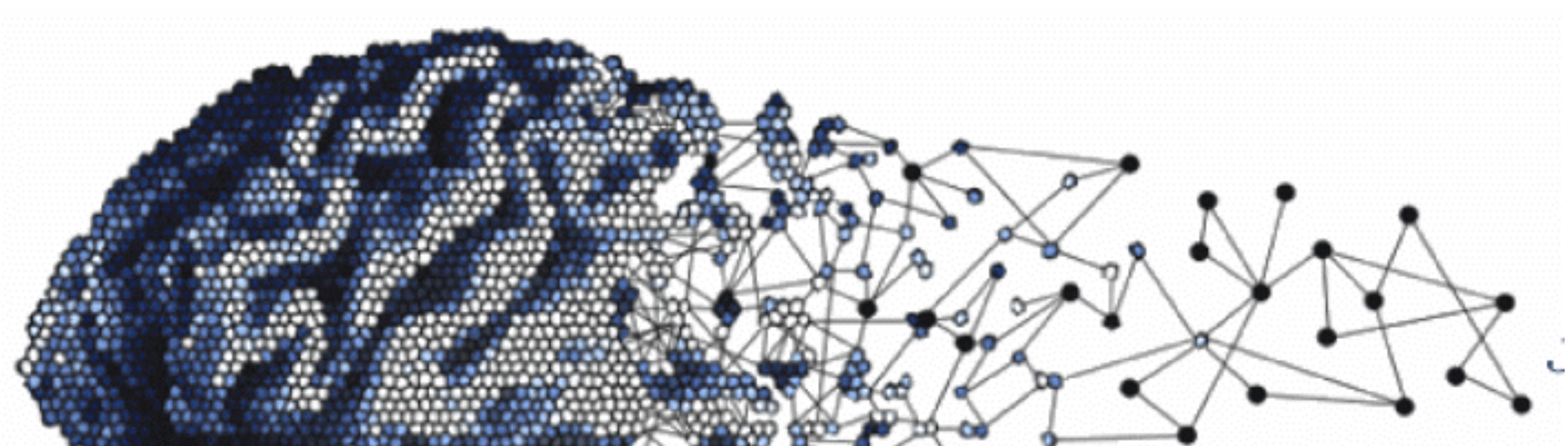
Applied Neuroscience

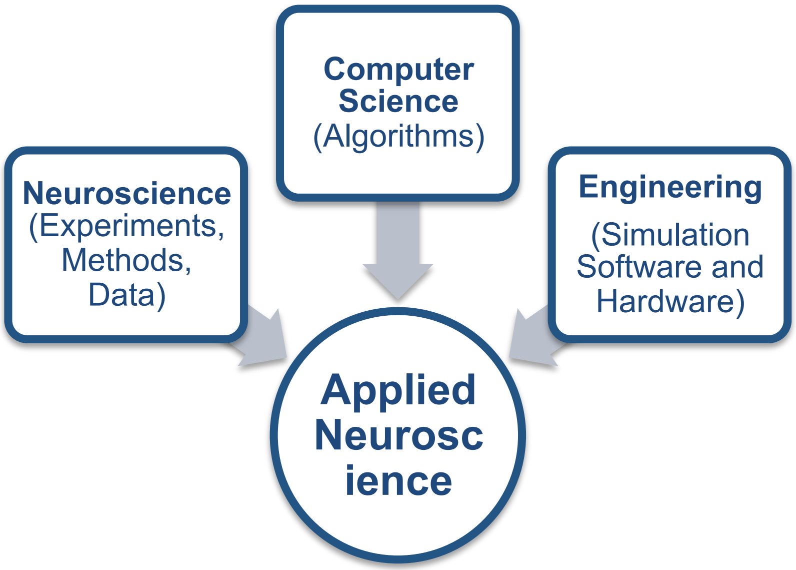
Columbia Science Honors Program
Fall 2016

Mathematical Models of Single Neurons



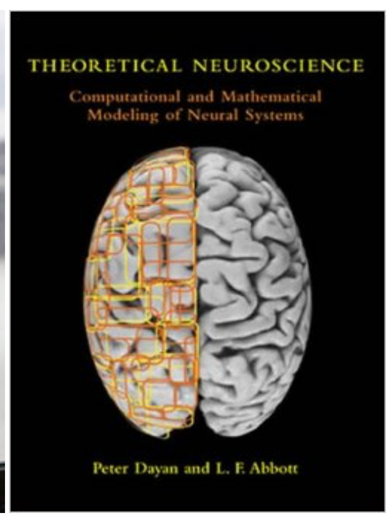
Computational Models of Brain Cells

How can we reproduce the behavior of a *single neuron* in a computer simulation?



Computational neuroscience provides tools and methods for "characterizing *what* nervous systems *do*, determining *how* they function, and understanding *why* they operate in particular ways" (Dayan and Abbott)

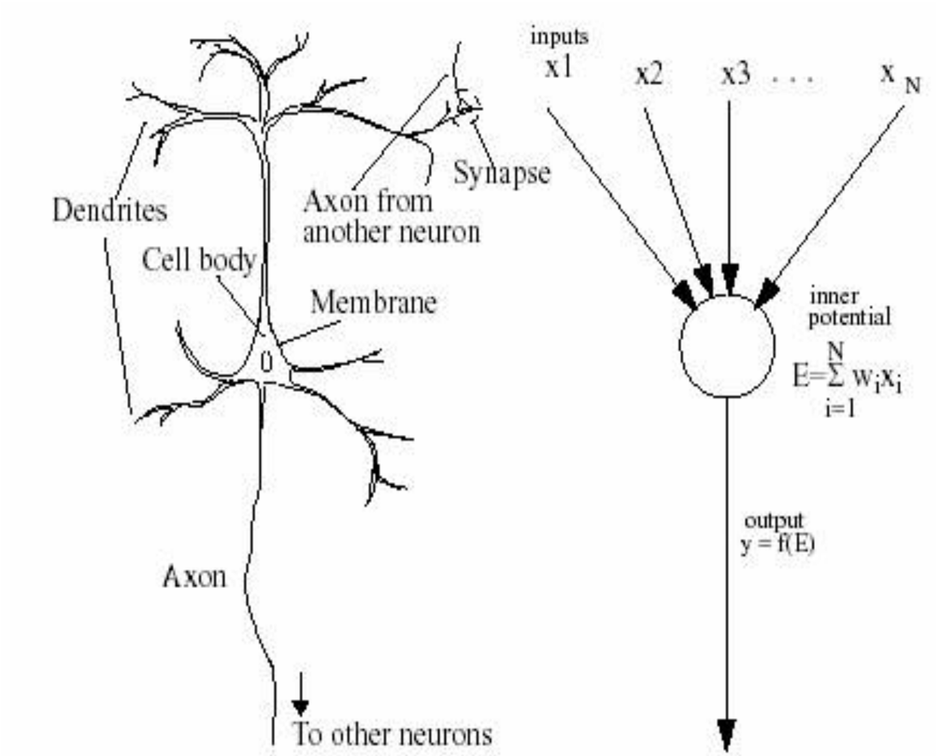
1. Description Models (*What*)
2. Mechanistic Models (*How*)
3. Interpretive Models (*Why*)



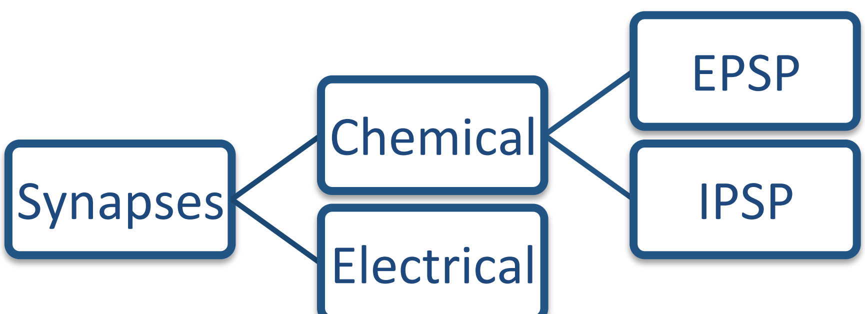
Guest Lecture:

Professor Larry Abbott
Center for Theoretical Neuroscience
Columbia University

Simulation of a Neuron



Neuronal Structure	Analogy
Dendritic Tree	Input (sums output signals received from surrounding neurons in the form of electric potential)
Soma	Processing
Axon	Output

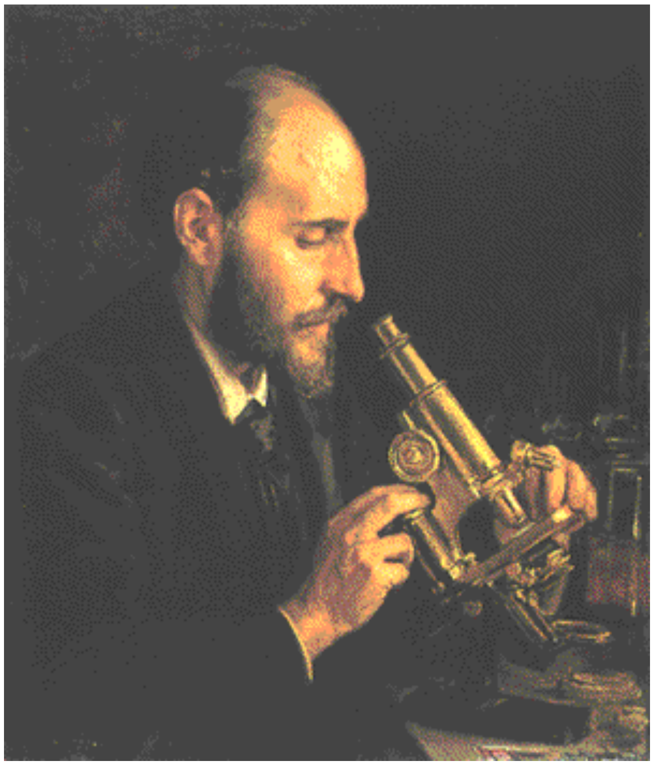


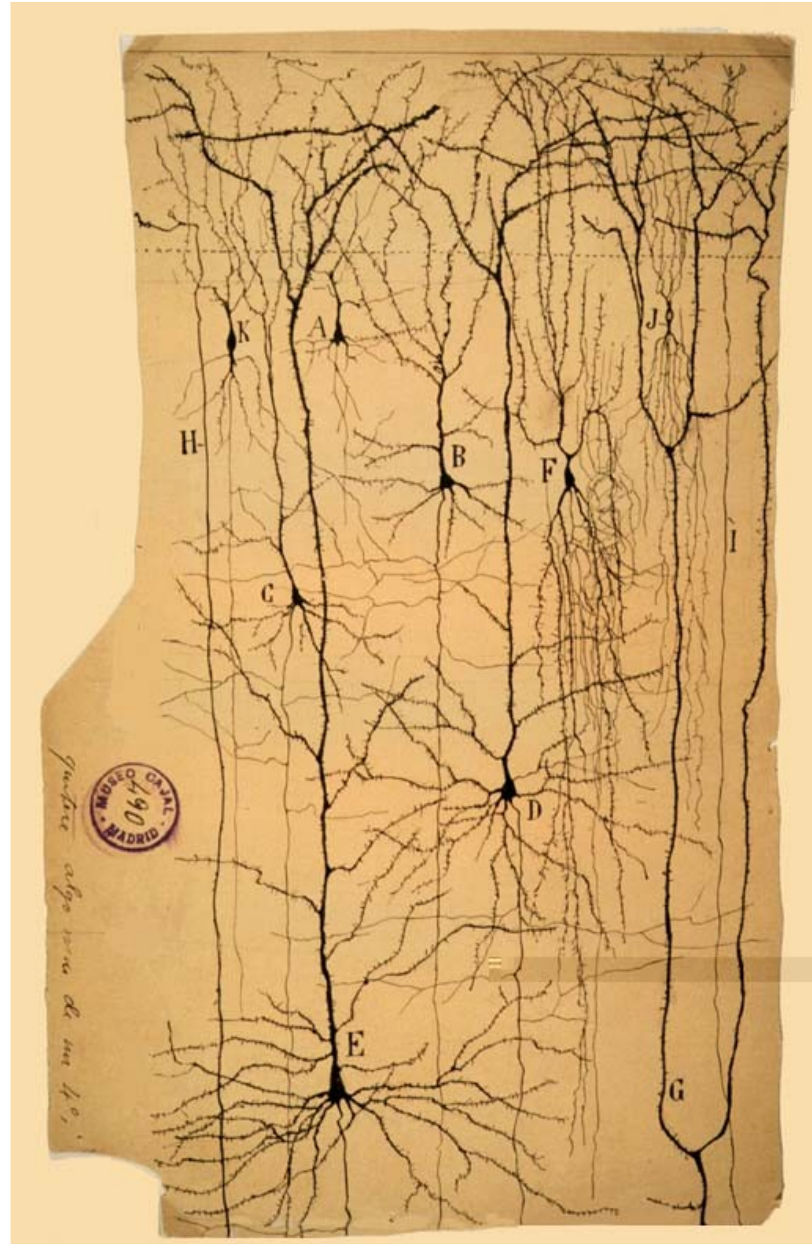
Input to Neuron:
Continuous Variable

Output to Neuron:
Discrete Variable

Golgi Stain

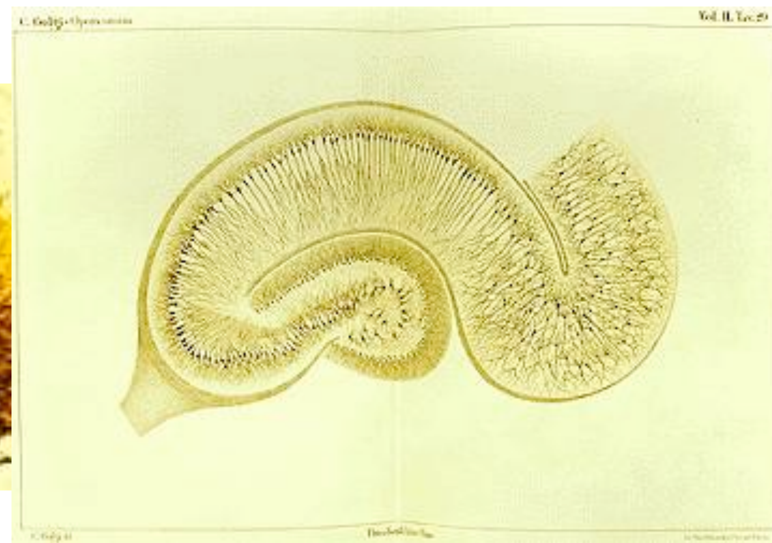
Santiago Ramon y Cajal
1852-1934





Golgi Stain

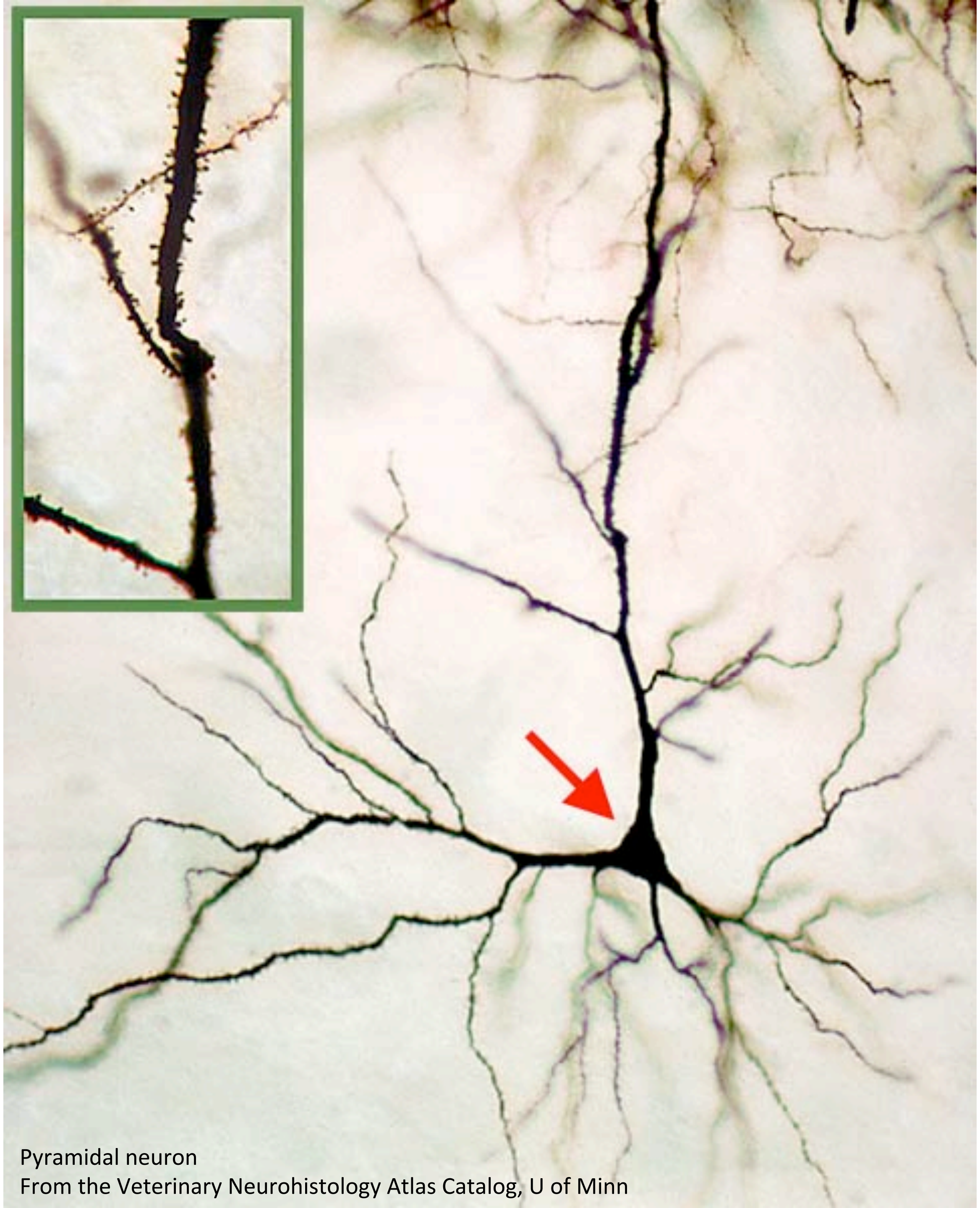
Hippocampus



Golgi Stain

Labels between 1 and 5% of all neuronal cells with oxidized heavy metal

Visualize cellular architecture of the brain



Pyramidal neuron
From the Veterinary Neurohistology Atlas Catalog, U of Minn

Golgi Stain

Labels between 1 and 5% of all neuronal cells with oxidized heavy metal

Visualize cellular architecture of the brain

Brain Scheme

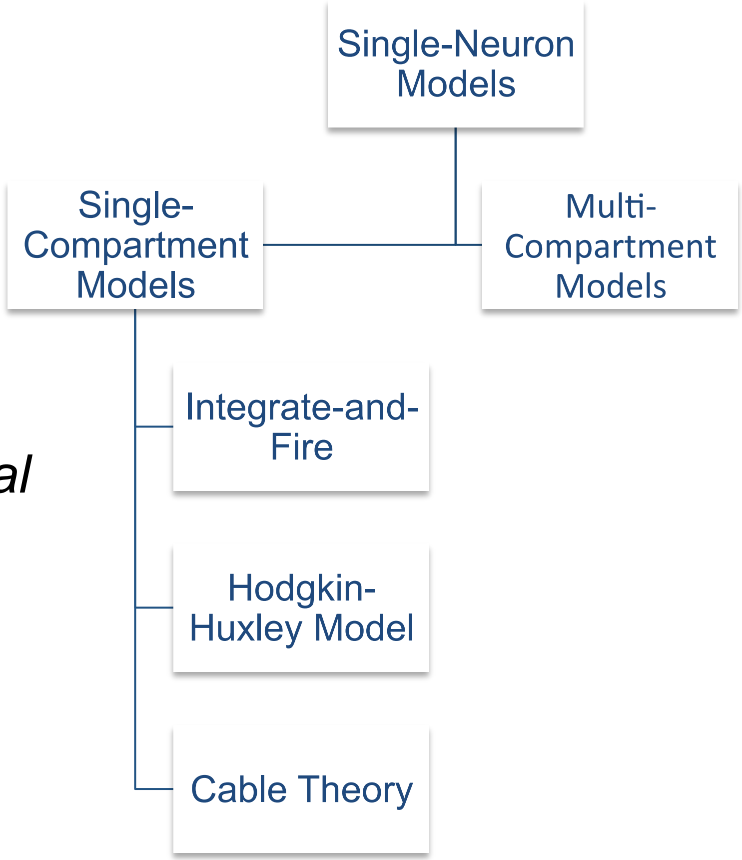
White matter = myelin (axon tracts)

Gray matter = neurons and dendrites

Simulation of a Neuron

To Model a Neuron:

1. Intrinsic properties of cell membrane
2. Morphology



Single-Compartment Models
describe the membrane potential of a single neuron by a single variable and ignore spatial variables

Multi-Compartment Models
describe how variables are transmitted among the compartments of a system

Simulation of a Neuron

Objective: Model the transformation from input to output spikes

Agenda:

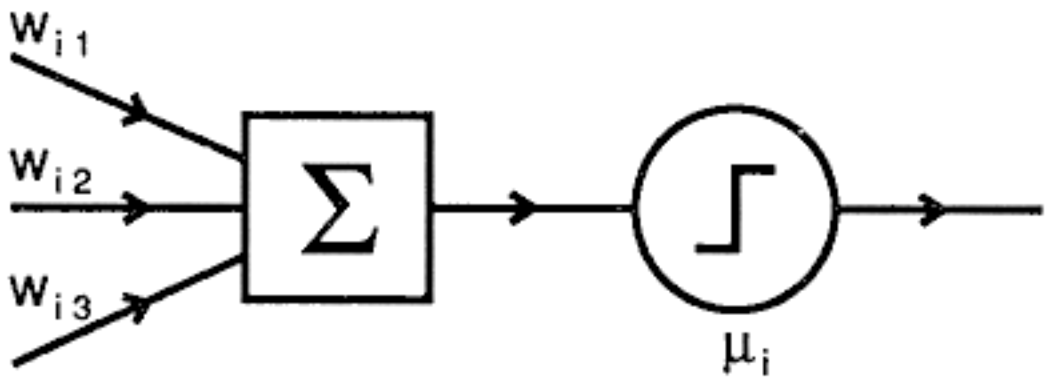
1. Model how the membrane potential changes with inputs
   Passive RC Membrane Model
2. Model the entire neuron as one component
   Integrate-and-Fire Model
3. Model the effects of inputs from synapses
4. Model active membranes
   Hodgkin-Huxley Model
5. Model the structure of neurons
   Dendrites, Cell Body, and Axon

Simple Model of a Neuron

Attributes of Artificial Neuron:

1. *m* binary inputs and a single output (binary)
2. Synaptic Weights m_{ij}
3. Threshold μ_i

Inputs

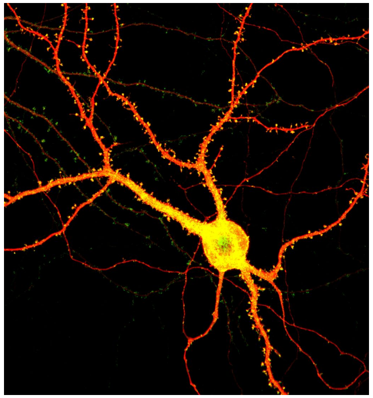


Output

Weighted Sum

Threshold

Electrophysiology of a Neuron

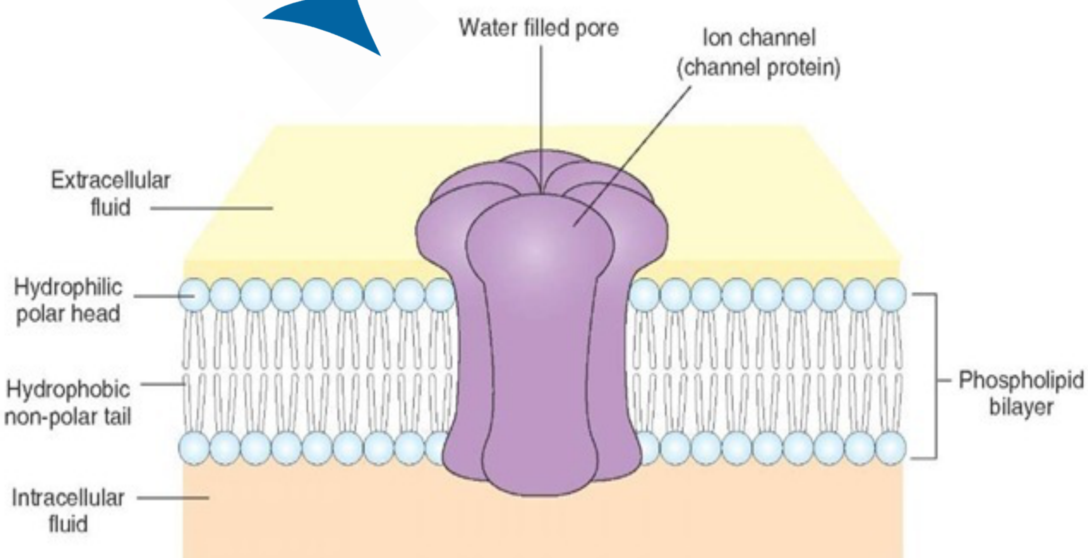


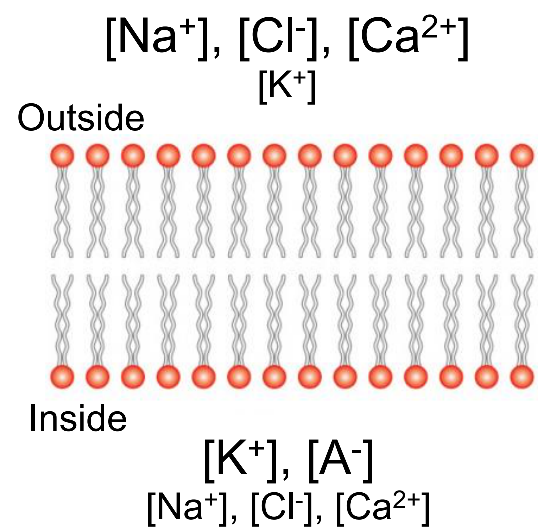
Nernst Equation

E = Membrane Potential at which current flow due to diffusion of ions is balanced by electric forces

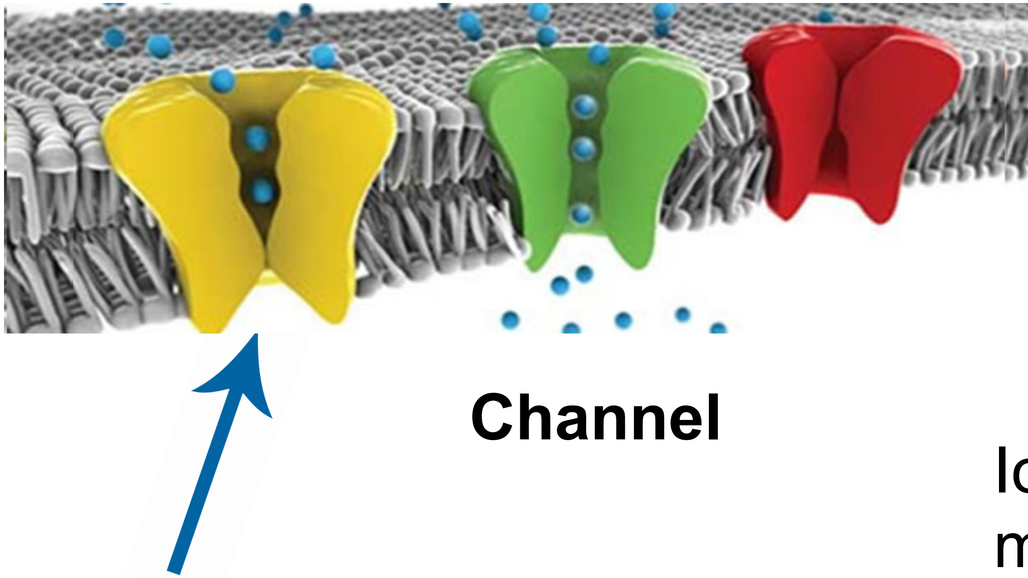
$$E = \frac{RT}{zF} \ln\left(\frac{[outside]}{[inside]}\right)$$

Cell Membrane





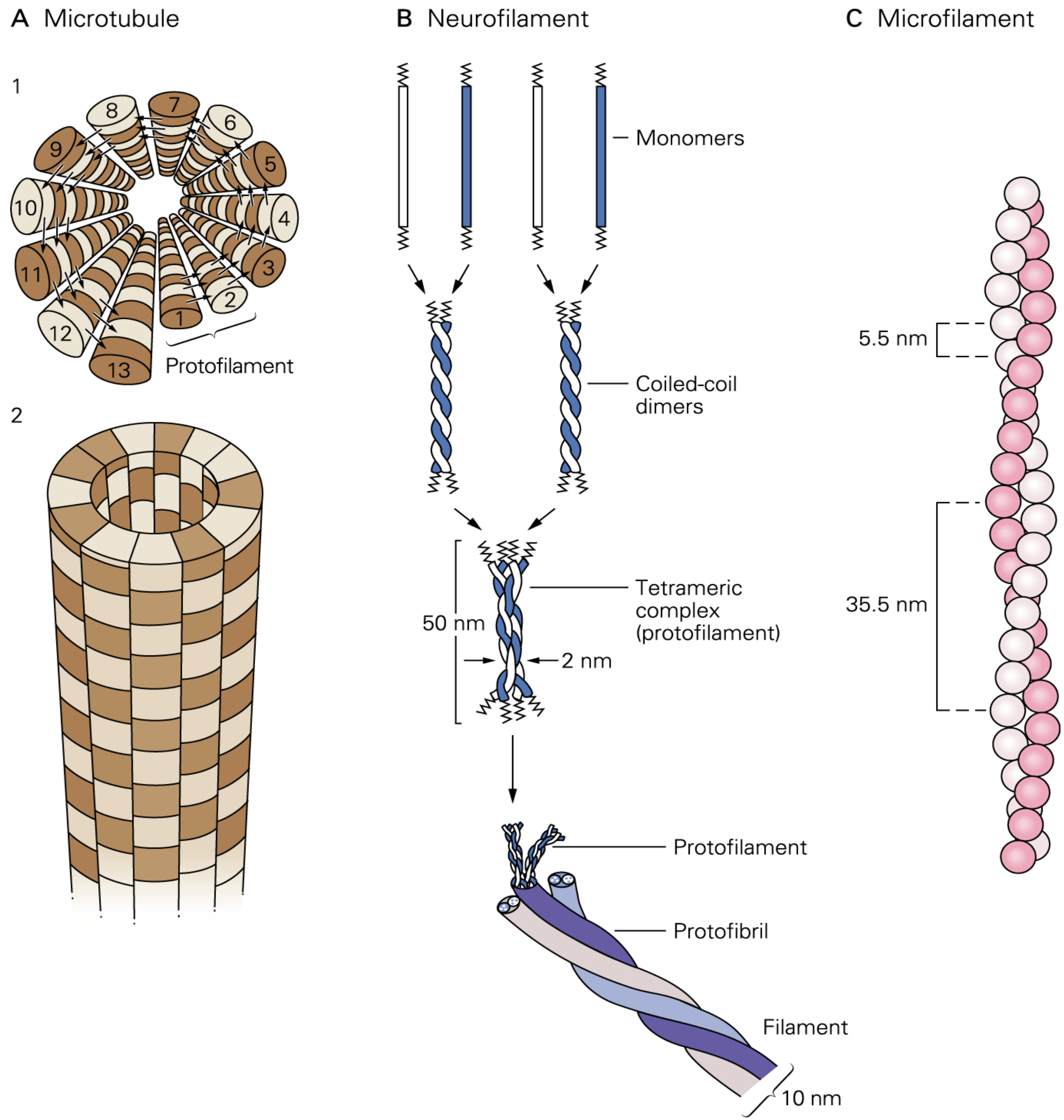
Ionic Channels



Ion Channels are modeled as conductance values g_i (enable current to flow in and out of the cell)

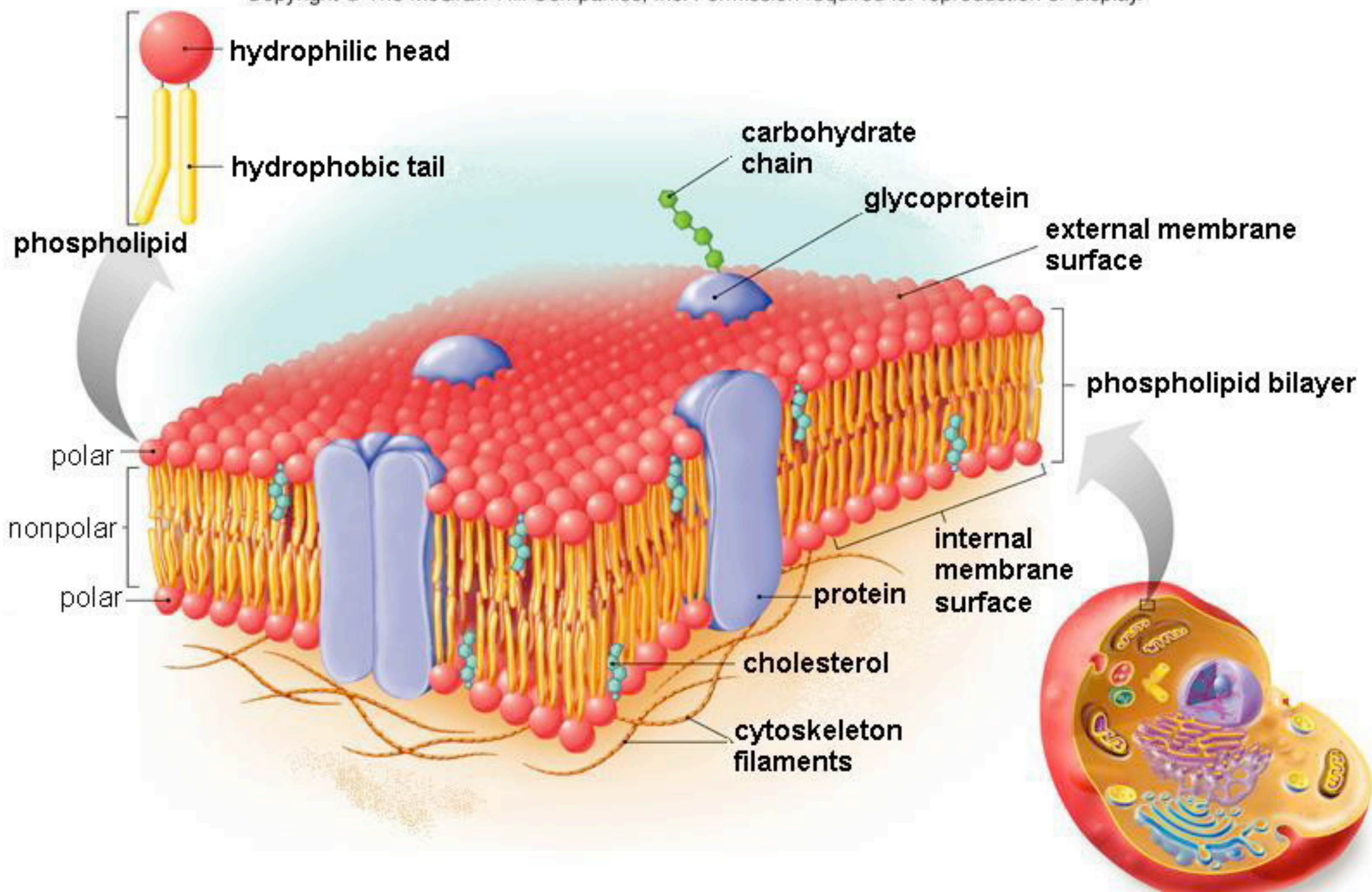
Cytoskeletal Architecture of a Neuron

Proteins are actively transported long distances in neurons

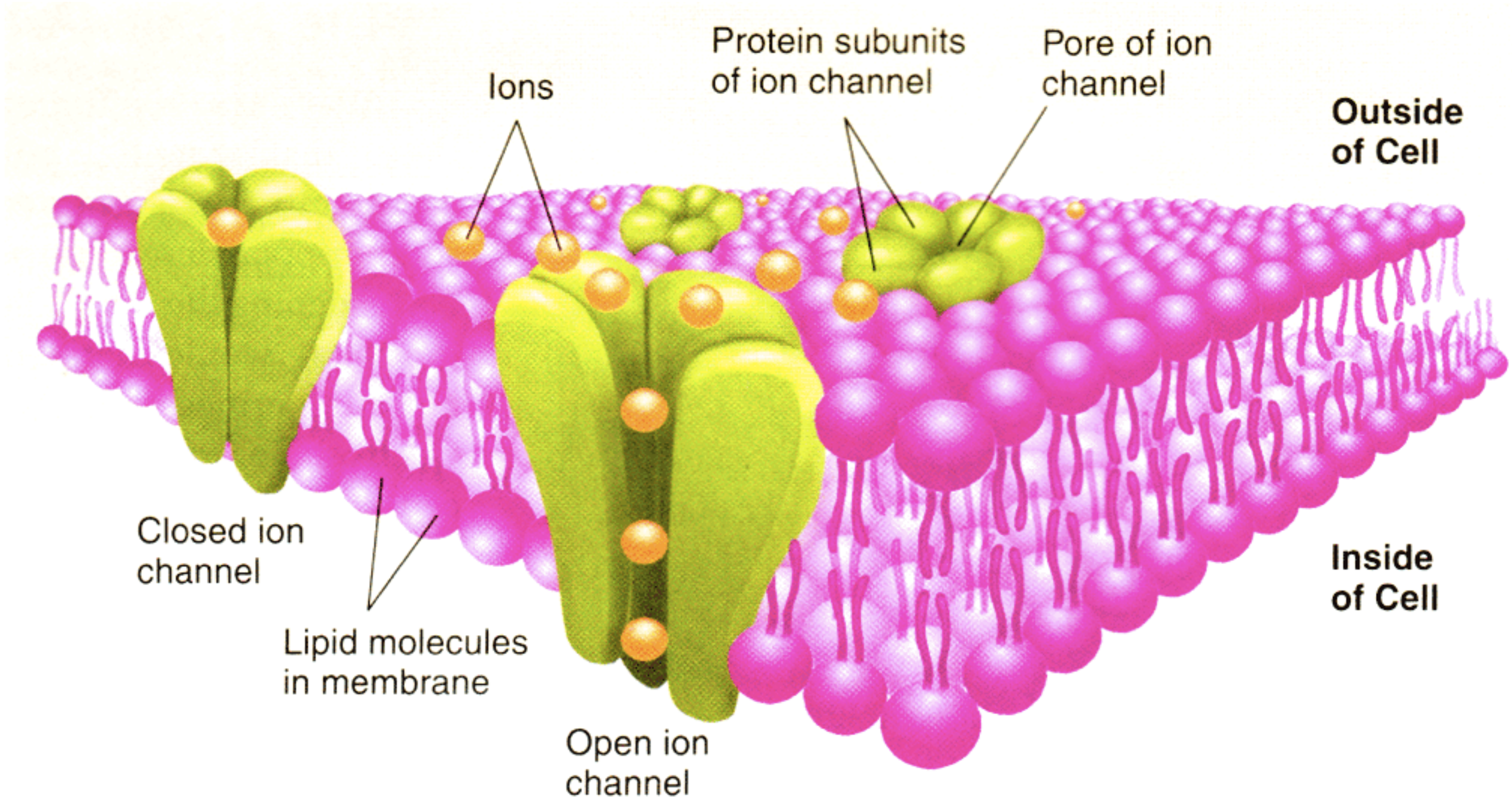


Principles of Neural Science, 4th Ed.; Fig. 4.5

Cell Membrane of a Neuron

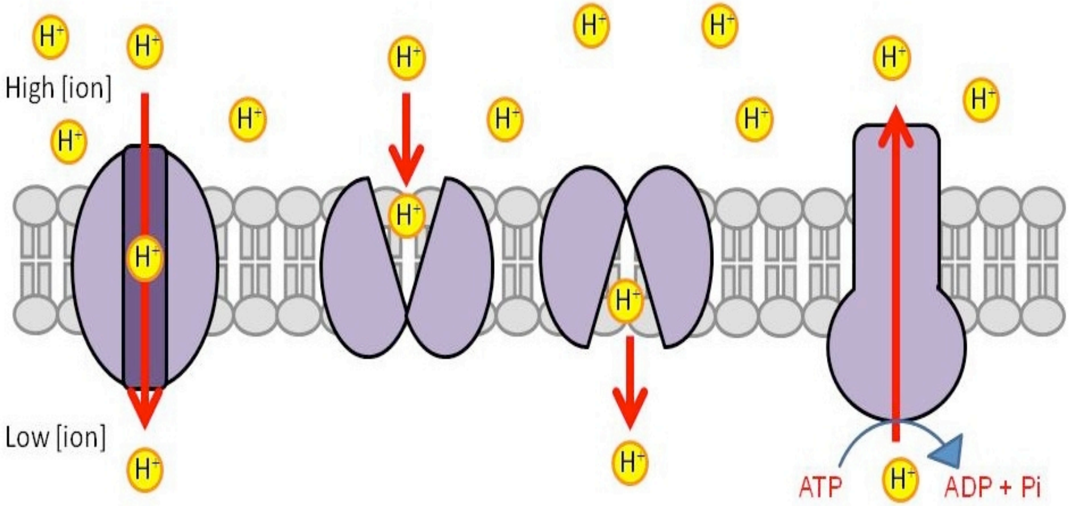


Ion Channels



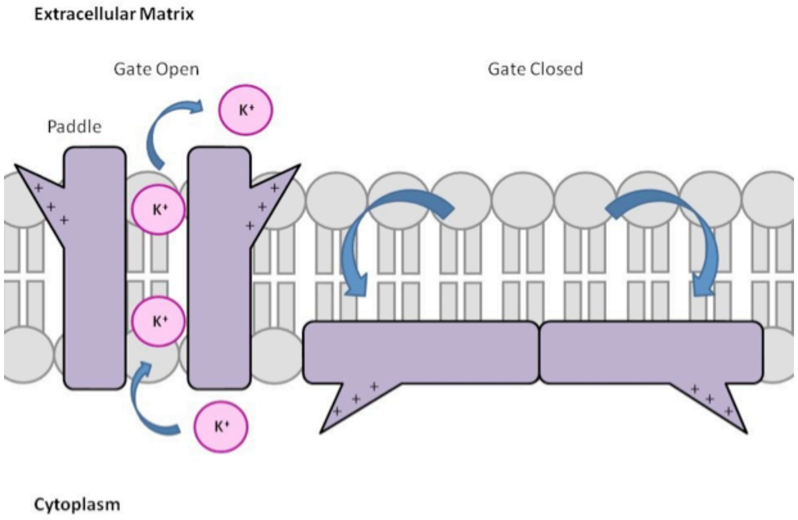
Ions cross the cell membrane through channels

Ion Channels are ***Gated***

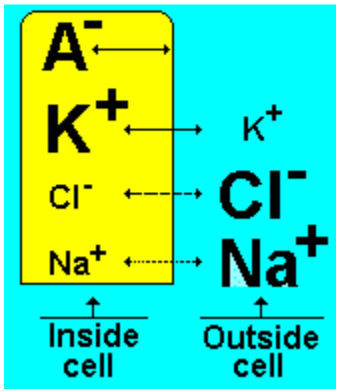


- Voltage-gated or ligand-gated, gated mechanically

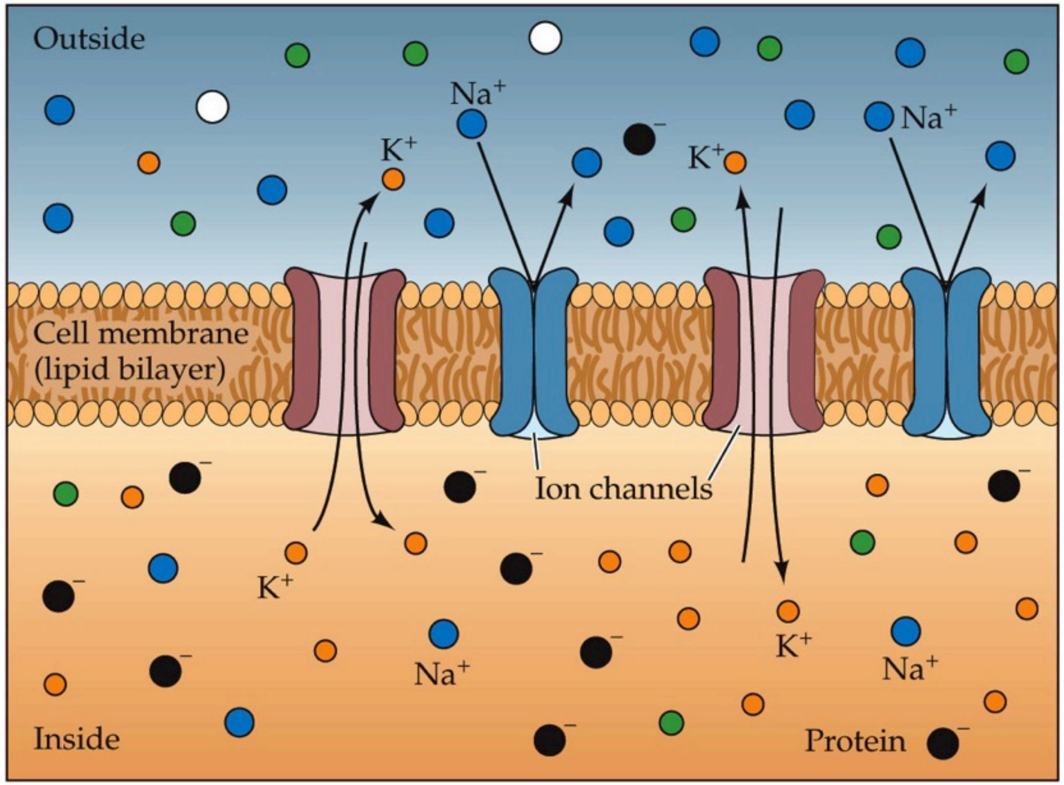
- 4 properties of ion channels:
  - Gated
  - Conductance
  - Selectivity
  - Pharmacology



SELECTIVE
PERMEABILITY



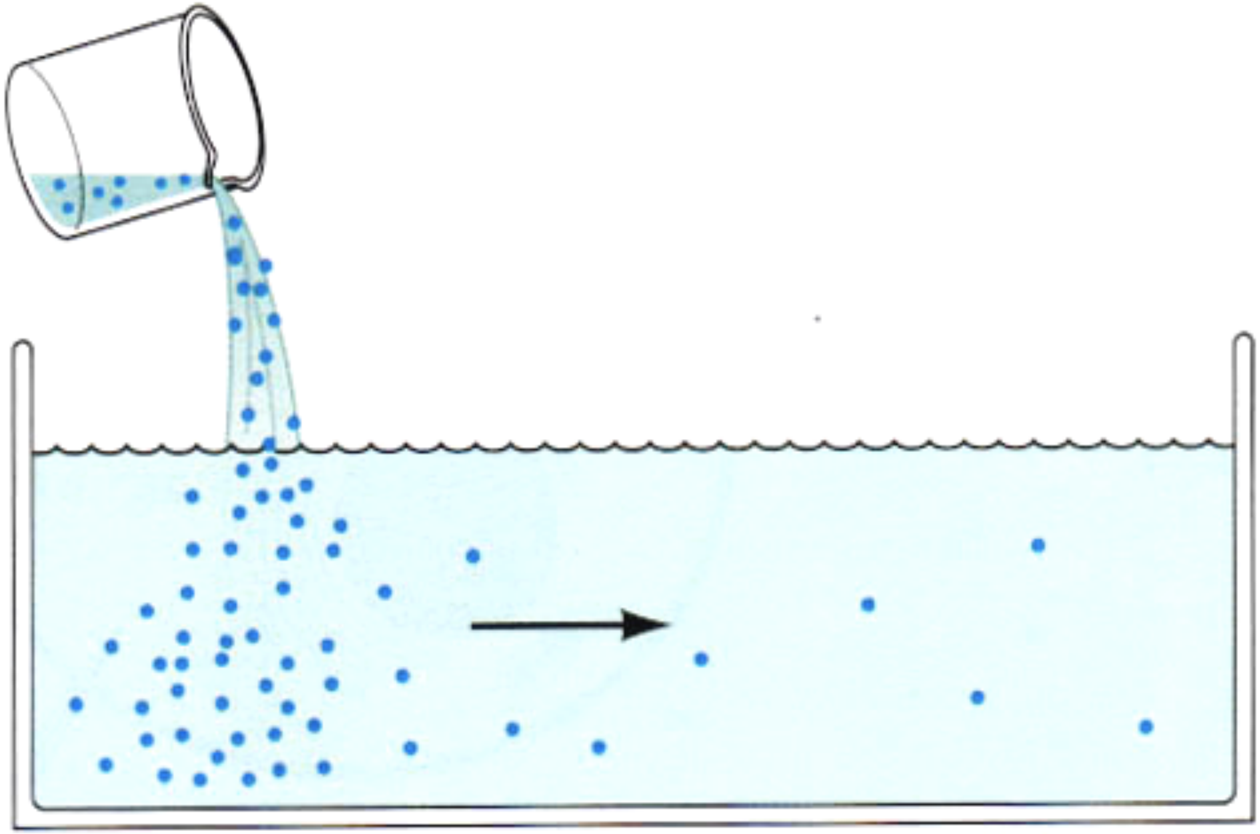
	Na⁺	K⁺	Cl⁻	Ca²⁺	Proteins
Outside cell	many	few	many	many	few
Inside cell	few	many	few	few	many



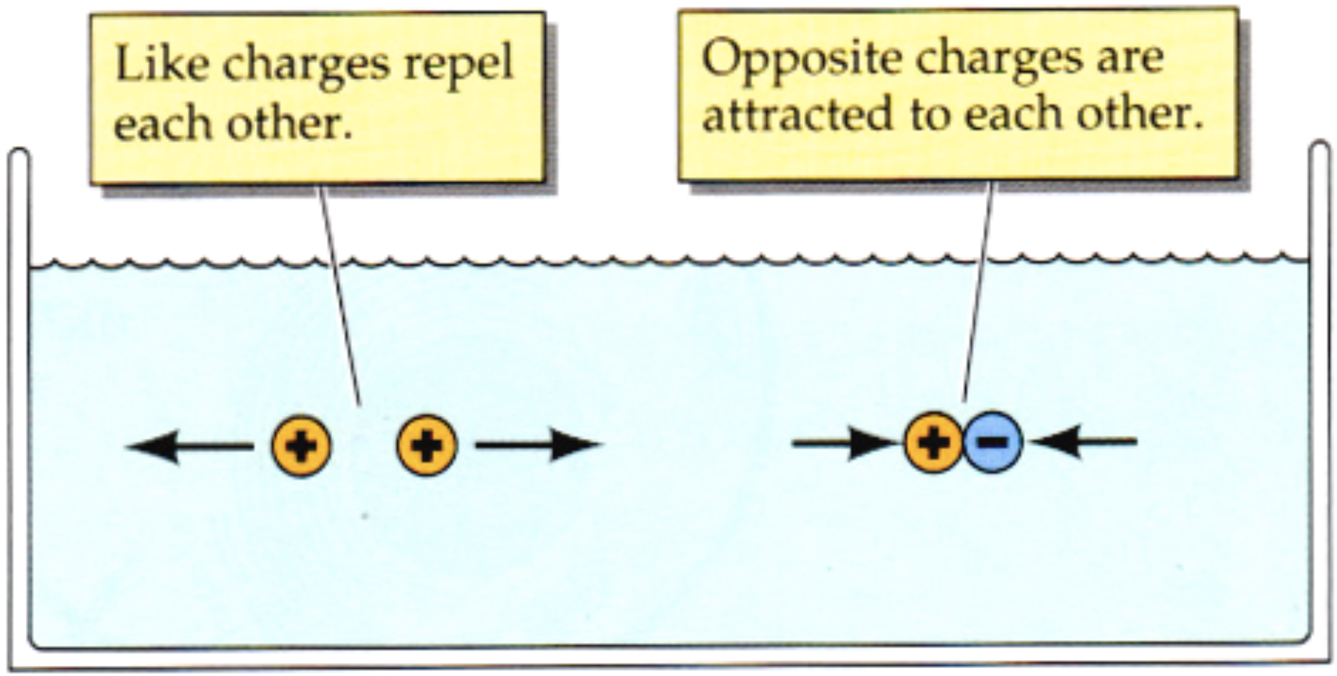
***Biological Psychology 6e*, Figure 3.4**

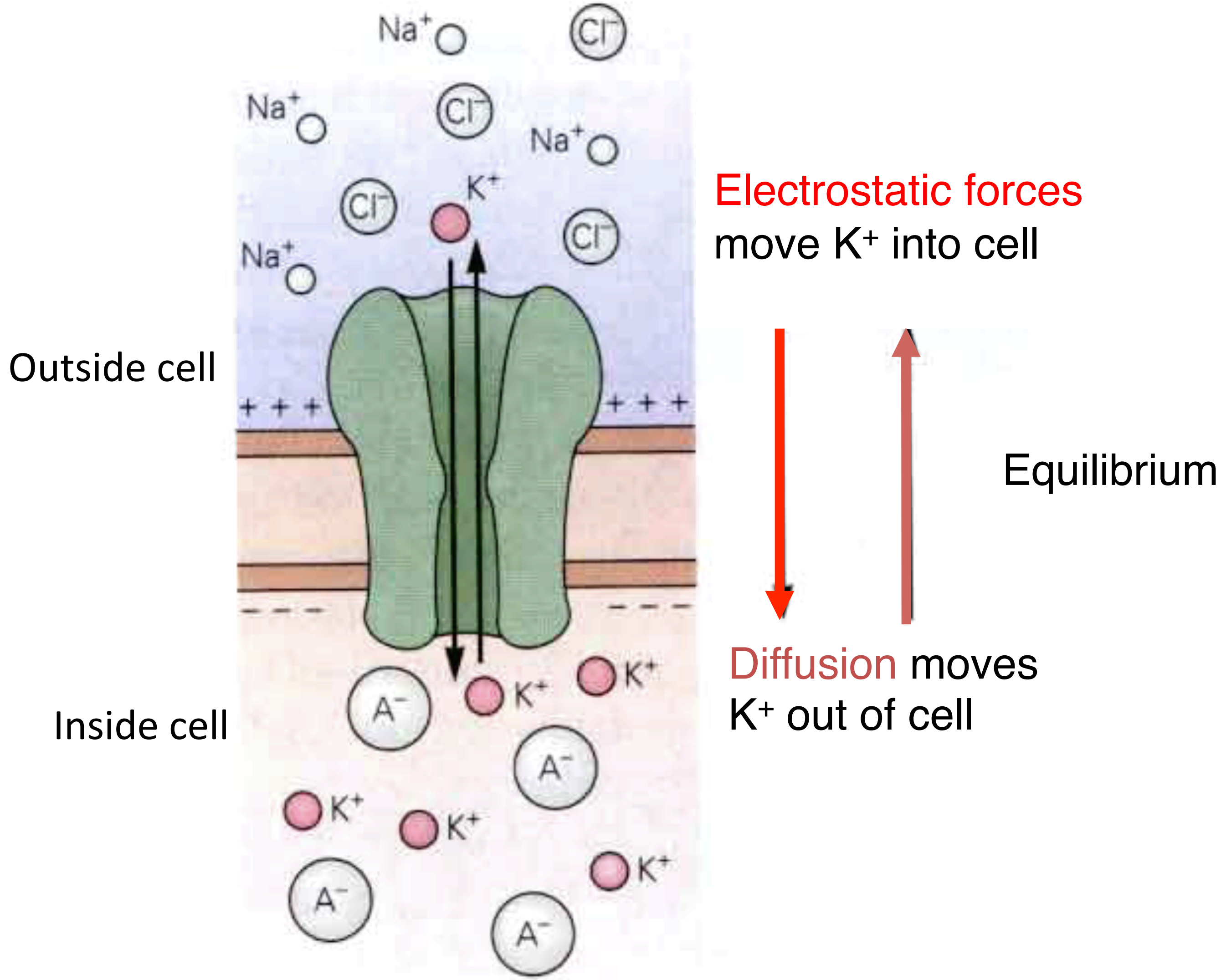
What are the 2 forces that act on ions to move them across the cell membrane?

1) Diffusion



2) Electrostatic forces



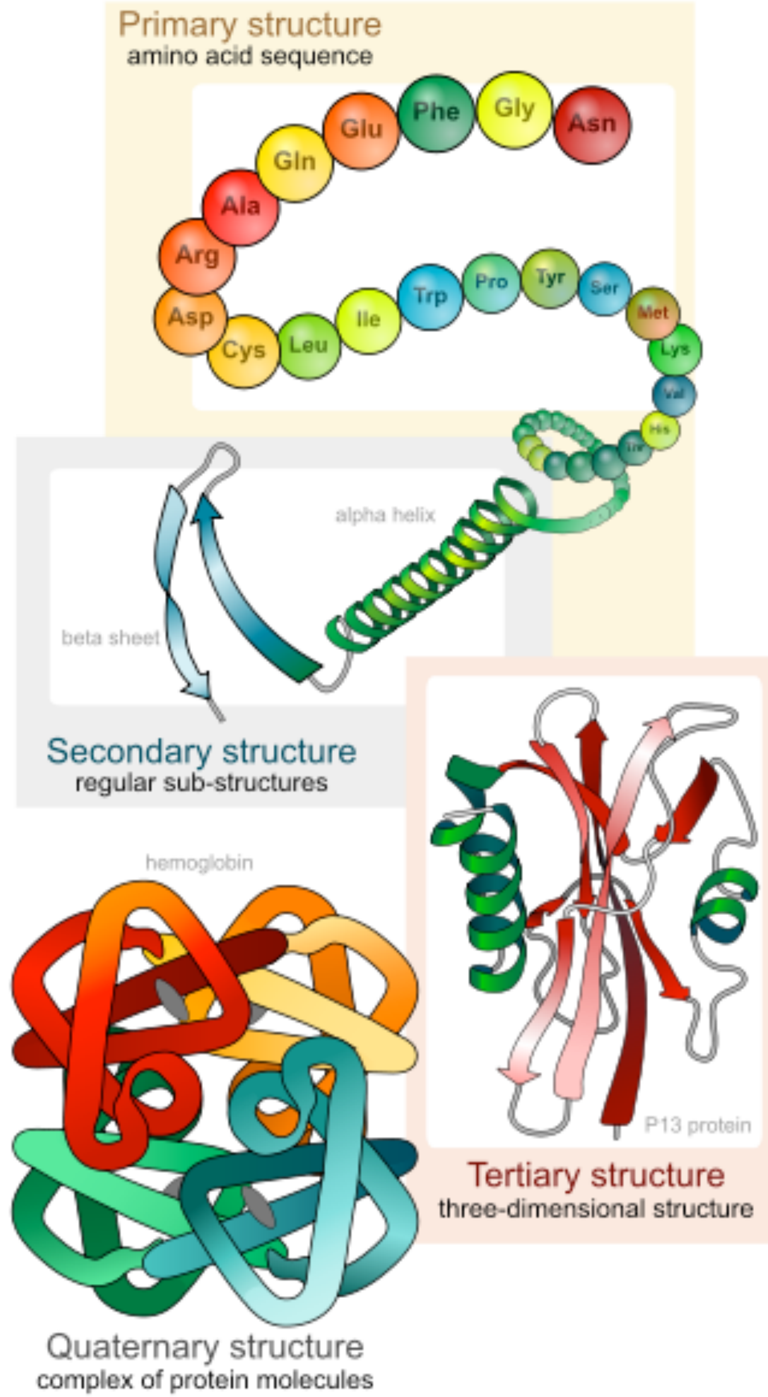


Ion Channel Scheme

Factors that Contribute to Resting Potential

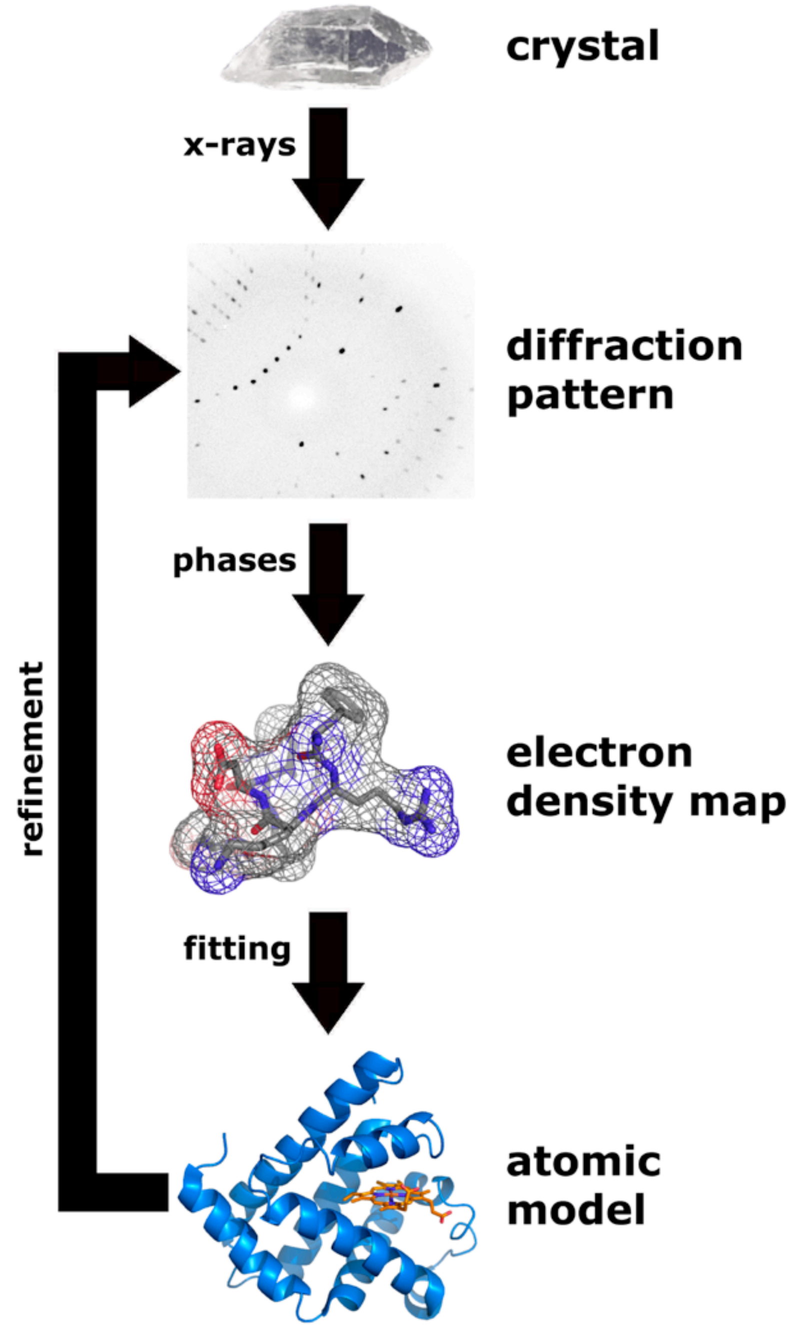
- Diffusion
- Electrostatic forces
- Selective permeability
- Ion pumps

Study of Ion Channels

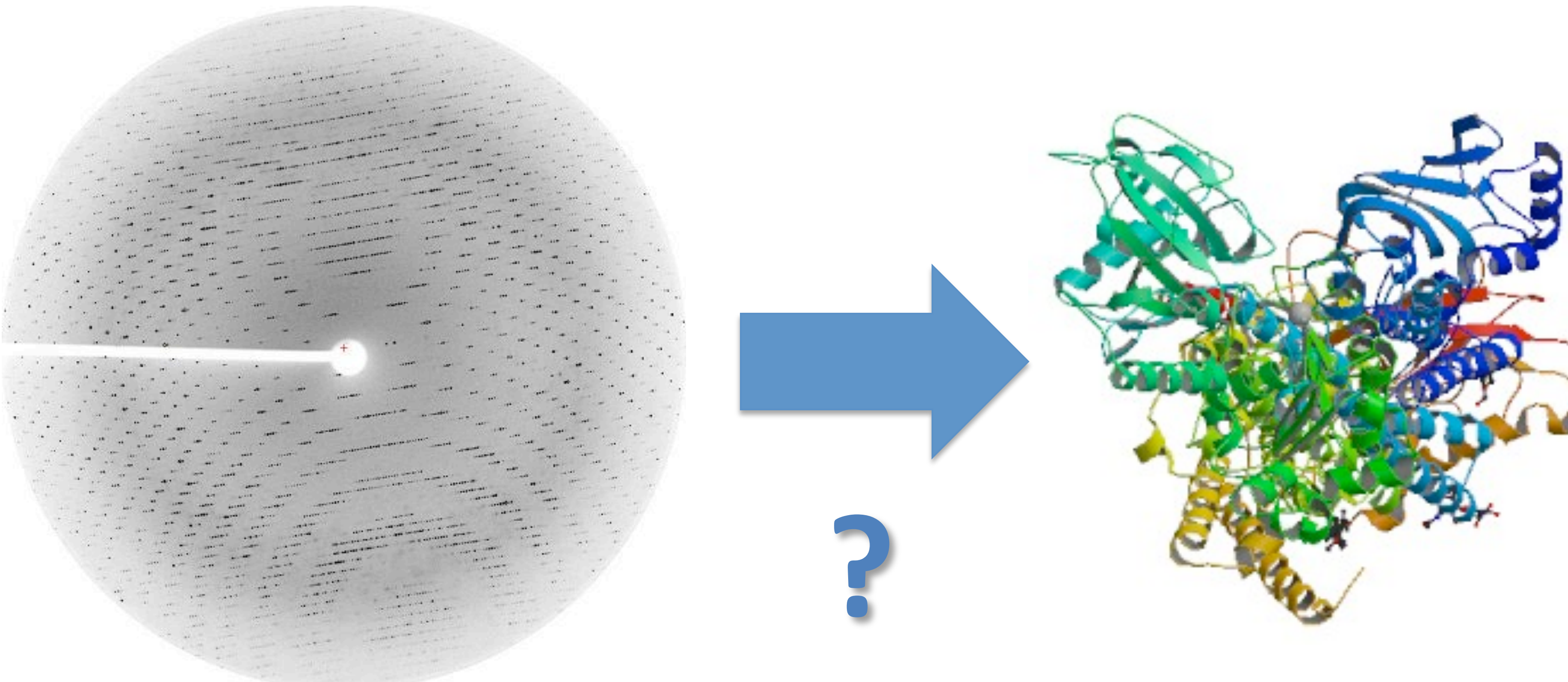


X- Ray Crystallography

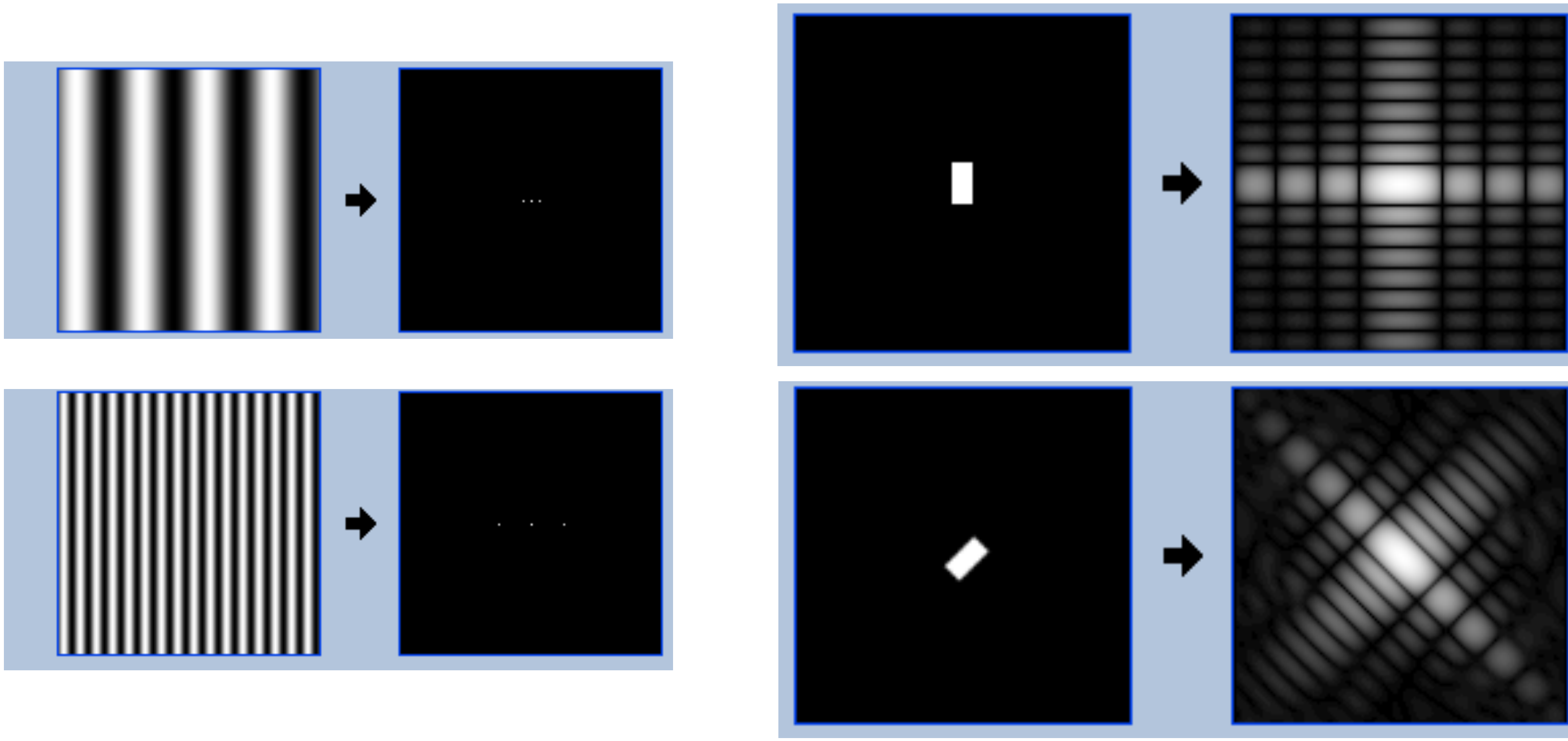
Ion Channel Structure



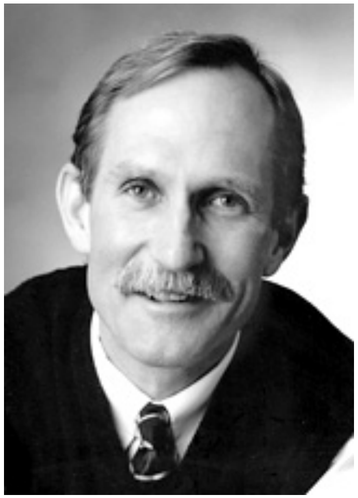
Ion Channel Structure



X-Ray Crystallography: Fourier Transform



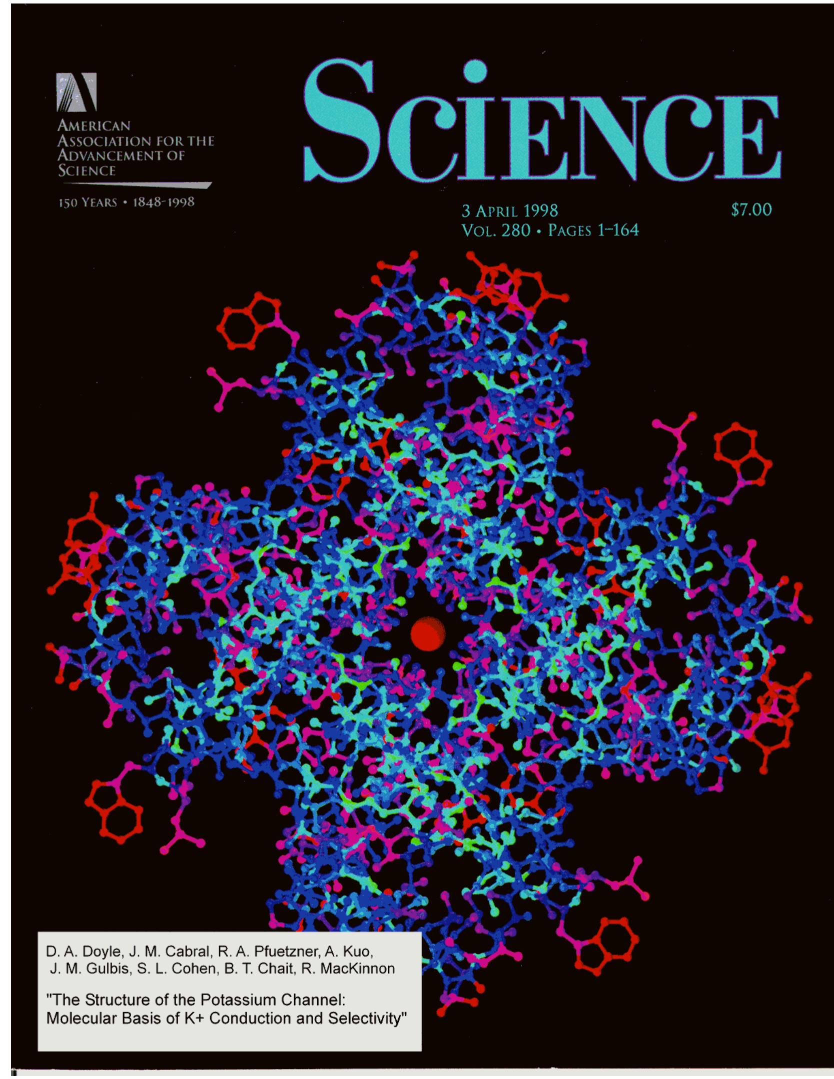
Nobel Prize in Chemistry 2003



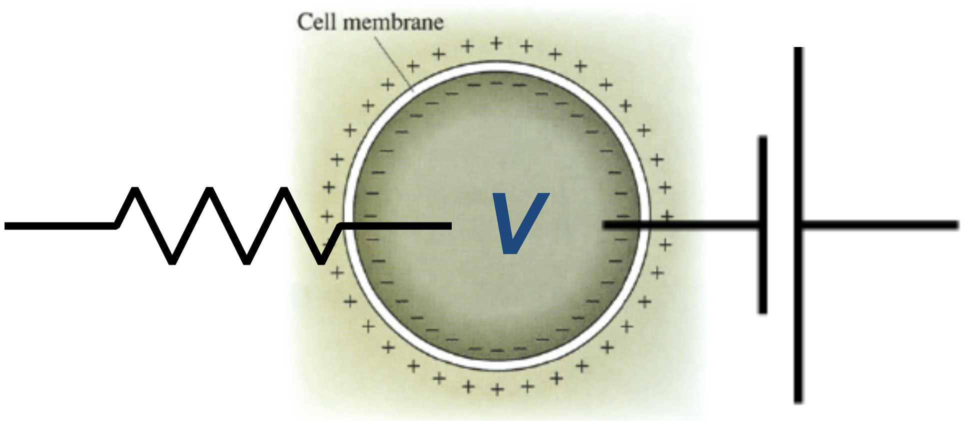
Peter Agre

Roderick MacKinnon

The Nobel Prize in Chemistry 2003 was awarded "for discoveries concerning channels in cell membranes" jointly with one half to Peter Agre "for the discovery of water channels" and with one half to Roderick MacKinnon "for structural and mechanistic studies of ion channels".



Modeling Neural Membranes



Membrane Current due to Ions ("Leak Current")

$$-i_m = c_m \frac{dV}{dt} = \frac{dQ}{dt}$$

$R_m = r_m / A$

$r_m \sim 1\ M\Omega\ mm^2$

(Specific Membrane Resistance)

$Q = C_m \frac{dV}{dt} V$

$C_m = c_m A$

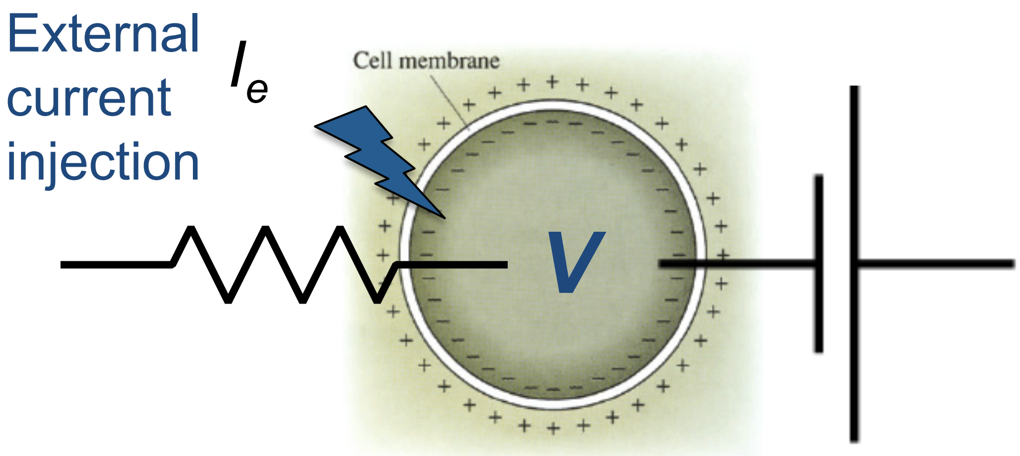
$c_m \sim 10\ nF/\ mm^2$

(Specific Membrane Capacitance)

Membrane Current with Leak Conductance Term

$$i_m = \sum_i g_i (V - E_i) = g_L (V - E_L) = \frac{(V - E_L)}{r_m}$$

Compartment Membrane Model



Membrane Time Constant

$\tau_m = r_m c_m$

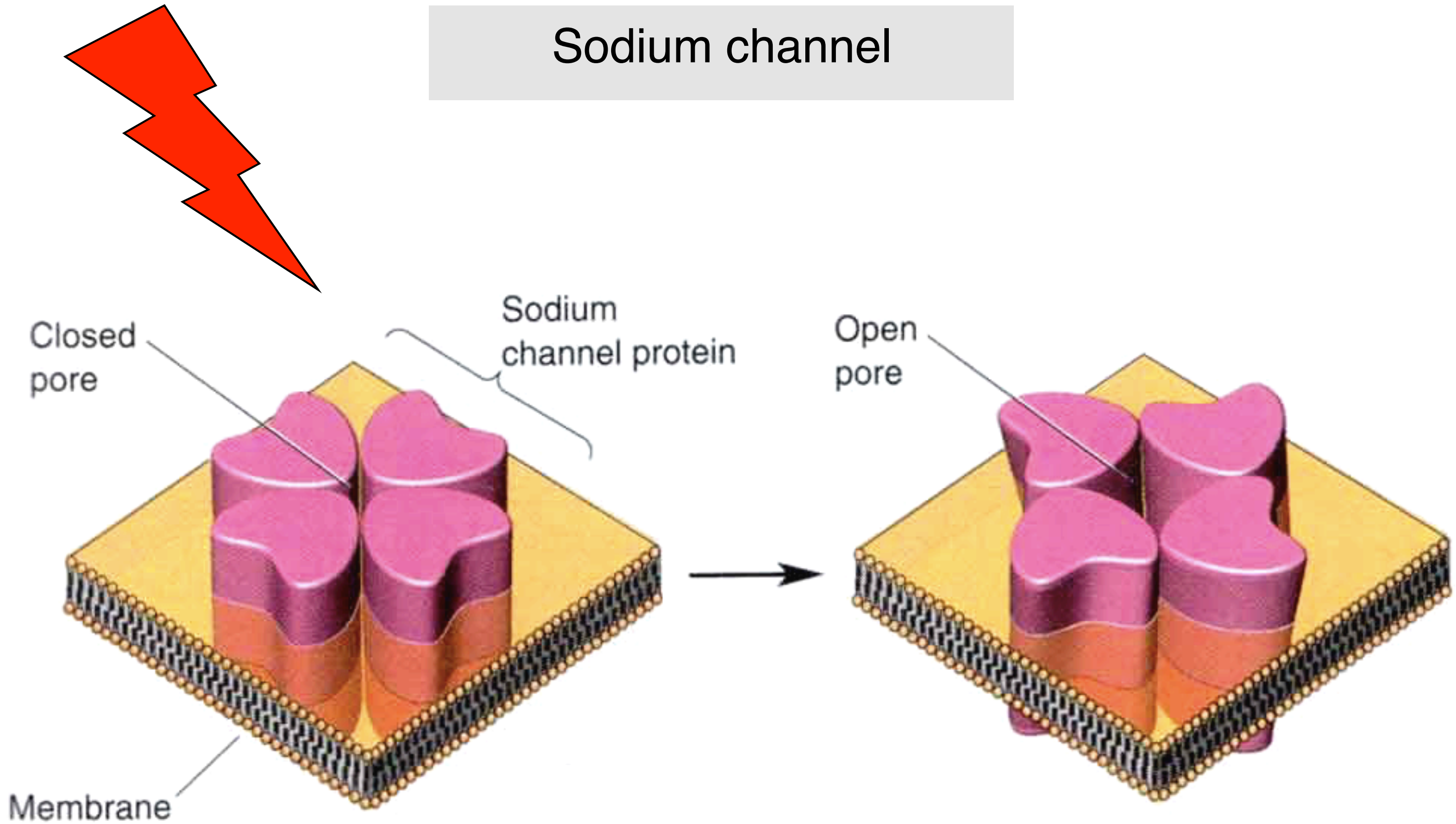
$$c_m \frac{dV}{dt} = -\frac{(V - E_L)}{r_m} + \frac{I_e}{A}$$

$R_m = r_m / A$
$r_m \sim 1$ MΩ mm^2
(Specific Membrane Resistance)

$Q = C_m V$
$C_m = c_m A$
$c_m \sim 10$ nF/ mm^2
(Specific Membrane Capacitance)

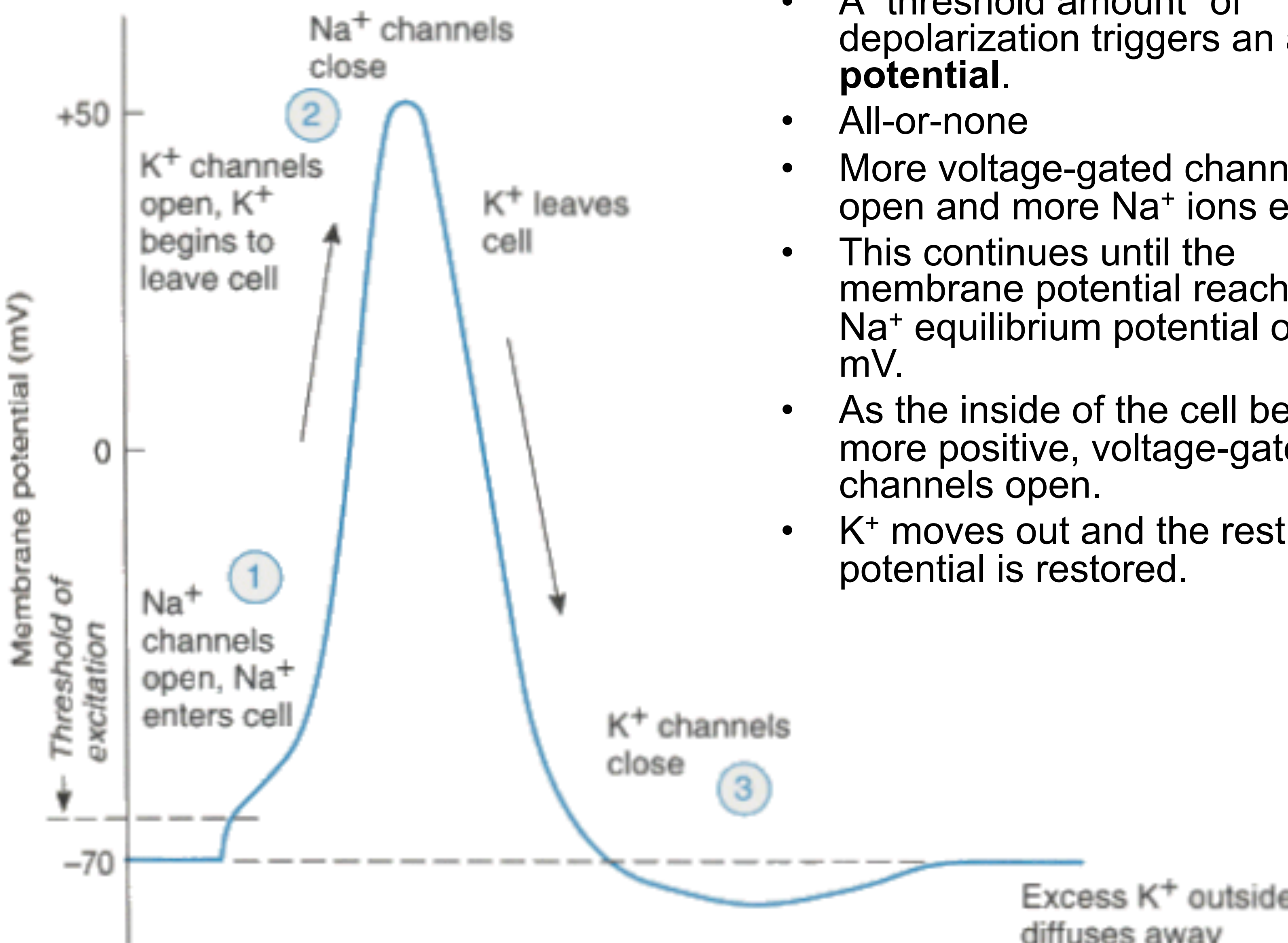
$$\tau_m \frac{dV}{dt} = -(V - E_L) + I_e R_m$$

Sodium channel



Gated (vs non-gated) channel

Action Potential

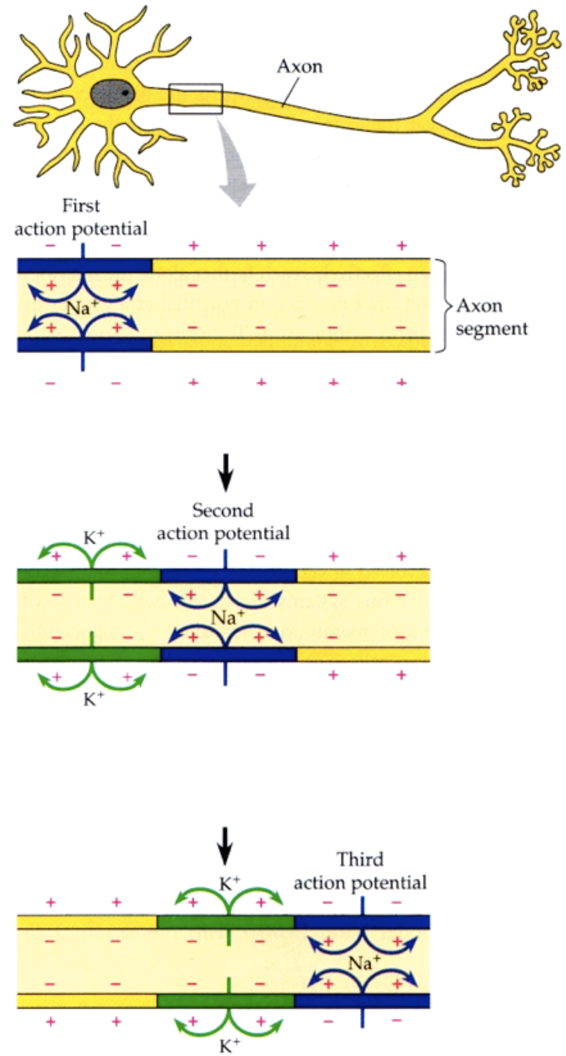


- A "threshold amount" of depolarization triggers an **action potential**.
- All-or-none
- More voltage-gated channels open and more Na^+ ions enter.
- This continues until the membrane potential reaches the Na^+ equilibrium potential of +50 mV.
- As the inside of the cell becomes more positive, voltage-gated K^+ channels open.
- K^+ moves out and the resting potential is restored.

The Action Potential is propagated down the axon

Voltage-gated sodium channels

Voltage-gated potassium channels

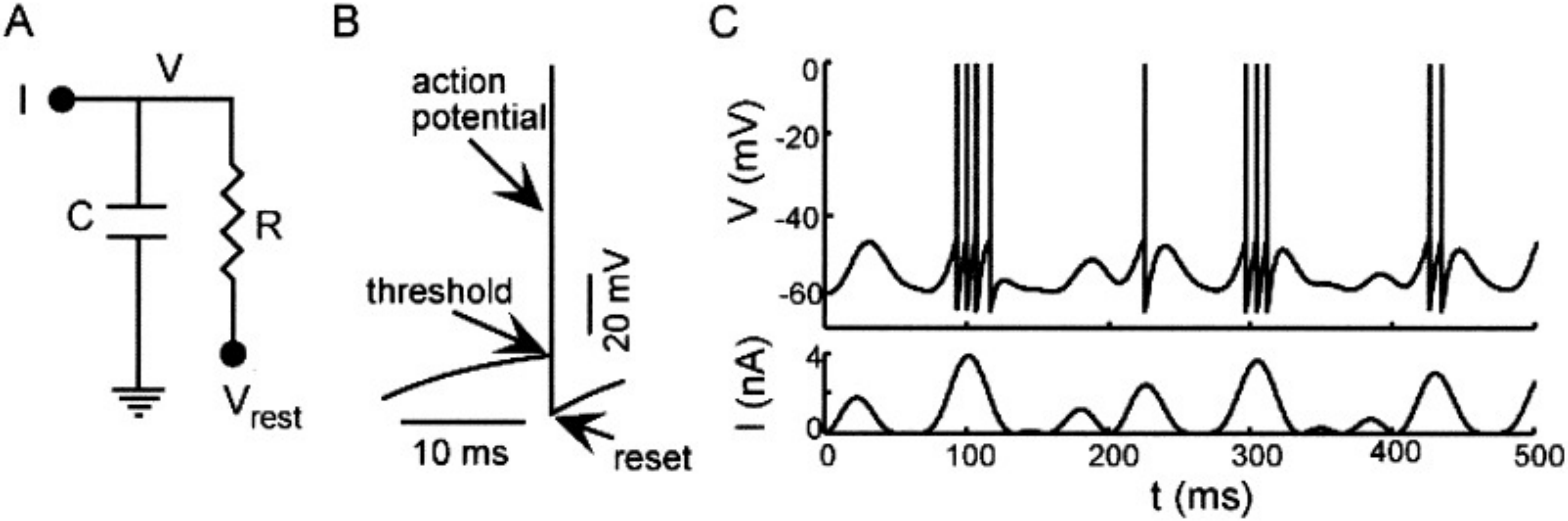


Neuropharmacology

- TTX (tetrodotoxin) → blocks Na+ channels
- Saxitoxin→ blocks voltage gated Na+ channels
- TEA (tetraethylammonium) → blocks K+ channels

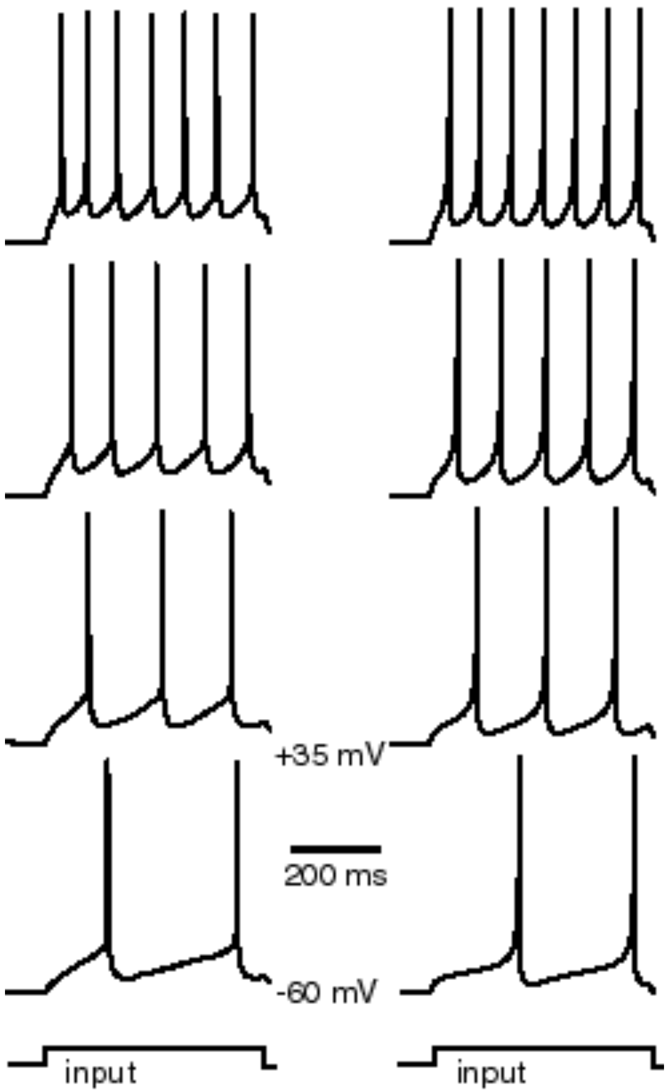
PUFFER FISH

Generating Spikes: Integrate-and-Fire Model

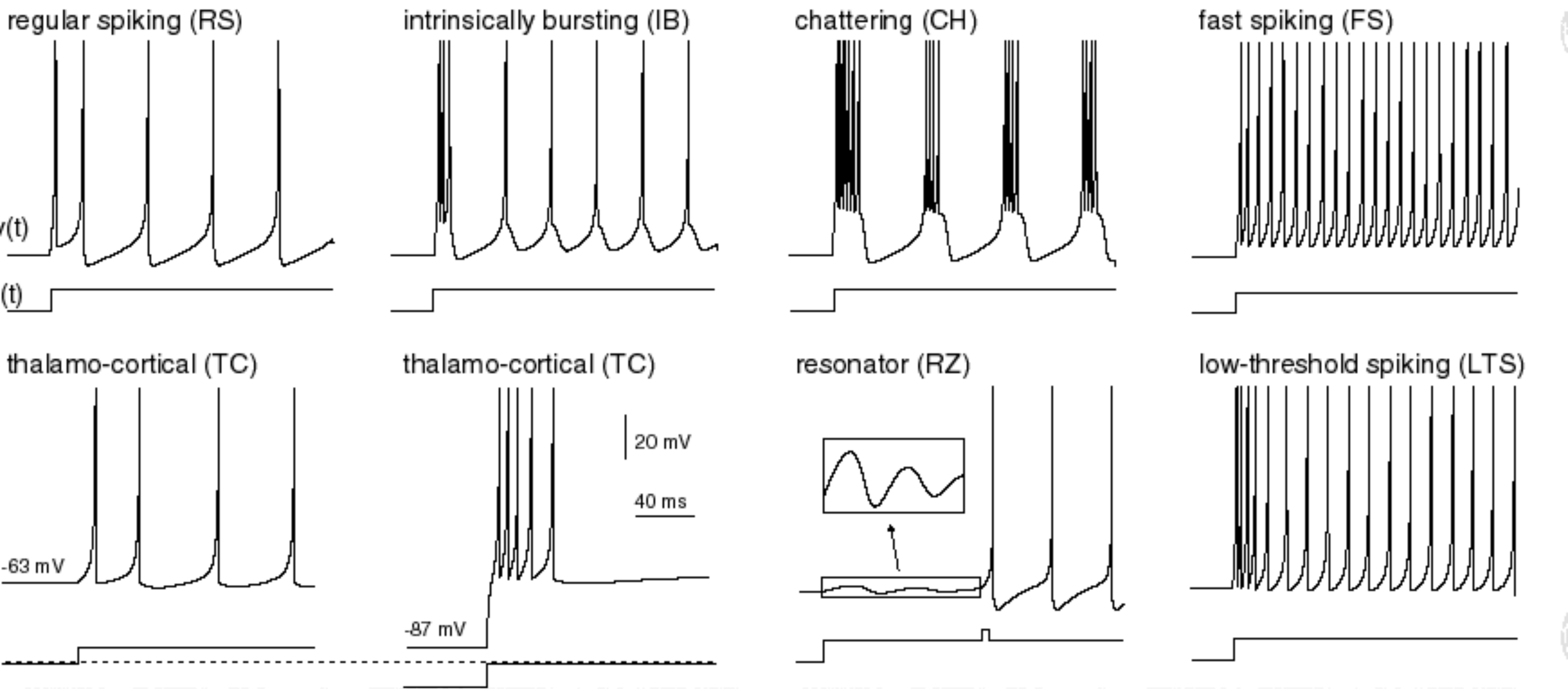


A. The equivalent circuit with membrane capacitance ***C*** and membrane resistance ***R. V*** is the membrane potential and ***V*** $_{\textbf{\textit{rest}}}$ is the resting membrane potential.
B. The voltage trajectory of the model. When ***V*** reaches a threshold value, an action potential is generated and ***V*** is reset to a sub-threshold value.
C. An integrate-and-fire model neuron driven by a time-varying current. The upper trace is the membrane potential and the bottom trace is the input current.

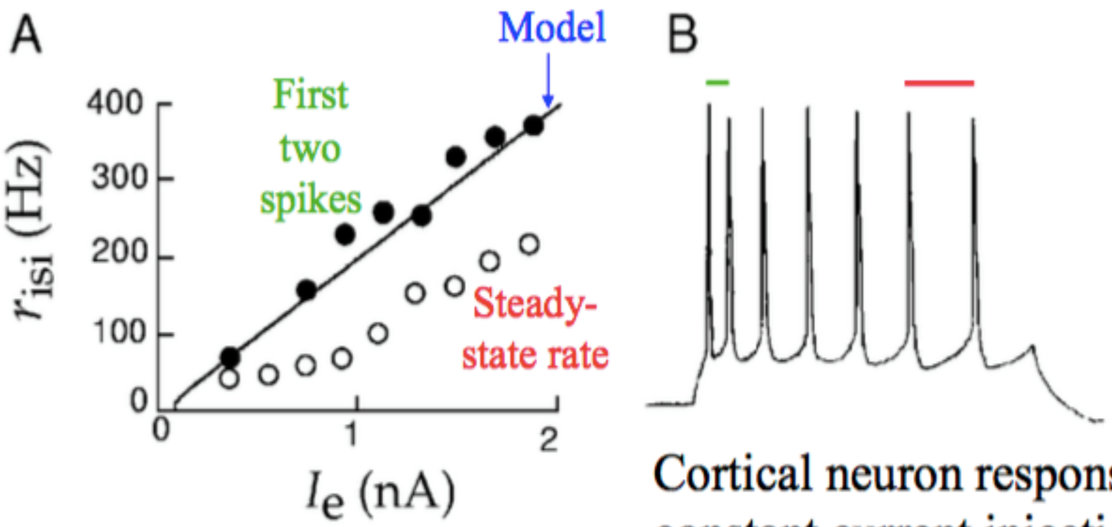
Which column represents real data?



Spiking Patterns of Neurons



Comparison of I & F Model to Data



Cortical neuron response to constant current injection

Real neuron exhibits spike-rate adaptation and refractoriness

Spike-Frequency Adaptation: When stimulated with a square pulse or step, many neurons show a reduction in the firing frequency of their spike response following an initial increase.
Sensory Adaptation: A change in responsiveness of a neural system when stimulated with a constant sensory stimulus.
Refractoriness: Property of neuron not to respond on stimuli (Amount of time it takes for neuron to be ready for a second stimulus once it returns to resting state following excitation)

Making the I & F Model More Realistic

$$\tau_m \frac{dV}{dt} = -(V - E_L) - r_m g_{sra}(V - E_K) + I_e R_m$$

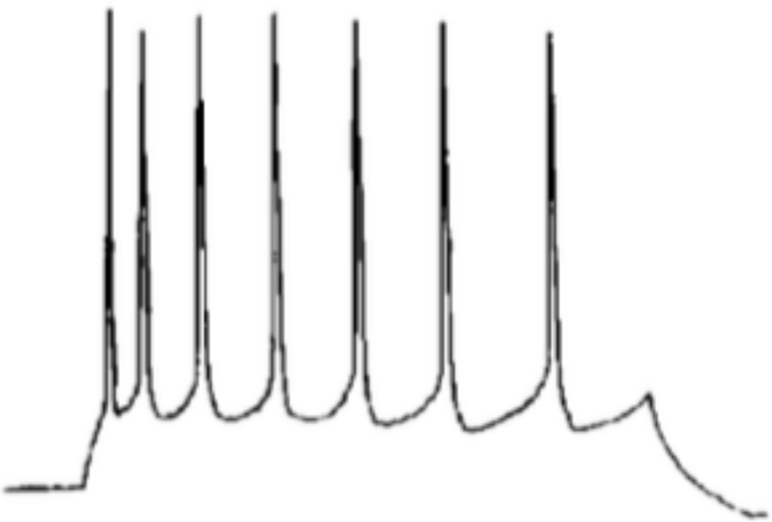
$$\tau_m \frac{dg_{sra}}{dt} = -g_{sra}$$

Spike-Rate Adaptation

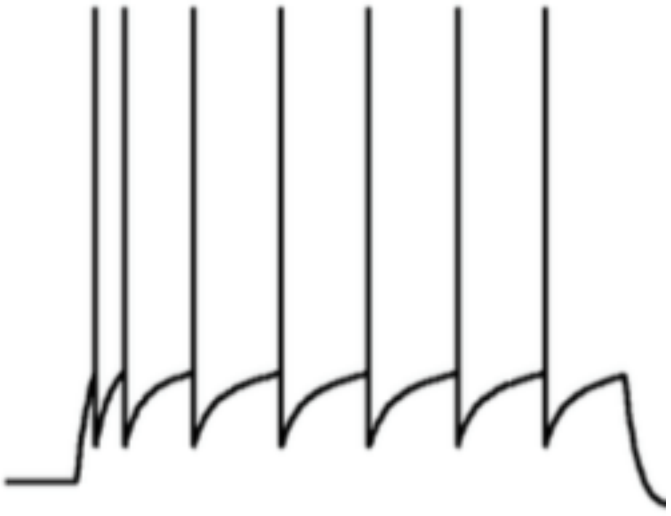
If $V > V_{threshold}$,
Spike and Set $g_{sra} = g_{sra} + \Delta g_{sra}$
Reset: $V = V_{reset}$

How would we add a term to model for refractoriness?

I & F Model with Spike-Rate Adaptation

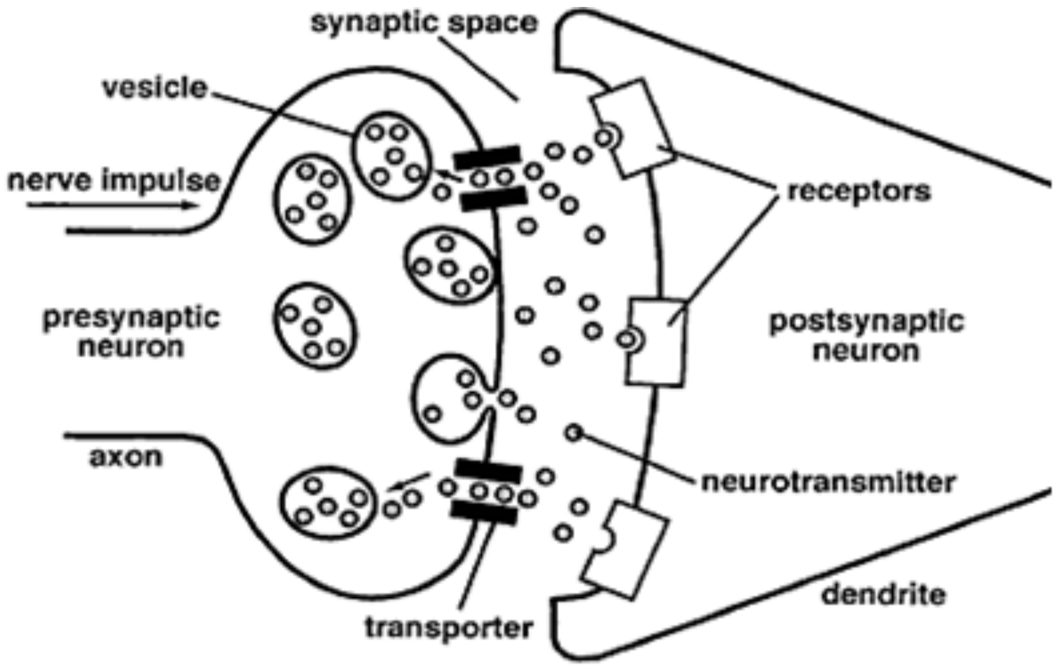


Cortical Neuron

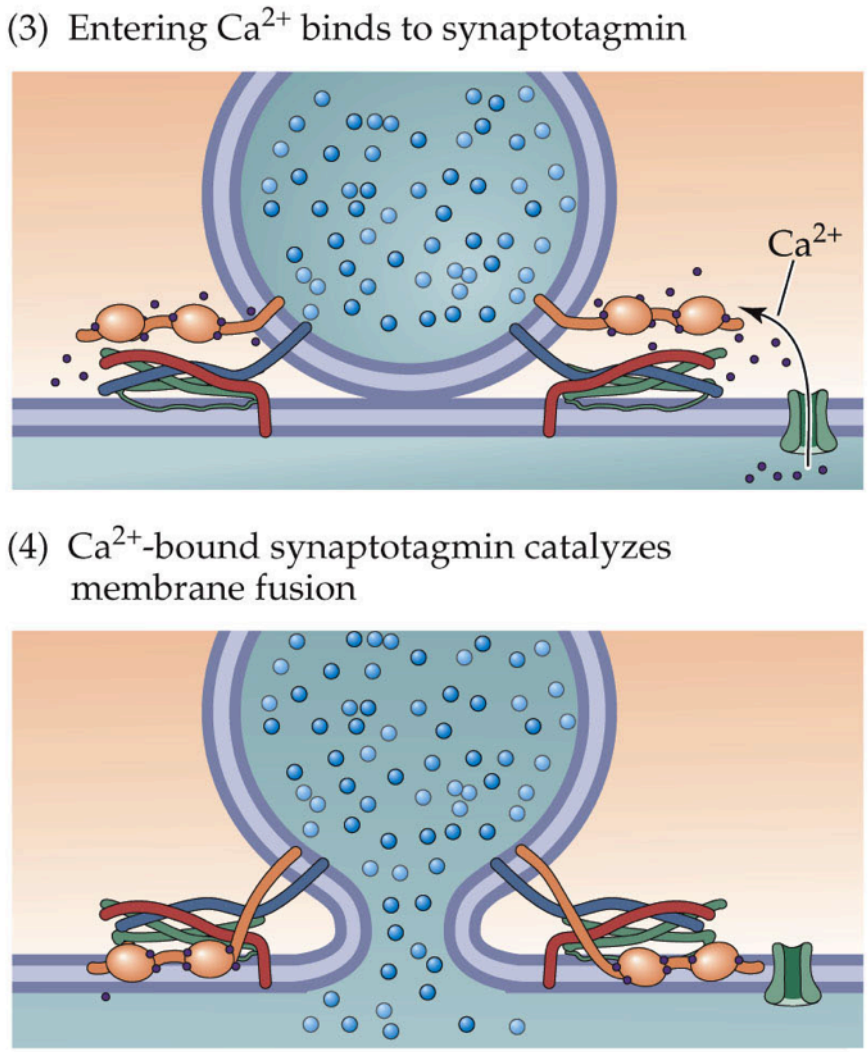


Integrate-and-Fire
Model with
Spike-Rate
Adaptation

Synapses: Modeling the Inputs to a Neuron



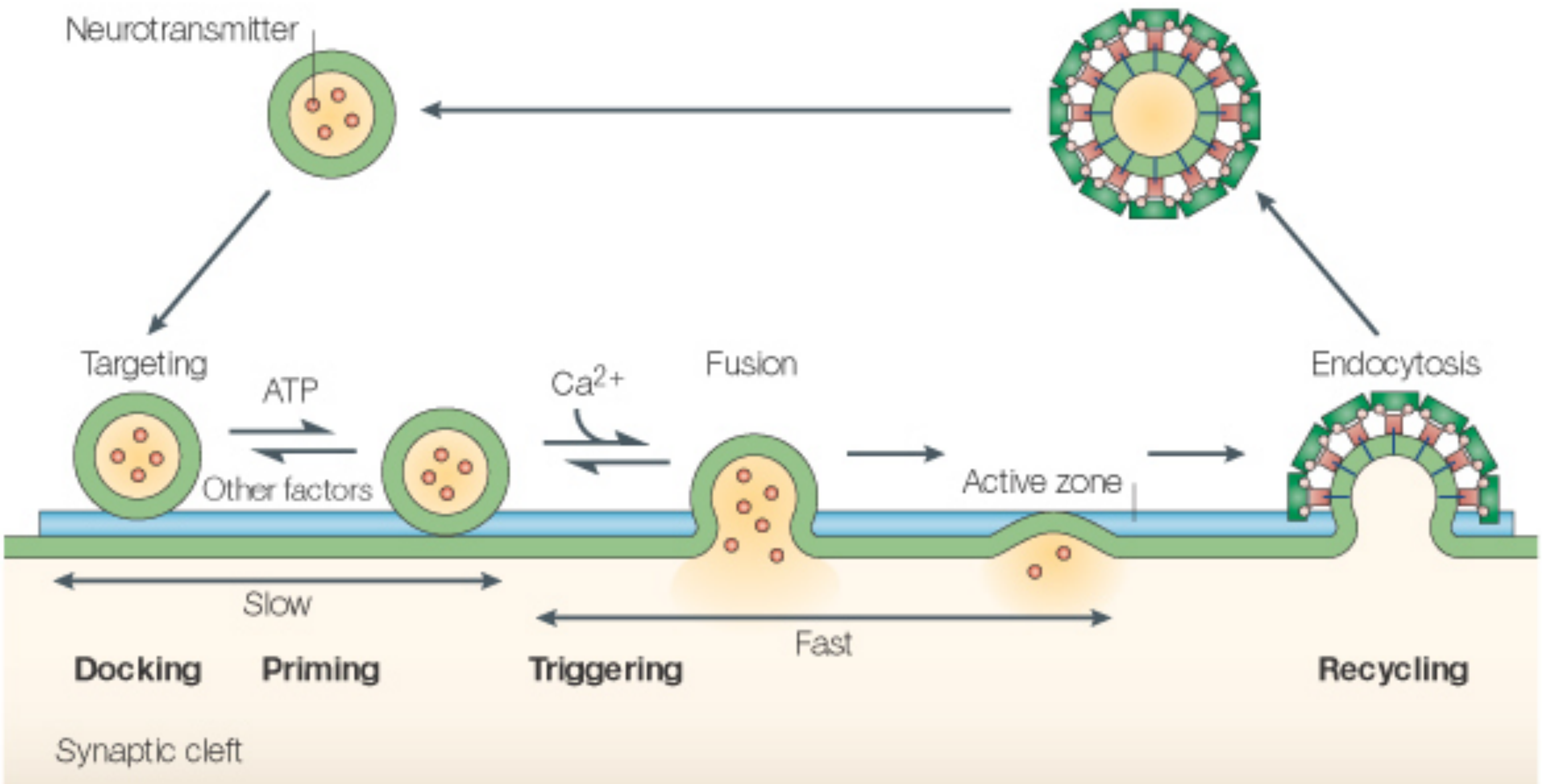
Vesicle Fusion is triggered by Calcium



EXOCYTOSIS

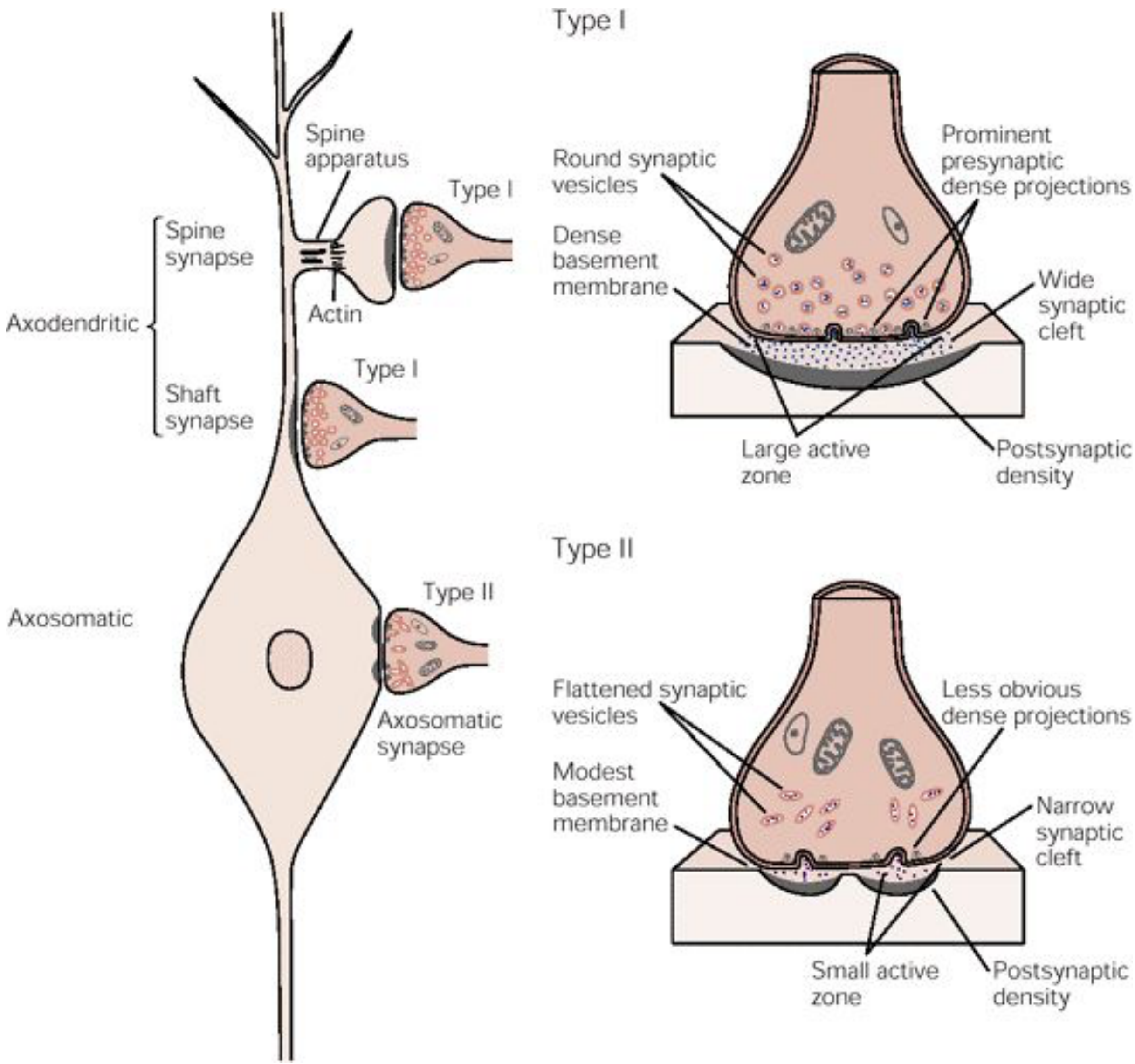
NEUROSCIENCE, Fourth Edition, Figure 5.14 (Part 3)

Endocytosis: Vesicle Retrieval



Nature Reviews | Molecular Cell Biology

Excitatory and Inhibitory Synapses



Type I Synapse: Found in dendrites and result in an excitatory response in the post-synaptic cell

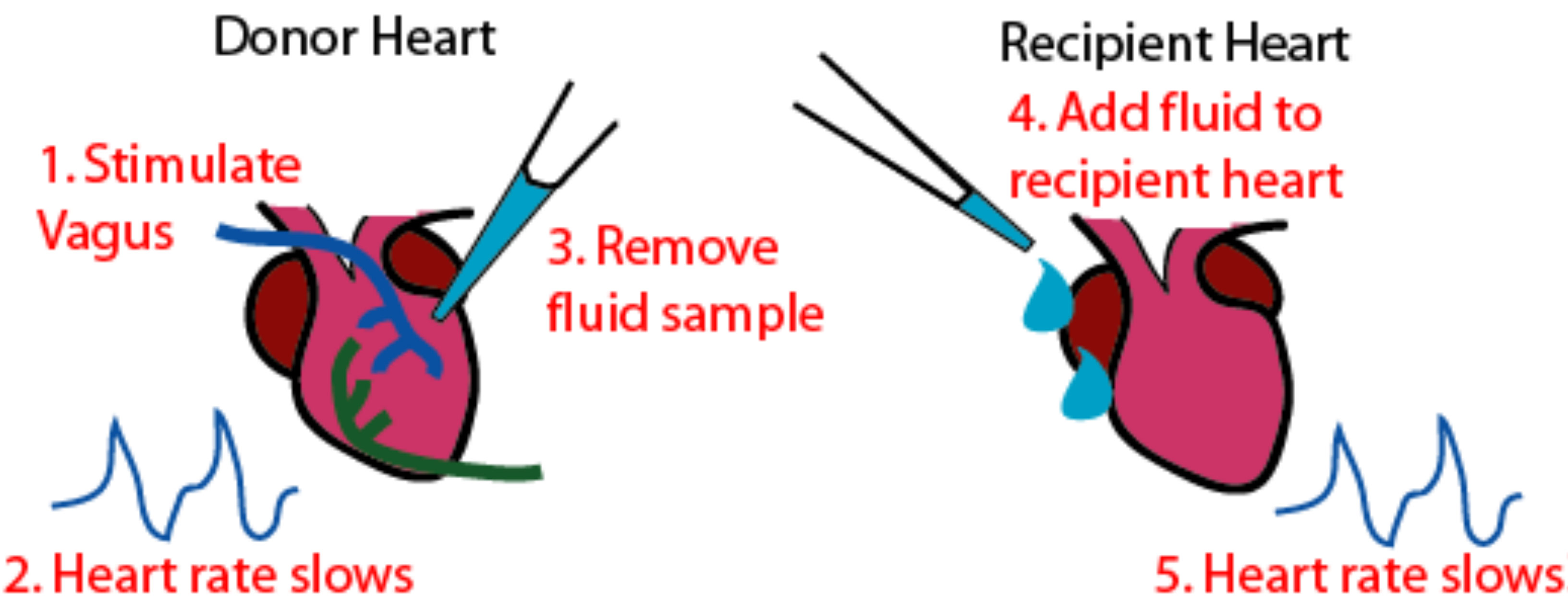
Type II Synapse: Found on soma and inhibit the receiving cell's activity

Definition of a Neurotransmitter

- Must be produced and found within a neuron
- Must be released upon depolarization
- Must act on a post-synaptic receptor and have a downstream biological effect
- If applied on a post-synaptic membrane, it should have the same effect
- It must be inactivated

Discovery of First Neurotransmitter

- Acetylcholine – Otto Loewi

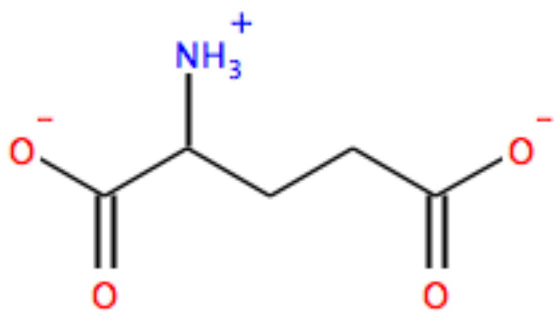


Three Main Groups of Neurotransmitter

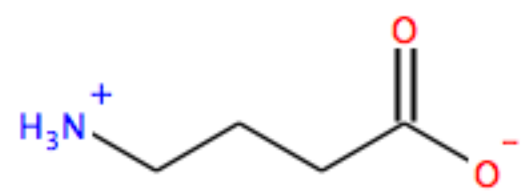
1) Excitatory neurotransmitter: Glutamate

2) Inhibitory neurotransmitter: GABA

3) Modulatory neurotransmitters: Dopamine, serotonin, acetylcholine, et al.



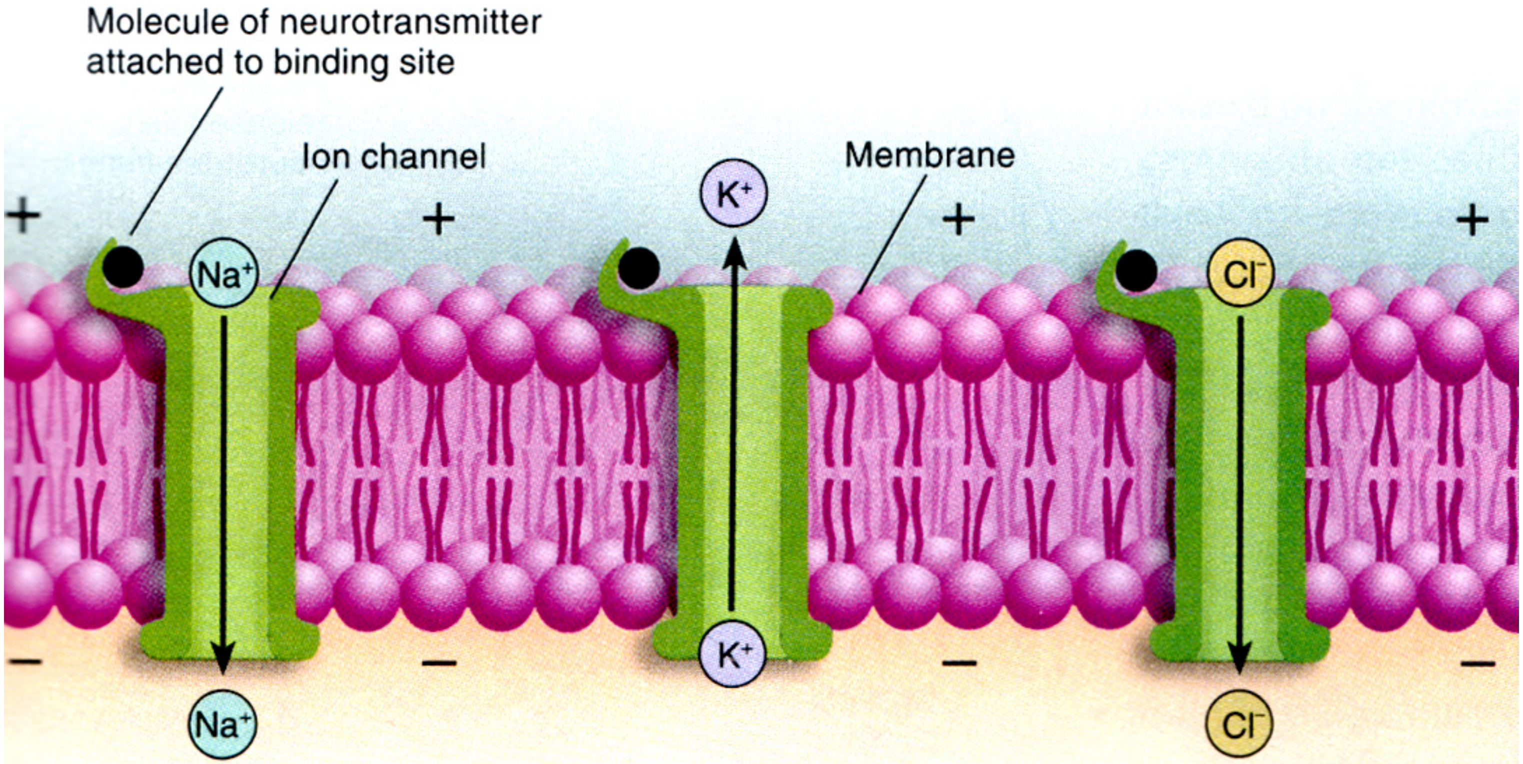
Glutamate



Gamma-aminobutryic acid (GABA)

Excitatory and Inhibitory Synapses

Excitatory Synapse	Inhibitory Synapse
1. Input Spike 2. Neurotransmitter release 3. Binds to Na channels, which open 4. Na^+ Influx 5. Depolarization due to EPSP (excitatory post-synaptic potential) Example: AMPA Synapse (allows both Na^+ and K^+ to cross membrane)	1. Input Spike 2. Neurotransmitter release 3. Binds to K channels 4. Change in synaptic conductance 5. K+ leaves cell 6. Hyperpolarization due to IPSP (inhibitory post-synaptic potential) Example: GABA Synapse, Glycine Synapse



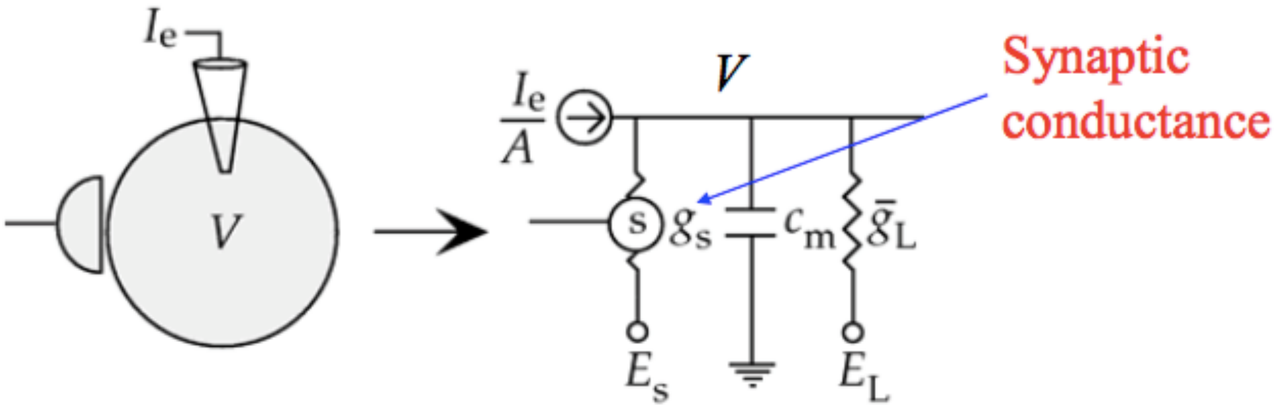
+	**−**	**−**
Excitatory postsynaptic potential **EPSP**	Inhibitory postsynaptic potential **IPSP**	Inhibitory postsynaptic potential **IPSP**

(depolarization) (hyperpolarization)

Inactivation of neurotransmitters

- **Diffusion out of the synaptic cleft**
- **Enzymatic Degradation** (structure of NT changed)
- **Reuptake by neuron or glial cell** (Transporter in presynaptic membrane)

Modeling a Synaptic Input to a Neuron



$$\tau_m \frac{dV}{dt} = -(V - E_L) - r_m g_{sra}(V - E_K) + I_e R_m$$

$$g_s = g_{s,\max} P_{rel} P_s$$

P_{rel} is the probability of post-synaptic channel opening (fraction of channels opened)

P_s is the probability of neurotransmitter release given an input spike

Basic Synapse Model

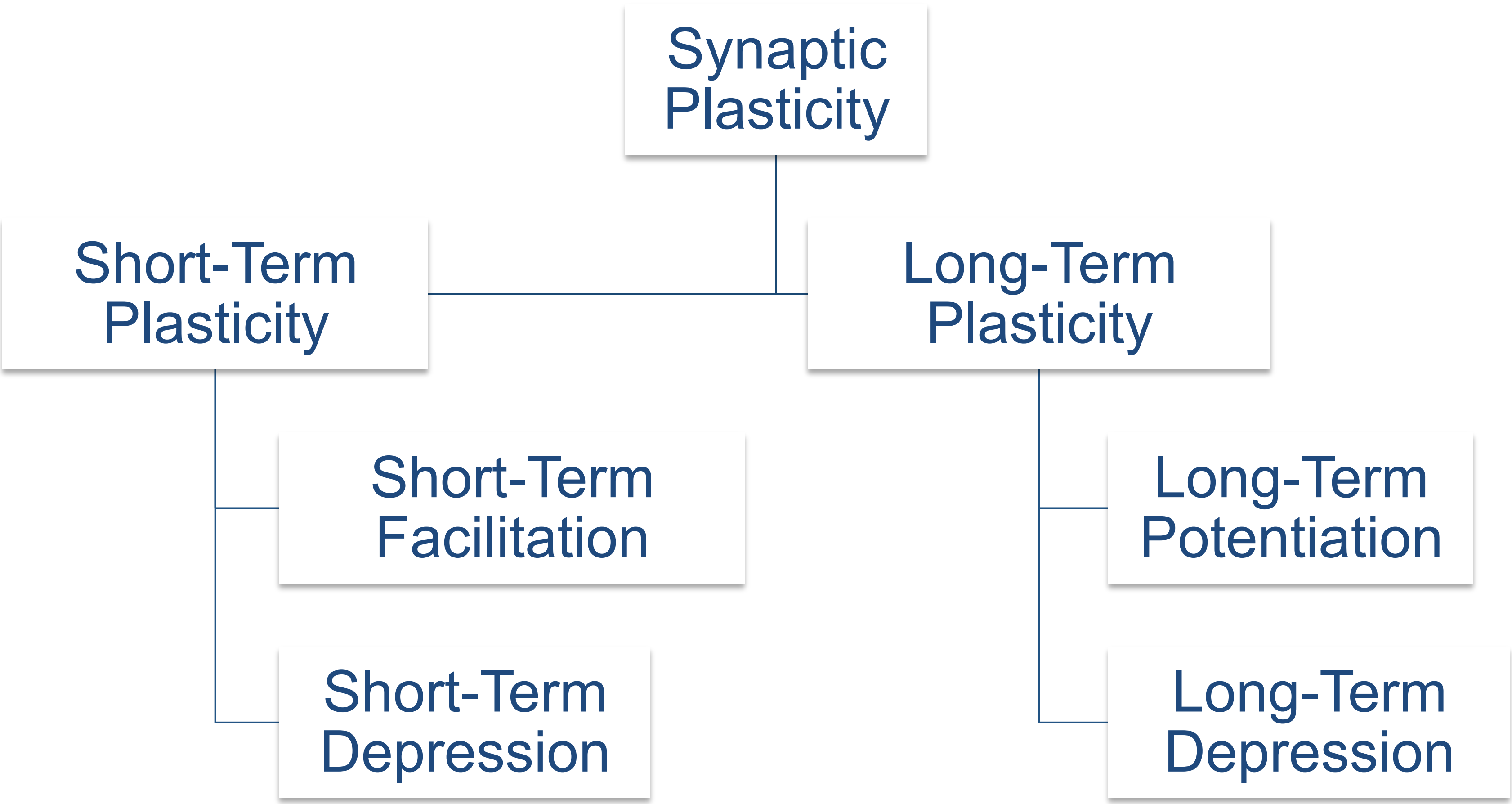
Assume $P_{rel} = 1$
Model the effect of a single spike input on P_s
Kinetic Model:

1. Closed $\xrightarrow{\alpha_s}$ Open
2. Open $\xrightarrow{\beta_s}$ Closed

$$\frac{dP_s}{dt} = \alpha_s (1 - P_s) - \beta_s P_s$$

α_s = Opening Rate
P_s = Fraction of channels closed
β_s = Closing Rate
P_s = Fraction of channels open

Synapse Primer



Synapse Primer

Short-Term Synaptic Plasticity:

(STP) Dynamic synapses, a phenomenon in which synaptic efficacy changes over time in a way that reflects the history of pre-synaptic effect

Short-Term Depression:

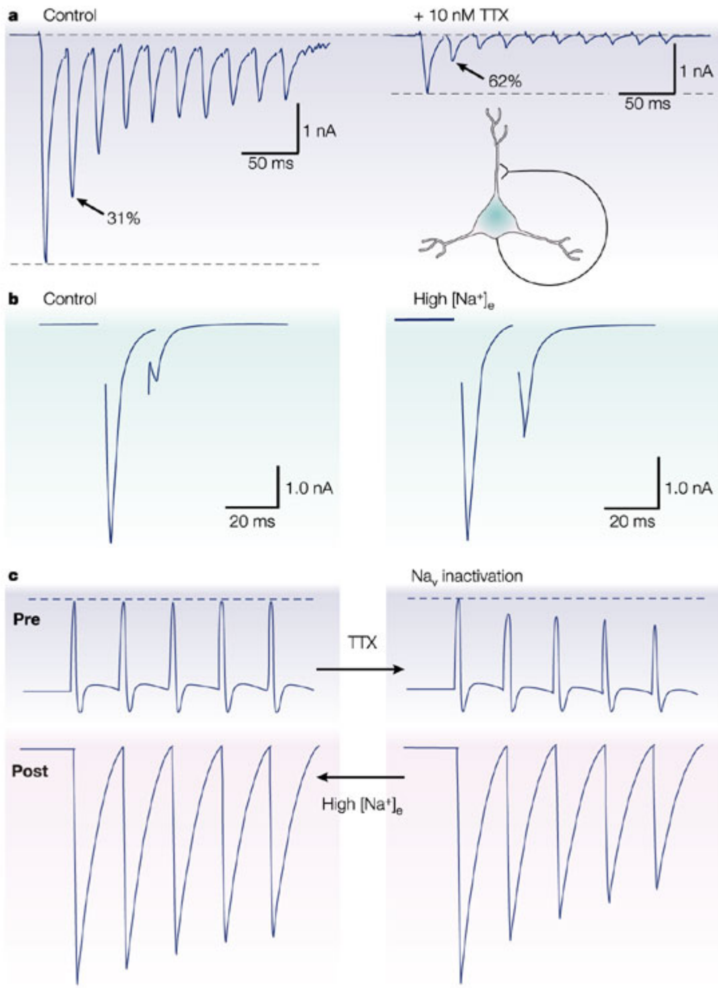
(STD) Result of depletion of neurotransmitters consumed during the synaptic signaling process at the axon terminal of a pre-synaptic neuron

Short-Term Facilitation:

(STF) Result of influx of calcium into the axon terminal after spike generation, which increases the release probability of neurotransmitters

What if there are multiple input spikes?

Biological synapses are dynamic
Linear summation of single spike inputs is not correct



A. Example of Short-Term Depression

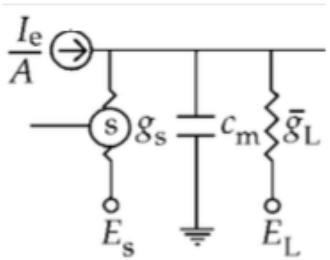
B. TTX Blocks Sodium Channels and Reduces synaptic transmission and enhances short-term depression

C. Hypothetical regulation of short-term depression by the modulation of activity-dependent attenuation of presynaptic spike amplitude. TTX attenuates spike train and enhances depression. Reduced inactivation opposes both pre-synaptic attenuation and short-term depression.

Modeling Dynamic Synapses

Recall the definition of synaptic conductance:

$$g_s = g_{s,\max} P_{rel} P_s$$



Idea: Specify how P_{rel} changes as a function of consecutive input spikes

$$\tau_P \frac{dP_{rel}}{dt} = P_o - P_{rel}$$

Between input spikes, P_{rel} decays exponentially back to P_o

If Input Spike:

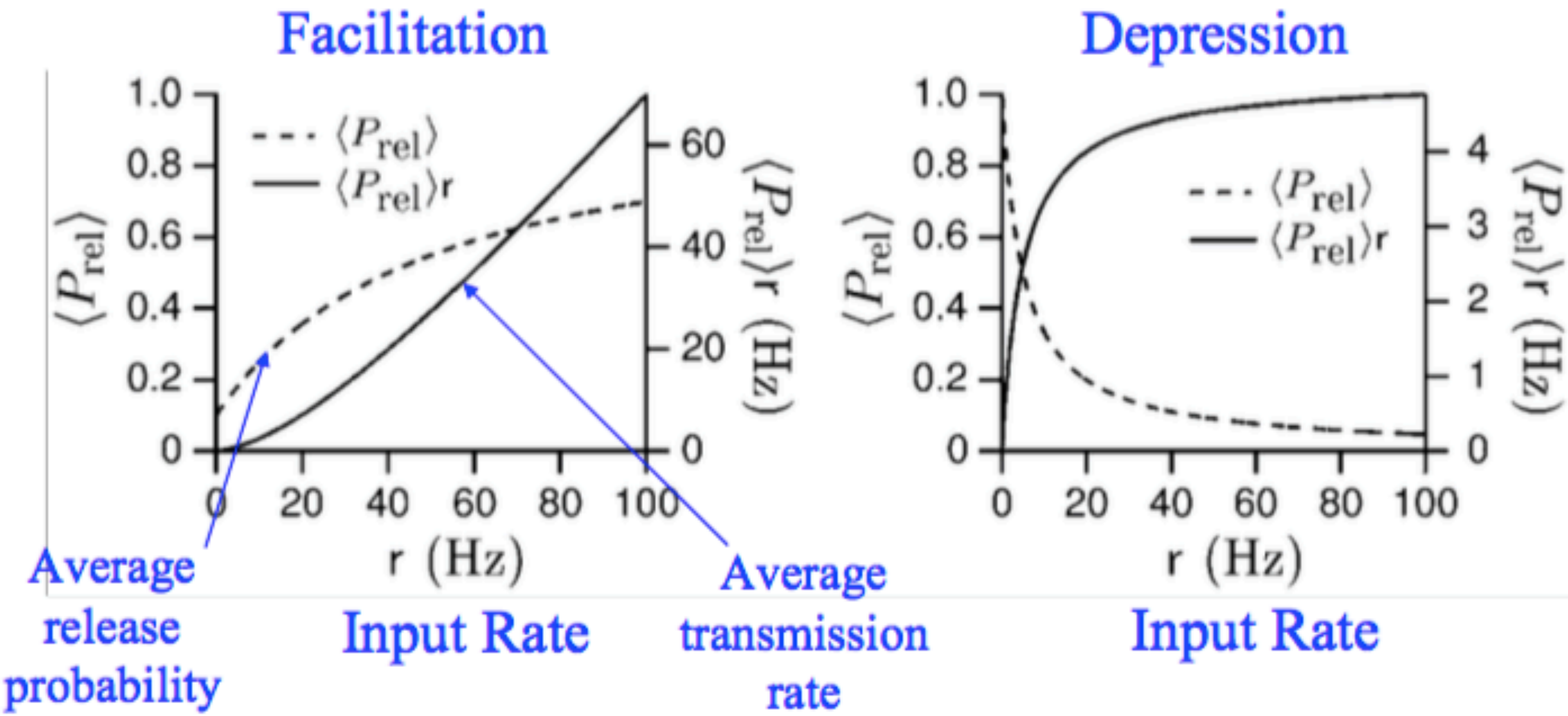
$$P_{rel} \sim f_D P_{rel}$$

Depression: Decrement P_{rel}

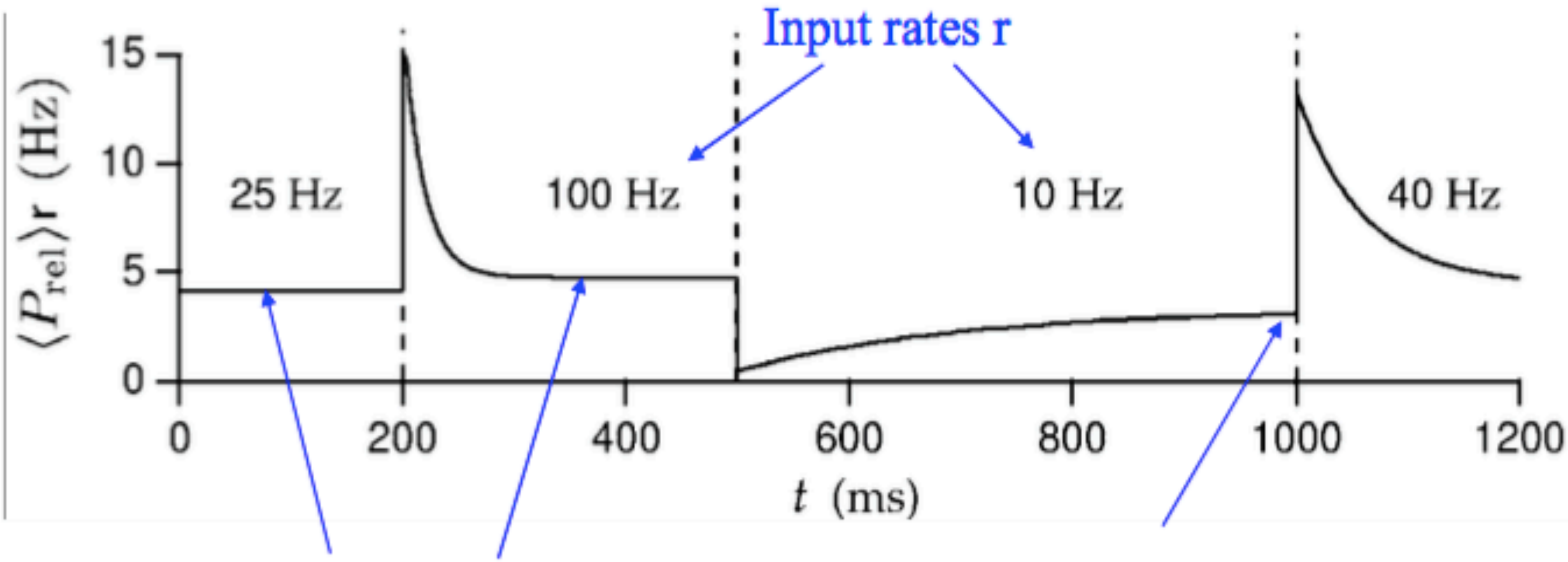
$$P_{rel} \sim P_{rel} + f_F (1 - P_{rel})$$

Facilitation: Increment P_{rel}

Effects of Synaptic Facilitation and Depression



Consequences of Synaptic Depression

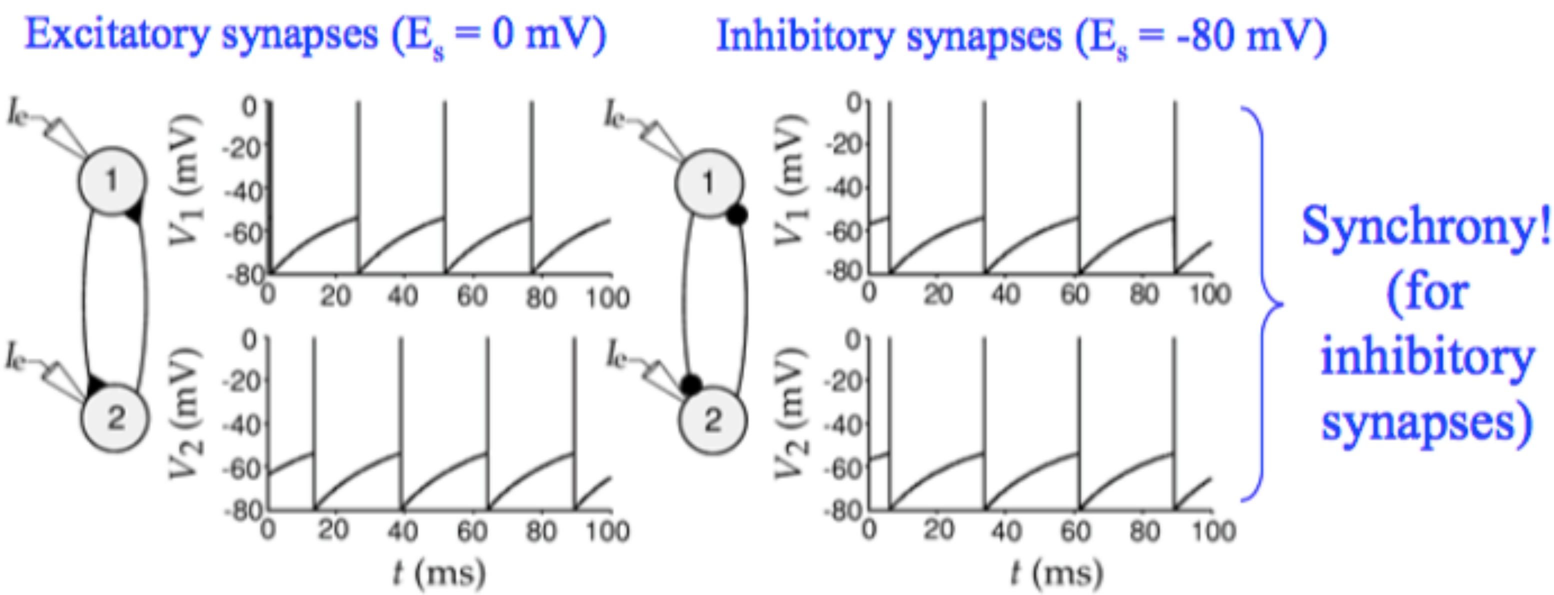


Steady-state transmission rates are similar for different rates

Transient inputs are amplified relative to steady-state inputs

Change in transmission rate ∝ $\Delta r/r$

Synapse Networks



Each Neuron:

$$\tau_m \frac{dV}{dt} = -(V - E_L) - r_m g_{s,\max} P_s (V - E_s) + I_e R_m$$

Synapses: Alpha Function model for P_s

Next Time:
Hodgkin-Huxley Model
Multi-Compartment Models