Mathematical Models in Neuroscience

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Outline

Types of Mathematical Models

Mathematical models in neuroscience can be categorized into three types:

- **Mechanistic (physics-type)**
- **Descriptive (statistical)**
- **Interpretive (normative)**

Encyclopedia of Computational Neuroscience [15]

Types of Mathematical Models

Mathematical models in neuroscience can be categorized into three types:

– **Mechanistic (physics-type):**

Aim to find out how properties of the system arise from the physical properties of the underlying parts.

\+ **Descriptive (statistical)**

\+ **Interpretive (normative)**

Encyclopedia of Computational Neuroscience [15]

Types of Mathematical Models

Mathematical models in neuroscience can be categorized into three types:

– **Mechanistic (physics-type):**

How neurons function?
How nervous systems operate on the basis of known anatomy, physiology, and circuitry?

\+ **Descriptive (statistical)**

\+ **Interpretive (normative)**

Theoretical Neuroscience [5]

Types of Mathematical Models

Mathematical models in neuroscience can be categorized into three types:

+ **Mechanistic (physics-type)**
− **Descriptive (statistical):**

  Used to summarize experimental data or encapsulate key properties compactly.

+ **Interpretive (normative)**

Encyclopedia of Computational Neuroscience [15]

Types of Mathematical Models

Mathematical models in neuroscience can be categorized into three types:

+ **Mechanistic (physics-type)**

− **Descriptive (statistical):**

What nervous systems do?

Summarize large amounts of experimental data compactly yet accurately, thereby characterizing what neurons and neural circuits do.

Their primary purpose is to describe phenomena, not to explain them.

+ **Interpretive (normative)**

Theoretical Neuroscience [5]

Types of Mathematical Models

Mathematical models in neuroscience can be categorized into three types:

+ **Mechanistic (physics-type)**
+ **Descriptive (statistical)**
– **Interpretive (normative):**

Aim to model the functional roles of neural systems, for example, relating neuronal responses to the task of processing useful visual information for the animal.

Encyclopedia of Computational Neuroscience [15]

Types of Mathematical Models

Mathematical models in neuroscience can be categorized into three types:

+ **Mechanistic (physics-type)**
+ **Descriptive (statistical)**
− **Interpretive (normative):**

  Why neurons operate in particular ways?
  Use computational and information-theoretic principles to explore the behavioral and cognitive significance of various aspects of nervous system function.

Theoretical Neuroscience [5]

Mechanistic Models

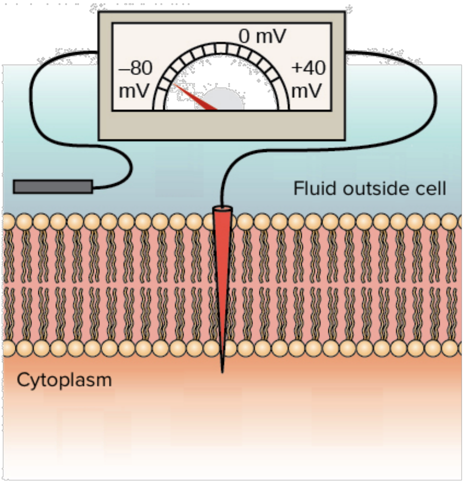
Hodgkin–Huxley Model

Before Development of Hodgkin and Huxley Ideas

It was known that [17]:

- Nerve cells had a low-resistance cytoplasm surrounded by a high-resistance membrane.
- The membrane had an associated electrical capacitance.
- There was an electrical potential difference between the inside and the outside of the cell: **Membrane Potential**

Membrane Potential



Before Development of Hodgkin and Huxley Ideas

Warning!

Until about 1940,
There was no way to measure the membrane potential directly [17].

Before that time, observations of nerve cell activity were made only with **extracellular electrodes**, which are capable of detecting **electrical activity** and **action potentials**, but only provide <u>indirect information</u> about the membrane potential itself [17].

Before Development of Hodgkin and Huxley Ideas

Background works

In 1939, researchers Cole and Curtis [2] used a Wheatstone bridge circuit, typically for measuring resistances, to study the squid giant axon's electrical properties.

Result

During an action potential, membrane conductance temporarily increased, while capacitance remained constant [2].

$\rightarrow$ Supported Bernstein's hypothesis of increased permeability.

Developments of Hodgkin and Huxley Ideas

Starting point: Cole's group at Columbia University 1939 - 1940

1939

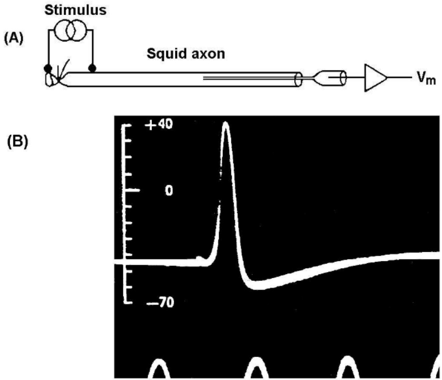
Hodgkin and Curtis almost succeeded in measuring V_m directly by tunneling along the giant axon with a glass micropipette [7].

1940

They found that not only did V_m rise transiently toward zero, but surprisingly, there was a substantial overshoot, such that the membrane potential reversed in sign at the peak of the action potential [4][7]

Developments of Hodgkin and Huxley Ideas

Starting point: Cole's group at Columbia University 1939 - 1940



First direct measurements of membrane potential in squid giant axon [7, 17]

1939 - 1945

Interruption by World War II

1939 - 1945

World War II...

Developments of Hodgkin and Huxley Ideas

1949-1950

- ⋆ Maintain uniform membrane voltage (V_m) for accurate membrane current measurement [1, 16]
- ⋆ Maintain membrane potential at desired voltage level to measure ionic currents [3]

$\Downarrow$

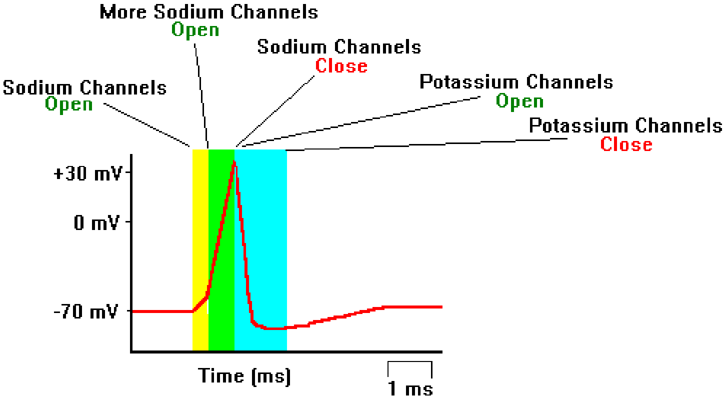
Identifying the individual contributions to I_{ion} from different ion species

Developments of Hodgkin and Huxley Ideas

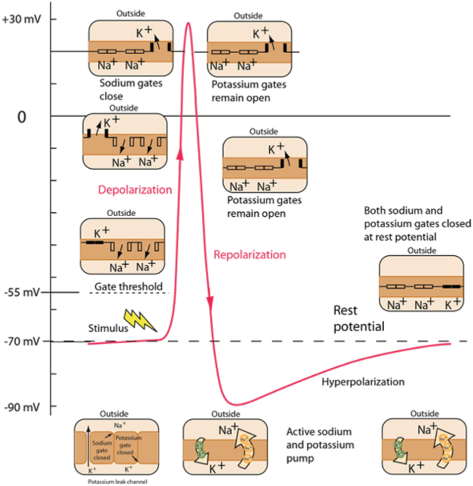
The effect of sodium ions on the electrical activity of the giant axon of the squid

1949 [10]

- ⋆ Showing the importance of both **sodium and potassium** contributions to the ionic current
- ⋆ Explaining why V_m overshoots zero during the action potential
- ⋆ The dependence of action potential amplitude on the <u>concentration of external sodium</u>
- ⋆ the decrease of sodium led to a lower peak for the action potential
- ⋆ The birth of Goldman-Hodgkin-Katz equation: the generalization of the Nernst equation to predict the steadystate potential when the membrane is permeable with different degrees to more than one ionic species.

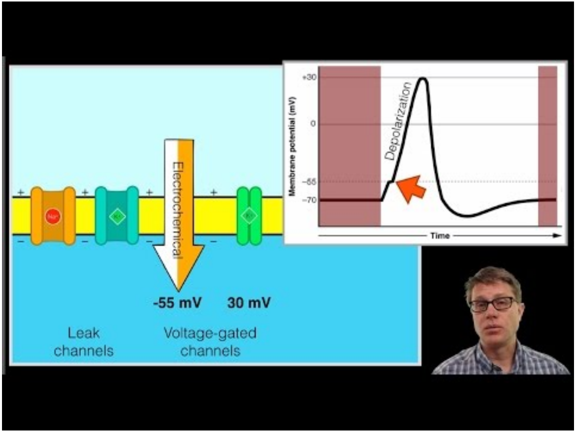


Contribution of Sodium and Potassium channels to Action Potentials



Changing the membrane potential for a giant squid by the Na channels and K channels

Action Potentials - Extra Info



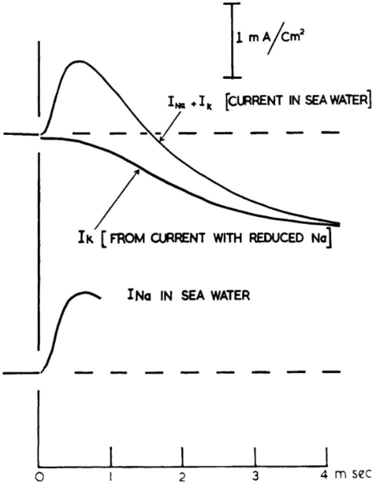
The Action Potential

Developments of Hodgkin and Huxley Ideas

The effect of sodium ions on the electrical activity of the giant axon of the squid

Sodium Hypothesis

V_m would tend to the Nernst potential for the ion to which the membrane was dominantly permeable, and this dominance could change with time [17]



Separation of ionic currents into I_{Na} and I_K [11][8]

Hodgkin and Huxley 1952 Series

1: Measurement of current–voltage relations in the membrane of the giant axon of Loligo [9]

2: Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo [11]

3: The components of membrane conductance in the giant axon of Loligo [12]

4: The dual effect of membrane potential on sodium conductance in the giant axon of Loligo [13]

5: A quantitative description of membrane current and its application to conduction and excitation in nerve [6]

Hodgkin and Huxley 1952 Series

Goal

To determine the laws which govern the movements of ions during electrical activity [9]

Paper 1: Introduction to experimental method, and the behaviour of the membrane in a normal ionic environment. [9]

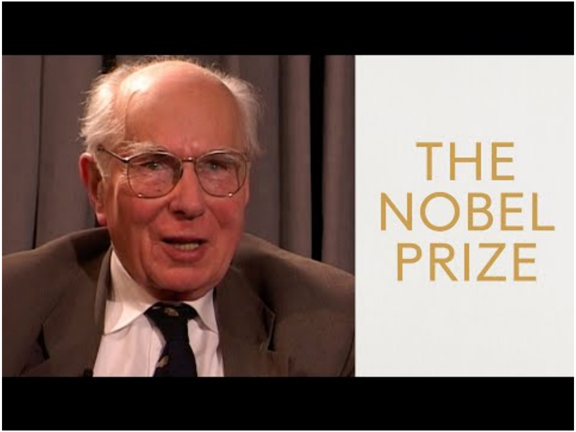
Paper 2: Identified sodium and potassium as the key ions driving the action potential. [11]

Paper 3: Detailed the kinetics of sodium and potassium conductances. [12]

Paper 4: Explained the dual regulation of sodium conductance by membrane potential. [13]

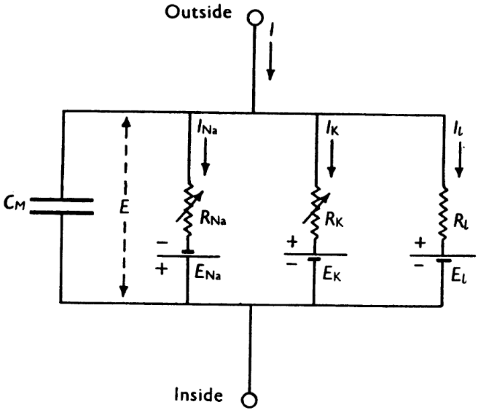
Paper 5: Unified the findings into a mathematical model that remains a cornerstone of neuroscience. [6]

1963 Nobel Prize in Physiology or Medicine



Andrew Huxley, Nobel Prize in Physiology or Medicine 1963: Nobel Prize Interview

Hodgkin and Huxley Model



Electrical circuit representing membrane. [6]

Hodgkin and Huxley Model

- $I = I_{\mathsf{Na}} + I_{\mathsf{K}} + I_{\mathsf{l}} + I_{\mathsf{C}}$
- $E - E_{\mathsf{ion}} = I_{\mathsf{ion}} R_{\mathsf{ion}}$ (Ohm law)
- $C_{\mathsf{M}} = Q/E$
- $I_C = \frac{dQ}{dt} = C_{\mathsf{M}} \frac{dE}{dt}$
- $g = 1/R$ (Ionic conductance)

$$\Rightarrow C_{\mathsf{M}} \frac{dE}{dt} = I - \sum_{\mathsf{ion}} g_{\mathsf{ion}} \left(E - |E_{\mathsf{ion}}|\right)$$

Hodgkin and Huxley Model

$$C_{\mathsf{M}} \frac{dV}{dt} = I - \sum_{\text{ion}} g_{\text{ion}} \left(V - V_{\text{ion}} \right)$$

where $V = E - E_r$, $V_{\text{ion}} = E_{\text{ion}} - E_r$,
and E_r is the absolute value of the resting potential.

Hodgkin and Huxley Model

What is E_{ion}?

Nernst Equation

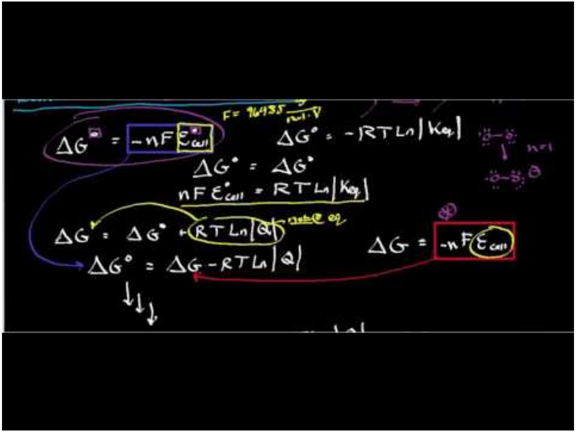
Introduction

- The Nernst equation calculates the equilibrium potential (E_{ion}) for a specific ion across a membrane.
- At equilibrium, the electrical driving force balances the chemical (concentration) gradient.
- Standard form (for monovalent ion at temperature T):

$$E_{\text{ion}} = \frac{RT}{zF} \ln\left(\frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}}\right) \quad \text{or} \quad E_{\text{ion}} = \frac{61.5\,\text{mV}}{z} \log_{10}\left(\frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}}\right)$$

at 37 °C.

Nernst Equation



Nernst Equation: Theory and Derivation

Nernst Equation

Derivation

1: Start from chemical potential difference: $\Delta\mu = RT \ln\left(\frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}}\right)$.

2: At equilibrium, $\Delta\mu = zF\,E_{\text{ion}}$, where z is ion valence.

3: Solve for E_{ion}:

$$E_{\text{ion}} = \frac{RT}{zF} \ln\left(\frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}}\right).$$

4: In physiology, often converted to base-10:

$$E_{\text{ion}} = \frac{2.303\,RT}{zF} \log_{10}\left(\frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}}\right).$$

Nernst Equation

Derivation

1: Main equation:

$$G = H - TS$$

where G is Gibbs free energy, H is enthalpy, T is temperature, and S is entropy.

2: $H = U + PV$ where U is inner energy, P is pressure, and V is volume.

3: First law of thermodynamic: $\Delta U = \Delta Q + \Delta W$ where $\Delta Q = T\Delta S$, $\Delta W = P\Delta V$

4: Ideal Gas Law: $PV = nRT$ where R is gas constant.

$$G = G^{\circ} + \frac{RT}{zF} \ln \left(\frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}} \right)$$

Nernst Equation

In Neuroscience

- Predicts equilibrium (reversal) potential for K^+, Na^+, Cl^-, etc.
- Example: For squid giant axon at 18 °C, $[\mathrm{K}^+]_{\text{out}} = 3\,\text{mM}$, $[\mathrm{K}^+]_{\text{in}} = 120\,\text{mM}$, $E_K \approx -75\,\text{mV}$.
- Limitation: Only valid for one ion at a time and assumes membrane is permeable solely to that ion.

Goldman–Hodgkin–Katz Equation

- The GHK equation extends Nernst to multiple permeant ions:

$$E_r = \frac{RT}{F} \ln \frac{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathsf{out}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathsf{out}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathsf{in}}}{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathsf{in}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathsf{in}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathsf{out}}}$$

- Resting membrane potential (E_r) depends on permeabilities (P_i) and concentrations of Na^+, K^+, Cl^-.

- At physiological temperature (37 °C), coefficient $RT/F \approx 26.7\,\mathrm{mV}$.

Hodgkin and Huxley Model

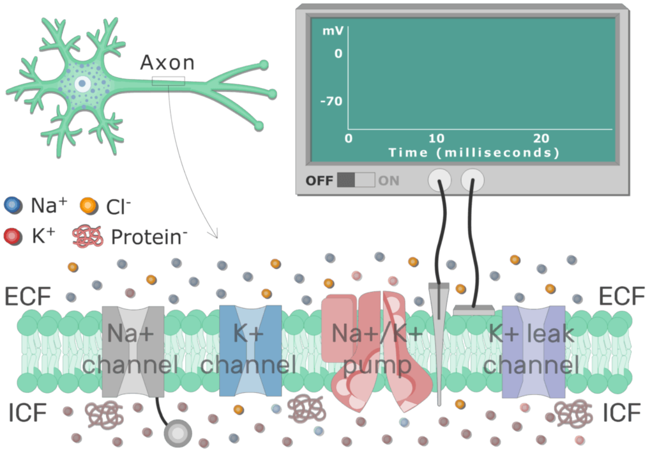
$$C_{\mathsf{M}} \frac{dV}{dt} = I - \sum_{\text{ion}} g_{\text{ion}} \left(V - V_{\text{ion}} \right)$$

where $V = E - E_r$, $V_{\text{ion}} = E_{\text{ion}} - E_r$,
and E_r is the absolute value of the resting potential.

Hodgkin and Huxley Model

What is g_{ion}?

Action Potentials - Extra Info



Hodgkin and Huxley Model

The ionic conductance

Each ion channel can be thought of as containing a small number of physical gates that regulate the flow of ions through the channel. [17]

An individual gate can be in one of two states [17]:

- **Permissive:** When all of the gates for a particular channel are in the permissive state, ions can pass through the channel, and the channel is open.
- **Non-permissive:** If any of the gates are in the non-permissive state, ions cannot flow, and the channel is closed.

Hodgkin and Huxley Model

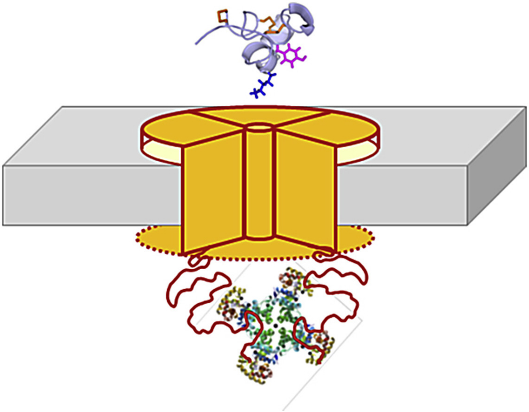
The potassium conductance

$$g_K \sim n^4$$

where n is the probability of a subgates being open. n^4 is the probability of the potassium channel being open.

Hodgkin and Huxley Model

The potassium channel



Assembly of four subunits to form a functional channel [18].

Hodgkin and Huxley Model

The potassium conductance

The permissive subgates can transmit to the non-permissive subgates, so over the period Δt we have

$$\Delta n = (1-n)\alpha_n(V)\Delta t - n\beta_n(V)\Delta t$$

where

- $\alpha_n(V)$ is the rate of transition from non-permissive to permissive.
- $\beta_n(V)$ is the rate of transition from permissive to non-permissive.

Hodgkin and Huxley Model

The potassium conductance

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

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

where $\bar{g}_K$ is the total/maximum conductance of the channels.

Hodgkin and Huxley Model

The potassium conductance

$$g_K = \bar{g}_K \cdot n^4$$
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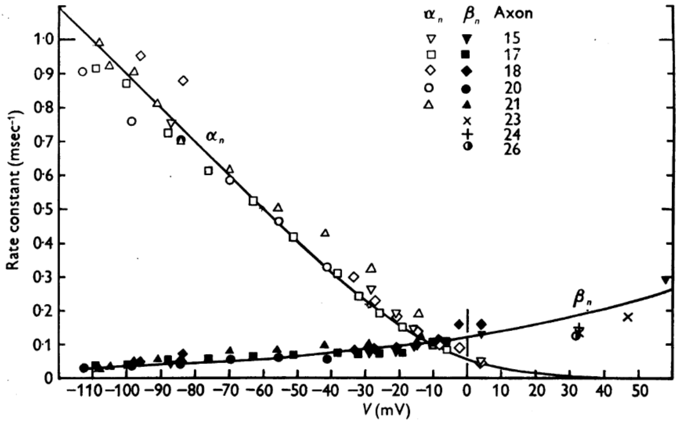
Hodgkin and Huxley Model

The potassium conductance



α_n, β_n vs V [6]

Hodgkin and Huxley Model

The potassium conductance

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

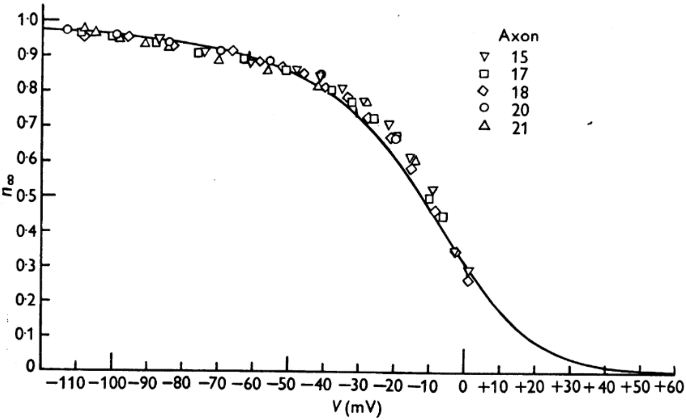
$$\tau_n \frac{dn}{dt} = n_\infty - n$$

where

- $n_\infty = \frac{\alpha_n(V)}{\alpha_n(V)+\beta_n(V)}$ is the equilibrium of the system
- $\tau_n = \frac{1}{\alpha_n(V)+\beta_n(V)}$

Hodgkin and Huxley Model

The potassium conductance



n_∞ vs V [6]

Hodgkin and Huxley Model

The sodium conductance

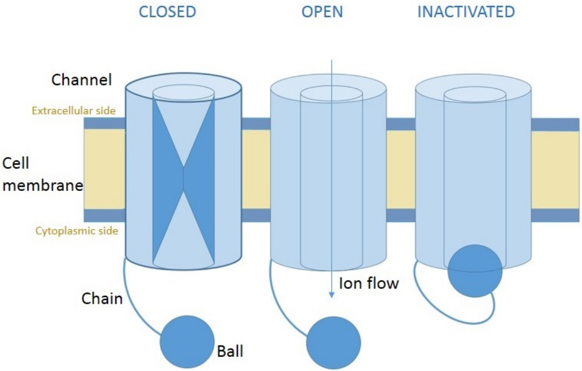
$$g_{Na} = \bar{g}_{Na} \cdot h \cdot m^3$$

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

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

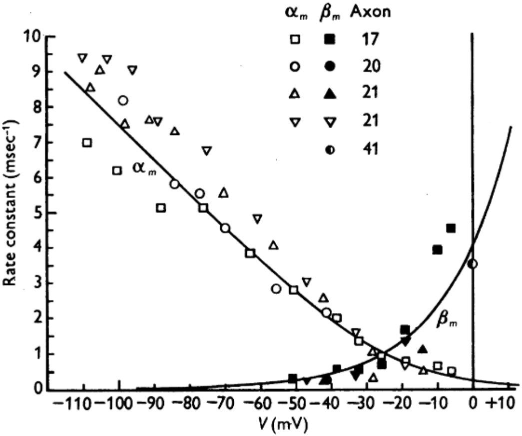
Hodgkin and Huxley Model

The sodium channel



Hodgkin and Huxley Model

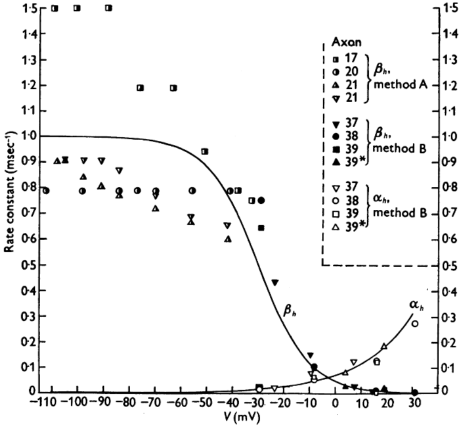
The sodium conductance



α_m, β_m vs V [6]

Hodgkin and Huxley Model

The sodium conductance



α_h, β_h vs V [6]

Hodgkin and Huxley Model

The sodium conductance

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

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

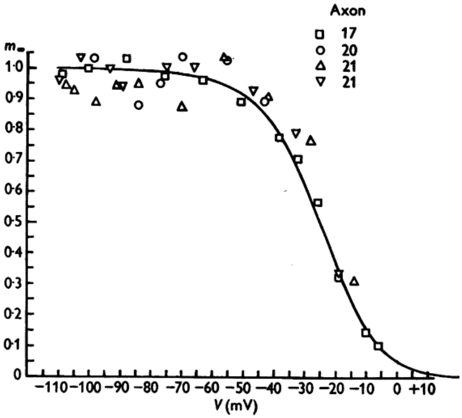
$$\tau_h \frac{dh}{dt} = h_\infty - h$$

where

- $m_\infty = \frac{\alpha_m(V)}{\alpha_m(V)+\beta_m(V)}$ and $h_\infty = \frac{\alpha_h(V)}{\alpha_h(V)+\beta_h(V)}$ is the equilibrium of the system
- $\tau_m = \frac{1}{\alpha_m(V)+\beta_m(V)}$ and $\tau_h = \frac{1}{\alpha_h(V)+\beta_h(V)}$

Hodgkin and Huxley Model

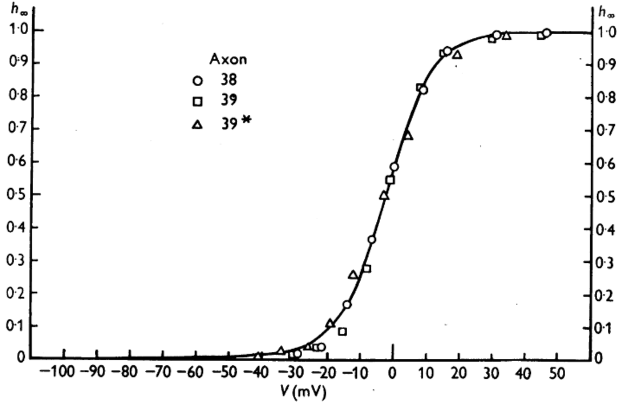
The sodium conductance



m_∞ vs V [6]

Hodgkin and Huxley Model

The sodium conductance



h_∞ vs V [6]

Hodgkin and Huxley Model

All in all

$$C_{\mathsf{M}} \frac{dV}{dt} = I - \sum_{\mathsf{ion}} g_{\mathsf{ion}} \big(V - V_{\mathsf{ion}} \big)$$

where $V = E - E_r$, $V_{\mathsf{ion}} = E_{\mathsf{ion}} - E_r$,
and E_r is the absolute value of the resting potential.

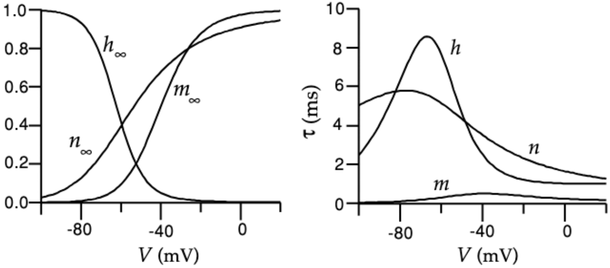
Hodgkin and Huxley Model

All in all

$$\begin{cases} C_{\mathsf{M}} \frac{dV}{dt} & = I - \bar{g}_{\mathsf{K}} \cdot n^4 \left(V - V_{\mathsf{K}}\right) - \bar{g}_{\mathsf{Na}} \cdot h \cdot m^3 \left(V - V_{\mathsf{Na}}\right) - \bar{g}_{\mathsf{l}} \left(V - V_{\mathsf{l}}\right) \\ \tau_n \frac{dn}{dt} & = n_\infty - n \\ \tau_m \frac{dm}{dt} & = m_\infty - m \\ \tau_h \frac{dh}{dt} & = h_\infty - h \end{cases}$$

Hodgkin and Huxley Model

All in all



The voltage-dependent functions of the Hodgkin-Huxley model [5]

Hodgkin and Huxley Model

All in all

$$\begin{cases} C_{\mathsf{M}} \frac{dV}{dt} & = I - \bar{g}_{\mathsf{K}} \cdot n^4 \big(V - V_{\mathsf{K}}\big) - \bar{g}_{\mathsf{Na}} \cdot h \cdot m^3 \big(V - V_{\mathsf{Na}}\big) - \bar{g}_{\mathsf{l}} \big(V - V_{\mathsf{l}}\big) \\ \frac{dn}{dt} & = (1-n)\alpha_n(V) - n\beta_n(V) \\ \frac{dm}{dt} & = (1-m)\alpha_m(V) - m\beta_m(V) \\ \frac{dh}{dt} & = (1-h)\alpha_h(V) - h\beta_h(V) \end{cases}$$

Potassium activation (n):

$$\alpha_n(V) = \frac{0.01(V+10)}{\exp\left(\dfrac{V+10}{10}\right) - 1}, \quad \beta_n(V) = 0.125 \exp\left(\frac{V}{80}\right),$$

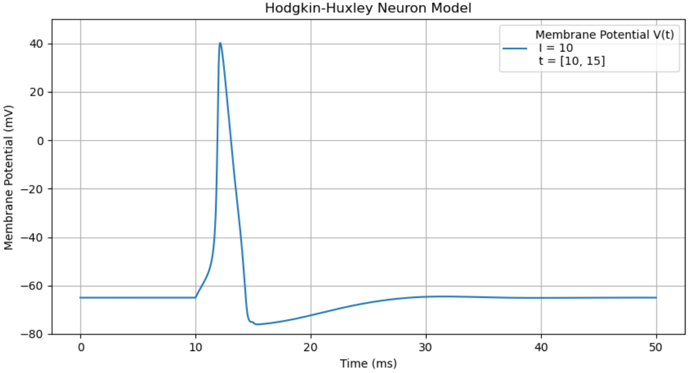
Sodium activation (m):

$$\alpha_m(V) = \frac{0.1(V+25)}{\exp\left(\dfrac{V+25}{10}\right) - 1}, \quad \beta_m(V) = 4 \exp\left(\frac{V}{18}\right),$$

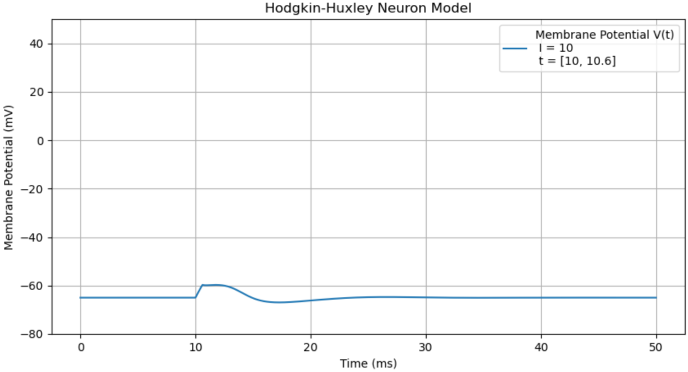
Sodium inactivation (h):

$$\alpha_h(V) = 0.07 \exp\left(\frac{V}{20}\right), \qquad \beta_h(V) = \left[\exp\left(\frac{V+30}{10}\right) + 1\right]^{-1}.$$

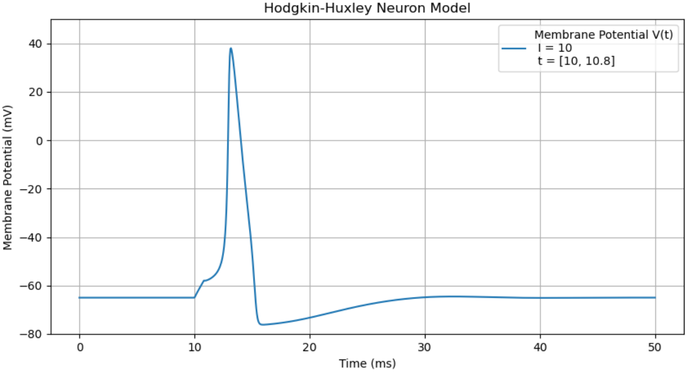
Hodgkin–Huxley Model



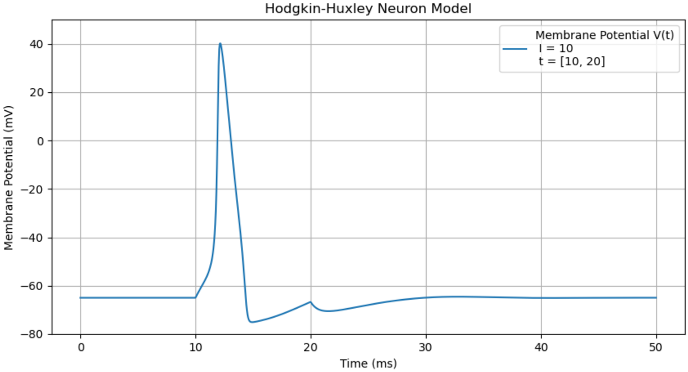
Hodgkin–Huxley Model



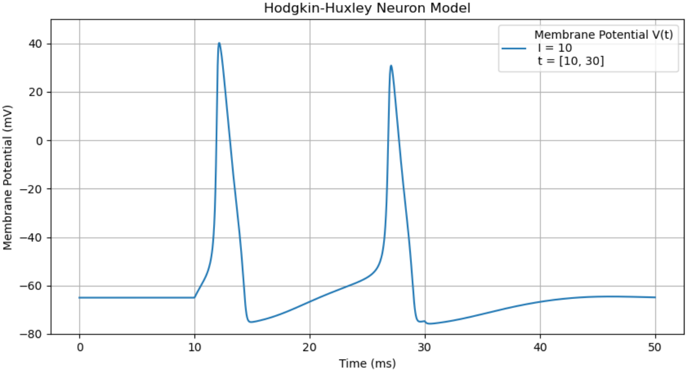
Hodgkin–Huxley Model



Hodgkin–Huxley Model



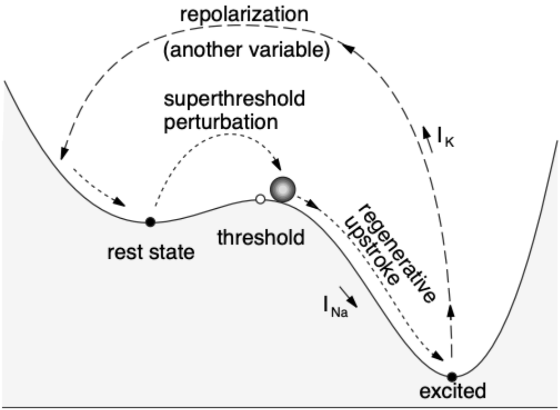
Hodgkin–Huxley Model



Neural Models

Could we simplify our model such that the overall **depolarization-repolarization-hyperpolarization** process stays the same? [14]

Neural Models



Mechanistic illustration of the mechanism of generation of an action potential [14]

Leaky integrate-and-fire model

$$C_M \dot{E} = I - g_{\mathsf{leak}} \left(E - E_{\mathsf{leak}} \right)$$

Leaky integrate-and-fire model

$$\dot{V} = b - V$$

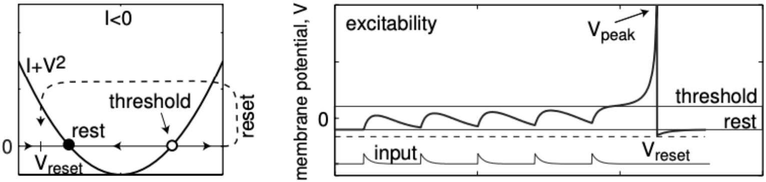
if $V = 1$, then $V \to 0$

Quadratic integrate-and-fire neuron

$$\dot{V} = V^2 - I,$$

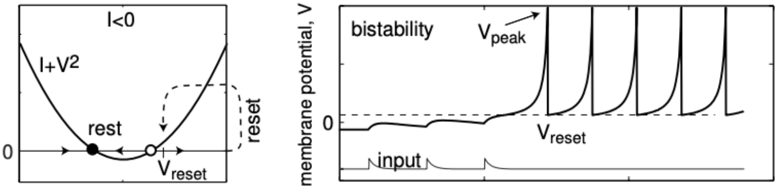
if $V \geq V_{\text{peak}}$ then $V \to V_{\text{rest}}$

Quadratic integrate-and-fire neuron



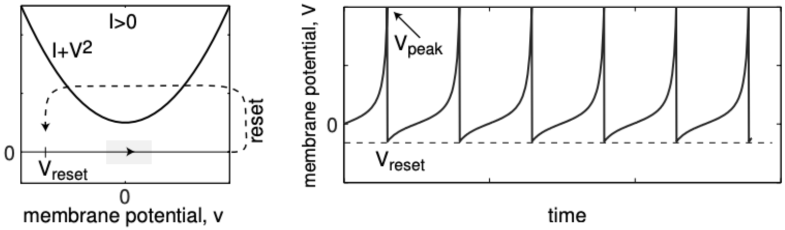
Quadratic integrate-and-fire neuron with time-dependent input. [14]

Quadratic integrate-and-fire neuron



Quadratic integrate-and-fire neuron with time-dependent input. [14]

Quadratic integrate-and-fire neuron



Quadratic integrate-and-fire neuron with time-dependent input. [14]

FitzHugh–Nagumo Model

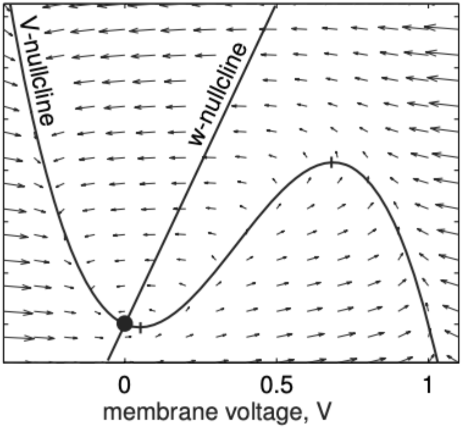
A two-dimensional simplification of Hodgkin–Huxley capturing the essential activation–recovery dynamics of neuronal spikes

FitzHugh–Nagumo Model

$$\dot{V} = I - V(V-1)(V-a) - w$$

$$\dot{w} = bV - cw$$

FitzHugh–Nagumo Model



Phase space of FitzHugh-Nagumo model [14]

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Thank you!