

# Hodgkin and Huxley (HH) Model Disease - Myotonia & Hyperkalemic Periodic Paralysis

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# Outline

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# Ion Channels as Resistors

Embedded within the neuronal membrane are specialized **protein ion channels** that regulate the flow of specific ions across the membrane.

- When a channel is **open**, ions pass freely, resulting in **low resistance** (high conductance).
- When a channel is **closed**, ion flow is restricted, leading to **high resistance** (low conductance).

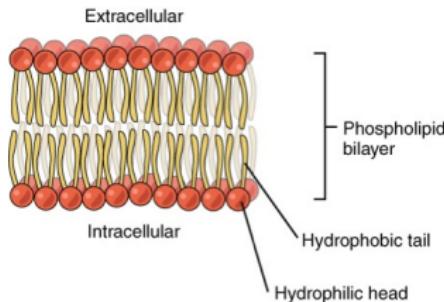
According to **Ohm's law**,

$$V = IR,$$

the voltage across the membrane depends on the ionic current and the effective membrane resistance/conductance.

# Membrane as 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 consequence, the membrane can store equal and opposite charges on its two sides, effectively functioning as a **capacitor**.

For a capacitor, we know:

$$Q = CV$$

# Ionic Diffusion via Non-selective pore

Both positively and negatively charged ions can diffuse across the membrane, driven by their **concentration gradients**.

As diffusion proceeds, ions move from regions of higher concentration to lower concentration, and the ionic concentrations on both sides of the membrane eventually **equalize**.

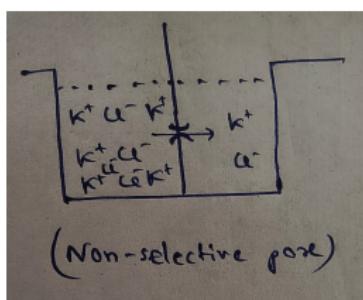


Figure: Non-selective pore

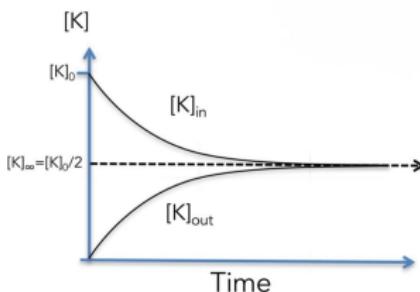


Figure: Concentration variation with time

# Ionic Diffusion via Ion-selective ( $K^+$ ) Pore

- In a  **$K^+$ -selective pore**, only  $K^+$  ions can diffuse across the membrane.
- Due to the concentration gradient,  $K^+$  ions diffuse **outward** from the cell.
- Outward movement of positive charge leaves behind **negatively charged ions** inside the cell.
- This charge separation generates an **electrical potential** across the membrane.
- The electrical gradient begins to **pull  $K^+$  inward**, opposing the concentration gradient.
- Eventually, the two forces balance, and **net ion movement stops**.
- The resulting voltage is the **equilibrium potential** (Nernst or reversal potential).

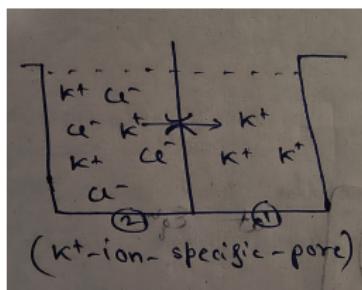


Figure:  $K^+$  ion-selective pore

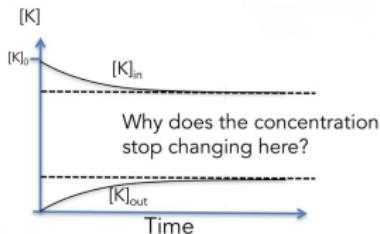


Figure: Concentration variation with time

# Where Does the Membrane “Battery” Come From?

**Thus, excitable cells have batteries!**

↪ This battery comes because of-

→ **Ion concentration gradients**

→ **Ion-selective pores/channels**

using Nernst equation at equilibrium we can estimate the reversal potential,

$$\Delta V = \frac{kT}{nq} \ln\left(\frac{[ion]_{out}}{[ion]_{in}}\right) \quad (\text{Nernst potential/ Reversal potential})$$

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:** Nernst potential data table

# Simple Model

In this simple model, we will consider only the membrane and a  $K^+$  ion-selective channel to examine what happens when an external current is injected.

## Why inject current?

We inject current to mimic how neurons naturally receive input (synaptic input, sensory stimuli).

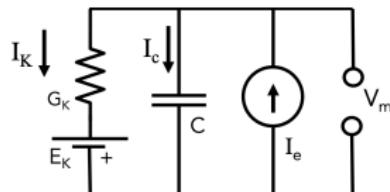


Figure: Equivalent circuit for the simple model

From Kirchhoff's current law:

$$I_K + I_C = I_e$$

where

$$I_K = \frac{(V_m - E_K)}{R_K}, \quad I_C = C \frac{dV_m}{dt}.$$

# Deriving the Membrane Equation

Thus,

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

Multiplying both sides by  $R_K$ :

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

At steady state ( $t \rightarrow \infty$ ), membrane voltage becomes constant:

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

Thus, the governing differential equation becomes:

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

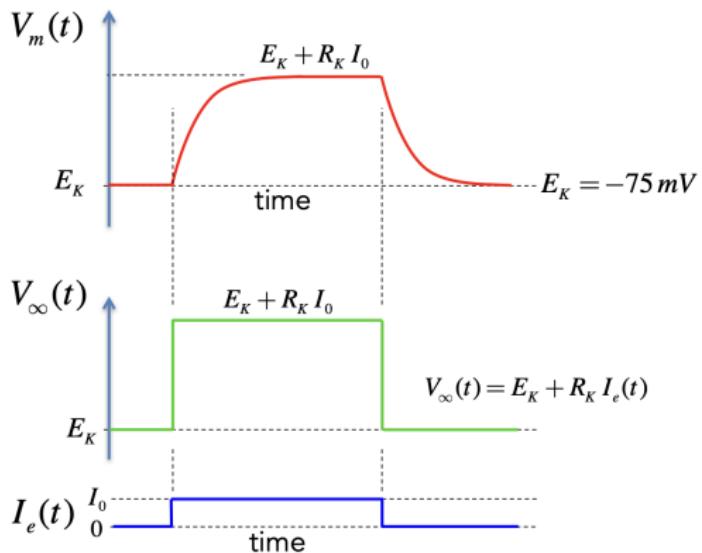
where

$$V_\infty = E_K + R_K I_e, \quad \tau = R_K C.$$

# Result

Integrating gives the time evolution of the membrane potential (for constant injected current):

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



# A Brief History

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

## 1. Julius Bernstein (1902): Membrane Theory

In the resting state, the nerve membrane is mainly permeable to  $K^+$  ions. As  $K^+$  ions diffuse outward (down their concentration gradient), a negative potential develops inside the cell, known as the **resting membrane potential**, which can be estimated by Nernst potential formula.

## 2. Cole & Curtis (1939)

- Using impedance measurements, showed that membrane resistance drops sharply during an action potential.
- First evidence that membrane **conductance increases** during excitation.
- Later developed the **voltage clamp** (with Hodgkin & Huxley, 1949). (discussed later)

## 3. Hodgkin & Huxley (1952)

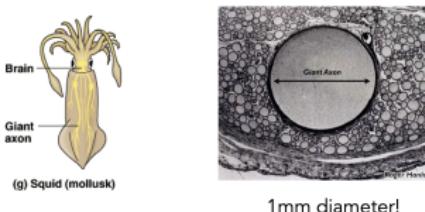
- Published a quantitative model describing the membrane as an electrical circuit.
- Explained the action potential via voltage- and time-dependent  $Na^+$  and  $K^+$  conductances.

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

# Hodgkin and Huxley model

# Hodgkin & Huxley: Experimental Insights

Working at Cambridge on the squid giant axon, Hodgkin and Huxley inserted a microelectrode into the axon and, using the **voltage-clamp** technique, held the membrane at fixed voltages to measure ionic currents directly — achieving the first intracellular recordings of membrane potential.



From their experiments, they inferred:

- Separate  $\text{Na}^+$  and  $\text{K}^+$  conductances must exist.
- Each conductance depends on both **voltage** and **time**.
- $\text{Na}^+$  conductance:
  - activates rapidly,
  - then **inactivates** even during sustained depolarization.
- $\text{K}^+$  conductance:
  - activates more slowly,
  - and does **not** inactivate like  $\text{Na}^+$ .
- These processes were modeled using gating variables **m**, **h**, **n**.

# Hodgkin & Huxley: Experimental Insights

Using the **voltage-clamp** technique, Hodgkin and Huxley clamped the membrane potential of the squid giant axon to desired values and measured the resulting ionic currents.

- By fixing  $V_m$  and measuring the current  $I$ , they could compute membrane conductance:

$$g = \frac{I}{V_m - E_{\text{ion}}}.$$

- Repeating this for many voltage levels allowed them to obtain conductance values at each  $V_m$ .
- Plotting **conductance vs. voltage** revealed characteristic activation curves.
- Fitting these curves led to empirical equations describing  $g(V)$ , forming the basis of the HH gating variables.

# Hodgkin & Huxley: Experimental Insights

To isolate individual ionic components, Hodgkin and Huxley replaced external  $\text{Na}^+$  with **choline chloride**, whose choline ions cannot pass through  $\text{Na}^+$  channels. Thus, any measured current under this condition arose primarily from  $\text{K}^+$  ions.

- The  **$\text{K}^+$ -only current** was recorded in choline solution.
- The **total current** was recorded under normal ionic conditions.
- Subtracting the two gave the  **$\text{Na}^+$  current**.

Having separated the ionic components, Hodgkin and Huxley yielded the voltage- and time-dependent conductances:

$$G_K(V, t) \quad \text{and} \quad G_{\text{Na}}(V, t),$$

which form the experimental basis of the HH model.

# Potassium Channel: Time and Voltage Dependence

Individual ion channels are either **open** or **closed**. Let:

$P_K$  = probability channel is open,  $N_K$  = total number of channels,  $\hat{g}_K$  = unitary conductance.

- Number of open channels:  $P_K N_K$
- Total  $K^+$  conductance:

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

All voltage and time dependence comes from  $P_K(V, t)$ .

they assumed a  $K^+$  channel has **4 independent subunits**. Let  $n$  = probability that one subunit is open.

$$P_K = n^4$$

Thus,

$$G_K = \bar{G}_K n^4, \quad \text{where } \bar{G}_K = \text{maximal conductance.}$$

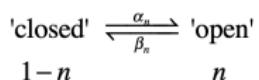
The potassium current becomes:

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

Hodgkin and Huxley called  $n$  the gating variable for  $K^+$  current.

## Gating Variable $n(V, t)$

At a given membrane potential  $V_m$ , the probability of a subunit moving from the **closed** to the **open** state changes instantly, but the actual conformational transition takes finite time. Thus, the open-state probability  $n(t)$  follows first-order kinetics.



- $\alpha_n(V_m)$ : rate of opening
- $\beta_n(V_m)$ : rate of closing
- $n$ : probability subunit is open
- $1 - n$ : probability subunit is closed

The rate equation is:

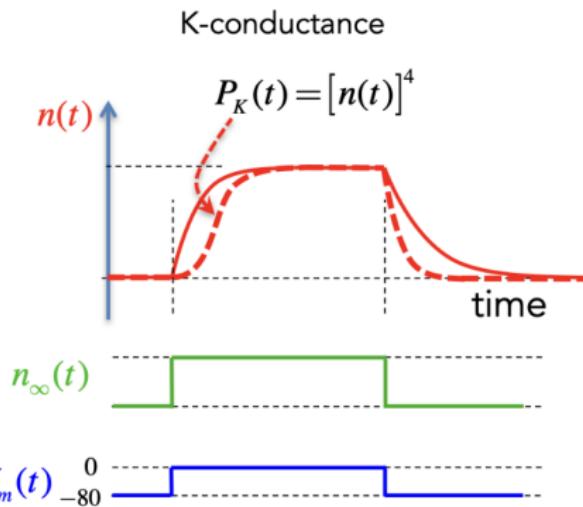
$$\frac{dn}{dt} = (\text{rate of opening}) - (\text{rate of closing})$$

# Gating Variable $n(V, t)$

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

on simplifying,

$$\frac{dn}{dt} = -\frac{1}{\tau_n}(n - n_\infty), \quad n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}, \quad \tau_n = \frac{1}{\alpha_n + \beta_n}.$$



## Gating variable ( $K^+$ ) Result

Hodgkin and Huxley found that  $K^+$  conductance fits the form  $G_K \propto n^4$ , implying four identical, independent subunits.

For each voltage, the steady-state value  $n_\infty(V)$  and time constant  $\tau_n(V)$  were obtained from voltage-clamp recordings:

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

By fitting the experimental data, Hodgkin and Huxley derived the empirical rate functions:

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

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

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

The  $\text{Na}^+$  channel behaves similarly to the  $\text{K}^+$  channel but includes an additional **inactivation** mechanism.

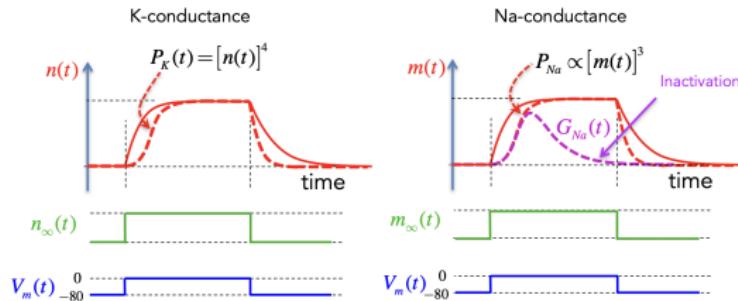


Figure:  $\text{K}^+$  vs.  $\text{Na}^+$  conductance.  $n(t)$ :  $\text{K}^+$  activation;  $m(t)$ :  $\text{Na}^+$  activation.

To capture  $\text{Na}^+$  activation and inactivation, Hodgkin and Huxley introduced:

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

where:

- $m$ : activation gating variable,
- $h$ : inactivation gating variable.

The factor  $m^3$  reflects the presence of three independent activation gates.

# Gating Variables of the Na<sup>+</sup> Channel

Similarly, Hodgkin and Huxley derived first-order kinetic equations for the Na<sup>+</sup> **activation** variable  $m$  and **inactivation** variable  $h$ , and obtained empirical expressions for their rate constants.

**For Na<sup>+</sup> activation ( $m$ ):**

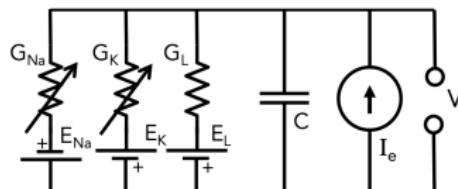
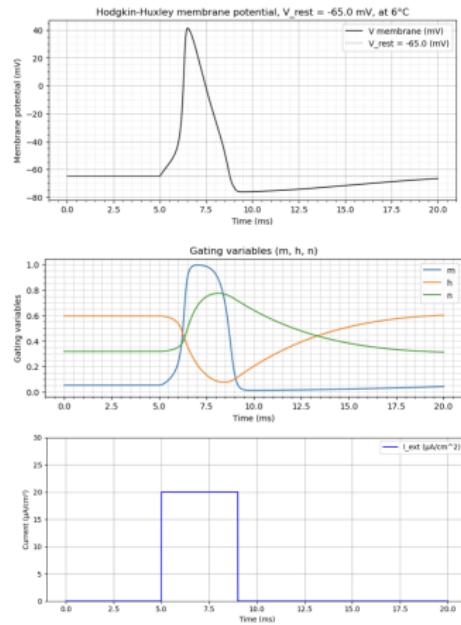
$$\alpha_m = 0.1 \frac{V + 25}{\exp\left(\frac{V+25}{10}\right) - 1}, \quad \beta_m = 4 \exp\left(\frac{V}{18}\right)$$

**For Na<sup>+</sup> inactivation ( $h$ ):**

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

# Hodgkin–Huxley Model: Action Potential Generation

The HH model describes membrane voltage dynamics using ionic currents through voltage-gated  $\text{Na}^+$  and  $\text{K}^+$  channels.



## Membrane equation:

$$C_m \frac{dV}{dt} = I_{\text{ext}} - (I_{\text{Na}} + I_{\text{K}} + I_{\text{L}})$$

## Ionic currents:

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

## Voltage-dependent conductances:

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

## Gating dynamics (for $x = m, h, n$ ):

$$\frac{dx}{dt} = \alpha_x(1-x) - \beta_x x \quad \Rightarrow \quad \tau_x \frac{dx}{dt} = x_\infty - x$$

## Rate constants ( $6.3^\circ\text{C}$ ):

$$\alpha_n = 0.01 \frac{V + 10}{e^{(V+10)/10} - 1}, \quad \beta_n = 0.125 e^{V/80}$$

$$\alpha_m = 0.1 \frac{V + 25}{e^{(V+25)/10} - 1}, \quad \beta_m = 4 e^{V/18}$$

$$\alpha_h = 0.07 e^{V/20}, \quad \beta_h = \frac{1}{e^{(V+30)/10} + 1}$$

# Disease - Myotonia and Hyperkalemic Periodic Paralysis

# Disease - Myotonia and HPP

Both disorders are **autosomal dominant** and caused by mutations in the **SCN4A** gene, which encodes the skeletal muscle  $\text{Na}^+$  channel. These mutations impair  $\text{Na}^+$  channel **inactivation**, producing a small but persistent inward  $\text{Na}^+$  current that alters muscle excitability.

## Clinical features:

- **Myotonia:** prolonged depolarization → delayed relaxation, stiffness, difficulty in initiating movement.
- **HPP:** episodic weakness/paralysis triggered by high  $\text{K}^+$ , rest after exercise, or  $\text{K}^+$ -rich foods.

**Experimental evidence:** Applying ATX-II (sea anemone toxin) to rat muscle fibers—known to block  $\text{Na}^+$  inactivation—produces a persistent  $\text{Na}^+$  current (1.2–2%), similar to that observed in patients.



Figure: sea anemone

# Disease - Myotonia & HPP



Figure: Myotonic Goat

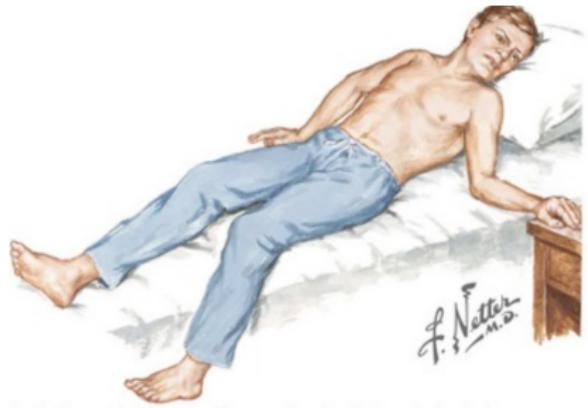


Figure: Hyperkalemic PP

# Two-Compartment Model for Skeletal Muscle

Each T-tubule connected to a unit area of surface membrane can be treated as a separate electrical compartment with a uniform potential  $V_T$ . The T-tubule system interacts with the surface membrane through **capacitive and resistive coupling**, forming the basis of the **two-compartment model**.

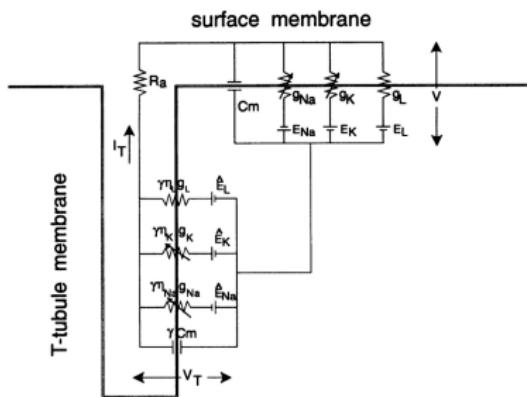


Figure: Equivalent circuit diagram (from original paper).

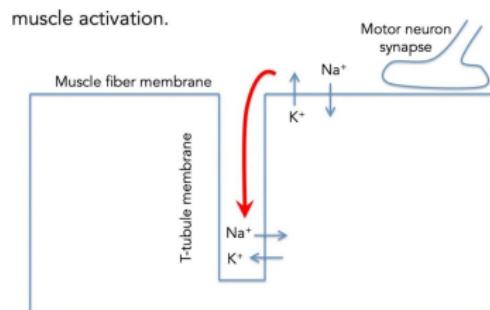


Figure: Coupling between surface and T-tubule membranes.

# Current Balance in the Two-Compartment Model

**Surface membrane:**

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

**T-tubule membrane:**

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

Voltage-gated channels in both membranes have the same **kinetics** and **conductance properties**, but may differ in **channel density**.

**Surface ionic current:**

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

**T-tubule ionic current (scaled by density factors):**

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

In the **surface membrane**,  $[K^+]_o$  and  $[K^+]_i$  remain nearly constant. In the **T-tubule**,  $[K^+]_o$  is restricted to a narrow lumen and can change dynamically, altering the local  $K^+$  reversal potential and affecting excitability.

# Dynamics of T-Tubular Potassium Accumulation

The T-tubule acts as a small extracellular compartment where  $K^+$  concentration  $[K^+]_t$  can change dynamically.  $K^+$  enters through voltage-gated  $K^+$  channels (plus a small leak component) and is removed by diffusion to the bulk extracellular space with time constant  $\tau_K \approx 350$  ms.

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

- $\zeta$  — T-tubule volume-to-area ratio ( $\sim 10^{-6}$  cm)
- 15% of contribution from leak current
- Diffusion term models passive exchange with bulk extracellular  $K^+$

During repetitive activity,  $K^+$  accumulates in the T-tubule, shifting  $E_K$  and causing sustained depolarization. When activity stops,  $K^+$  diffuses out and the membrane potential returns exponentially to rest, with half-time determined by  $\tau_K$ .

# Modified $\text{Na}^+$ Current for Defective Inactivation

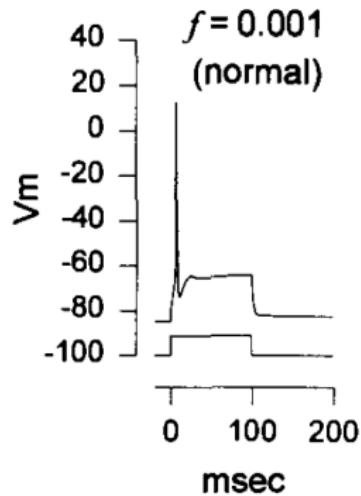
To model incomplete  $\text{Na}^+$  inactivation, the sodium current is written as:

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

## Interpretation:

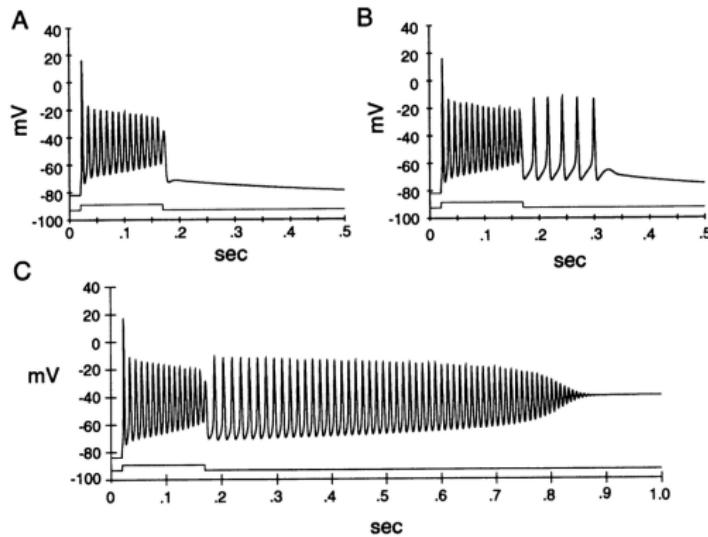
- $f = 0$  : normal muscle (all  $\text{Na}^+$  channels inactivate normally)
- $0 \leq f \leq 1$  : fraction of channels that **fail to inactivate**

# Results



**Figure:** Normal muscle fiber ( $f = 0$ ): normal excitability and full recovery after stimulus.

# Results



**Figure:** Effect of increasing non-inactivating  $\text{Na}^+$  fraction  $f$ : (A)  $f = 0.015$  — myotonic firing during stimulus; (B)  $f = 0.018$  — myotonic burst persisting briefly after stimulus; (C)  $f = 0.020$  — HPP-like depolarization block with slow recovery.

## Interpretation, ( $f = 0$ )

- Initially, the membrane is at its resting potential.
- A long-duration injected current depolarizes the cell, triggering an **action potential**.
- Voltage-gated  $\text{Na}^+$  channels open rapidly → fast depolarization.
- After the spike,  $\text{Na}^+$  channels inactivate and  $\text{K}^+$  channels open.
- $\text{K}^+$  efflux repolarizes the membrane.
- Slow closing of  $\text{K}^+$  channels produces an **after-hyperpolarization**.
- Once  $\text{K}^+$  channels close, the membrane approaches a new equilibrium voltage set by the injected current (exponentially).
- When the stimulus is removed, the equilibrium shifts back toward rest.
- Membrane potential decays exponentially to the original resting value.

# Interpretation, ( $f = 0.015$ )

- About 1.5% of  $\text{Na}^+$  channels are **non-inactivating**, leaving a small persistent inward  $\text{Na}^+$  current.
- After an AP,  $\text{K}^+$  channels open and repolarize the membrane as outward  $\text{K}^+$  current dominates.
- As  $\text{K}^+$  channels begin to close, the small inward  $\text{Na}^+$  current continues.
- After AP,  $\text{K}^+$  accumulates inside the T-tubule lumen. This shifts the local reversal potential  $E_K$  to more depolarized values.
- This residual  $\text{Na}^+$  influx slightly depolarizes the membrane and triggers a **second, smaller AP**.
- The limited number of non-inactivating  $\text{Na}^+$  channels produces APs of reduced amplitude.
- $\text{K}^+$  channels reopen during each spike, pushing the membrane back toward a slightly depolarized equilibrium.
- This interplay between slowly closing  $\text{K}^+$  channels and persistent  $\text{Na}^+$  current leads to **repetitive firing**—the hallmark of myotonia.

## Role of T-tubular $\text{K}^+$ accumulation:

- After every AP,  $\text{K}^+$  accumulates inside the T-tubule lumen.
- This shifts the local reversal potential  $E_K$  to more depolarized values.
- The baseline membrane potential becomes slightly more depolarized after each spike.

## When the stimulus is removed:

- The small  $\text{Na}^+$  current is no longer sufficient to reach threshold → firing stops.
- Accumulated  $\text{K}^+$  diffuses out of the T-tubule.
- The membrane potential returns exponentially to its normal resting level.

# Interpretation, ( $f = 0.018$ )

## During stimulation:

- Behavior is similar to the  $f = 0.015$  case: persistent  $\text{Na}^+$  current + slowly closing  $\text{K}^+$  channels → repetitive firing.
- $\text{K}^+$  progressively accumulates in the T-tubule lumen.

## After stimulus removal:

- More  $\text{K}^+$  has accumulated in the T-tubule compared to  $f = 0.015$ .
- Elevated T-tubular  $[\text{K}^+]_t$  makes  $E_K$  less negative.
- $\text{K}^+$  current can temporarily **reverse direction** → inward  $\text{K}^+$  flow.
- Inward  $\text{K}^+$  + persistent  $\text{Na}^+$  current pushes the membrane above threshold.
- Result: **self-sustained APs** continue briefly even without stimulation.

## Termination of the burst:

- $\text{K}^+$  gradually diffuses from the T-tubule into bulk extracellular space.
- The  $\text{K}^+$  gradient dissipates → inward  $\text{K}^+$  current declines.
- Persistent  $\text{Na}^+$  current alone cannot reach threshold.
- APs stop, and the membrane potential slowly returns to rest.

**Observation:** AP frequency is **higher during stimulation** than after stimulus removal, because  $\text{K}^+$  buildup is stronger when external current drives repeated firing.

# Interpretation ( $f = 0.02$ )

## During stimulation:

- Initial behavior similar to  $f = 0.018$ .
- Higher persistent  $\text{Na}^+$  current ( $\sim 2\%$ )  $\rightarrow$  larger spikes.
- Each spike drives more  $\text{K}^+$  into the T-tubule  $\rightarrow$  strong  $\text{K}^+$  accumulation.

## After stimulus removal:

- Persistent  $\text{Na}^+$  current + inward  $\text{K}^+$  current depolarize the membrane above threshold.
- Spontaneous action potentials continue without stimulation.
- AP frequency becomes **higher than during stimulation**:
  - Positive feedback: AP  $\rightarrow$  more  $\text{K}^+$  buildup  $\rightarrow$  stronger inward  $\text{K}^+$  current  $\rightarrow$  more APs.

# Interpretation ( $f = 0.02$ )

## Termination of firing:

- Slowly inactivating  $\text{Na}^+$  channels eventually become fully inactivated.
- No  $\text{Na}^+$  current remains → further APs cannot be generated.

## Depolarization block (HPP state):

- Large  $\text{K}^+$  buildup keeps  $E_K$  depolarized.
- Inward  $\text{K}^+$  current maintains a **sustained depolarized membrane potential**.
- $\text{Na}^+$  channels remain inactivated → muscle becomes **temporarily inexcitable**.

## Recovery:

- Excess  $\text{K}^+$  slowly diffuses out of the T-tubule.
- $E_K$  gradually normalizes.
- Membrane potential decays back to rest → excitability returns.

**Why AP amplitude increases after stimulus removal?** During stimulation, APs rely mainly on the small persistent  $\text{Na}^+$  current → smaller spikes. After removal, inward  $\text{K}^+$  current adds to  $\text{Na}^+$  current → **larger spikes**.

# Refrence

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Thank You