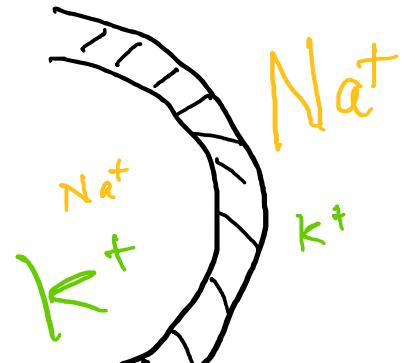


Q355/Q590
Today: Single neuron
models and
neurophysiology of
learning

Recap

$$V_m = V_{in} - V_{out}$$

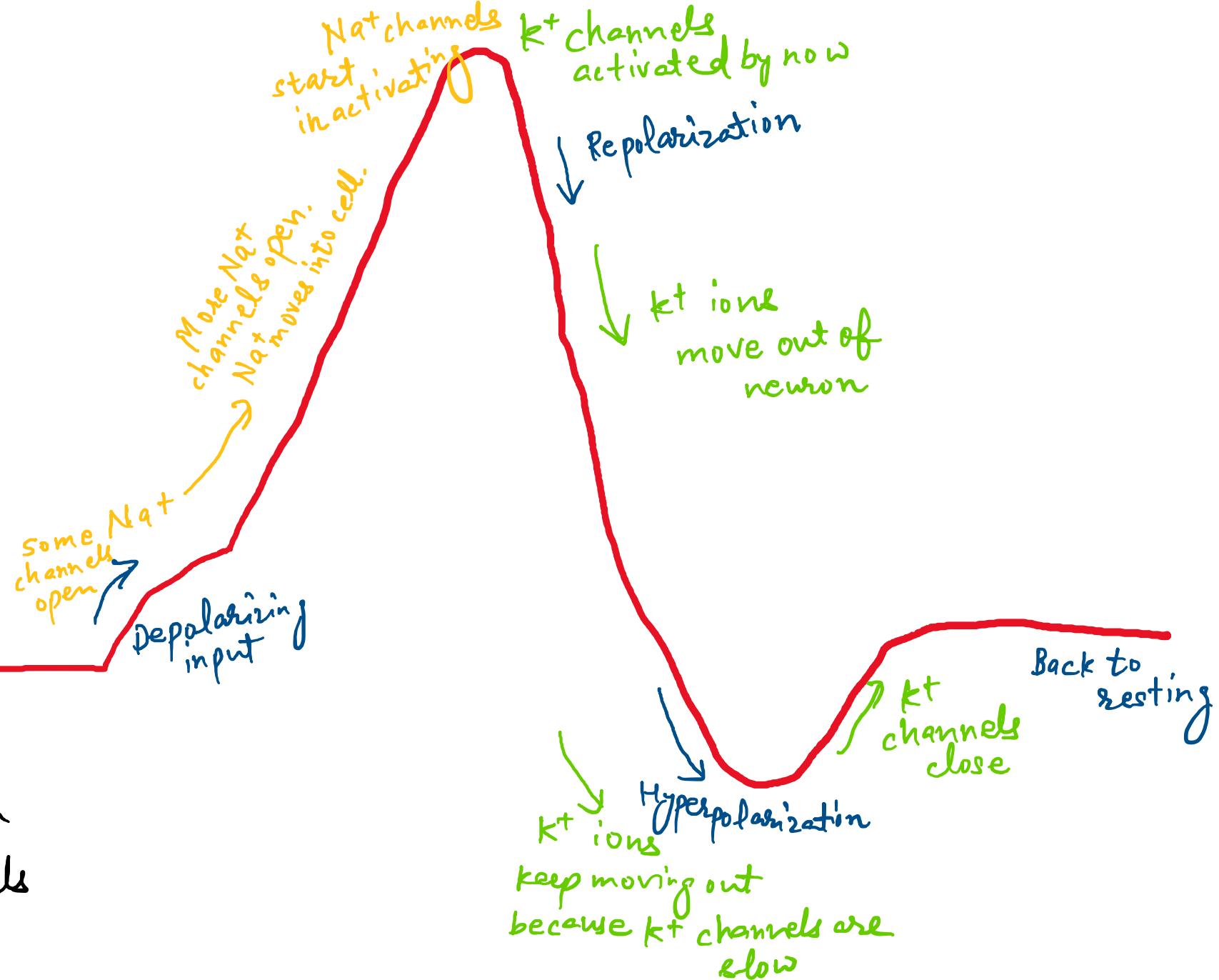


Membrane

Resting membrane

- Passive K^+ channels open

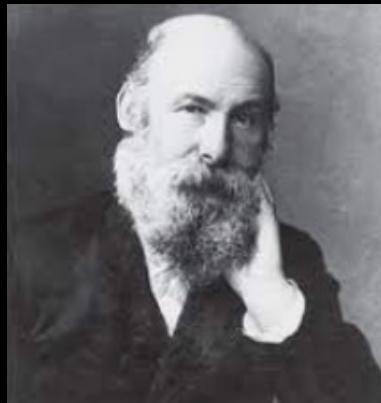
- leaky channels



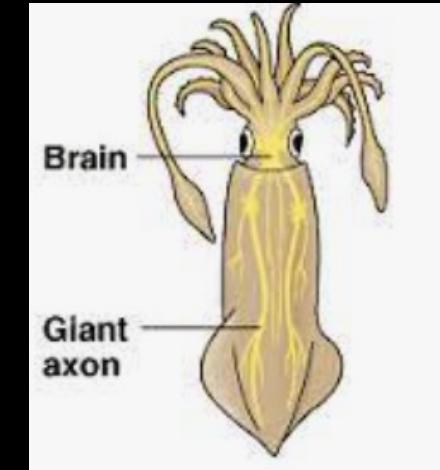
Mathematical models of action potential

- Hodgkin & Huxley model
- Izhikevich model
- Integrate & fire model
- Rate coded model

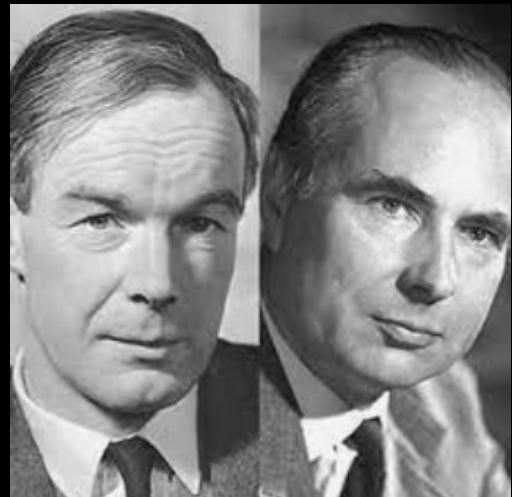
Hodgkin - Huxley and the discovery of neurophysiological events of an action potential



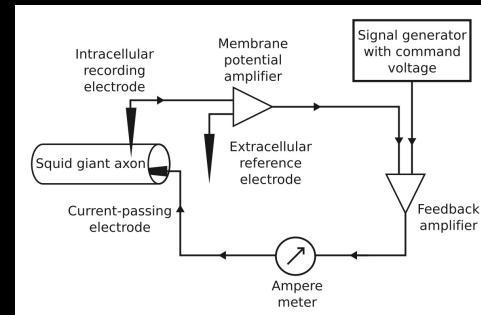
Julius Bernstein – Ionic theory of action potential generation (1902)



John Zachary Young – Discovery of the giant squid axon (1936)



Alan Hodgkin (left) and Andrew Huxley (right) – Hodgkin & Huxley model of action potential generation (1952)



Voltage clamp technique



Brunsviga calculating machine

Brunsviga machine



Hodgkin & Huxley model

- Conductance based model
- Membrane approximated as an RC circuit with resistances (that is, conductances) dependent on the membrane voltage
- Every sodium channel has 3 activation gates, and one inactivation gate.

m = probability that its activation gate is open h = probability that its inactivation gate is open

What is the probability that a sodium channel is open? $\rightarrow m^3h$

- Every potassium channel has 4 activation gates.

n = probability that potassium activation gate is open

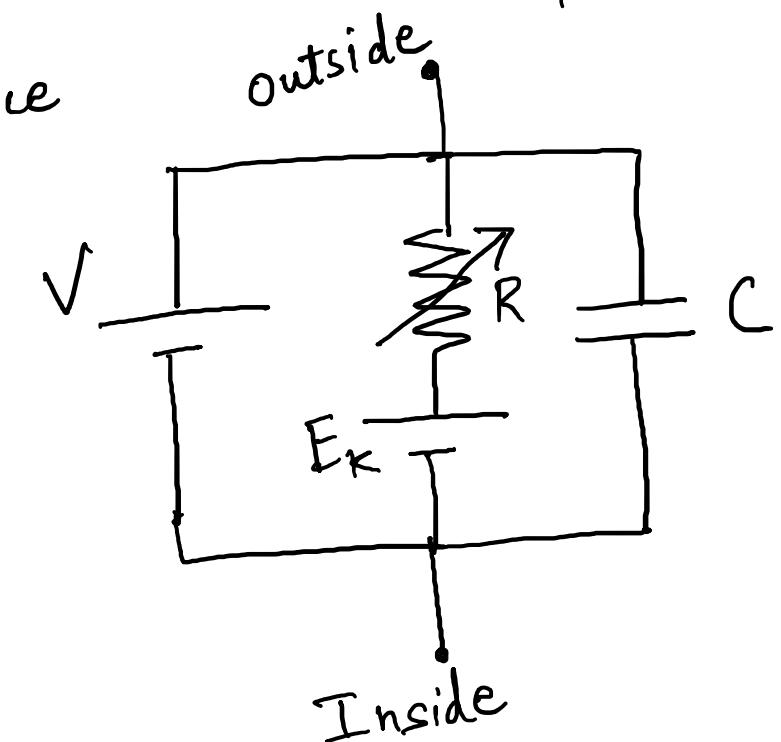
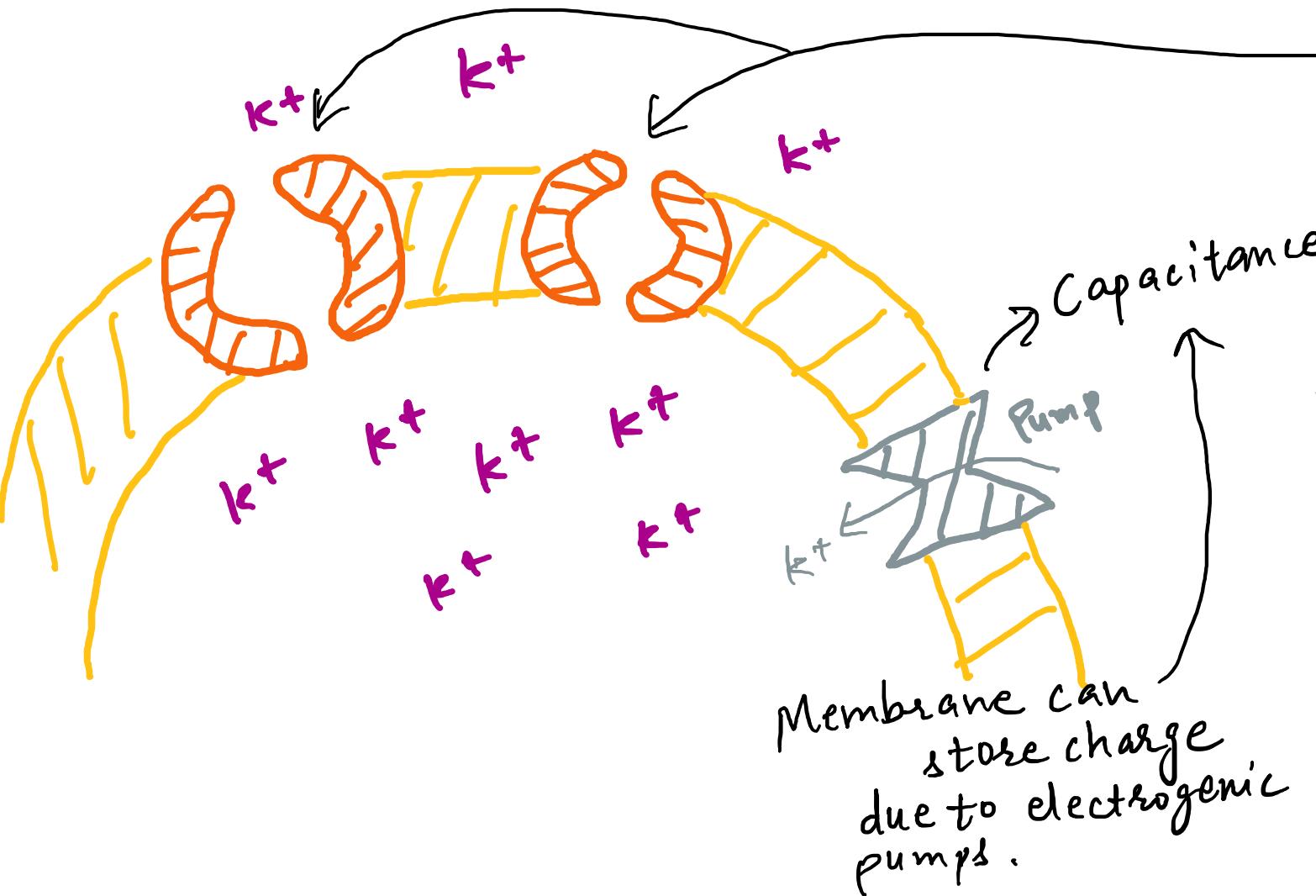
n^4 = Probability that a potassium channel is open

V : Membrane Voltage

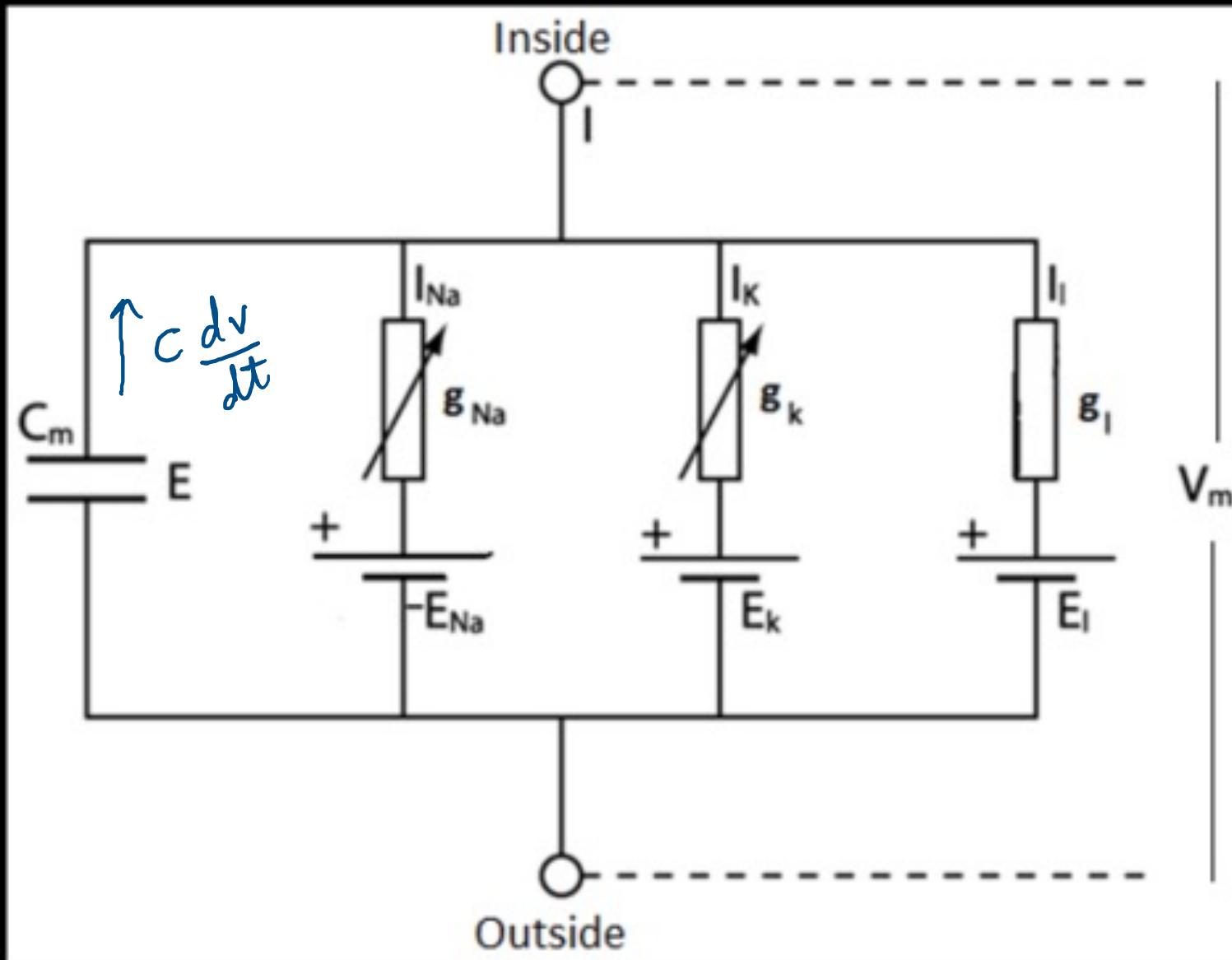
E_K : " necessary to match the K^+ chemical pot difference

$$\left. \begin{array}{l} I_K = g_K (V - E_K) \\ \downarrow \\ \text{Conductance of } K^+ \text{ across the membrane} \end{array} \right\}$$

(Depends on number of open K^+ channels)



HH model: Equivalent circuit and model equations



$$I =$$

$$C \frac{dV_m}{dt} + I_{Na} + I_K + I_L$$

$$\begin{aligned}
 C\dot{V} &= I - \overbrace{\bar{g}_K n^4 (V - E_K)}^{I_K} - \overbrace{\bar{g}_{Na} m^3 h (V - E_{Na})}^{I_{Na}} - \overbrace{g_L (V - E_L)}^{I_L} \\
 \dot{n} &= \alpha_n(V)(1-n) - \beta_n(V)n \\
 \dot{m} &= \alpha_m(V)(1-m) - \beta_m(V)m \\
 \dot{h} &= \alpha_h(V)(1-h) - \beta_h(V)h ,
 \end{aligned}$$

$$\alpha_n(V) = 0.01 \frac{10 - V}{\exp(\frac{10-V}{10}) - 1},$$

$$\beta_n(V) = 0.125 \exp\left(\frac{-V}{80}\right),$$

$$\alpha_m(V) = 0.1 \frac{25 - V}{\exp(\frac{25-V}{10}) - 1},$$

$$\beta_m(V) = 4 \exp\left(\frac{-V}{18}\right),$$

$$\alpha_h(V) = 0.07 \exp\left(\frac{-V}{20}\right),$$

$$\beta_h(V) = \frac{1}{\exp(\frac{30-V}{10}) + 1}.$$

V: Membrane potential

E_x: Nernst potential of ion X

g_x: Maximum conductance of ion X

(Conductance when all channels of X are open)

m, h: probability that the activation and inactivation gates are open in a sodium channel, respectively

g_{Na}*m³h = Average sodium conductance at some values m and h (that is, at a given V)

n: probability that activation gate of a potassium channel is open

g_K*n⁴ = Average potassium conductance at a given value of n (that is, at a given V)

HH model: Gating variables kinetics

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

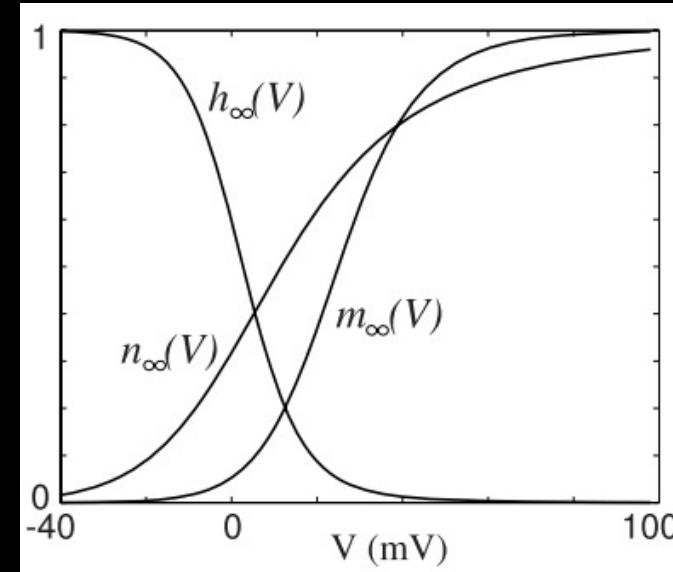
$$\frac{dn}{\alpha_n - (\alpha_n + \beta_n)n} = dt$$

$$\frac{-1}{\alpha_n + \beta_n} \ln \left(\frac{\alpha_n - (\alpha_n + \beta_n)n}{\alpha_n} \right) = dt$$

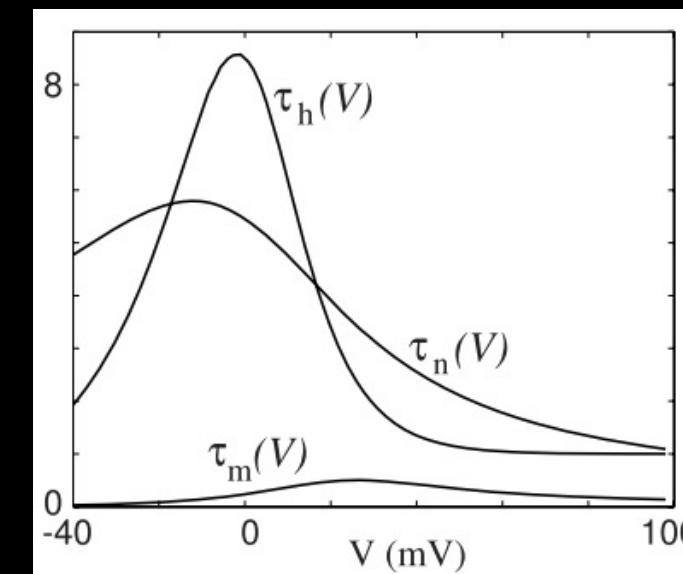
$$n = \frac{\alpha_n}{\alpha_n + \beta_n} \left(1 - e^{-t(\alpha_n + \beta_n)} \right)$$

$$\boxed{z_n} = \frac{1}{\alpha_n + \beta_n}; \text{ As } t \rightarrow \infty \quad n \rightarrow \boxed{n_\infty} = \frac{\alpha_n}{\alpha_n + \beta_n}$$

$z_m, z_h, m_\infty, \& h_\infty$ will look same
but with different subscripts.



Steady state values of gating variables, m, h, and n



Time constants of gating variables, m, h, and n
(Larger value \rightarrow slower dynamics)

$$\text{Consider, } C \frac{dV_m}{dt} = I - g_K n^4 (V_m - E_K) - g_{Na} m^3 h (V_m - E_{Na}) - g_L (V_m - E_L)$$

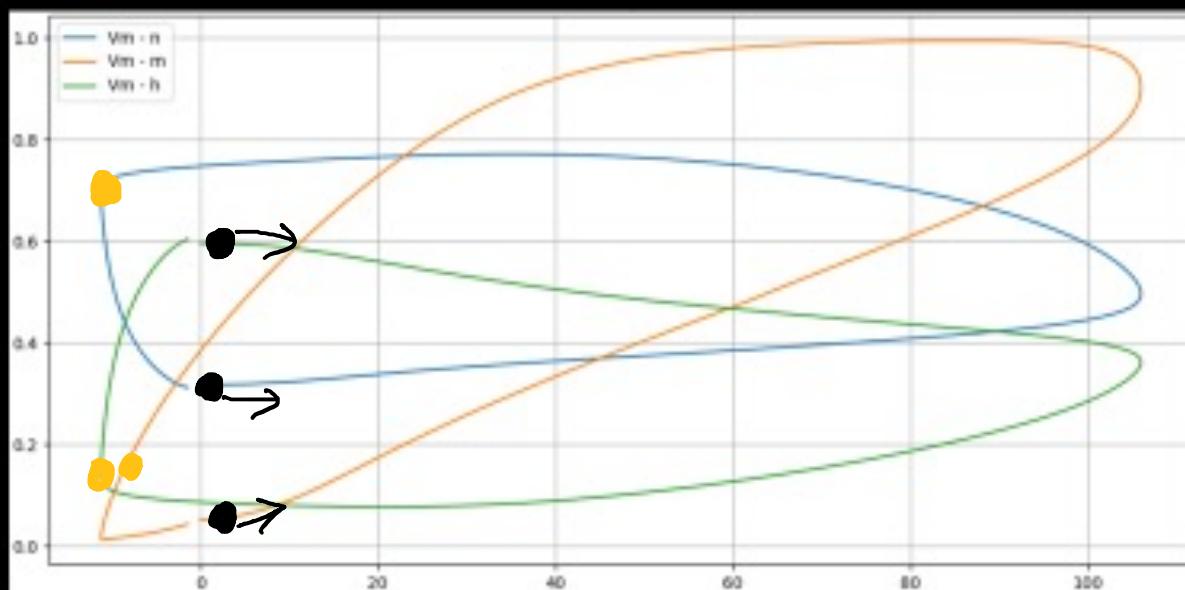
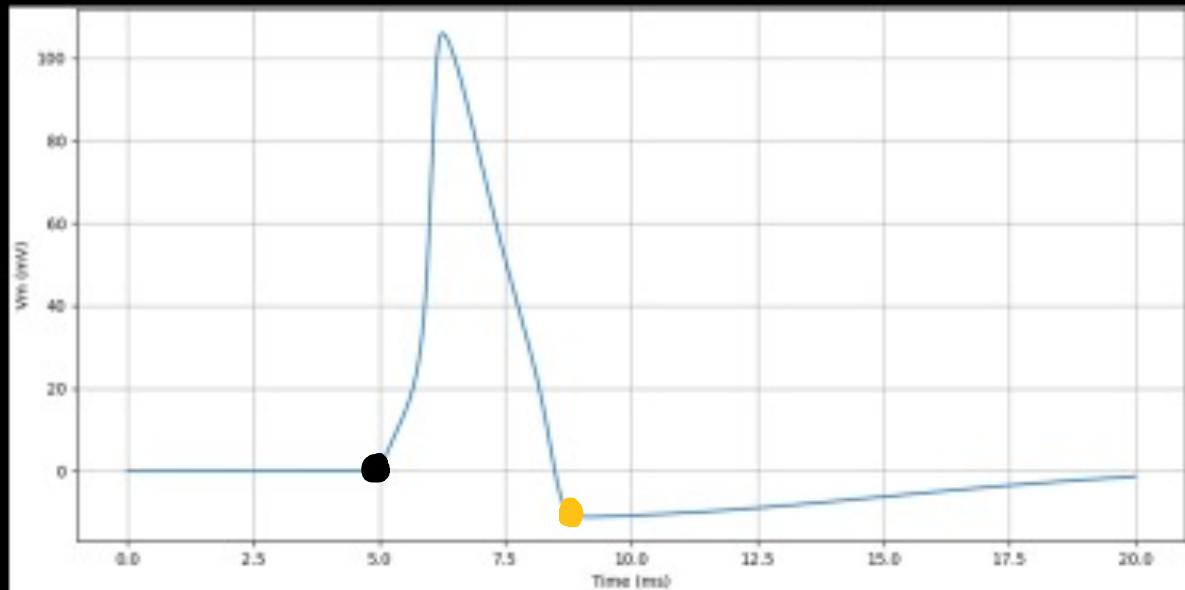
At equilibrium, $\frac{dV_m}{dt} = 0, I = 0$

$$V_m \underset{\text{(at equilibrium)}}{=} \frac{g_K n^4 E_K + g_{Na} m^3 h E_{Na} + g_L E_L}{g_K n^4 + g_{Na} m^3 h + g_L}$$

If equilibrium conductances are known, then $V_{m,eqm}$ is weighted sum of nernst potentials, $E_K, E_{Na} \& E_L$, with those conductances as the weights.

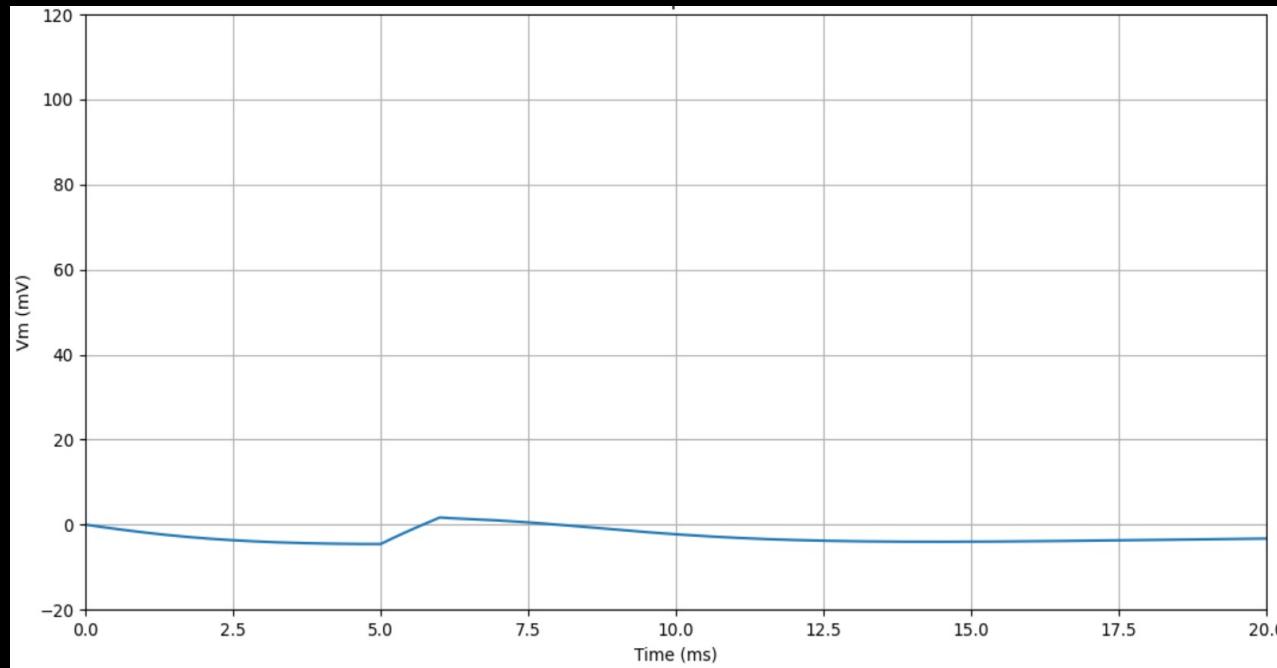
HH model simulations

Input = 30



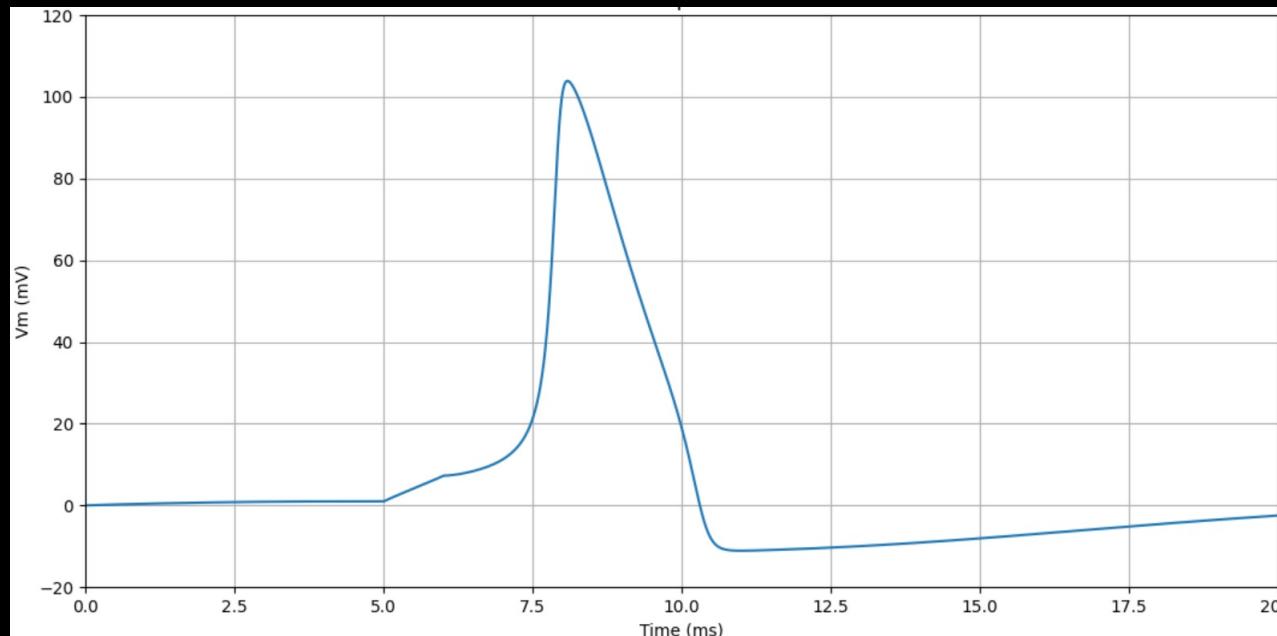
gL decreased to 0.1
(original value = 0.3)

Input = 7



gK was decreased to
32 (Original value = 36)

Input = 7



HH model: Drawbacks

- Hodgkin-Huxley neurons are computationally expensive
- Thus, non-scalable

Towards simple models . . .

How can the HH model be simplified while still retaining spiking dynamics?

Better question:

What are the basic requirements to generate spiking?

The 'm'
in HH
model

'h' and 'n'
in HH
model

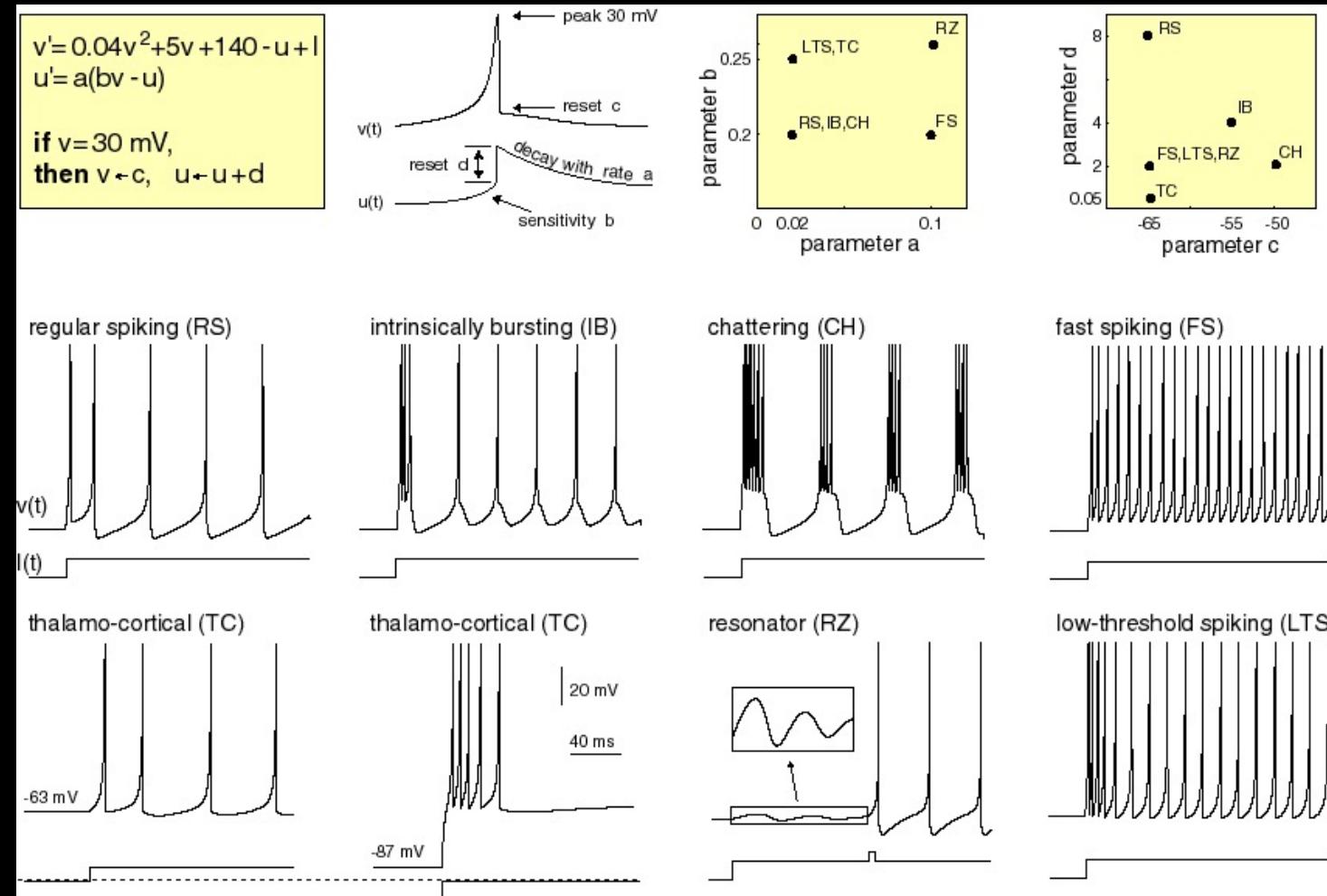
Answer: At least,

- One fast excitation variable
- One slow recovery variable

Izhikevich neuron
model

Izhikevich neuron model

- Not as biologically detailed
 - More computationally efficient than Hodgkin-Huxley
 - 2 state variables, plus integrate-and-fire



What if we are only interested to know whether an action potential happened or not? We are not interested in detail on how it came about. → Integrate and Fire Neuron

In that case, we can just see when the neuronal membrane reaches V_{thresh} ; We can consider the neuron to have generated an action potential when the former happens.

$I_{\text{ion}} \approx 0$ when V is close to V_{rest}

$$C \frac{dV}{dt} = I \Rightarrow \frac{dV}{dt} = \frac{I}{C}$$

$$V(t+1) = V(t) + \frac{I}{C}$$

if $V(t) > V_{\text{thresh}}$

$$V(t) = V_{\max}, V(t+1) = V_{\min}$$

Perfect
Integrate
& fire

Leaky integrate & fire

$$C \frac{dV}{dt} = I - I_l$$

$$= I - g_l V$$

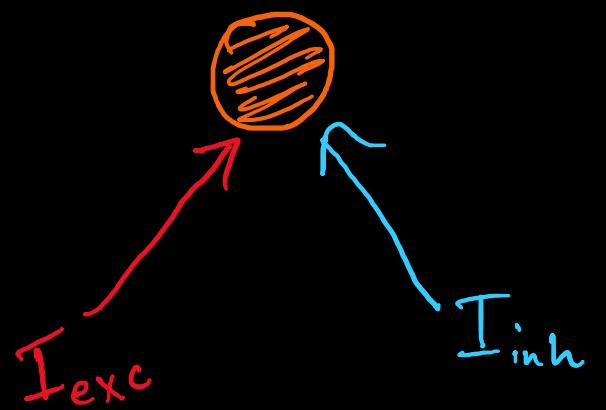
$$V(t+1) = V(t) + \frac{I}{C} - \frac{g_l V(t)}{C}$$

if $V(t) > V_{\text{thresh}}$

$$V(t) = V_{\max}, V(t+1) = V_{\min}$$

What if we are not even interested to know whether an action potential happened or not? We only care about frequency of action potential generation.

→ Rate-coded model



X : Firing rate
of neuron
(No. of spikes per sec)

$$\frac{dx}{dt} = (1-x) I_{exc} - x (A + I_{inh})$$

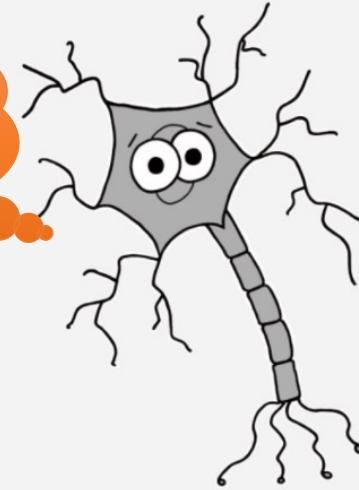
$$\frac{dx}{dt} = I_{exc} - x (I_{exc} + I_{inh} + A)$$

$$x = \frac{I_{exc}}{I_{exc} + I_{inh} + A} \left(1 - e^{-t(I_{exc} + I_{inh} + A)} \right)$$

As $t \rightarrow \infty$

$$x \rightarrow \frac{I_{exc}}{I_{exc} + I_{inh} + A}$$

I have some questions!



Q1. Which of the following models has parameters that have direct correspondence with the physiological properties of the neuronal membrane?

- A. Integrate & Fire model
- B. Hodgkin and Huxley model
- C. Izhikevich model
- D. Rate-coded model

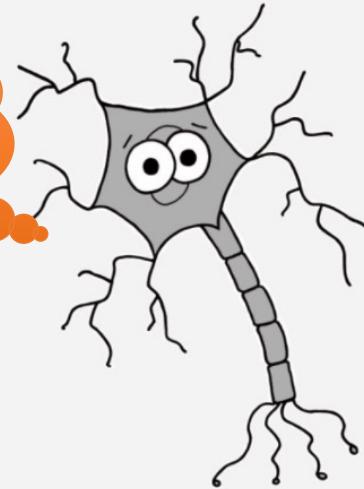
Q2. Consider that certain drug affects the excitability of neurons in certain part of brain. I have data on neuron dynamics from single neuron recordings with or without the drug applied to a neuron from this region.

Using a neuron model and modifying the model to add the effect of drug, I want to understand how the drug affects the neuron – Which ionic currents get affected? Does it affect sodium channels or potassium channels? How exactly does it affect the kinetics of channel opening/closing?

Which of the following would be the best choice to model the neuron in this case?

- A. Integrate & Fire model
- B. Conductance based model (Hodgkin & Huxley)
- C. Izhikevich model
- D. Rate-coded model

I have some questions!



Q3. Say, I have a network of neurons connected to each other via excitatory/inhibitory connections.



Under different input conditions, I want to find the pattern of activity at which this network settles.

Which of the following would be the best choice to model the neurons in this case?

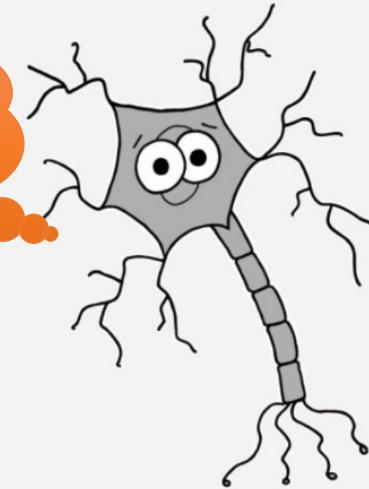
A. Integrate & Fire model

C. Izhikevich model

B. Conductance based model (Hodgkin & Huxley)

D. Rate-coded model

I have some questions!



Q4. Consider that you are constructing a multilayered network of visual cortex. The input layer is retinal ganglion neurons – the layer is meant to signal amount of contrast in input images.

Say, you are told that the ganglion neurons have greater frequency of firing to a greater contrast – so the information about the contrast is in the frequency (rate) of firing.

Which of the following would be the best choice to model the neurons in this layer?

A. Integrate & Fire model

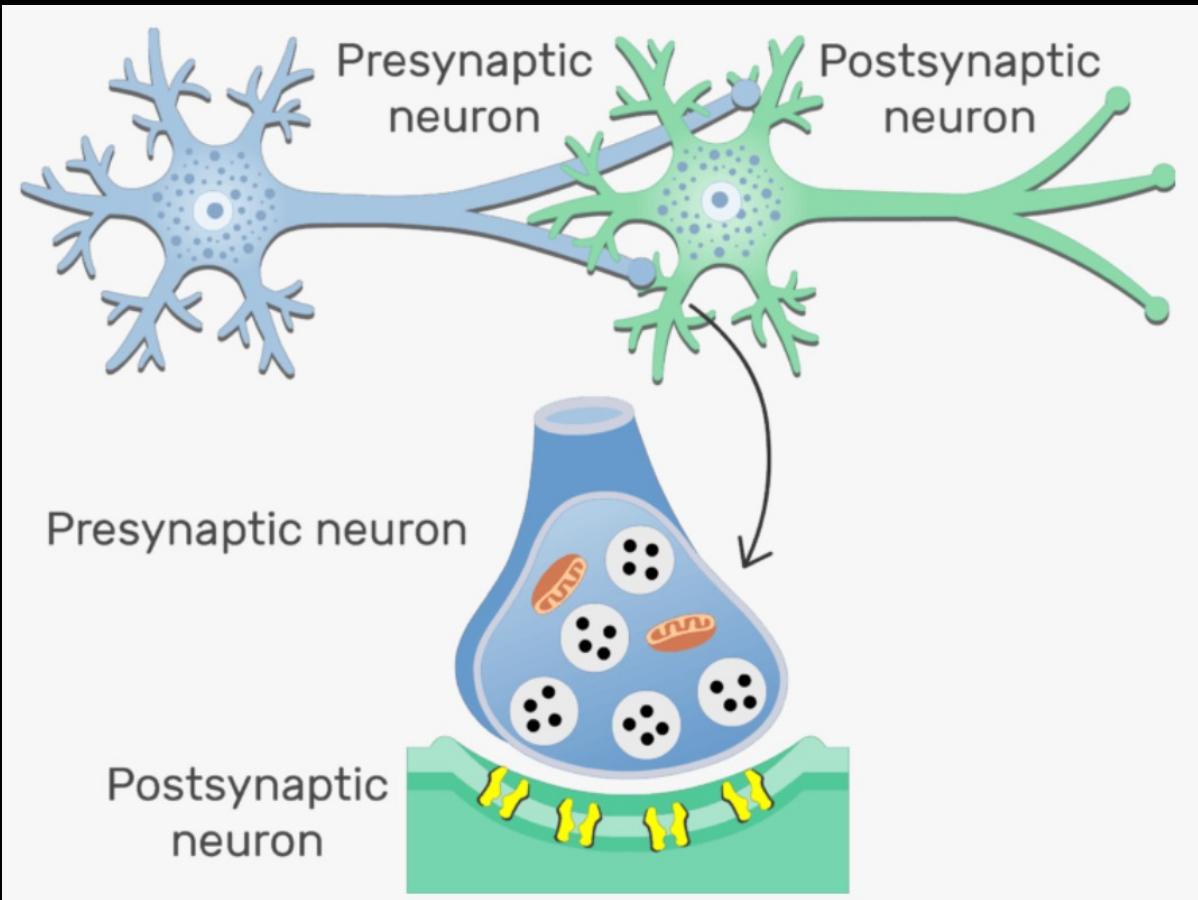
C. Izhikevich model

B. Conductance based model (Hodgkin & Huxley)

D. Rate-coded model

How do neurons communicate?

Synapse: The junction between 2 neurons where the communication happens



What is the nature of the signal between one neuron and the other?

- A. Chemical *mostly*
- B. Electrical
- C. Physical

Synaptic transmission: Soup vs spark debate – 1930s



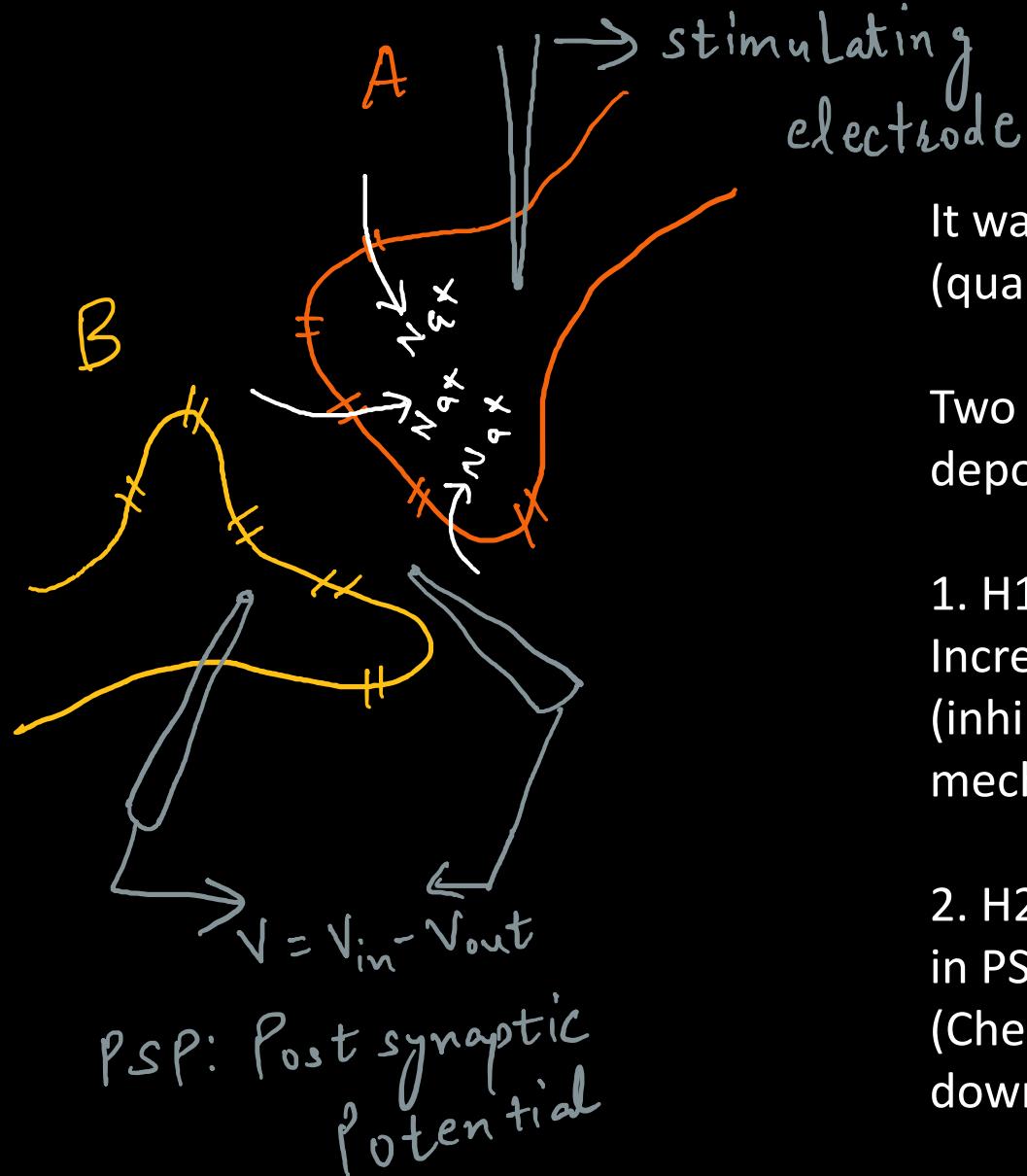
Sir Henry Hallett Dale (1875 – 1968)

Proponent of chemical neurotransmission



Sir John Carew Eccles (1903 – 1997)

Proponent of electrical neurotransmission



John Eccles experiment with cat motoneurons

It was known that A (hamstring sensory neuron) inhibited B (quadriceps motoneuron)

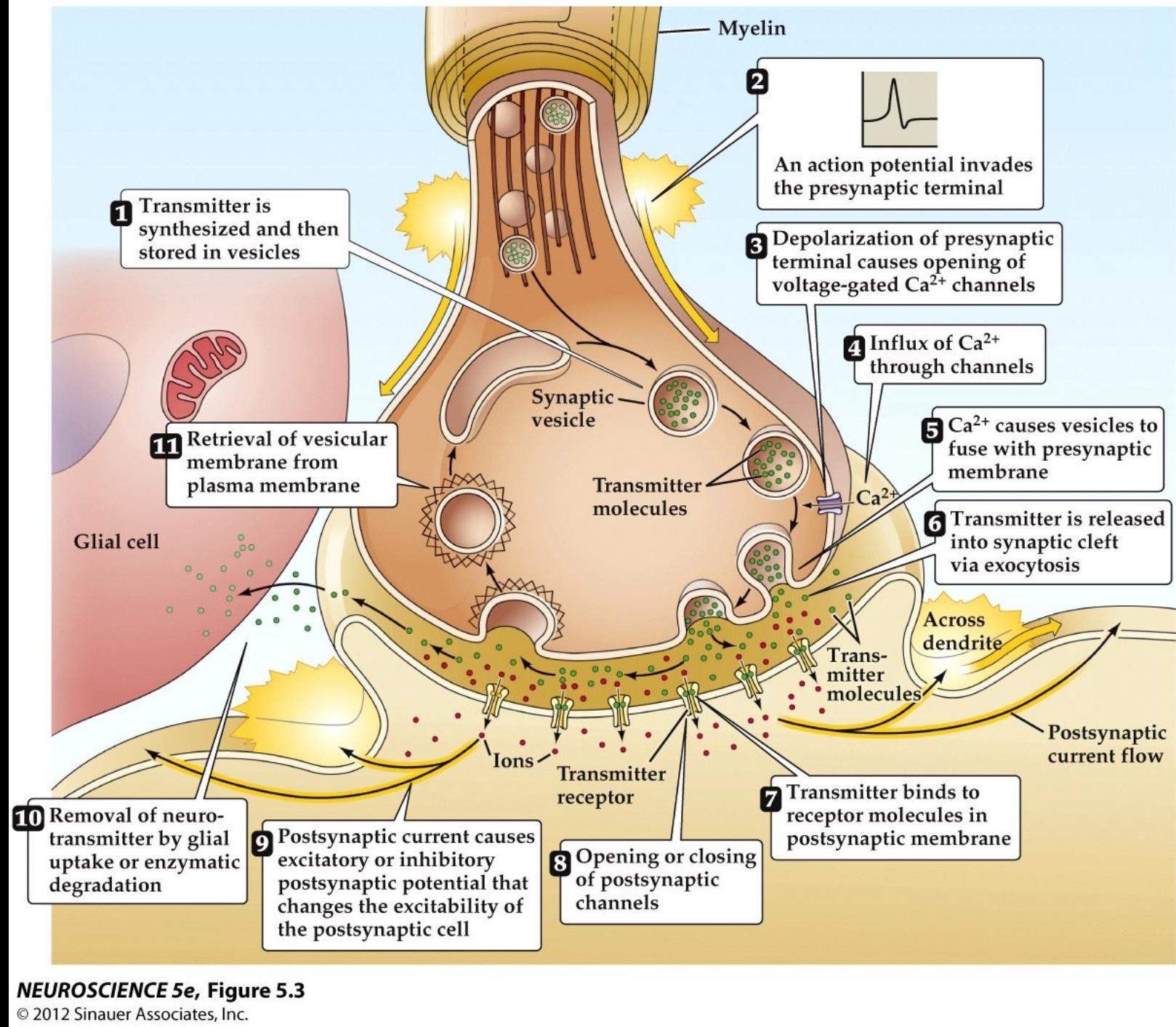
Two hypotheses: When A is stimulated (so that the axonal terminal depolarizes) -

1. H1: Electrical neuronal transmission happens from A to B; → Increase in PSP indicates H1 is true
(inhibitory effect of A on B is brought about by some downstream mechanisms)
2. H2: Chemical neurotransmission happens from A to B → Decrease in PSP indicates H2 is true
(Chemical neurotransmission can do inhibition directly – no downstream mechanisms required)

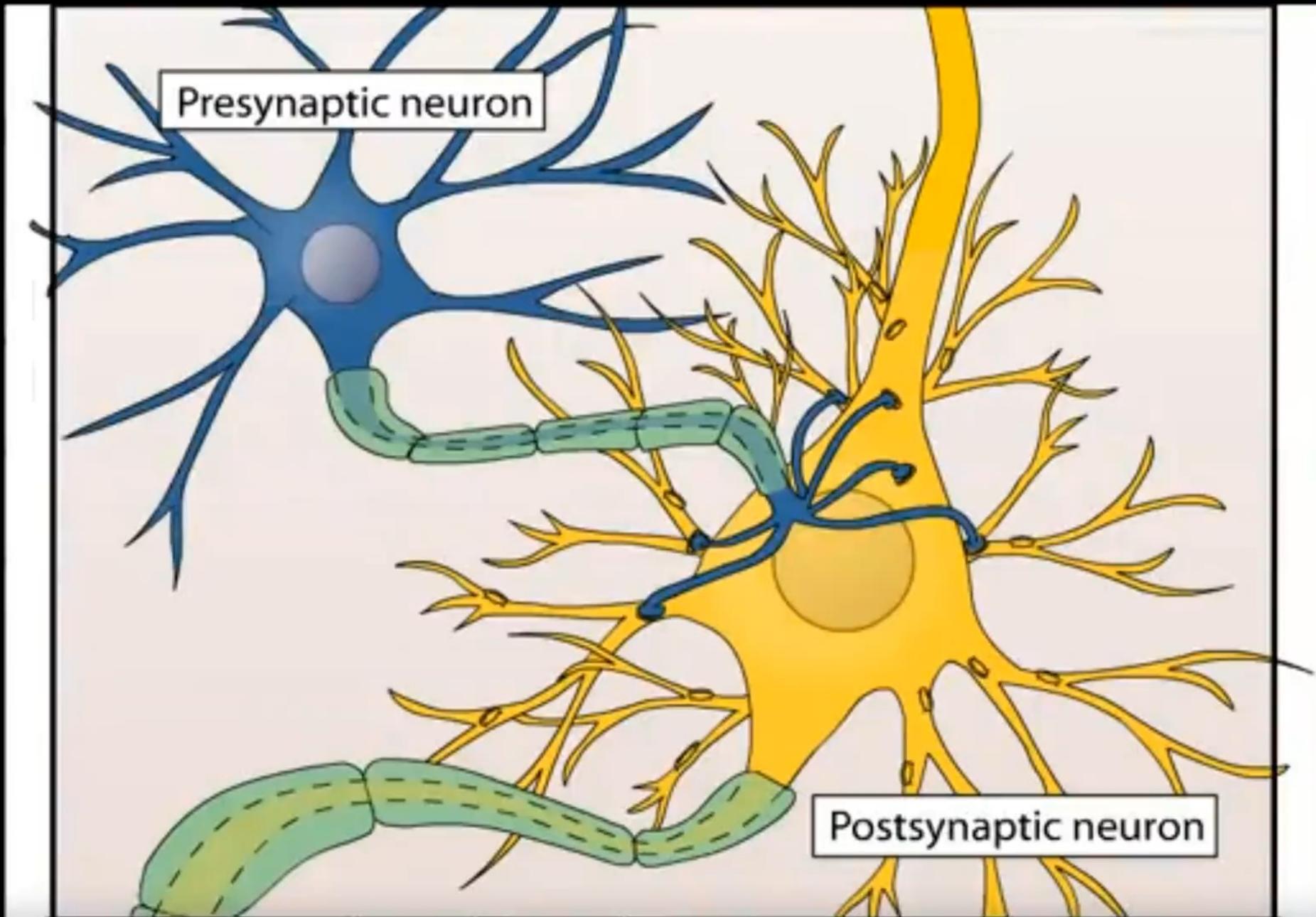
Decrease in PSP observed → chemical neurotransmission

Neurons also need to have some chemistry in order to understand each other's feelings fillings!

So, what exactly happens at the synapse?



Transmitter release - animation

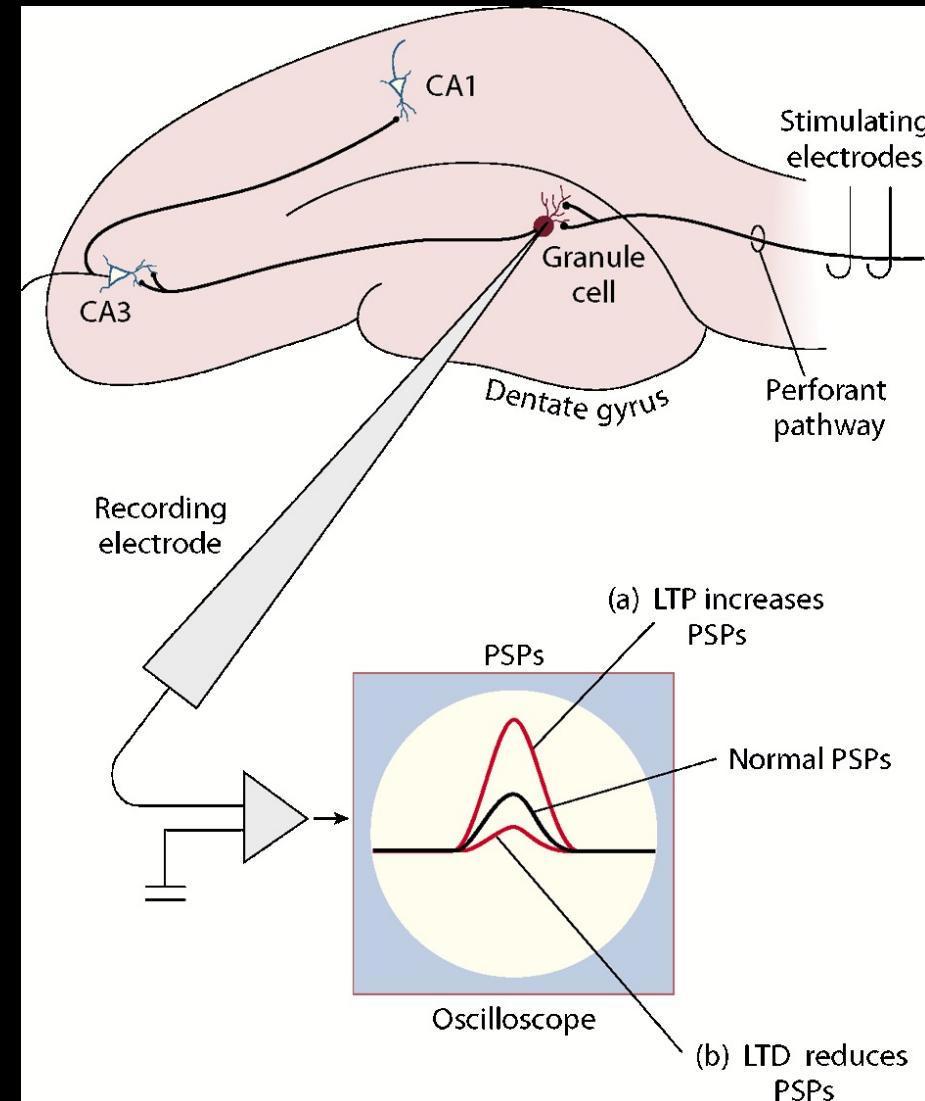


Synaptic plasticity



Patient H.M.

Underwent surgical removal of parts of middle temporal lobe including hippocampus to treat epilepsy – suffered from anterograde amnesia as a result.

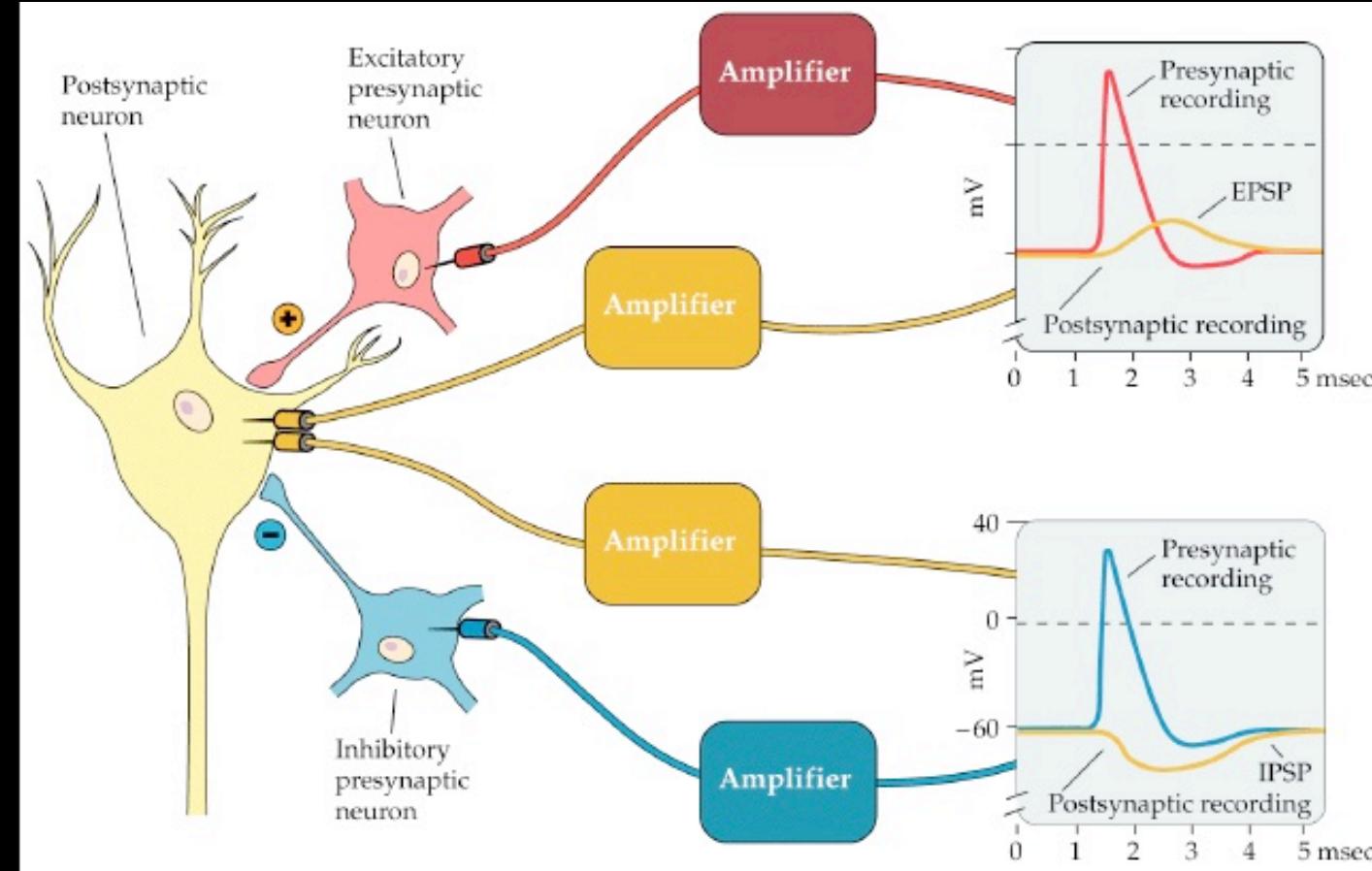


LTP discovered in Rabbit hippocampus by Terje Lømo in 1966

Excitation vs. Inhibition

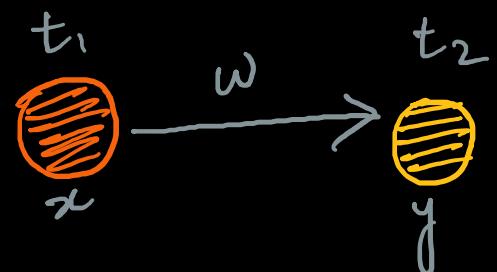
EPSP –
excitatory
post-synaptic
potential

IPSP – inhibitory
post-synaptic
potential



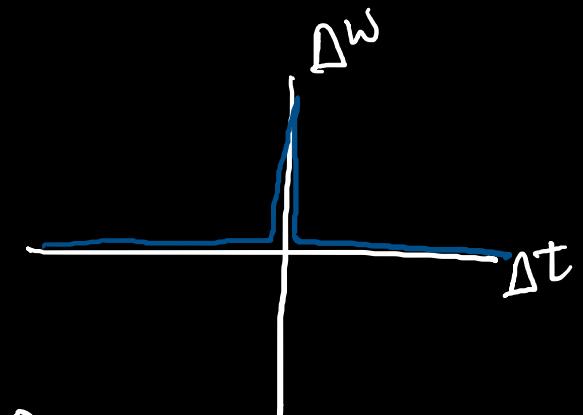
Long-term potentiation: Increased EPSP of post-synaptic neuron after repeated excitation of the pre-synaptic neuron.

Two of the theoretical models of synaptic plasticity



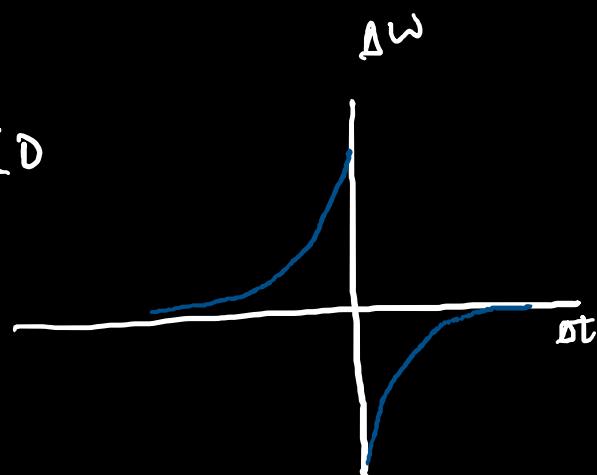
$$y = f(wx) ; \text{ Let } y = wx$$

1. Hebbian learning $\Rightarrow \Delta w = w_0 (e^{nxyt} - 1)$

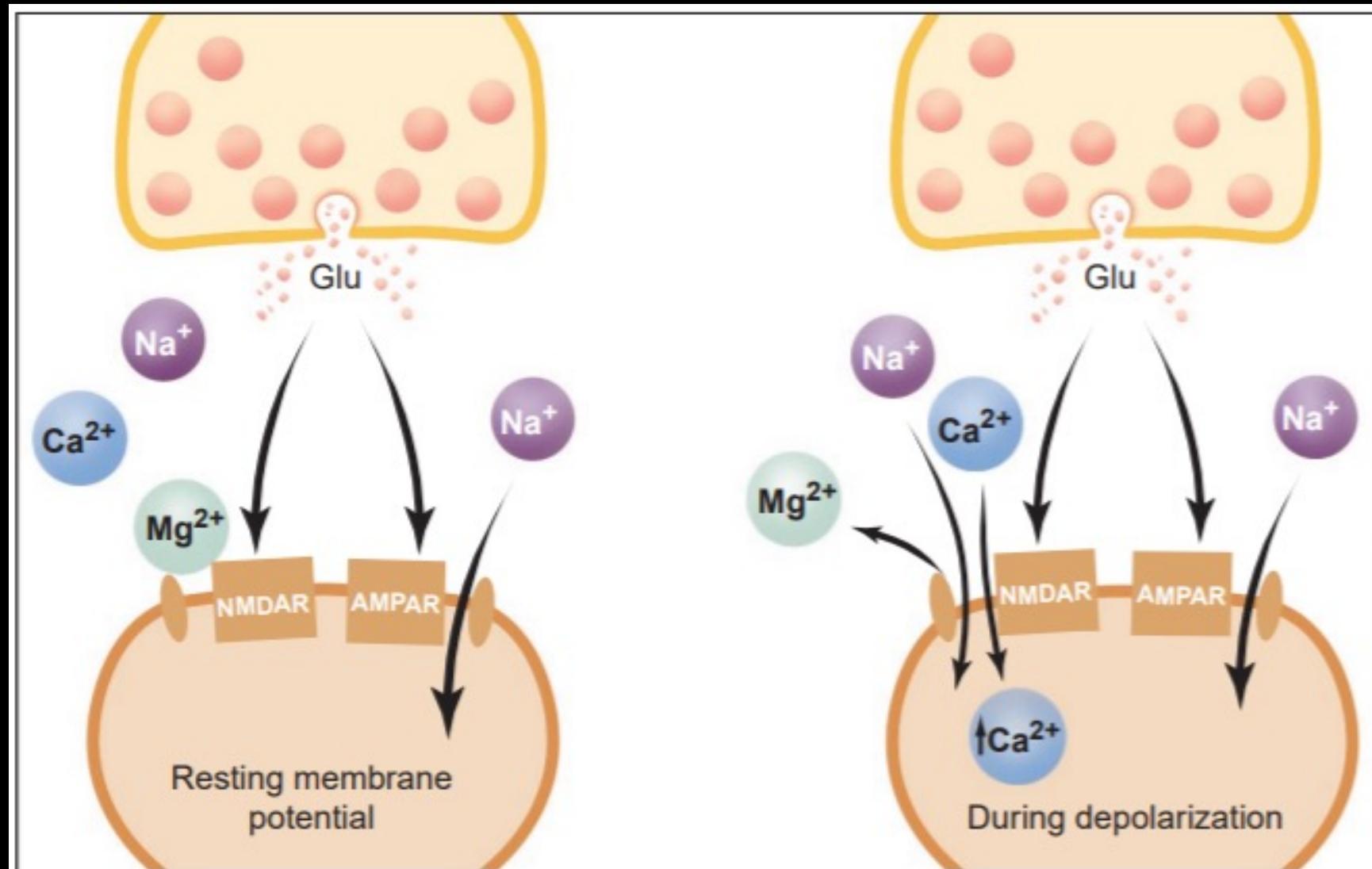


2. Spike timing dependent plasticity (STDP) $\Rightarrow \Delta w = \begin{cases} A_1 e^{\frac{\Delta t}{\tau_1}}, & \text{if } \Delta t > 0 \\ -A_2 e^{-\frac{\Delta t}{\tau_2}}, & \text{if } \Delta t < 0 \end{cases}$

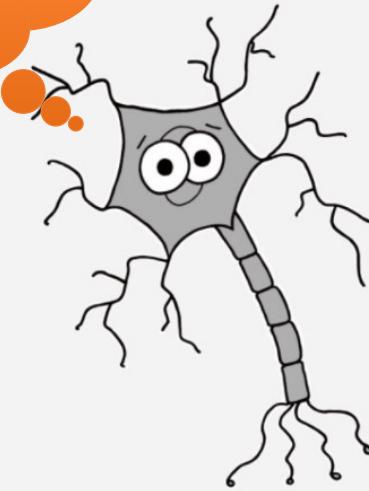
$\Delta t = t_2 - t_1$



NMDA mediated LTP in hippocampus



I have some questions!



Q1. When the neurotransmitter GABA binds to the GABA receptors on post-synaptic neuron membrane, it allows the flow of chloride ions across the membrane. What is the effect of GABA on post-synaptic neuron?

A. Excitatory

B. Inhibitory

Q2. Which among the following is a 'coincidence detector' in one type of LTP in hippocampus that we discussed in this class?

A. AMPA receptors
B. Calcium ions

C. NMDA receptors
D. Magnesium ions

Q3. Cocaine inhibits the reuptake of dopamine by blocking dopamine transporter proteins. What does this do to the dopamine concentration in synaptic cleft?

A. It gets high

B. Stays the same

C. It decreases

Adios neurophysiology ...

(for now)



AND AN AXON, YEAH YEAH

Neuron song by students at American University
Performed by Jason Sager (<http://jasonsager.net>)
Lyrics by Jason Sager and David Jangraw