Models of Neurons 2: The Hodgkin-Huxley Model

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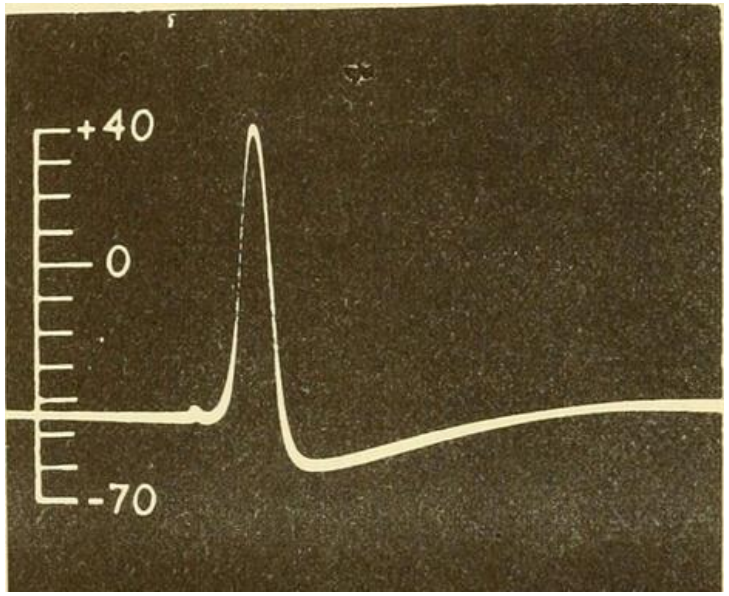
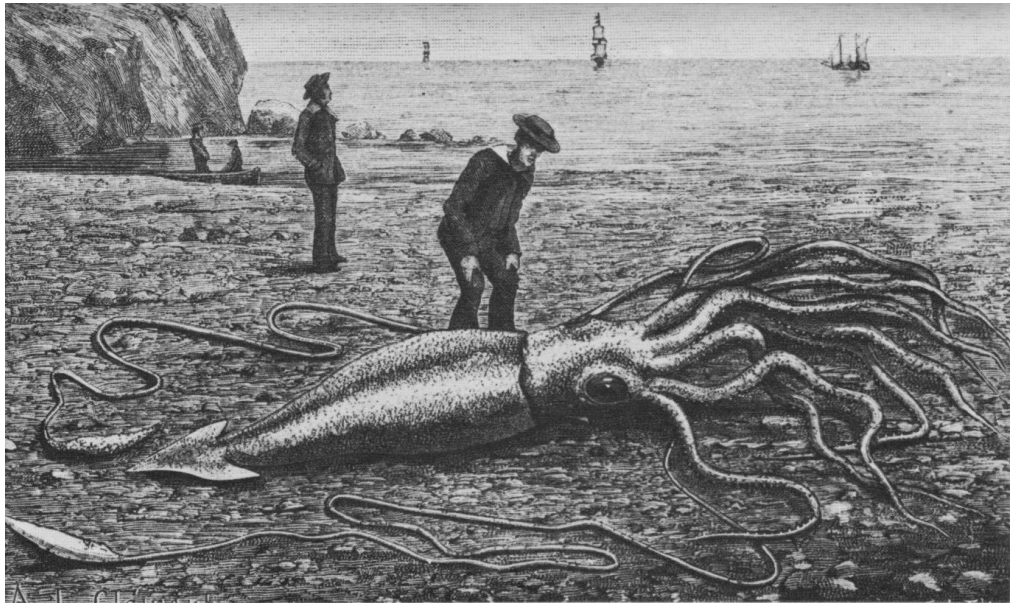
Computational Neuroscience (Lecture 4, 2023/2024)

Outline of Lecture

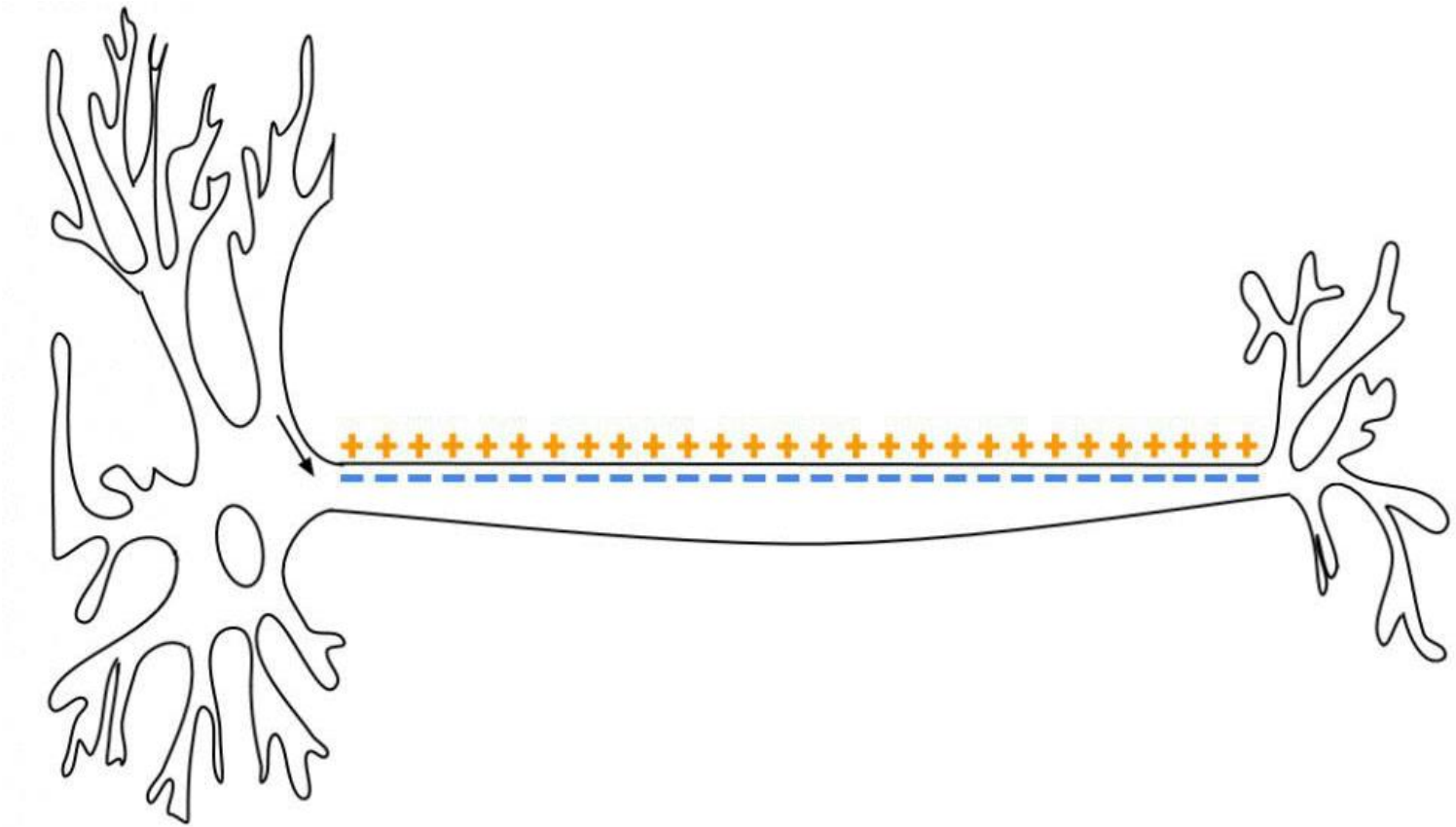
- Action potentials
- The voltage clamp
- Voltage-gated ion channels
- Markov models for ion channel gating
- The Hodgkin-Huxley model





Action Potentials (or “Spikes”)

- Action potentials propagate from the soma down the axon.
- The speed of action potential propagation is generally quite slow (metres per second)
- Action potentials are a noise-robust and energetically efficient method for communication over long distances



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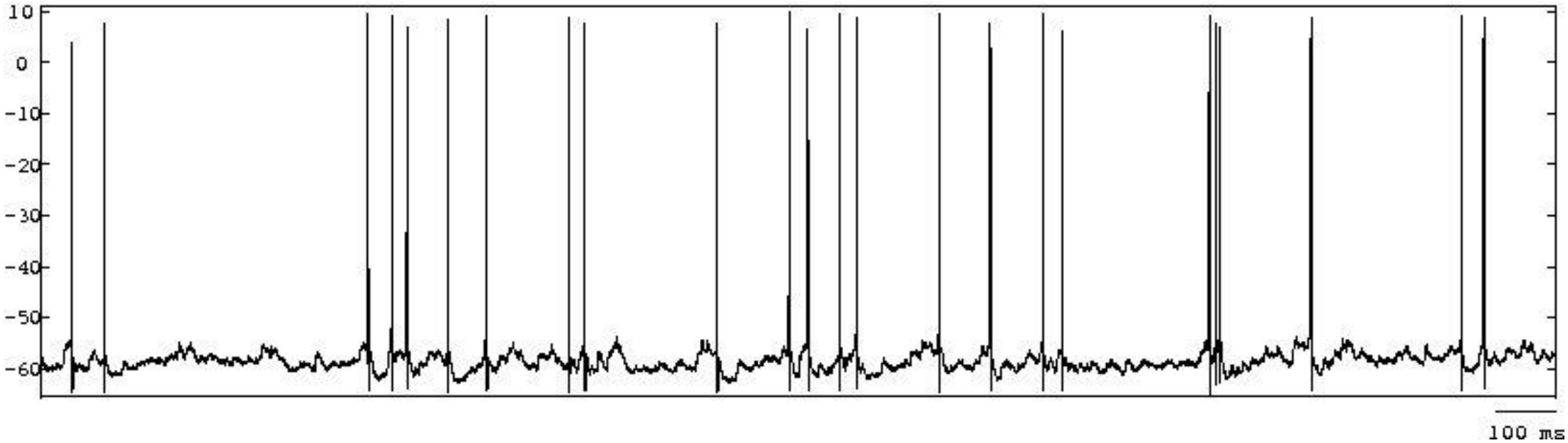

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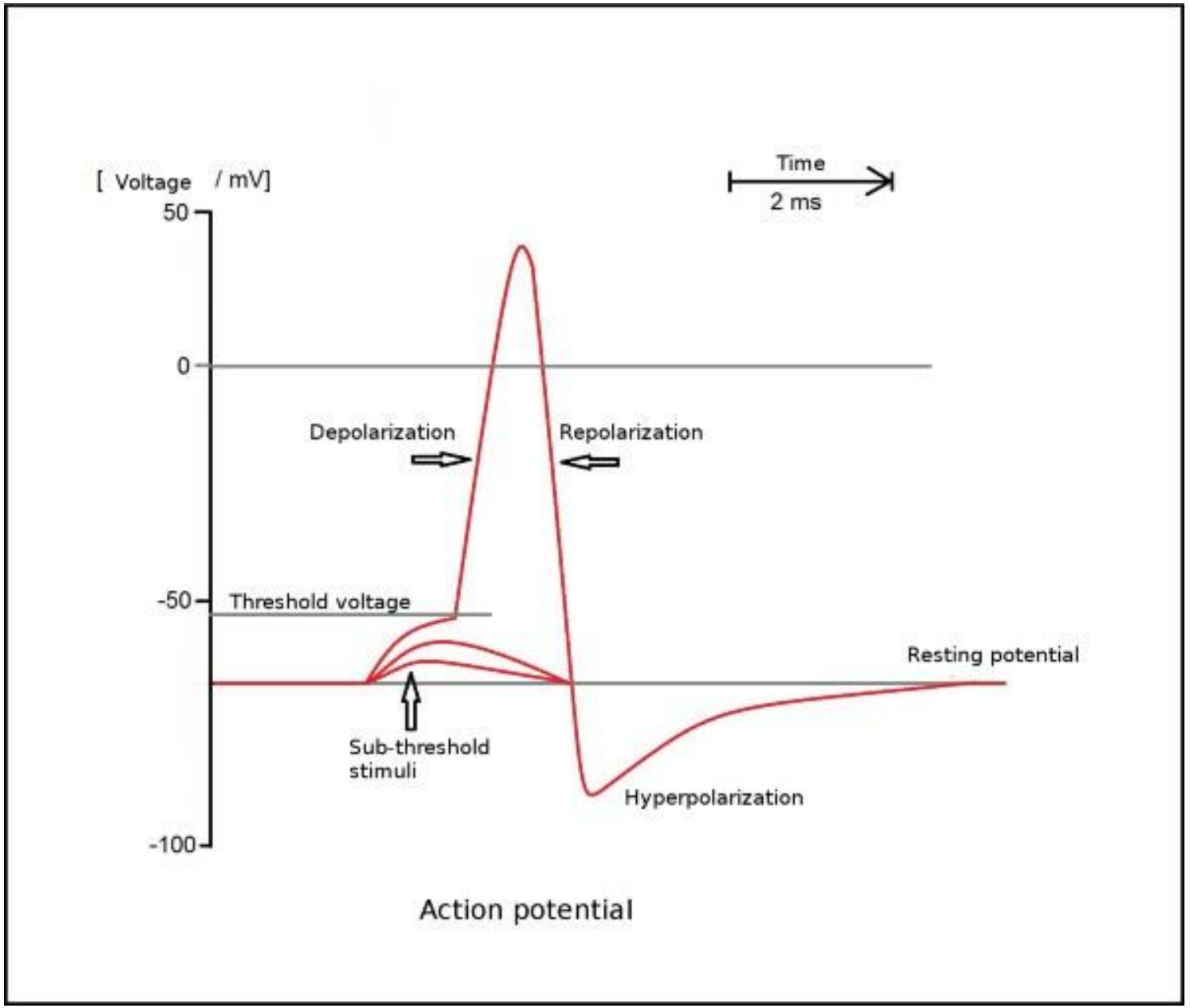

Recap – Membrane Potential

- Neurons have multiple species of ions inside and outside, with different concentrations
- Ions can flow in and out through open ion channels, due to concentration gradient and voltage
- At the resting potential, no net current flows across the cell membrane
- Using Ohm's law, we find an equation for the dynamics of the membrane potential
- This equation predicts a membrane time constant of around 20 ms, and can't explain spikes which last around 1 ms

Recap – Membrane Potential Equations

Membrane current: $I_m(V) = \sum_i I_i(V) \qquad I_i(V) = g_i(V - E_i)$

Membrane potential dynamics: $C_m \frac{dV}{dt} = -\sum_i g_i(V - E_i) + I_{ext}$

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Rewriting in terms of a single membrane conductance: $\tau_m \frac{dV}{dt} = -(V - E_m) + I_{ext}/g_m$

$$\tau_m = \frac{C_m}{\sum_i g_i} \qquad E_m = \frac{\sum_i g_i E_i}{\sum_i g_i}$$

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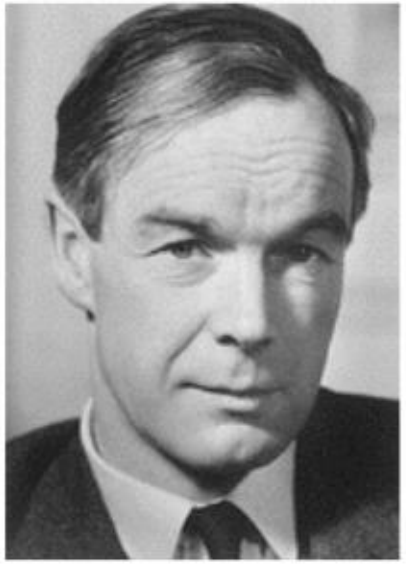
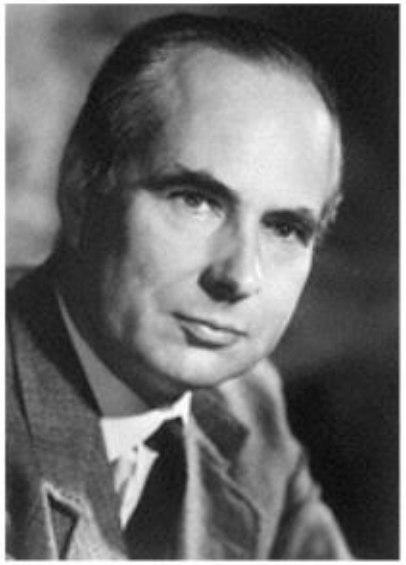
How can we decrease the time constant to get fast spikes? 1) Decrease *Cm* 2) Increase *g's*…

1 is not biologically plausible, but 2 turns out to be basis of action potential!

Some History

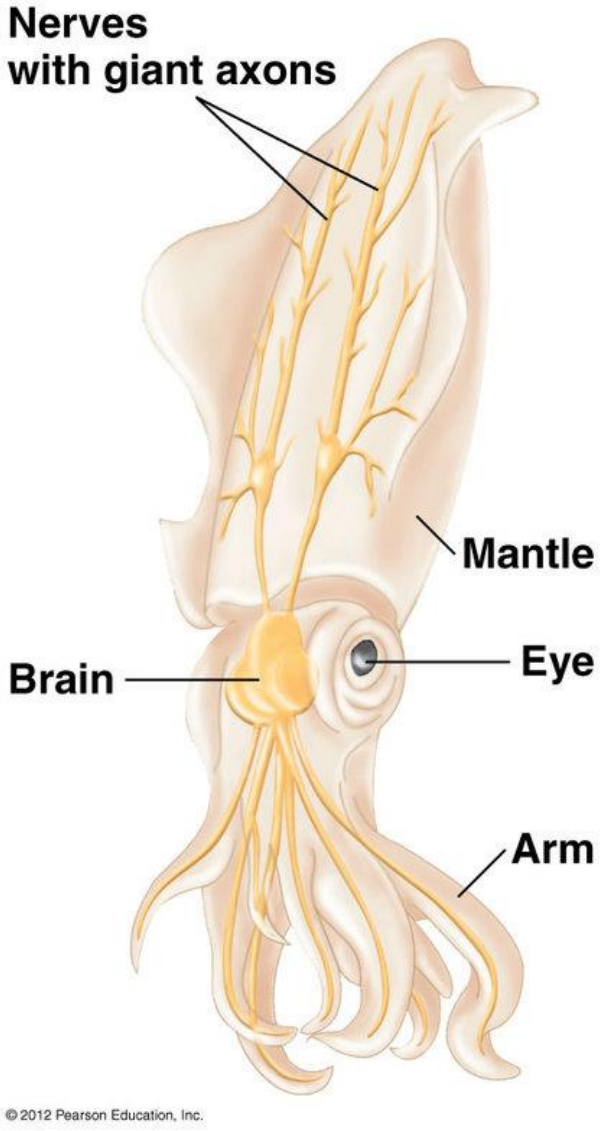
- Alan Hodgkin and Andrew Huxley, working to discover the ionic basis of the action potential (1930s-1940s)
- Working with the squid giant axon as a model system
- Developing methods to record from and control the axon
- They developed a mathematical model for the biophysics of the action potential and tested it experimentally
- They won the Nobel Prize for this work in 1963





The Squid Giant Axon

- The squid has a giant axon running through its whole body (diameter ~0.5 mm)
- Why? Wider axons transmit signals faster, and this axon sends a signal to squirt water for jet propulsion to escape predators!
- Hodgkin and Huxley could place an electrode directly inside the axon
- They developed clever methods to study the various ionic currents that flow through the axon membrane, and came up with an elegant mathematical model to describe them



The Voltage Clamp

- How can we measure the relationship between membrane potential and current flow experimentally? If we inject current to try to move the membrane potential to a set value, the neuron will start to spike!

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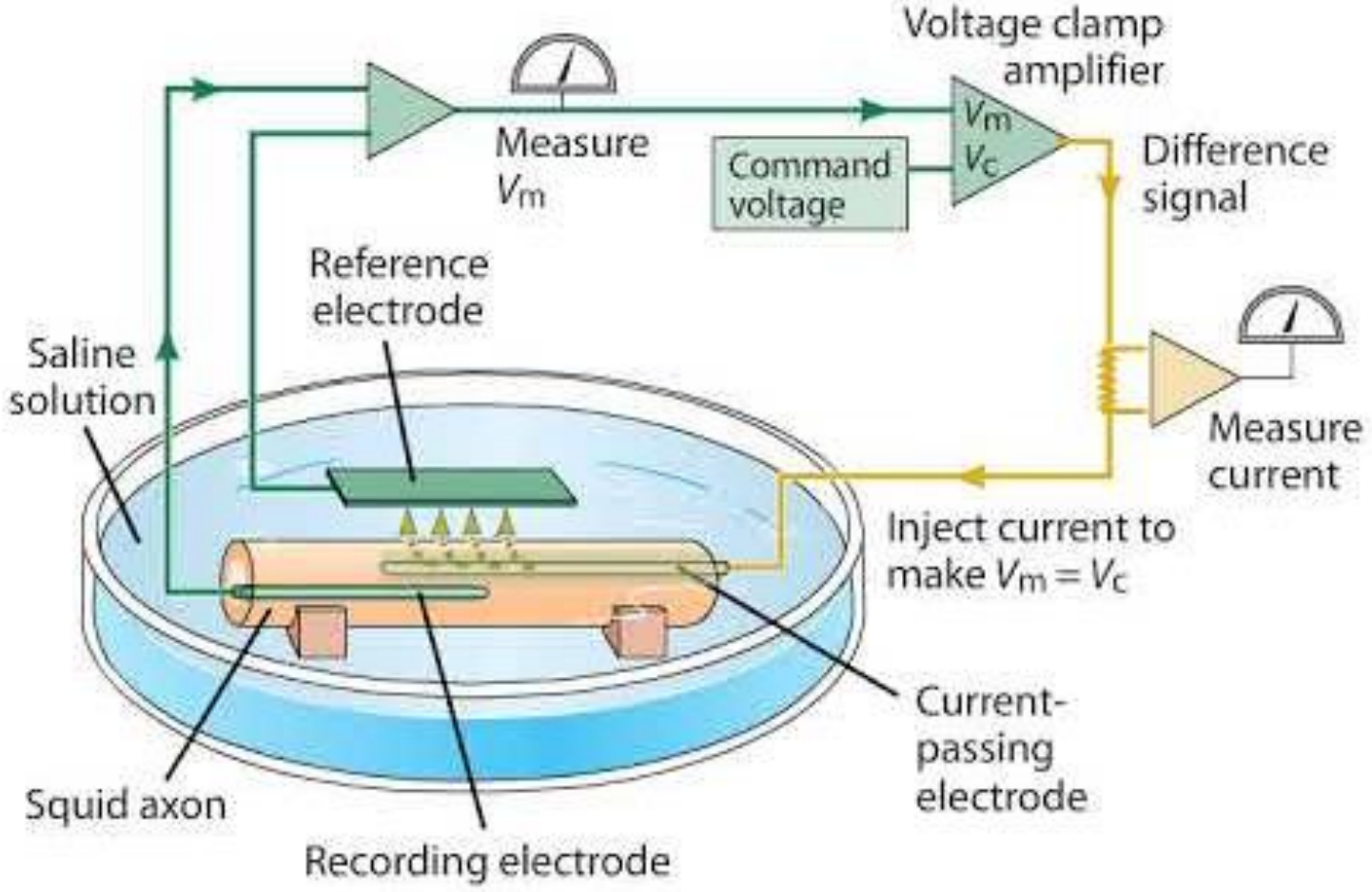
- Answer: the voltage clamp - use a feedback control system to rapidly adjust the injected current to keep the membrane potential at a set value.



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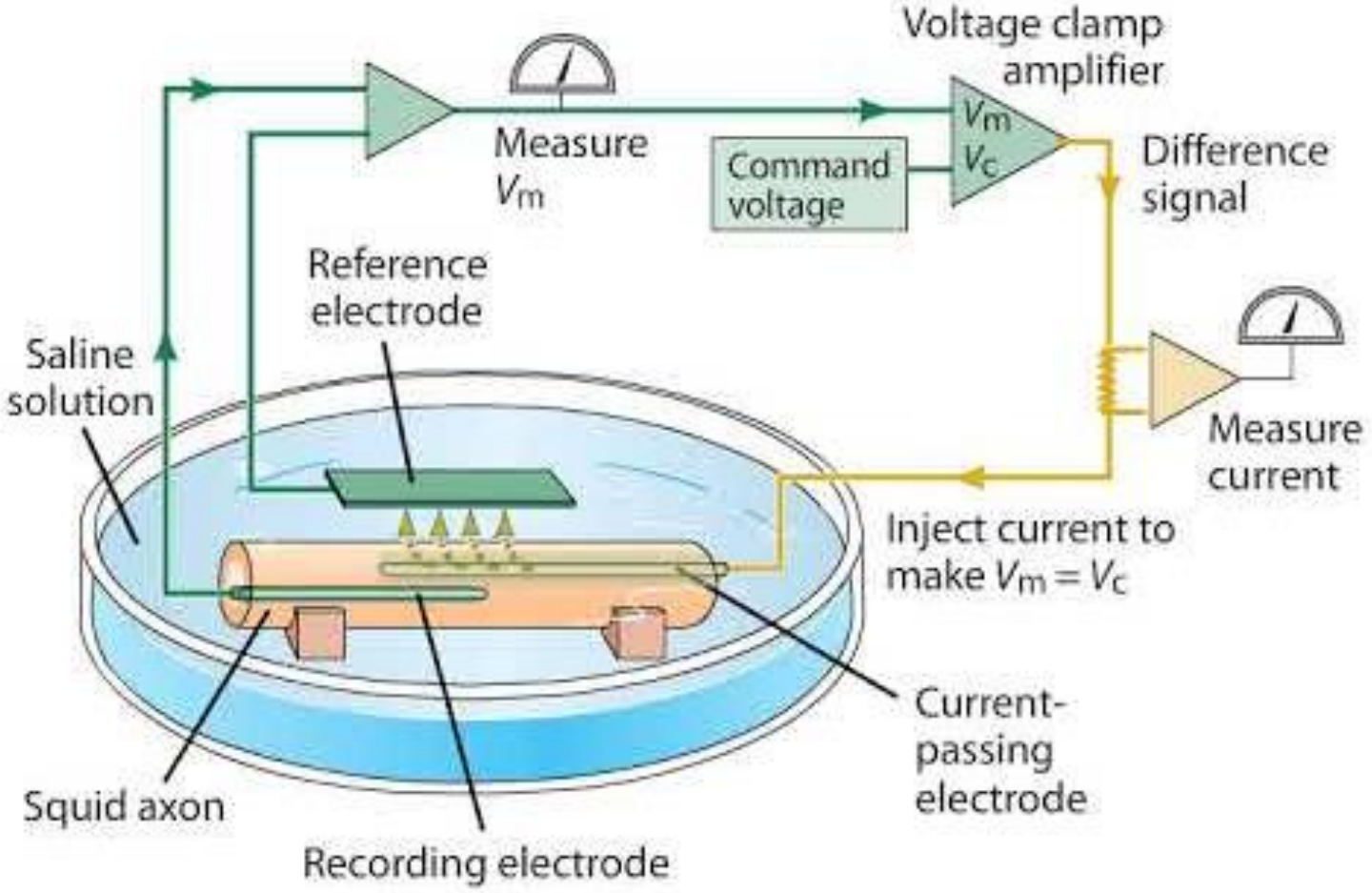

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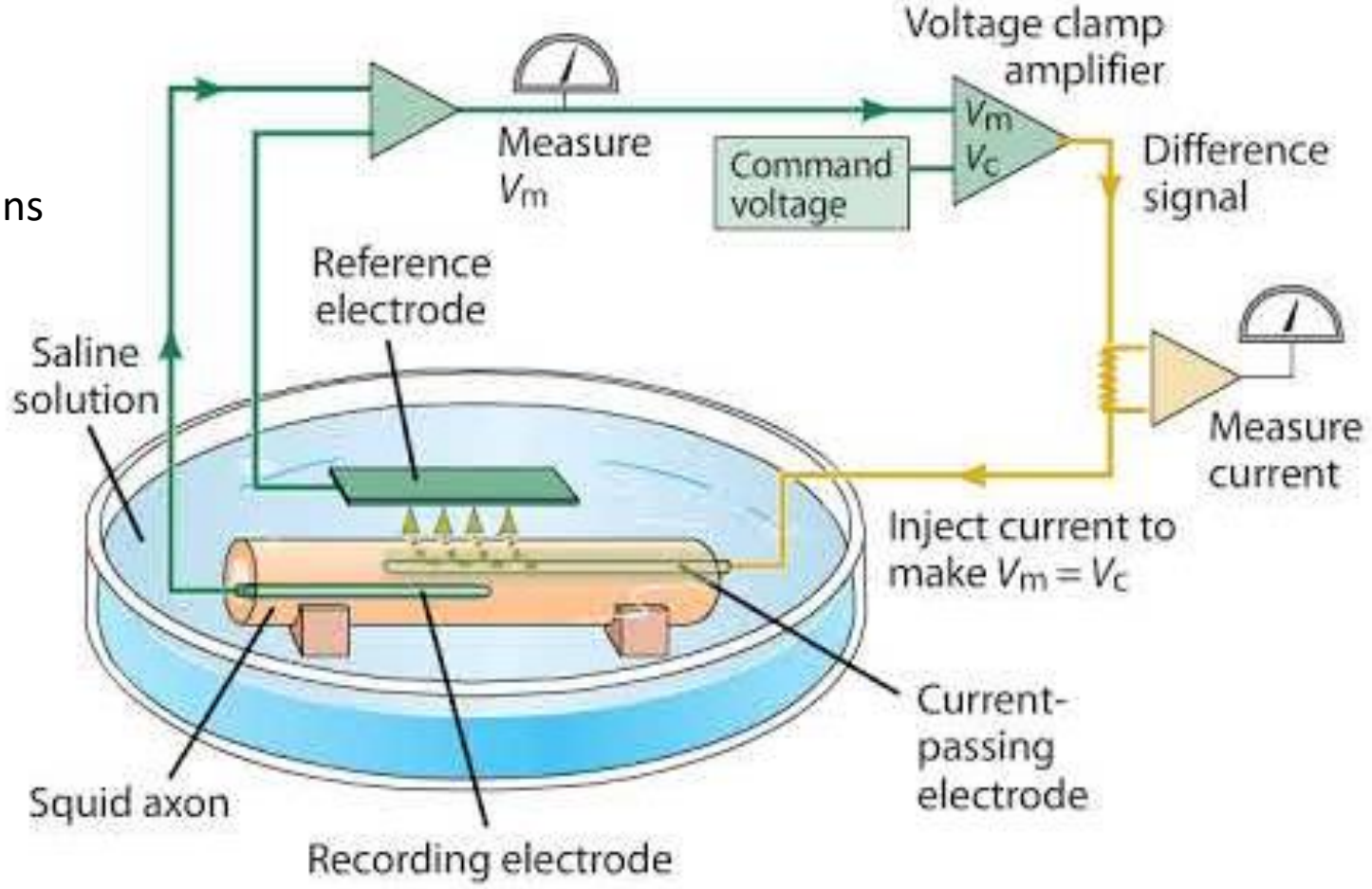
Set this

Can vary ion concentrations to set these

$$I(V) = \sum_i g_i(V)(V - E_i)$$

Measure this

Can block ion channels pharmacologically to set some to zero.



Hodgkin-Huxley Model Equations

- The membrane current is modelled as three ionic currents plus an external input current

$$c_m \frac{dV(t)}{dt} = -g_{leak}[V(t) - E_{leak}] - g_{Na}(V,t)[V(t) - E_{Na}] - g_K(V,t)[V(t) - E_K] + I_{ext}$$

- The first term represents the leak current, i.e. any current through ion channels with fixed conductances (mostly chloride)

- The second and third term represent the current flow through sodium and potassium channels, with conductances that depend on voltage and time

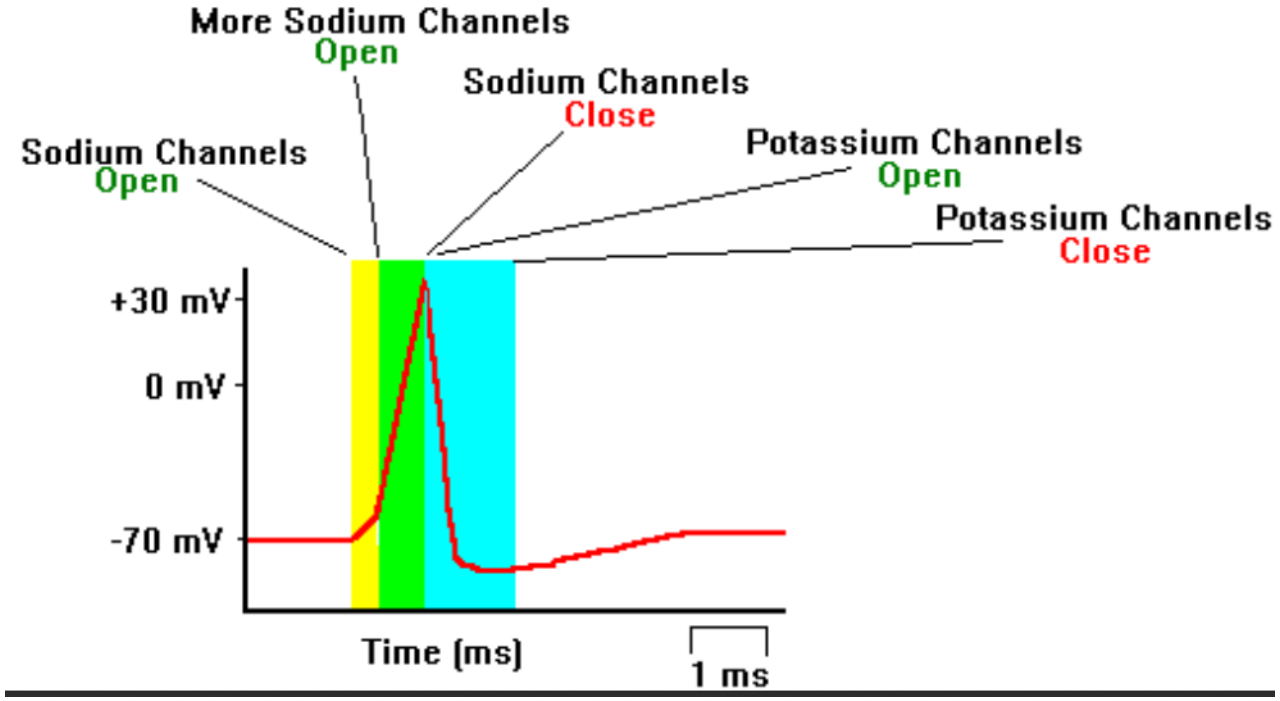
- Hodgkin and Huxley combined experiment and mathematical modelling to find equations for these conductances

The Hodgkin-Huxley Model

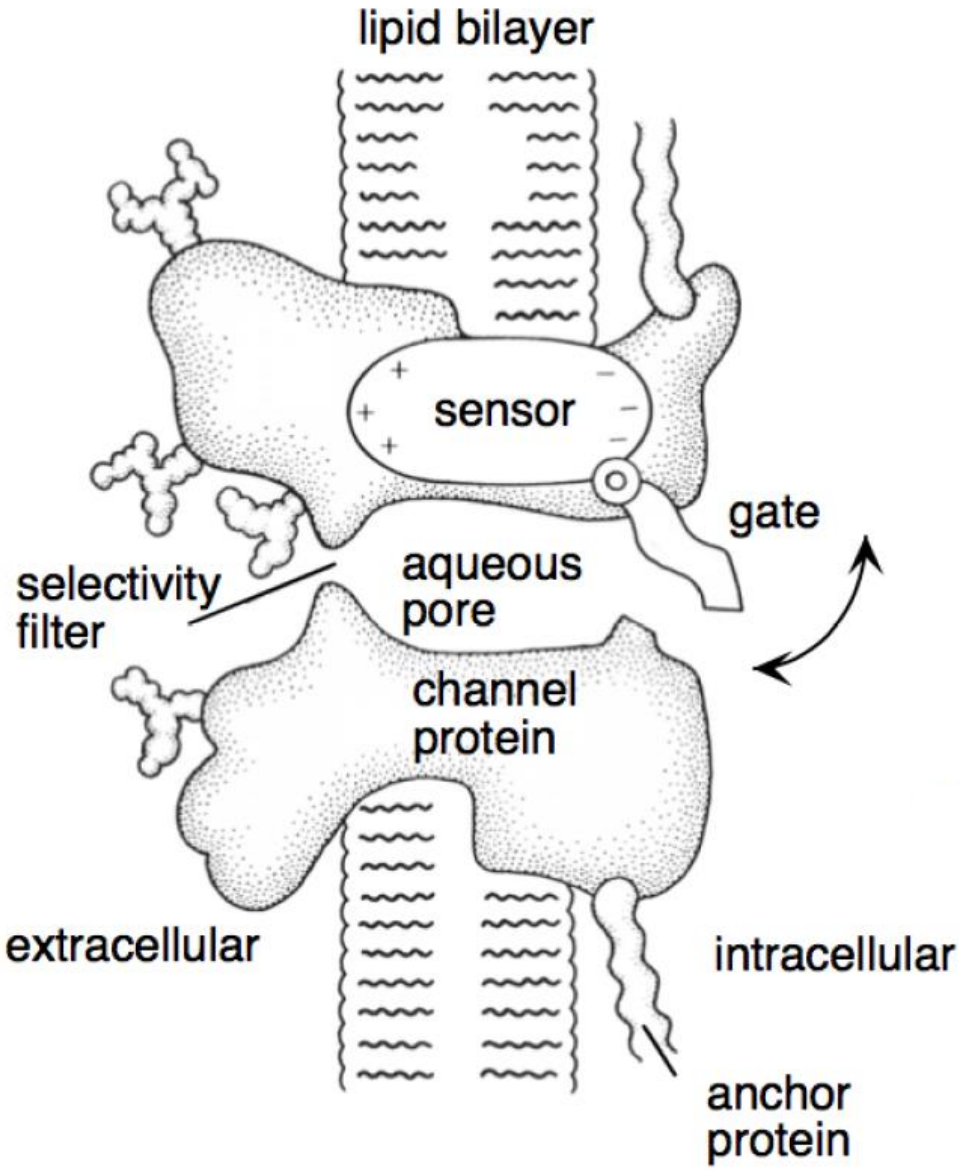
- Hodgkin and Huxley hypothesised that the permeability of ion channels is voltage-dependent
- Sodium channels are closed at the resting potential but open at higher membrane potentials
- When open, sodium ions flow into the cell, further increasing the membrane potential. As the membrane potential increases:

1) More sodium channels open, creating a positive feedback loop
2) potassium channels open, creating negative feedback
3) sodium channels close, halting positive feedback
(a "safety mechanism")

Together, 1-3) explain the rapid rise and decay of the action potential



Active Ion Channels

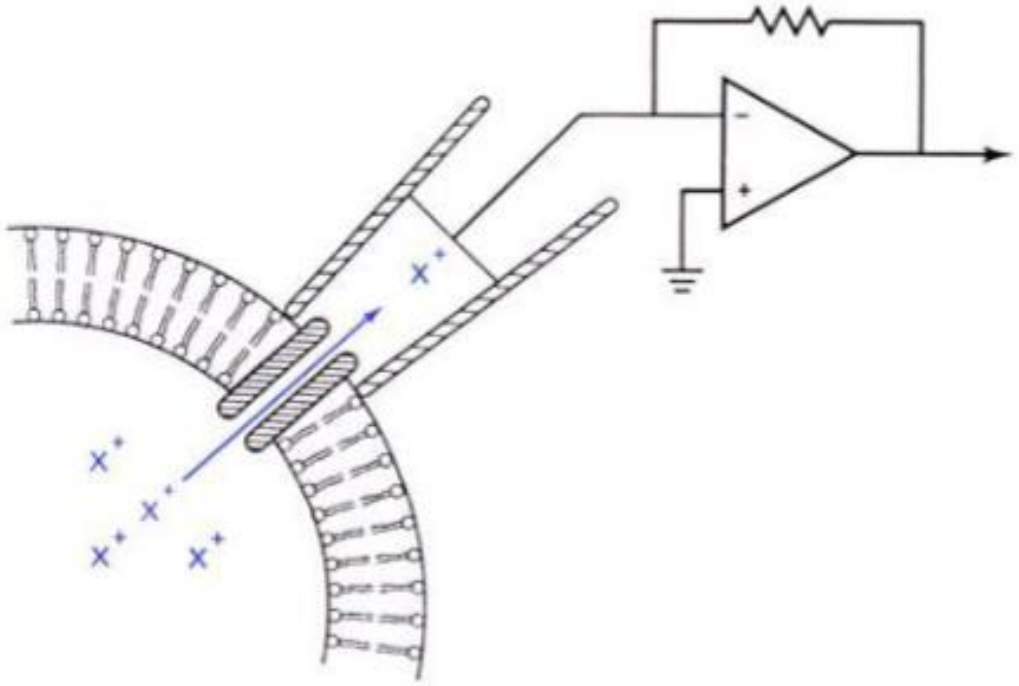


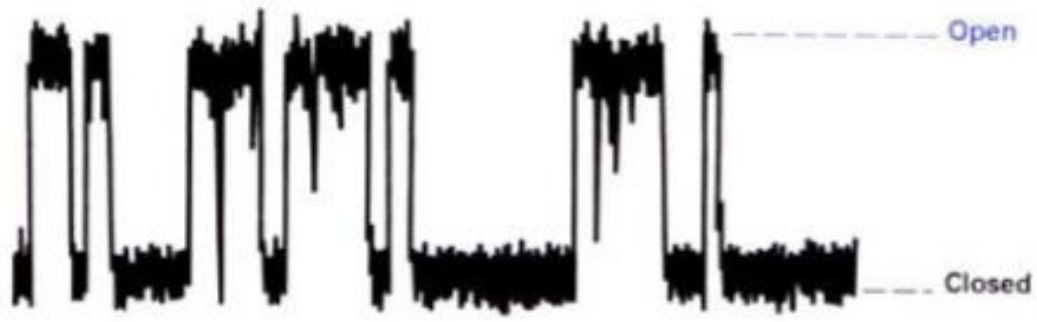
Ion channels may open and close, actively controlling the flow of current into and out of the cell.

Various factors cause opening and closing – voltage, molecules that bind to the ion channel, and random/stochastic processes.

This figure shows a potassium channel, with a voltage sensor that opens a gate at high membrane potentials. It has a “selectivity filter” that only allows potassium through.

Active Ion Channels





We can now measure current through single ion channels – this was not possible at the time of Hodgkin and Huxley!

Membrane Conductance Revisited

Last lecture, we considered the membrane conductance for the cell membrane to each species of ion. We considered membranes with fixed conductances (“passive membranes”)

How does the conductance change when ion channels open and close?

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How does the conductance change when ion channels open and close?

The total conductance depends on the number of open channels and the conductance of each channel:

$$g = N_{\text{open}} g^0 = N_{\text{channel}} P_{\text{open}} g^0 = \bar{g} P_{\text{open}}$$

number of open channels

conductance per channel

number of channels

probability of channel being open

conductance if all channels are open

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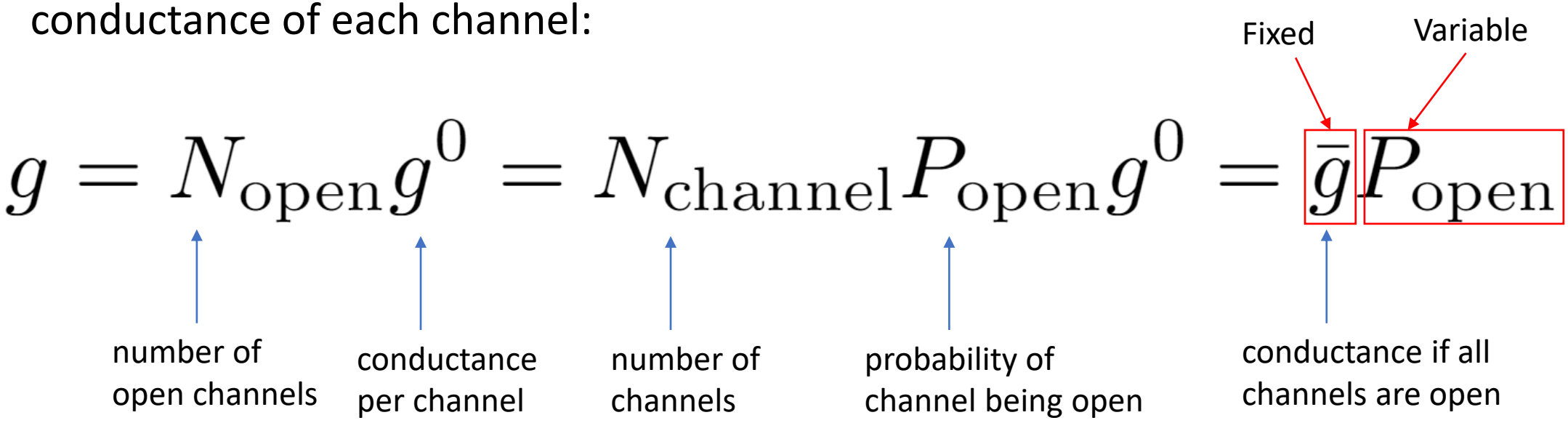
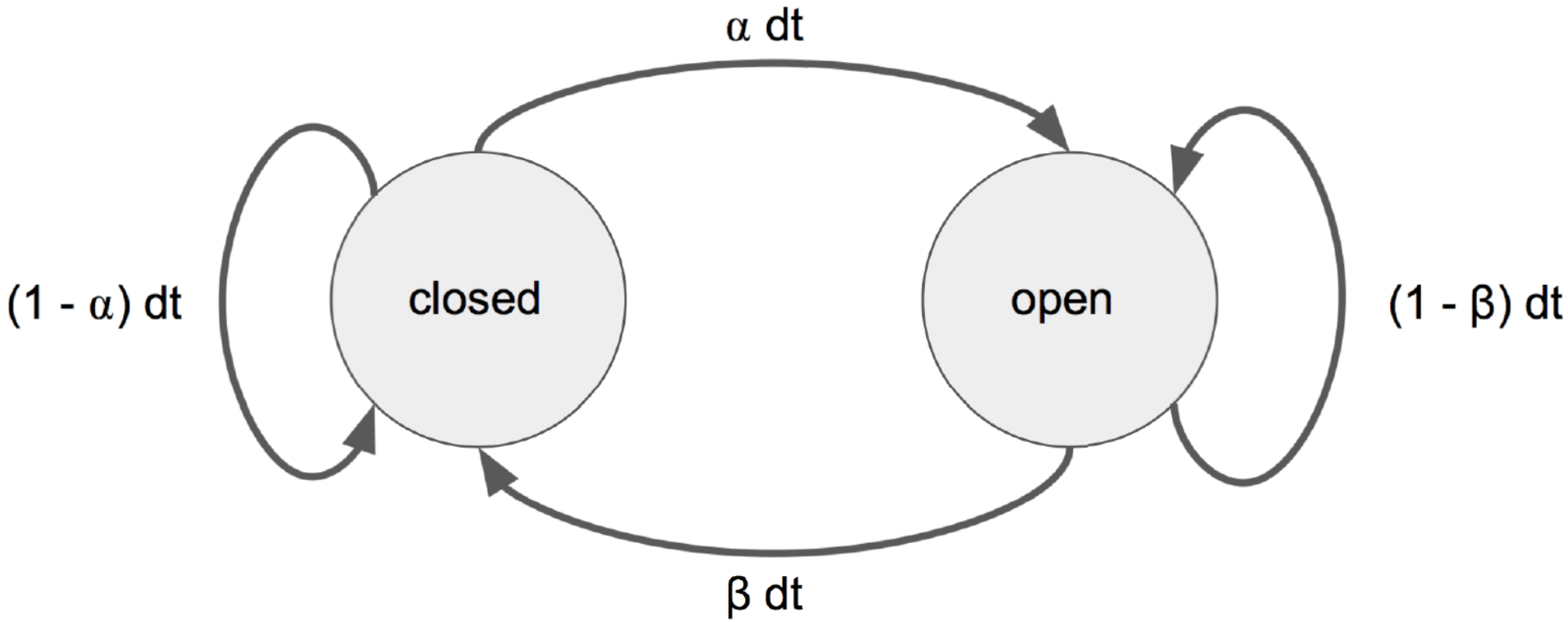


Markov Model For Channel Opening/Closing



Markov assumption: probability of state (open/closed) at time *t+dt* depends only on state at time *t*.

$$\begin{cases} p(\text{closed} \rightarrow \text{open}) & = \alpha(V)dt \\ p(\text{open} \rightarrow \text{closed}) & = \beta(V)dt. \end{cases}$$

Markov Model For Channel Opening/Closing

closed open

$$[A] \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} [A^*]$$

change in number open open to closed closed to open

$$d[A^*]/dt = -\beta[A^*] + \alpha[A]$$

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change in number open open to closed closed to open

$$d[A^*]/dt = -\beta[A^*] + \alpha[A]$$

Fraction open + fraction closed = 1

$$[A] + [A^*] = 1$$

$$d[A^*]/dt = -\beta[A^*] + \alpha(1 - [A^*])$$

Solution to Markov Model

The Markov equation is of the same form as the passive membrane potential dynamics equation - we can rewrite as:

$$\tau \frac{d\left[A^*\right]}{dt} = -\left[A^*\right] + \left[A^*\right]_\infty$$

$$\left[A^*\right]_\infty = \alpha/(\alpha+\beta) \qquad \tau = 1/(\alpha+\beta)$$

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So we already know the solution:

$$\left[A^*\right](t) = \left[A^*\right]_\infty + \left(\left[A^*\right]_0 - \left[A^*\right]_\infty\right)\exp(-t/\tau)$$

Summary Markov Models for Ion Channel Gating

- Ion channels stochastically open and close
- A simple model is to assume that opening/closing occurs at a fixed rate, with no history- or time-dependence (Markov assumption)
- This model predicts that the fraction of open gates will relax exponentially towards a fixed asymptotic value
- The asymptotic value and relaxation time constant depend on the Markov transition rates

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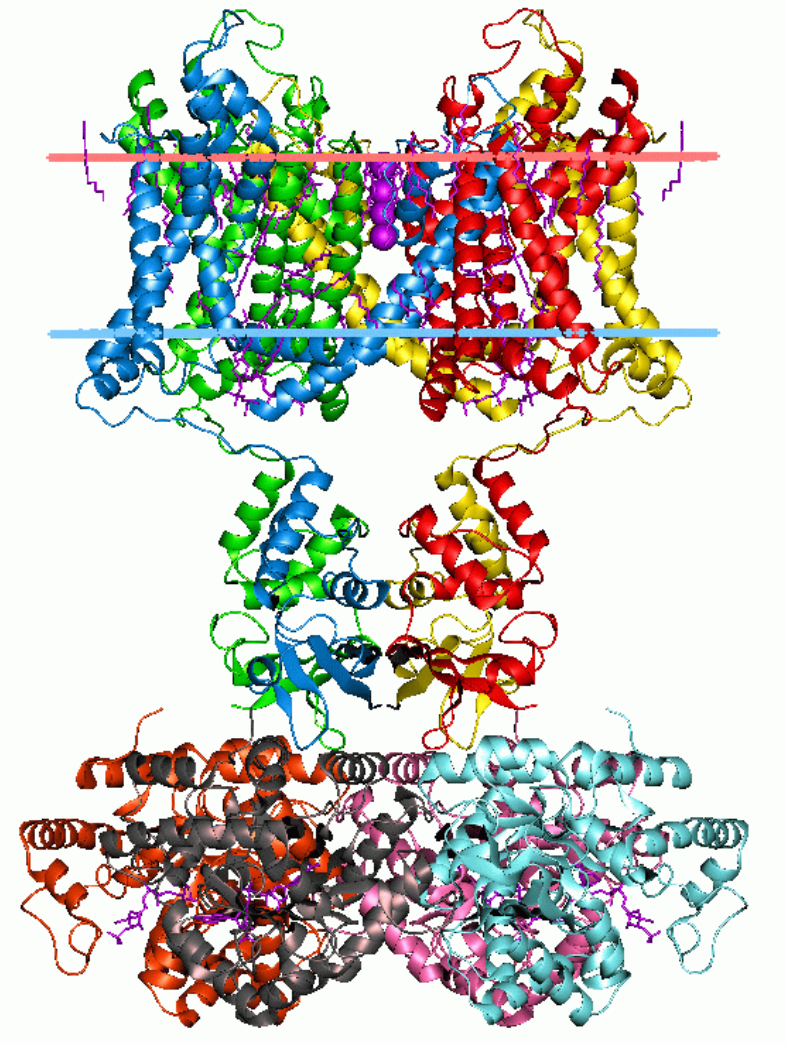
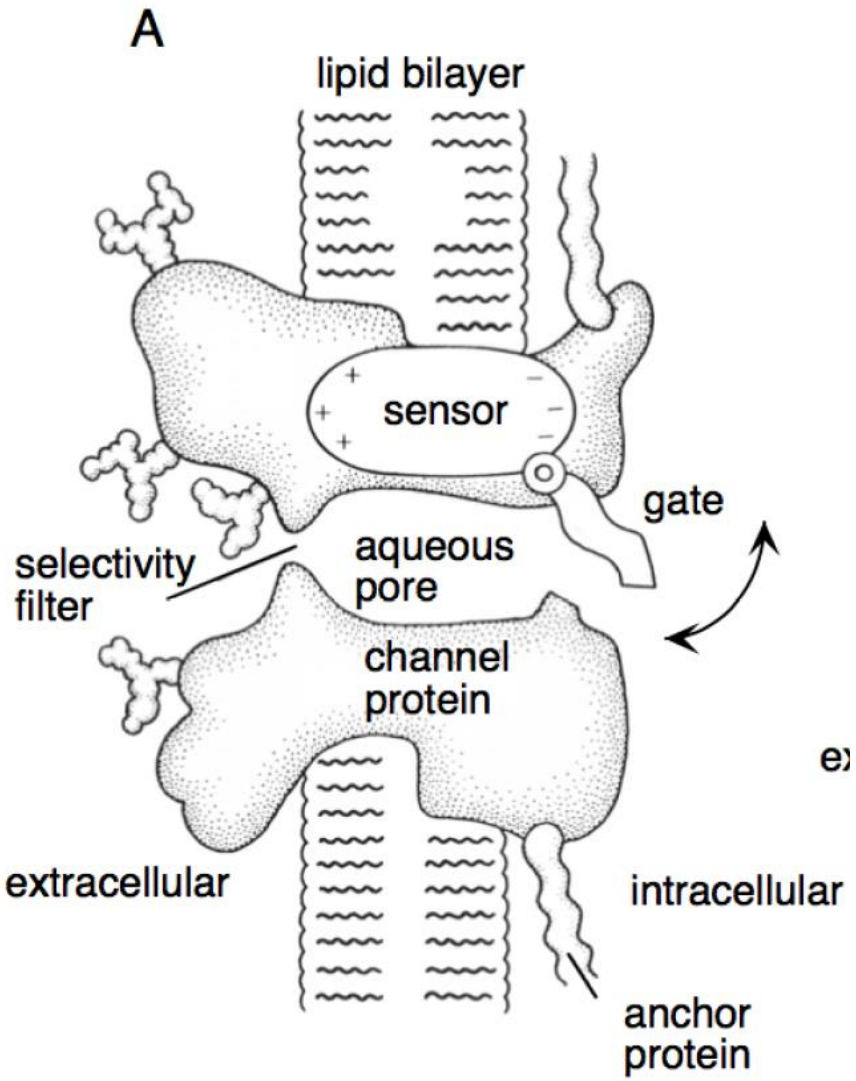
- This model predicts that the fraction of open gates will relax exponentially towards a fixed asymptotic value
- The asymptotic value and relaxation time constant depend on the Markov transition rates
- BUT!!! This turns out to be insufficient to explain ion channels for two reasons:

  1) Transition rates are voltage-dependent 2) Ion channels have multiple gates

Voltage-Gated Potassium Channels

Molecular structure of a voltage-gated potassium channel





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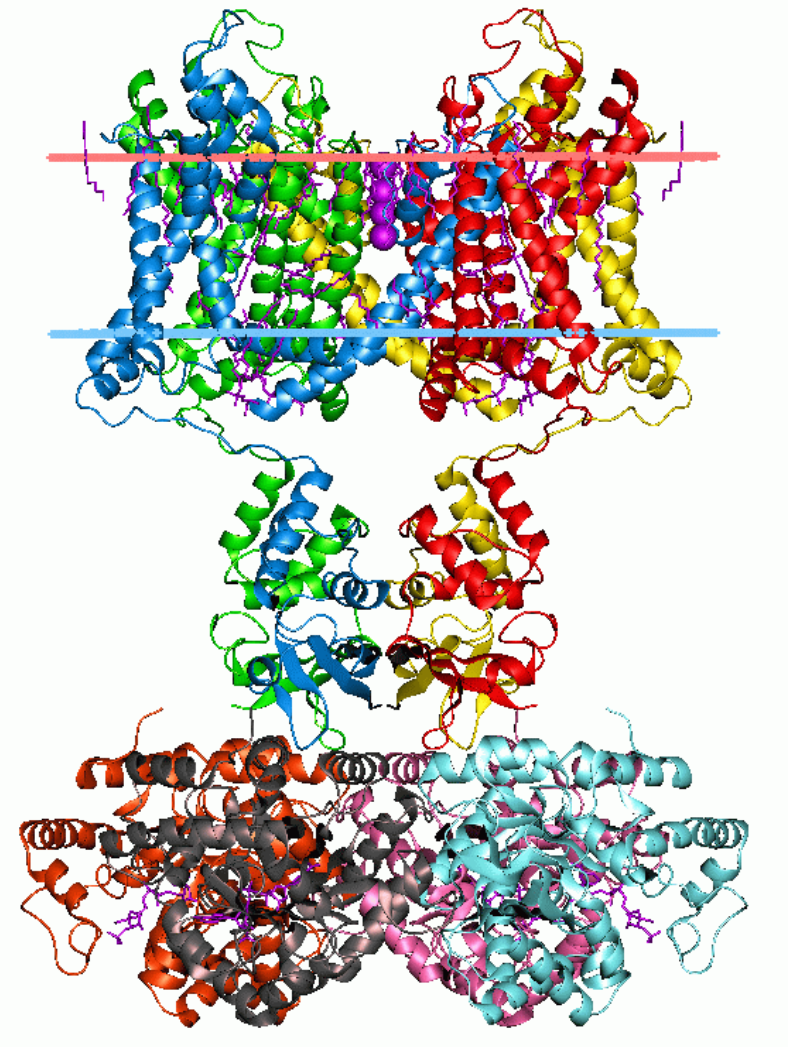

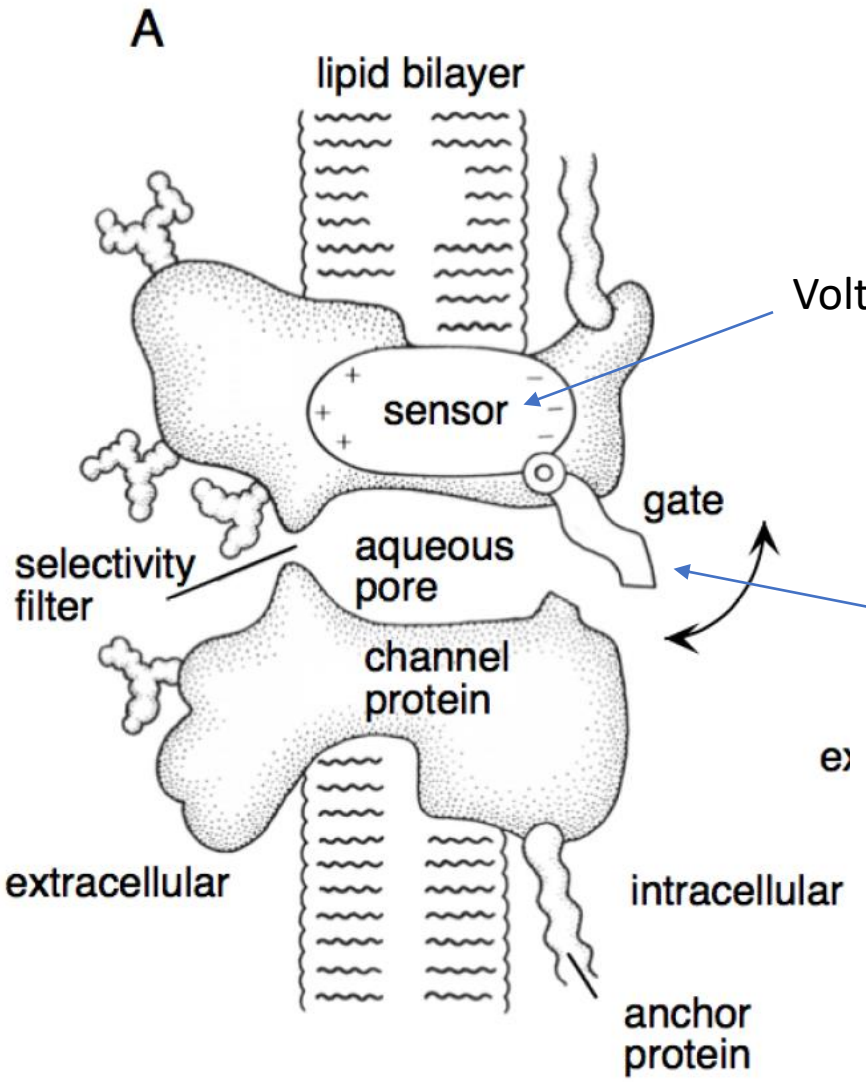

Voltage-Sensor

There are actually 4 of these!!!
The channel is only open when all 4 gates are open…

Application to Potassium Channels

$$g_K(V,t) = \bar{g}_K P_{\text{open}}(V,t)$$

$$P_{\text{open}}(V,t) = n^4(V,t)$$

Each potassium channel has 4 gates, all of which need to be open for ions to pass through

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

Markov dynamics for each gate

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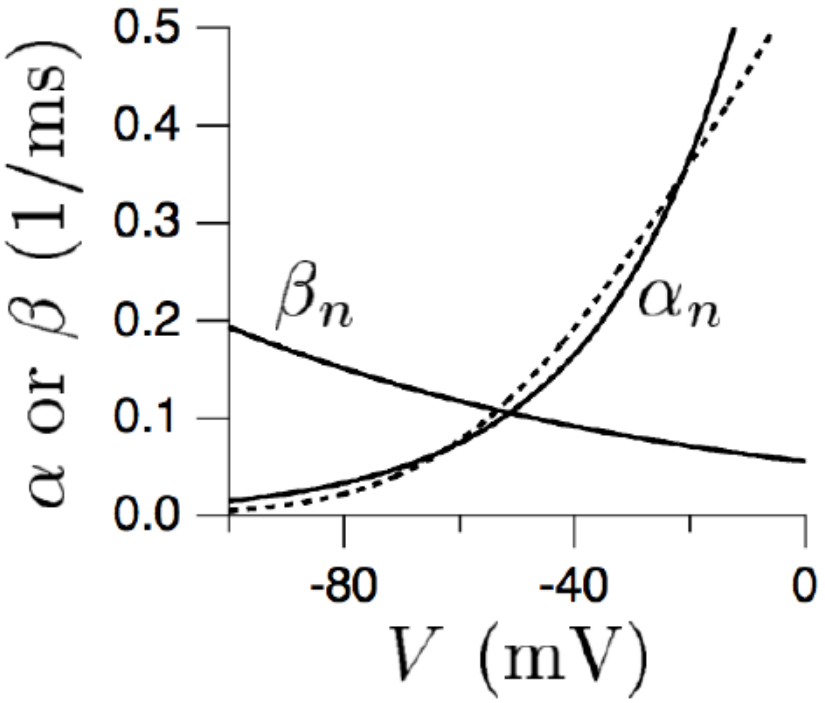
Markov dynamics for each gate

$$\alpha_n = \frac{(10-V)/100}{\exp[0.1(10-V)]-1}$$

$$\beta_n = 0.125\,\mathrm{e}^{-V/80}$$

These functions are essentially fit to data based on voltage clamp experiments

Fitting the Model to Potassium Channels



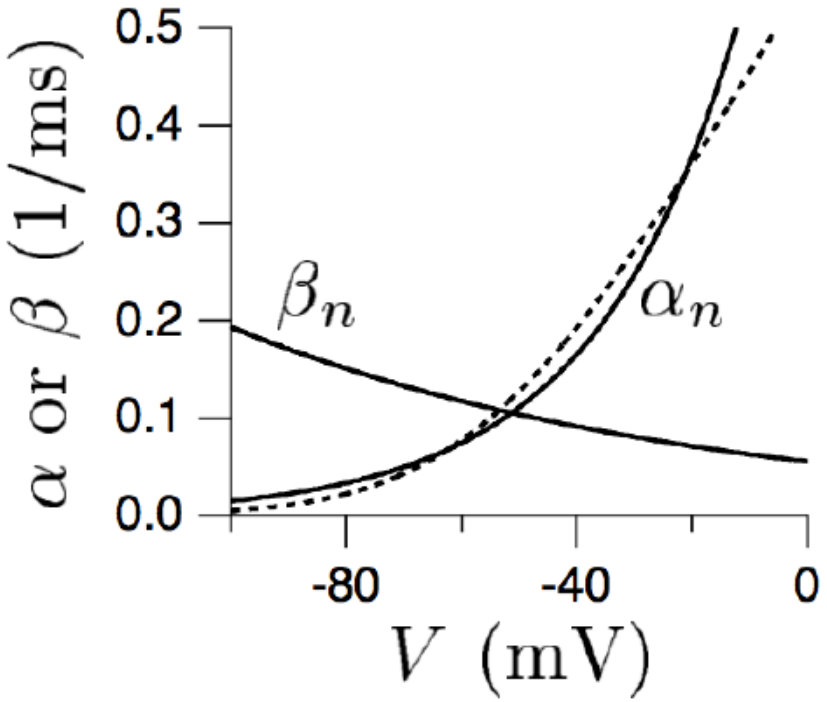
Fitting the Model to Potassium Channels

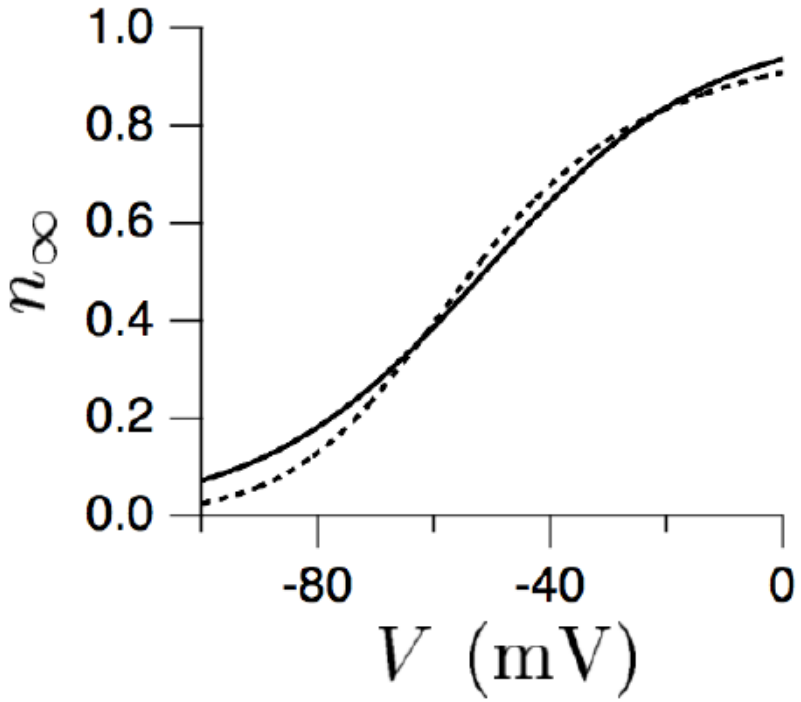
Fraction open at equilibrium
(clamped at V)

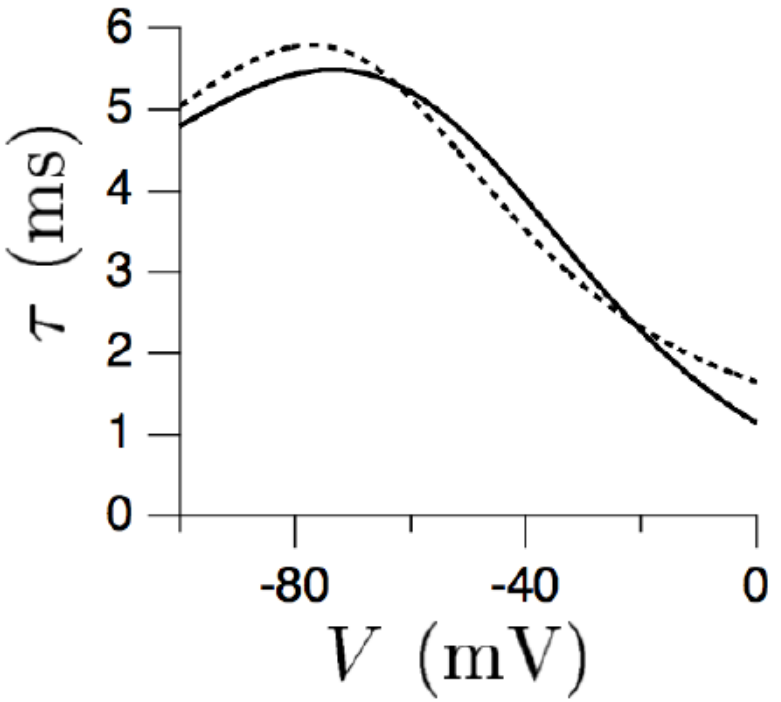
$$n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}$$

Time to approach equilibrium
(clamped at V)

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

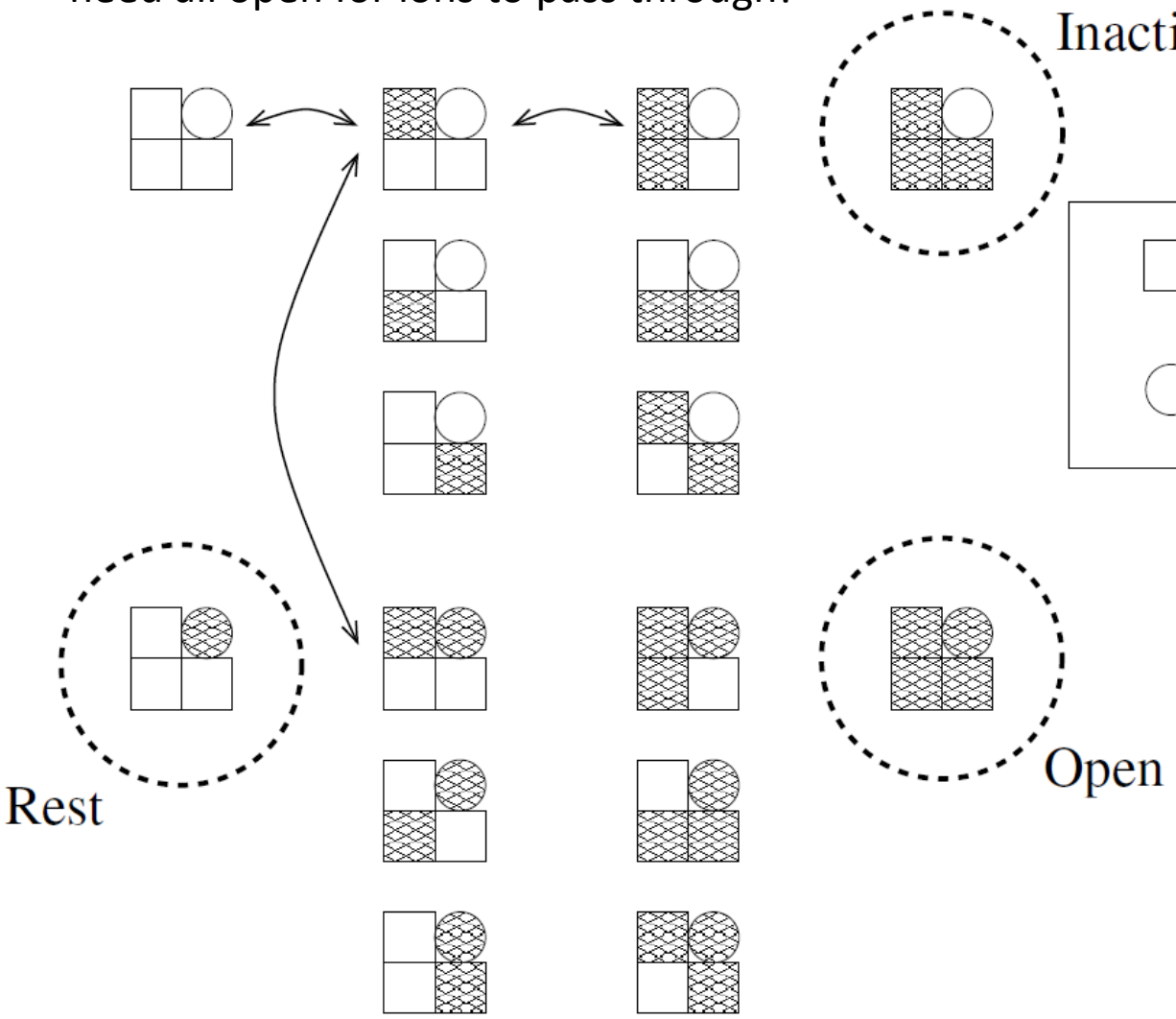


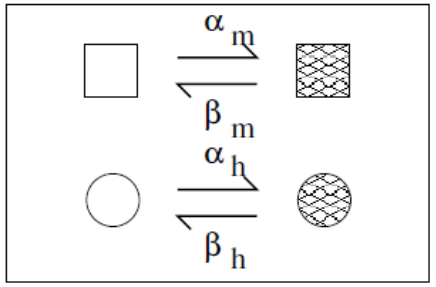




Sodium Channels

3 activation gates (m) + 1 inactivation gate (h)
– need all open for ions to pass through!





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

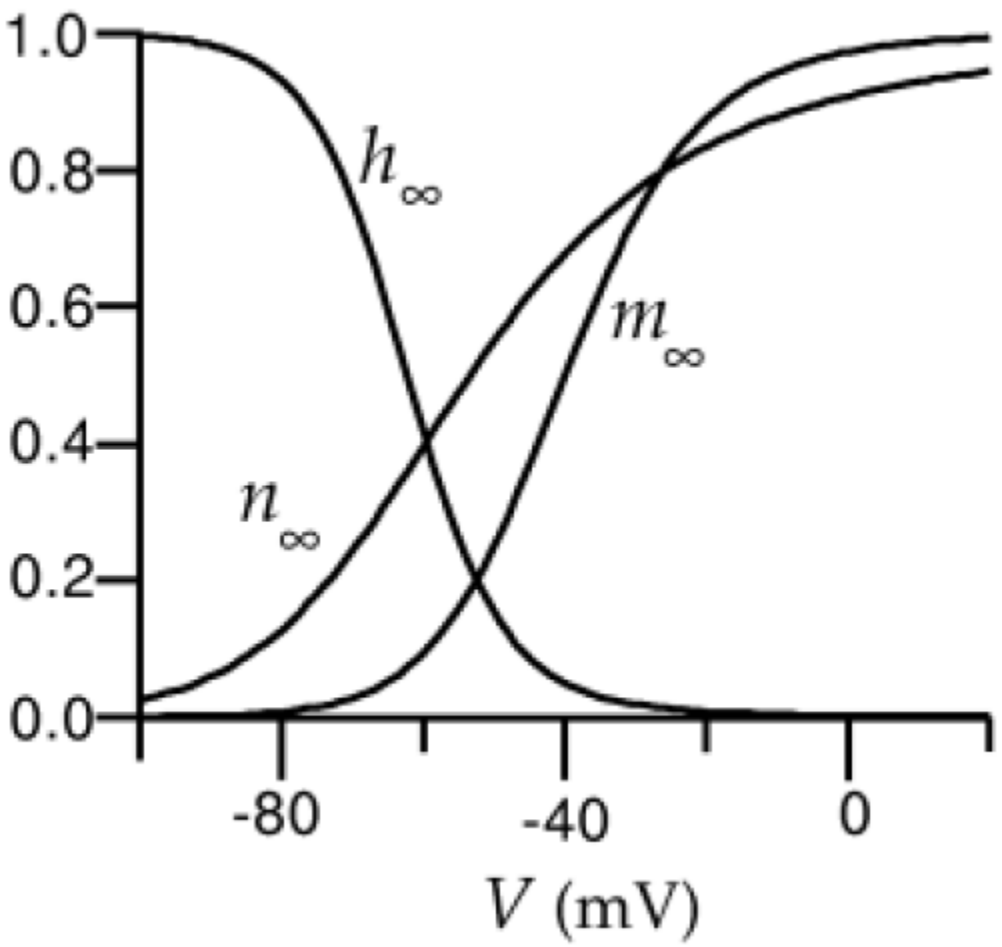
$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$

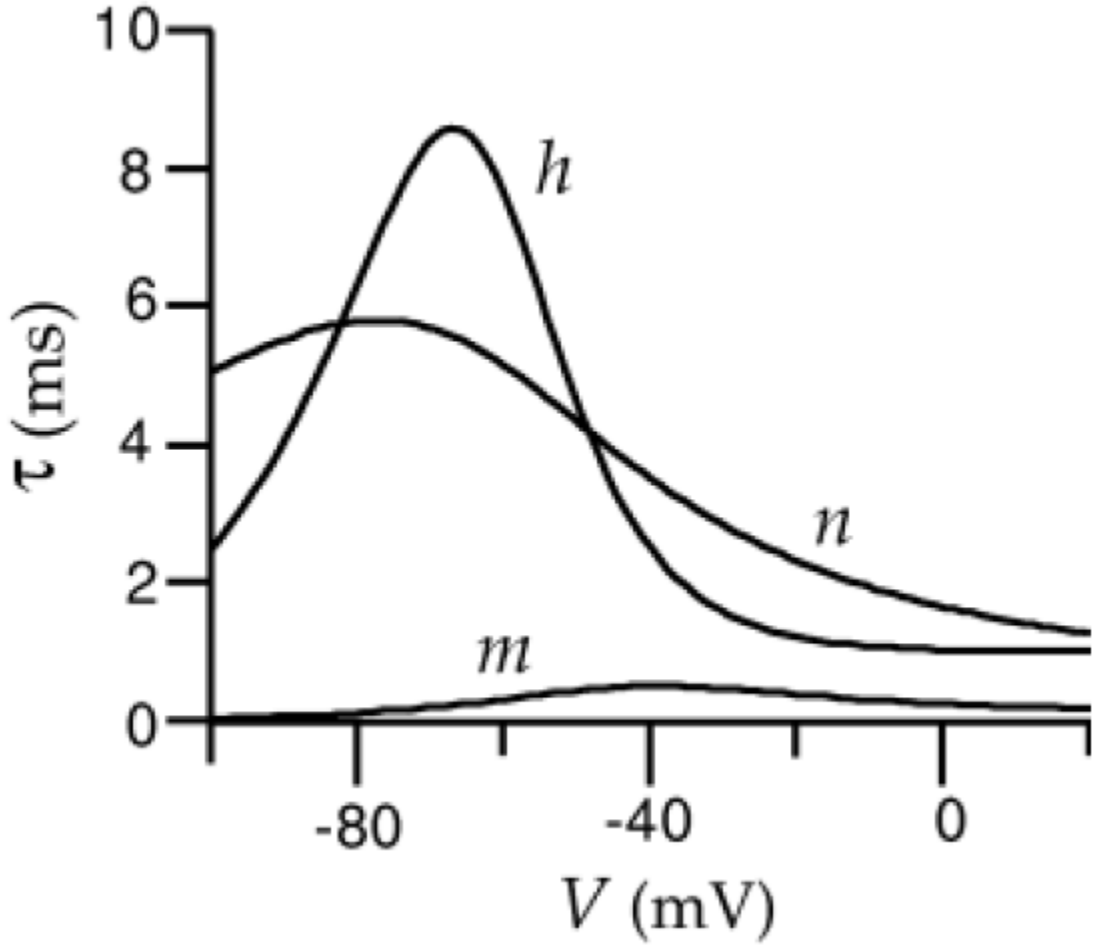
$$g_{Na} = \bar{g}_{Na} P_{\text{open}}(V,t)$$

$$P_{\text{open}} = m^3(V,t)h(V,t)$$

Sodium Channels

The *h* and *m* sodium variables are modelled/fit in the exactly the same as way as the *n* potassium variables, but with different experimentally-derived parameter values:





Putting it all together…

The Hodgkin-Huxley model is a set of 4 coupled nonlinear differential equations (1 voltage + 3 gating variables)

$$c_m \frac{dV(t)}{dt} = -g_{leak}[V(t) - E_{leak}] - \bar{g}_{Na} m^3(V,t) h(V,t)[V(t) - E_{Na}] - \bar{g}_K n^4(V,t)[V(t) - E_K] + I_{ext}$$

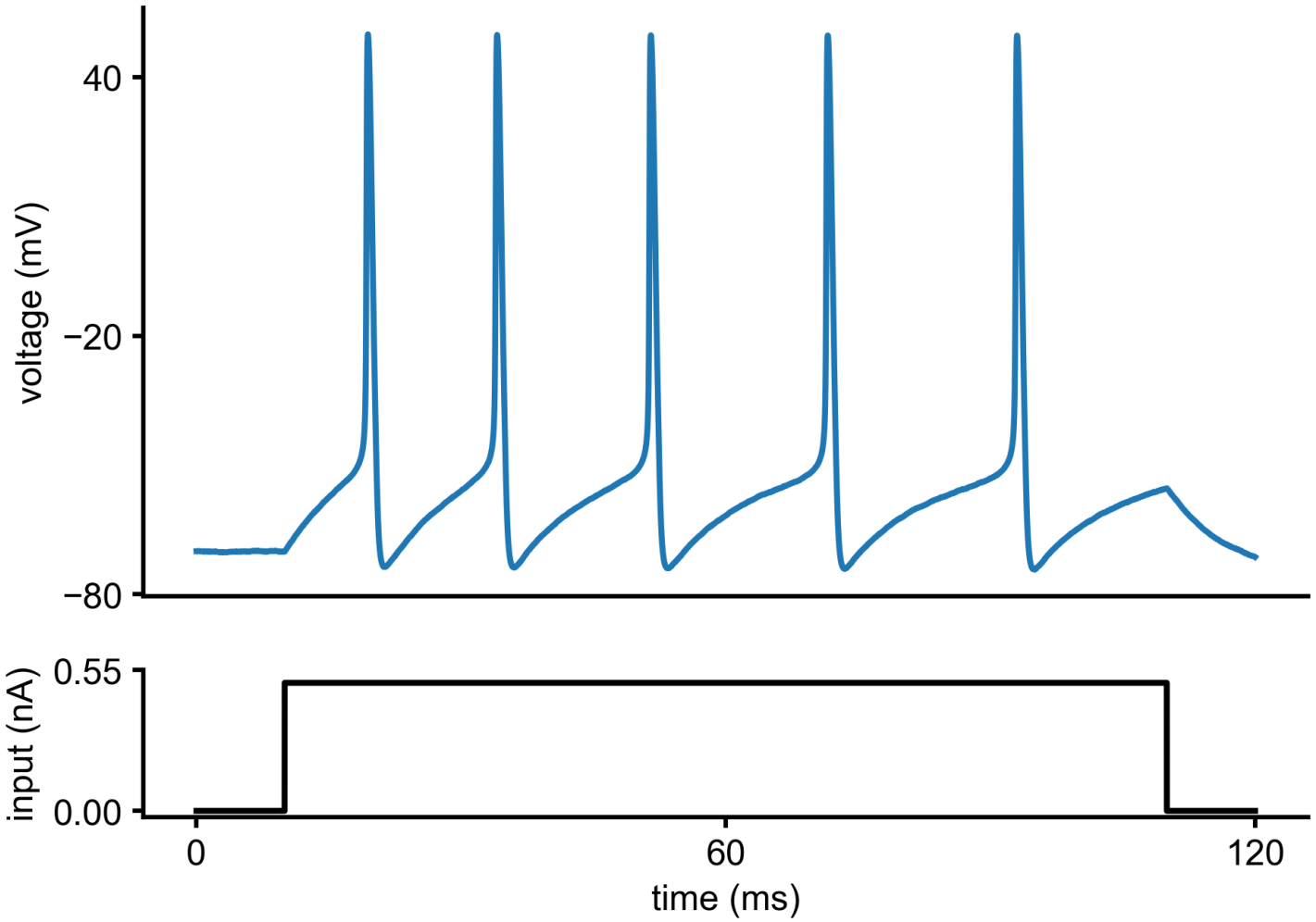
$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$ Potassium gate

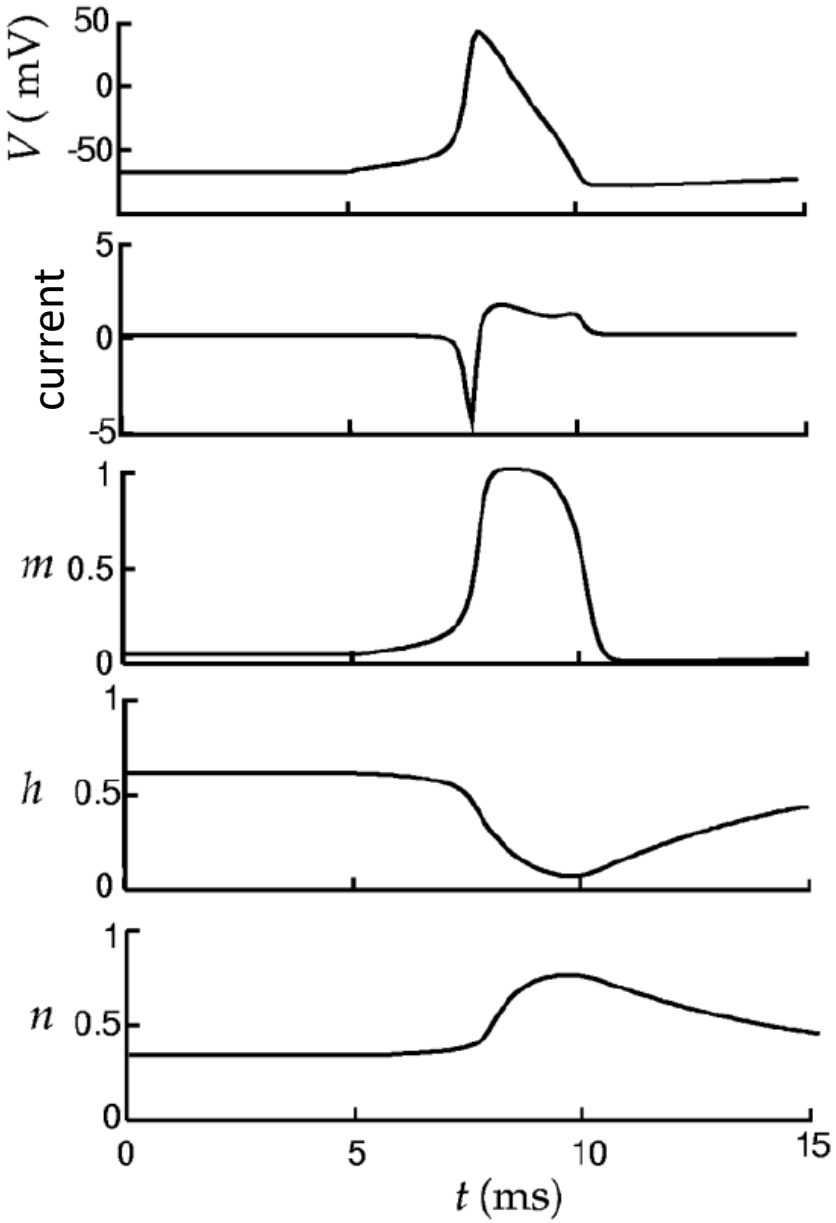
$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$ Sodium activation gate

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

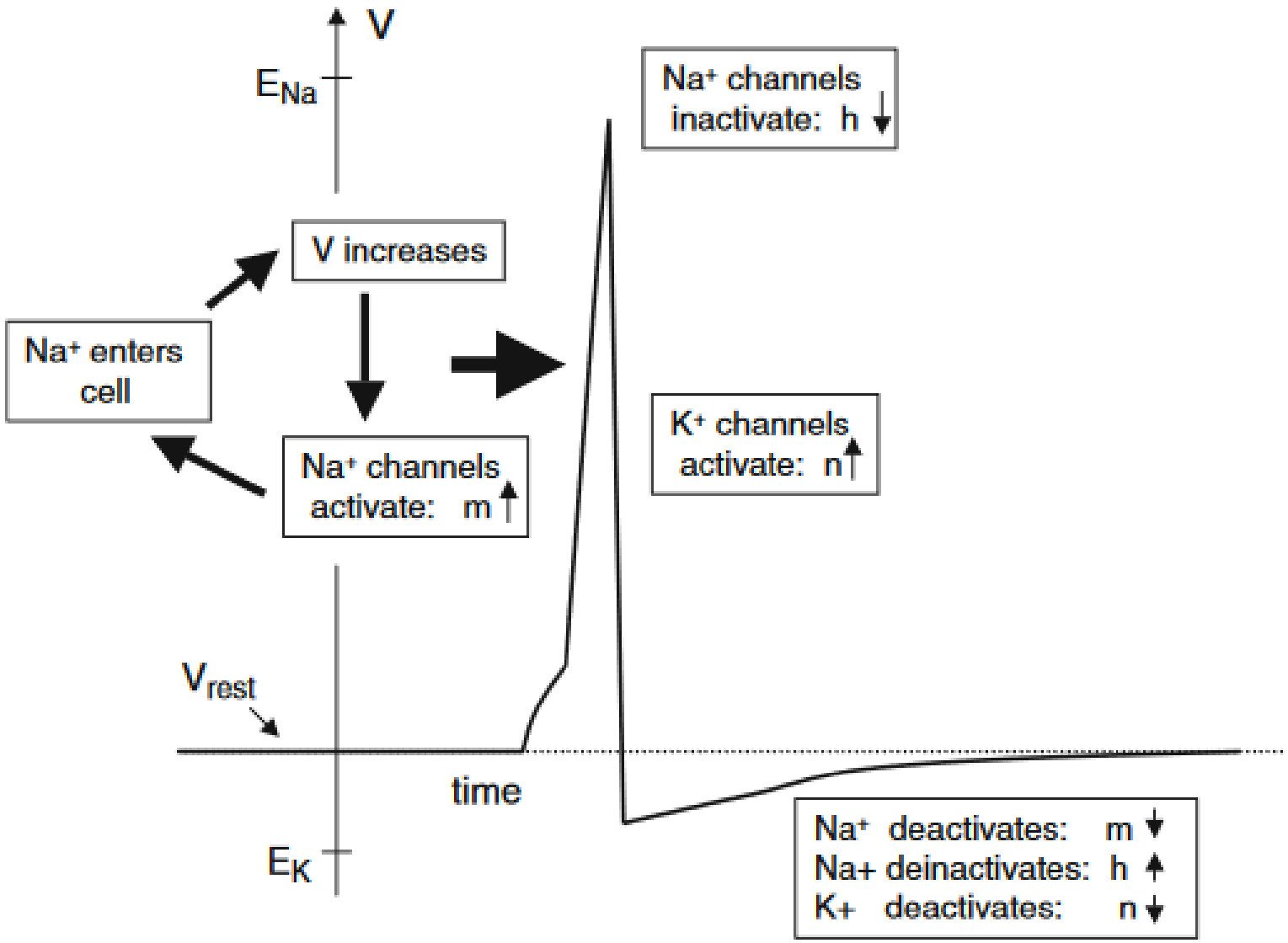
It has no known analytical solution. It can be solved numerically using the Euler method (or other ODE solvers).

Behaviour of the Hodgkin-Huxley Model



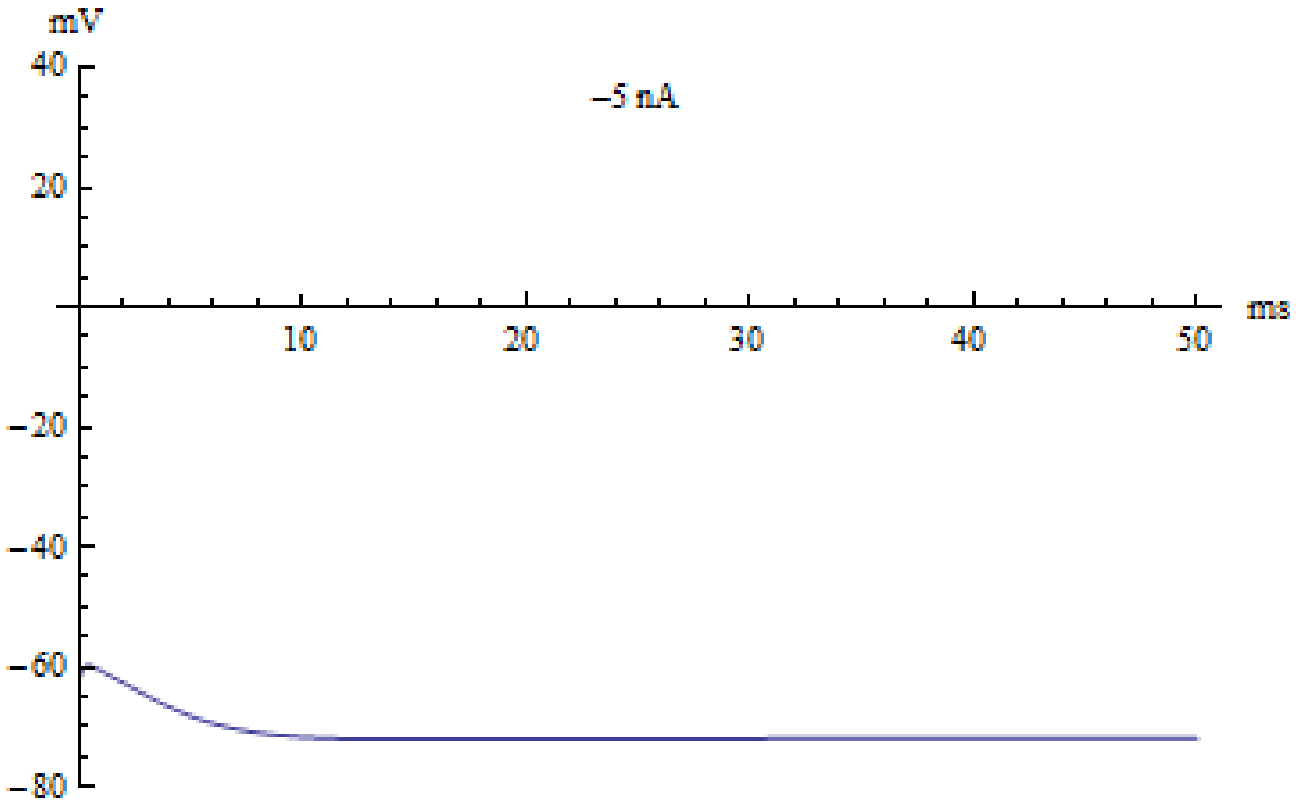


Overview of the Hodgkin-Huxley Model



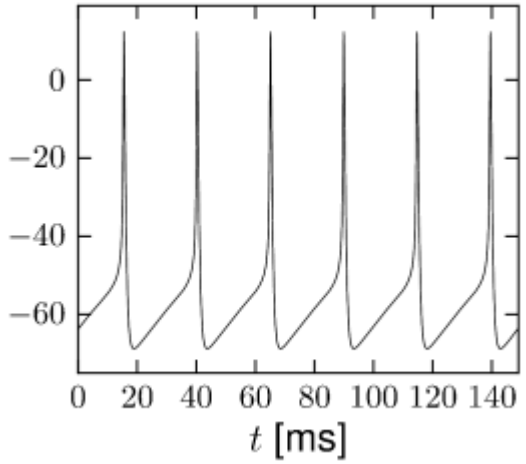
The “Threshold” in the Hodgkin-Huxley Model

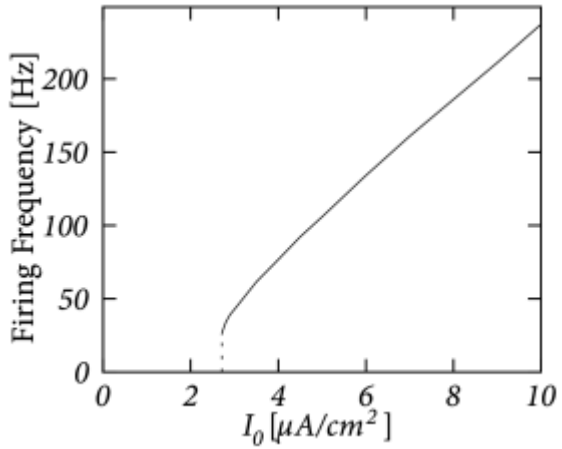
- If the Hodgkin-Huxley neuron is injected with a constant input current, it will not fire any action potentials below a certain strength of current
- The current strength at which the neuron switches from non-spiking to spiking is called the threshold
- There is no well-defined voltage threshold in the Hodgkin-Huxley model, only a current threshold

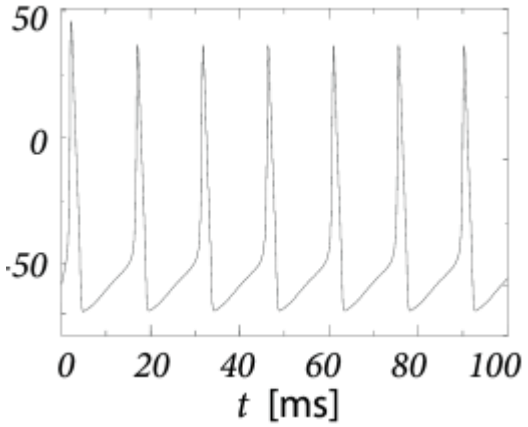


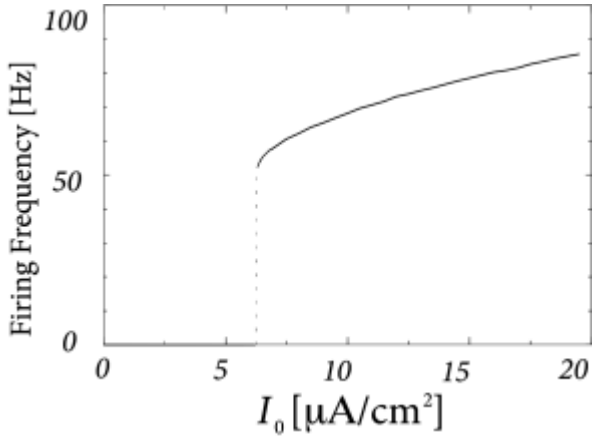
The f-I Curve in the Hodgkin-Huxley Model

- Changes in model parameters can produce different types of firing rate vs input current (f-I curves)
- Different neurons in the brain also exhibit these different f-I curves









Why is the Hodgkin-Huxley Model a Good Model?

- The Hodgkin-Huxley model is one of the most successful models in neuroscience to date
- They were awarded the Nobel Prize in 1963
- It has led to many experimental predictions that have been subsequently confirmed (e.g., in terms of kinetics of ion channels, changes with temperature, blocking with TTX, etc.)
- It can be augmented to account for many more biological phenomena – additional currents, more complex cellular morphology, stochastic ion channels gating, etc.
- It provides crucial insight into the biophysical processes which govern electrical signalling in neurons

Summary

- Action potentials are generated via the interplay of two voltage-gated ion channels (sodium and potassium)
- Voltage changes cause ion channels to open or close, which causes current to flow or stop, which causes voltage to change
- The dynamics of these processes can be described by the Hodgkin-Huxley model – a 4D dynamical system describing the time evolution of the membrane potential and sodium and potassium channel states
- The model is too complex to be solved analytically – it has to simulated, or approximated by simpler models (e.g., Fitzhugh-Nagumo, integrate and fire)

Bibliography

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