

# **COMS30127/COMSM2127**

## ***Computational Neuroscience***

### **Lecture 17: Ion channels and Hodgkin Huxley**

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**Links to lecture videos:**

**Part 1:** <https://mediasite.bris.ac.uk/Mediasite/Play/9c70f721207d4be388e5d8da73a901851d>

**Part 2:** <https://mediasite.bris.ac.uk/Mediasite/Play/c9547b06b0f74945944d1a5a401116131d>

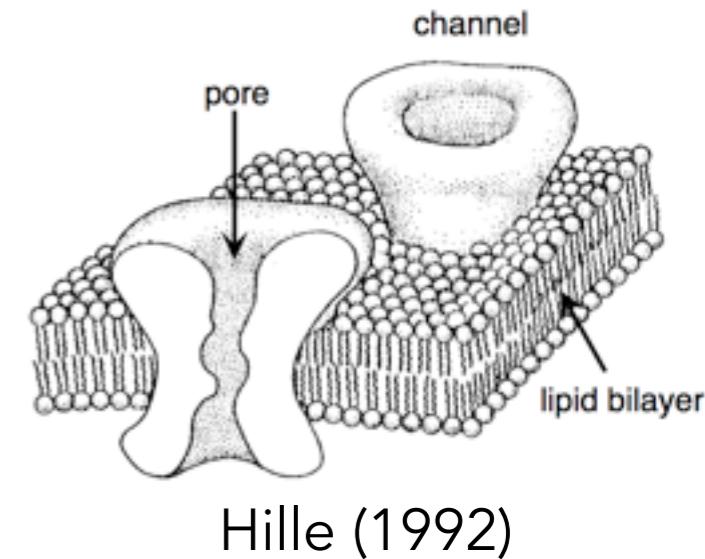


# What we will cover today

- What are ion channels and what do they do?
- Modelling ion channels.
- How ion channels make the neuron's input-output function nonlinear.
- The Hodgkin-Huxley model of the action potential:
  - what is in it.
  - what it does.
  - what it doesn't do.

# What are ion channels?

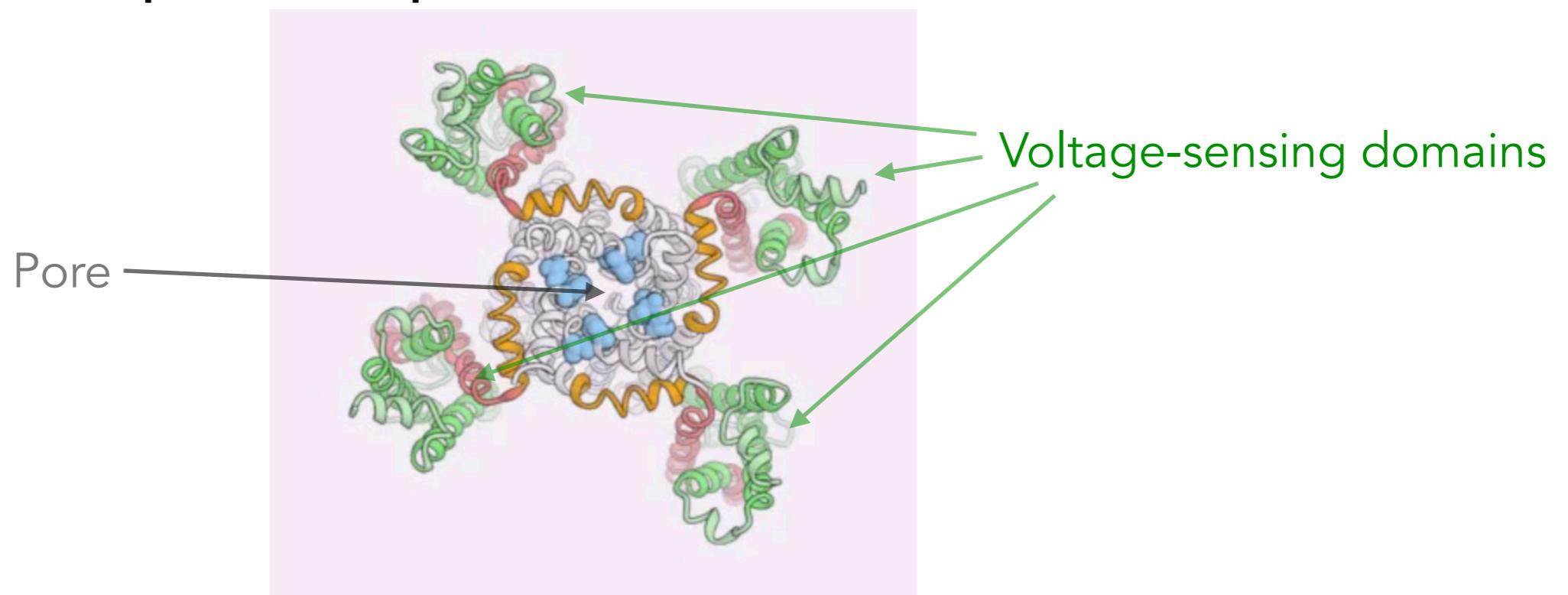
- Ion channels are ion-permeable pores in the lipid membrane of cells.
- A single neuron typically has hundreds of thousands to millions of ion channels embedded in its membrane.
- They open and close in response to stimuli (**voltage**, neurotransmitters, intracellular chemicals, pH, mechanical forces, temperature...), passing ions like  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cl}^-$ .
- Their currents mediate electrical signalling in the nervous system.
- The conductance of single ion channels vary between ~0.1 and 100 picoSiemens. For most channels it's around 10 pS.
- The flux through a single open channel can be millions of ions per second.



# What are ion channels?

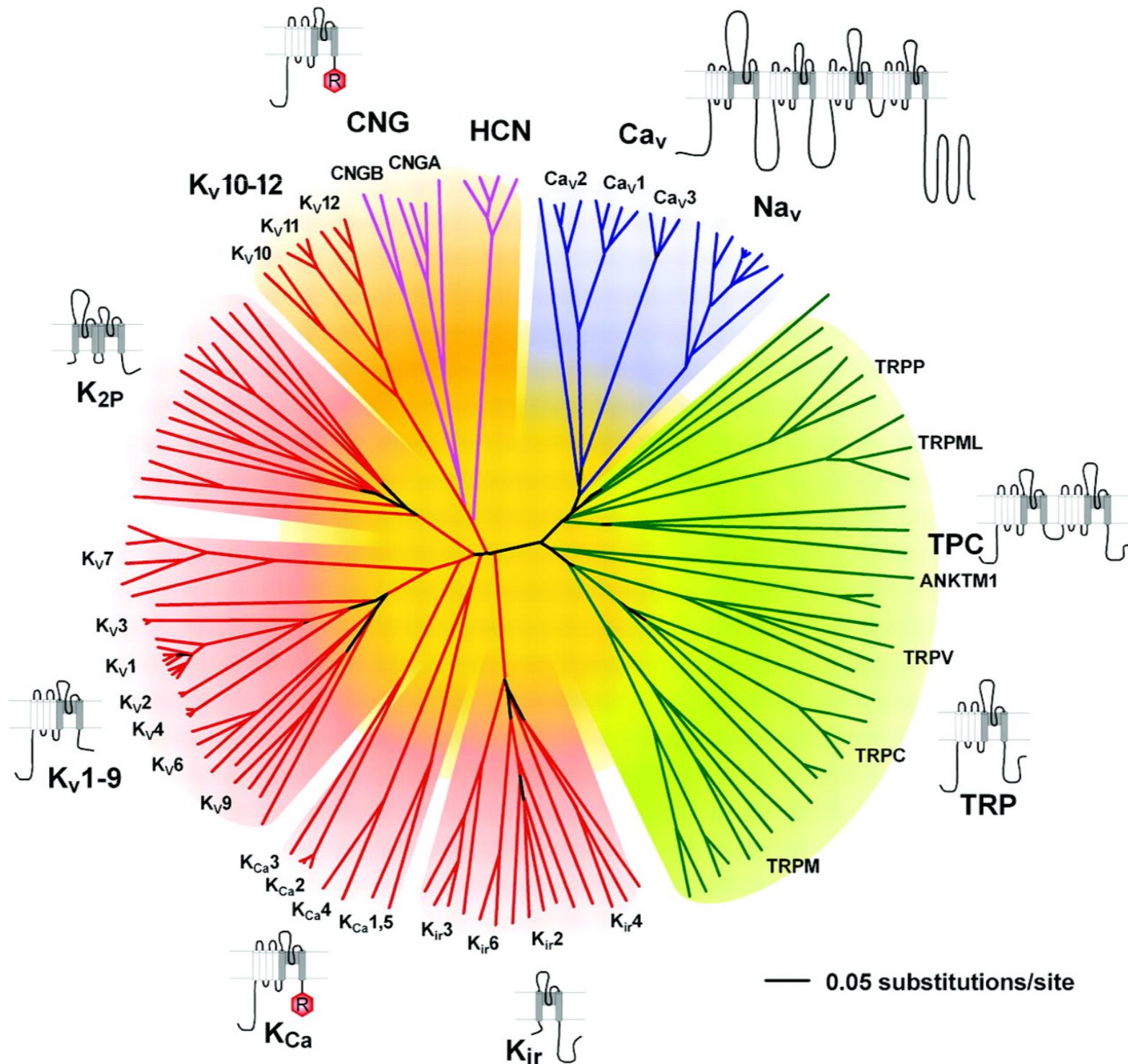
- Voltage-gated ion channels typically have a pore domain made up of four identical, or similar, channel subunits arranged in a ring. The ion pore is made along the axis where they meet.
- The channel also has secondary voltage-sensing domains, that deform in response to changes in the transmembrane voltage. These drag the pore-domain components to switch the channel open or closed.

**Bottom-up view of a potassium channel (from inside the cell)**



# Ion channel types

# The ion channel zoo



# Ion channel types

- Sodium ( $\text{Na}^+$ ) channels mediate inward currents that depolarise the voltage.
  - Fast gating and activated by depolarisation (positive feedback).
  - Responsible for upswing of the action potential, and boosting subthreshold inputs in dendrites.
  - Targets for some anaesthetics (e.g. lidocaine, pufferfish venom)
- Potassium ( $\text{K}^+$ ) channels mediate outward currents that hyperpolarise the voltage.
  - Can be fast or slow gating, activated by depolarisation (negative feedback).
  - Voltage-independent  $\text{K}^+$  channels mediate the 'leak' current.
  - Very genetically diverse (around 50 types in mammals).
- Calcium ( $\text{Ca}^{2+}$ ) channels, like sodium, mediate inward currents that depolarise the voltage.
  - Fast gating, but not as strongly expressed as sodium so have weaker effect on the voltage.
  - Responsible for some forms of dendritic spikes.
  - Generate intracellular calcium signals that the cell uses to monitor its electrical activity.
- Other channels include
  - Chloride ( $\text{Cl}^-$ ) channels: involved in setting resting voltage.
  - HCN channels: mixed sodium/potassium permeability, active at resting voltage, inactivated by depolarisation (negative feedback), heavily expressed in dendrites).

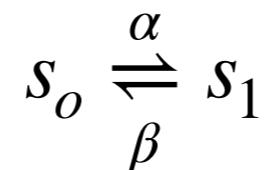
# Modelling ion channels

# Modelling ion channels

- In most neuroscience applications we don't care about all the molecular details of the ion channel, we just want a simple model that captures their dynamics.
- Usually this involves state-based modelling.
- We assume that each channel can be in one of a small number of discrete states. The channel can transition between states, with transition rates that depend on the cell's voltage.

# Modelling ion channels

Consider a 2-state ion channel model with transitions between the closed  $s_0$  and open  $s_1$  states, with transition rates  $\alpha$  and  $\beta$ :



If we imagine a large population of such channels, we could think of  $s_1$  as representing the proportion of the population in the open state.  
Then we can write down a differential equation to describe its dynamics:

$$\frac{ds_1(t)}{dt} = \alpha s_0(t) - \beta s_1(t)$$

The steady state value  $s_\infty$  is found by setting  $ds_1/dt = 0$ :  $s_\infty = \frac{\alpha}{\alpha + \beta}$

Then we can rewrite the right hand side of the dynamics equations as

$$\frac{ds_1(t)}{dt} = \frac{s_\infty - s_1(t)}{\tau}$$

Where we have introduced the time constant  $\tau = \frac{1}{\alpha + \beta}$

# Modelling ion channels

- The previous slide showed a very simple 2-state channel example. Most real channels are too complicated to describe so compactly, so their models often have many more states.
- The voltage dependence is built into these channel models by making the transitions rate ( $\alpha$  and  $\beta$ ) functions of voltage.
- We will go through a famous example of this later: the Hodgkin-Huxley squid axon model.
- You can find lots of example computational models of ion channel types in several good online repositories:
  - ModelDB: <https://senselab.med.yale.edu/modeldb/>
  - Channelpedia: <https://channelpedia.epfl.ch>
  - ICGenealogy: <https://icg.neurotheory.ox.ac.uk>

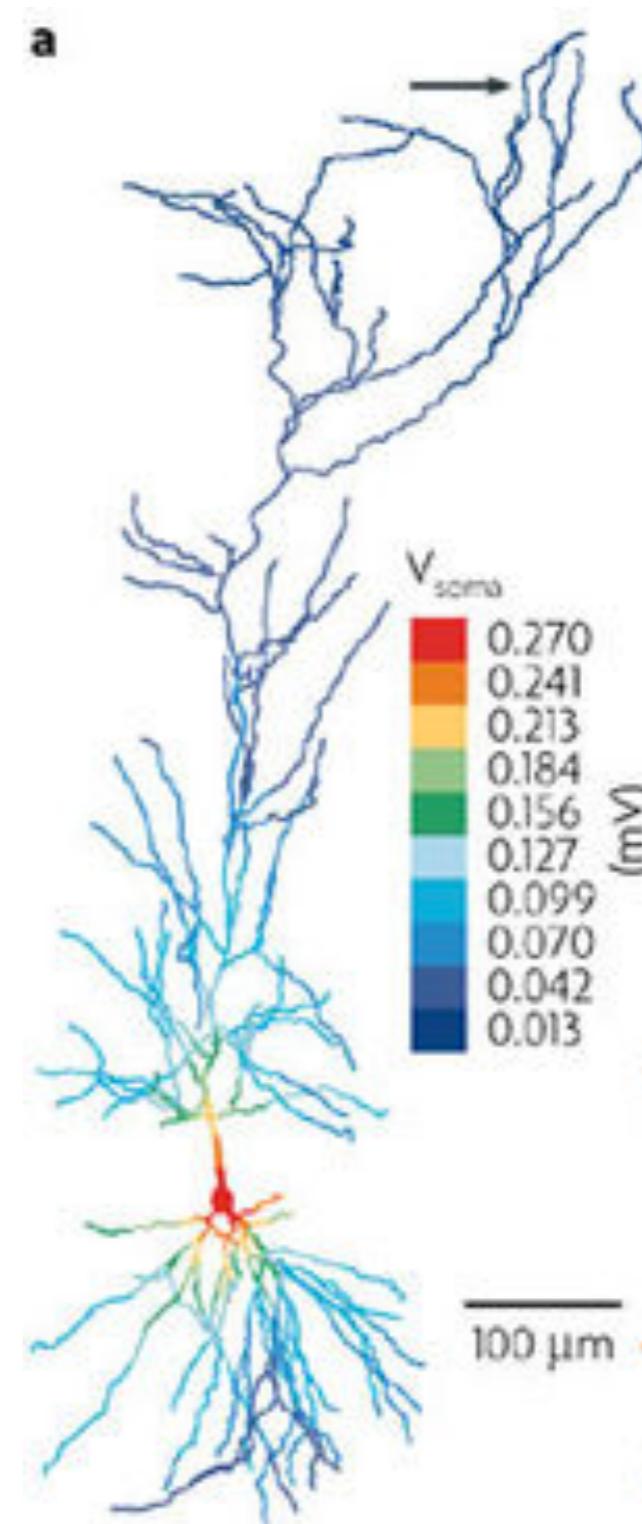
The neuron's input-output function  
a.k.a. synaptic integration

# Non-linear synaptic integration

- Neurons receive multiple temporal patterns of spike trains as input, and produce a single spike train as output.
- “Point” neuron models (like the integrate-and-fire) assume that the soma performs a weighted linear sum of the synaptic currents.
- However, real neurons differ from this idealisation in two key aspects:
  1. Neurons have dendrites, which implies a **spatial layout of synaptic inputs**.
  2. Dendrites have voltage-dependent (active) ion channels which makes **synaptic integration non-linear**.

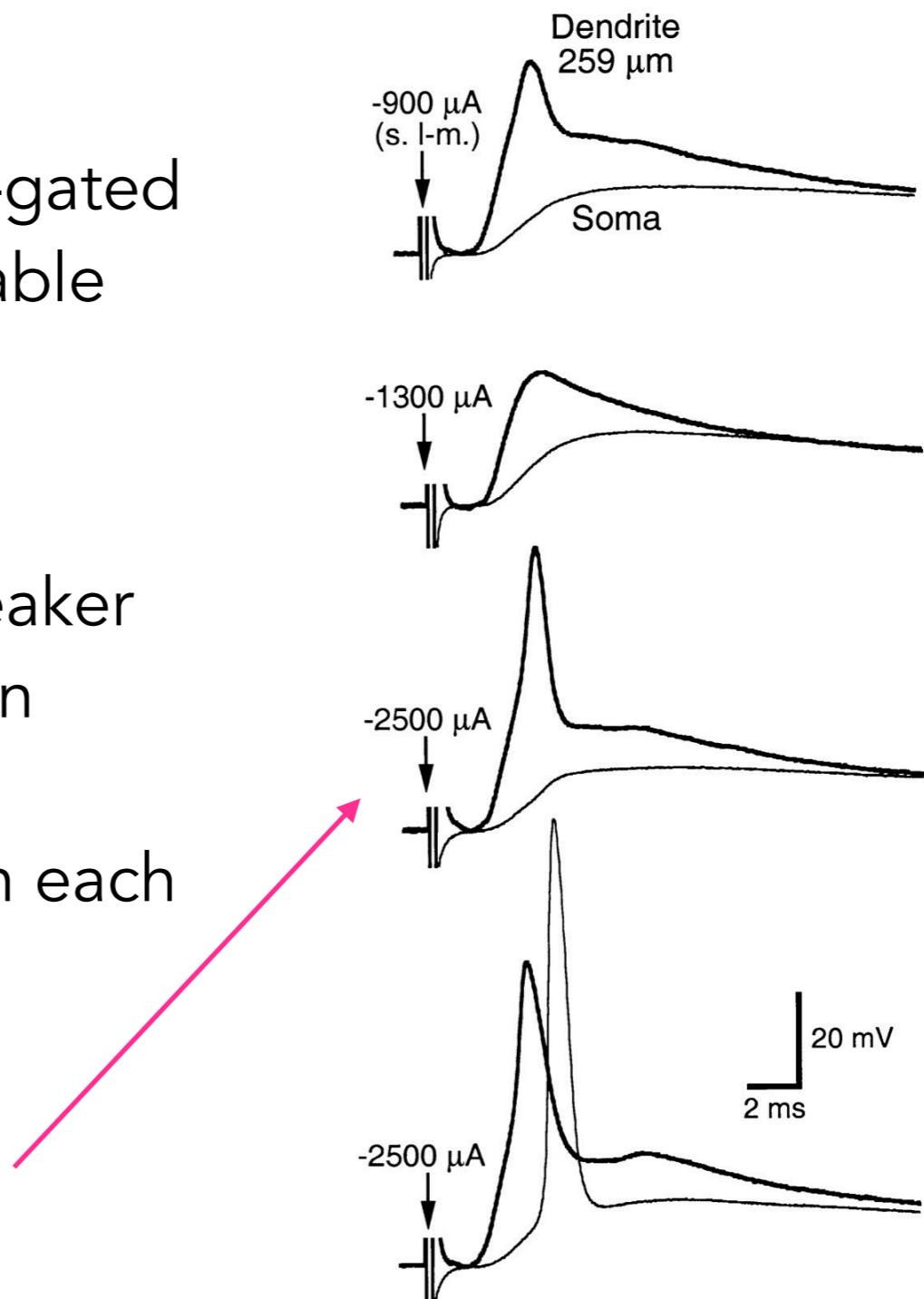
# Synaptic location matters

- The figure on the right is a trace of the dendritic tree of a CA1 pyramidal cell from a rat.
- The colour indicates the amplitude of the voltage response (EPSP) at the soma, when the synapse is placed at the corresponding location on the dendritic tree.
- Without any “boosting”, a synapse would give a smaller somatic response if it was located at a distal dendritic site.
- However it turns out that voltage-dependent ion channels in dendrites can boost synaptic inputs to amplify their effect at the soma.

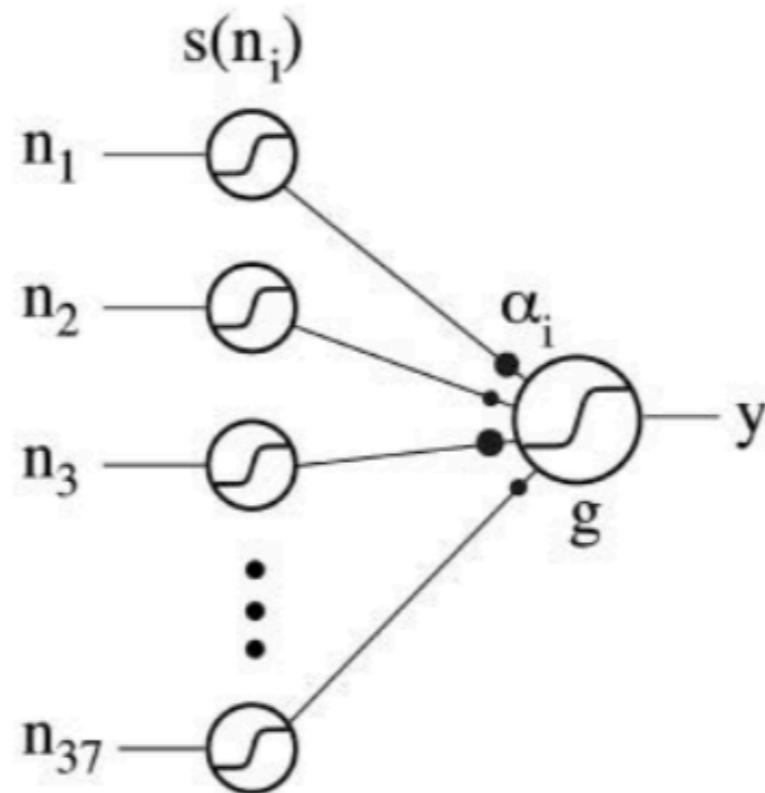
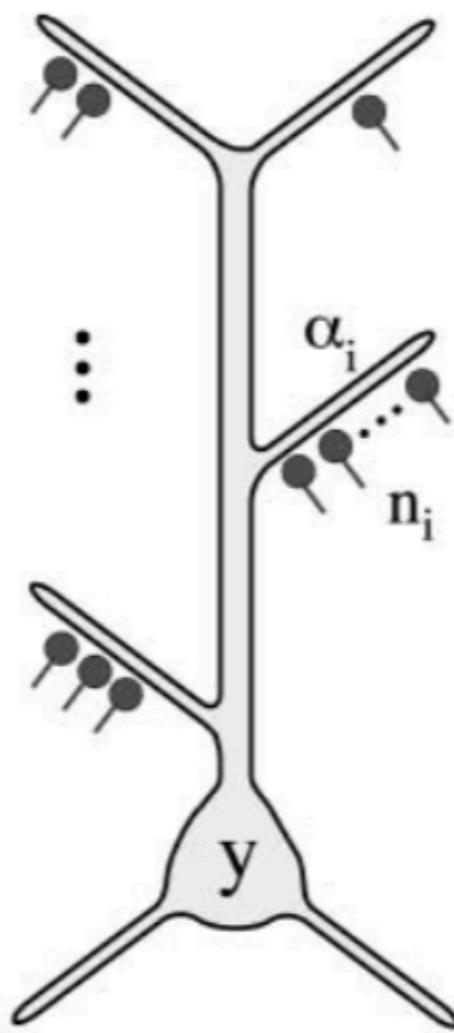


# Dendritic spikes

- Some neurons have enough voltage-gated ion channels in their dendrites to enable purely dendritically-generated action potentials.
- These dendritic spikes tend to be weaker and less all-or-none than axonal action potentials  
(note variable dendritic amplitudes in each plot on right).
- A single dendritic spike is not always sufficient to trigger an axonal spike.



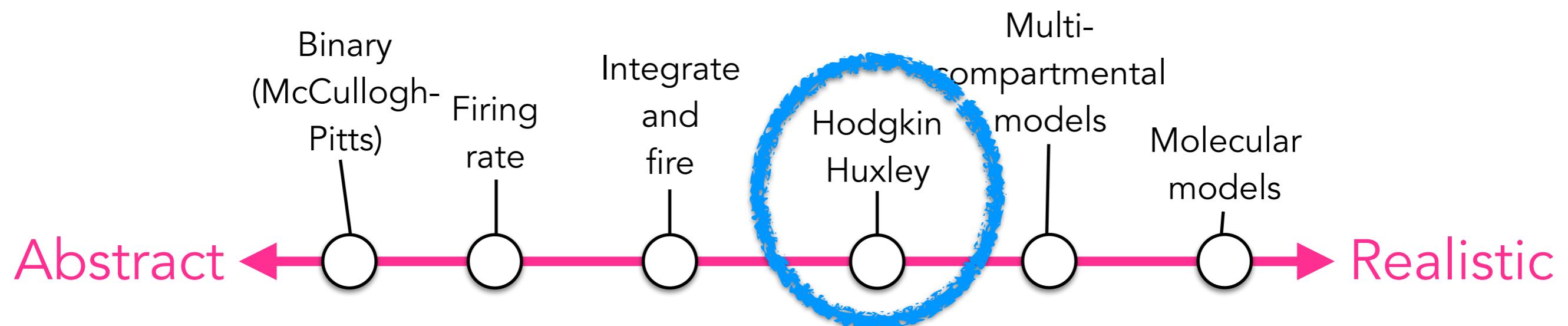
# The single neuron as two-layer neural network



- The existence of dendritic spikes means we can almost think of a single pyramidal neuron as a multi-layer neural network. Each dendritic does a nonlinear operation on its inputs before passing the signal to the soma.
- Voltage-gated ion channels expand the brain's computational power.

# The Hodgkin-Huxley model

# Model neuron types (recap)



## Abstract models

- Simple vs Hard to relate to biology
- Few parameters vs Few parameters
- Fast simulation vs Mathematical analysis
- Generic vs Generic

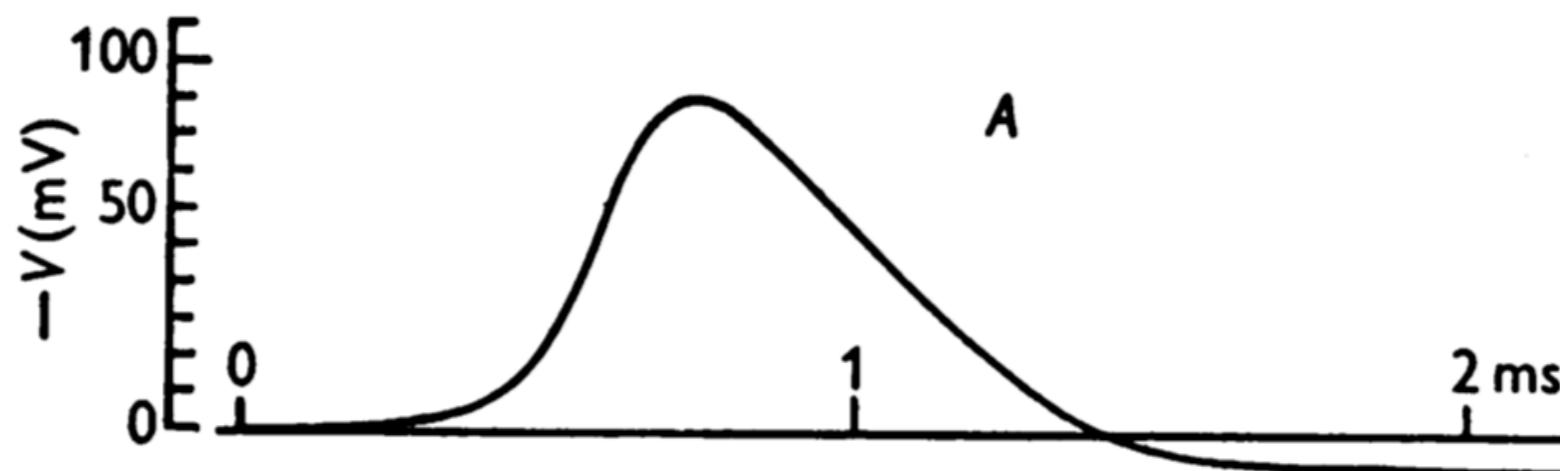
## Realistic models

- Detailed vs Contains stuff you could measure
- Lots of parameters vs Slow simulation
- Intractable vs Specific

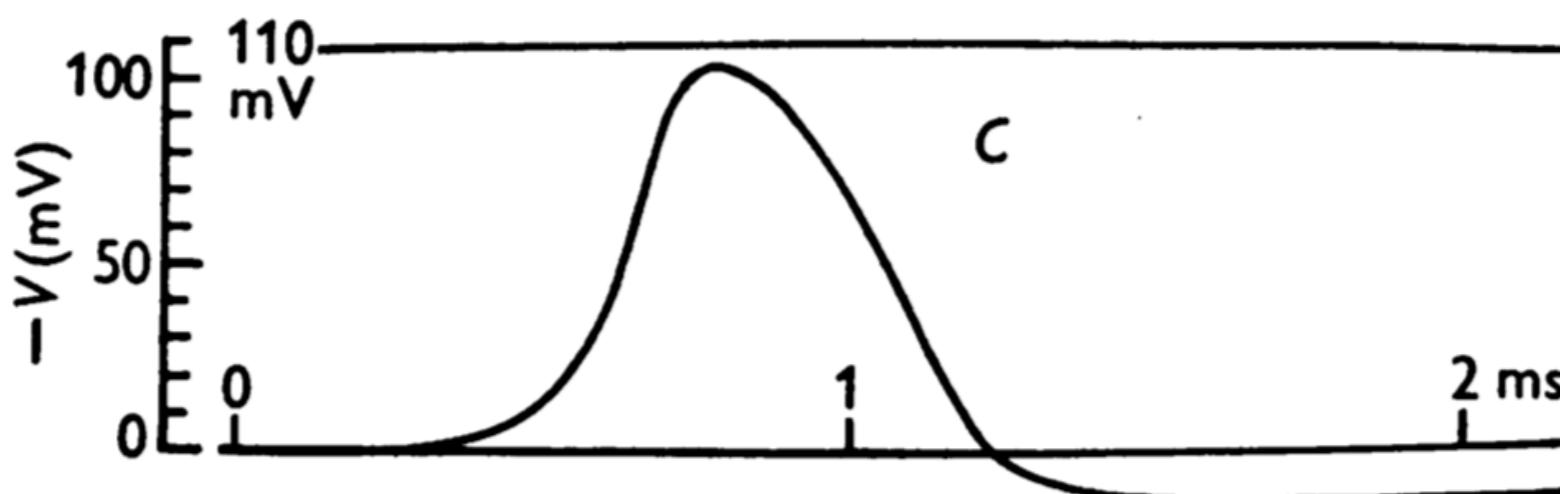
# What is the Hodgkin-Huxley model?

- The original Hodgkin-Huxley model is a mathematical model of the electrical dynamics of the 'giant' axon of the squid *Loligo forbesii*.
- Its key success was to demonstrate that **two voltage-gated membrane conductances** were sufficient to explain the **action potential**.
- These days people often use the term "Hodgkin-Huxley style model" more loosely to mean any mathematical model of any neuron that is built using **conductance-based dynamics**.
- The Hodgkin-Huxley model stands as one of the outstanding successes of computational neuroscience.

Model



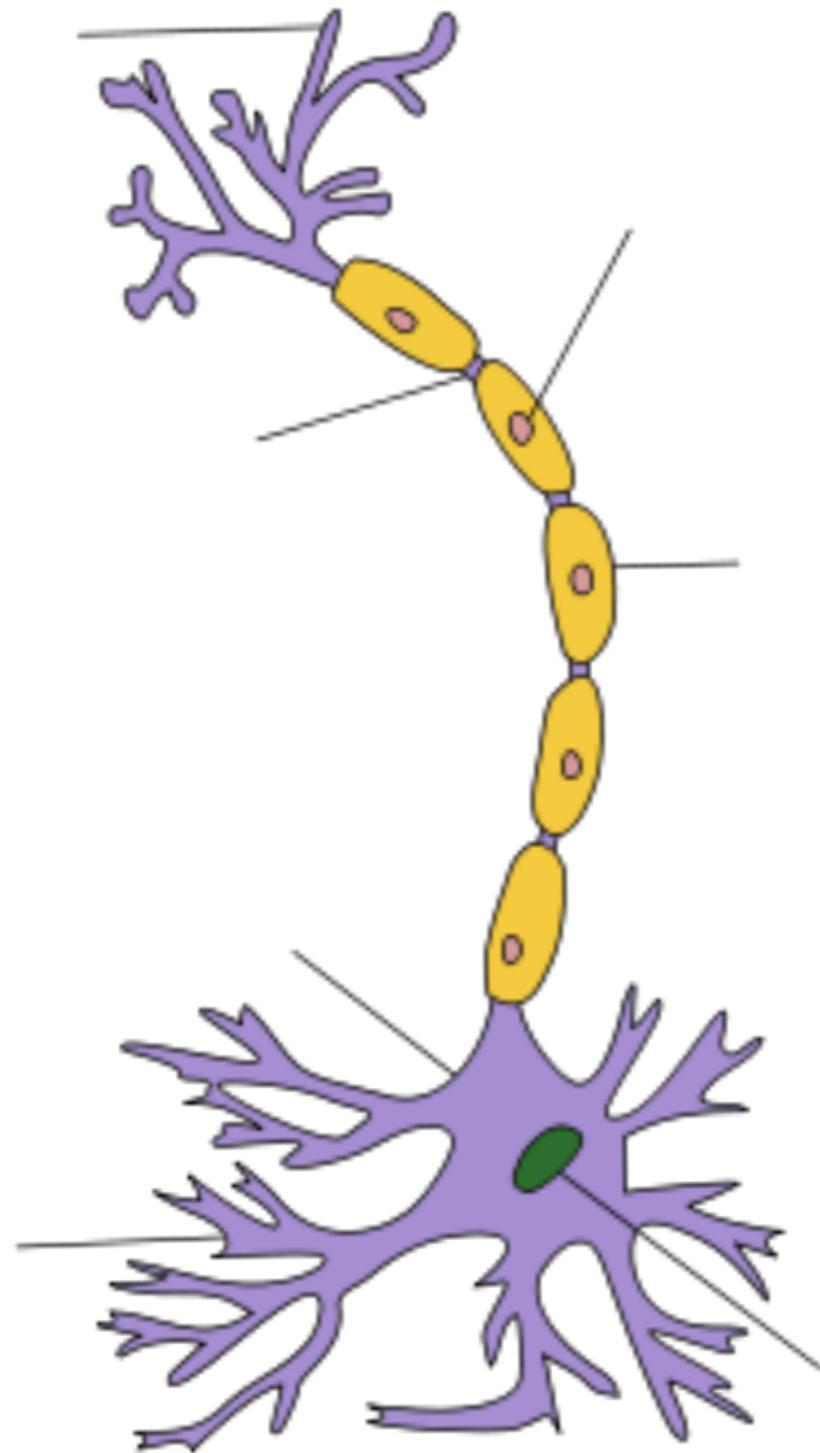
Data



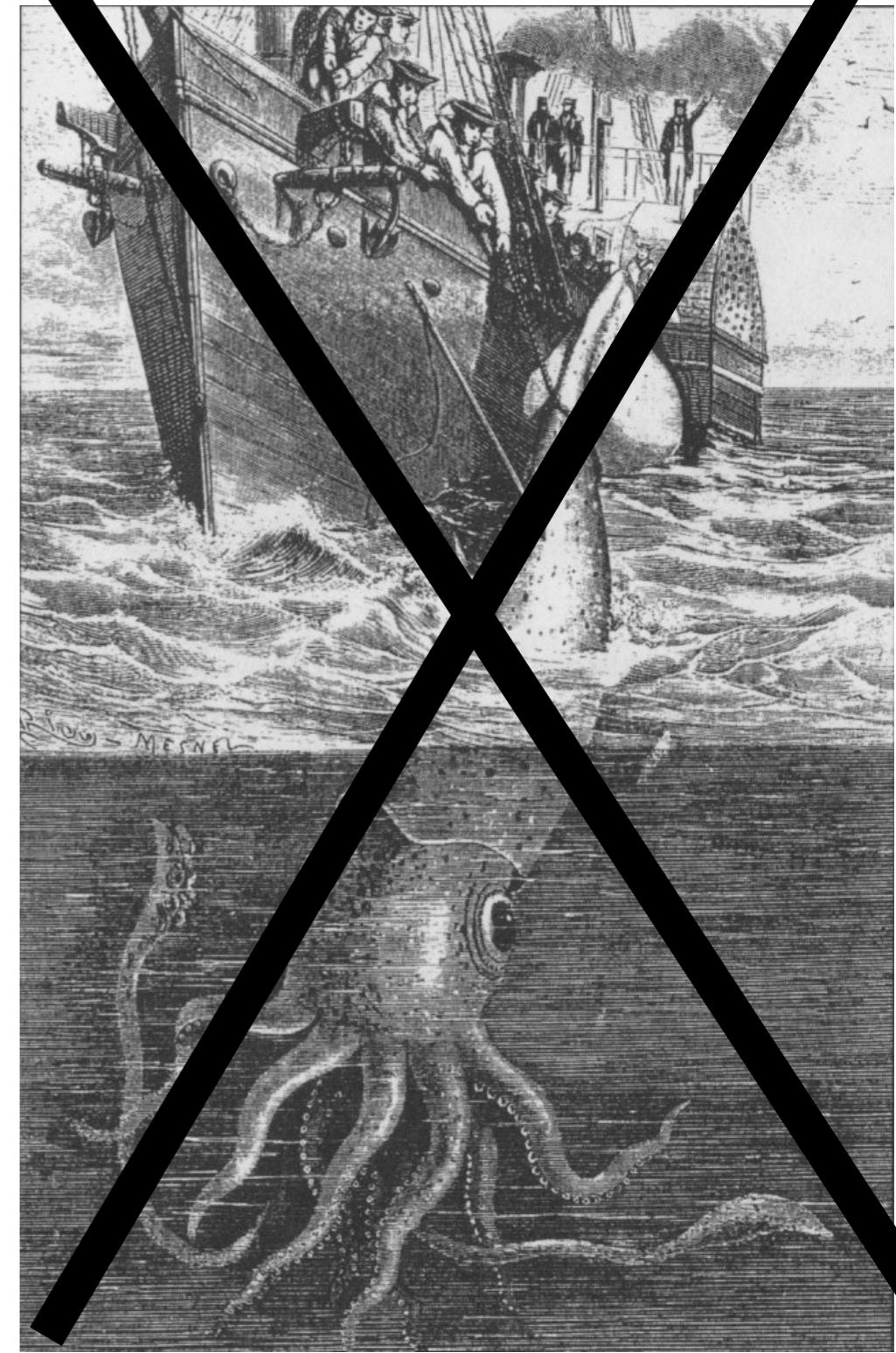
*Loligo forbessi*



(Squid) giant axon

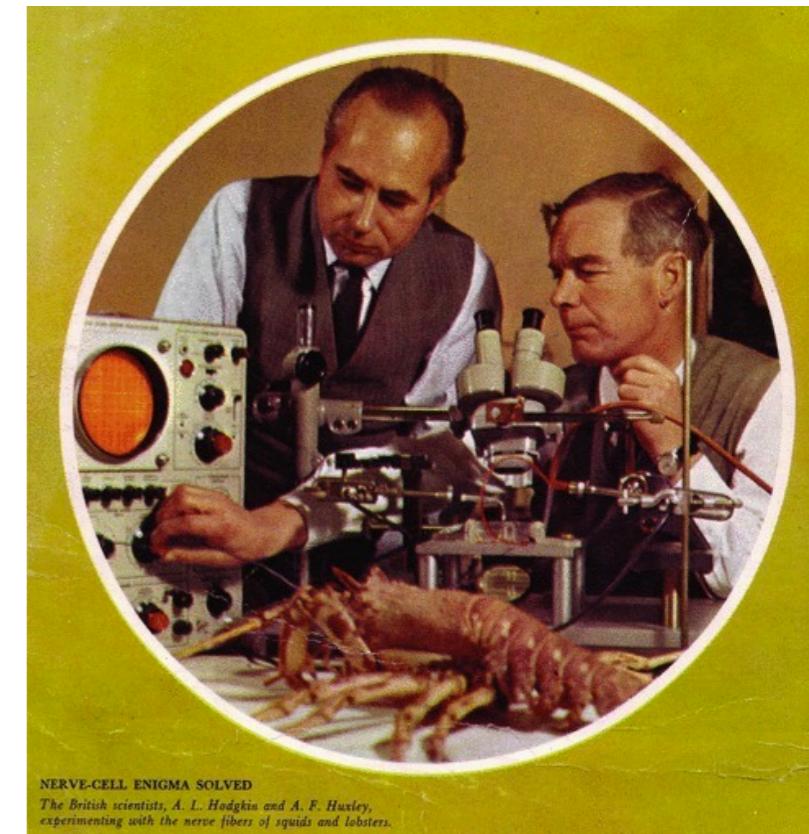


Giant squid (axon)



Who were Hodgkin and Huxley?

# Alan Hodgkin & Andrew Huxley

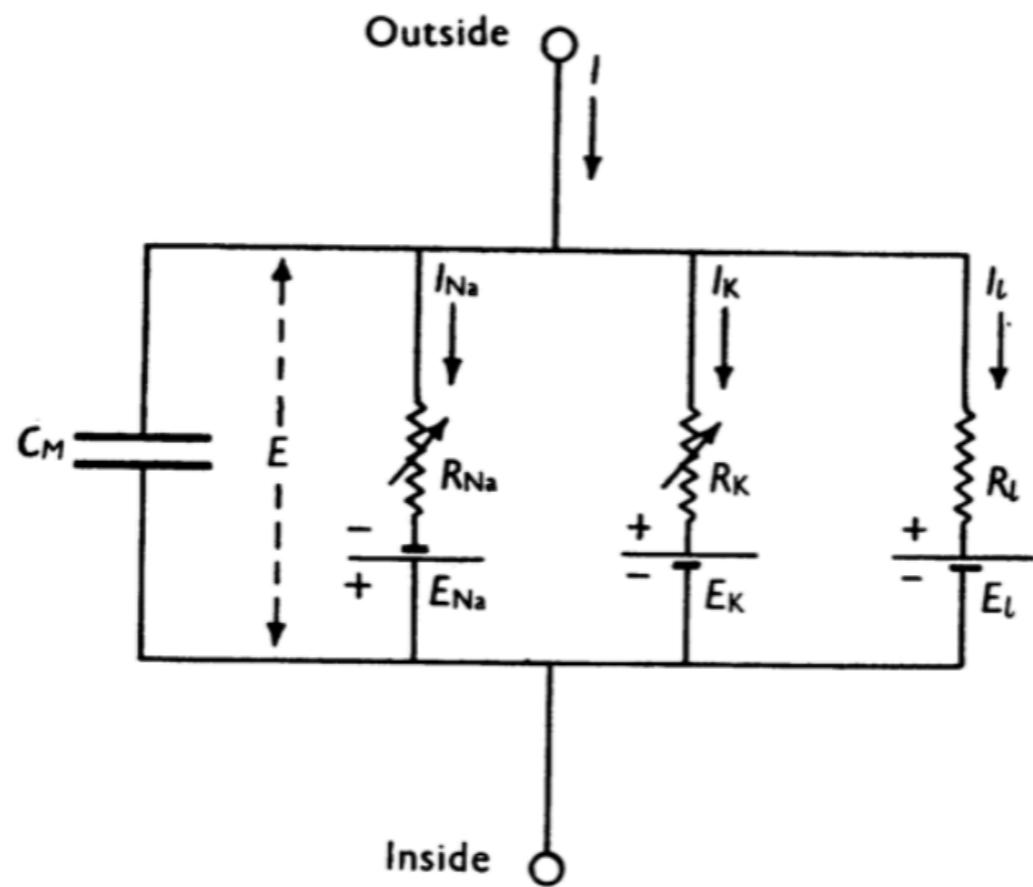


NERVE-CELL ENIGMA SOLVED  
The British scientists, A. L. Hodgkin and A. F. Huxley,  
experimenting with the nerve fibers of squids and lobsters.

- Physiologists based at Cambridge and Plymouth.
- Published a series of five landmark papers on the squid axon model of the action potential in 1952.
- Began working together in 1938/9 but were interrupted for seven years by WW2.
- Awarded the 1963 Nobel Prize in Physiology or Medicine (along with John Eccles) "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"

What does the model consist of?

# The HH model



$$C_M \frac{dV}{dt} = I_{Na} + I_K + I_l$$

$$I_x = g_x(E_x - V) \quad \dots \text{where } x \text{ is Na, K or } l$$

$g_x = ?$

How do we model the conductances?

How do we model the conductances?

*Using time and voltage-dependent gating variables.*

$$g_{Na} = \bar{g}_{Na} m^3(V, t) h(V, t)$$

$$g_K = \bar{g}_K n^4(V, t)$$

How do the gating variables evolve in time?

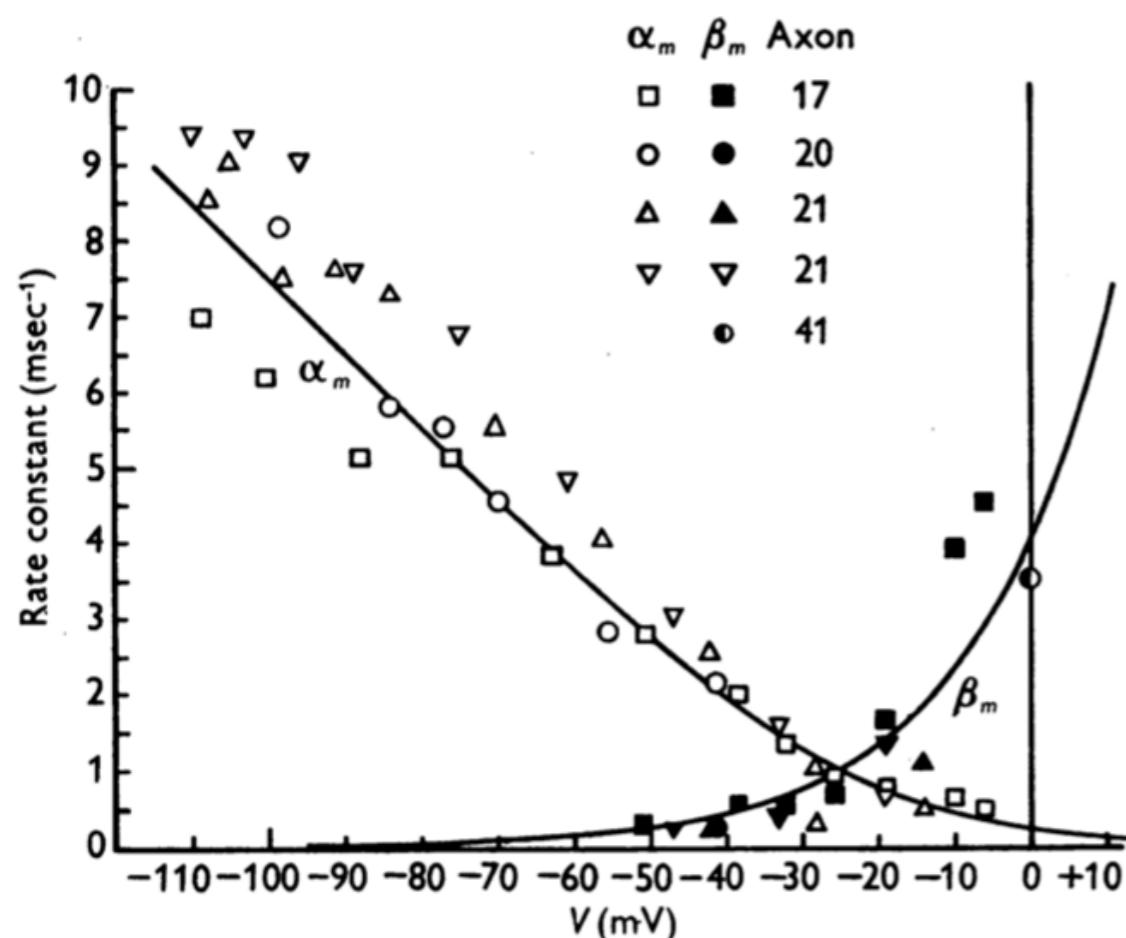
$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)}$$

How do the steady-state values and time constants depend on voltage?

$$m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)}$$

$$\tau_m(V) = \frac{1}{\alpha_m(V) + \beta_m(V)}$$

How do the forward and backward rate constants depend on voltage?  
*Hodgkin and Huxley fit them to match their voltage-clamp data.*



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

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

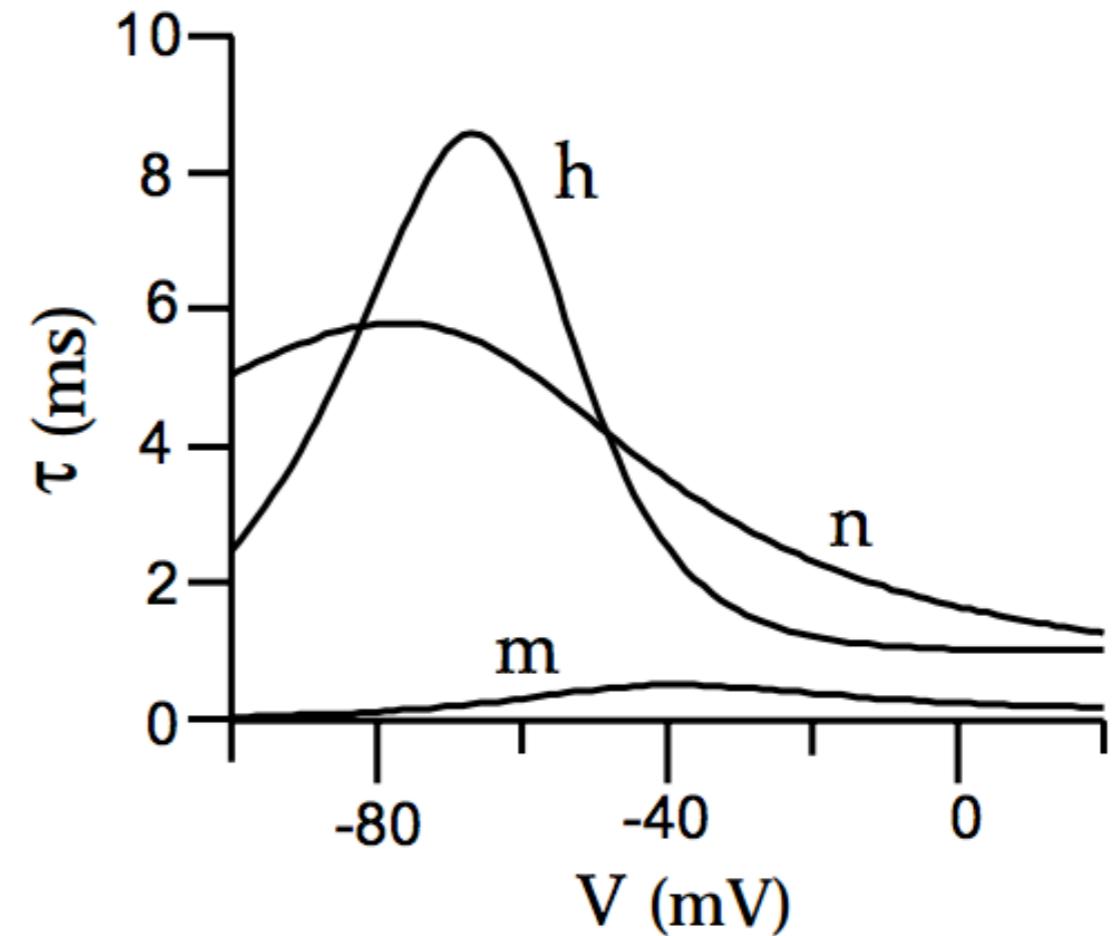
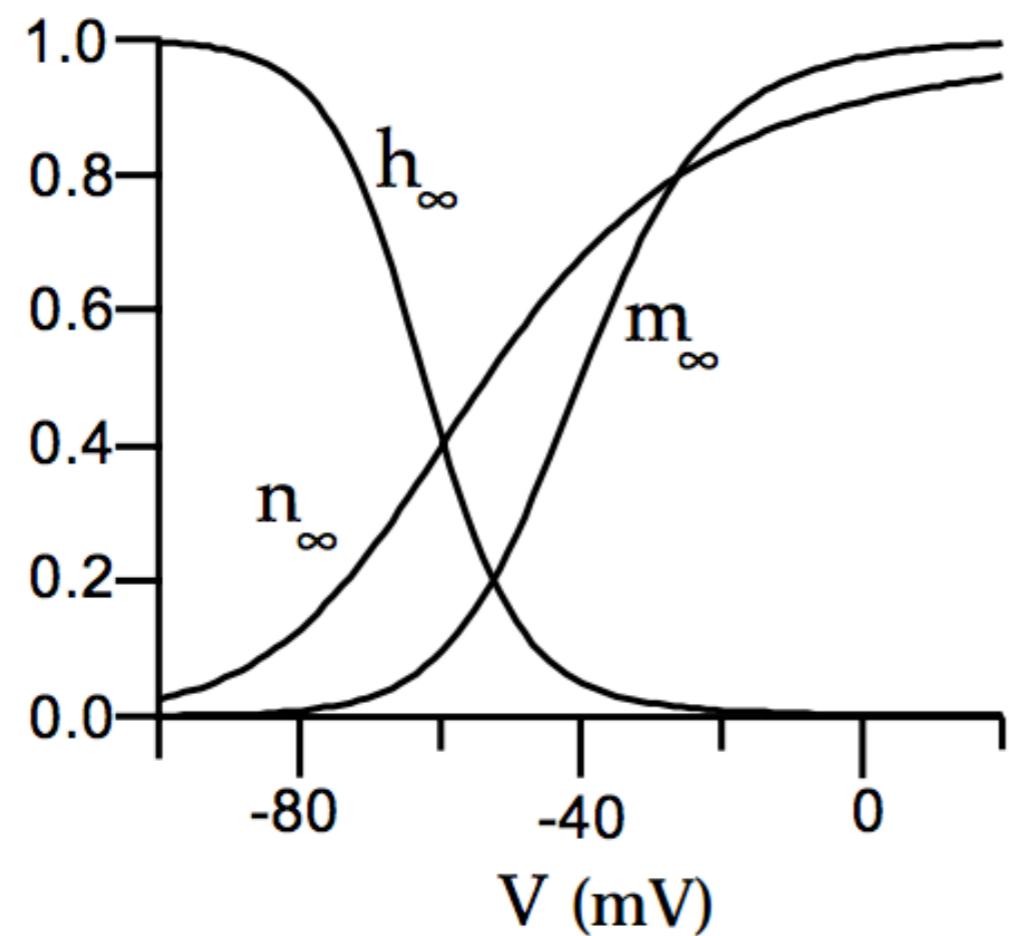
$$\alpha_n(V) = \frac{0.01(V + 55)}{1 - e^{-(V+55)/10}}$$

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

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

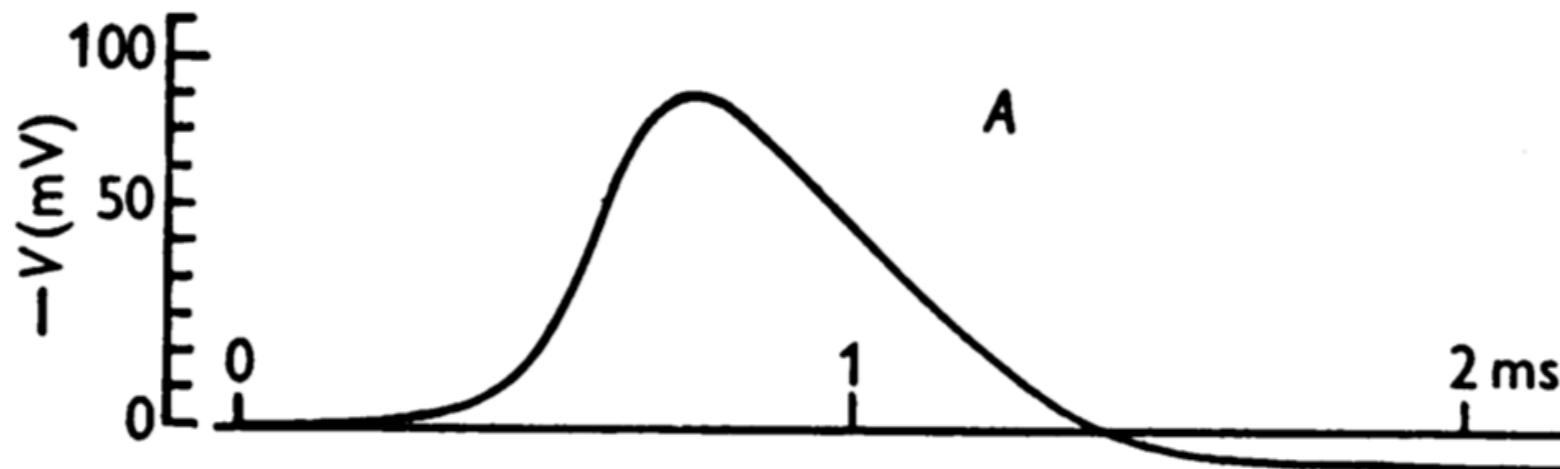
$$\beta_n(V) = 0.125e^{-(V+65)/80}$$

## Gating variables steady-state values and time constants as a function of voltage

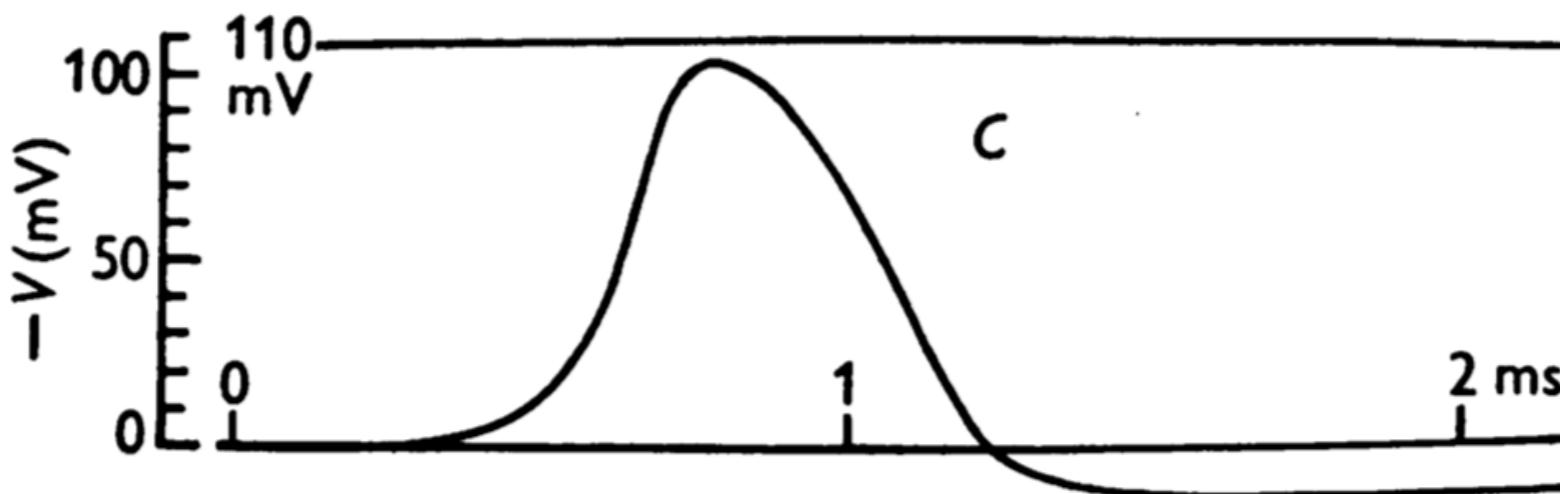


# What does the HH model do?

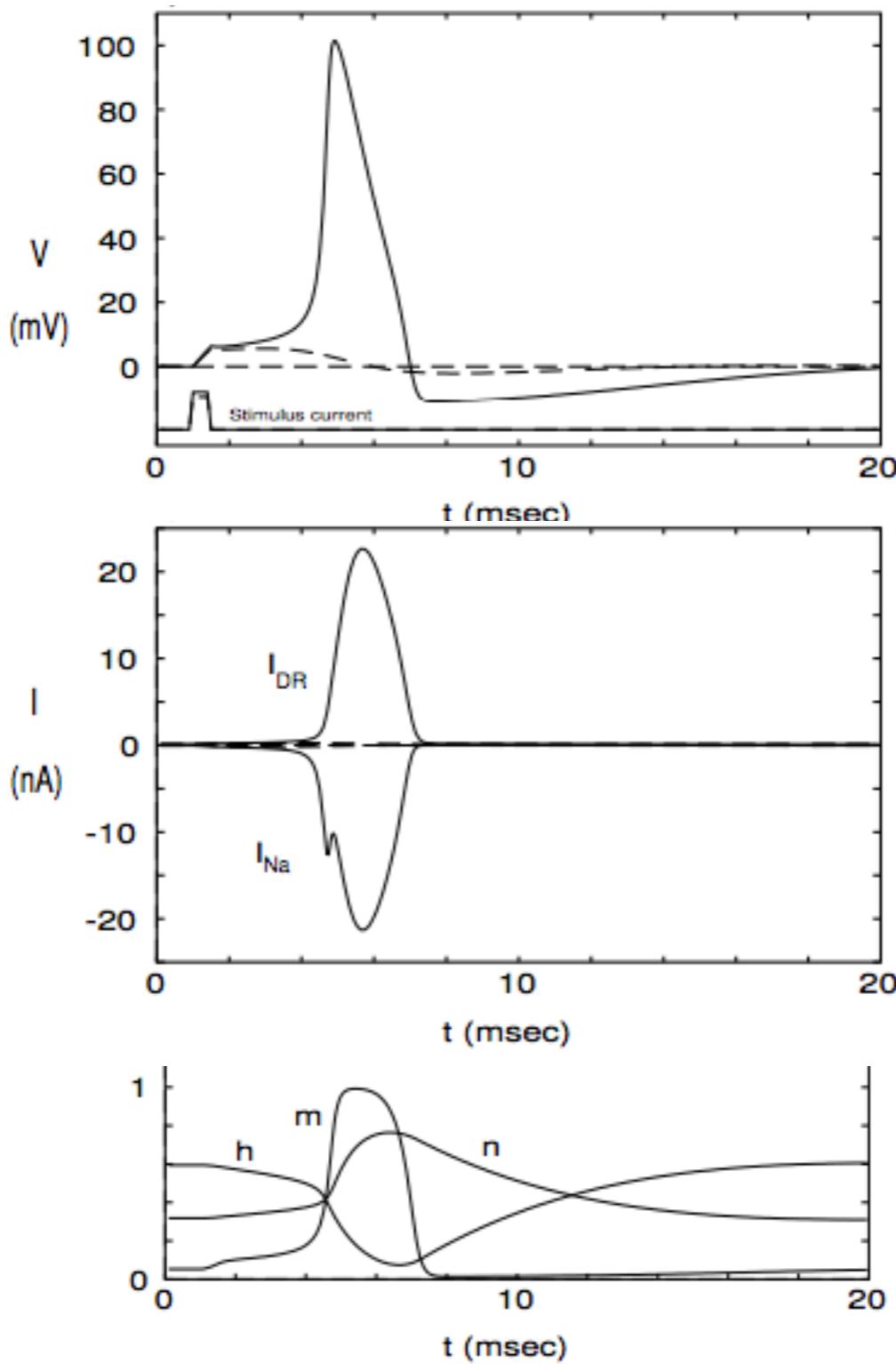
Model



Data



# What does the HH model do?



# What else does the HH model do?

- It is a “Type 2” model neuron:
  - Discontinuous fi-curve (unlike the integrate-and-fire model). The firing rate jumps from 0 Hz to  $\sim$ 50Hz at some threshold value.
  - Has membrane potential oscillations.
- Both of these properties come from its underlying dynamical properties, it undergoes a “Hopf bifurcation” at spike threshold.

# What does the HH model *not* do?

- It is unlike the action potentials in mammalian neurons:
  - different ion channels
  - different waveform
  - energy inefficient
  - extremely leaky resting conductance
- Not a good model for myelinated axons
- It is deterministic.  
We now know that ion channels are discrete (Neher and Sakmann) and noisy.
- Description of multiple independent gates per channel type is biophysically unrealistic.
- If you want a single-compartment model of spiking, integrate-and-fire can actually be considered *more* realistic by some measures (Brette, *PLoS Comp Biol* 2015).

End