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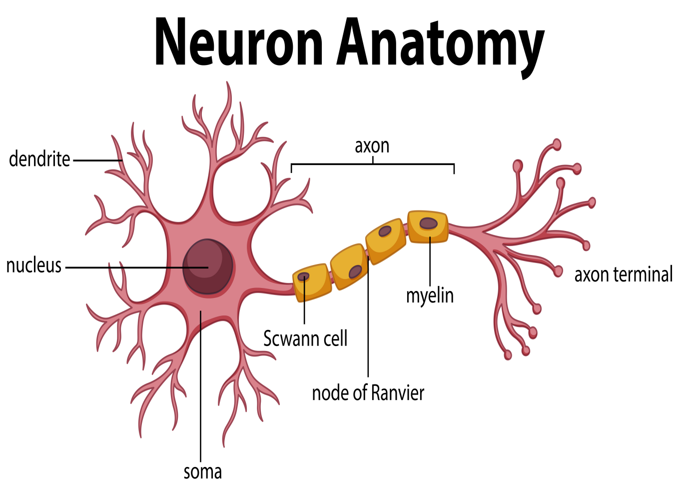
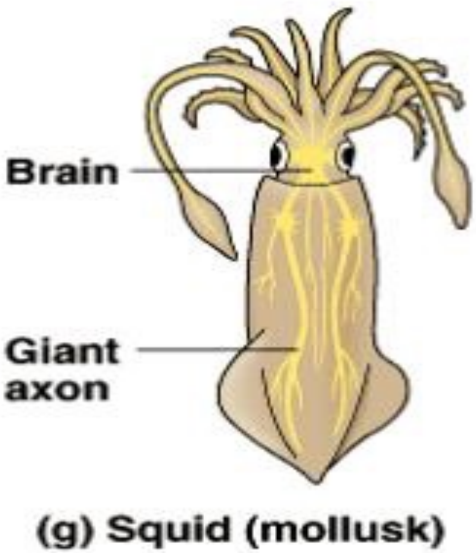
Numerical Approximations of the Hodgkin–Huxley Model



Miya Spinella

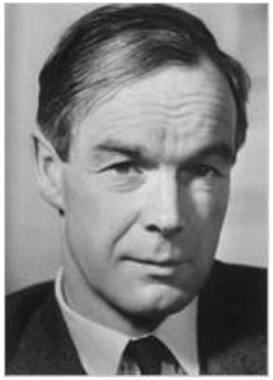


Overview

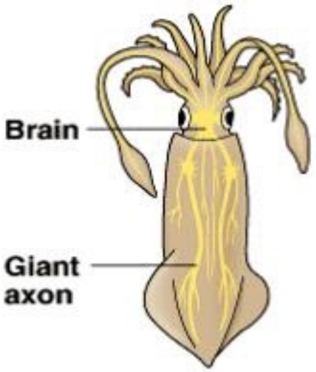
- **History** of the Hodgkin-Huxley Model
- **Background** information about neurons and action potentials
- **Equations** in the Hodgkin-Huxley Model
- **Numerical Analysis** of the Hodgkin-Huxley Model

History of Hodgkin-Huxley Model

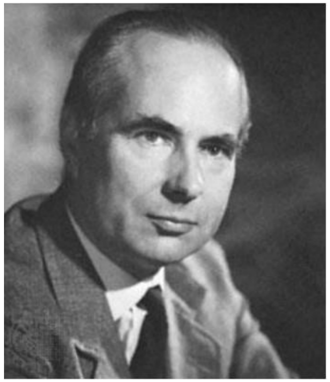
- Describes the process of an action potential
- Created by Alan Lloyd Hodgkin and Andrew Huxley with research about modelling the action potentials through the squid giant axon
- Awarded Nobel Prize in 1963



Alan Lloyd Hodgkin

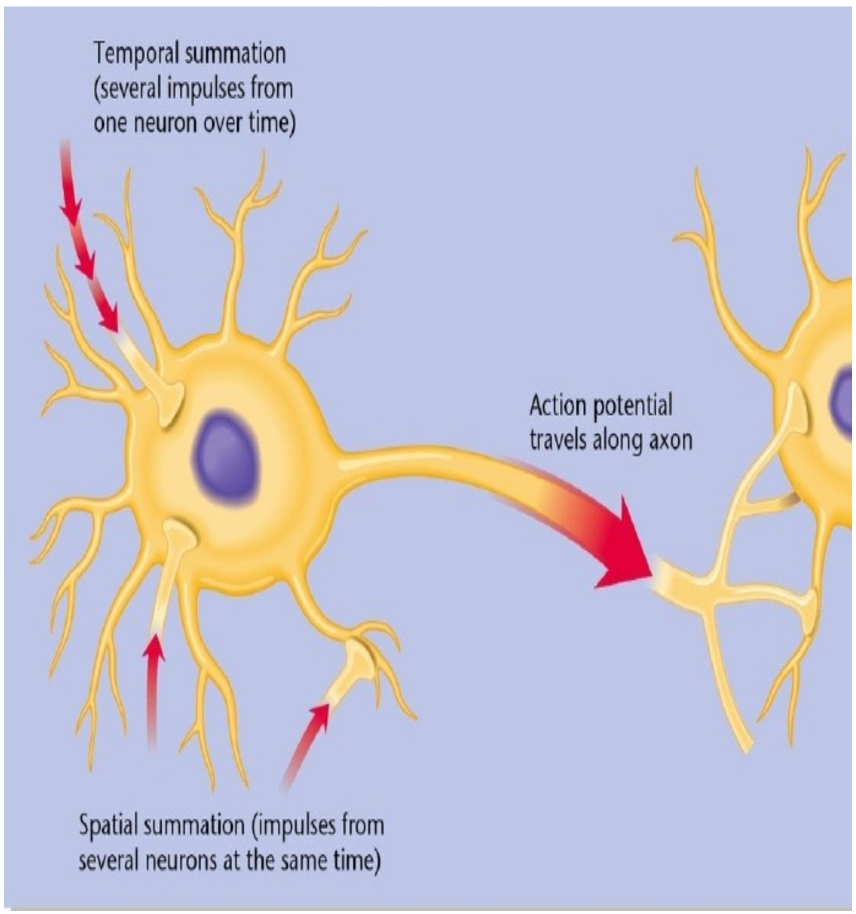


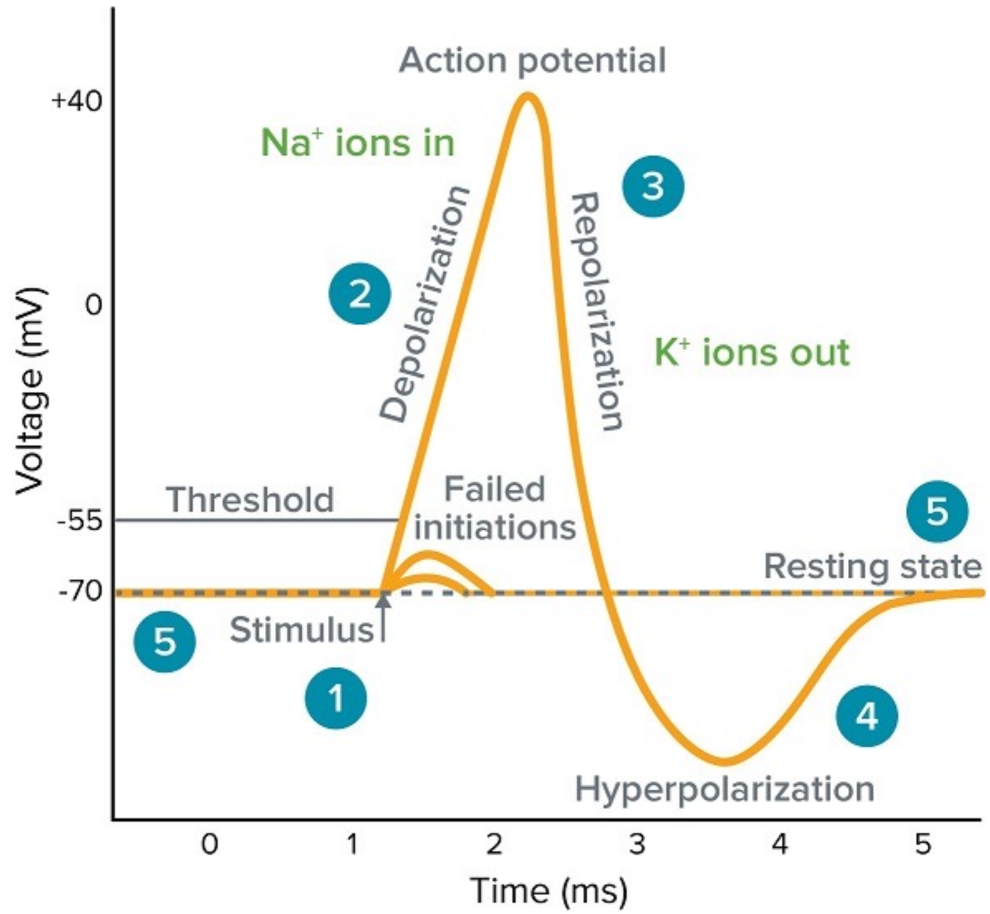
(g) Squid (mollusk)



Andrew Huxley

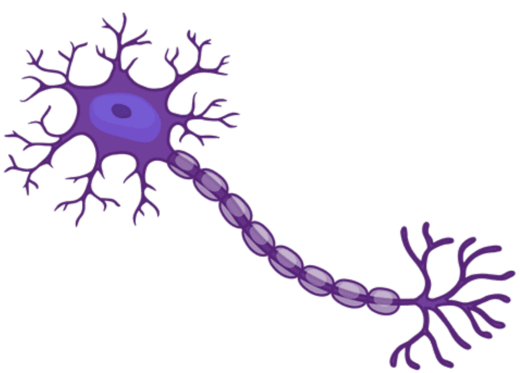
Action Potentials

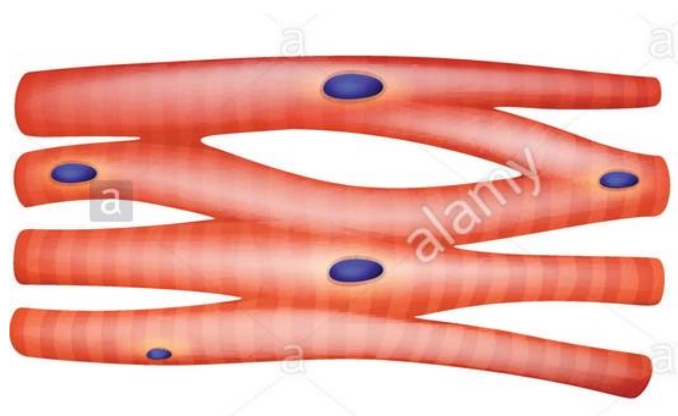


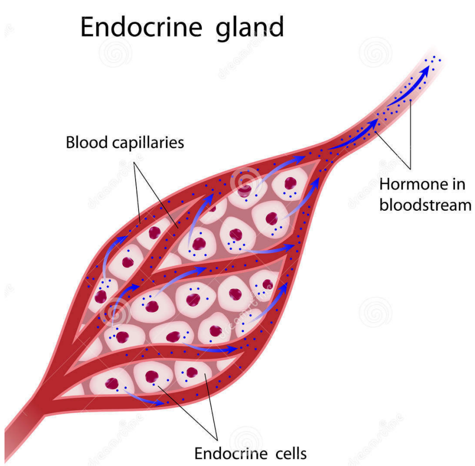


Action Potentials: Definition

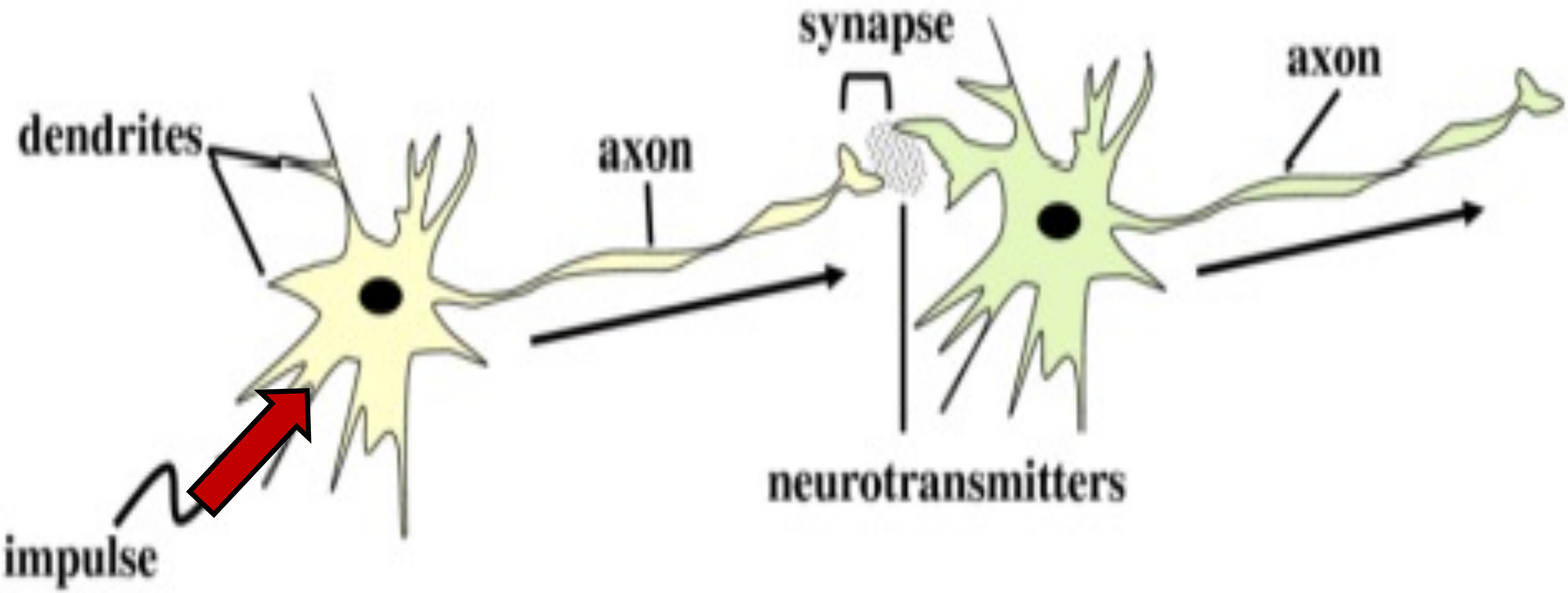
- Explosion of depolarizing current moving across a cell
- Send impulses or signals to other cells to relay information
- Occurs in excitable cells





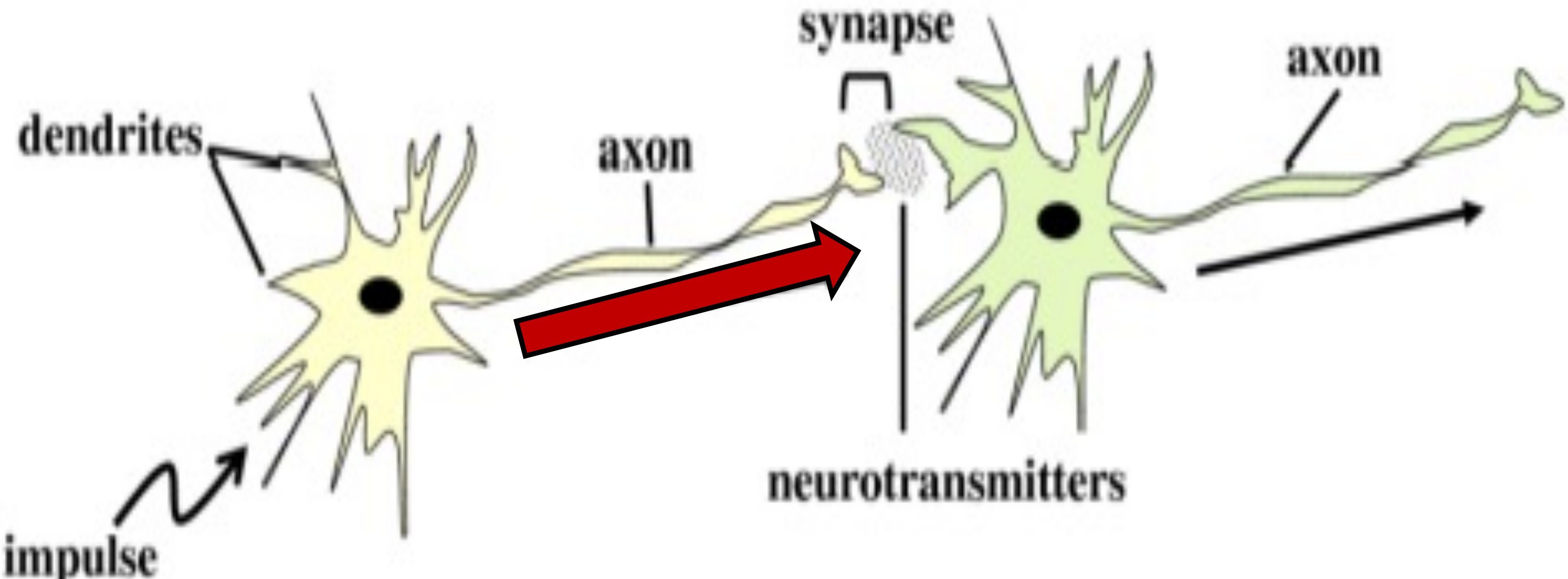


Neuron Anatomy



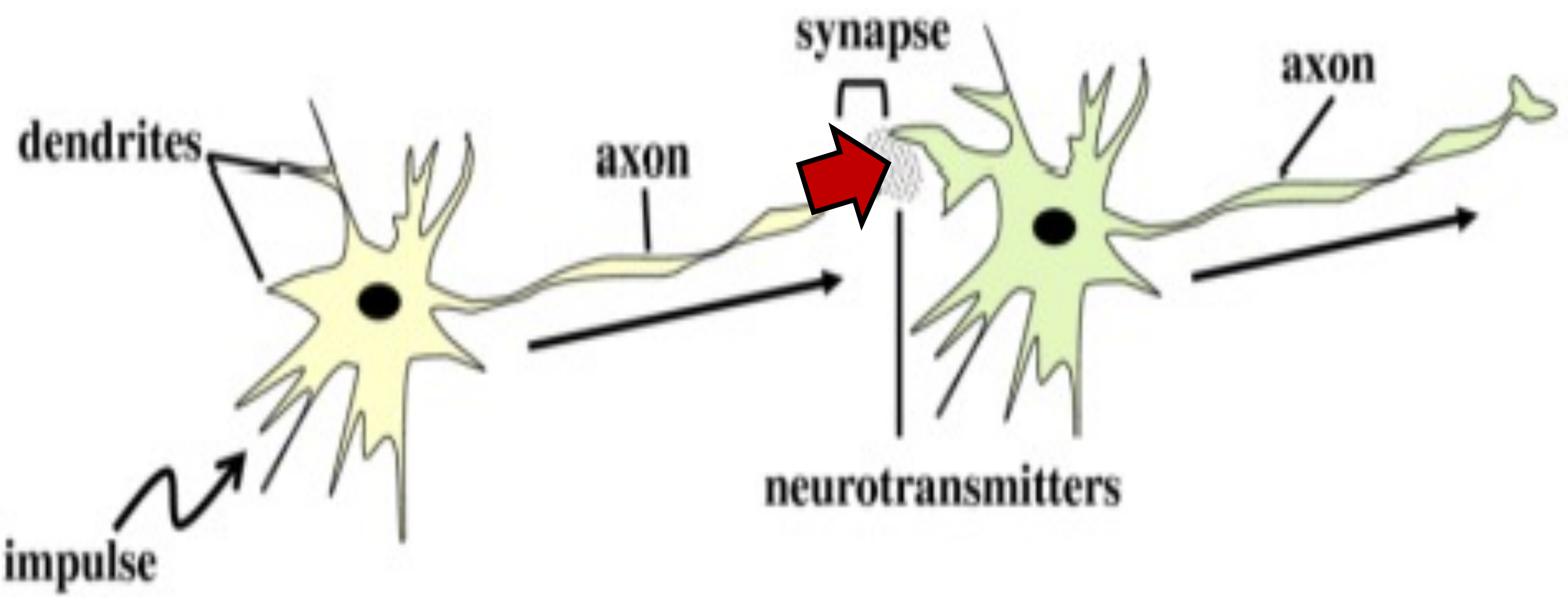
Signal Received!

Neuron Anatomy



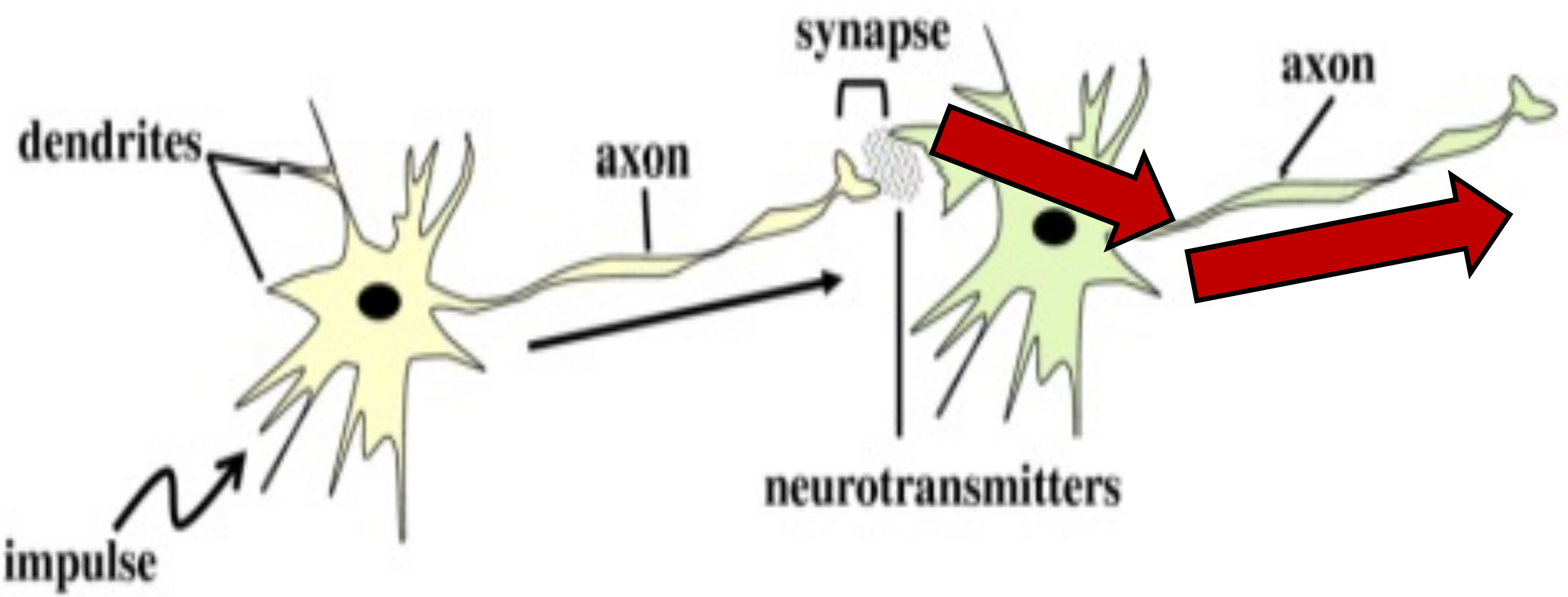
Signal Travels!

Neuron Anatomy



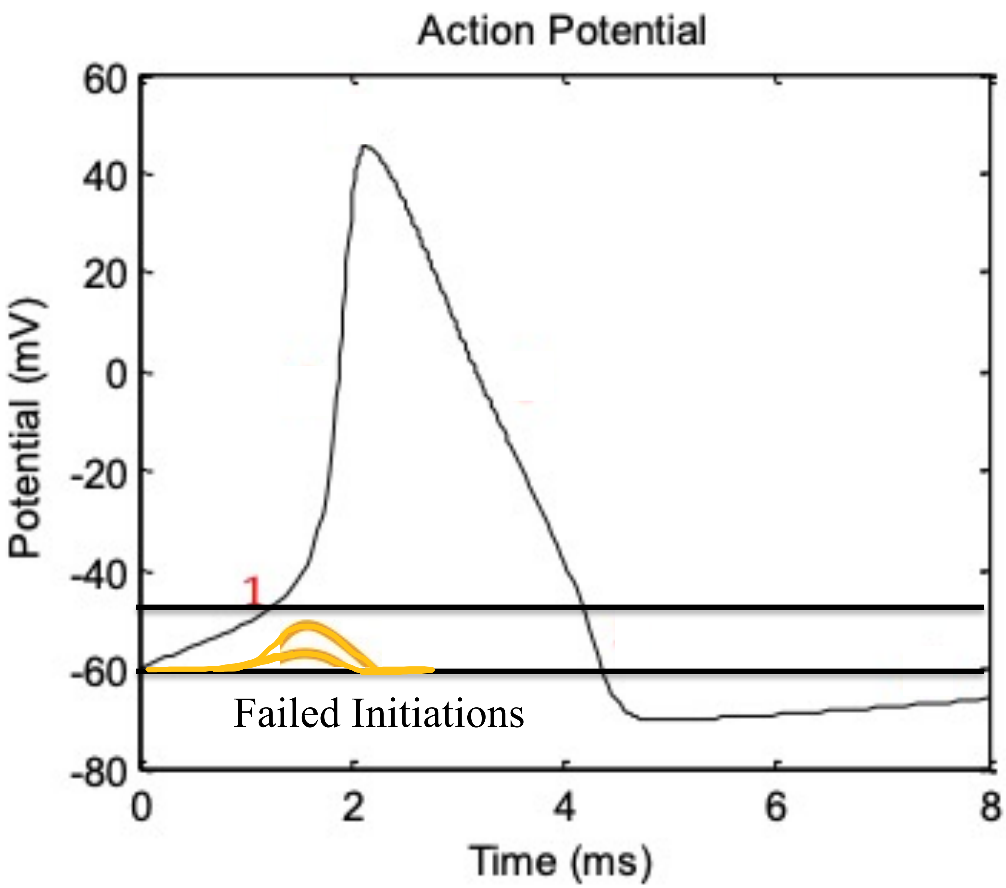
Action Potential Begins!

Neuron Anatomy



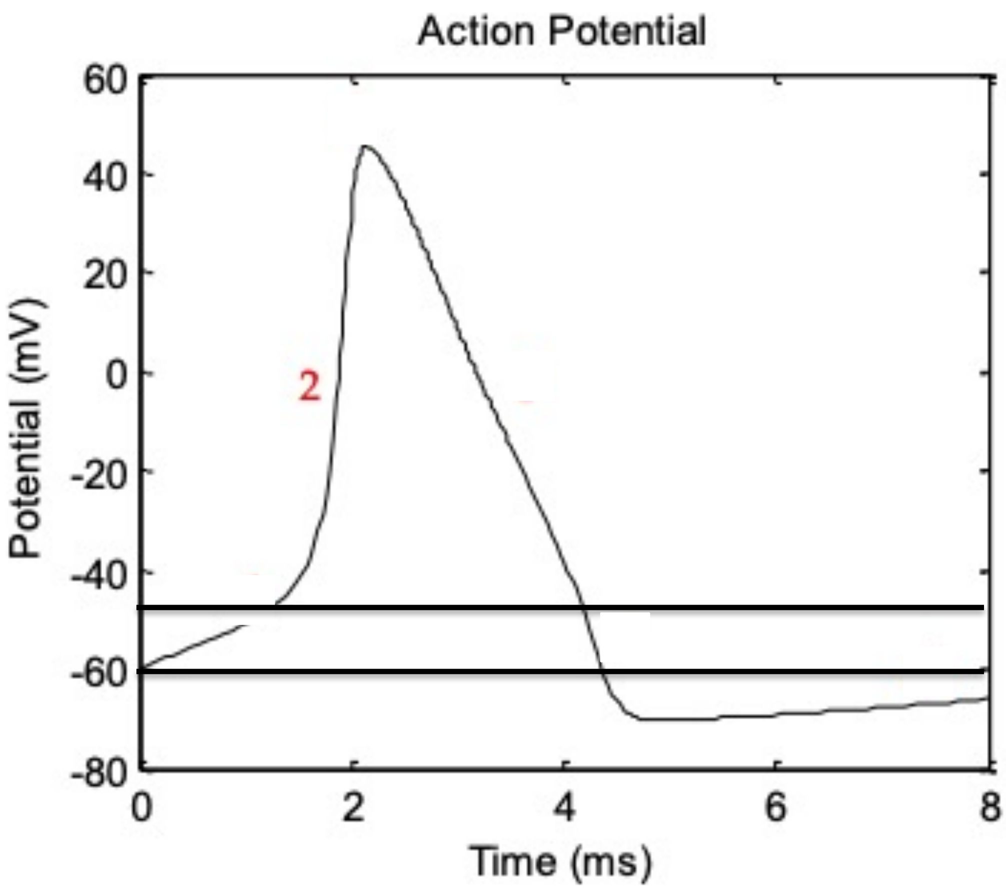
Cycle Continues!

Voltage of Action Potential



Voltage increases until firing potential reached

Voltage of Action Potential



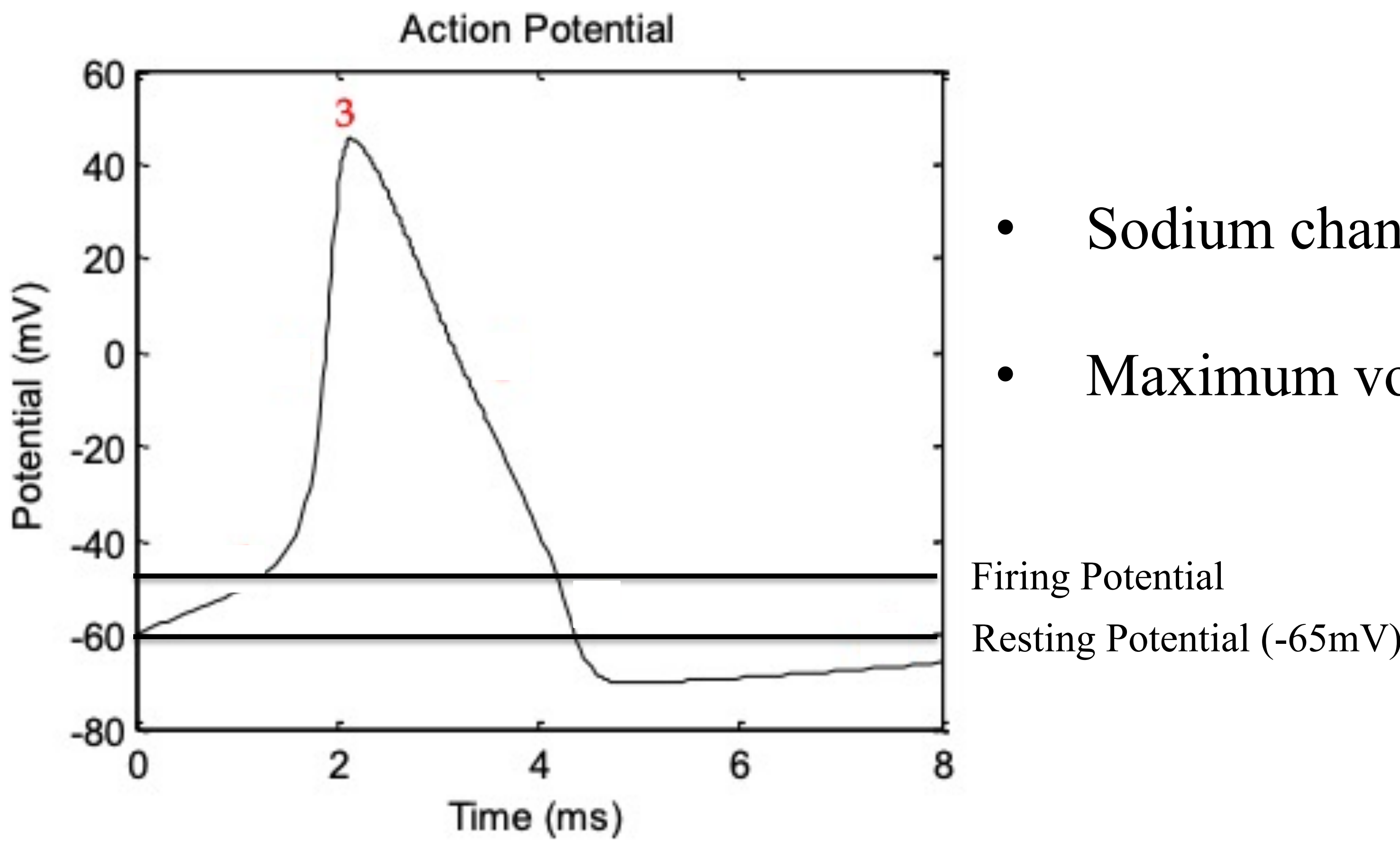
Depolarization Phase

- Sodium channels open
- Sodium (Na+) enters cell
- Cell becomes more positive

Firing Potential

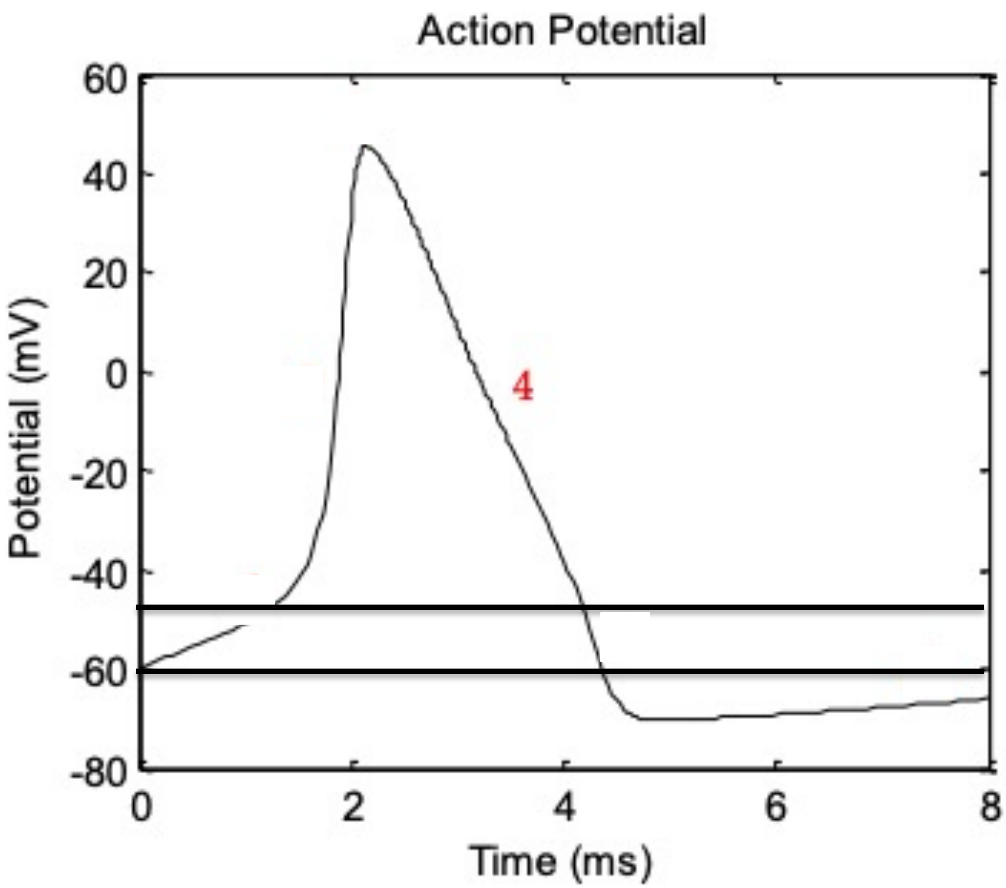
Resting Potential (-65mV)

Voltage of Action Potential



- Sodium channels close
- Maximum voltage reached

Voltage of Action Potential



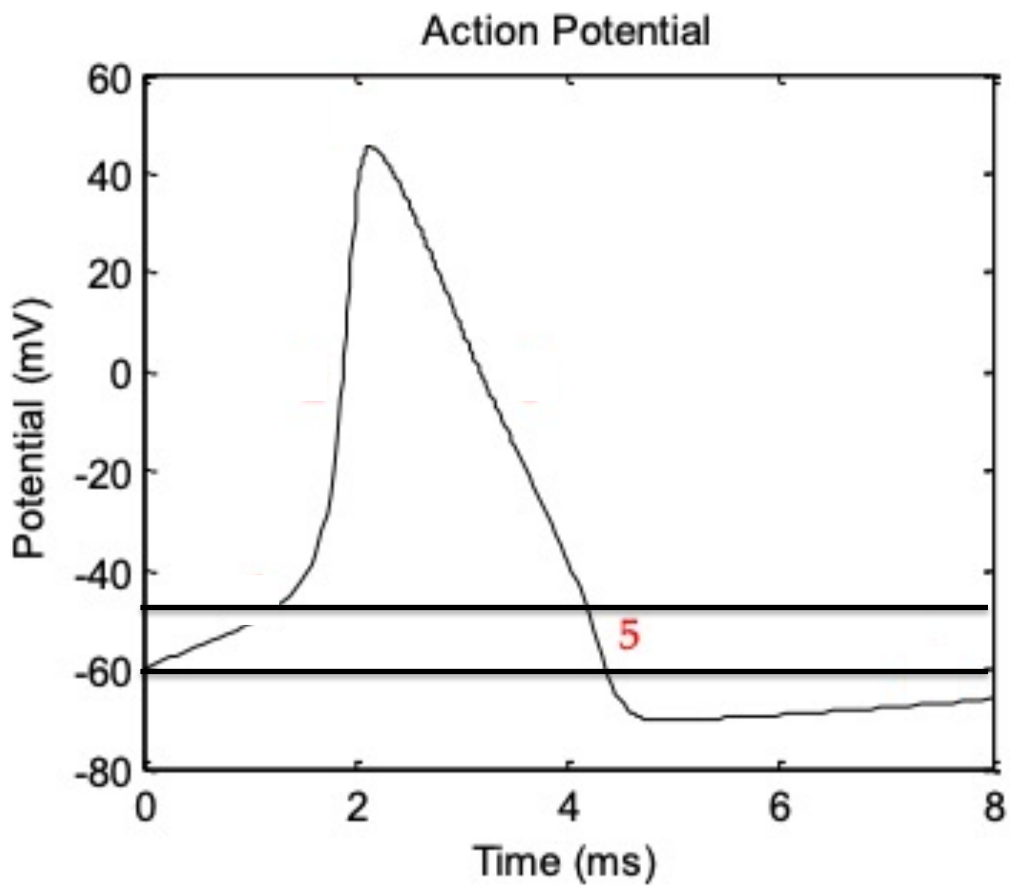
Firing Potential

Resting Potential (-65mV)

Repolarization Phase

- Potassium channels open
- Potassium (K+) exits cell
- Voltage decreases

Voltage of Action Potential



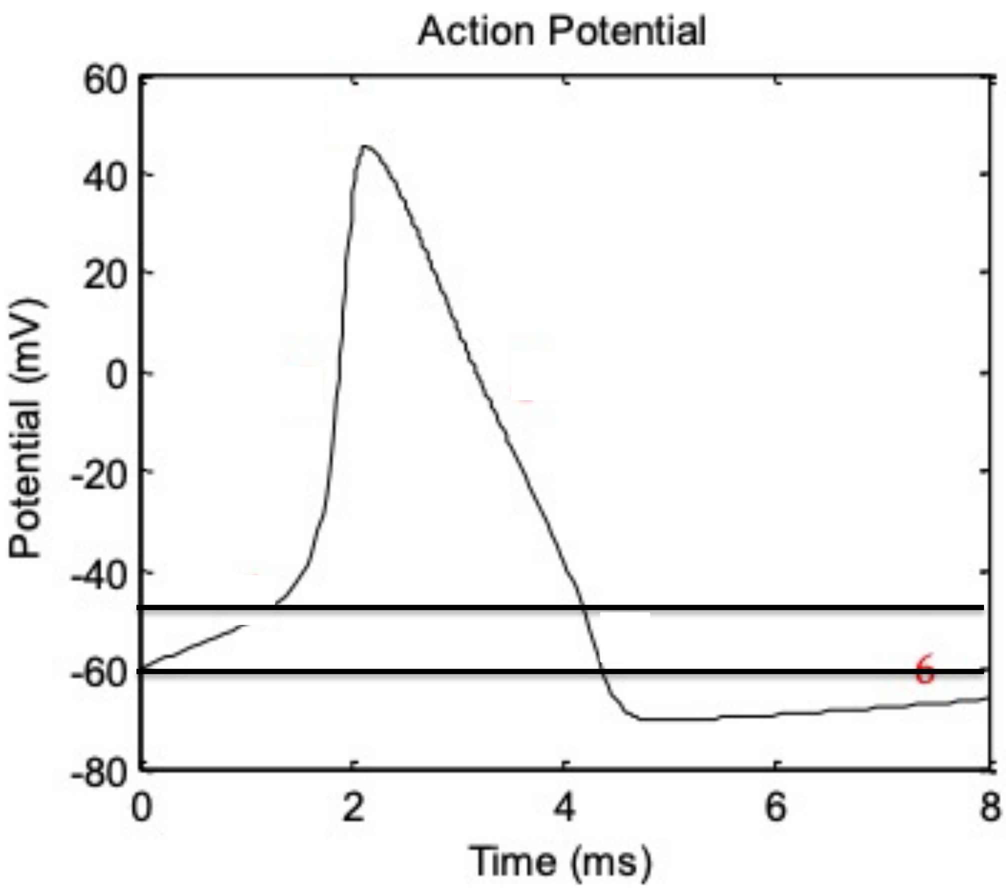
Firing Potential

Resting Potential (-65mV)

Hyperpolarization Phase

- Potassium channels close
- Voltage decreases below resting potential

Voltage of Action Potential



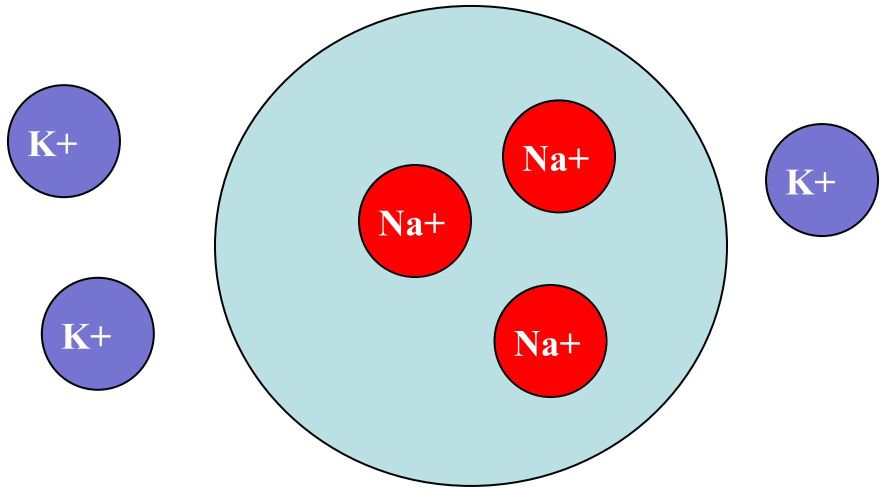
Firing Potential

Resting Potential (-65mV)

- Voltage slightly increases
- Voltage returns to resting potential

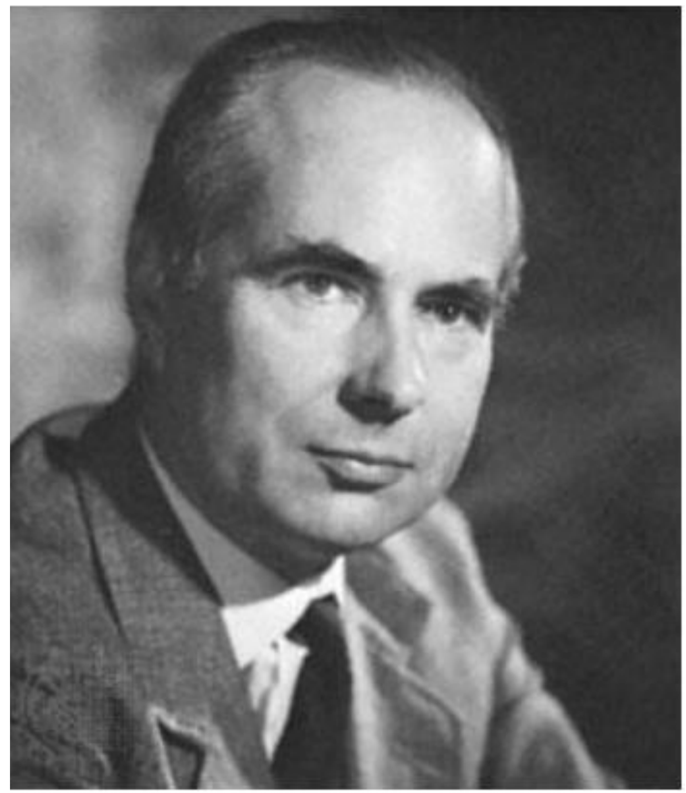
Other Action Potential Facts

- Action potentials are always the same size
- Membrane has increased conductivity during action potential



Hodgkin-Huxley Model

Alan Lloyd Hodgkin



Andrew Huxley

Purpose and Definition

- Mathematical model that describes how action potentials are fired in neurons
- Involves system of 4 nonlinear differential equations
  - $\frac{dv}{dt}$ measures voltage difference between inside and outside of cell
  - $\frac{dn}{dt}, \frac{dm}{dt}, \frac{dh}{dt}$ model the activation level of the ion channels
  - t represents time, v represents membrane potential

Model Equations

$$\frac{dv}{dt} = \frac{1}{C_m}\left(I - \overline{g}_{Na} m^3 h (v - E_{Na}) - \overline{g}_K n^4 (v - E_K) - \overline{g}_L (v - E_L)\right)$$

6 different supporting functions

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

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

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

11 different constants

Ion Channel Constants

n, m, h

1. Dimensionless quantities between 0 and 1 associated with potassium channel activation, sodium channel activation, and sodium channel inactivation, respectively.
2. Defines gates for specific channel
   - eg. Sodium channel has 3 m gates and 1 h gate

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Supporting Functions

$\alpha_n(v) = \frac{0.01(v+50)}{1-e^{\left(\frac{-(v+50)}{10}\right)}}$	Rate constants for the n ion channel
$\beta_n(v) = 0.125e^{\left(\frac{-(v+60)}{80}\right)}$	
$\alpha_m(v) = \frac{0.1(v+35)}{1-e^{\left(\frac{-(v+35)}{10}\right)}}$	Rate constants for the m ion channel
$\beta_m(v) = 4e^{(-0.0556(v+60))}$	
$\alpha_h(v) = 0.07e^{(-0.05(v+60))}$	Rate constants for the h ion channel
$\beta_h(v) = \frac{1}{1+e^{(-0.1(v+30))}}$	

Constants

Equilibrium Potentials	
$E_{Na} = 55.17mV$	Sodium (Na) channels
$E_K = -72.14mV$	Potassium (K) channels
$E_L = -49.42mV$	Leakage (L) channels

$$I = 0.1\,\frac{\mu F}{cm^2}$$

Input current per unit area

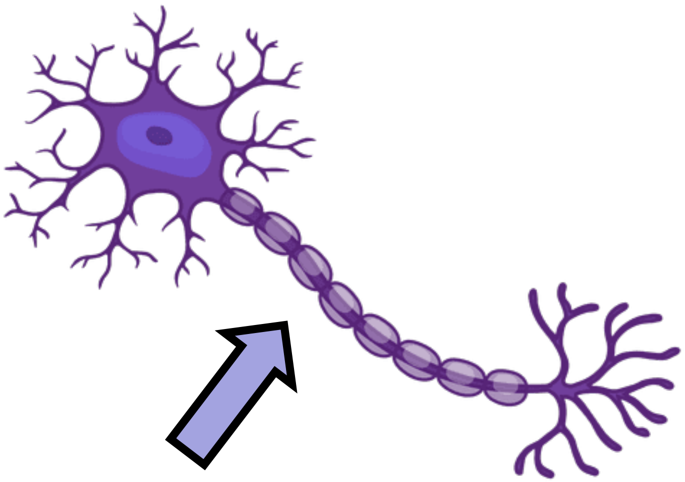
$$C_m = 0.01\,\frac{\mu F}{cm^2}$$

Capacitance of the membrane

Maximum Conductance	
$\overline{g}_{Na} = 1.2\,\frac{mS}{cm^2}$	all the sodium (Na) channels are open
$\overline{g}_K = 0.36\,\frac{mS}{cm^2}$	all the potassium (K) channels are open
$\overline{g}_L = 0.003\,\frac{mS}{cm^2}$	all the leakage (L) channels are open

Capacitance

- **Capacitance** - "Ratio of the amount of electric charge stored on a conductor to a difference in electric potential"
- Axon membrane imagined as long thin cylindrical capacitor



Axon

$$C_m = 0.01\,\frac{\mu F}{cm^2}$$

Capacitance of the membrane

Maximum Conductance

- **Conductance** – "potential for a substance to conduct electricity"
- Each $\overline{g}$ is maximum conductance for a specified channel

$\overline{g}_{Na} = 1.2 \dfrac{mS}{cm^2}$	all the sodium (Na) channels are open
$\overline{g}_{K} = 0.36 \dfrac{mS}{cm^2}$	all the potassium (K) channels are open
$\overline{g}_{L} = 0.003 \dfrac{mS}{cm^2}$	all the leakage (L) channels are open

Equilibrium Potential

- Each E is equilibrium potential, or reversal potential, for a specified channel
- Equal to the voltage value required to form the boundary between the currents flowing inward and outward of cell

$E_{Na} = 55.17mV$	Sodium (Na) channels
$E_K = -72.14mV$	Potassium (K) channels
$E_L = -49.42mV$	Leakage (L) channels

Numerical Methods

Euler's Methods

Forward Euler	$y_{n+1} = y_n + \Delta t f(t_n, y_n)$
Backward Euler	$y_{n+1} = y_n + \Delta t f(t_{n+1}, y_{n+1})$
Modified Euler	$y_{n+1} = y_n + \frac{\Delta t}{2}\left(f(t_{n+1}, y_{n+1}) + f(t_n, y_n)\right)$

- Simplest methods and involve little computational time
- However, some of the most unstable and inaccurate methods
  - More iterations needed compared to other methods to achieve the same error

4th Order Runge-Kutta (RK4)

$$y_{n+1} = y_n + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

where

$$k_1 = \Delta t f(t_n, y_n)$$

$$k_2 = \Delta t f\left(t_n + \frac{1}{2}\Delta t, y_n + \frac{1}{2}k_1\right)$$

$$k_3 = \Delta t f\left(t_n + \frac{1}{2}\Delta t, y_n + \frac{1}{2}k_2\right)$$

$$k_4 = \Delta t f(t_n + \Delta t, y_n + k_3)$$

Most commonly used Runge-Kutta method

Involves using the previous solution value and weighted averages of four increments, $k_1, k_2, k_3,$ and k_4, to find approximate value of solution at the next time step

Adams-Bashforth-Moulton 4th Order Predictor-Corrector (ABMPC4)

$$y_{n+1} = y_c + \frac{19}{270}(y_p - y_c)$$

where

$$y_p = y_n + \frac{\Delta t}{24}(55f_n + 59f_{n-1} - 37f_{n-2} + 9f_{n-3})$$

$$y_c = y_n + \frac{\Delta t}{24}(9f_{n+1} + 19f_n - 5f_{n-1} + f_{n-2})$$

$$f_{n+1} = f(t + \Delta t, y_p)$$

Requires four previous function values or terms to get the first calculated n+1 term, y_{n+1}

RK4 is used to find the first 4 terms, then ABMPC4 is used afterwards

Background for ABMPC4

Any **Adam-Type scheme** is of the form:

$$\frac{y_{i+1} - y_i}{\Delta t} = \beta_0 f_{i+1} + \beta_1 f_i + \cdots + \beta_m f_{i-m+1}$$

Predictor-Corrector Method:

Algorithm which involves two separate steps:

1. Initial, commonly explicit **predictor equation** y_p, fitted to function and derivative values to approximate function value at next time step
2. Implicit **correction equation**, y_c, that refines approximated function value by using another method, which is the 4th Order Adams-Bashforth-Moulton method in this case.

ODE45

Built-in Matlab function that solves systems of DE

Utilizes Runge-Kutta method and a variable time step for efficiency

[t, y] = ode45(odefun, tspan, y0)

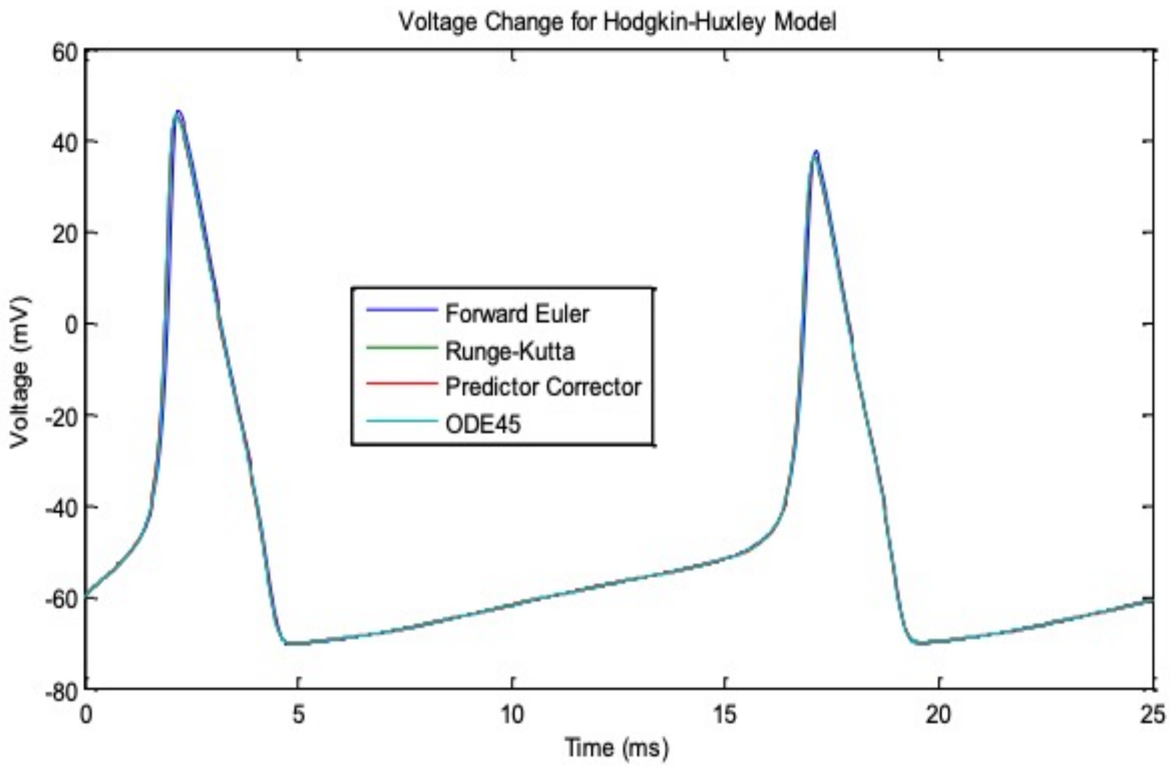
Inputs

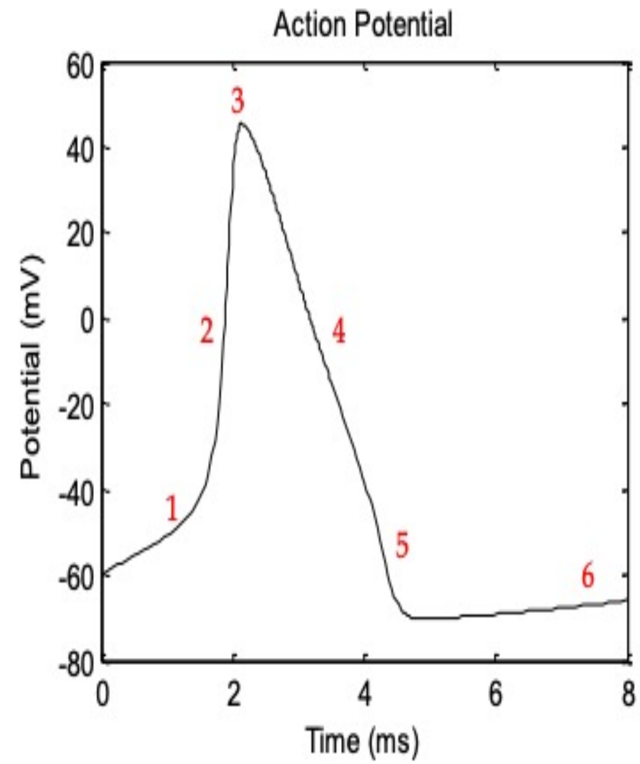
odefun	function that has system of DE(s)
tspan	time span from t_0 to t_n.
y0	initial condition

Outputs

t	column vector with time steps
y	array with the solution values for each time step

Numerical Analysis





Numerical Analysis Overview

- Performed on a simplified version of model
- Appr. Solution found using all 6 methods for:

N = 10, 20, 40, 80, 160, 320 from

$t_0 = 0\,ms$ to $t_n = 25\,ms$

- Average error and average order calculated

Simplified Model

- Na and K Conductance ($\overline{g}_{Na}, \overline{g}_K$) are 0

$$\frac{dv}{dt} = \frac{1}{C_m}\left(I - \overline{g}_{Na}m^3h(v - E_{Na}) - \overline{g}_K n^4(v - E_K) - \overline{g}_L(v - E_L)\right)$$

$$\Downarrow$$

$$\boxed{\frac{dv}{dt} = \frac{1}{C_m}\left(I - \overline{g}_L(v - E_L)\right)}$$

Simplified Model

Since $\overline{g}_{Na}, \overline{g}_K = 0$:

$$\frac{dv}{dt} = \frac{1}{C_m}\Big(I - \underbrace{\boxed{\overline{g}_{Na} m^3 h(v - E_{Na})}}_{0} - \underbrace{\boxed{\overline{g}_K n^4 (v - E_K)}}_{0} - \overline{g}_L (v - E_L)\Big)$$

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

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

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

Model simplifies to only:

0 supporting functions

$$\frac{dv}{dt} = \frac{1}{C_m}\Big(I - \overline{g}_L (v - E_L)\Big)$$

4 constants

Exact Solution

$$\frac{dv}{dt} = \frac{1}{C_m}\left(I - \overline{g}_L(v - E_L)\right)$$

can be solved through separation of variables.

Solution to DE with IC: $v_0 = -60mV$

$$v = \frac{1}{\overline{g}_L}\left(-e^{\left(-\frac{\overline{g}_L}{C_m}t\right)}\left(I + 60\overline{g}_L + \overline{g}_L E_L\right) + I + \overline{g}_L E_L\right)$$

$I = 0.1\ \frac{\mu F}{cm^2}, C_m = 0.01\frac{\mu F}{cm^2},\ \overline{g}_L = 0.003\frac{mS}{cm^2}, E_L = -49.42mV$

Euler's Methods

N	h	error	observed order
10.00000	2.50000	32.93500	NaN
20.00000	1.25000	16.46750	1.00000
40.00000	0.62500	8.23375	1.00000
80.00000	0.31250	4.11688	1.00000
160.00000	0.15625	2.05844	1.00000
320.00000	0.07812	1.02922	1.00000

Forward Euler

1st Order Method

10.00000	2.50000	4.54066	NaN
20.00000	1.25000	2.63571	0.78471
40.00000	0.62500	1.40353	0.90913
80.00000	0.31250	0.72915	0.94477
160.00000	0.15625	0.37136	0.97341
320.00000	0.07812	0.18749	0.98600

Backward Euler

1st Order Method

10.00000	2.50000	2.59512	NaN
20.00000	1.25000	0.50513	2.36107
40.00000	0.62500	0.10907	2.21135
80.00000	0.31250	0.02540	2.10248
160.00000	0.15625	0.00613	2.05119
320.00000	0.07812	0.00151	2.02546

Modified Euler

2nd Order Method

RK4 and ABMPC4 Methods

N	h	error	observed order
10.00000	2.50000	0.07705	NaN
20.00000	1.25000	0.00362	4.41252
40.00000	0.62500	0.00019	4.21954
80.00000	0.31250	0.00001	4.11084
160.00000	0.15625	0.00000	4.05594
320.00000	0.07812	0.00000	4.02807

RK4

4^{th} Order Method

N	h	error	observed order
10.00000	2.50000	0.09098	NaN
20.00000	1.25000	0.00477	4.25339
40.00000	0.62500	0.00020	4.54895
80.00000	0.31250	0.00001	4.69306
160.00000	0.15625	0.00000	4.78594
320.00000	0.07812	0.00000	4.89295

ABMPC4

4^{th} Order Method

Average Error and Order

Method	Paper's Average Error	Average Error	Average Order
Forward Euler	0.034984	10.80680	1
Backward Euler	-	1.64465	0.91960
Modified Euler	-	0.54039	2.15031
RK4	1.0155e-7	0.01348	4.16538
ABMPC4	1.2004e-8	0.01599	4.63486
ODE45	3.0036e-4	0.00589	0.05527

Coding Difficulties

- Numerical Analysis and Exact Solution not coded
- Calculation to find average error and order not implemented
- Forward and Backward Euler Methods were not analyzed in original paper

N	h	error	observed order
10.00000	2.50000	0.00521	NaN
20.00000	1.25000	0.00521	0.00000
40.00000	0.62500	0.00792	-0.60583
80.00000	0.31250	0.00534	0.56944
160.00000	0.15625	0.00738	-0.46633
320.00000	0.07812	0.00430	0.77907

ODE45

Conclusions

- Hodgkin-Huxley Model is important to understanding action potentials
- Simplifying the model made numerical analysis possible
- Numerical Methods ranked worst to best at approximating the solution:

1. Forward Euler
2. Backward Euler
3. Modified Euler
4. RK4
5. ABMPC4
6. ODE45

References

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Thank you, Professor Gottlieb, for providing the base code necessary for most of the numerical analysis!