Neuro 80 Lecture 6

September 23

Nernst: $E_{ion} = \frac{RT}{zF} \ln\left(\frac{[C]_{out}}{[C]_{in}}\right)$

- increasing permeability: ↑ # of ion-specific leak channels
- if membrane was only permeable to one ion, resting potential = equilibrium potential

Ohm's Law: Voltage = I (current) · Resistance

$I = V/R$

$R = 1/g$ where g is conductance (similar to permeability in GHK)

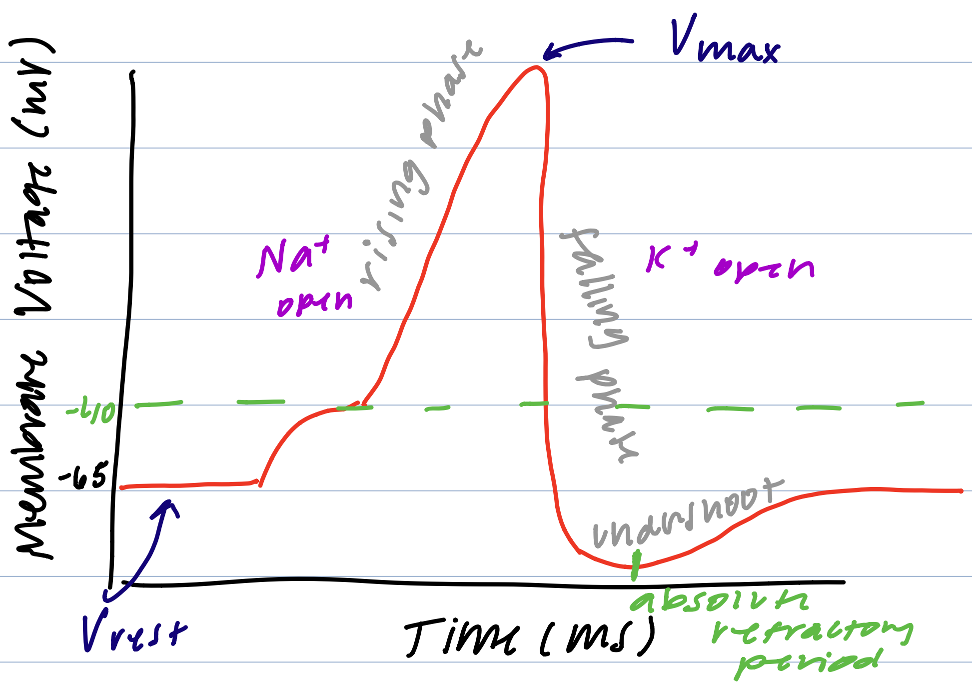
V = electrical driving force = $V_{memb} - E_{ion}$

membrane potential

ion eq potential

$I_{ion} = g_{ion} \times (V_{memb} - E_{ion})$

ionic current = ion's conductance × driving force



Rising Phase (Na^+)

synapses
receptor potentials
local potentials

Depolarization → $\uparrow g_{Na}$ → Depolarization

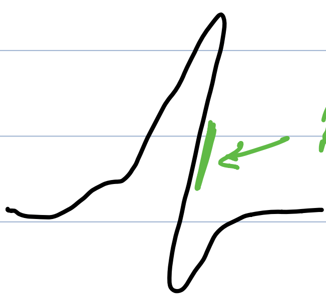
1. g_{Na} increases
2. $P_K >> P_{Na}$
3. Na^+ moves into cell
4. V_m approaches E_{Na}

Na^+ conductance highest here

Falling Phase (K^+)

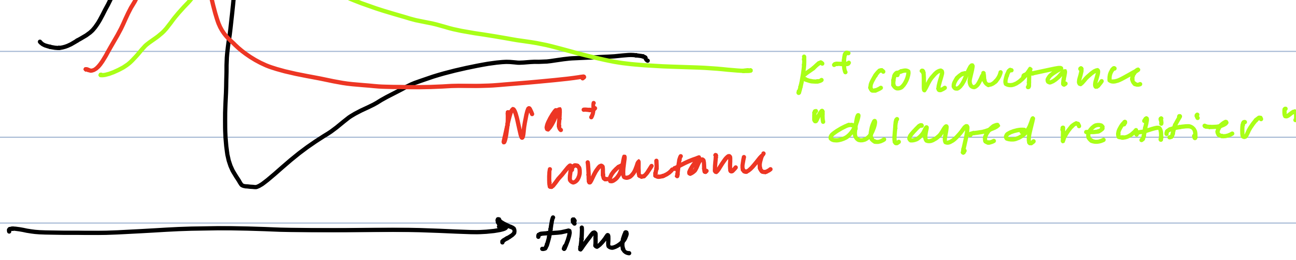
I_{Na} depolarizing the membrane potential

Depolarization → (delayed) $\uparrow g_K$ & $\downarrow g_{Na}$ → ($I_K \uparrow$, $I_{Na} \downarrow$) hyperpolarization → $\downarrow g_K$ → ($I_K \downarrow$) resting pot.



K^+ conductance highest here

1. g_K increases, g_{Na} decreases
2. V_m moves towards E_K

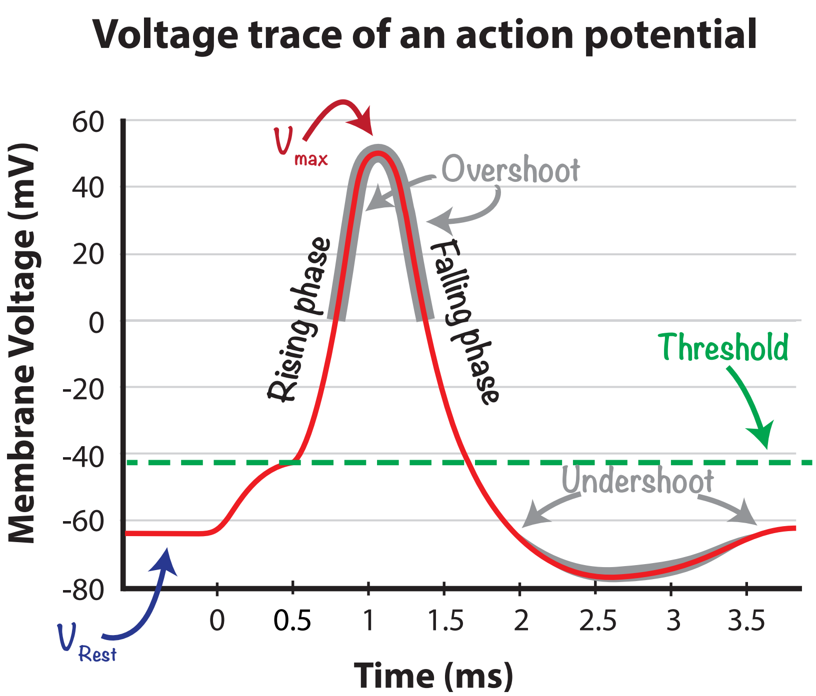


Lecture 6 - The Action Potential

Pre-class notes for September 23, 2019

Reading: *Neuroscience* by Purves et al., pages **46-48**, **49-56**

The brain needs to be able to quickly and faithfully send signals over long distances. Consider the distance from your spine to your lower leg, if the nervous system depended on diffusion alone to propagate a signal that distance it would take over a decade. Simple, passive electrical signaling is fast, but since the membrane is leaky (especially to K^+ ions), a brief, passive increase in the potential would dissipate in less than a millimeter. Thus **Action Potentials**, electrical signals generated by neurons which arise from dramatic changes in ion conductance, propagate signals along the axon and allow for long-range transmission of information. In an action potential, a rapid depolarization is followed by a rapid hyperpolarization. These rapid changes are caused by the opening and closing of voltage gated ion channels in a specific order, which leads to the different phases of the action potential:



Rising Phase - rapid depolarizing stage of the action potential when the there is an increase in Na^+ current and membrane potential quickly rises from around -65 mV (resting potential) to almost +60 mV.

Overshoot - part of the action potential when the membrane potential is greater than 0 mV.

Falling Phase - phase of action potential after the peak (V_{max}) when the Na^+ current decreases and the K^+ current increases causing the membrane potential to hyperpolarize and fall to or below the resting potential (V_{rest})

Undershoot - part of the action potential when the membrane potential is below the resting potential. During the undershoot the membrane potential (Vm) will approach E_K.

Threshold - minimal membrane potential that a neuron must be depolarized to open voltage gated channels and generate an action potential. Typically around -45 mV. Since action potentials are an “all or none” event, if the threshold voltage is reached, an action potential *will* fire. A *local depolarization*, often synaptic potentials or a sensory stimulation will bring the neuron to the threshold voltage.

Refractory Period - the period of time after an action potential when it is more difficult (i.e. needs more depolarization) to reach threshold. This period is divided into the absolute and relative segments. The absolute refractory period is when it is impossible to generate another action potential. The relative refractory period is when more current, is required to generate another action potential.

Since opening additional sodium channels will cause sodium to enter the cell and depolarize the membrane, there is a dynamic relationship between potential and ion flow (or ionic current).

Resistance (**R**) - relative difficulty in passing an electric current through a material. Units = Ohms (Ω**)**

Conductance (**g**) - relative ability of charge to move or pass through a material. *Conductance* is the inverse of *resistance* (**R** = 1/**g**) and can be thought as analogous to permeability in the GHK equation. Units = siemens (S)

Current (**I**) - flow or movement of electric charge. Units = Amperes, amps (A)

Driving Force - the difference between the *membrane potential* and the *equilibrium potential* for a specific ion species.

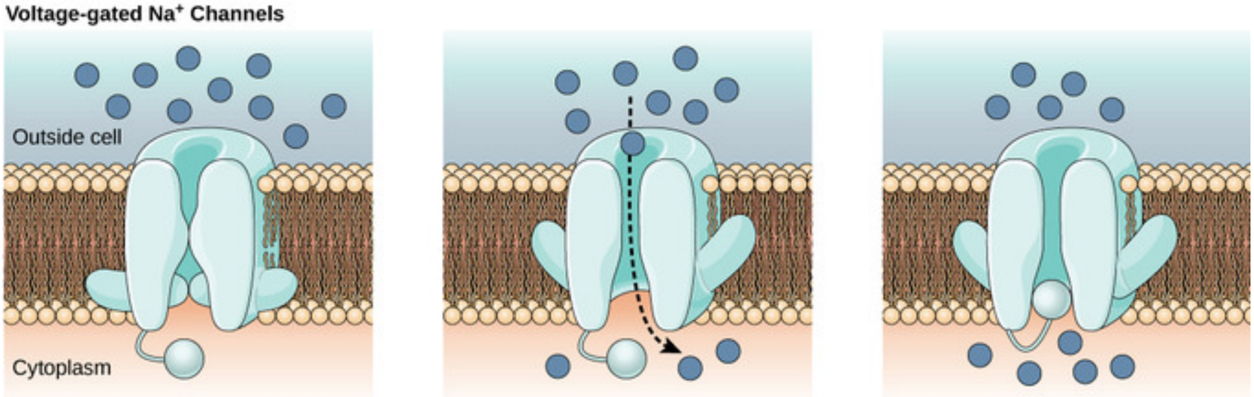
Ohm's Law - relationship of current and voltage through any conducting medium. Traditionally **V = IR**.

$$\underbrace{I_{ion}}_{\text{Current}} = \underbrace{g_{ion}}_{\text{Conductance}}\overbrace{(V_m - E_{ion})}^{\text{Driving Force}}$$

The dramatic increase in sodium conductance during the rising phase of the action potential is due to opening of **Voltage-gated ion channels** - channels whose *conductance* (ability to pass ions) is dependent on membrane voltage. Both voltage-gated Na^+ channels and K^+ channels play critical roles in the action potential and need to be *depolarized* from the resting potential to open. The voltage-gated sodium channels open first and drive the rising phase. Then after about 1 ms, two things happen: the voltage-gated sodium channels *inactivate* and the voltage-gated potassium channels open.

The voltage gated sodium channel consists of a single, long polypeptide that contains 4 domains. Each domain has 6 transmembrane α-helixes (S1-S6). The voltage sensor of each domain is S4, which twists away from the inside when the cell is depolarized from rest (from rest ~-65 mV to ~-40mV). The twist causes the channel to open and allows an inrush of Na^+ into the cell, as the channel is 12 times more permeable to Na^+ than K^+. A millisecond or so after the depolarization induced opening of the channel, one of the cytoplasmic loops (likely the link between domains D3 and D4) swings up and blocks the pore, *inactivating* the channel and stopping the flow of Na^+ ions.

Voltage-gated Na^+ Channels



Closed At the resting potential, the channel is closed.

Open In response to a nerve impulse, the gate opens and Na^+ enters the cell.

Inactivated For a brief period following activation, the channel does not open in response to a new signal.

Inactivation - property of some depolarization-gated ion channels whose conductance goes to zero even though the membrane is depolarized. Voltage-gated Na^+ channels inactivate shortly after opening. The membrane must *hyperpolarize* for the channels to *de-inactivate* and return to their closed conformation before they can open again.

Tetrodotoxin (TTX) - voltage gated sodium channel *antagonist*. Toxin found in some puffer fish that eliminates action potentials.

Voltage-gated potassium channels, as their name suggests, are also opened by depolarization. However, they open slower than voltage-gated Na^+ channels and drive the rate of the falling phase. Since E_K is hyperpolarized relative to E_{Na}, they rectify or return the membrane potential to a negative value and are known as **delayed rectifiers**.

Learning Objectives: (By the end of Lecture 6 you should be able answer the following)

1. Define driving force, conductance and current and know how they are related by Ohm's law.
2. Diagram an action potential as a function of voltage over time and label the following stages:
   i. resting potential
   ii. rising phase
   iii. falling phase
   iv. overshoot
   v. undershoot
3. Describe or illustrate how changes in Na^+ and K^+ conductances influence the membrane potential and lead to an action potential.
4. Describe the ionic events (which channels are involved, direction and magnitude of ion flow) that lead to:
   i. rapid depolarization of an action potential (rising phase)
   ii. rapid hyper polarization (falling phase)
   iii. hyper polarization (undershoot)
5. Define and describe the biological mechanism for each of the following:
   i. threshold
   ii. all-or-none property of action potentials
   iii. absolute refractory period

MCB/Neuro 80 - Neurobiology of Behavior

Today's Topic:

Circuits of the Nervous System

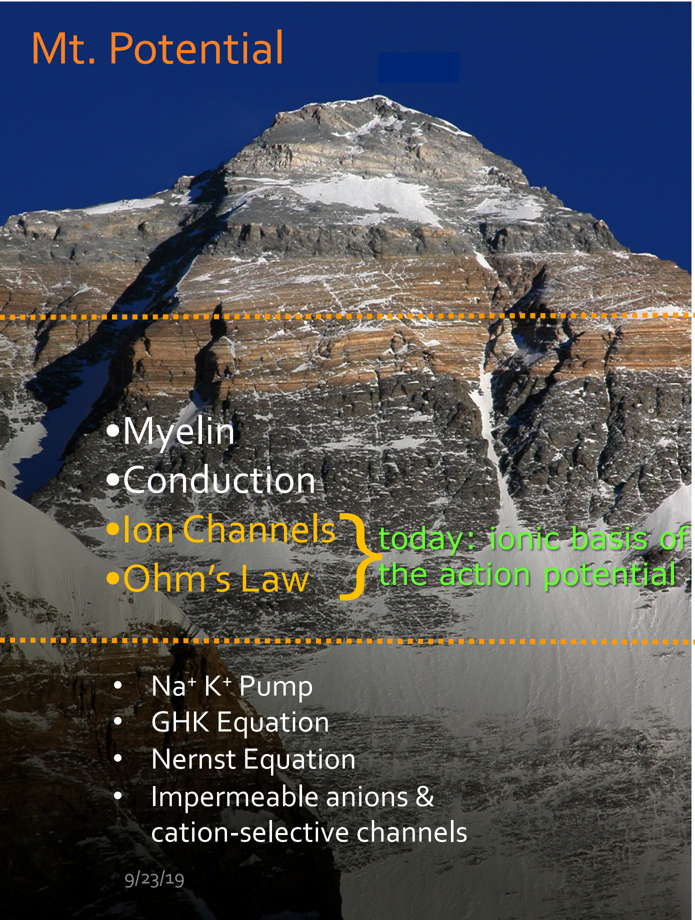
Lecture

Optional reading: Purves et al., Neuroscience 6th pages

Lecture notes, review questions, office hour times available at:

https://canvas.harvard.edu/courses/59120

Mt. Potential



Synaptic Potential

- Myelin
- Conduction
- Ion Channels
- Ohm's Law

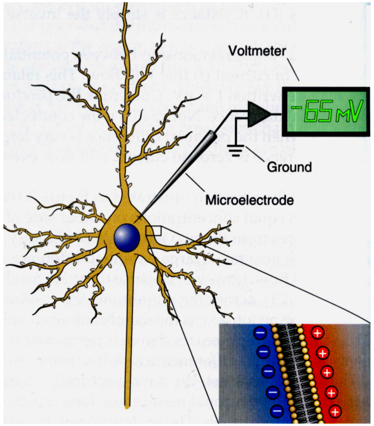
$\left.\begin{array}{l}\text{Ion Channels}\\ \text{Ohm's Law}\end{array}\right\}$ today: ionic basis of the action potential

Action Potential

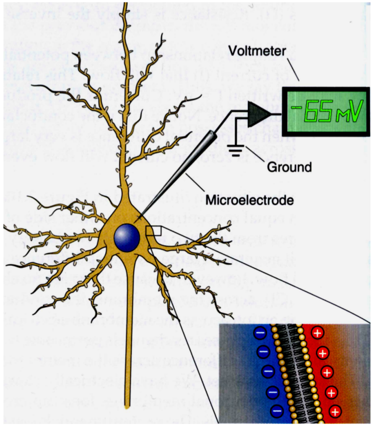
- Na^+ K^+ Pump
- GHK Equation
- Nernst Equation
- Impermeable anions & cation-selective channels

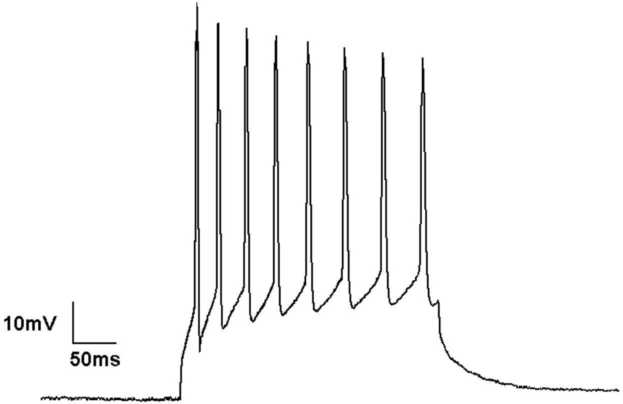
Resting Potential

Intracellular recording of action potentials: rapid fluctuations in membrane potential



Intracellular recording of action potentials: rapid fluctuations in membrane potential





How Does This Occur???

Remember Nernst potentials

$$E_{ion} = \frac{RT}{zF} ln \frac{[C_{out}]}{[C_{in}]}$$

Outside Conc.	Inside Conc	Ratio Out:In	Eq. Potential (37°C)
$[K^+]_o$ = 5 mM	$[K^+]_i$ = 107 mM	1:20	-80 mV
$[Cl^-]_o$ = 150 mM	$[Cl^-]_I$ = 13 mM	11.5:1	-65 mV
$[Na^+]_o$ = 150 mM	$[Na^+]_i$ = 15 mM	10:1	60 mV

- If “left to its own devices” i.e., if the membrane was only permeable to just one of these ions, the resting potential would do what?

If a cell's membrane was permeable to only one type of its ion, its membrane potential would

only be figured out using the GHK equation

be exactly the Nernst potential for that ion species

be 0 mV

be hyperpolarized

Remember Nernst potentials

$$E_{ion} = \frac{RT}{zF} ln \frac{[C_{out}]}{[C_{in}]}$$

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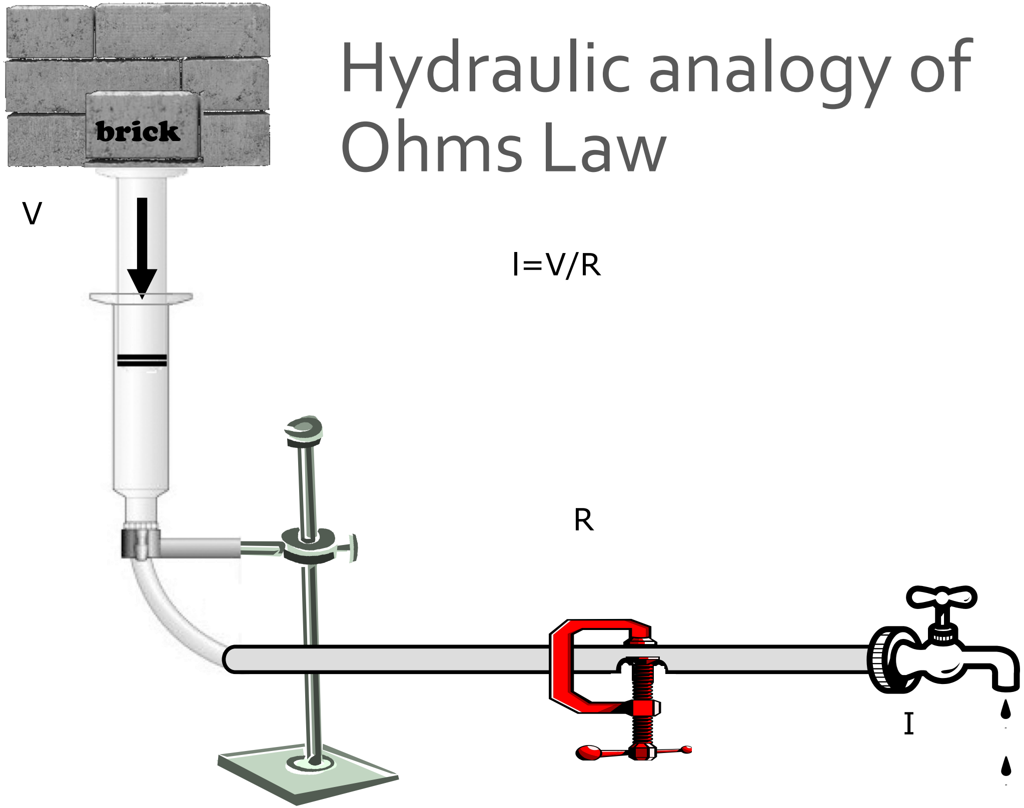
- If "left to its own devices" i.e., if the membrane was only permeable to just one of these ions, the resting potential would be the same as that equilibrium potential. (A glial cell is only permeable to K^+ and its Resting potential is determined by the Nernst Potential of K^+)
- At rest in neurons: $P_K > P_{Cl} > P_{Na}$ and the membrane potential is near E_K (GHK)
- If the relative amount of Na^+ channels suddenly increased what would happen?
- The membrane potential would move toward E_{Na}^+ because of a Sodium Current

Ohm's law: a way to figure out ionic currents

- V (voltage) = I (current) x R (resistance)
- 1 volt (V) = 1 amp (A) x 1 ohm (Ω)
- or I=V/R

Hydraulic analogy of Ohms Law

$I=V/R$



Ohm's law

- V (voltage) = I (current) x R (resistance)
- 1 volt (V) = 1 amp (A) x 1 ohm (W)
- or I=V/R
- R= 1/g (g is "conductance" and similar to permeability in GHK, thus I=gV)
- V is the electrical "driving force" which is the difference between the membrane potential (Vmemb) and the ion's equilibrium potential (Eion)
- So, ionic current = the ion's conductance x its driving force
  - $I_K = g_K * (V_{mem} - E_K)$

Let's do the same for the other ions

Ohm's law

- V (voltage) = I (current) x R (resistance)
- 1 volt (V)   = 1 amp (A) x 1 ohm (W)
- or I=V/R
- R= 1/g (g is "conductance" and similar to permeability in GHK, thus I=gV)
- V is the electrical "driving force" which is the difference between the membrane potential (Vmemb) and the ion's equilibrium potential (Eion)
- So, ionic current = the ion's conductance x its driving force
  - $I_K = g_K * (V_{mem} - E_K)$
  - $I_{Na} =$
  - $I_{Cl} =$

Based on Ohm's law then, the amount of current (I_{ion}) is affected by 2 things:

1. The driving force on the ion which is the difference between:

   Membrane Potential (V_m)

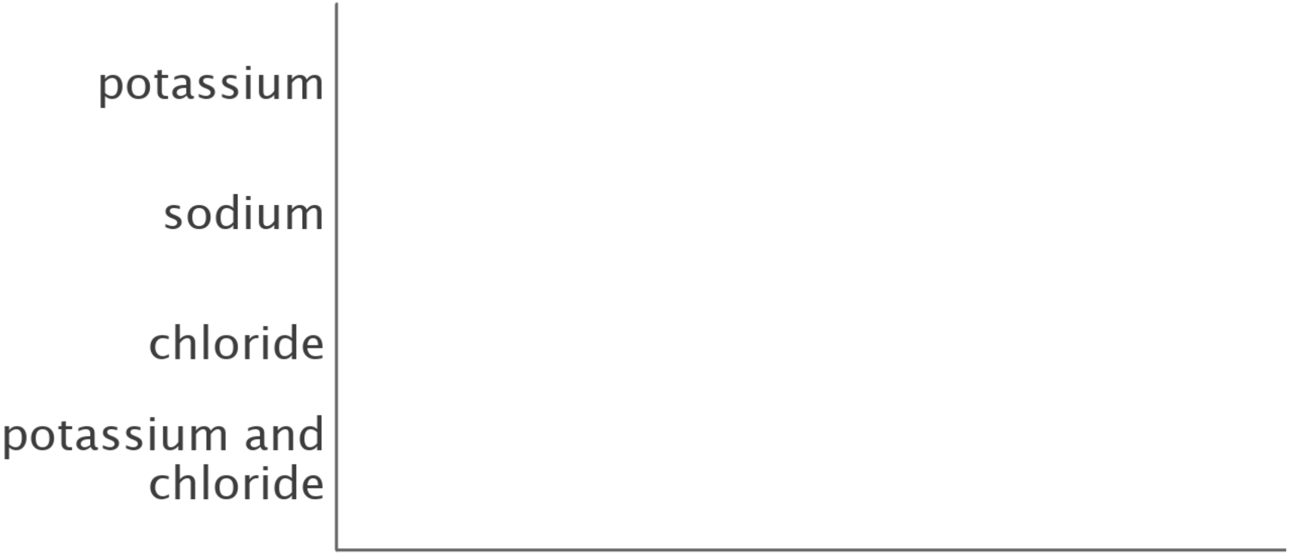
   &

   Ion's equilibrium potential (E_{ion})

2. The conductance (g_{ion})

Remember Ohm's relation $I_{ion} = g_{ion}\,(V_{memb} - E_{ion})$

If the membrane potential of a neuron is at +60mV which ion or ions has or have the smallest driving force? (one best answer)



Certain chloride channels are always open; what happens to the chloride current when the membrane potential reaches +60mV?

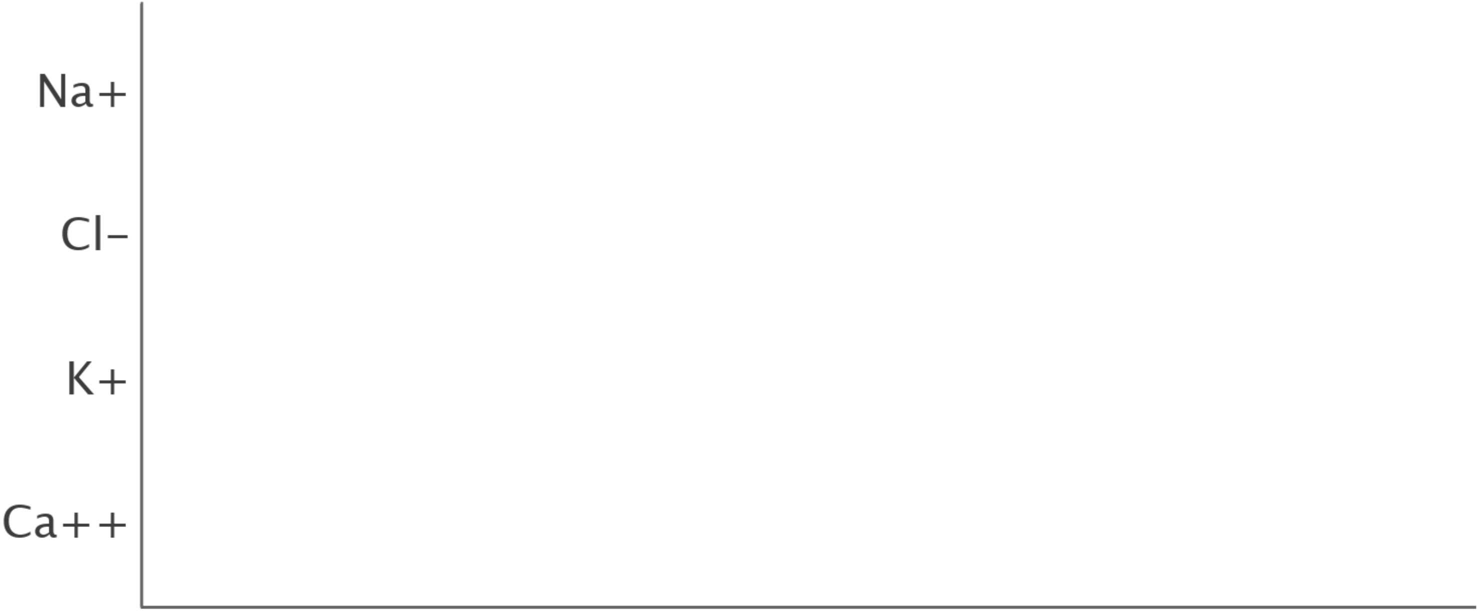
It increases as chloride flows out of the cell

it dramatically decreases

It increases as chloride flows into the cell

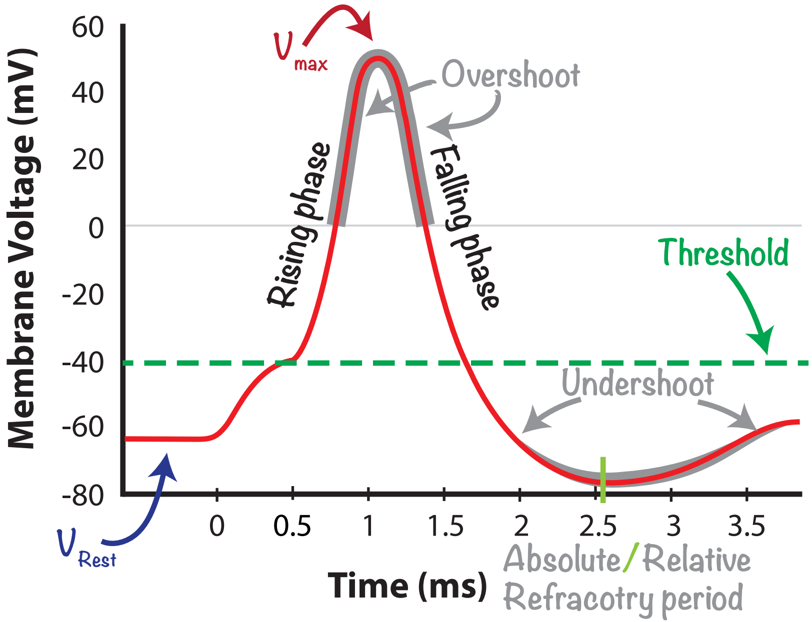
Chloride cant flow because of very low conductance and permeability

At resting potential, which ion has the largest driving force?

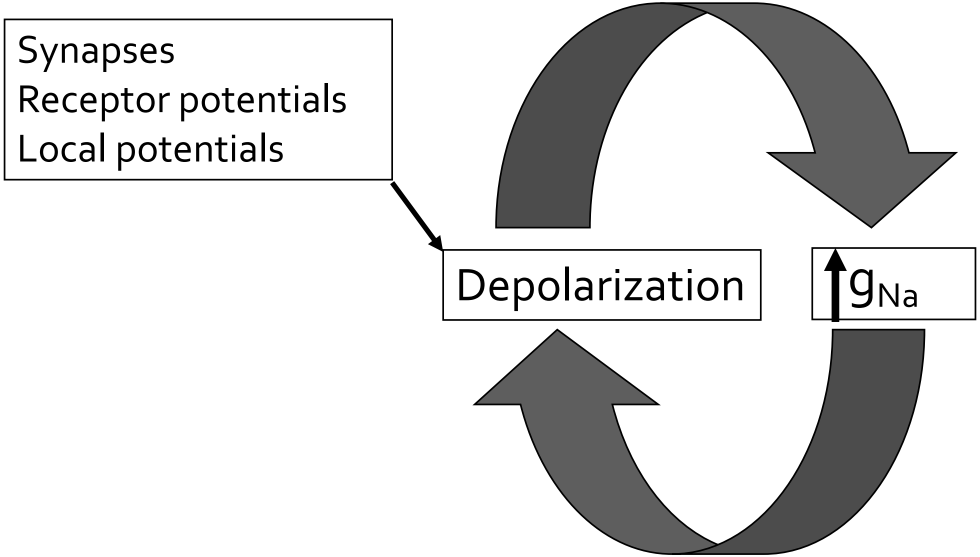


I_{Na+} and I_{K+} (which are based on their conductances and driving forces) are responsible for the shape of the action potential

Action potential – explained by a causal relation between Na^+ and K^+ currents



Rising Phase: all about Na^+ - Positive feedback in the action potential

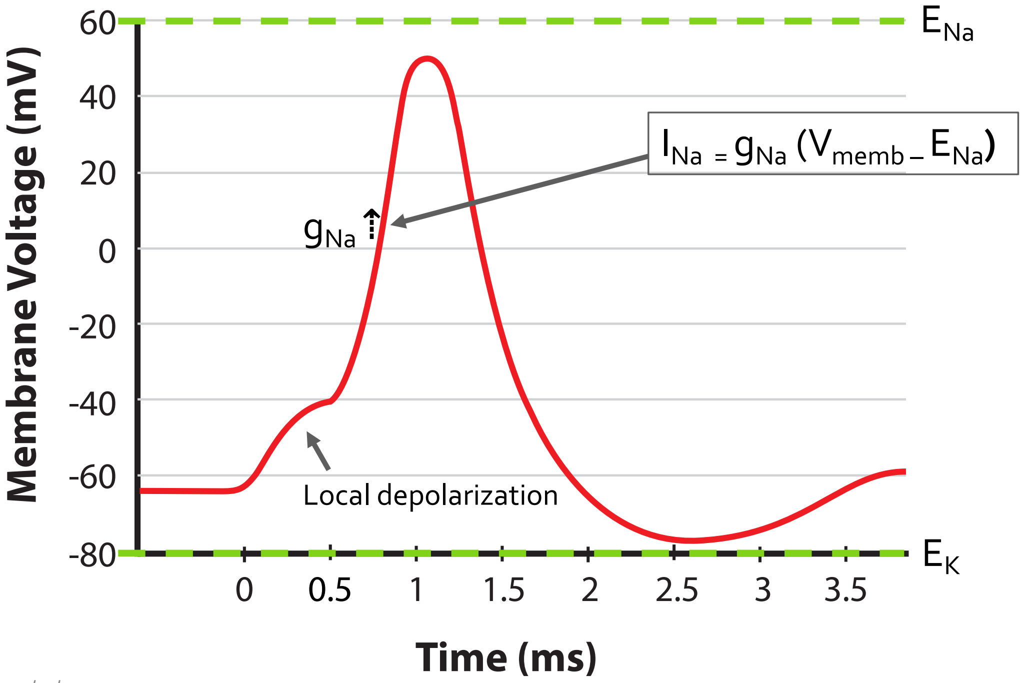


What will happen to the sodium current (I_{Na}) when g_{Na+} rises?

What will happen to the membrane potential when Na^+ current (I_{Na+}) rises?

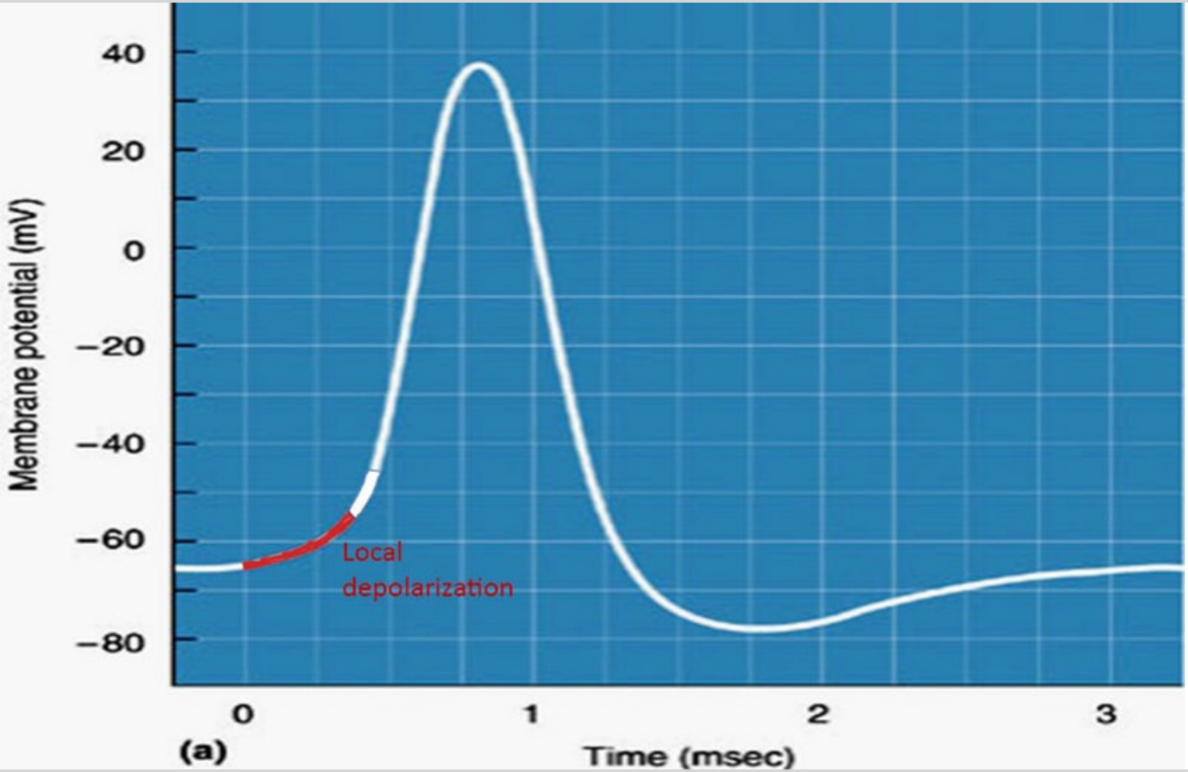
"Regenerative" in the sense that depolarization begets more depolarization

Rising phase

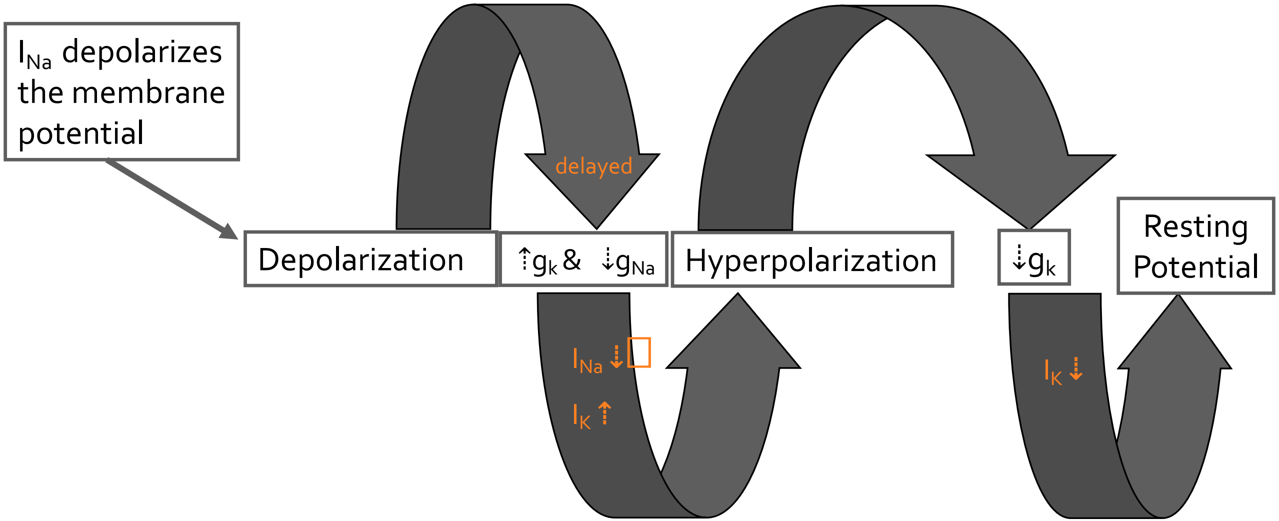


- If local depolarization causes V_m to go above threshold, g_{Na} increases
- $P_K >> P_{Na}$
- Na^+ moves into the cell
- V_m approaches E_{Na}

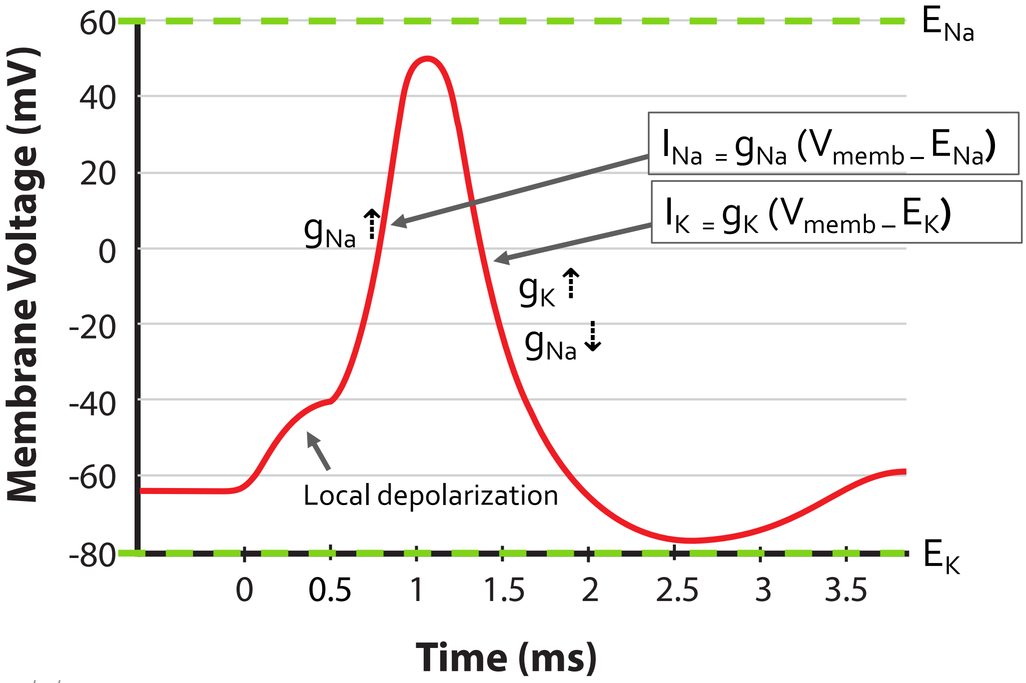
Where is Na current (I_Na) greatest?



Falling Phase: all about K$^+$
Negative feedback in the action potential



Falling phase

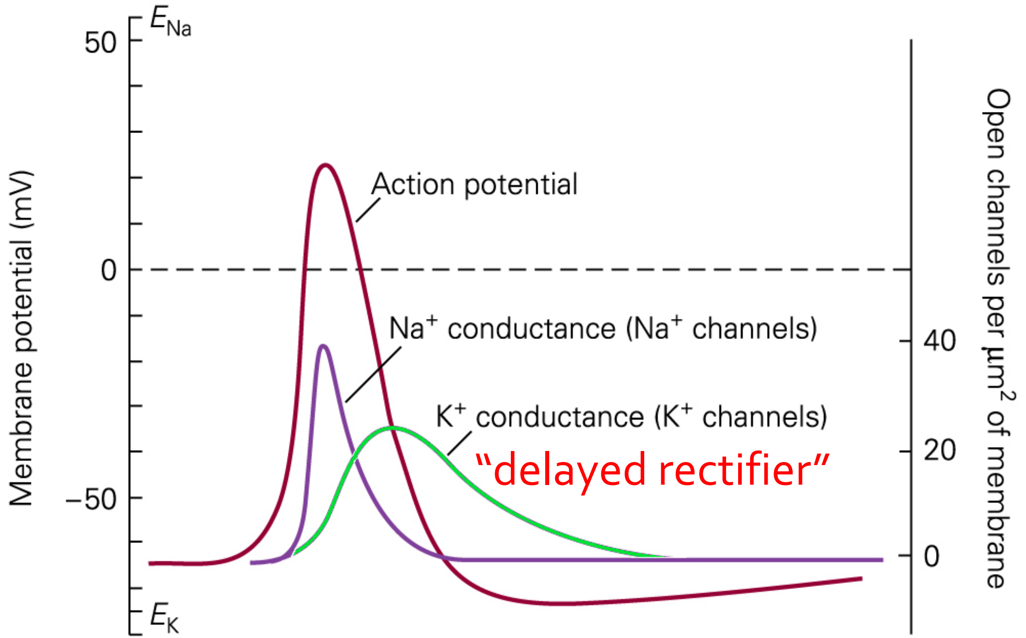


Approximately 1 ms after start of the action potential

- g_K increases
- g_{Na} decreases
- V_m moves toward E_K

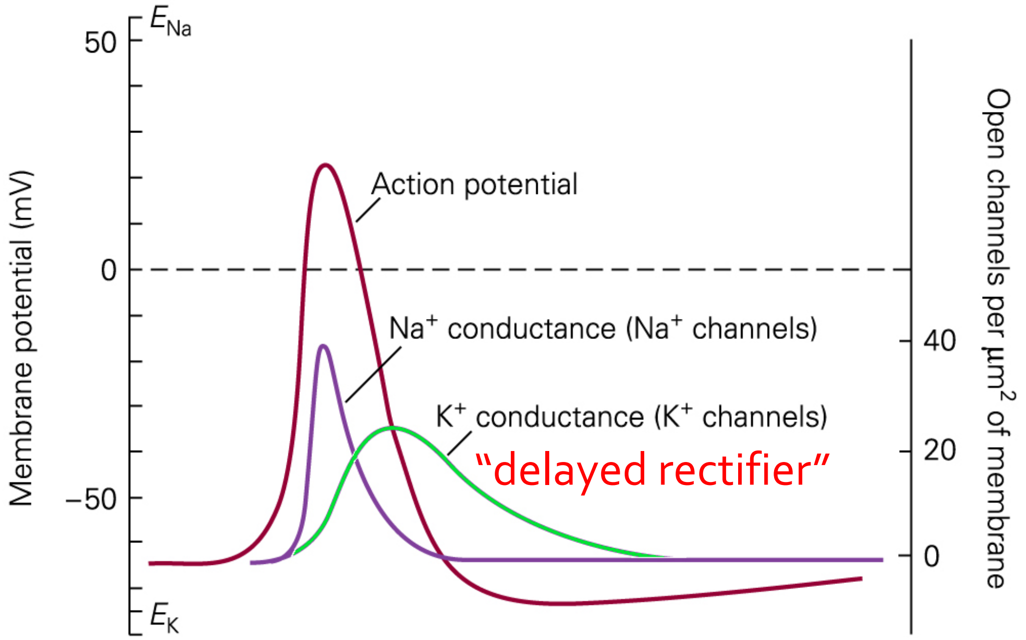
- Which direction do the K^+ ions flow?

Hodgkin and Huxley's model (via voltage clamp experiments)



Q: Why does g_{Na} go up and
why does g_{Na} go down?
A: Voltage-gated Na channels open and then inactivate

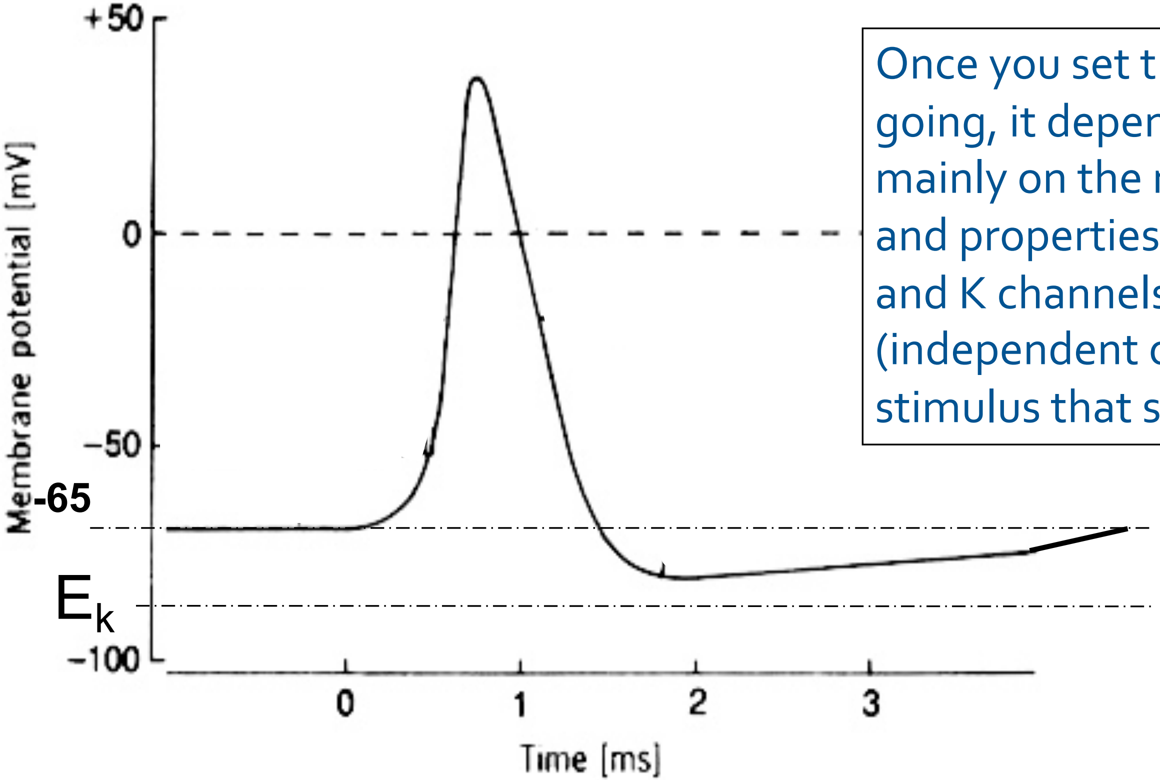
Hodgkin and Huxley's model (via voltage clamp experiments)



Q: Why is there an undershoot?

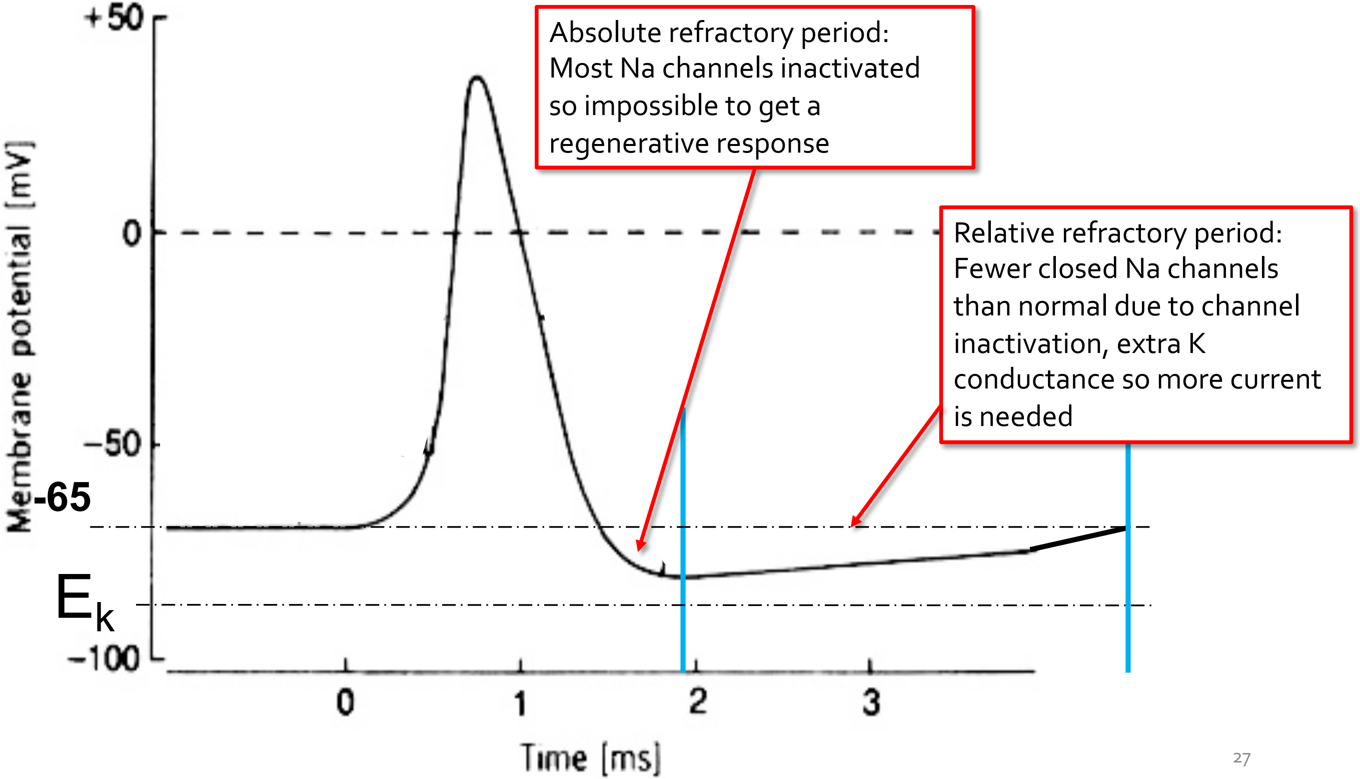
A: Delayed Rectifier Channel

All-or-none property of action potentials



Once you set the AP going, it depends mainly on the number and properties of Na and K channels (independent of the stimulus that starts it)

Refractory Period



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  - absolute refractory period