Propagation of Nerve Impulses : The Hodgkin–Huxley model

Amardeepsingh H Kushwah (19MS165)

A quantitative description of membrane current and its application to conduction and excitation in nerve.

Hodgkin AL, Huxley AF. The Journal of physiology. 1952 Aug 8;117(4):500

The Nobel Prize in Physiology or Medicine 1963

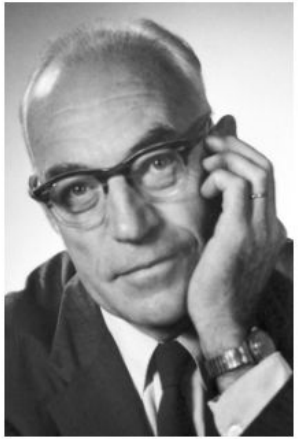
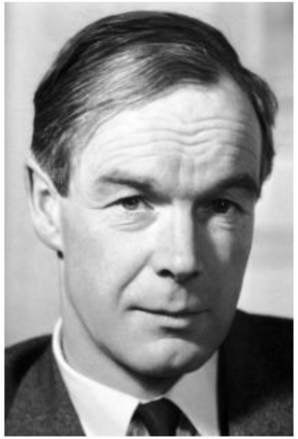


Photo from the Nobel Foundation archive.

Sir John Carew Eccles

Prize share: 1/3



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Alan Lloyd Hodgkin

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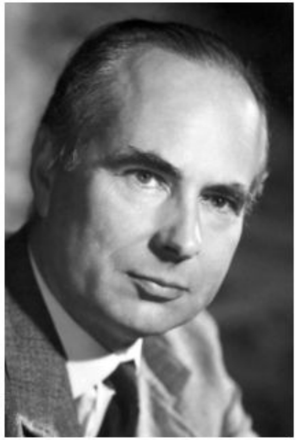

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Andrew Fielding Huxley

Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1963 was awarded jointly to Sir John Carew Eccles, Alan Lloyd Hodgkin and Andrew Fielding Huxley "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"

Preceding papers

- HODGKIN, A. L., HUXLEY, A. F. & KATZ, B. (1952). Measurement of current-voltage relations in the membrane of the giant axon of Loligo. J. Physiol. 116, 424-448.
- HODGKIN, A. L. & HUXLEY, A. F. (1952a). Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. J. Physiol. 116, 449-472.
- HODGKIN, A. L. & HUXLEY, A. F. (1952b). The components of membrane conductance in the giant axon of Loligo. J. Physiol. 1I6, 473-496.
- HODGKIN, A. L. & HUXLEY, A. F. (1952c). The dual effect of membrane potential on sodium conductance in the giant axon of Loligo. J. Physiol. 116, 497-506.

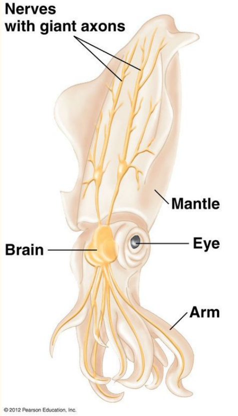
Model system

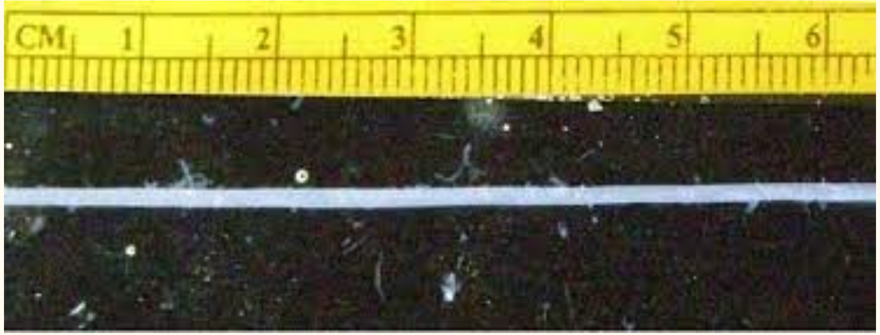
1. Squid giant axon was chosen as the model system due to its large size.

2. This axon controls part of the water jet propulsion system in squid, which is a part of defence mechanism to escape from predator.

3. As its length of the axon increases the time taken for propagation of action potential increases, this is where its large diameter comes to rescue.

4. Larger area of conduction increases conductance along its length.





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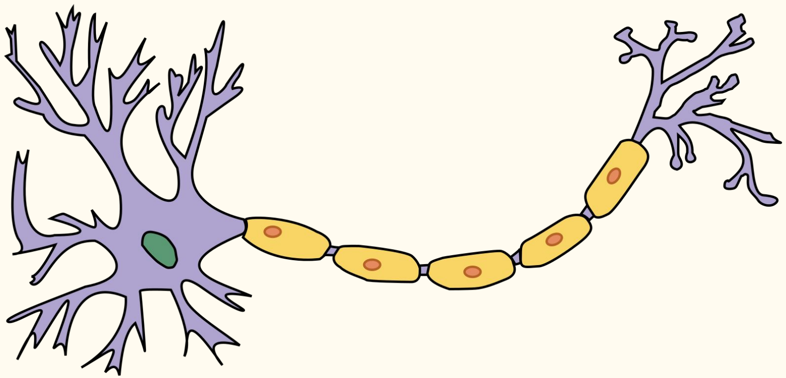
Model system

1. This is different from the structure of neuron found in human body

2. Human neurons have myelin sheath along the length of axon, this helps in increased speed of conduction



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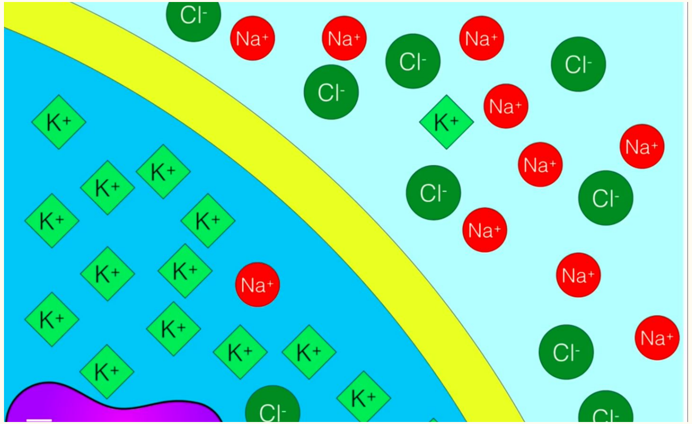
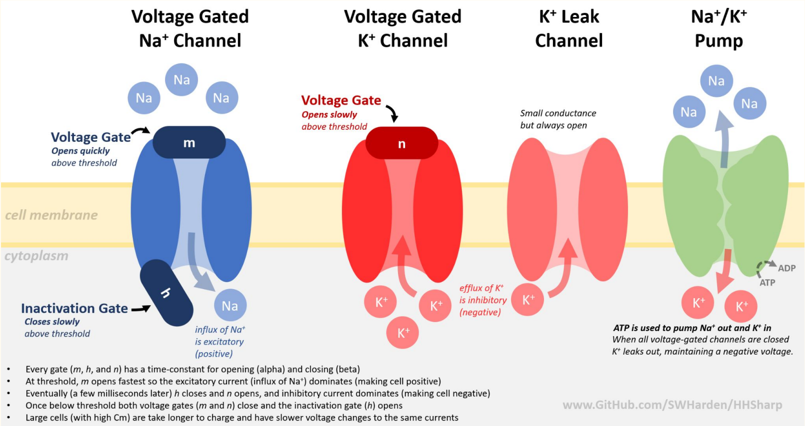
Model system

1. The model system setup initially has higher sodium concentration on the outside and higher potassium conc on the inside of the axon.

2. The membrane has several passage ways for these ions, which include sodium and potassium leak channels, voltage gated potassium channels, voltage gated sodium channel with inactivation gate, membrane also has sodium potassium pump.





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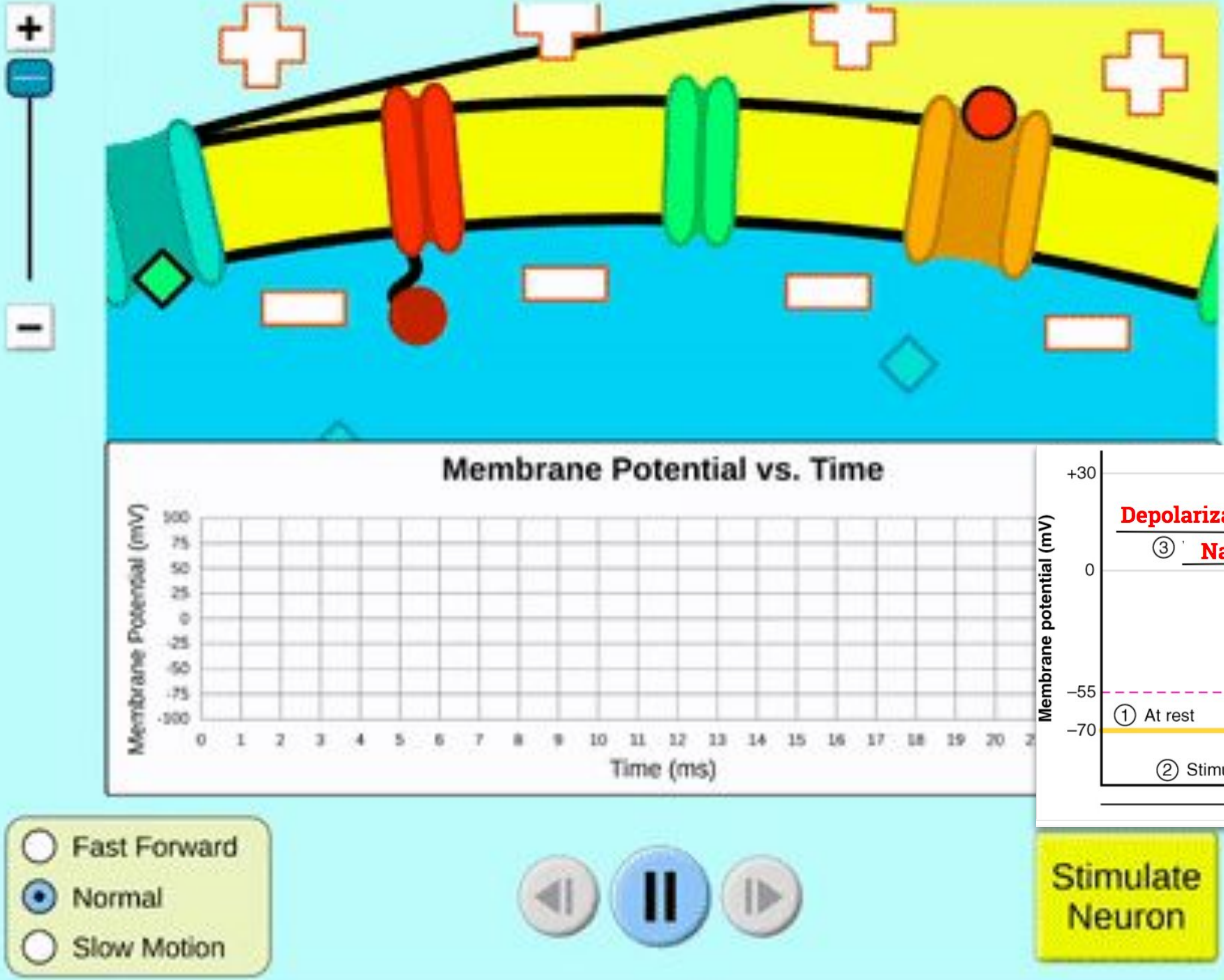
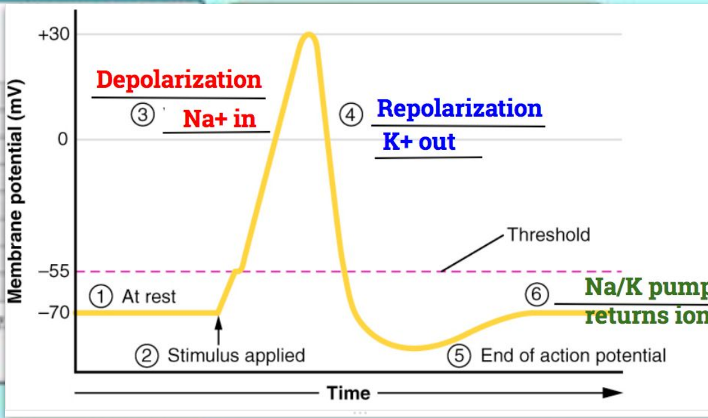
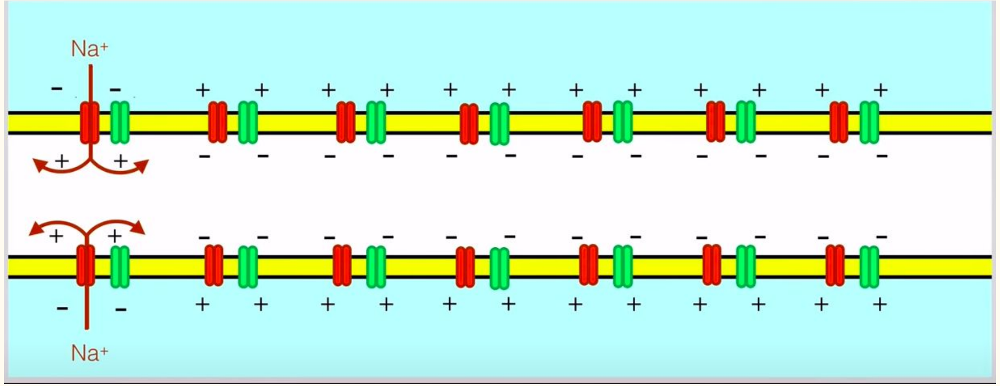
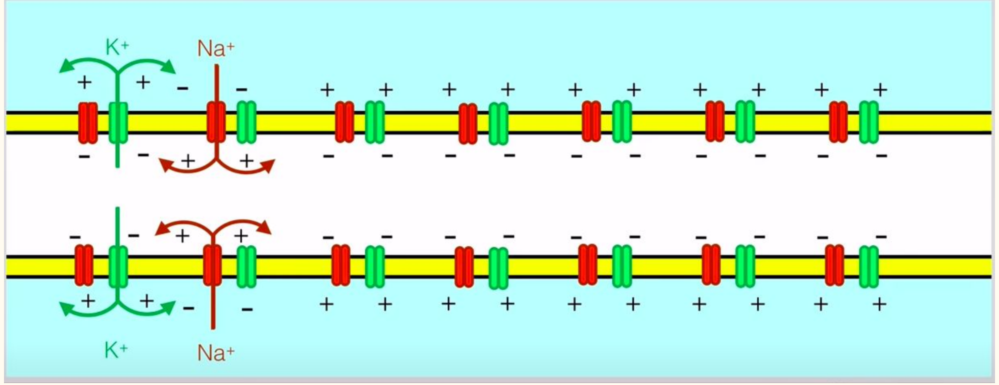




Credit : PhET interactive simulations
https://phet.colorado.edu/sims/html/neuron/latest/neuron_en.html





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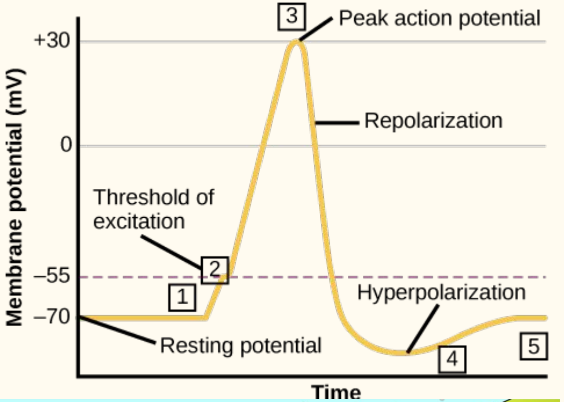

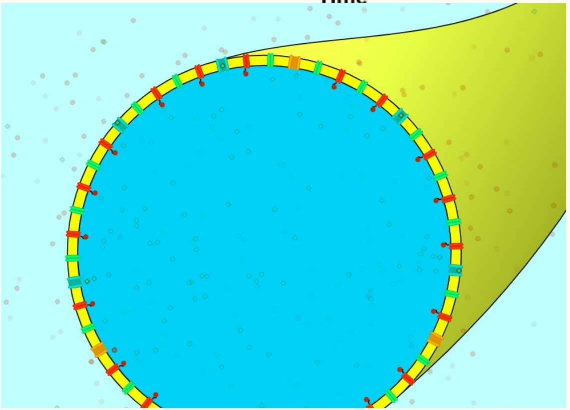

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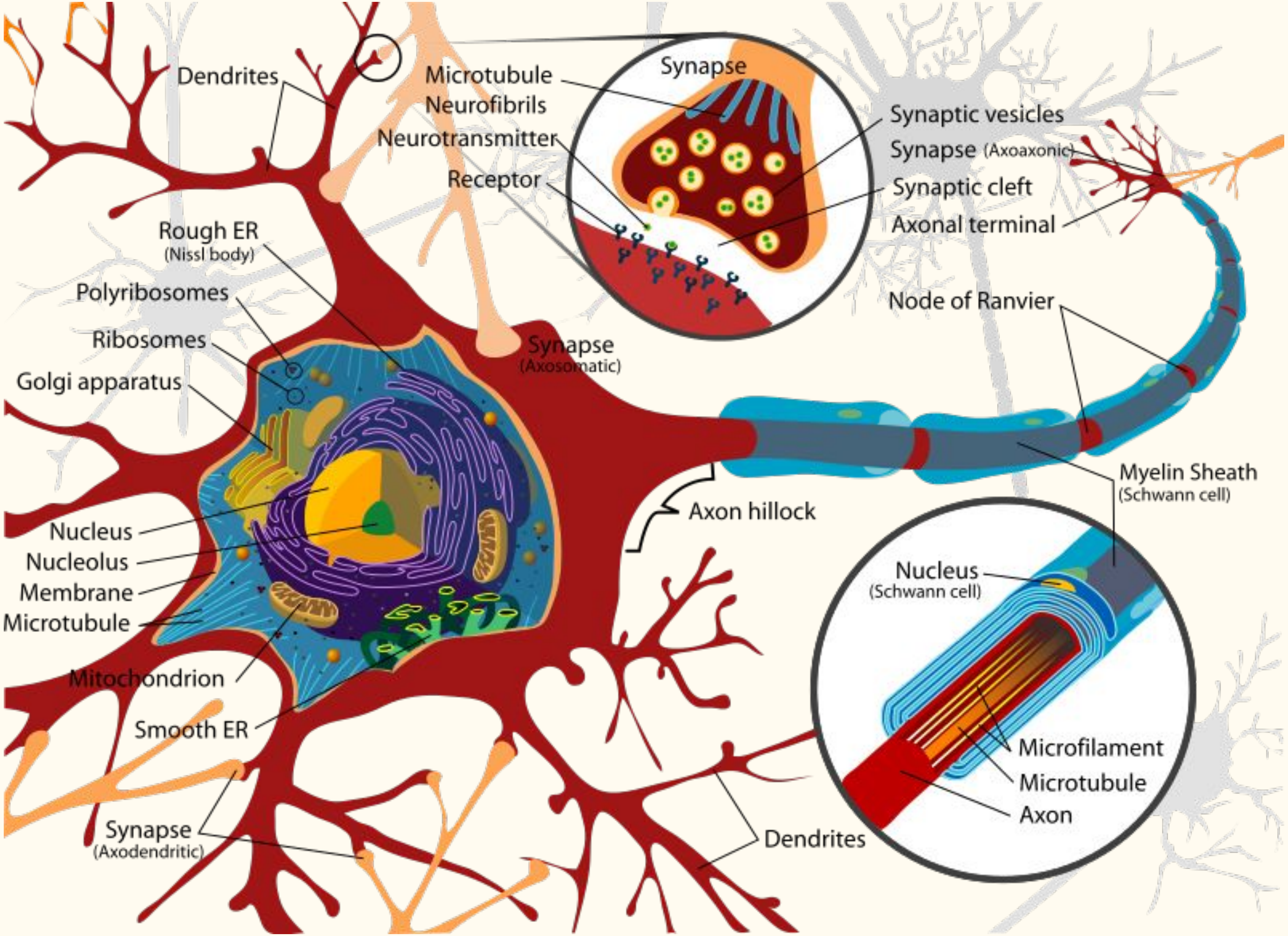
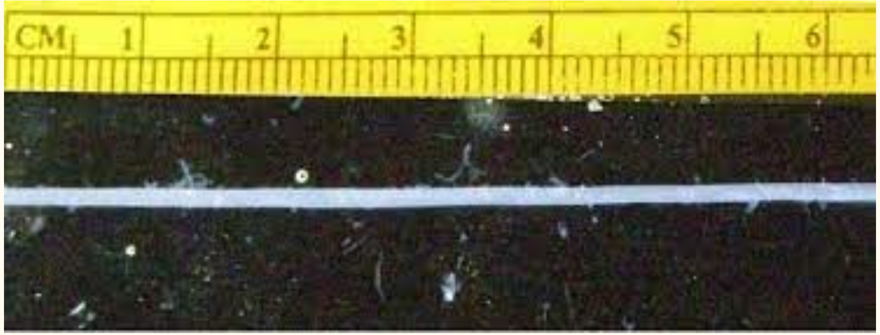
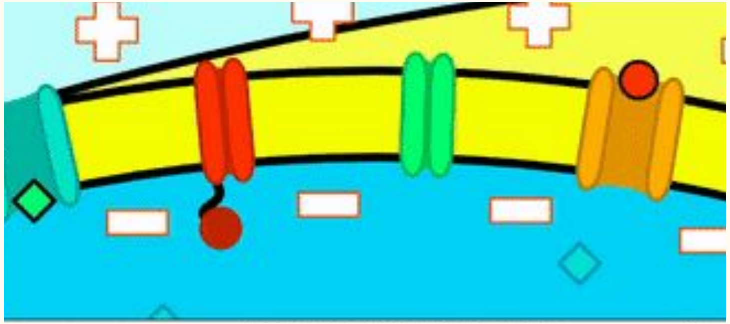

Dendrites
Microtubule
Neurofibrils
Neurotransmitter
Receptor
Synapse
Synaptic vesicles
Synapse (Axoaxonic)
Synaptic cleft
Axonal terminal
Rough ER
(Nissl body)
Polyribosomes
Ribosomes
Golgi apparatus
Synapse
(Axosomatic)
Node of Ranvier
Myelin Sheath
(Schwann cell)
Axon hillock
Nucleus
Nucleolus
Membrane
Microtubule
Nucleus
(Schwann cell)
Mitochondrion
Smooth ER
Microfilament
Microtubule
Axon
Synapse
(Axodendritic)
Dendrites

So how do we get from ….



to



?

Some conclusions made in previous papers..

Na^+ & K^+ are responsible for conduction of action potential

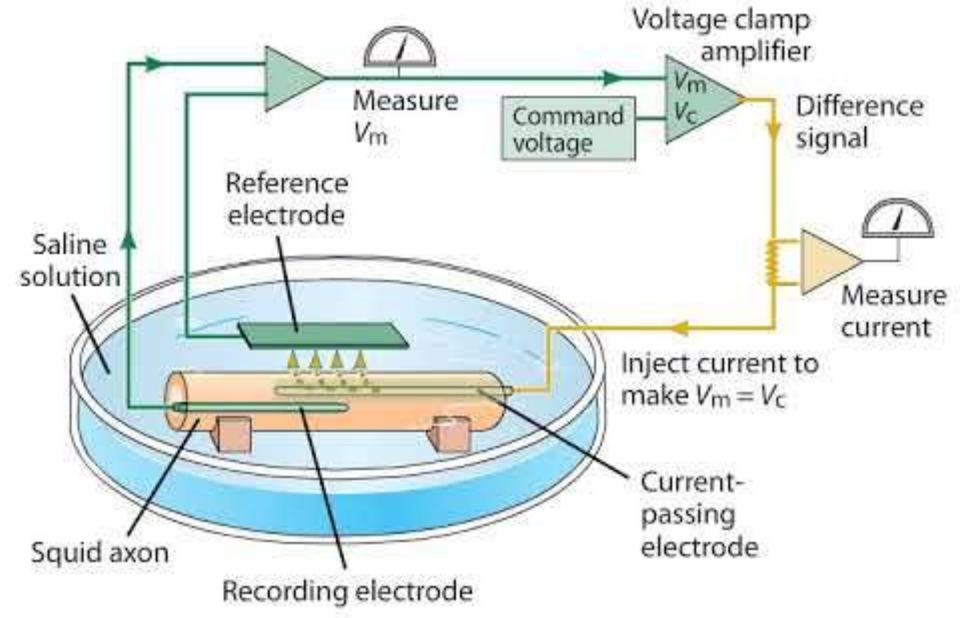
(As suggested by katz in his 1947 paper, the concentration of Na^+ affected axon conduction velocity)

- Hodgkin rigorously tested this theory and arrived at a conclusion that it was indeed the case.
- Here they noticed positive feedback mechanism whereby membrane depolarisation increases Na^+ permeability allowing Na^+ influx, which causes more depolarisation.
- He also noted that that the action potential vanishes in Na^+ free seawater.
- They performed similar experiments with K^+

Some conclusions made in previous papers..

Development of Voltage Clamp

- It creates a continuous length of membrane with constant membrane potential
- This voltage could be varied according to the need and currents could be measured



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Some conclusions made in previous papers..

Breaking down membrane current into its components namely sodium current, potassium current and leak current

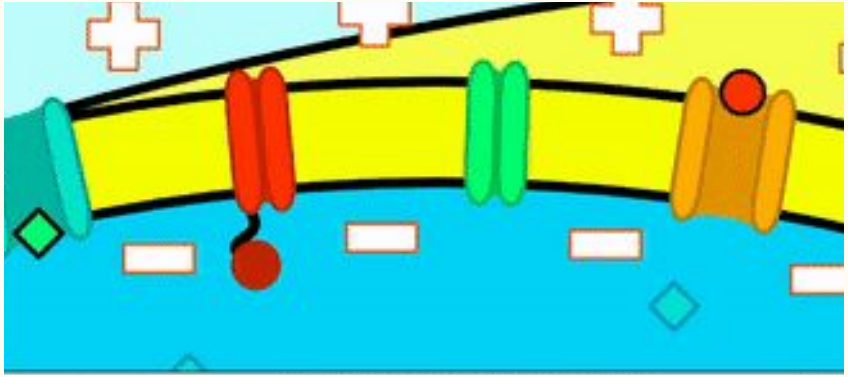
- Voltage clamp along coupled with careful observation of the membrane current under varying ionic concentration lead to the conclusion that there are two parts of the membrane current

- They concluded there was an inward component (the early current) followed by a sustained outward current

- Applying mathematical tools they were able to isolate sodium current, potassium current and leak current

Some conclusions made in previous papers..

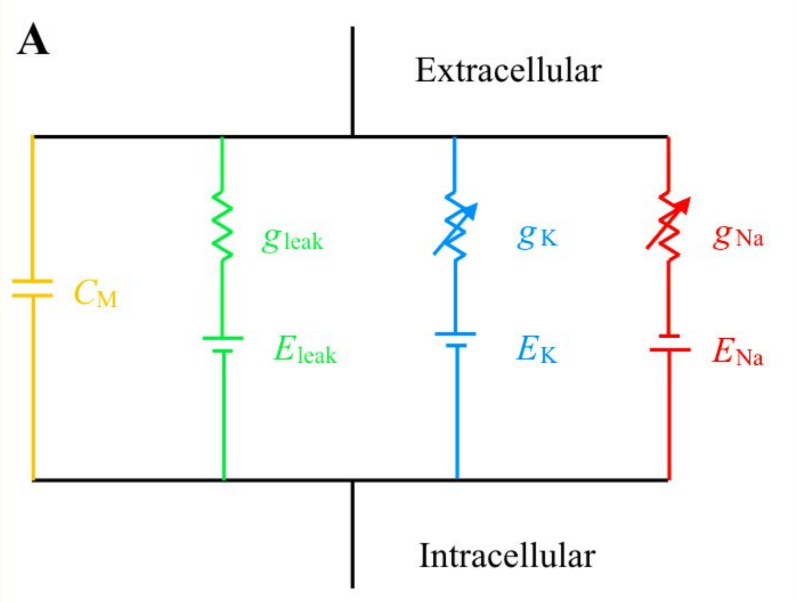
They also observed dual effect of membrane potential on sodium conductance



- During depolarisation of the membrane the sodium conductance first increased then decreased without change in direction of depolarisation
- Further studying this phenomenon lead to the hypothesis of inactivation of sodium conduction channel

So now we have some idea and data about how the axons behave under different conditions, lets make our own mathematical model which behaves in the same manner

The electrical model



$$I = C_{\mathrm{M}}\frac{\mathrm{d}V}{\mathrm{d}t} + \bar{g}_{\text{leak}}\left(V - E_{\text{leak}}\right) + \bar{g}_{\mathrm{K}} n^4 \left(V - E_{\mathrm{K}}\right) + \bar{g}_{\mathrm{Na}} m^3 h \left(V - E_{\mathrm{Na}}\right)$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(1-n) - \beta_n n$$
$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1-m) - \beta_m m$$
$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1-h) - \beta_h h$$

$$\alpha_n = 0.01\frac{(V+55)}{1-e^{\left[\frac{-(V+55)}{10}\right]}}$$
$$\beta_n = 0.0555 e^{\left(\frac{-V}{80}\right)}$$
$$\alpha_m = \frac{0.1(V+40)}{1-e^{\left(\frac{-V+40}{10}\right)}}$$
$$\beta_m = 0.108 e^{\left(\frac{-V}{18}\right)}$$
$$\alpha_h = 0.0027 e^{\left(\frac{-V}{20}\right)}$$
$$\beta_h = \frac{1}{1-e^{\left(\frac{-V+35}{10}\right)}}$$

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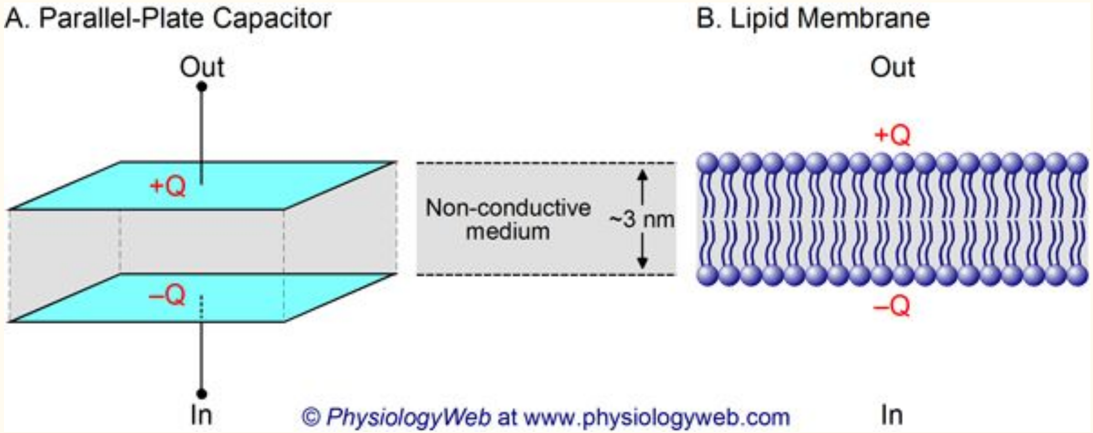
$$I_m = C_m dV/dt + I_{ionic}$$

$$C_m dV/dt$$



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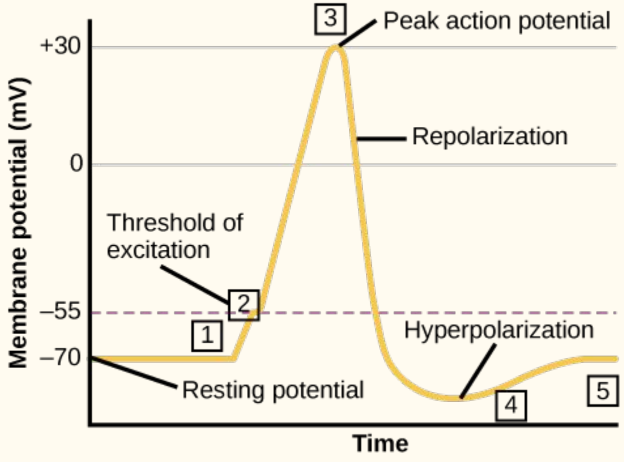
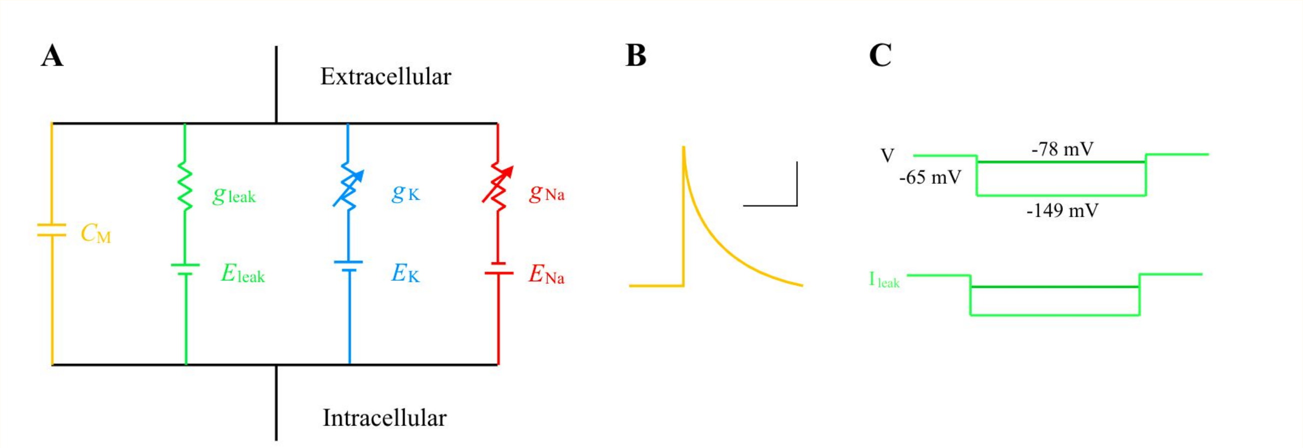
$$I_{ionic} = I_{Na} + I_K + I_{leak}$$

$$I_{leak} = g_{leak}(V - E_{leak})$$





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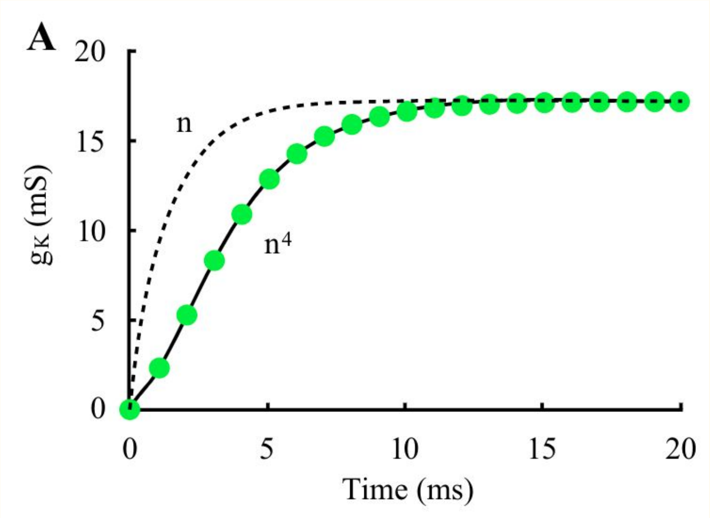
Potassium conduction



g_k at -20mV

$$\left(1 - e^{\frac{-t}{t_n}}\right)^n$$

n = 4

- HH proposed that movement of K through the membrane occurred via gates,which were voltage sensitive, such that membrane depolarization favored the switching from a closed state to an open state.
- The opening of the gate was controlled by four gating particles,which they named n.
- Each of which had to be aligned appropriately for the gate to open.

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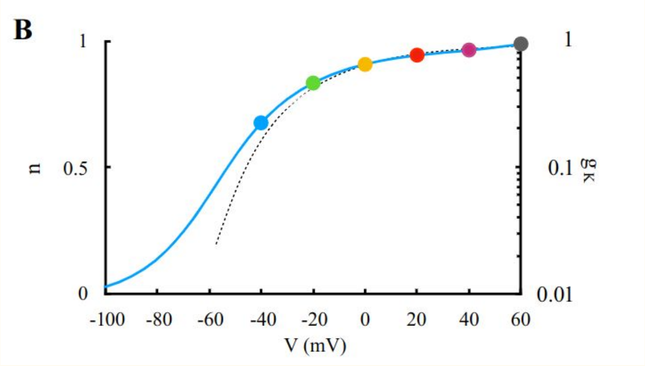
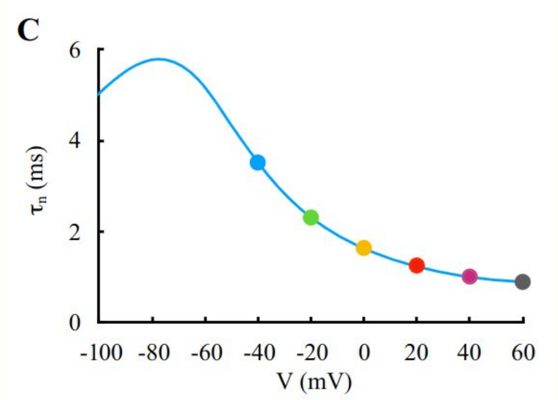
Potassium conduction



$$g_{\mathrm{K}} = \left[g_{\mathrm{K}\infty}{}^{\frac{1}{4}} - \left(g_{\mathrm{K}\infty}{}^{\frac{1}{4}} - g_{\mathrm{K}0}{}^{\frac{1}{4}} \right) e^{\frac{-t}{\tau n}} \right]^4$$

$$g_{\mathrm{K}} = \bar{g}_{\mathrm{K}} n^4$$

$$n = \sqrt[4]{\frac{g_{\mathrm{K}}}{\bar{g}_{\mathrm{K}}}}$$



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$$C \underset{\beta_n}{\overset{\alpha_n}{\rightleftarrows}} O$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_{\mathrm{n}}(1 - n) - \beta_n n$$

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

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

$$\alpha_n = \frac{n_\infty}{\tau_n}$$

$$\beta_n = \frac{1 - n_\infty}{\tau_n}$$

$$\alpha_n = 0.01 \frac{(V + 55)}{1 - e^{\left[\frac{-(V+55)}{10}\right]}}$$

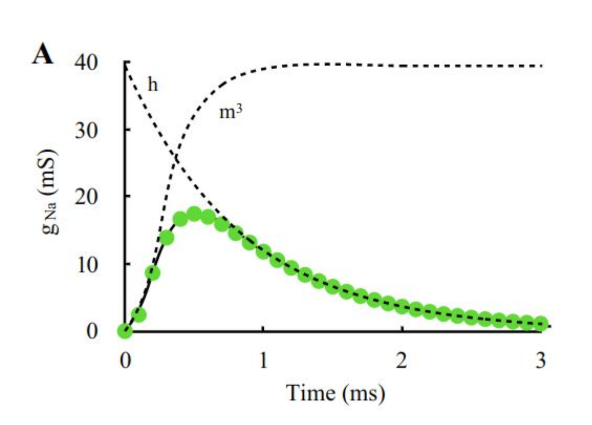
$$\beta_n = 0.0555 e^{\left(\frac{-V}{80}\right)}$$

$$I_{\mathrm{K}} = \bar{g}_{\mathrm{K}} n^4 \left(V - E_{\mathrm{K}}\right)$$

Sodium conduction

During rising phase best fit can be obtained by

$$g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} \left[1 - e^{\left(\frac{-t}{\tau_m}\right)}\right]^3$$



During falling phase, best fit was obtained by raising factor h to power 1

$$g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} \left[1 - e^{\left(\frac{-t}{\tau_m}\right)}\right]^3 e^{\left(\frac{t}{\tau_h}\right)}$$

Conductance at depolarisation at -20mV

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

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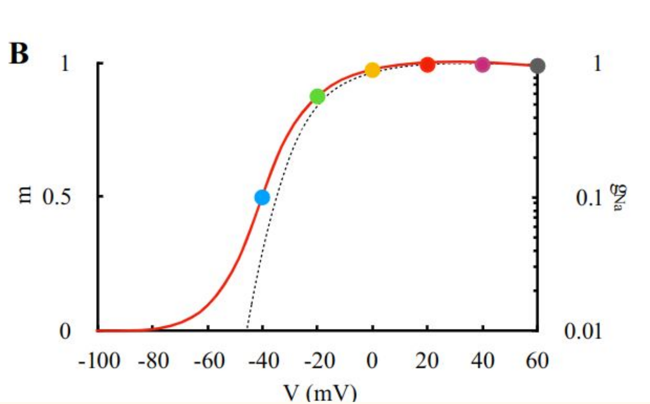
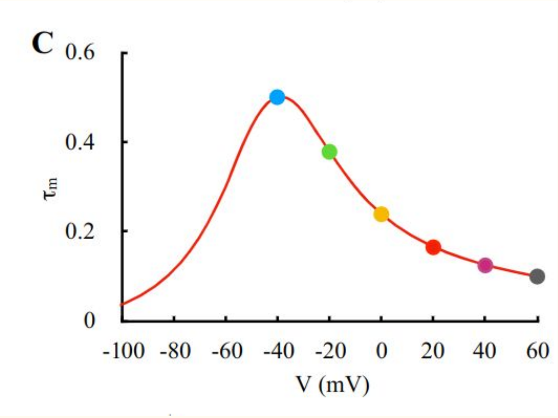
Sodium conduction





For initial curve fitting they fixed h=1

$$m = \sqrt[3]{\left[\frac{g_{\mathrm{Na}}}{\bar{g}_{\mathrm{Na}}}\right]}$$

$$g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}}\left[1 - e^{\left(\frac{-t}{\tau_m}\right)}\right]^3$$

$$\tau_m = \frac{1}{\alpha_m + \beta_m}$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}$$

$$\alpha_m = \frac{m_\infty}{\tau_m}$$

$$\beta_m = \frac{1 - m_\infty}{\tau_m}$$

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Sodium conduction

$$g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} \left[1 - e^{\left(\frac{-t}{\tau_m}\right)}\right]^3 e^{\left(\frac{t}{\tau_h}\right)}$$

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

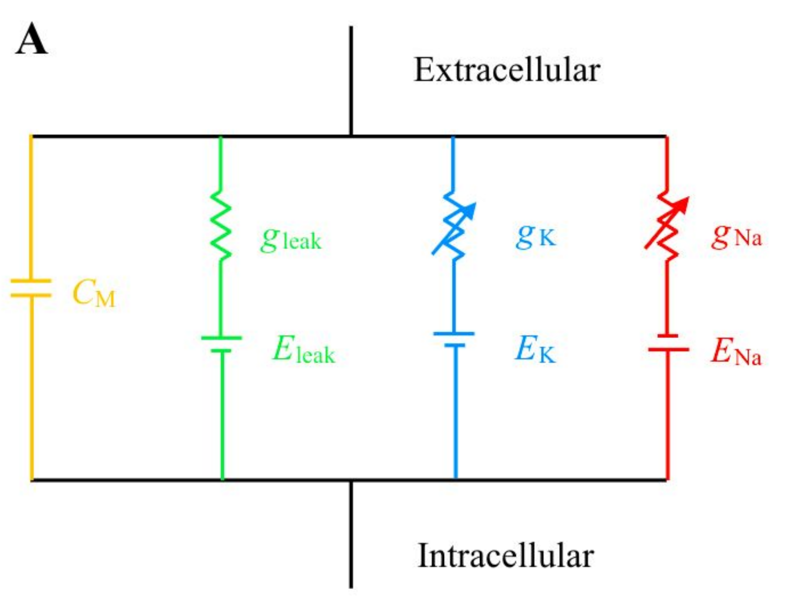
$$\tau_h = \frac{1}{\alpha_h + \beta_h}$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}$$

$$\alpha_h = \frac{h_\infty}{\tau_h}$$

$$\beta_h = \frac{1 - h_\infty}{\tau_h}$$

$$I_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} m^3 h \left(V - E_{\mathrm{Na}}\right)$$



$$I = C_{\mathrm{M}}\frac{\mathrm{d}V}{\mathrm{d}t} + \bar{g}_{\mathrm{leak}}\left(V - E_{\mathrm{leak}}\right) + \bar{g}_{\mathrm{K}}n^4\left(V - E_{\mathrm{K}}\right) + \bar{g}_{\mathrm{Na}}m^3h\left(V - E_{\mathrm{Na}}\right)$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(1-n) - \beta_n n$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1-m) - \beta_m m$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1-h) - \beta_h h$$

$$\alpha_n = 0.01\frac{(V+55)}{1-e^{\left[\frac{-(V+55)}{10}\right]}}$$

$$\beta_n = 0.0555e^{\left(\frac{-V}{80}\right)}$$

$$\alpha_m = \frac{0.1(V+40)}{1-e^{\left(\frac{-V+40}{10}\right)}}$$

$$\beta_m = 0.108e^{\left(\frac{-V}{18}\right)}$$

$$\alpha_h = 0.0027e^{\left(\frac{-V}{20}\right)}$$

$$\beta_h = \frac{1}{1-e^{\left(\frac{-V+35}{10}\right)}}$$

E_{Na}=50mV
E_K=77 mV
E_{leak}=54.4 mV
g_{Na}= 120 $mScm^{-2}$
g_K=36 $mScm^{-2}$
g_{leak}= 0.3 $mScm^{-2}$
C_M= 0.9 μFcm^{-2}

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References

A color-coded graphical guide to the Hodgkin and Huxley papers Amy J. Hopper, Hana Beswick-Jones and Angus M. Brown ,Advances in Physiology EducationVolume 46, Issue 4Dec 2022

A quantitative description of membrane current and its application to conduction and excitation in nerve A. L. Hodgkin and A. F. Huxley, J Physiol. 1952 Aug 28; 117(4): 500–544.

Chapter 2-7 - A companion guide to the Hodgkin-Huxley papers Angus M Brown

Thank You

Sodium conduction

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

$$m = \sqrt[3]{\left[\frac{g_{\mathrm{Na}}}{\bar{g}_{\mathrm{Na}}}\right]}$$

$$\tau_h = \frac{1}{\alpha_h + \beta_h}$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}$$

$$\alpha_h = \frac{h_\infty}{\tau_h}$$

$$\beta_h = \frac{1 - h_\infty}{\tau_h}$$

$$g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} \left[1 - e^{\left(\frac{-t}{(m)}\right)}\right]^3$$

$$\tau_m = \frac{1}{\alpha_m + \beta_m}$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}$$

$$\alpha_m = \frac{m_\infty}{\tau_m}$$

$$\beta_m = \frac{1 - m_\infty}{\tau_m}$$

$$g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} \left[1 - e^{\left(\frac{-t}{\tau_m}\right)}\right]^3 e^{\left(\frac{t}{\tau_h}\right)}$$

$$I_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} m^3 h \left(V - E_{\mathrm{Na}}\right)$$

$$I = C_{\mathrm{M}}\frac{\mathrm{d}V}{\mathrm{d}t}+\bar{g}_{\text{leak}}\left(V-E_{\text{leak}}\right)+\bar{g}_{\mathrm{K}}n^{4}\left(V-E_{\mathrm{K}}\right) + \bar{g}_{\mathrm{Na}}m^{3}h\left(V-E_{\mathrm{Na}}\right)$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(1-n)-\beta_n n$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1-m)-\beta_m m$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1-h)-\beta_h h$$

$$\alpha_n = 0.01\frac{(V+55)}{1-e^{\left[\frac{-(V+55)}{10}\right]}}$$

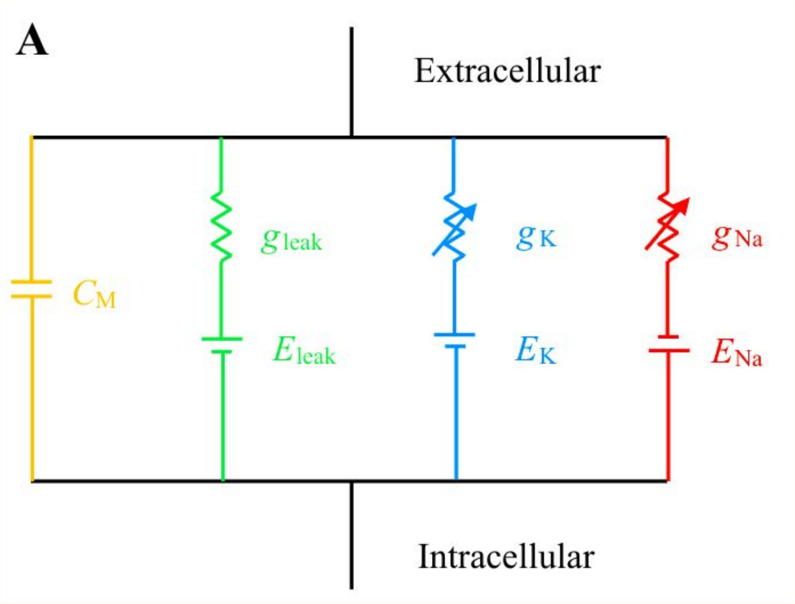
$$\beta_n = 0.0555e^{\left(\frac{-V}{80}\right)}$$

$$\alpha_m = \frac{0.1(V+40)}{1-e^{\left(\frac{-V+40}{10}\right)}}$$

$$\beta_m = 0.108e^{\left(\frac{(-V}{18}\right)}$$

$$\alpha_h = 0.0027e^{\left(\frac{-V}{20}\right)}$$

$$\beta_h = \frac{1}{1-e^{\left(\frac{-V+35}{10}\right)}}$$



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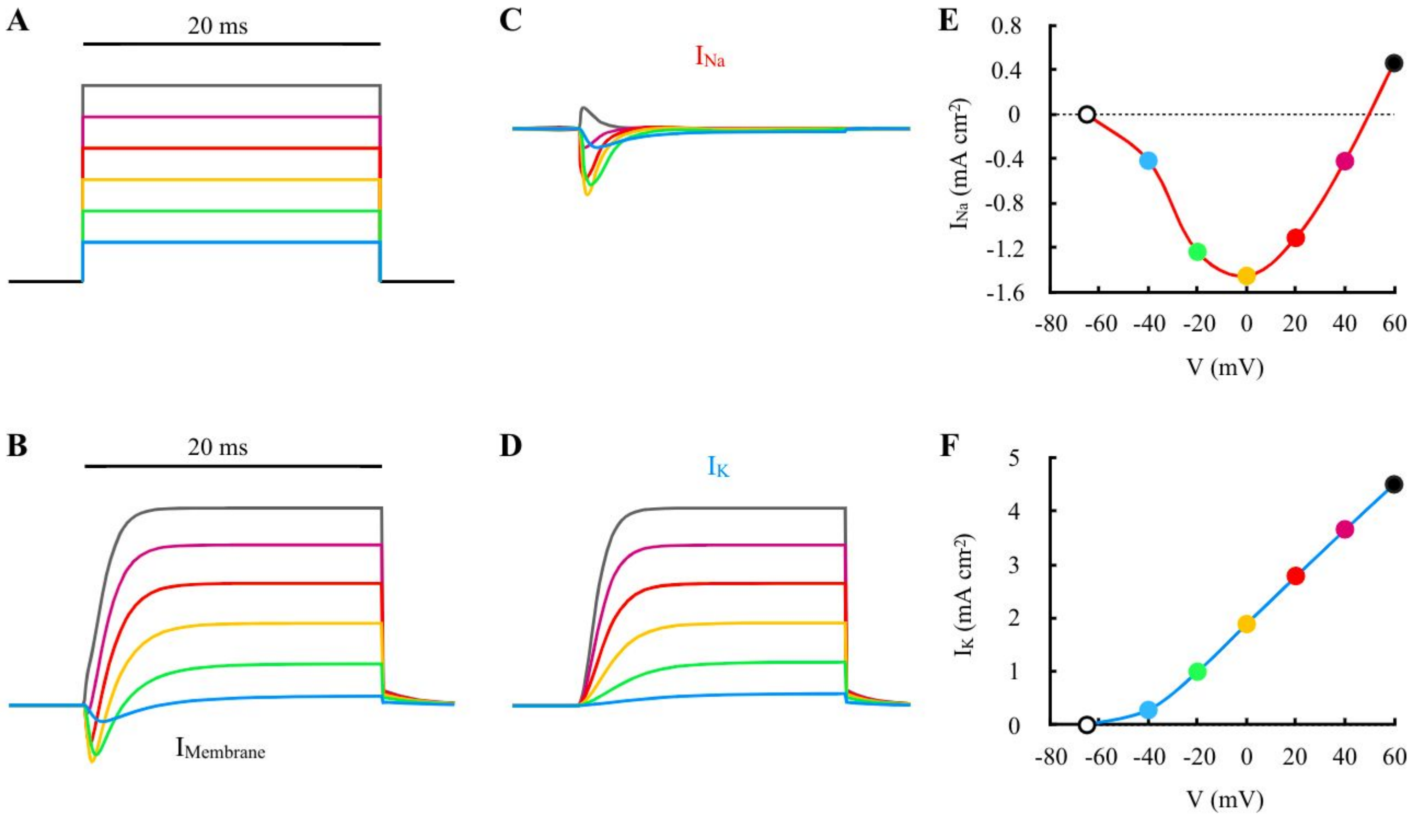

Figure 2. Membrane currents evoked by depolarization. *A*: single depolarizing pulses of 20-ms duration from rest (−65 mV) were imposed with the voltage-clamp technique. The voltage steps proceed from −40 mV (blue) to +60 mV (gray) in 20-mV steps. The evoked currents are color coded according to the voltage step in all panels. *B*: the resulting membrane current ($I_{Membrane}$) comprised 2 components, a transient early inward current followed by a later persistent outward current. *C* and *D*: reducing the Na^+ in the seawater to 10% or 30% and replacing it with choline allowed separation of the current into the early Na^+ (I_{Na}; *C*) and late K^+ (I_K; *D*) components. *E*: plotting peak I_{Na} vs. membrane potential (*V*) produced a nonlinear steady-state current-voltage (*I-V*) relationship that reversed polarity at the Na^+ equilibrium potential (E_{Na}). *F*: the maximum steady-state I_K vs. membrane potential produced an almost linear *I-V* relationship. The open data points at −65 mV describe the current evoked at rest (traces not shown in *B–D*).

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