W5-Note

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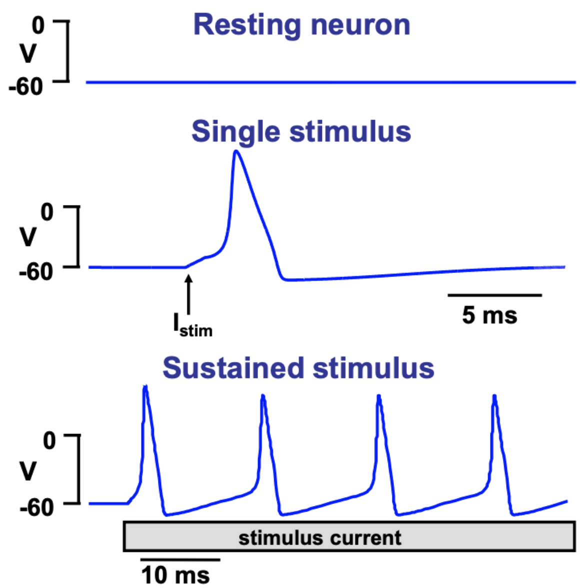
W5. Modelling Electrical Signaling

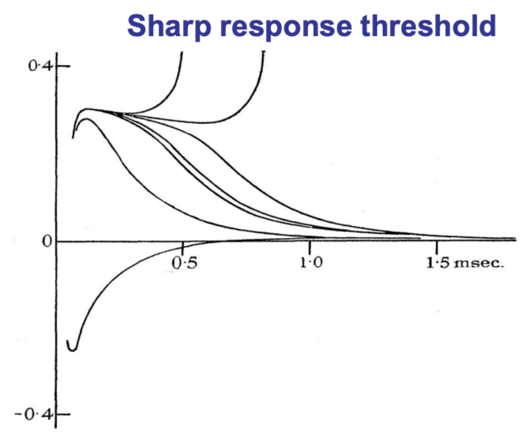
Q1. Mathematical models of action potentials

- Interesting nonlinear behaviours of excitable cells
- Definition of terms
- Electrochemical potential and driving force

Action potentials in squid giant axon

They exhibit unusual nonlinear behavior



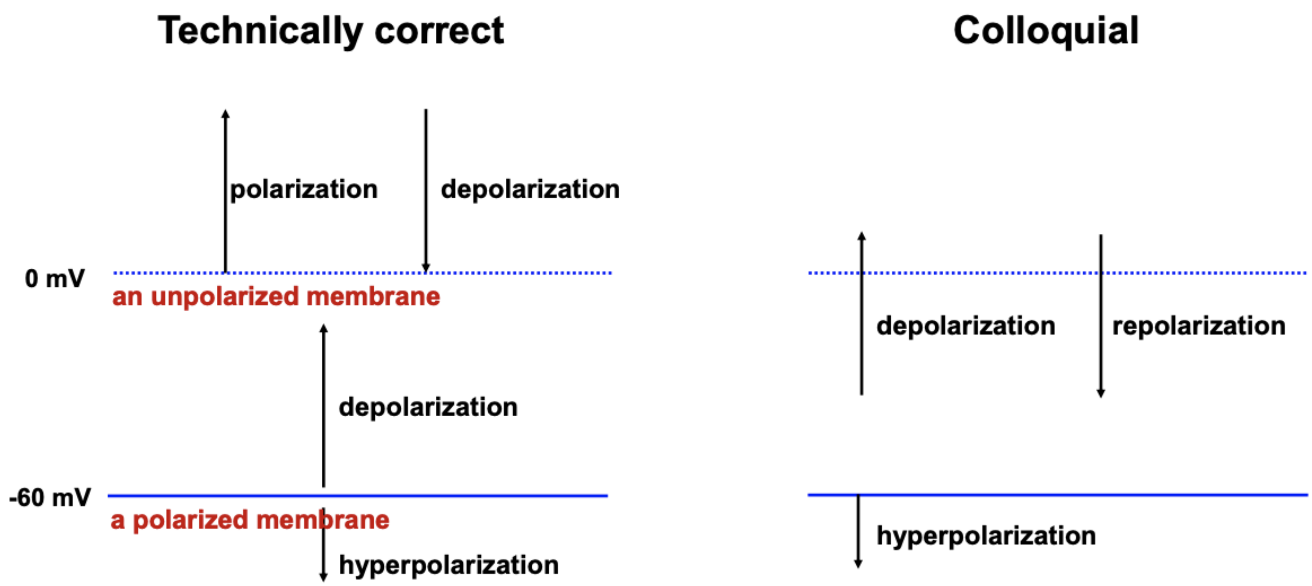


Hodgkin (1938), *Proc. Roy. Soc. B* 126:87-121.

How to account for this behaviour quantitatively?

Important definition of terms

Depolarization, repolarization, and hyperpolarization

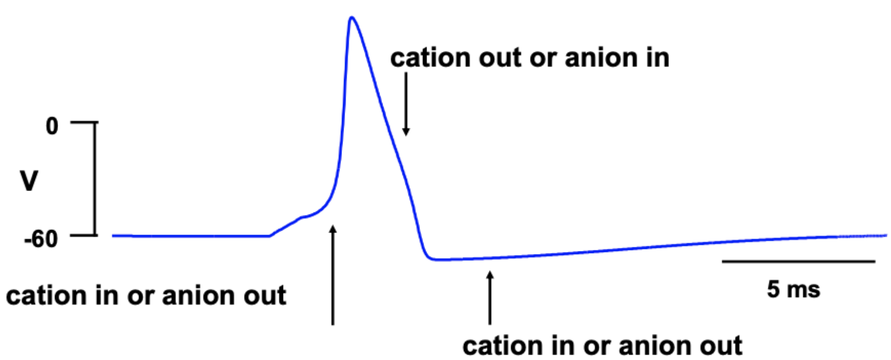


Voltage changes result from ion movements

Cations flowing in depolarize the membrane

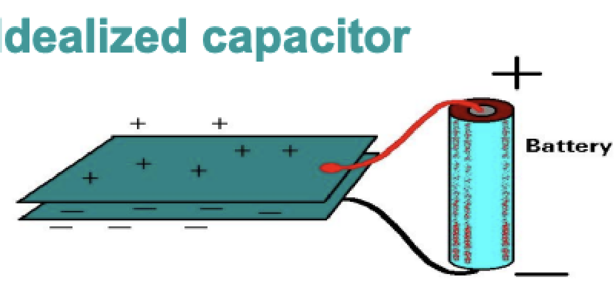
Cations flowing out repolarize / hyperpolarize the membrane

Ions: Cations: (+) & Anions: (-)



- How to describe depolarization / repolarization quantitavely?
- Which ions are the most likely candidates?

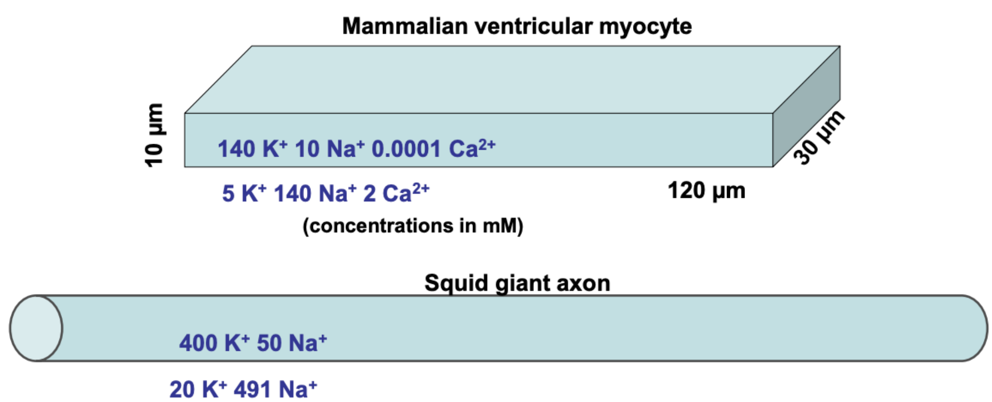
$$C\frac{dV}{dt} = I$$



The cell membrane is a capacitor

$$C_m \frac{dV}{dt} = -I_{ion}$$

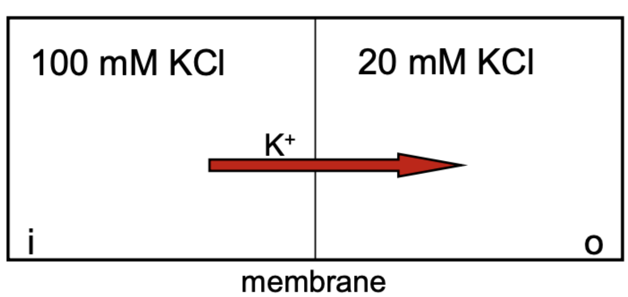
Our differential equation for membrane voltage:



Ionic concentrations in cells

- Thus, diffusion will drive Na+ inward, K+ outward.
- These movements will depolarize or hyperpolarize the membrane respectively.

Concentration cell: membrane permeable to K+ not to CI-



Qualitatively, what happens when [KCI] on left is increased?

1. K+ ions flow from left to right
2. Excess positive ions on right produce voltage difference

3. Voltage difference opposes left -> right movement of K+
4. Eventually, an equilibrium is reached.

More quantitatively ->

Electrochemical potential

$$\mu = \mu^0 + RT \ln C + zFV$$

What is the significance of each term?

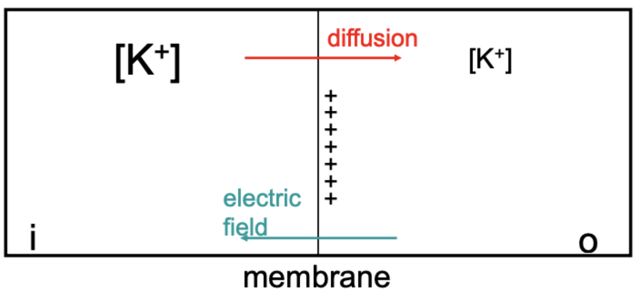
μ^0 **this is the "standard" electrochemical potential**

(same on both sides, can ignore)

$RT \ln C$ **this term describes diffusion: a higher concentration leads to a higher electrochemical potential**

zFV **this term describes electrical effects: greater voltage means greater electrochemical potential, for positively charged species only (z > 0)**

Function in membrane



At equilibrium, $\mu_i = \mu_o$

$$RT \ln C_i + zFV_i = RT \ln C_o + zFV_o$$

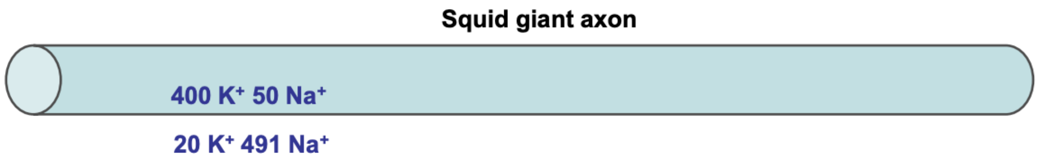
Then, rearranging terms:

$$zF(V_i - V_o) = RT(\ln C_o - \ln C_i)$$

$$V_i - V_o = \frac{RT}{zF} \ln \frac{C_o}{C_i}$$

This is definition of equilibrium or Nernst potential

Function in squid giant axon



Each ion associated with a Nernst potential

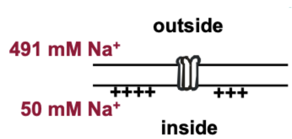
$$E_X = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}$$

$E_K = -72$ mV $\qquad E_{Na} = +55$ mV

The distance away from the reversal potential, V-Ex is the "driving force" for ion X.

This is basically converting electrochemical potential from units of J/mol to units of volts (J/C), i.e. $V - E_X = \frac{\delta \mu_x}{F}$.

Driving force and ionic currents: $V - E_{Na}$



If $V - E_{Na} > 0$, $\Delta\mu_{Na} > 0$, Na^+ moves out of the cell

If $V - E_{Na} < 0$, $\Delta\mu_{Na} < 0$, Na^+ moves into the cell

Ionic current can then be calculated as: $I_{Na} = g_{Na}(V - E_{Na})$.

By convention, inward current is negative.

In general, g_x can be dependent on both V and time.

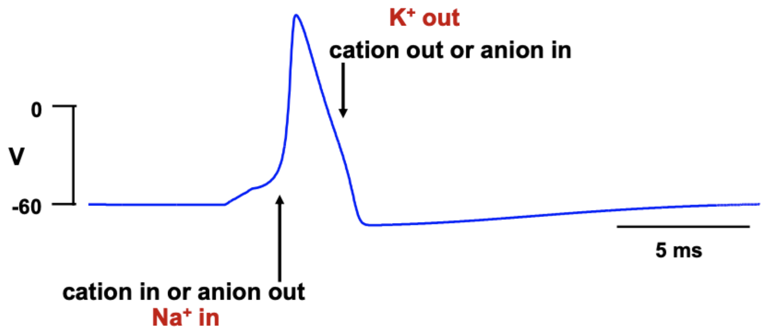
Units:

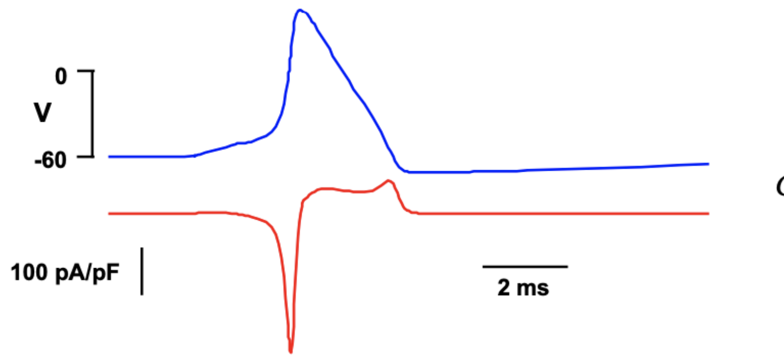
V, E_{Na}: mV
I_{Na}: μA/cm^2 (μA/μF)
g_{Na}: mS/cm^2 (mS/μF)

- Neurons exhibit complex non-linear behavior that is challenging to describe mathematically.
- Changes in membrane potential (voltage) result from ion movements across the cell membrane.
- Electrochemical potentials determine which direction ions move, with the Nernst potential representing equilibrium.

Q2. Voltage clamp was the key advance that made the Hodgkin-Huxley model possible.

Voltage changes result from ion movements

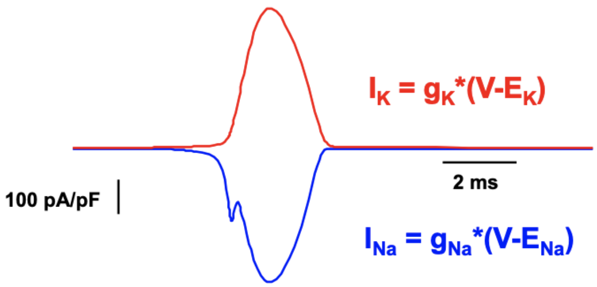


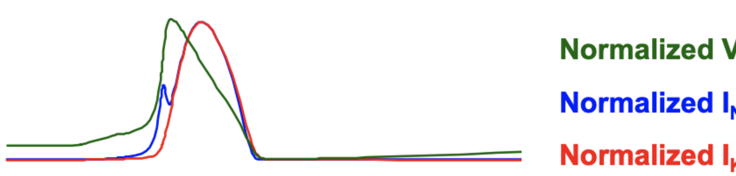


Suppose we can separate Na+ and K+ currents:

=> Change in current could result from:

- Change in conductance gx, or
- Change in driving force V - Ex





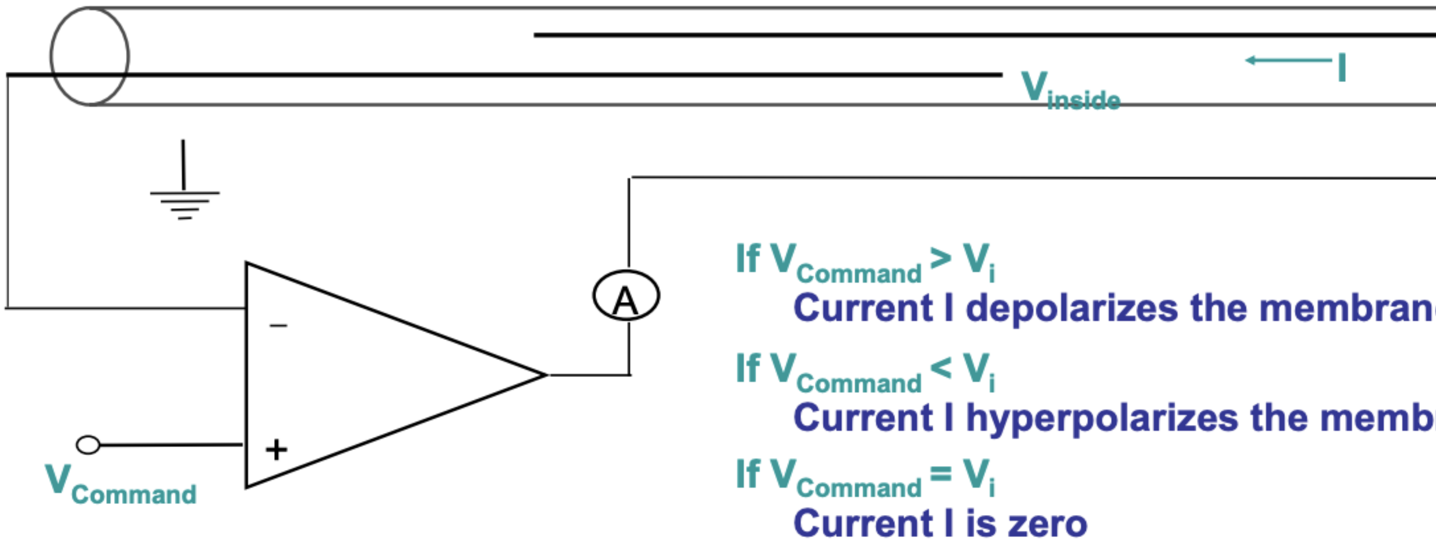
Now let's plot V, lK, and INa all on the same scale:

The problem is:

1. a change in voltage causes a change in current
2. a change in current causes a change in voltage

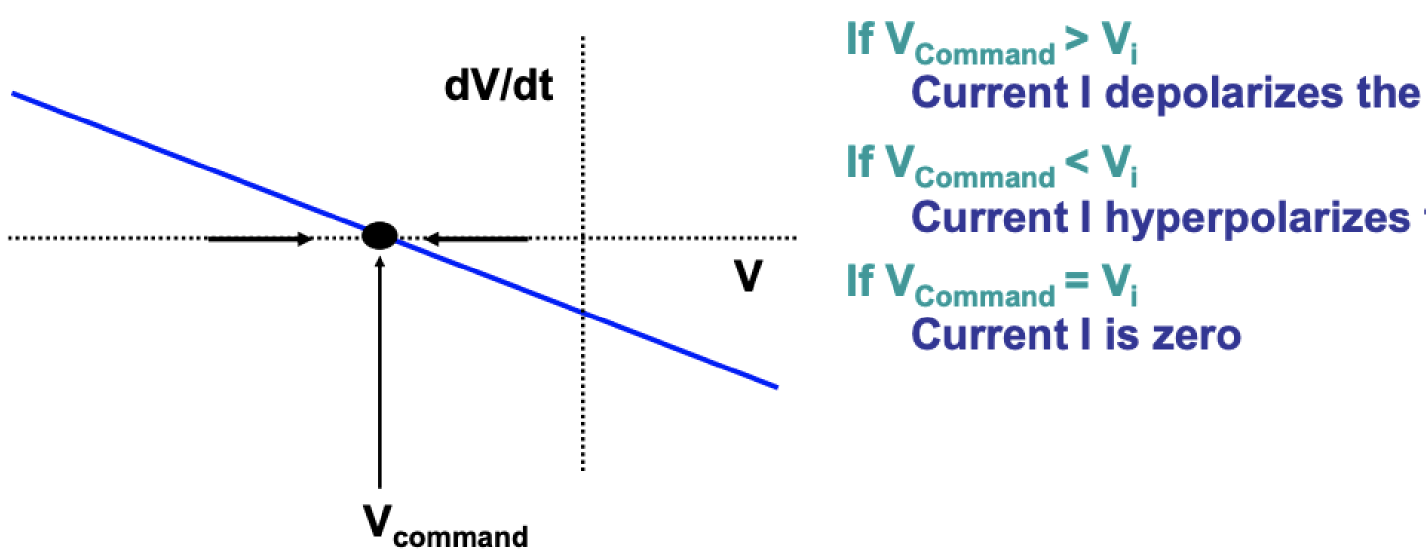
This makes it difficult to separate.

Voltage clamp of squid giant axon



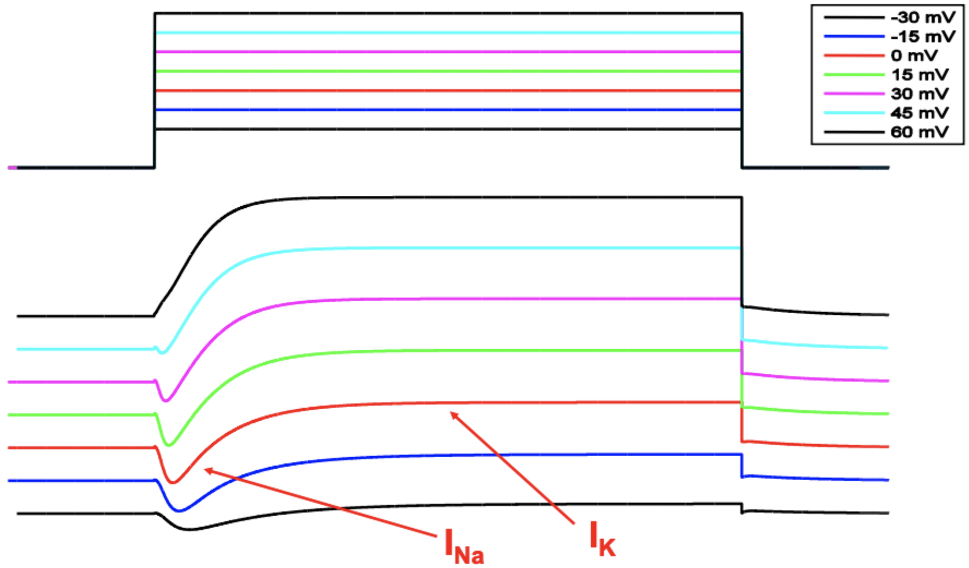
Current I required to keep Vcommand = Vi is equal in magnitude to current flowing across the membrane.

Voltage clamp as 1D dynamical system

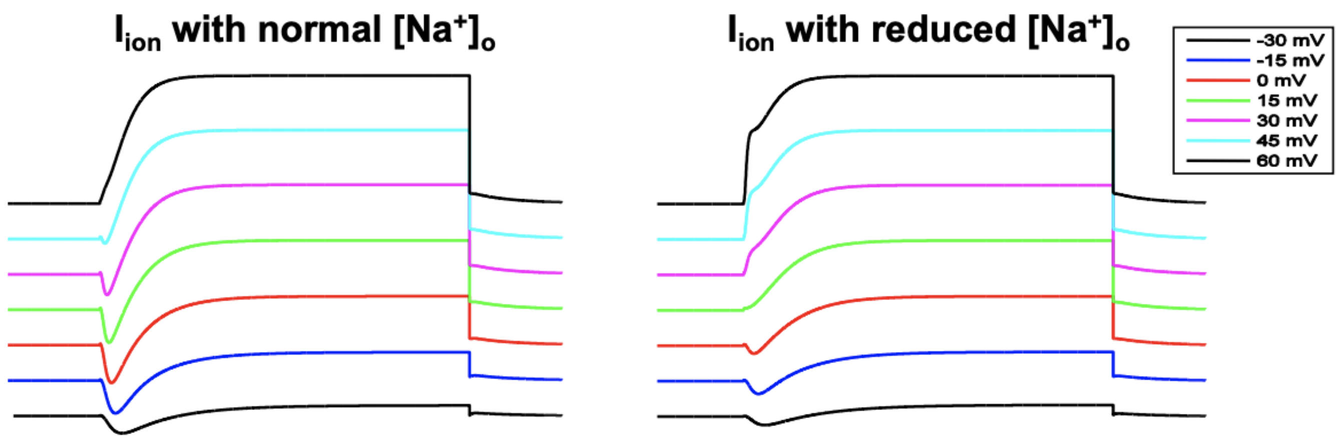


Command voltage therefore constitutes a stable fixed point.

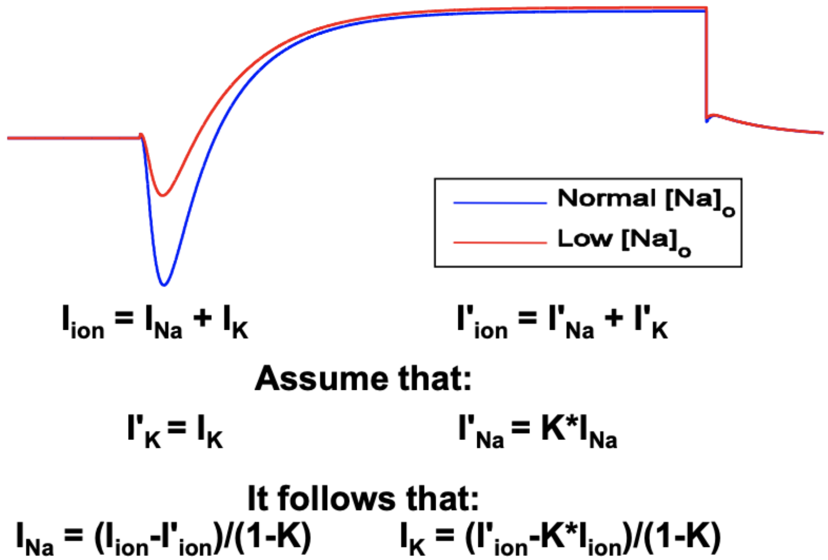
Currents record under voltage clamp

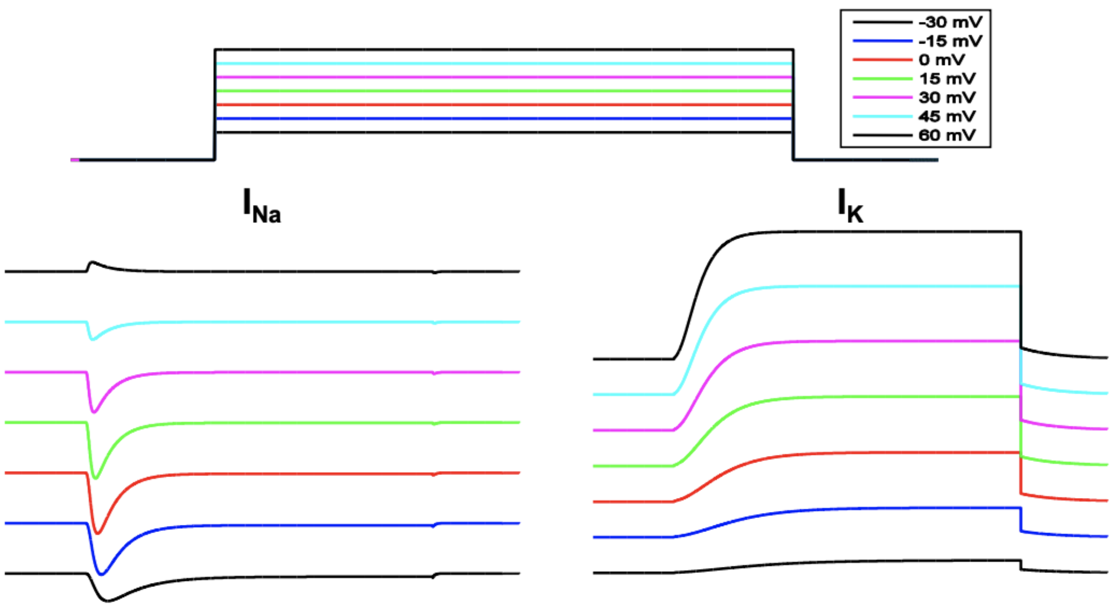


=> A clever technique for separating INa and IK



Assume that changing $[Na^+]_o$ only affects I_{Na}, not I_K



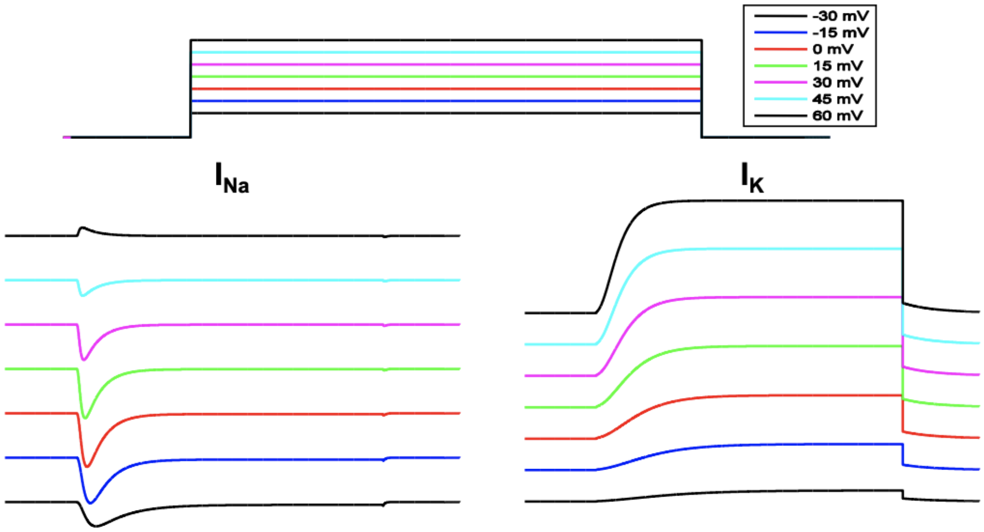


- Membrane voltage and ionic currents in neurons are interdependent, which makes it difficult to develop mathematical representations.
- The voltage clamp method, pioneered by Hodgkin and Huxley, allows for the currents to be recorded while voltage is controlled.
- Voltage clamp was the key advance that made the Hodgkin-Huxley model possible.

Q3. The Hodgkin-Huxley (1952) action potential model

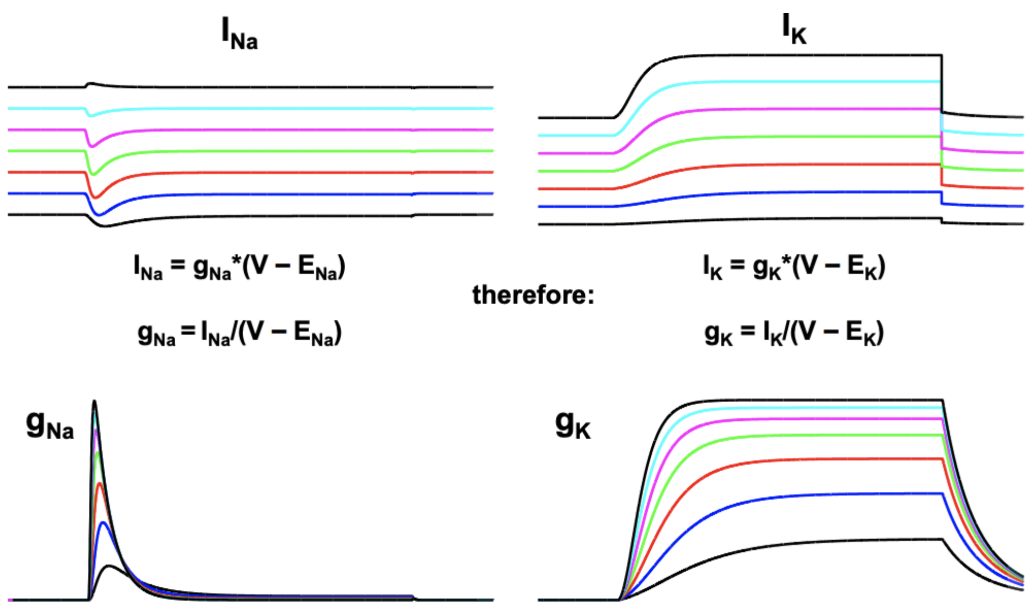
- Deriving the model equations form the experimental records
- Converting from currents to conductances
- K+ conductance: increases with a delay
- Na+ conductance: increases then decreases (inactivates)

INa and IK at different membrane potentials

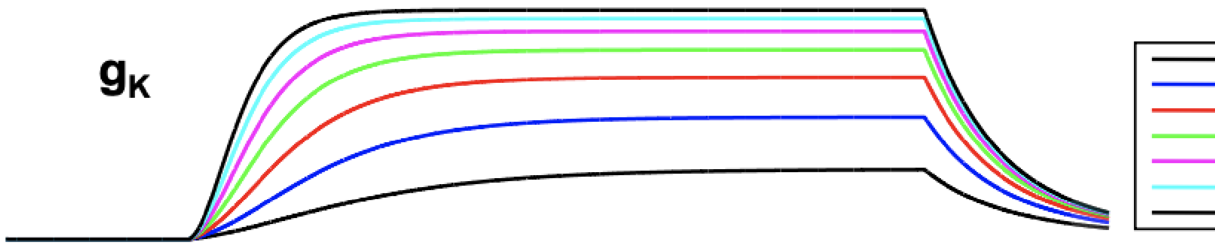


$I_X = g_X*(V-E_X)$, change in current can reflect conductance or driving force

Convert from currents to conductances:

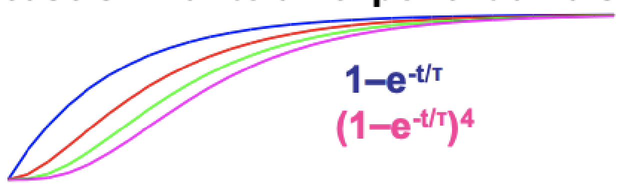


Focus on potassium conductance



1) Changing V changes both steady-state g_K and rate of rise

2) Time course of g_K increase similar to an exponential raised to a power



The facts suggest the model:

- n = fraction of particles in "permissive" state
- conductance proportional to n^4

$$g_K = g_{K,max} n^4$$

$$(1-n) \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} n$$

$$dn/dt = \alpha(1-n) - \beta n$$

α and β are functions of voltage

- Gating variable n always between 0 and 1.

Determine $\alpha(V)$ **and** $\beta(V)$

$$dn/dt = \alpha(1-n) - \beta n = \alpha - (\alpha + \beta)n$$

This equation has the steady-state (t=∞) solution:

$$n_\infty = \alpha/(\alpha + \beta)$$

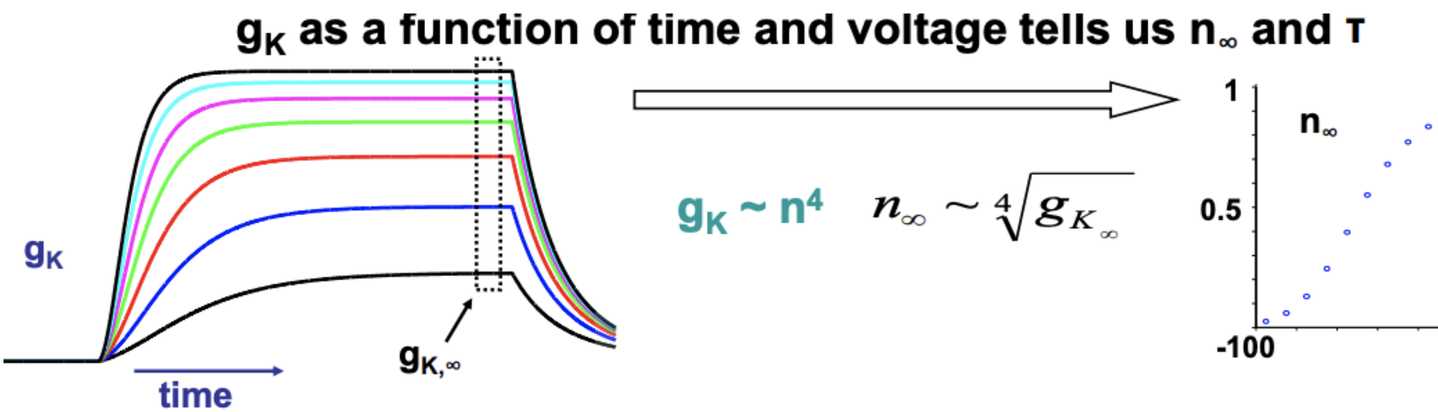
The steady-state value is reached with a time constant:

$$\tau = 1/(\alpha + \beta)$$

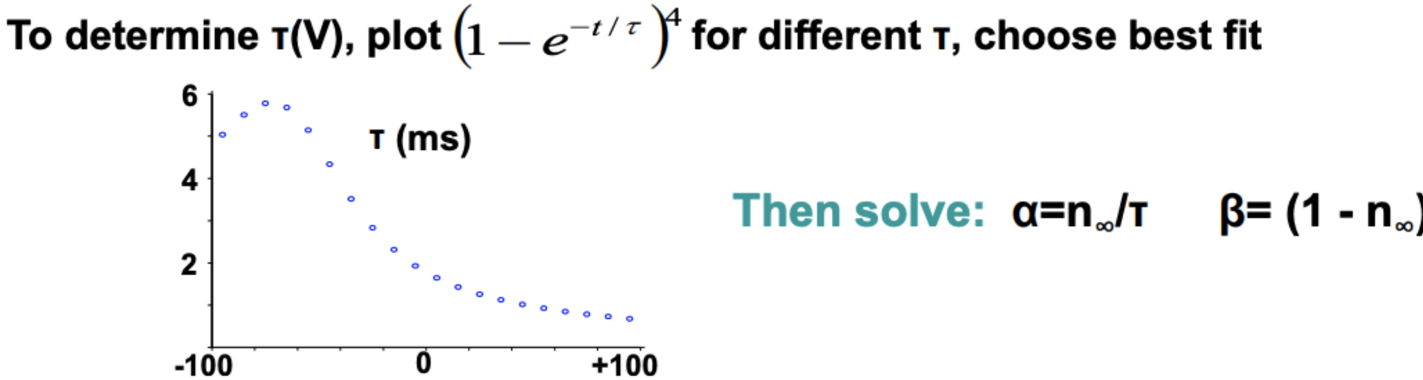
Rearranging terms: $\alpha = n_\infty/\tau \quad \beta = (1 - n_\infty)/\tau$

Thus, we know $n_\infty(V)$ and $T(V)$, we can determine $\alpha(V)$ and $\beta(V)$

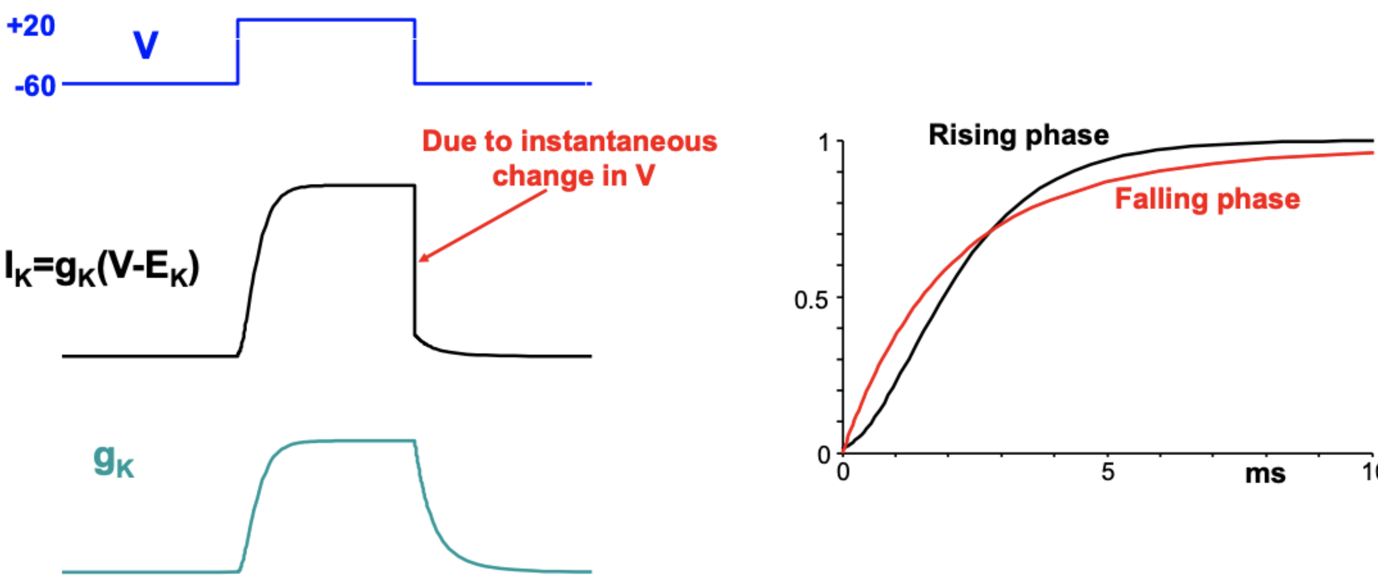
$n_\infty(V)$:

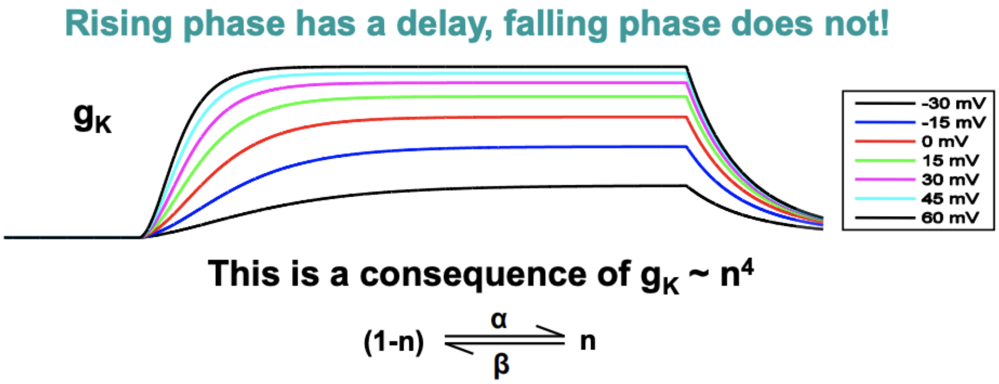


$T(V)$:



Time course of conductance changes: <u>Rising phase has a delay, failing phase does not.</u>

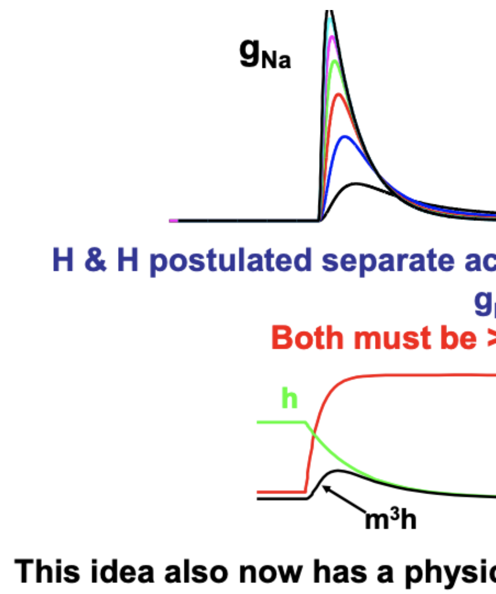




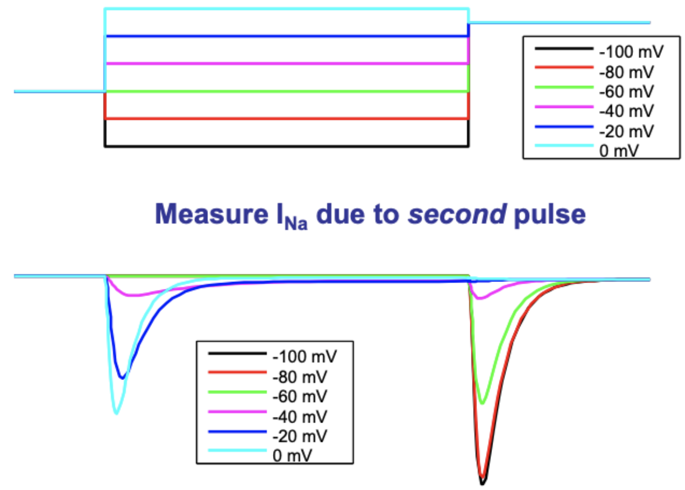
- When conductance **increases**, **all 4** charged particles must **move**.
- When conductance **decreases**, **1 out of 4** is **sufficient**.

The model now has a well-established physical basis, namely that as most ion channels are tetramers.

Focus on sodium conductance: slightly more complicated than gK



1. How to explain both the increase and decrease at constant voltage?



If first pulse is long, this gives value of steady-state inactivation, h_∞

2. How to derive both m and h from the data?

- Changes in K+ conductance and Na+ conductance can be described by "gating variables" that range from 0 to 1.
- K+ conductance is described by a single variable (n). Na+ conductance is described by the product of an activation variable (m) and an inactivation variable (h).
- The terms describing how gating variables depend on voltage are extracted directly from the experimental voltage clamp data.

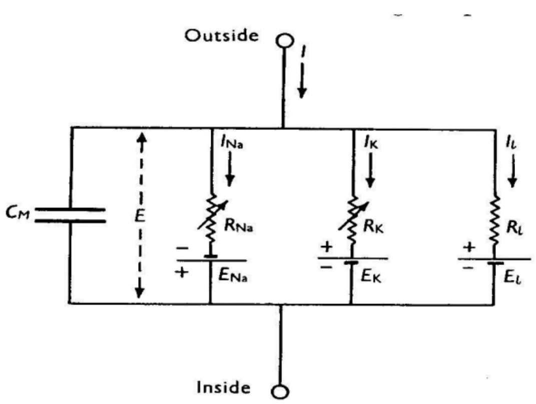
Q4. Example results with Hodgkin-Huxley model

- Sub-threshold and supra-threshold responses
- Refractoriness
- Anode break excitation

Theme: Each of these simulations represented an independent validation of the model.

Overall Hodgkin-Huxley model

1. Membrane represented as parallel conductances



2. Four ODEs

$$C_m \frac{dV}{dt} = -g_L(V - V_L) - \bar{g}_{Na} m^3 h (V - V_{Na}) - \bar{g}_K n^4 (V - V_K)$$

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

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

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

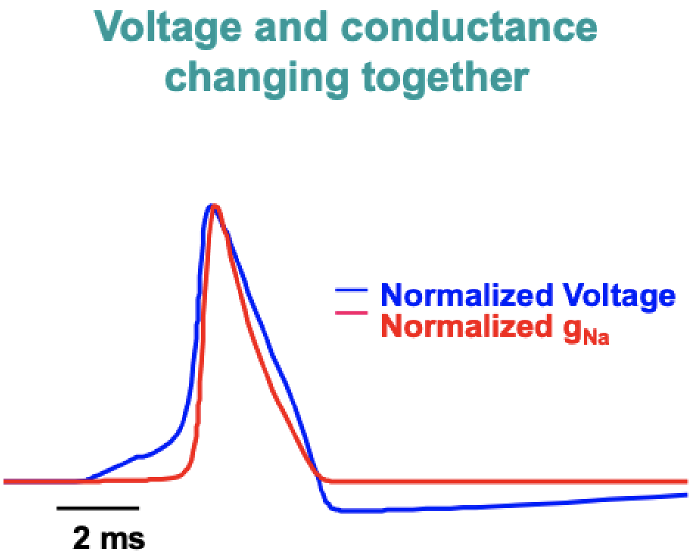
3. Voltage-dependent rate constants

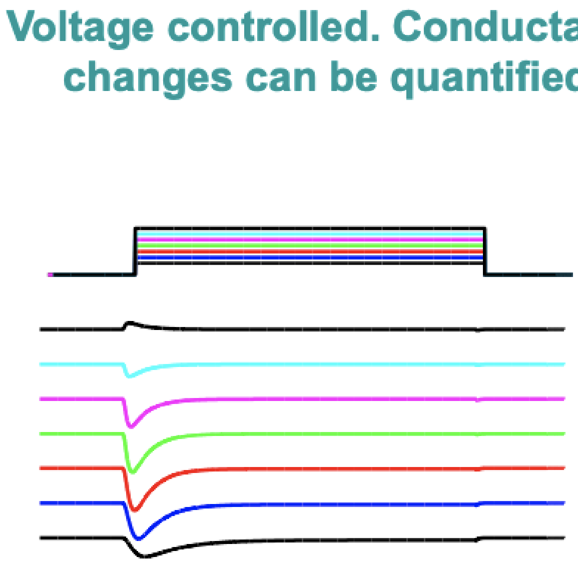
$$\alpha_m = 0.1(V_m + 35.0)/(1. - e^{(-(V_m+35.0)/10.0)})$$
$$\beta_m = 4.0\, e^{(-(V_m+60.0)/18.0)}$$

$$\alpha_h = 0.07\, e^{(-(V_m+60.0)/20.0)}$$
$$\beta_h = 1./(1 + e^{(-(V_m+30.0)/10.0)})$$

$$\alpha_n = 0.01(V_m + 50.0)/(1 - e^{(-(V_m+50.0)/10.0)})$$
$$\beta_n = 0.125\, e^{(-(V_m+60.0)/80.0)}$$

Why was voltage clamp transformative?





Simulation of simplified experiments was critical for both model development and understanding.