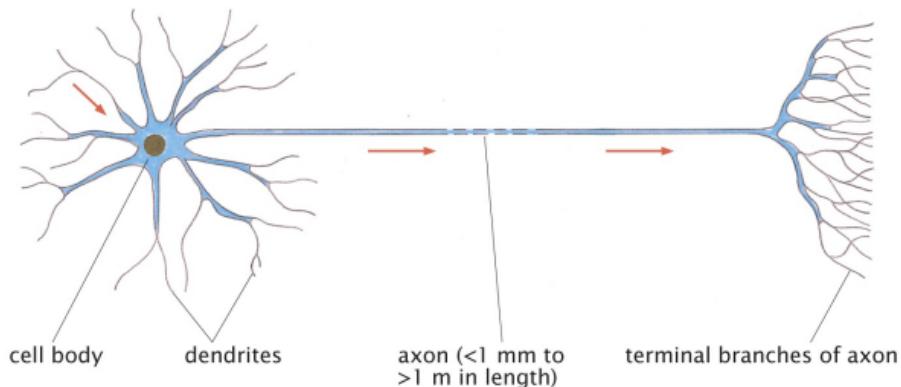
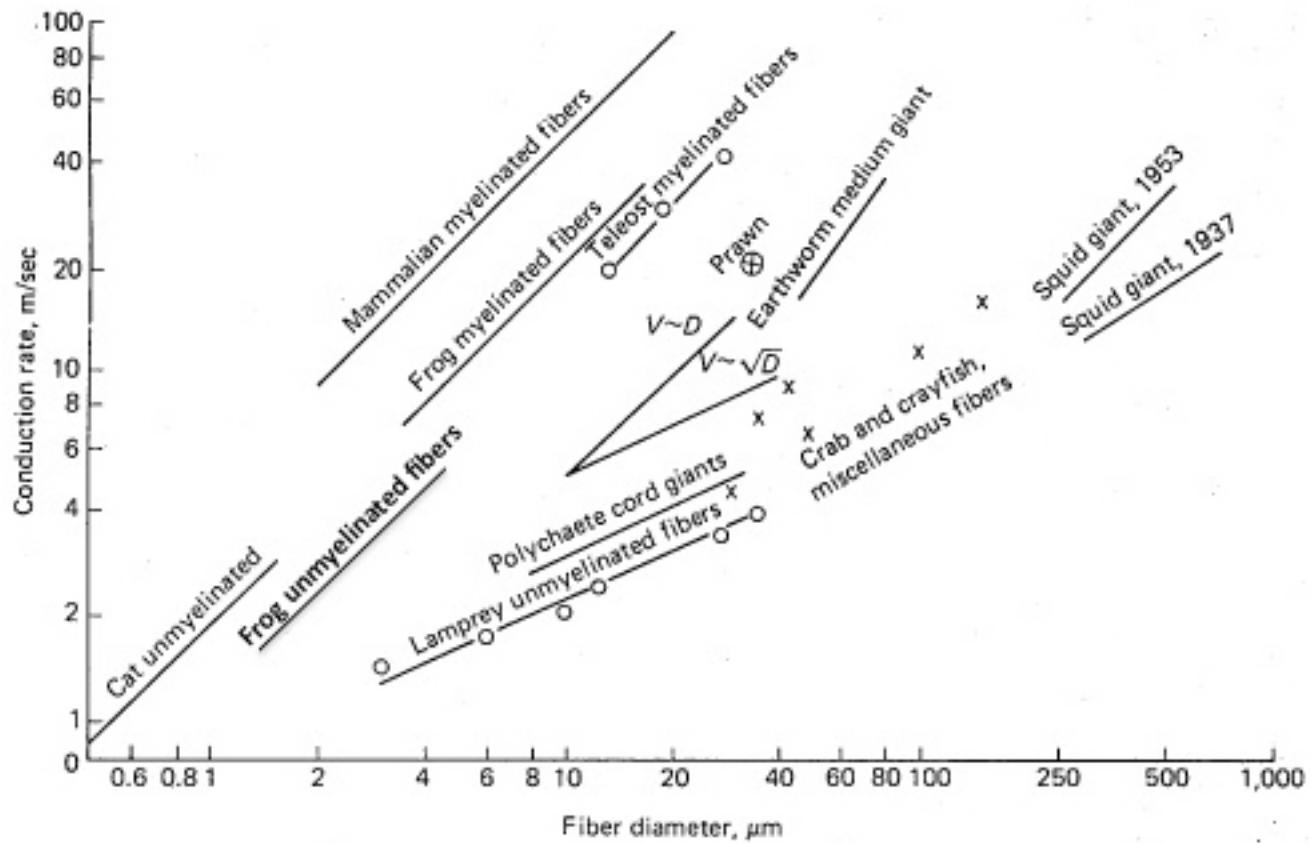
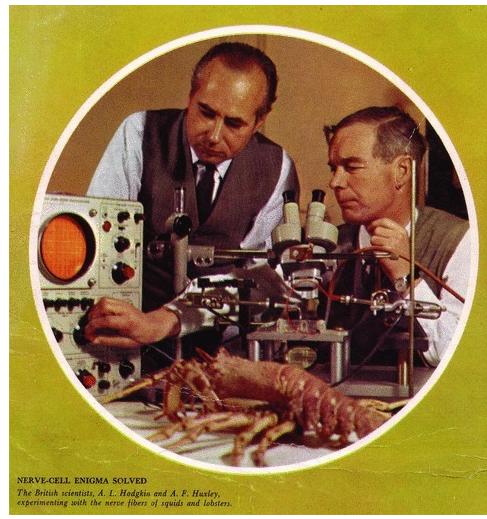


Membrane potential and neurons: structures for information transfer and processing



Hodgkin and Huxley
1939-1952, Nobel 1963



The neuron is the structural and functional unit of the brain

Humans: 10^{11} neurons

Each neuron has between 10^3 and 10^4 synapses... so total over 10^{14} synapses.

Total “wiring”, mostly axons, approx $4 \cdot 10^5$ km (larger than earth-moon).

1mm³ of cortex contains many km of axons. 10^5 nerve cells, 10^8 or 10^9 synapses

The brain is a supercomputer

made of oil, salt, proteins and water

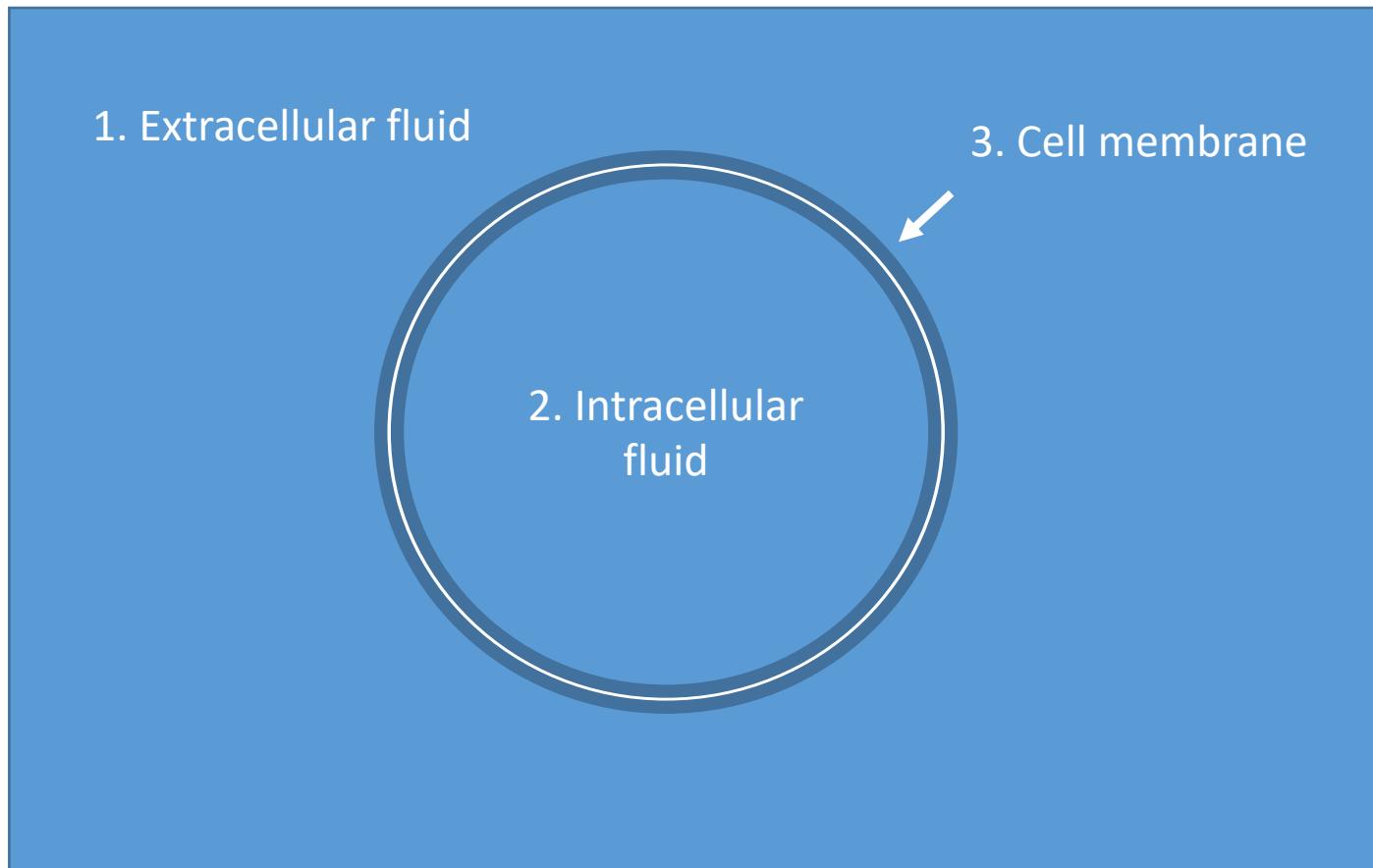


Largest commercial chip in 2019 has $4 \cdot 10^{10}$ transistors, packed at $0.3 \cdot 10^9 / \mu\text{l}$

Speed CPU: 10^9 Hz brain: 10Hz uhm...

Many differences: In the brain, data and processing share the architecture; synapses can change.

The main components – and their electrical properties



1 and 2: volume conductors. 3: “leaky” capacitor

Membrane potentials

There are differences in ion concentration across membranes (that's one of their functions!).

The **Nernst equation** relates the voltages across a septum that allows only positive ions to cross:

$$V_2 - V_1 = \frac{k_B T}{ze} \ln \frac{c_1}{c_2}$$

c_1, c_2 are the concentrations at either side

ze is the charge on the ion

$k_B T / e$ approx. 25 mV

Voltages across membranes of neurons are in the range 10–100 mV so thermal effects can be important.

Imagine two compartments, initially charge neutral, initially isolated. Then an opening, semipermeable to positive ions. For example K^+ and Cl^- in the two compartments.

→ Competition of entropy and electrostatic potential energy.

c_1, c_2 change so little that we keep their initial values.

Data		Data		Plugging into Nernst eq.
Ion species	Intracellular concentration (mM)	Extracellular concentration (mM)	Nernst potential (mV)	
K ⁺	155	4	-98	
Na ⁺	12	145	67	
Ca ²⁺	10 ⁻⁴	1.5	130	
Cl ⁻	4	120	-90	

→ problem.

In equilibrium, the Nernst potentials should all be the same... they don't even all have the same signs...

So if not equilibrium.... Something must be supplying energy.

Ion pumps (chemically fuelled, ion selective) and channels (can be ion-selective).

... there are >> 100 types of ion channel coded in the human genome!



Figure 4.25 (part 1 of 2) Physical Biology of the Cell, 2ed. (© Garland Science 2013)

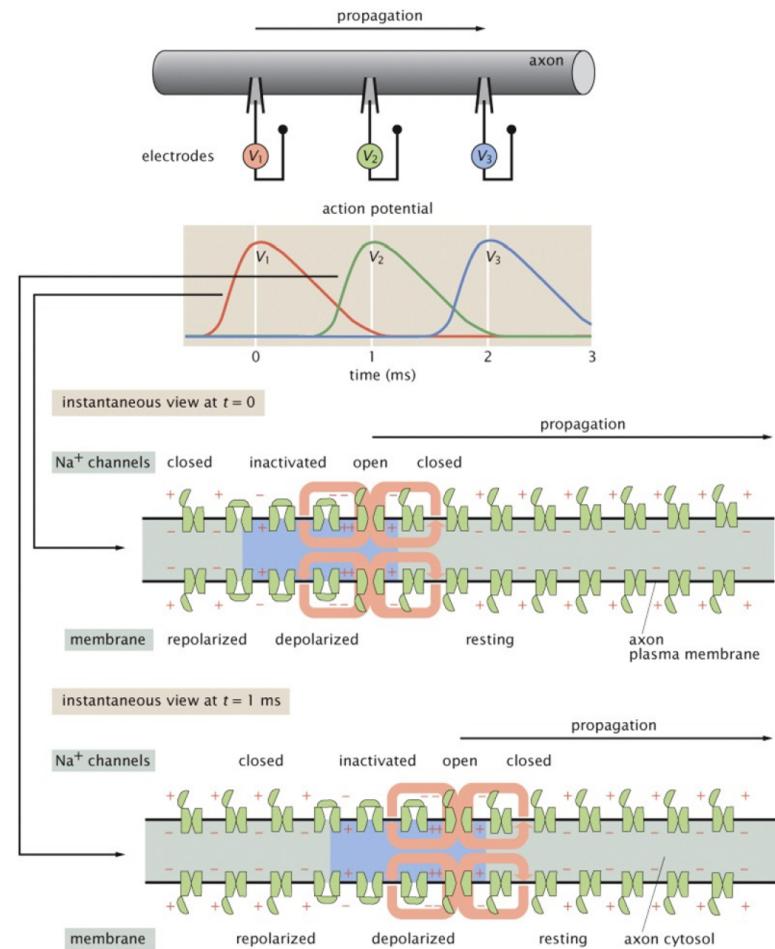
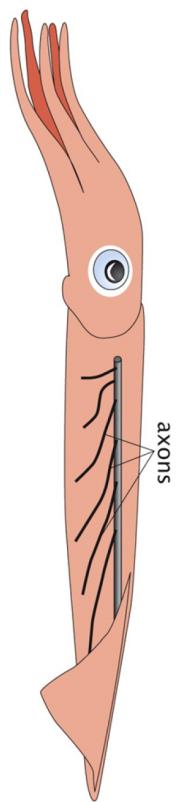
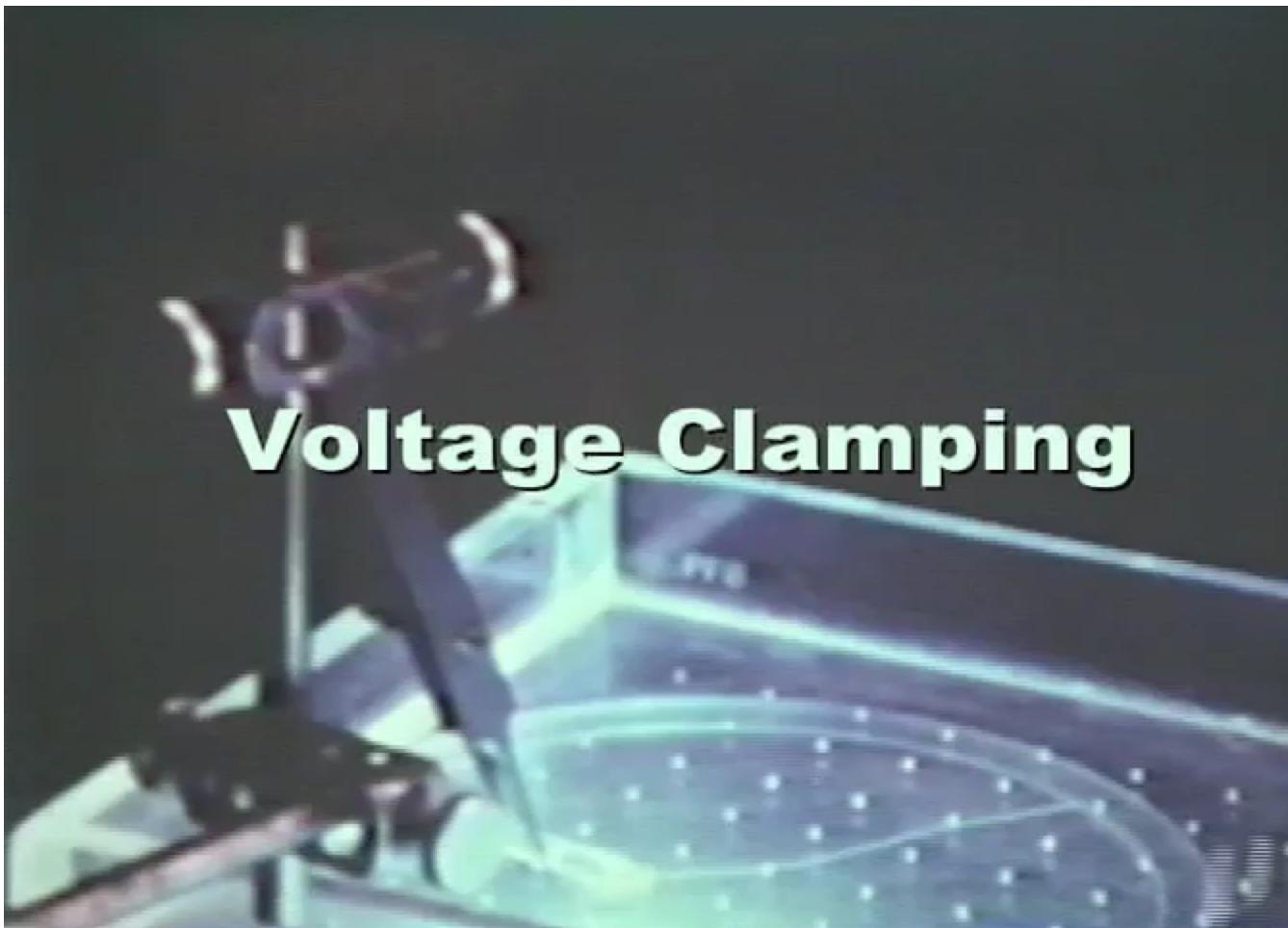
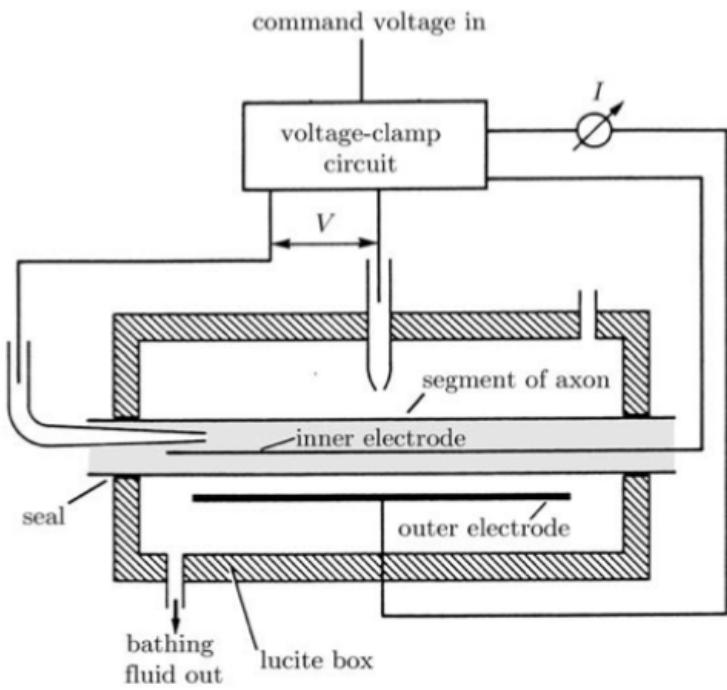


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Hodgkin-Huxley voltage clamping



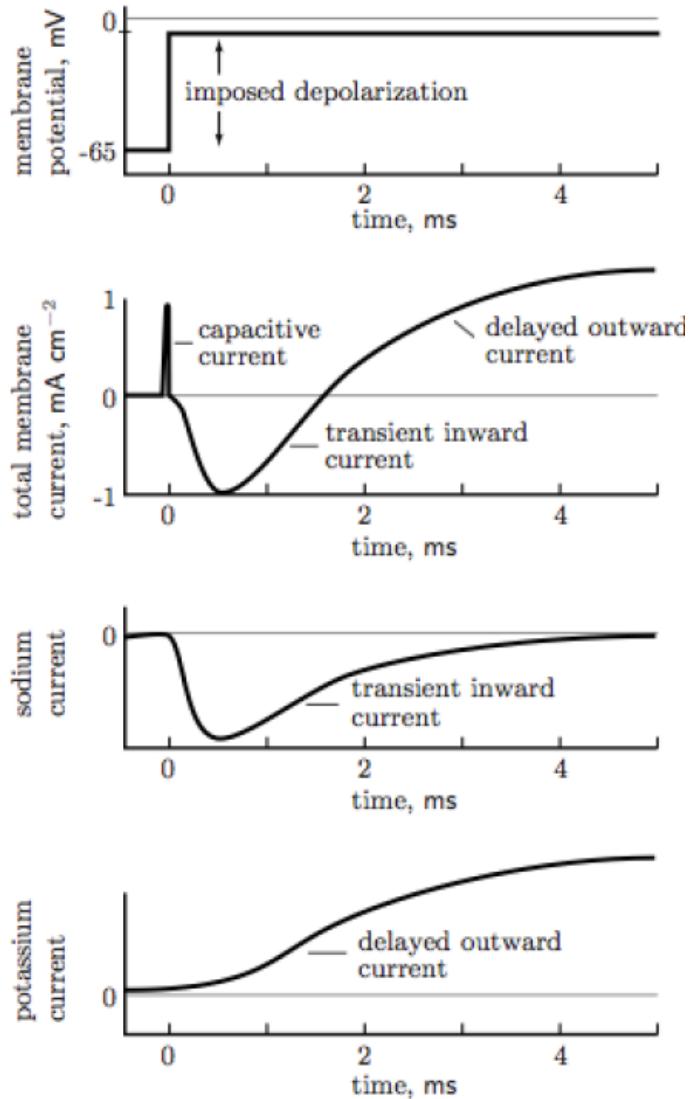
Hodgkin-Huxley voltage clamping



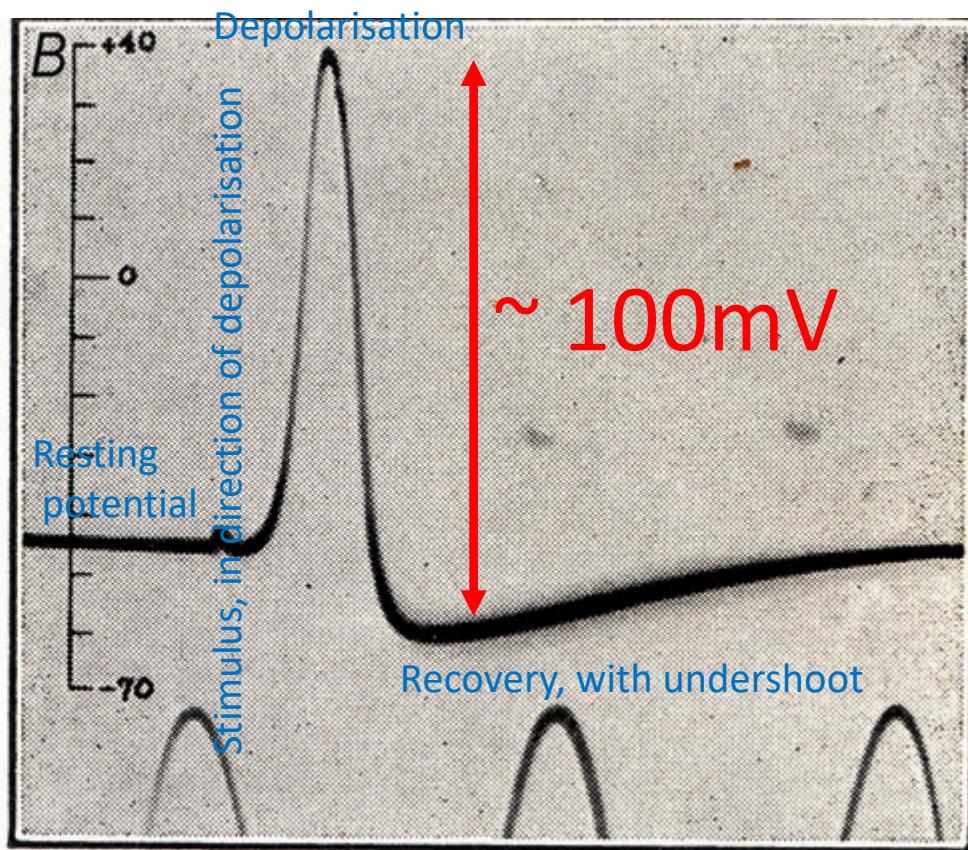
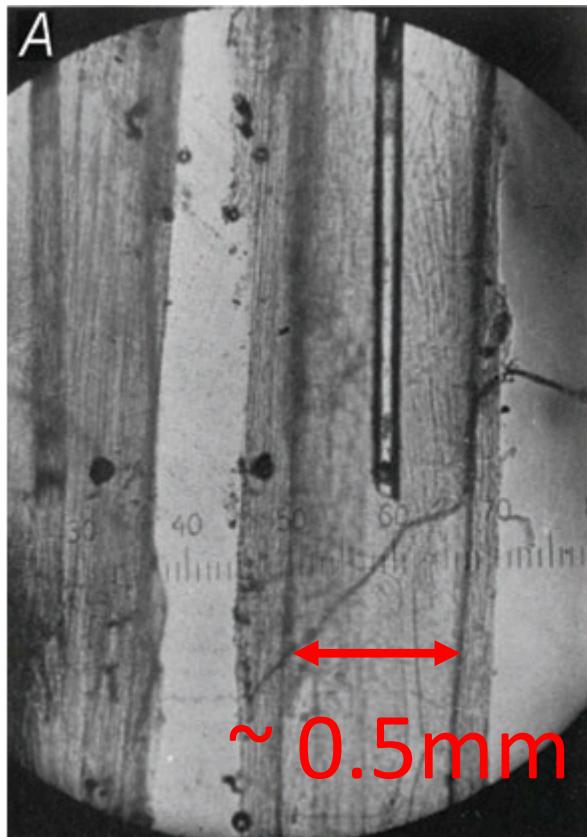
Space clamping. Squid axon long enough for a long wire to be threaded through them, allowing spatially uniform potential along axon. This eliminates gradients, and propagation.

Voltage clamping. A feedback circuit monitors V , the transmembrane voltage, and adjusts I to maintain V at a fixed voltage in the experiment.

Separation of effects of different ion currents. This is possible by adjusting the concentration of an ion species such that its Nernst potential is equal to the set voltage.



The “spike” – action potential.



Enables information to be carried. It's an analogue to digital conversion. All-or-none.

What are the membrane structures that enable this dynamics?

Voltage can propagate as a signal. These signals are typically pulses of around 50 mV in amplitude, and of width between 1 and 500 ms depending on the organism and cell type.

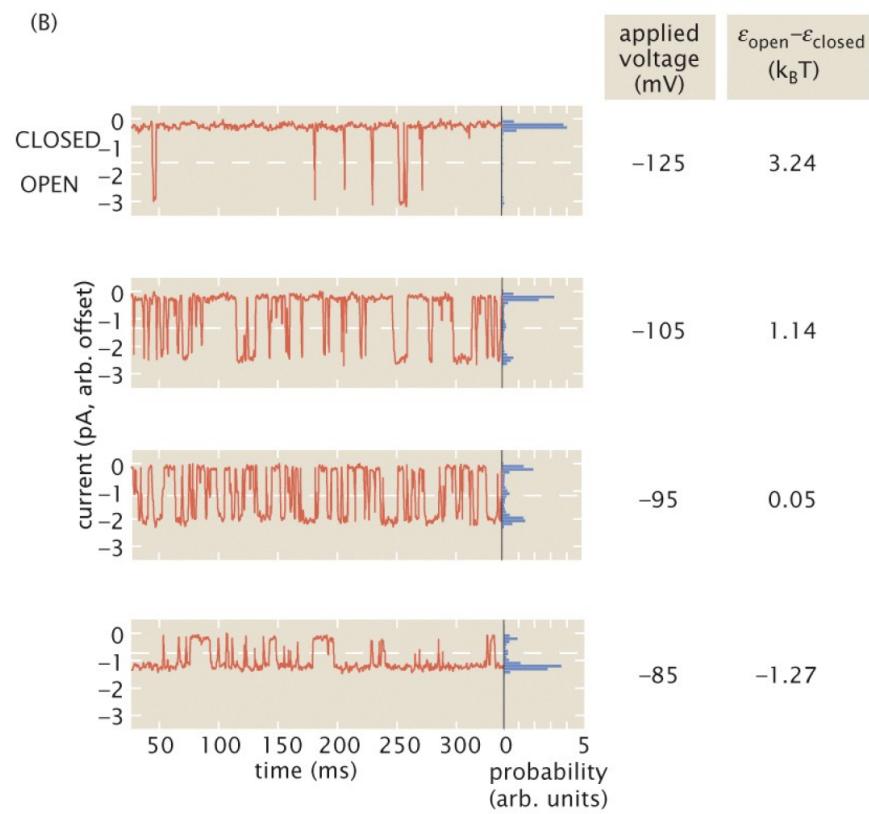
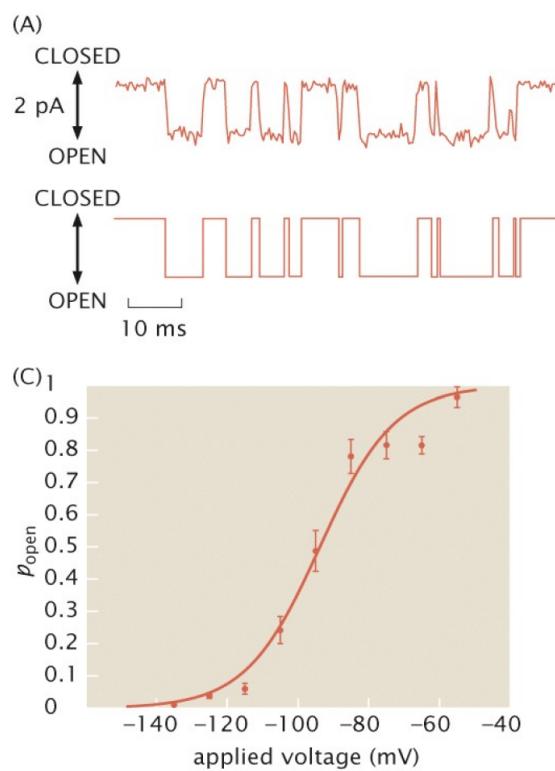
This pulse travels down the axon without changing shape, at speeds between 10 and 100 m/s.

A threshold value of voltage is required to trigger the action potential.

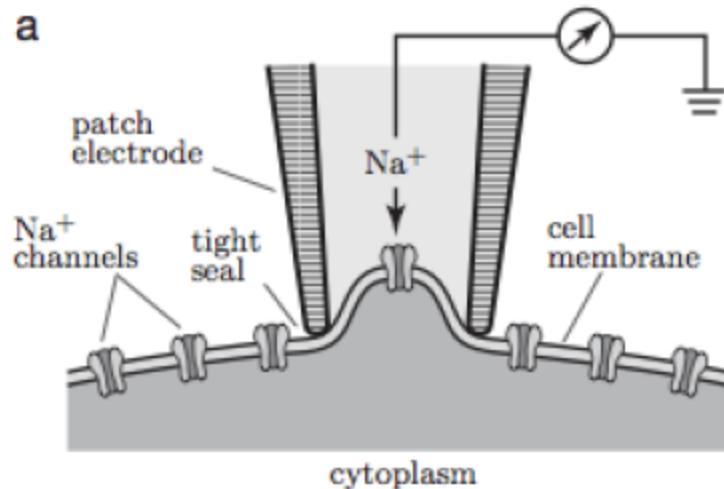
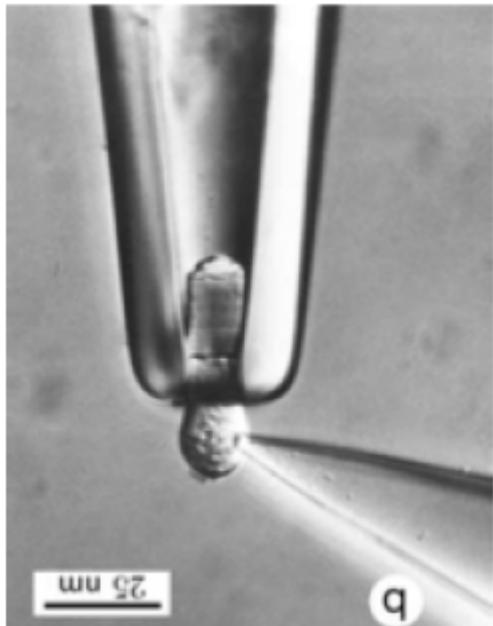
It is the transient (due to opening and closing of the channels) permeability to K^+ and Na^+ ions that lies at the heart of the action potential.

The opening and closing are regulated by voltage (in other contexts, they can also be regulated by mechanical forces, membrane tension, ligand binding, phosphorylation).

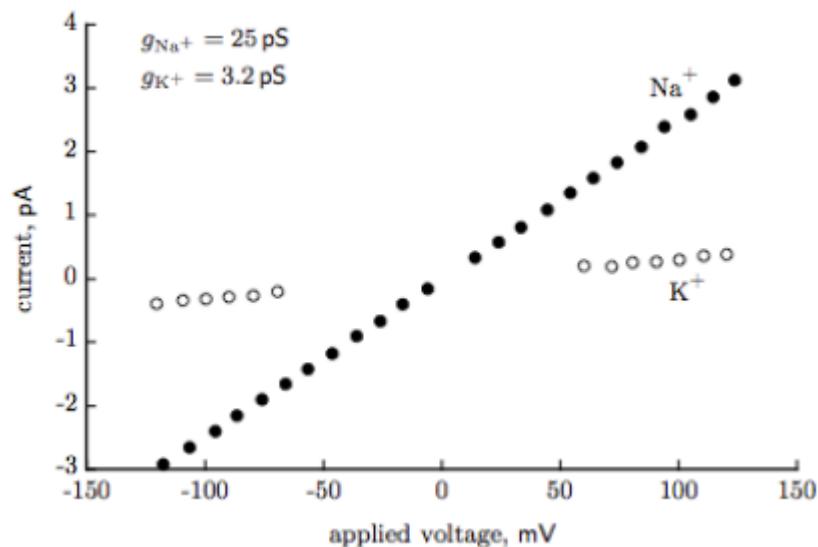
Membrane voltage keeps the channels closed, and their ‘preferred’ configuration (in absence of voltage) is open.



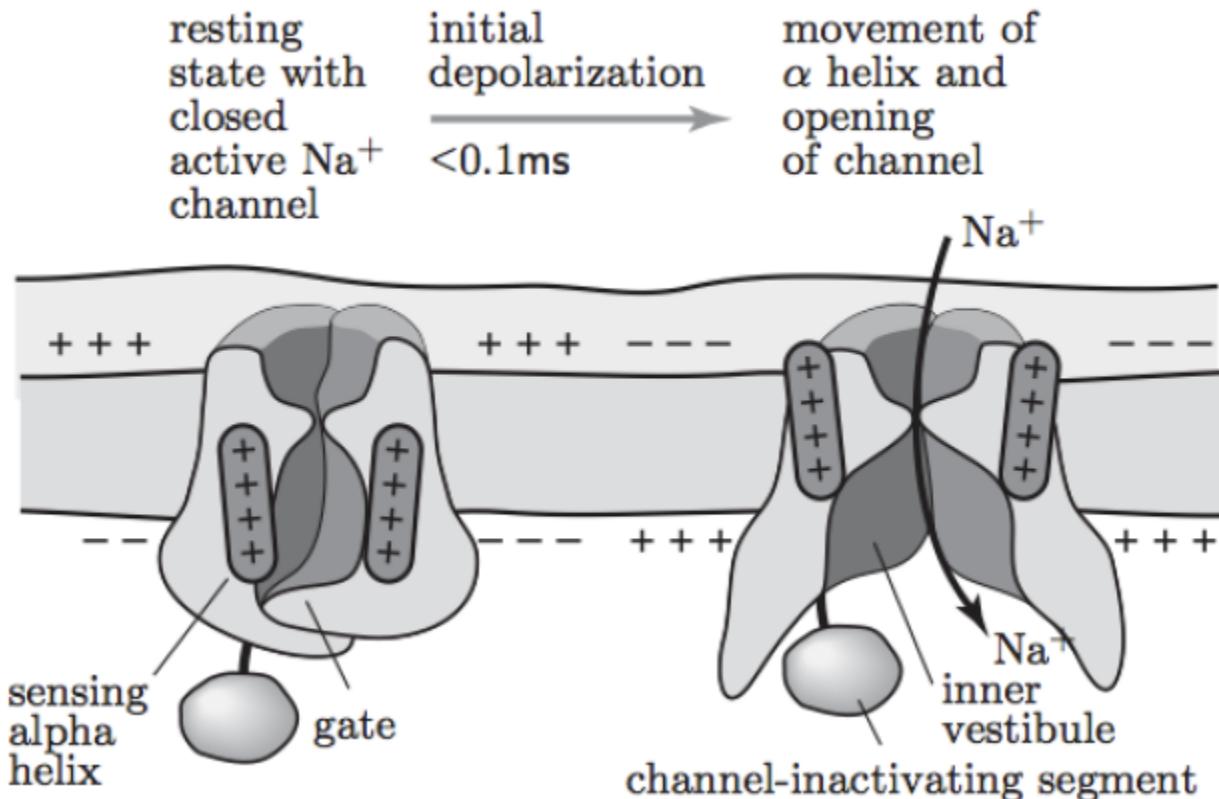
Patch clamping



Micropipette aspirates a patch of membrane.
Electrical/ionic seal on the glass.
One (or few) channel only in the patch.
By keeping channels artificially open,
experiments find that channels are
highly ion-specific.
Data for sodium channel →



Channel modelled as a two state system



Channel modelled as a two state system

If $\Delta\epsilon$ is the energy difference between states, preferring the open configuration, the probability of the channel being open is:

$$p_{open} = \frac{e^{-\beta\Delta\epsilon}}{1 + e^{-\beta\Delta\epsilon}}.$$

These energies are voltage dependent:

$$\Delta\epsilon = \Delta\epsilon_{conf} - QfV_{mem},$$

$$\begin{array}{ccc} & \uparrow & \uparrow \\ \text{Energies of} & & \text{Energy from moving} \\ \text{protein} & & \text{charge } Q \text{ across the} \\ \text{conformation} & & \text{potential} \end{array}$$

If the membrane has thickness d , then we have a field $E=V_{mem}/d$.

fV_{mem} is equal to fEd and is the drop in potential experienced by the charges on the channel, when the channel switches from open to closed.

V_{mem} less negative (depolarisation) means smaller potential drop to go to closed state, which eventually favours the open state.

Channel modelled as a two state system

$$p_{open} = \frac{e^{-\beta \Delta \epsilon}}{1 + e^{-\beta \Delta \epsilon}}.$$

$p_{open} = 1/2$ for $\Delta \epsilon = 0$, so

$$V^* = \frac{\Delta \epsilon_{conf}}{Qf}.$$

We can re-write as

$$p_{open} = \frac{1}{1 + e^{\beta q(V^* - V_{mem})}},$$

with $q = Qf$.

This is a sigmoid shape (non-linear) in V_{mem} , a key ingredient in the action potential.

Need to consider two channel / pumps in the membrane

1. The sodium-potassium pump.

This pump consumes the energy of an ATP molecule ($20 k_B T$ for hydrolysis of ATP) and uses that to pump 3 Na^+ ions out of the cell, and 2 K^+ ions inside.

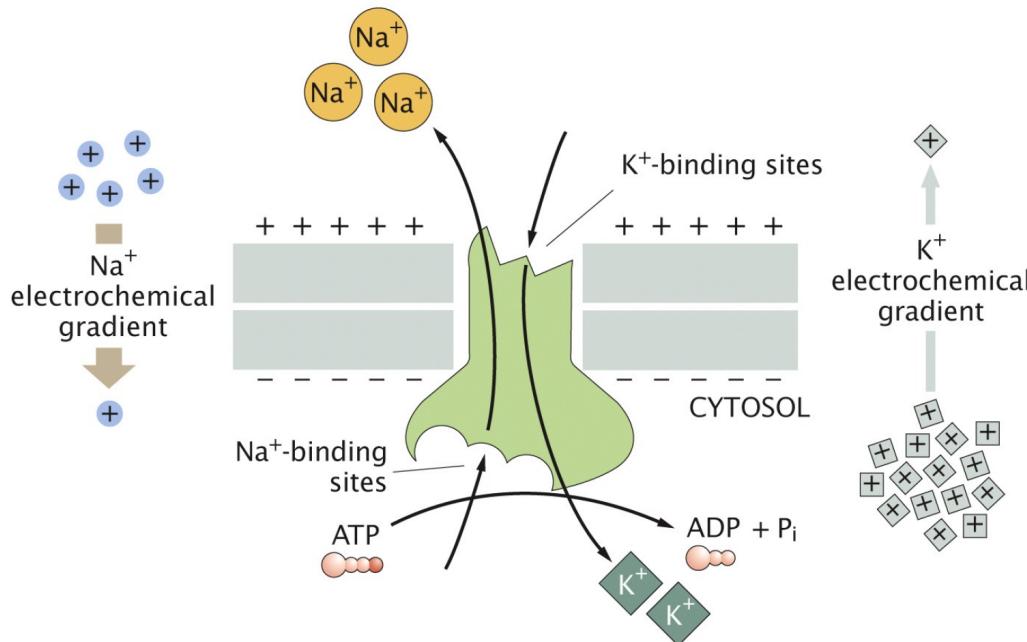


Figure 17.8 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

2. The potassium (and sodium) “leak” channels, which selectively allows potassium (or sodium) to transport through.

If a potassium 'leak channel' is open, K⁺ escape the cell following their concentration gradient.

However, this change reduces the magnitude of the membrane potential.

Potassium will reach a balance close to its Nernst potential.

Now if a sodium channel opens, sodium will move both in response to its own concentration gradient, and also to re-equilibrate the charge lost by the potassium.

Sodium will reach a balance close to its Nernst potential.

The sodium channels are normally closed. They open transiently and locally, if a neighboring patch of membrane has been depolarised.

These ideas can be made into a quantitative model.

The capacitance of a patch of the membrane is

$$C_{patch} = \frac{Q_{patch}}{V_{mem}},$$

where Q_{patch} is the excess charge on either side of the membrane patch.

In terms of charge density σ , and patch area, we have $Q_{patch} = \sigma A_{patch}$.

In a parallel plate capacitor the field is uniform and given by $\sigma/\epsilon_0\epsilon_r$, so with membrane thickness d we have

$$V_{mem} = \frac{\sigma d}{\epsilon_0\epsilon_r},$$

So substituting both into the top equation we have

$$C_{patch} = \frac{\epsilon_0\epsilon_r A_{patch}}{d}.$$

Values? $\epsilon_r=2$ and $d = 5\text{nm}$ so capacitance per unit area around $0.4 \mu\text{F}/\text{cm}^2$ (real membranes measure around $1 \mu\text{F}/\text{cm}^2$)

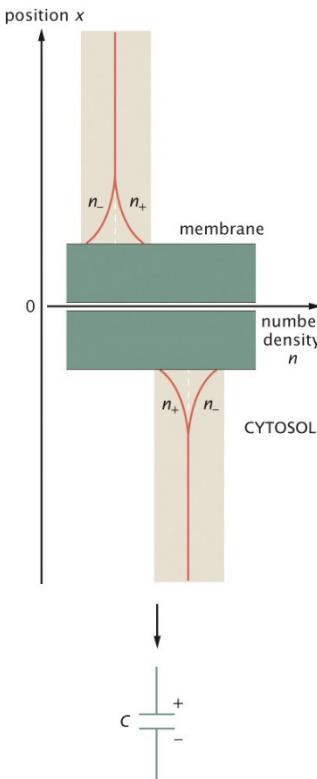


Figure 17.12 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

How many charges move during a depolarisation of 100mV?

We take capacitance per unit area of $c = 1 \mu\text{F}/\text{cm}^2$

Take a cylindrical cell radius $r = 25 \mu\text{m}$ and length l

$$\begin{aligned}\Delta Q_{\text{patch}} &= \Delta V_{\text{mem}} c 2\pi r l \\ &= 10^{10} e l / \text{cm}\end{aligned}$$

with $e = 1.6 \cdot 10^{-19} \text{ C}$

How many charges are *inside* the cell? Take $c_{\text{in}} = 100 \text{ mM}$

$$\begin{aligned}Q_{\text{in}} &= e c_{\text{in}} \times \pi r^2 l \\ &= 10^{15} e l / \text{cm}\end{aligned}$$

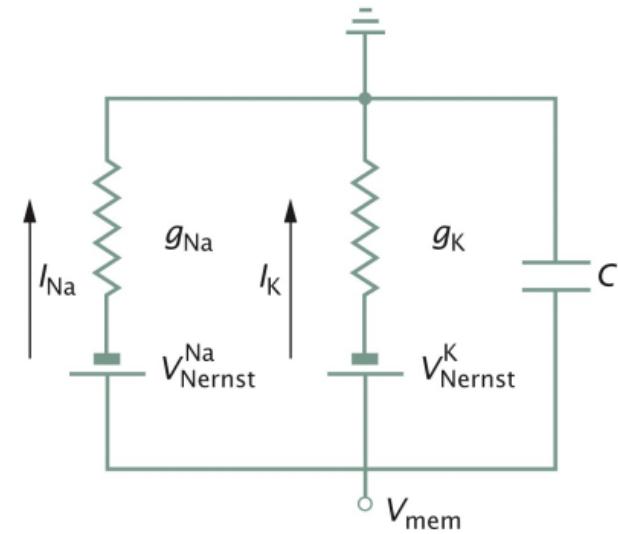
So...

$$\Delta Q_{\text{patch}} / Q_{\text{in}} = 10^{-5}$$

Independent of l

Small, so we don't need to worry about changes in Q_{in}

Electrical circuit analog of the model we are building is this



ionic current across the membrane

$$I = g \left(\frac{k_B T}{ze} \ln \frac{c_{in}}{c_{out}} + V_{in} - V_{out} \right)$$

With g the conductance per unit area.

Positive I is a flow of positive ions out of the cell.

We had define V_{Nernst} as from the Nernst equation and V_{mem} so that:

$$I = g(V_{\text{mem}} - V_{\text{Nernst}})$$

This is an Ohm law.

Connections in parallel for each ion species.

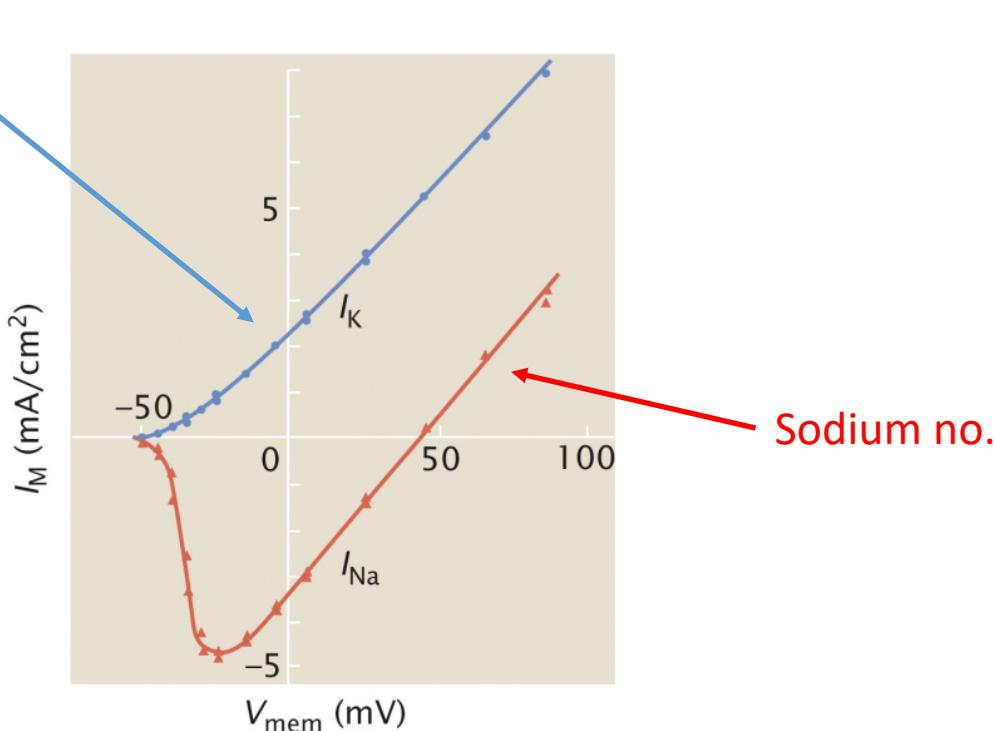
How do the channels regulate current?

If G_1 is the conductance of one channel in open state

Then in a patch we have

$$g_{\text{patch}} = N_{\text{patch}} p_{\text{open}} G_1$$

If p_{open} is always =1 then we expect Ohm conductance, i.e. linear I-V.
Potassium does this pretty ok.

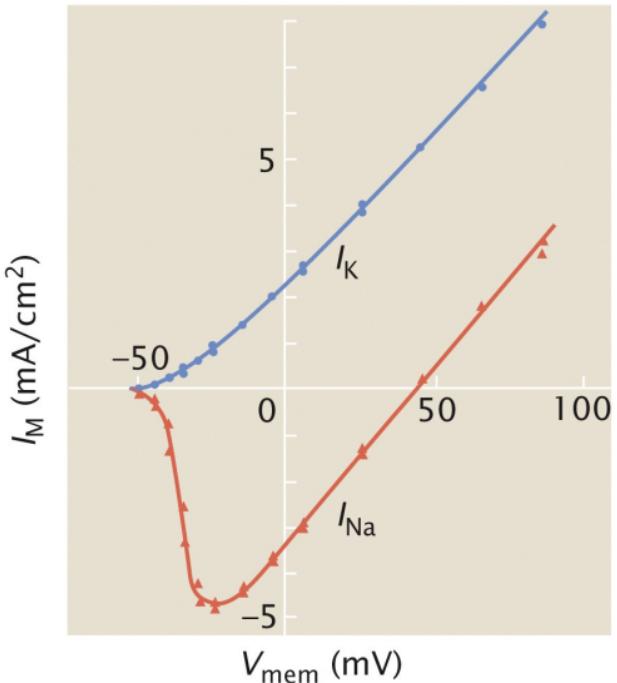


How do the channels regulate current?

Sodium

If p_{open} does a step change, opening at a voltage V^*
→ g will jump to a higher value
→ The current will drop at the voltage V^* .

Below and above V^* we expect the current to grow linearly.



Bistability of membrane voltage

Considering both potassium and sodium currents, we have

$$\Delta Q = - (I_K + I_{Na}) \Delta t$$

$$\Delta Q = C \Delta V_{mem}$$

Combining: $C \frac{dV_{mem}}{dt} = g_K(V_{Nernst}^K - V_{mem}) + g_{Na}(V_{Nernst}^{Na} - V_{mem})$

Steady state: $V_{mem} = \frac{g_K V_{Nernst}^K + g_{Na} V_{Nernst}^{Na}}{g_K + g_{Na}}$

Bistable!

If $g_K \gg g_{Na}$ then $V_{mem} = V_{Nernst}^K$

If $g_{Na} \gg g_K$ then $V_{mem} = V_{Nernst}^{Na}$

The ion species with the highest conductance through the membrane sets the membrane potential to its Nernst potential.

The conductances are of course related to the open/closed balance of the channels, and we have seen that this is Voltage regulated.

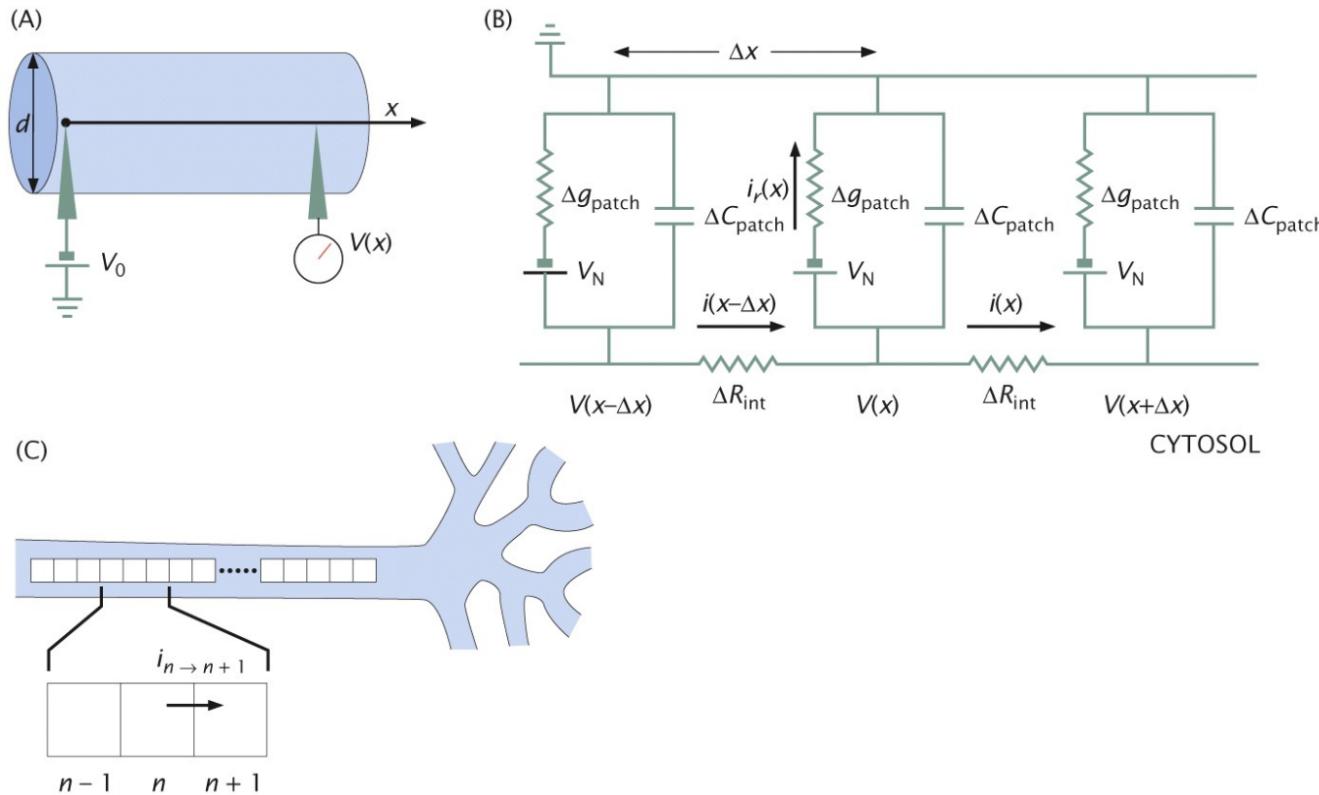
An approximation is to consider the potassium conductance as fixed; this is justified because its dynamics is slower than the dynamics of the sodium channel. Then, we have that the sodium conductance is proportional to its own p_{open} .

For $V_{mem} < V^*$ this gives a low conductance, and therefore the membrane will take the Nernst potential of **potassium**.

If $V_{mem} > V^*$ the sodium channels open, sodium conductance dominates. The membrane potential goes to the Nernst voltage of **sodium**, a positive value.

Cable equation

We can model the spatial transmission of signal by considering a series of circuits



The change of voltage along the axon is connected to the longitudinal current:

$$V(x + \Delta x) - V(x) = -i(x) \Delta R_{int}$$

$i(x)$ can change along the axon due to currents in the radial direction, $i_r(x)$ but conserving:

$$i(x - \Delta x) - i(x) = i_r(x) = \Delta g_{patch} (V(x) - V_{Nernst})$$

Information encoding

The action potential (spike) is the elementary unit of signal transmission.

The form of the spike does not carry information – it is essentially indistinguishable.

The number and timing of spikes matter.

We want to understand how axons are able to transmit this kind of wave.

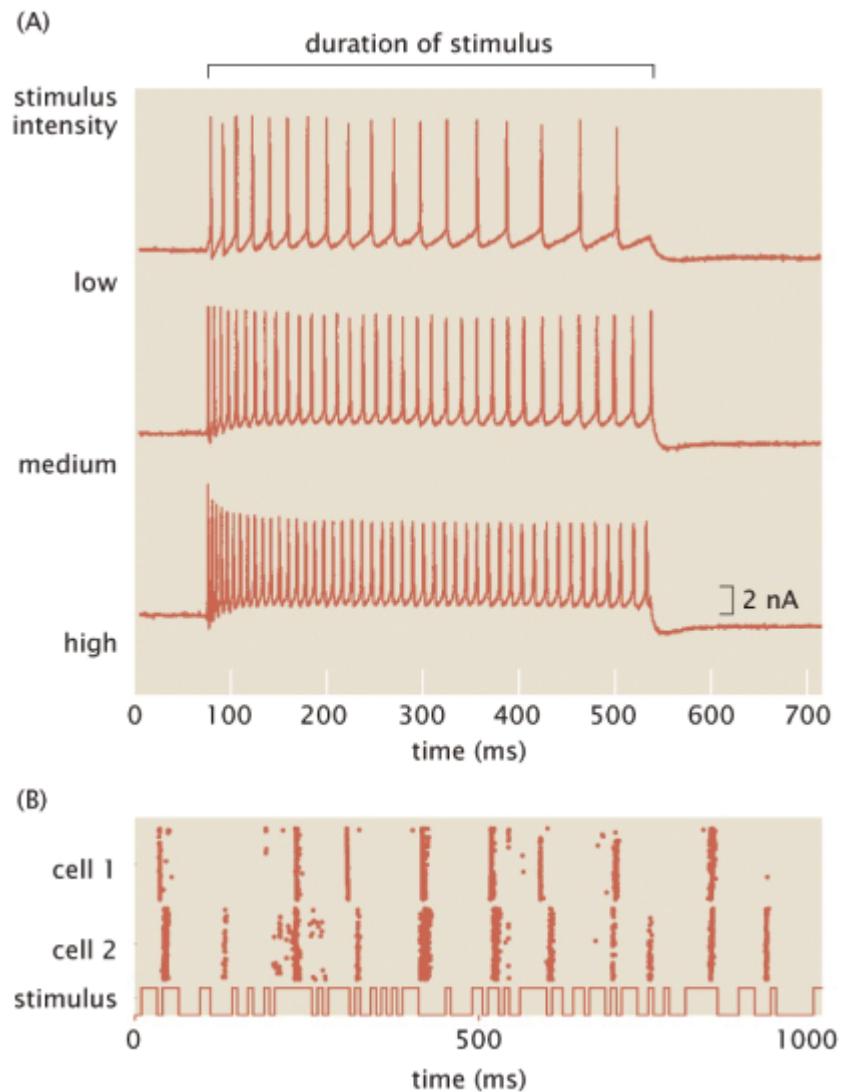


Figure 17.22 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Cable equation

$$V(x + \Delta x) - V(x) = -i(x) \Delta R_{\text{int}}$$

$$i(x - \Delta x) - i(x) = i_r(x) = \Delta g_{\text{patch}} (V(x) - V_{\text{Nernst}})$$

We have $\Delta R_{\text{int}} = \rho \Delta x / (\pi d^2 / 4)$ and $\Delta g_{\text{patch}} = g \pi d \Delta x$

Where

d is the axon diameter

Squid

0.5 mm

ρ is the resistivity of intracellular medium

0.3 Ω m

g conductance per unit area

5 $\Omega^{-1}\text{m}^{-2}$

So: $dV(x)/dx = -(\Delta R_{\text{int}}/\Delta x) i(x)$

$$d i(x)/dx = -(\Delta g/\Delta x) (V(x) - V_{\text{Nernst}})$$

Taking x derivative of the first, and subbing the second, gives:

$$\frac{d^2V(x)}{dx^2} = \frac{1}{\lambda^2} (V(x) - V_{\text{Nernst}})$$

with

$$\lambda = \sqrt{\frac{d}{4\rho g}}$$

λ gives the exponential decay of the voltage perturbation, along the axon.

It is $\simeq 9$ mm in the squid axon.

Depolarisation Waves

To describe waves on the axon we have to combine the voltage bistability property with the cable equation.

Generalising the current equation to include two types of channels, and the capacitance current, gives:

$$\begin{aligned} i(x - \Delta x, t) - i(x, t) &= \Delta g_{patch}^{Na} (V(x, t) - V_{Nernst}^{Na}) + \\ &+ \Delta g_{patch}^K (V(x, t) - V_{Nernst}^K) + \Delta C_{patch} \frac{\partial V(x, t)}{\partial t}. \end{aligned}$$

Again making the simplification that potassium conductance is a constant with voltage, and low.

The sodium conductance has the form described earlier, and values that switch from below the potassium to very high, increasing voltage.

The resulting equation, generalising the Cable equation to give time dependence, is:

$$\lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} - \tau \frac{\partial V(x, t)}{\partial t} = (V(x, t) - V_{Nernst}^K) + \frac{g_{Na}(V(x, t))}{g_K} (V(x, t) - V_{Nernst}^{Na}),$$

with λ as above, and $\tau = C/g$ with the conductances set by potassium.

Depolarisation Waves

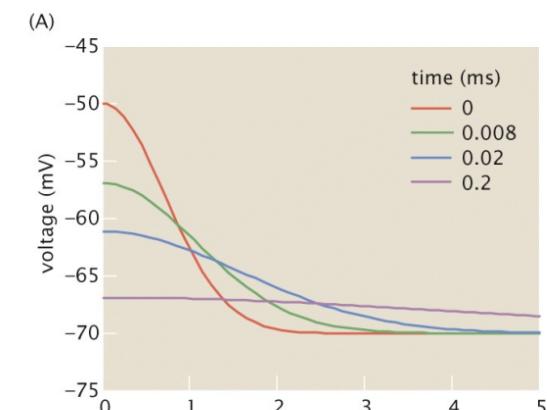
$$\lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} - \tau \frac{\partial V(x, t)}{\partial t} = (V(x, t) - V_{Nernst}^K) + \frac{g_{Na}(V(x, t))}{g_K} (V(x, t) - V_{Nernst}^{Na}),$$

with λ as above, and $\tau = C/g$ with the conductances set by potassium.

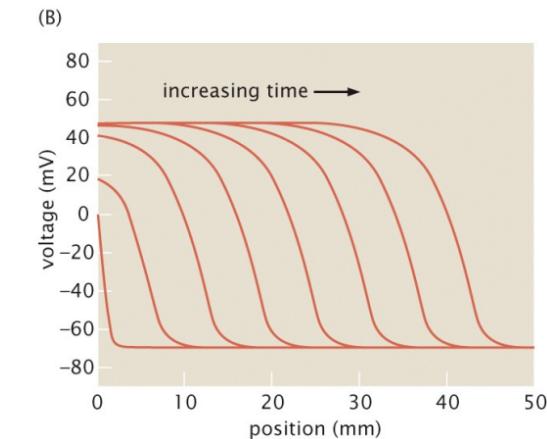
I.h.s. is the diffusion equation.

If we imagine a localised current injected at $x = 0$ in a small region, then there can be two cases.

(A) If the membrane voltage remains below the threshold to open the sodium channels. Then the r.h.s. remains small (negligible) and we simply have a diffusive relaxation of the voltage.



(B) If the voltage rises above the threshold to open the sodium channels, then the membrane potential near $x = 0$ changes to the Nernst potential of sodium. This then leads to a propagating front.



The speed is λ/τ , and we had $\lambda \sim \sqrt{d}$, so large axons propagate signals faster.

A Hodgkin-Huxley model for spike propagation

A typical signal traveling in an axon has a conserved and local envelope - this is called a spike.

To describe a spike, the missing concept from the equation so far is the inactivation of the sodium channels.

In the membrane, sodium channels remain open for about 2 ms. After closing, they remain 'inactive' for few tens of ms.

The voltage gated potassium channels are slower to open (several ms) but remain open as long as depolarisation is maintained.

This time-asymmetry in the sodium response leads to uni-directional motion of the signal down the axon.

Information is coded as a frequency of spikes. i.e. a more intense input current is turned into a more rapid train of spikes compared to a low input current, with the shapes of the spikes being quite comparable.

This process turns an analog input into a digital signal.

We now add inactivation of the sodium channels, with the concept of the inactive state, to complete the model.

A Hodgkin-Huxley model for spike propagation

There are three states for the sodium channel, and the transitions between them can be described by:

$$\begin{aligned}\frac{dp_C}{dt} &= -k_{open} p_C \\ \frac{dp_O}{dt} &= k_{open} p_C - k_{inactive} p_O \\ \frac{dp_I}{dt} &= k_{inactive} p_O.\end{aligned}$$

Note that we have not allowed inactive→closed nor open→closed, so this simplification can only describe a single spike.

We take the rate of opening to be proportional to the probability of an open channel (same logic as elsewhere in the course, e.g. in regulating gene expression):

$$k_{open} = k_{open}^{max} \frac{1}{1 + e^{\beta q(V^* - V(x,t))}}$$

and the inactivation rate as a constant.

The sodium conductance now depends on the state of the channels, and has the form:

$$g_{Na} = g_{Na}^{open} p_O + g_{Na}^{closed} p_C.$$

A Hodgkin-Huxley model for spike propagation

The sodium conductance now depends on the state of the channels, and has the form:

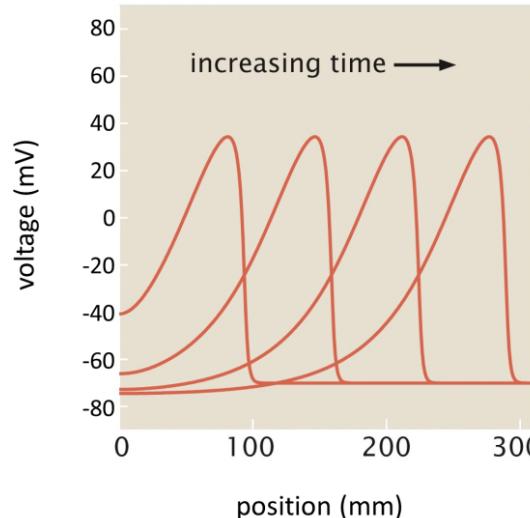
$$g_{Na} = g_{Na}^{open} p_O + g_{Na}^{closed} p_C.$$

Crucially for the system to work, the parameters have evolved such that the open state conductivity of sodium channels is about 20 times larger than g_K (potassium), and the closed state is about 20 times lower than potassium.

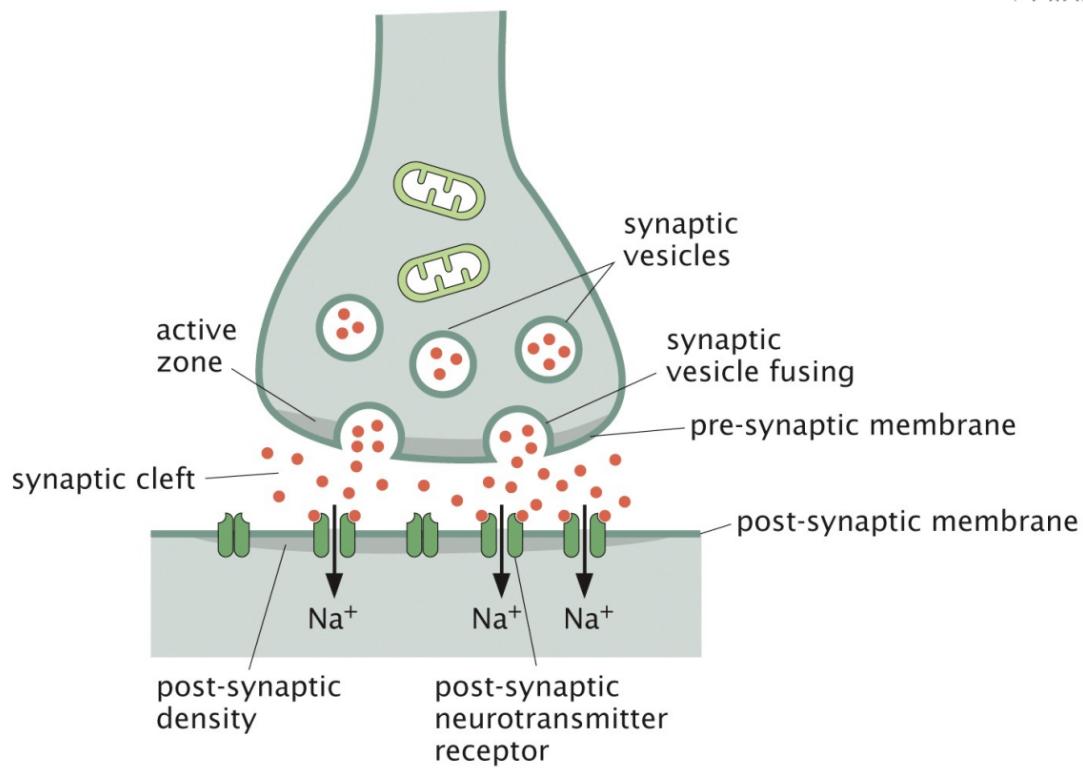
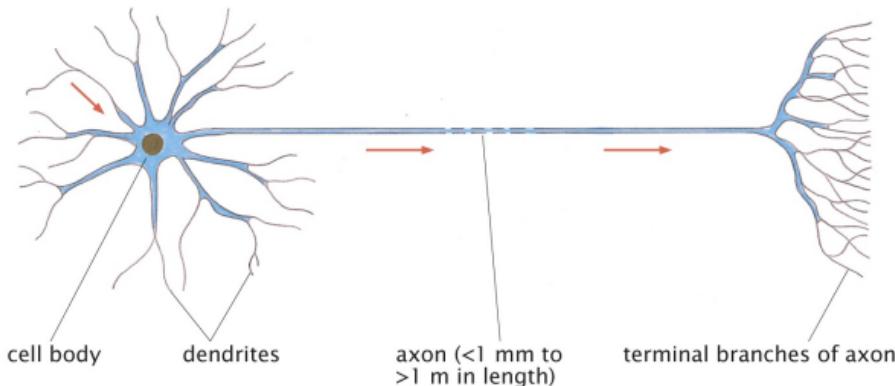
This more complex sodium conductivity, function of the voltage, and hence space and time, needs to be considered in

$$\lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} - \tau \frac{\partial V(x, t)}{\partial t} = (V(x, t) - V_{Nernst}^K) + \frac{g_{Na}(V(x, t))}{g_K} (V(x, t) - V_{Nernst}^{Na})$$

The equation is readily solved numerically and the solutions are traveling spikes:



What is a synapse? What happens there?



Note: advances in neuroscience possible with optogenetics, GM of light-responsive channels.

Towards networks of neurons – computation and information processing

The HH model described so far is representative of a family of HH models, where researchers have added more and more biological detail. A neuron has a lot more degrees of freedom e.g. through modulating the properties of its channels. This brings many more timescales to the behaviour of neural systems.

Another aspect that is simplified in HH is the physical chemistry of the ions. E.g. their timescales for diffusion. There are models that aim to address this too.

But already the simple HH we derived can be too complex if one wants to simulate the behaviour of a large network.

For this, one can replace neurons in a model by a simpler “integrate and fire” rule:

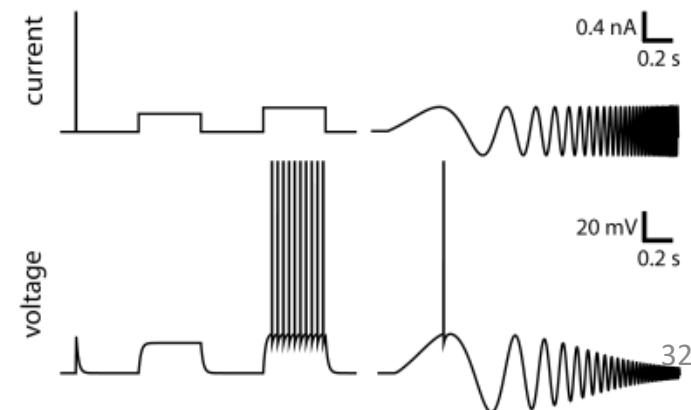
Neuron accumulates current $I(t)$,
and increases its voltage $V(t)$.

A spike is emitted when V
reaches a threshold, and the
potential is reset to V_r

$$V(t) = V_r + \frac{1}{C} \int_{t_0}^t I(s) ds$$

$$\frac{dV}{dt} = \frac{1}{C} I(t)$$

when $V(t) > V_T$ then $V(t) \rightarrow V_r$



How is computation achieved?

Hopfield 1986

A model of 7 connected neurons

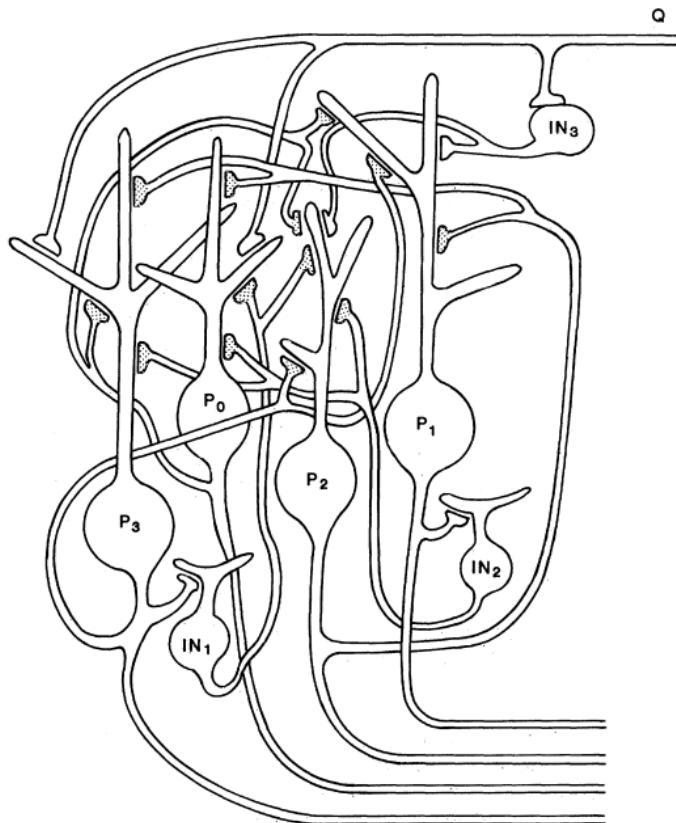


Fig. 1. "Anatomy" of a simple model neural circuit. Input axon Q has excitatory synapses (direct or effective) on each of the principal neurons P₀ through P₃. Each of these principal neurons has inhibitory synapses (direct or indirect) with all other principal neurons. Inhibitory synapses are shaded. IN₁ to IN₃, intrinsic interneurons.

Table 1. Effective synaptic strengths for the circuit in Fig. 1.

Post-synaptic neuron	Presynaptic neuron				
	P ₀	P ₁	P ₂	P ₃	Q
P ₀	-2	-2	-4	-8	+1
P ₁	-2	-8	-8	-16	+2
P ₂	-4	-8	-32	-32	+4
P ₃	-8	-16	-32	-8	+8

In this simplified model of neurons, two variables describe the state of neuron *i*:

- The effective input potential u_i
- The output firing rate $f_i(u_i)$

The synapses have weights, so that the effect of *j* on *i* is $T_{ij}f_j(u_j)$

$$C_i \frac{du_i}{dt} = \sum_{j=1}^N T_{i,j} f_j(u_j) - \frac{u_i}{R_i} + I_i \quad (i = 1, \dots, N)$$

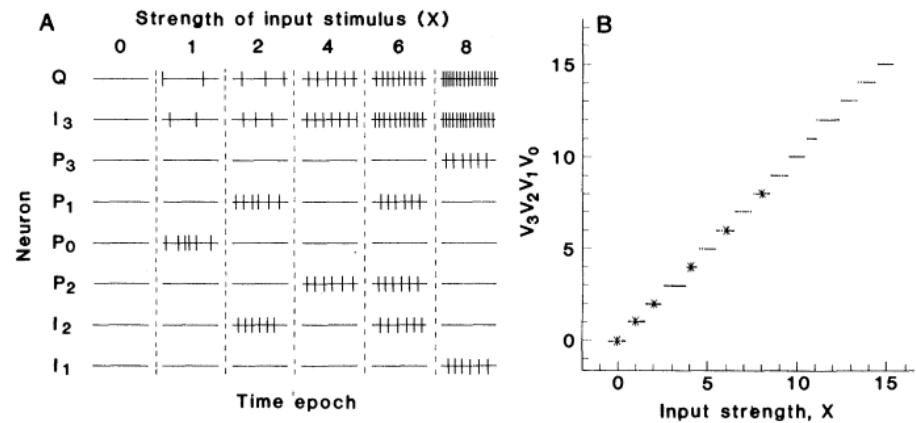


Fig. 2. (A) Results of an experiment in which the activity in each neuron in the circuit of Fig. 1 was simultaneously recorded (by simulation) as a function of the strength of the input stimulus on axon Q. The strength of the input stimulus is indicated by the numbers above each time epoch. (B) A selective rearrangement of the data in (A) illustrating the analog-binary computation being performed by the circuit. The digital word $V_3V_2V_1V_0$ is calculated from the records.

It is set up so that either directly or indirectly (through an IN neuron, the P neurons inhibit each other).

Electrical circuit analogous to the Neural circuit in Fig.1

Firing rate $f_i(u_i)$ is replaced by the output voltage V_i of amplifier i :

$$V_i = V_i^{\max} g_i(u_i)$$

With $g_i(u_i)$ having a sigmoid shape, like $f_i(u_i)$

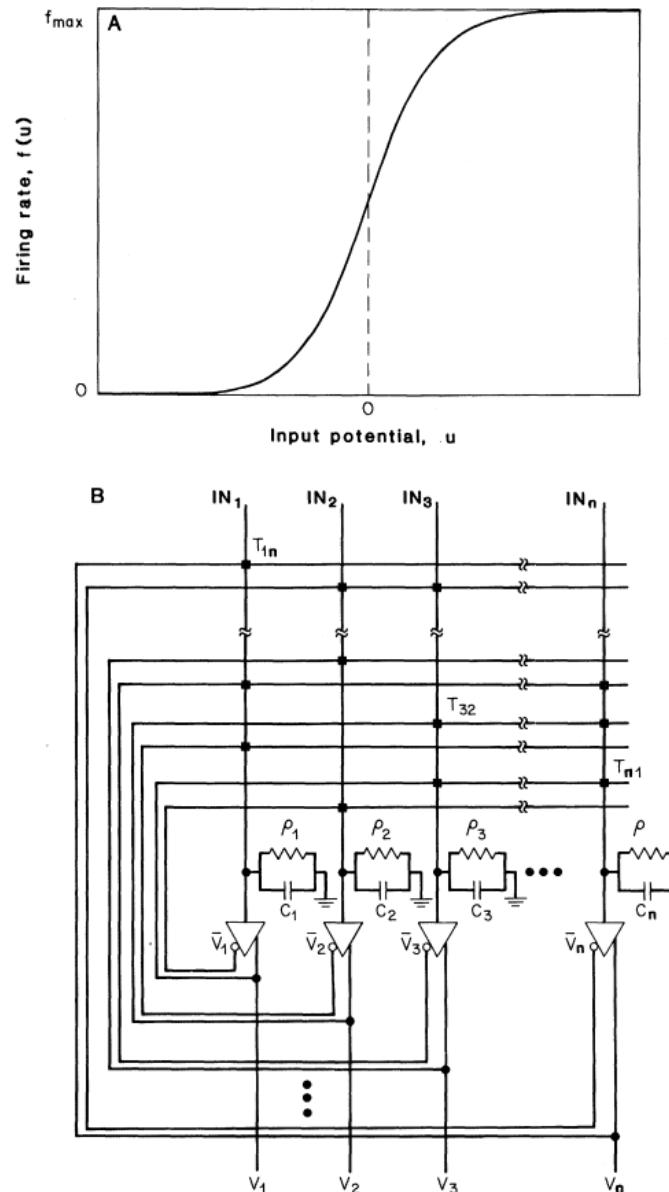


Fig. 3. (A) The sigmoid monotonic input-output relation used for the model neurons. (B) The model neural circuit in electrical components. The output of any neuron can potentially be connected to the input of any other neuron. Black squares at intersections represent resistive connections (with conductance T_{ij}) between outputs and inputs. Connections between inverted outputs (represented by the circles on the amplifiers) and inputs represent negative (inhibitory) connections.

A “Computational power” of such networks can be defined.

The network can be adapted to solve a variety of optimisation problems by changing just the synaptic strengths (forward engineering).

If you have a network that is pre-optimised for a task, it will be way more efficient than a general purpose computer.

In neuroscience, often the challenge is one of reverse engineering.