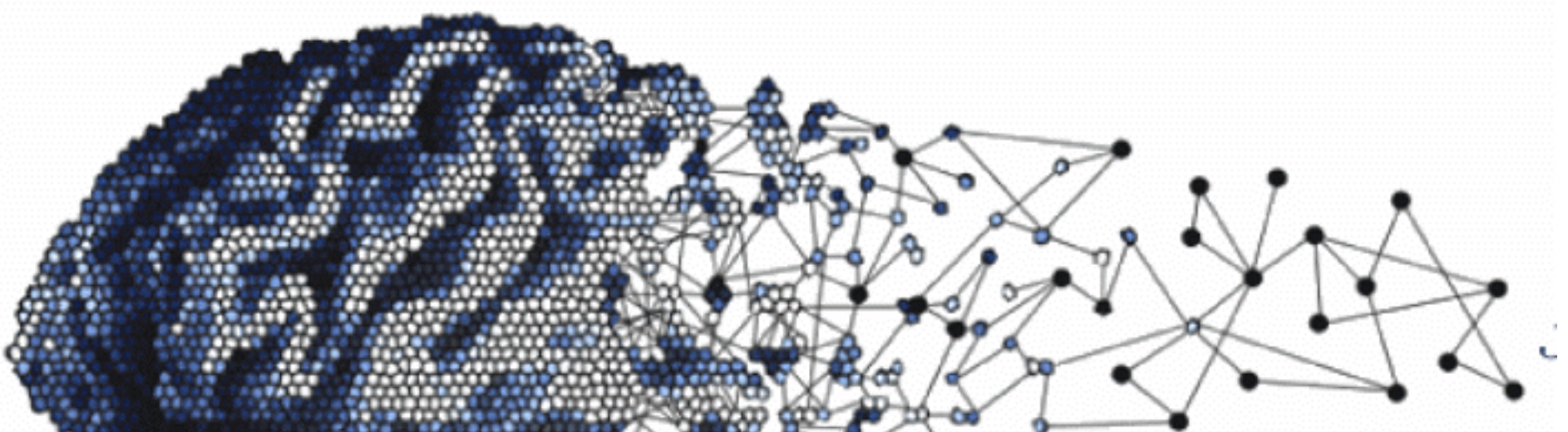
Applied Neuroscience

Columbia Science Honors Program

Fall 2017

Biophysical Models of Neurons and Synapses



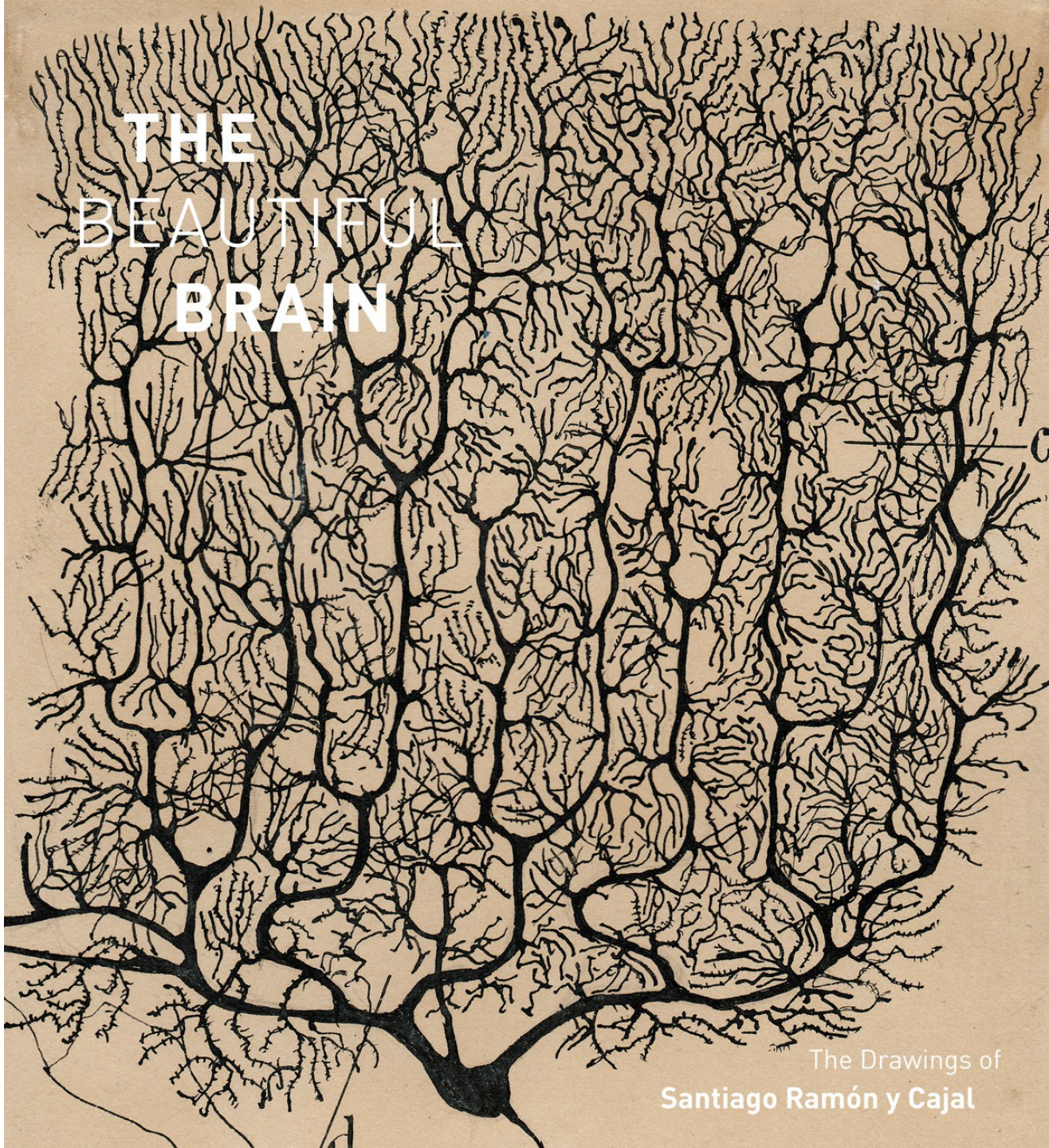
Guest Lecture
by Roger Traub

"Why is the brain so hard to understand?"

Art Exhibition
by Cajal Institute

January 09, 2018
To
March 31, 2018

Class Trip



Biophysical Models of Neurons and Synapses

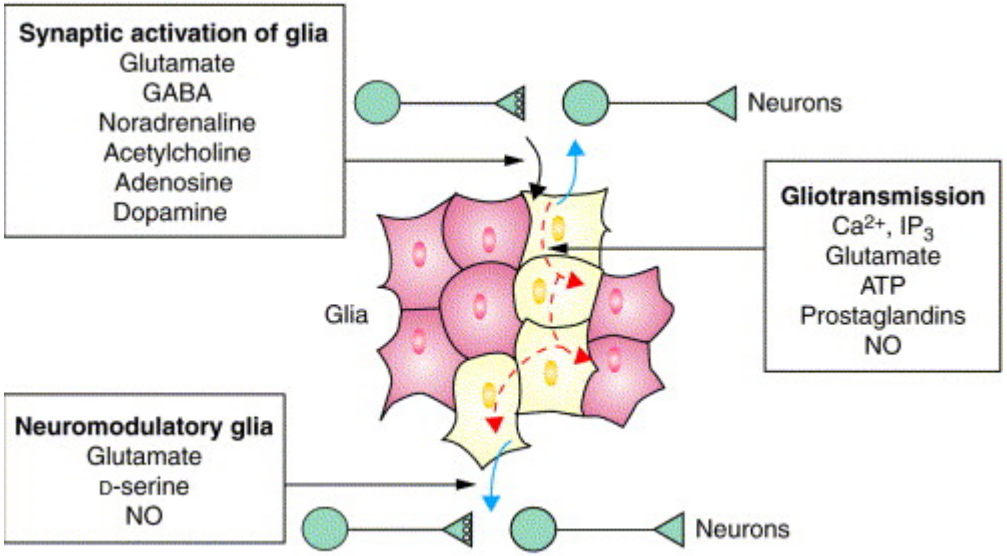
Objective: Model the transformation from input to output spikes

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 active membranes
   Hodgkin-Huxley Model
4. Model the effects of inputs from synapses
   Synaptic Model

Why use models?

- Quantitative models force us to think about and formalize hypotheses and assumptions
- Models can integrate and summarize observations across experiments and laboratories
- A model done well can lead to *non-intuitive* experimental predictions
- A quantitative model, implemented through simulations, can be useful from an engineering standpoint
  i.e. face recognition
- A model can point to important missing data, critical information, and decisive experiments



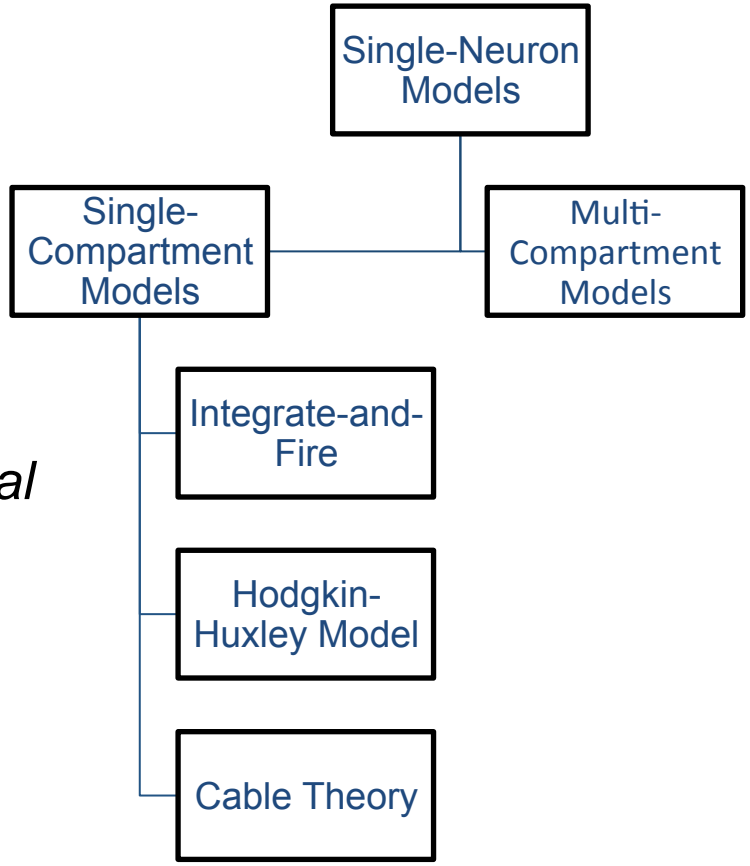
Case Study: Neuron-Glia Signaling Network in Active Brain

Chemical signaling underlying neuron-glia interactions. Glial cells are believed to be actively involved in processing information and synaptic integration. This opens up new perspectives for understanding the pathogenesis of brain diseases. For instance, inflammation results in known changes in glial cells, especially astrocytes and microglia.

Simulation of a Neuron

To Model a Neuron:

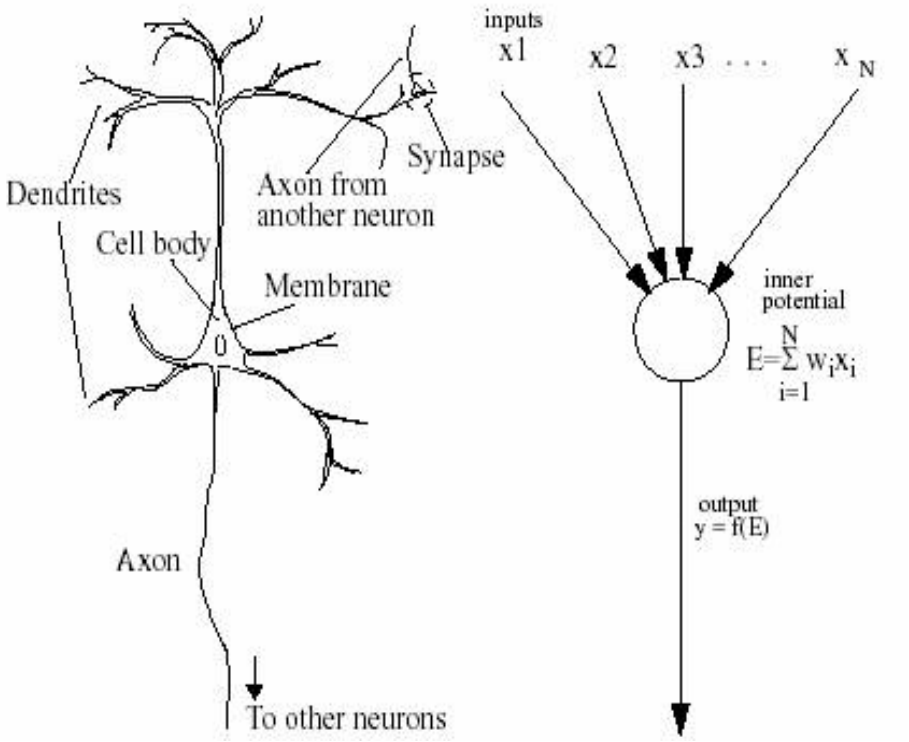
1. Intrinsic properties of cell membrane
2. Morphology



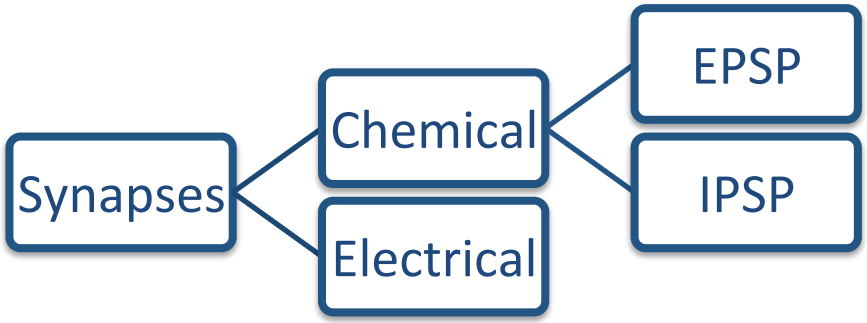
Single-Compartment Models
describe the membrane potential of a single neuron by a single variable and ignore spatial variables

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

Simulation of a Neuron



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

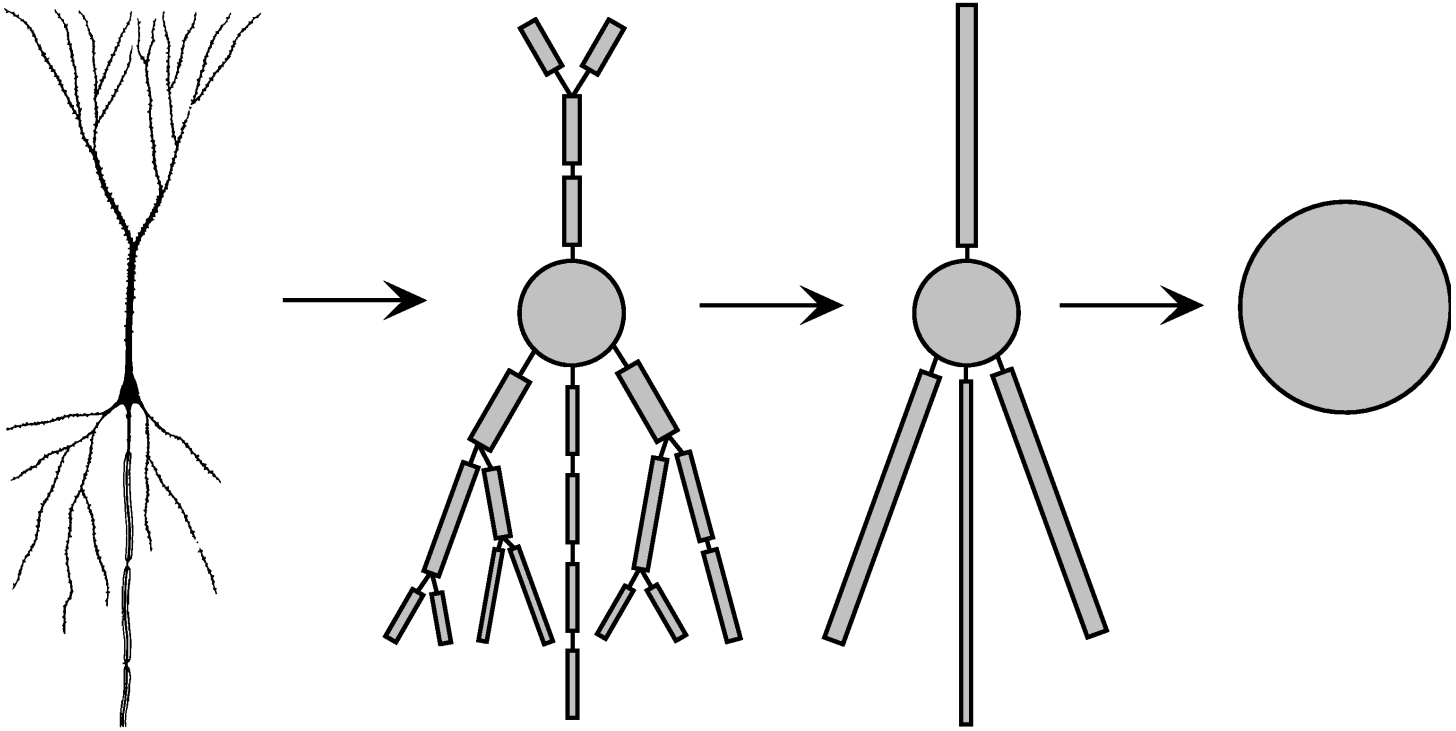
Output to Neuron:
Discrete Variable

Single Neuron Models

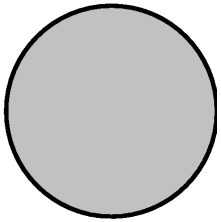
***Central Question**:* What is the correct level of abstraction?

- Filter Operations
- Integrate-and-Fire Model
- Hodgkin-Huxley Model
- Multi-Compartment Models
- Models of Spines and Channels

Abstract thought depicted in Inside Out by Pixar.



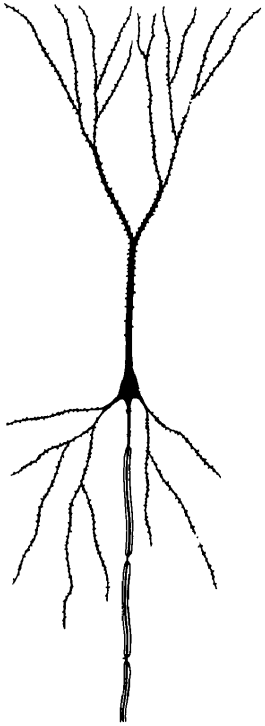
Single Neuron Models



Artificial Neuron Model: aims for computational effectiveness and consists of

- an input with some synaptic weight vector
- an activation function or transfer function inside the neuron determining output

$$O_j = f(\sum w_{ij} e_i)$$



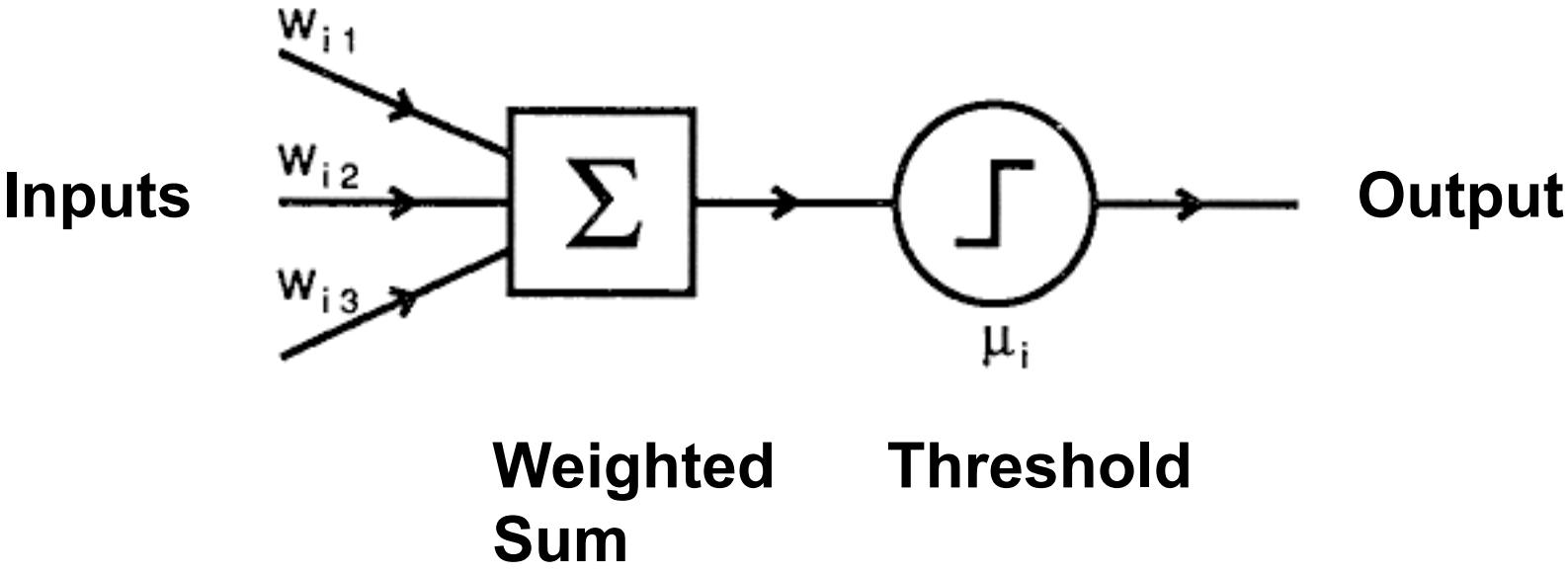
Biological Neuron Model: mathematical description of the properties of neurons

- physical analogs are used in place of abstractions such as “weight” and “transfer function”
- ion current through the cell membrane is described by a physical time-dependent current *I(t)*
- Insulating cell membrane determines a capacitance C_m
- A neuron responds to such a signal with a change in voltage, resulting in a voltage spike (action potential)

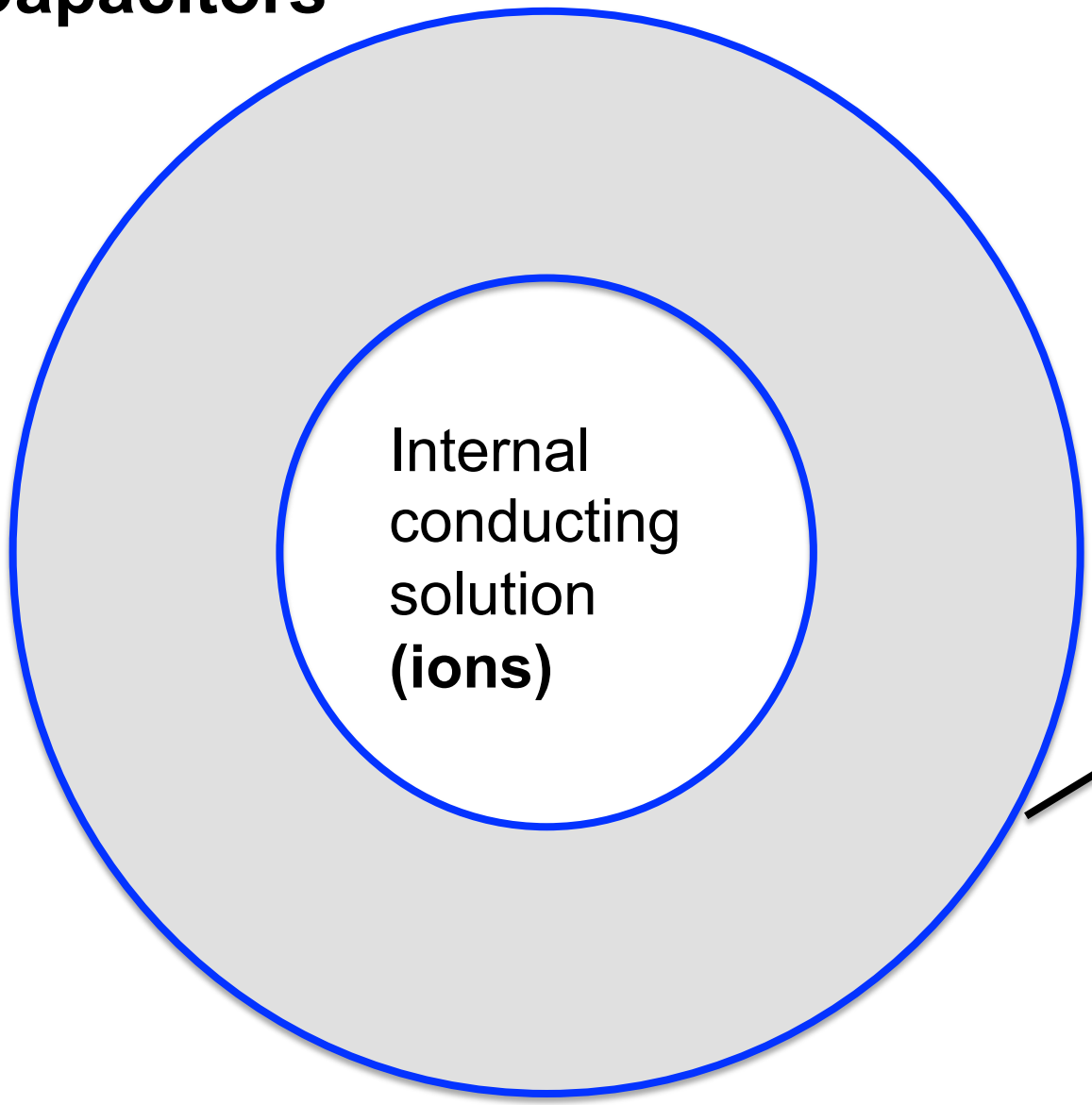
Simple Model of a Neuron

Attributes of Artificial Neuron:

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



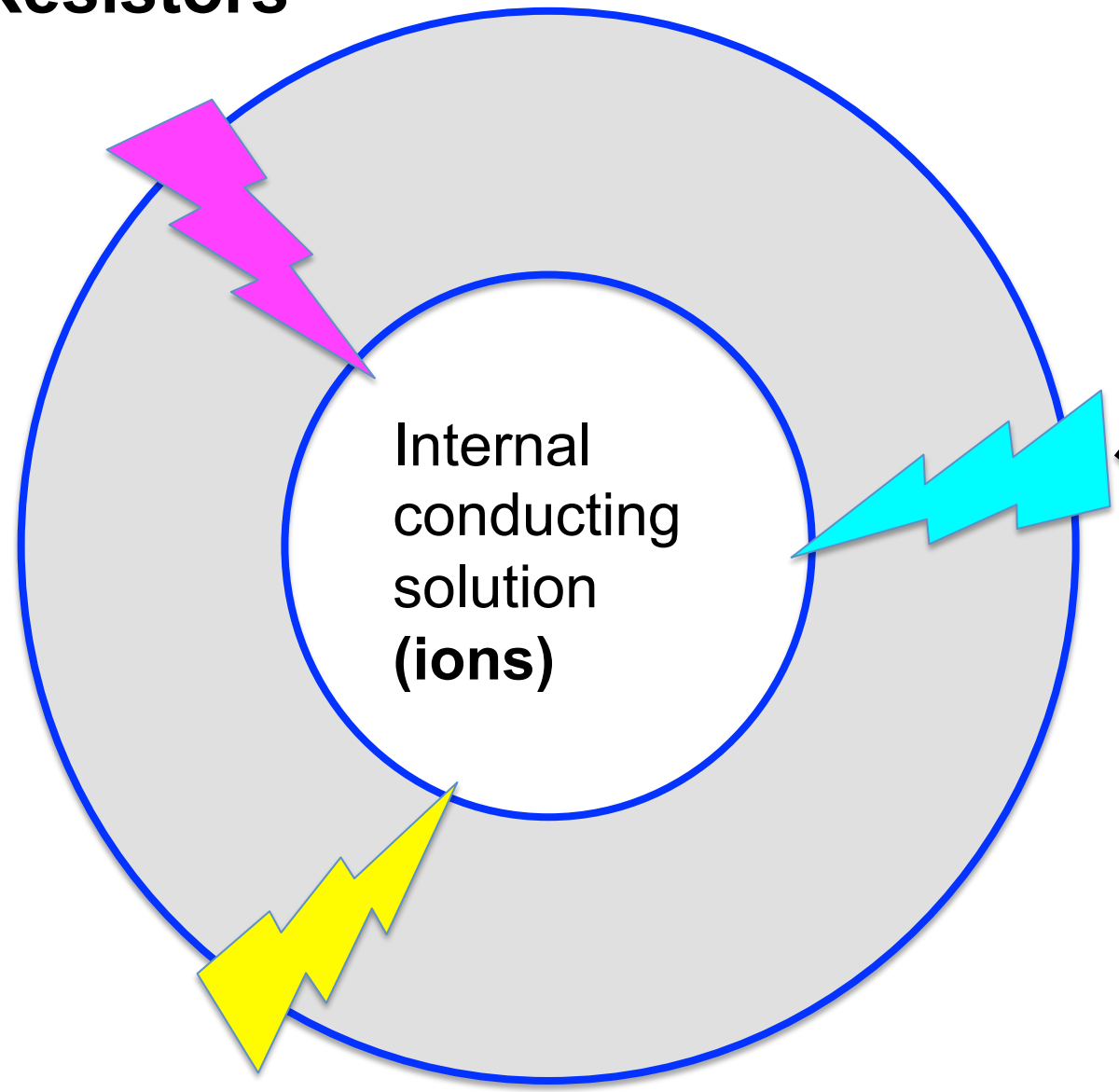
Modeling Neural Membranes as Capacitors



External
conducting
solution
(ions)

Thin
insulating
layer
**(membrane,
4 nm)**

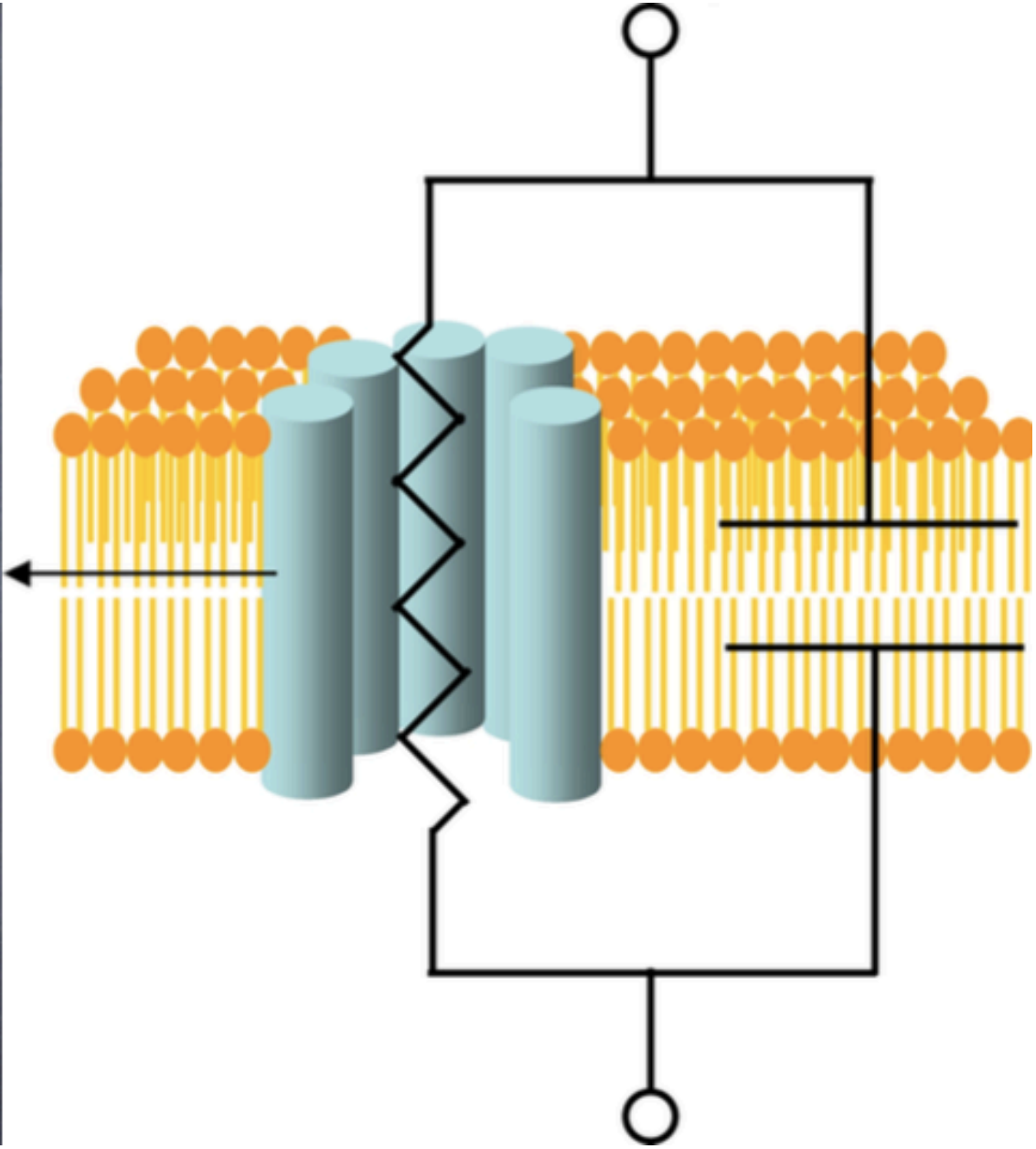
Modeling Neural Membranes as Resistors



External conducting solution **(ions)**

Ion channels **(voltage-gated and chemically-gated)**

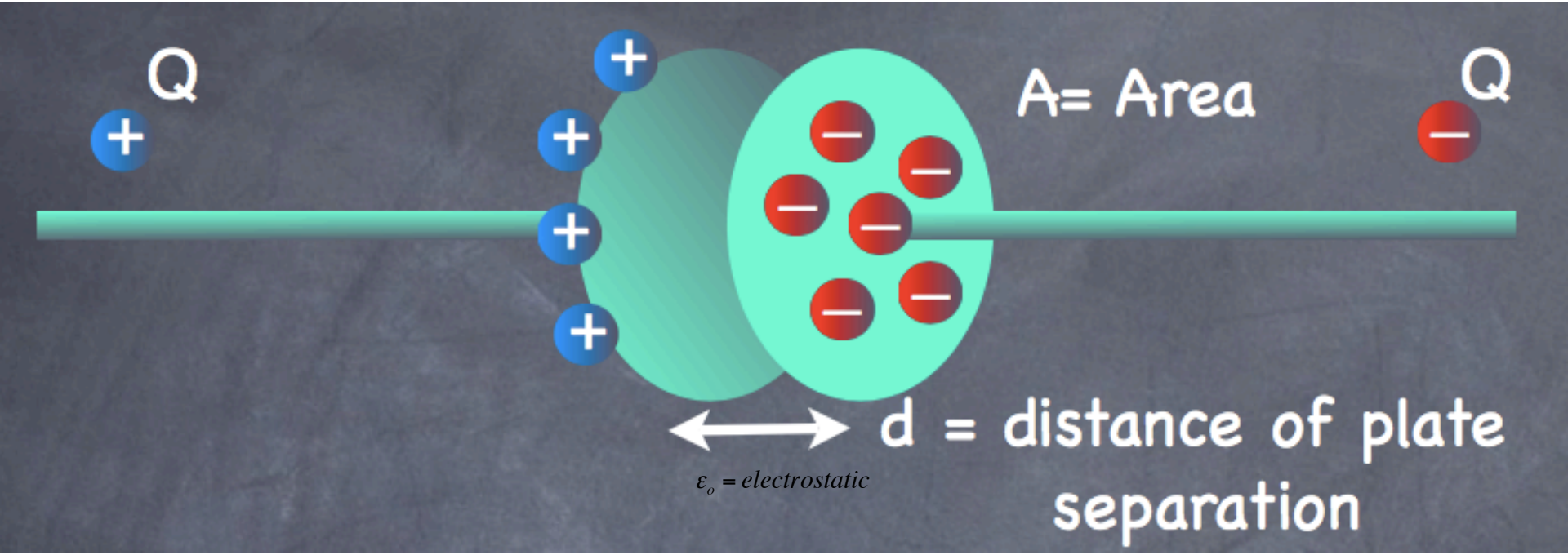
Passive RC Membrane Model

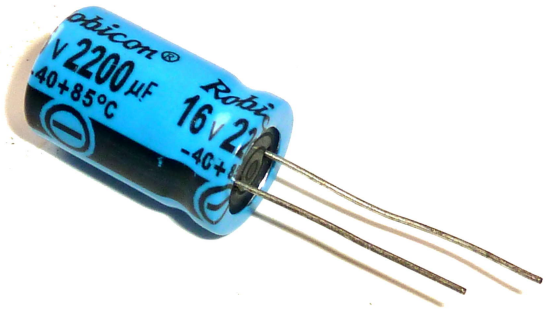


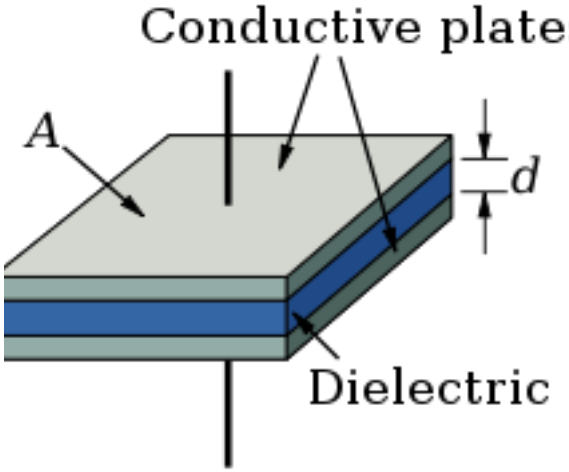
The RC membrane model represents the passive electrical properties of a neuron:

1. **R** *is* **Resistor (Ion Channels)**
2. **C** *is* **Capacitor (Cell Membrane)**

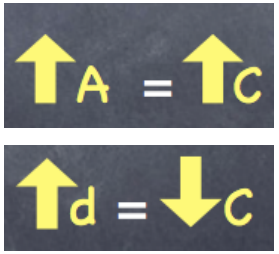
Capacitors



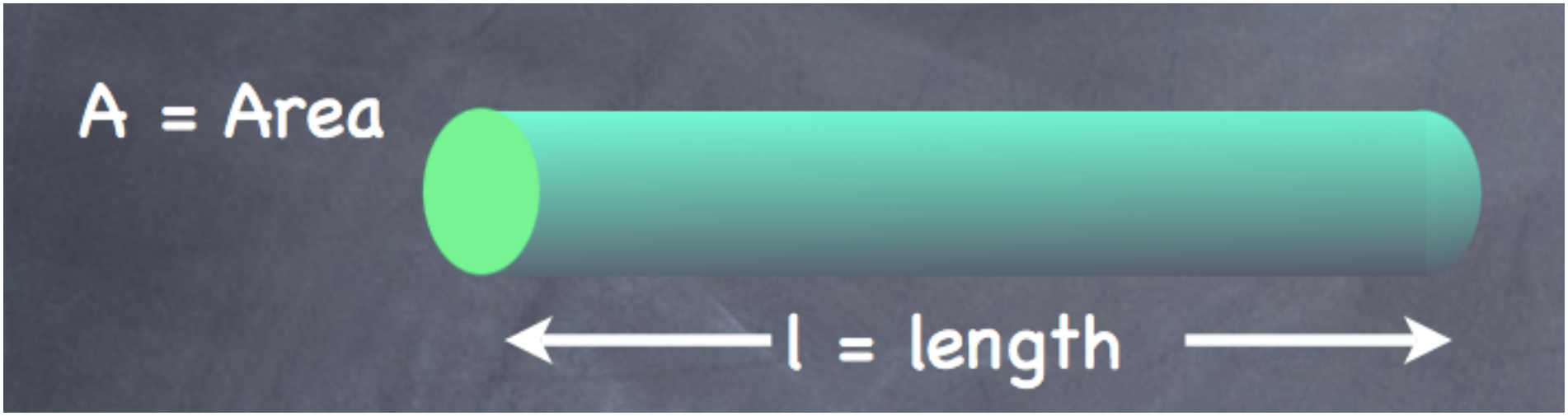




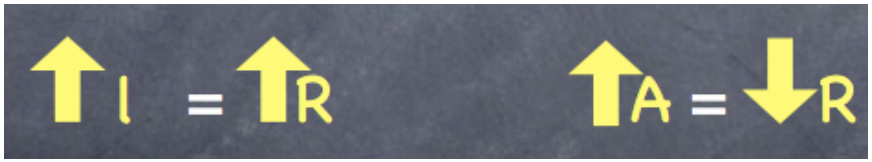
$$C = \frac{Q}{V} = \varepsilon_o \frac{A}{d}$$



Resistors

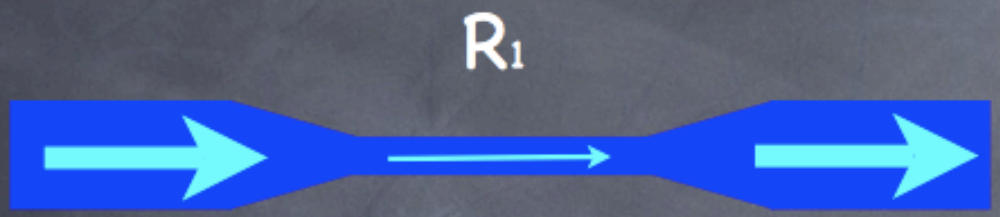


$$R = \frac{V}{I} = \rho \frac{L}{A}$$



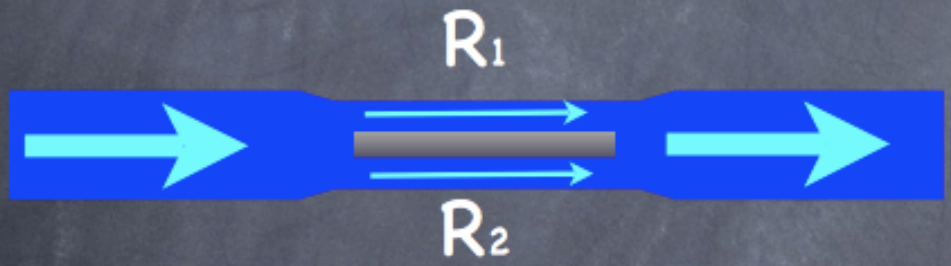
For the same current, a larger *R* produces a larger *V.*

Ion Channels as Resistors



For ion channels is better to think in terms of conductance

$$R_1 = 1/g_1$$

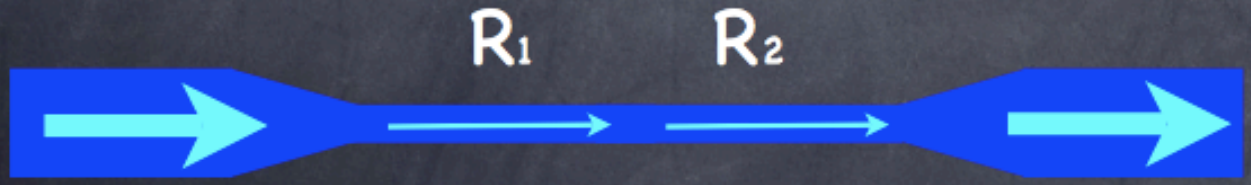


As the # of Rs in parallel increases RT decreases!

$$1/R_T = 1/R_1 + 1/R_2$$

More (open) channels in the membrane more conductance

$$g_T = g_1 + g_2$$



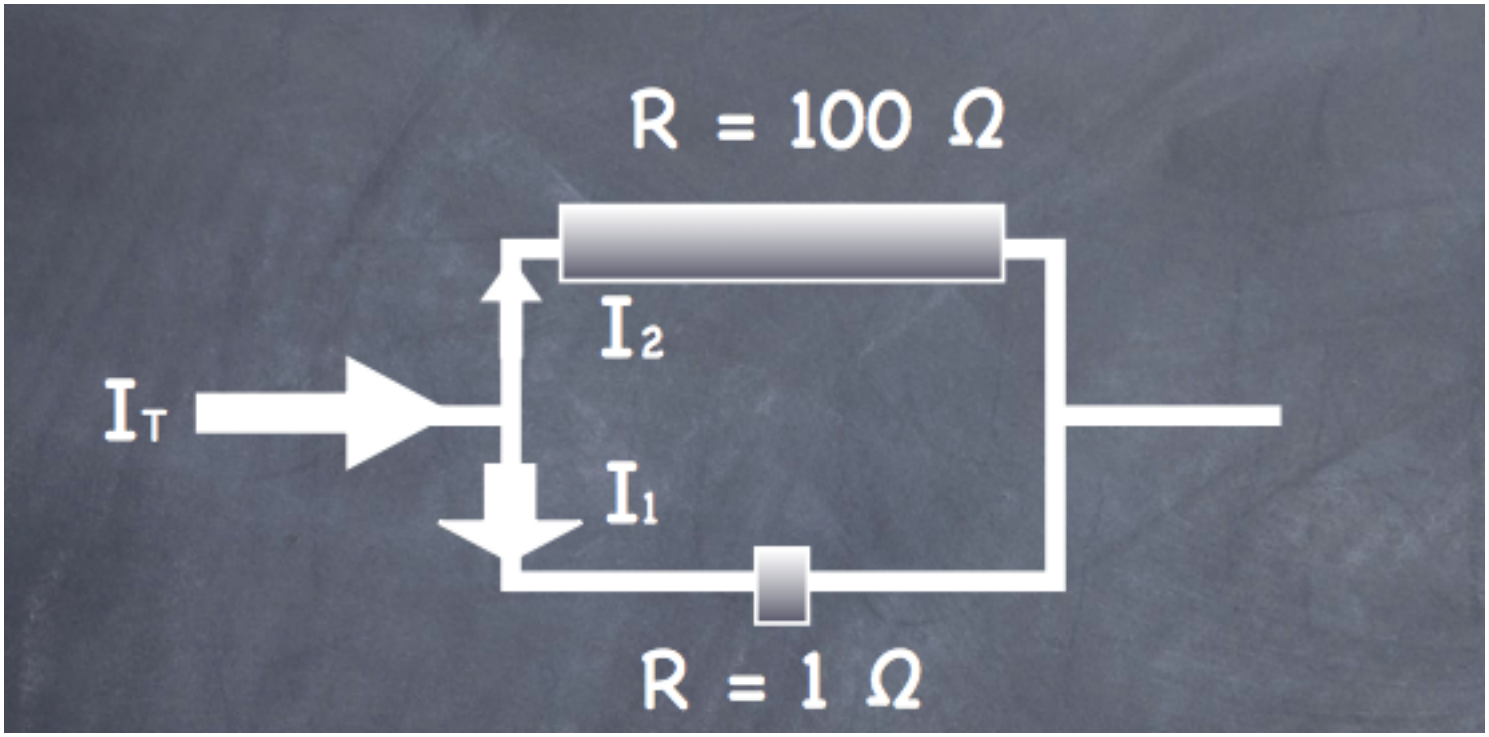
$$R_T = R_1 + R_2$$

Long, thin parts of a neuron have large resistance!

Circuits Primer

Value	Equation
Current	I = Coulombs/ second or Amperes (A)
Ohm's Law	V = IR
Capacitance	C = Q/V = Coulombs/Volts (F)
Voltage across capacitor	V = Q/C
Changing the voltage in a capacitor	$\Delta V = \Delta Q / C$
We change the charge by passing current	$I_c = \Delta Q / \Delta t$
The change in V depends on the duration of I_c	$\Delta V = I_c \Delta t / C$

Kirchhoff's Current Law

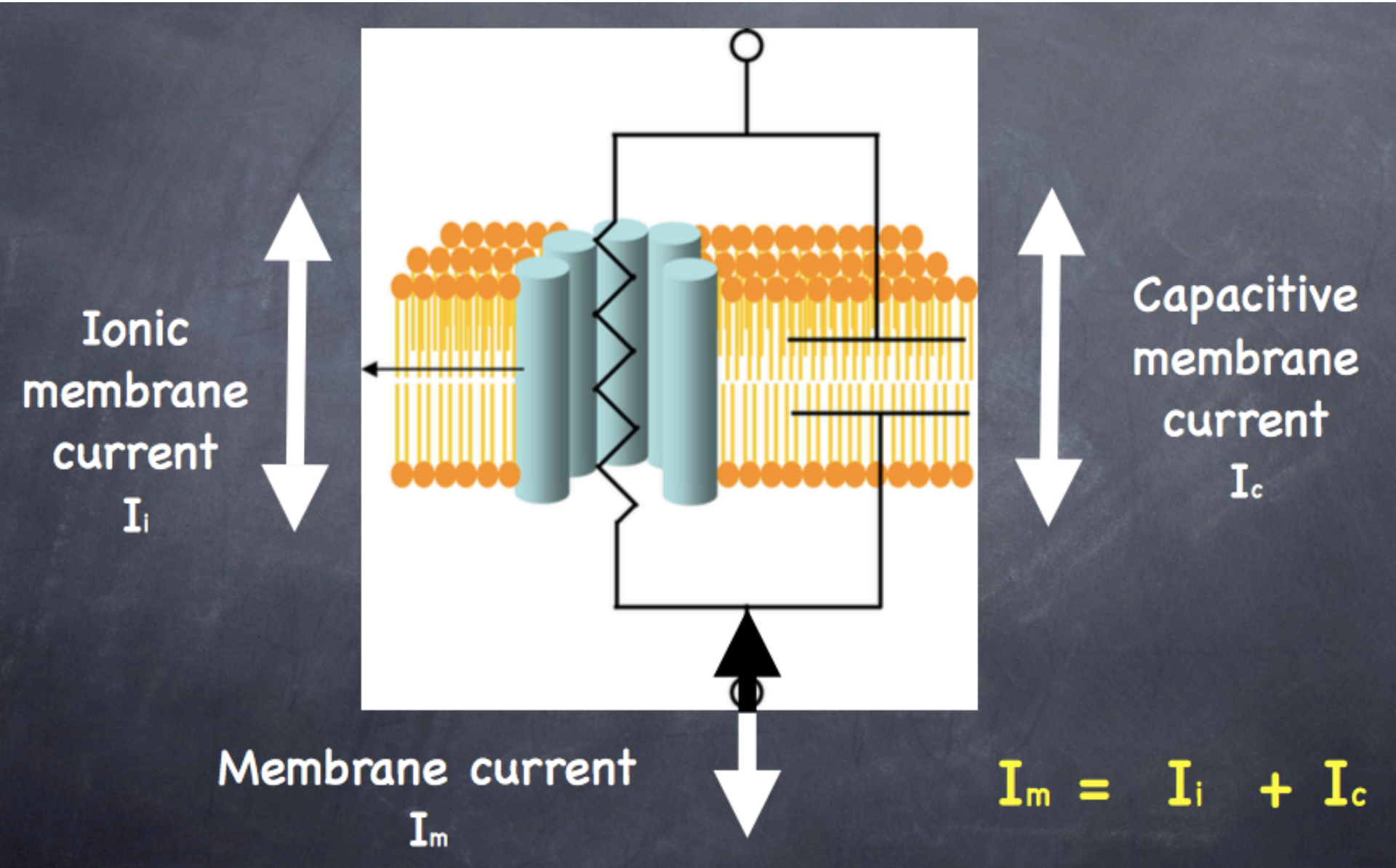


Current flows through the path of least resistance

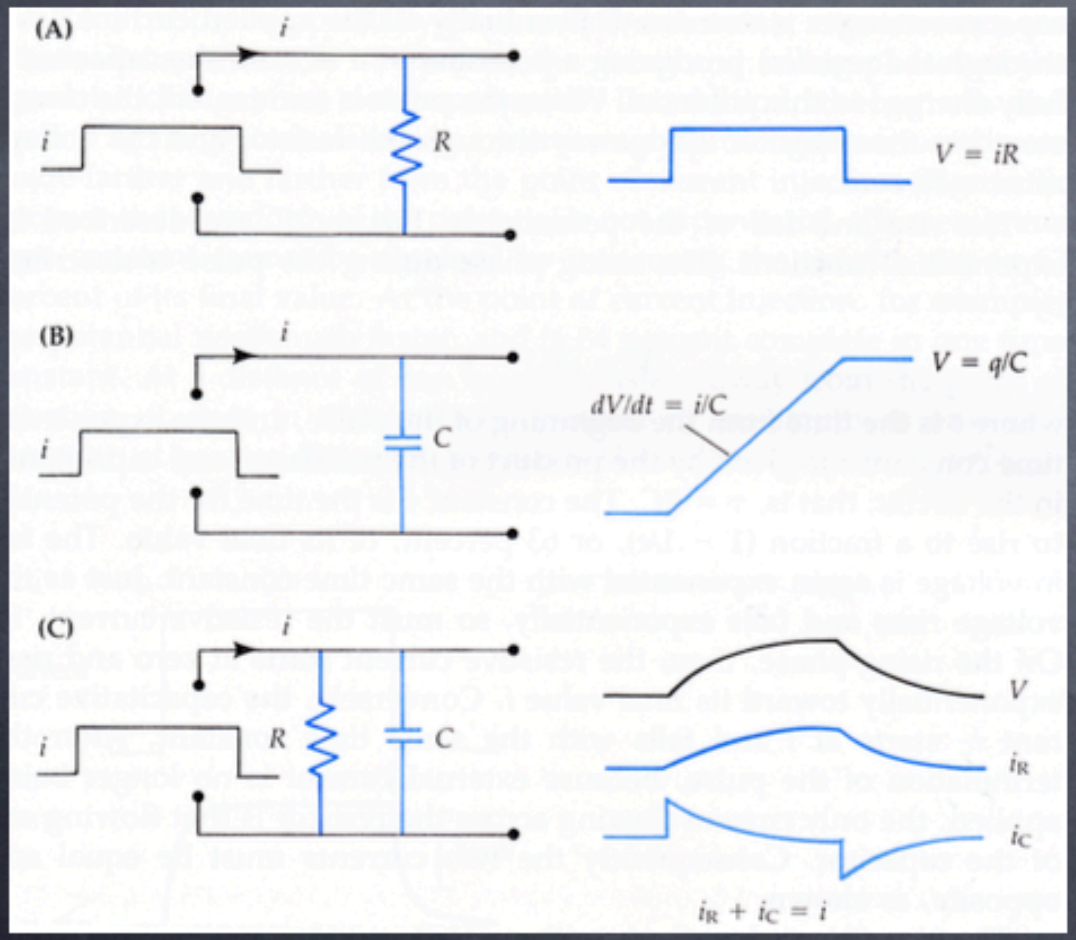
and $I_T = I_1 + I_2$

Electrical Model of the Cell Membrane

Total current is the sum of the currents of each component.



Current in RC Circuits



V changes instantaneously with I

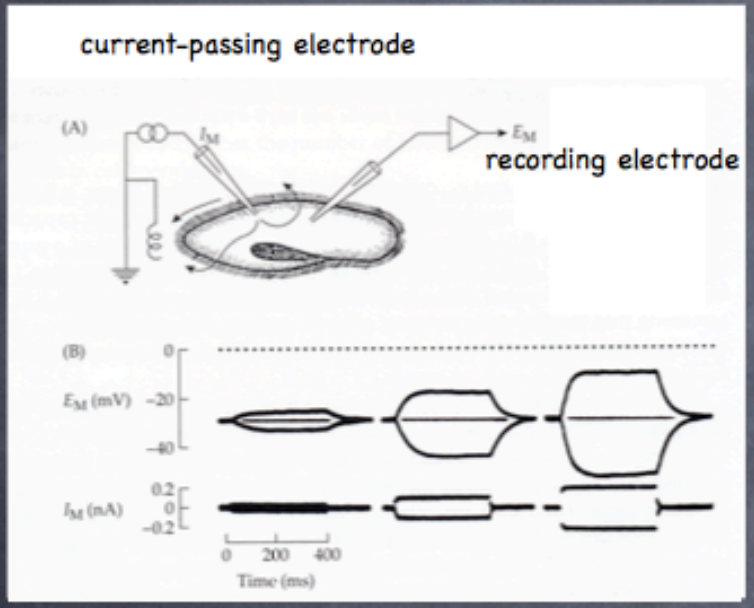
V changes linearly in time with I

V changes exponentially with a time constant = RC

The RC model of a neuronal membrane has voltage that changes exponentially over time.

Electrical Recordings in Paramecium

Passing current and recording the membrane potential from a paramecium

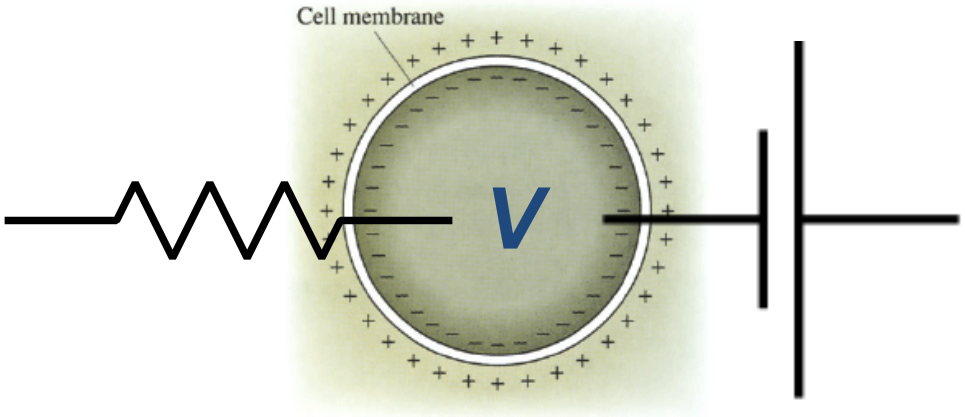


"electrotonic potential"

Negative current makes the membrane potential more negative hyperpolarization

Positive current makes the membrane potential more positive depolarization

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)

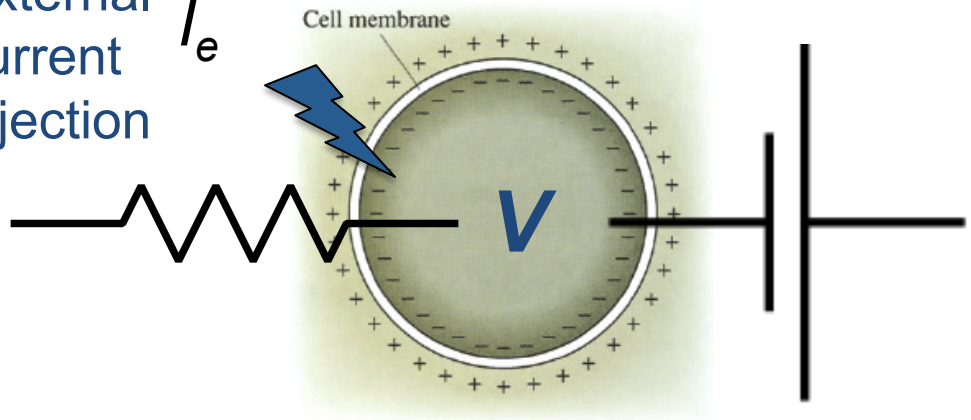
$Q = C_m V$
$C_m = c_m A$
$c_m \sim 10\ nF / mm^2$
(Specific Membrane Capacitance)

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

External current injection I_e



Membrane Time Constant

$\tau_m = r_m c_m$

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

$R_m = r_m / A$

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

(Specific Membrane Resistance)

$Q = C_m V$

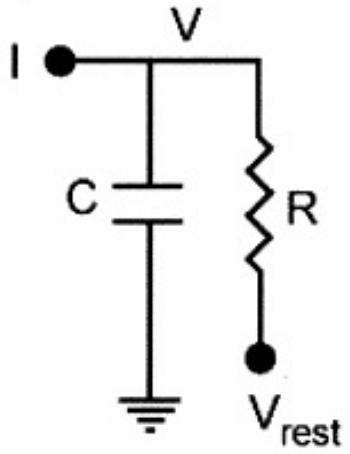
$C_m = c_m A$

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

(Specific Membrane Capacitance)

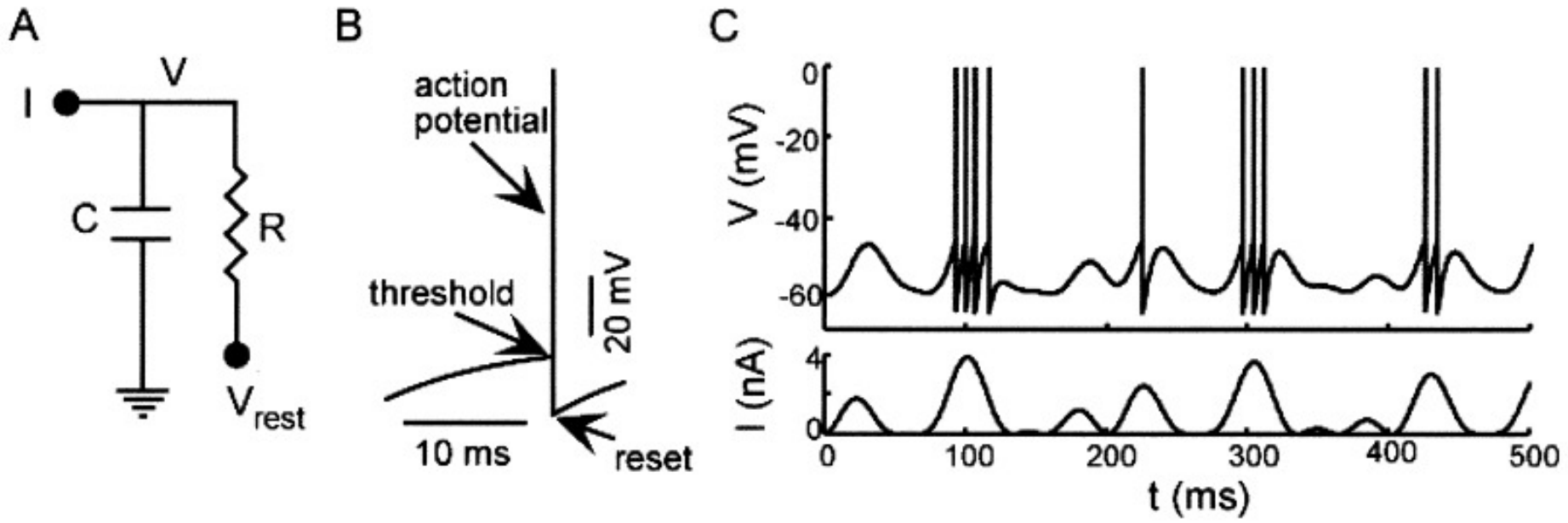
$$\tau_m \frac{dV}{dt} = -(V - E_L) + I_e R_m$$

Integrate-and-Fire Neuron Model



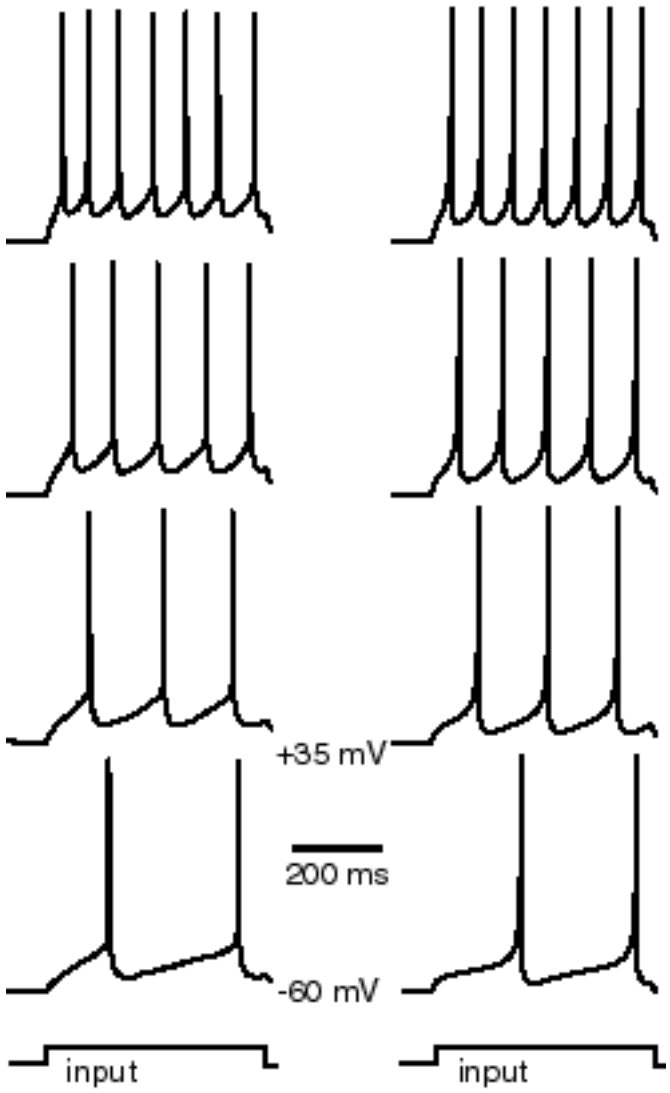
- Proposed in 1907 by Louis Lapicque
- Model of a single neuron using a circuit consisting of a parallel capacitor and resistor
- When the membrane capacitor was charged to a certain threshold potential
  - an action potential would be generated
  - the capacitor would discharge
- In a biologically realistic neuron model, it often takes multiple input signals in order for a neuron to propagate a signal.
- Every neuron has a certain threshold at which it goes from stable to firing.
- When a cell reaches its threshold and fires, its signal is passed onto the next neuron, which may or may not cause it to fire.
- *Shortcomings of Model:*
  - an input, which may arise from pre-synaptic neurons or from current injection, is integrated linearly, independently of the state of post-synaptic neuron
  - no memory of previous spikes is kept

Generating Spikes: Integrate-and-Fire Model

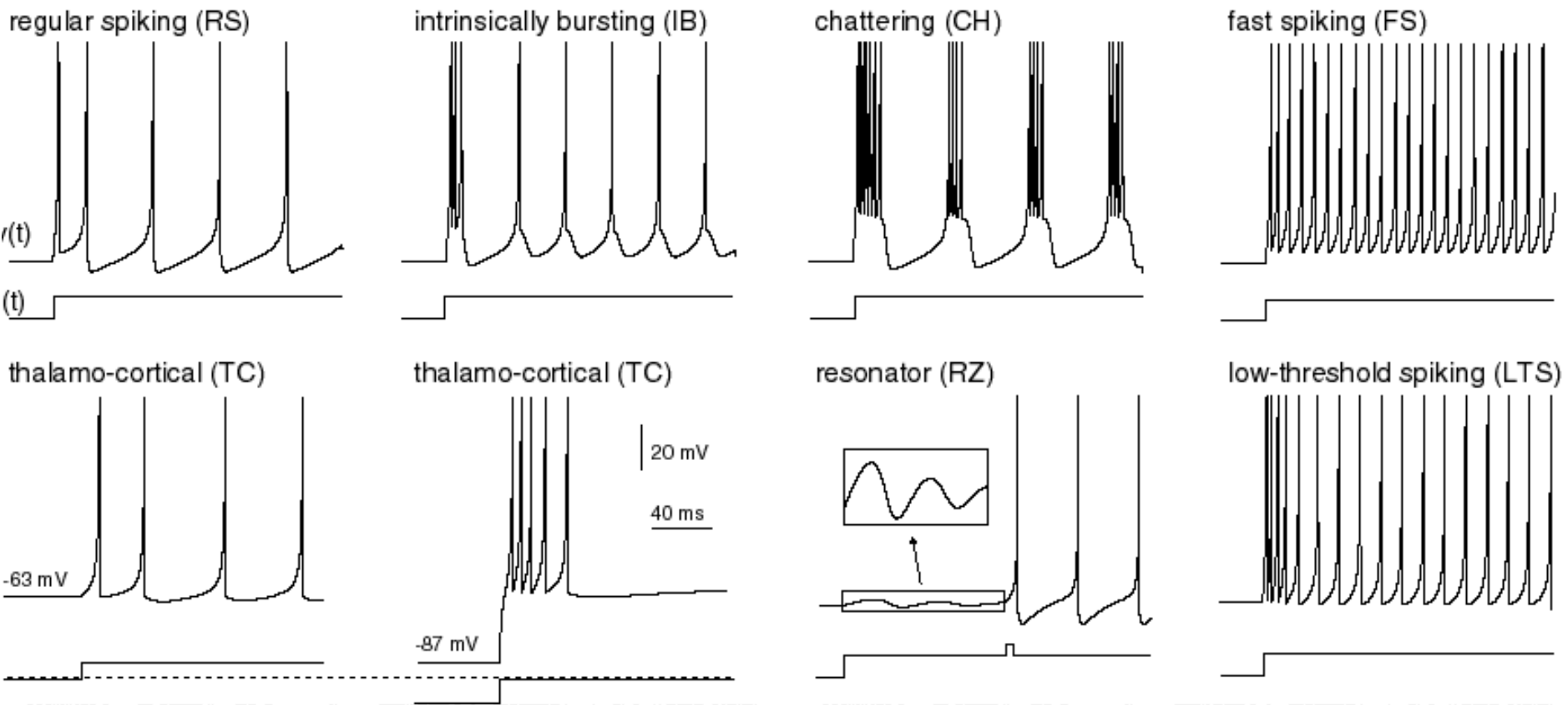


A. The equivalent circuit with membrane capacitance ***C*** and membrane resistance ***R.*** ***V*** is the membrane potential and $\boldsymbol{V}_{\boldsymbol{rest}}$ is the resting membrane potential.
B. The voltage trajectory of the model. When ***V*** reaches a threshold value, an action potential 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.

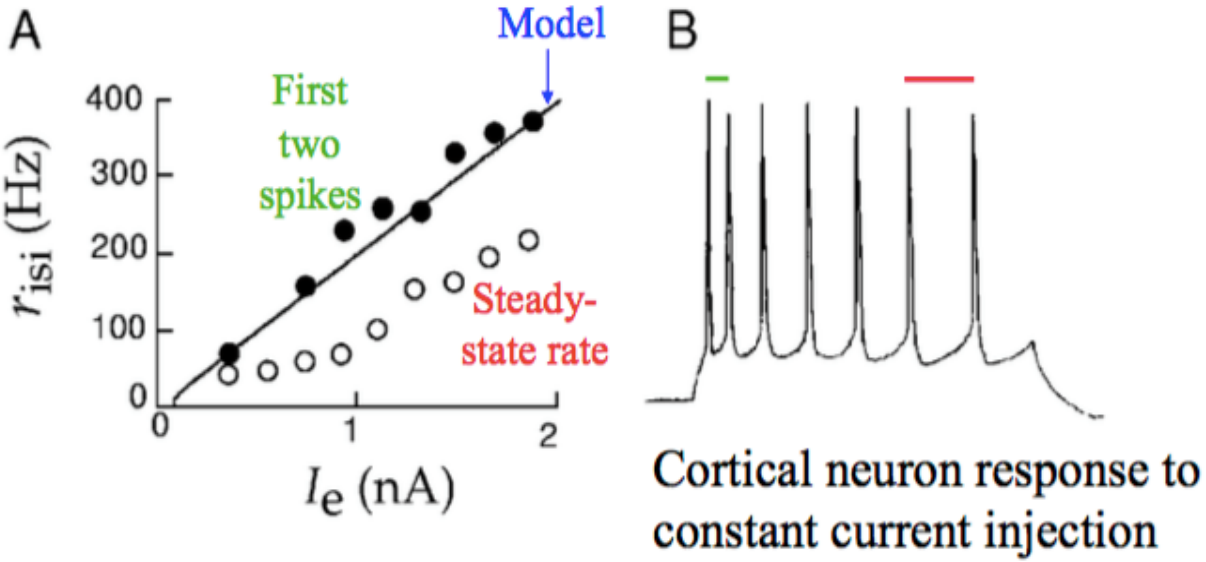
Which column represents real data?



Spiking Patterns of Neurons



Comparison of I & F Model to Data



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

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

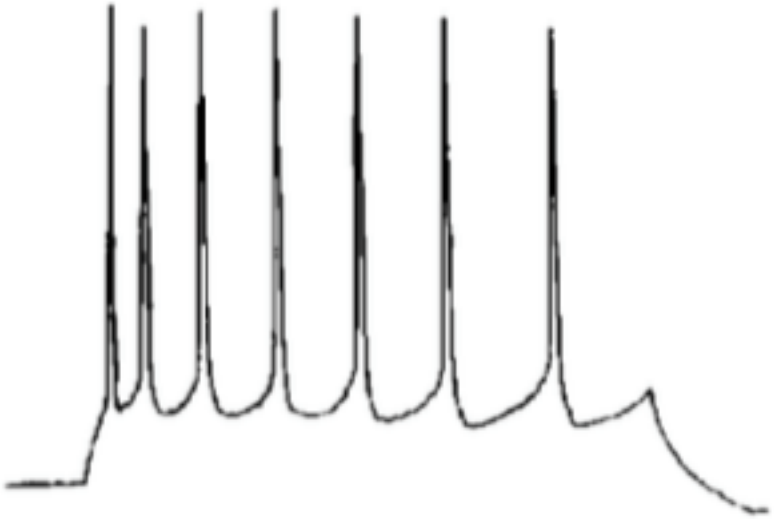
$$\tau_m \frac{dg_{sra}}{dt} = -g_{sra}$$

Spike-Rate Adaptation

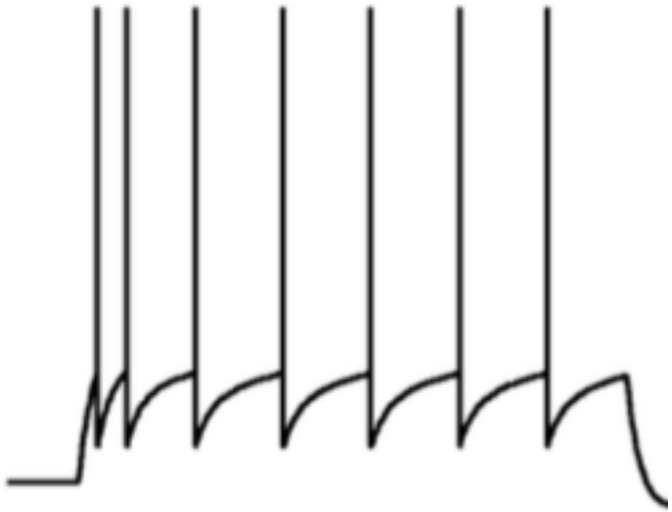
If $V > V_{threshold}$,
Spike and Set $g_{sra} = g_{sra} + \Delta g_{sra}$
Reset: $V = V_{reset}$

How would we add a term to model for refractoriness?

I & F Model with Spike-Rate Adaptation



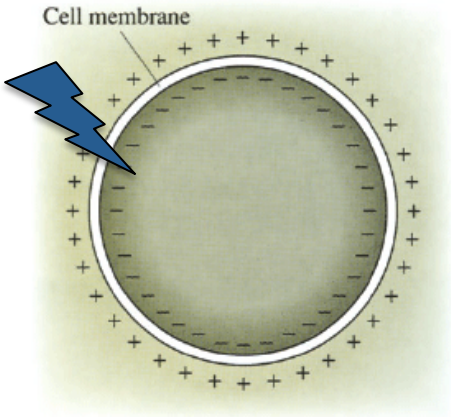
Cortical Neuron

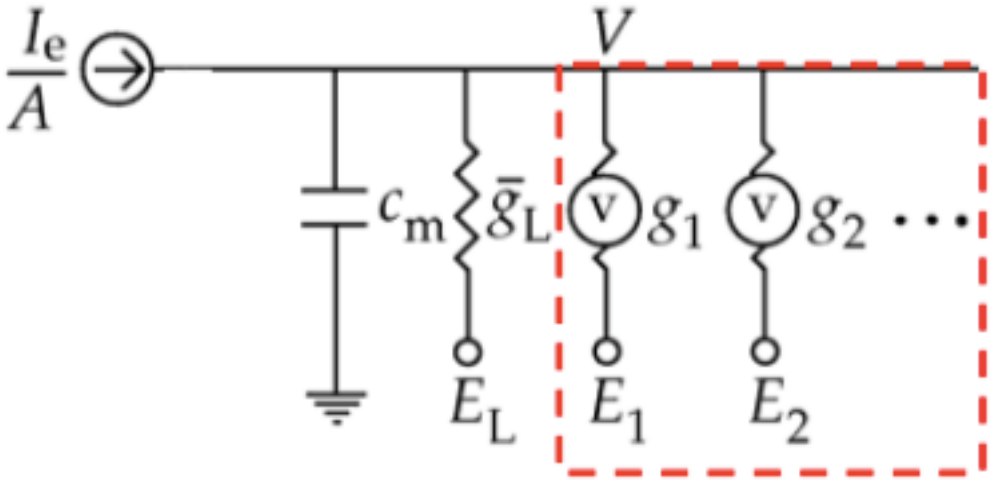


Integrate-and-Fire Model with Spike-Rate Adaptation

Modeling Active Membranes

External current injection I_e





$$\tau_m \frac{dV}{dt} = -(V - E_L) - r_m g_1 (V - E_1) \ldots + I_e R_m$$

$$g_1 = g_{1,\max} P_1$$

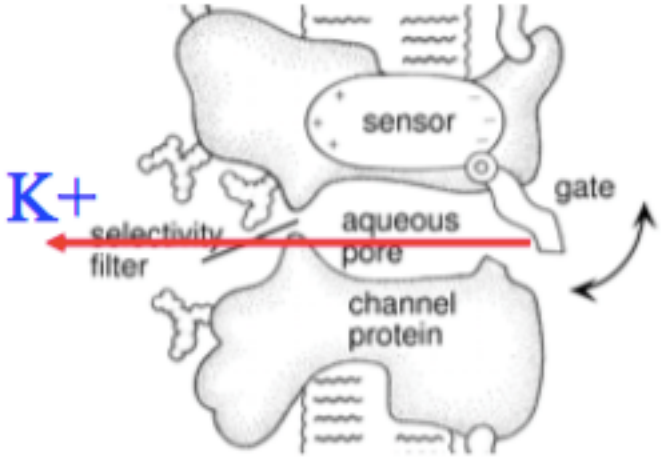
$g_{1,max}$ represents maximum possible conductance

P_1 represents the fraction of ion channels open

Example 1: Delayed-Rectifier K^+ Channel

$$g_K = g_{K,\max} P_K$$

$$P_K = n^4$$



4 **=** indicates 4 independent subunits are necessary for K^+ channel to open

$$\frac{dn}{dt} = \alpha_n(V_1)(1-n) - \beta_n(V_2)n$$

V_1 **=** opening rate
n **=** fraction of channels open
1 – n **=** fraction of channels closed
V_2 **=** closing rate

Example 2: Transient Na^+ Channel

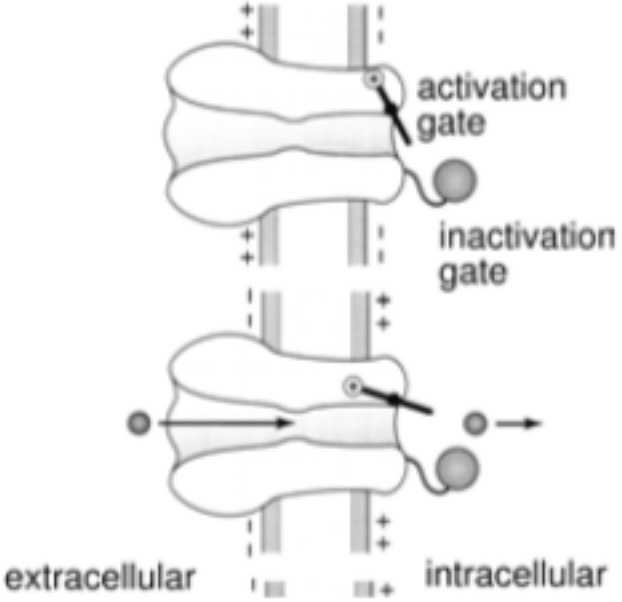
$$g_{Na} = g_{Na,\max} P_{Na}$$

$$P_{Na} = m^3 h$$

***m* =** Activation

***3* =** indicates 3 independent subunits are necessary for Na^+ channel to be activated

***h* =** Inactivation

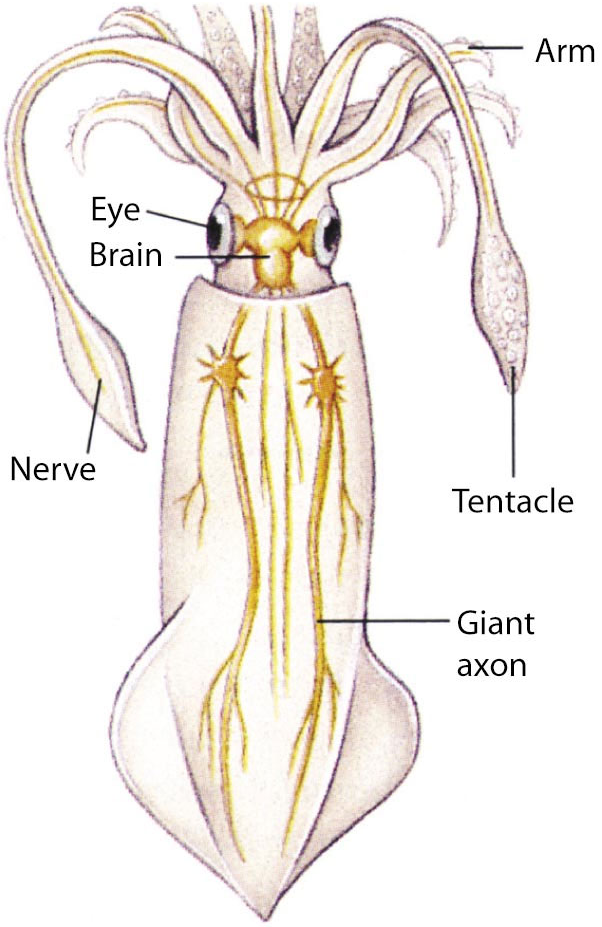


$$\frac{dm}{dt} = -(\alpha_m + \beta_m)m + \alpha_m$$

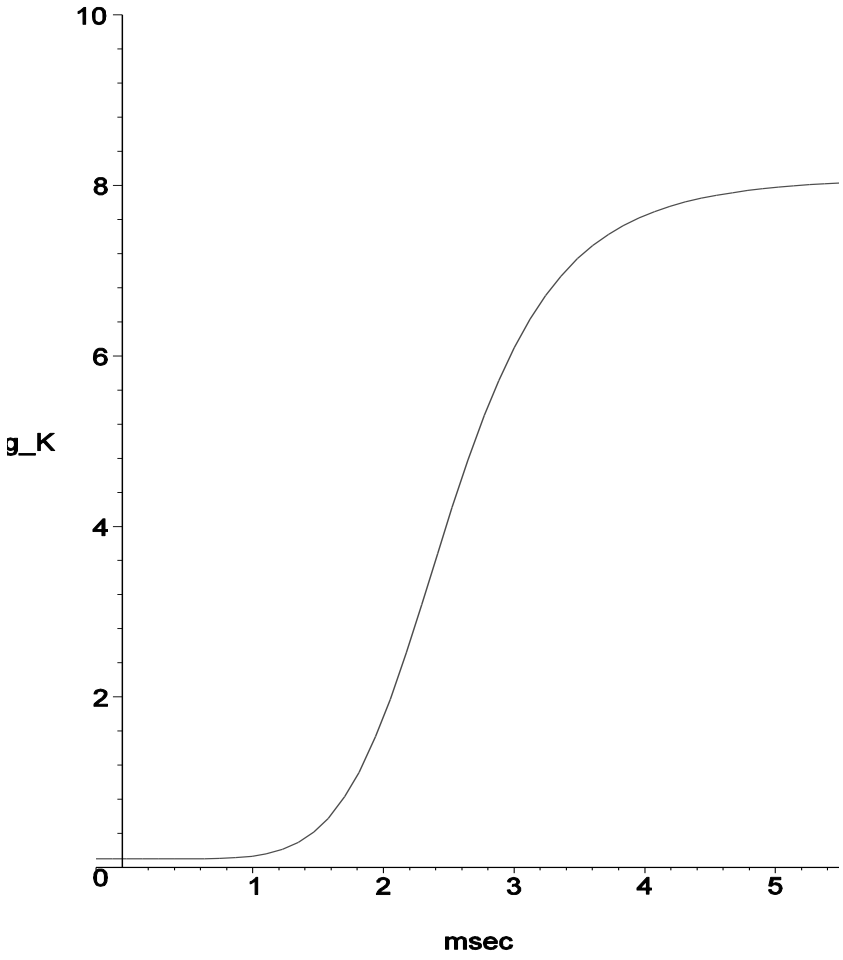
$$\frac{dh}{dt} = -(\alpha_h + \beta_h)h + \alpha_h$$

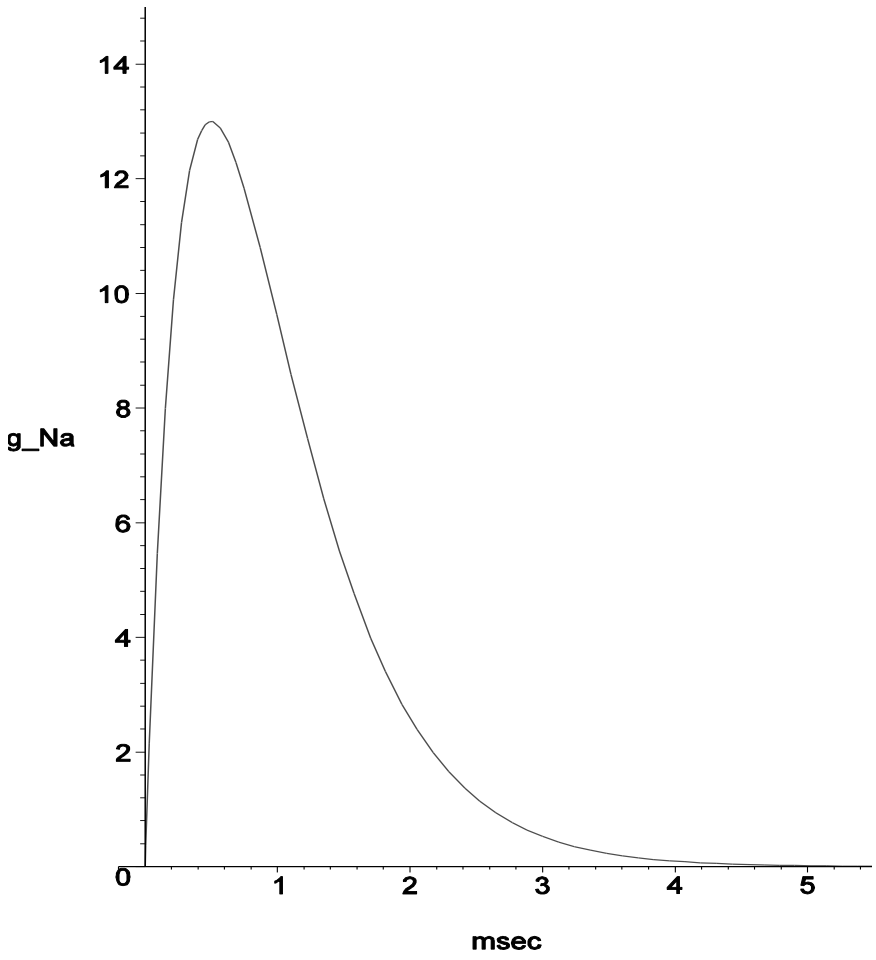
Hodgkin-Huxley Model

Alan Hodgkin, Andrew Huxley, John Eccles
Nobel Prize in Physiology (1963) for discovery of mechanisms of the giant squid neuron cell membrane



Variable Conductance

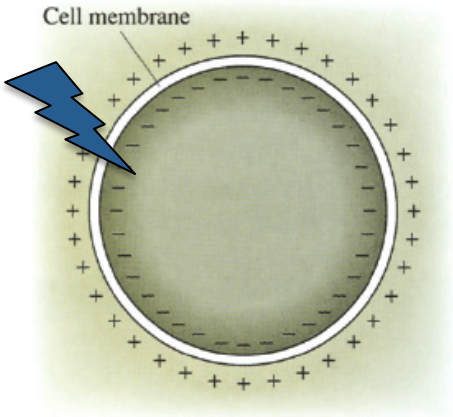


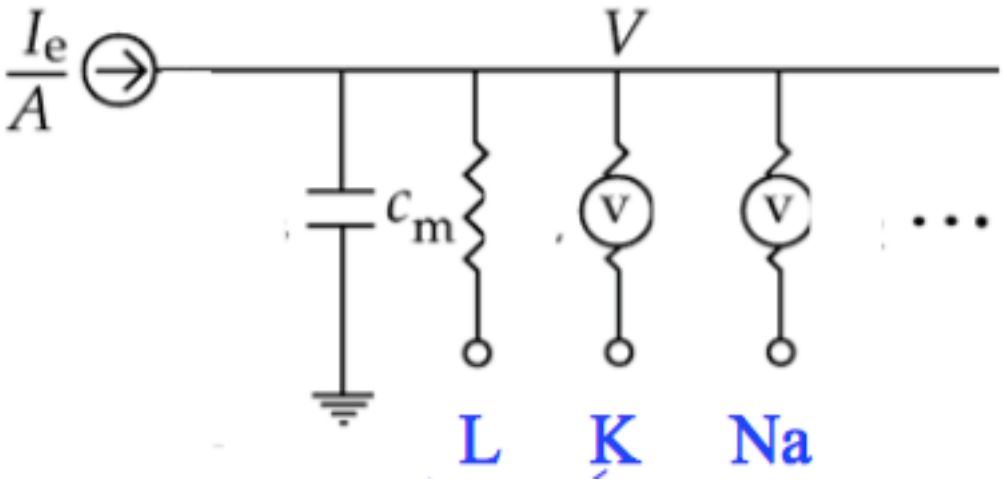


Experiments illustrated that g_K and g_{Na} varied with time *t* and voltage *V*. After stimulus, Na responds much more rapidly than K.

Hodgkin-Huxley Model

External current injection I_e



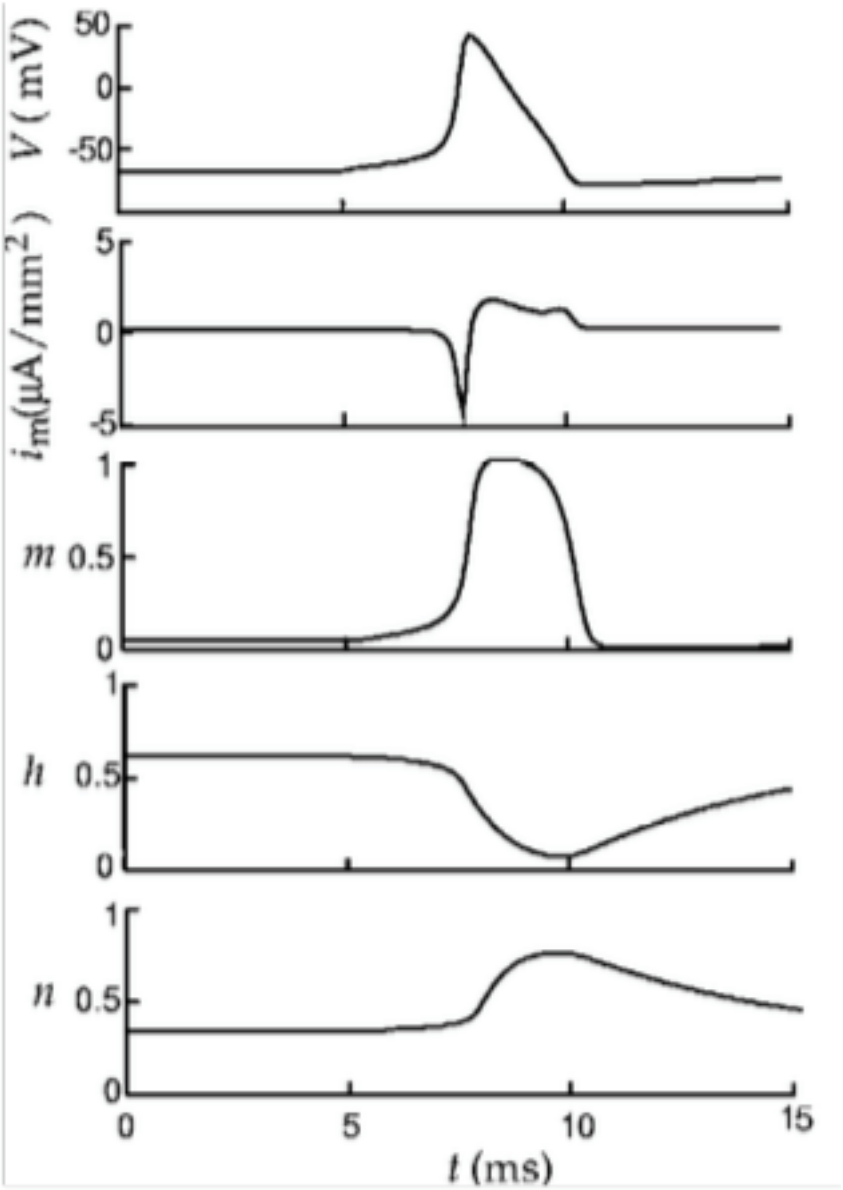


$$c_m \frac{dV}{dt} = -i_m + \frac{I_e}{A}$$

$$i_m = g_{L,\max}(V - E_L) + g_{K,\max} n^4 (V - E_K) + g_{Na,\max} m^3 h (V - E_{Na})$$

E_L = -54 mV
E_K = -77 mV
E_{Na} = +50 mV

Hodgkin-Huxley Model Dissected



Action Potential (Spike)

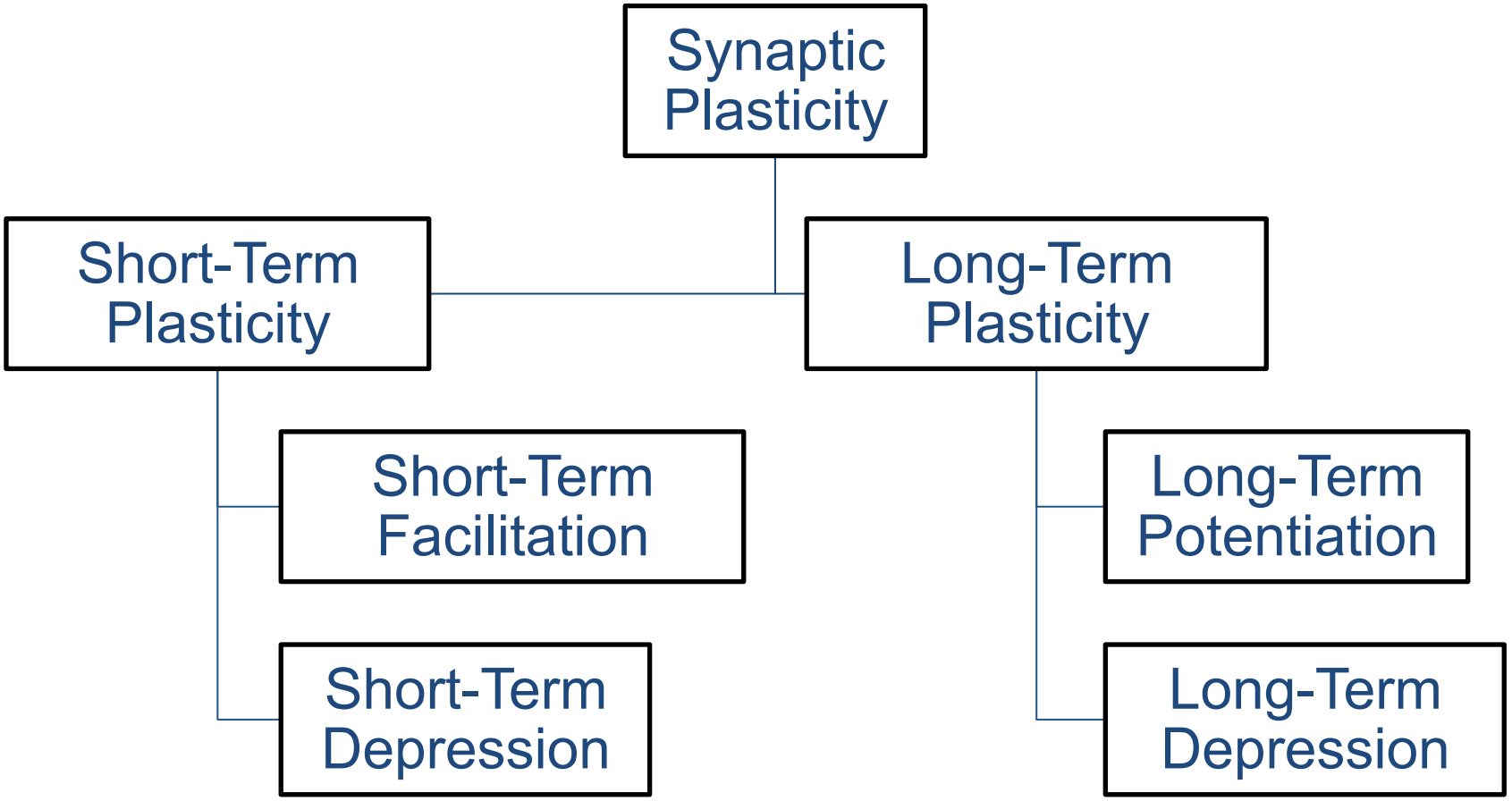
Membrane Current

Na^+ Activation (m)

Na^+ Inactivation (h)

K^+ Activation (n)

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

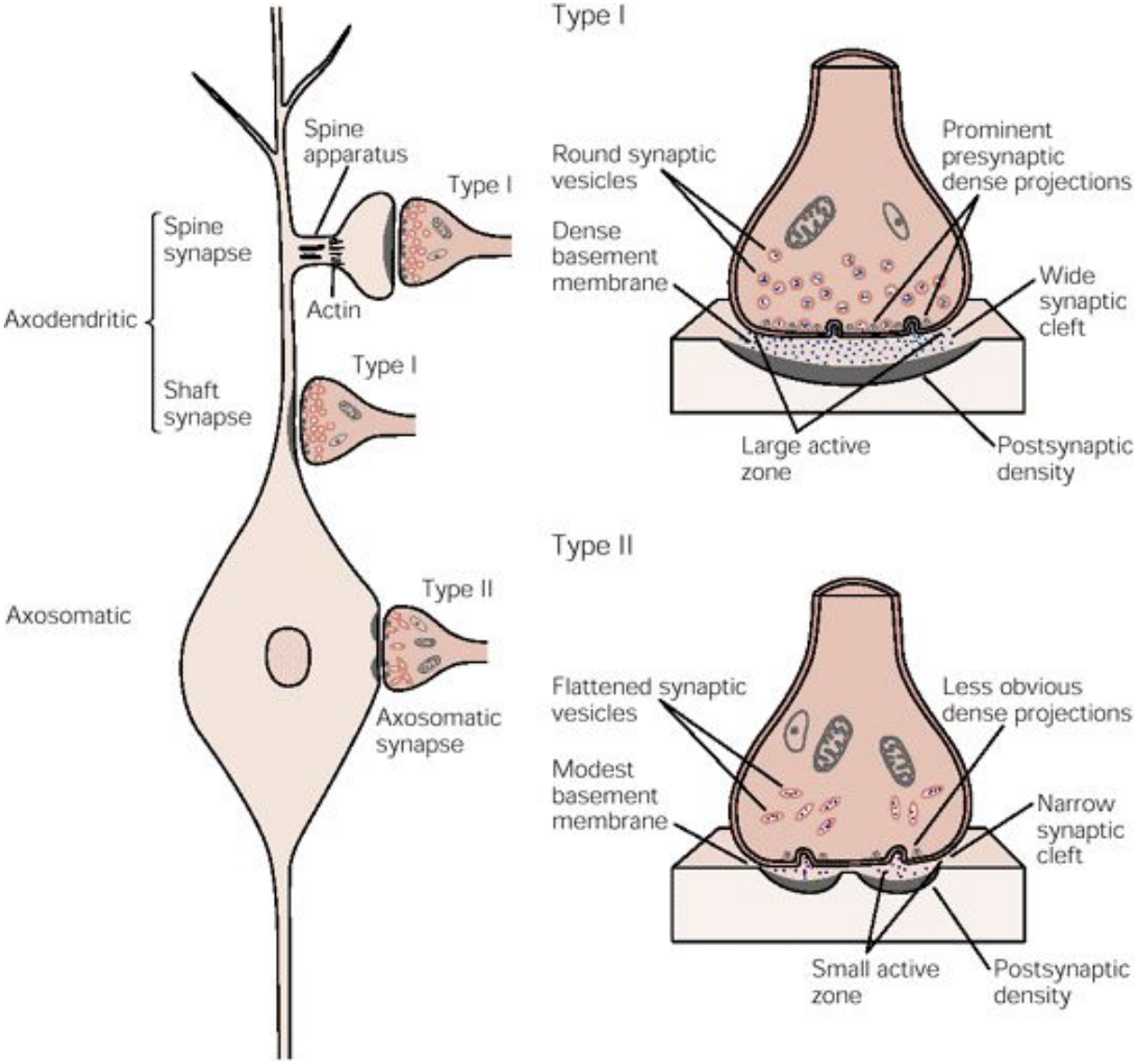
Short-Term Depression:

(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

Excitatory and Inhibitory Synapses



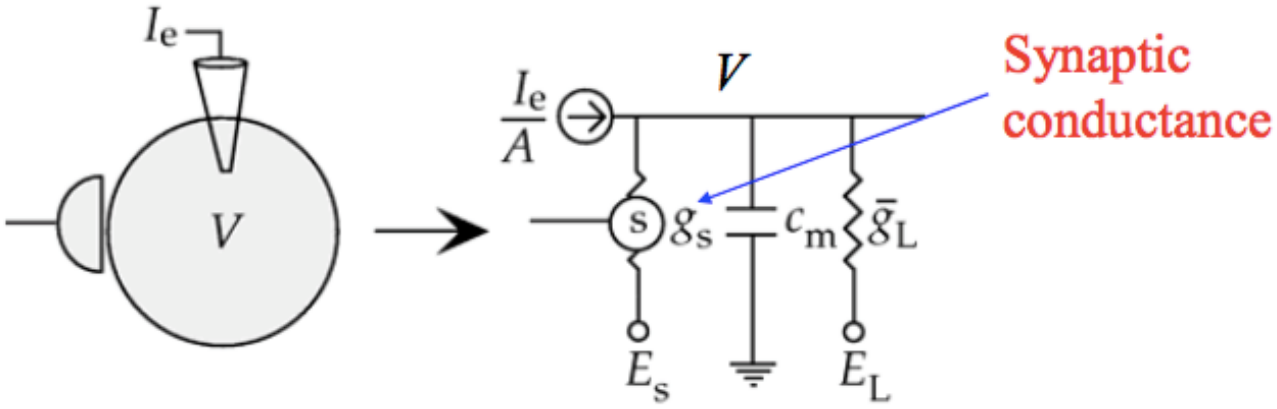
Type I Synapse:
Found in dendrites and result in an excitatory response in the post-synaptic cell

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

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

Modeling a Synaptic Input to a Neuron



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

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

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

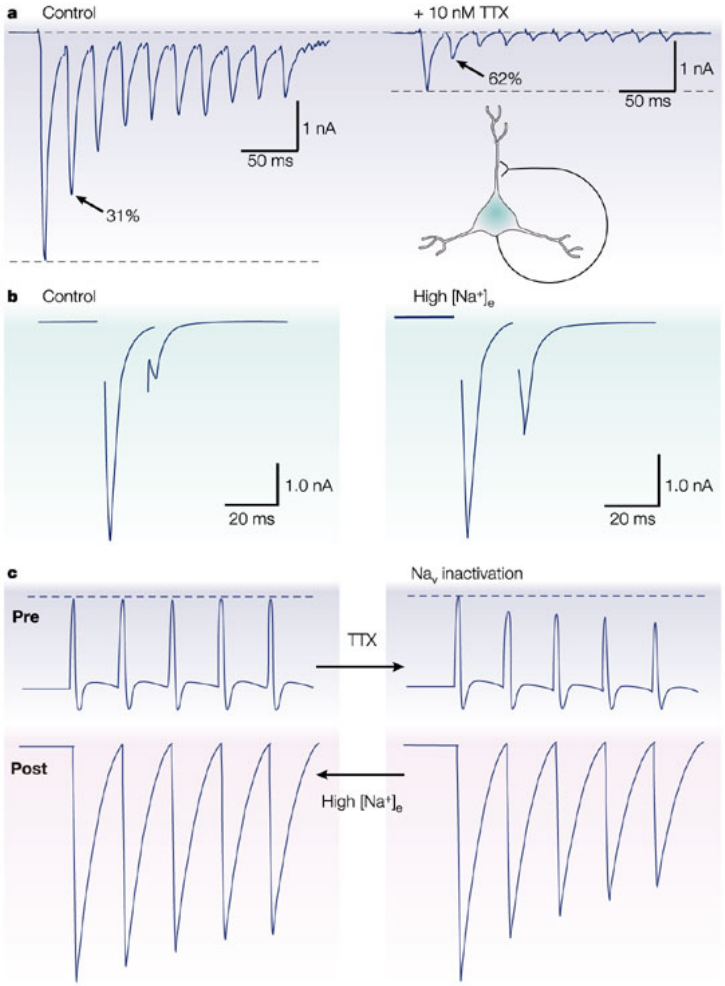
P_s = Fraction of channels closed

β_s = Closing Rate

P_s = Fraction of channels open

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

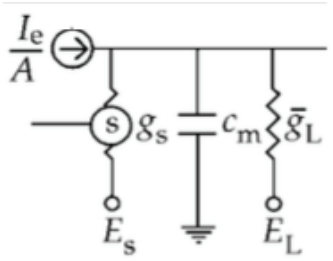
B. TTX Blocks Sodium Channels and Reduces synaptic transmission and enhances short-term depression

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:

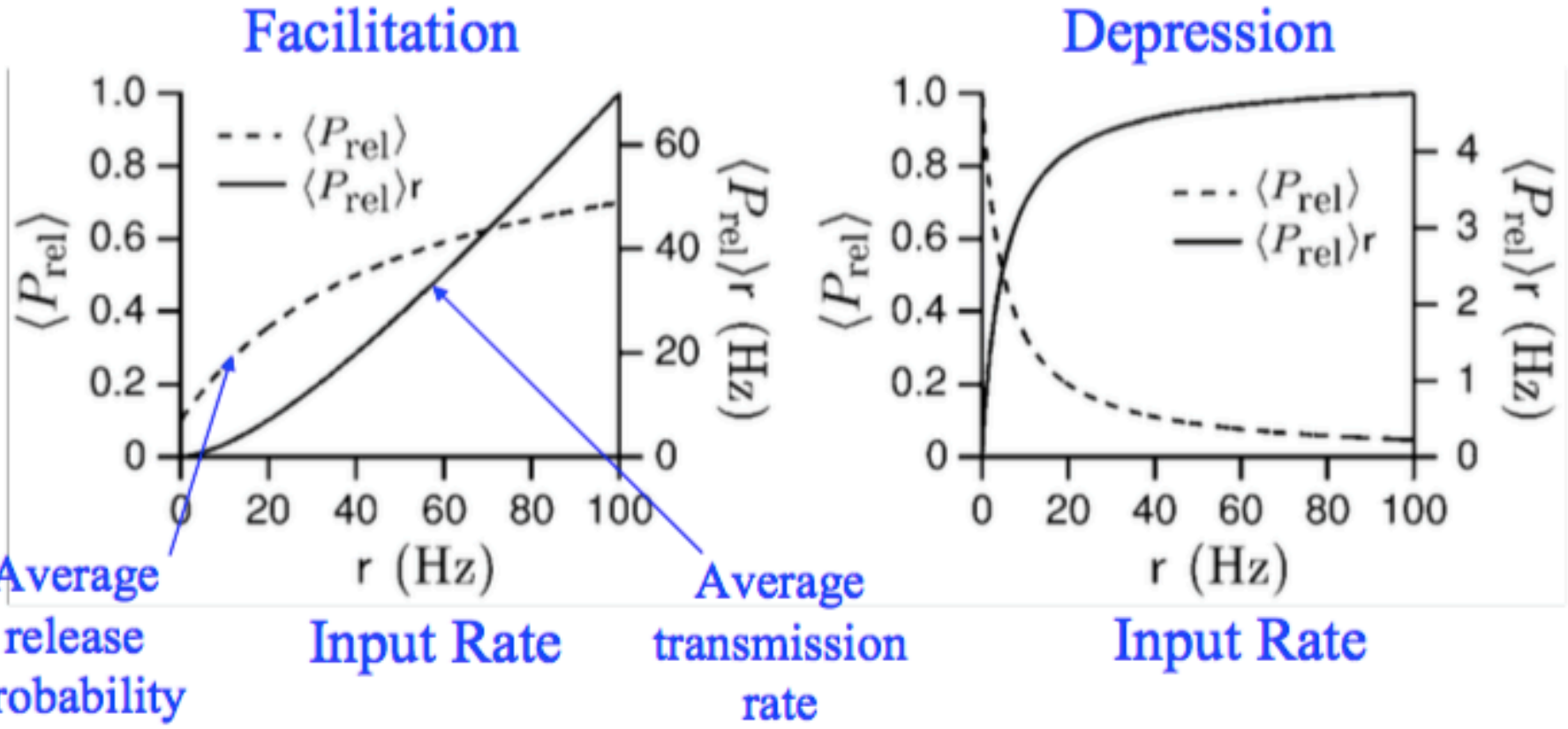
$$P_{rel} \sim f_D P_{rel}$$

Depression: Decrement P_{rel}

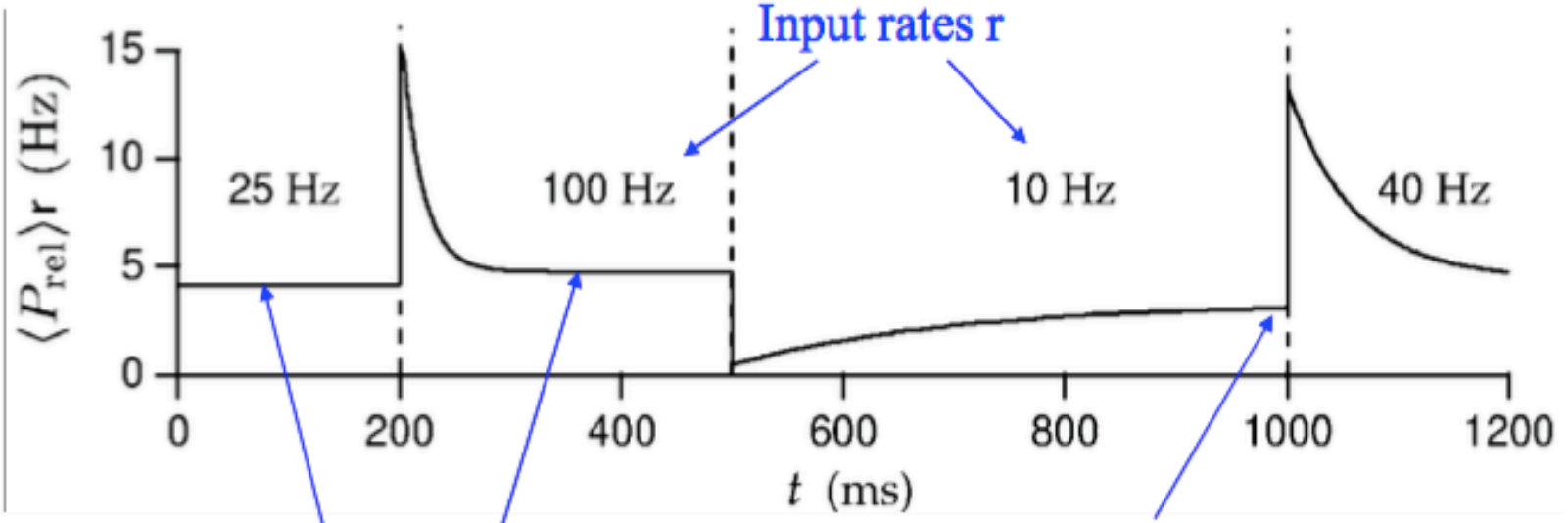
$$P_{rel} \sim P_{rel} + f_F (1 - P_{rel})$$

Facilitation: Increment P_{rel}

Effects of Synaptic Facilitation and Depression



Consequences of Synaptic Depression

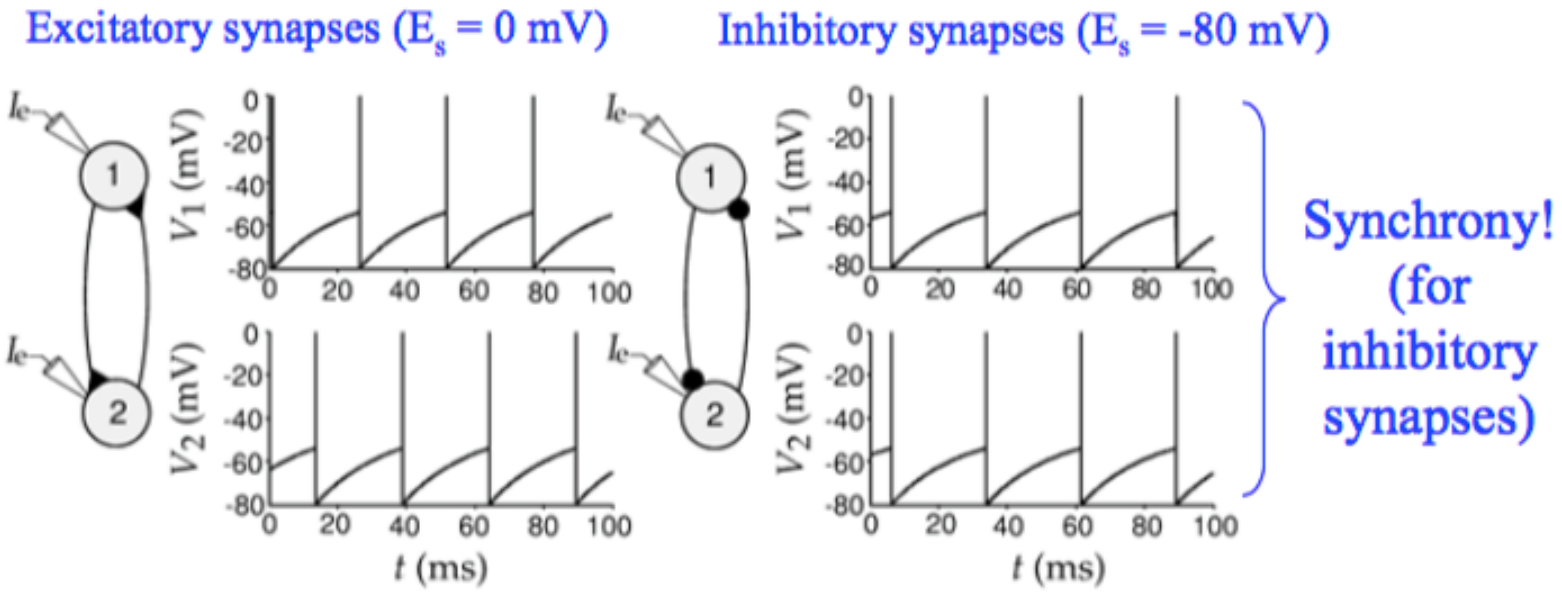


Steady-state transmission rates are similar for different rates

Transient inputs are amplified relative to steady-state inputs

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

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:

Tour of Laboratory of Paul Sajda