

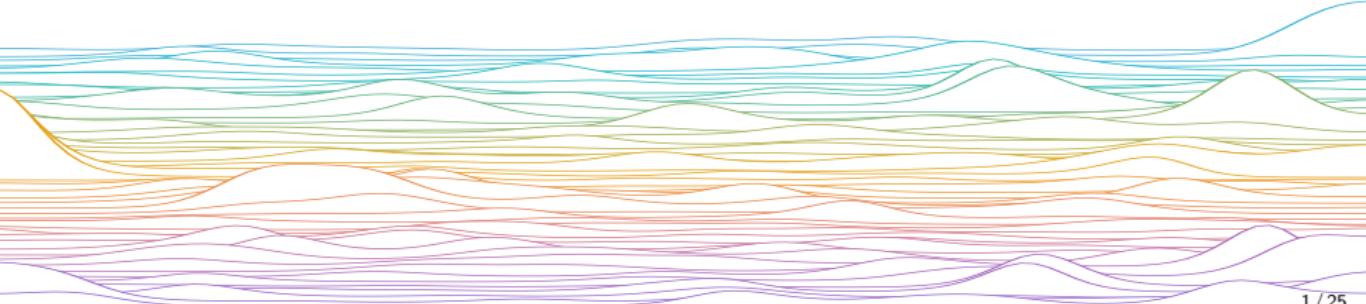
The Hodgkin–Huxley model of the action potential

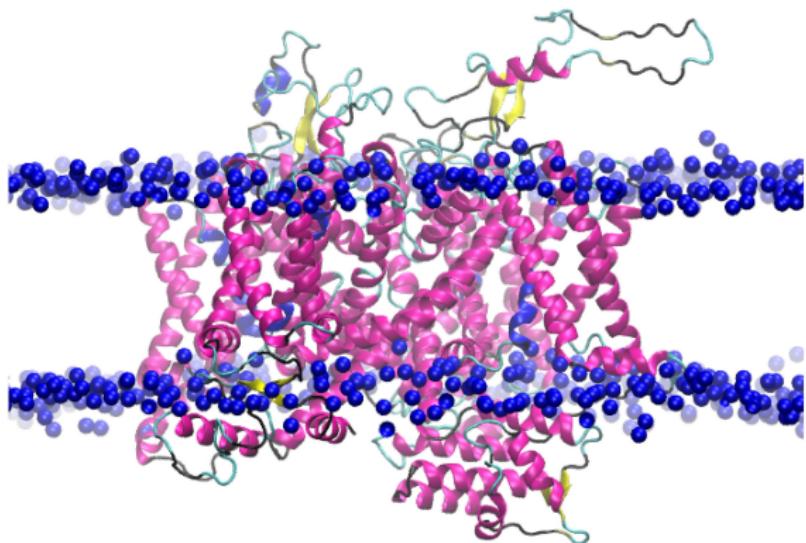
Computational Neuroscience
University of Bristol

M Rule

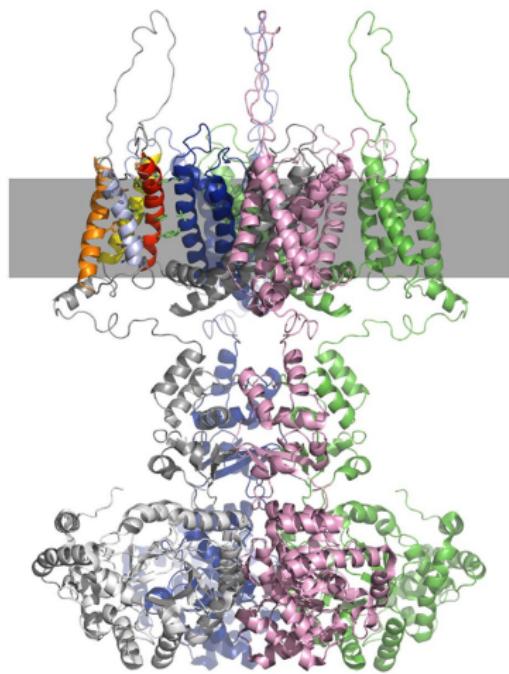
Learning outcomes:

- ▶ Write & analyse computer code that numerically simulates the Hodgkin–Huxley model of the action potential
- ▶ Be able to sketch the voltage dependences and reason about the dynamics of the key variables in the model.

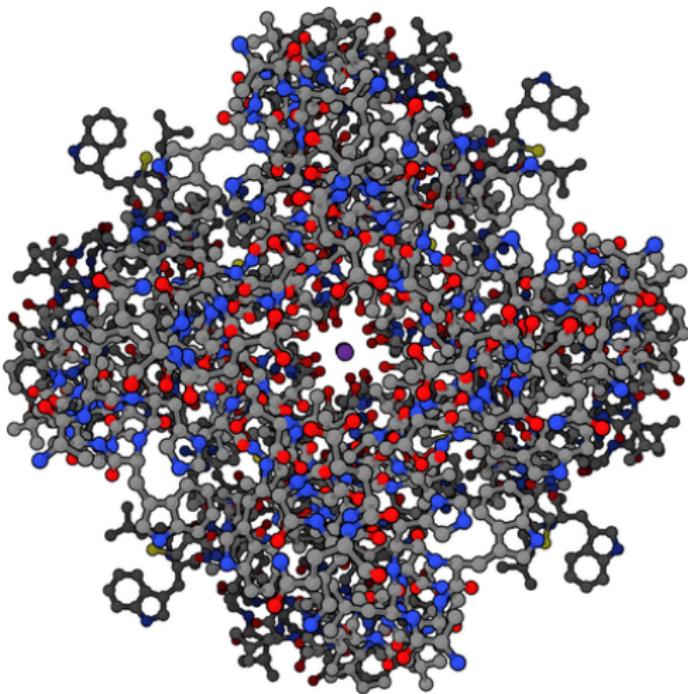




Na_v1.1; image from Montanino, Annalaura, et al. (2020)



Open Kv1.1; image from Hasan, Sonia, et al. (2017)



Potassium channel from streptomyces lividans

ION CHANNELS

Potassium



Sodium

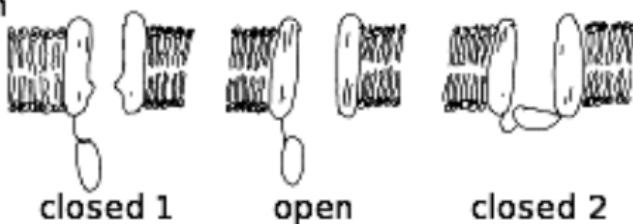
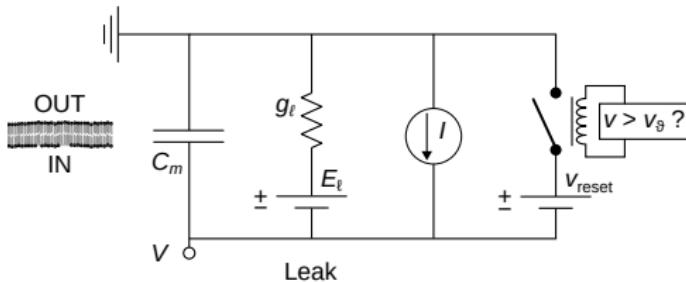
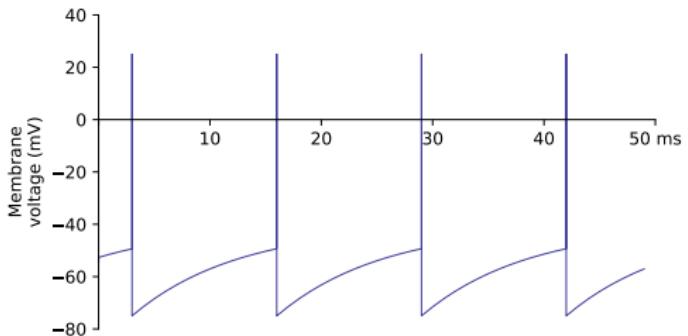


Illustration by Conor Houghton

Leaky Integrate-and-Fire (LIF)

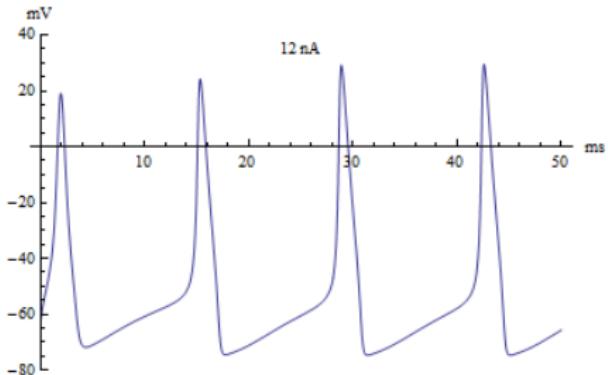
Departs from physiology, but sufficient to build intuition
Easy to integrate



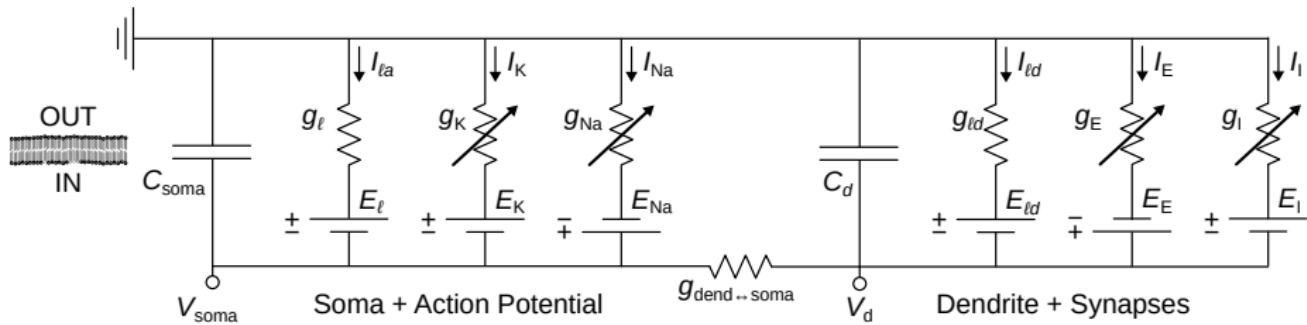
Full Conductance Model e.g. Hodgkin–Huxley

Nonlinear, action potential
costly to simulate

Study role of ion channels,
conductances, dendritic
morphology (shape), etc.



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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 forbessi*.

It showed that two voltage-gated membrane conductances were sufficient to explain the action potential.

We now use the term "Hodgkin-Huxley style model" loosely to refer to conductance-based models of voltage dynamics.

The Hodgkin-Huxley model stands as one of the outstanding successes of computational neuroscience.

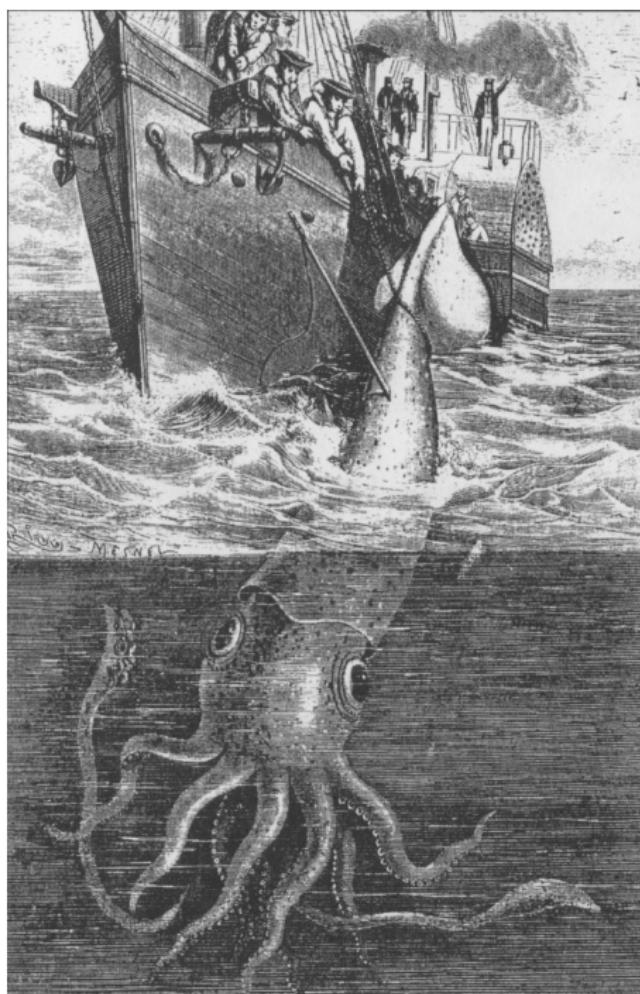
Who were Hodgkin and Huxley?

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"





$$RC\dot{v} = E_\ell - v + RI$$

$$C\dot{v} = \frac{1}{R}(E_\ell - v) + I$$

$$C\dot{v} = g_\ell(E_\ell - v) + I$$

$$C\dot{v} = g_1(E_1 - v) + g_2(E_2 - v) + \dots + I$$

$$C\dot{v} = g_\ell(E_\ell - v) + g_K(t)(E_K - v) + g_{Na}(t)(E_{Na} - v) + I$$

Maximal Conductance

- ▶ Conductance (1/resistance) if *all* available channels are open
- ▶ We denote using a “bar” \bar{g} here but you may see other conventions
- ▶ Multiply \bar{g} by *gating term* to get actual conductance

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

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

Gating term

Time-varying *fraction of channels open* $\in [0, 1]$

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

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

Raising the gating variables to 4th and (3+1)th powers in the potassium and sodium gating terms, respectively, is sometimes interpreted as reflecting interactions between the channel protein sub-domains, but in practice these powers are fit to experimental data and may be fractional if this provides a better fit.

Hodgkin–Huxley Gating variables

- ▶ n : Fraction potassium K^+ open
- ▶ m : Fraction sodium Na^+ open
- ▶ h : Fraction sodium Na^+ *active*

Gating variable dynamics:

$$\dot{n} = \alpha_n(v) \cdot (1 - n) - \beta_n(v) \cdot n$$

$$\dot{m} = \alpha_m(v) \cdot (1 - m) - \beta_m(v) \cdot m$$

$$\dot{h} = \alpha_h(v) \cdot (1 - h) - \beta_h(v) \cdot h$$

What are $\alpha_p(v)$ and $\beta_p(v)$ for $p \in \{n, m, h\}$?

What are $\alpha_p(v)$ and $\beta_p(v)$ for $p \in \{n, m, h\}$?

- α : Rate of decay toward “on” state ($p \rightarrow 1$)
- β : Rate of decay toward “off” state ($p \rightarrow 0$)

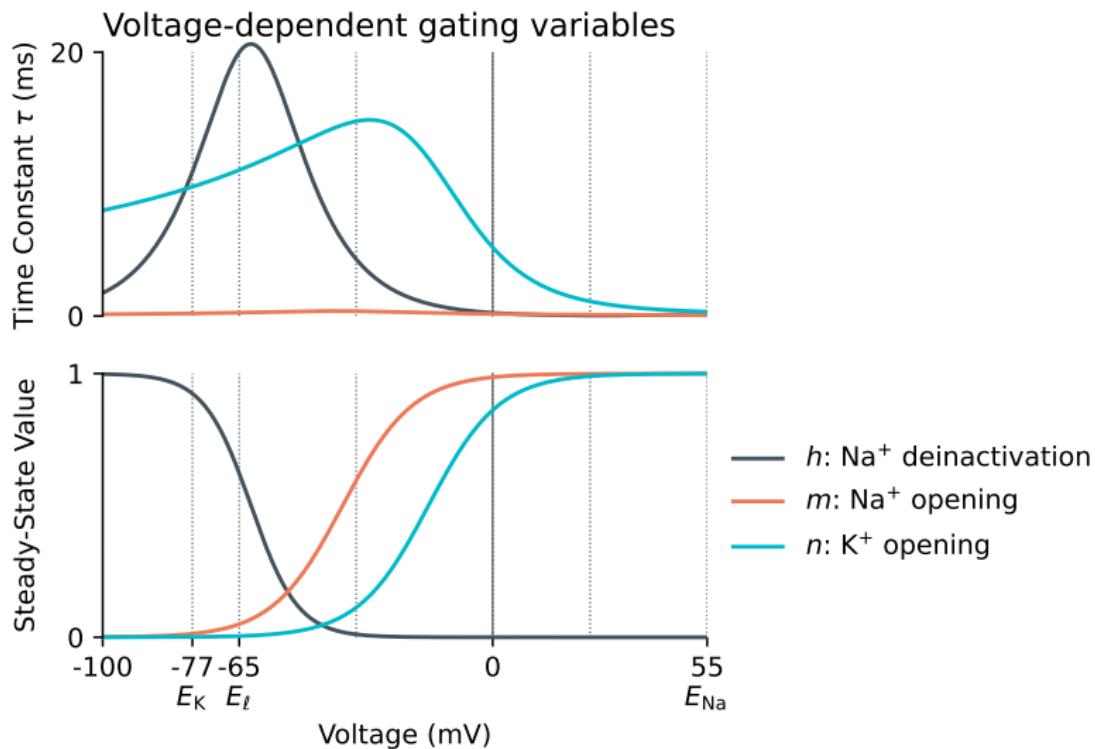
$$\dot{p} = \alpha \cdot (1 - p) - \beta \cdot p$$

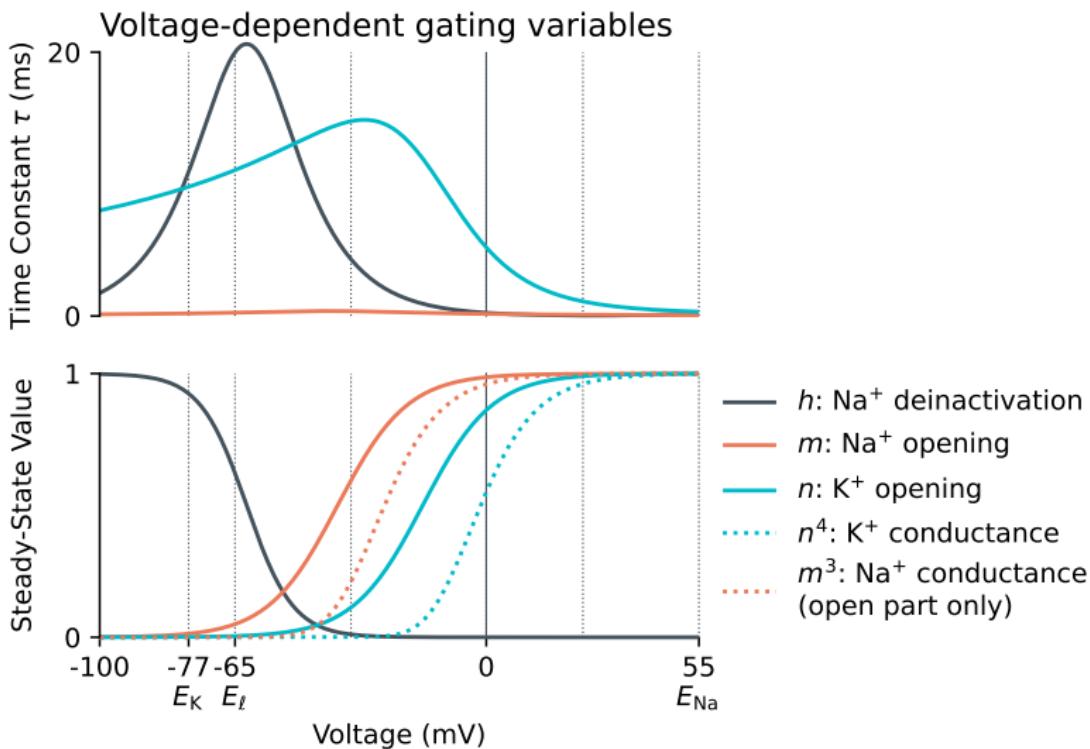
$$\dot{p} = \alpha - (\alpha + \beta) \cdot p$$

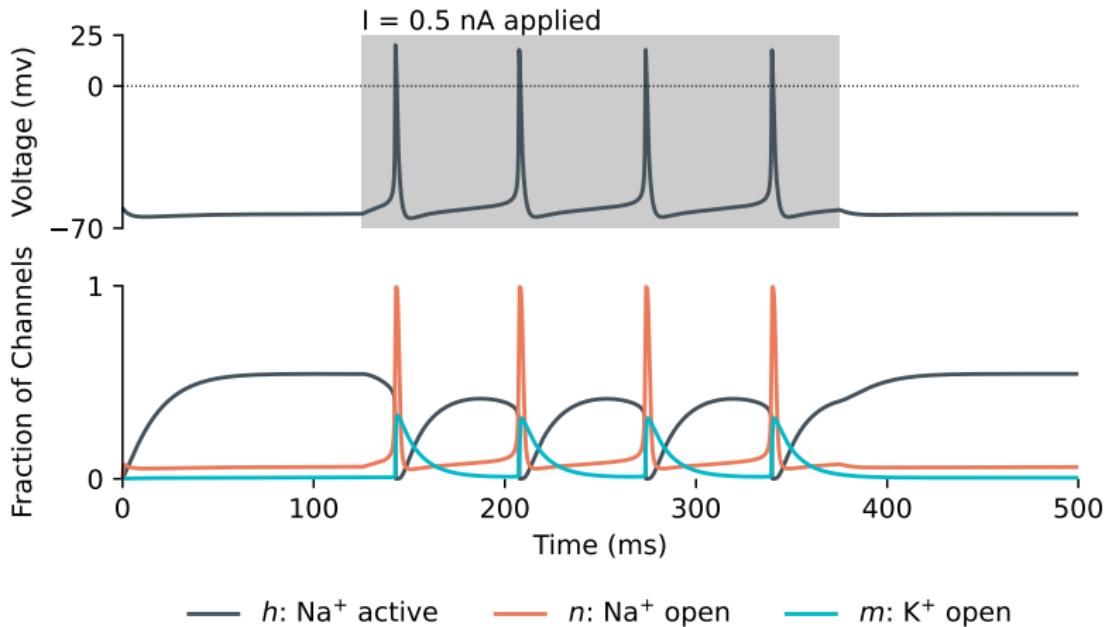
$$\underbrace{\frac{1}{\alpha + \beta} \dot{p}}_{\tau_p} = \underbrace{\frac{\alpha}{\alpha + \beta}}_{p_\infty} - p$$

	$\alpha(u)$	$\beta(u)$
n	$0.02(u - 25)/[1 - e^{-(u-25)/9}]$	$-0.002(u - 25)/[1 - e^{(u-25)/9}]$
m	$0.182(u + 35)/[1 - e^{-(u+35)/9}]$	$-0.124(u + 35)/[1 - e^{(u+35)/9}]$
h	$0.25e^{-(u+90)/12}$	$0.25e^{(u+62)/6}/e^{(u+90)/12}$

Parameters for excitatory pyramidal cell in rat cortex via Table 2.1 in Gerstner et al. (2004)
from Mainen et al. (1995), Huguenard et al. (1988), and Hamill et al. (1991)







$$RC\dot{v}=E_\ell-v+RI$$

$$C\dot{v}=\frac{1}{R}(E_\ell-v)+I$$

$$C\dot{v}=g_\ell(E_\ell-v)+I$$

$$C\dot{v}=g_1(E_1-v)+g_2(E_2-v)+\cdots +I$$

$$C\dot{v}=g_\ell(E_\ell-v)+g_{\rm K}(t)(E_{\rm K}-v)+g_{\rm Na}(t)(E_{\rm Na}-v)+I$$

$$g_{\rm K}(t)=\bar{g}_{\rm K}n(t)^4$$

$$\dot{n} = \alpha_n\left(v\right) \cdot \left(1-n\right) - \beta_n\left(v\right) \cdot n$$

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

$$\dot{m} = \alpha_m(v)\cdot(1-m)-\beta_m(v)\cdot m$$

$$\dot{h} = \alpha_h\left(v\right) \cdot \left(1-h\right) - \beta_h\left(v\right) \cdot h$$

Modelling synaptic conductances

These are typically modelled as a current, applied to a dendrite or to the same (somatic) compartment that has the voltage-gated sodium and potassium currents to generate action potentials.

$$\tau_{\text{syn}} \dot{g}_{\text{syn}}(t) = -g_{\text{syn}}(t)$$

if presynaptic cell spikes at time t

$$g_{\text{syn}}(t) \leftarrow g_{\text{syn}}(t) + 1$$

$$C\dot{v} = (\text{leak and spike conductances}) + g_{\text{syn}}(t)(E_{\text{syn}} - v)$$

The Hodgkin-Huxley model

Voltage-gated Na^+ , K^+ channels → action potential.

Typical parameters produce “Type 2” model neuron:

- ▶ Discontinuous f - I curve: Jumps from 0 to ~50 Hz at threshold*
- ▶ Has membrane potential oscillations (Hopf bifurcation)

Modern use: HH-style conductance models

- ▶ Dynamic, voltage-gated conductances in feedback with passive membrane

Drawbacks

- ▶ Even when recalibrated to match mammalian cells
 - Non-uniform channel densities?
 - Key ion channels with special behaviours (e.g. HCN)?
 - Myelinated axons, saltatory conduction
- ▶ HH is a deterministic “mean field”: Real ion channels are noisy
- ▶ Extra computational cost, not always more accurate
 - Some 1-compartment models, LIF arguably better (Brette &al. 2015).

Exam Question

[22/50 marks] The Hodgkin–Huxley Model: (10–20 minutes) The voltage in the Hodgkin Huxley model of the action potential evolves according to the following differential equations.

$$C\dot{v} = g_\ell(E_\ell - v) + \bar{g}_K n^4(E_K - v) + \bar{g}_{\text{Na}} m^3 h(E_{\text{Na}} - v) + I$$

$$\dot{n} = \alpha_n(v) \cdot (1 - n) - \beta_n(v) \cdot n$$

$$\dot{m} = \alpha_m(v) \cdot (1 - m) - \beta_m(v) \cdot m$$

$$\dot{h} = \alpha_h(v) \cdot (1 - h) - \beta_h(v) \cdot h$$

- i. What part of the action potential does the gating variable h capture? Which ionic conductance does it affect?
- ii. Assume that $v(t)$ is constant, so that $\alpha_h(v)$ and $\beta_h(v)$ are also constants. Find the steady-state value for the gating variable h , denoted as $h_\infty = \lim_{t \rightarrow \infty} h(t)$
- iii. Assume that α_h and β_h are constants. Re-write the differential equation for the sodium gating variable $\dot{h} = \alpha \cdot (1 - h) - \beta \cdot h$ in the form $\tau \dot{h} = h_\infty - h$. Give an expression for τ and h_∞ in terms of α_h and β_h .

$$C\dot{v} = g_\ell(E_\ell - v) + \bar{g}_K n^4 (E_K - v) + \bar{g}_{Na} m^3 h (E_{Na} - v) + I$$
$$\dot{n} = \alpha_n(v) \cdot (1 - n) - \beta_n(v) \cdot n$$
$$\dot{m} = \alpha_m(v) \cdot (1 - m) - \beta_m(v) \cdot m$$
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Exam Preparation

If shown a system of ODEs for the HH model, be able to state which terms are

- ▶ Maximal conductances
- ▶ Gating variables (what do each of n , m , and h do?)
- ▶ Maximal+gating combined to obtain time-varying Na^+ , K^+ conductances
- ▶ Voltage gated vs. leak conductances
- ▶ Be able to describe the *biological meaning of all the above*

HH: Good excuse to test 1st-order linear ODEs in context

- ▶ n , m , h at constant v follow a 1st-order linear ODE
- ▶ v with constant n , m , h , I follows a 1st-order linear ODE

Describe advantages/disadvantages of a conductance-based spike model like HH compared to e.g. LIF

end