

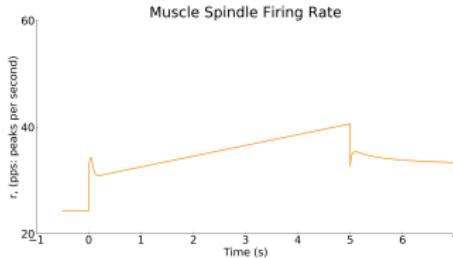
Neuromechanics of Human Motion

Action Potentials

Joshua Cashaback, Ph.D.

Recap — Sensory Organs

1. Should know about the visual, vestibular, somatosensory organs
2. Know the pathways to the central nervous system (e.g., spinal cord, cranial nerves)
3. Know some common sensory reflexes
4. Understand why sensory feedback is important (and what happens without it)
5. Muscle spindle model



Lecture Objectives — Action Potentials

1. Nerve Anatomy
2. Ions, Passive and Active Transport
3. Resting Membrane Potential
4. Action Potentials
5. Hodgkins-Huxley Model

History and Nobel Prize



Hodgkin, Huxley, & Eccles won the Nobel Prize for Physiology or Medicine in 1963

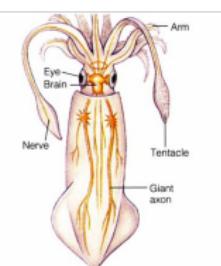
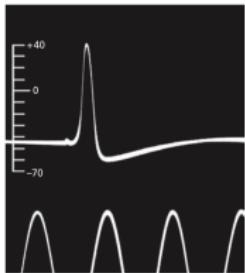
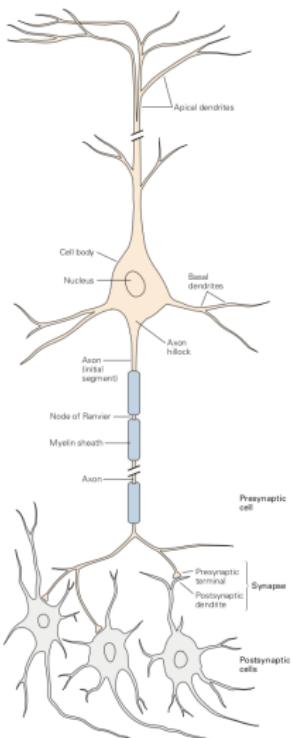


Figure 2-2 This historic tracing is the first published intracellular recording of an action potential. It was recorded in 1939 by Hodgkin and Huxley from a squid giant axon, using

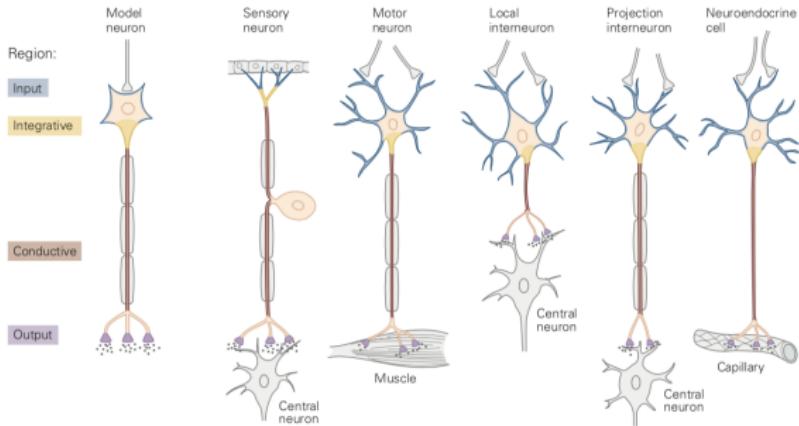
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Neuron Anatomy



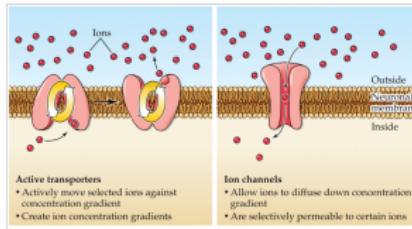
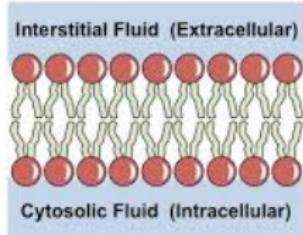
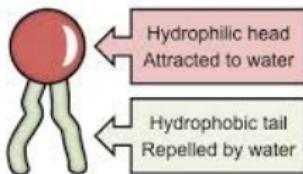
1. Neurons similarities to other cells
 - a. Phospholipid bilayer cell
 - b. cell body, nucleus
2. Neurons are unique!
 - a. morphology: dendrites & axons
 - b. Electrically excitable!

Neuron Anatomy



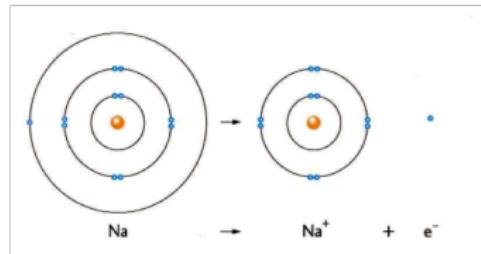
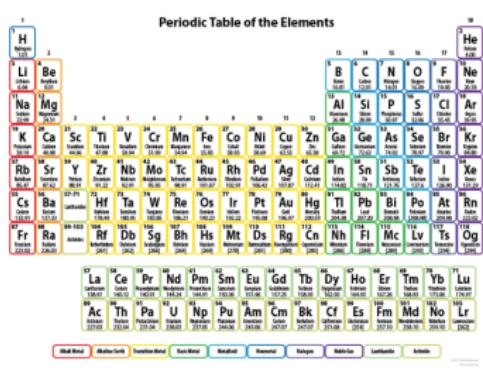
1. "Form follows function" - neurons come in many shapes and sizes
2. Integration - initial segment (not axon hillock) initiates AP
3. neuroendocrine - release message molecules (hormones) into the blood.

Neural Cell Membranes



1. hydrophilic (attracted to water)
2. hydrophobic (afraid of water)
3. proteins allow ions to flow and be pumped out of cell

Sodium and Potassium Ions



1. Sodium (Na^+) ions have a + charge (11 protons, 10 electrons)
2. Potassium (K^+) ions have a + charge (19 protons, 18 electrons)
3. Na^+ and K^+ ions create concentration gradients and electrical gradients across the cell membrane

Ion Concentrations

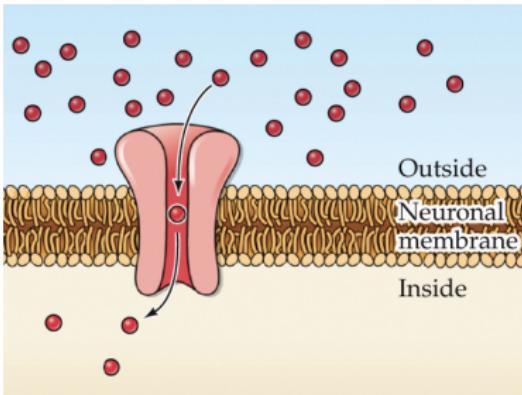


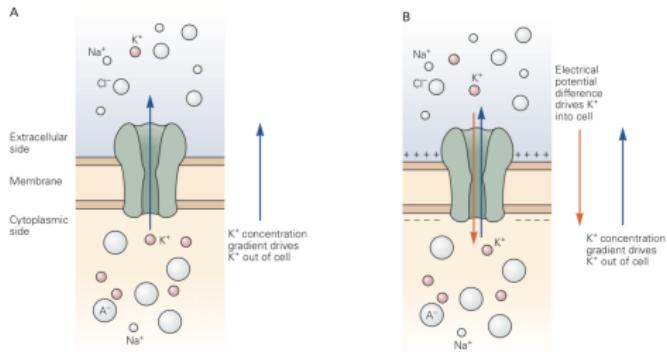
TABLE 2.1 ■ Extracellular and Intracellular Ion Concentrations

Ion	Concentration (mM)	
	Intracellular	Extracellular
Squid neuron		
Potassium (K^+)	400	20
Sodium (Na^+)	50	440
Chloride (Cl^-)	40–150	560
Calcium (Ca^{2+})	0.0001	10
Mammalian neuron		
Potassium (K^+)	140	5
Sodium (Na^+)	5–15	145
Chloride (Cl^-)	4–30	110
Calcium (Ca^{2+})	0.0001	1–2

REPRODUCED FROM Table 2.1
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1. more K^+ inside the cell (intracellular)
2. more Na^+ outside the cell (extracellular)
3. Contributions from Cl^- and Ca^{++}

Electrochemical Gradients



1. **concentration gradients** - ions want to move from high to low concentrations (e.g., K^+ in to out, Na^+ out to in)
2. **electrical gradients** - ions have a charge which can lead to electrical forces (e.g., since inside of cell negative: K^+ wants to stay in & Na^+ out to in)
3. **Equilibrium potential (of an ion):** concentration forces = opposing electrical forces

Resting Membrane (approx. -65mV)

Membrane Potential: the difference in electrical charge between the inside and outside of the cell

- depends on concentration of ions on inside and outside of the cell

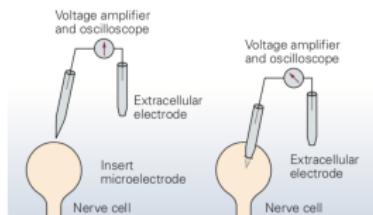


Figure 6-2A The recording setup.

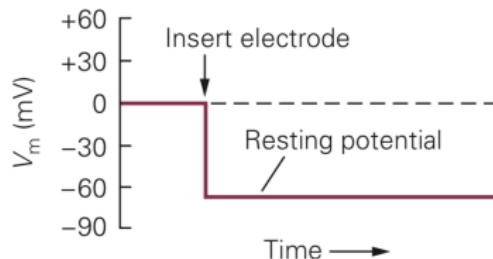


Figure 6-2B Oscilloscope display.

Resting Membrane (approx. -65mV)

Membrane Potential: the difference in electrical charge between the inside and outside of the cell

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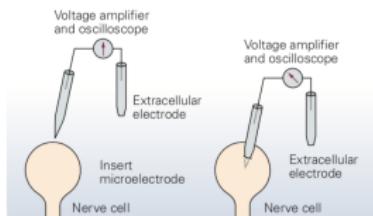


Figure 6-2A The recording setup.

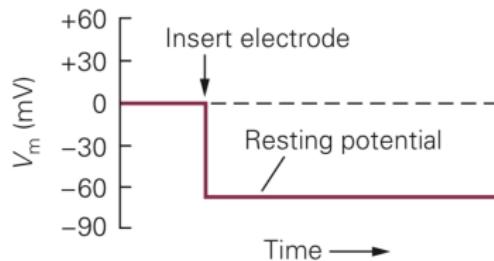
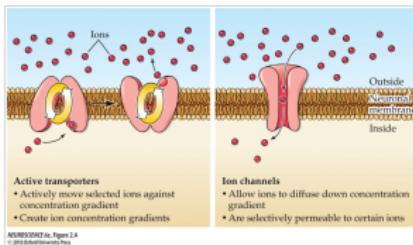


Figure 6-2B Oscilloscope display.

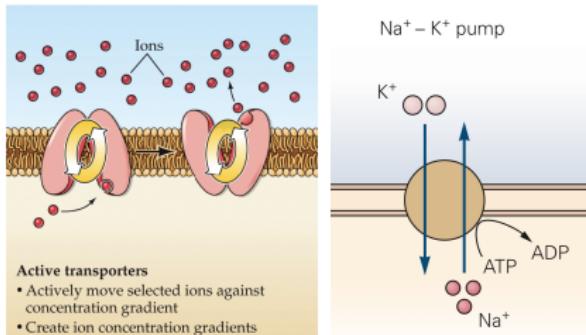
Different trans-membrane protein channels regulate ion flow and are critical to maintaining membrane potential

Trans-Membrane Protein Channels and Pumps



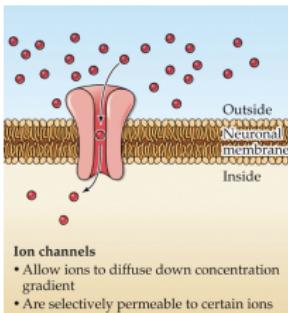
1. **Active Transport** - Ions move against the net *electrochemical gradient*
 - a. Na-K pump
2. **Passive Transport** - Ions move with the net electrochemical gradient
 - a. Leak Channels
 - b. Voltage-Gated Channels

NA-K Pumps



1. Pumps move ions *against* the net electrochemical gradient
2. Requires energy (ATP - adenosine triphosphate)
3. $1 \text{ ATP} = 2 \text{ } K^+ \text{ in and } 3 \text{ } Na^+ \text{ out}$
4. Maintains imbalance of K^+ and Na^+ inside and outside the cell
5. intracellular (-charge), extracellular (+charge): more positive ions leaving

Leak Channels



1. “Leak” trans-membrane protein channels always in an ‘open’ state
2. **Ion specific** flow *with* the net electrochemical gradient
3. Leak channels for all types of ions, however, K^+ has the largest effect on the resting membrane potential (membrane more permeable to K^+ than Na^+)
4. Contribute to resting membrane potential

Ion Equilibrium Potential

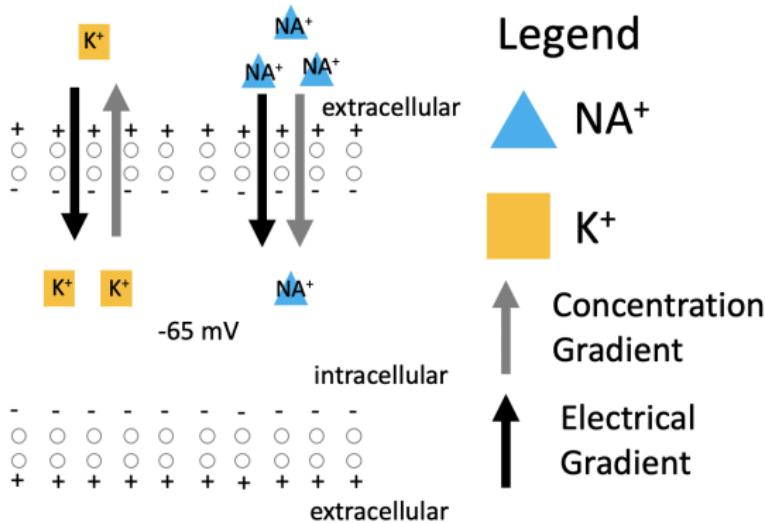
Table 6-1 Distribution of the Major Ions Across a Neuronal Membrane at Rest: The Giant Axon of the Squid

Species of ion	Concentration in cytoplasm (mM)	Concentration in extracellular fluid (mM)	Equilibrium potential ^a (mV)
K ⁺	400	20	-75
Na ⁺	50	440	+55
Cl ⁻	52	560	-60
A ⁻ (organic anions)	385	none	none

^aThe membrane potential at which there is no net flux of the ion species across the cell membrane.

1. Equilibrium potential (of a specific ion): concentration forces = opposing electrical forces (given that other ions states are constant)
2. Nernst equation - calculate membrane potential in static conditions
3. An ion's equilibrium potential depends on ion concentrations, # of leaky channels, membrane potential
4. cell more permeable to K^+ than Na^+ (note: A^- cannot leave cell)
5. K^+ leak channels main contributor to resting MP (e.g., -70mv)

Resting Membrane Potential



1. Note concentration and electrical gradients

Resting Membrane Potential

1. Approximately -65mV (variable - species, neuron)
2. Goldman Equation: Calculate resting membrane potential (static)
3. Leak channels for all ions contribute to resting membrane potential (K⁺ most influential)
4. Na-K pumps also contribute to resting potential

Resting Membrane Potential

1. Approximately -65mV (variable - species, neuron)
2. Goldman Equation: Calculate resting membrane potential (static)
3. Leak channels for all ions contribute to resting membrane potential (K⁺ most influential)
4. Na-K pumps also contribute to resting potential

Video on membrane resting potentials (too long for class)

<https://www.khanacademy.org/science/health-and-medicine/nervous-system-and-sensory-information/neuron-membrane-potentials-topic/v/neuron-resting-potential-mechanism>

* copy and paste into your browser

Action Potential

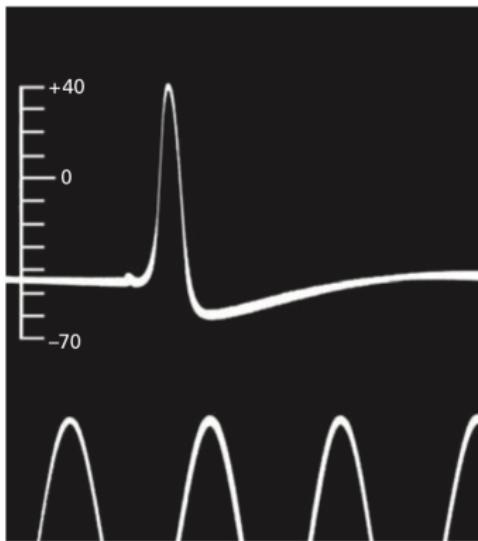
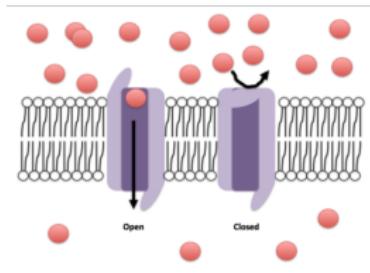


Figure 2-2 This historic tracing is the first published intra-cellular recording of an action potential. It was recorded in 1939 by Hodgkin and Huxley from a squid giant axon, using

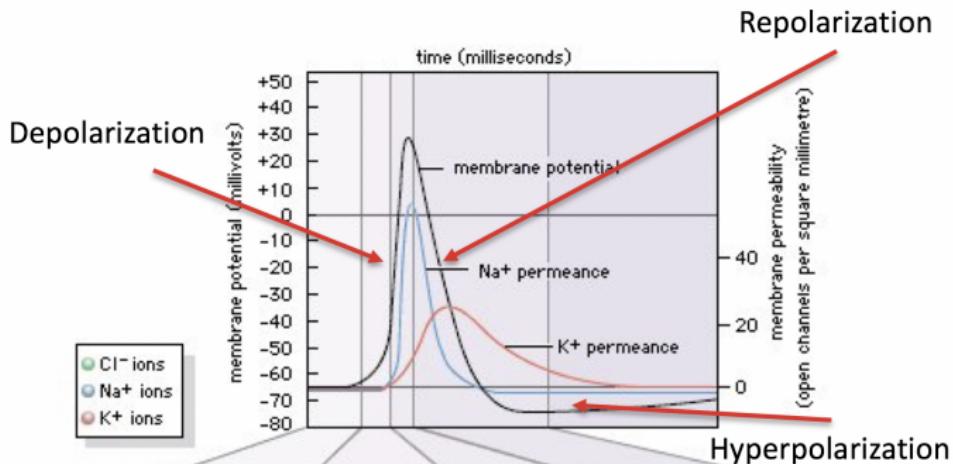
APs can occur because of voltage-gated channels

Gated Channels



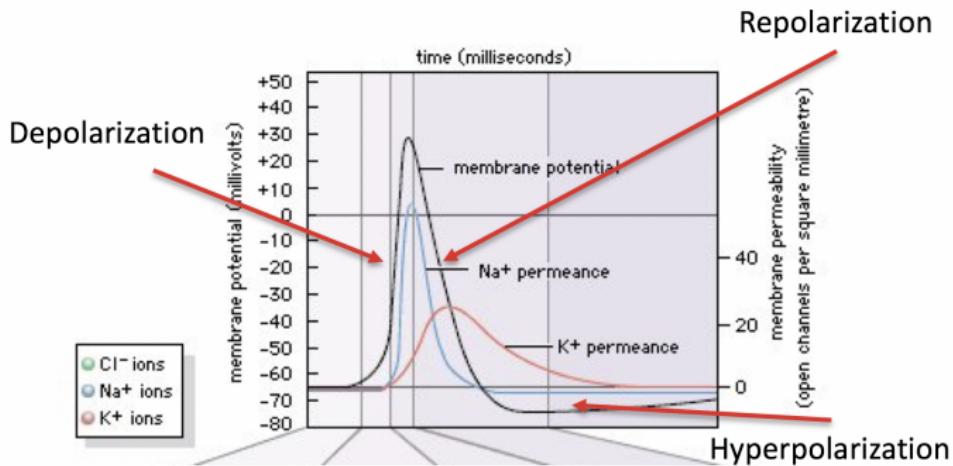
1. Many types of ion gating (mechanical, thermal, **voltage**, etc.)
2. “Gated” trans-membrane protein channels have different “states”
3. States: open, closed, inactive
4. **Voltage-Gated channels critical for generation of action potentials (e.g., nerve firing)**

Action Potential



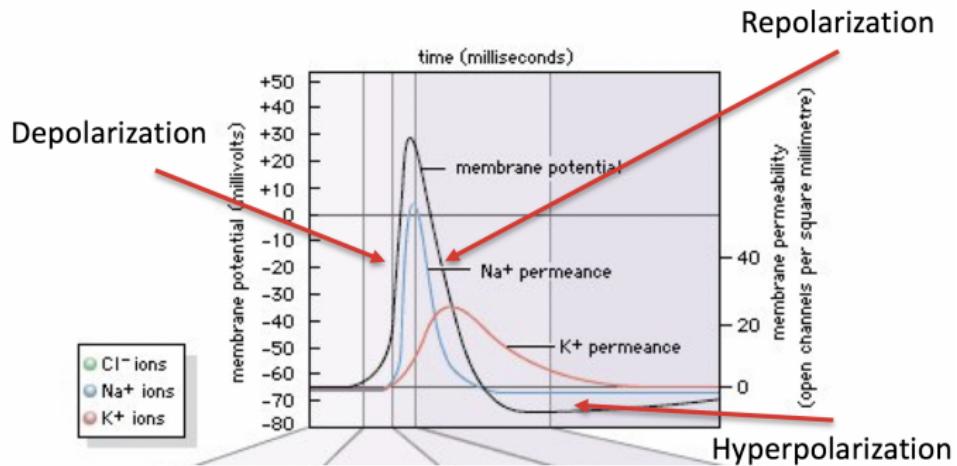
1. Initial segment integrates inputs (voltage) from dendrites
2. If voltage crosses a threshold = Na and K voltage gates open
3. **ALL OR NONE RESPONSE!!!**

Action Potential



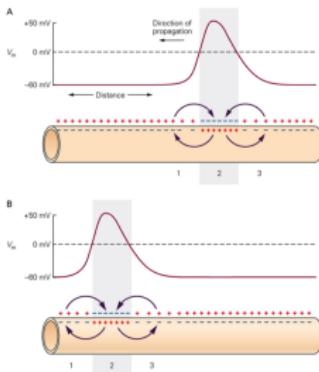
1. Na voltage-gates open and close at a fast rate (depolarization - towards Na equilibrium potential)
2. K open and close at a slow rate (repolarization, hyperpolarization - towards K equilibrium potential)

Refractory Period



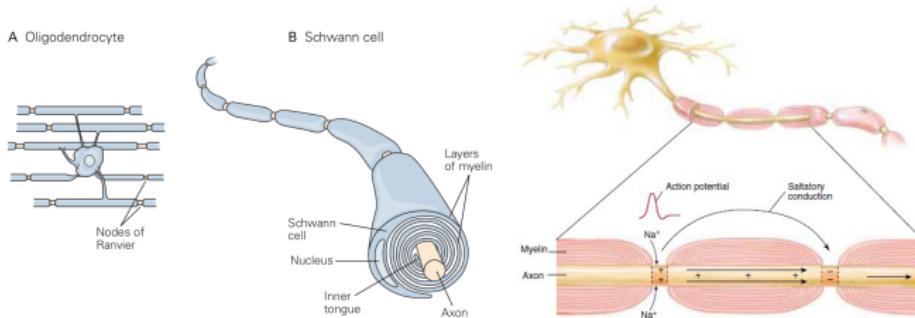
1. Na channels inactive during hyperpolarization
2. Cell cannot repolarize during this 'refractory period'
3. Prevents APs from flowing in backwards direction

Propagation



1. Until now, viewing APs temporally (at a specific location) not spatially
2. Spatially adjacent voltage-gates open, allowing the AP to propagate
3. Single direction

Myelin



1. Glial cells
 - a. Oligodendrocyte - central nervous system
 - b. Schwann Cell - peripheral nervous system
2. lipids, insulation
3. Action Potentials move faster by jumping over myelin and depolarizing at the Nodes of Ranvier

Action Potentials — Video and Demo

Video

<https://www.youtube.com/watch?v=7EyhsOewnH4>

Demo - University of Alberta

<https://neuromembrane.ualberta.ca/account/login>

NOW TO THE FUN STUFF! HODGKIN-HUXLEY MODEL

Hodgkin-Huxley Model

Major Innovation

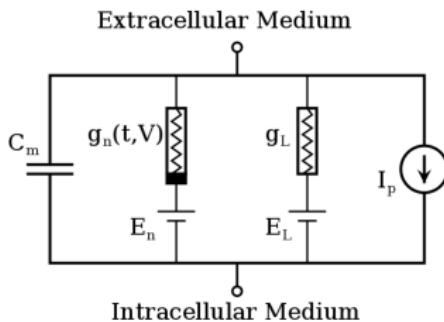
1. Action Potential Thresholding
2. “All-or-None response”

Electrical Circuit

$$\frac{dE}{dt} = \frac{I}{C}$$

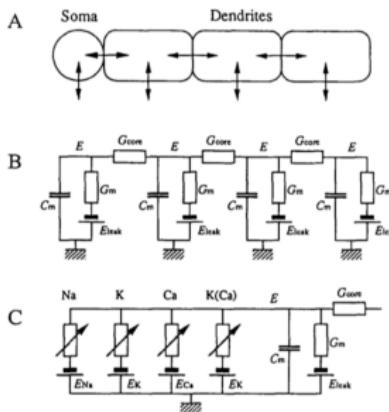
1. E : Voltage (e.g., water pressure in a pipe)
2. I : Current (e.g., flow through a pipe)
3. C : Capacitance (ability to store an electrical charge)

Nerve Model — Electrical Circuit



1. C_m : Lipid bilayer is represented as a capacitance (ability to store an electrical charge)
2. g_n and g_L voltage-gated and leak channels represented as nonlinear and linear conductances
3. E electrochemical gradients from ions represented as batteries
4. I_p ion pumps represented by current sources

Nerve Model — Electrical Circuit



- A) Modelling dendrites different distances from Soma
 - B) Soma, dendrites modelled as electrical compartments
 - C) depiction of soma, with different ion channels
- We're just going to model the Soma

HH model (Ekeberg et al., 1991)

$$\frac{dE}{dt} = \frac{(E_{\text{leak}} - E)G_m + \Sigma(E_{\text{comp}})G_{\text{core}} + I_{\text{channels}}}{C_m}$$

1. dE/dt = Voltage (membrane potential) change over time (Ekeberg's notation)
2. Passive leakage current
3. Electrical coupling of different compartments
4. Currents of the various channels
5. Membrane Capacitance

Modelling Just the Soma

$$\frac{dE_{soma}}{dt} = \frac{(E_{leak} - E_{soma})G_m + I_{channels}}{C_m}$$

1. Ignoring multiple dendrites
2. $E_{leak} = -7.0 \times 10^{-2}$
3. $G_m = 3.0 \times 10^{-9}$
4. $C_m = 3.0 \times 10^{-11}$

Adding External Current

$$\frac{dE_{soma}}{dt} = \frac{(E_{leak} - E_{soma})G_m + I_{channels} + I_{ext}}{C_m}$$

1. Sum of dendrite currents (not currently modelled), or
2. Ejecting current as in a patch-clamp experiment

Channel Current

Hodgkin-Huxley Model:

$$I_{channels} = I_{Na} + I_K$$

Sodium Channels — Current

$$I_{Na} = (E_{Na} - E_{soma})G_{Na}m^3h$$

1. I_{Na} : sodium current
2. m : activation of the sodium channel
3. h : inactivation of the sodium channel
4. E_{Na} : sodium reversal potential
5. G_{Na} : maximal sodium conductance
6. E_{soma} : soma membrane potential

Sodium Channels — Activation

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

1. α_m : rate channel goes from closed to open state
2. β_m : rate channel goes from open to closed state

$$\alpha_m = \frac{A_{\alpha_m}(E_{soma} - B_{\alpha_m})}{1 - e^{(B_{\alpha_m} - E_{soma})/C_{\alpha_m}}}$$

$$\beta_m = \frac{A_{\beta_m}(B_{\beta_m} - E_{soma})}{1 - e^{(E_{soma} - B_{\beta_m})/C_{\beta_m}}}$$

Note: α_m and β_m on right side of these two equations are all subscripts (not parameters)

Model Parameters

Table 1. Parameters used in describing the ion channels

		Na ⁺		K ⁺	Ca ²⁺	NMDA
		<i>m</i>	<i>h</i>	<i>n</i>	<i>q</i>	<i>p</i>
α	<i>A</i> (mV ⁻¹ ms ⁻¹)	0.2	0.08		0.02	0.08
	<i>B</i> (mV)	-40	-40		-31	-10
	<i>C</i> (mV)	1	1		0.8	11
β	<i>A</i> (mV ⁻¹ ms ⁻¹)	0.06	0.4 (ms ⁻¹)	0.005	0.001	0.1 (ms ⁻¹)
	<i>B</i> (mV)	-49	-36		-28	-10
	<i>C</i> (mV)	20	2		0.4	0.5

Table 2. Parameters used for the neuron simulations in this paper. The parameters correspond to those of excitatory interneurons in the simulations of the spinal locomotor network of the lamprey

Passive Properties		Active Properties			
E_{leak}	-70 mV	E_{Na}	50 mV	ϱ_{AP}	4 s ⁻¹ mV ⁻¹
G_m , Soma	0.003 μS	G_{Na}	1.0 μS	δ_{AP}	30 s ⁻¹
C_m , Soma	0.03 nF	E_K	-90 mV	ϱ_{NMDA}	0.5 s ⁻¹ mV ⁻¹
G_m , Dendrites	0.01 μS	G_K	0.2 μS	δ_{NMDA}	3 s ⁻¹
C_m , Dendrites	0.3 nF	E_{Ca}	150 mV	$G_{\text{K}(\text{Ca})}$	0.01 μS
G_{core}	0.04 μS	G_{Ca}	0 μS		

Sodium Activation Parameters

1. $E_{Na} = 5.0 \times 10^{-2}$
2. $G_{Na} = 1.0 \times 10^{-6}$
3. $A_{\alpha m} = 2.0 \times 10^{+5}$
4. $B_{\alpha m} = -4.0 \times 10^{-2}$
5. $C_{\alpha m} = 1.0 \times 10^{-3}$
6. $A_{\beta m} = 6.0 \times 10^{+4}$
7. $B_{\beta m} = -4.9 \times 10^{-2}$
8. $C_{\beta m} = 2.0 \times 10^{-2}$

Sodium Channels — Inactivation

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

$$\alpha_h = \frac{A_{\alpha_h}(B_{\alpha_h} - E_{soma})}{1 - e^{(E_{soma} - B_{\alpha_h})/C_{\alpha_h}}}$$

$$\beta_h = \frac{A_{\beta_h}}{1 + e^{(B_{\beta_h} - E_{soma})/C_{\beta_h}}}$$

Sodium Inactivation Parameters

1. $A_{\alpha h} = 8.0 \times 10^{+4}$
2. $B_{\alpha h} = -4.0 \times 10^{-2}$
3. $C_{\alpha h} = 1.0 \times 10^{-3}$
4. $A_{\beta h} = 4.0 \times 10^{+2}$
5. $B_{\beta h} = -3.6 \times 10^{-2}$
6. $C_{\beta h} = 2.0 \times 10^{-3}$

Potassium Channels

$$I_K = (E_K - E_{soma}) G_K n^4$$

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

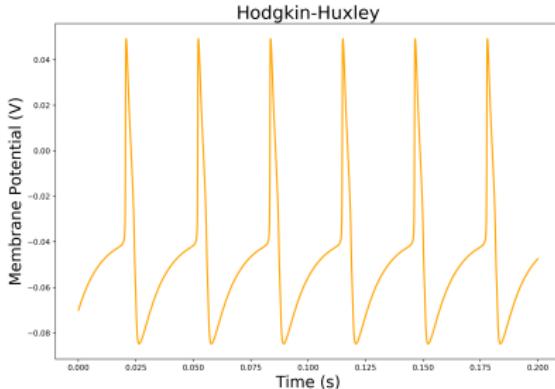
$$\alpha_n = \frac{A_{\alpha_n}(E_{soma} - B_{\alpha_n})}{1 - e^{(B_{\alpha_n} - E_{soma})/C_{\alpha_n}}}$$

$$\beta_n = \frac{A_{\beta_n}(B_{\beta_n} - E_{soma})}{1 - e^{(E_{soma} - B_{\beta_n})/C_{\beta_n}}}$$

Potassium Parameters

1. $E_K = -9.0 \times 10^{-2}$
2. $G_K = 2.0 \times 10^{-7}$
3. $A_{\alpha n} = 2.0 \times 10^{+4}$
4. $B_{\alpha n} = -3.1 \times 10^{-2}$
5. $C_{\alpha n} = 8.0 \times 10^{-4}$
6. $A_{\beta n} = 5.0 \times 10^{+3}$
7. $B_{\beta n} = -2.8 \times 10^{-2}$
8. $C_{\beta n} = 4.0 \times 10^{-4}$

Hodgkin-Huxley Model Output



1. $I_{ext} = 1.0 \times 10^{-10}$
2. $ss, dur = 0.00001, 0.2 \# stepsize(s), duration(s)$
3. $n = int(dur/ss) \# numberofsteps$
4. $E_{soma0}, m0, h0, n0, t0 =$
 $-70 \times 10^{-3}, 0, 1, 0, 0 \# InitialConditions$

Ekeberg (1991) — Long-Lasting Afterhyperpolarization

Afterhyperpolarization: the hyperpolarizing phase of the neuron's action potential when the voltage is less than the resting membrane potential.

Two additional channels:

1. Ca
2. K(Ca)

Channel Current

Hodgkin-Huxley Model:

$$I_{channels} = I_{Na} + I_K$$

Channel Current

Hodgkin-Huxley Model:

$$I_{channels} = I_{Na} + I_K$$

Ekeberg (1991) Model:

$$I_{channels} = I_{Na} + I_K + I_{Ca} + I_{K(Ca)}$$

Calcium Channel

$$I_{Ca} = (E_{Ca} - E_{soma}) G_{Ca} q^5$$

$$\frac{dq}{dt} = \alpha_q(1 - q) - \beta_q q$$

$$\alpha_q = \frac{A_{\alpha_q}(E_{soma} - B_{\alpha_q})}{1 - e^{(B_{\alpha_q} - E_{soma})/C_{\alpha_q}}}$$

$$\beta_q = \frac{A_{\beta_q}(B_{\beta_q} - E_{soma})}{1 - e^{(E_{soma} - B_{\beta_q})/C_{\beta_q}}}$$

Potassium Parameters

1. $E_{Ca} = 150 \times 10^{-03}$
2. $G_{Ca} = 1.0 \times 10^{-08}$
3. $A_{\alpha q} = 0.08 \times 10^{+06}$
4. $B_{\alpha q} = -10 \times 10^{-03}$
5. $C_{\alpha q} = 11 \times 10^{-03}$
6. $A_{\beta q} = 0.001 \times 10^{+06}$
7. $B_{\beta q} = -10 \times 10^{-03}$
8. $C_{\beta q} = 0.5 \times 10^{-03}$

Calcium dependent Potassium Channels

$$I_{K(Ca)} = (E_K - E_{soma}) G_{K(Ca)} [Ca_{AP}]$$

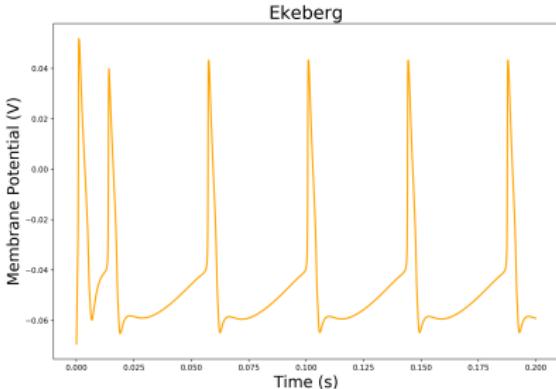
Intracellular calcium level:

$$\frac{d [Ca_{AP}]}{dt} = (E_{Ca} - E_{soma}) \varrho_{AP} q^5 - \delta_{AP} [Ca_{AP}]$$

Calcium dependent Potassium Channel Parameters

1. $G_{K(Ca)} = 0.01 \times 10^{-6}$
2. $\varrho_{ap} = 4.0 \times 10^{+03}$
3. $\delta_{ap} = 30.0$

Ekeberg Model Output



1. $I_{ext} = 2.0 \times 10^{-9}$
2. $ss, dur = 0.00001, 0.2 \# stepsize(s), duration(s)$
3. $n = int(dur/ss) \# numberofsteps$
4. $Esoma0, m0, h0, n0, q0, CaAP0, t0 =$
 $-70 \times 10^{-3}, 0, 1, 0, 0, 0, 0 \# InitialConditions$

read Ekeberg et al. (1991)

Ekeberg et al. (1991) A computer based model for realistic simulations of neural networks: I. The single neuron and synaptic interaction. Volume 65, Issue 2, pp 81-90.

1. Read to get a better sense of the model
2. Double check equations
3. Double check parameters
4. Start working on this assignment early...

Ekeberg Model — Pseudo Code

```
import numpy, math, matplotlib
from pylab import *
ss, dur = 0.00001, 0.2 # step size (s), duration (s)
n = int(dur / ss) # number of steps
E_soma0, m0, h0, n0, q0, CaAP0, t0 = -70e-03, 0, 1, 0, 0, 0, 0 # Initial Conditions
E_SOMA, M, H, N, Q, CAAP, T = np.zeros(n), np.zeros(n), np.zeros(n), np.zeros(n), np.zeros(n), np.zeros(n)
I_ext = 2.0e-9 #I_ext = 100.0e-10
for i in arange(0,n,1):
    t1 = t0 + ss
    #####
    # sodium activation channel
    # define alpha_m term
    A_alpha_m, B_alpha_m, C_alpha_m = 2.0e+5, -4.0e-2, 1.0e-3
    # define beta_m term
    A_beta_m, B_beta_m, C_beta_m = 6.0e+4, -4.9e-2, 2.0e-2
    # define Na activation channel — differential equation here
    #####
    # sodium inactivation channel
    # define alpha_h term
    A_alpha_h, B_alpha_h, C_alpha_h = 8.0e+4, -4.0e-2, 1.0e-3
    # define beta_h term
    A_beta_h, B_beta_h, C_beta_h = 4.0e+2, -3.6e-2, 2.0e-3
    # define Na inactivation channel — differential equation
    #####
    # define Na channel current
    E_Na, G_Na = 5.0e-2, 1.0e-6
```

Ekeberg Model — Pseudo Code Cont'd

```
#####
# potassium channel
# define alpha_n term
A_alpha_n, B_alpha_n, C_alpha_n = 2.0e+4, -3.1e-2, 8.0e-4
# define beta_n term
A_beta_n, B_beta_n, C_beta_n = 5.0e+3, -2.8e-2, 4.0e-4
# define K channel — differential equation
#####
# define K channel current
E_K, G_K = -9.0e-2, 2.0e-7
#####
# calcium channel
# define alpha_n term
A_alpha_q, B_alpha_q, C_alpha_q = 0.08e+06, -10e-03, 11e-03
# define beta_n term
A_beta_q, B_beta_q, C_beta_q = 0.001e+06, -10e-03, 0.5e-03
# define K channel —— differential equation
#####
# define Ca channel current
E_Ca, G_Ca = 150e-03, 1.0e-08
#####
# define intracellular Ca —— differential equation
rho_ap, delta_ap = 4.0e+03, 30.0
#####
# define Ca dependent Potassium channel current
G_K_Ca = 0.01e-06
```

Ekeberg Model — Pseudo Code Cont'd

```
#####
# sum current from all channels (e.g., I_Na + I_K)
#####
# leak current
E_leak, G_m, C_m = -7.0e-2, 3.0e-09, 3.0e-11
# define (E_soma) membrane current — differential equation
#####
# update differential equation terms from n+1 to n
```

Summary

1. Basic nerve anatomy
2. Know what contributes to resting membrane potential
 - a. ions, electrochemical gradients, leak channels and Na-K pumps
3. Understand how action potentials occur
 - a. voltage gates, depolarization, repolarization, hyperpolarization (refractory period)
4. Hodgkin-Huxley Model

QUESTIONS???

Next Classes

1. (Multi)Sensory Illusions
2. Bayesian Integration

Assignment

1. See Handout

Acknowledgements

Dinant Kistemaker

Paul Gribble

Ryan Peters

References

Kandel (2021)