The Hodgkin–Huxley model of the action potential

SEMT30003/4

This lecture covers:

- Hodgkin–Huxley model of the action potential and numerical integration thereof

Learning goals:

1. Be able to write or analyse computer code that numerically simulates the Hodgkin–Huxley model of the action potential
2. Be ready to approach numerical simulation other conductance-based models of voltage dynamics

Building on:

First-order ordinary differential equations

Membrane voltage dynamics

Leaky Integrate-and-Fire (LIF)

Building up to:

Maths for *Topics in Computer Science* final exam question

Modelling Scales

Physiological,
Quantitative

Biological
Realism,
Data needed
to identify
parameters

⋮

Chemistry

Biochemistry

Conductance Models:

- Hodgkin–Huxley

Leaky Integrate and Fire

Rate Neurons

Neural Mass/Field Models

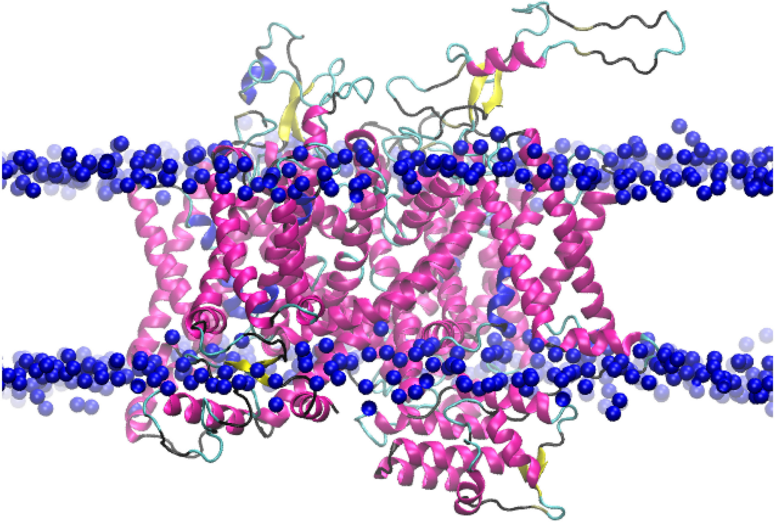
Cognitive Neuroscience

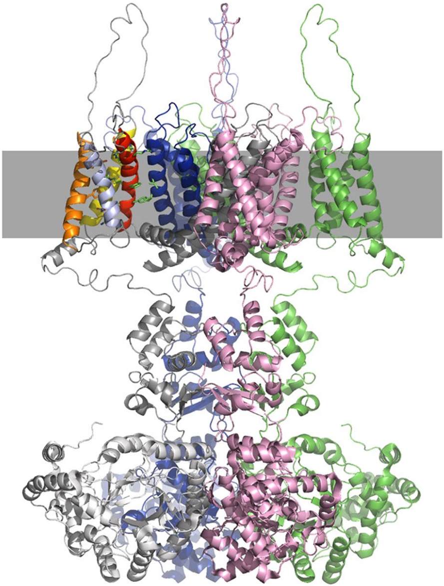
⋮

Computational
Efficiency,
Mathematical
Tractability

Phenomenological,
Qualitative

NA_v 1.1 SODIUM CHANNEL

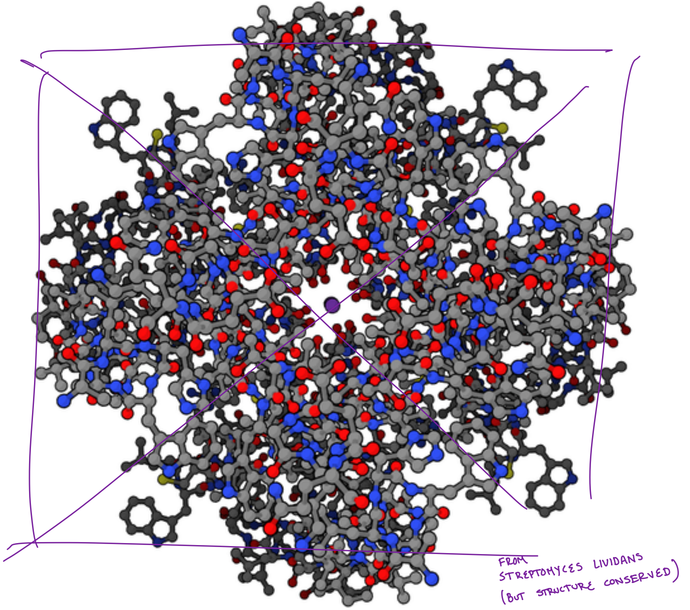




Open $K_v1.1$; image from Hasan, Sonia, et al. (2017)

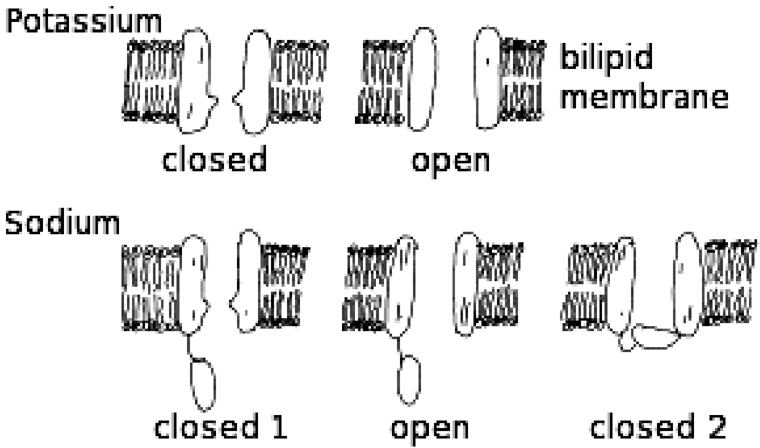
FOUR SUBUNITS

n^4



FROM
STREPTOMYCES LIVIDANS
(BUT STRUCTURE CONSERVED)

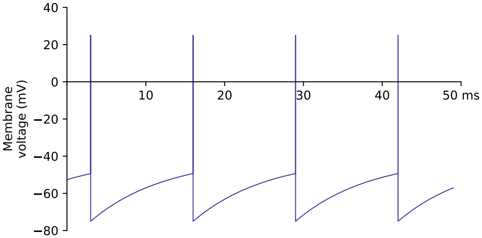
ION CHANNELS

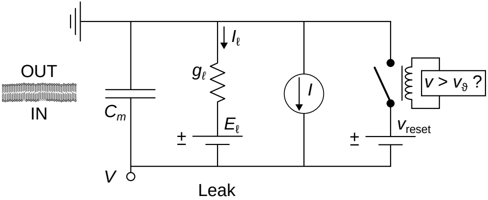


Leaky Integrate-and-Fire (LIF)

Departs from physiology, but sufficient to build intuition

Easy to integrate

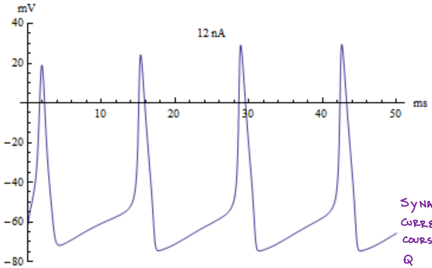




Full Conductance Model e.g. Hodgkin–Huxley

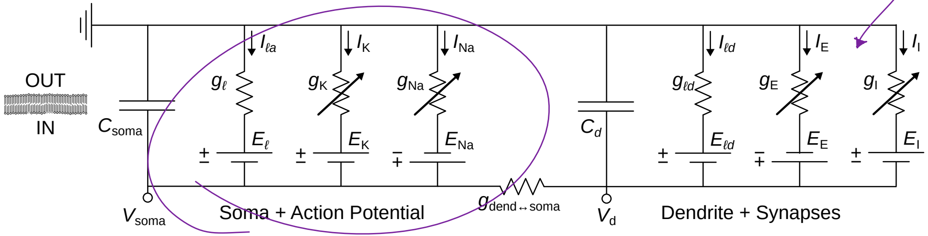
Nonlinear, action potential costly to simulate

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



SYNAPTIC CURRENTS FOR COURSEWORK Q

Wikimedia Commons



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$\frac{1}{R} = g$

OTHER CURRENTS ?

LIF
$$\left\{ C\dot{v} = g_\ell(\mathcal{E}_\ell - v) + I \right.$$

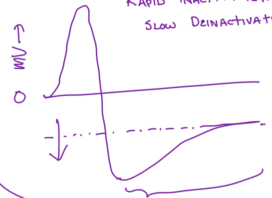
OPEN @ ~ -55 mV

$$\begin{aligned} C\dot{v} = {} & g_{Na}(t)(\mathcal{E}_{Na} - v) \\ & + g_K(t)(\mathcal{E}_K - v) \\ & + g_\ell(\mathcal{E}_\ell - v) \\ & + I(t) \end{aligned}$$

Na^+: RAPID OPENING

RAPID INACTIVATION

SLOW DEINACTIVATION



K^+ RELATIVE REFRACT

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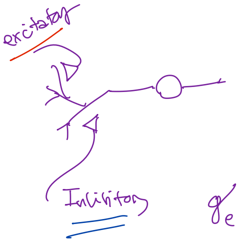
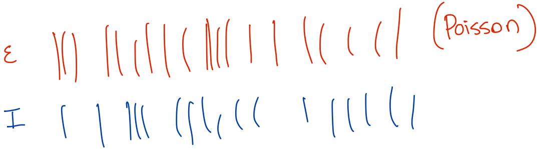
COURSEWORK Q3



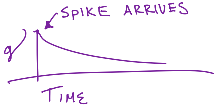


$$g_e(t)\left(E_e - v\right)$$

resting voltage $\qquad s \in \{e, i\}$

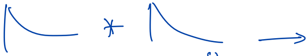
$$g_i(t)\left(E_e - v\right)$$

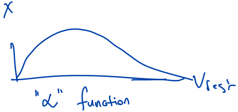
$$\tau_s \dot{g}_s = g_e(t) - g$$



SPIKE SUMMATION

$$C\dot{v} = \left(\text{leak}, \cancel{\text{action potential}}\right) + g_s\left(E_s - v\right)$$





SOMETIMES CONDUCTANCE & VOLTAGE RESPONSE COMBINED (CONVOLUTION) —

NOT QUITE CORRECT (effective membrane time "constant" τ not actually constant)

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

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

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

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

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

(t, v)

With lots of excitatory & Inhibitory input: high conductance state

+++ Inh

--- Exc

$\underline{g_e}(\sim)$ $\underline{g_i}(\sim)$

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

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

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

Gating term

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

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

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

$\in [0, 1]$

inactivation

$n \sim \Pr(1\ \mathrm{K}$ channel unit open$)$

Raising the gating variables to 4^{th} and $(3+1)^{\text{th}}$ 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.

1

0

$0.5 \times \bar{g}_{Na}$

Hodgkin–Huxley Gating variables

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

$m^3 h$ n^4

Gating variable dynamics:

Pull to "open" 1 Pull to "0" (closed or inactive)

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

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

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

$\Delta t \sim 0.01$ ms

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 ($p \longrightarrow 1$)
- β: Rate of decay toward "off" state ($p \longrightarrow 0$)

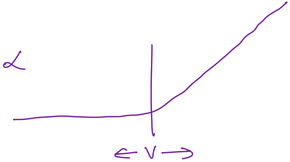
$\tau \dot{p} = p_\infty - p$

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

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

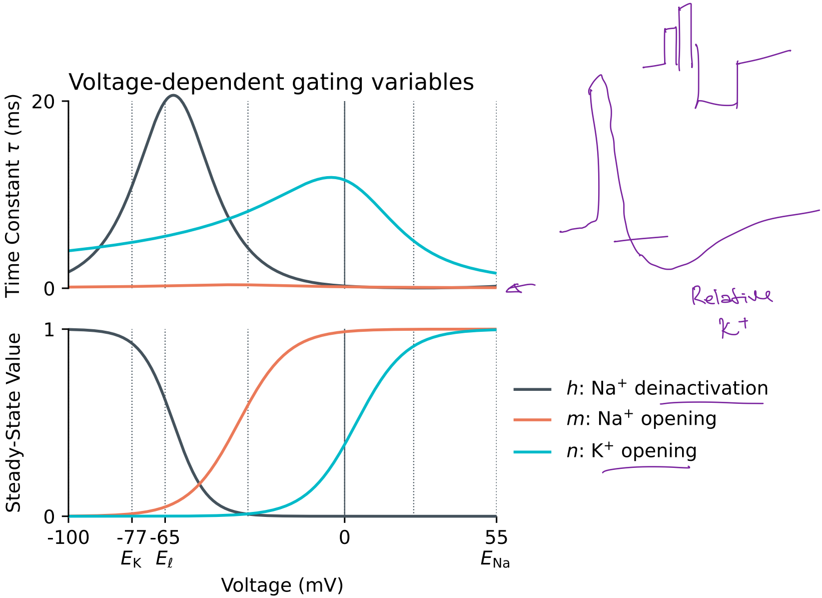
$$\underbrace{\frac{1}{\alpha + \beta}}_{\tau_p} \dot{p} = \underbrace{\frac{\alpha}{\alpha + \beta}}_{p_\infty} - p$$

$$\frac{v - v_0}{1 - e^{-(v - v_0)/c}}$$



		α (u / mV) [ms^{-1}]	β (u / mV) [ms^{-1}]
K^+	n	$0.02\,(u - 25) \,/\, \left[1 - e^{-(u-25)/9}\right]$	$-0.002(u - 25) \,/\, \left[1 - e^{(u-25)/9}\right]$
Na^+	m	$0.182\,(u + 35) \,/\, \left[1 - e^{-(u+35)/9}\right]$	$-0.124(u + 35) \,/\, \left[1 - e^{(u+35)/9}\right]$
	h	$0.25\; e^{-(u+90)/12}$	$0.25\; e^{(u+62)/6} \,/\, e^{(u+90)/12}$

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)



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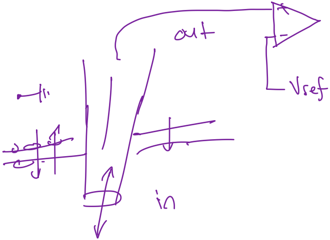
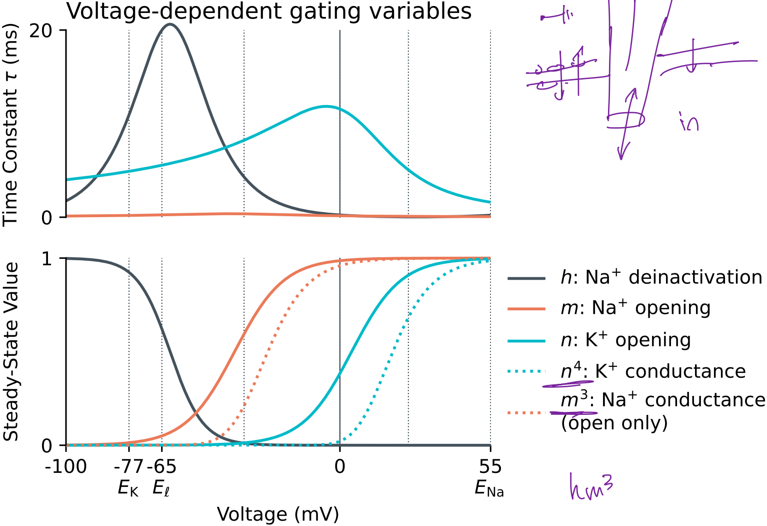
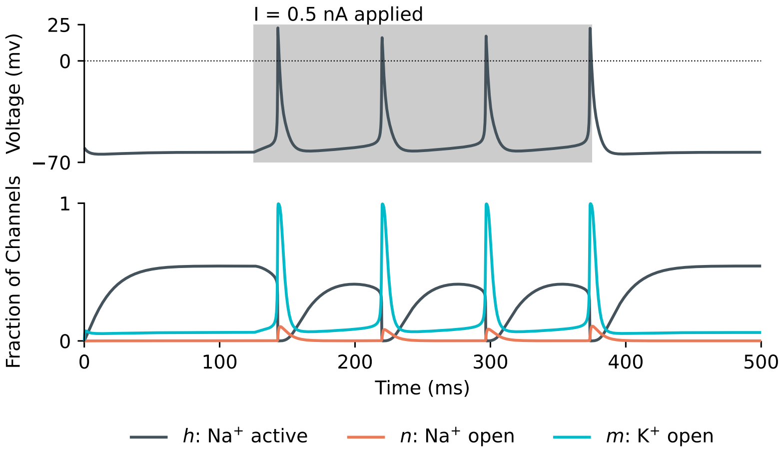




hm^3

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)

Todo: Put online



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$$
\begin{aligned}
RC\dot{v} &= E_\ell - v + RI \quad \leftarrow \text{LIF} \\
C\dot{v} &= \frac{1}{R}(E_\ell - v) + I \\
C\dot{v} &= g_\ell(E_\ell - v) + I \quad \leftarrow \\
C\dot{v} &= g_1(E_1 - v) + g_2(E_2 - v) + \cdots + I \\
C\dot{v} &= g_\ell(E_\ell - v) + \underline{g_\mathrm{K}(t)(E_\mathrm{K} - v)} + \underline{g_\mathrm{Na}(t)(E_\mathrm{Na} - v)} + I \\
g_\mathrm{K}(t) &= \bar{g}_\mathrm{K} n(t)^4 \\
\dot{n} &= \alpha_n(v) \cdot (1 - n) - \beta_n(v) \cdot n \\
g_\mathrm{Na}(t) &= \bar{g}_\mathrm{Na} m(t)^3 h(t) \\
\dot{m} &= \alpha_m(v) \cdot (1 - m) - \beta_m(v) \cdot m \\
\dot{h} &= \alpha_h(v) \cdot (1 - h) - \beta_h(v) \cdot h
\end{aligned}
$$

0 1

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.

? ? m? h?

$$
\begin{aligned}
C\dot{v} &= g_\ell(E_\ell - v) + \bar{g}_\mathrm{K} n^4 (E_\mathrm{K} - v) + \bar{g}_\mathrm{Na} m^3 h (E_\mathrm{Na} - v) + I \\
\dot{n} &= \alpha_n(v)\cdot(1-n) - \beta_n(v)\cdot n \\
\dot{m} &= \alpha_m(v)\cdot(1-m) - \beta_m(v)\cdot m \\
0 = \cancel{\dot{h}} &= \alpha_h(v)\cdot(1-h) - \beta_h(v)\cdot h
\end{aligned}
$$

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 $h_\infty = \lim_{t\to\infty} h(t)$

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.

$$
\begin{aligned}
C\dot{v} &= g_\ell(E_\ell - v) + \bar{g}_{\mathrm{K}} n^4 (E_{\mathrm{K}} - v) + \bar{g}_{\mathrm{Na}} m^3 h (E_{\mathrm{Na}} - v) + I \\
\dot{n} &= \alpha_n(v) \cdot (1 - n) - \beta_n(v) \cdot n \\
\dot{m} &= \alpha_m(v) \cdot (1 - m) - \beta_m(v) \cdot m \\
\dot{h} &= \alpha_h(v) \cdot (1 - h) - \beta_h(v) \cdot h
\end{aligned}
$$

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let $\dot{h} = 0$

$\alpha(1-h) = \beta h_\infty$

$\alpha - \alpha h = \beta h_\infty$

$\alpha = (\alpha + \beta) h_\infty$

$h_\infty = \dfrac{\alpha}{\alpha + \beta}$

$$
\begin{aligned}
C\dot{v} &= g_\ell(E_\ell - v) + \bar{g}_{\mathrm{K}} n^4 (E_{\mathrm{K}} - v) + \bar{g}_{\mathrm{Na}} m^3 h (E_{\mathrm{Na}} - v) + I \\
\dot{n} &= \alpha_n(\cancel{v}) \cdot (1 - n) - \beta_n(\cancel{v}) \cdot n \\
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\dot{h} &= \alpha_h(\cancel{v}) \cdot (1 - h) - \beta_h(\cancel{v}) \cdot h
\end{aligned}
$$

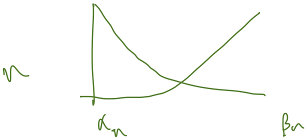
iii. Assume that α_h and β_h are constants. Re-write the differential equation for the sodium gating variable $\dot{h} = \alpha \cdot (1-h) - \beta \cdot h$ in the form $\tau \dot{h} = h_\infty - h$. Give an expression for τ and h_∞ in terms of α_h and β_h.

$h_\infty = \dfrac{\alpha}{\alpha+\beta}$

$0 \longleftrightarrow 1$

$\beta \qquad \alpha$

$\dfrac{\alpha \cdot 1 + \beta \cdot 0}{\alpha+\beta}$



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

$\dot{h} = \alpha - \alpha h - \beta h$

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

$\underbrace{\dfrac{1}{\alpha+\beta}}_{\tau_h} \dot{h} = \underbrace{\dfrac{\alpha}{\alpha+\beta}}_{h_\infty} - h$

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 1^{st}-order linear ODEs in context

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

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