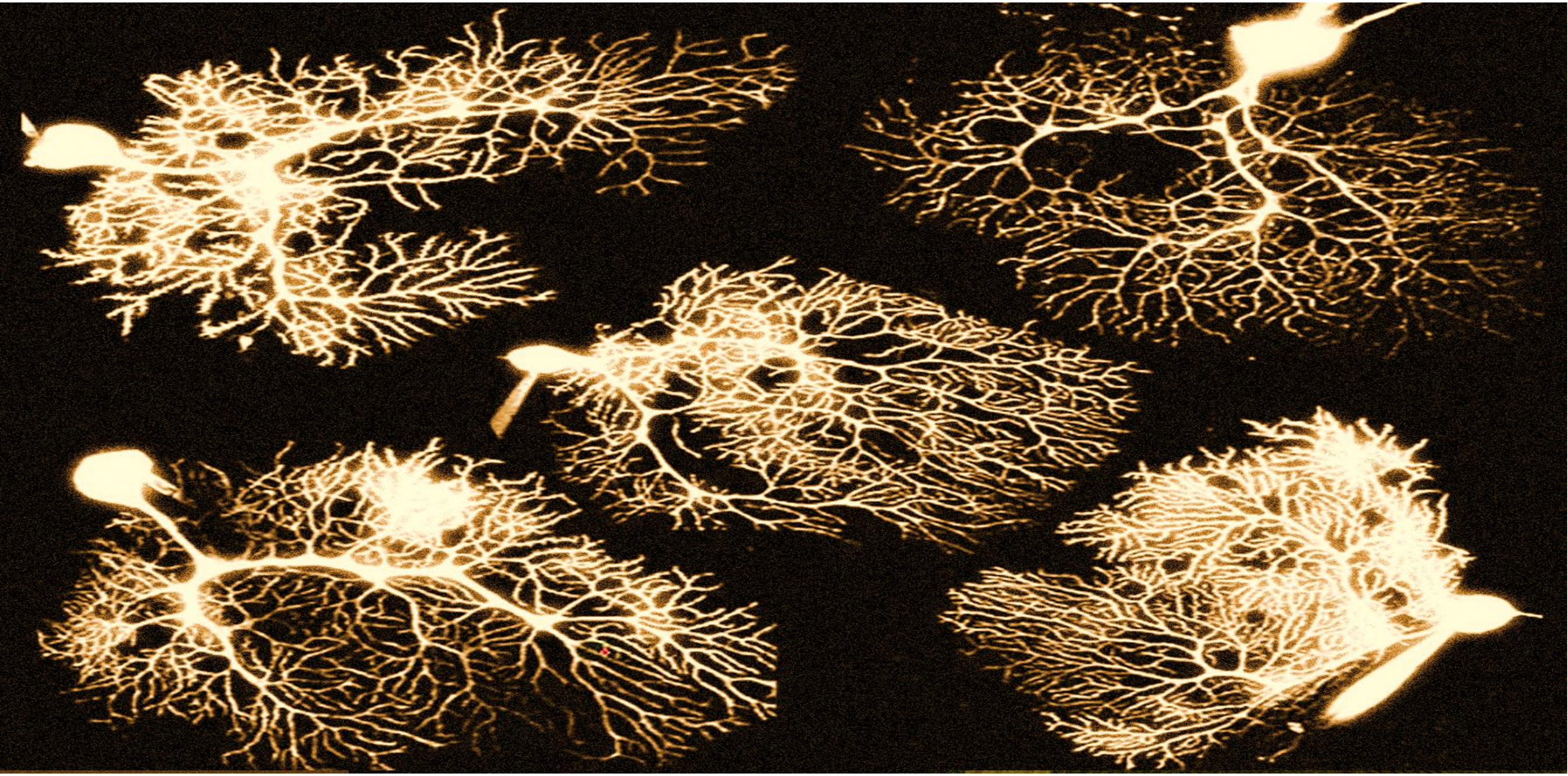
Neuroscience of Learning, Memory, Cognition

Part I: Neuronal Networks



1

Neuron Models

Set II

Outline

- Sensing & perception
- Neurons & spikes
- The Hudgkin-Huxley equation
- Modeling neuronal dynamics

Some slides credit:

- Adrienne Fairhall, Rajesh Rao, UW course material 2013-2017
- Wulfram Gerstner, EPFL course material 2018

Other credits as noted on slides

Cover slide drawing: Santiago Ramon Y Cajal

Textbooks:

- Peter Dayan & Larry Abbott "Theoretical Neuroscience", 2005
- Wulfram Gerstner "Neuronal Dynamics", 2014
- Eugene Izhikevich "Dynamical Systems in Neuroscience", 2010

Reference book:

- Paul Miller "An Introductory Course in Computational Neuroscience", 2018

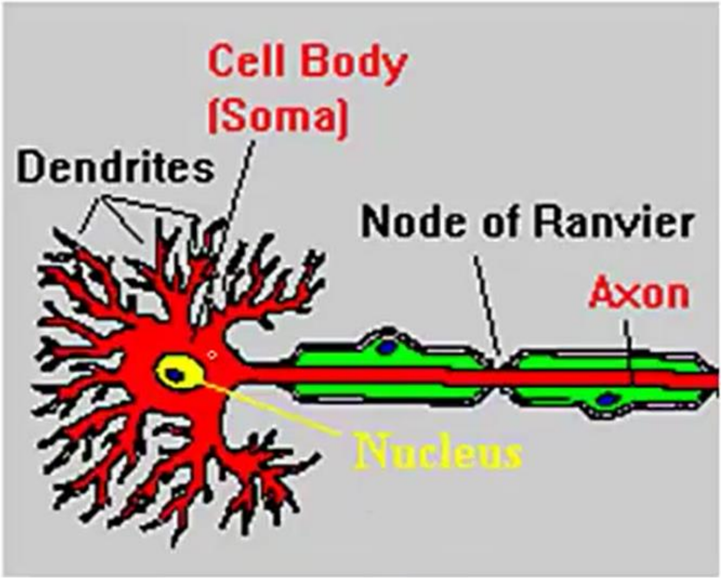
Outline

- Sensing & perception
  - Neurons in the brain
  - Visual cortex & receptive fields
  - Vision & perception
- Neurons & spikes
  - **Electrical personality of a neuron**
  - **Ionic channels**
  - **Action potential**
- The Hudgkin-Huxley equation
  - **The passive membrane**
  - **Voltage-gated channels**
  - **Anatomy of a spike**
- Neuronal dynamics
  - **Phase portrait models**
  - **Fixed points and their stability**
  - **Bifurcation (saddle-node / Hopf)**
  - **Simplified 2D models**

Electrical Personality of a Neuron

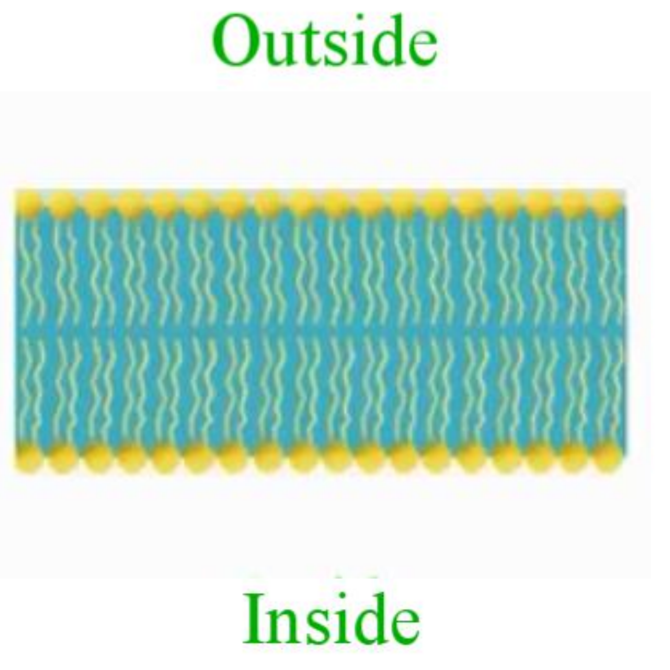
What is a Neuron?

- A “leaky bag of charged liquid”
- Contents of the neuron enclosed within a *cell membrane*



What is a Neuron?

- A “leaky bag of charged liquid”
- Contents of the neuron enclosed within a *cell membrane*
- Cell membrane is a *lipid* bilayer
- Bilayer is impermeable to charged ion species such as Na^+, Cl^-, and K^+

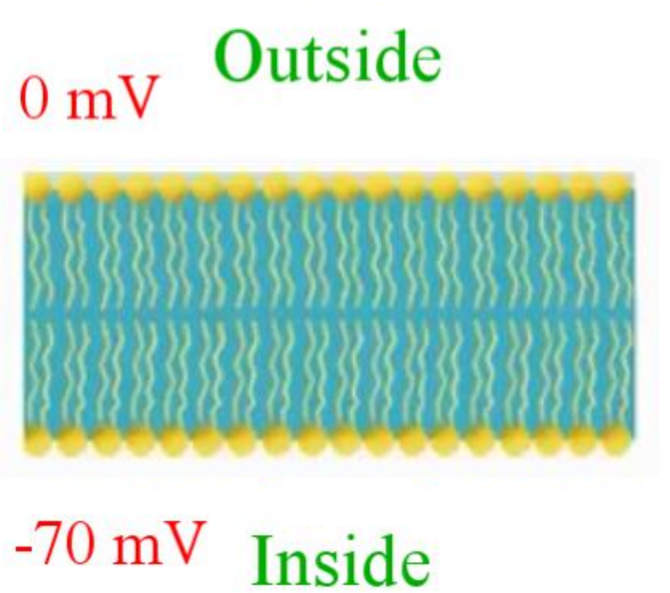


Adapted from Wikipedia

The Electrical Personality of a Neuron

- Each neuron maintains a *potential difference* across its membrane

  → Inside is about -70 mV relative to outside ***(Resting Potential)***



Adapted from Wikipedia

The Electrical Personality of a Neuron

- Each neuron maintains a *potential difference* across its membrane

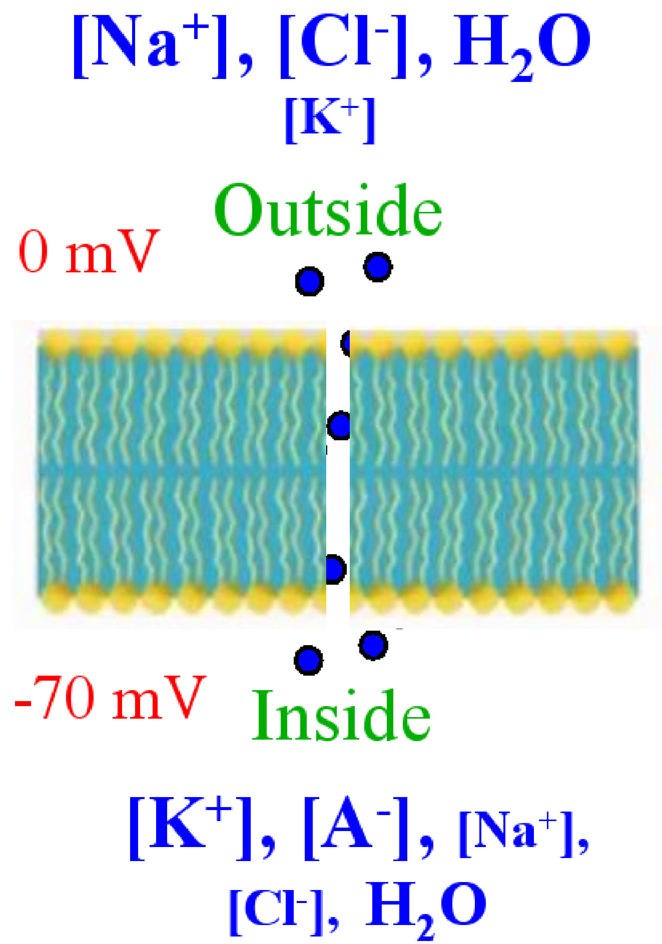
  → Inside is about -70 mV relative to outside *(Resting Potential)*

$[\mathrm{Na}^+]$ and $[\mathrm{Cl}^-]$ are higher outside; $[\mathrm{K}^+]$ and organic anions $[\mathrm{A}^-]$ are higher inside

(**This causes *osmosis* forces**)

Ionic pump maintains -70 mV difference by expelling $[\mathrm{Na}^+]$ out and allowing $[\mathrm{K}^+]$ ions in

(This is driven by *electric* forces)

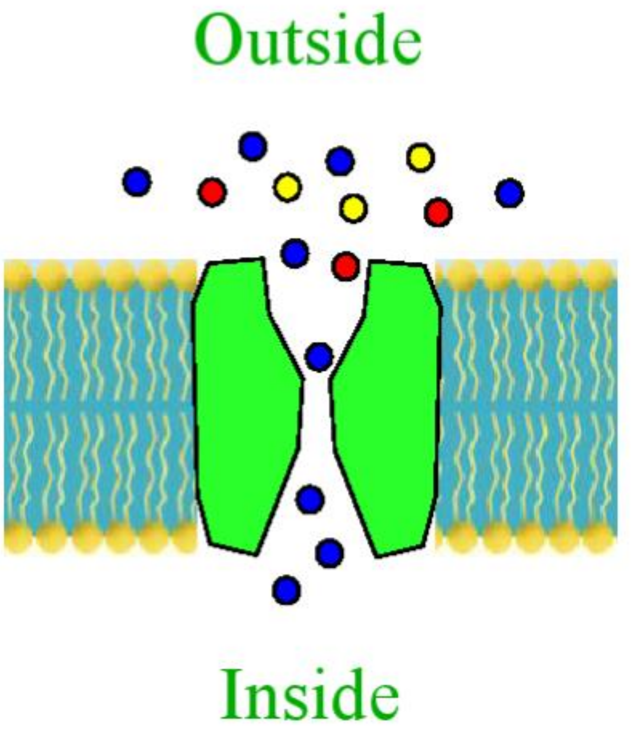


Adapted from Wikipedia

Ionic Channels

Ionic Channels: The Gatekeepers

- Ionic channels in membranes are proteins that are *selective* and allow only specific ions to pass through
  - E.g. Pass Na^+ but not K^+ or Cl^-



Adapted from Wikipedia

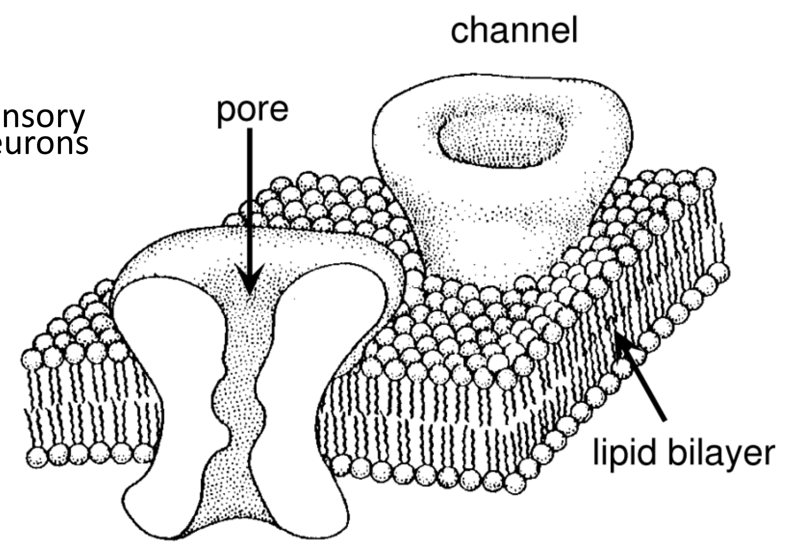
Currents Flow through Ion Channels

- Ion channels distinguish between different ions

→ Different ions have different rates of transport between inside and outside the neuron

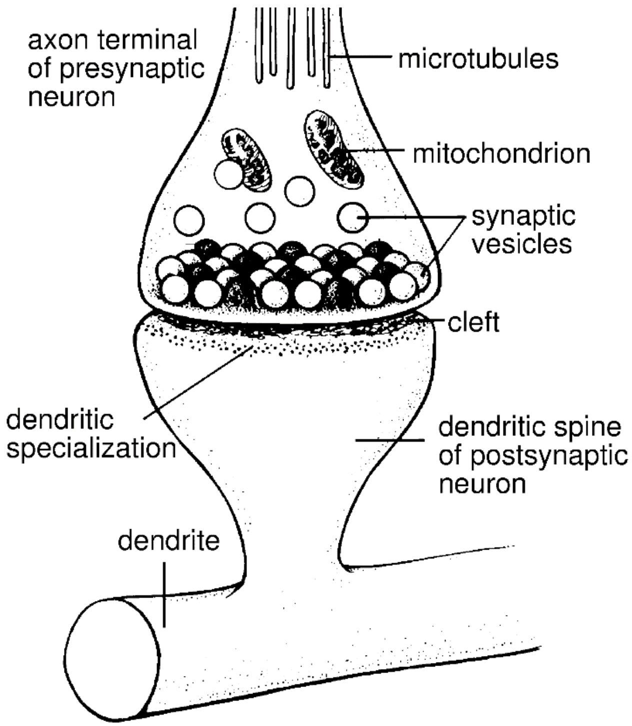
- Ion channels are of many types:
  - Neurotransmitter-dependent (synaptic)
  - Voltage-dependent
  - Ca-dependent
  - Mechanosensitive
  - Heat sensitive

Sensory neurons

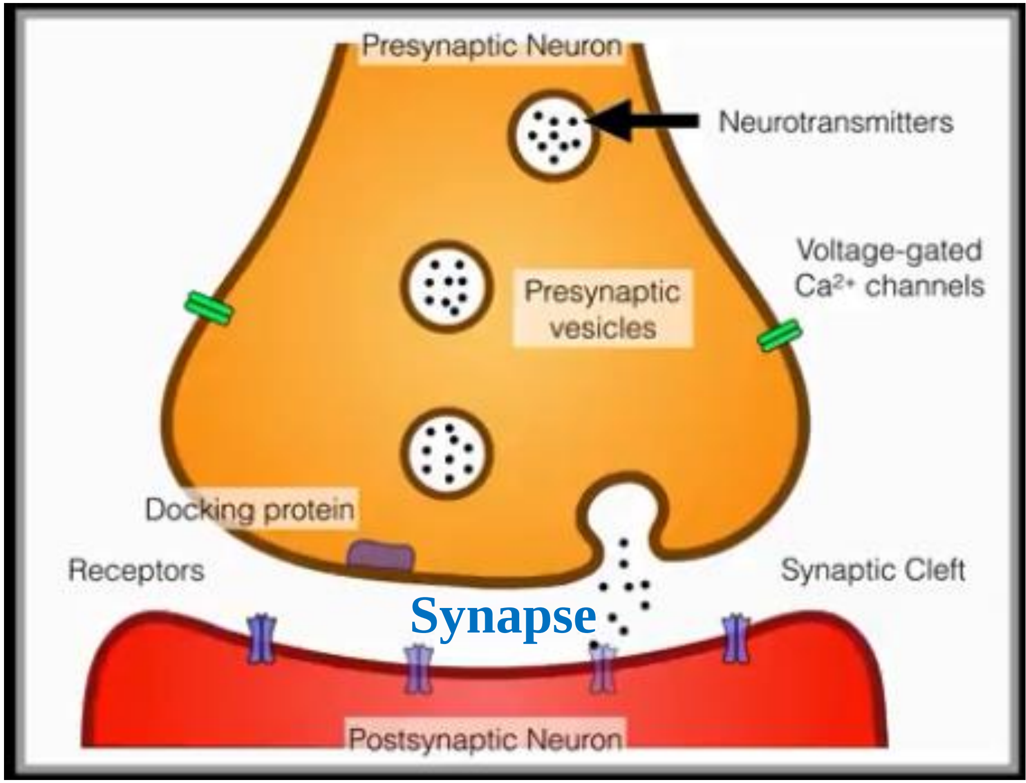


Gated Channels Allow Neuronal Signaling

Inputs from other neurons → *Chemically-gated channels* (at ***synapses***) open → Changes in local membrane potential



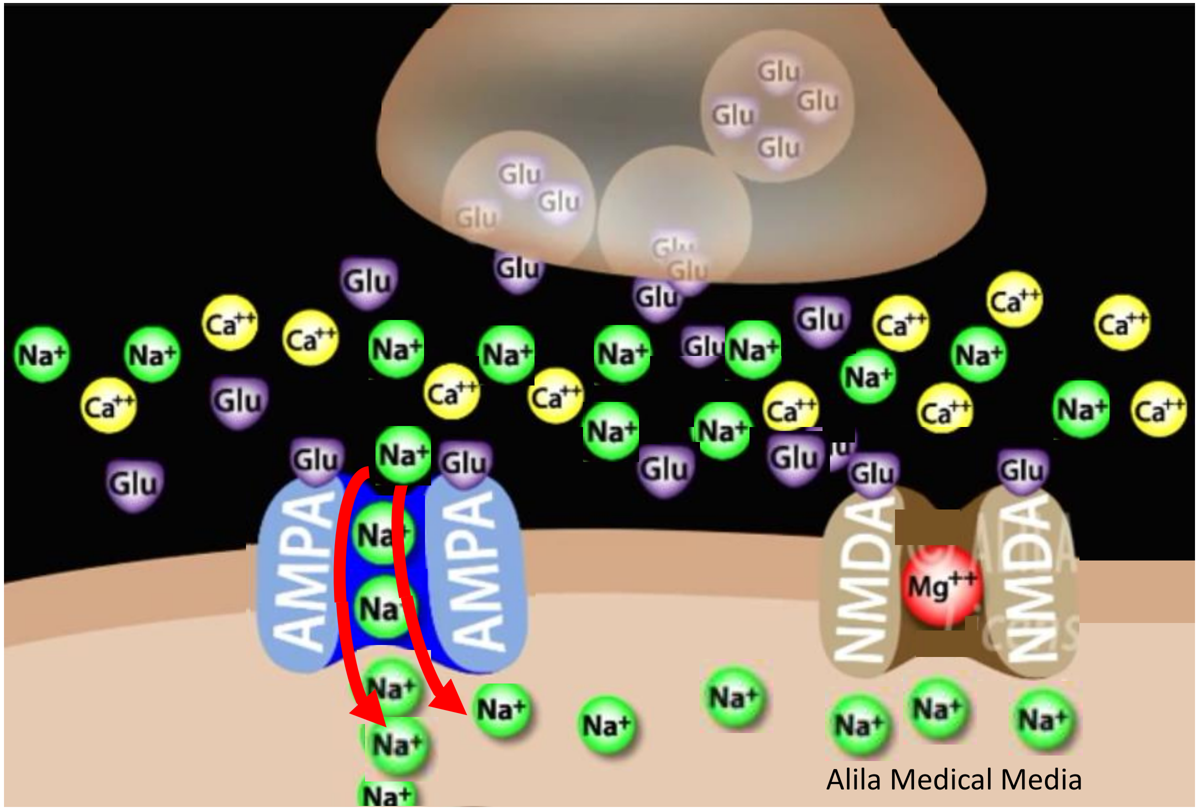
Dayan & Abbott, 2005



Paul Andersen, BozemanScience.com

Gated Channels Allow Neuronal Signaling

Inputs from other neurons → *Chemically-gated channels* (at ***synapses***) open → Changes in local membrane potential

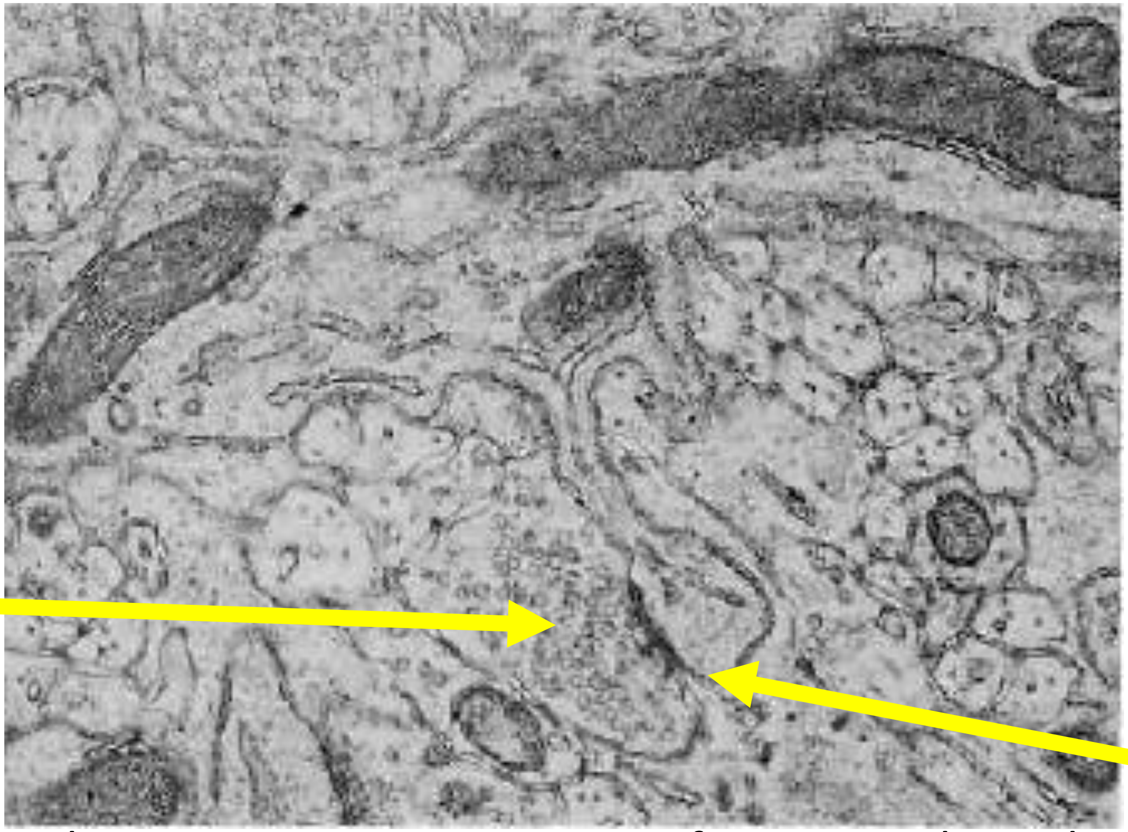


Alila Medical Media

How Synapses Work

Two membrane surfaces, of an axon and a dendrite, come together at a synapse: A 20 nm cleft separates them

Axon filled with tiny round synaptic vesicles, in which neurotransmitter is stored

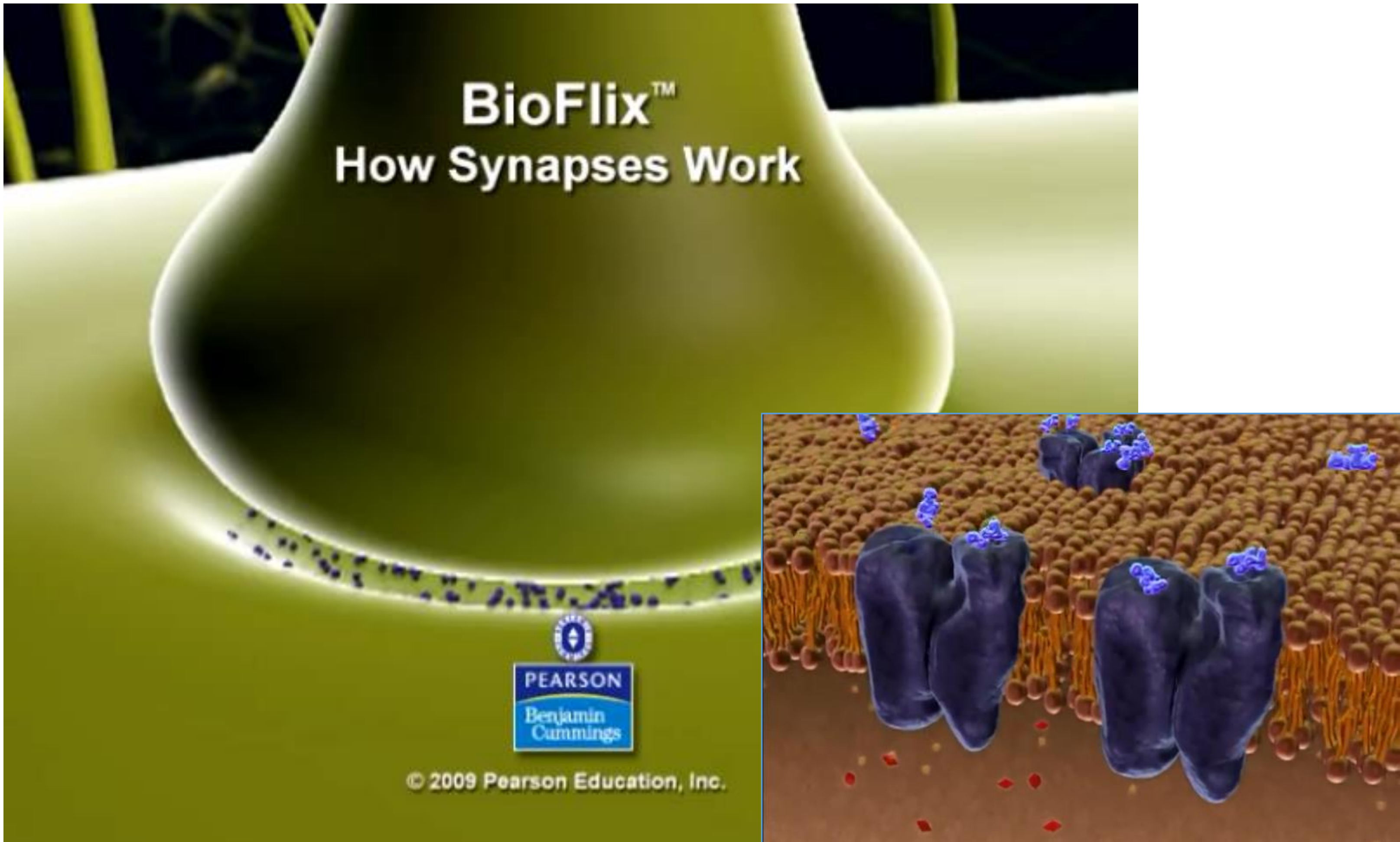


A synapse

Electron microscope picture of a section through cerebellar cortex of a rat

David Hubel "Eye, Brain, and Vision", 1995

How Synapses Work



https://www.youtube.com/watch?v=Ibzfwtdtong

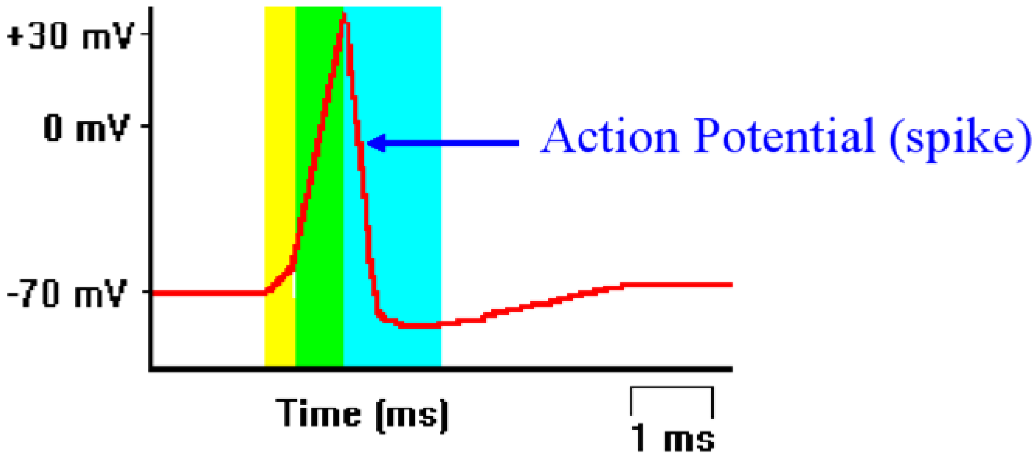
(Video to watch later)

Source: Pearson Education, Inc.

Action Potential

Action Potential

The Output of a Neuron: Action Potential (Spike)



- Change of potential due to synaptic activity causes opening/closing of *voltage-gated channels*
  (in body, axon, dendrites)

→ Further *Depolarization* (positive change in voltage)

- Strong enough depolarization causes a spike or ***action potential***

The Output of a Neuron: Action Potential (Spike)

- *Voltage-gated channels* cause action potentials (spikes)

1. Strong *depolarization* opens Na^+ channels, causing rapid Na^+ influx and more channels to open (positive feedback)
2. At higher potentials, Na^+ channels inactivate while K^+ outflux reduces and restores membrane potential

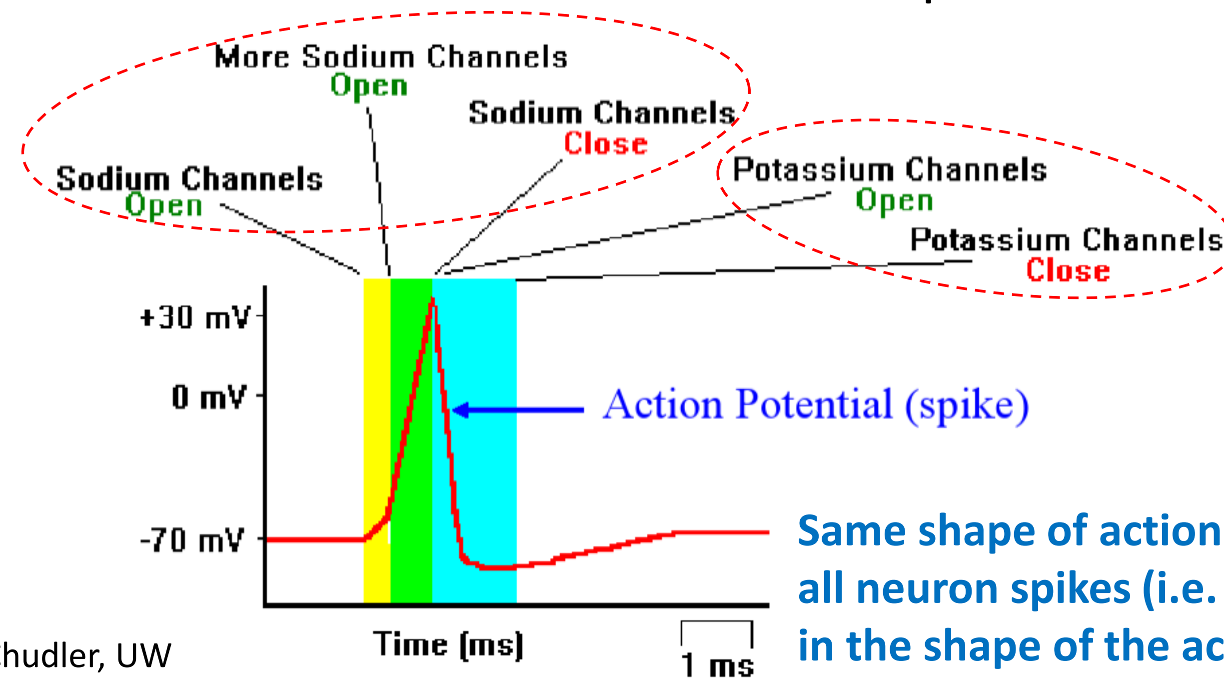
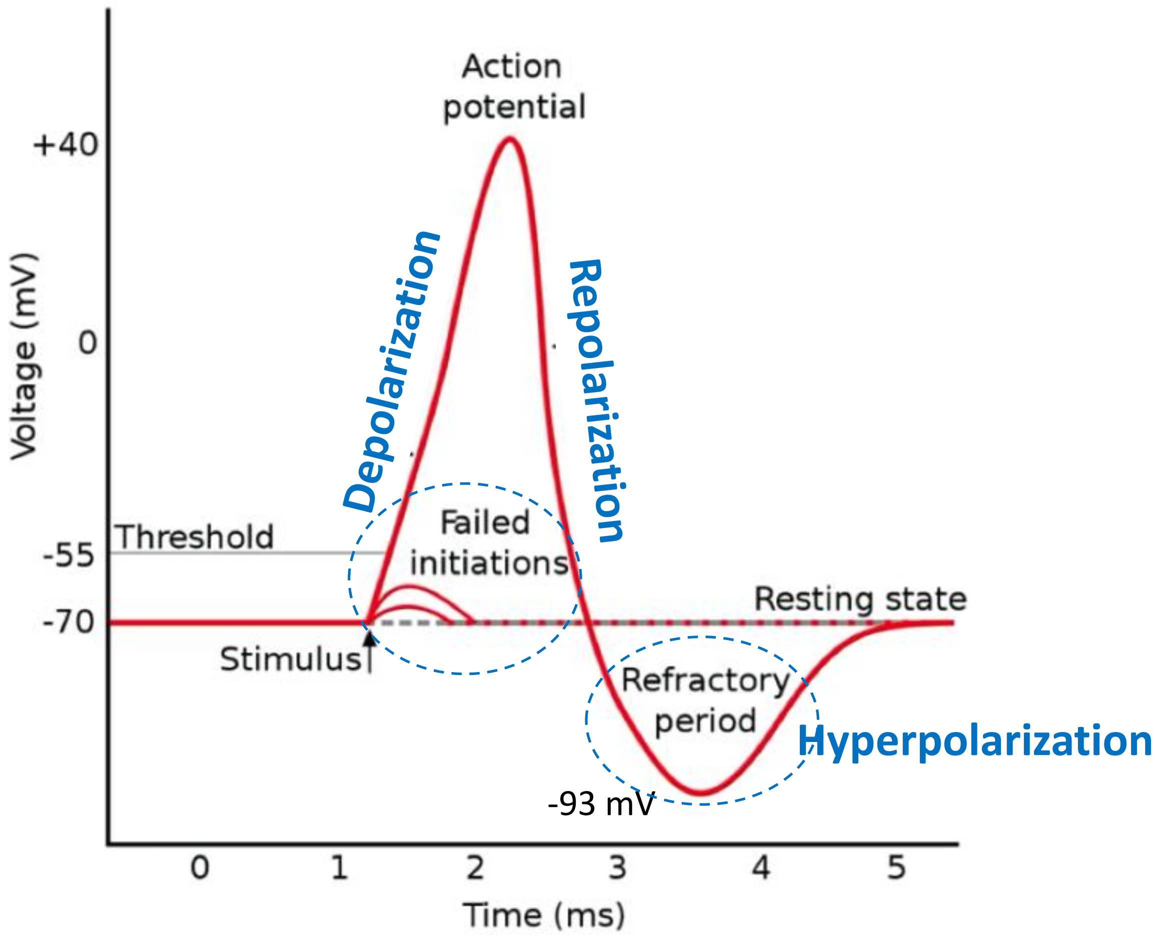


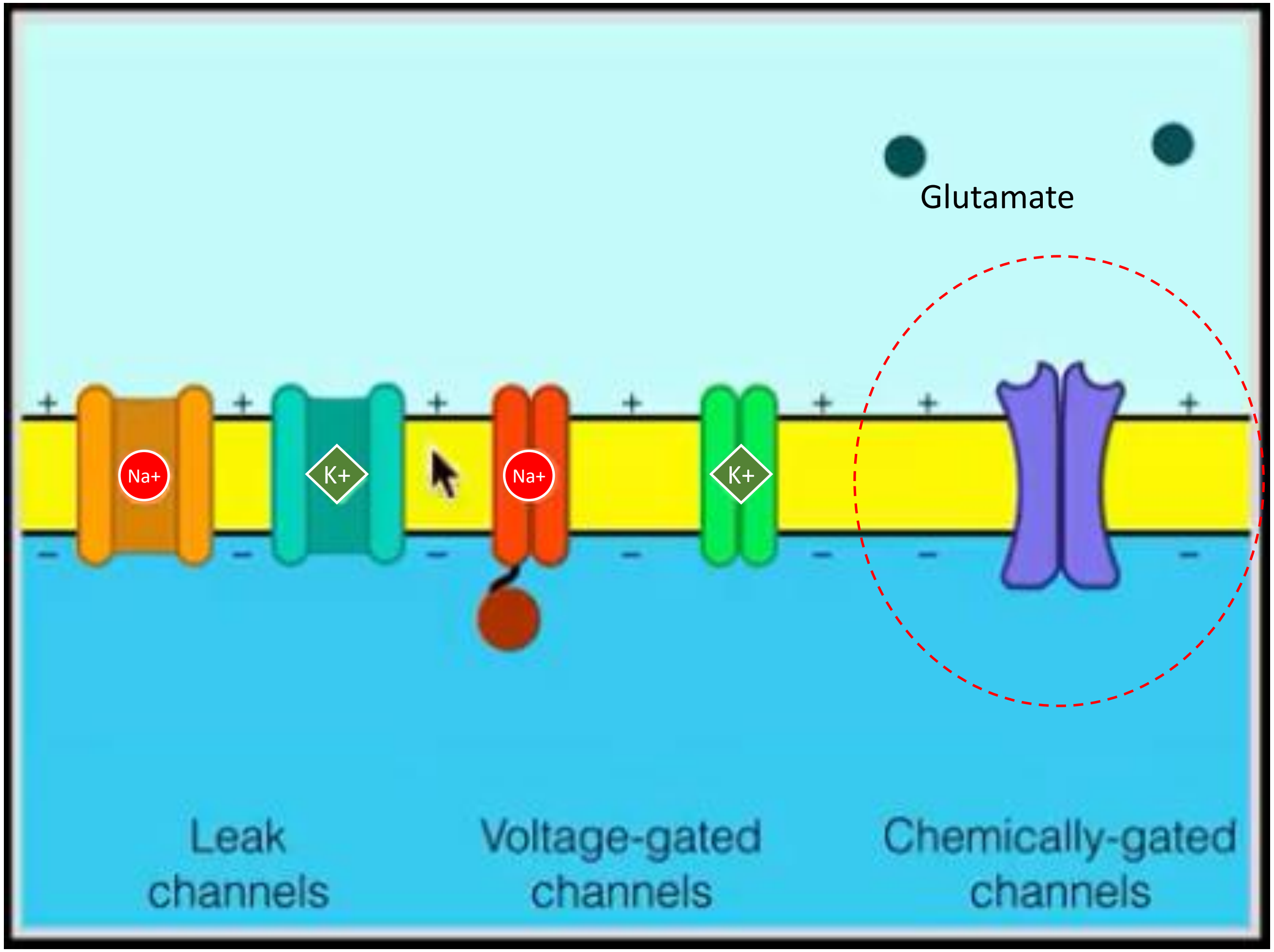
Image by Eric Chudler, UW

Same shape of action potential for all neuron spikes (i.e. no information in the shape of the action potential)

The Output of a Neuron: Action Potential (Spike)



Ionic Channels – Chemically-Gated Channels (Synapses)



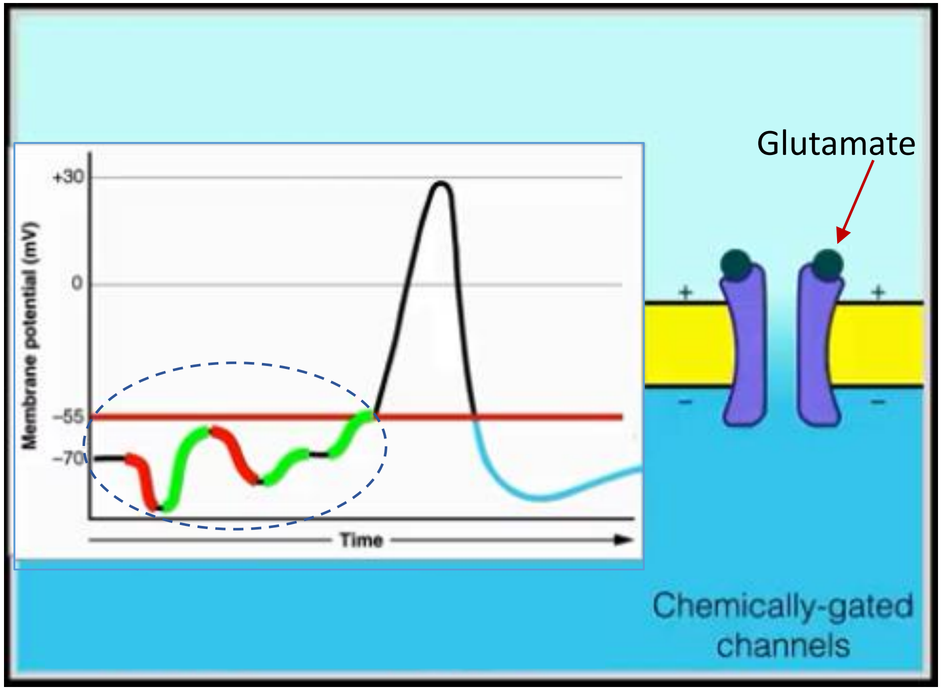
https://www.youtube.com/watch?v=L41TYxYUqqs
(Video to watch later)

Paul Andersen, BozemanScience.com

Ionic Channels –
Chemically-Gated Channels (Synapses)

Two types of chemically-gated channels:

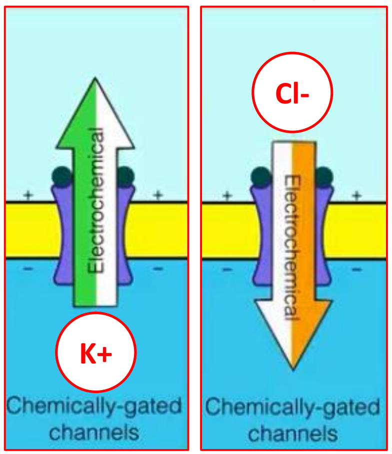
- Excitatory channels tend to increase the membrane potential
- Inhibitory channels decrease the membrane potential



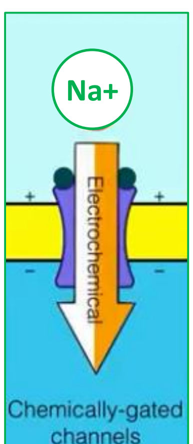
Paul Andersen, BozemanScience.com

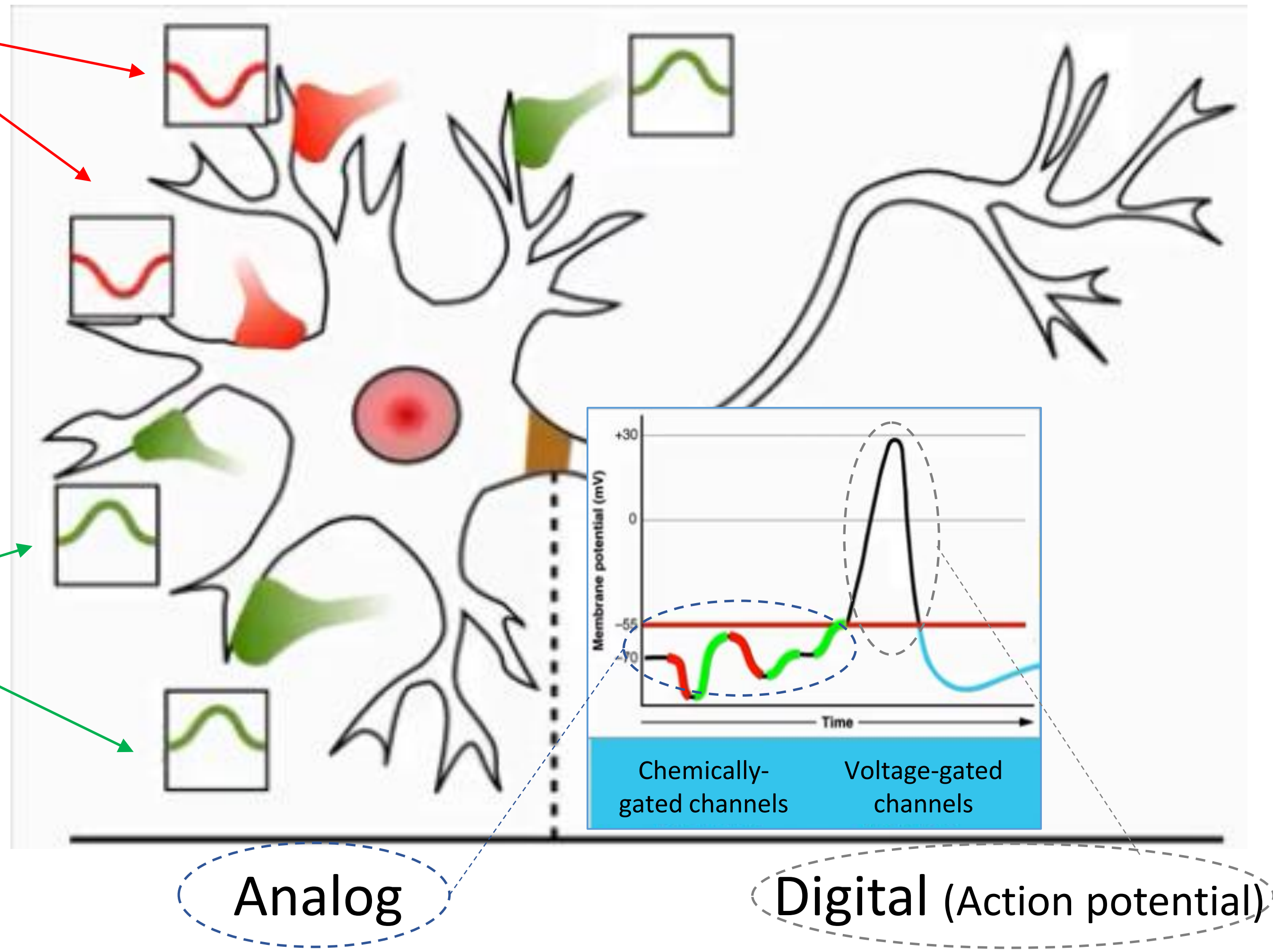
Ionic Channels –
Chemically-Gated Channels (Synapses)

Inhibitory



Excitatory

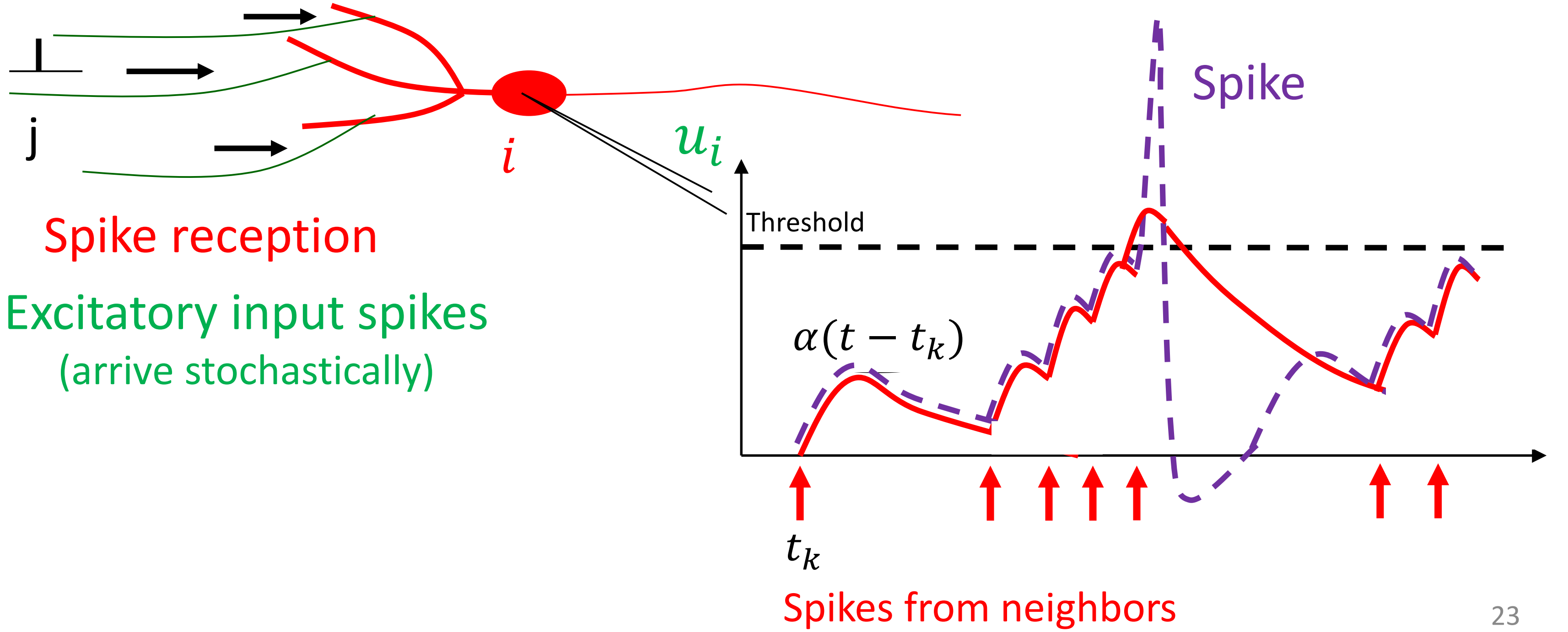




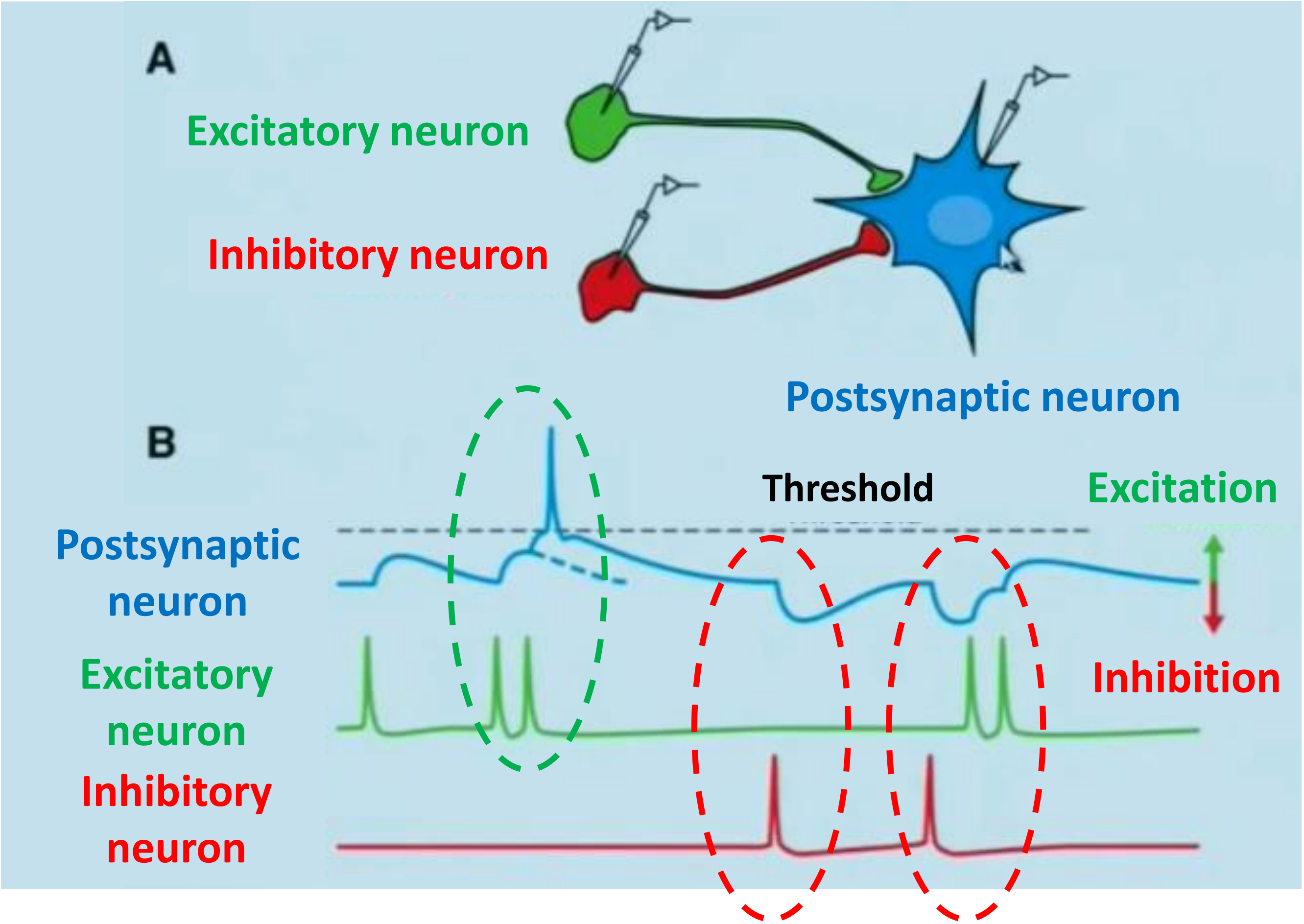
Paul Andersen, BozemanScience.com

Modeling A Neuron

- **Integrate and fire model:** A neuron takes a weighted sum of its inputs and fires a spike if the sum exceeds a threshold

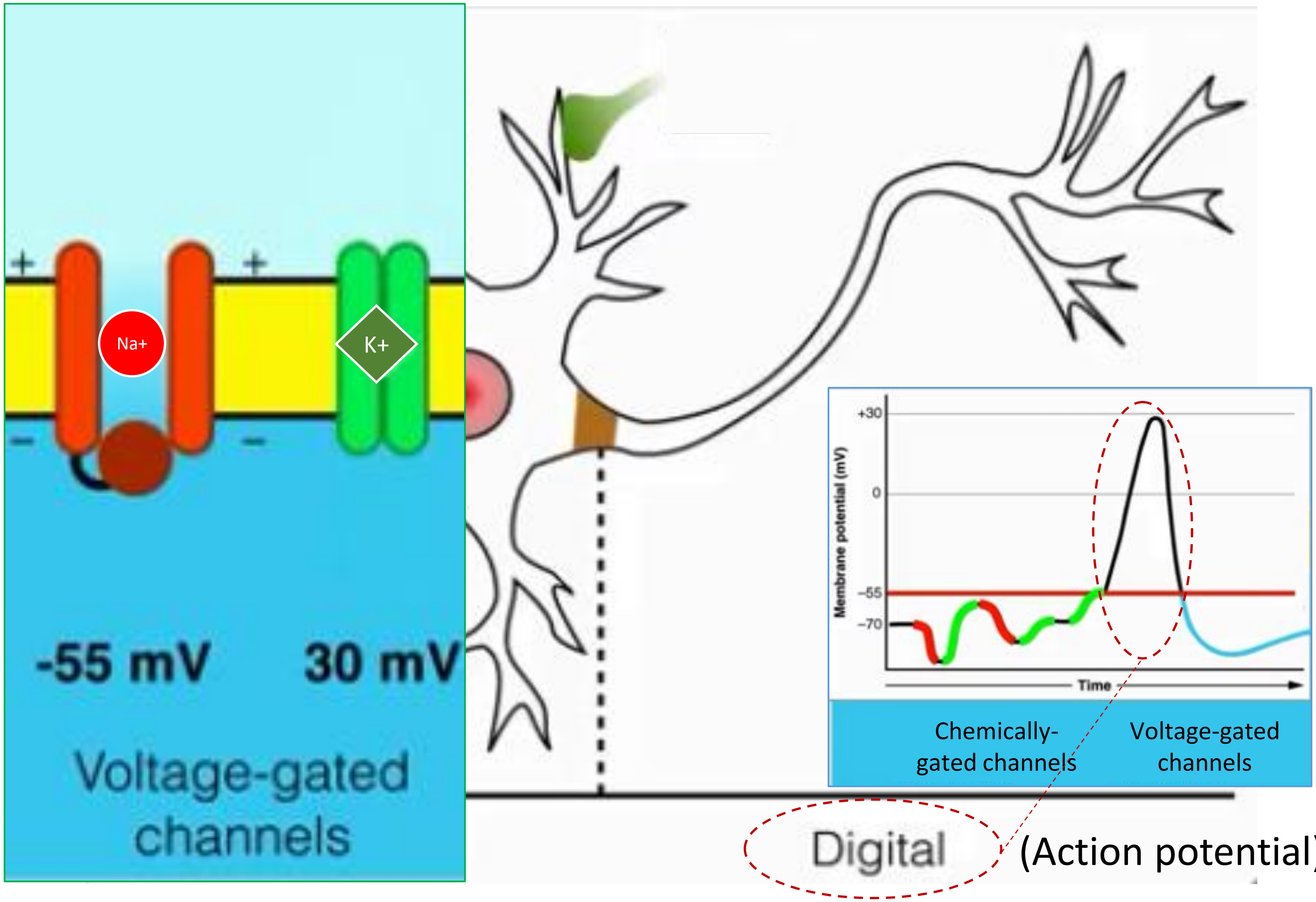


Ionic Channels –
Chemically-Gated Channels (Synapses)



John Byrne, Univ. Texas

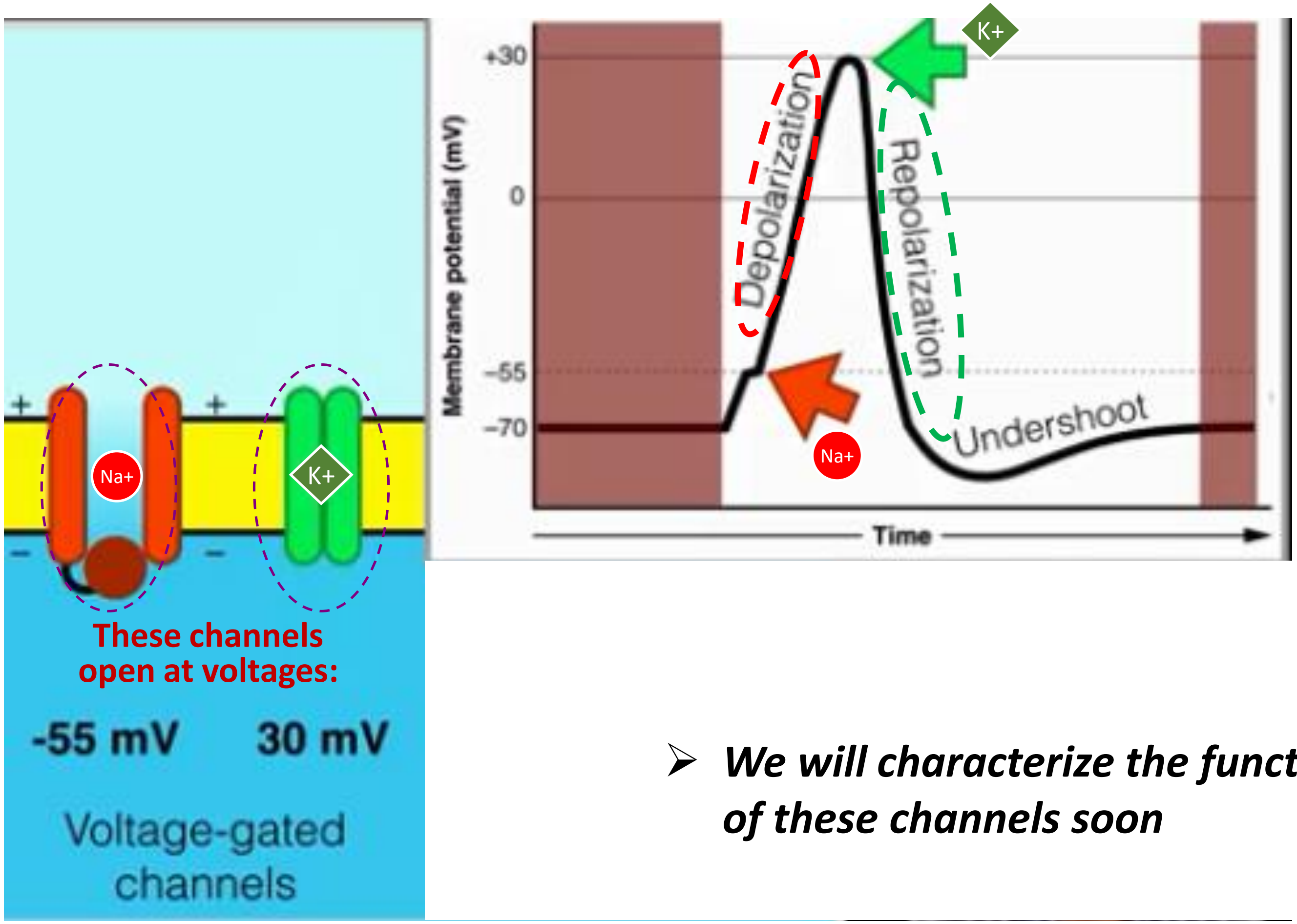
Ionic Channels –
Voltage-Gated Channels (Action Potential)



(Action potential)

Paul Andersen, BozemanScience.com

Ionic Channels – Voltage-Gated Channels (Action Potential)



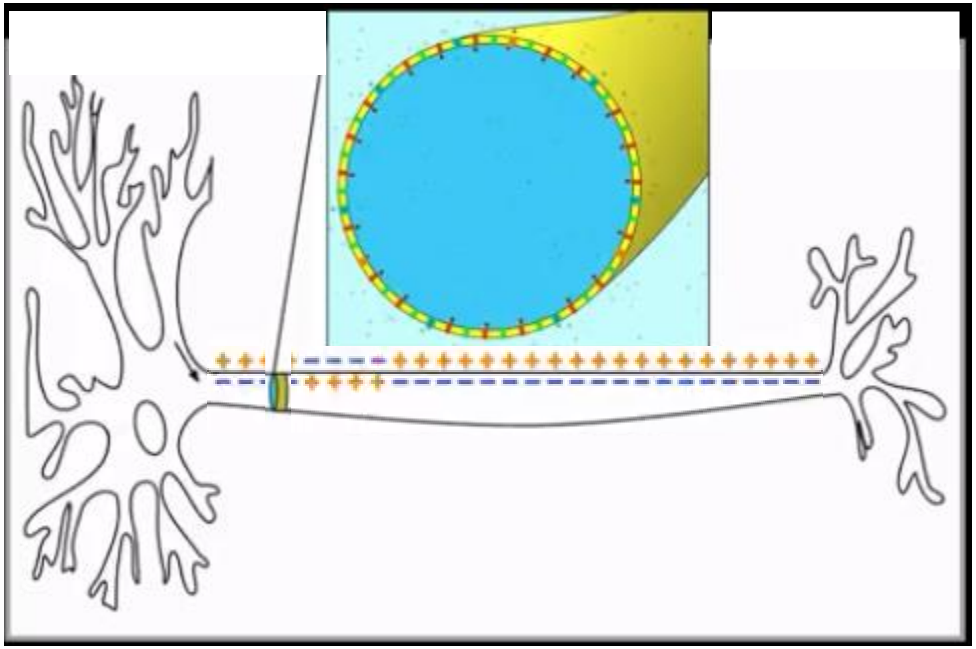
- ***We will characterize the function of these channels soon***

https://www.youtube.com/watch?v=HYLyhXRp298

(Video to watch later)

Paul Andersen, BozemanScience.com

Axon – Transmission of Action Potential

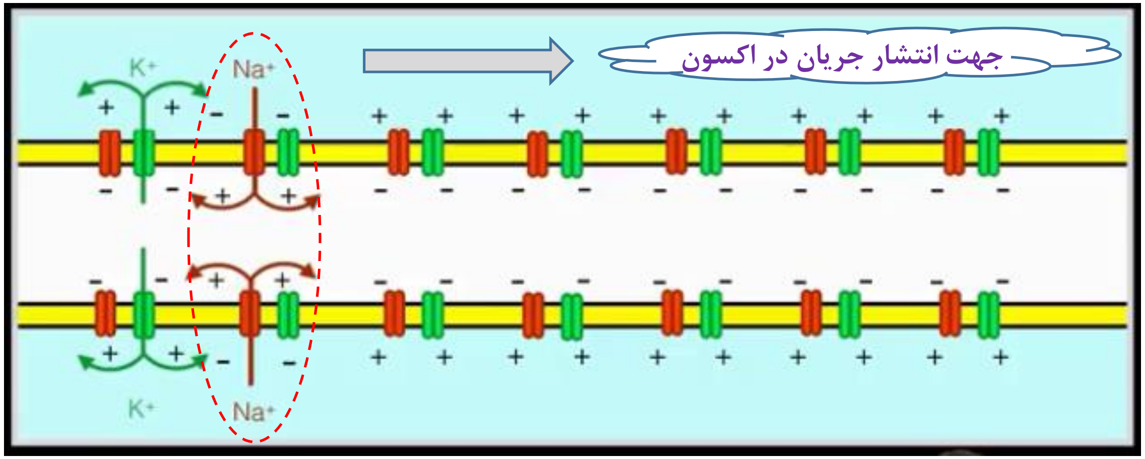


- The action potential moves across the axon
- This is performed by:
  - Voltage-gated Na^+ and K^+ channels
  - The role of myelin cover

Paul Andersen, BozemanScience.com

Axon –
Transmission of Action Potential

To neuron’s soma



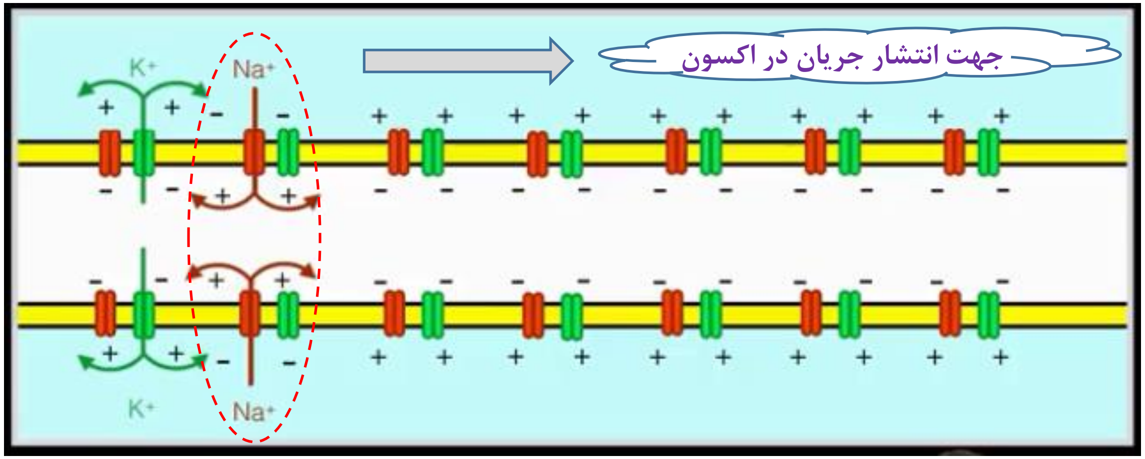
To other neurons synapses

- As the activation threshold is reached, sodium channels open
- The Na^+ ions move away from each other due to their charges
    - The charges moving down the axon cause voltage increase → The subsequent sodium channels open
    - Charges moving the other way do not cause any effect (since potassium channels have opened there causing voltage drop)

Paul Andersen, BozemanScience.com

Axon –
Transmission of Action Potential

To neuron’s soma



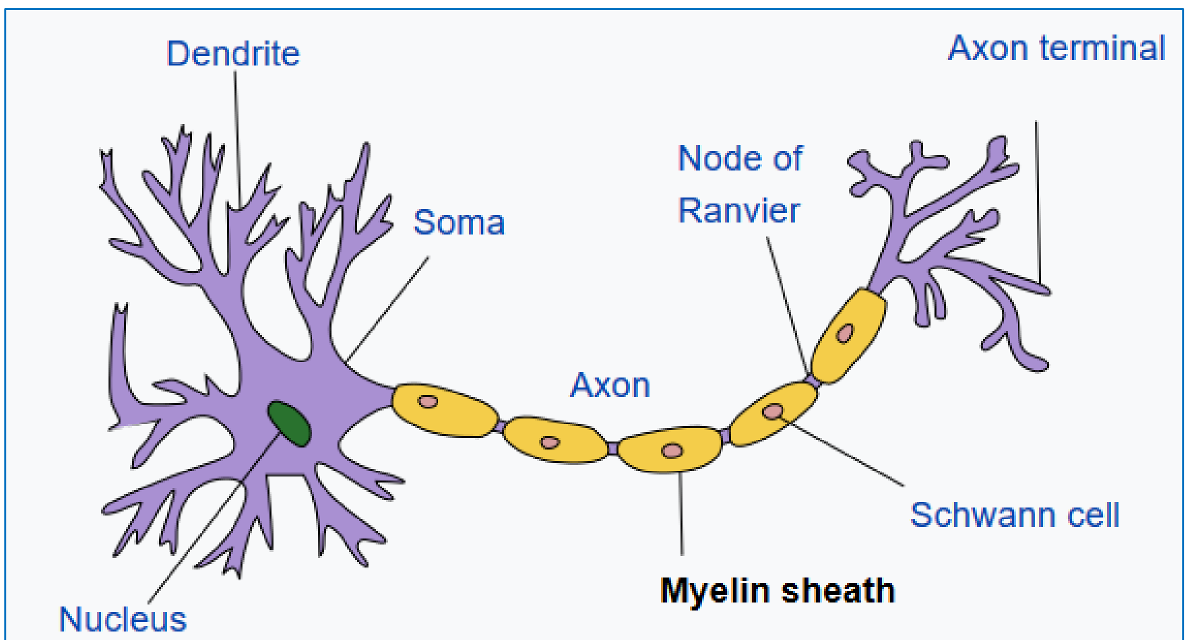
To other neurons synapses

- Given the length of a typical axon, and the large number of channels:
  - ➢The transmission of action potential along the axon will be slow (causing long delays in transmission of data or commands across neuronal networks)

Paul Andersen, BozemanScience.com

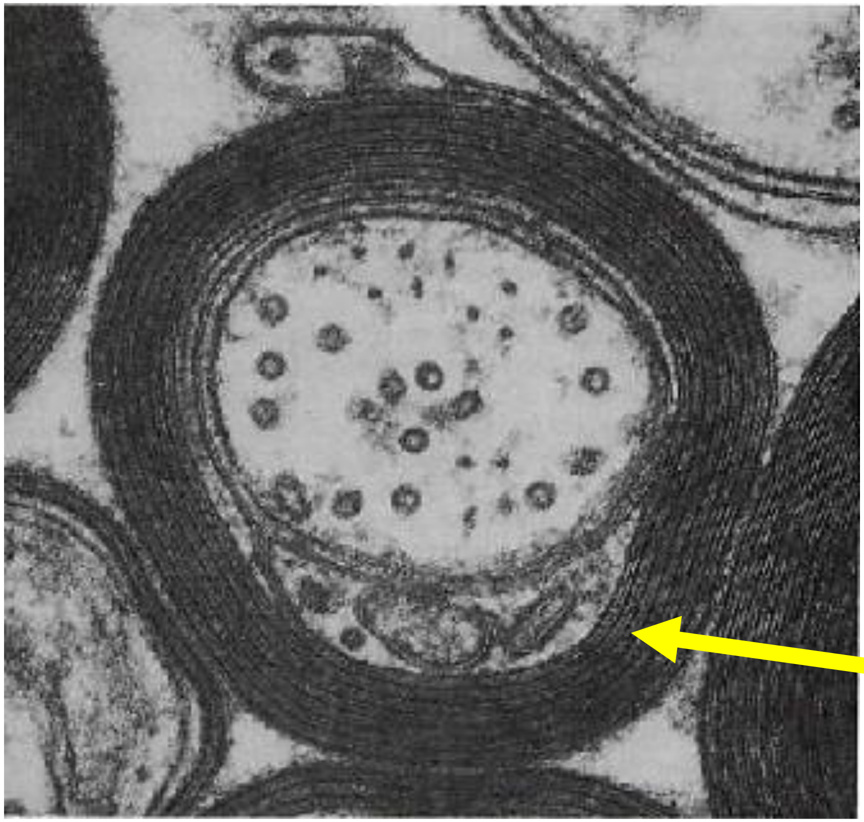
Active Wiring: Myelination of Axon

- Many axons in vertebrates are covered with an insulating sheath of ***myelin***



Active Wiring: Myelination of Axon

The myelin sheath consists of many layers of glial cell membrane wrapped around the axon:

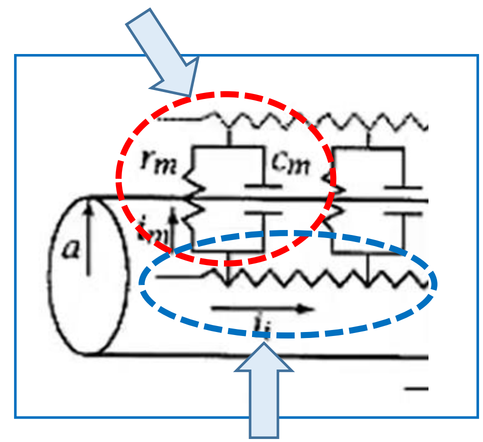


Myelin

David Hubel "Eye, Brain, and Vision", 1995

This results in:

- A very high membrane resistance (to prevent passage of charges through the membrane)
- A small membrane capacitance (to prevent accumulation of charges on the membrane)

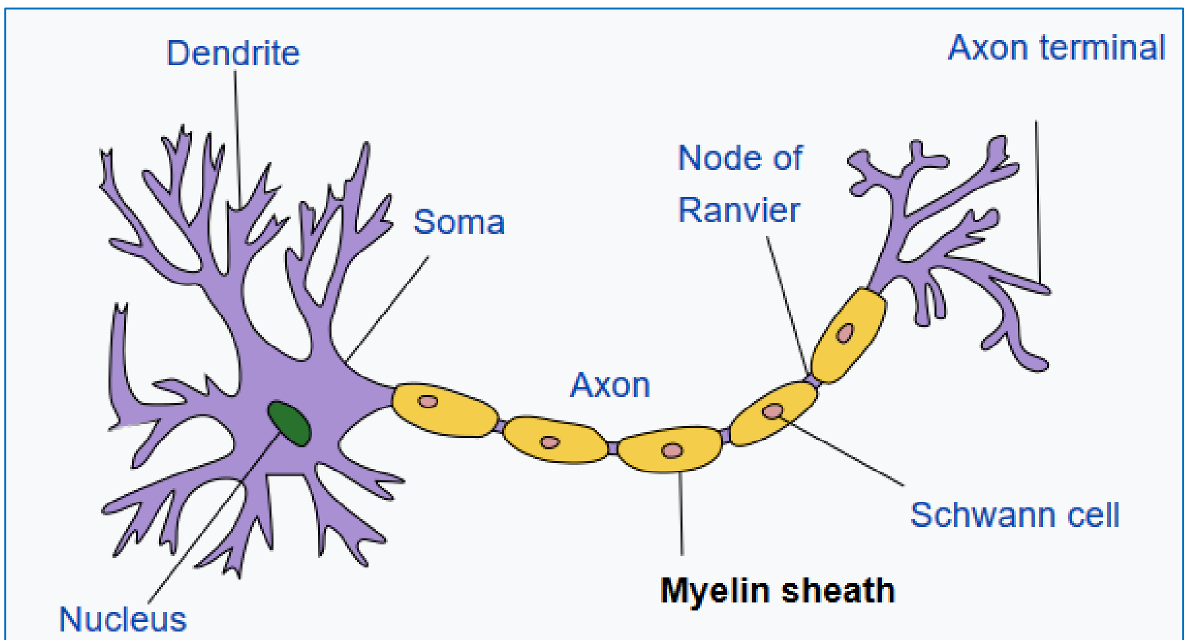


But the voltage drops along the axon

Myelin speeds nerve impulses by promoting charges to travel along the axon

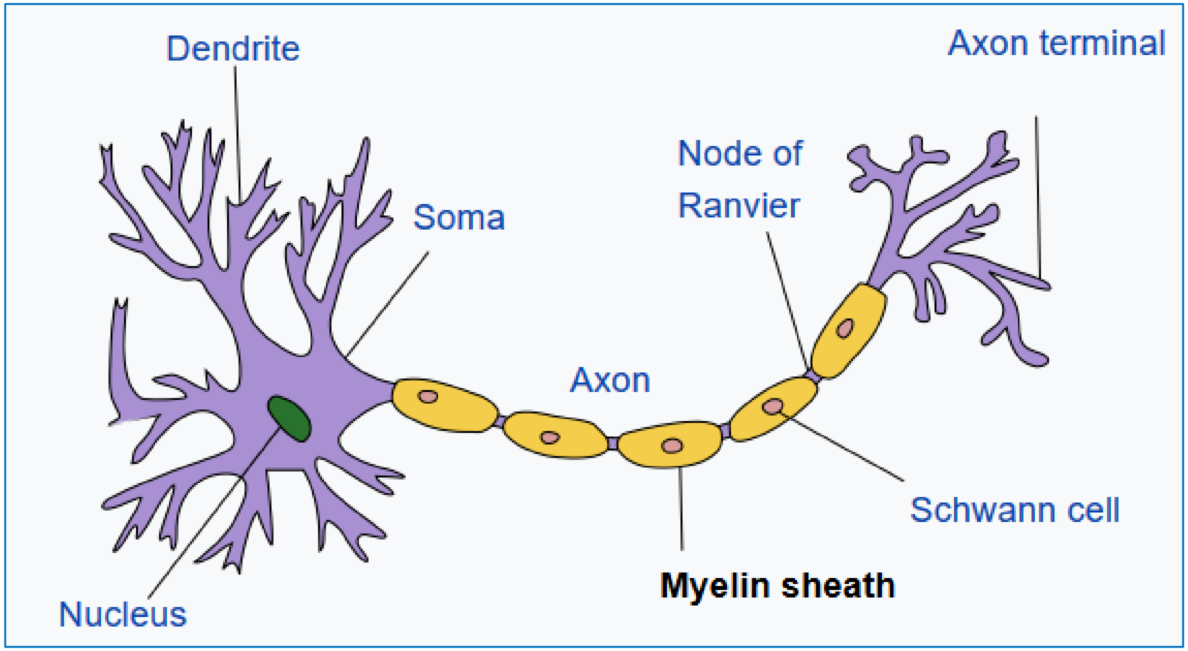
Active Wiring: Myelination of Axon

- Many axons in vertebrates are covered with an insulating sheath of ***myelin***
  - Myelin covers the axon except at gaps (called the ***nodes of Ranvier***)
  - There is a high density of fast voltage-dependent Na+ channels at these nodes



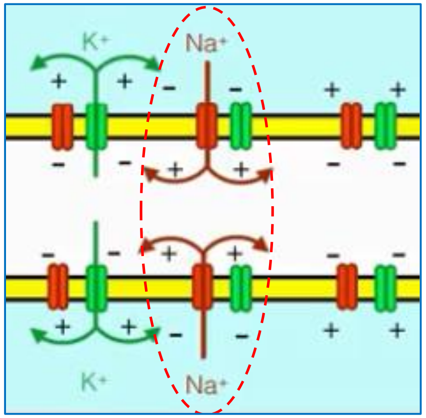
Active Wiring: Myelination of Axon

- ***Propagation of action potential:***
  1. Membrane's potential depolarization is transferred ***passively*** down the myelin-covered sections of the axon **(This is fast transmission since it does not involve chemical channels)**

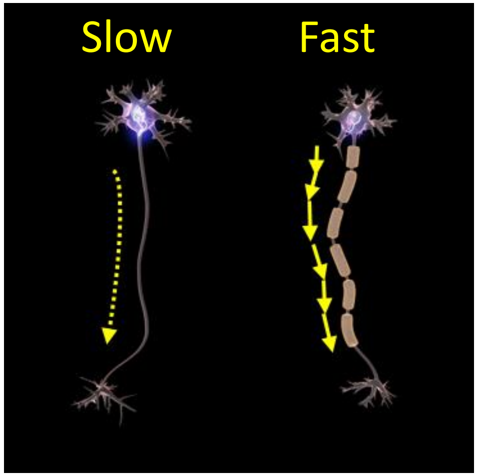


Active Wiring: Myelination of Axon

- ***Propagation of action potential:***
  1. Membrane's potential depolarization is transferred ***passively*** down the myelin-covered sections of the axon
     (This is fast transmission since it does not involve chemical channels, but the voltage drops due to resistance to moving charges along the axon)
  2. Action potentials are ***actively*** regenerated at the nodes of Ranvier
     (This compensates for the voltage drop caused by passive transmission in myelinated axon regions)



- This type of transfer is slow
- It only occurs at the nodes of Ranvier

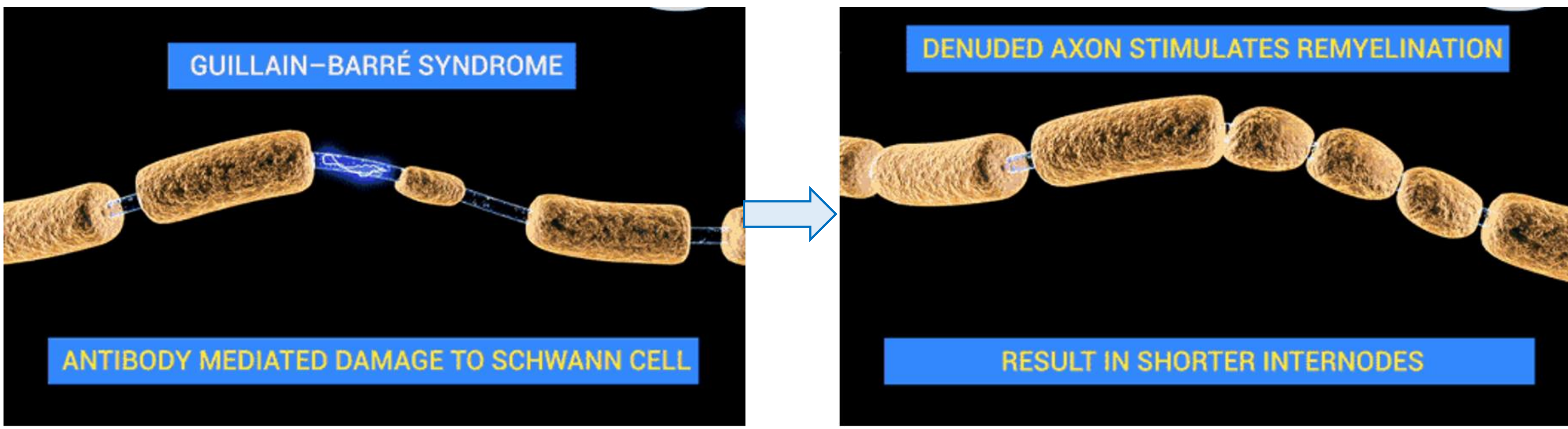


Wikipedia Dr. Jana

Active Wiring: Myelination of Axon

Extra Info

- In **MS (multiple sclerosis)**, the body's auto-immune response damages the myelin, causing the neurons to lose efficient communication



- **Guillain–Barré syndrome (GBS)** is a rapid-onset muscle weakness as a result of damage to the peripheral nervous system

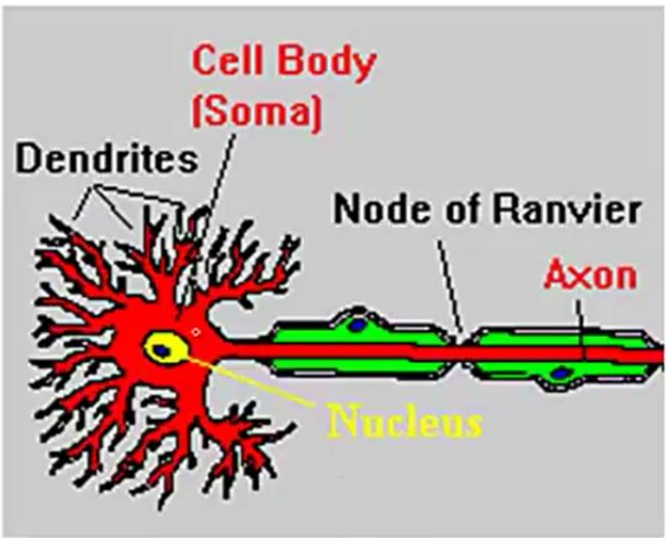
Image source: Doctor Jana – Wikipedia Commons

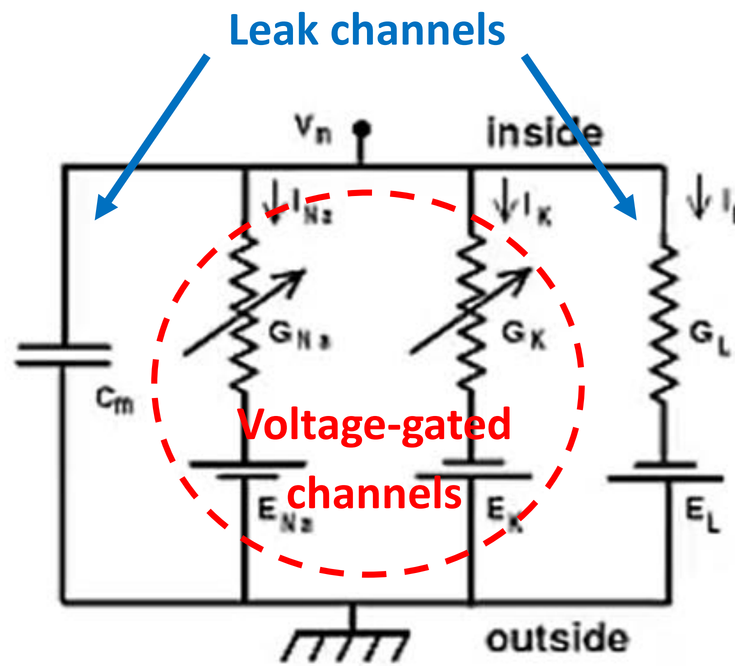
Outline

- Sensing & perception
  - Neurons in the brain
  - Visual cortex & receptive fields
  - Vision & perception
- Neurons & spikes
  - Electrical personality of a neuron
  - Ionic channels
  - Action potential
- The Hudgkin-Huxley equation
  - **The passive membrane**
  - **Voltage-gated channels**
  - **Anatomy of a spike**
- Neuronal dynamics
  - **Phase portrait models**
  - **Fixed points and their stability**
  - **Bifurcation (saddle-node / Hopf)**
  - **Simplified 2D models**

The Passive Membrane

Equivalent Circuit Model

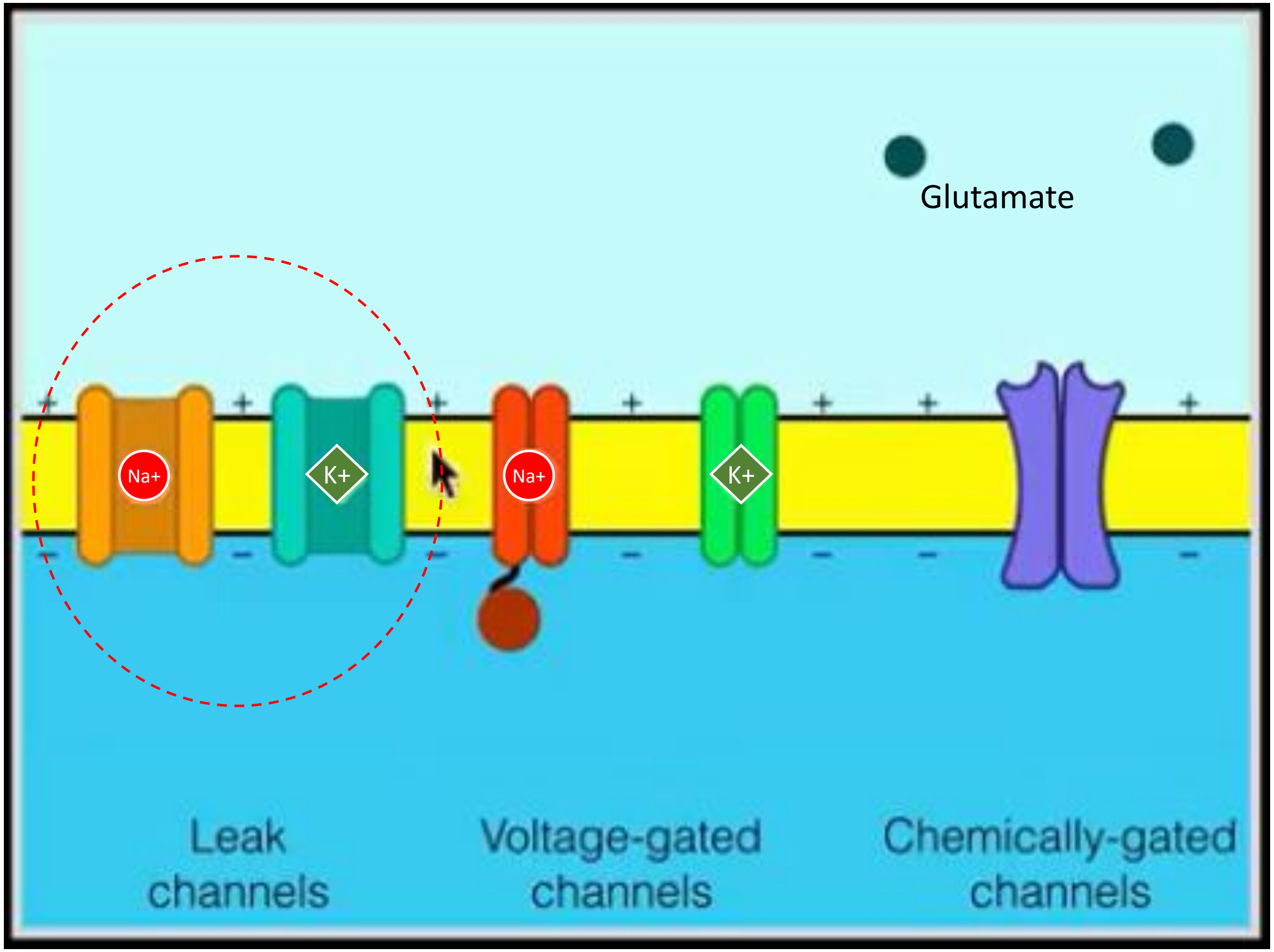




- We will derive a model for the function of a neuron
- The mathematical tool will be differential equations
- Hudgkin and Huxley won nobel prize for deriving such a model

Eric Chudler, UW

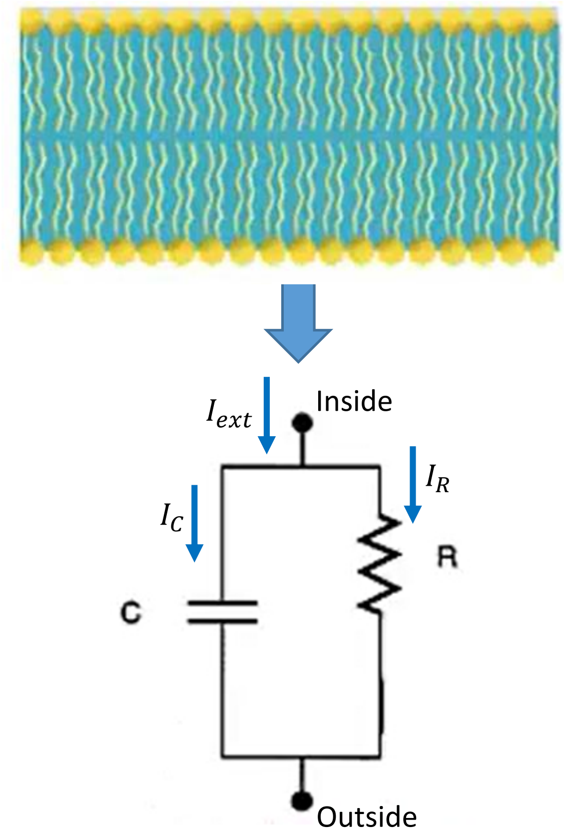
Ionic Channels –
Passive Membrane and Leak Channels



Paul Andersen, BozemanScience.com

The Passive Membrane

- We will first derive a model for the current that leaks through the membrane itself:
  - The lipid bilayer acts like a ***capacitor***
  - Some charge pass through, which can be modeled as a conductance by a ***resistor***

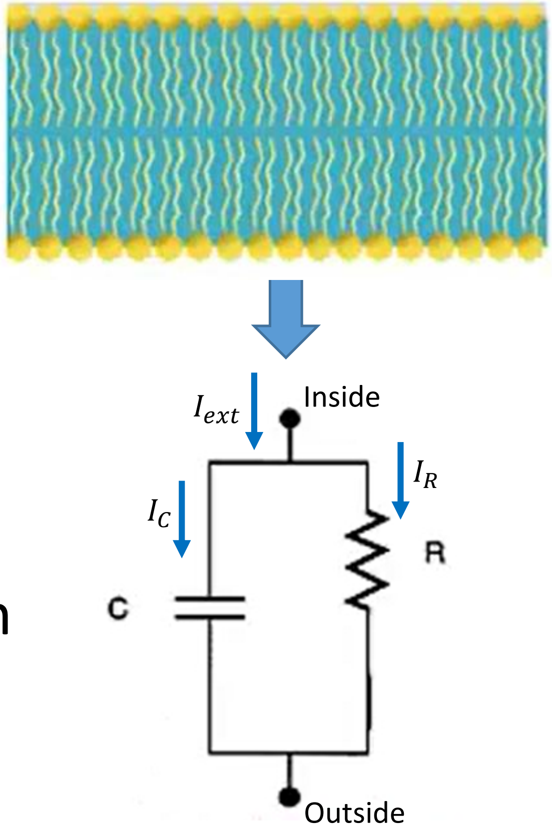


(For a review, see Extra Info on next page)

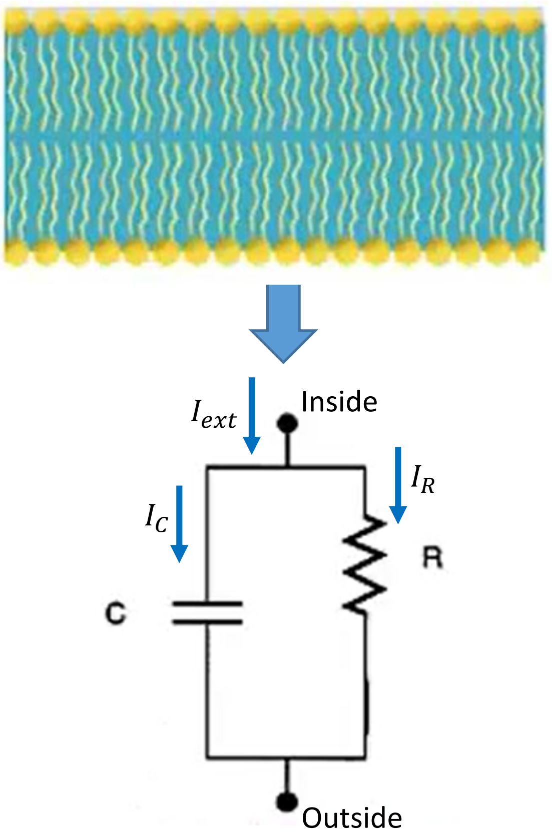
RC Circuits

- At a junction of wires, the total (input/output) current is zero
- The potential changes by a fixed amount across a battery symbol
- The potential across a resistor is proportional to the current going through it (Ohm's law: $V = IR$ or $I = Vg$)
- The current through a capacitor is proportional to the derivative of the potential across it:

$$I_C = \frac{dQ}{dt} = C\frac{dV}{dt}$$



The Passive Membrane



At the node: $I_{ext} = I_C + I_R$

Ohm's law: $V = I_R R$

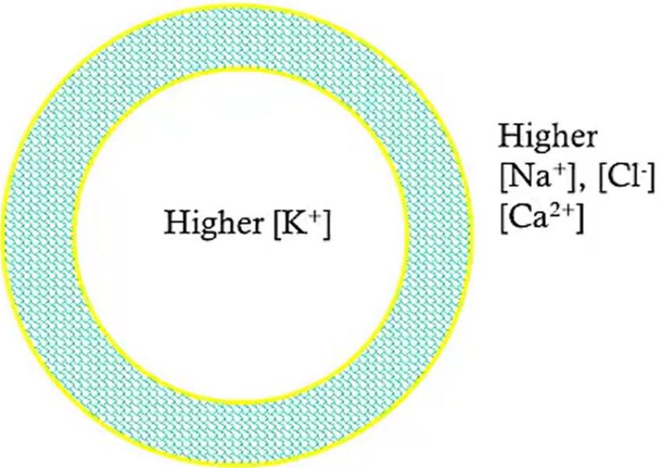
For capacitor: $C = Q/V$

$$I_C = \frac{dQ}{dt} = C\frac{dV}{dt}$$

$$\boxed{C\frac{dV}{dt} = -\frac{V}{R} + I_{ext}}$$

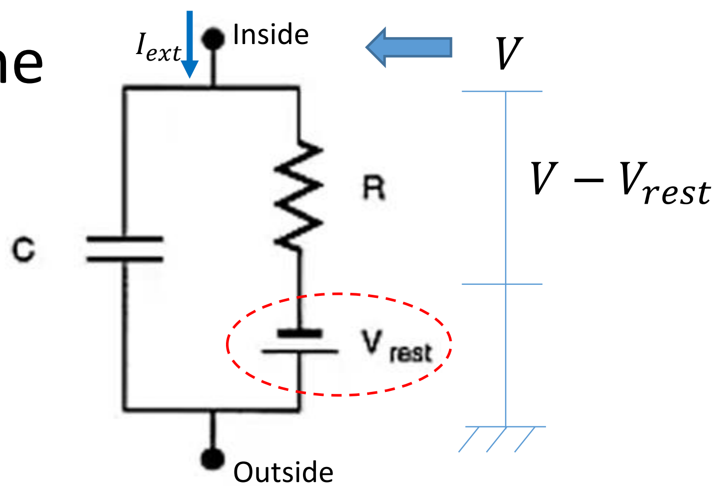
Leak Channels – The Cell Has A Battery

- The membrane encloses a solution in which concentrations of ions are different from outside



- This difference in ion concentrations can be modeled by a **potential difference** V_{rest} across the membrane

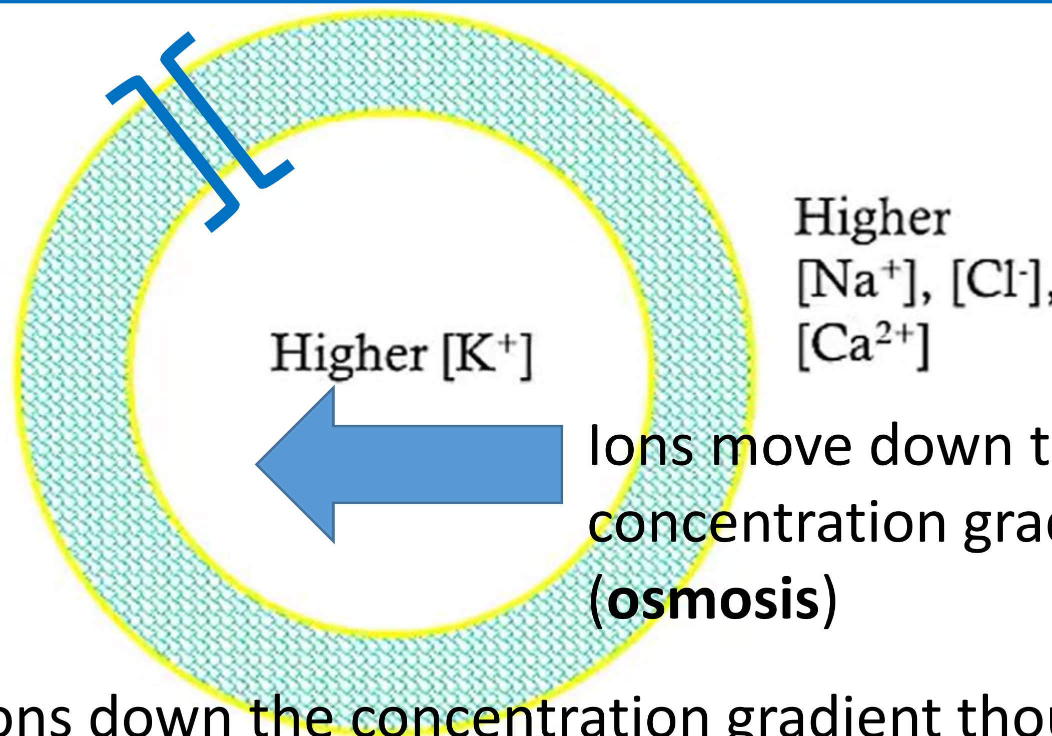
$$\boxed{C\frac{dV}{dt} = -\frac{(V - V_{rest})}{R} + I_{ext}}$$



➢ ***Let's see how this potential difference is derived***

Leak Channels –
The Cell Has A Battery

Until opposed by **electrostatic** forces

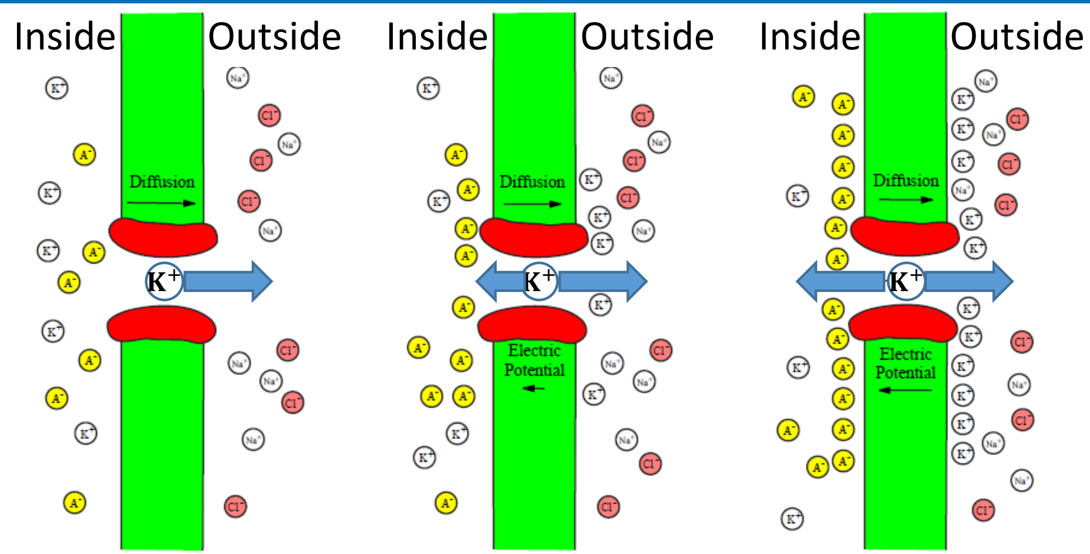


Ions move down their concentration gradient (**osmosis**)

- ***Diffusion*** of K^+ ions down the concentration gradient though the membrane (due to osmosis)
- This creates an ***electric potential*** force directed at the opposite direction
- And continues until the diffusion and electrical forces ***counter each other***

Eugene Izhikevich “Dynamical Systems in Neuroscience”, 2010

Leak Channels –
The Cell Has A Battery



(a) (b) (c)

- The resulting transmembrane potential is referred to as ***Nernst equilibrium potential*** for K^+

- Each ion type has its own equilibrium potential (i.e. if only that ion was allowed to diffuse through the membrane)

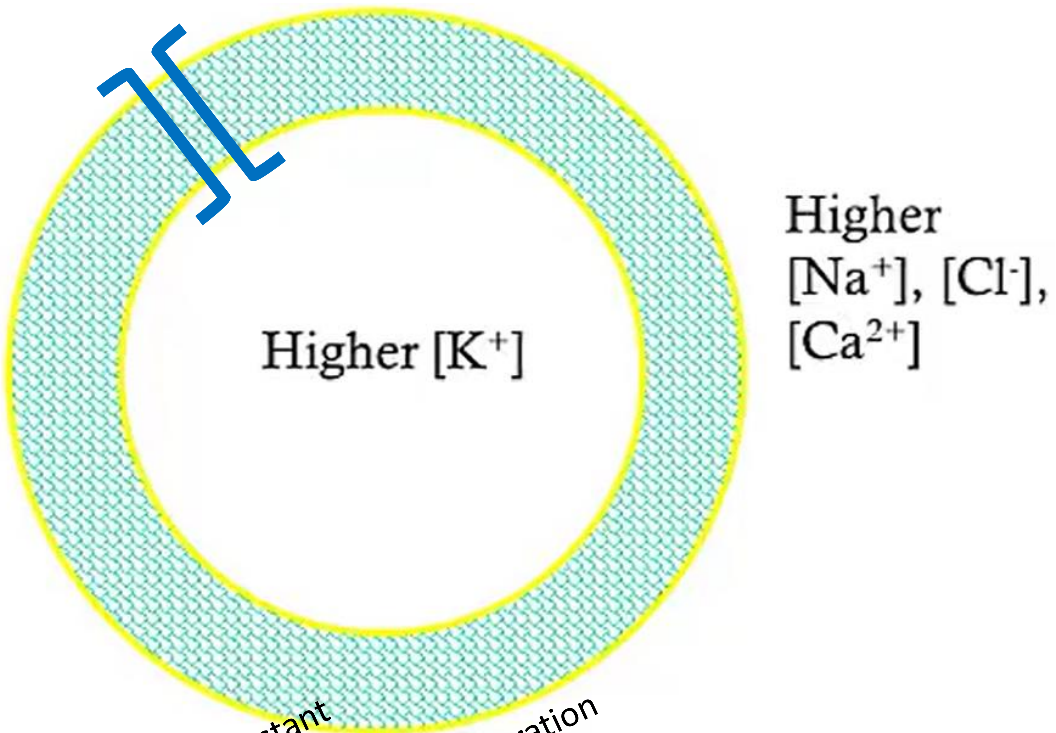
$$\boldsymbol{E_{Na} \sim 50\ mV}$$
$$E_{Ca} \sim 150\ \mathrm{m}V$$
$$\boldsymbol{E_K \sim -80\ mV}$$
$$E_{Cl} \sim -60\ \mathrm{m}V$$

→ Resulting in an equivalent potential (the neuron's resting potential) about $\boldsymbol{-70\ mV}$

Eugene Izhikevich "Dynamical Systems in Neuroscience", 2010

Leak Channels – The Cell Has A Battery

Extra Info



At equilibrium:

Boltzman's constant
Temperature
Ion concentration inside

Nernst potential: $E = \frac{K_B T}{z\,q} \ln \frac{[\text{inside}]}{[\text{outside}]} = \frac{V_T}{z} \ln \frac{[\text{inside}]}{[\text{outside}]}$

No. of protons
Charge of proton
Ion concentration outside

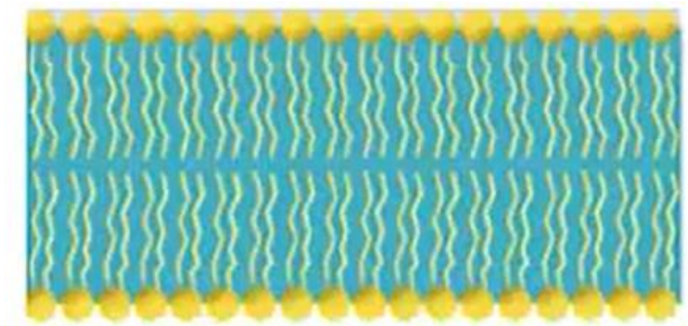
$$E_{Na} \sim 50\text{ mV}$$
$$E_{Ca} \sim 150\text{ mV}$$
$$E_K \sim -80\text{ mV}$$
$$E_{Cl} \sim -60\text{ mV}$$

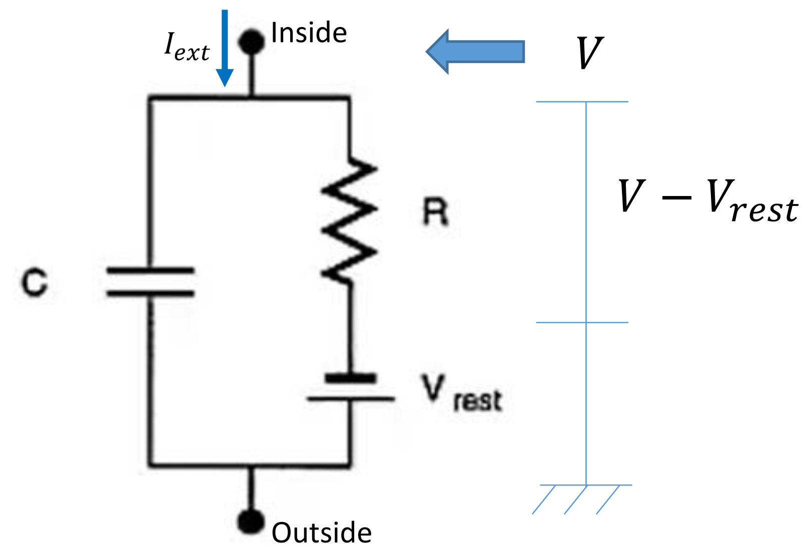
(This equilibrium potential is calculated for each ion type)

V_T is around 24-27 mV

Leak Channels –
The Cell Has A Battery

- The voltage drop across the resistor is decreased by the amount V_{rest} (i.e. it will be $V - V_{rest}$)



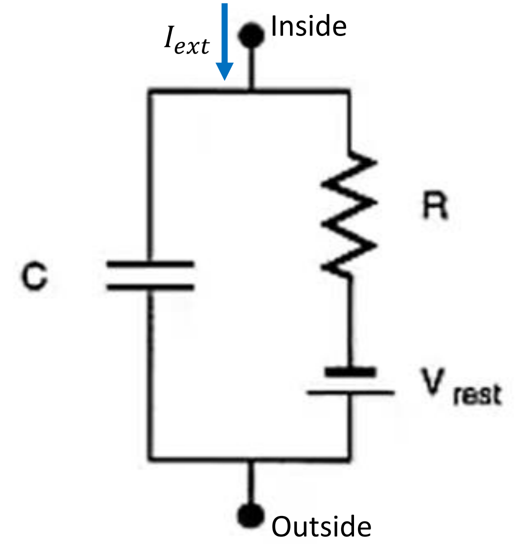


$$C\frac{dV}{dt} = -\frac{(V - V_{rest})}{R} + I_{ext}$$

Leak Channels –
The Cell Has A Battery

- Let's compare the form of the differential equation with a familiar form:

$$C\frac{dV}{dt} = -\frac{(V - V_{rest})}{R} + I_{ext}$$



Define:

$$\tau = RC$$

V_∞: steady state solution

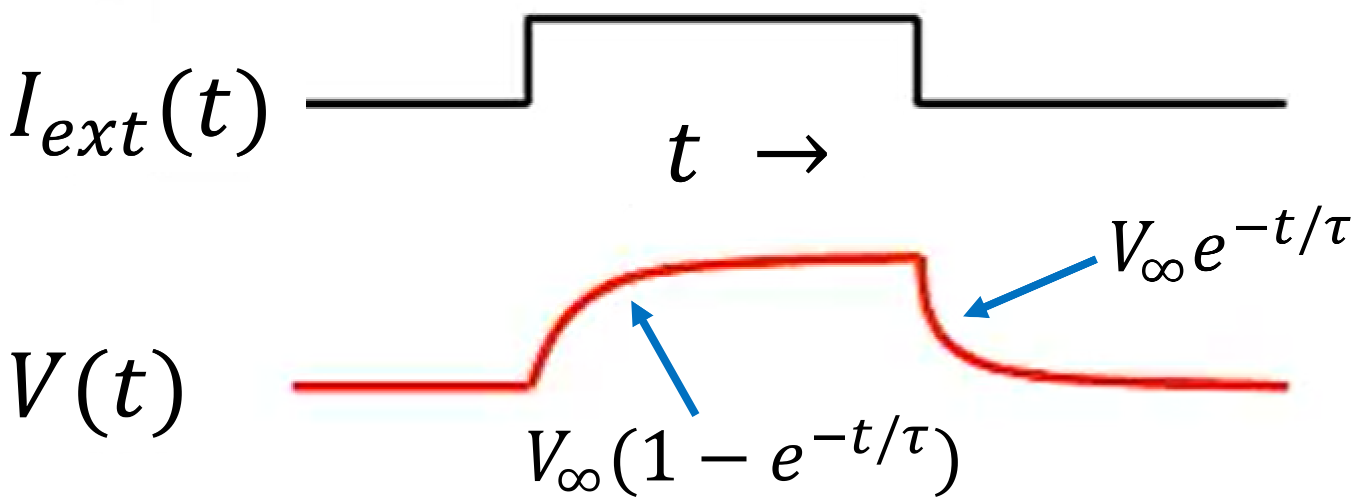
$$\left(\frac{dV}{dt} = 0\right) \rightarrow \quad V_\infty = V_{rest} + RI_{ext}$$

$$\boxed{\tau\frac{dV}{dt} = -V + V_\infty \quad , \quad V_\infty = V_{rest} + RI_{ext}}$$

Leak Channels – The Cell Has A Battery

$$\tau \frac{dV}{dt} = -V + V_\infty \qquad\qquad V_\infty = V_{rest} + RI_{ext}$$

- For an input current in the form of a pulse:



Voltage-gated Channels

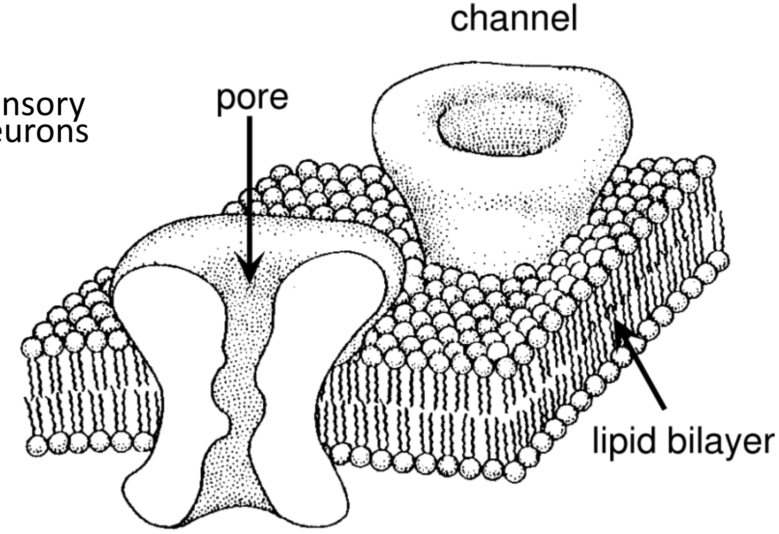
Currents Flow through Ion Channels

- Ion channels distinguish between different ions

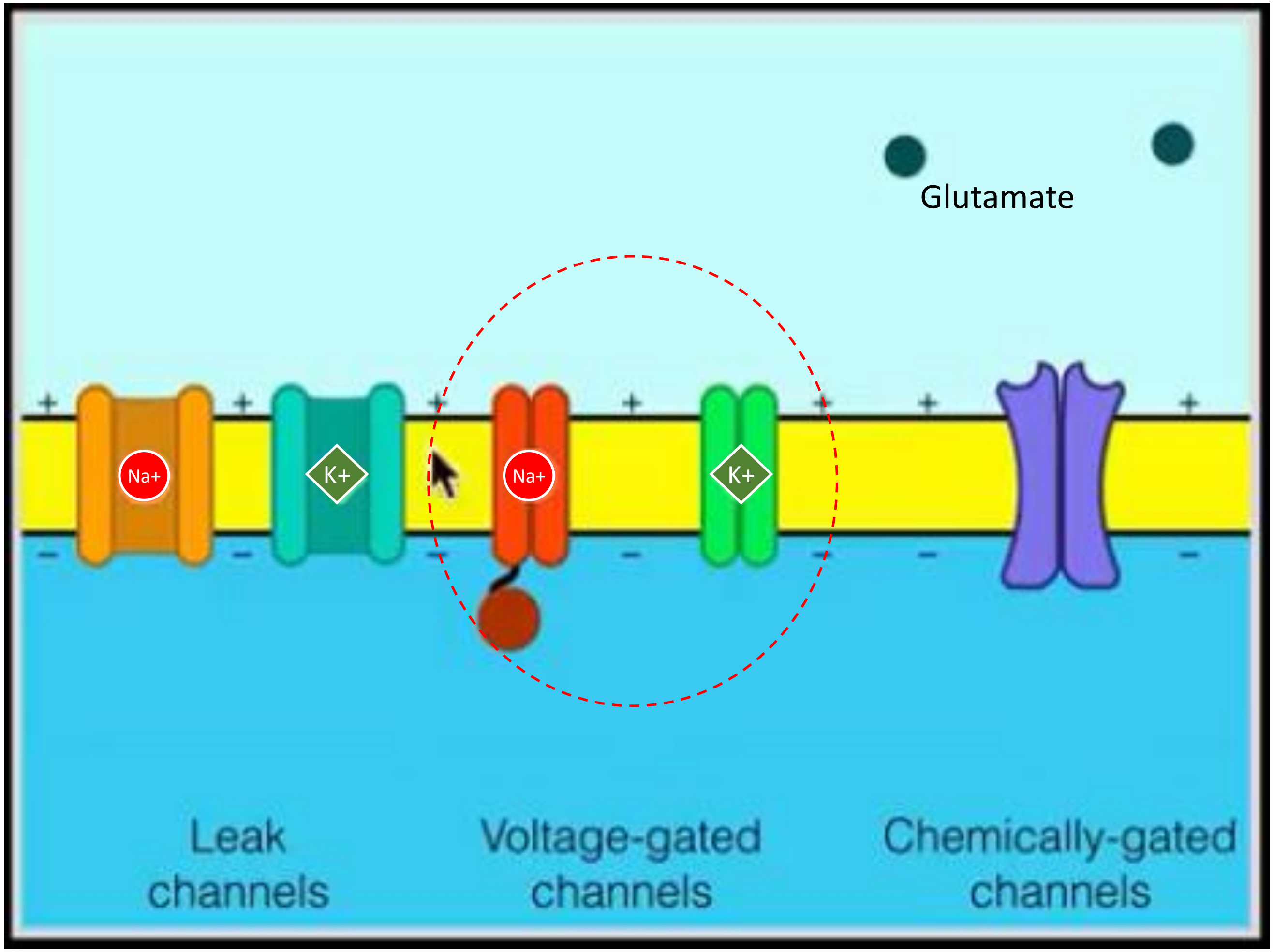
→ Different ions have different rates of transport between inside and outside the neuron

- Ion channels are of many types:
  - Neurotransmitter-dependent (synaptic) ←(we'll model these later)
  - Voltage-dependent ←(we'll first learn about these)
  - Ca-dependent
  - Mechanosensitive
  - Heat sensitive

Sensory neurons



Ionic Channels –
Voltage-Gated Channels



Paul Andersen, BozemanScience.com

Voltage-Gates Channels –
A Battery for Each Ion Type

- Different ion channels have associated ***conductances***
- A given conductance tends to move the membrane potential toward the equilibrium potential for that ion

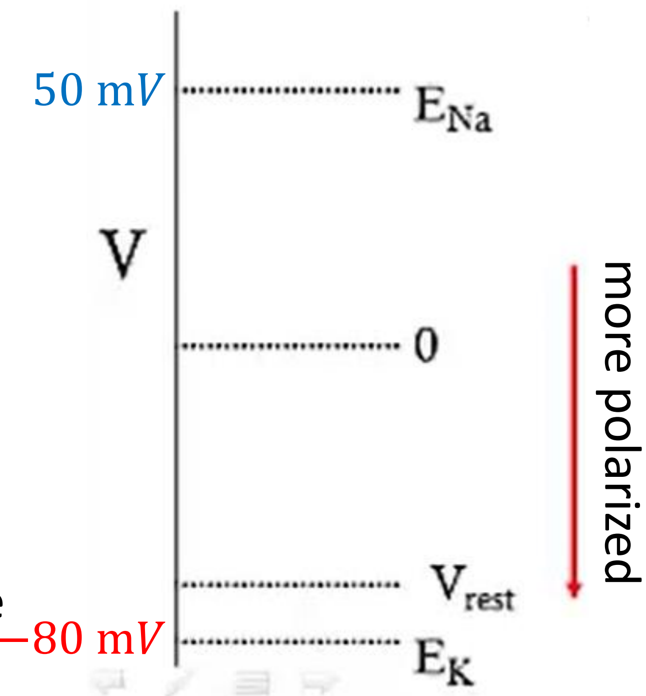
$$E_{Na} \sim 50\ \mathrm{m}V$$

$$E_{Ca} \sim 150\ \mathrm{m}V$$

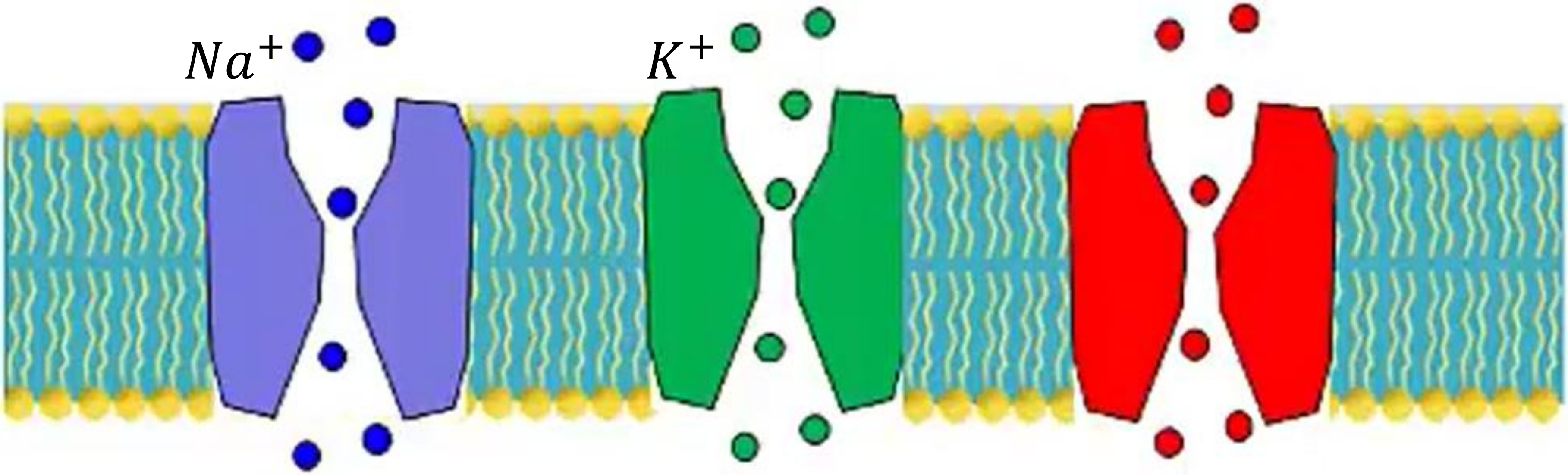
$$E_K \sim -80\ \mathrm{m}V$$

$$E_{Cl} \sim -60\ \mathrm{m}V$$

- We will focus on Na and K currents:
  - Na current tends to ***depolarize*** the membrane (i.e. move it towards more positive potentials)
  - K current tends to ***hyperpolarize*** the membrane (i.e. move it towards more negative potentials)

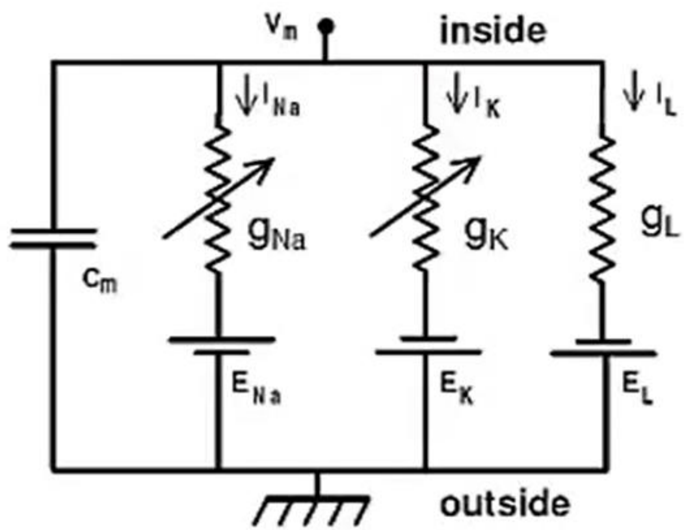


Equivalent Circuit Model



Parallel paths for different ions:

$$I_i = g_i(V - E_i)$$

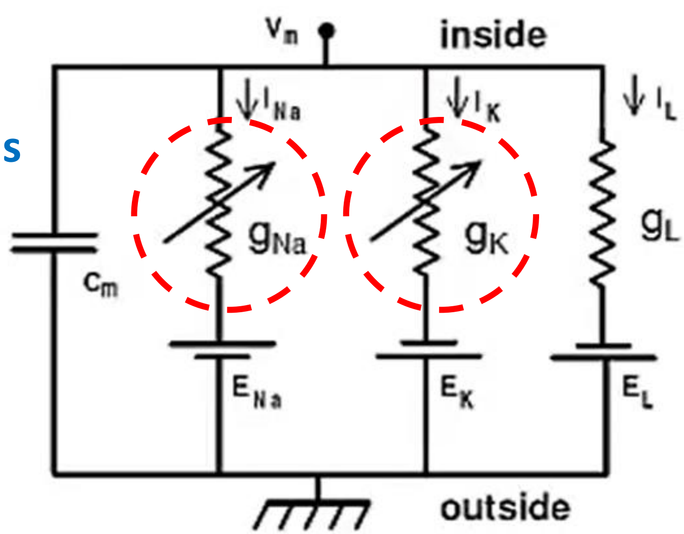


Leakage conductance

Equivalent Circuit Model

- The ***variable conductances*** associated with the ion channels make the model much more interesting

Variable conductances of *Na* and *K* channels

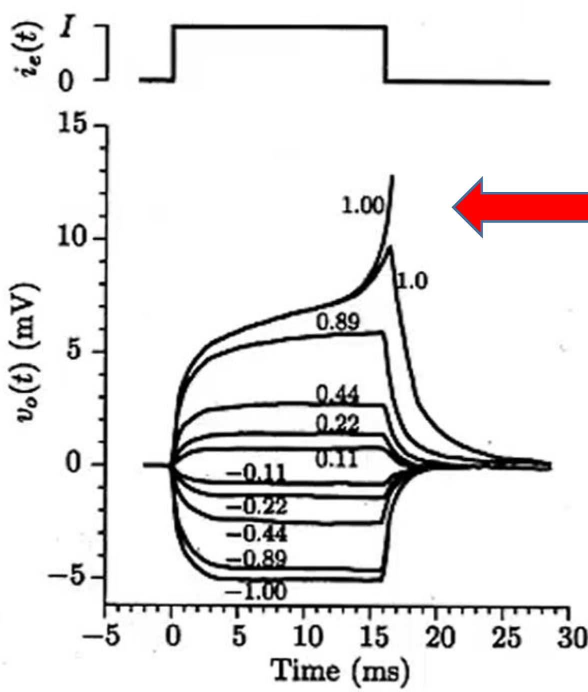


Leakage conductance

What Makes a Neuron To Compute?

- Instead of producing a linear response to the input, the neuron responds in an interesting fashion
- This is due to the ***nonlinearities*** of the ion channel conductances

Voltage response to various values of input current

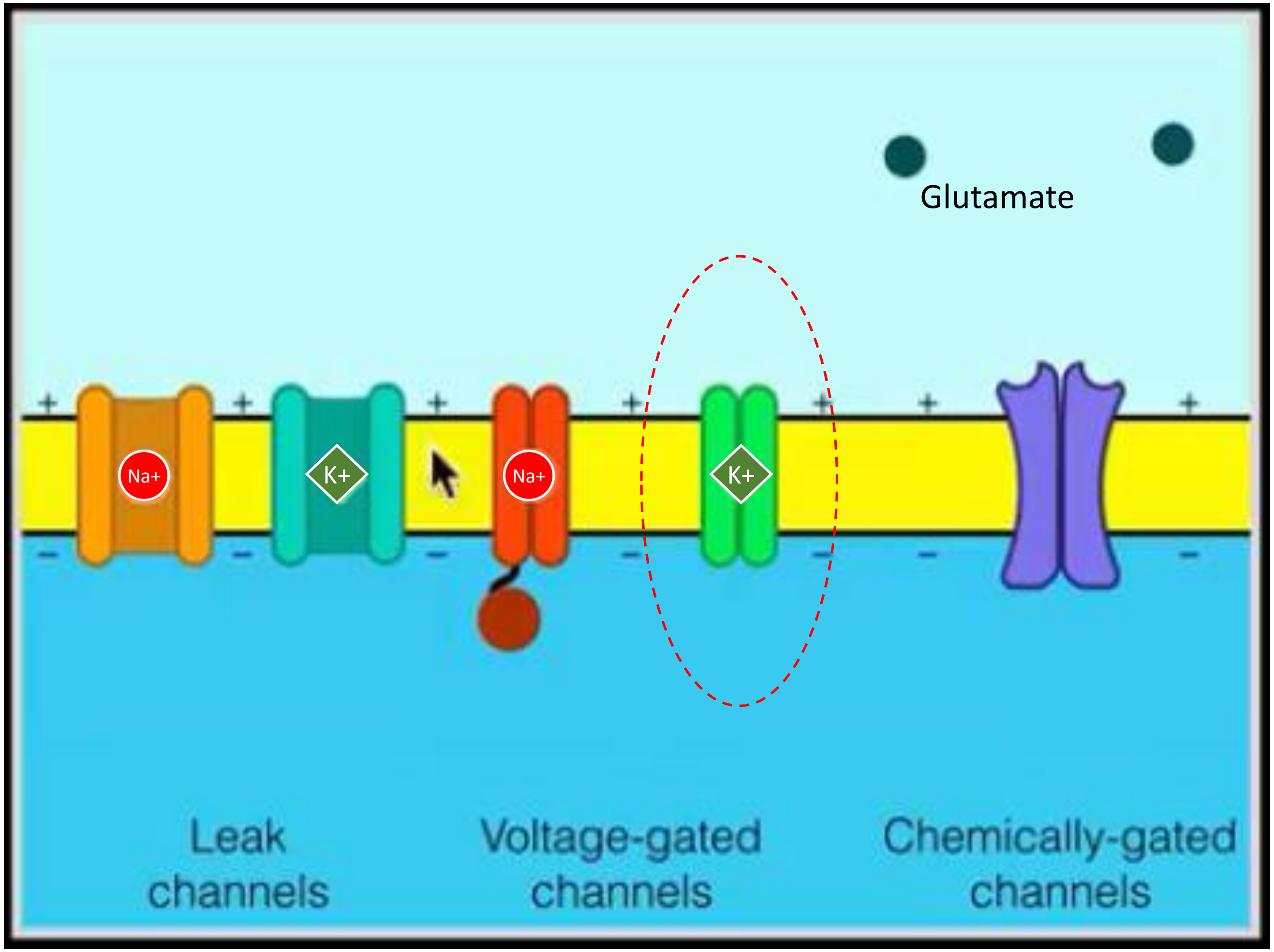


Excitability

Linear behavior

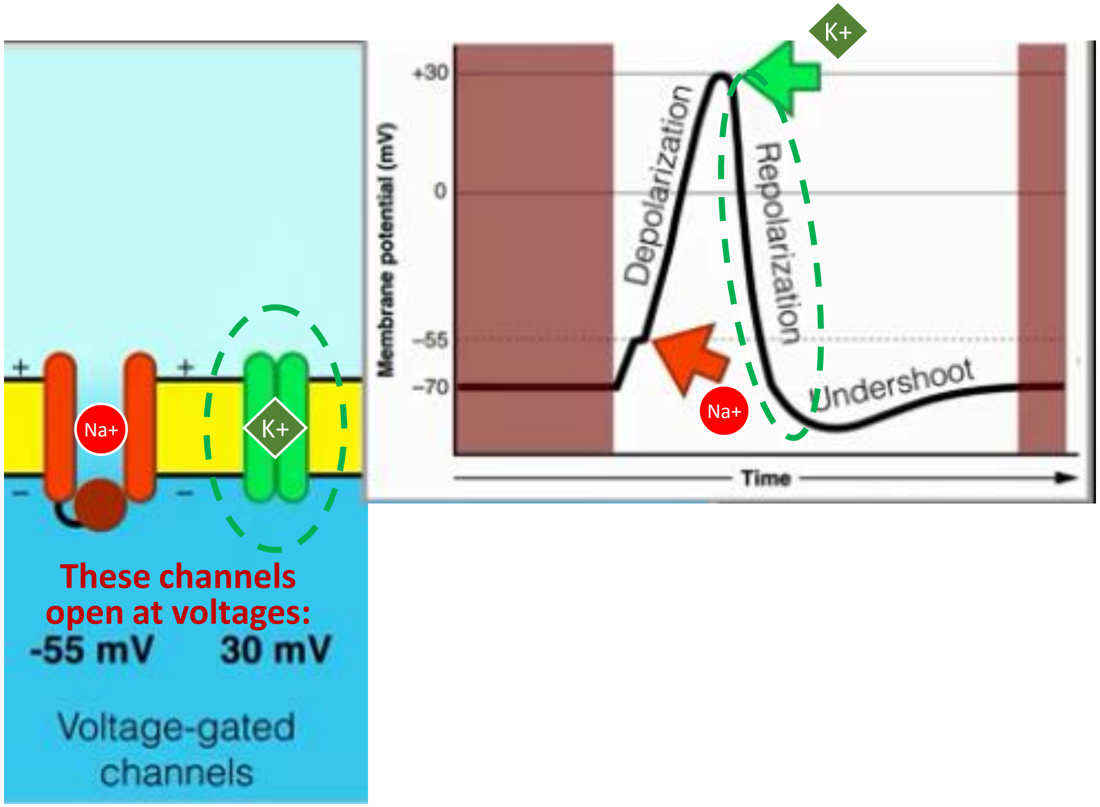
➢ ***We will see how the nonlinear behavior leads to spiking***

Voltage-Gated Channels –
The Potassium Channel



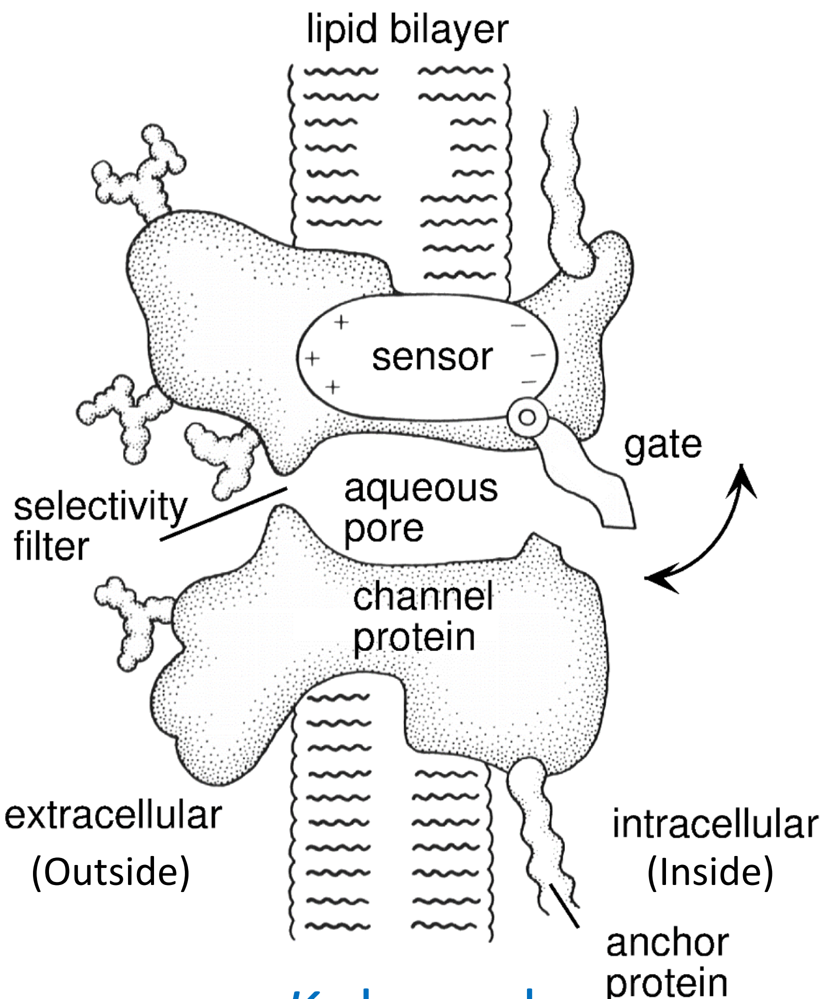
Paul Andersen, BozemanScience.com

Voltage-Gated Channels – The Potassium Channel



Paul Andersen, BozemanScience.com

The Potassium Channel –
A Cool Molecular Machine



K channel

- The potassium channel contains:
  - **A gate:** Controls the entrance of ions
  - **A voltage sensor:** Controls the configuration of the gate
- The probability of ***gate open*** increases when the neuron is **depolarized** (i.e. with increasing voltage)

The Potassium Channel – A Cool Molecular Machine

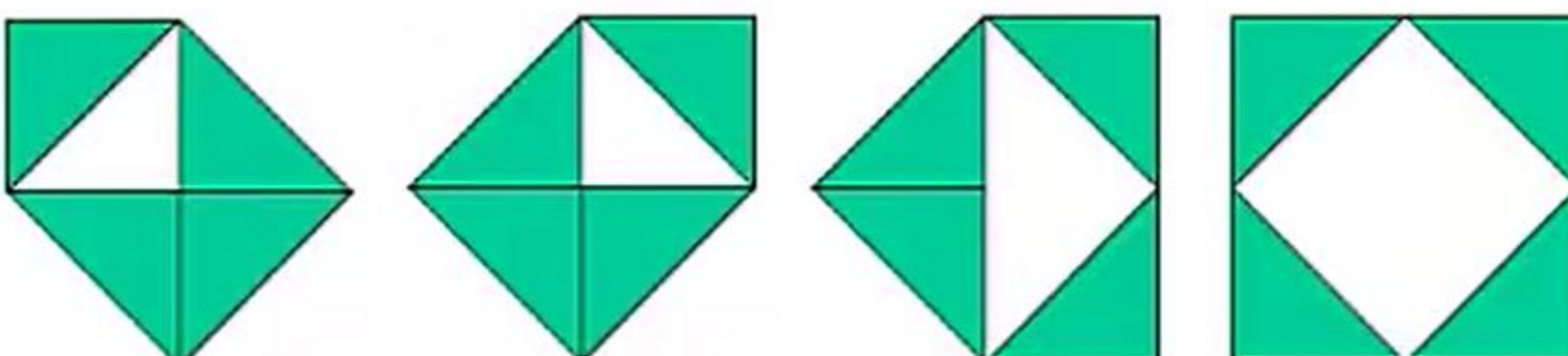
A simplified model for the gate

- The gate has 4 sub-units
  - All 4 need to be in the correct configuration for the ions to go through
- Let n describe the status of a sub-unit:

  n: open probability

  $1 - n$: closed probability
- For the channel to be open (assume independent sub-units):

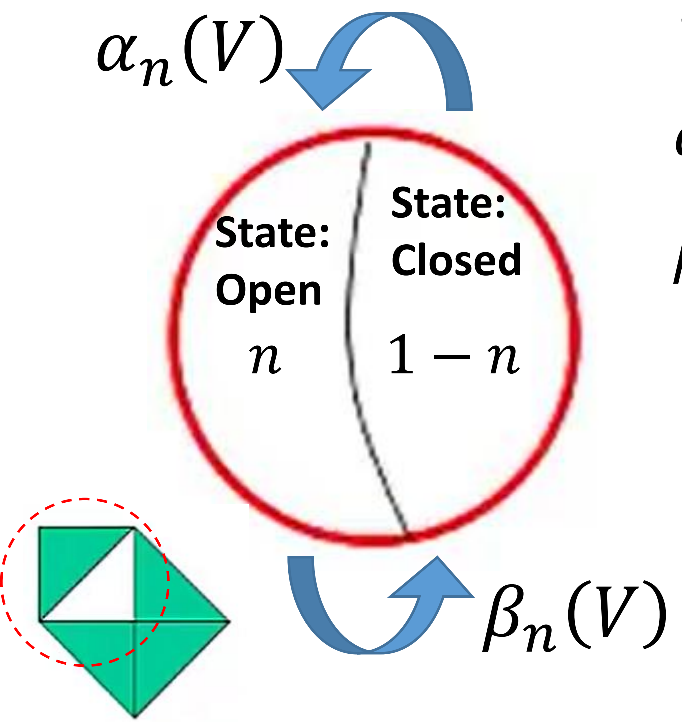
$$\boxed{P_K \sim n^4}$$



One sub-unit open Two sub-units open All sub-units open

The Potassium Channel – A Cool Molecular Machine

- To calculate the dynamics of the probability of having a sub-unit open:
  - We need to consider transitions between the states of the sub-unit

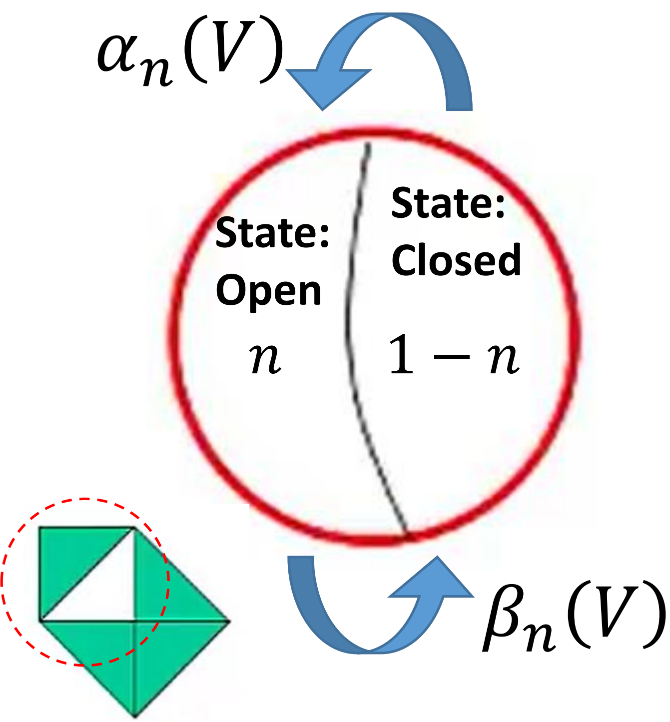


- Transitions between states occur at ***voltage-dependent*** rates:

$\alpha_n(V)$: Rate of transition from **Closed to Open**

$\beta_n(V)$: Rate of transition from **Open to Closed**

The Potassium Channel – A Cool Molecular Machine



- Probability that a sub-unit **opens** over a short interval Δt: $(1-n)\,\alpha_n(V)\Delta t$

  Probability of being closed
  x Rate of transition from closed to open
  x Time interval

- Probability that a sub-unit **closes** over a short interval Δt: $n\,\beta_n(V)\Delta t$

  Probability of being open
  x Rate of transition from open to closed
  x Time interval

- The ***open probability*** of a sub-unit changes over Δt as:

$$\Delta n = [\alpha_n(V)(1-n) - \beta_n(V)n]\Delta t$$

- The **rate** at which the open probability of a sub-unit changes over time:

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

The Potassium Channel – A Cool Molecular Machine

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

- Rewrite the differential equation in the familiar form:

$$\frac{dn}{dt} = -n\big(\alpha_n(V) + \beta_n(V)\big) + \alpha_n(V)$$

(Dividing both sides by $\alpha_n(V) + \beta_n(V)$):

$$\Rightarrow \quad \frac{1}{\alpha_n(V) + \beta_n(V)} \frac{dn}{dt} = -n + \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}$$

- In canonical form:

$$\tau_n(V)\frac{dn}{dt} = -n + n_\infty(V)$$

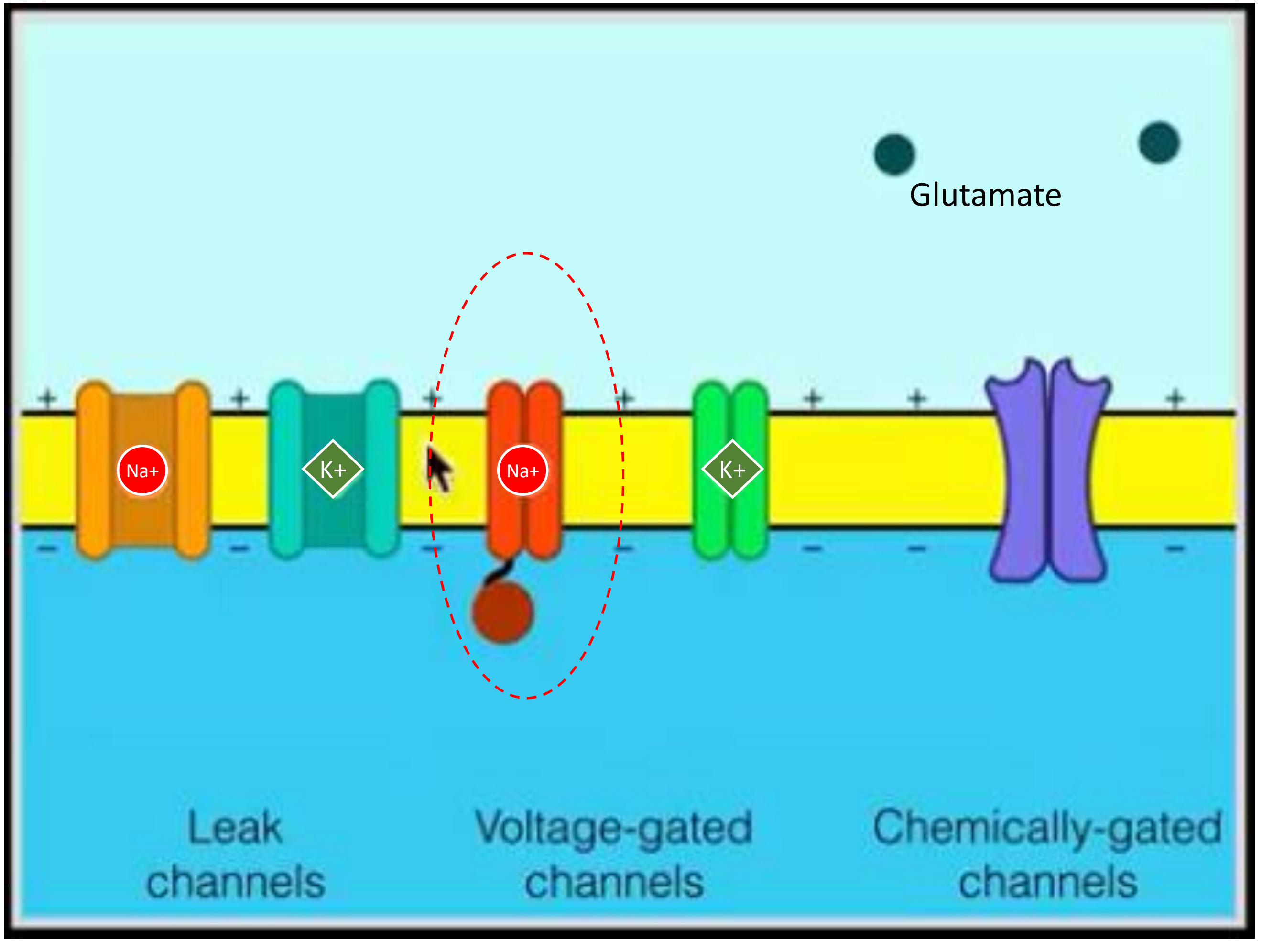
where:

$$\tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)} \qquad n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}$$

Note: $n_\infty(V)$ is the steady-state value of n (when $\frac{dn}{dt} = 0$)

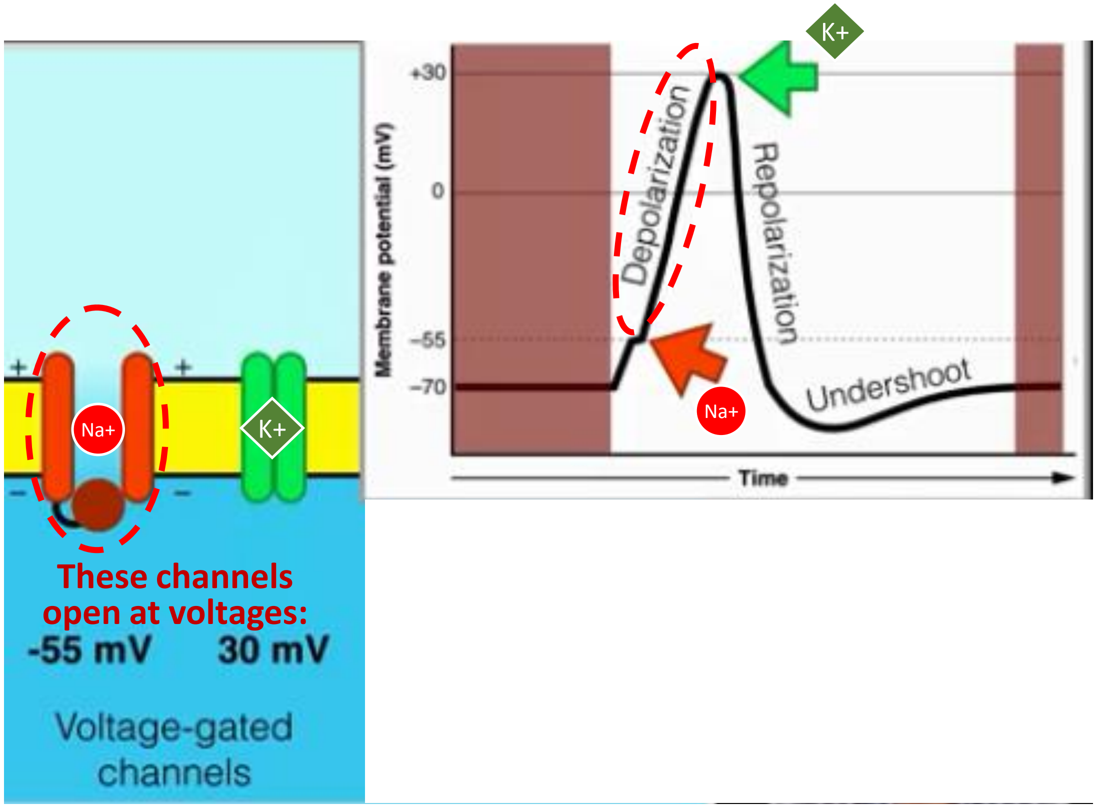
➢ ***We will next derive a similar model for the sodium channel***

Voltage-Gated Channels –
The Sodium Channel



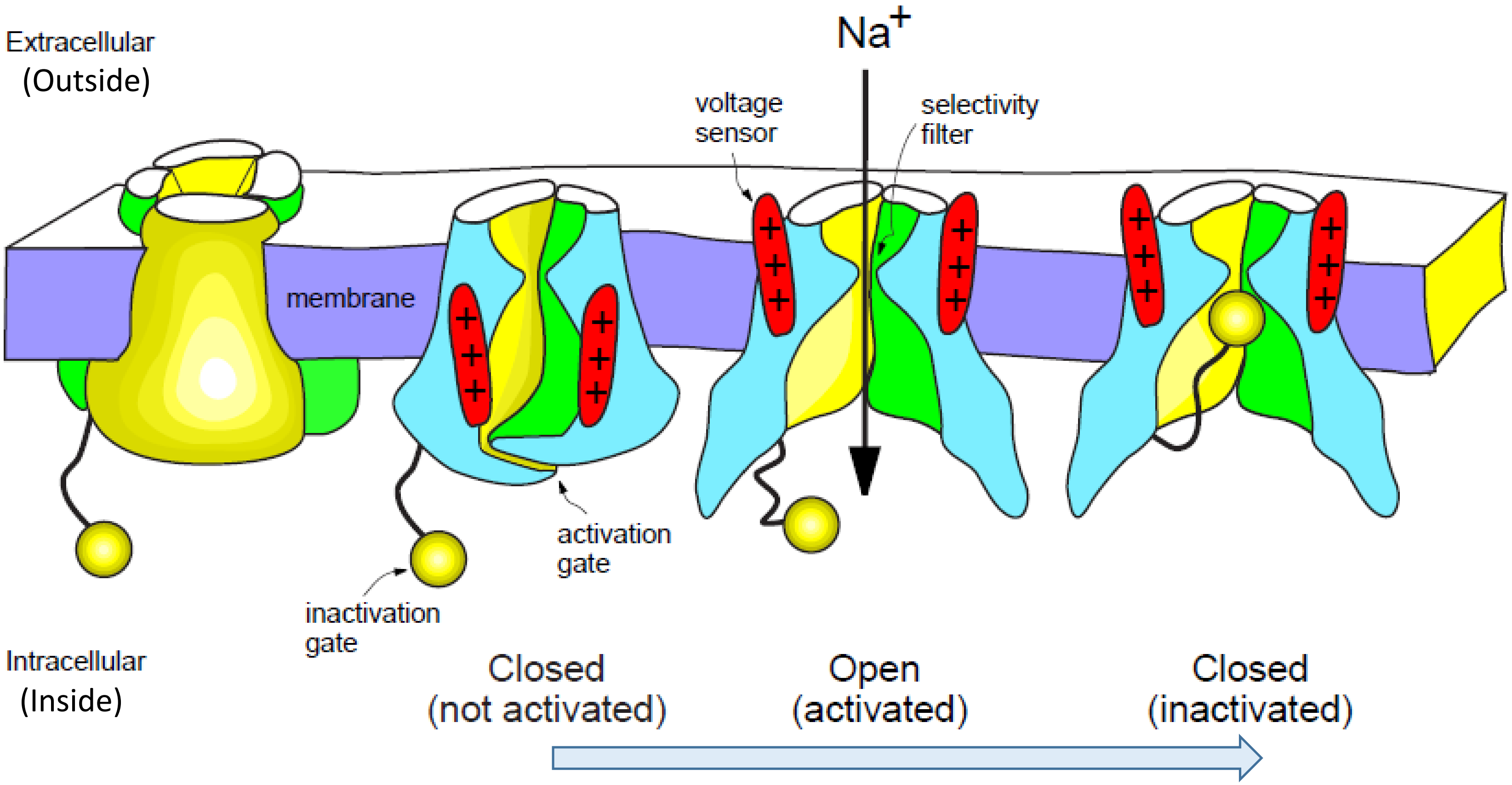
Paul Andersen, BozemanScience.com

Voltage-Gated Channels –
The Sodium Channel



Paul Andersen, BozemanScience.com

Voltage-Gated Channels –
The Sodium Channel

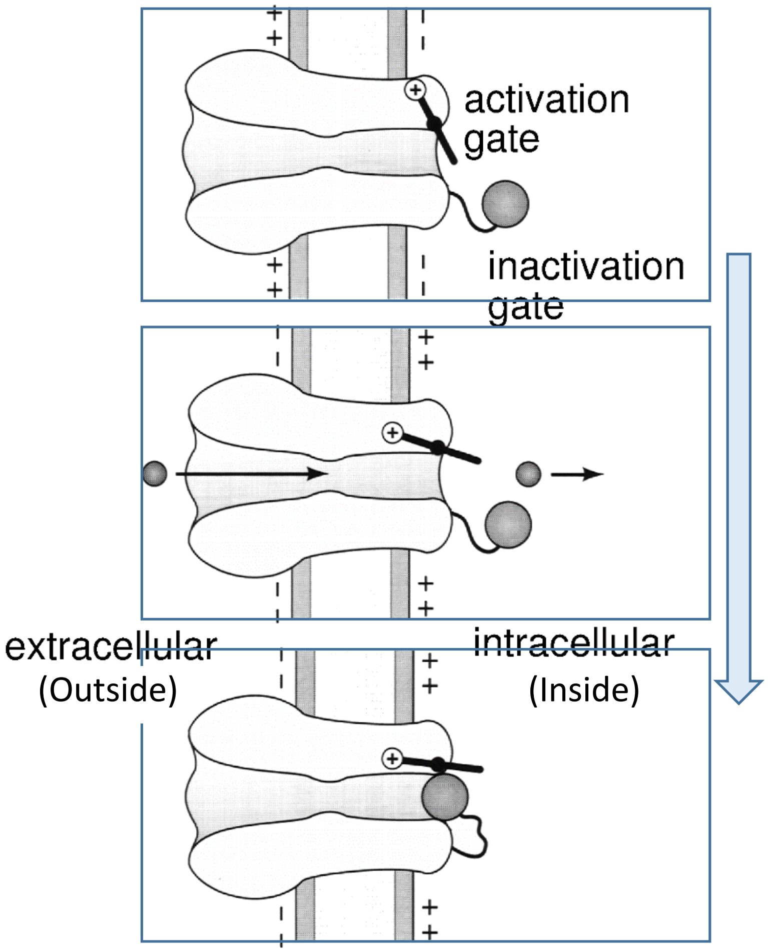


The sodium channel contains 2 different gates:

- **An activation gate**
- **An inactivation gate**

Eugene Izhikevich "Dynamical Systems in Neuroscience", 2010

The Sodium Channel – Transient Conductances



Na channel

- The sodium channel contains 2 different gates:
  - **An activation gate:** Controls the entrance of ions (like in the potassium channel) with **3 sub-units**

    (Probability of each sub-unit being open: m)

  - **An inactivation gate:** An additional gate which can block the channel when closed

    (Probability of gate being not closed: h)

- For the channel to be open:

$$\boxed{P_{Na} \sim m^3 h}$$

Dynamics of Activation and Deactivation

- we can write canonical forms for the sodium gates m and h (in terms of time constants and steady-state values):

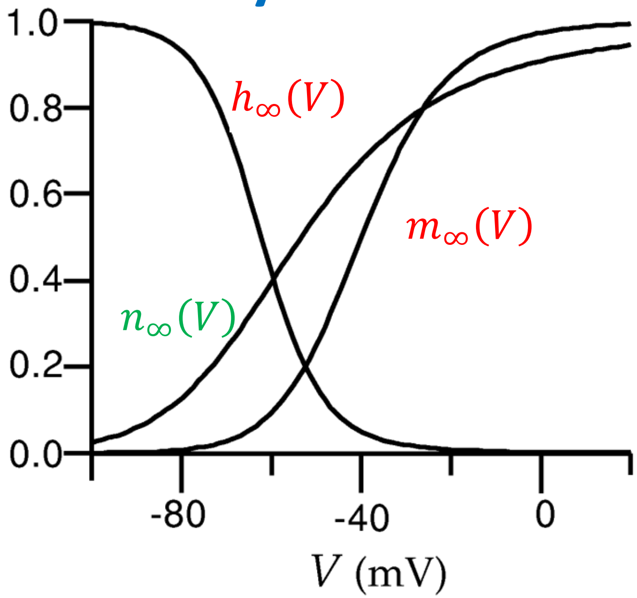
$$\tau_m(V)\frac{dm}{dt} = m_\infty(V) - m \qquad \tau_m(V) = \frac{1}{\alpha_m(V) + \beta_m(V)}, m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)}$$

$$\tau_h(V)\frac{dh}{dt} = h_\infty(V) - h \qquad \tau_h(V) = \frac{1}{\alpha_h(V) + \beta_h(V)}, \quad h_\infty(V) = \frac{\alpha_h(V)}{\alpha_h(V) + \beta_h(V)}$$

Dynamics of Activation and Inactivation

$\boxed{n_\infty(V), m_\infty(V), h_\infty(V)}$

Steady state values



- ***m* and *h* have opposite voltage dependencies:**
- **Depolarization (voltage increase):**
  - **Increases *m***
  - **Decreases *h***

→ There is an activation window for *Na* channel

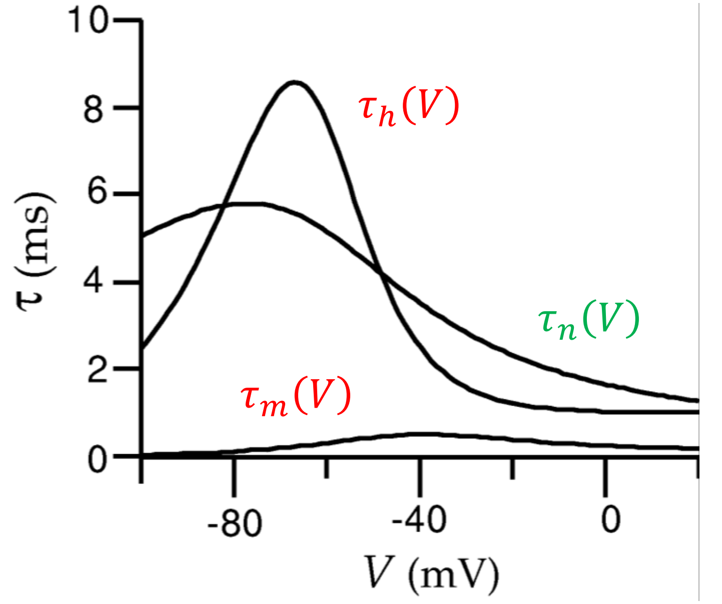
This is where each variable is going with change of voltage

- Activation steady-state values depend on voltage
- They all have sigmoidal forms

Dynamics of Activation and Inactivation

$\boxed{\tau_n(V), \tau_m(V), \tau_h(V)}$

Time constants



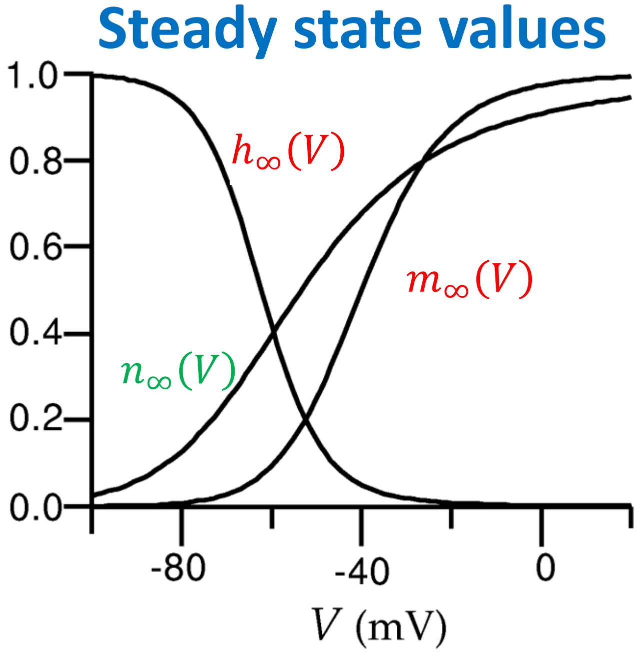
This is how fast it gets there

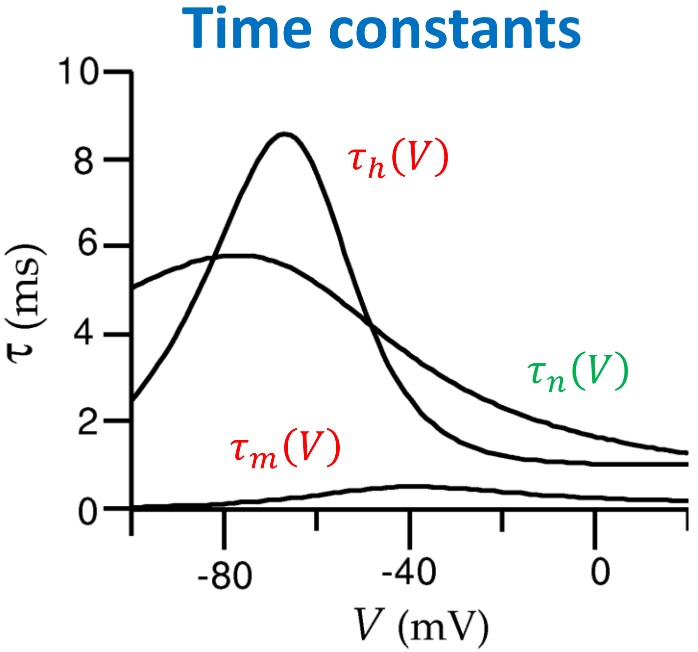
- Time constant values also depend on voltage
- The sodium activation channel m has the shortest time constant (it rapidly opens with an increase in voltage)

Dynamics of Activation and Inactivation

$n_\infty(V), m_\infty(V), h_\infty(V)$

$\tau_n(V), \tau_m(V), \tau_h(V)$





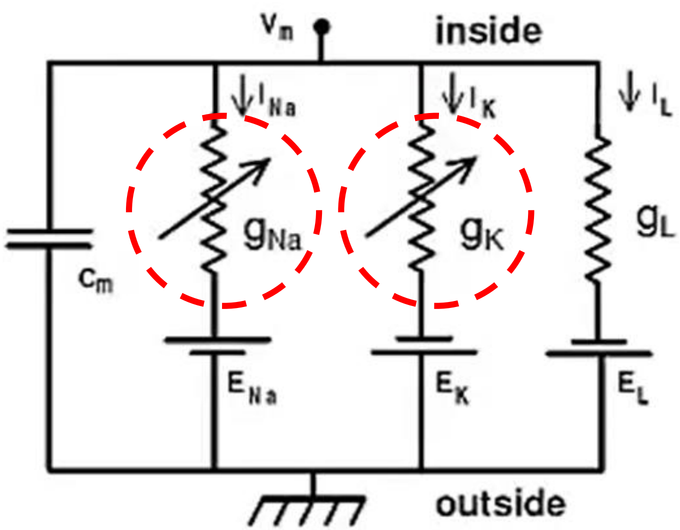
This is where each variable is going with change of voltage

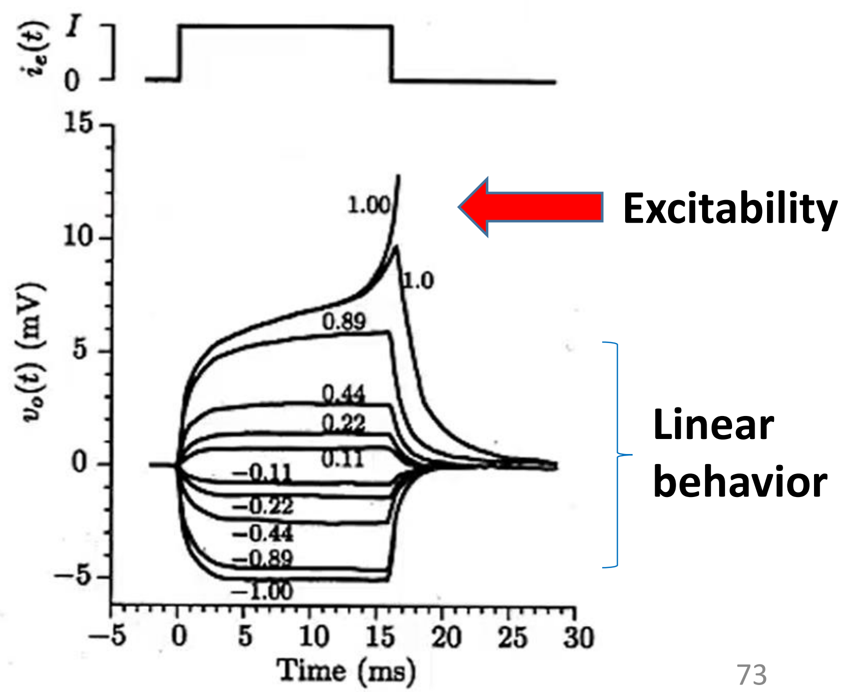
This is how fast it gets there

Anatomy of A Spike

Equivalent Circuit Model

- The ***variable conductances*** associated with the ion channels make the model much more interesting
- This is due to the ***nonlinearities*** of the ion channel conductances





Dynamics of Activation and Deactivation

- Conductances of the channels:

$$g_K(V) = \overline{g_K}\, n^4$$

$$g_{Na}(V) = \overline{g_{Na}}\, m^3 h$$

$\overline{g_K}$ and $\overline{g_{Na}}$ are the total (maximum) conductances of the channels

are thus ***voltage dependent***

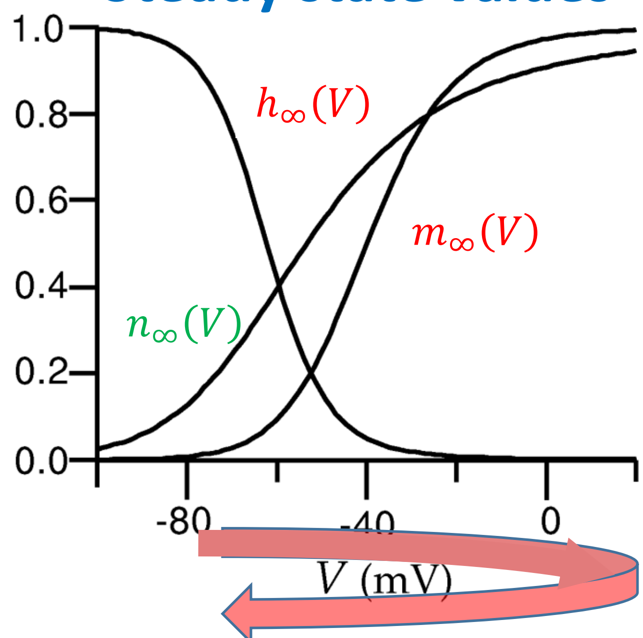
- All n, m and h values have ***time constants*** in their dynamic behavior

$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n$$
$$\tau_m(V)\frac{dm}{dt} = m_\infty(V) - m$$
$$\tau_h(V)\frac{dh}{dt} = h_\infty(V) - h$$

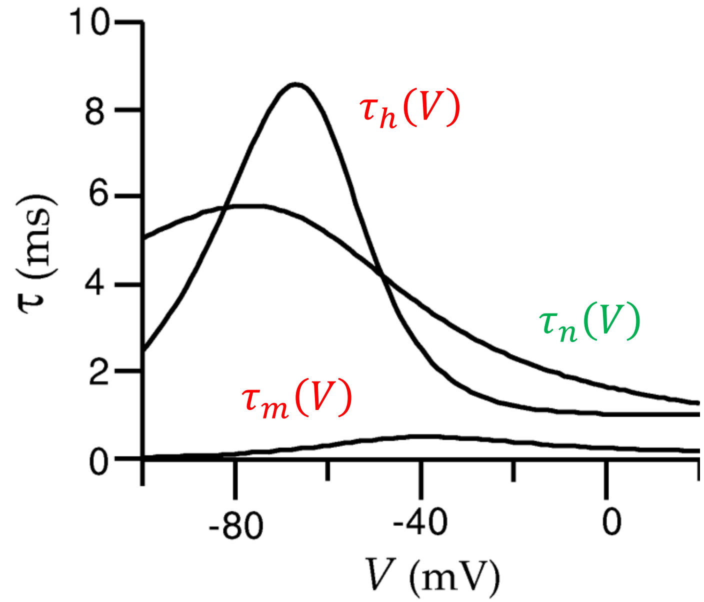
→ This causes the channel conductances g_K and g_{Na} to also depend on these time dynamics

Dynamics of Activation and Inactivation

Steady state values



Time constants



As voltage increases:

Rapid increase in voltage and then slowing

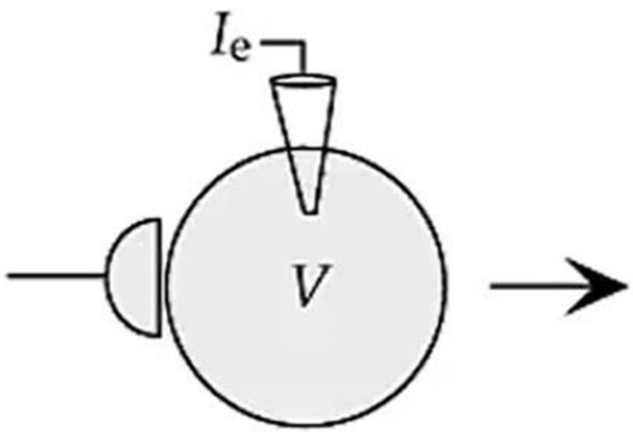
- The sodium channel <u>first</u> opens (a small τ_m) → $m_\infty \to 1$
- But <u>then</u> closes (a larger τ_h) → $h_\infty \to 0$

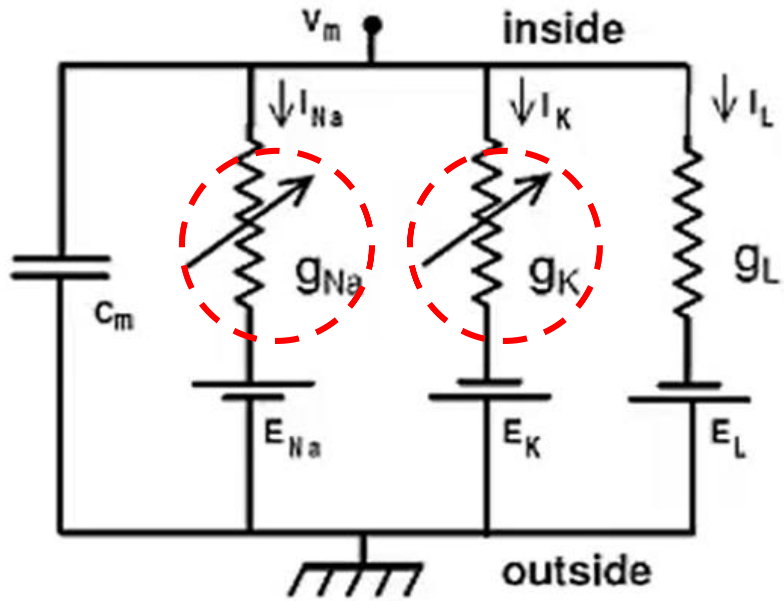
$m^3 h \to 0$

Decrease in voltage towards hyperpolarization

- The potassium channel is activated <u>after</u> the opening of the sodium channel ($\tau_n > \tau_m$), and has a higher probability of being open for larger voltages → $n_\infty \to 1$

Equivalent Circuit Model – Summary





(Leakage current)

Ohm's law for conductances:

$$V - E_i = R_i \, I_i \quad \rightarrow \quad I_i = g_i(V - E_i)$$

All currents:

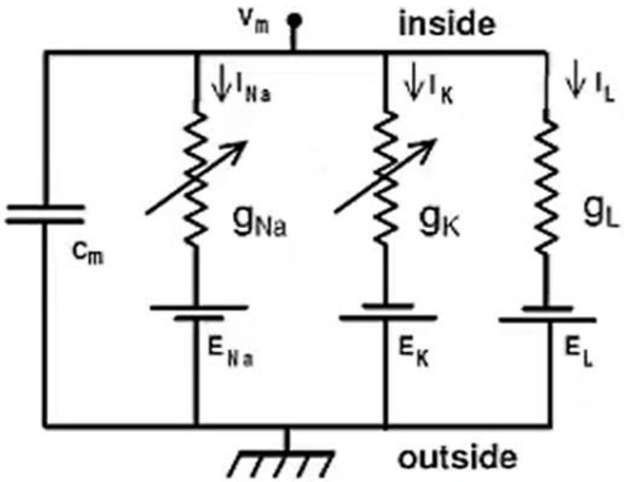
$$C_m \frac{dV}{dt} + \sum_i g_i(V - E_i) = I_{ext}$$

Capacitive current Ionic currents Externally applied current

Hudgkin and Huxley's Nobel Equation

$$C_m \frac{dV}{dt} = -\sum_i g_i(V - E_i) + I_{ext}$$

$$-C_m \frac{dV}{dt} = g_L(V - E_L) + \overline{g_K}\, n^4(V - E_K) + \overline{g_{Na}}\, m^3 h(V - E_{Na}) - I_e$$



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

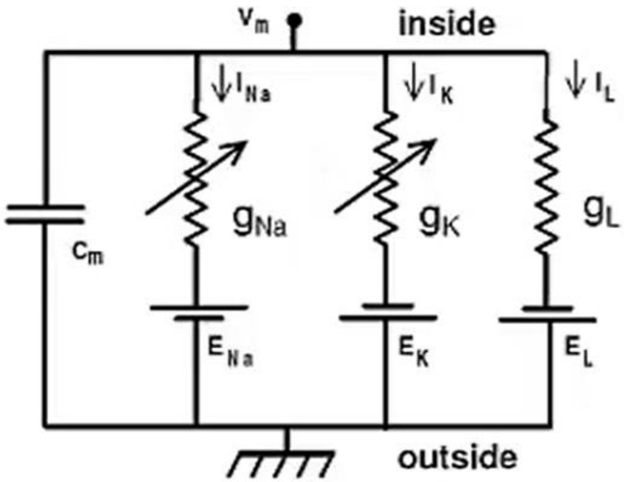
$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m$$

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

Hudgkin and Huxley's Nobel Equation

$$C_m \frac{dV}{dt} = -\sum_i g_i (V - E_i) + I_{ext}$$

$$-C_m \frac{dV}{dt} = g_L(V - E_L) + \overline{g_K}\, n^4 (V - E_K) + \overline{g_{Na}}\, m^3 h (V - E_{Na}) - I_e$$



- The dynamics are explained by a differential equation with 2 nonlinear effects:
  1. Multiplicative factors relating the sub-unit behavior to channel conductances
  2. Voltage dependence of the sub-unit dynamics

Hudgkin and Huxley’s Nobel Equation

Studies of spike-generation mechanism in “giant squid axons” won Alan Hodgkin and Andrew Huxley the 1963 Nobel prize in physiology or medicine

Eugene Izhikevich “Dynamical Systems in Neuroscience”, 2010

Variants of Hudgkin and Huxley's Equation

$$C_m \frac{dV}{dt} = I_e - g_L(V - E_L) - g_{Na} m^3 h\,.(V - E_{Na}) - g_K n^4\,.(V - E_K)$$

- General form of the Hudgkin-Huxley gate model:

$$I = \bar{g} m^a h^b (V - E)$$

See Izhikevich Sec. 5.1 and 5.1.2

- A variant of the Hudgkin-Huxley equation:

$$C_m \frac{dV}{dt} = I_e - \underbrace{g_L(V - E_L)}_{\text{Leak } I_L} - \underbrace{g_{Na} m_\infty(V)\,.\,(V - E_{Na})}_{\textbf{Instantaneous } I_{Na,p}} - \underbrace{g_K n\,.(V - E_K)}_{\text{Slower } I_K}$$

with a second equation modeling the slower potassium channel dynamics:

$$\tau(V)\frac{dn}{dt} = -n + n_\infty(V)$$

- This is called the $I_{Na,p} + I_K$ (**Persistent *Na* plus *K***) model
  - **Persistent current**: No inactivation gate involved (no h gate) for *Na* channel
  - **Instantaneous current**: Small time constant τ_m (i.e. $m_\infty(V)$ is reached instantly)

The Output of a Neuron: Action Potential – Summary

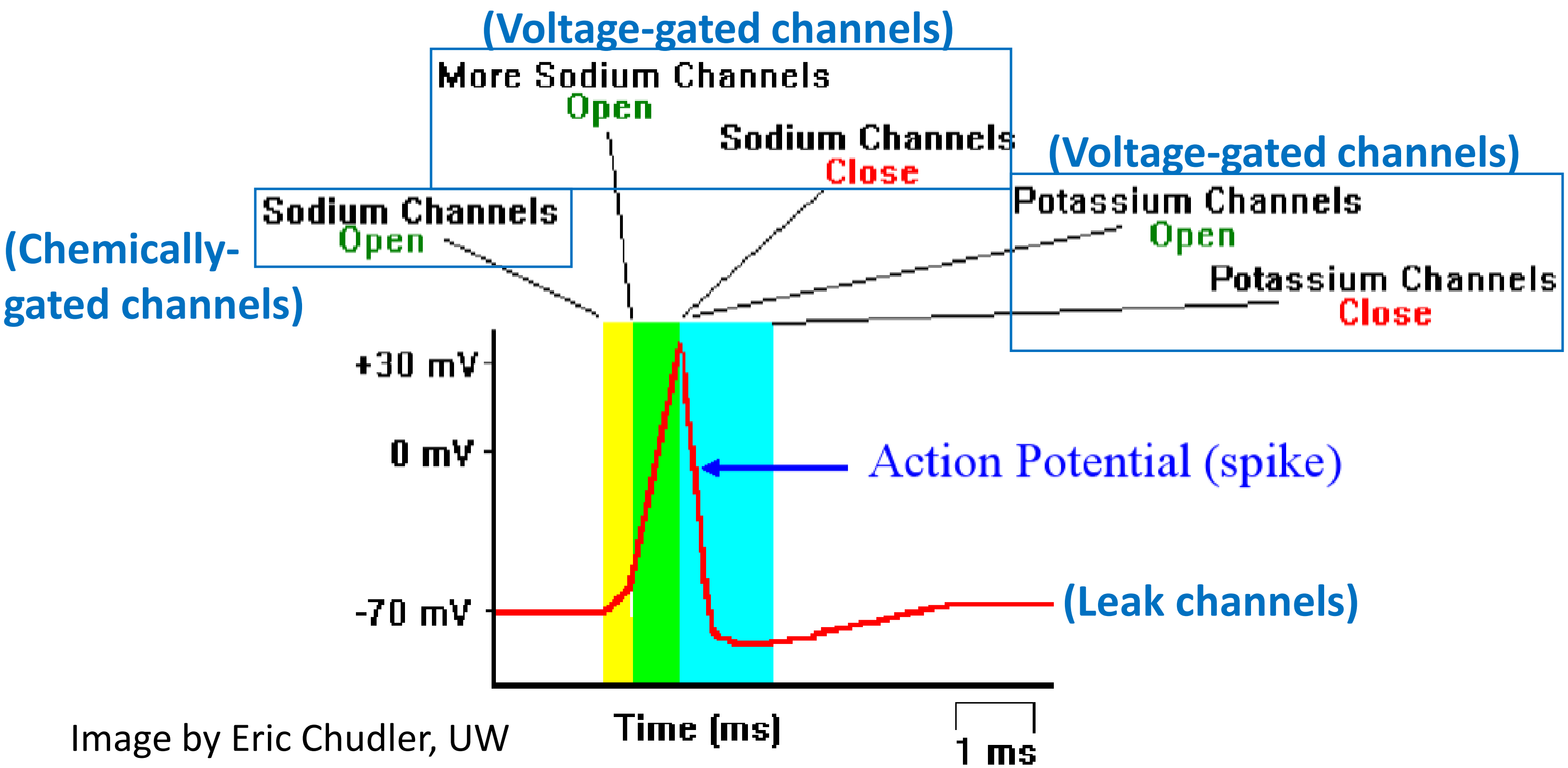
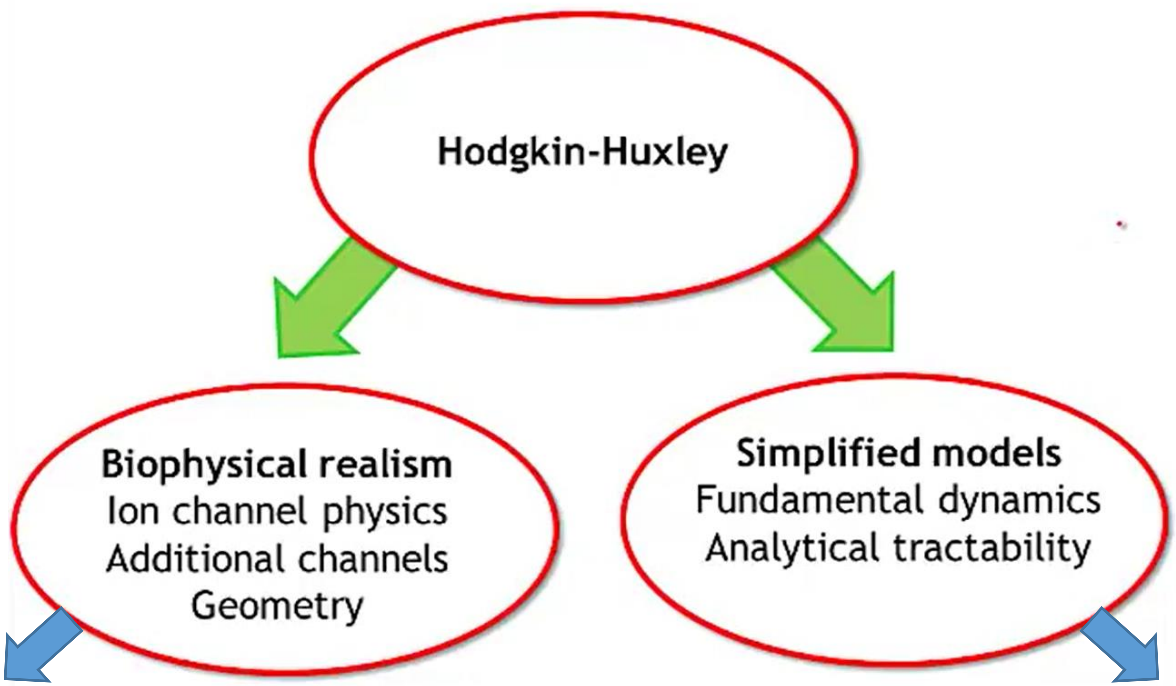


Image by Eric Chudler, UW

Where To Go As A Modeler?



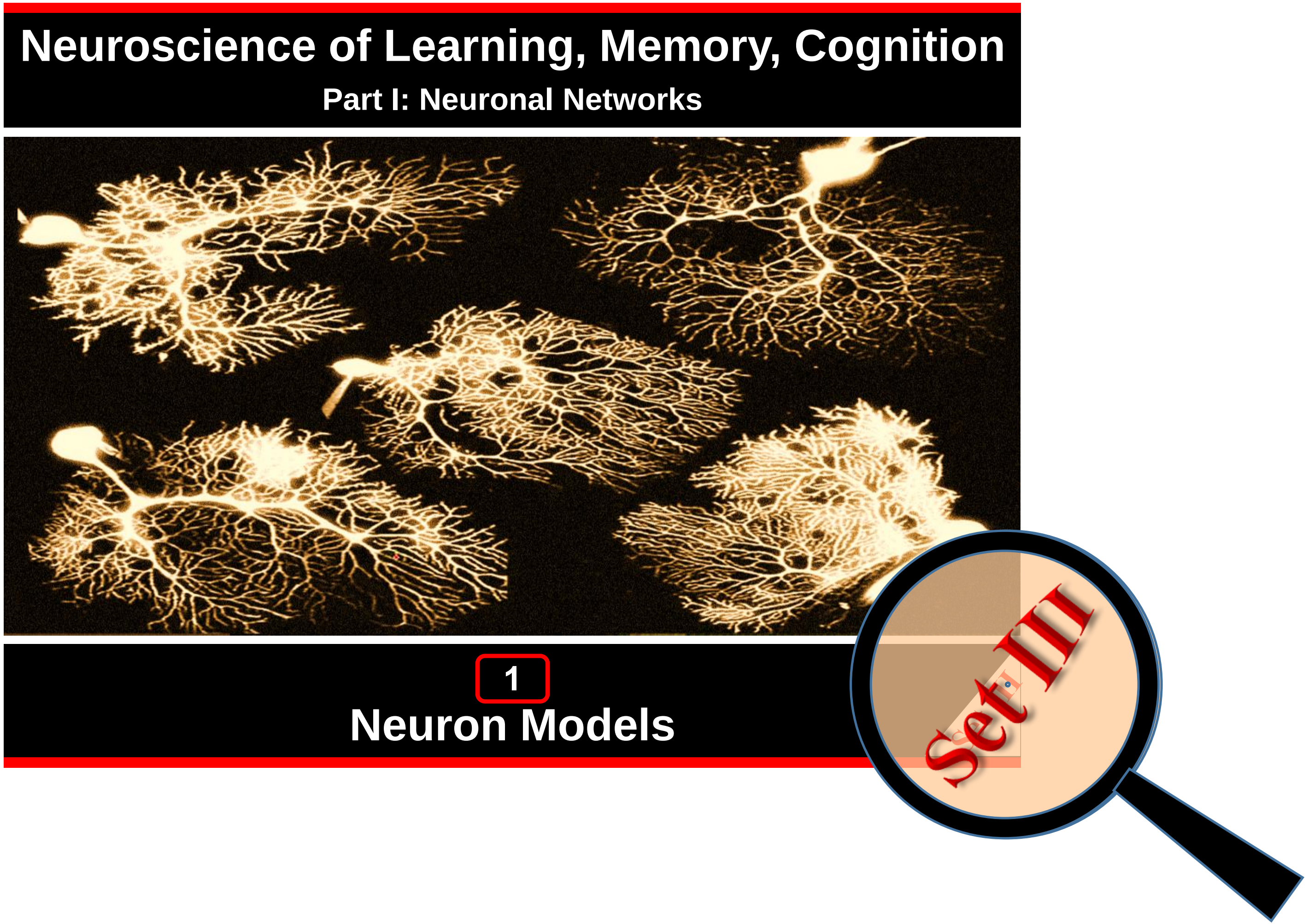
- What are the molecular level dynamics of neural activity?
- How do the around 100 different types of channels work?
- A neuron is not just a simple membrane, how does the **geometry** influence the operation of a neuron?

- ➢ Can simpler models capture the essence of the neural dynamics?
- ➢ Can we have models which can be analyzed mathematically?
- ➢ Which may also allow for running large-scale simulations?

Outline

- Sensing & perception
  - Neurons in the brain
  - Visual cortex & receptive fields
  - Vision & perception
- Neurons & spikes
  - Electrical personality of a neuron
  - Ionic channels
  - Action potential
- The Hudgkin-Huxley equation
  - The passive membrane
  - Voltage-gated channels
  - Anatomy of a spike
- Neuronal dynamics
  - **Phase portrait models**
  - **Fixed points and their stability**
  - **Bifurcation (saddle-node / Hopf)**
  - **Simplified 2D models**

Next


Neuroscience of Learning, Memory, Cognition
Part I: Neuronal Networks
1
Neuron Models
Set III