

# Biologisk Fysikk UiO

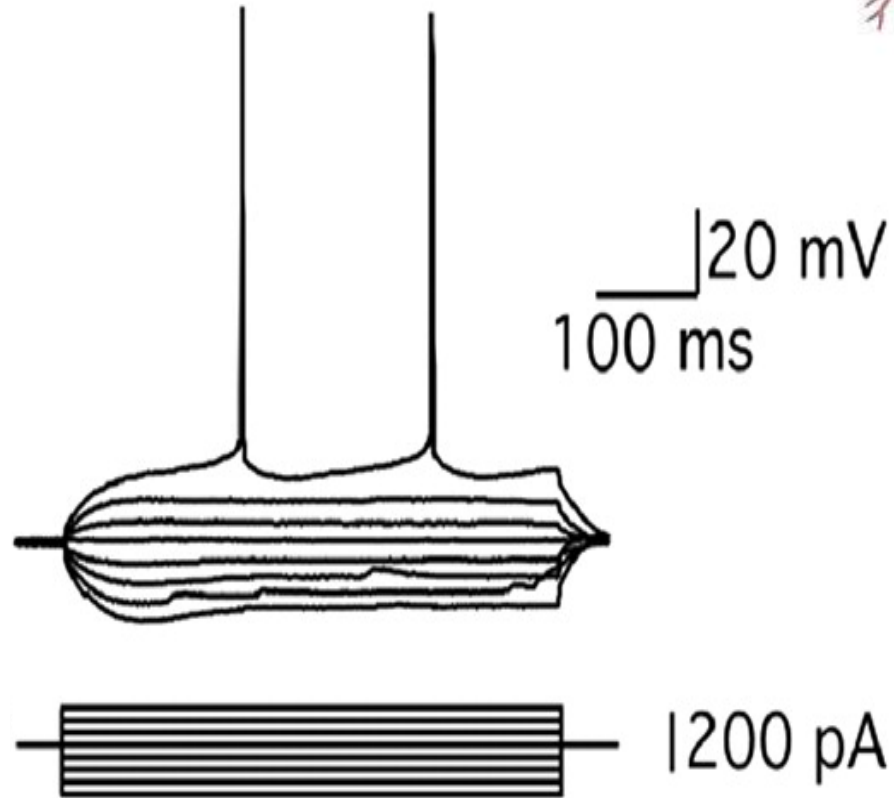
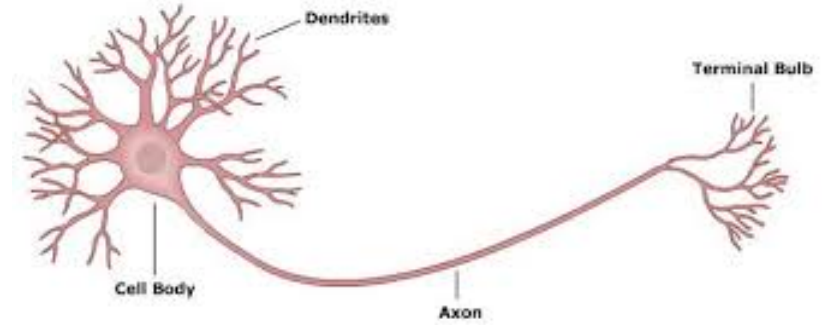
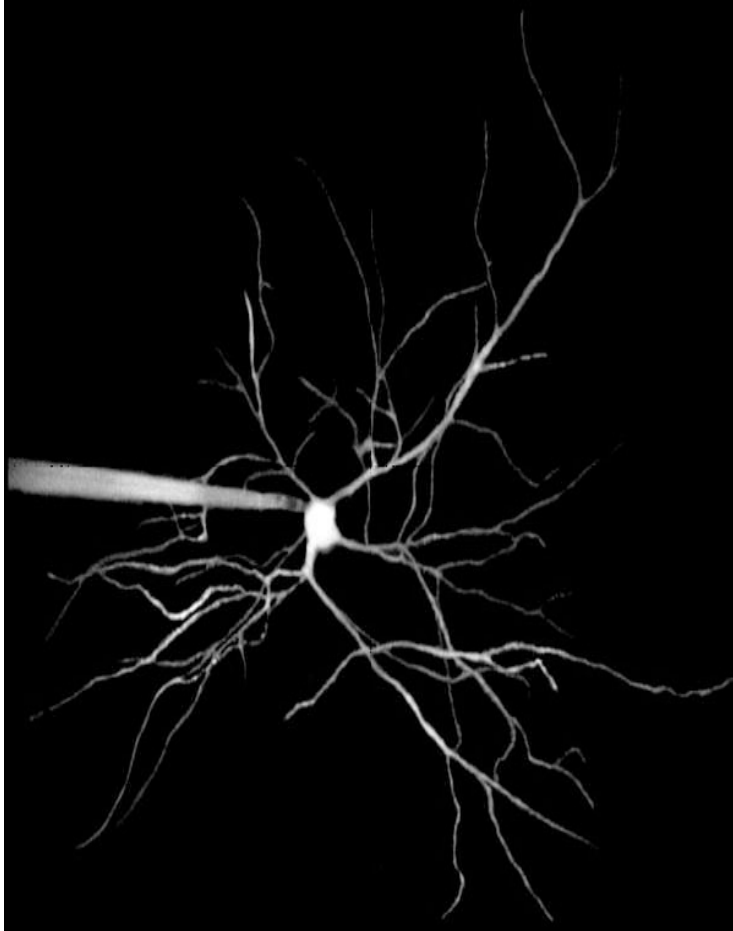
## *Hodgkin-Huxley-model*

*Geir Halnes*

Norwegian University of Life Sciences,

# #0: Introduction

# Action potentials

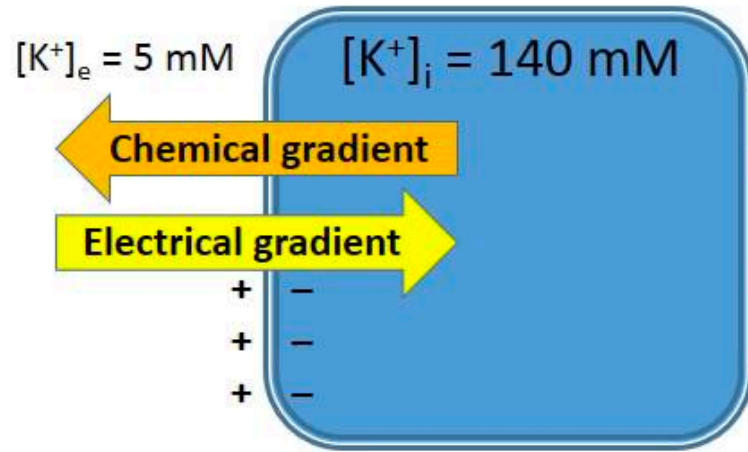


Neurons fire so-called action potentials.

The generation of these will be the main topic of this lecture.

ACTION-POTENTIAL-CURRENT-CLAMP

# Reversal (Nernst) - Potential



## Typical values:

$$E_K \sim -80 \text{ mV}$$

$$E_{Na} \sim 50 \text{ mV}$$

$$E_{Cl} \sim -60 \text{ mV}$$

$$E_{Ca} \sim 120 \text{ mV}$$

## Equilibrium between diffusion and electric drift:

One species: 
$$E_{eq,K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i},$$

Several species:

$$E_m = \frac{RT}{F} \ln \left( \frac{P_{Na^+} [Na^+]_o + P_{K^+} [K^+]_o + P_{Cl^-} [Cl^-]_i}{P_{Na^+} [Na^+]_i + P_{K^+} [K^+]_i + P_{Cl^-} [Cl^-]_o} \right)$$

## Resting neuron:

$$V_m \sim -65 \text{ mV}$$

$I_K$  will be hyperpolarizing.

$I_{Na}$  and  $I_{Ca}$  depolarizing.

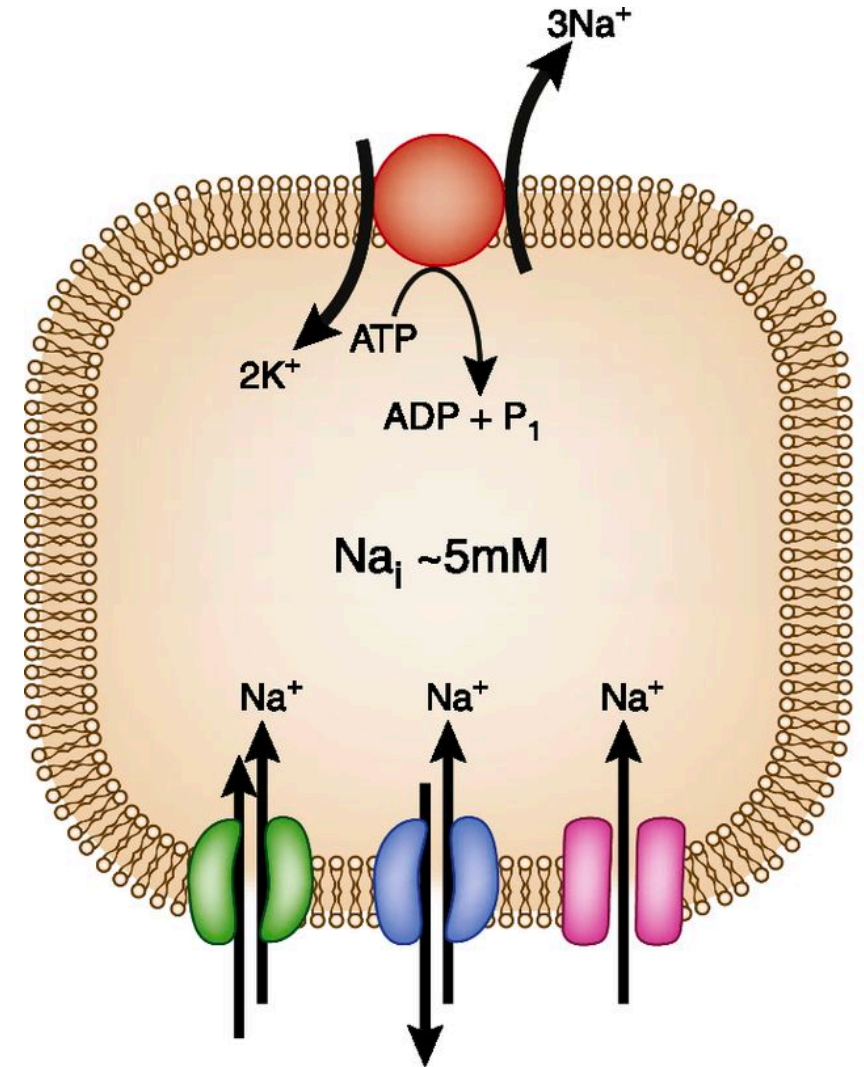
# Constant ion concentrations?

## Reason for concentration gradients:

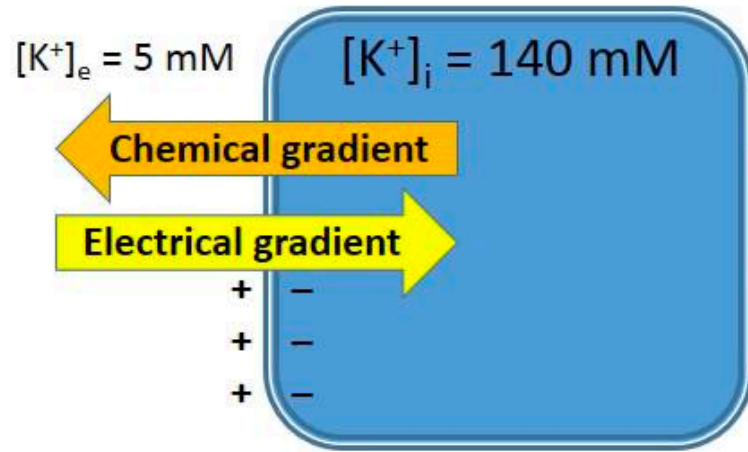
- Ion pumps & co-transporters.
  - Use energy to pump ions against gradients.
- Example:  $\text{Na}^+/\text{K}^+$  exchanger (ATPase)-pump

## Constant concentrations:

- A normal assumption in neuroscience is that the ion concentrations are constant!
- Reason:
  - Number of e.g.,  $\text{Na}^+$  that cross the membrane during an action potential so small that it doesn't change the concentration much
  - Pump resets original balance between action potentials
  - Exceptions sometimes made for  $\text{Ca}^{2+}$ .



# Reversal (Nernst) - Potential



One species: 
$$E_{eq,K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i},$$

Several species:

$$E_m = \frac{RT}{F} \ln \left( \frac{P_{Na^+} [Na^+]_o + P_{K^+} [K^+]_o + P_{Cl^-} [Cl^-]_i}{P_{Na^+} [Na^+]_i + P_{K^+} [K^+]_i + P_{Cl^-} [Cl^-]_o} \right)$$

## Reason for concentration gradients:

- Ion pumps & co-transporters.
- Use energy to pump ions against gradients.

## Constant concentrations:

Typical values:

$$E_K \sim -80 \text{ mV}$$

$$E_{Na} \sim 50 \text{ mV}$$

$$E_{Cl} \sim -60 \text{ mV}$$

$$E_{Ca} \sim 120 \text{ mV}$$

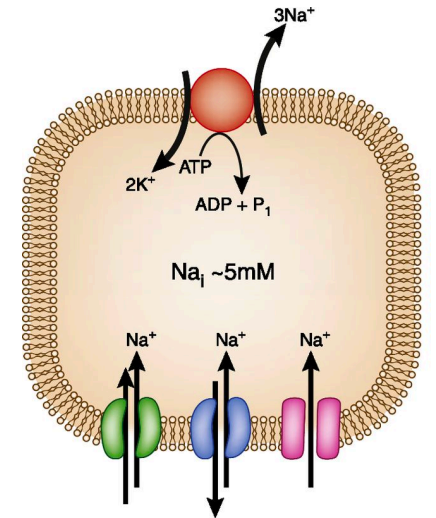
Resting neuron:  $V_m \sim -65 \text{ mV}$

$I_K$  will be hyperpolarizing.

$I_{Na}$  and  $I_{Ca}$  depolarizing.

Reason for concentration gradients:

Ion pumps & co-transporters



# Passive (RC) neuron model

Group all pumps and passive leakage currents into one current:

$$I_L = g_L(V_m - E_L)$$

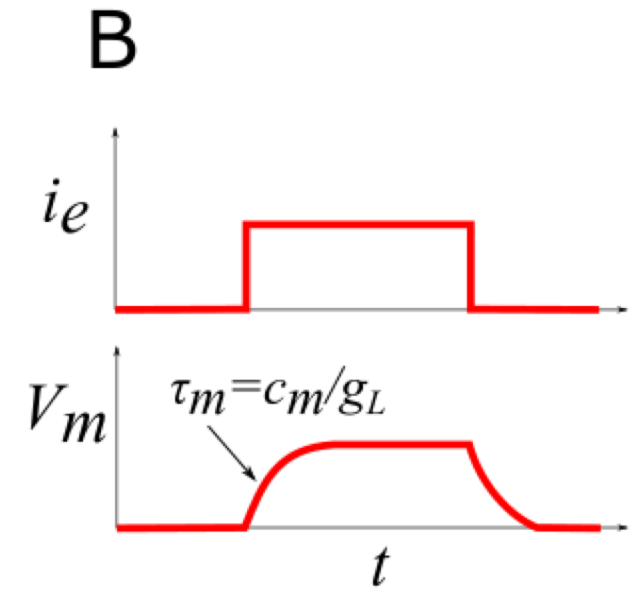
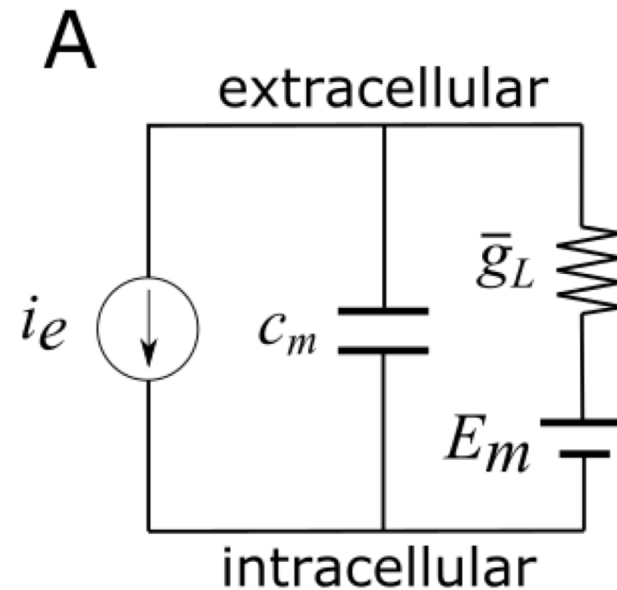
**Quasi-Ohmic:**

Linear with deviance from  $E_L$ .  
Ok approximation.

When  $I_L$  is the only ionic current,  
 $E_L$  will be identical to the resting potential

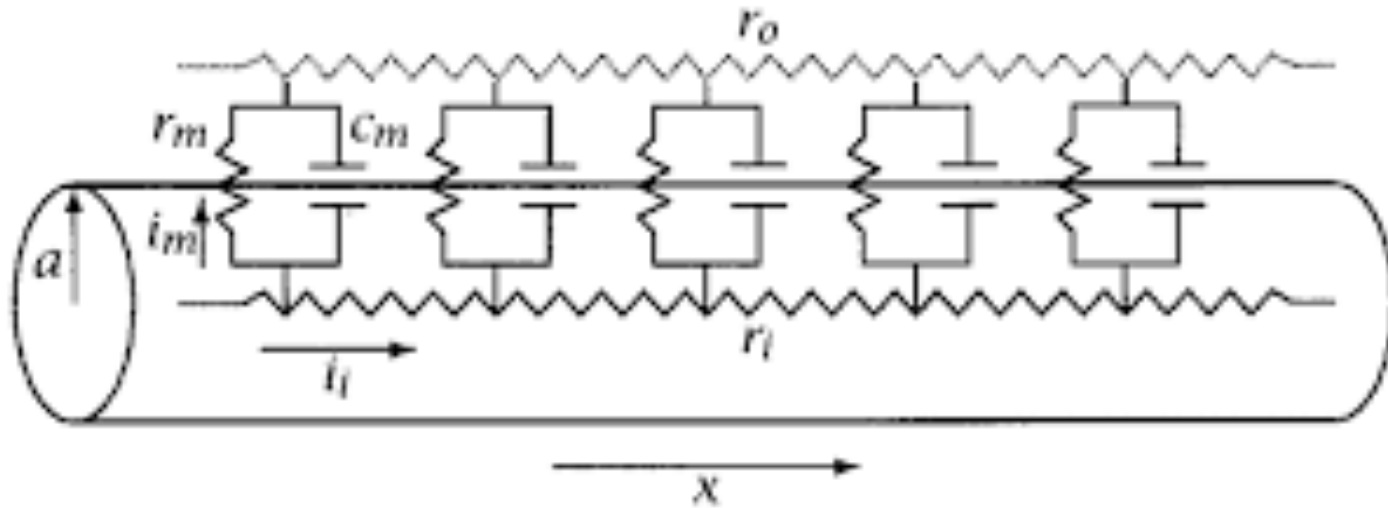
**Circuit equation:**

$$c_m \frac{dV_m}{dt} = -g_L(V_m - E_L) - i_{stim}$$



# Cable equation

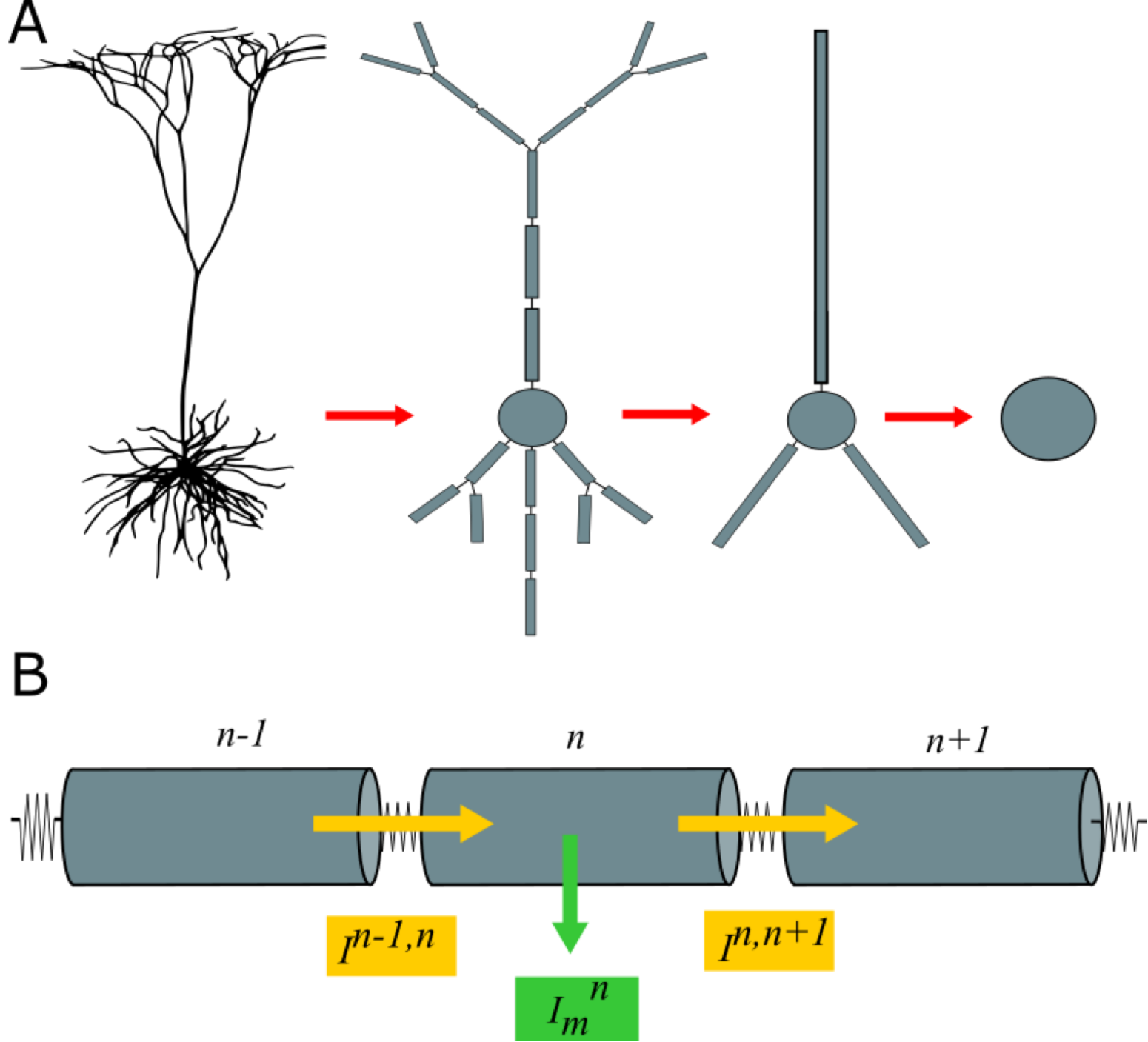
Connect many RC's together, to get «cable»:



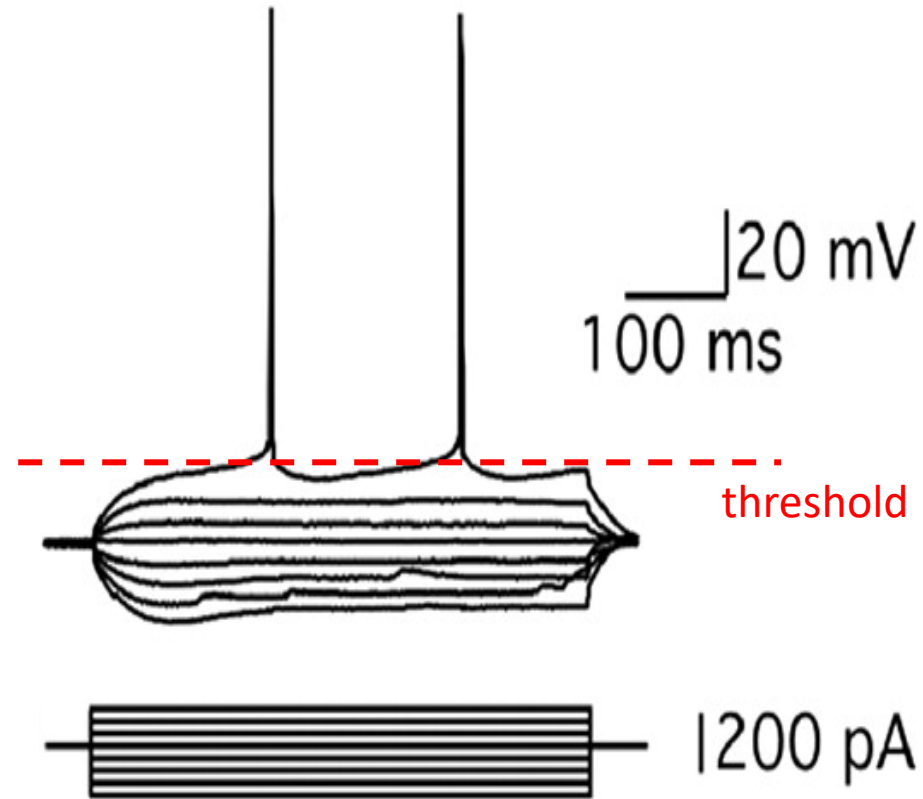
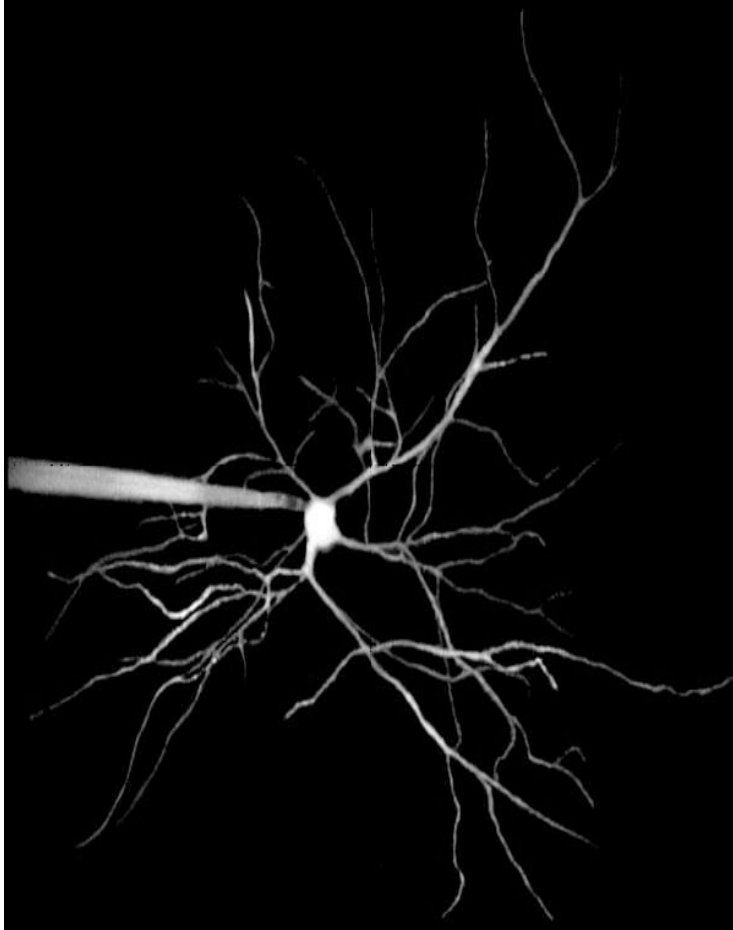


Used for multicompartments models of neurons,  
To model signal propagation in dendrites and axons.

I will stay «single-compartment»  
in this lecture.



# Action potentials:

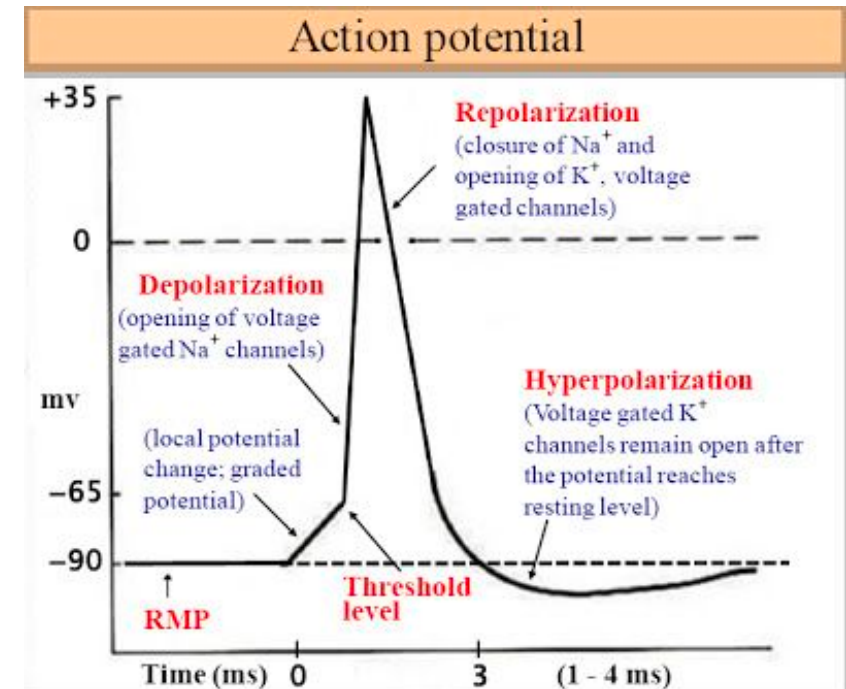
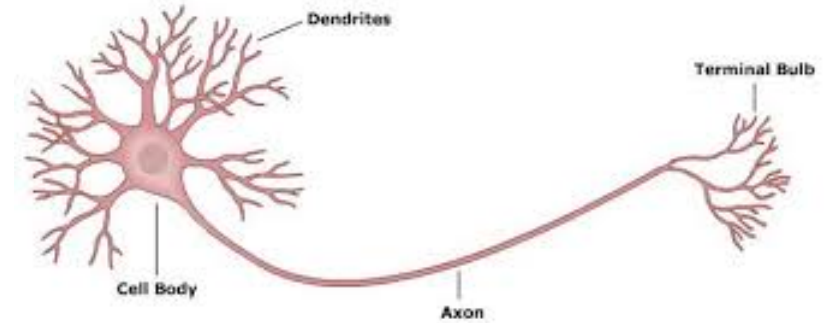


Passive model ok for small current injections, but **exciting** things happen when the membrane potential is depolarized up to a certain threshold

ACTION-POTENTIAL-CURRENT-CLAMP

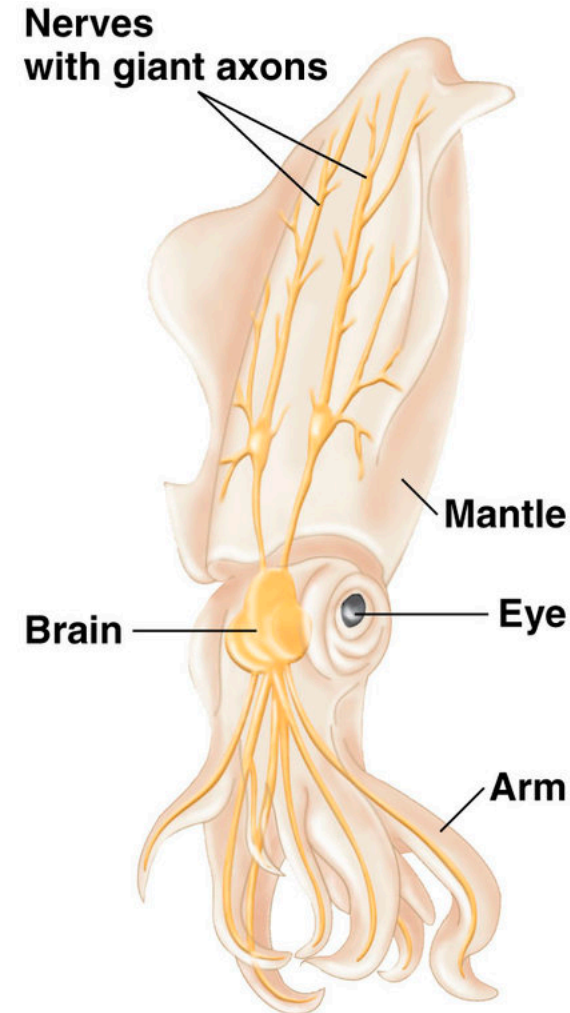
# Action potential (AP)

- The main communication «unit» in the brain
- Key features of the AP
  - Rapid depolarization followed by rapid repolarization (often also hyperpolarization) of the membrane potential
  - Propagate down the axon with little loss in shape



# Hodgkin & Huxley (HH)

- Hodgkin & Huxley (1952) made model of AP generation and propagation in squid giant axons
  - Among the first qualitatively successful theories in neuroscience
  - Predicted AP shape and propagation speed
  - Circuit model
  - Got the Noble prize for this work.
  - Formalism still in use



© 2012 Pearson Education, Inc.



# Space-clamp configuration

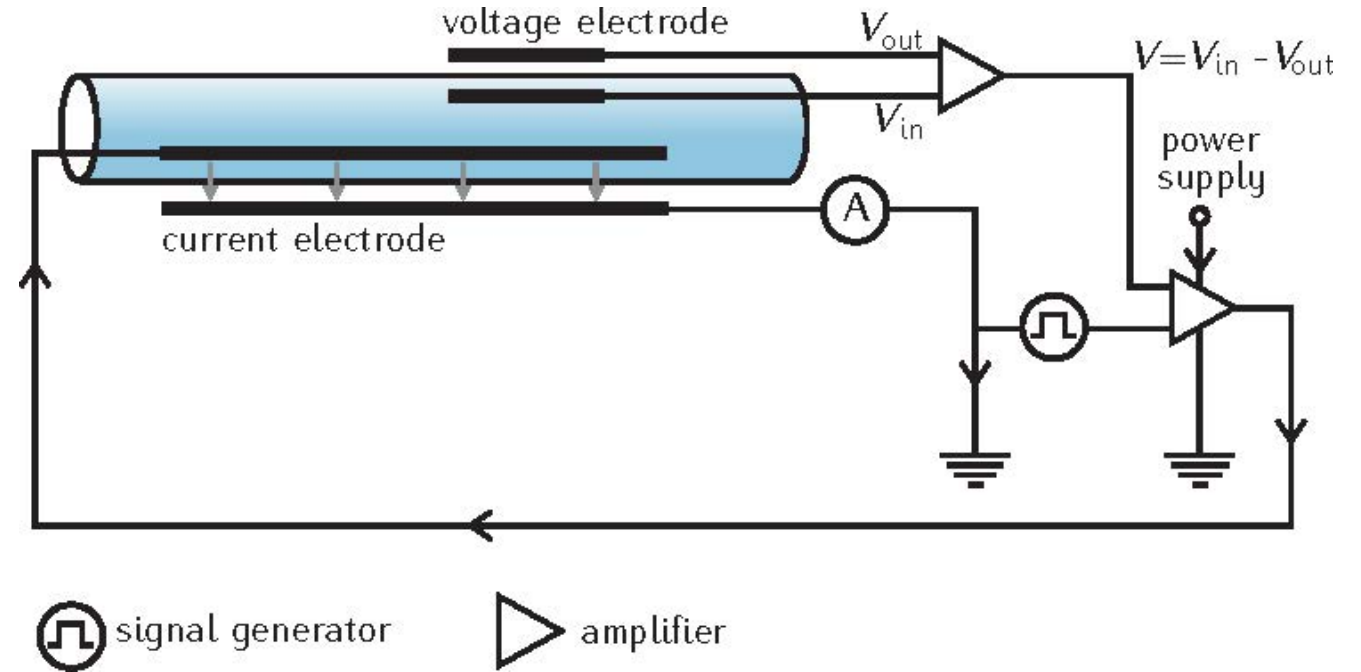
Experiments on squid giant axons because these were the thickest axons one knew of

Could short-circuit the axon by sticking a copper wire into it

Thus – the whole thing was isopotential, so one had full control of the voltage everywhere.

No axial currents.

Essentially then – a real single-compartment neuron.

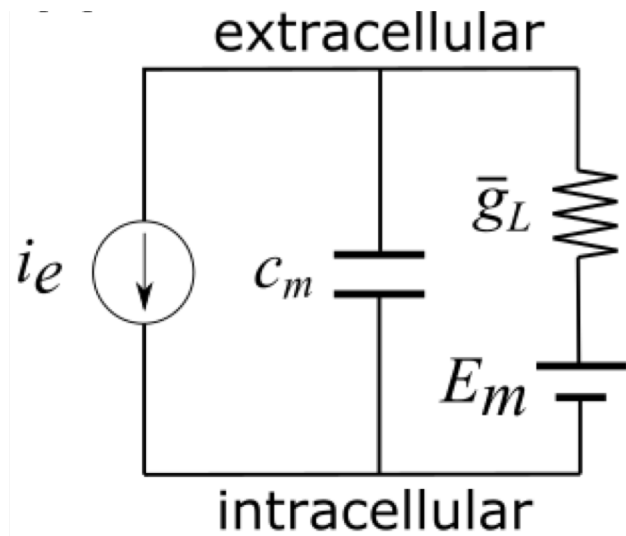


# #1. HH circuit model for single compartment.

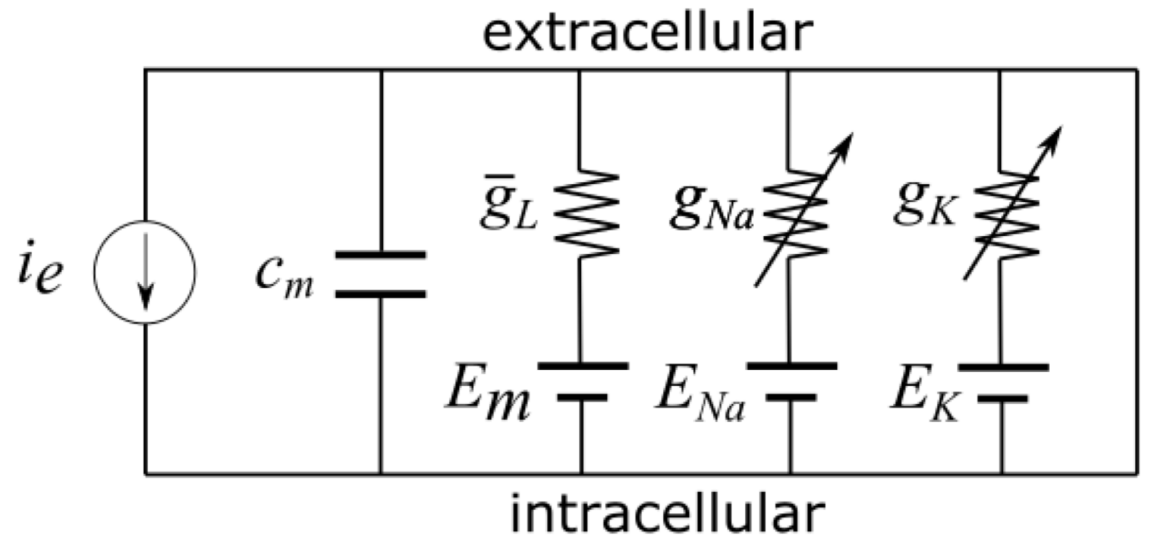
## Action potential as:

- $\text{Na}^+$  current entering the neuron (upstroke),
- Followed by a  $\text{K}^+$  current leaving it (downstroke).

## PASSIVE



## HH



# #1. HH circuit model for single compartment

$$C_m \frac{dV_m}{dt} = \underbrace{-\bar{g}_L \cdot (V_m - E_L)}_{\text{Passive components}} - \overbrace{g_{Na} \cdot (V_m - E_{Na})}^{i_{Na}} - \overbrace{g_K \cdot (V_m - E_K)}^{i_K}$$

Passive components

The bar over  $g$  indicates that it's a constant

Active components

Sodium & Potassium channels making APs

## Interpretation of active components:

Time and voltage dependent conductances:

$$g_{Na}(V_m, t) \quad g_K(V_m, t)$$

- Conductances can be written as

$$g_x(V_m, t) = \bar{g}_x \cdot p_x(V_m, t)$$

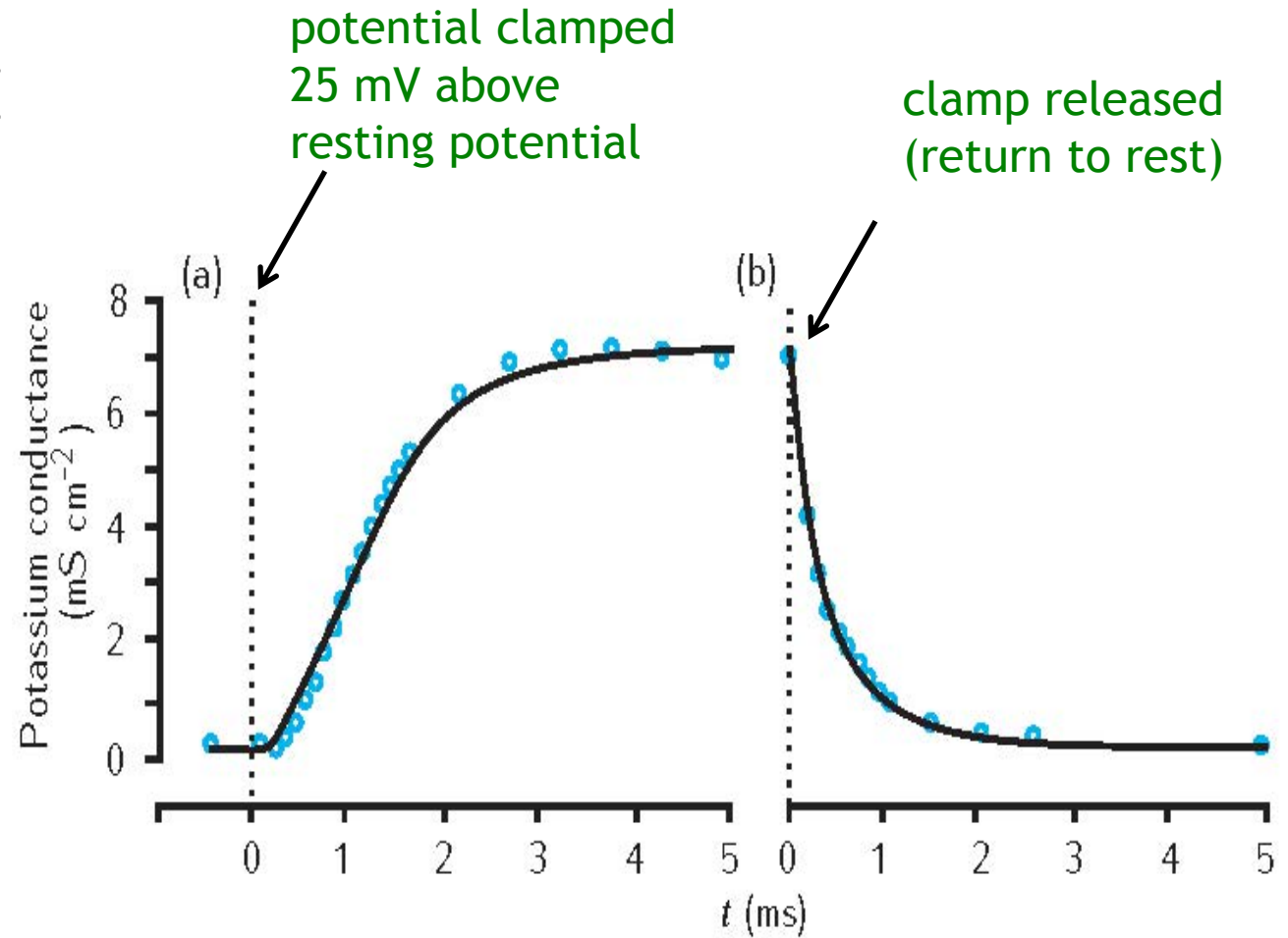
- For a single ion channel
  - $p_x$  is the probability that it is open
- For many ion channels of same type (x)
  - $p_x$  is the fraction of the total channels that are open.

-

# #2: Potassium current

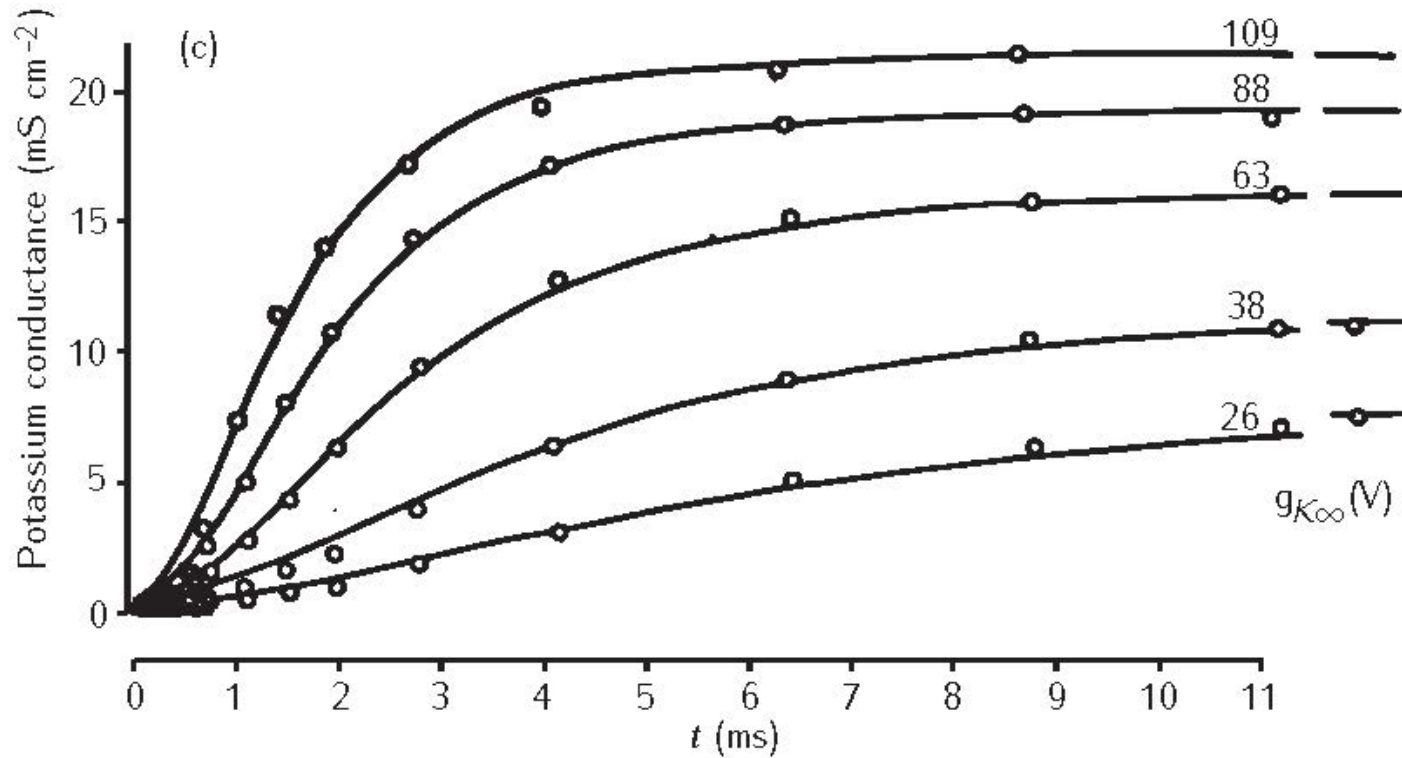
How to determine  $g_K(V_m, t)$  ?

1. Manipulate conditions so that one knows that  $I_K$  is the only current passing through the membrane.
2. Control  $V_m$ : Set it to a «holding-potential»  $V_h$
3. Measure  $I_K$  for this holding potential.
4. Derive conductance from:  $g_K = \frac{I_K}{(V_h - E_K)}$
5. Repeat for many  $V_h$ .





## #2: Potassium current



### Observation:

For a given  $V_h$ ,  $g_K$  increases w/ time and reaches a steady state (SS) value  $g_{K\infty}(V_h)$ .

SS depends on  $V_h$ .

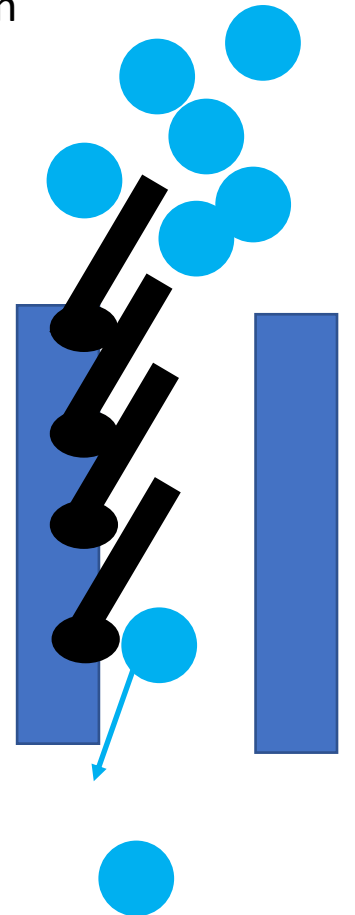
Time to reach SS also depends on  $V_h$ .

We must fit some conceptual model to these observations!

## #2: Potassium current

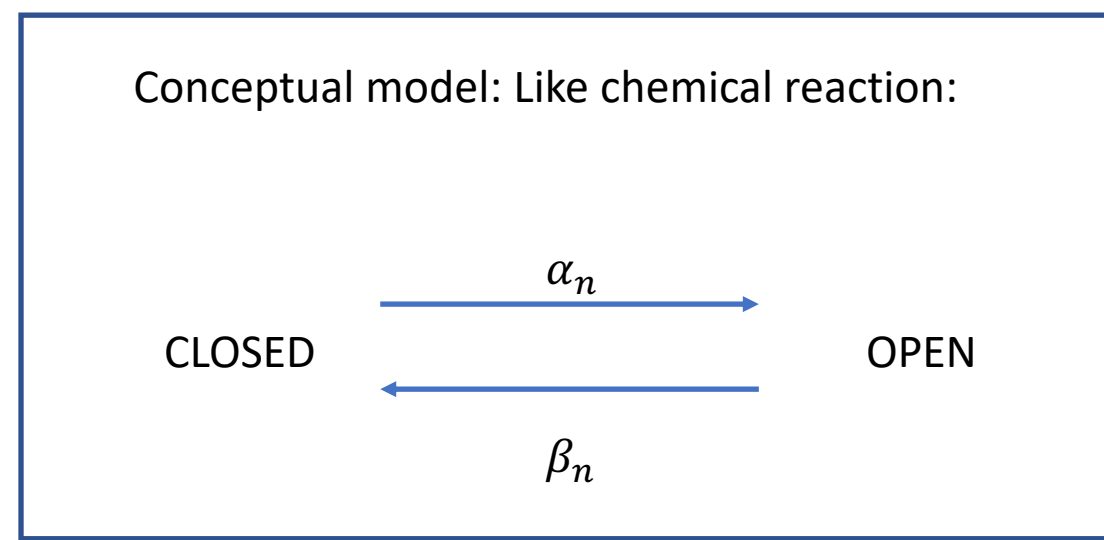
- Conceptual model (by HH)
  - Each  $K^+$ -channel is controlled by four so-called *gating particles*.
    - Four, simply because that gave best fit to data.
  - Each gating particle is in either an **open** or **closed** state.
  - $n$  is the probability that a particular gate is open
  - For large numbers of ion channels  $n$  is the fraction of gates that are open.
  - For the channel to be open, all four gates must be open.
  - $n^4$  should then be the fraction of  $K^+$  channels that are open.
- That should give us:  $I_K = \bar{g}_K n^4 (V - E_K)$ .

4 activation  
gates



# #2: Potassium current

- Dynamics of the gating particles



- First order kinetics equation:

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

- Alternative form:

$$\frac{dn}{dt} = \underbrace{\left(\frac{\alpha_n}{\alpha_n + \beta_n} - n\right)}_{n_\infty} \underbrace{(\alpha_n + \beta_n)}_{1/\tau_n}$$

- So that:

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

- Interpretation:

- $n$  approaches  $n_\infty$  with time constant  $\tau_n$ .
- $n_\infty$  is the open probability for given  $V_h$  when  $t \rightarrow \infty$ .

# #2: Potassium current

- SUMMARY

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

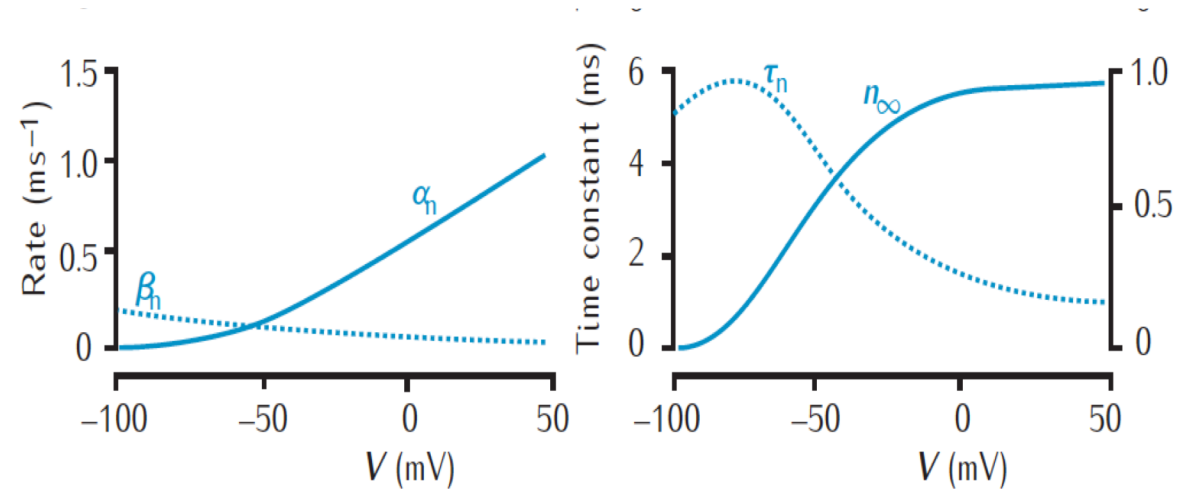
- $\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n$

- Fits:

- $\alpha_n = 0.01 \frac{V+55}{1 - e^{-(V+55)/10}}$

- $\beta_n = 0.125 e^{-(V+65)/80}$

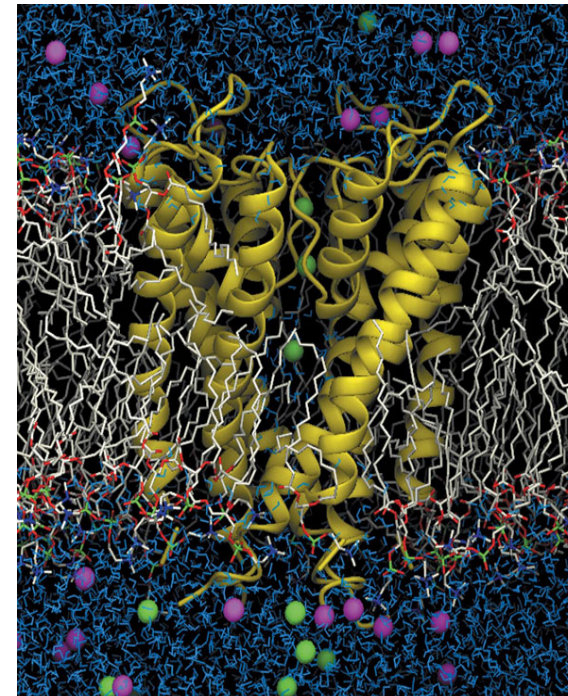
- $V$  must be inserted with units mV



The rate variables  $\alpha_n$  and  $\beta_n$  are basically just curves fitted to experimental data.

It was during this curve fitting that HH realized that a number of 4 gates gave best agreement.

Much later it was seen that the  $K^+$  channel contains 4 sub-units, giving a structural explanation to the data.



*Model of  $K^+$  ion channel embedded in cell membrane (Berneche & Roux, Nature, 2001)*

# #3: Sodium current

Unlike for  $K^+$ , the  $Na^+$  current is transient.

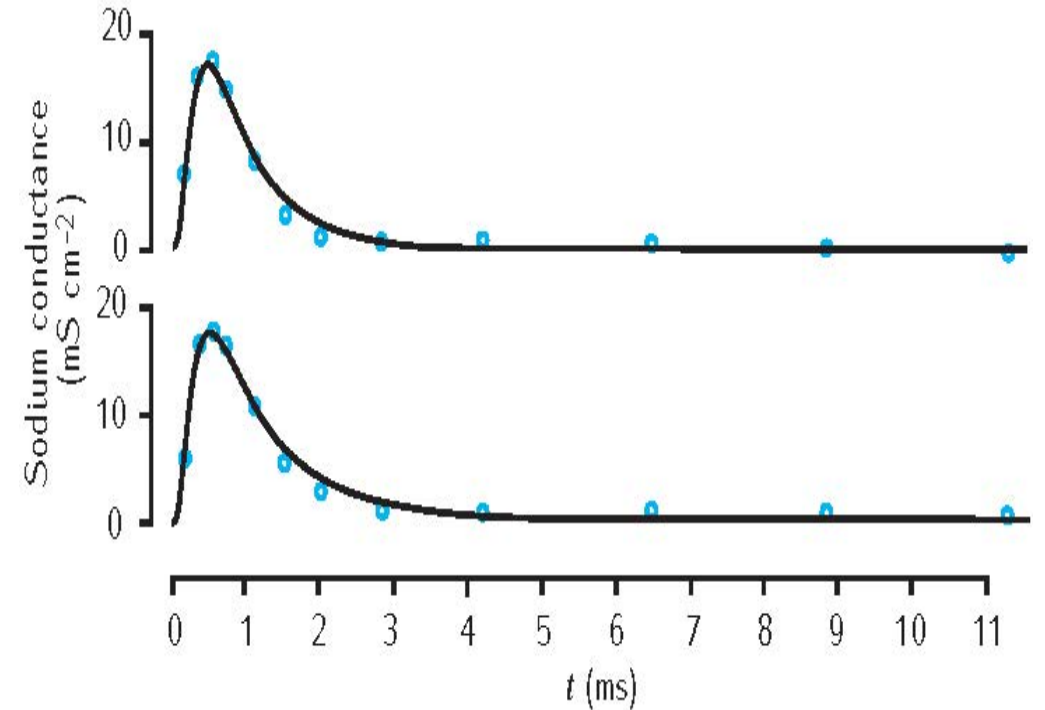
For a given  $V_h$ , it peaks and then decays to zero

Something opens (activates) it

Then something else closes (inactivates it).

Hodgkin & Huxley introduced

- Activation variable  $m$  (like  $n$  for  $K^+$ ).
- Inactivation variable  $h$  (brand new)



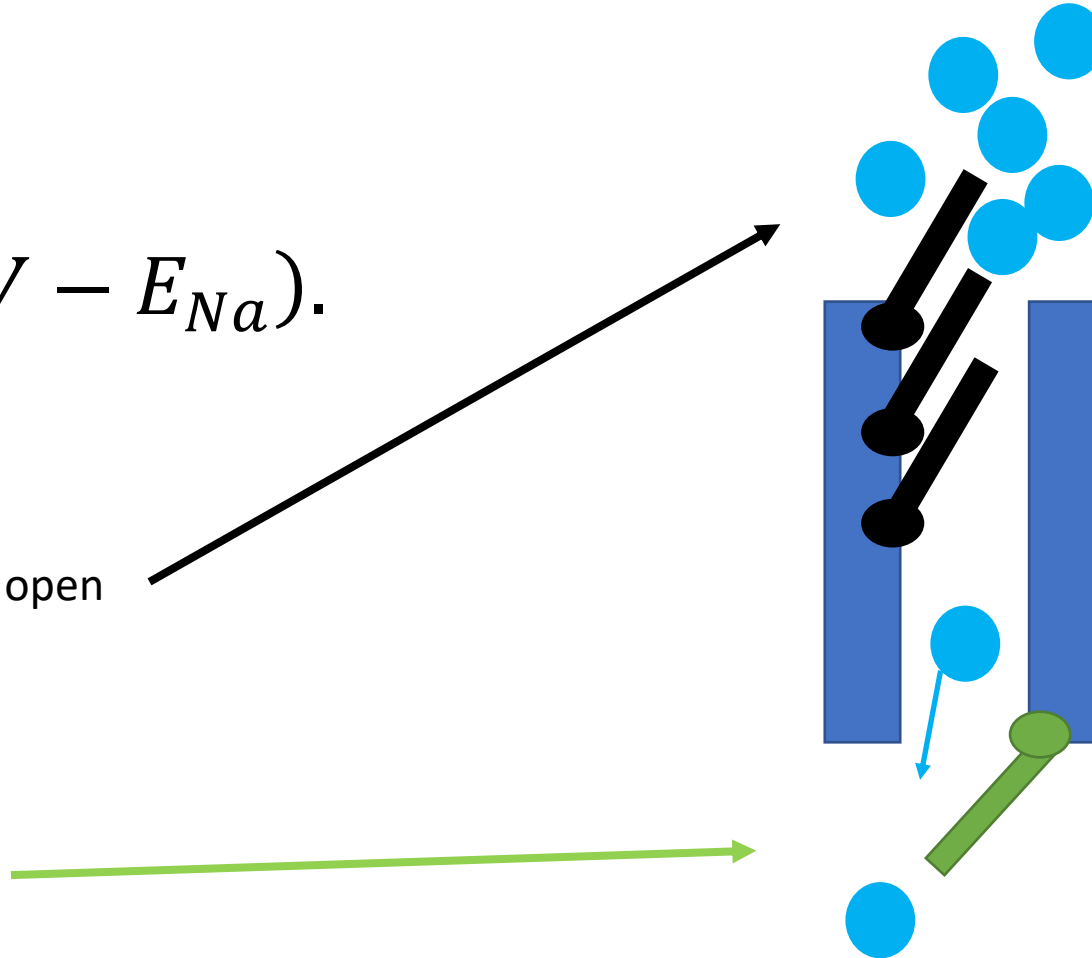
# #3: Sodium current

- Model

$$I_{Na} = \bar{g}_{Na} m^3 h (V - E_{Na}).$$

3 activation gates: Are closed at rest, but open when the voltage is increased

1 inactivation gate: Is open at rest, but closes when the voltage is increased.



Again, the numbers 3 and 1 come from curve-fitting to data

## #3: Sodium current

- Model for  $Na^+$ -channel

- $g_{Na} = g_{Na} \bar{m}^3 h$

- $\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m$

- $\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h$

- FITS:

- $\alpha_m = 0.1 \frac{V+40}{1 - e^{-(V+40)/10}}$

- $\beta_m = 4e^{-(V+65)/18}$

- $\alpha_h = 0.07e^{-(V+65)/20}$

- $\beta_h = \frac{1}{1 + e^{-(V+35)/10}}$

- $V$  must be inserted with units mV

# #4: Full HH model

$$c_m \frac{dV_m}{dt} = -\bar{g}_L(V_m - E_L) - \bar{g}_{Na}m^3h(V_m - E_{Na}) - \bar{g}_K n^4(V_m - E_K)$$

Passive components

The bar over  $g$  indicates that it's a constant

Active components

Sodium & Potassium channels making APs

$$\frac{dx(V_m, t)}{dt} = \frac{x_\infty(V_m) - x}{\tau_x(V_m)}, \text{ for } x = \{m, h, n\}$$

$$x_\infty(V_m) = \frac{\alpha_x(V_m)}{\alpha_x(V_m) + \beta_x(V_m)}, \text{ for } x = m, n, h \quad \tau_x = 1/(\alpha_x + \beta_x)$$

$$\alpha_n = \frac{0.01\text{ms}^{-1}V_m + 55\text{mV}}{1 - e^{-(V_m+55\text{mV})/10\text{mV}}}$$

$$\beta_n = 0.125\text{ms}^{-1}e^{-(V_m+65\text{mV})/80\text{mV}}$$

$$\alpha_m = \frac{0.1\text{ms}^{-1}V_m + 40\text{mV}}{1 - e^{-(V_m+40\text{mV})/10\text{mV}}}$$

$$\beta_m = 4\text{ms}^{-1}e^{-(V_m+65\text{mV})/18\text{mV}}$$

$$\alpha_h = 0.07\text{ms}^{-1}e^{-(V_m+65\text{mV})/20\text{mV}}$$

$$\beta_h = \frac{1\text{ms}^{-1}}{1 + e^{-(V_m+35\text{mV})/10\text{mV}}}$$

$$c_m = 1.0\mu\text{F}/\text{cm}^2$$

$$\bar{g}_{Na} = 120\text{mS}/\text{cm}^2$$

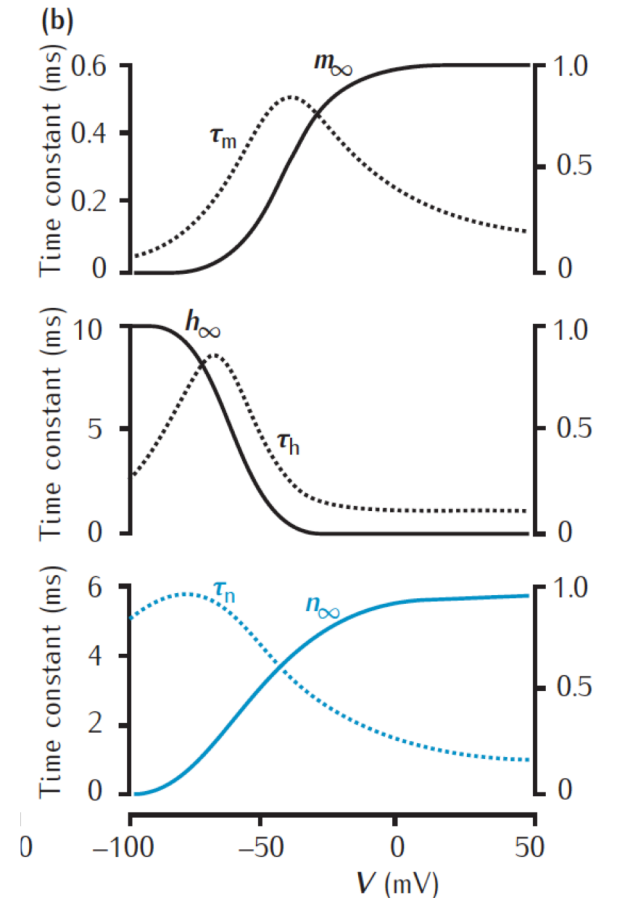
$$\bar{g}_K = 36\text{mS}/\text{cm}^2$$

$$\bar{g}_L = 0.3\text{mS}/\text{cm}^2$$

$$E_{Na} = 50\text{mV}$$

$$E_K = -77\text{mV}$$

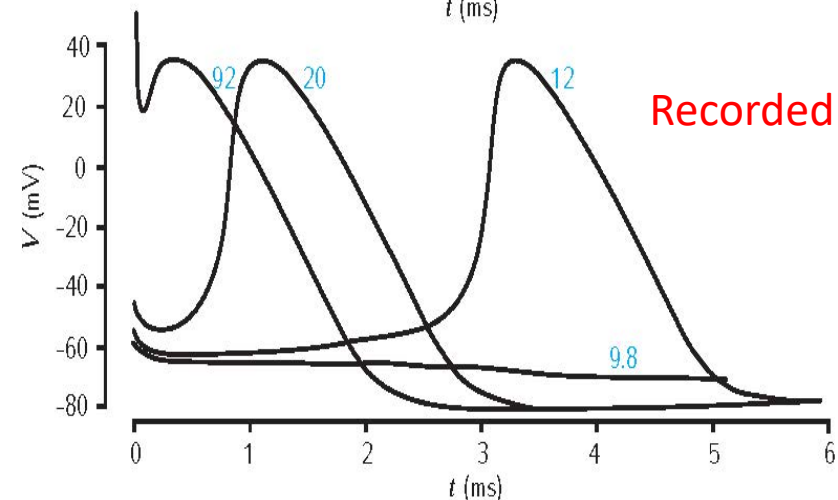
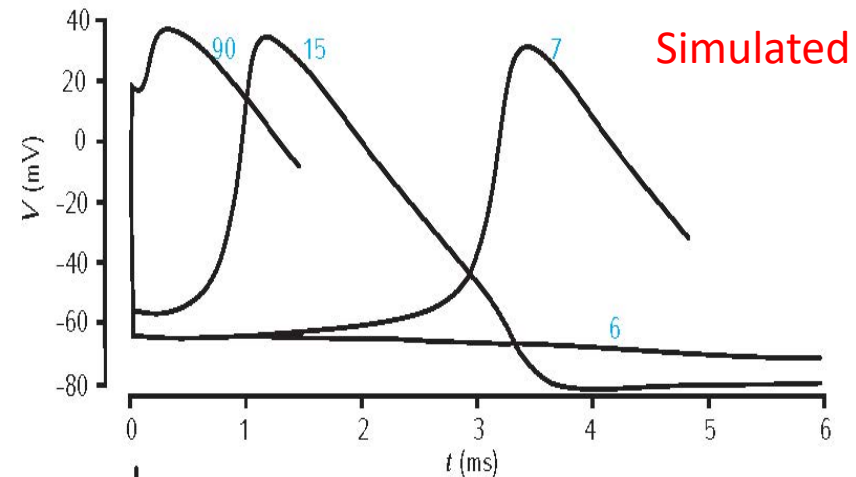
$$E_L = -54.4\text{mV}$$





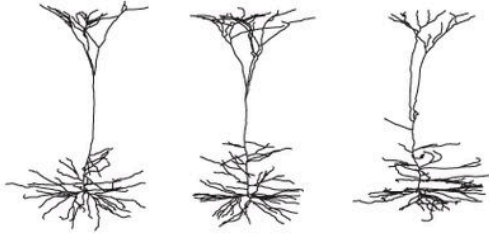
# #4: Full HH model

- **Simulated vs. experimentally recorded** responses to induced depolarizations of the membrane
- **Blue numbers** = depolarized to this many millivolts above the resting potential

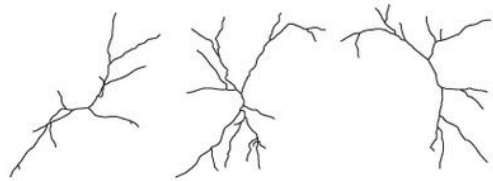


# #5. HH-type models

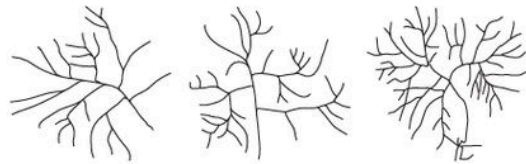
Pyramidal cells



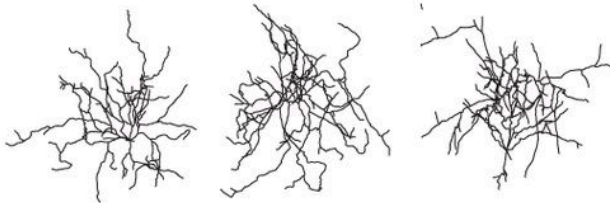
Tripolar cells



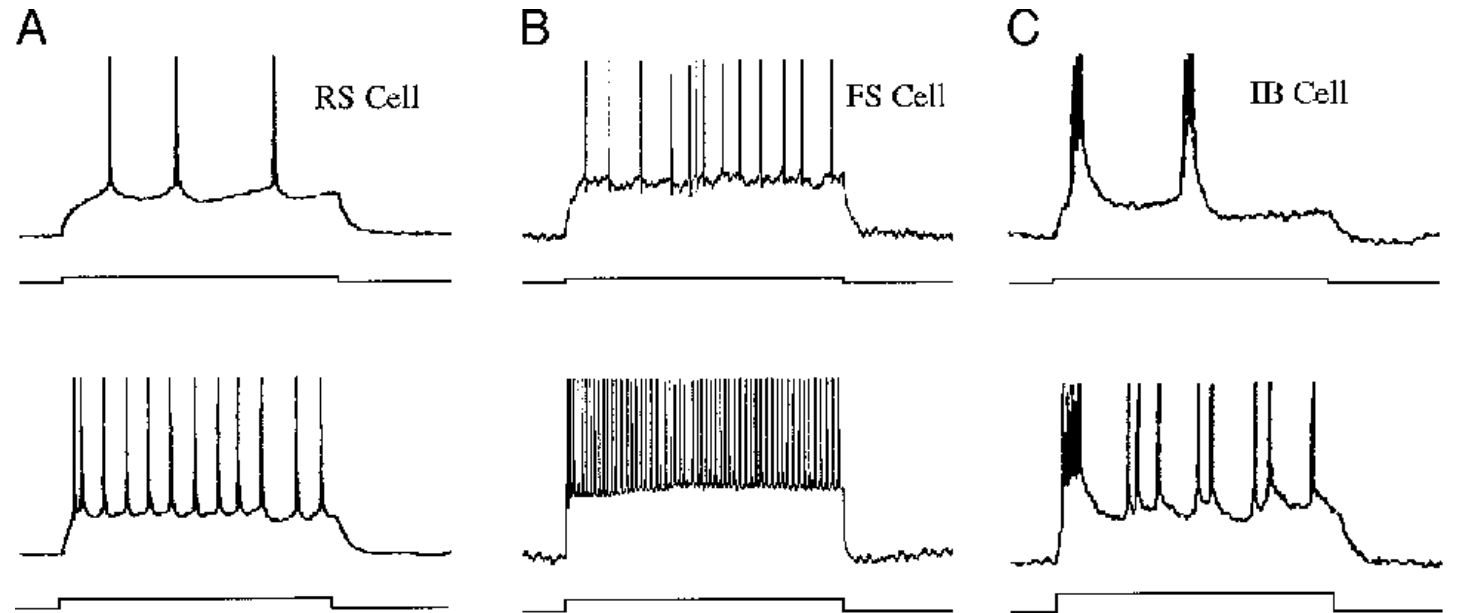
Purkinje cells



Stellate neuron



- Many neuron types exist.
  - Different morphologies.
  - Different firing properties.
- Not all of them are well described by the HH model
  - Many ion channels exist besides  $I_K$  and  $I_{Na}$  in HH.
- Good news: Most of them can be modelled with a HH-type formalism



# #5. HH-type models

HH-type formalism means that ion channels are modelled as:

$$i_x = \bar{g}_x m_x^\alpha h_x^\beta (V_m - E_x).$$

Conductance for fully open channel

A number  $\beta$  of inactivation gates.

A number  $\alpha$  of activation gates.

Reversal potential for ion species running through the channel x.

# #5. HH-type models

Different ion channels explain different features of the firing patterns of neurons

$I_h$ : Initial «sags»

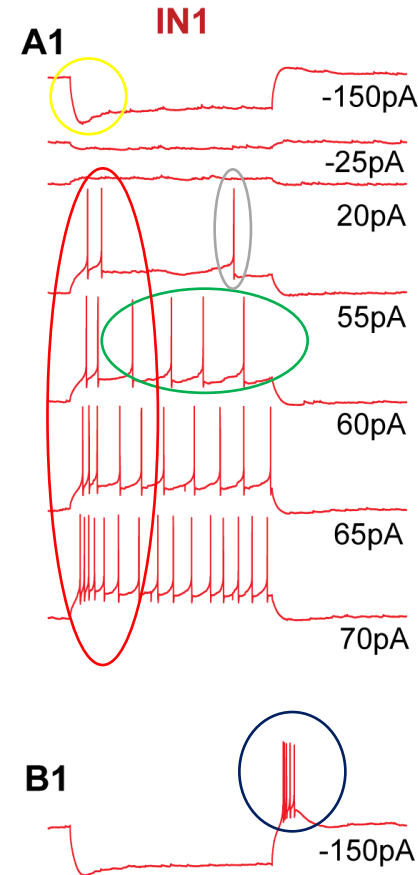
$I_{Na}$ ,  $I_K$ ,  $I_A$ : AP-shape

$I_{Na}/I_K$ : regular AP-firing

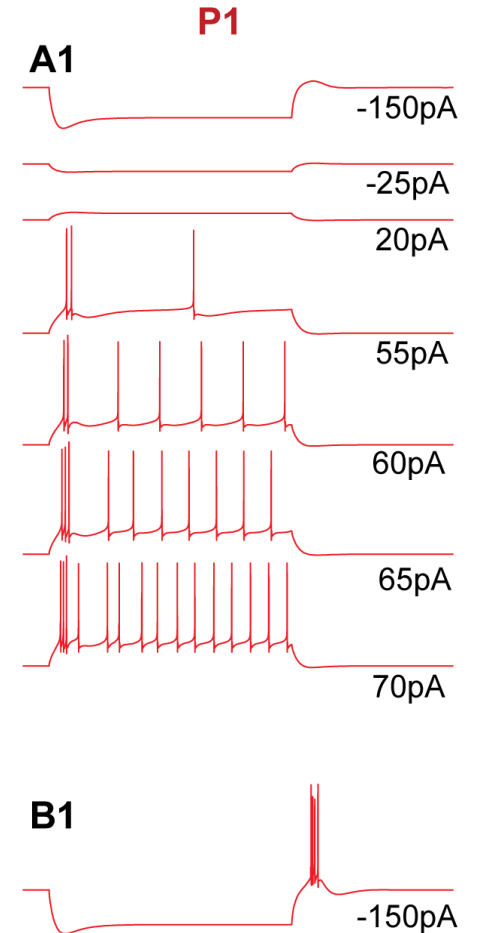
$I_T$ ,  $I_L$ ,  $I_{AHP}$ ,  $I_M$ ,  $I_{CAN}$ :  
Spike frequency adaptation & initial bursts

$I_T, I_h$ : Rebound Bursts

DATA



MODEL WITH 7 ION CHANNELS



# #6. Calcium channel

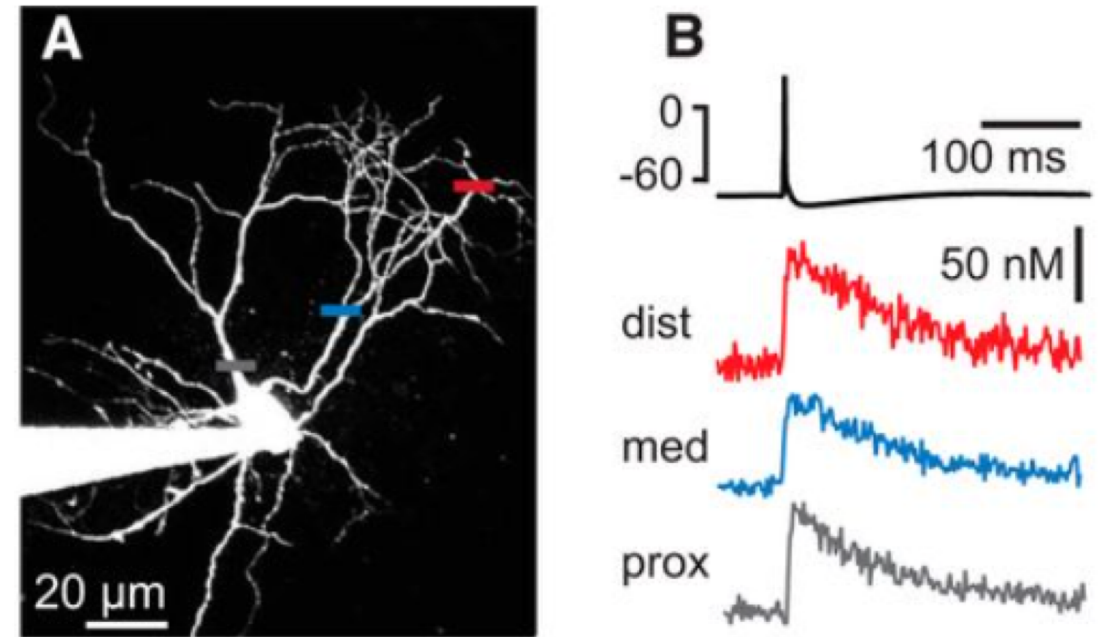
- Inside neurons:
  - $[\text{Na}^+]_i \sim 15 \text{ mM}$  and  $[\text{K}^+]_i \sim 140 \text{ mM}$
  - $[\text{Ca}^{2+}]_i \sim 100 \text{ nM}$
- $I_K$  and  $I_{\text{Na}}$  do not affect ion concentrations much.
  - E.g., the number of  $\text{Na}^+$  ions needed to charge  $V_m$  by 80 mV (action pot.) changes  $[\text{Na}^+]_i$  by (much) less than 1 %.
  - We therefore normally assume that  $[\text{Na}^+]_i$  and  $[\text{K}^+]_i$  are constant.
- But:  $I_{\text{Ca}}$  can change  $[\text{Ca}^{2+}]_i$  dramatically.

# #6. Calcium channel

- $\text{Ca}^{2+}$ 
  - Used by neurons as a signalling molecule
    - Synaptic plasticity
    - Biochemical reactions
    - $\text{Ca}^{2+}$  gated ion channels
    - Seen in  $\text{Ca}^{2+}$  imaging experiments
- High-voltage activated  $\text{Ca}^{2+}$  channels (here called  $I_{\text{Ca}}$ )
  - Many neurons have these
  - These open during action potentials and let some  $\text{Ca}^{2+}$  into the neurons.
  - For neurons that have these, action potentials can be seen as fluctuations in intracellular  $\text{Ca}^{2+}$ .

# #6. Calcium channel

- Two-photon calcium imaging
- Let's say we want to model the soma in the experiment to the right
  - Need calcium channel for calcium influx
  - Need to model the dynamics calcium concentration



Stephanie Rudolph, Court Hull and Wade G. Regehr  
Journal of Neuroscience 25 November  
2015, 35 (47) 15492-15504

# #6. Calcium channel

- Simplest HH-type model of  $I_{Ca}$ :

$$I_{Ca} = \bar{g}_{Ca} s^2 (V - E_{Ca}).$$

Two activation gates  
No inactivation gates

Calcium reversal potential  
~ 120 mV

- Simplest model for  $[Ca^{2+}]_i$ :

$$\frac{d[Ca^{2+}]_i}{dt} = -\alpha I_{Ca} - \frac{[Ca^{2+}]_i - [Ca^{2+}]_{basal}}{\tau_{Ca}}$$

- $\alpha$  converts current to concentration change
  - Depends on volume, membrane area and buffering processes
- $\tau_{Ca} \sim 50$  ms is the  $Ca^{2+}$  decay time constant
  - Due to pumps & buffering



# Tomorrow

- Exercise:
  - I will give you a python script with the original HH model
  - You will modify it
    - Speed up kinetics
    - Add calcium channel
    - Add calcium dynamics
    - Try to model a Ca-imaging experiment

Thank you

# HH-equation

$$g_x = \bar{g}_x$$

$$C_m \frac{dV_m}{dt} = -\bar{g}_L(V_m - E_L) - \overbrace{\bar{g}_{Na} m^3 h (V_m - E_{Na})}^{i_{Na}} - \overbrace{\bar{g}_K n^4 (V_m - E_K)}^{i_K}$$

Passive components

The bar over  $g$  indicates that it's a constant

Active components

Sodium & Potassium channels making APs

## Interpretation of active components:

Time and voltage dependent conductances:

$$g_{Na}(V_m, t) = \bar{g}_{Na} m^3 h \quad g_K(V_m, t) = \bar{g}_K n^4$$

-  $m$ ,  $h$  and  $n$  are called gating variables. Functions of  $V_m$  &  $t$ .

- The Na-channel has 3 gates of type  $m$  and one of type  $h$ .

-  $m$  &  $n$  take values between 0 & 1.

- Indicate the **probability** that the particular gate is open.

- For channel to be open, all gates must be open. The product  $m^3 h$  is the prob. that a given Na-channel is open.

- For many Na-channels (large numbers),  $m^3 h$  interprets as the fraction of channels that are open.

