

# Hodgkin and Huxley Model

*Disease: Myotonia & Periodic Paralysis*

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# 1 History

By the early 1900s, scientists knew that nerves transmit electrical signals, but the exact mechanism was unclear.

## 1.1 Julius Bernstein (1902): Membrane Theory

In the resting state, the nerve membrane is mainly permeable to  $K^+$  ions. Inside the neuron, there is a high concentration of  $K^+$  ions and negatively charged proteins, while outside the neuron,  $Na^+$  ions are at a higher concentration. As  $K^+$  ions diffuse outward (down their concentration gradient), a negative potential develops inside the cell, known as the **resting membrane potential**. Mathematically, Bernstein used the **Nernst equation** to relate ionic concentration to membrane potential:

$$E = \frac{RT}{F} \ln \left( \frac{[K^+]_{\text{outside}}}{[K^+]_{\text{inside}}} \right)$$

During excitation, the membrane temporarily loses its selective permeability and becomes leaky to all ions. Thus, the potential drops to zero (since ionic distributions would equalize), leading to the so-called **membrane breakdown hypothesis**.

## 1.2 Cole & Curtis (1939)

1. Cole and Curtis measured the electrical impedance of the squid giant axon and found that during an action potential, membrane resistance ( $R_m$ ) drops sharply.
2. The change was reversible and lasted only during the spike.
3. This gave the first evidence that membrane conductance increases during excitation, though polarity reversal was not directly measured.

Later Cole collaborated with Hodgkin and Huxley and developed the **Voltage Clamp method (1949)** (Later discussed).

## 1.3 Hodgkin & Huxley (1952)

1. In a series of five landmark papers (*Journal of Physiology*, 1952), Hodgkin and Huxley presented a **mathematical model** describing the neuronal membrane as an electrical circuit.
2. They showed that the **action potential** arises from **voltage- and time-dependent changes** in  $Na^+$  and  $K^+$  conductances across the membrane.
3. The membrane potential overshooting zero was first ever recorded by Hodgkin and Huxley, it is the hallmark of the action potential, and it conclusively disproved Bernstein's membrane breakdown theory.

Their work laid the **foundation of modern neuroscience** and they were awarded the **Nobel Prize in Physiology or Medicine (1963)**.

## 2 Electric circuit elements

### 2.1 Ion-channels

Ion Channels ↔ Resistors

Embedded within the neuronal membrane are specialized **protein ion channels** that regulate the flow of specific ions across the membrane. These channels act as *gates* that can open or close in response to various stimuli such as changes in membrane potential. When a channel is **open**, ions can pass freely through it, resulting in **low electrical resistance** or equivalently, **high conductance**. Conversely, when the channel is **closed**, ion flow is restricted, leading to **high resistance** or **low conductance**.

According to Ohm's law,

$$V = IR,$$

where  $V$  is the potential difference across the membrane,  $I$  is the ionic current, and  $R$  is the resistance. Since conductance  $G$  is the reciprocal of resistance ( $G = 1/R$ ), the relationship can be rewritten as

$$I = GV.$$

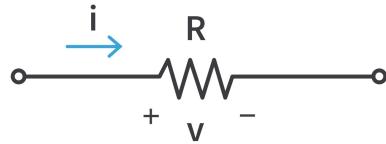


Figure 1.1: Resistor circuit

### 2.2 Membrane

Membrane ↔ Capacitor

The **phospholipid bilayer** forms the basic structure of the cell membrane. The interior of the bilayer is **electrically insulating**, while both the inner (cytoplasmic) and outer (extracellular) surfaces are in contact with **conductive fluids**. As a result, the membrane can store equal and opposite charges on its two sides, effectively functioning as a **capacitor** that stores electrical energy. The **membrane potential** is therefore the potential difference across this capacitor, given by:

$$Q = CV$$

where  $Q$  is the charge stored,  $C$  is the membrane capacitance, and  $V$  is the potential difference across the membrane.

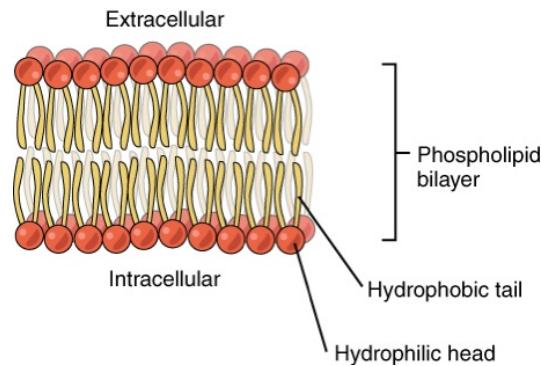


Figure 1.2: Bilayer-membrane

Differentiating the relation  $Q = CV_m$ , we obtain:

$$I_c = C \frac{dV_m}{dt}$$

where  $I_c$  is the **capacitive current**,  $V_m$  is the **membrane potential**, and  $C$  is the **membrane capacitance**.

### What is Capacitive Current?

General Explanation: When positive charges are injected into the cell, the membrane potential changes, leading to a redistribution of charges (or ions) on both sides of the membrane surface. This redistribution gives the appearance of a current "passing through" the membrane, even though no ions actually cross the lipid bilayer itself.

Intuitive Explanation: When we inject a current into a neuron, positive charges accumulate on the inside of the membrane. These repel positive charges on the outer surface, causing a local shift of charges. This rearrangement mimics the behavior of a current flowing through the membrane capacitor.

### Why Inject Current?

To understand neuronal behavior, we often inject current experimentally to mimic how neurons in the brain receive current naturally — either through **synaptic input** from other neurons or in response to **sensory stimuli**.

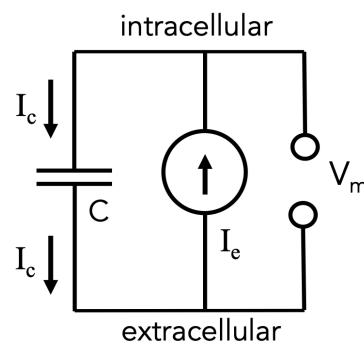


Figure 1.3: Equivalent circuit diagram

### 3 Reversal Potential

#### 3.1 Non-selective pore

In a **non-selective pore**, both positively and negatively charged ions can diffuse across the membrane driven by their concentration gradients. As diffusion continues, the ionic concentrations on both sides of the membrane eventually equalize which is illustrated in the figures below.

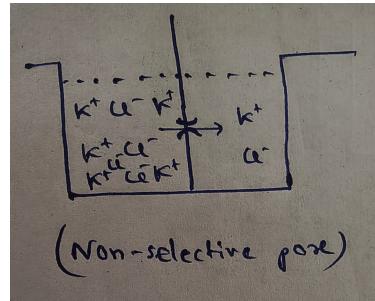


Figure 1.4: Non-selective pore

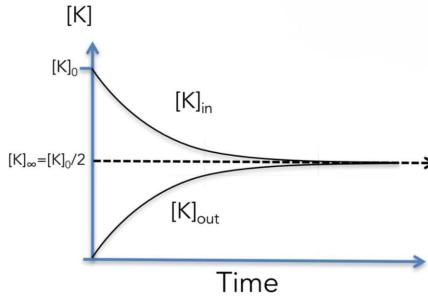


Figure 1.5: Concentration variation with time

#### 3.2 Ion-selective ( $K^+$ ) pore

In a  $K^+$  **ion-selective pore**, only  $K^+$  ions diffuse outward due to the concentration gradient. As a result, positive charge inside the cell decreases and increases outside, leaving behind negatively charged ions inside. This charge separation generates an electrical potential across the membrane. Eventually, the **concentration gradient** driving  $K^+$  outward and the **electrical gradient** pulling it inward balance each other. At this point, net ion movement stops, and an **equilibrium potential**—also known as the **Nernst potential** or **reversal potential**—is established. This process is illustrated in the figures below.

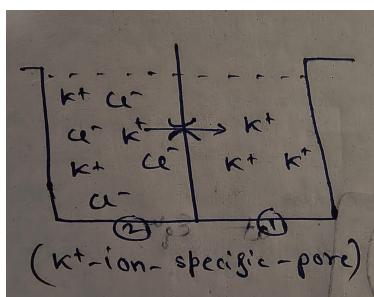


Figure 1.6:  $K^+$  ion-selective pore

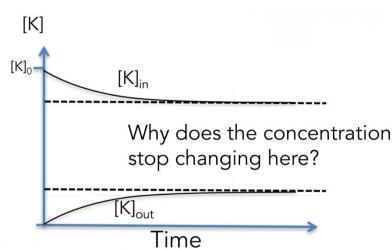


Figure 1.7: Concentration variation with time

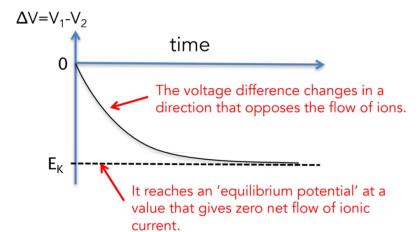


Figure 1.8: Voltage variation with time

## The Nernst Potential

One can use Ohm's law and Fick's first law to derive the **Nernst potential**.

- At this voltage, the drift current in the electric field exactly balances the current due to diffusion.

$$I_{\text{Tot}} = I_{\text{Drift}} + I_{\text{Diffusion}} = 0$$

**Ohm's Law**

**Fick's First Law**

$$I_{\text{Drift}} = \frac{Aq^2\varphi(x)D}{kT} \frac{\Delta V}{L}, \quad I_{\text{Diffusion}} = -AqD \frac{\partial \varphi}{\partial x}$$

Here,  $\varphi(x)$  denotes the **ion concentration function** (i.e., the spatial concentration profile of ions across the membrane).

$$\Delta V = \frac{kT}{q} \ln \left( \frac{\varphi_{\text{out}}}{\varphi_{\text{in}}} \right) \quad \text{at equilibrium.}$$

**Thus, Neurons have batteries!**

↪ Where does this battery come from?

- Ion concentration gradient
- Ion-selective pores/channels

Ion	Cytoplasm (mM)	Extracellular (mM)	Nernst (mV)
K <sup>+</sup>	400	20	-75
Na <sup>+</sup>	50	440	+55
Cl <sup>-</sup>	52	560	-59
Ca <sup>++</sup>	10 <sup>-4</sup>	2	+124

Figure 1.9: Nernst potential data table

## 4 Modeling ion-selective ( $K^+$ ) pore

Let us model the  $K^+$  channel only. The channel can be represented as a **resistor** in parallel with an **intrinsic battery** associated with it, corresponding to the **reversal (Nernst) potential**.

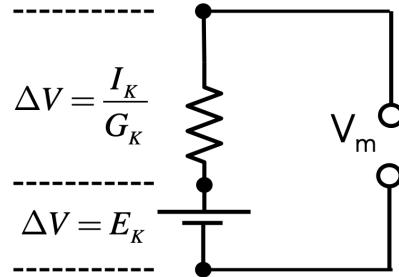


Figure 1.10: Equivalent circuit diagram

From the equivalent circuit diagram, we can write:

$$\Delta V_{(\text{across resistor})} + E_K = V_m$$

Using Ohm's law,

$$\Delta V_{(\text{across resistor})} = \frac{I_K}{G_K}$$

where  $I_K$  is the potassium current and  $G_K$  is the potassium conductance.

Substituting this into the first equation, we get:

$$I_K = G_K(V_m - E_K)$$

$$I_K = G_K \underbrace{(V_m - E_K)}_{\text{Driving Potential}}$$

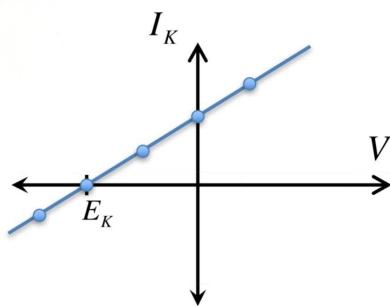


Figure 1.11: I-V curve for the above circuit

### Physical Interpretation:

- If the membrane potential is held **above equilibrium** ( $V_m > E_K$ ),  $K^+$  ions flow **outward**, producing a **positive current**.
- If the membrane potential is held **below equilibrium** ( $V_m < E_K$ ),  $K^+$  ions flow **inward**, resulting in a **negative current**.

## 5 Simple Model

In this simple model, we will consider only the membrane and a K<sup>+</sup> ion-selective channel to examine what happens when an external current is injected. The equivalent circuit is shown below.

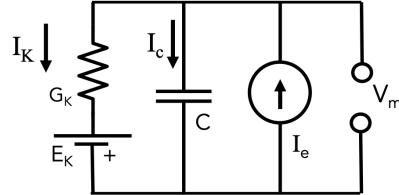


Figure 1.12: Equivalent circuit for the simple model

From the equivalent circuit, we can write (by applying Kirchhoff's current law):

$$I_K + I_C = I_e$$

where  $I_K$  is the potassium ionic current,  $I_C$  is the capacitive current, and  $I_e$  is the externally injected current.

Using the previously derived expressions, we substitute directly:

$$\frac{(V_m - E_K)}{R_K} + C \frac{dV_m}{dt} = I_e$$

Multiplying through by  $R_K$  and simplifying:

$$V_m + R_K C \frac{dV_m}{dt} = E_K + R_K I_e$$

At steady state ( $t \rightarrow \infty$ ), the membrane potential becomes constant, hence:

$$\frac{dV_m}{dt} = 0 \quad \Rightarrow \quad V_m = E_K + R_K I_e = V_\infty$$

Thus, the governing differential equation can be written as:

$$V_m + \tau \frac{dV_m}{dt} = V_\infty$$

where

$$V_\infty = E_K + R_K I_e \quad \text{and} \quad \tau = \underbrace{R_K C}_{\text{dimension of time}}$$

Finally, rearranging gives:

$$\frac{dV_m}{dt} = -\frac{1}{\tau} (V_m - V_\infty)$$

If the injected current  $I_e$  is **constant in time**, then the steady-state potential  $V_\infty$  is also constant in time.

$$\frac{dV_m}{dt} = -\frac{1}{\tau}(V_m - V_\infty)$$

Rewriting,

$$\frac{d}{dt}(V_m - V_\infty) = -\frac{1}{\tau}(V_m - V_\infty)$$

Integrating both sides:

$$\int_{V_0}^{V_m(t)} \frac{d(V_m - V_\infty)}{(V_m - V_\infty)} = \int_0^t -\frac{1}{\tau} dt$$

Simplifying, we get:

$$\ln \left( \frac{V_m(t) - V_\infty}{V_0 - V_\infty} \right) = -\frac{t}{\tau}$$

Exponentiating both sides gives:

$$V_m(t) - V_\infty = (V_0 - V_\infty)e^{-t/\tau}$$

Hence, the time evolution of the membrane potential is:

$$V_m(t) = V_\infty + (V_0 - V_\infty)e^{-t/\tau}$$

Now, let us inject a constant current and observe the behavior of the membrane potential by plotting the graph for the derived equation.

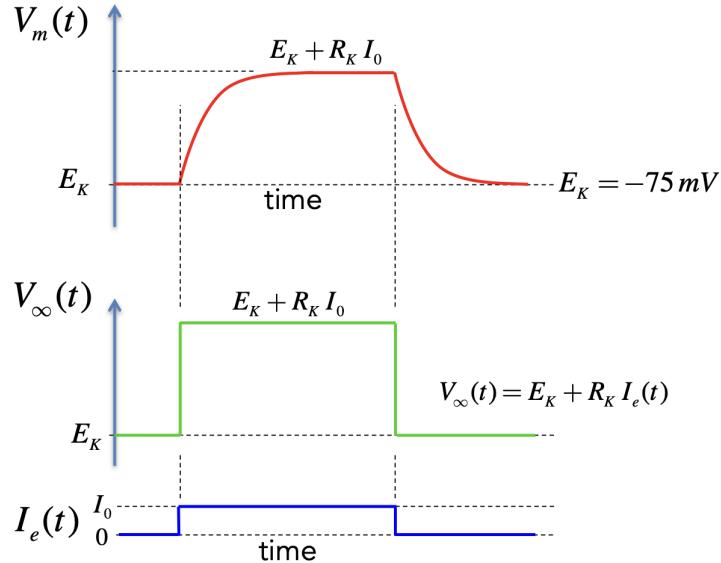


Figure 1.13: Response of membrane potential to a constant injected current.

### Important Points:

- **Resting potential (at  $I_e = 0$ ):**  $V_{\text{rest}} = E_K$
- **Steady-state potential (at  $t \rightarrow \infty$ ):**  $V_{\text{steady}} = E_K + R_K I_e = V_\infty$

### Theoretical Interpretation:

- At  $I_e = 0$ :  $V_m = E_K$

At rest, the **diffusive force** (arising from the concentration gradient that drives K<sup>+</sup> outward) is exactly balanced by the **electrical force** (arising from the membrane potential that pulls K<sup>+</sup> inward).

- At  $I_e = I_0$  and  $t \rightarrow \infty$ :

- Injecting K<sup>+</sup> increases the intracellular K<sup>+</sup> concentration, making the **electrical force** stronger than the **diffusive force**.
- As a result, K<sup>+</sup> ions begin to flow outward through the membrane until a new equilibrium is reached.
- Eventually, the two forces balance again, but at a shifted potential where the magnitudes of the opposing forces are different from their original resting values.

Thus, the new equilibrium occurs at a different steady-state voltage, and the system settles at a new membrane potential:

$$V_{\text{new}} = E_K + R_K I_e = V_\infty$$

This shift represents the **steady-state depolarization** caused by the injected current, where the balance between electrical and diffusive forces is re-established at a new potential.

## 6 Hodgkin and Huxley(HH) Model

### 6.1 Introduction

Working at Cambridge with the **squid giant axon**, they inserted a microelectrode inside the axon. Using the voltage-clamp technique, Hodgkin and Huxley were able to hold the membrane at fixed voltages and measure ionic currents directly. achieving the first **direct intracellular recording** of membrane potential.

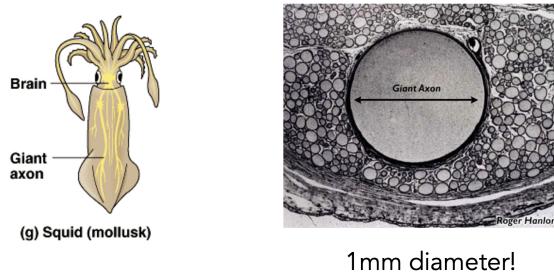


Figure 1.14: Left: squid, Right: squid giant axon with diameter 1mm

- From these experiments, they inferred:
  - There must be separate sodium ( $\text{Na}^+$ ) and potassium ( $\text{K}^+$ ) conductances.
  - Each conductance depends on both voltage and time.
  - The  $\text{Na}^+$  conductance activates rapidly and then inactivates even if the depolarization continues.
  - The  $\text{K}^+$  conductance activates more slowly and does not inactivate in the same way.
- They modeled these processes using gating variables ( $m$ ,  $h$ , and  $n$ ), which served as the mathematical forerunners of the open, closed, and inactivated states discussed in modern channel theory.

#### Note :

- The concept of discrete ion channels with physical gates emerged later, in the 1970s–1980s, through the development of the patch-clamp technique by Neher and Sakmann (Nobel Prize, 1991).
- These experiments provided direct evidence that ion channels “flicker” between open and closed states, thereby confirming what Hodgkin and Huxley had mathematically inferred decades earlier.

## 6.2 Voltage Clamp Technique

One straightforward approach to study membrane conductance is to apply a desired voltage across a giant axon and measure the corresponding current. Repeating this process for multiple voltage values allows us to calculate the conductance for each case. Plotting **conductance vs. voltage** and fitting the resulting curve helps us determine an empirical equation that models the conductance as a function of voltage.

However, this simple method faces a major problem: as soon as the potential is applied, the membrane rapidly depolarizes and generates an **action potential**, thereby altering the membrane potential almost immediately (typically, the time interval between two action potentials is about 1 ms). This makes it difficult to maintain a constant membrane potential long enough to measure steady-state currents.

To overcome this issue, **Kenneth Cole** collaborated with **Alan Hodgkin** and **Andrew Huxley** in 1949 to develop the **voltage clamp technique**. A simplified schematic of the setup is shown below for conceptual understanding.

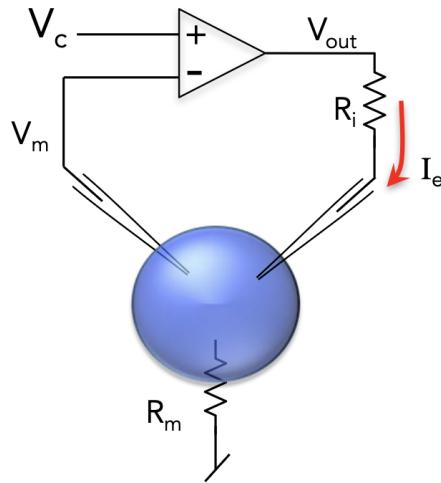


Figure 1.15: Schematic representation of the voltage clamp setup.

In this setup, the **voltage clamp** maintains the membrane potential at any desired **command voltage**  $V_c$ . The core of the system is an **operational amplifier**, which amplifies the difference between the command voltage  $V_c$  and the actual membrane potential  $V_m$  by a gain factor  $G$ , producing an output voltage  $V_{out}$ .

- If  $V_m < V_c$ , then  $V_{out} \gg 0$ . The amplifier injects a positive current  $I_e$ , causing  $V_m$  to rise toward  $V_c$ .
- If  $V_m > V_c$ , then  $V_{out} \ll 0$ . The amplifier drives a negative  $I_e$ , pulling  $V_m$  down toward  $V_c$ .

This forms a **negative feedback loop** that continuously adjusts  $I_e$  to ensure that

$$V_m \rightarrow V_c.$$

Hence, the membrane potential is effectively clamped at the desired value.

With  $V_m$  held constant, we can now accurately measure the **ionic current** corresponding to each  $V_c$ .

### 6.3 Separation of Ionic Currents and Conductance Measurement

From the voltage clamp experiment, when the membrane potential is switched from  $-65$  mV to  $-9$  mV, a clear variation in the total ionic current is observed. It was already known that the intracellular concentration of  $K^+$  ions is much larger, whereas the extracellular concentration of  $Na^+$  is much larger. Therefore, the total ionic current can be considered as the sum of three components:

$$I_{\text{total}} = I_{\text{Na}} + I_{\text{K}} + I_{\text{L}},$$

where  $I_{\text{Na}}$  and  $I_{\text{K}}$  are the currents carried by sodium and potassium ions, respectively, and  $I_{\text{L}}$  is a small leakage current mainly due to chloride and other minor ions.

To isolate the individual ionic components, **Hodgkin and Huxley** removed sodium ions by immersing the squid giant axon segment in a **choline chloride** solution, which replaces external  $Na^+$  with impermeable choline ions. Under this condition, any measured ionic current primarily arises from  $K^+$  ions. By subtracting this potassium-only current from the total current recorded under normal conditions, the sodium current can be obtained.

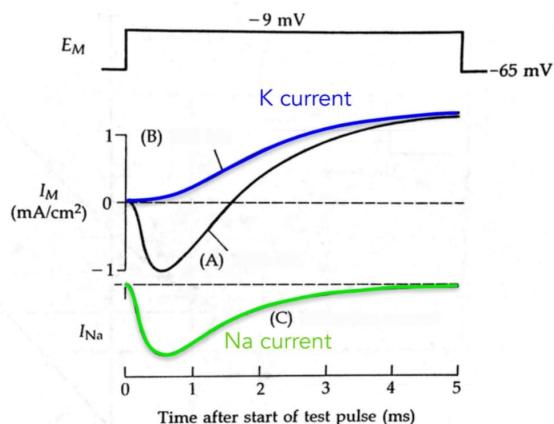
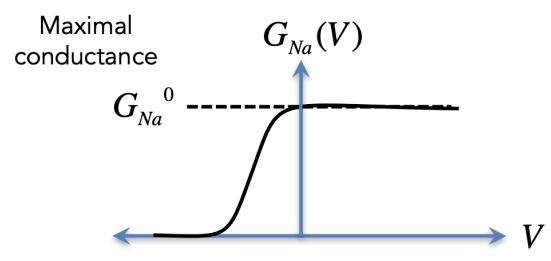
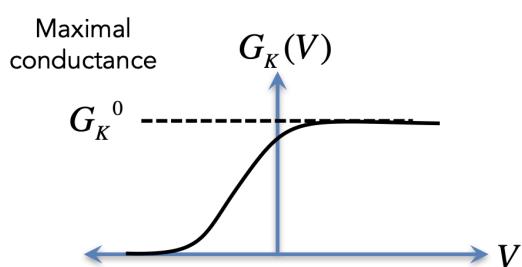
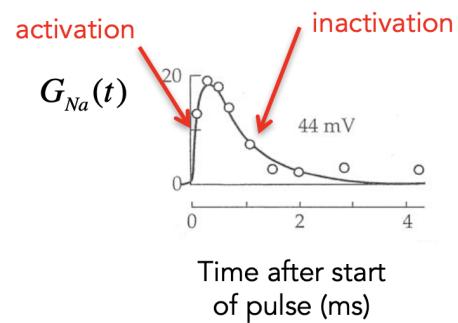
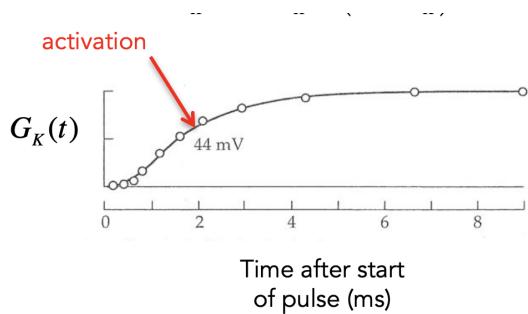


Figure 1.16: Isolation of sodium and potassium currents using the voltage clamp technique.  
 (A) is ionic current, (B) is K current and (C) is Na current

Having separated the two ionic components, Hodgkin and Huxley measured the **current–time response** for various clamped voltages for both  $Na^+$  and  $K^+$  ions. From these recordings:

- The **peak current** at each voltage was extracted.
- The corresponding **conductance values** were calculated using Ohm's law.

Thus, the variations of  $K^+$  conductance ( $G_K$ ) and  $Na^+$  conductance ( $G_{\text{Na}}$ ) with both **membrane voltage** and **time** were obtained experimentally, as illustrated below.



Finally, with this experimental data in hand, Hodgkin and Huxley proceeded to derive an **empirical model** describing how conductance varies with voltage and time.

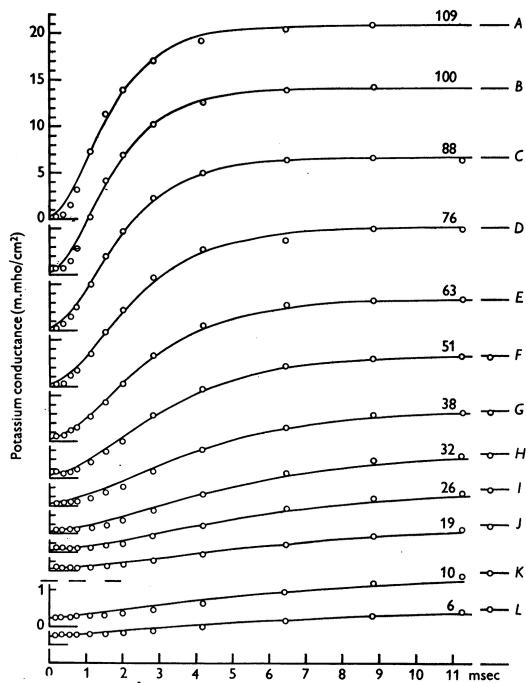


Fig. 3. Rise of potassium conductance associated with different depolarizations. The circles are experimental points obtained on axon 17, temperature 6–7°C, using observations in sea water and choline sea water (see Hodgkin & Huxley, 1952a). The smooth curves were drawn from eqn. (11) with  $g_{K0}=0.24$  m.mho/cm<sup>2</sup> and other parameters as shown in Table 1. The time scale applies to all records. The ordinate scale is the same in the upper ten curves (A to J) and is increased fourfold in the lower two curves (K and L). The number on each curve gives the depolarization in mV.

Figure 1.21: From Original Paper: Potassium conductance with time for different potentials.

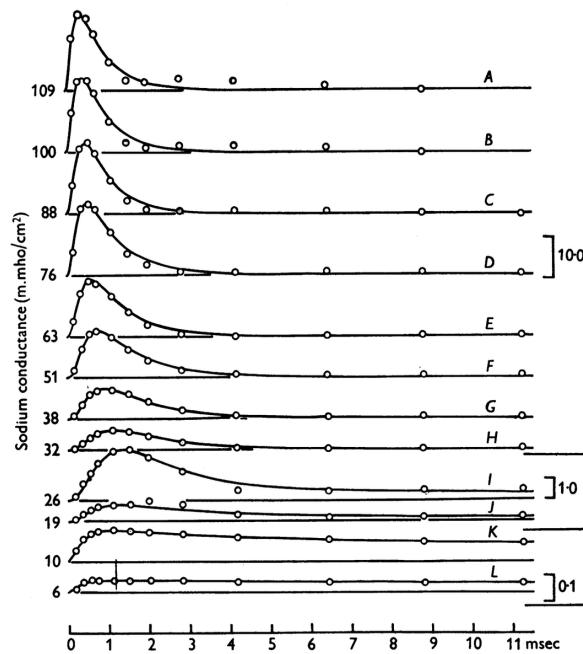


Fig. 6. Changes of sodium conductance associated with different depolarizations. The circles are experimental estimates of sodium conductance obtained on axon 17, temperature 6–7°C (cf. Fig. 3). The smooth curves are theoretical curves with parameters shown in Table 2; A to H drawn from eqn. 19, I to L from 14, 17, 18 with  $\bar{g}_{Na}=70.7$  m.mho/cm<sup>2</sup>. The ordinate scales on the right are given in m.mho/cm<sup>2</sup>. The numbers on the left show the depolarization in mV. The time scale applies to all curves.

Figure 1.22: From original paper: Sodium conductance with time for different potentials.

## 6.4 Time and Voltage dependence of $K^+$ channel

### Introduction to the Gating Variable

Individual ion channels are either **open** or **closed**. The total conductance through a membrane is given by the total number of open channels times the conductance of a single ion channel.

$P_K$  = probability of being 'open'

$N_K$  = total number of ion channels

$\hat{g}_K$  = unitary conductance

Thus, the total number of open ion channels =  $P_K N_K$

The total potassium conductance is then:

$$G_K = P_K(V, t)N_K\hat{g}_K$$

*All of the interesting time and voltage dependence arises from  $P_K(V, t)$ .*

### Properties of the $K^+$ Channel

The  $K^+$  channel exhibits the following properties:

- The pore of a  $K^+$  channel is formed by four identical subunits.
- Each subunit contains a voltage sensor and a gate that regulates the channel's open or closed state.
- Each subunit can exist in one of two states: *open* or *closed*.

*Note:* In the original Hodgkin–Huxley model, the assumption of four identical and independent subunits was introduced empirically to best fit the experimental data. Remarkably, later structural studies confirmed that real  $K^+$  channels indeed consist of four homologous subunits.

Let  $n$  denote the probability that a single subunit is open. For the entire channel to be permeable, all four subunits must simultaneously be in the open state.

Assuming independence among subunits, the probability that all four are open is:

$$P_K = n^4$$

Hence, the total  $K^+$  conductance becomes:

$$G_K = \bar{G}_K n^4$$

where  $\bar{G}_K$  is the maximal (fully open) conductance.

Finally, the  $K^+$  current can be written as:

$$I_K = \bar{G}_K n^4 (V - E_K)$$

$I_K = \bar{G}_K n^4 (V - E_K)$

Hodgkin and Huxley referred to  $n$  as the **gating variable** for the potassium current.

## Voltage dependence of Gating Variable

From the Graph of  $G_k$  with  $V_m$ , we can sketch the model for the  $K^+$  channel as below,

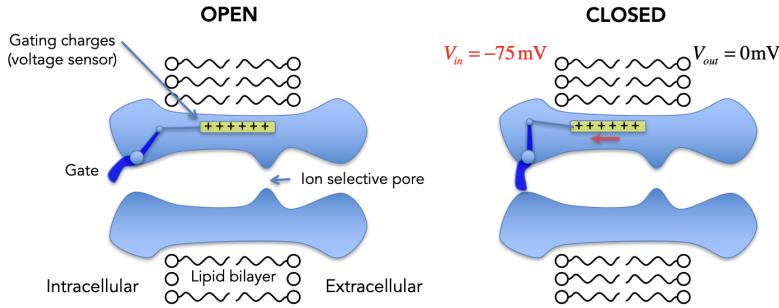


Figure 1.23:  $K^+$  channel model

At 0 mV, the gating charges in the channel protein experience no net electrical force that would favor closure — so the “gate” remains open and allows ions to pass freely.

The flickering mentioned means the channel is constantly fluctuating due to thermal energy  $kT$ , but the probability is strongly biased toward the open configuration.

When  $V_m$  becomes negative, these positive gating charges are pulled inward — stabilizing the closed conformation.

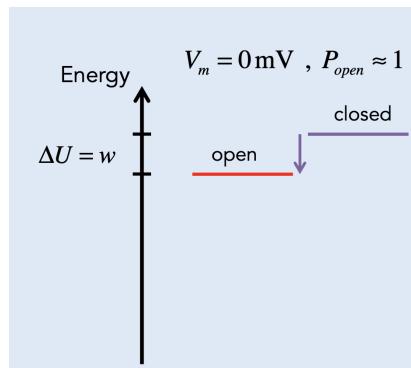


Figure 1.24: At depolarized potential ( $V_m = 0 \text{ mV}$ ), the energy of the open state is lower than the closed state ( $U_{\text{open}} < U_{\text{closed}}$ ), hence the channel prefers to be open.

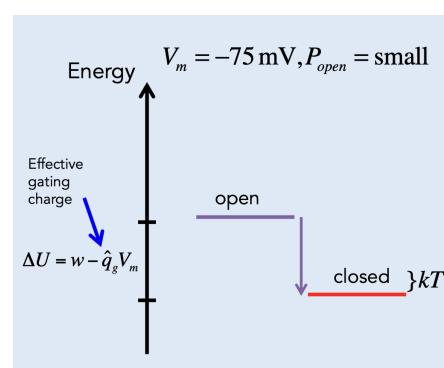


Figure 1.25: At hyperpolarized potential ( $V_m = -75 \text{ mV}$ ), the energy of the open state becomes higher than the closed state ( $U_{\text{open}} > U_{\text{closed}}$ ), and the channel remains closed.

From **Boltzmann relation**, The probability of being in either state(open or closed) depends on the energy difference between the two states.

$$\frac{P_{\text{open}}}{P_{\text{closed}}} = e^{-\frac{U_{\text{open}} - U_{\text{closed}}}{kT}} = e^{-\frac{(w - qgV_m)}{kT}}$$

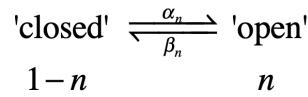
$$n = P_{\text{open}} = \frac{1}{1 + \frac{P_{\text{closed}}}{P_{\text{open}}}} = \frac{1}{1 + e^{\frac{(w - q_g V_m)}{kT}}}$$

$$n = \frac{1}{1 + e^{\frac{(w - q_g V_m)}{kT}}}$$

Here,  $w$  represents the intrinsic energy difference between the open and closed states at zero membrane potential, and  $q_g$  is the effective gating charge that senses the membrane voltage  $V_m$ . On fitting this equation with the experimental data we can estimate the value of  $w$  and  $q_g$ .

### Time dependence of Gating Variable

Let us consider that the membrane potential  $V_m$  is changed such that it favors the transition of a subunit from the closed state to the open state. Although the voltage change instantaneously alters the probability of a subunit being open, the physical process of conformational rearrangement takes a finite time. Therefore, we describe the time evolution of the probability  $n(t)$ , which represents the fraction of open subunits, by a first-order kinetic model.



Here,

- $\alpha_n(V_m)$ : rate constant for transition from closed to open state,
- $\beta_n(V_m)$ : rate constant for transition from open to closed state,
- $n$ : probability that a subunit is in the open state,
- $1 - n$ : probability that a subunit is in the closed state.

Note: No. of open subunits is  $(1)n$  and No. of closed subunit is  $(1)(1 - n)$

The change in the number of open subunits per unit time can be expressed as:

$$\frac{dn}{dt} = (\text{rate of opening}) - (\text{rate of closing})$$

Thus,

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

Expanding the expression, we get:

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

At steady state ( $\frac{dn}{dt} = 0$ ), the fraction of open subunits is given by:

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}$$

where  $n_\infty$  represents the steady-state (voltage-dependent) open probability.

We can also define a time constant  $\tau_n$ , which determines how fast the variable  $n(t)$  approaches its steady-state value:

$$\tau_n = \frac{1}{\alpha_n + \beta_n}$$

Using these definitions, the original equation can be rewritten in a compact form:

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

or equivalently,

$$\frac{dn}{dt} = -\frac{1}{\tau_n(V_m)}(n(t) - n_\infty(V_m))$$

Both  $n_\infty$  and  $\tau_n$  are voltage-dependent quantities, as the transition rates  $\alpha_n$  and  $\beta_n$  themselves depend on the membrane potential  $V_m$ .

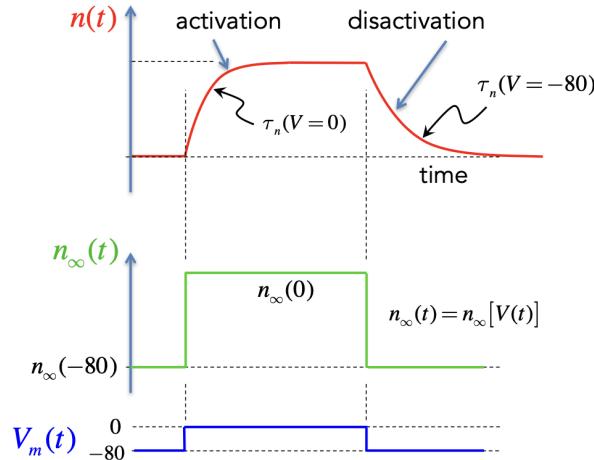


Figure 1.26: for a constant  $V_m$ , variation of  $K^+$  gating variable ( $n$ ) and it's steady state value

### Rate constant's Empirical expressions

Since the experimental graph of  $G_K(t)$  versus time fitted best with the relation  $G_K \propto [n(t)]^4$ , Hodgkin and Huxley proposed that the potassium channel is composed of four identical and independent subunits. They determined the corresponding rate constants empirically from voltage-clamp experiments. For each membrane potential,  $n_\infty(V)$  and  $\tau_n(V)$  were obtained by fitting the time course of the potassium conductance. Using the relations

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}, \quad \tau_n = \frac{1}{\alpha_n + \beta_n},$$

the rate constants  $\alpha_n(V)$  and  $\beta_n(V)$  were then calculated for each voltage. By fitting these experimentally derived values, Hodgkin and Huxley obtained the following empirical expressions:

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

where, Potential  $V$  in  $mV$  and  $\alpha_n, \beta_n$  in  $ms^{-1}$

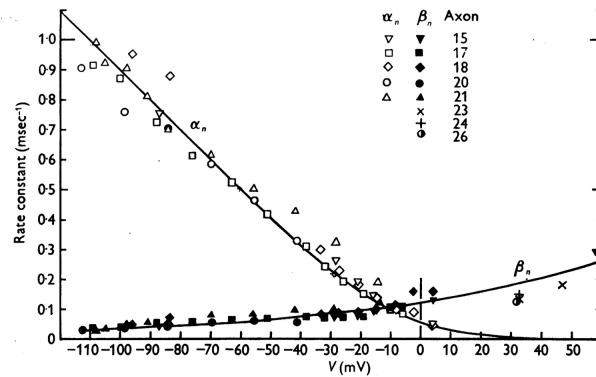


Fig. 4. Abscissa: membrane potential minus resting potential in sea water. Ordinate: rate constants determining rise ( $\alpha_n$ ) or fall ( $\beta_n$ ) of potassium conductance at 6°C. The resting potential was assumed to be 4 mV higher in choline sea water than in ordinary sea water. Temperature differences were allowed for by assuming a  $Q_{10}$  of 3. All values for  $V < 0$  were obtained by the method illustrated by Fig. 3 and Table 1; those for  $V > 0$  were obtained from the decline of potassium conductance associated with an increase of membrane potential or from repolarization to the resting potential in choline sea water (e.g. Fig. 2). Axons 17–21 at 6–11°C, the remainder at about 20°C. The smooth curves were drawn from eqns. (12) and (13).

Figure 1.27: From Original paper: Rate constant,  $\alpha_n$  and  $\beta_n$  variation with different clamped Voltages

## Flow of Calculation

At a given membrane potential  $V = V_0$ :

1. Evaluate the rate constants  $\alpha_n(V_0)$  and  $\beta_n(V_0)$  using their empirical expressions.
2. Compute the steady-state value and time constant:

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}, \quad \tau_n = \frac{1}{\alpha_n + \beta_n}.$$

3. Determine the time evolution of the gating variable  $n(t)$ :

$$n(t) = n_\infty - [n_\infty - n(0)]e^{-t/\tau_n}.$$

4. Calculate the potassium conductance:

$$G_K(t) = \bar{G}_K[n(t)]^4.$$

5. Finally, obtain the potassium current:

$$I_K(t) = G_K(t)(V - E_K).$$

## 6.5 Time and Voltage dependence of $\text{Na}^+$ channel

### Introducing Gating Variables of $\text{Na}^+$ Channel

The  $\text{Na}^+$  channel can be understood similarly to the  $\text{K}^+$  channel, except that it includes an additional *inactivation* process.

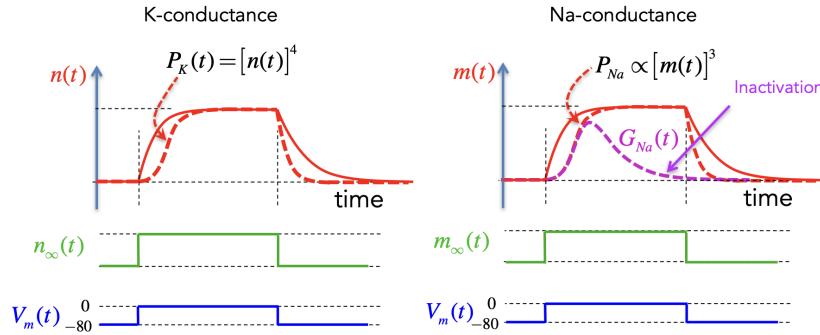


Figure 1.28: Comparison between the  $\text{K}^+$  and  $\text{Na}^+$  channel conductances. The variable  $n(t)$  represents the gating variable for  $\text{K}^+$  channels, while  $m(t)$  is the activation gating variables for  $\text{Na}^+$  channels, respectively.

To account for this, Hodgkin and Huxley introduced another gating variable  $h$ , known as the inactivation gating variable. Thus, the sodium channel conductance is modeled as

$$P_{\text{Na}} = m^3 h,$$

where  $m$  is the activation gating variable and  $h$  is the inactivation gating variable. The cubic term ( $m^3$ ) arises because experimental data show that three activation gates are required to fit the activation kinetics accurately.

### Activation Gating Variable

From the  $\text{K}^+$  channel analogy, the gating dynamics for  $m$  are given by

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

where

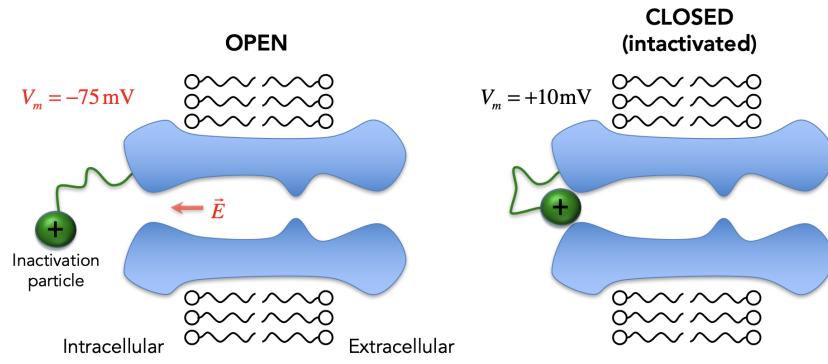
$$\tau_m = \frac{1}{\alpha_m + \beta_m}, \quad m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}.$$

The empirical rate constants obtained from voltage-clamp experiments are

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

### Inactivation Gating Variable

The inactivation process of the  $\text{Na}^+$  channel is represented by the gating variable  $h$ , which decreases over time following depolarization, thereby reducing the  $\text{Na}^+$  conductance even when the activation variable  $m$  remains high. The schematic below illustrates this inactivation mechanism.

Figure 1.29:  $\text{Na}^+$  channel model.

The inactivation gating variable  $h$  follows a similar kinetic equation:

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

where

$$\tau_h = \frac{1}{\alpha_h + \beta_h}, \quad h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}.$$

The corresponding empirical rate constants are

$$\alpha_h = 0.07 \exp\left(\frac{V}{20}\right), \quad \beta_h = \frac{1}{\exp\left(\frac{V+30}{10}\right) + 1}.$$

## Flow of Calculations

- For  $V = V_0$ , evaluate  $\alpha_m$ ,  $\beta_m$ ,  $\alpha_h$ , and  $\beta_h$ .
- Determine steady-state and time constant values:

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \quad h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}$$

$$\tau_m = \frac{1}{\alpha_m + \beta_m}, \quad \tau_h = \frac{1}{\alpha_h + \beta_h}$$

- Solve for  $m(t)$  and  $h(t)$  at  $V = V_0$  using:

$$\tau_m \frac{dm}{dt} = m_\infty - m, \quad \tau_h \frac{dh}{dt} = h_\infty - h$$

- Compute sodium conductance:

$$G_{\text{Na}}(t) = \bar{G}_{\text{Na}} m^3 h$$

- Determine sodium current:

$$I_{\text{Na}} = G_{\text{Na}}(t) (V - E_{\text{Na}})$$

## 6.6 HH Model for Action potential generation

The Hodgkin–Huxley (HH) model describes the time evolution of the membrane potential  $V(t)$  in terms of ionic currents through voltage-gated ion channels.

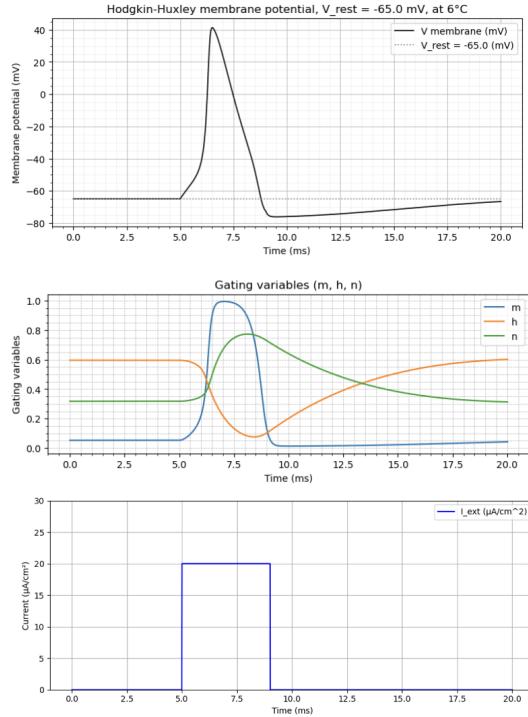


Figure 1.30: Typical action potential generated using the HH model code.

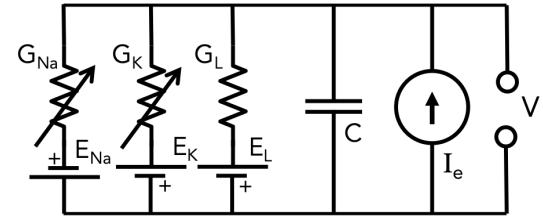


Figure 1.31: Equivalent electrical circuit representing the HH model.

### 1. Membrane Equation

$$C_m \frac{dV}{dt} = I_{\text{ext}} - \underbrace{(I_{\text{Na}} + I_{\text{K}} + I_{\text{L}})}_{\text{Membrane current } (I_m)}$$

where

- $C_m$  — membrane capacitance per unit area ( $\approx 1 \mu\text{F}/\text{cm}^2$ )
- $I_{\text{ext}}$  — externally applied current density ( $\mu\text{A}/\text{cm}^2$ )
- $I_{\text{Na}}, I_{\text{K}}, I_{\text{L}}$  — sodium, potassium, and leakage current densities ( $\mu\text{A}/\text{cm}^2$ )

### 2. Ionic Currents

$$I_{\text{Na}} = G_{\text{Na}}(V - E_{\text{Na}}), \quad I_{\text{K}} = G_{\text{K}}(V - E_{\text{K}}), \quad I_{\text{L}} = G_{\text{L}}(V - E_{\text{L}})$$

where

- $G_{\text{Na}}, G_{\text{K}}, G_{\text{L}}$  — conductances per unit area ( $\text{mS}/\text{cm}^2$ )
- $E_{\text{Na}}, E_{\text{K}}, E_{\text{L}}$  — reversal potentials (mV)

### 3. Voltage-dependent Conductances

$$G_{\text{Na}} = \bar{G}_{\text{Na}} m^3 h, \quad G_{\text{K}} = \bar{G}_{\text{K}} n^4, \quad G_{\text{L}} = \bar{G}_{\text{L}}$$

where

- $\bar{G}_{\text{Na}}, \bar{G}_{\text{K}}, \bar{G}_{\text{L}}$  — maximum conductances ( $\bar{G}_{\text{Na}} = 120, \bar{G}_{\text{K}} = 36, \bar{G}_{\text{L}} = 0.3 \text{ mS/cm}^2$ )
- $m, h, \text{ and } n$  — gating variables (dimensionless, between 0 and 1)

### 4. Gating Variable Dynamics

Each gating variable  $x = m, h, n$  follows:

$$\frac{dx}{dt} = \alpha_x(V)[1 - x] - \beta_x(V)x$$

or equivalently,

$$\tau_x \frac{dx}{dt} = x_\infty - x$$

where

$$x_\infty = \frac{\alpha_x}{\alpha_x + \beta_x}, \quad \tau_x = \frac{1}{\alpha_x + \beta_x}$$

and  $\tau_x$  has units of ms.

### 5. Empirical Rate Constants (at 6.3°C)

For Potassium ( $\text{K}^+$ ) activation variable  $n$ :

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

For Sodium ( $\text{Na}^+$ ) activation variable  $m$ :

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

For Sodium ( $\text{Na}^+$ ) inactivation variable  $h$ :

$$\alpha_h = 0.07 \exp\left(\frac{V}{20}\right), \quad \beta_h = \frac{1}{\exp\left(\frac{V+30}{10}\right) + 1}$$

where membrane potential  $V$  is measured in mV.

### 6. Typical Parameters

- $E_{\text{Na}} = -115 \text{ mV}$
- $E_{\text{K}} = +12 \text{ mV}$
- $E_{\text{L}} = -10.613 \text{ mV}$
- $C_m = 1 \mu\text{F}/\text{cm}^2$

## 7. Final Expression for Membrane Potential Dynamics

$$C_m \frac{dV}{dt} = I_{\text{ext}} - \bar{G}_{\text{Na}} m^3 h (V - E_{\text{Na}}) - \bar{G}_{\text{K}} n^4 (V - E_{\text{K}}) - \bar{G}_{\text{L}} (V - E_{\text{L}})$$

### Units Summary:

$$\begin{aligned} V &: \text{mV}, & t &: \text{ms}, & C_m &: \mu\text{F}/\text{cm}^2, \\ G_x &: \text{mS}/\text{cm}^2, & I_x &: \mu\text{A}/\text{cm}^2, & x = m, h, n &: \text{dimensionless} \end{aligned}$$

### Note:

Modified empirical formula of rate constants (at 6.3°C):

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

$$\beta_n(V) = 0.125 \exp(-(V + 65)/80),$$

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

$$\beta_m(V) = 4 \exp(-(V + 65)/18),$$

$$\alpha_h(V) = 0.07 \exp(-(V + 65)/20),$$

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

The “modern” Hodgkin–Huxley empirical formulas differ from the original 1952 paper only because we now express membrane voltage relative to the external medium (65 mV at rest) rather than relative to the resting potential (0 mV) considered in the paper.

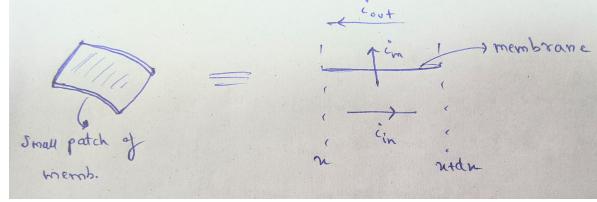
This change introduces:

1. A voltage offset (+65 mV) in all arguments, and
2. A sign flip in exponential terms (since the direction of voltage change is redefined).

The underlying kinetics, time constants, and steady-state gating behaviors remain identical.

## 6.7 HH model for Action potential propagation

- $i_{in}$  : Membrane current per unit length along the fiber,  
 $r_1$  : External (extracellular) resistance per unit length along the fiber,  
 $r_2$  : Internal (axial) resistance per unit length along the fiber,  
 $x$  : Distance along the fiber.



Inside the fiber:

since current is propagating down the axon, thus we can write the equation,

$$\begin{aligned} V(x) - V(x + dx) &= (r_2 dx) i_{in} \\ \frac{V(x + dx) - V(x)}{dx} &= -r_2 i_{in} \\ \frac{\partial V_{in}}{\partial x} &= -r_2 i_{in} \end{aligned}$$

similarly, Outside the fiber:

$$\frac{\partial V_{out}}{\partial x} = +r_1 i_{out}$$

Total potential difference:

$$\begin{aligned} V &= V_{in} - V_{out} \\ \frac{\partial V}{\partial x} &= \frac{\partial V_{in}}{\partial x} - \frac{\partial V_{out}}{\partial x} = -r_2 i_{in} - r_1 i_{out} \\ \boxed{\frac{\partial^2 V}{\partial x^2} = -r_2 \frac{\partial i_{in}}{\partial x} - r_1 \frac{\partial i_{out}}{\partial x}} &\quad (\text{Eq. } \textcircled{1}) \end{aligned}$$

Inside the fiber,

$$i(x) - i(x + dx) = i_m dx$$

as *current loss* equal to the current leaving through the membrane. Hence,

$$\frac{i(x + dx) - i(x)}{dx} = -i_m \Rightarrow \frac{\partial i_{in}}{\partial x} = -i_m$$

Similarly, for the outside medium,

$$\frac{\partial i_{out}}{\partial x} = -i_m$$

as *current gain* corresponds to the current entering through the membrane.  
Substituting these relations into Eq. (1), we obtain

$$\frac{\partial^2 V}{\partial x^2} = (r_1 + r_2) i_m$$

or,

$$i_m = \frac{1}{(r_1 + r_2)} \frac{\partial^2 V}{\partial x^2}$$

Since the extracellular medium has very high conductivity, we can neglect  $r_1$  with respect to  $r_2$ . Thus, the equation simplifies to:

$$i_m = \frac{1}{r_2} \frac{\partial^2 V}{\partial x^2}$$

By definition,

$$i_m = \frac{I}{dx}$$

Multiplying and dividing by the membrane circumference  $2\pi a$ , we get

$$i_m = \frac{I}{dx} \left( \frac{2\pi a}{2\pi a} \right)$$

where  $I_m$  is the *membrane current density* (current per unit membrane area) leaving radially through the cylindrical surface. Thus,

$$i_m = I_m (2\pi a)$$

From the earlier relation,

$$i_m = \frac{1}{r_2} \frac{\partial^2 V}{\partial x^2}$$

we obtain

$$I_m (2\pi a) = \frac{1}{r_2} \frac{\partial^2 V}{\partial x^2}$$

or,

$$I_m = \frac{1}{r_2 (2\pi a)} \frac{\partial^2 V}{\partial x^2}$$

Since the internal resistance per unit length is related to the specific resistance  $R$  by

$$r_2 = \frac{R}{\pi a^2},$$

we can write

$$I_m = \frac{a}{2R} \frac{\partial^2 V}{\partial x^2}$$

$$I_m = \frac{a}{2R} \frac{\partial^2 V}{\partial x^2}$$

where

- $I_m$ : Membrane current density ( $\text{A}/\text{cm}^2$ ),
- $a$ : Axon radius ( $\text{cm}$ ),
- $R$ : Specific resistance of the axoplasm ( $\Omega \cdot \text{cm}$ ).

Since the action potential propagates along the axon without changing its shape, the membrane potential  $V(x, t)$  can be described as a traveling wave. Hence, the spatial and temporal variations of  $V$  are related by the wave equation:

$$\frac{\partial^2 V}{\partial x^2} = \frac{1}{\theta^2} \frac{\partial^2 V}{\partial t^2},$$

where  $\theta$  is the *velocity of propagation* of the action potential.

Substituting this into the earlier expression for the membrane current density,

$$I_m = \frac{a}{2R} \frac{\partial^2 V}{\partial x^2},$$

we obtain

$$I_m = \frac{a}{2R\theta^2} \frac{\partial^2 V}{\partial t^2}.$$

Now, the total current balance across the membrane is given by

$$I_m = C_m \frac{dV}{dt} + I_K + I_{Na} + I_L,$$

which leads to the following ordinary differential equation for the membrane potential:

$$\frac{a}{2R\theta^2} \frac{d^2 V}{dt^2} = C_m \frac{dV}{dt} + I_K + I_{Na} + I_L$$

This equation represents the dynamic balance of membrane currents during the propagation of an action potential.

### Note:

The derived ODE not only models the voltage dynamics of the axon membrane but also allows one to compute the propagation velocity ( $\theta$ ) of the action potential. By numerically solving this equation under realistic biophysical parameters such as  $C_m$ ,  $R$ ,  $a$ ,  $I_K$ ,  $I_{Na}$ , and  $I_L$ , one can determine the value of  $\theta$ , the *velocity of action potential propagation* along the axon.

## 7 Modeling Disease

We will use the Hodgkin–Huxley (HH) model to simulate the effects of defective voltage-gated  $\text{Na}^+$  channel inactivation, which is implicated in certain inherited muscle disorders such as *Myotonia* and *Hyperkalemic Periodic Paralysis (HPP)*.

### 7.1 Intro to Disease – Myotonia & Hyperkalemic Periodic Paralysis

Myotonia and Hyperkalemic Periodic Paralysis are **autosomal dominant** disorders caused by mutations in the **SCN4A** gene, which encodes the skeletal muscle  $\text{Na}^+$  channel. These mutations lead to a defect in channel inactivation—specifically, a slowed or incomplete inactivation of a fraction of  $\text{Na}^+$  channels. As a result, persistent inward sodium currents can occur, altering the excitability of muscle fibers.

#### Clinical Manifestations:

In **Myotonia**, the defective inactivation of  $\text{Na}^+$  channels results in prolonged depolarization of muscle fibers after stimulation. This causes delayed relaxation following voluntary contraction, leading to symptoms such as muscle stiffness, difficulty in initiating movement, and delayed relaxation after gripping or blinking.

In contrast, **Hyperkalemic Periodic Paralysis (HPP)** is characterized by episodes of muscle weakness or transient paralysis, often triggered by elevated serum potassium levels, rest after exercise, or ingestion of potassium-rich food. During these attacks, sustained depolarization leads to inexcitability of muscle fibers.

#### Experimental Evidence:

To investigate whether defective inactivation alone is sufficient to reproduce the symptoms of Myotonia and HPP, researchers have applied ATX-II toxin (derived from sea anemone) to rat muscle fibers. ATX-II selectively disrupts  $\text{Na}^+$  channel inactivation. It was observed that at approximately 10  $\mu\text{M}$  concentration, the toxin produced a persistent  $\text{Na}^+$  current of about 1.2–2%, closely matching the activity levels seen in patients.



Figure 1.32: Sea Anemone

## 7.2 Model development

### Two-Compartment Model for Skeletal Muscle

**Assumption 01:** The internal resistance of the muscle fiber is assumed to be zero.

**Meaning:** The fiber is *space-clamped*, meaning there is no potential difference along its length and therefore no physical propagation of the action potential. This assumption is justified because previous studies have shown that action potential propagation properties remain largely unchanged between normal and myotonic muscle fibers, making this simplification reasonable for analysis.

**Note:** Experimental evidence also indicates that Myotonia, under various conditions—such as exposure to ATX-II toxin or reduced chloride conductance (as observed in myotonic goats)—is strongly influenced by the function of the **T-tubule** system. Thus, to accurately capture the behavior of skeletal muscle, it is essential to include the T-tubule dynamics in the model.

**Assumption 02:** The T-tubule membrane is space-clamped radially.

**Meaning:** Each T-tubule connected to a unit area of the surface membrane can be represented as a single electrical compartment characterized by a uniform potential  $V_T$ . This allows the T-tubule system to be modeled as a distinct compartment that interacts with the surface membrane through capacitive and resistive coupling, **forming the basis of the two-compartment model**.

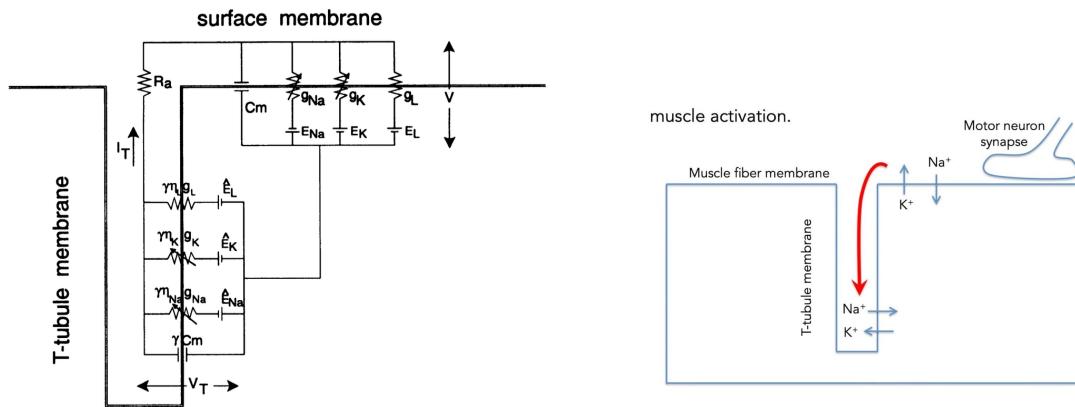


Figure 1.33: Equivalent circuit diagram of the two-compartment model.  
**(From Original Paper)**

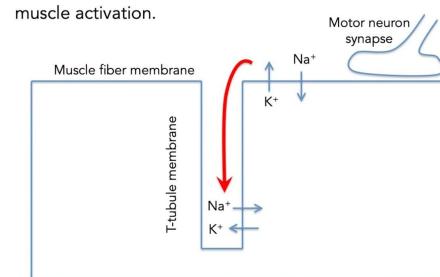


Figure 1.34: Schematic representation of the coupling between surface and T-tubule membranes.

## Surface Membrane Current Balance Equation

$$I_m = I_C + I_{\text{ionic}} + I_t$$

Where:

- $I_m$  : Total membrane current per unit surface area
- $I_C$  : Capacitive current per unit area
- $I_{\text{ionic}}$  : Sum of ionic currents ( $I_{Na}$ ,  $I_K$ ,  $I_{Cl}$ , etc.) per unit area
- $I_t$  : Current entering or leaving the T-tubule system per unit area

Let,

$$I_t = \frac{V - V_t}{R_a}$$

Where:

- $V$  : Surface membrane potential
- $V_t$  : T-tubular membrane potential

If the surface membrane potential ( $V$ ) and T-tubule potential ( $V_t$ ) differ, a current flows between them through the coupling resistance  $R_a$  (representing the resistance at the mouth of the T-tubule,  $R_a \approx 150 \Omega \text{ cm}^2$ ).

**Therefore**, the equation describing the time evolution of the surface membrane voltage can be written as:

$$I_m = C \frac{dV}{dt} + I_{\text{ionic}} + \frac{V - V_t}{R_a}$$

## T-tubular Membrane Current Balance Equation

$$\frac{V - V_t}{R_a} = \gamma \left( C \frac{dV_t}{dt} + I_{\text{ionic},t} \right)$$

Where:

- $V$  : Surface membrane potential
- $V_t$  : T-tubular membrane potential
- $R_a$  : Access resistance between the surface and T-tubule membranes
- $C$  : Membrane capacitance per unit area
- $\gamma$  : Ratio of T-tubule membrane area to surface membrane area

Typically,

$$\gamma \approx 4.8$$

**Assumption (3):** Voltage-gated ionic channels in the T-tubule and surface membrane have the same *kinetics* and *conductance properties*, but the *density of ion channels* is not necessarily identical.

$I_{\text{ionic}}$  includes the contributions from the leaky,  $K^+$ , and  $Na^+$  currents, where the ionic conductances are approximated by the classical **Hodgkin–Huxley (HH) model equations**. Hence, the total ionic current per unit area is given by:

$$I_{\text{ionic}} = g_K(V - E_K) + g_{Na}(V - E_{Na}) + g_L(V - E_L)$$

The conductances and reversal potentials are expressed as:

$$\begin{aligned} g_{Na} &= \bar{g}_{Na}m^3h, \\ g_K &= \bar{g}_Kn^4, \\ E_{Na} &= \frac{RT}{F} \ln \left( \frac{[Na^+]_o}{[Na^+]_i} \right), \\ E_K &= \frac{RT}{F} \ln \left( \frac{[K^+]_o}{[K^+]_i} \right), \\ E_L &= \frac{RT}{F} \ln \left( \frac{[K^+]_o + 0.01[Na^+]_o}{[K^+]_i} \right) \end{aligned}$$

**Note:** Although  $E_L$  is written in a form resembling a  $K^+$  reversal potential, the true resting potential in mammalian skeletal muscle fibers is primarily determined by  $Cl^-$  permeability. This expression is used here mainly as a mathematical approximation to reproduce the correct resting-slope conductance behavior.

### T-tubular Membrane Ionic Current

$$I_{\text{ionic},t} = \eta_L g_L(V_t - \hat{E}_L) + \eta_K g_K(V_t - \hat{E}_K) + \eta_{Na} g_{Na}(V_t - \hat{E}_{Na})$$

Here,  $\eta$  denotes the ratio of T-tubule to surface channel density:

- $\eta_L$  : Ratio of leak channel density
- $\eta_K$  : Ratio of potassium channel density
- $\eta_{Na}$  : Ratio of sodium channel density

**Note:** In the **surface membrane**,  $[K^+]_o$  and  $[K^+]_i$  are considered nearly constant due to the large extracellular and intracellular volumes. In contrast, in the **T-tubule membrane**,  $[K^+]_i$  remains approximately constant, but  $[K^+]_o$  is confined within the narrow T-tubule lumen and can therefore vary dynamically during muscle activity. Consequently,  $[K^+]_t$  can deviate from  $[K^+]_o$ , causing dynamic changes in the local  $K^+$  reversal potential and influencing membrane excitability.

## Modified Sodium Current for Defective Inactivation

$$I_{Na} = (1 - f) \bar{g}_{Na} m^3 h(V - E_{Na}) + f \bar{g}_{Na} m^3 (1)(V - E_{Na})$$

where:

- $f = 0$  : Normal muscle (all  $\text{Na}^+$  channels inactivate properly)
- $0 \leq f \leq 1$  : Fraction of non-inactivating  $\text{Na}^+$  channels, proportional to inactivation defect

To account for the sodium current with defective inactivation, we simply replace

$$g_{Na} = \bar{g}_{Na} m^3 h \quad \longrightarrow \quad g_{Na} = \bar{g}_{Na} [(1 - f)m^3 h + f m^3 (1)],$$

## Modeling accumulation of $\text{K}^+$ in the T-tubule

The model treats the T-tubule as a small extracellular compartment where potassium concentration  $[K^+]_t$  can change dynamically. Potassium entering the T-tubule through voltage-gated  $\text{K}^+$  channels (and a small fraction of leak current) increases  $[K^+]_t$ , while diffusion back to the bulk extracellular fluid removes  $\text{K}^+$  with a time constant ( $\tau_K$ ) of approximately 350 ms. These two processes determine the rate of change of  $[K^+]_t$ . Because the T-tubule volume is restricted,  $[K^+]_t$  can rise significantly during repetitive activity, shifting the  $\text{K}^+$  reversal potential and influencing membrane excitability.

$$\frac{d[K^+]_t}{dt} = \frac{\eta_K g_K (V_t - \hat{E}_K) + 0.15 \eta_l (V_t - \hat{E}_l)}{F \zeta} - \frac{[K^+]_t - [K^+]_o}{\tau_K}$$

where,  $\zeta$  is the volume to surface area ratio for the T-tubule ( $\approx 10^{-6} \text{ cm}$ ).

About 15% of the total contribution is taken from the leaky channel.

The diffusion of  $\text{K}^+$  between the T-tubular space and the bulk extracellular space is modeled as a passive first-order rate process characterized by the time constant  $\tau_K$ .

During repeated activity,  $\text{K}^+$  accumulates within the T-tubule, leading to a sustained depolarization of the membrane. When the activity ceases,  $\text{K}^+$  diffuses out of the T-tubule into the bulk extracellular space. As this diffusion occurs, the membrane potential exponentially decays back to its resting level. The half-time of this decay represents the rate of  $\text{K}^+$  clearance and provides a direct measurement of the time constant  $\tau_K$ .

All the coupled differential equations described above were solved numerically to study the time evolution of the membrane potentials and ionic concentrations.

The model parameter values were taken from the original paper, which were derived from experimental data on mammalian skeletal muscle—primarily from rat and human preparations. Sodium channel activation and inactivation properties were adjusted according to mammalian measurements rather than the original amphibian Hodgkin–Huxley (HH) values. Temperature corrections were incorporated using appropriate  $Q_{10}$  factors to account for the faster gating kinetics at mammalian body temperatures.

The principal free parameters in the model are the ratios of channel densities between the T-tubule and surface membranes, which control how effectively T-tubular depolarization propagates to the surface. Overall, the key behaviors of the model are robust and do not depend critically on fine-tuning of individual parameters.

The classical HH model was based on squid axon experiments performed at low temperatures (approximately 6°C), whereas mammalian skeletal muscle operates within a physiological range of 22–37°C. To simulate mammalian muscle behavior more accurately, the gating rate constants were scaled by a temperature-dependent factor derived from the  $Q_{10}$  relationship:

$$Q_{10} = \left( \frac{\text{rate at } T_2}{\text{rate at } T_1} \right)^{\frac{10}{T_2 - T_1}}.$$

A typical  $Q_{10}$  value of 2.5 indicates that ion-channel kinetics increase approximately 2.5-fold for every 10°C rise in temperature.

### 7.3 Results and Biophysical Interpretation

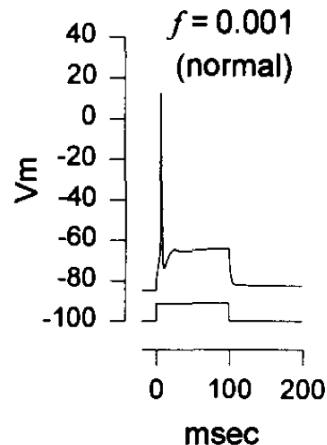


Figure 1.35: Simulated membrane potential response of a normal muscle fiber ( $f = 0$ ), showing regular excitability and complete recovery to the resting potential after the stimulus is removed.

(From Original Paper)

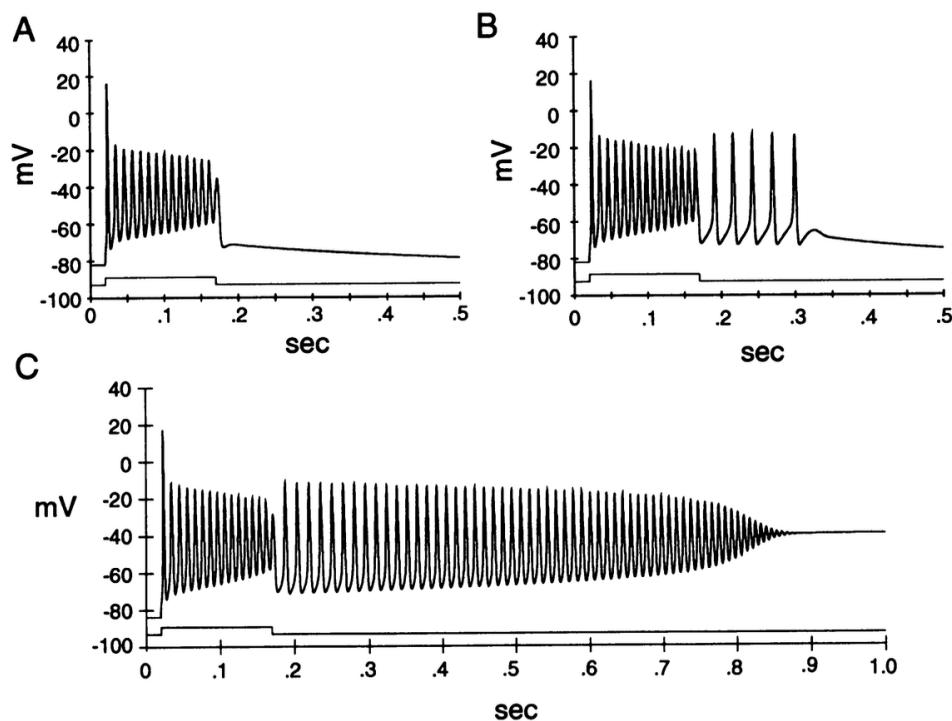


Figure 1.36: Simulated responses for different fractions of non-inactivating  $\text{Na}^+$  channels ( $f$ ): (A)  $f = 0.015$  — Myotonic response characterized by repetitive firing during stimulation, returning to rest once the stimulus is removed. (B)  $f = 0.018$  — Myotonic burst, showing self-sustained repetitive firing that persists briefly after stimulus removal before returning to rest. (C)  $f = 0.02$  — Hyperkalemic Periodic Paralysis (HPP) behavior, where the membrane remains depolarized for an extended period before gradually repolarizing.

(From Original Paper)

### Fig 1.35 biophysical explanation

Initially, the membrane is at its resting potential. When a long-duration current is injected, an action potential (AP) is generated as voltage-gated  $\text{Na}^+$  channels open and rapidly depolarize the membrane. Following the spike, all  $\text{Na}^+$  channels become inactivated, and voltage-gated  $\text{K}^+$  channels open to repolarize the cell. Since  $\text{K}^+$  channels close slowly, a brief undershoot (after-hyperpolarization) occurs with respect to the new equilibrium set by the injected current. Once the  $\text{K}^+$  channels close, the membrane potential approaches a new equilibrium value determined by the injected current, following an exponential time course.

When the stimulus is removed, the equilibrium potential shifts back toward the normal resting potential, and the membrane potential decays exponentially to its original resting state.

### Fig 1.36 (A) biophysical explanation

When the membrane is initially at its resting potential and a long-duration current is injected, an action potential (AP) is generated. In this case, approximately 1.5% of the  $\text{Na}^+$  channels are non-inactivating, meaning a small fraction of  $\text{Na}^+$  channels remain open even after the spike. Following depolarization, voltage-gated  $\text{K}^+$  channels open, causing the membrane potential to fall as the outward  $\text{K}^+$  current dominates. When the  $\text{K}^+$  channels begin to close, a small inward  $\text{Na}^+$  current persists due to the few non-inactivating  $\text{Na}^+$  channels. As a result, the potential reaches a minimum that is slightly depolarized, which triggers another AP. However, this subsequent AP has a smaller amplitude since it is generated only by the limited number of  $\text{Na}^+$  channels that remain open.

#### Why do all $\text{Na}^+$ channels not reopen after the first AP?

Because most  $\text{Na}^+$  channels remain inactivated immediately after the first AP. For them to reopen, the membrane must repolarize sufficiently to remove inactivation.

As the  $\text{Na}^+$  current again reaches a peak, the  $\text{K}^+$  channels reopen and drive the membrane back toward a new equilibrium potential that is slightly depolarized relative to the original resting level. This cyclic interaction between the slowly closing  $\text{K}^+$  channels and the small persistent  $\text{Na}^+$  current produces repetitive firing, characteristic of myotonic behavior.

**Note:** After each AP,  $\text{K}^+$  ions accumulate within the T-tubule lumen and gradually diffuse out into the bulk extracellular space. This accumulation shifts the local T-tubular reversal potential  $\hat{E}_K$  toward more depolarized values. Consequently, after every AP, the baseline membrane potential becomes slightly more depolarized.

When the stimulus is removed, the small inward  $\text{Na}^+$  current alone is insufficient to bring the membrane potential to threshold, so no further APs are generated. Meanwhile, the accumulated  $\text{K}^+$  in the T-tubule lumen diffuses out to the extracellular space, allowing the membrane potential to decay exponentially back to the normal resting level. The half-time of this decay corresponds to the characteristic diffusion time constant  $\tau_K$ .

### Fig 1.35 (B) biophysical explanation

For  $f = 0.018$ , the overall mechanism is similar to the previous case ( $f = 0.015$ ) during stimulation. However, the key difference appears once the stimulus is removed. A larger amount of  $\text{K}^+$  accumulates within the T-tubule lumen and diffuses out slowly. Because the extracellular  $\text{K}^+$  concentration in the T-tubule lumen becomes significantly elevated relative to the intracellular space, the  $\text{K}^+$  current temporarily reverses direction, producing an inward  $\text{K}^+$  flow. Together

with the small persistent inward  $\text{Na}^+$  current, this inward flux is sufficient to surpass the threshold potential and trigger additional action potentials even after the stimulus has ceased.

**Note:** The fraction of non-inactivating  $\text{Na}^+$  channels increases with  $f$ , leading to a larger inward  $\text{Na}^+$  current w.r.t. the previous case. Consequently, AP exhibits a slightly larger amplitude w.r.t. the previous case, causing greater  $\text{K}^+$  accumulation in the T-tubule lumen w.r.t. the previous case.

Since each AP drives  $\text{K}^+$  efflux into the T-tubule lumen, one might expect this process to continue indefinitely. However, diffusion of  $\text{K}^+$  into the bulk extracellular space gradually dominates. As the  $\text{K}^+$  gradient dissipates, the inward  $\text{K}^+$  current diminishes, and the small  $\text{Na}^+$  current alone becomes insufficient to reach threshold. As a result, no further APs are generated, and the membrane potential slowly decays back to its resting level.

**Observation:** The frequency of APs during stimulation is higher than after stimulus removal, indicating that  $\text{K}^+$  accumulation is enhanced in the presence of a driving current but gradually decreases once the stimulus is withdrawn.

### Fig 1.35 (C) biophysical explanation

For  $f = 0.02$ , the behavior initially follows the same trend as in the  $f = 0.018$  case during stimulation. However, a significant difference emerges once the stimulus is removed. At this higher fraction of non-inactivating  $\text{Na}^+$  channels (approximately 2%), the persistent inward  $\text{Na}^+$  current becomes larger, producing higher-amplitude spikes and consequently greater  $\text{K}^+$  accumulation within the T-tubule lumen.

When the stimulus is withdrawn, the combined inward flux of  $\text{Na}^+$  and  $\text{K}^+$  ions depolarizes the membrane sufficiently to trigger spontaneous action potentials. With each AP, additional  $\text{K}^+$  accumulates in the T-tubule lumen. In this regime, the frequency of APs after the stimulus is removed becomes *higher* than during stimulation, indicating that diffusion is no longer the dominant process.. Instead, the system enters a positive feedback loop: each AP enhances  $\text{K}^+$  accumulation, which in turn increases the inward  $\text{K}^+$  current and further promotes repetitive firing.

Eventually, the slowly inactivating  $\text{Na}^+$  channels also become fully inactivated, terminating action potential generation. However, by this point, a large amount of  $\text{K}^+$  has accumulated in the T-tubule lumen. This excess  $\text{K}^+$  diffuses outward very slowly into the bulk extracellular space while simultaneously driving a continuous inward  $\text{K}^+$  current. Because all  $\text{Na}^+$  channels are now inactivated, no further APs can be produced. The elevated  $\text{K}^+$  concentration in the T-tubule lumen keeps the local reversal potential  $\hat{E}_K$  depolarized, holding the membrane at a sustained depolarized state in which  $\text{Na}^+$  channels remain inactivated.

Consequently, the cell becomes temporarily inexcitable—a condition known as **Hyperkalemic Periodic Paralysis (HPP)**. Over time, as diffusion gradually clears  $\text{K}^+$  from the T-tubule lumen,  $\hat{E}_K$  slowly returns toward its normal value, and the membrane potential decays exponentially back to its resting state, restoring excitability.

**Why is there a sudden increase in AP amplitude when the stimulus is removed?** During stimulation, subsequent APs are generated primarily by the few open  $\text{Na}^+$  channels that persist after inactivation, resulting in smaller amplitudes. Once the stimulus is turned off, however, APs arise from the combined effect of the persistent  $\text{Na}^+$  current and the additional inward  $\text{K}^+$  current, producing larger spikes immediately after stimulus removal.

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