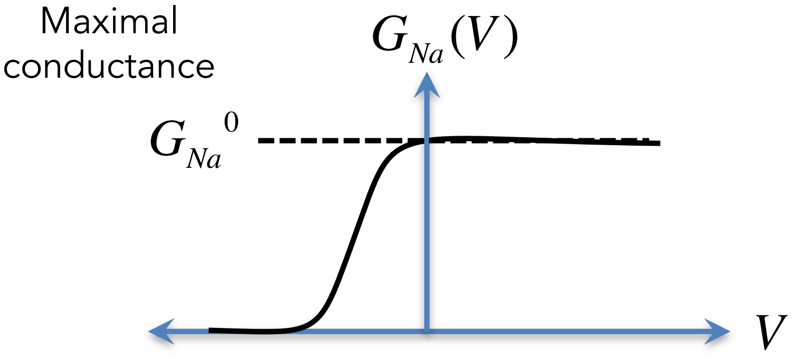


Maximal conductance

$G_K(V)$

$G_K^{\ 0}$

V



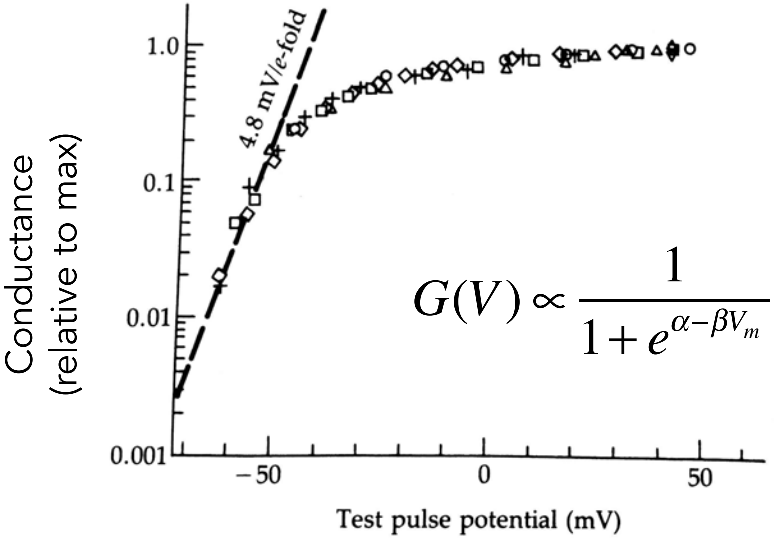
Maximal conductance

$G_{Na}(V)$

$G_{Na}^{\ 0}$

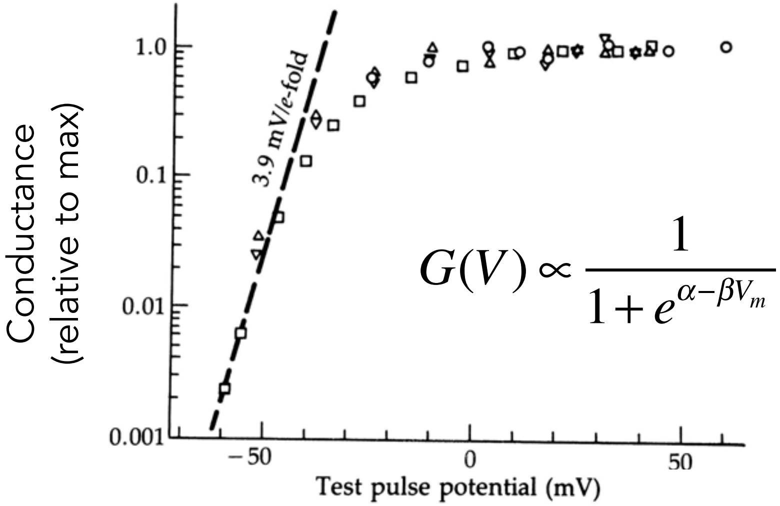
V

K conductance



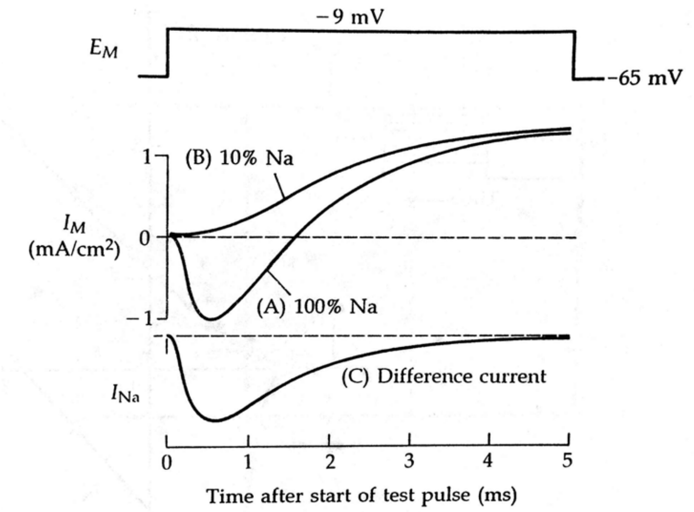
$$G(V) \propto \frac{1}{1+e^{\alpha-\beta V_m}}$$

Na conductance



$$G(V) \propto \frac{1}{1+e^{\alpha-\beta V_m}}$$

Ionic currents (time dependence)

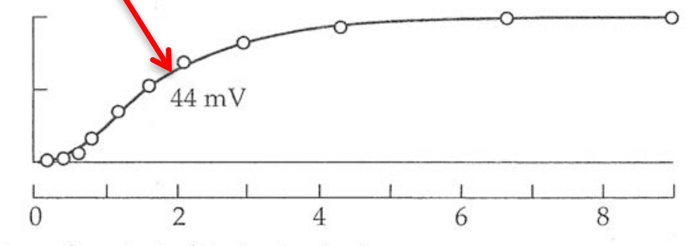


$$I_K(t) = G_K(t)\left(V - E_K\right)$$

$$I_{Na}(t) = G_{Na}(t)\left(V - E_{Na}\right)$$

activation

$G_K(t)$

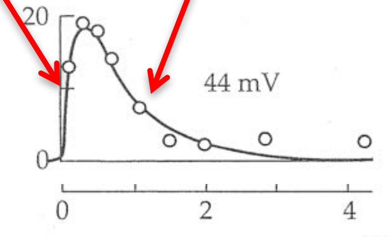


Time after start
of pulse (ms)

activation

inactivation

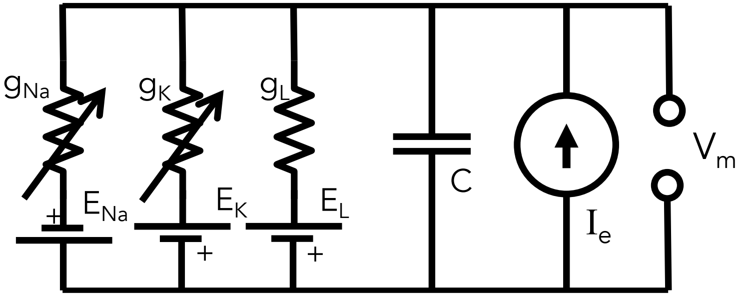
$G_{Na}(t)$

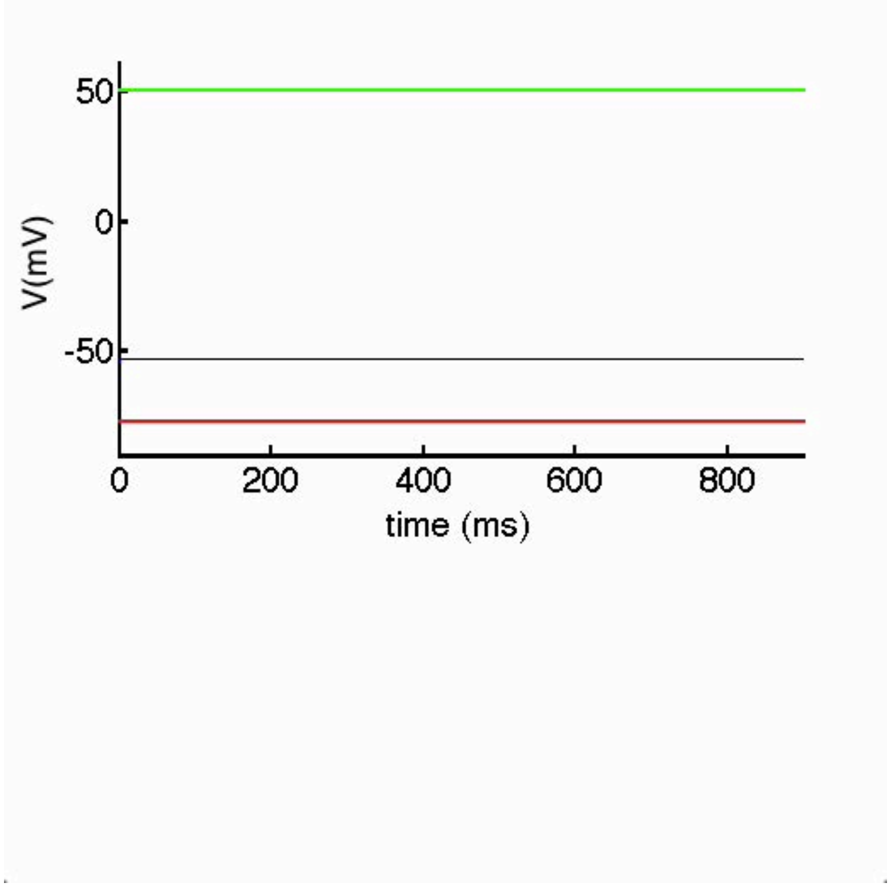


Time after start
of pulse (ms)

Outline of HH model

Voltage and time-dependent ion channels are the ‘knobs’ that control membrane potential.





- Some ion channels push the membrane potential positive.
- Other ion channels push the membrane potential negative.
- Together these channels give the neural machinery flexible control of voltage!

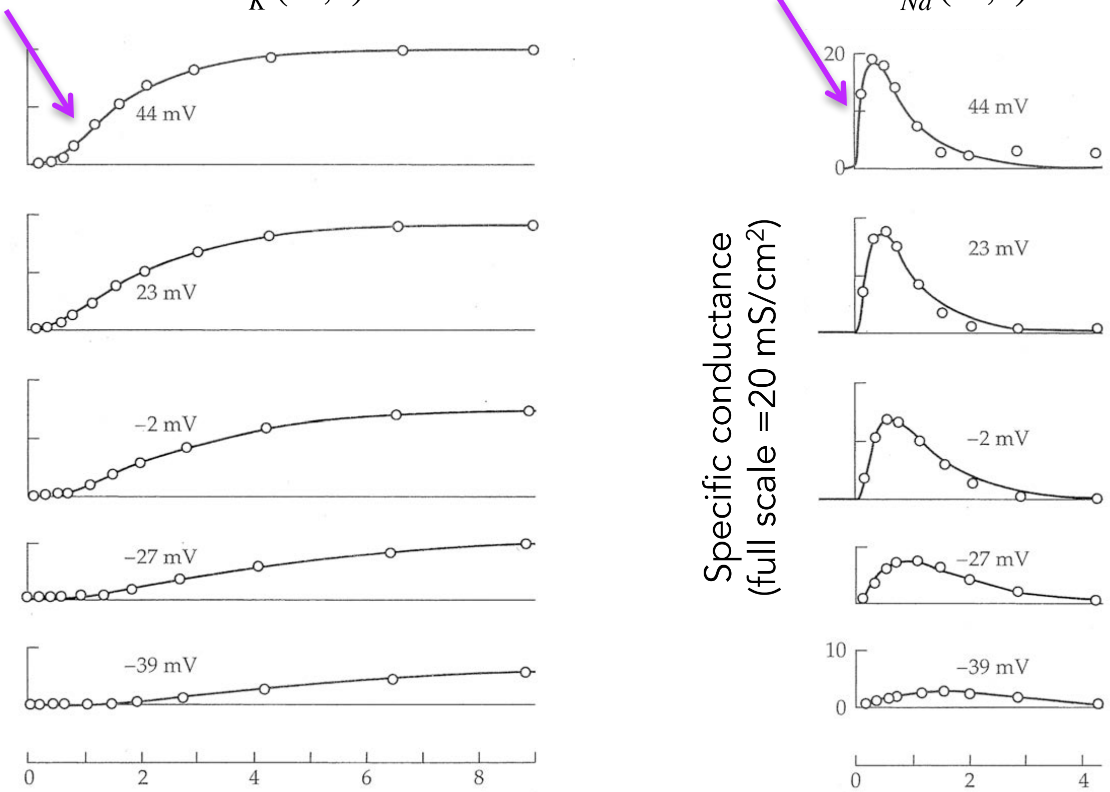
Ionic currents (time and voltage dependence)

$G_K(V,t)$

$G_{Na}(V,t)$

Delayed activation

Fast activation



Specific conductance (full scale =20 mS/cm^2)

Specific conductance (full scale =20 mS/cm^2)

Time after start of pulse (ms)

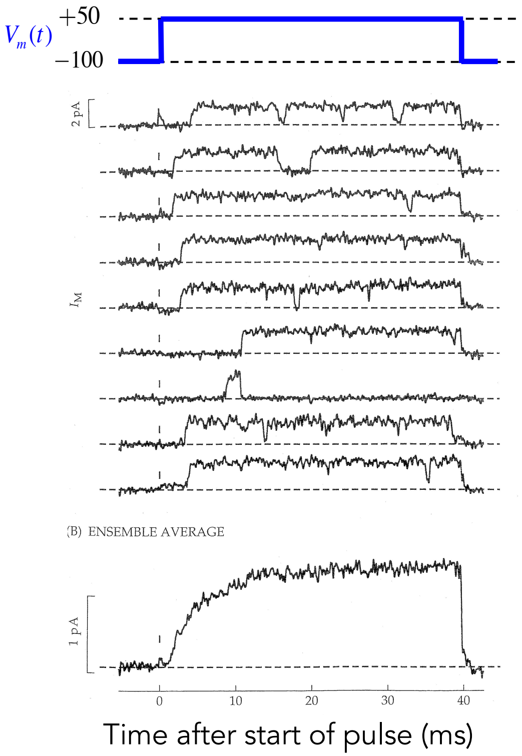
Ionic Currents (time and voltage dependence)

- Now we are going to develop a detailed understanding of where these voltage and time-dependencies come from!
- We are going to derive equations for the voltage dependence
- And differential equations for the time dependence.
- Once we do that, we will be able to write down a system of equations that allows us to simulate an action potential!

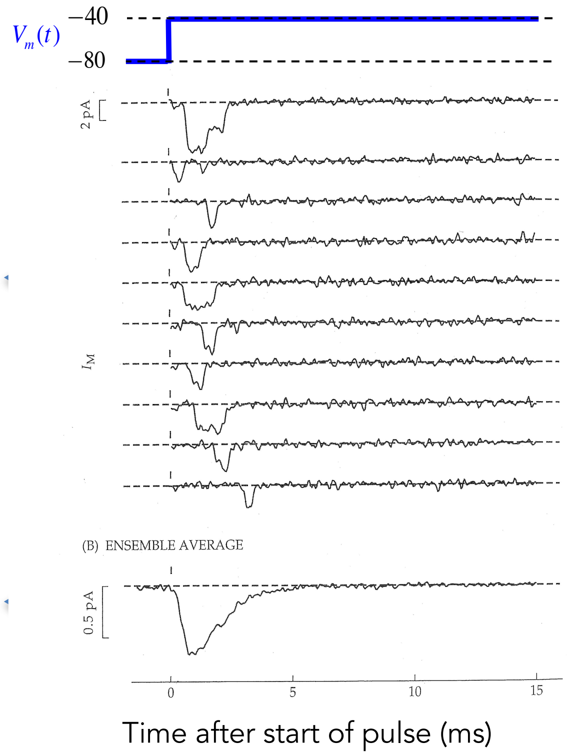
Single Channels

So far, we have been discussing total currents into a neuron. However, these total currents result from ionic flow through thousands of individual ion channels.

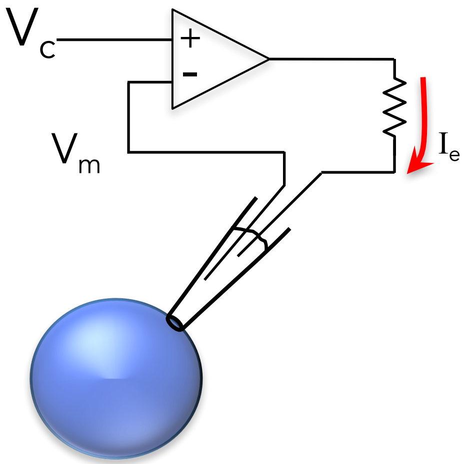
Single channel K-current



Single channel Na-current



It is possible to record from single ion channels using a ‘patch clamp’.



Neher & Sakmann

Ionic conductance in terms of single channels

Individual ion channels are either OPEN or CLOSED.

The total conductance through a membrane is given by the total number of open channels times the conductance one ion channel.

P_K = probability of being ‘open’

N_K = total number of ion channels

$\hat{g}_K$ = unitary conductance

Number of ‘open’ ion channels $= P_K N_K$

Total K conductance:

$$G_K = P_K(V,t)\, N_K\, \hat{g}_K$$

Remember, K current is:

$$I_K = G_K(V,t)\,(V - E_K)$$

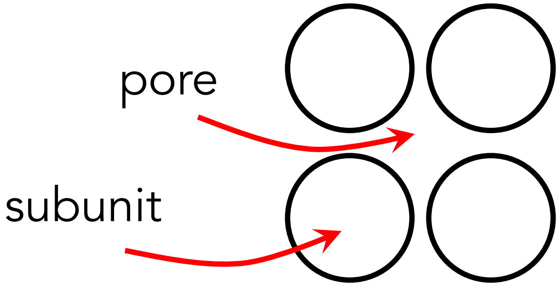
All of the interesting time and voltage dependence comes from here

Ionic conductance in terms of single channels

How do we describe the probability that a channel is open?

Lets start with the K channel.

The pore of a K^+ channel is formed by 4 identical subunits.



Each subunit has a voltage sensor and gate to turn the channel on and off.

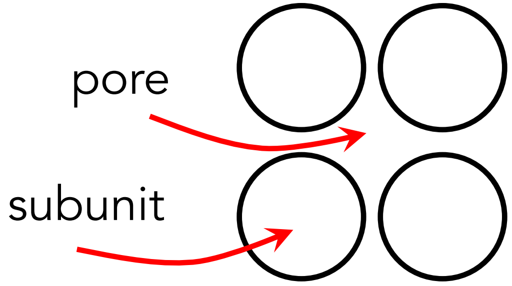
Each subunit has two states: ‘open’ and ‘closed’.
‘n’ is the probability that a subunit is open.

Finally, all subunits must be in the ‘open’ state for the channel to be permeable.

Ionic conductance in terms of single channels

How do we describe the probability that a channel is open?

If ‘n’ is the probability that one subunit is open, then the probability that all four subunits is open is given by:



$$P_K = n^4$$

Assuming independence

We can now write down the conductance of our K channels as:

$$G_K = \bar{G}_K n^4$$

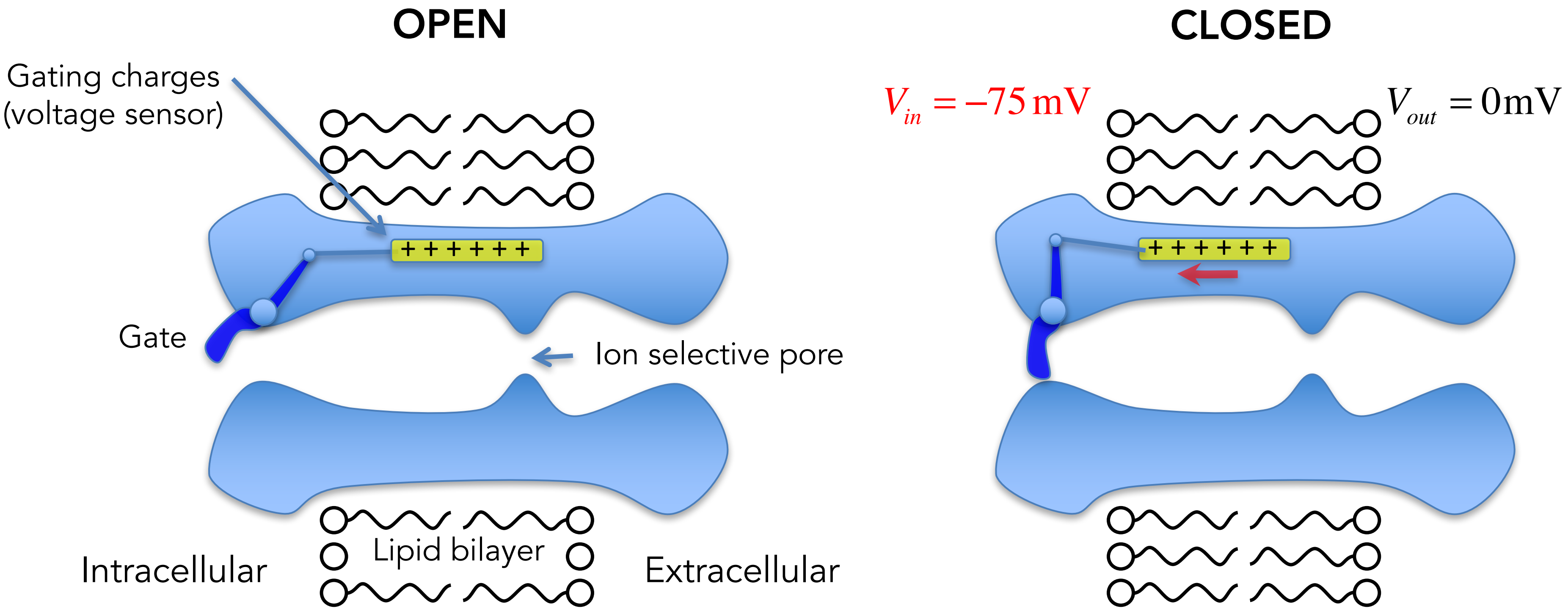
$\bar{G}_K$ is the maximal open conductance

And we can write the K current as:

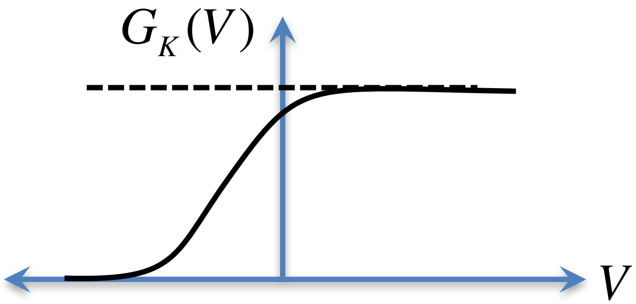
$$\boxed{I_K = \bar{G}_K n^4 (V - E_K)}$$

H & H called n the ‘gating variable’ for the potassium current

Ionic conductance in terms of single channels



We are going see how to derive the voltage-dependence from first principles!

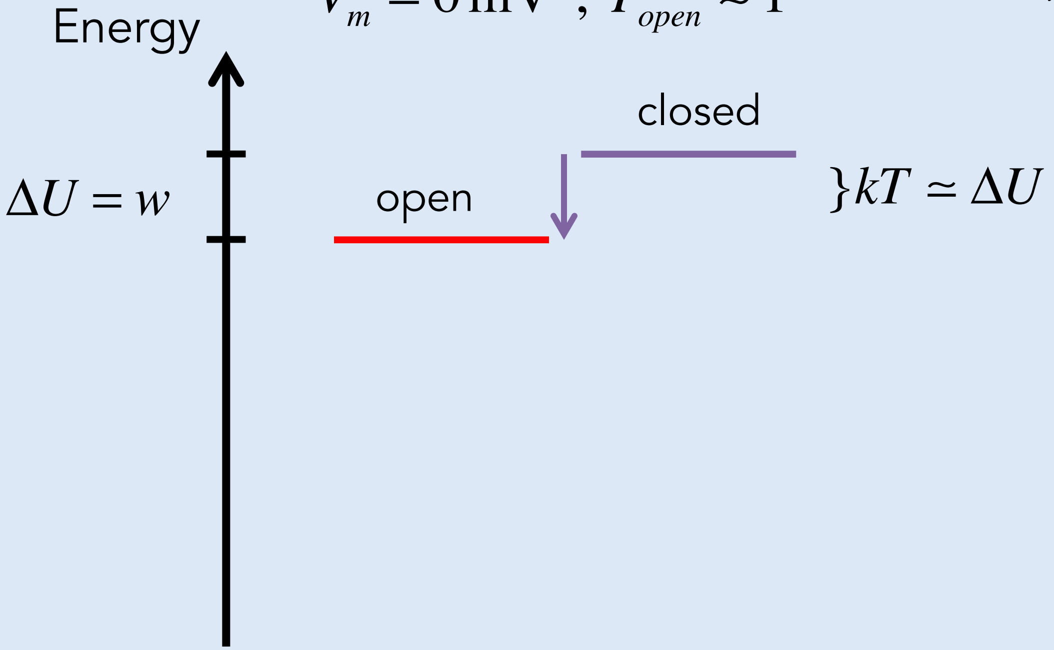


Ionic conductance in terms of single channels

Ion channels are stochastic. They are either open or closed, and flicker back and forth between the open and closed states.

Lets see if we can predict the voltage-dependence of an ion channel!

$V_m = 0\,\mathrm{mV}$, $P_{open} \approx 1$

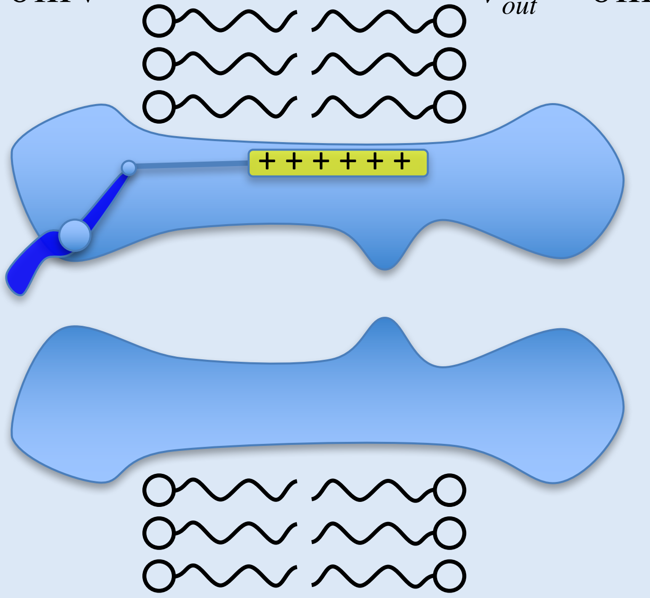


$\Delta U = w$

$\}kT \simeq \Delta U$

OPEN

$V_{in} = 0\mathrm{mV}$ $V_{out} = 0\mathrm{mV}$



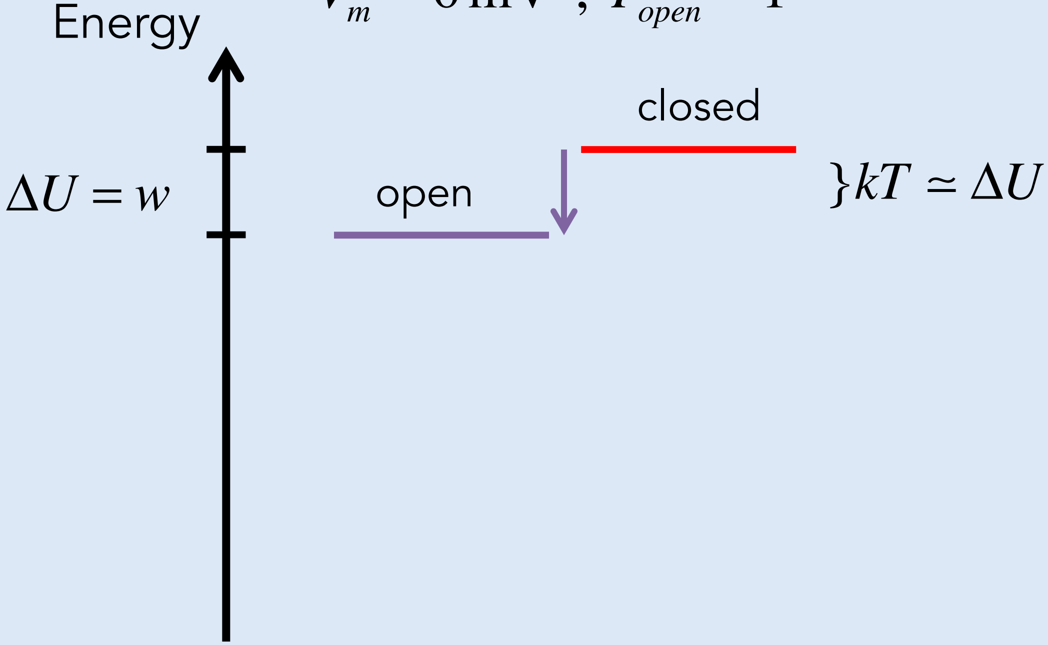
$$\Delta U = U_{open} - U_{closed}$$

Ionic conductance in terms of single channels

Ion channels are stochastic. They are either open or closed, and flicker back and forth between the open and closed states.

Lets see if we can predict the voltage-dependence of an ion channel!

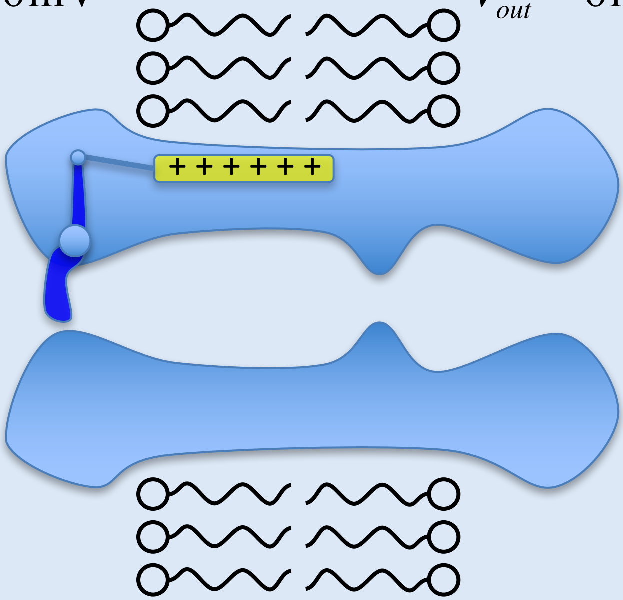
$$V_m = 0\,\mathrm{mV}\ ,\ P_{open} \approx 1$$



CLOSED

$V_{in} = 0\mathrm{mV}$

$V_{out} = 0\mathrm{mV}$

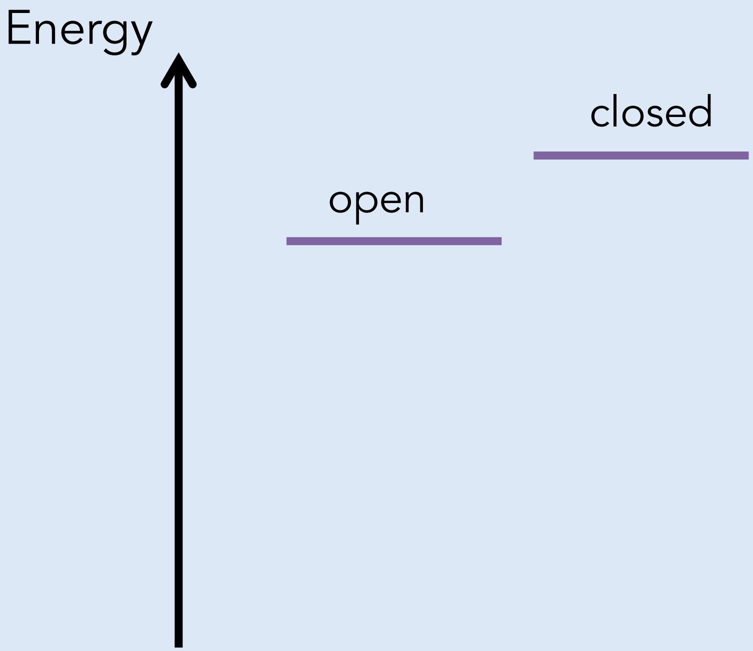


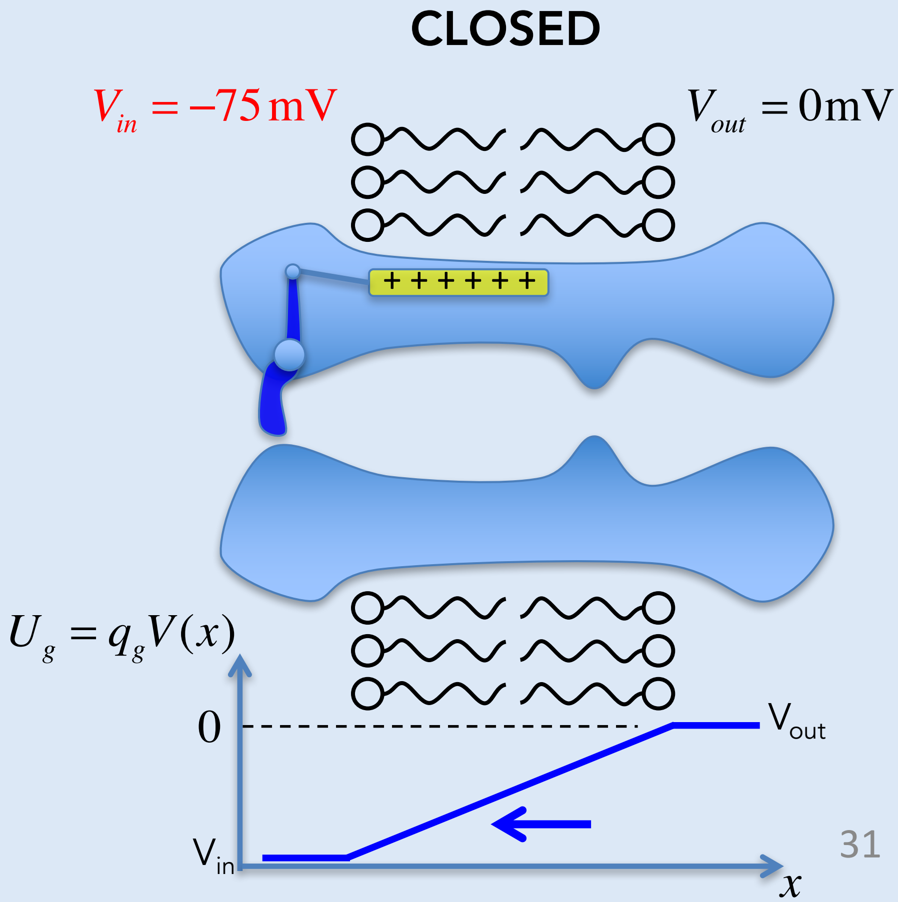
$$\Delta U = U_{open} - U_{closed}$$

Ionic conductance in terms of single channels

Ion channels are stochastic. They are either open or closed, and flicker back and forth between the open and closed states.

Lets see if we can predict the voltage-dependence of an ion channel!





Ionic conductance in terms of single channels

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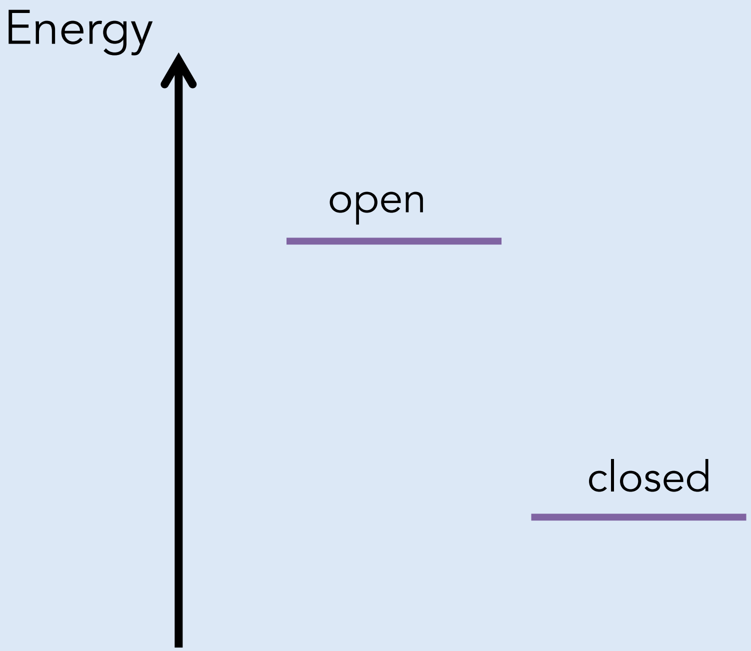

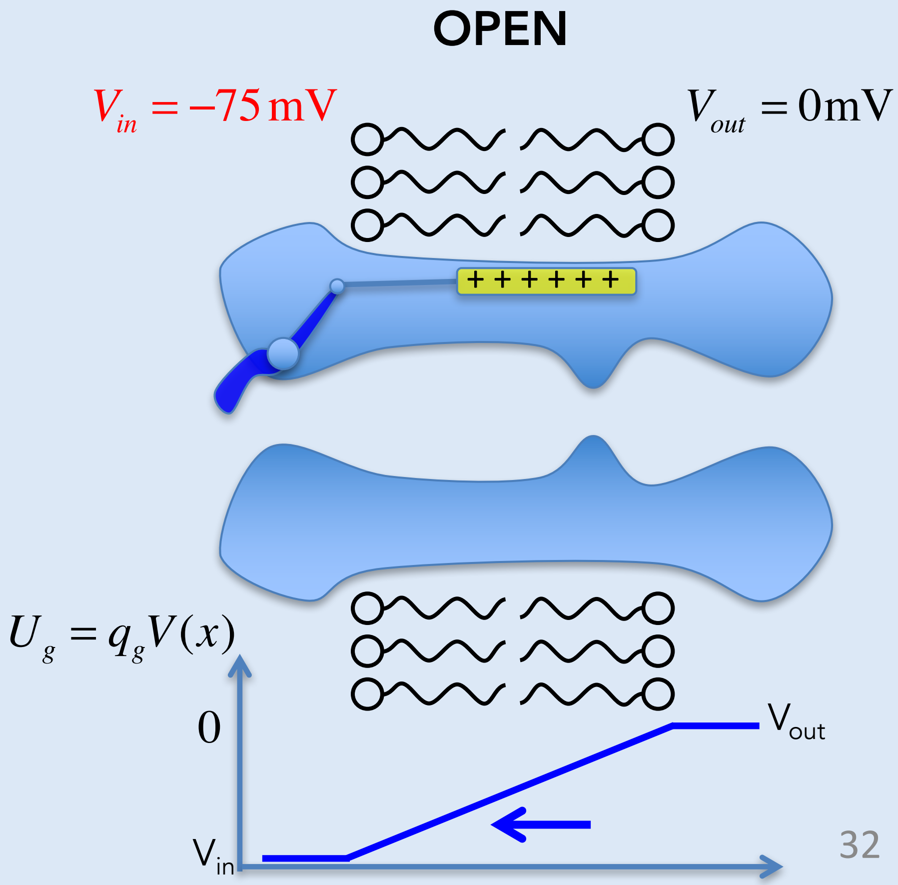

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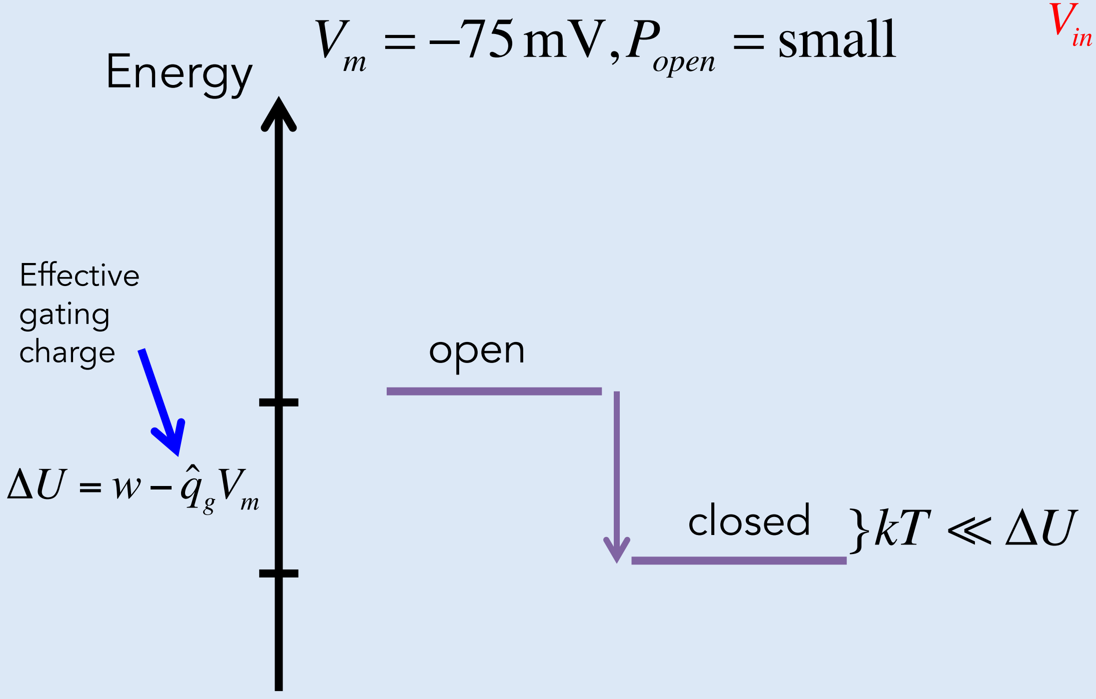


$V_m = -75\,\mathrm{mV}, P_{open} = \text{small}$

Energy

Effective gating charge

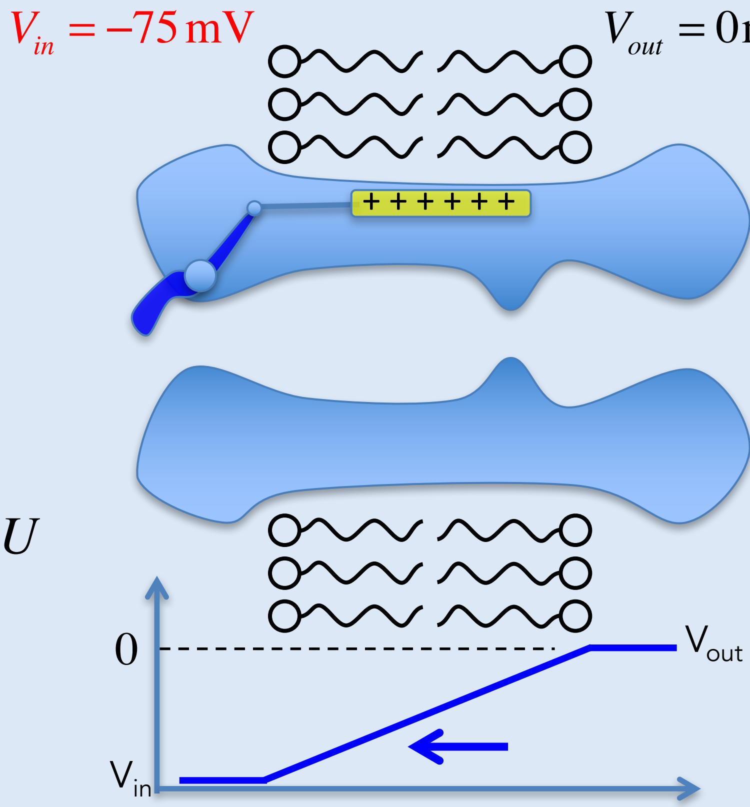
$\Delta U = w - \hat{q}_g V_m$

open

closed $\}kT \ll \Delta U$

$\Delta U = U_{open} - U_{closed}$

OPEN



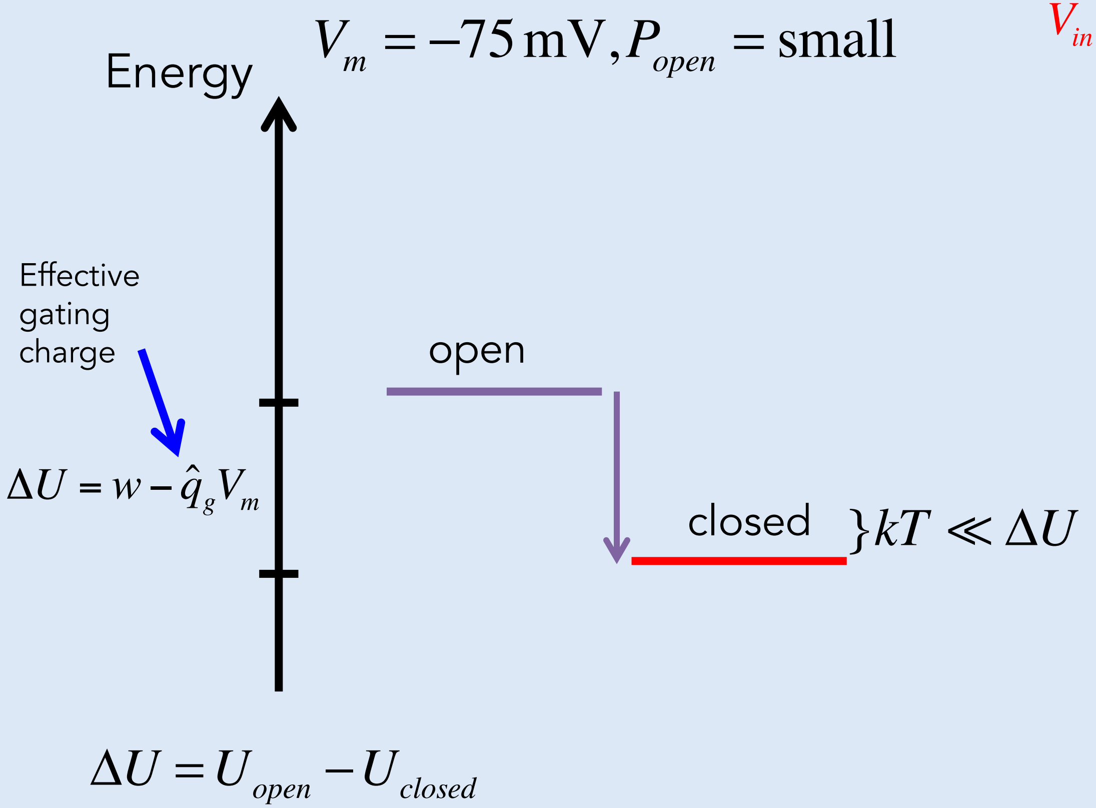
$V_{in} = -75\,\mathrm{mV}$

$V_{out} = 0\mathrm{mV}$

Ionic conductance in terms of single channels

Ion channels are stochastic. They are either open or closed, and flicker back and forth between the open and closed states.

Lets see if we can predict the voltage-dependence of an ion channel!



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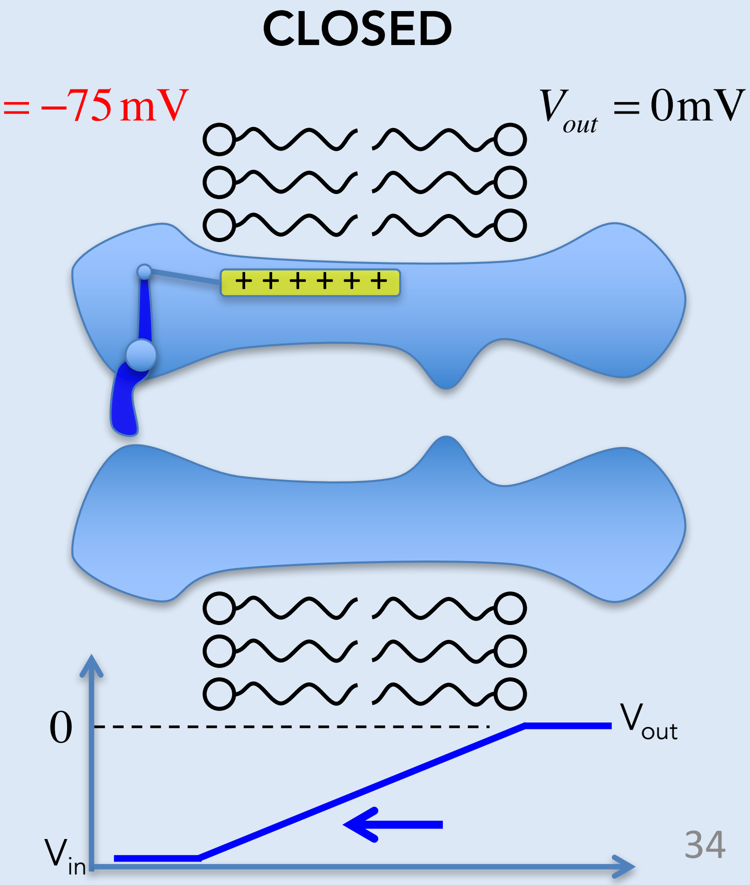
CLOSED

$V_{in} = -75\,\mathrm{mV}$



$V_{out} = 0\mathrm{mV}$

To derive the voltage dependence: boltzmann equation

We can use the Boltzmann equation to describe the ratio of probabilities of being in the open or closed state:

$$\frac{P_{open}}{P_{closed}} = e^{-\left(\frac{U_{open} - U_{closed}}{kT}\right)} \qquad \frac{P_{open}}{P_{closed}} = e^{-\left(\frac{w - q_g V_m}{kT}\right)}$$

The probability of having an open subunit is:

$$n = P_0 = \frac{P_o}{P_o + P_c} = \frac{1}{1 + \frac{P_c}{P_o}} = \frac{1}{1 + e^{(w - q_g V_m)/kT}}$$

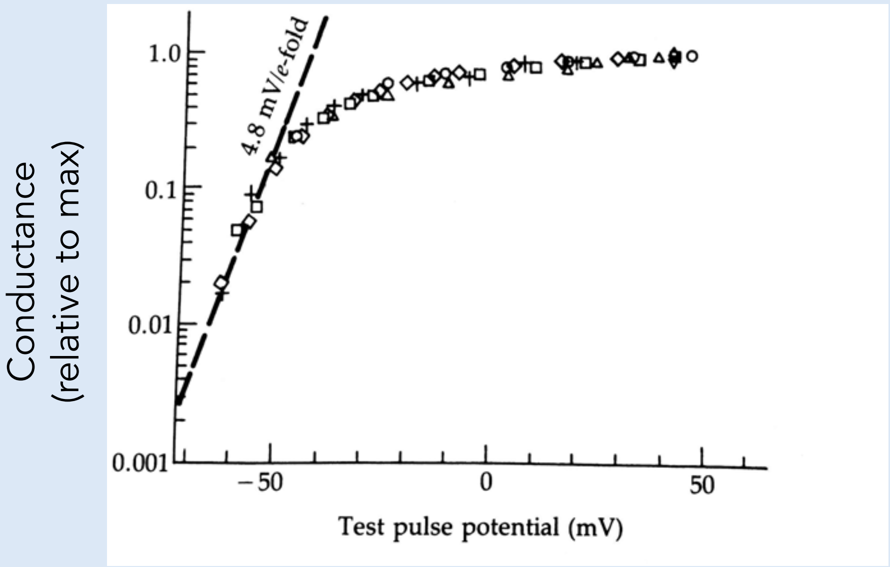
To derive the voltage dependence: boltzmann equation

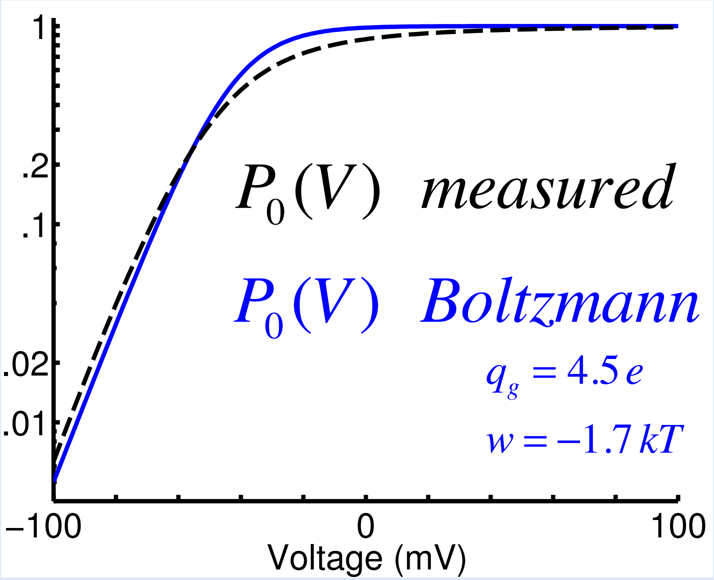
$$P_o(V) = \frac{1}{1+e^{(w-q_g V_m)/kT}}$$

Is this the observed voltage-dependence?

YES!

K conductance





Now get the time dependence!

Note that for any given subunit or channel, when we change the voltage, the energy levels shift (nearly) instantaneously. The probability of making a transition changes instantly, however the number of open channels does not changes instantly.

We still have to wait for thermal fluctuations to kick the channel or subunit open, or wait for the subunit to make a conformational change.

This takes time!

voltage-dependent!

$$\begin{array}{ccc} \text{'closed'} & \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} & \text{'open'} \\ 1-n & & n \end{array} \qquad \alpha_n, \beta_n \text{ are transition rates}$$

Probability per unit time;

units are 1/s

We are going to model the transitions between open and closed states with a simple rate equation. We can do this because we have many channels to average over.

$$\text{'closed'} \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} \text{'open'} \qquad \alpha_n, \beta_n \text{ are transition rates}$$

$$1-n \qquad\qquad\qquad n$$

Change in the number of open subunits = The number of closed subunits that open − The number of open subunits that close

Change in the number of open subunits

per unit time

=

The number of closed subunits (1-n)

times

the probability that a closed subunit opens

per unit time (α_n)

−

The number of open subunits (n)

times

the probability that an open subunit closes

per unit time (β_n)

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

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

Remember: n is the probability that a subunit is open.

Let’s rewrite this equation as follows:

$$= \alpha_n - \alpha_n n - \beta_n n$$

$$= \alpha_n - (\alpha_n + \beta_n)n$$

$$\underbrace{\frac{1}{(\alpha_n + \beta_n)}}_{}\frac{dn}{dt} = \underbrace{\frac{\alpha_n}{(\alpha_n + \beta_n)}}_{} - n$$

The steady state solution!

$$\boxed{n_\infty = \frac{\alpha_n}{(\alpha_n + \beta_n)}}$$

A time constant!

$$\boxed{\tau_n = \frac{1}{(\alpha_n + \beta_n)}}$$

Thus, we can rewrite this equation in terms of the steady state open probability and a time constant:

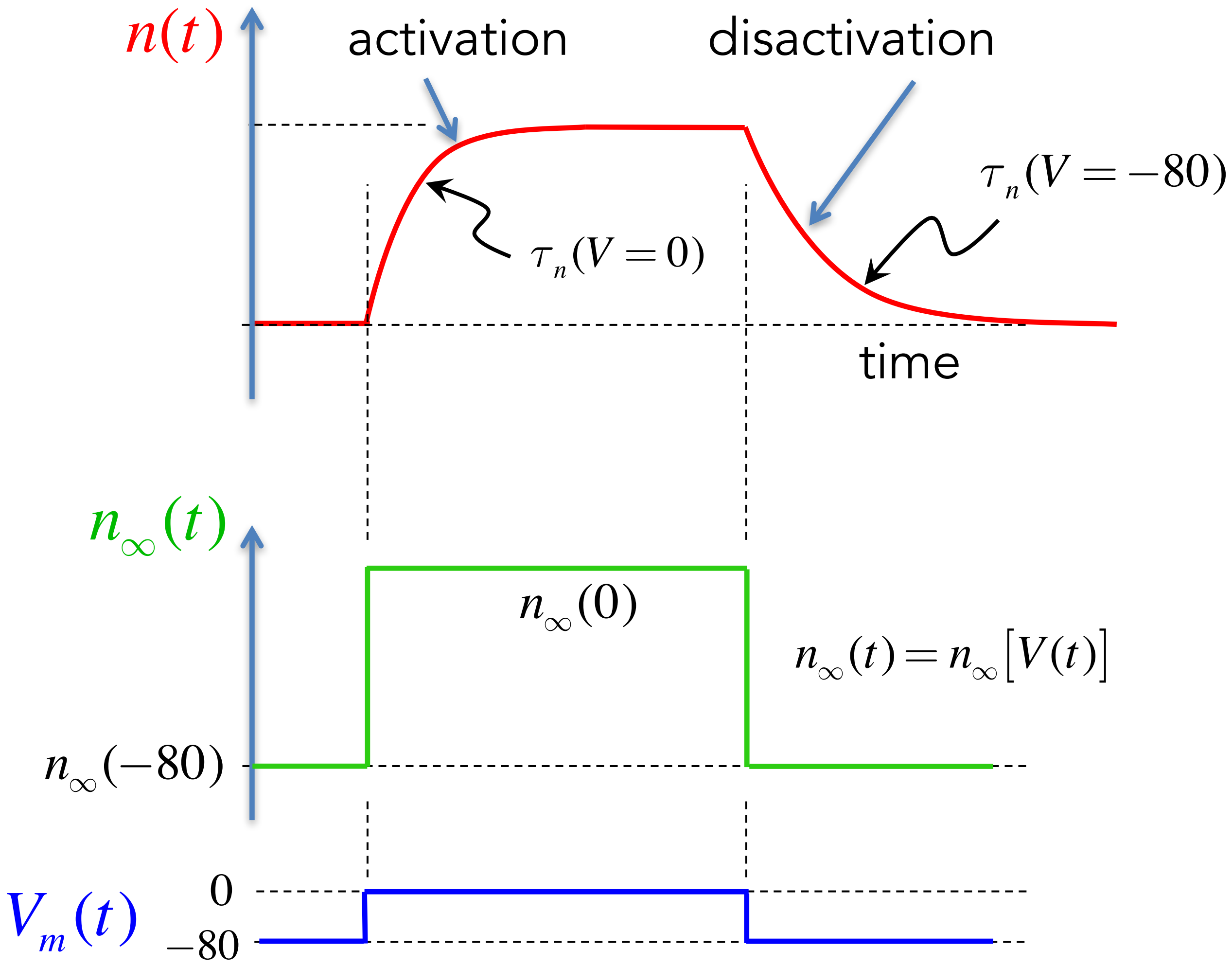
$$\boxed{\tau_n \frac{dn}{dt} = n_\infty - n}$$

But we just derived $n_\infty(V)$!

Remember… $\alpha_n, \beta_n, n_\infty, \tau_n$ are all voltage dependent

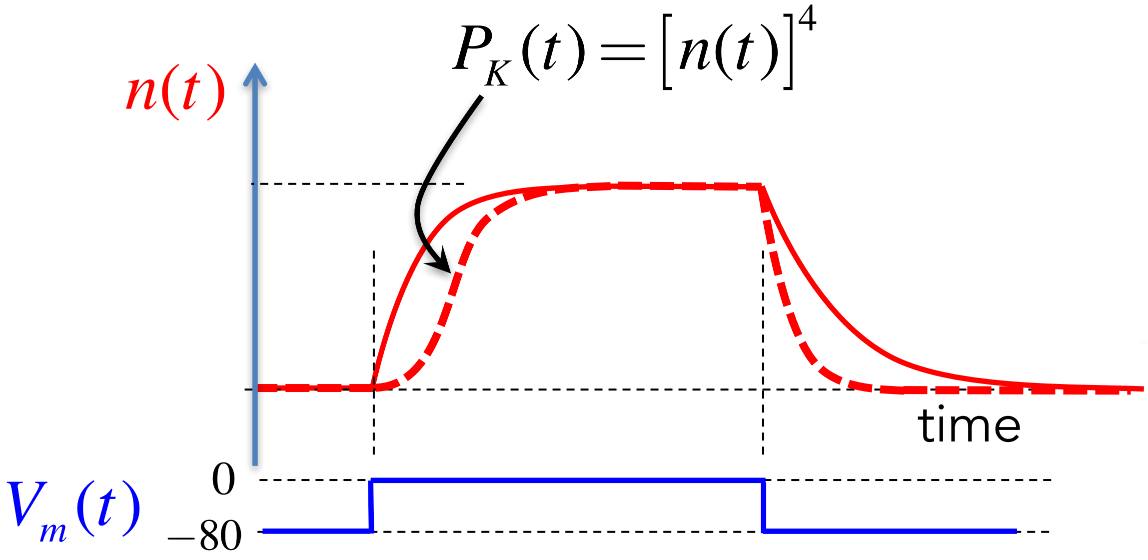
Response to voltage change

How does the gating variable ‘n’ change as we step the membrane potential?

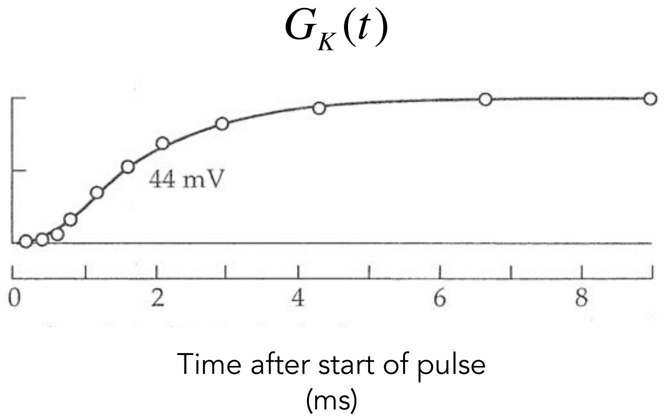


Response to voltage change

How does the ‘open’ probability change as we step the membrane potential?

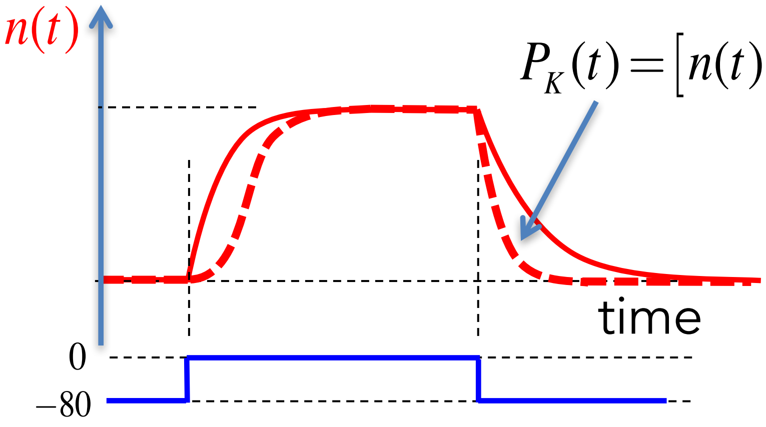


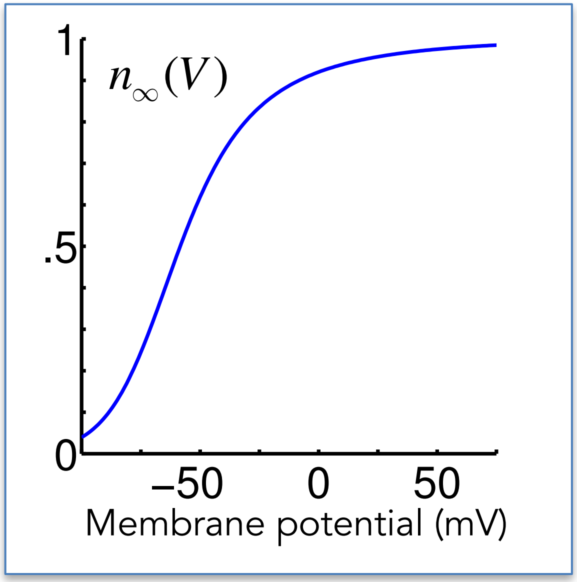
$$P_K(t) = [n(t)]^4$$



- The shape of the K conductance was well fit by a rising exponential raised to the fourth power.
- H & H inferred from this that the K-current was governed by four independent first-order processes! (They didn’t know about the structure of K-channels at the time!)

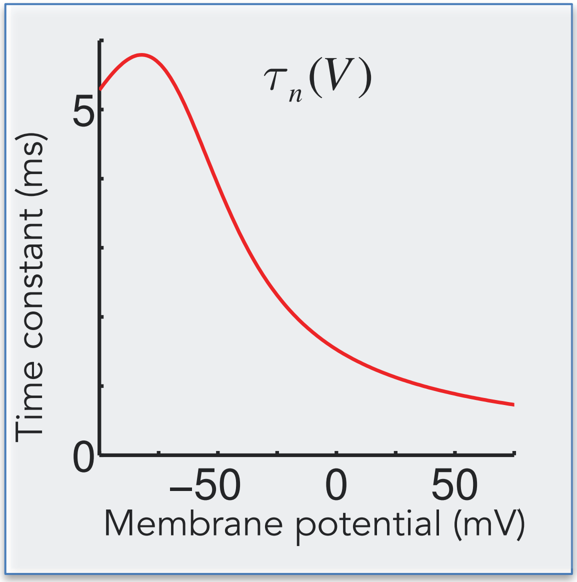
Measuring the parameters





- By measuring the persistent conductance at different voltages, they were able to measure n_∞ as a function of voltage.

- By measuring the time course of the conductance at onset and offset of the voltage steps, they were able to measure τ_n as a function of voltage.



Measuring the parameters

Hodgkin and Huxley summarized their data using algebraic expressions for the rate functions $\alpha_n(V)$, $\beta_n(V)$

$$\alpha_n(V) = \frac{1}{1 - \exp\left(-0.1(V + 55)\right)}$$

$$\beta_n(V) = 0.125 \exp\left(-0.0125(V + 65)\right)$$

V is in mV

α_n, β_n are in ms^{-1}

Remember that…

$$n_\infty = \frac{\alpha_n}{(\alpha_n + \beta_n)}$$

$$\tau_n = \frac{1}{(\alpha_n + \beta_n)}$$

Measuring the parameters

Why did we do all of this?

Because once we have expressions for $n_\infty(V)$ and $\tau_n(V)$, we can integrate the differential equation for n :

$$\tau_n \frac{dn}{dt} = n_\infty - n$$

to get the potassium conductance:

$$G_K = \bar{G}_K n^4$$

and the potassium current:

$$I_K = \bar{G}_K n^4 (V - E_K)$$

We are going to write down an algorithm for how a neuron spikes!

For now here the parts related to the potassium current…

Start with V_m at time step t

Compute $n_\infty(V)$ and $\tau_n(V)$

Integrate $\frac{dn}{dt}$ one time step to get $n(t)$

Compute K current: $I_K = \bar{G}_K n^4 (V - E_K)$

Compute total membrane current $I_m = I_K + I_{Na} + I_L$

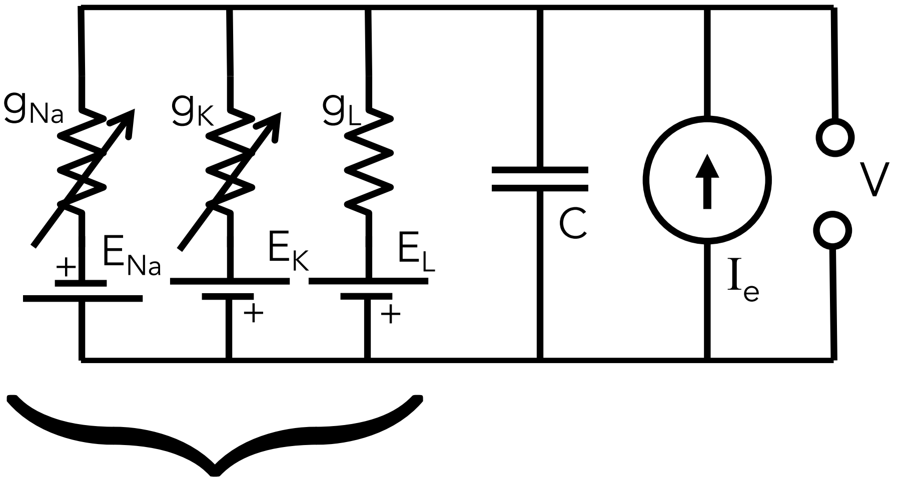
Compute V_∞

Integrate $\frac{dV_m}{dt}$ to get V_m at next time step

Learning objectives for Lecture 2

- To be able to draw the circuit diagram of the HH model
- Understand what a voltage clamp is and how it works
- Be able to plot the voltage and time dependence of the potassium current and conductance
- Be able to explain the time and voltage dependence of the potassium conductance in terms of Hodgkin-Huxley gating variables

Outline of HH model



$$I_m = I_{Na} + I_K + I_L$$

$$I_m(t) + C\frac{dV(t)}{dt} = I_e(t)$$

$$I_{Na} = G_{Na}(V,t)\left(V - E_{Na}\right)$$

The sodium conductance is time-dependent and voltage-dependent

$$E_{Na} = +55mV$$

$$I_K = G_K(V,t)(V - E_K)$$

The potassium conductance is time-dependent and voltage-dependent

$$E_K = -75mV$$

$$I_L = G_L(V - E_L)$$

The leak conductance is neither time-dependent nor voltage-dependent

$$E_L = -50mV$$

9.40 Introduction to Neural Computation
Spring 2018