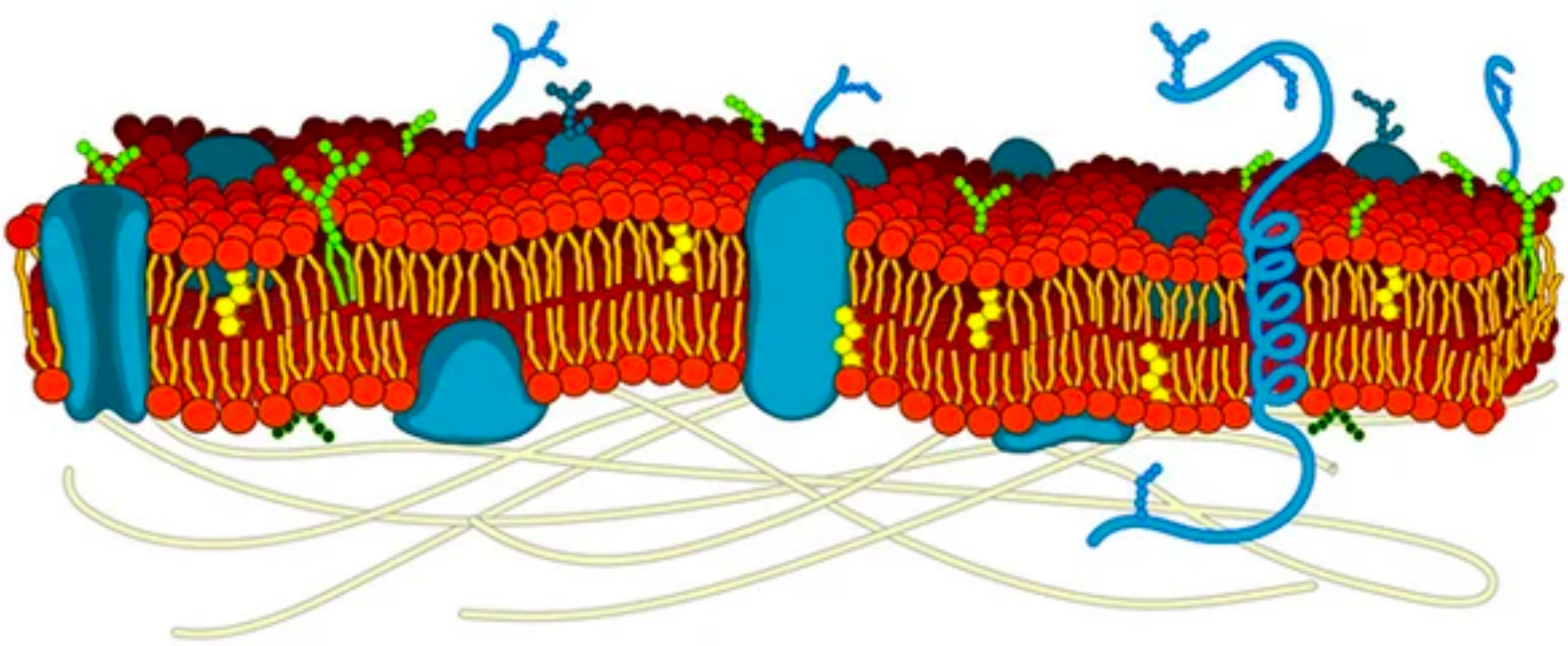


Membrane Excitability and Synaptic Plasticity

Suhita Nadkarni, IISER Pune, suhita@iiserpune.ac.in

Hippocrates

“And men ought to know that from nothing else but from the brain come joys, delights, laughter and sports, and sorrows, griefs, despondency, and lamentations.

And by this, in an especial manner, we acquire wisdom and knowledge, and see and hear, and know what are foul and what are fair, what are bad and what are good, what are sweet, and what unsavory...

And by the same organ we become mad and delirious, and fears and terrors assail us... All these things we endure from the brain, when it is not healthy...

In these ways I am of the opinion that the brain exercises the greatest power in the man. This is the interpreter to us of those things which emanate from the air, when it [the brain] happens to be in a sound state.”

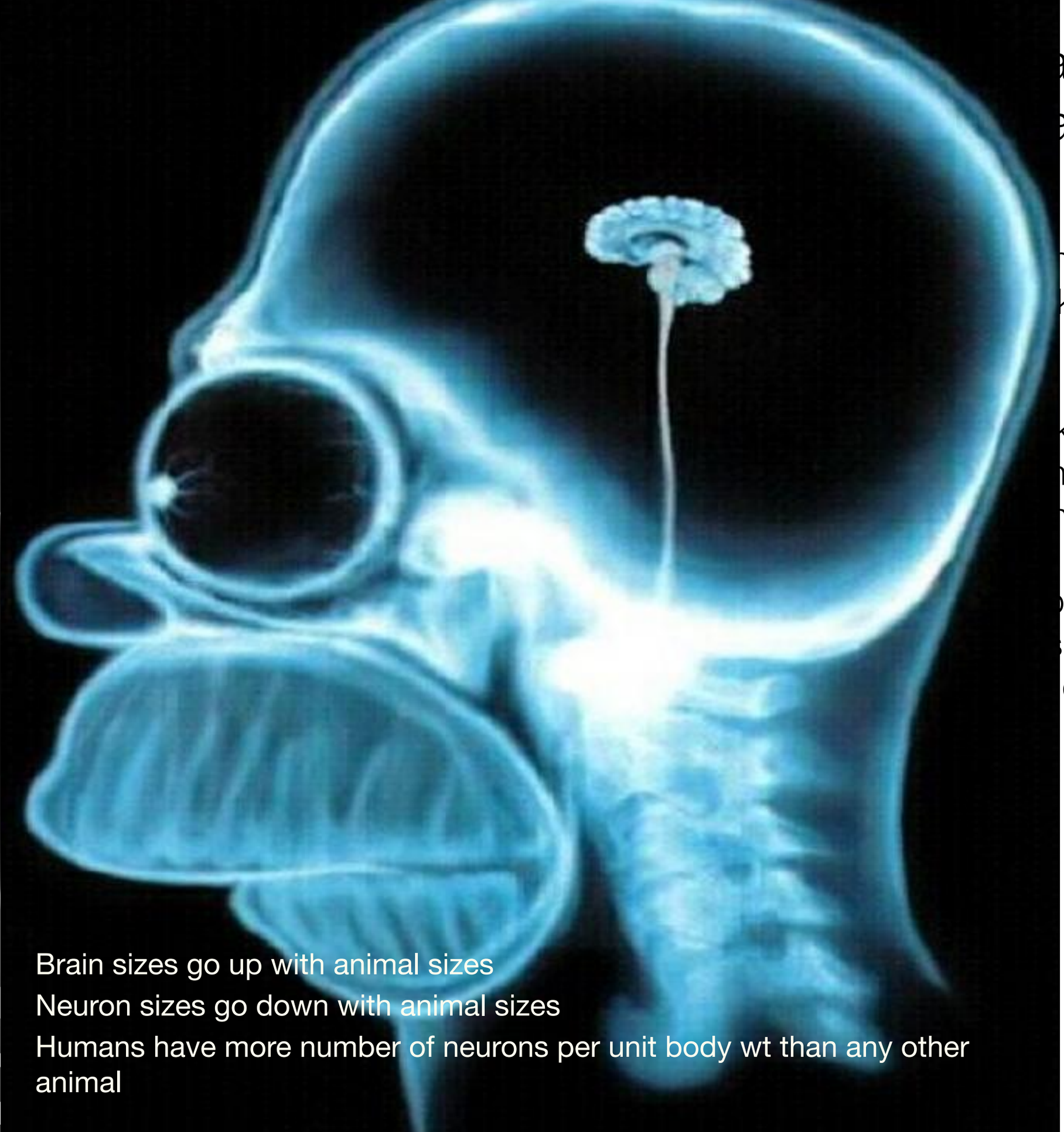
How much do we really know??

10^{10} to 10^{11} neurons (~200 Billion Stars)
Each neuron makes 10^{3} to 10^{4} connections
Switching Time 10^{-3} S(10^{-10} for new computers)
Switching Energy 10^{-16} joules/operation (10^{-6})
Consumes 25% of body's energy accounts for 1-2% of Wt.(3 lbs and 1400 cm^{3} volume)
0.1 Sec to recognize your mother!!!!!

Yet, we know very little about how the brain processes information

10 times as many glial cells as neurons in elaborate and well defined arrangement with
neurons

Largest cerebral cortex (logical reasoning abstract reasoning)



Brain sizes go up with animal sizes

Neuron sizes go down with animal sizes

Humans have more number of neurons per unit body wt than any other animal

a Neuroscientist:
and brain function

n: 1.5 kg
kg

king from the movement
n (until you have to stand up
n public)

ecial about the human
s is it that we study animals
em studying us?

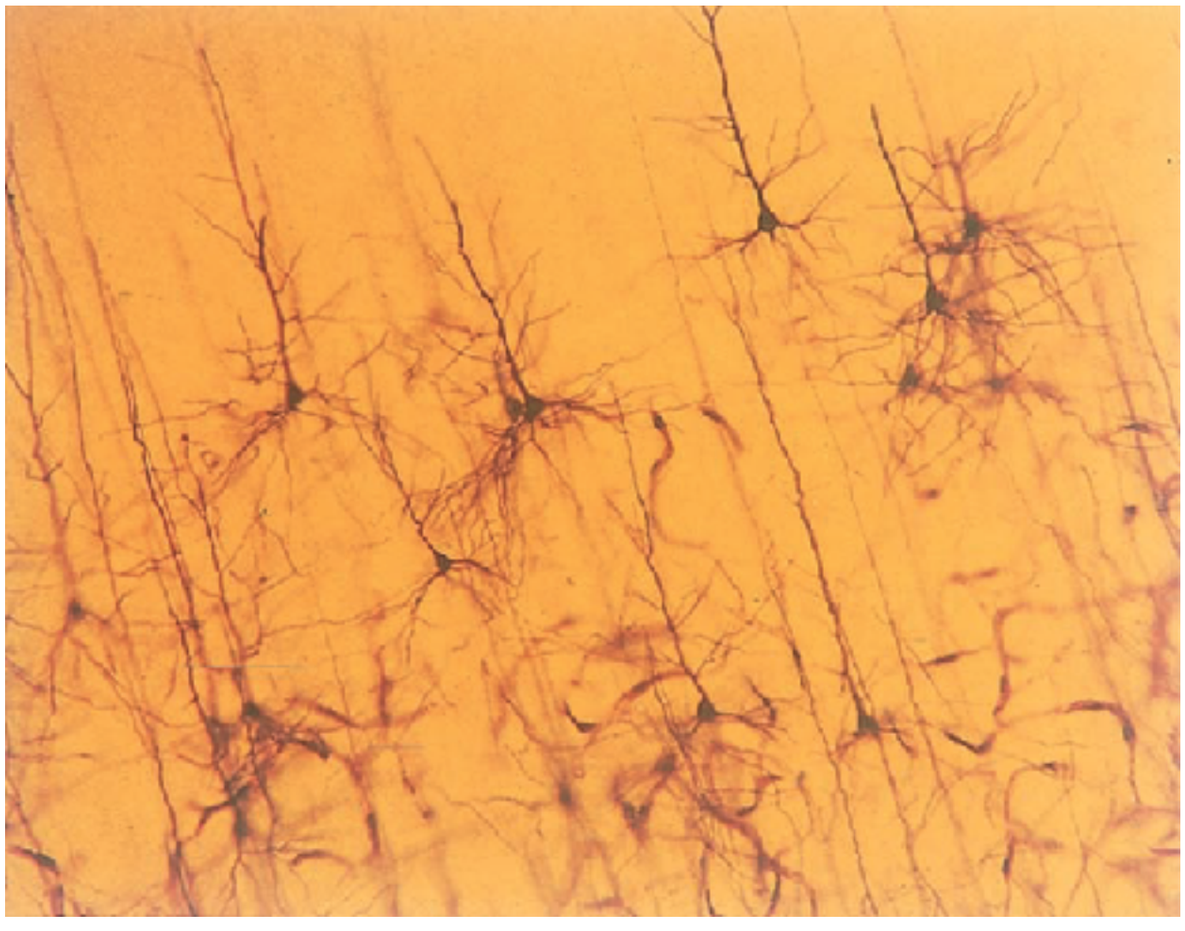
Birth of modern Neuroscience

In 1870s, Camillo Golgi invented the staining method that launched modern neuroscience

Gailed to grasp that each neuron was a discrete unit

Golgi stain (Golgi 1846- 1926)

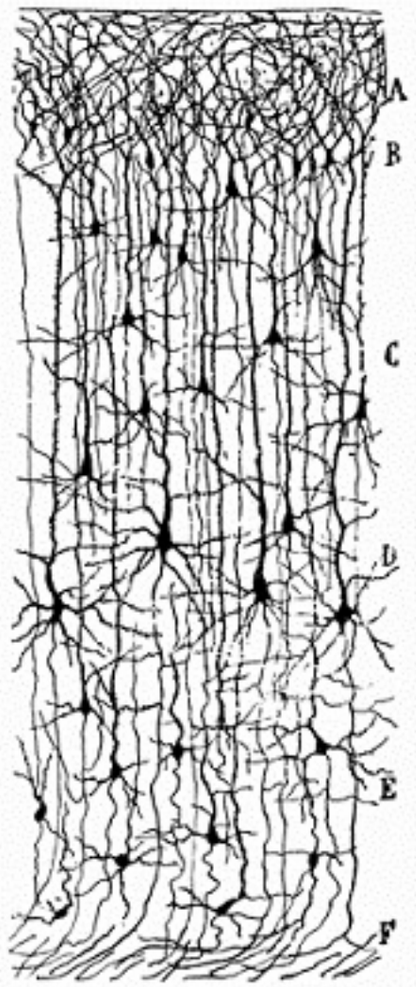
Soaking brain tissue in a silver chromate solution, a small percentage of neurons became darkly colored in their entirety



Reticular theory - Golgi's theory: neurons form a continuum like arteries and veins of the circulatory system

15 years later, Cajal had a different idea

It all started here



Santiago Ramón y Cajal : Father of modern Neuroscience, May 1852 – 18 October 1934) was a Spanish pathologist, histologist, neuroscientist, and Nobel laureate, 1906.

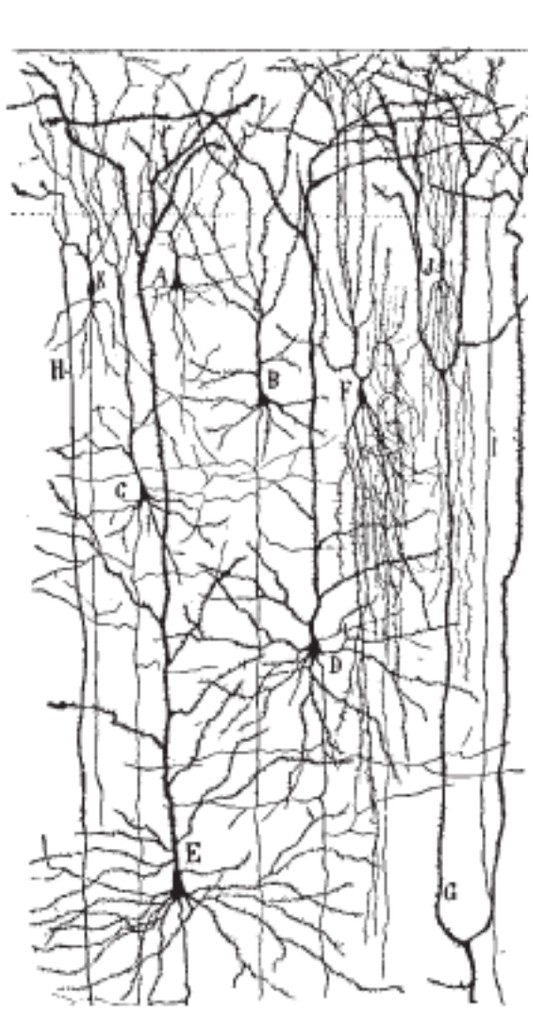
Cajal's drawings provided the foundation of modern neuroanatomy by showing that the nervous system is composed of individual nerve cells as opposed to a web of continuous elements.

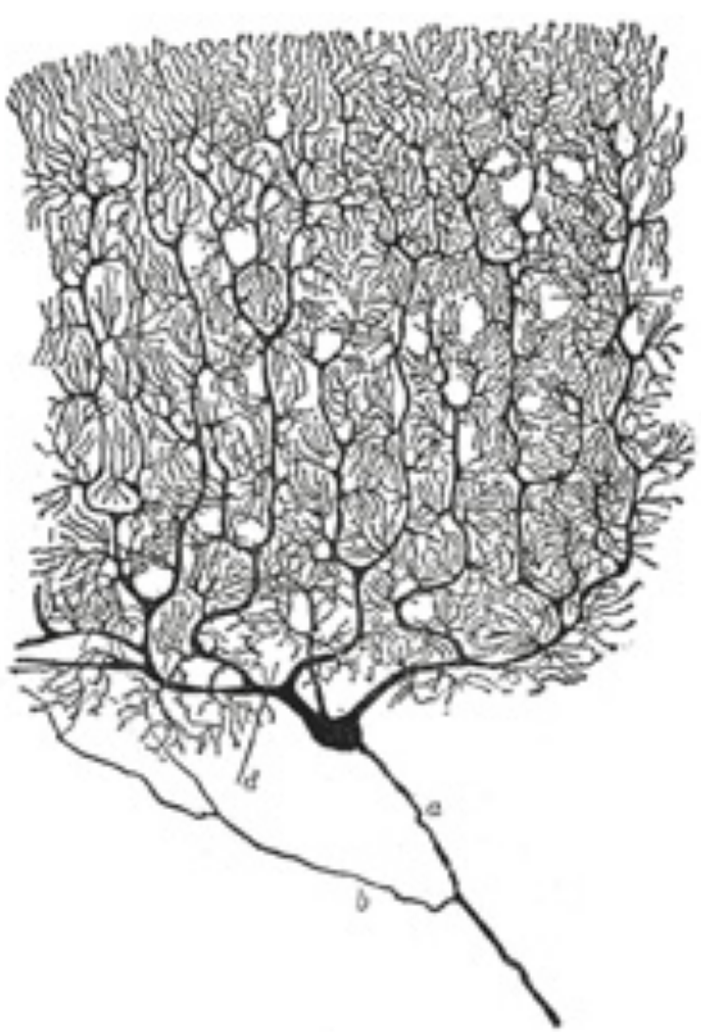
https://en.wikipedia.org/wiki/Santiago_Ram%C3%B3n_y_Cajal

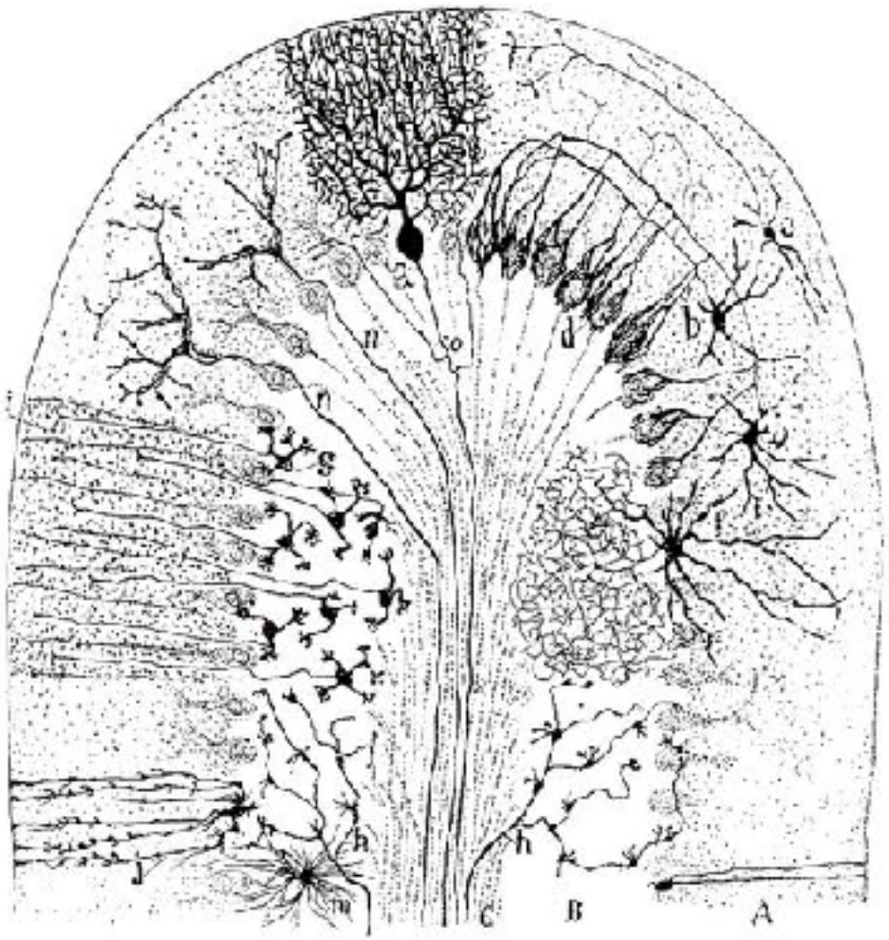
Father of modern Neuroscience: Santiago Ramon y Cajal (1852-1934)

Worked out circuitry of many regions of the brain using improved Golgi stain

The neuron doctrine is the concept that the nervous system is made up of discrete individual cells: special case of cell theory





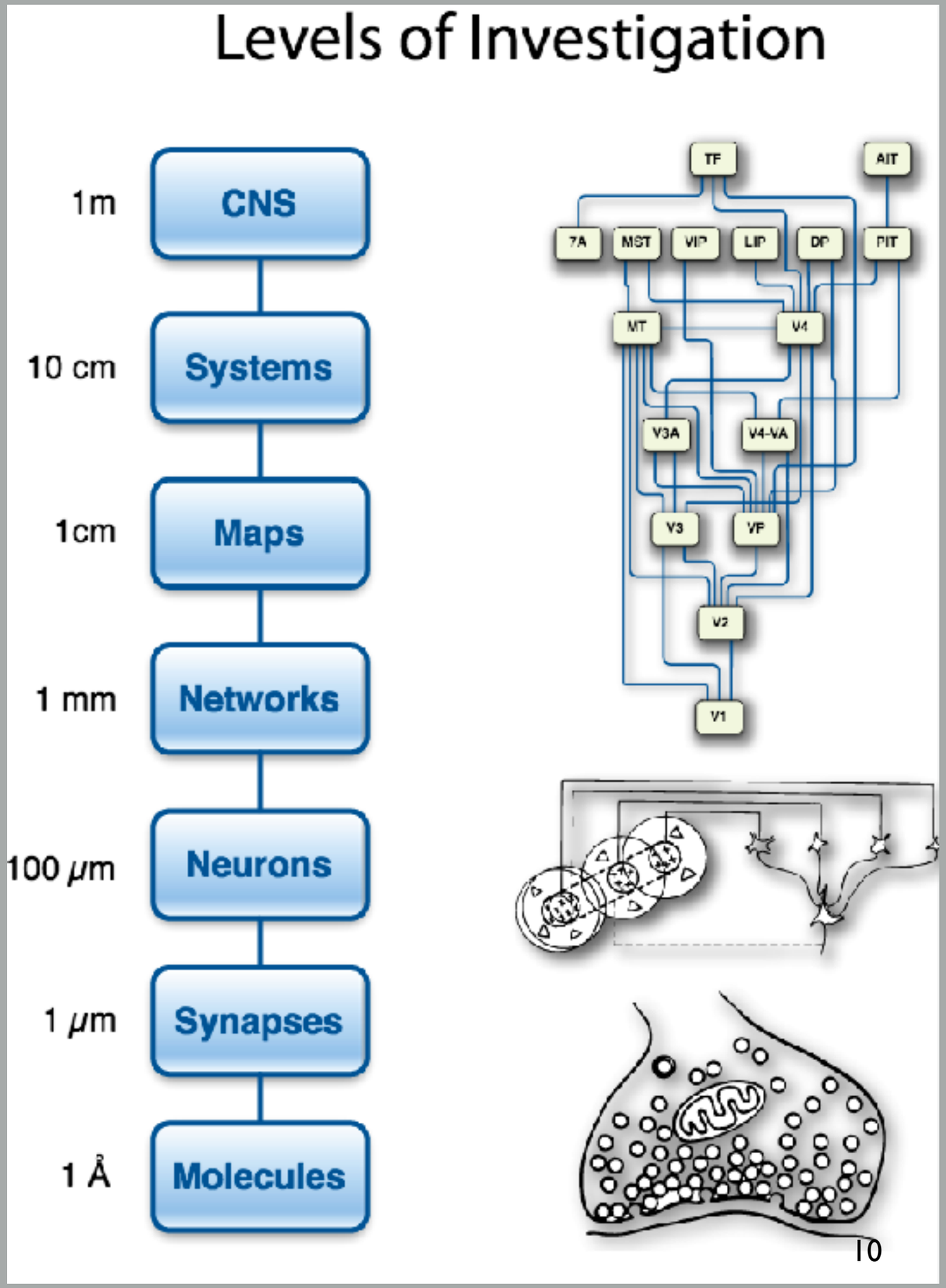


Glia, more than just brain-glue ?

The prejudice that the relation between neuroglial fibers and neuronal cells is similar to the relation between connective tissue and muscle or gland cells, that is, a passive weft for merely filling and support (and in the best case, a gangue for taking nutritive juices), constitutes the main obstacle that the researcher needs to remove to get a rational concept about the activity of the neuroglia.

—S Ramon y Cajal
Nobel Prize 1906

Neuroscience is a truly modern and multidisciplinary subject which seeks to understand the most complex organ in the body; the brain.



Modern Neuroscience research is a truly multidisciplinary subject that draws from biology, chemistry, physics mathematics, computer science, philosophy and psychology

Hierarchy of organizational levels is convenient but an oversimplification

Major hurdle to a better understanding of the brain is incomplete understanding of molecular principles that govern networks and behavior

Image: Terry Sejnowski


CAUTION

The New York Times

The Opinion Pages

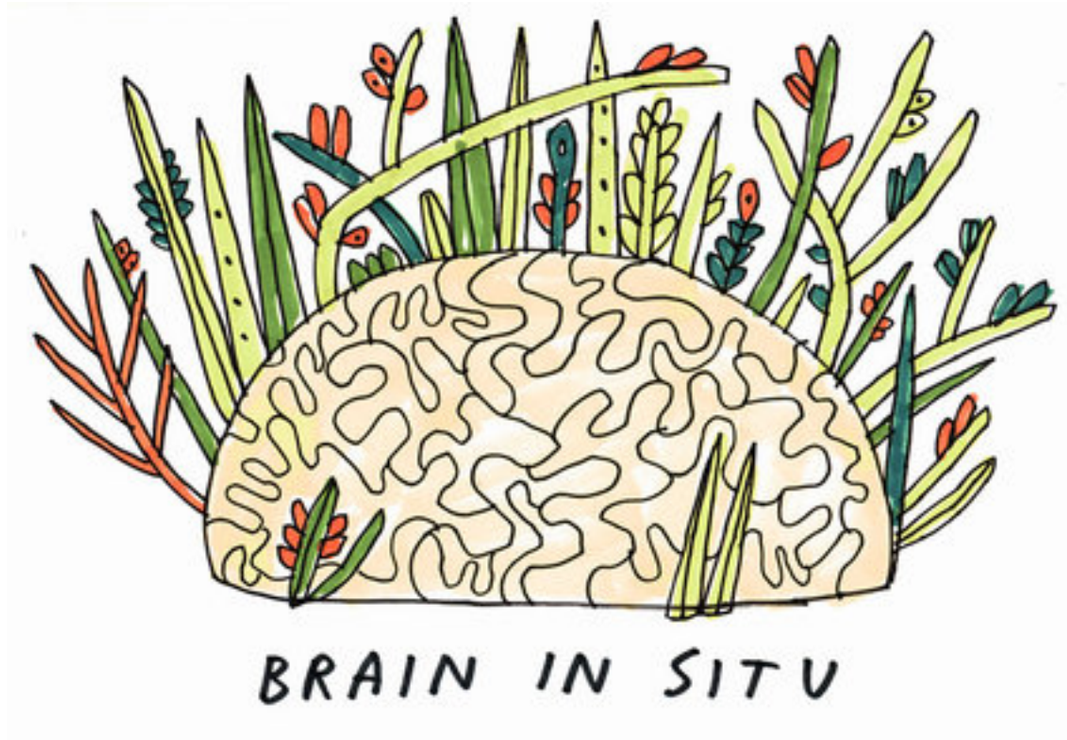
Opinionator

The Stone is a forum for contemporary philosophers and other thinkers on issues both timely and timeless.

THE STONE

Bursting the Neuro-Utopian Bubble

By BENJAMIN Y. FONG AUGUST 11, 2013 9:31 PM 387 Comments

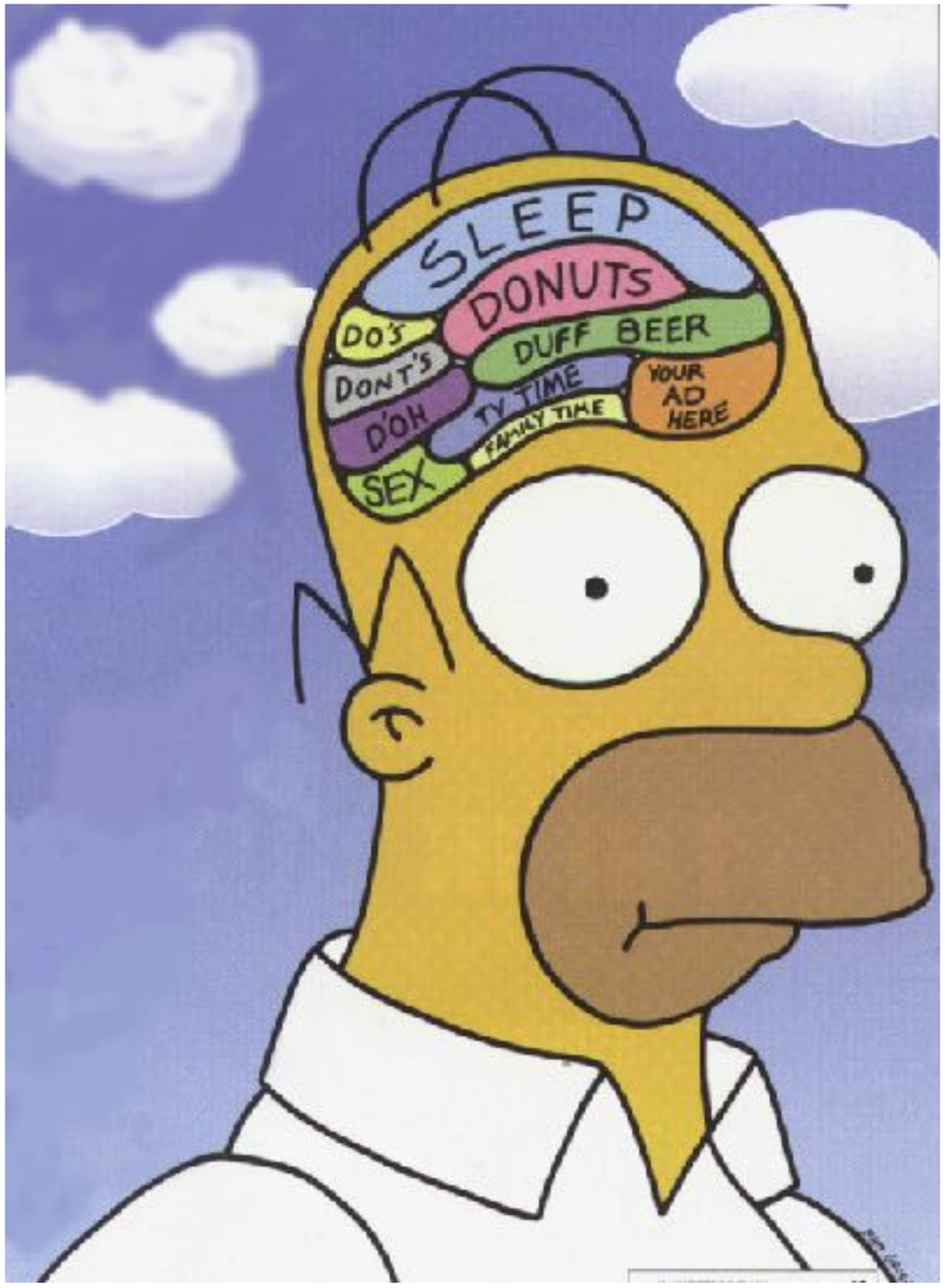


Neuroscience and psychology represent two radically different “modes” of science (“instrumental control” vs “critical reflection”); that neuroscience has been usurping psychology’s role in explaining human life; and that neuroscience is unable and unwilling to speak to concerns about personal and societal well-being, and so shuts down conversations about these issues.

“That it is somehow more realistic, “scientifically,” to find a way to change the human being itself than it is to work together to change the kind of environment that lends itself to the emergence of a disorder like schizophrenia.

What are brains for?

The kidneys make piss but brains make epistemology



Understanding the brain and the way it performs its function stretches our scientific and linguistics abilities

Neurological diseases remain the most challenging frontiers in Medicine

So whats the point?

No two brains are identical!

Yet, all brains have a lot in common that we can draw on.
A single cell protozoan: Paramecium is similar our nerve cells

Chemical sensing : oldest sense (bacteria use it). So is olfaction

Mechanisms that make the sensory detection events such taste smell sound are also somewhat conserved across phylogenies.

Use model systems (Drosophila) Argument: Understanding the workings of invertebrates is critical to understanding our own brain. Some experiments possible only in invertebrates.

Evolution has produced a large variation so as to accomplish specific tasks and solve problems :Larger variation in invertebrates than mammals

All organisms are limited in what whey can and this limitation comes from what brains can do: Explore these boundaries

Paramecium:Ionic currents

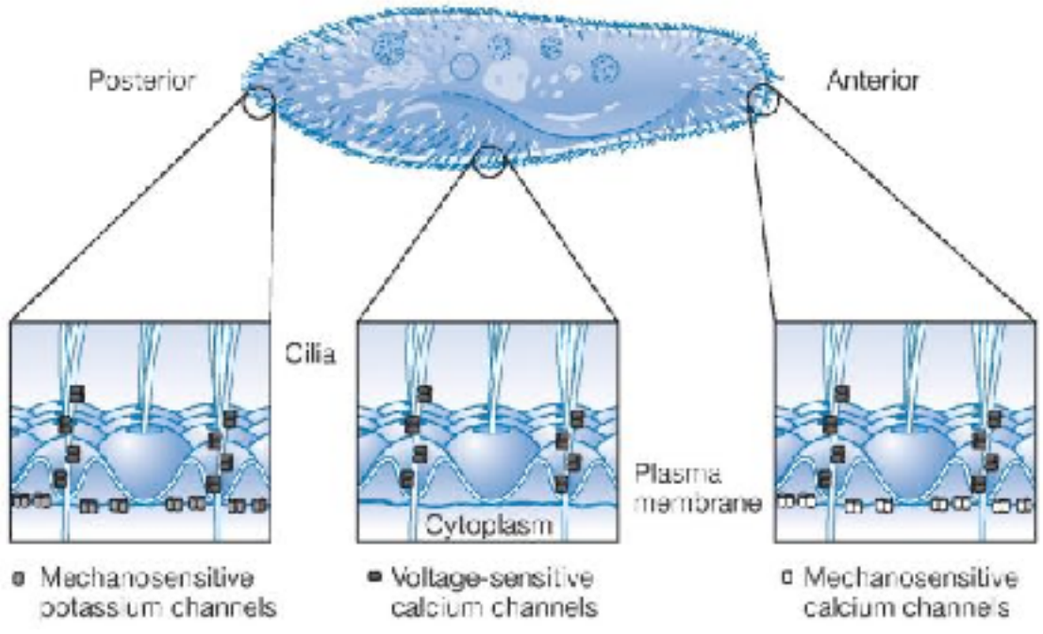
Paramecium: A unicellular organism shows very complex behavior
This behavior arises out of electrical signals identical to neurons coursing through them

Live in ponds, stagnant pools where they swim, consume bacteria, avoid predators and occasionally mate, sense variety of stimuli

It swims with thousands of cilia covering their single cell bodies.
When bumped from behind : it speeds up
Bumped into from front : backs up and changes direction

Sense temperature and chemical composition

They use the same currency that complex nervous systems do: electrical signals carried by charged ions Na+ Ca+ Cl-, K+ etc.



An Introduction to Nervous Systems (Textbook)
by Ralph J. Greenspan

Physics of neural signaling

Charge difference (an electrical potential) across cell membrane drives the movement of ions : inside more negatively charged compared to outside of the cell, -30 mV in normal pond water.

Excess of K+ inside and Ca+ and Na+ higher outside

Charge difference arises out of

1) -vely charged groups on many proteins inside the cell
2) Proteins called transporters and pumps on cell membrane actively pump ions out of the cell's cytoplasm
3) Selective permeability of the cell membrane that allows ions to diffuse out
4) Ions and proteins cannot penetrate hydrophobic lipids that comprises cell membranes : insulator

Basic chronology of electrical signaling

Membrane protein when induced to open creates pore through the lipid membrane that permits ions to pass.

Some of these ion channels are very selective.

When Na+ channel opens Na+ ions in. Creates net +ve current inside, membrane potential becomes +ve.

K+ go out making the cell more -ve etc.

The charges are not immediately flushed out because of the insulating properties of the cell membrane and this local signal can spread.

Eventually the cell goes back to its original state when the pumps pump the excess ions out.

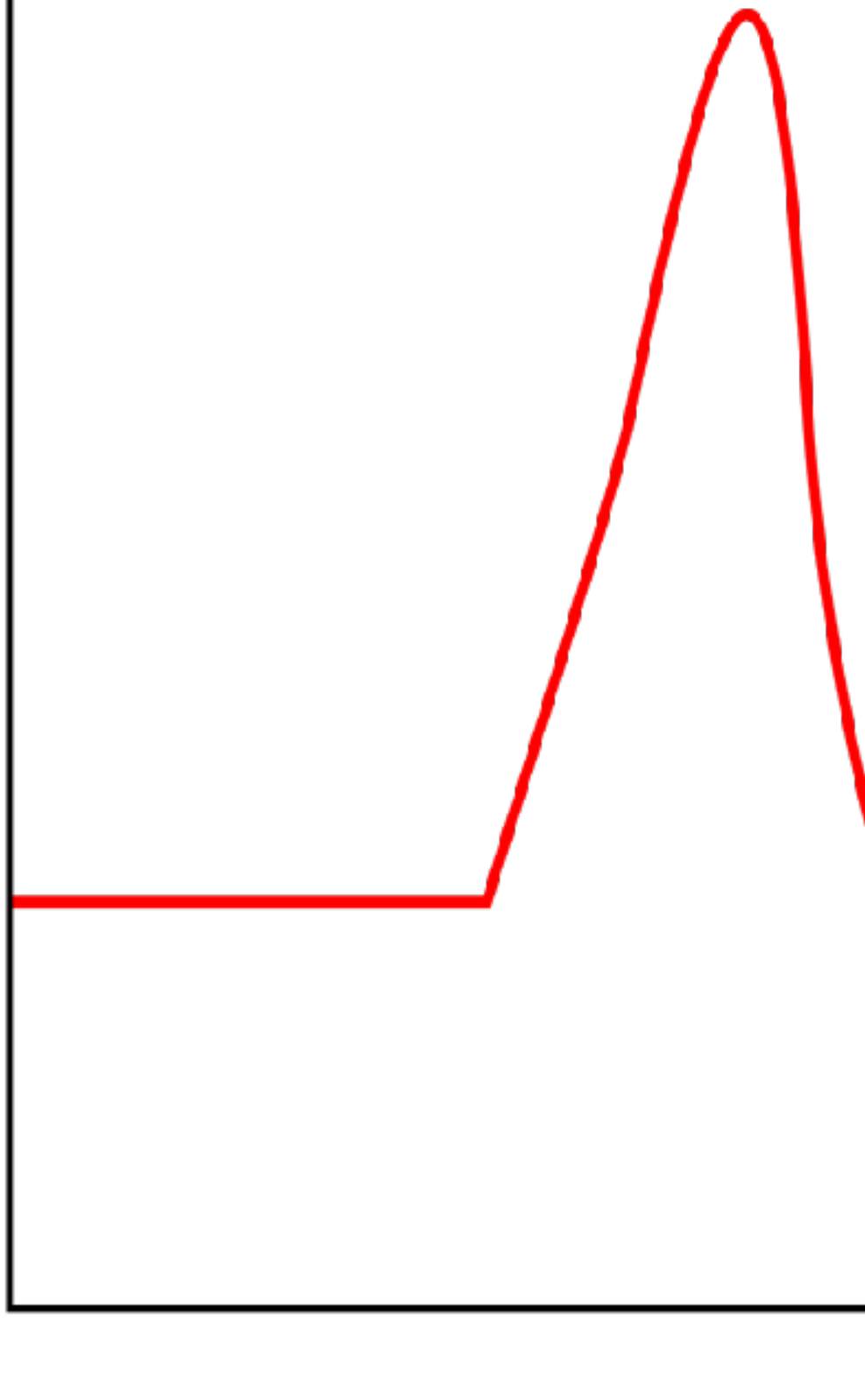
MIND Guest Blog

Exclusive: Oliver Sacks, Antonio Damasio and Others Debate Christof Koch on the Nature of Consciousness

A few neurologists and brain scientists are proposing that the secret underlying all conscious activity must lie with the way cells respond to stimuli they receive from their environment. In a response to this suggestion, Christof Koch asserts that much more is required for a full theory of consciousness

By Oliver Sacks, Antonio Damasio, Gil B. Carvalho, Norman D. Cook, Harry T. Hunt, Christof Koch on June 17, 2015

Action Potentials



Action potentials are not graded, on/off response. Do not degrade. Fixed size and duration: simplistic view - morse code.

Qualitative description: Electrical and chemical signaling across cellular barriers over ion channels and synaptic transmission

The cells capable of carrying out APs are called excitable. All the activity happens at the boundary between inside and outside because of the differences in concentration and electric potentials

The Nernst-Planck equation (NPE)

The ion flux under the influence of both concentration gradient and electric field is

$$\begin{aligned} J &= J_{\text{drift}} + J_{\text{diff}} \\ &= -\mu z[\mathrm{C}]\frac{\partial V}{\partial x} - D\frac{\partial[\mathrm{C}]}{\partial x} \end{aligned}$$

Einstein's relation allows us to express the diffusion coefficient in terms of mobility

$$J = -\left(\mu z[\mathrm{C}]\frac{\partial V}{\partial x} + \frac{\mu kT}{q}\frac{\partial[\mathrm{C}]}{\partial x}\right) \qquad \textbf{(NPE)}$$

NPE in current density form

$$I = \mathbf{J} \cdot zF = -\left(uz^2F[\mathrm{C}]\frac{\partial V}{\partial x} + uzRT\frac{\partial[\mathrm{C}]}{\partial x}\right)$$

The Nernst equation (NPE)

When the membrane is at rest

$$I = -\left(uz^2F[\mathrm{C}]\frac{\partial V}{\partial x} + uzRT\frac{\partial [\mathrm{C}]}{\partial x}\right) = 0$$

$$V_{\mathrm{in}} - V_{\mathrm{out}} = \frac{RT}{zF}\ln\frac{[\mathrm{C}]_{\mathrm{out}}}{[\mathrm{C}]_{\mathrm{in}}}$$

Nernst equation

	Inside (mM)	Outside (mM)	Equilibrium Potential (NE) $E_i = \frac{RT}{zF} \ln \frac{[C]_{out}}{[C]_{in}}$
Frog muscle (Conway 1957)			$T = 20°C = 293°K$
K^+	124	2.25	$58 \log \frac{2.25}{124} = -101$ mV
Na^+	10.4	109	$58 \log \frac{109}{10.4} = +59$ mV
Cl^-	1.5	77.5	$-58 \log \frac{77.5}{1.5} = -99$ mV
Ca^{2+}	$4.9^\dagger$	2.1	$29 \log \frac{2.1}{10^{-4}} = +125$ mV
Squid axon (Hodgkin 1964)			
K^+	400	20	$58 \log \frac{20}{400} = -75$ mV
Na^+	50	440	$58 \log \frac{440}{50} = +55$ mV
Cl^-	40–150	560	$-58 \log \frac{560}{40-150} = -66 - (-33)$ mV
Ca^{2+}	$0.4^\dagger$	10	$29 \log \frac{10}{10^{-4}} = +145$ mV
Typical mammalian cell			$T = 37°C = 310°K$
K^+	140	5	$62 \log \frac{5}{140} = -89.7$ mV
Na^+	5–15	145	$62 \log \frac{145}{5-15} = +90.7 - (+61.1)$ mV
Cl^-	4	110	$-62 \log \frac{110}{4} = -89$ mV
Ca^{2+}	$1–2^\dagger$	2.5–5	$31 \log \frac{2.5-5}{10^{-4}} = +136 - (+145)$ mV

$^\dagger(10^{-4})$ free

The Goldman-Hodgkin-Katz (GHK) model

$$I = PzF\xi\left(\frac{[\mathrm{C}]_{\mathrm{in}} - [\mathrm{C}]_{\mathrm{out}}e^{-\xi}}{1 - e^{-\xi}}\right)$$

GHK current equation

$$\text{efflux}: I_{\mathrm{out}} = PzF\xi\frac{[\mathrm{C}]_{\mathrm{in}}}{1 - e^{-\xi}},$$

$$\xi \stackrel{\text{def}}{=} \frac{zVF}{RT}$$

and

$$\text{influx}: I_{\mathrm{in}} = -PzF\xi\frac{[\mathrm{C}]_{\mathrm{out}}e^{-\xi}}{1 - e^{-\xi}}.$$

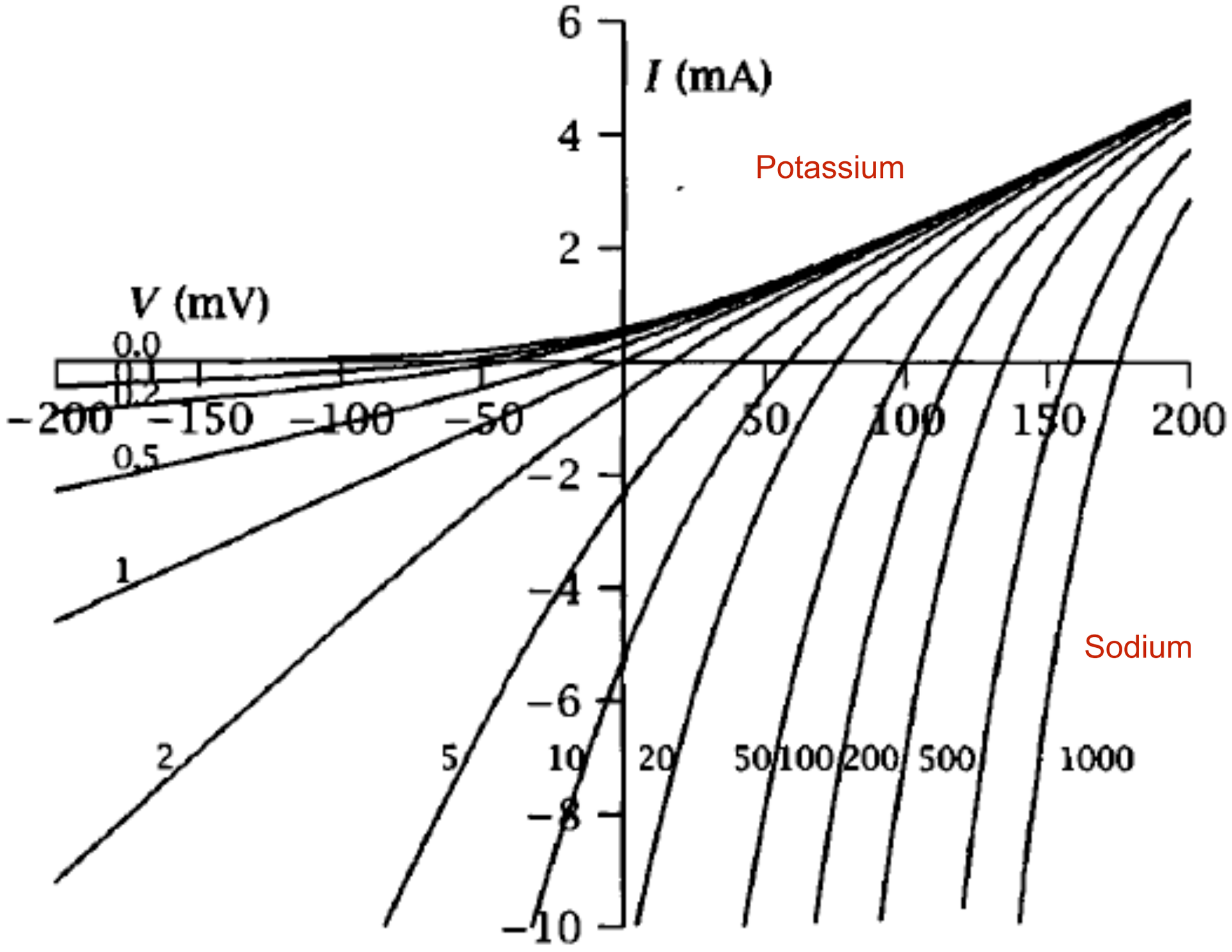
GHK current equation predicts that the membrane current is a nonlinear function of membrane potential

The current-voltage relation depends on the ratio [C]out/[C]in.

When [C]out/[C]in = 1, Current=constant times V and the I-V relation is linear.
When [C]out/[C]in < 1, I-V relation shows outward rectification, slope increases with membrane voltages
When [C]out/[C]in >1, I-V relation shows inward rectification, slope decreases with membrane voltages

IV relationship for GHK

Inward and Outward Rectification



Johnston and Wu, Foundations of cellular Neurophysiology

For a cell that is permeable to K+, Na+, and Cl- ions,

$$
\begin{aligned}
I &= I_K + I_{Na} + I_{Cl} \\
&= P_K z F \xi \frac{[\mathrm{K}^+]_{\mathrm{in}} - [\mathrm{K}^+]_{\mathrm{out}} e^{-\xi}}{1 - e^{-\xi}} + P_{Na} z F \xi \frac{[\mathrm{Na}^+]_{\mathrm{in}} - [\mathrm{Na}^+]_{\mathrm{out}} e^{-\xi}}{1 - e^{-\xi}} \\
&\quad + P_{Cl} z F \xi \frac{[\mathrm{Cl}^-]_{\mathrm{in}} - [\mathrm{Cl}^-]_{\mathrm{out}} e^{-\xi}}{1 - e^{-\xi}}
\end{aligned}
$$

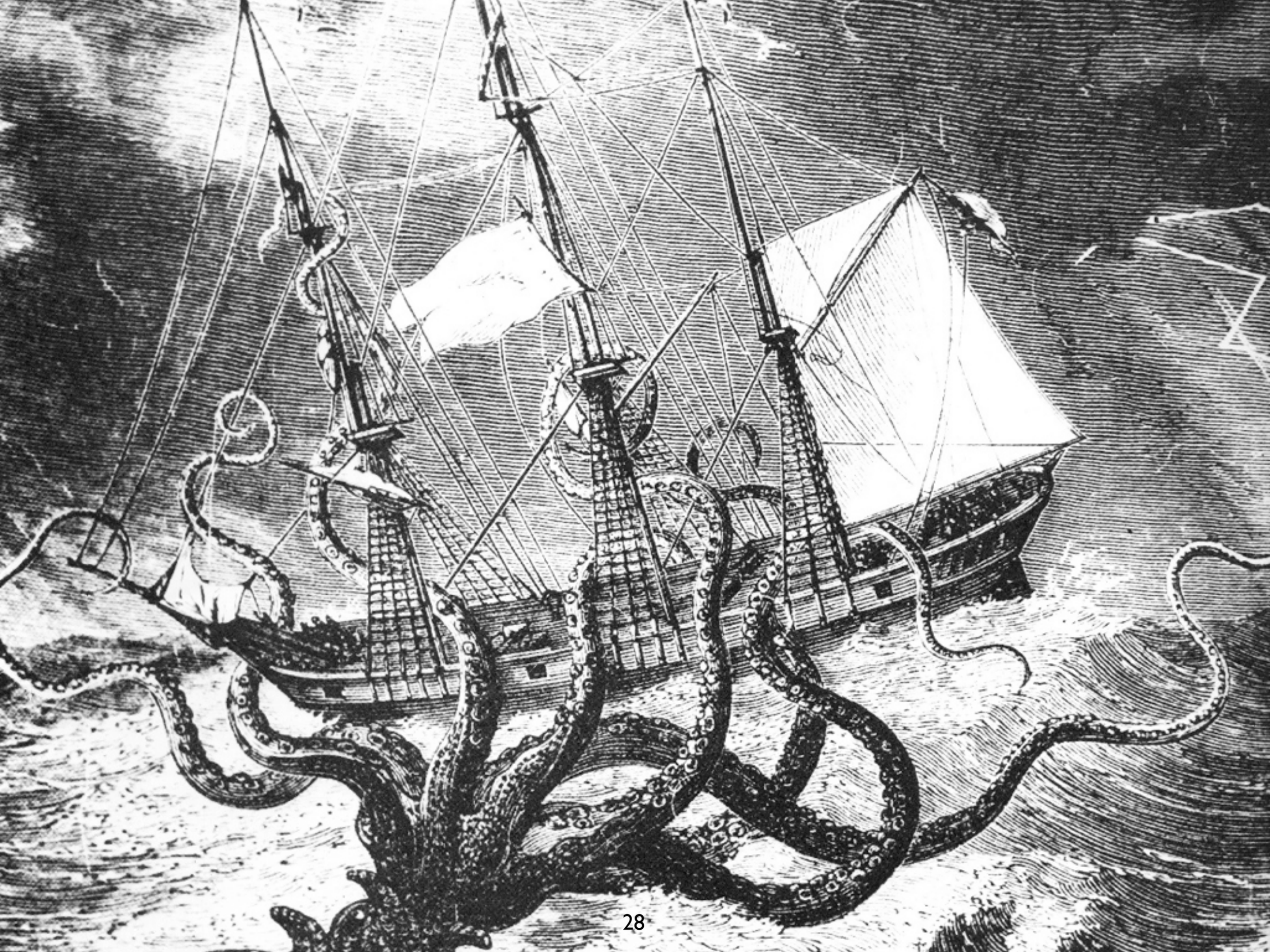
The resting potential of the cells can be calculated by setting the total current across the membrane equal to zero.

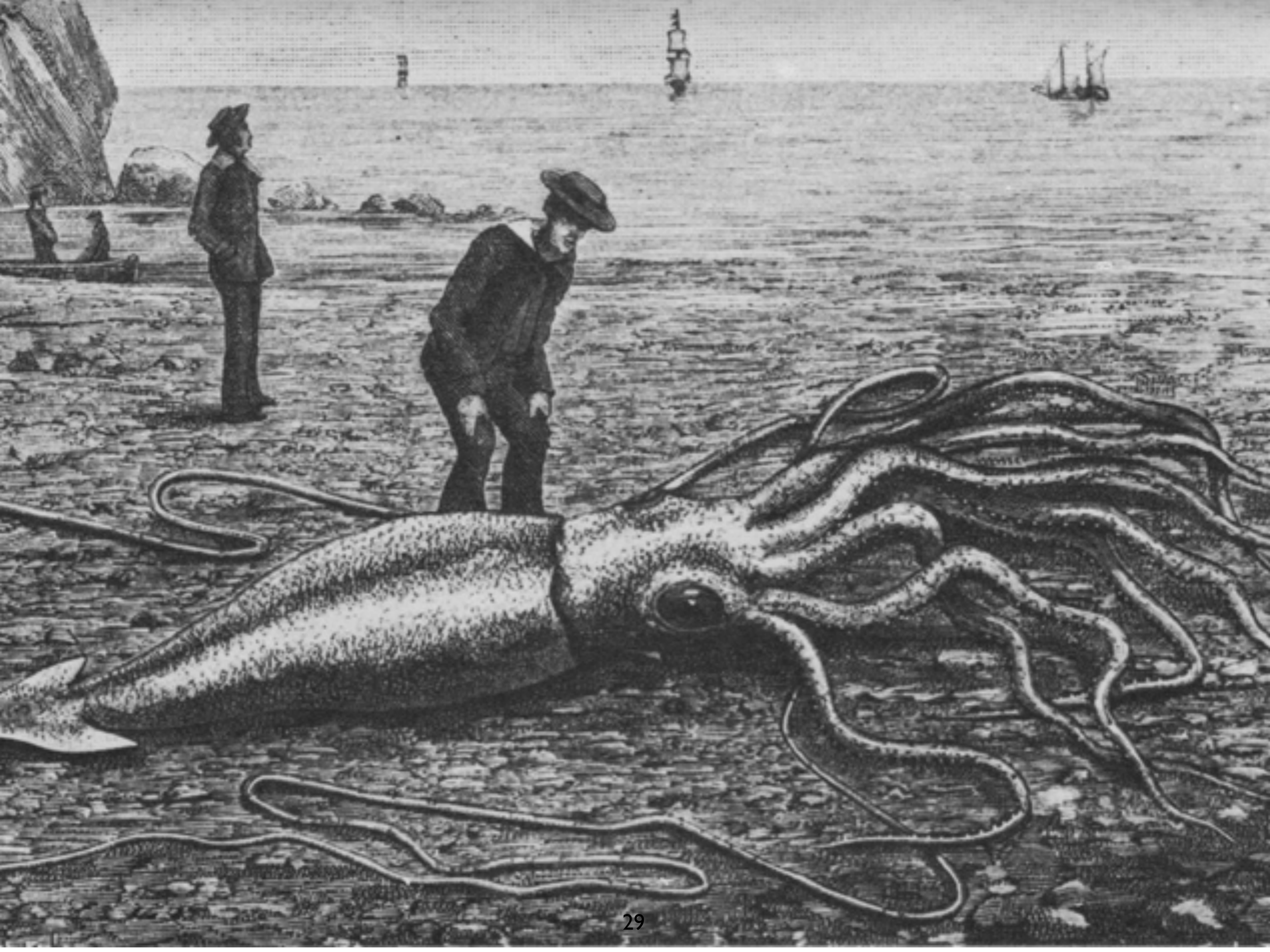
$$
V = \frac{RT}{\mathrm{F}} \ln \frac{P_K[\mathrm{K}^+]_{\mathrm{out}} + P_{Na}[\mathrm{Na}^+]_{\mathrm{out}} + P_{Cl}[\mathrm{Cl}^-]_{\mathrm{in}}}{P_K[\mathrm{K}^+]_{\mathrm{in}} + P_{Na}[\mathrm{Na}^+]_{\mathrm{in}} + P_{Cl}[\mathrm{Cl}^-]_{\mathrm{out}}}.
$$

GHK voltage equation

At rest, the ratio of permeabilities for a squid giant axon PK : PNa : PCl = 1: 0.03 : 0.1 and leads to a prediction of resting voltage to be -70 mV (Compare that to the K reversal)

Hodgkin and Huxley's Analysis of the Squid Giant Axon: Architeuthis?





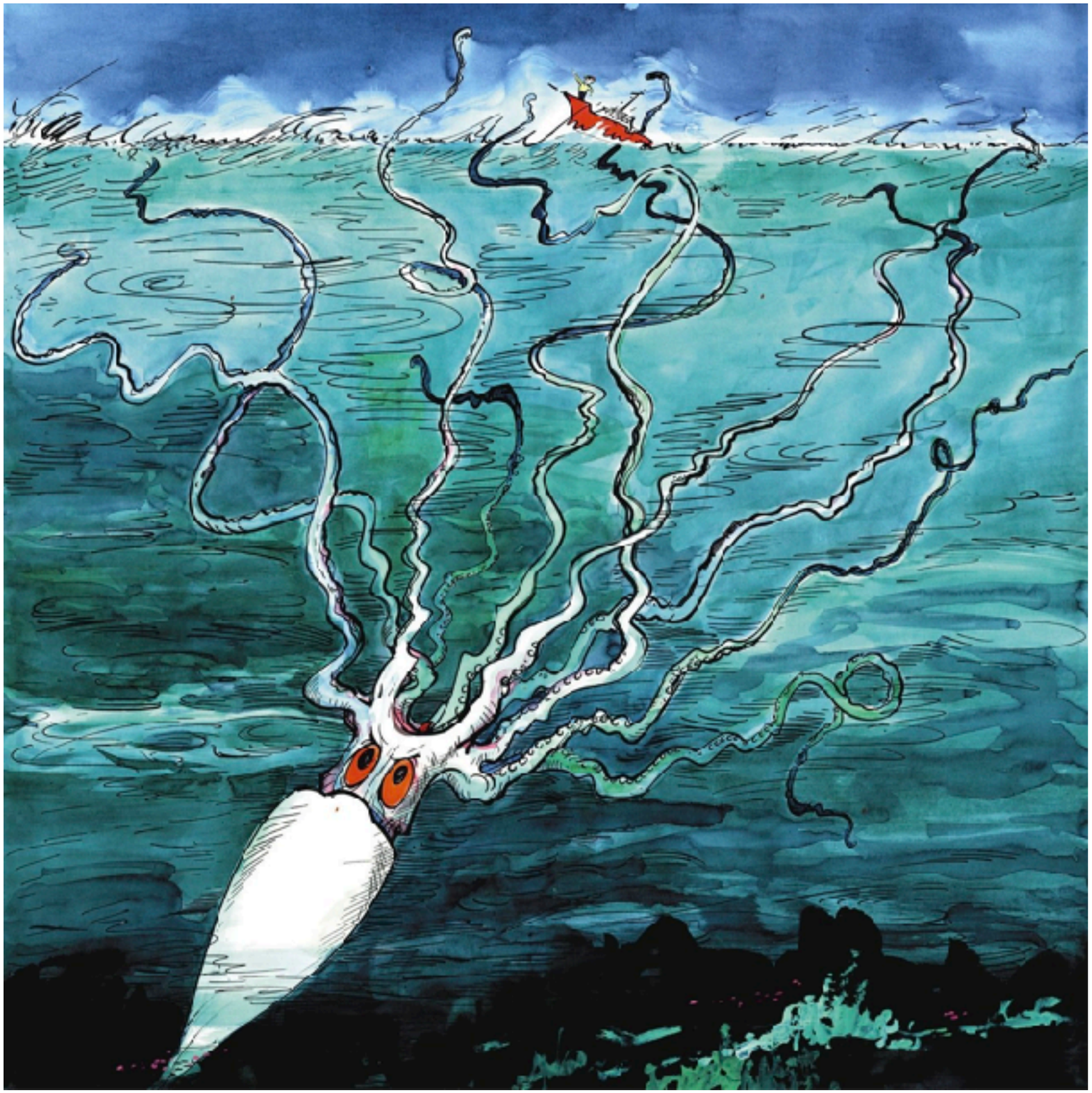
A REPORTER AT LARGE | MAY 24, 2004 ISSUE

THE SQUID HUNTER

Can Steve O'Shea capture the sea's most elusive creature?

BY DAVID GRANN

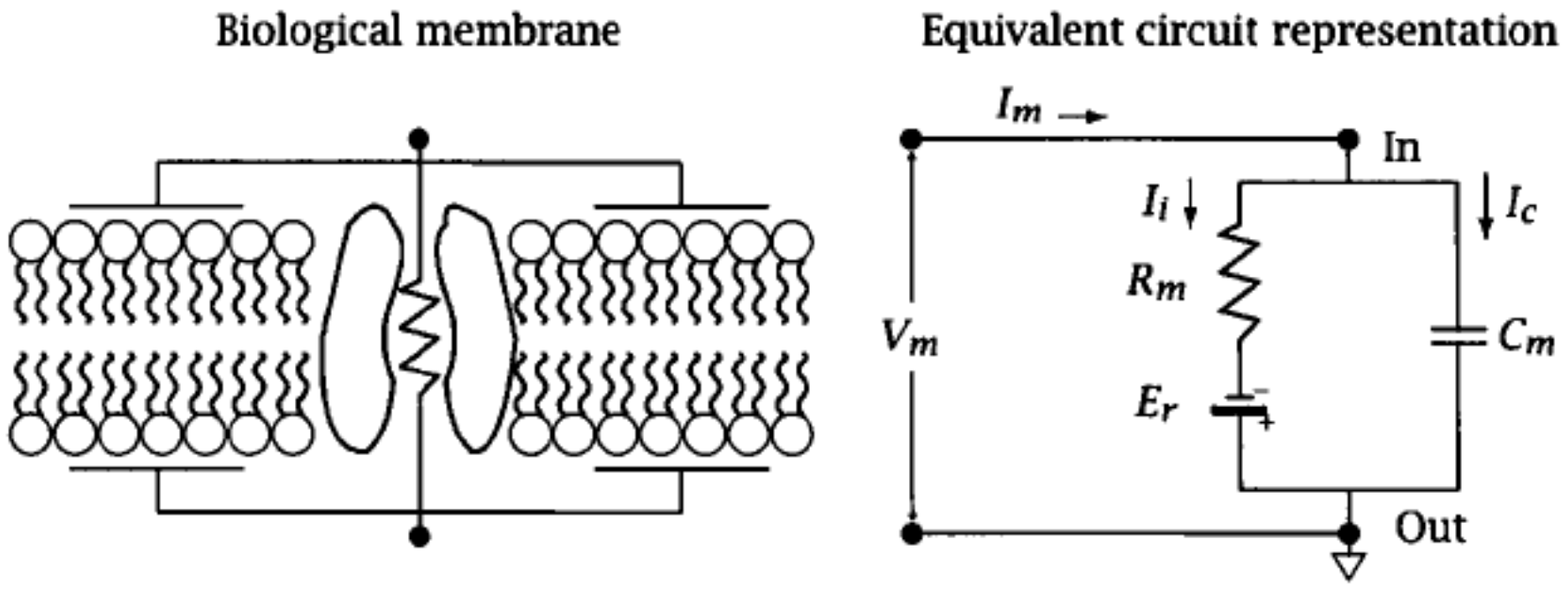
TABLE OF CONTENTS »



In a famous scene in “20,000 Leagues Under the Sea,” Jules Verne depicts a battle between a submarine and a giant squid that is twenty-five feet long, with eight arms and blue-green eyes —“a terrible monster worthy of all the legends about such creatures.”

Peter Benchley, in his thriller “Beast,” describes a giant squid that “killed without need, as if Nature, in a fit of perverse malevolence, had programmed it to that end.”

Circuit representation of the biological membrane

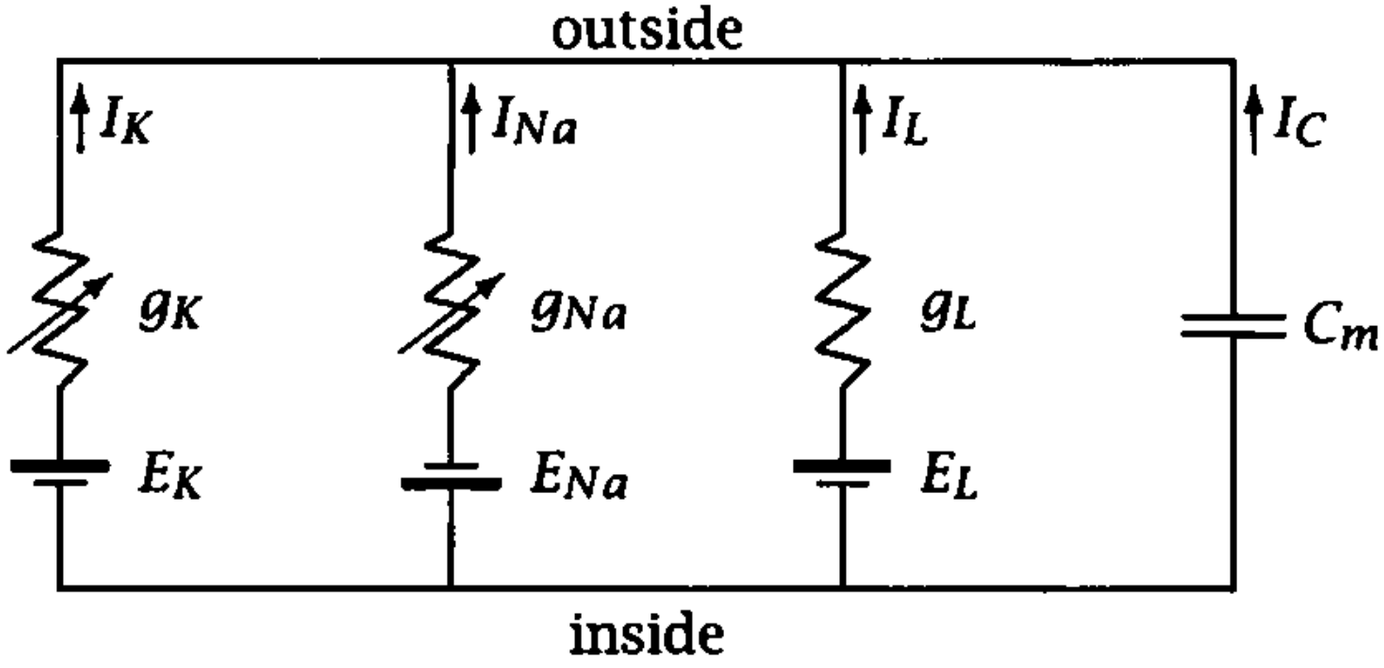


Electrical behavior of biological membranes can be described in terms of electric circuits.

Using Kirchhoff's laws :

$$I_m = I_C + I_i = C_m \frac{dV_m}{dt} + \frac{(V_m - E_r)}{R_m}$$
$$= C_m \frac{dV_m}{dt} + G_m(V_m - E_r).$$

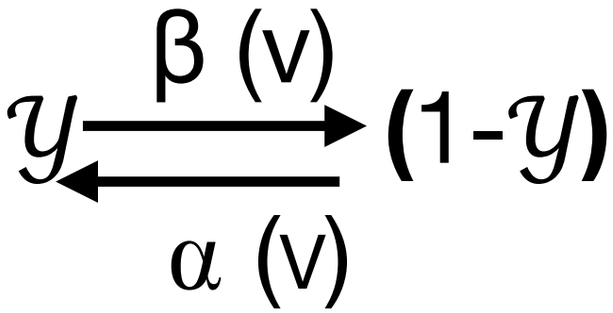
Johnston and Wu, Foundations of cellular Neurophysiology



$$I_m = C_m \frac{dV}{dt} + g_K(V,t)(V - E_K) + g_{Na}(V,t)(V - E_{Na}) + g_L(V - E_L).$$

$$g_K(t) = \bar{g}_K n^4 ;$$

$$g_{Na}(t) = \bar{g}_{Na} m^3 h$$



J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

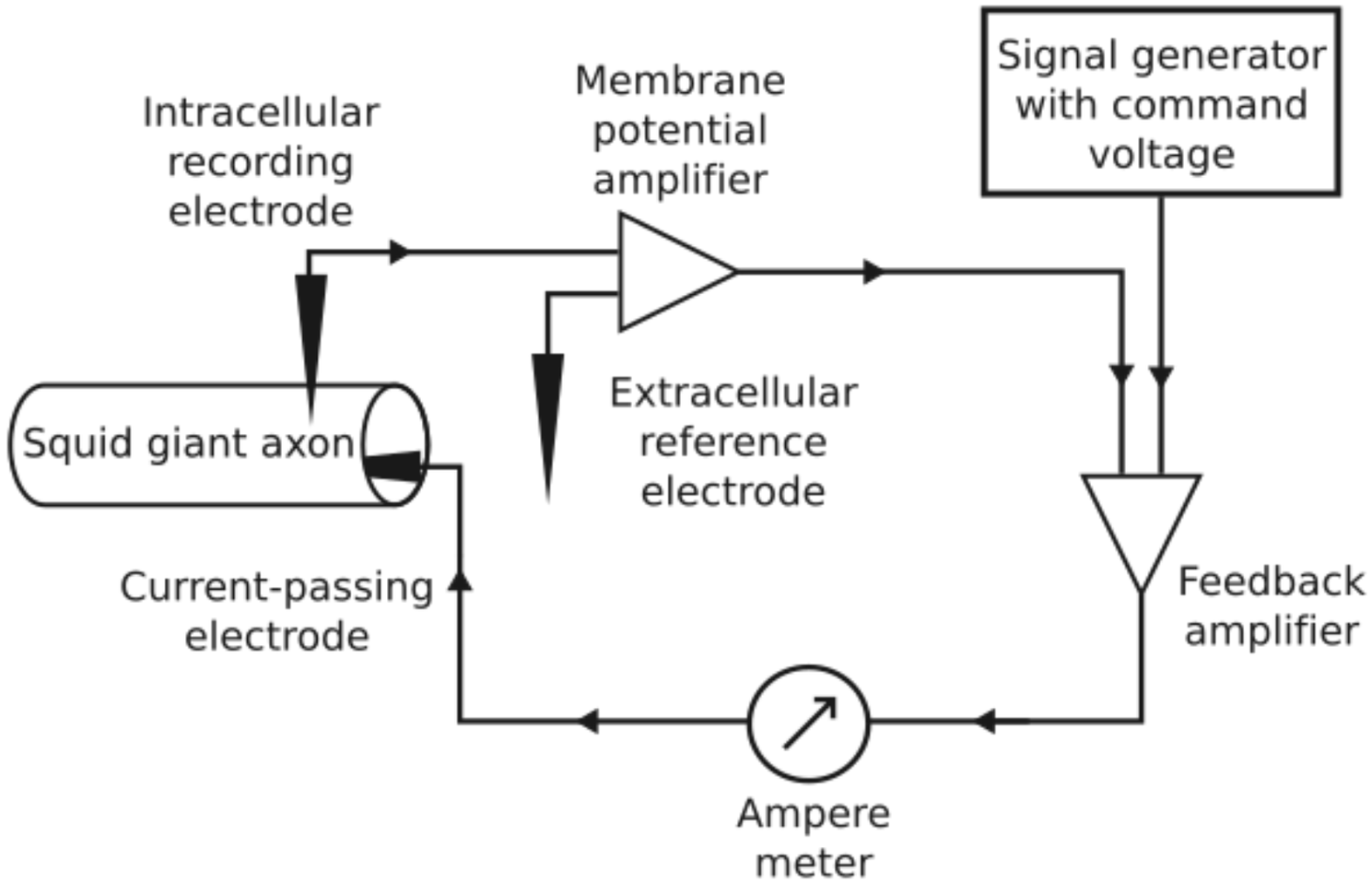
By A. L. HODGKIN and A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

(*Received* 10 *March* 1952)

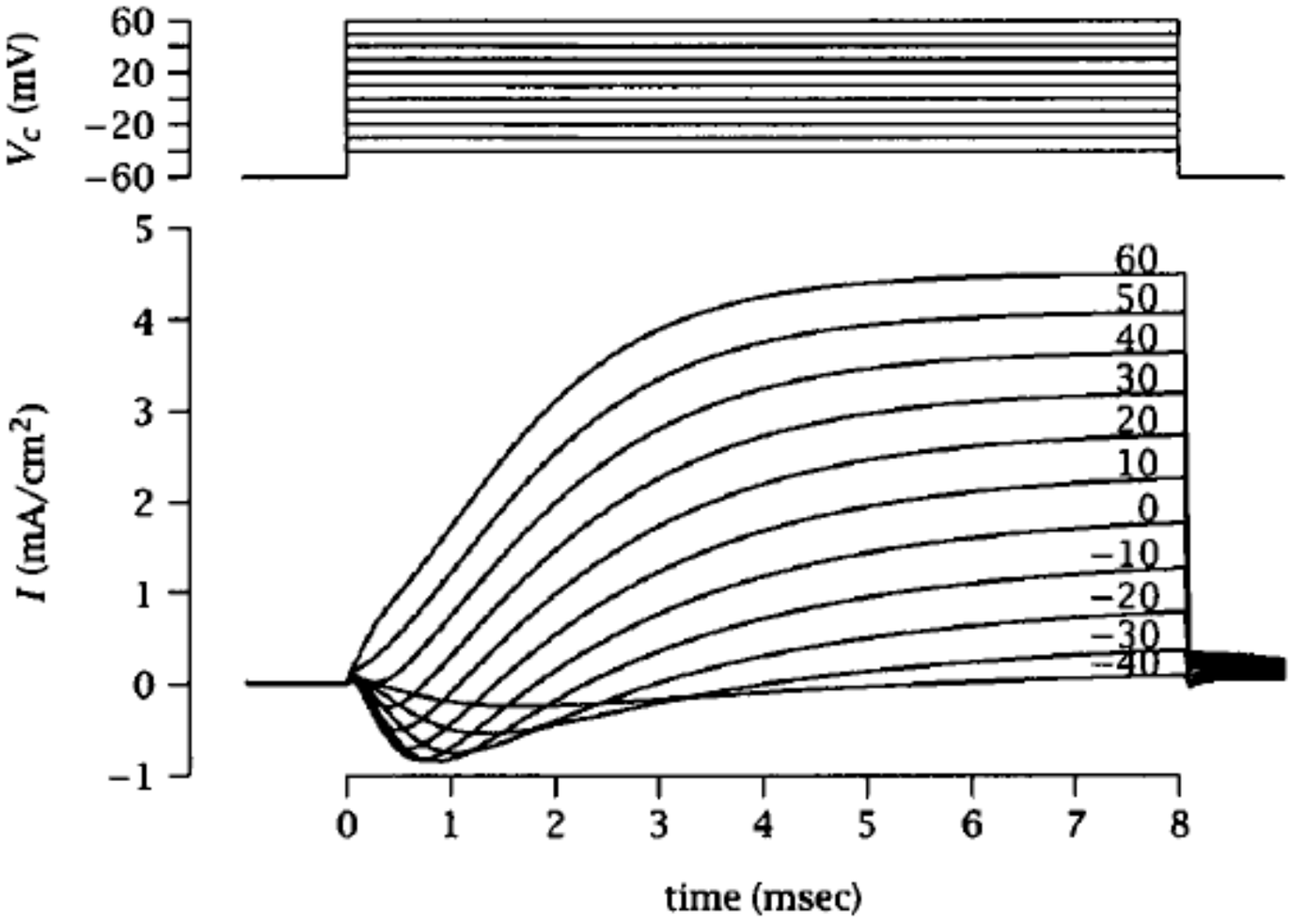
This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952 *a–c*). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).

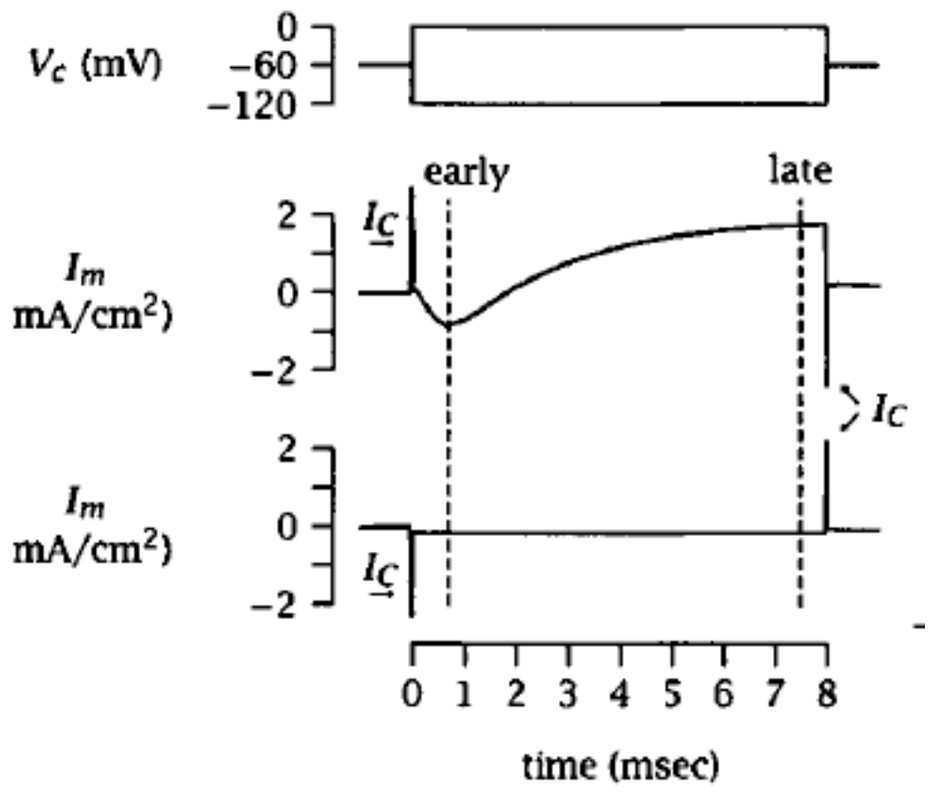
Voltage Clamp



Voltage-clamp Experiments

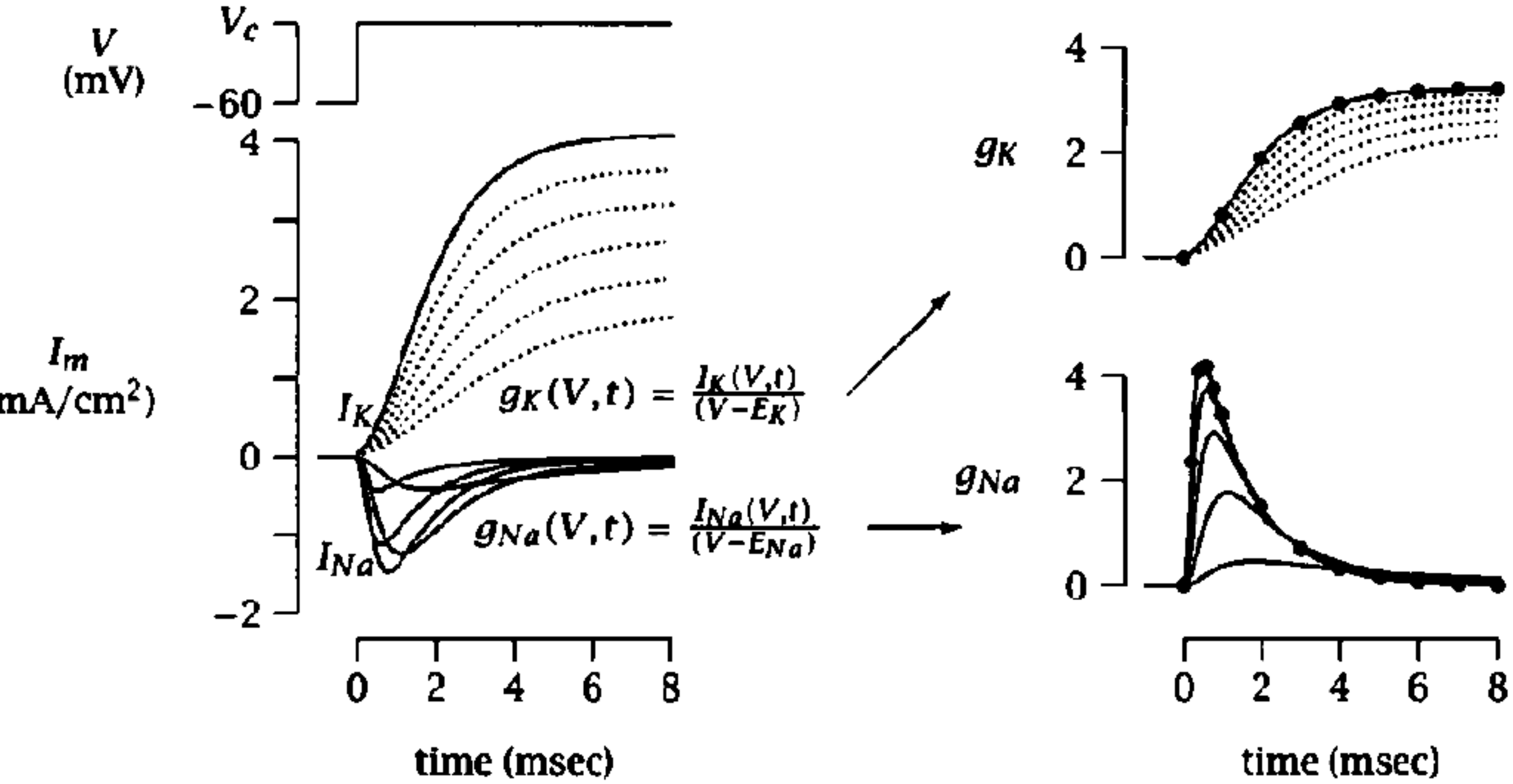
Current records of the squid axon when the voltage is stepped
from a holding voltage (VH) to a command voltage (Vc) of various levels.





The early onset inward current mediated by Na+ (see above -30 mV)and the late onset outward current mediate by K+ (pharmacological agents TTX and TEA)

calculating gNa/gK for every instant:response to single pulse

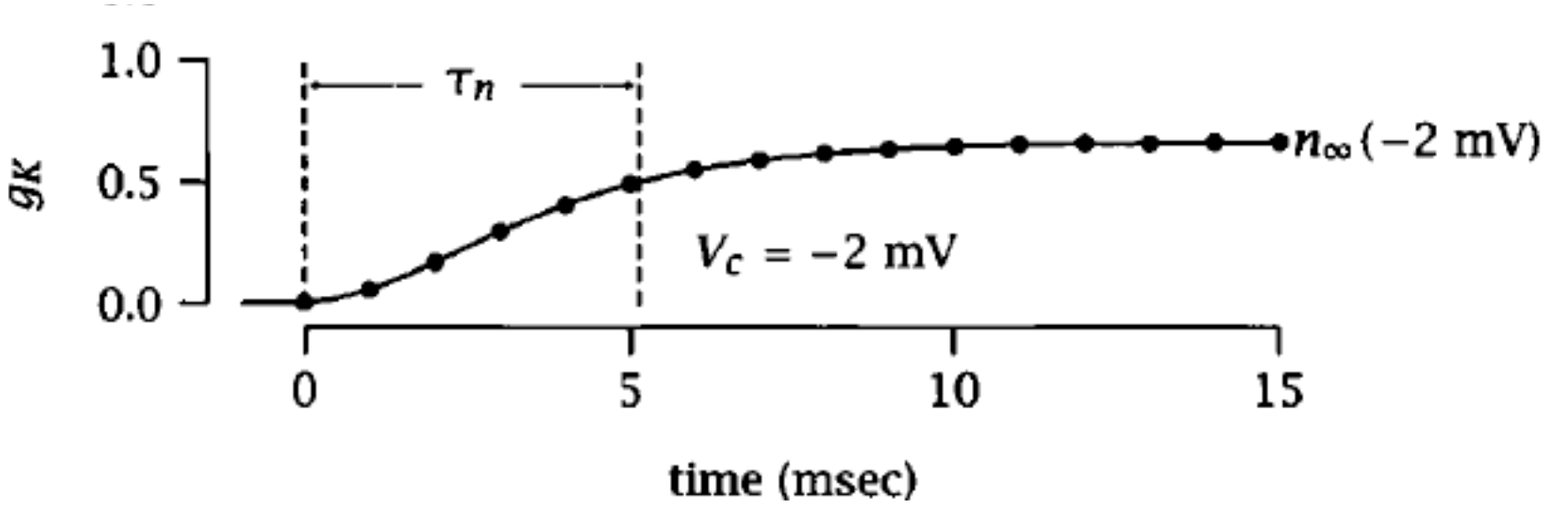


Each family of lines for either I_K and I_Na describes various holding voltages V.

Since experimentally it was seen that instantaneous conductance is linear, g=I/V (Ohms law)

Johnston and Wu, Foundations of cellular Neurophysiology

Calculate values of α and β for several voltages from expt. data



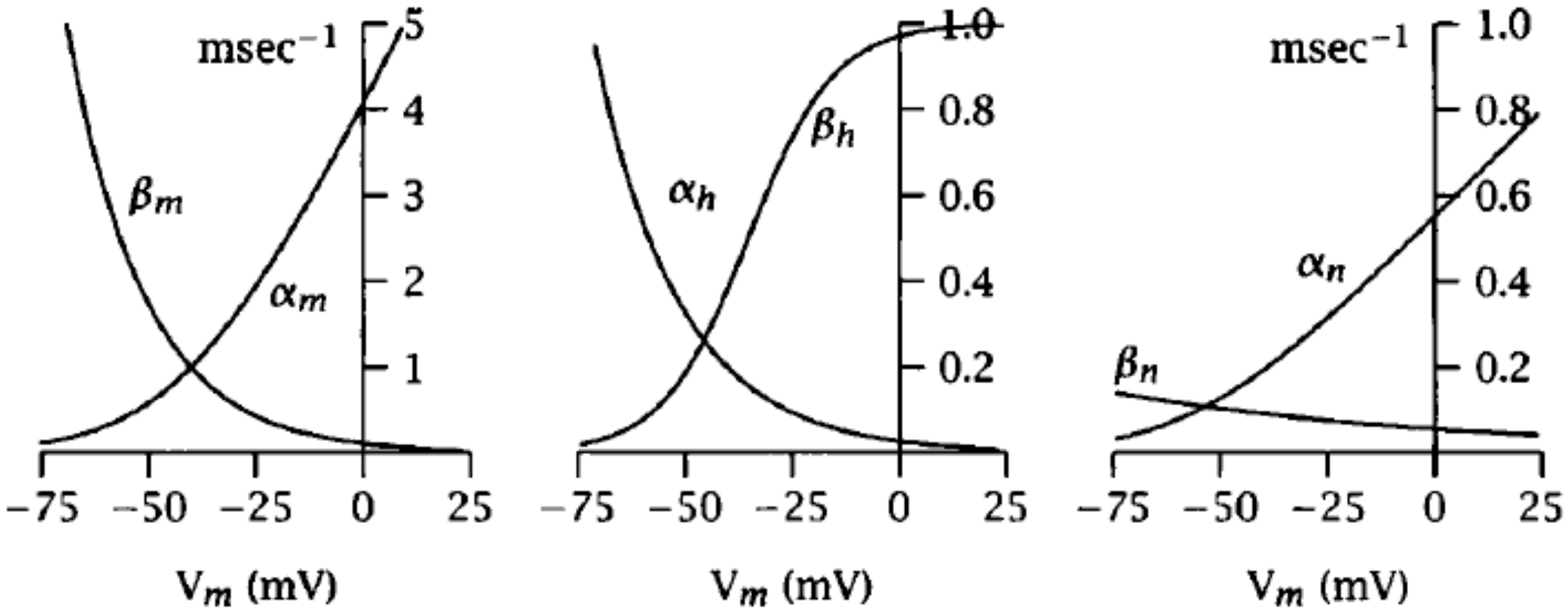
$$g_K(t) = \bar{g}_K n^4 = \bar{g}_K \left[n_0 - (n_0 - n_\infty)(1 - e^{-t/\tau_n}) \right]^4. \qquad (6.3.5)$$

$$\begin{aligned} g_{Na}(t) &= \bar{g}_{Na} m^3 h \\ &= \bar{g}_{Na} \left[m_0 - (m_0 - m_\infty)(1 - e^{-t/\tau_m}) \right]^3 \left[h_\infty + (h_0 - h_\infty) e^{-t/\tau_h} \right] \\ &= \bar{g}_{Na} m_\infty^3 h_0 \left(1 - e^{-t/\tau_m} \right)^3 e^{-t/\tau_h}, \qquad (6.3.6) \end{aligned}$$

$$\begin{aligned} \alpha_n &= n_\infty/\tau_n \qquad \beta_n = (1 - n_\infty/\tau_n), \\ \alpha_m &= m_\infty/\tau_m \qquad \beta_m = (1 - m_\infty)/\tau_m, \\ \alpha_h &= h_\infty/\tau_h \qquad \beta_h = (1 - h_\infty)/\tau_h. \end{aligned}$$

Calculate alpha and beta for each V_c

Plot Alphas and Betas them and fit a function to it



functions α and β follow gate model prediction (m and n activated by depolarization, h inactivated by depolarization)

$$\beta_n(V) = 0.125e^{\frac{-V}{80}},$$

$$\alpha_m(V) = 0.1(-V + 25)/\left(e^{\frac{-V+25}{10}} - 1\right),$$

$$\beta_m(V) = 4e^{\frac{-V}{18}},$$

$$\alpha_h(V) = 0.07e^{\frac{-V}{20}},$$

$$\beta_h(V) = 1/\left(e^{\frac{-V+30}{10}} + 1\right).$$

Hodgkin and Huxley equations

$$I_m = C_m \frac{dV}{dt} + \overline{g}_K n^4 (V - E_K) + \overline{g}_{Na} m^3 h (V - E_{Na}) + g_L (V - E_L).$$

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

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

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

$$\alpha_n(V) = 0.01(-V + 10) / \left[e^{\frac{-V+10}{10}} - 1 \right]$$

$$\beta_n(V) = 0.125 e^{\frac{-V}{80}},$$

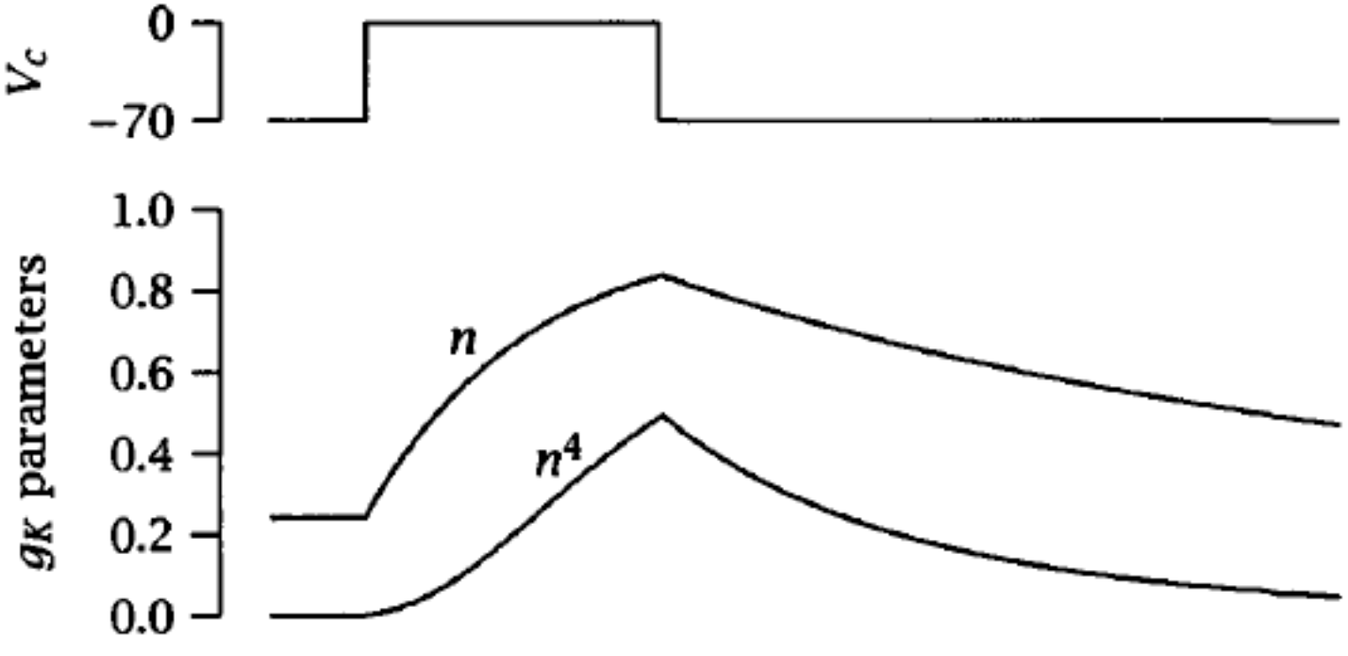
$$\alpha_m(V) = 0.1(-V + 25) / \left(e^{\frac{-V+25}{10}} - 1 \right),$$

$$\beta_m(V) = 4 e^{\frac{-V}{18}},$$

$$\alpha_h(V) = 0.07 e^{\frac{-V}{20}},$$

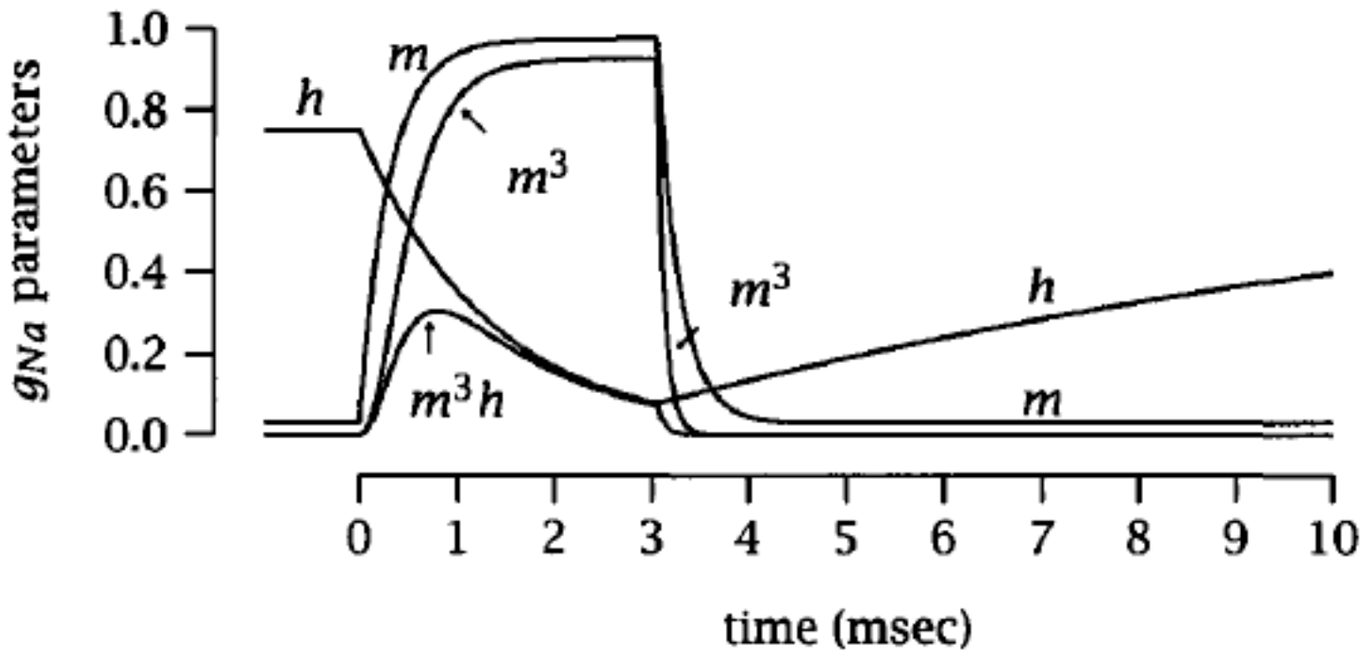
$$\beta_h(V) = 1 / \left(e^{\frac{-V+30}{10}} + 1 \right).$$

Plotting the solutions of m,n and h gates



$$n(t) = n_0 - \left[(n_0 - n_\infty)\left(1 - e^{-t/\tau_n}\right)\right],$$

$$m(t) = m_0 - \left[(m_0 - m_\infty)\left(1 - e^{-t/\tau_m}\right)\right],$$



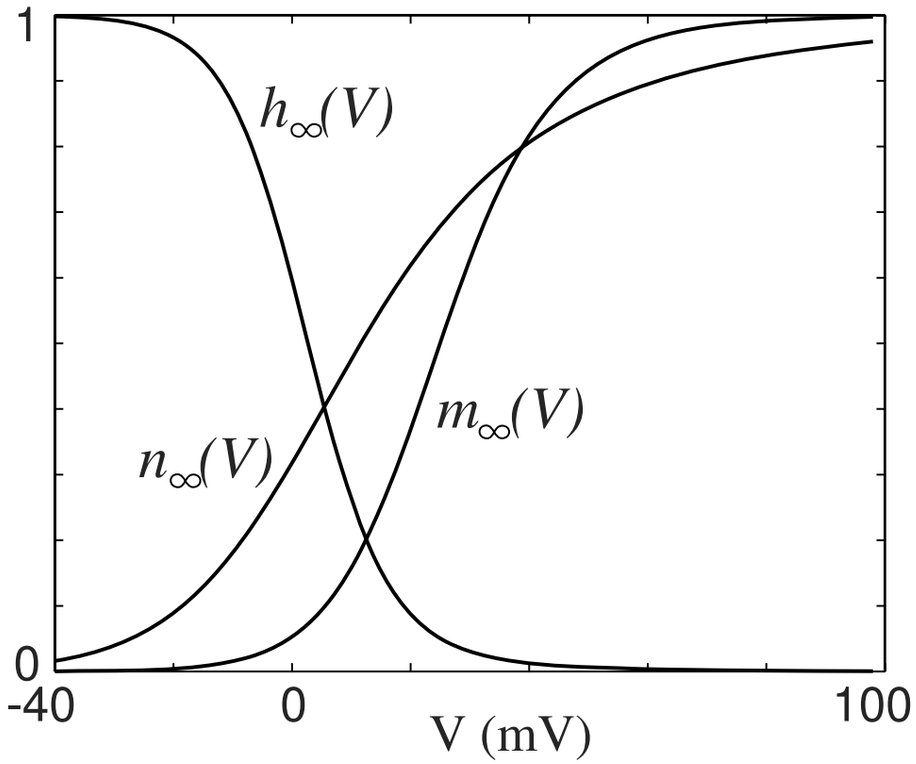
and

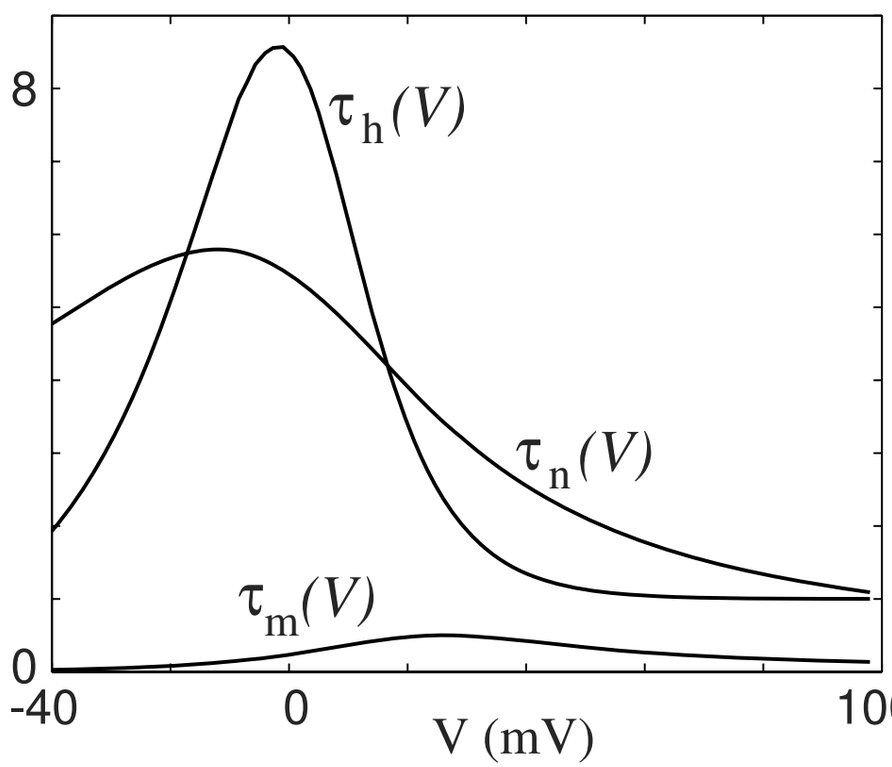
$$h(t) = h_0 - \left[(h_0 - h_\infty)\left(1 - e^{-t/\tau_h}\right)\right],$$

or

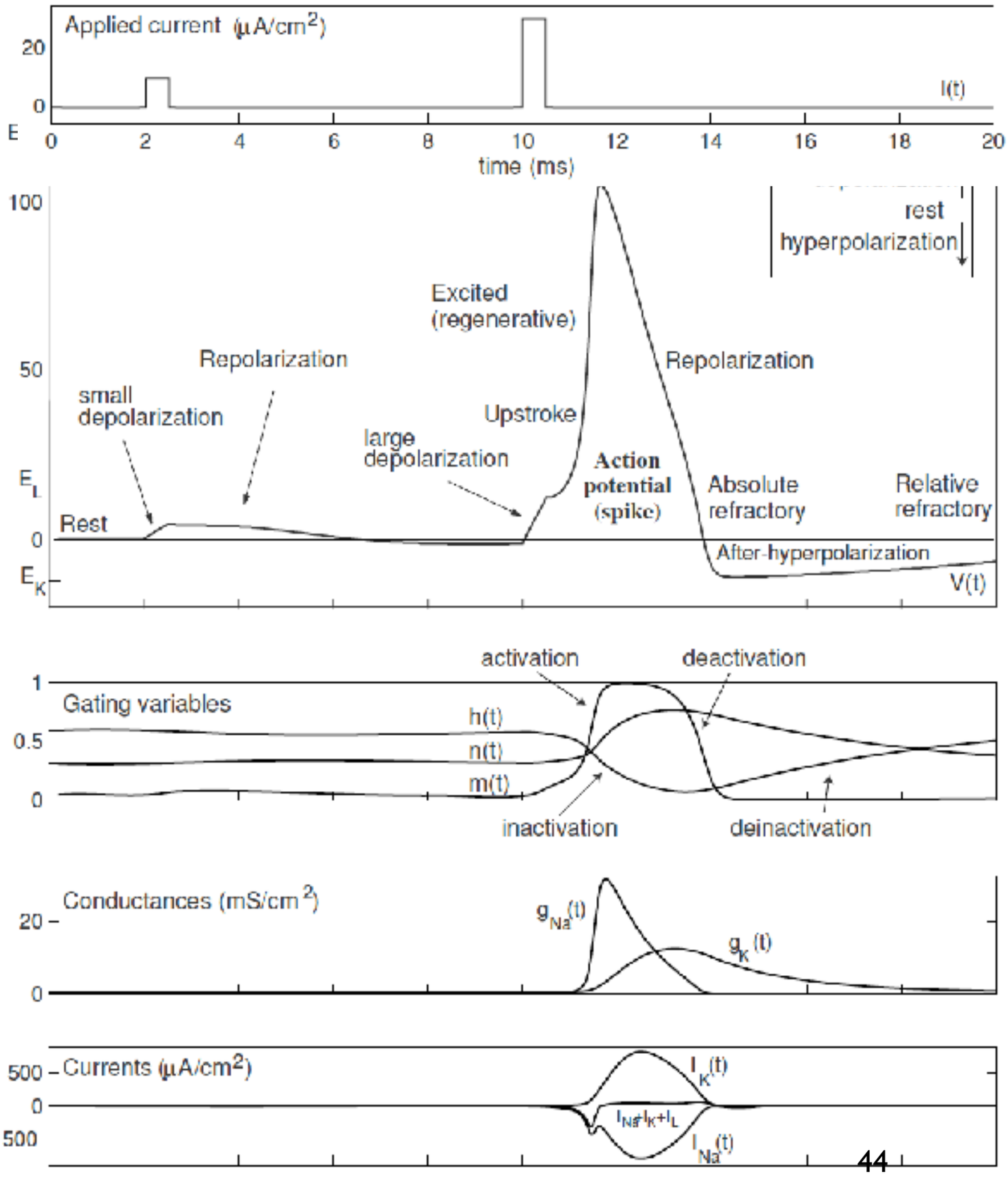
$$h(t) = h_\infty + \left[(h_0 - h_\infty)e^{-t/\tau_h}\right].$$

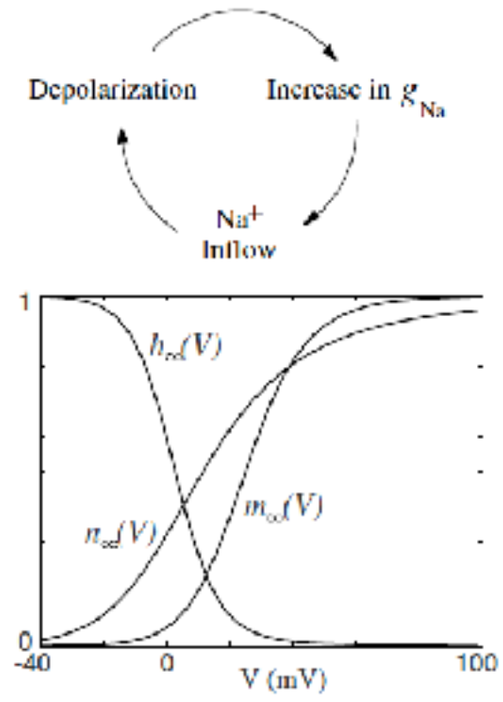
Activation of Sodium and Potassium ion channels

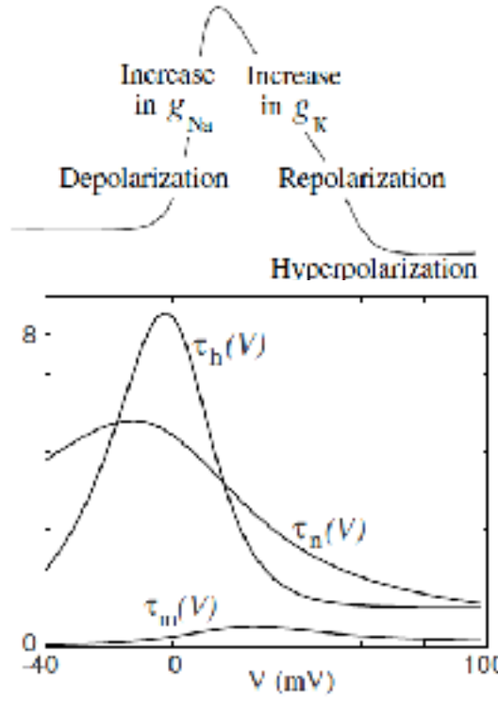




Action Potential







Local Anesthesia

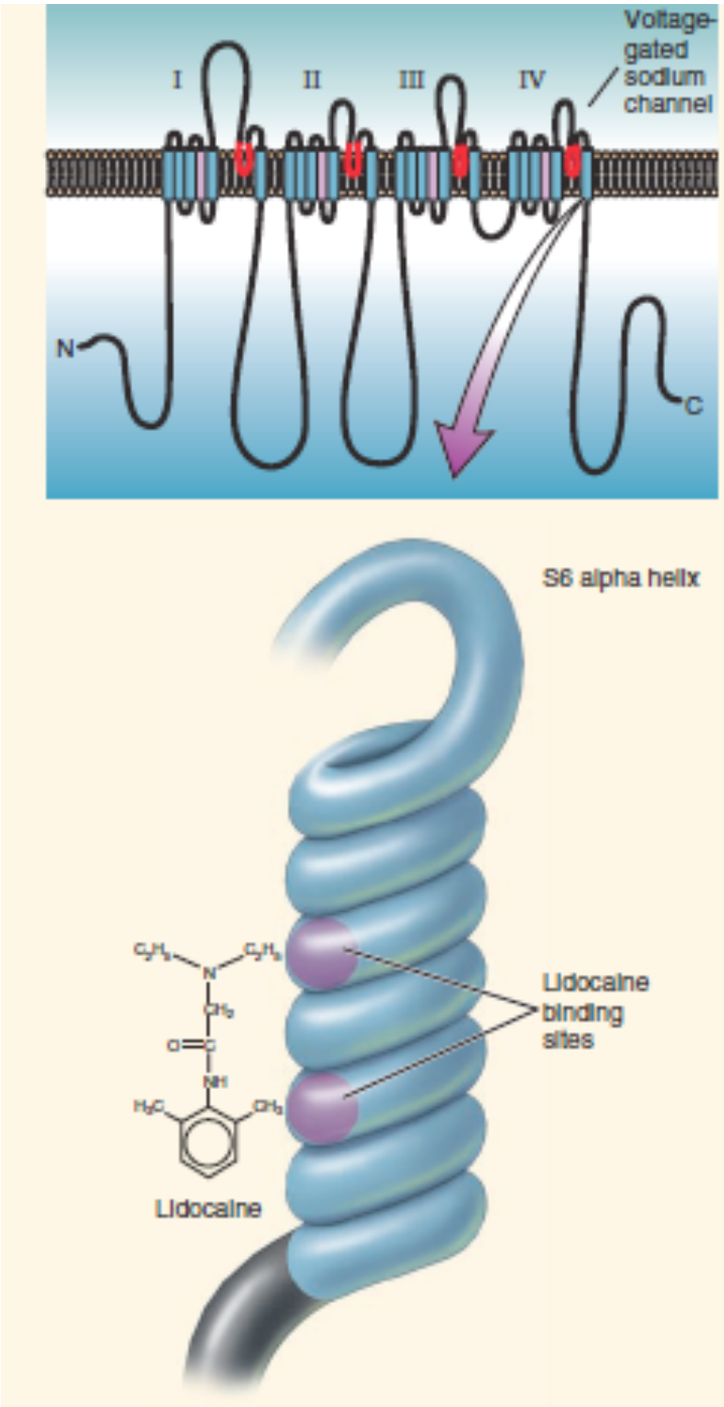


FIGURE A
Lidocaine's mechanism of action. (Source: Adapted from Hardman et al., 1996, Fig. 15-3.)

Ion Channels in Neurological Disorders

Pravir Kumar [1], Dhiraj Kumar [2], Saurabh Kumar Jha [2], Niraj Kumar Jha [2], Rashmi K Ambasta [2]

Affiliations + expand

PMID: 26920688 DOI: 10.1016/bs.apcsb.2015.10.006

Abstract

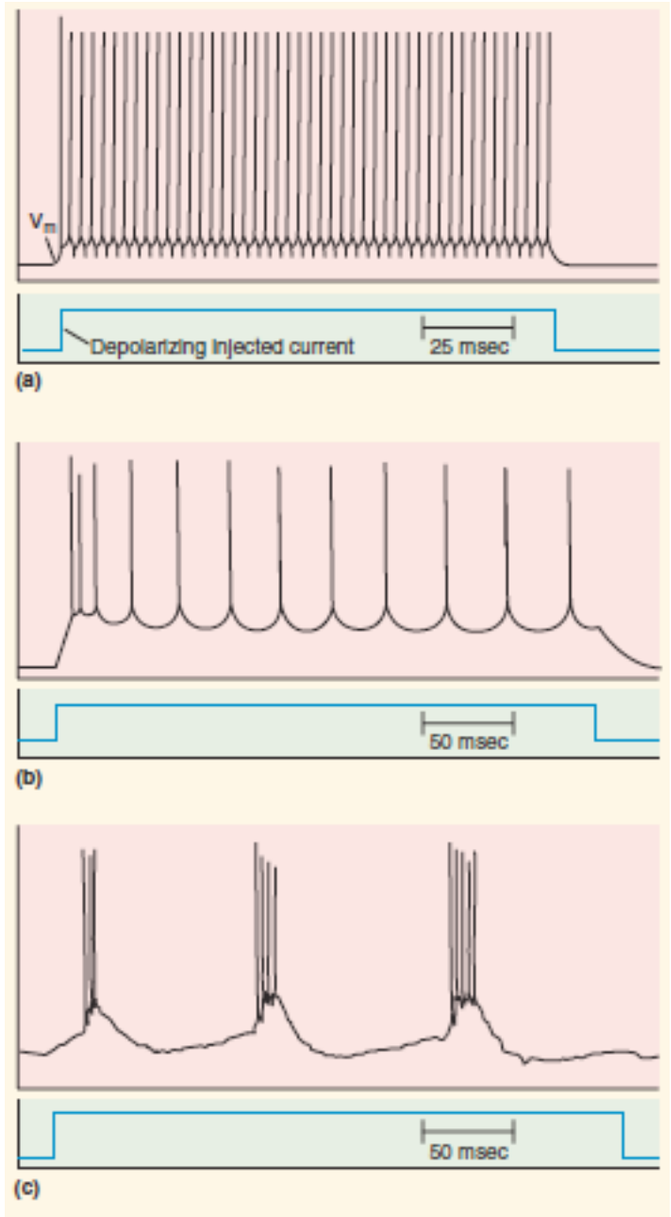
The convergent endeavors of the neuroscientist to establish a link between clinical neurology, genetics, loss of function of an important protein, and channelopathies behind neurological disorders are quite intriguing. Growing evidence reveals the impact of ion channels dysfunctioning in neurodegenerative disorders (NDDs). Many neurological/neuromuscular disorders, viz., Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, and age-related disorders are caused due to altered function or mutation in ion channels. To maintain cell homeostasis, ion channels are playing a crucial role which is a large transmembrane protein. Further, these channels are important as it determines the membrane potential and playing critically in the secretion of neurotransmitter. Behind NDDs, losses of pathological proteins and defective ion channels have been reported and are found to aggravate the disease symptoms. Moreover, ion channel dysfunctions are eliciting a range of symptoms, including memory loss, movement disabilities, neuromuscular sprains, and strokes. Since the possible mechanistic role played by aberrant ion channels, their receptor and associated factors in neurodegeneration remained elusive; therefore, it is a challenging task for the neuroscientist to implement the therapeutics for targeting NDDs. This chapter reviews the potential role of the ion channels in membrane physiology and brain homeostasis, where ion channels and their associated factors have been characterized with their functional consequences in neurological diseases. Moreover, mechanistic role of perturbed ion channels has been identified in various NDDs, and finally, ion channel modulators have been investigated for their therapeutic intervention in treating common NDDs.

Cocaine from coca leaves in1860 by Dr. Niemann, Freud (mind altering mechanism is distinct)

Lidocaine: synthetic substitute, blocks Na channels

Prevents action potentials by binding VDSCs

Eclectic electric behavior of neurons



sustained firing by stellate cells

rapid and then slowing down by pyramidal cells

burst by pyramidal neurons

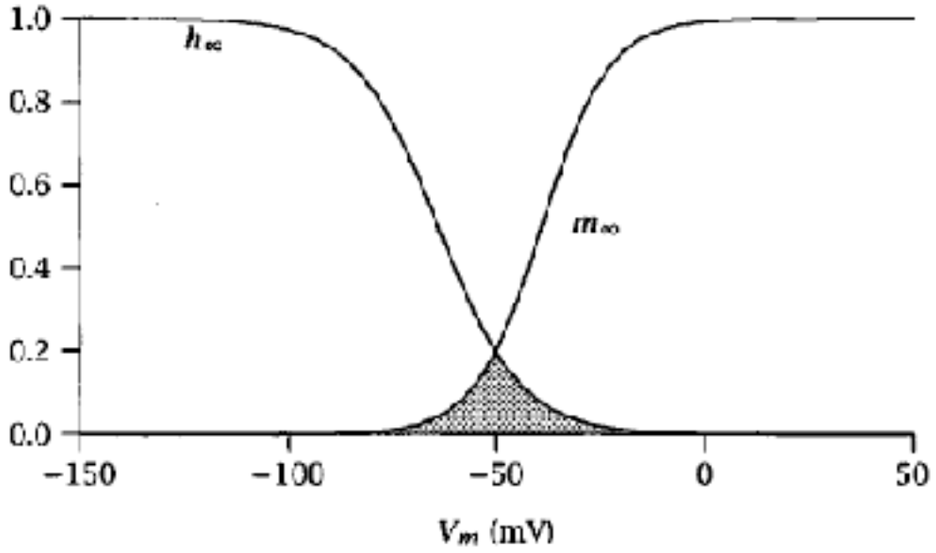
The firing repertoire is governed the biophysical properties of ion channels and their number

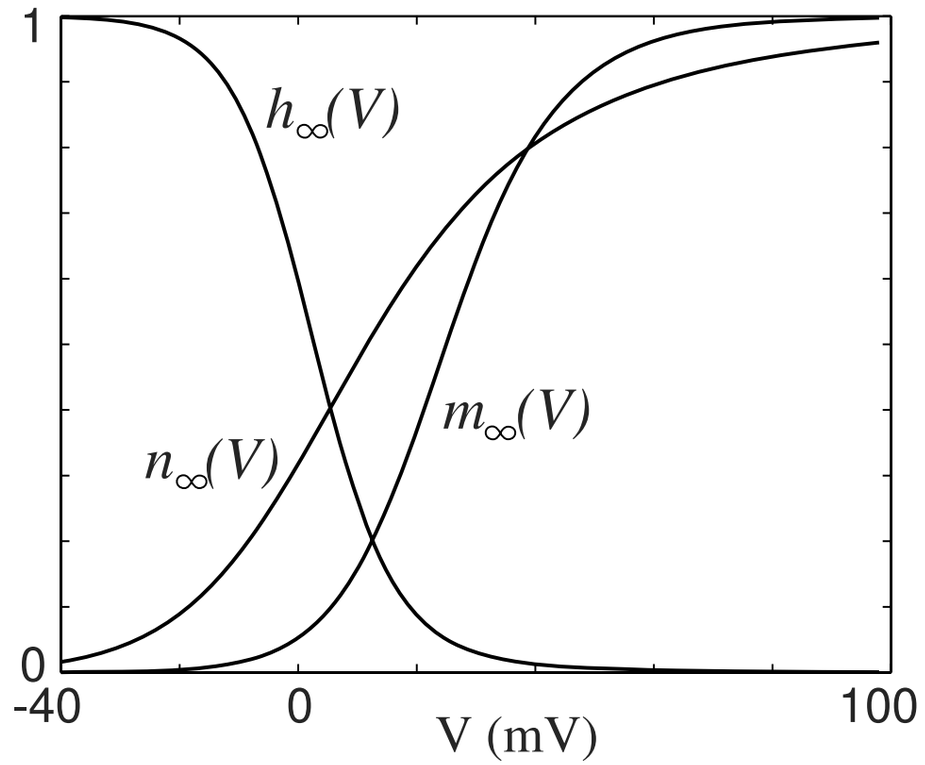
Zoo of ion channels

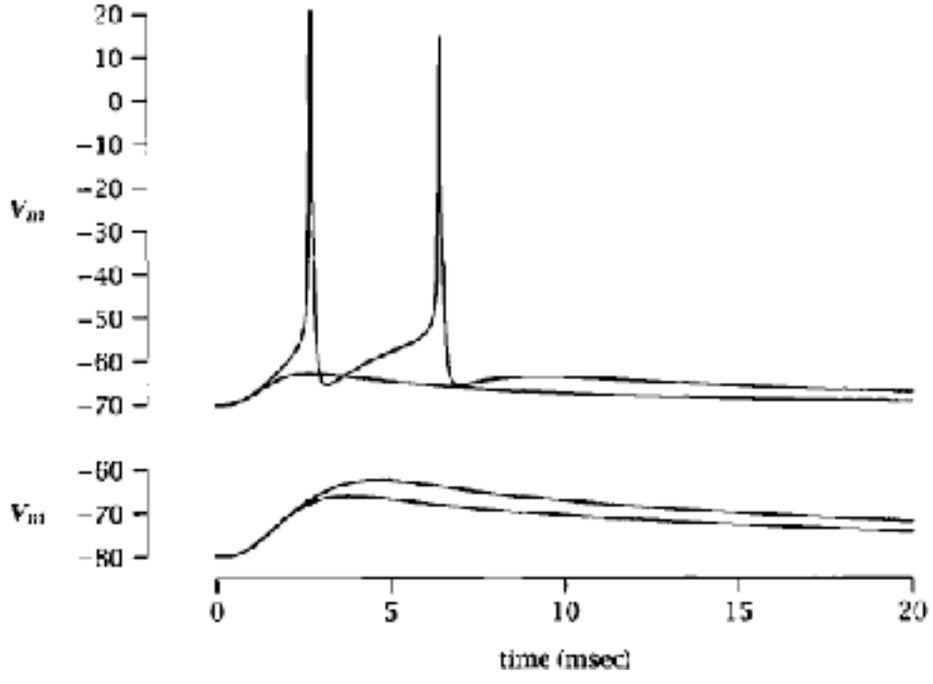
Table 7.1 Voltage-gated ionic currents in cortical neurons

Current	Symbol	Ion	V_{th}	Inactivation	Blocked by	Modulation	Function
1. Voltage-gated (depolarization)							
Na^+ currents							
Fast	$I_{Na(fast)}$	Na^+	−50	Fast	TTX		spike
Slow	$I_{Na(slow)}$	Na^+	−65	Slow	TTX		prepotential
Ca^{2+} currents							
High-threshold	$I_{Ca(L)}$	Ca^{2+}	−15	Slow Ca^{2+}-dep	Cd^{2+} DHP	NE (+) ACh (−)	spike
Low-threshold	$I_{Ca(T)}$	Ca^{2+}	−40	Fast V-dep	Ni^{2+}	ACh (+)	burst firing
High-threshold	$I_{Ca(N)}$	Ca^{2+}	−25	Medium V & Ca^{2+}-dep	Cd^{2+} ωCTX-GVIA	NE (+,−) Aden. (−) Others (−)	spike (?) presyn. (?)
High-threshold	$I_{Ca(P)}$	Ca^{2+}	−20	Slow	ωAga-IVA		presyn. (?)
K^+ currents							
Delayed rectifier	$I_{K(DR)}$	K^+	−40	Slow	TEA (10 mM)		
Transient	$I_{K(A)}$	K^+	−60	Fast	4-AP (> 0.1 mM)	ACh (−)	spike repolar.
Delay current	$I_{K(D)}$	K^+	−75	Slow	4-AP (< 0.1 mM)	DTX	delayed firing, spike repolar.
M current	$I_{K(M)}$	K^+	−65	None	Ba^{2+}	ACh (−) 5-HT (−) Somato. (+)	spike train accommod. *m*AHP

Current	Symbol	Ion	V_{th}	Inactivation	Blocked by	Modulation	Function
2. Voltage-gated (hyperpolarization)							
Slow inward rectifier	I_Q, I_h, I_f	Na + K	−60	None	Cs^+, THA		rest V_m
Fast inward rectifier	$I_{K(IR)}$	K^+	−80	Slow	Cs^+, Ba^{2+}	G_o (+)	
Time-depend. Cl^- currents	$I_{Cl(V)}$	Cl^-	−20	None	Cd^{2+}	PBs	dendrites (?)
		Cl^-	−60	None	Cd^{2+}		
3. Ca^{2+}*-gated*							
Fast K^+ current	$I_{K(C)}$	K^+	−40	None	TEA (1 mM)		spike repolar. *f*&*m*AHP
Slow K^+ current	$I_{K(AHP)}$	K^+	None	None	Ba^{2+}	ACh (−) NE (−) 5-HT (−) Hist. (−)	spike train accommod. *s*AHP
Cl^- current	$I_{Cl(Ca)}$	Cl^-					
Cation current		Na + K				ACh (+)	AHP (?)
4. Other currents							
Leak (?)	$I_{K(L)}$	K^+	None	None	Ba^{2+}	ACh (−)	rest V_m
Cl^-	I_{Cl}	Cl^-					
Anoxic	$I_{K(ATP)}$	K^+					hyperpol.
Na^+ Act. K^+	$I_{K(Na)}$	K^+					
Stretch		Na + K					mechanorec.







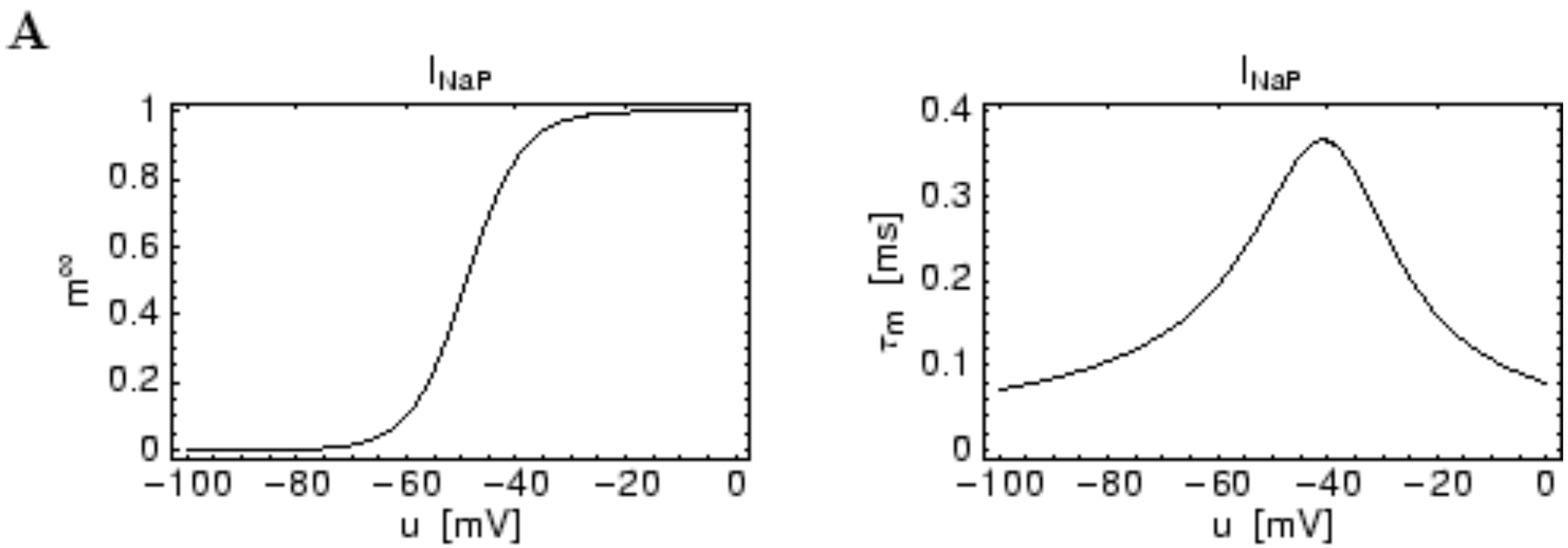
Sodium currents I_Na(slow)

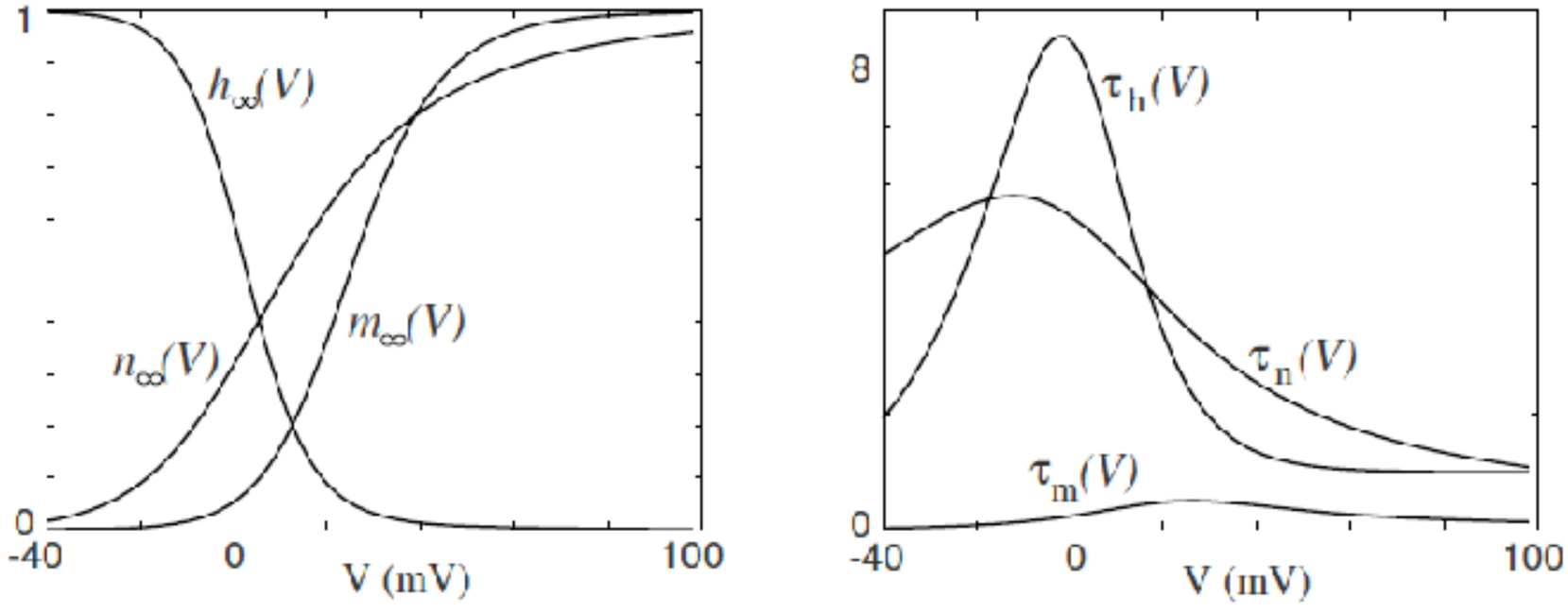
Function:
Amplify small depolarizations
(activated near resting potential)
Sustain repetitive firing and bursting

$$g_{Na} = (0.2)^3(0.2) \cdot \overline{g}_{Na} \simeq 0.002\overline{g}_{Na},$$

At Vm=-50 mV

Sodium currents non-inactivating





Function:
Increases overall excitability

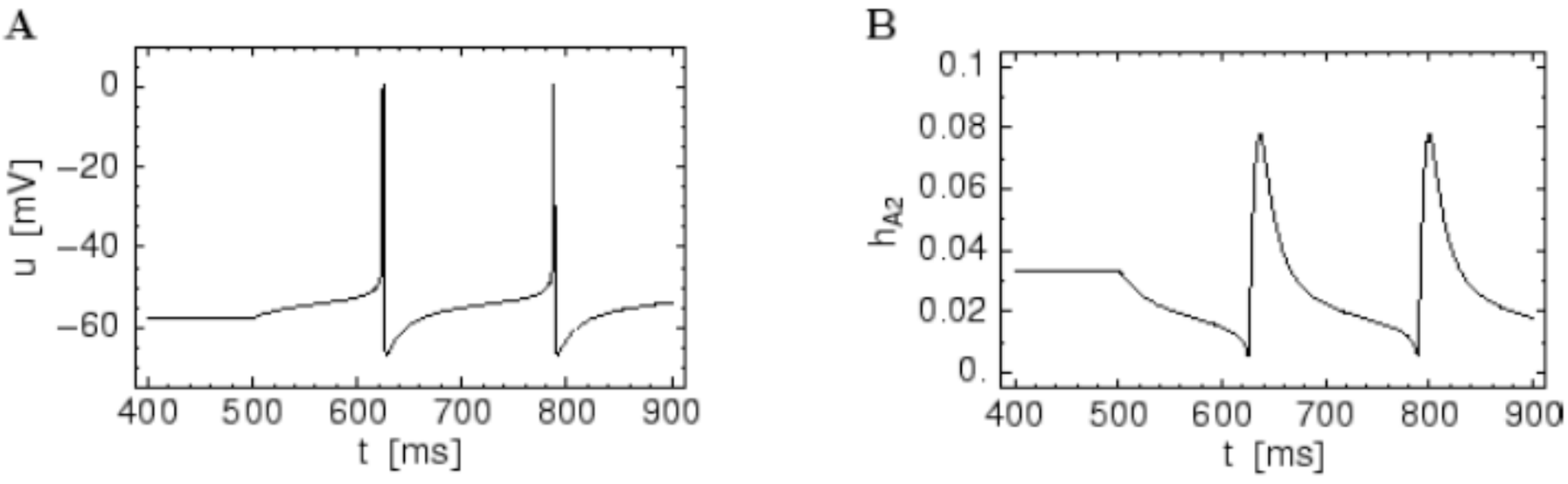
$$I_{\mathrm{NaP}} = \bar{g}_{\mathrm{NaP}}\ m\ (u - E_{\mathrm{Na}})\ .$$

Potassium currents

Greatest diversity

examples:
Rapidly inactivating I_A , tau_A=10 ms
Slowly inactivating I_K, tau_K=20-2000ms

I_A : A large class of transient K currents



Since this has hyperpolarizing effect, slows down firing: For a weak stimulus,

APs occur only after I_A has died down, can cause long delay: Increases threshold of AP

Dynamics here comparable to Na but opposite effect of hyperpolarization:

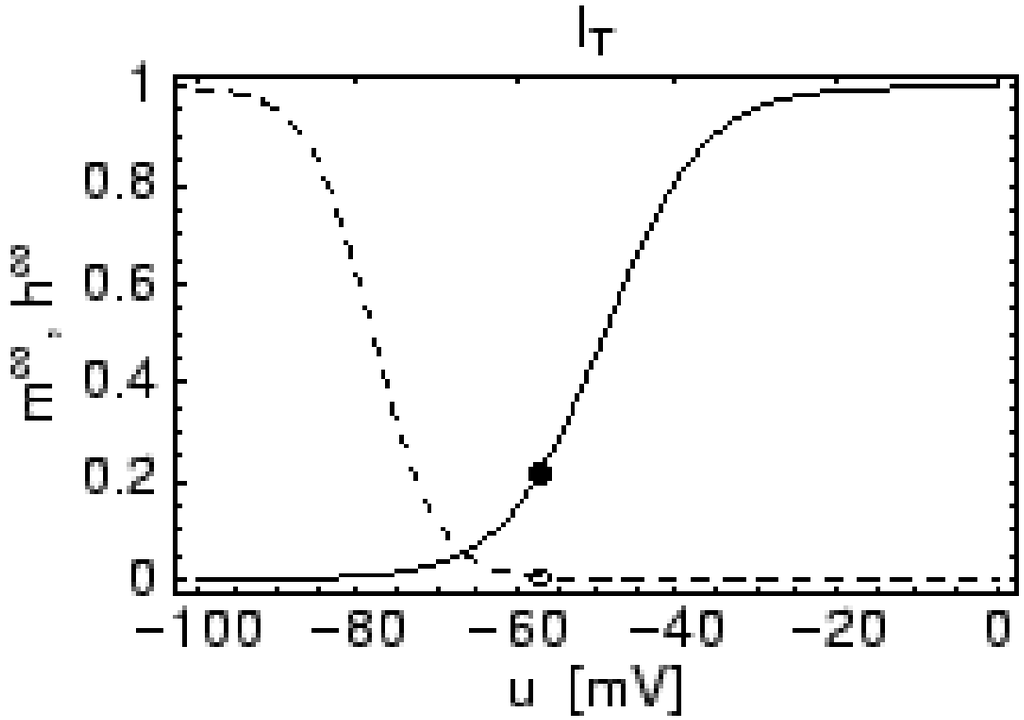
Calcium currents

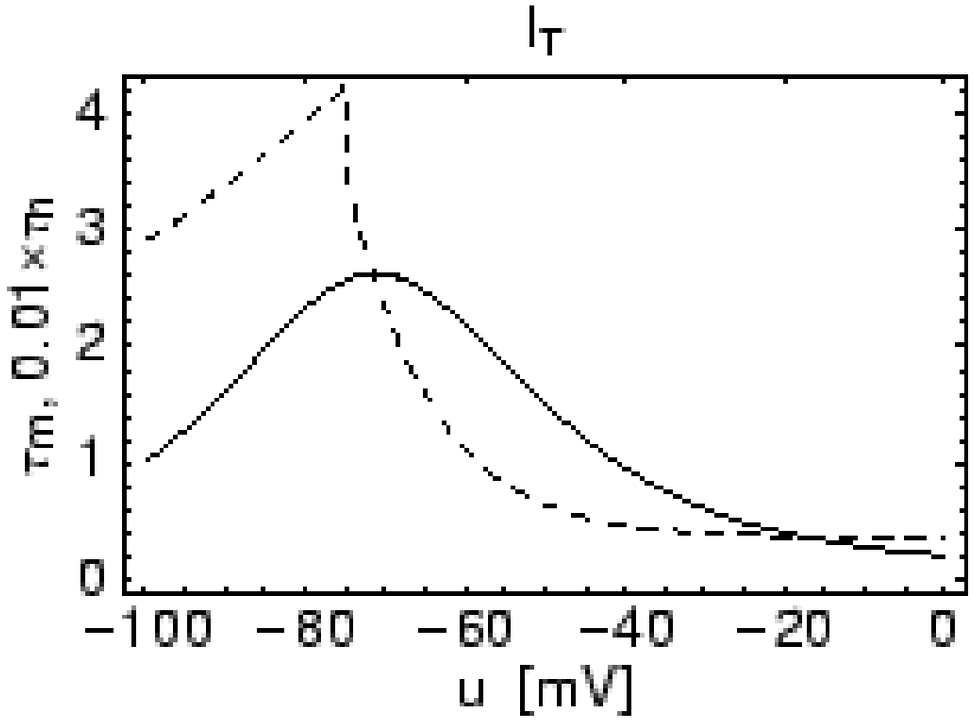
Reversal potential of 150 mV, however hard to measure experimentally as very few calcium ions inside the cell, Types, L, T, P, Q, N etc.

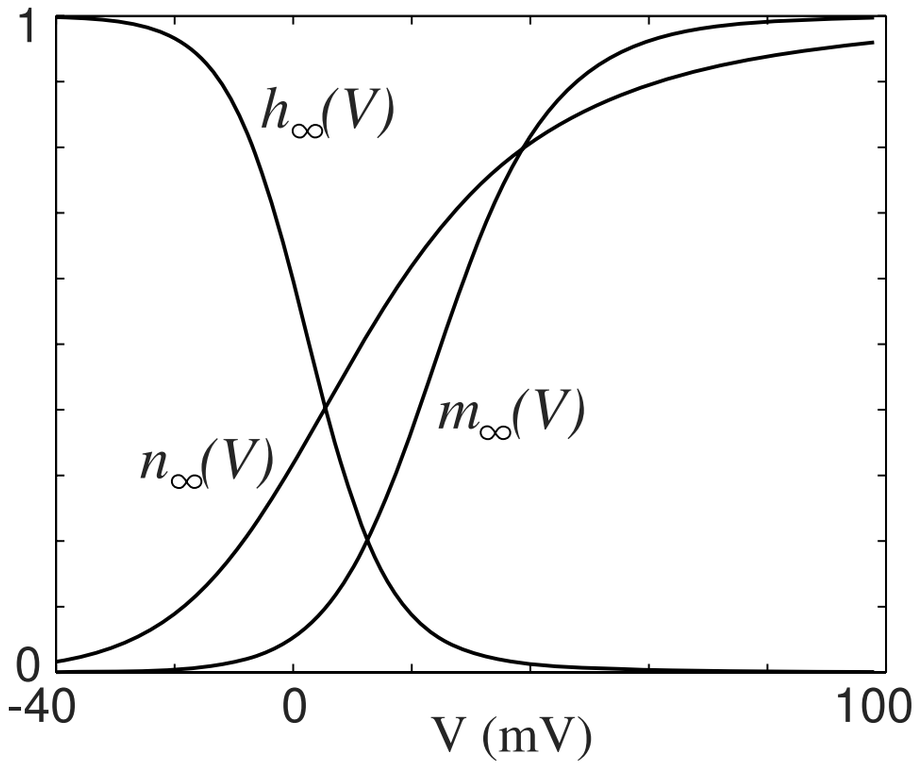
Two types:
Low-threshold calcium current : post-inhibitory rebound.
High-threshold calcium current:

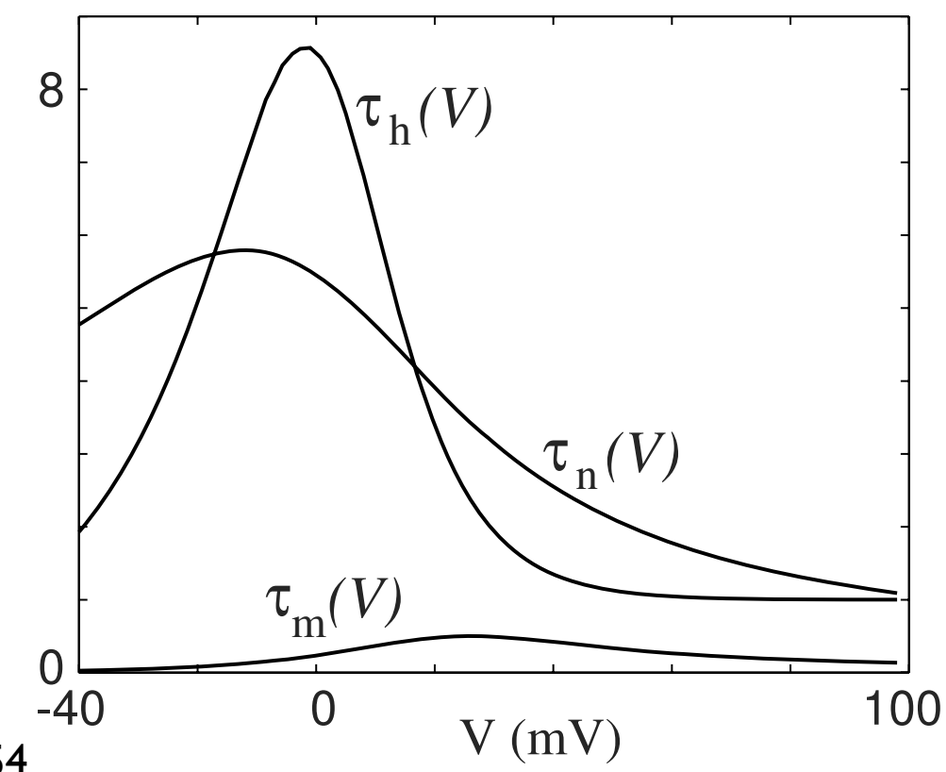
Low threshold and post-inhibitory rebound

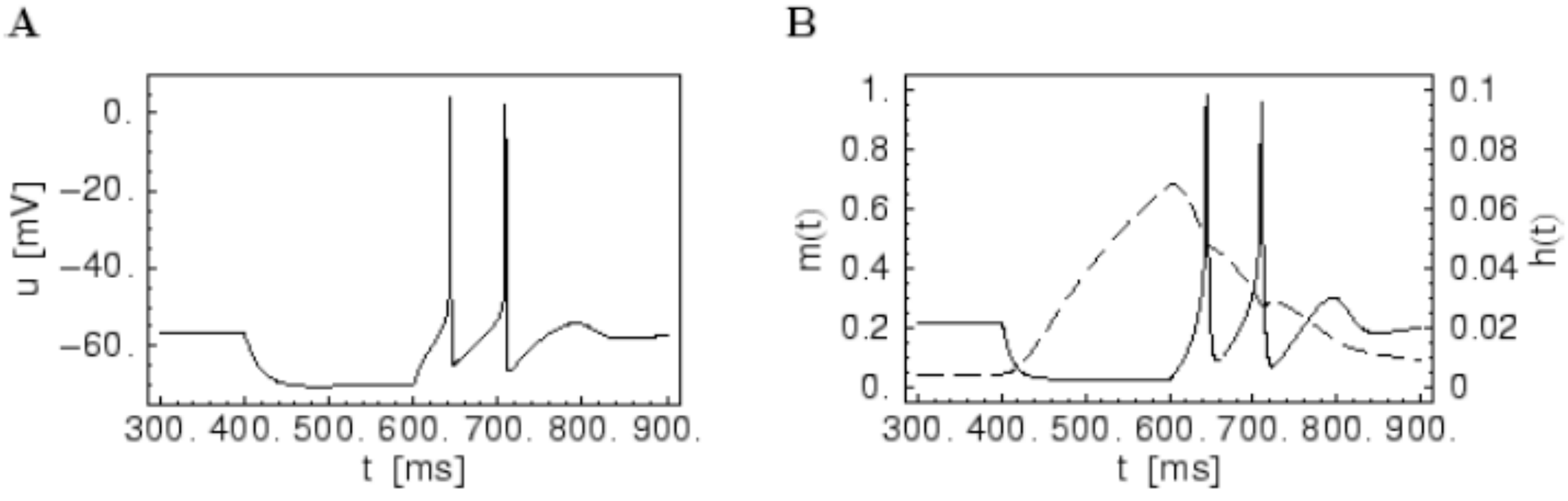
C











Hyperpolarizing current that is suddenly switched off/on leads to spiking: triggered by inhibitory input

Activation and Inactivation curves shifted towards left

At appropriate hyperpolarizing potentials the the block by depolarization inactivation variable is removed

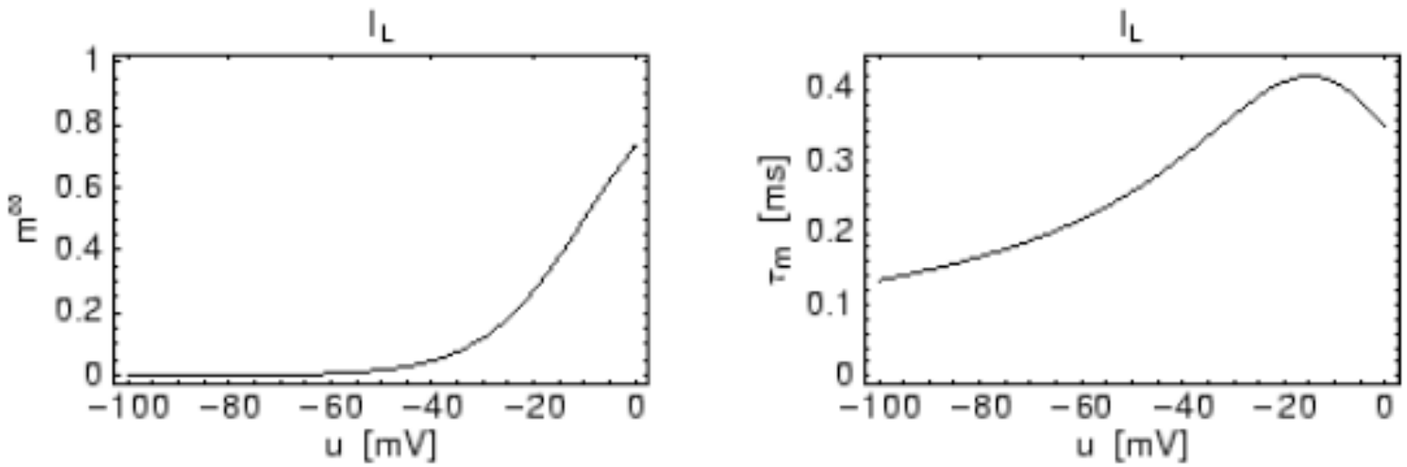
As the membrane potential travels back to equilibrium activation gate transiently opens before inactivation gate closes due to depolarization

Because activation is much faster than inactivation variable: Ca comes in

This depolarization can lead to Na entry and spike

Response occurs after delay

High threshold Calcium current

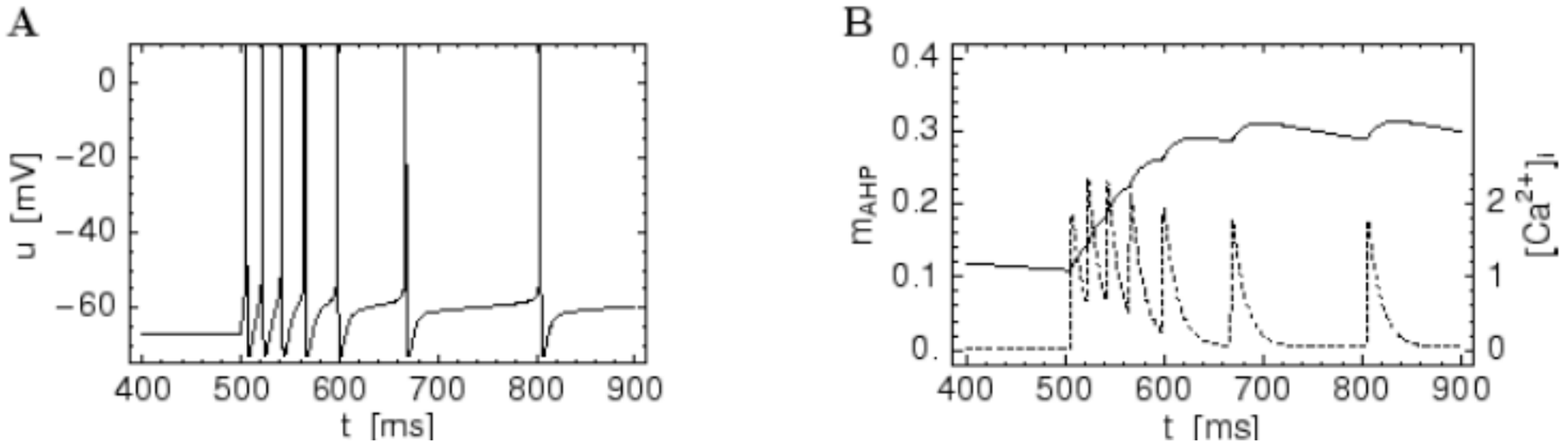


Non inactivating and long lasting but activated at high depolarization, during AP

Carry +ve charge

Crucial secondary messenger for all kinds of plasticity

Ca activated K and adaptation I_AHP

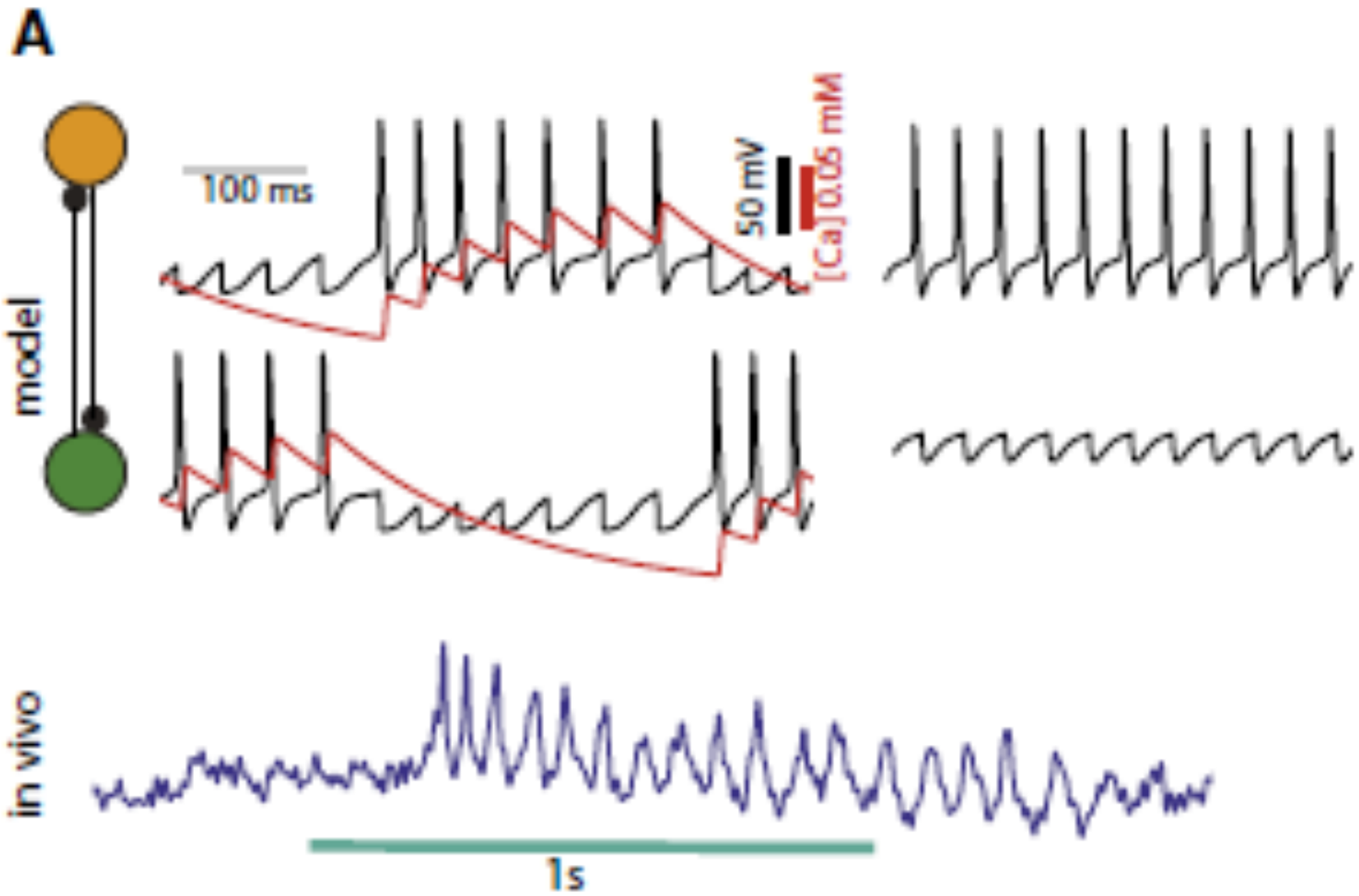


Slow current (after hyperpolarization) voltage independent, calcium dependent

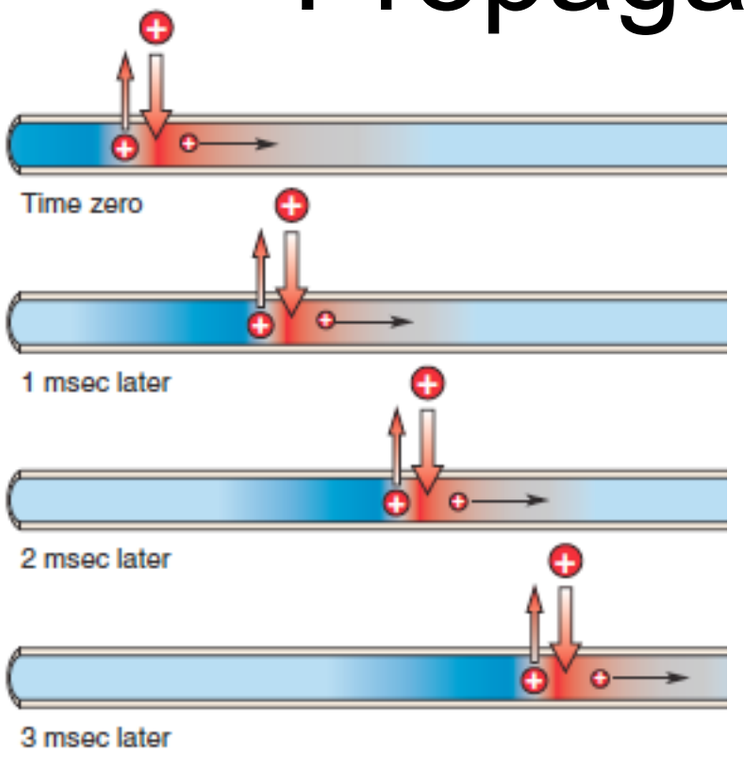
Because of the fact that the AHP-channels are not inactivating and slow, each AP increases the activation m by a fixed amount.

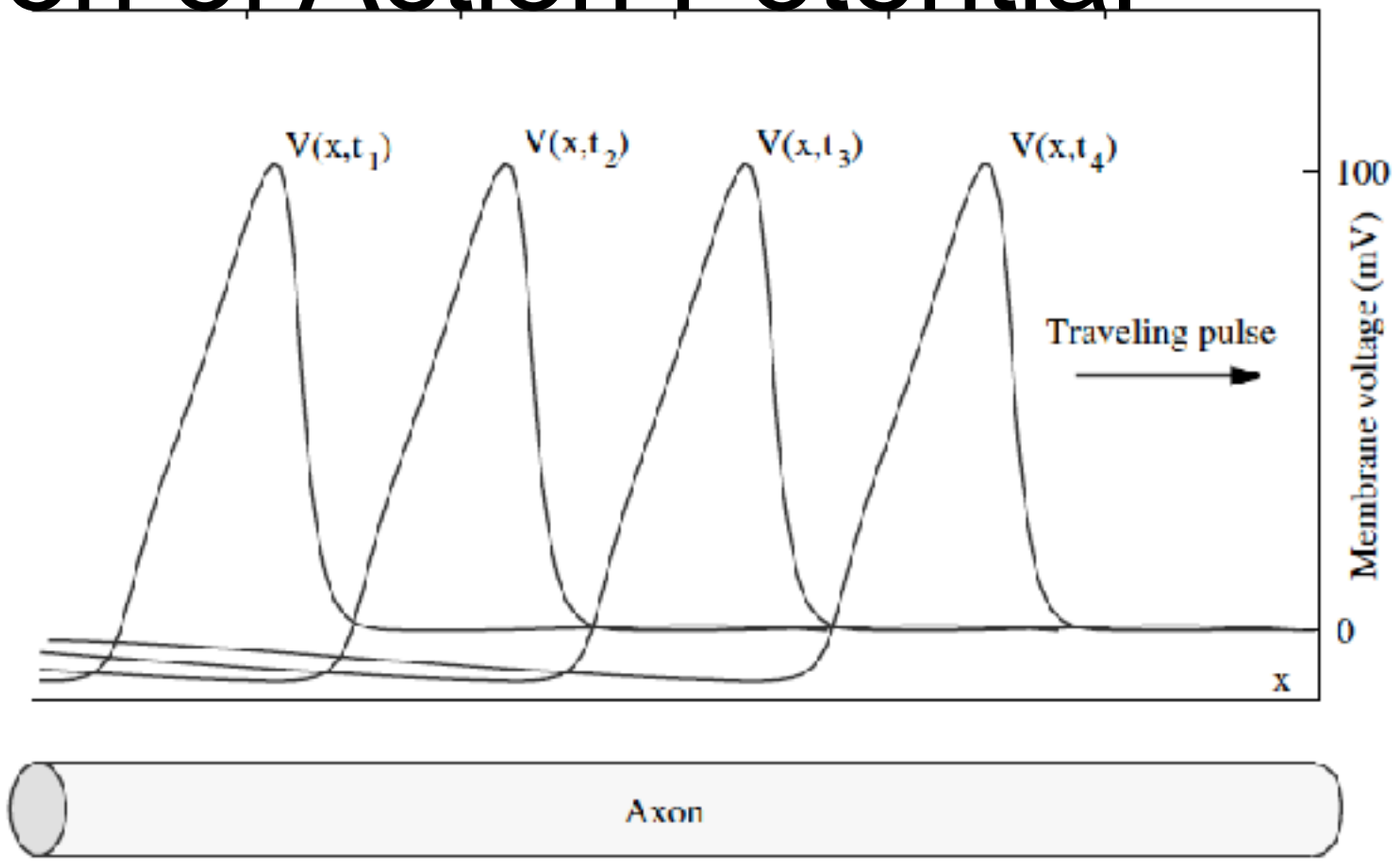
If the neuron is stimulated by a constant depolarizing current each action potential increases the amount of open AHP-channels and the corresponding potassium current subtracts from the applied stimulus.

The firing frequency is thus decreasing, a phenomenon that is known as firing frequency adaptation


A
100 ms
50 mV
[Ca] 0.05 mM
model
in vivo
1s

Propagation of Action Potential





Absolute refractory period of action potential ensures that action potential movement is unidirectional (orthodromic)

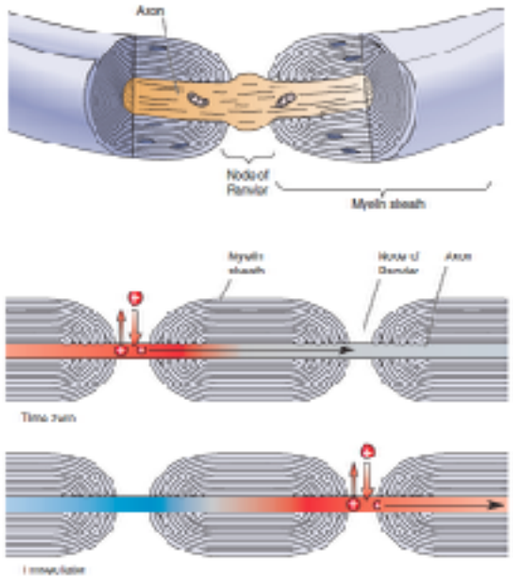
Action potential conduction velocity increases with axon diameter, fat axons lead to big fat head, too big to carry around! (10 m/sec)

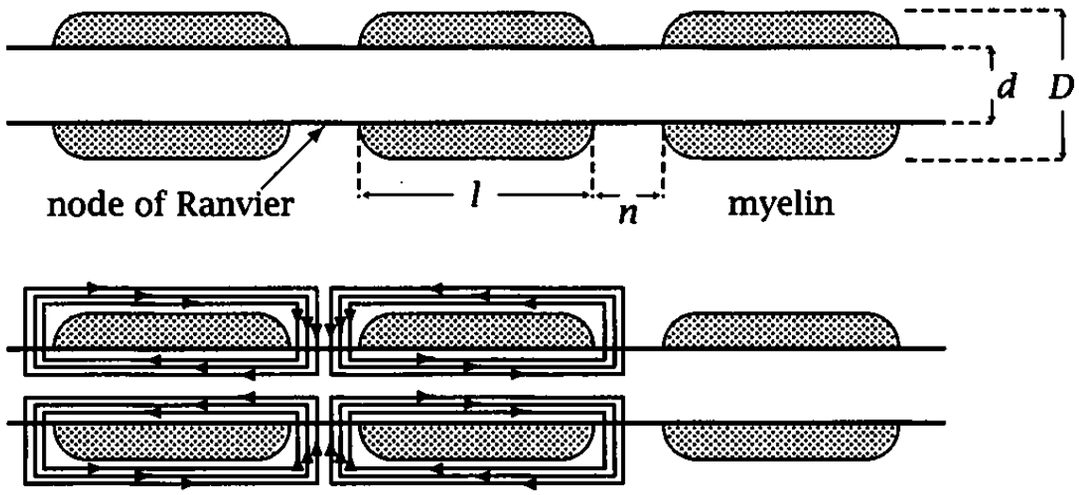
Smaller axons need more voltage dependent channels for AP

$$C\,V_t = \frac{a}{2R}\,V_{xx} + I - I_{\mathrm{K}} - I_{\mathrm{Na}} - I_{\mathrm{L}}$$

Hodgkin and Huxley Cable equation
a= radius, R=intracellular resisitivity

Propagation of Action Potential in axons with Myelin





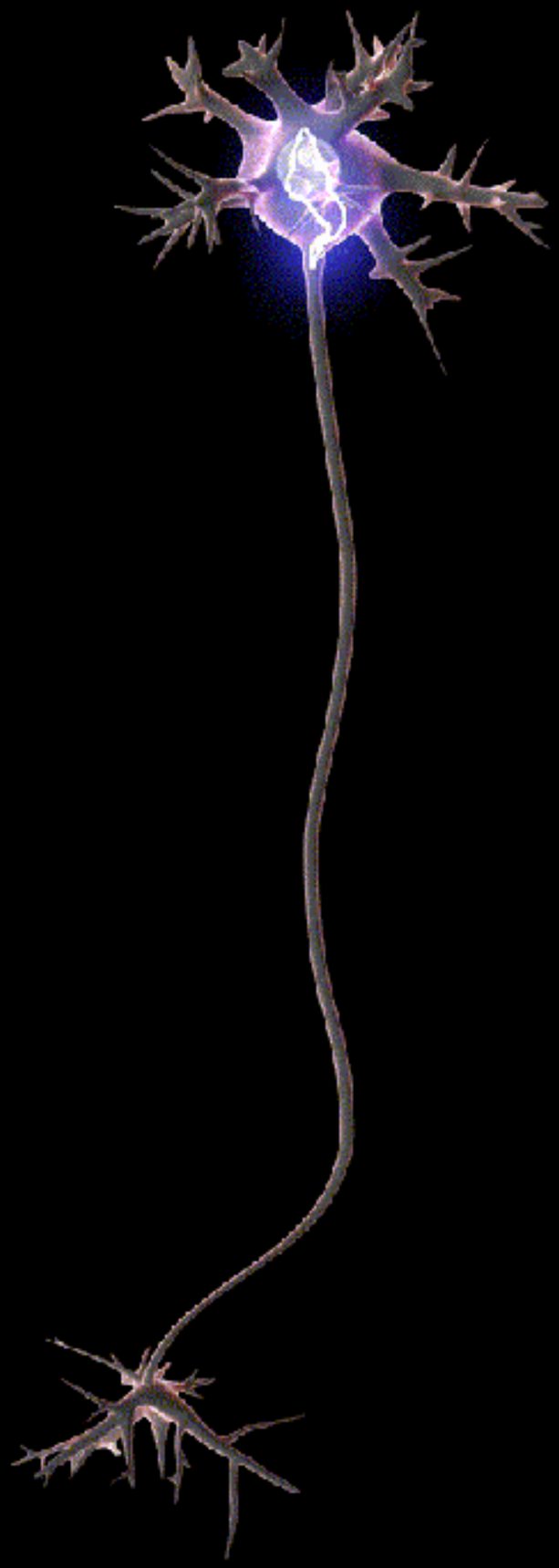
Another solution: Insulation (Myelin) provided by glia (Schwann (PNS) and Oligodendrocytes (CNS))

Myelin sheath does not extend continuously. Breaks in the insulation (nodes of Ranvier) where ions can go across the membrane to generate AP. Saltatory conduction:Like skipping

Distance between n of R is 0.2-2.0 mm, Conduction speed 10 meters/second

Multiple sclerosis is marked by poorer conduction velocities seen as a result of damaged myelin

High concentration of Na+ channels in n of R



Synaptic Transmission

Charles Sherrington (1897): The process of information transfer at a synapse is called synaptic transmission.

Process of information transfer between neurons is synaptic transmission

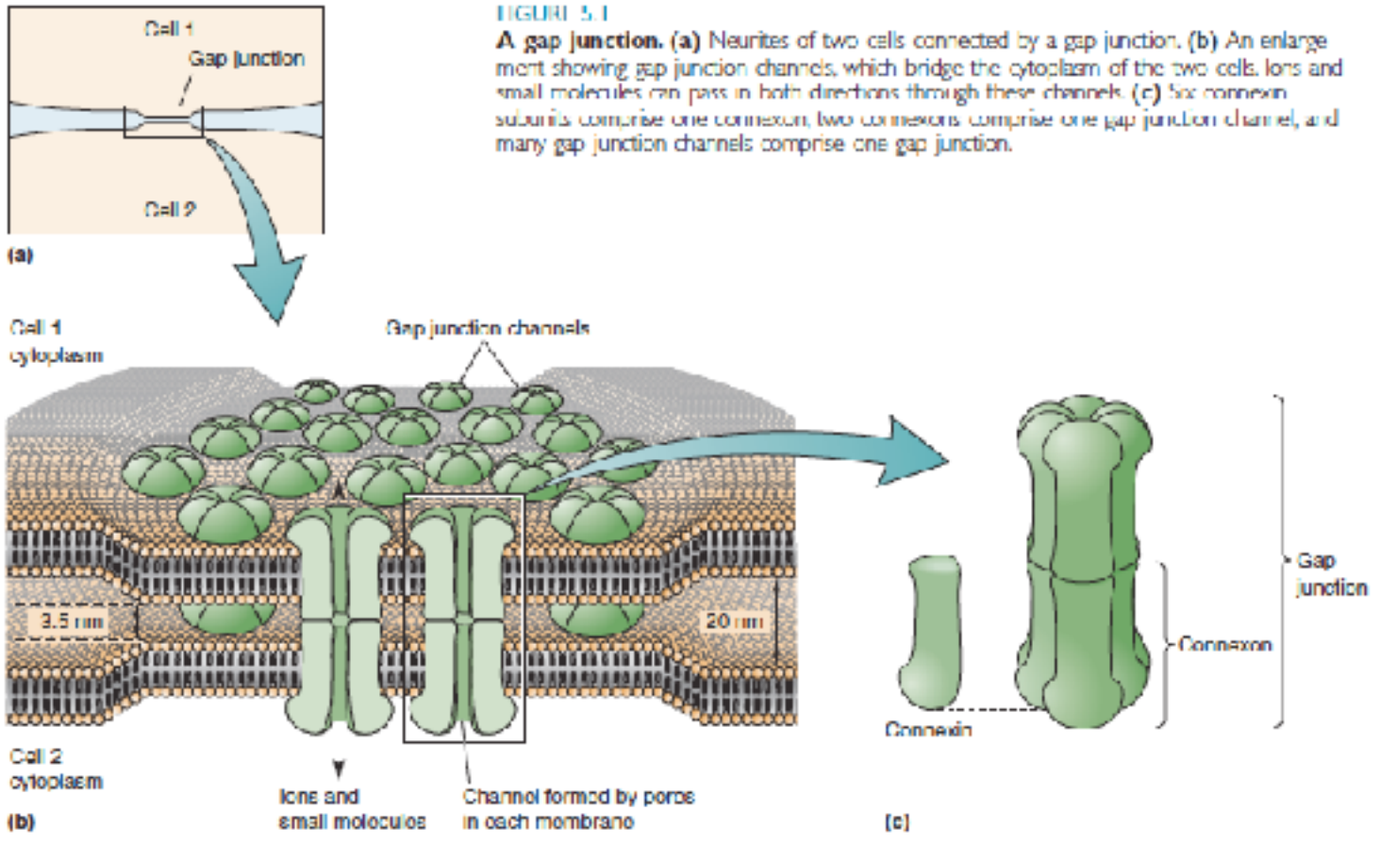
Synaptic transmission is a large and fascinating topic, it is the basis of learning and memory

Electrical Synaptic Transmission

Transfer ionic current from one cell to the next via gap junctions.

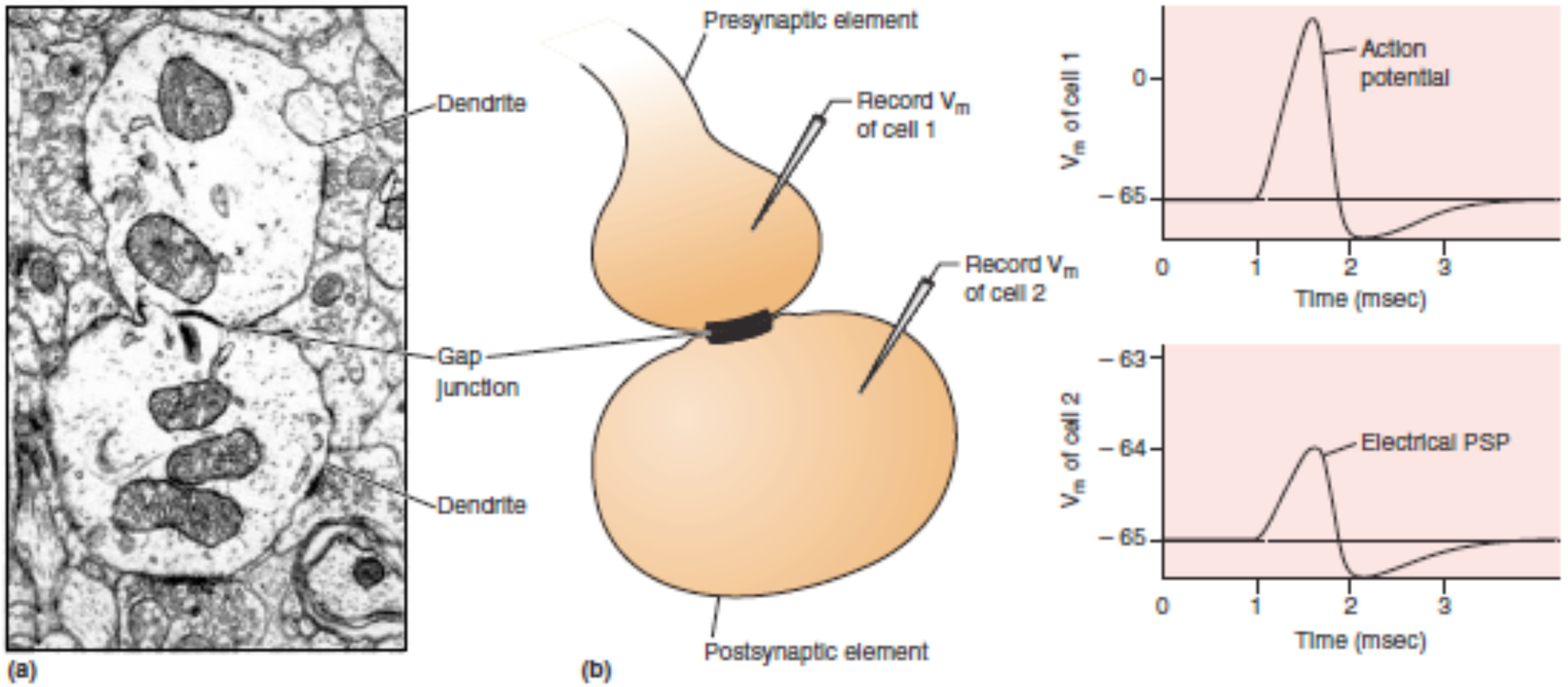
Membranes separated by ~ 3 nm, contains clusters of special proteins called **connexins**. Six connexins combine to form a channel called a connexon , and two connexons (one from each cell) combine to form a gap junction channel.

Large bidirectional pores 1–2 nm.



A gap junction. (a) Neurites of two cells connected by a gap junction. **(b)** An enlargement showing gap junction channels, which bridge the cytoplasm of the two cells. Ions and small molecules can pass in both directions through these channels. **(c)** Six connexin subunits comprise one connexon, two connexons comprise one gap junction channel, and many gap junction channels comprise one gap junction.

Electrical Synapses: Invertebrate and vertebrate brains



Invertebrates (crayfish): Found between sensory and motor neurons in neural pathways mediating **escape reflexes**. This mechanism enables an animal to beat a hasty retreat when faced with a dangerous situation.

Electrical synapses are common in every part of the mammalian CNS.

Soup versus Sparks

Electrical transmission: allows for sub threshold signals to be transmitted, **bidirectional, fast and Reliable**.

Found where normal function requires that the activity of neighboring neurons be highly synchronized. Its common during brain development : allow neighboring cells to share both electrical and chemical signals that may help coordinate their growth and maturation.

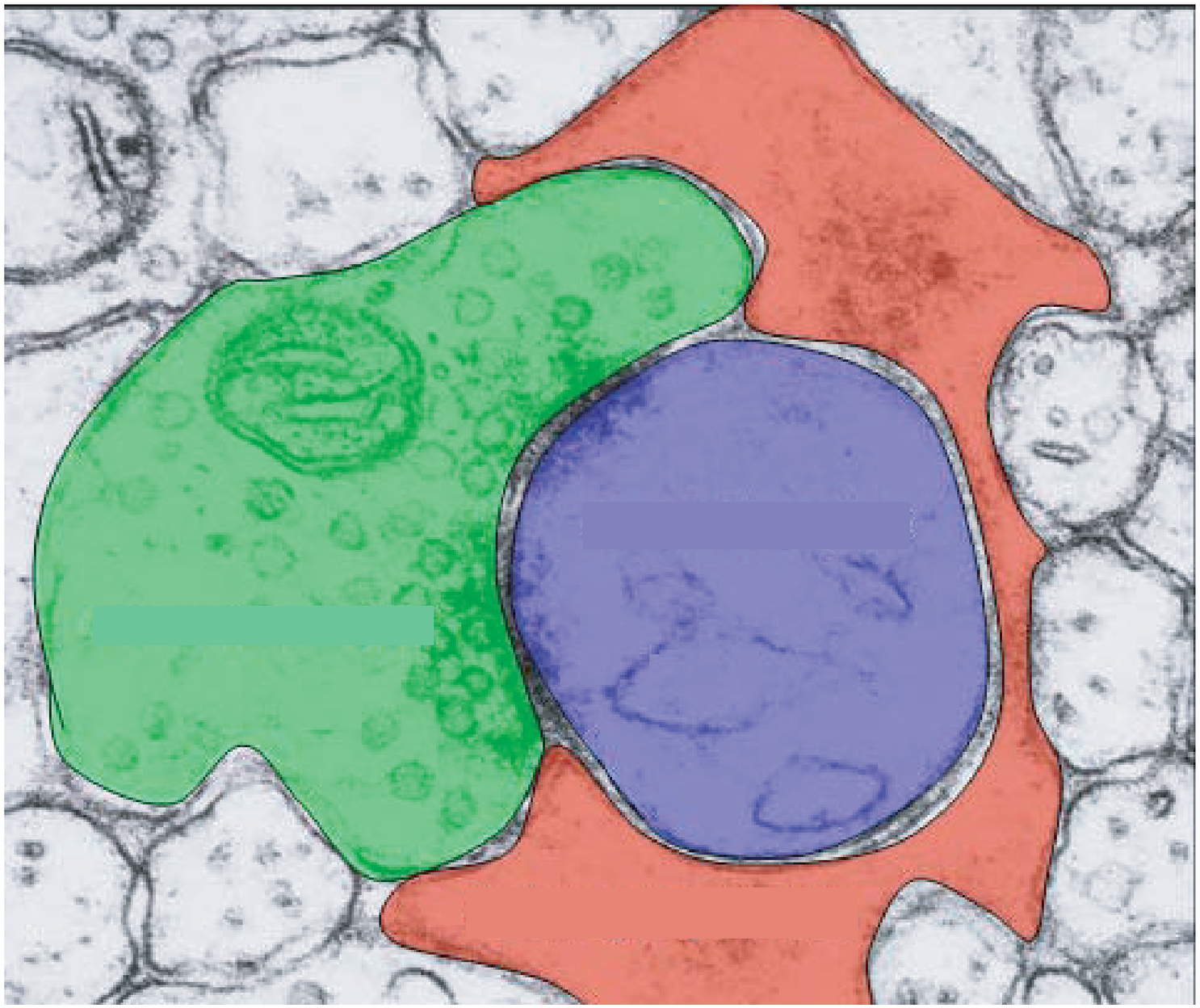
Gap junctions also interconnect many non-neural cells, including glia, epithelial cells, smooth and cardiac muscle cells, liver cells, and some glandular cells.

History: Chemical Synaptic Transmission

Otto Loewi (1921): Concept of chemical synapses. Electrical stimulation of axons innervating the frog's heart caused the release of a chemical and that this chemical could mimic the effects of neuron stimulation on the heartbeat (electrically stimulated vagus nerve, Vagusstoff)

Bernard Katz: Demonstrated that fast transmission at the synapse between a motor neuron axon and skeletal muscle was chemically mediated.

John Eccles (1951): Synaptic transmission of mammalian central nervous system (CNS) using a new tool, the glass micro electrode



Chemical Transmission: Most synaptic transmission in the mature human nervous system.

synaptic cleft that is 20–50 nm wide

The terminal typically contains several small membrane-enclosed spheres, each about 50 nm in diameter, called synaptic vesicles

Dense accumulations of proteins adjacent to and within the membrane on either side of the cleft: Active Zones and Postsynaptic Densities

Table 5.1 The Major Neurotransmitters		
AMINO ACIDS	AMINES	PEPTIDES
Gamma-aminobutyric acid (GABA) Glutamate (Glu) Glycine (Gly)	Acetylcholine (ACh) Dopamine (DA) Epinephrine Histamine Norepinephrine (NE) Serotonin (5-HT)	Cholecystokinin (CCK) Dynorphin Enkephalins (Enk) N-acetylaspartylglutamate (NAAG) Neuropeptide Y Somatostatin Substance P Thyrotropin-releasing hormone Vasoactive intestinal polypeptide (VIP)

Amino acids and Amines (small organic molecules with one nitrogen atom) thru vesicles

Large peptides thru **dense core vesicles**

Both seen in same axons

Fast synaptic transmission in CNS is Glutamate, GABA and at NMJ its Ach

Crucial requirements of chemical synaptic transmission

Mechanism for SV proteins to be manufactured and delivered to the presynaptic terminal

Mechanism for synthesizing neurotransmitter and packing it into the synaptic vesicles,

Mechanism for causing vesicles to spill their contents into the synaptic cleft in response to a presynaptic action potential,

Mechanism for producing an electrical or biochemical response to neurotransmitter in the postsynaptic neuron

Mechanism to retrieve the membrane after fusion

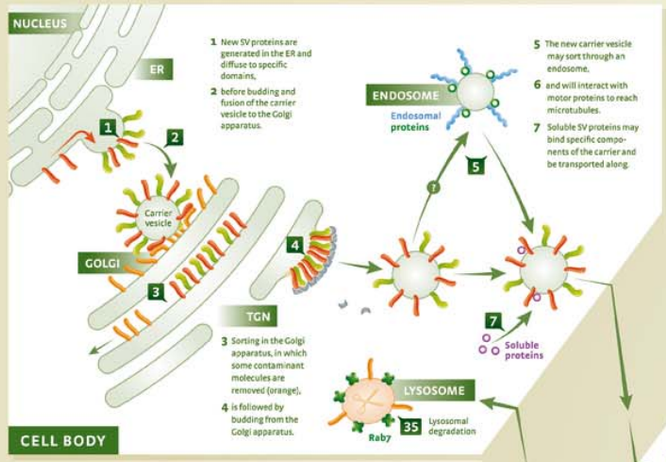
Mechanism for removing neurotransmitter from the synaptic cleft.

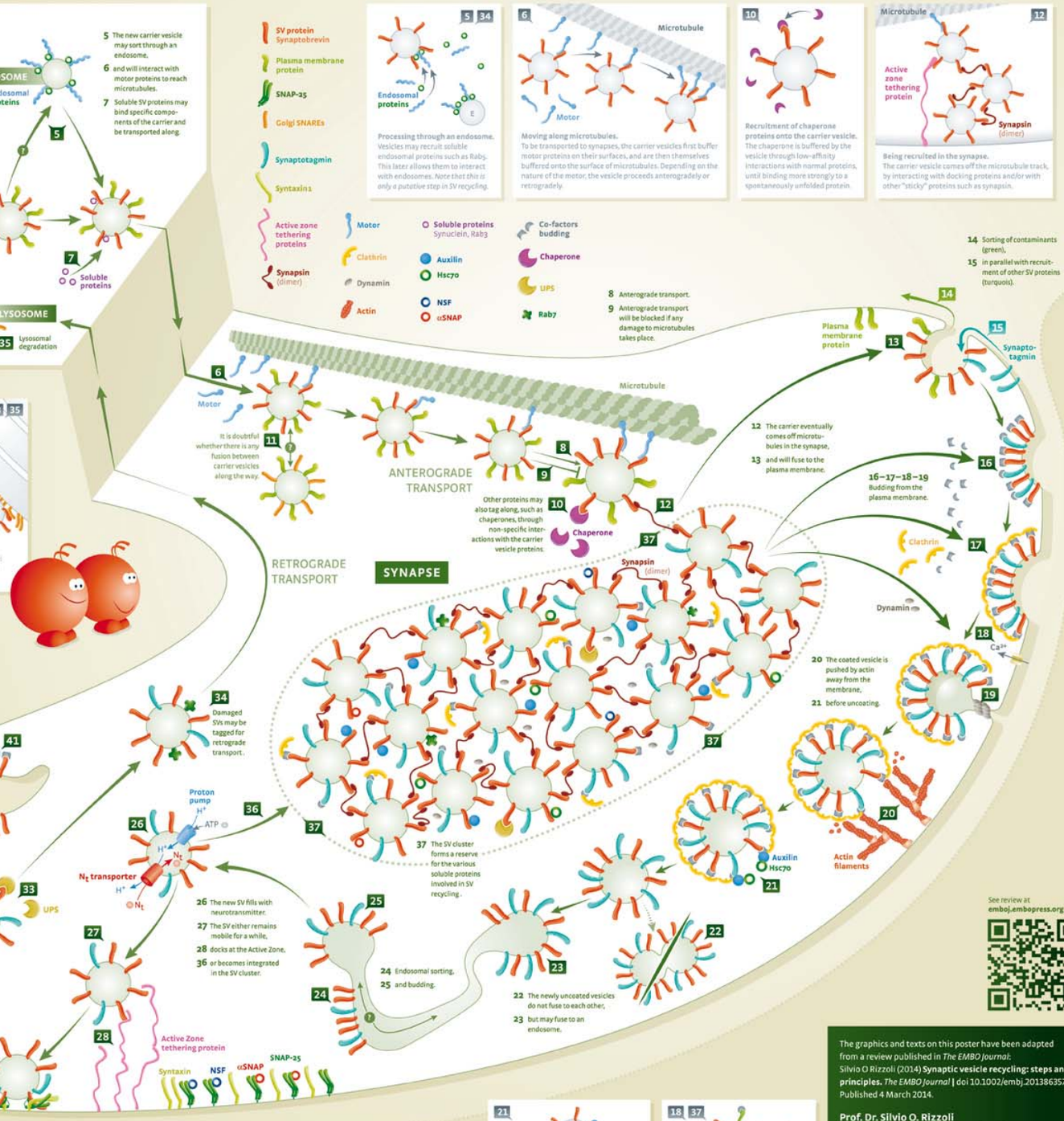
Speed: To be useful for sensation, perception, and the control of movement, all these things must occur very rapidly.

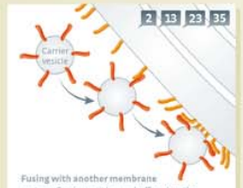
Synaptic vesicle recycling

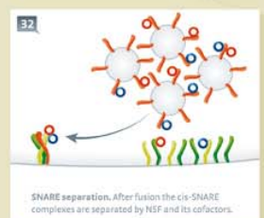
Steps and principles by Silvio O. Rizzoli

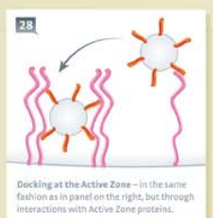
THE EMBO JOURNAL

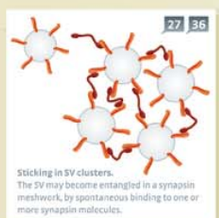


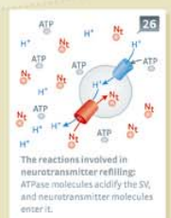


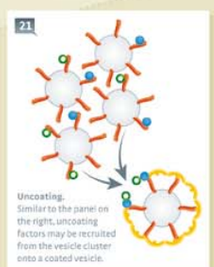


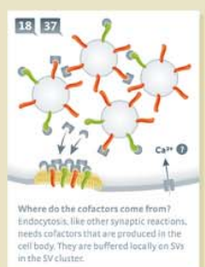












See review at emboj.embopress.org

The graphics and texts on this poster have been adapted from a review published in *The EMBO Journal*:
Silvio O Rizzoli (2014) **Synaptic vesicle recycling: steps and principles.** *The EMBO Journal* | doi 10.1002/embj.201386357
Published 4 March 2014.

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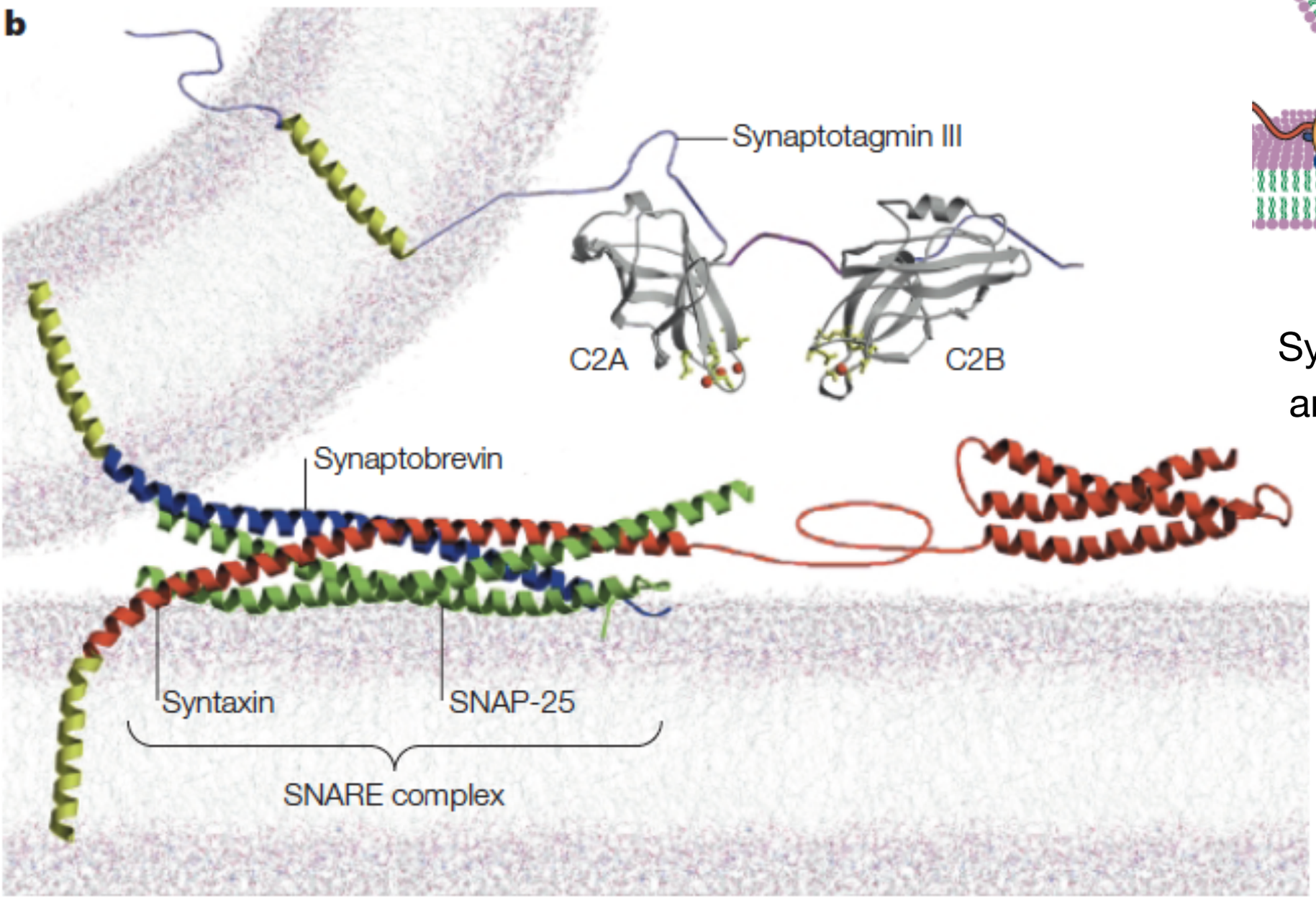
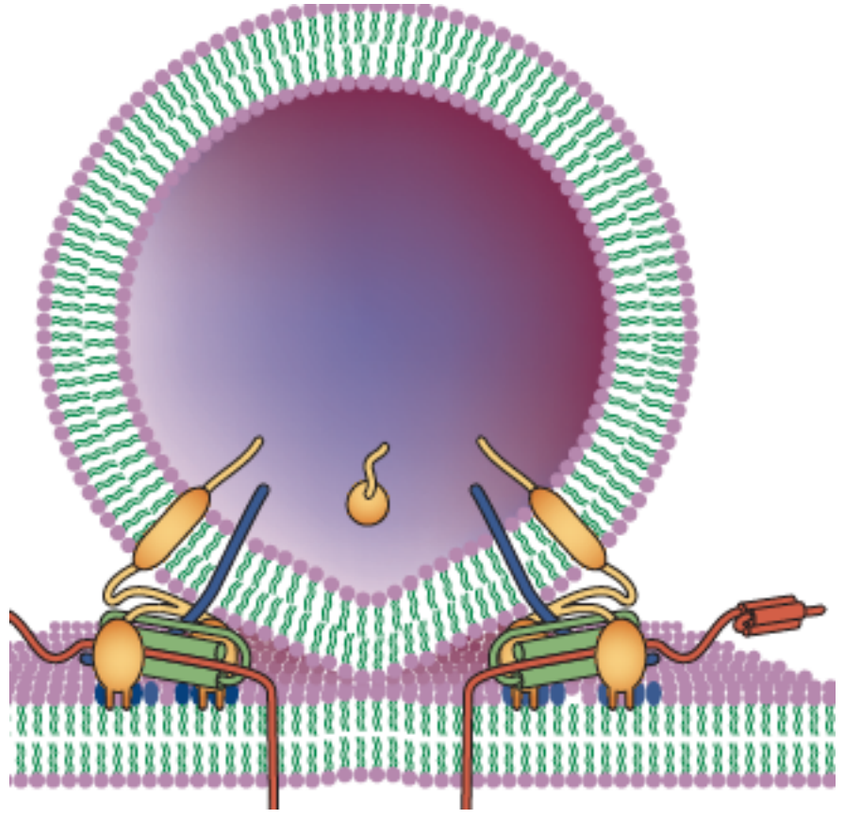
EMBOpress

A scale model of the components of the fusion apparatus





Syt C2 domains bind syntaxin and the SNARE complex

ER Chapman, Nat. Rev. Molecular cell Biology 2002

Vesicle Fusion

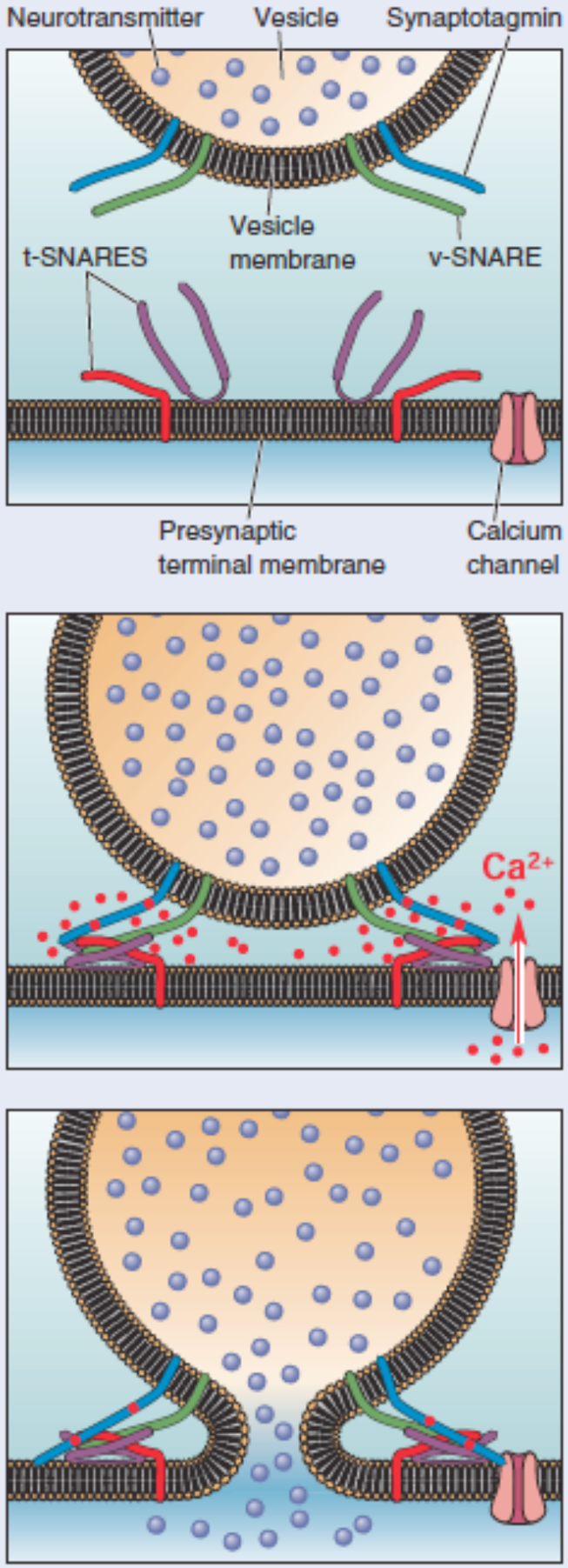
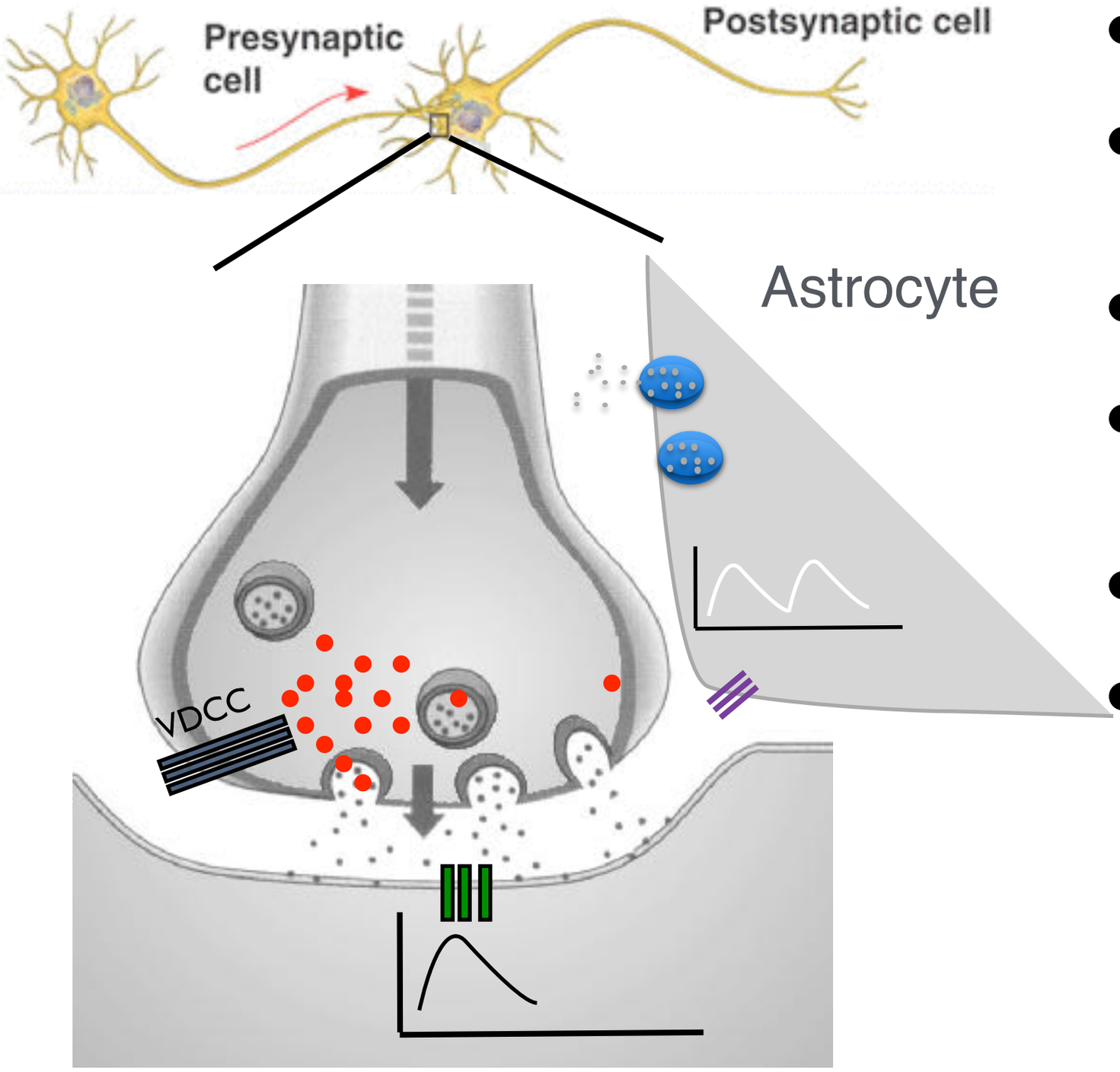


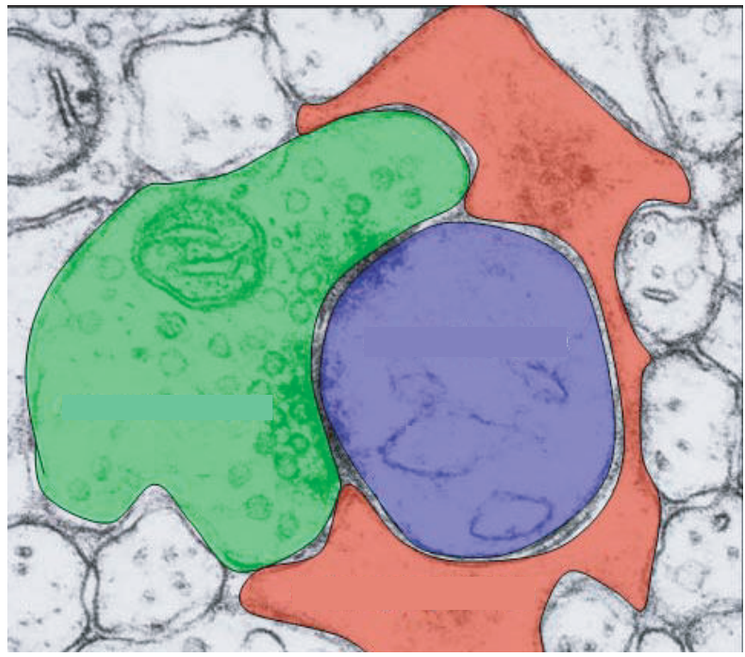
FIGURE A
SNAREs and vesicle fusion.

Sudhof 2013

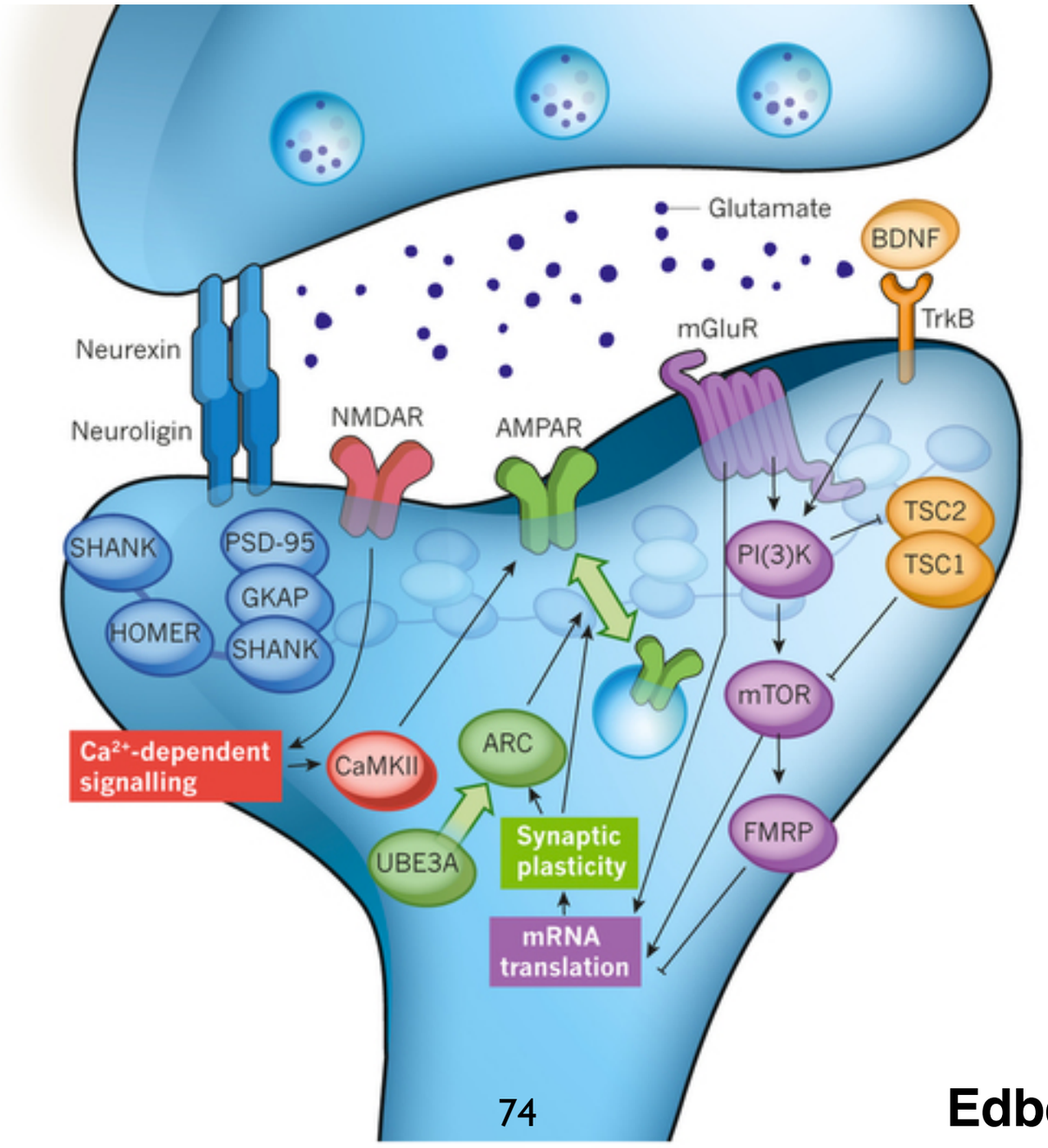
Synaptic transmission at a tripartite synapse



- Calcium signal necessary and sufficient for neurotransmitter release
- Action potential arrives
- Voltage Dependent Calcium Channels (VDCC) open
- Increase in intracellular [Ca^{2+}]
- Stochastic release of neurotransmitter vesicle
- Astrocytes sense neurotransmitter respond by elevated calcium
- Modulation of release probability of neurotransmitter

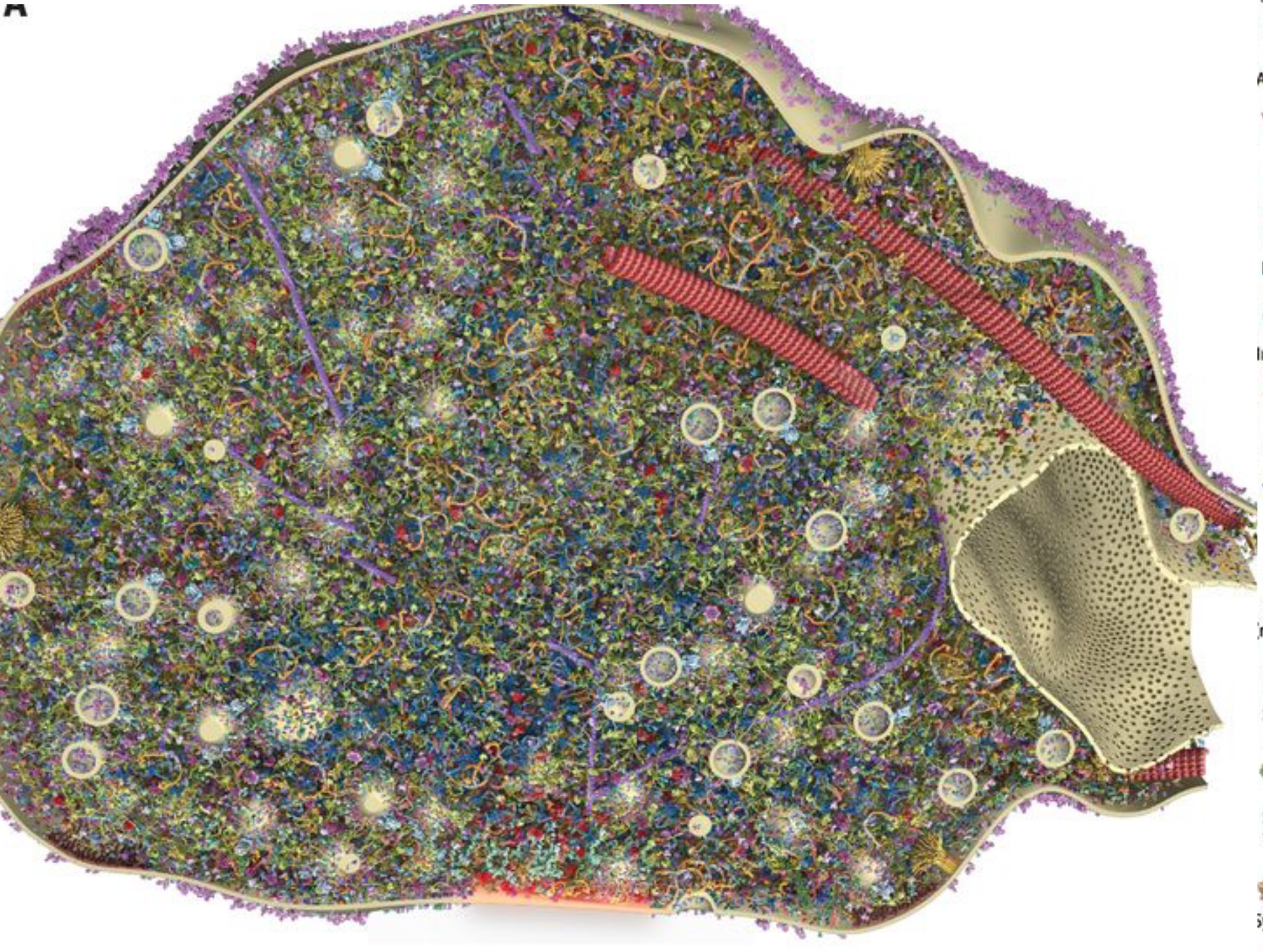


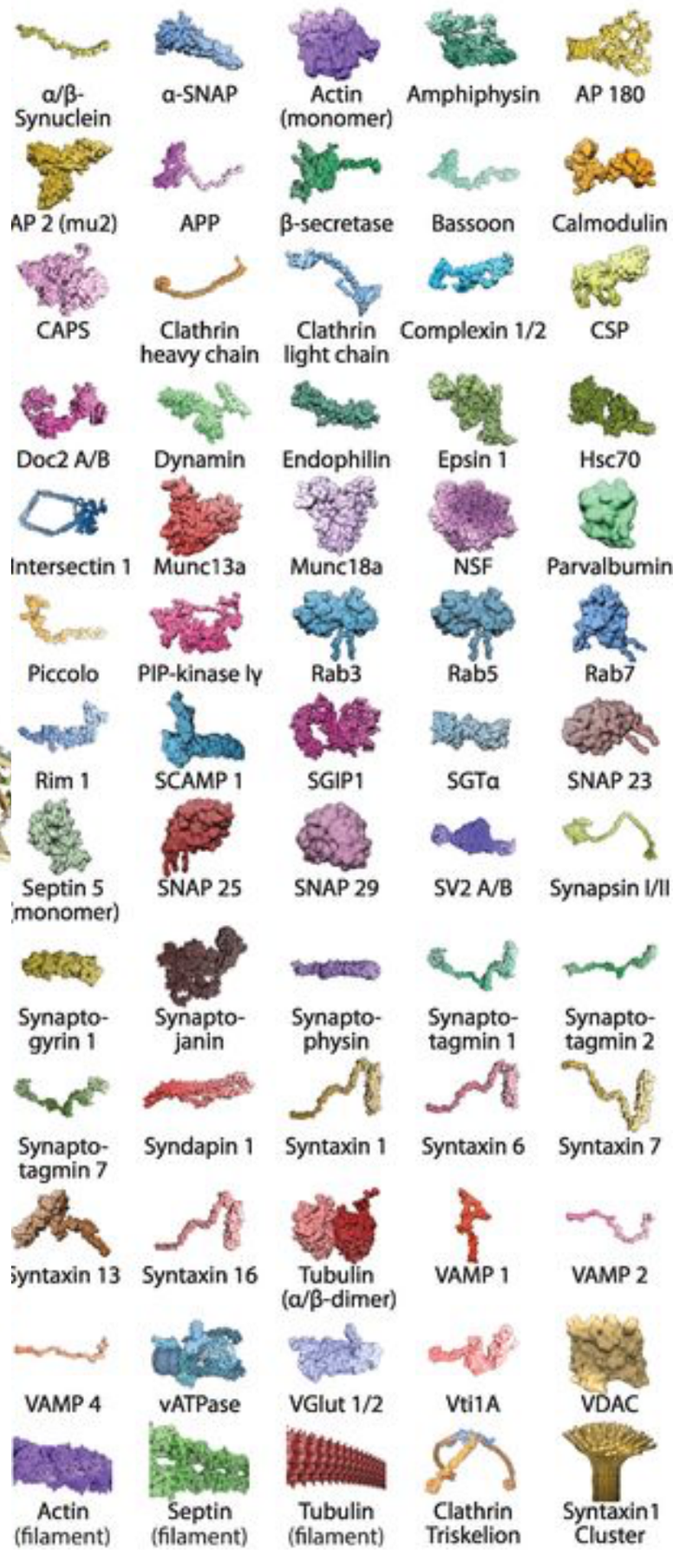
Presynaptic terminal; merely an on-off faucet?



Edbert et al., Nature, 2013

Sophisticated Bouton





Wilheim et al. 2014

Whats the point?

Changes in strength of synaptic transmission (Synaptic Plasticity) is the cellular underpinning of learning and memory: Rigorously quantify mechanisms associated with plasticity

Most neurological disorders seem to have synaptic basis: Use disease models to understand normal function. WHO estimated that neurological disorders affect up to one billion people worldwide.

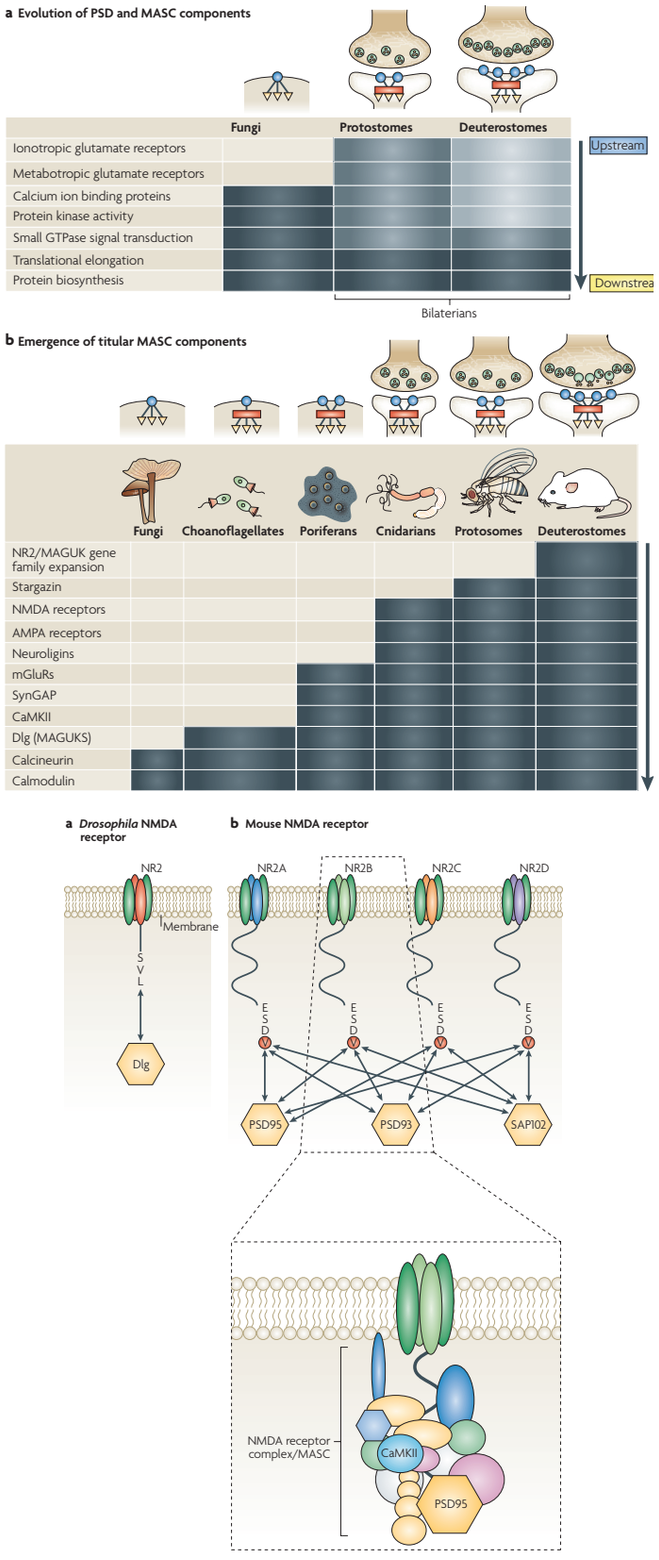
Given the high dimensional space and the degrees of freedom, use computational models may give an intuition about what to look for and where

A popular choice of model synapse: CA3-CA1 synapse, a small synapse in the hippocampus: Prototype for plasticity mechanisms; Direct sub-synaptic measurements difficult

"What I cannot create, I do not understand" -- *Richard Feynman*

Philosophical Approach: Understanding through simulation

Evolution of synapses



Complexity increases in a coordinated fashion not just increase in number and connections

Proteomic studies of the composition of mammalian synapses have revealed a high degree of complexity.

The postsynaptic and presynaptic terminals are molecular systems with highly organized protein networks producing emergent physiological and behavioral properties

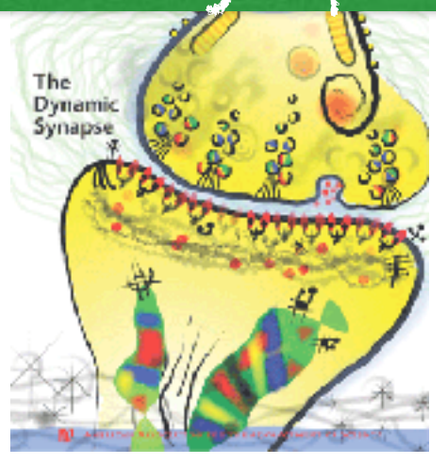
Proposal: Evolution of synapse complexity around a core proto-synapse has contributed to invertebrate-vertebrate differences and to brain specialization.

Evolution of the synapse complement might have enabled the increase of neuronal cell types and, in turn, the neuronal network complexity of the human brain.

Ryan and Grant, Nat Rev Neurosci. 2009

General approaches:

Sophisticated Synapses



1. Devise detailed 3D biophysical models for in-silico experiments

2. Calibrate and test these models with experimental data that can then be used to make testable predictions

3. Postdiction! Make sense of extant data

4. Big challenge: relevance of each degree of freedom/constraint for each functional module

Understanding of higher function can be based on making sense of the complexity and dynamics at the level of synapse

through

hippocampal

neuropil

A 3-D reconstruction of 180 cubic microns
of CA1 stratum radiatum in adult rat.

Realistic Model of Synapses in Hippocampal

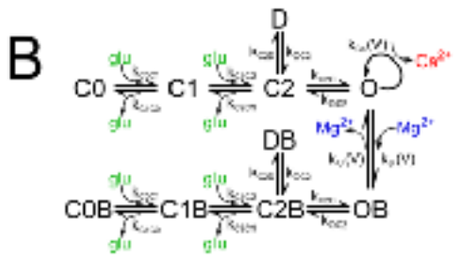
The simulation includes:

100nM resting Ca^{2+} level
PMCA pumps and Na^{+}/Ca^{2+} exchangers
postsynaptic L & R type VDCCs
NR2A and NR2B type NMDA receptors at the PSD
AMPA receptors at the PSD
Diffusible Calbindin-D28k in the cytosol
Calmodulin
CAMKII
Calcineurin
SERCA pumps
IP_3 and RyR receptors
Mitochondrial Ca^{2+} pumps
presynaptic P/Q type VDCCs
presynaptic vesicular release pathway with SNARE complex

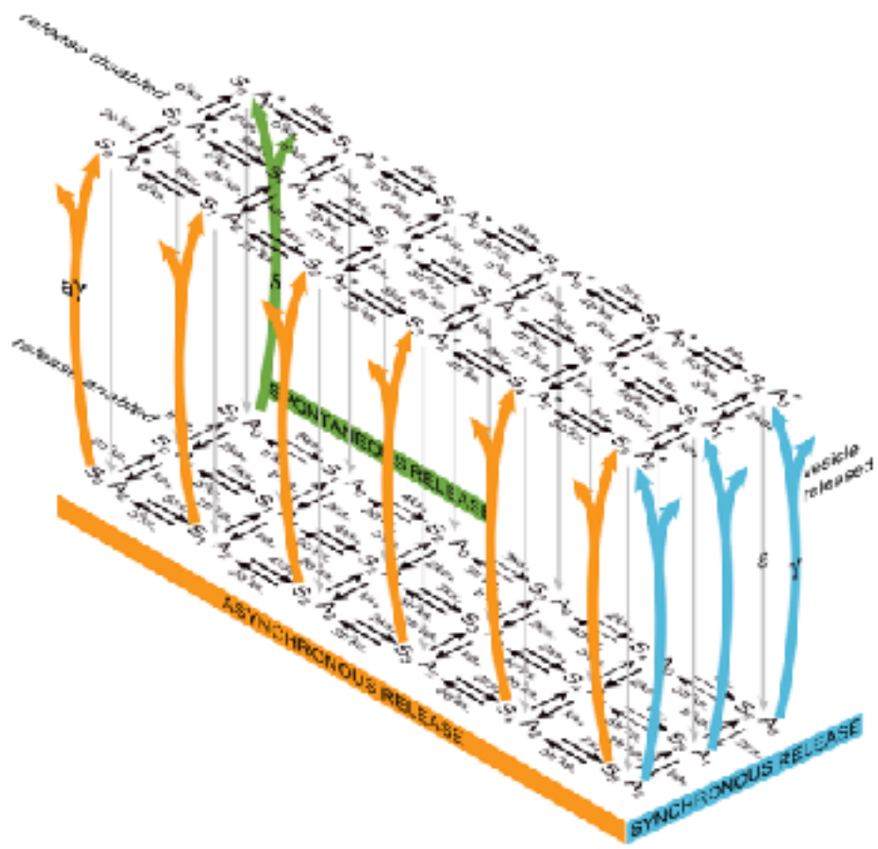
Rules of engagement

Experimental estimates of reaction kinetics and subcellular distributions for relevant molecules

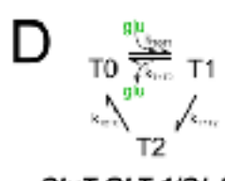
AMPAR-GLUR1



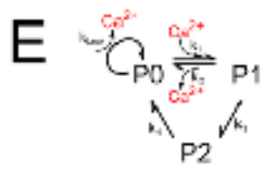
NMDAR-NR2A



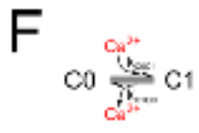
L-type, R-type, and P/Q type VDCC



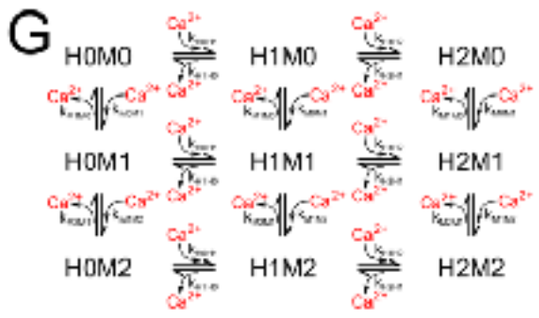
GluT GLT-1/GLAST



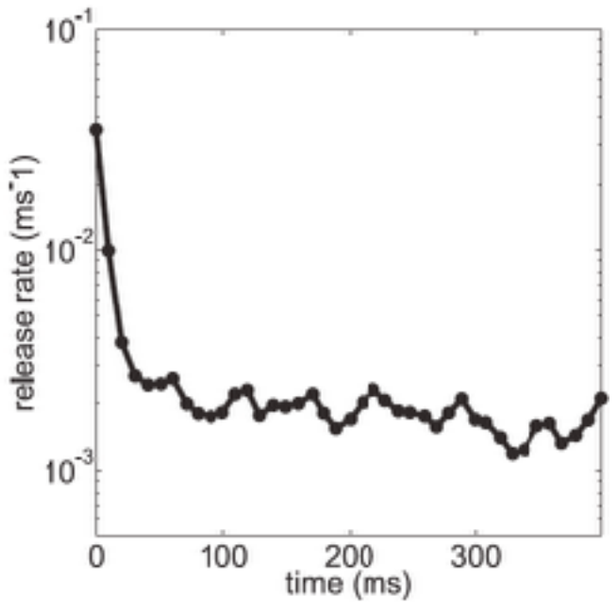
PMCA, NCX, SERCA



Endogenous CBP

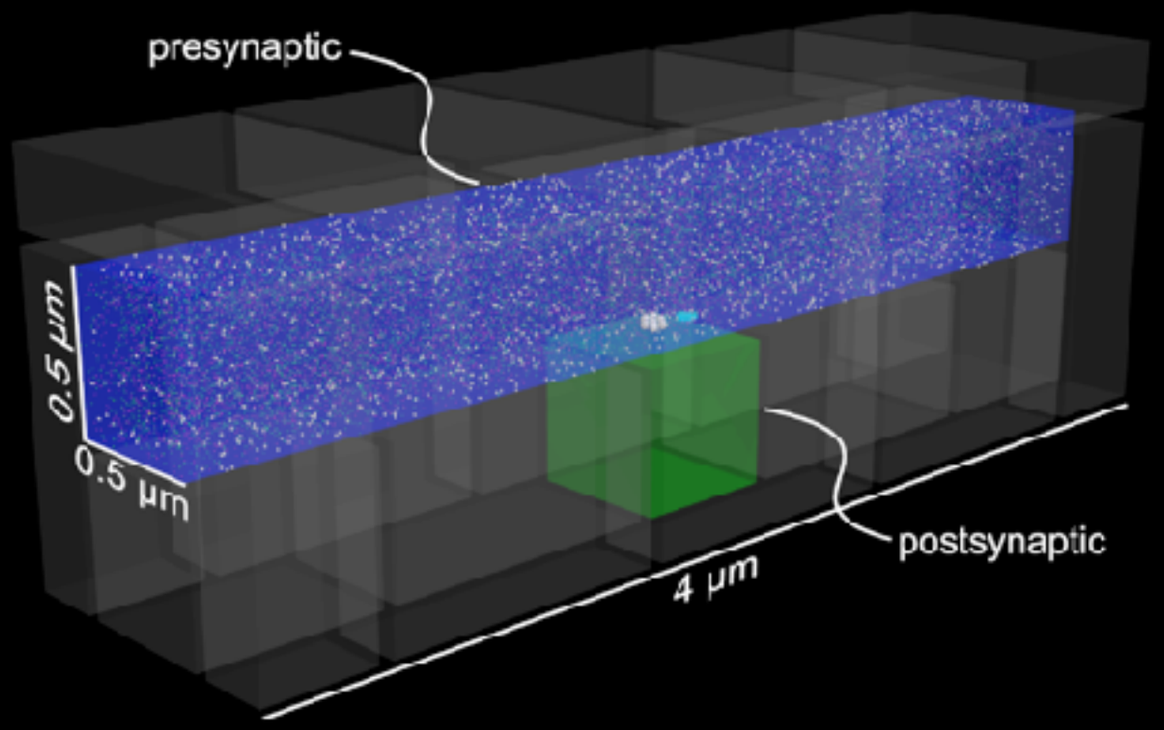


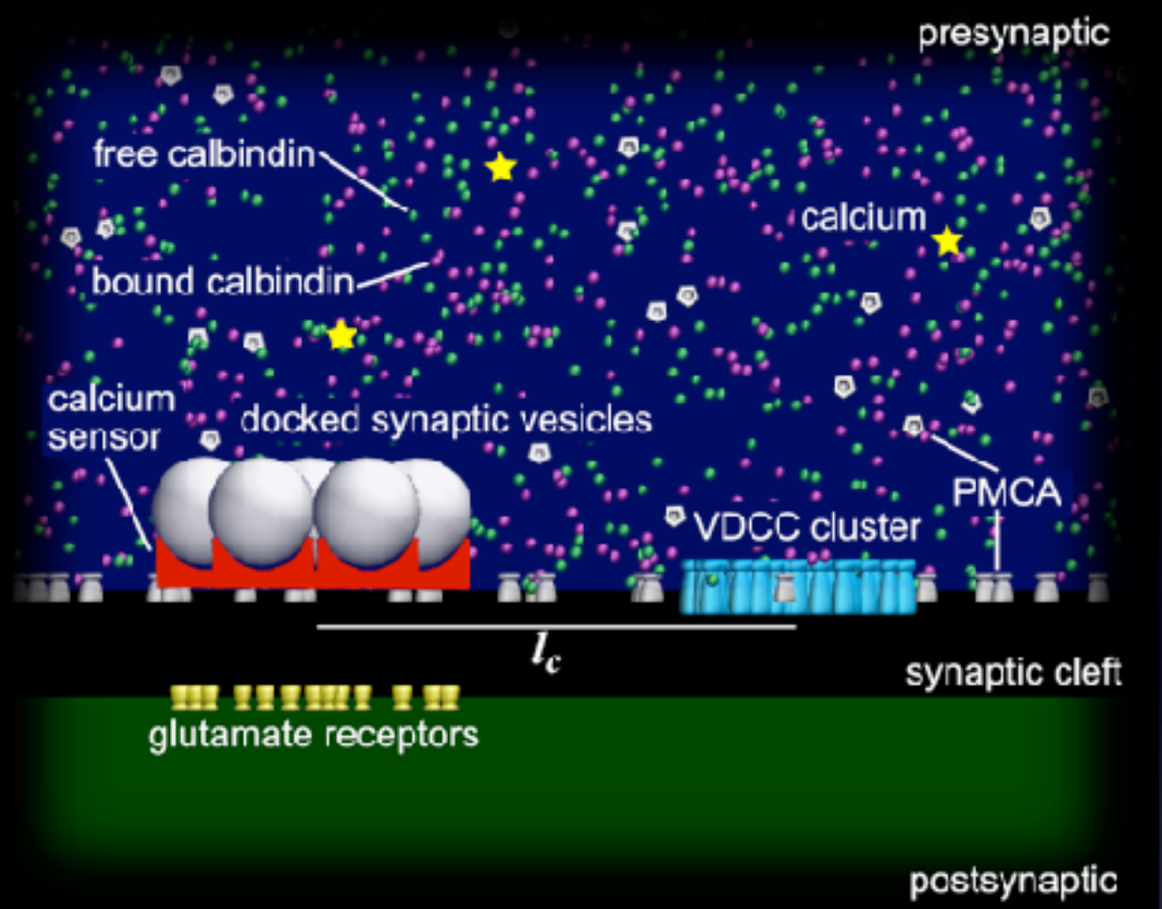
Calbindin-D28k

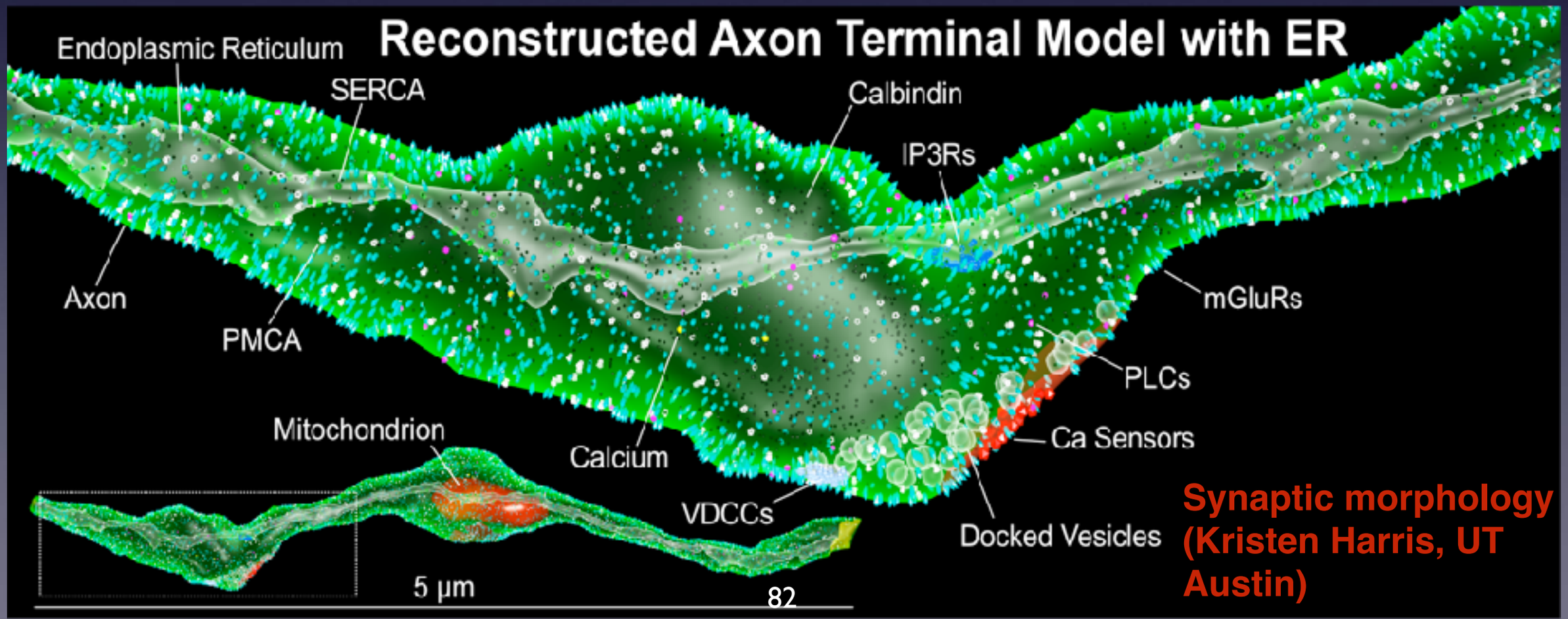


Use MCell (mcell.org), specialized Monte Carlo simulator for reaction diffusion trajectories in cells

Canonical Axon Terminal Model







Synaptic morphology (Kristen Harris, UT Austin)

Modeling pipeline

Model Geometry

canonical geometry

3D surfaces from CAD
blender, solid edge

mesh generation
netgen, meshmorph

mesh analysis
meshalyzer

mesh annotation
blender, DReAMM

geometries MDL

realistic geometry

EM serial thin sections

segment images in 2D contours
reconstruct

reconstruct 3D surfaces
contour_tiler

Model Biophysics

construct reaction networks
extant data, models, collaborations

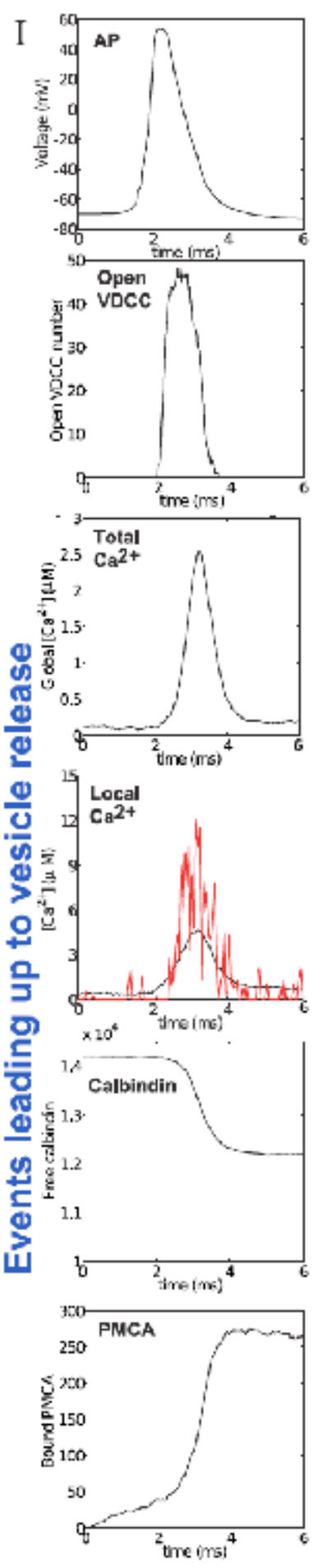
define molecules, concentrations, placement and diffusion constants

merge geometry, molecules, reactions, biophysical properties
specify initial conditions
complete model

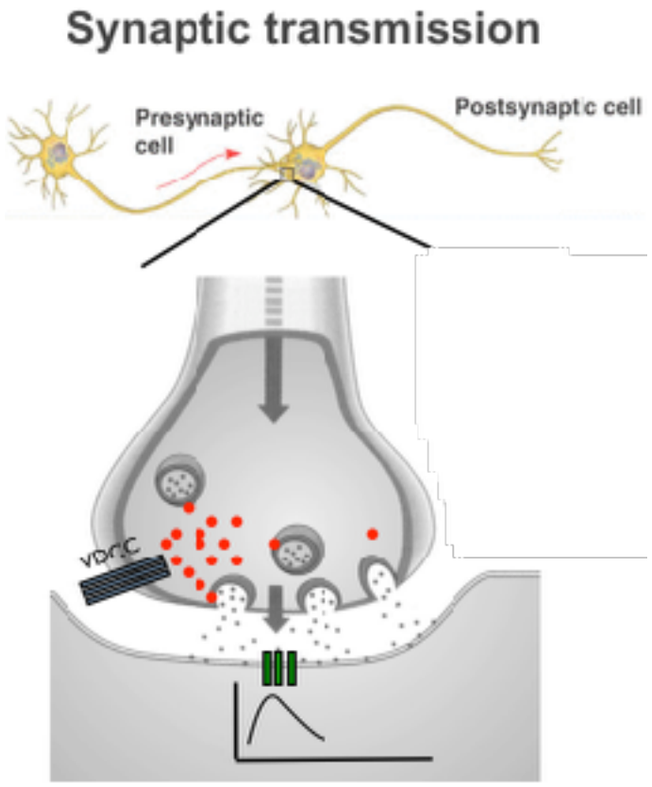
compute monte carlo simulations
analyze results from several trajectories

“What I cannot create I cannot understand”-- Richard Feynman

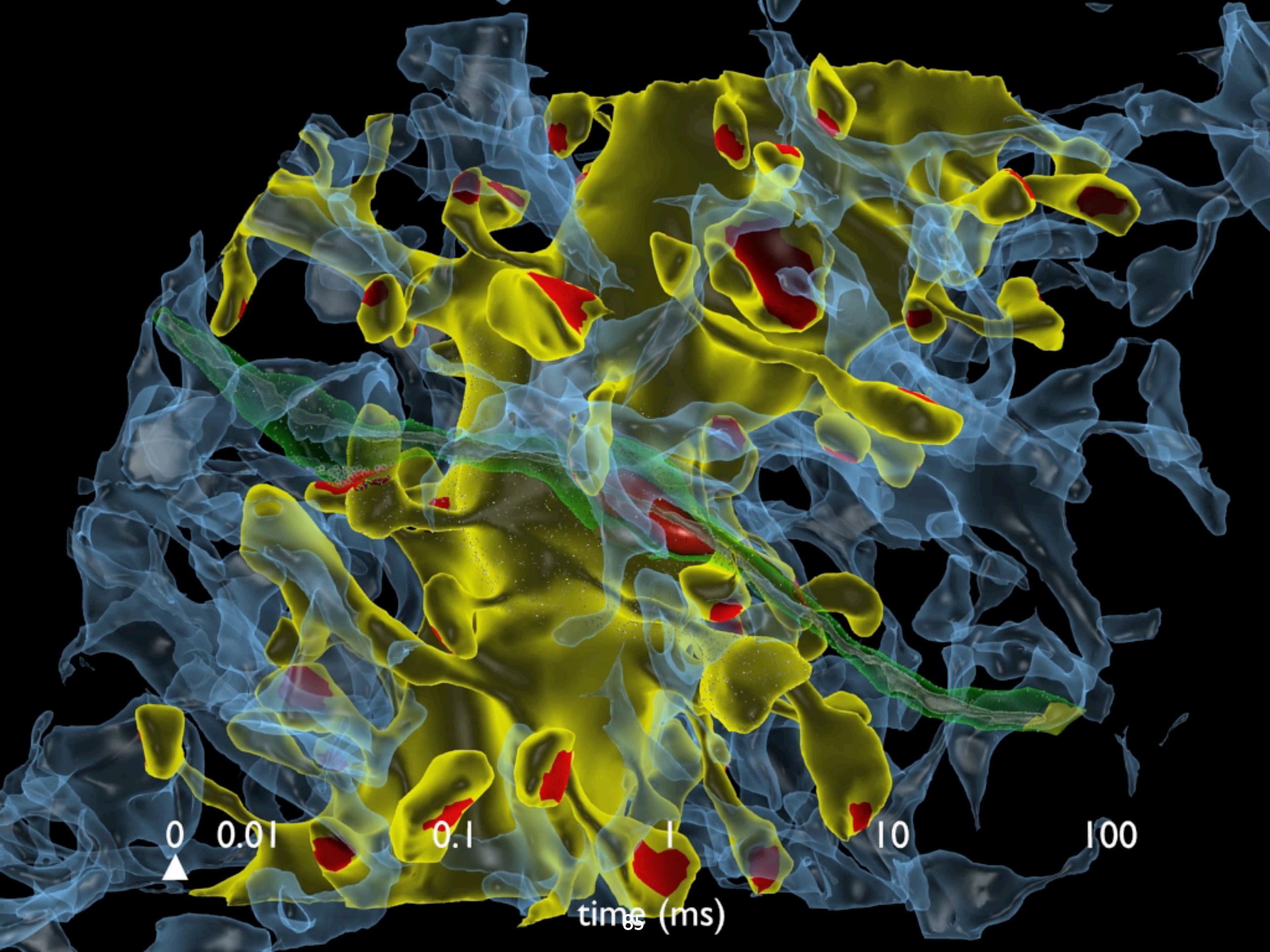
In-Silico experiments on CA3-CA1 synapse

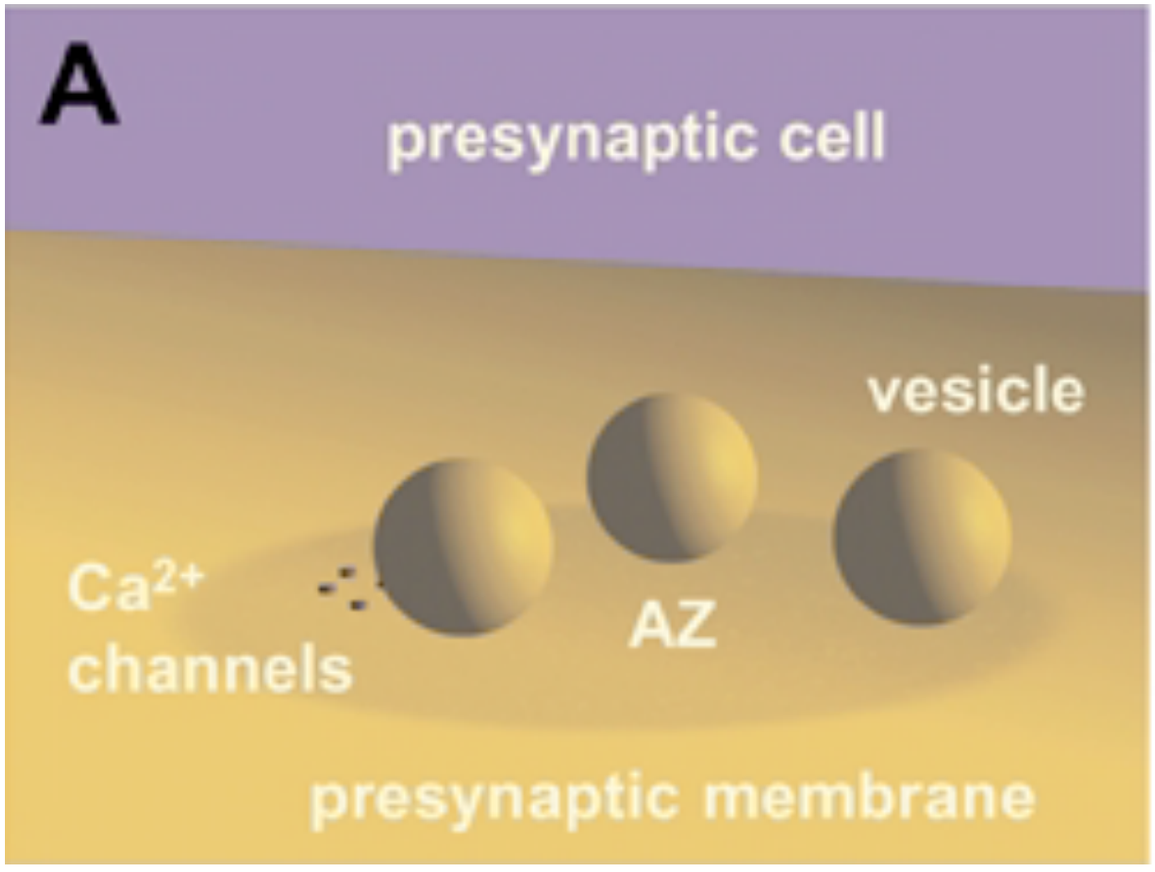


- Time series data on chronology of events leading up to a vesicle release.
- Concentrations, kinetics rates and diffusion constants are well constrained by physiologic data.
- Effective diffusion constant of Ca^{2+} that falls out of the model synapse is consistent with measured experimental values - validates the model.



Its Alive!


0
0.01
0.1
1
10
100
time (ms)



The geometrical relationship between ca channels and its sensors determines the precise nature of the physiological response to this signal

These scales may be beyond the current resolution of ca imaging

Christoph J. Meinrenken, J. Gerard G. Borst* and Bert Sakmann, Journal of Physiology, 2003

Nanodomain coupling between Ca^{2+} channels and sensors of exocytosis at fast mammalian synapses

Emmanuel Eggermann, Iancu Bucurenciu, Sarit Pati Goswami and Peter Jonas

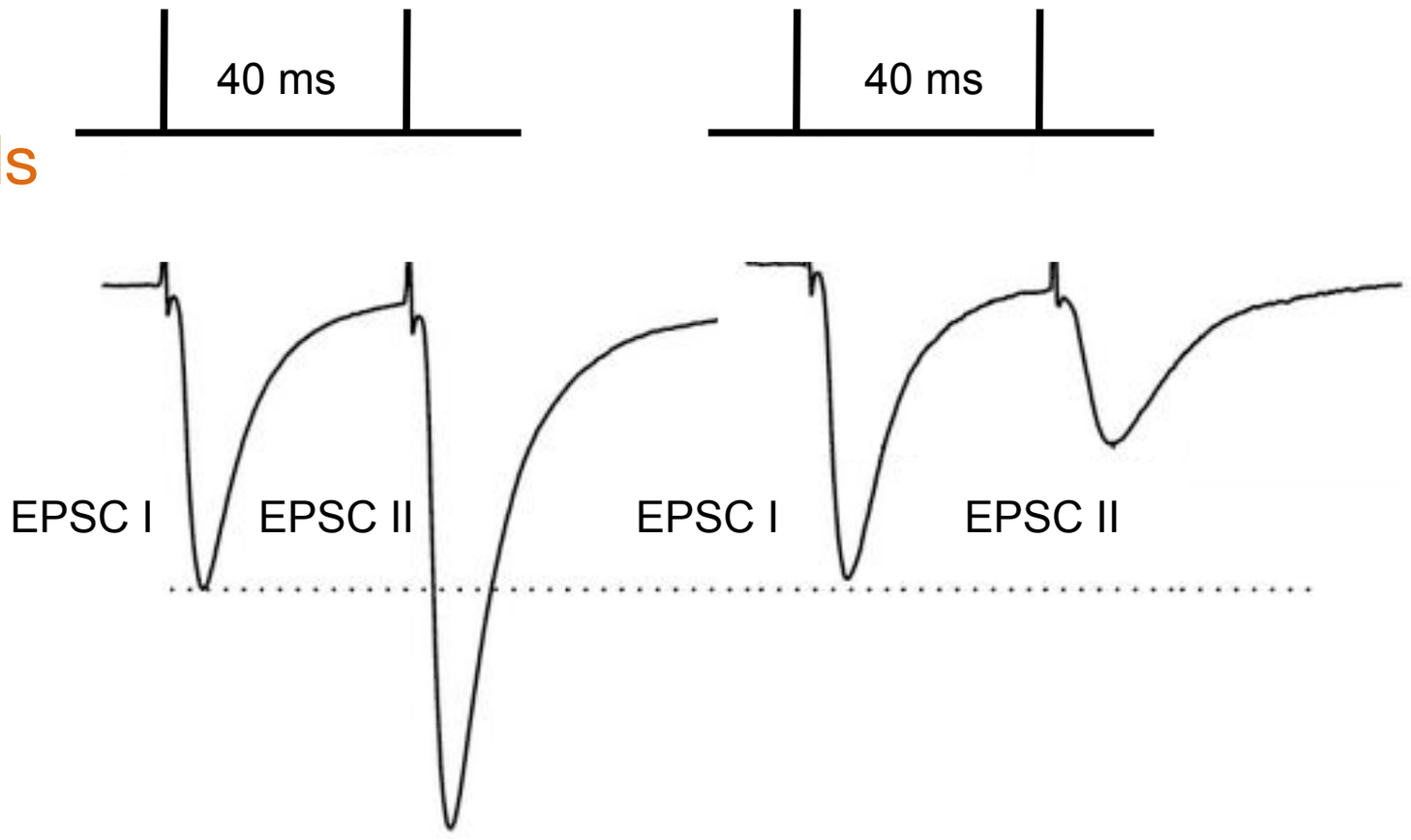
Abstract | The physical distance between presynaptic Ca^{2+} channels and the Ca^{2+} sensors that trigger exocytosis of neurotransmitter-containing vesicles is a key determinant of the signalling properties of synapses in the nervous system. Recent functional analysis indicates that in some fast central synapses, transmitter release is triggered by a small number of Ca^{2+} channels that are coupled to Ca^{2+} sensors at the nanometre scale. Molecular analysis suggests that this tight coupling is generated by protein–protein interactions involving Ca^{2+} channels, Ca^{2+} sensors and various other synaptic proteins. Nanodomain coupling has several functional advantages, as it increases the efficacy, speed and energy efficiency of synaptic transmission.

At a fast inhibitory synapse, a close nanodomain coupling allows for fast high fidelity transmission

Does the functional plasticity requirements at this synapse constrain the geometrical arrangement between channels and the AZ?

Paired Pulse Ratio

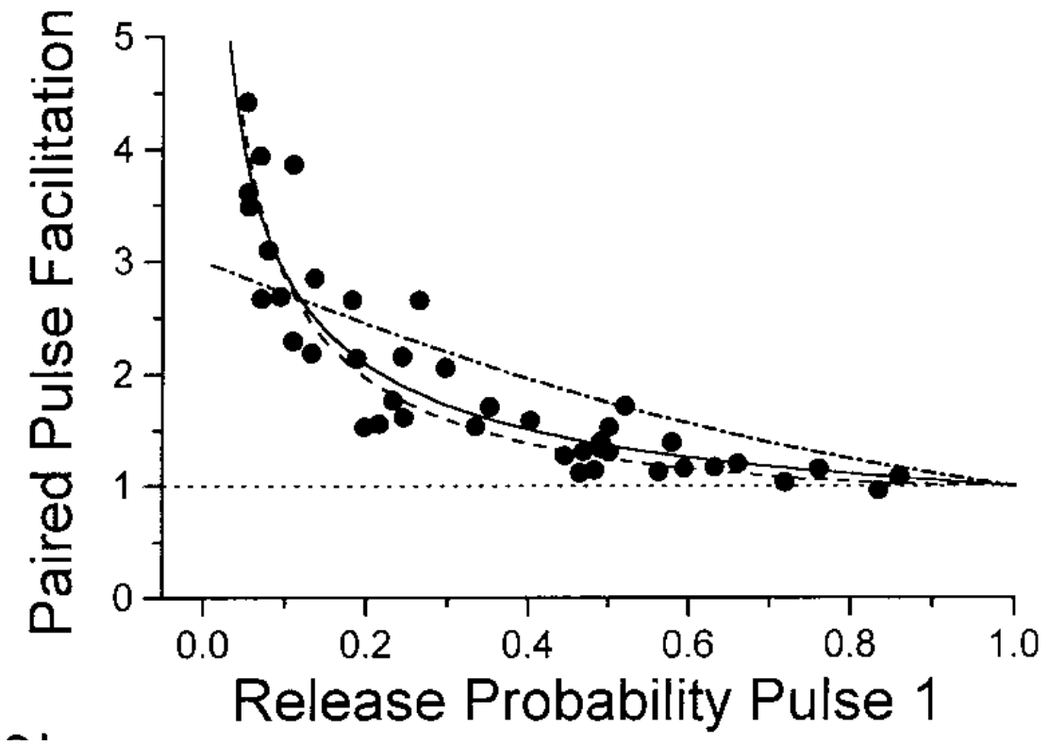
Excitatory Postsynaptic Current (EPSC) responses to a pair stimuli

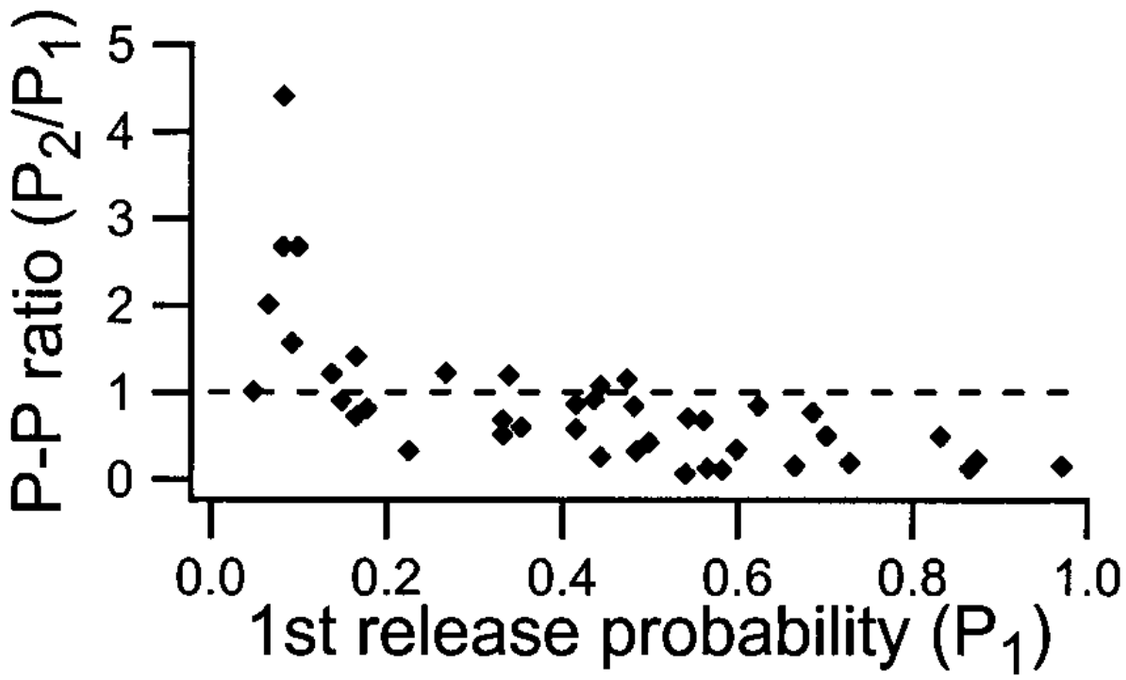


Paired Pulse Facilitation (PPF)

Paired Pulse Depression (PPD)

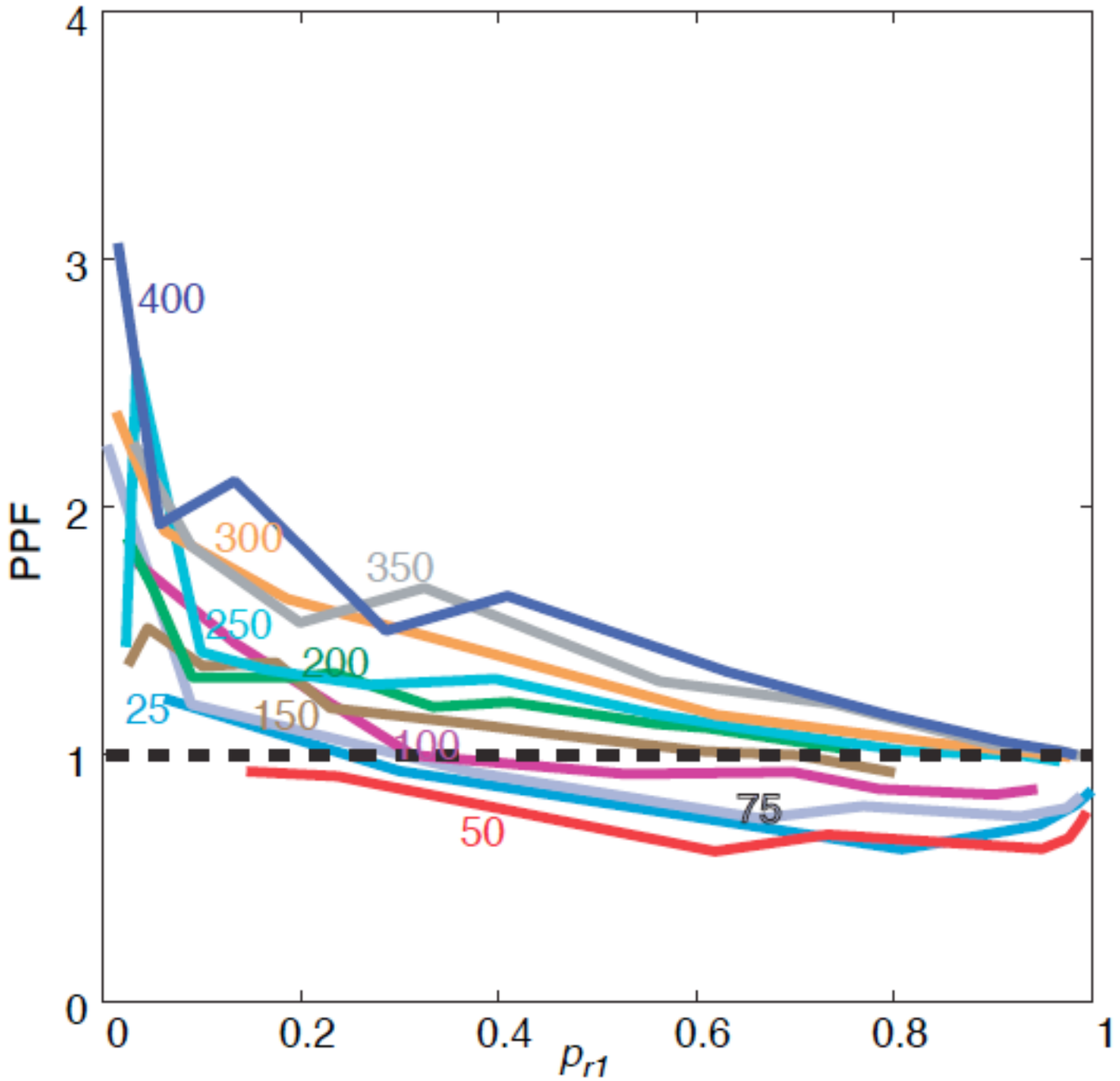
Paired Pulse Ratio= EPSCII / EPSC I





Dobrunz and Stevens, Neuron, 1999 and Hanse and Gustafson, J of NeuroSci., 2001

Structural correlates of plasticity



- If Lc is large, need large global Ca signal to reach threshold at sensor, implies facilitation of next pulse. If Lc is small, tight coupling allows release with localized peak, which decays quickly; depletion dominates at large pr

- Only large Lc can account for PPF seen in experimental data

Short-term plasticity constrains spatial organization of a hippocampal presynaptic terminal

Suhita Nadkarni[a,b], Thomas M. Bartol[a,b], Charles F. Stevens[b], Terrence J. Sejnowski[a,b,c], and Herbert Levine[a,1]

[a]Center for Theoretical Biological Physics, University of California at San Diego, La Jolla, CA 92093; [b]Salk Institute for Biological Studies, La Jolla, CA 92037; and [c]Howard Hughes Medical Institute, Salk Institute for Biological Studies, La Jolla, CA 92037

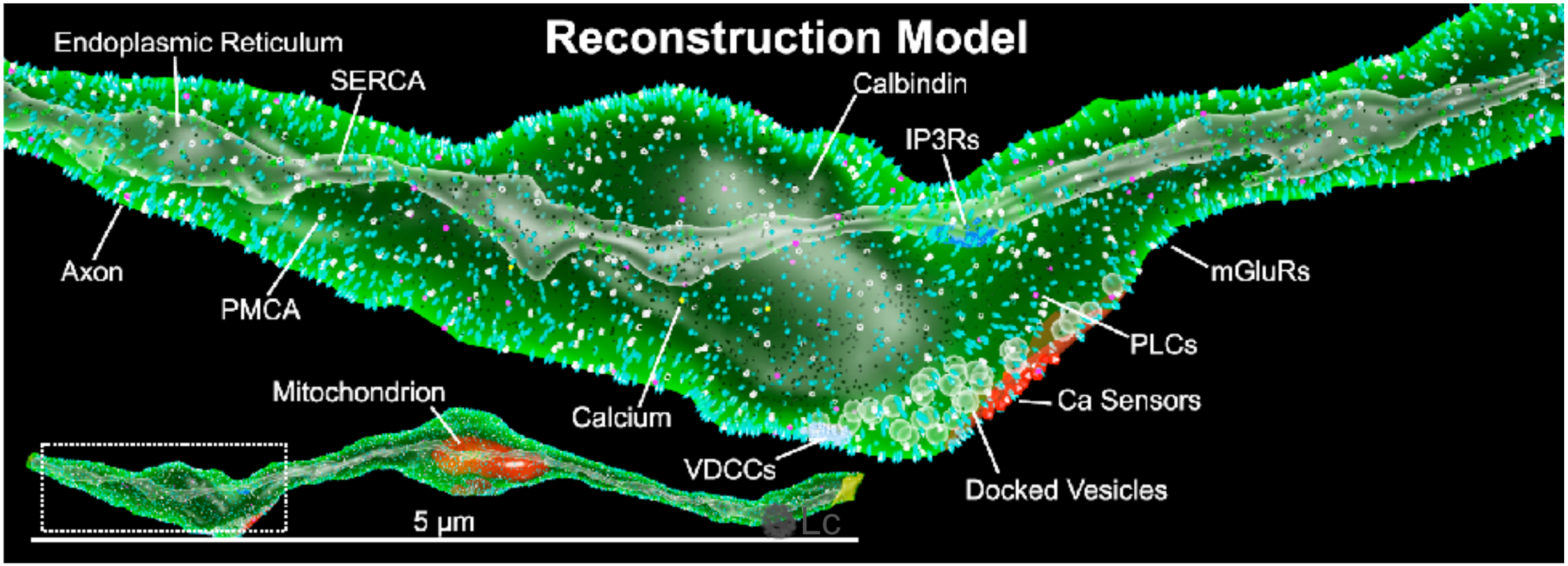
PNAS | **September 4, 2012** | vol. 109 | no. 36 | **14657–14662**

Loose Coupling Between Ca^{2+} Channels and Release Sensors at a Plastic Hippocampal Synapse

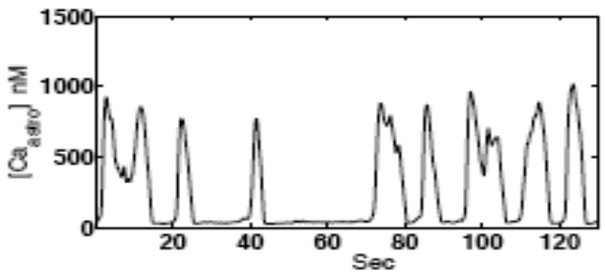
Nicholas P. Vyleta and Peter Jonas*

www.sciencemag.org **SCIENCE** VOL 343 7 FEBRUARY 2014

Ca^{2+} induced Ca^{2+} release (CICR)

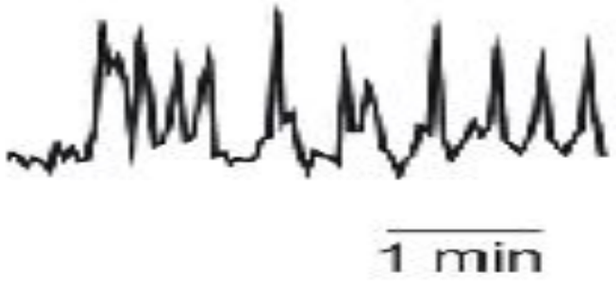


Activation of RyR by VDCC Ca

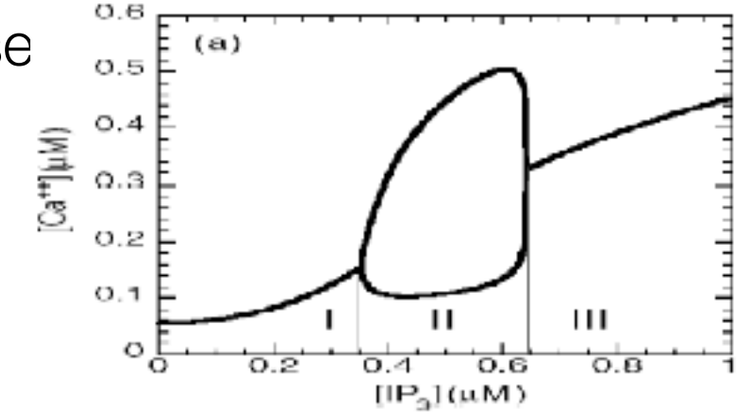


Activation of mGluRs by glutamate in extracellular space

Production of IP_3 - an important secondary messenger

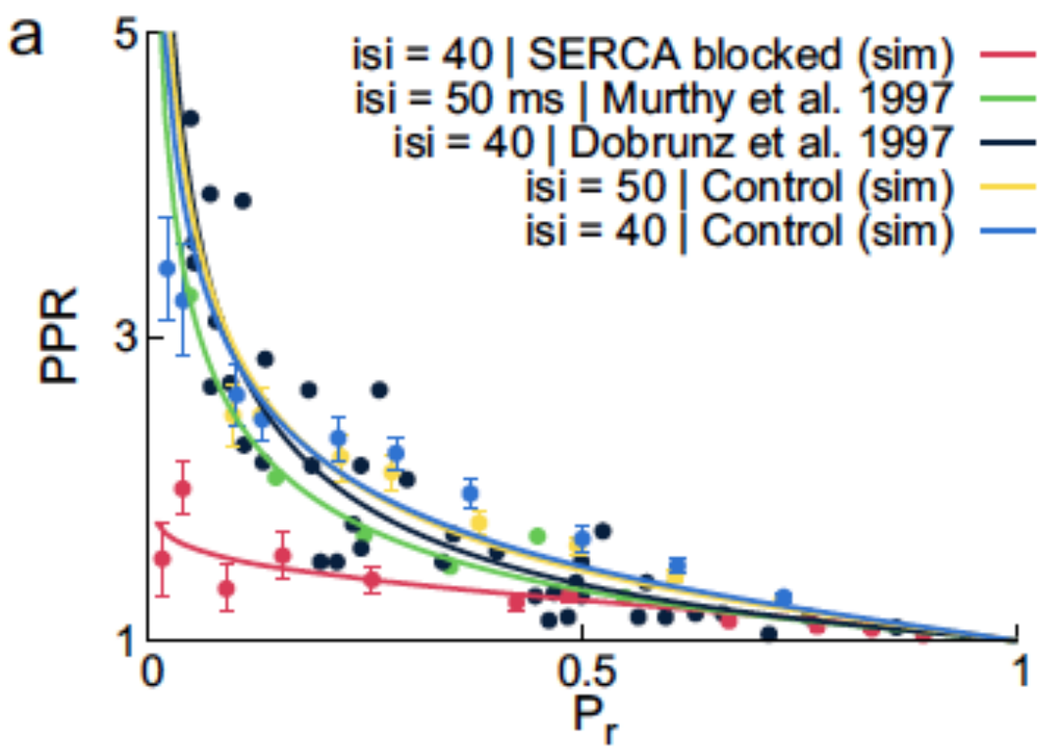


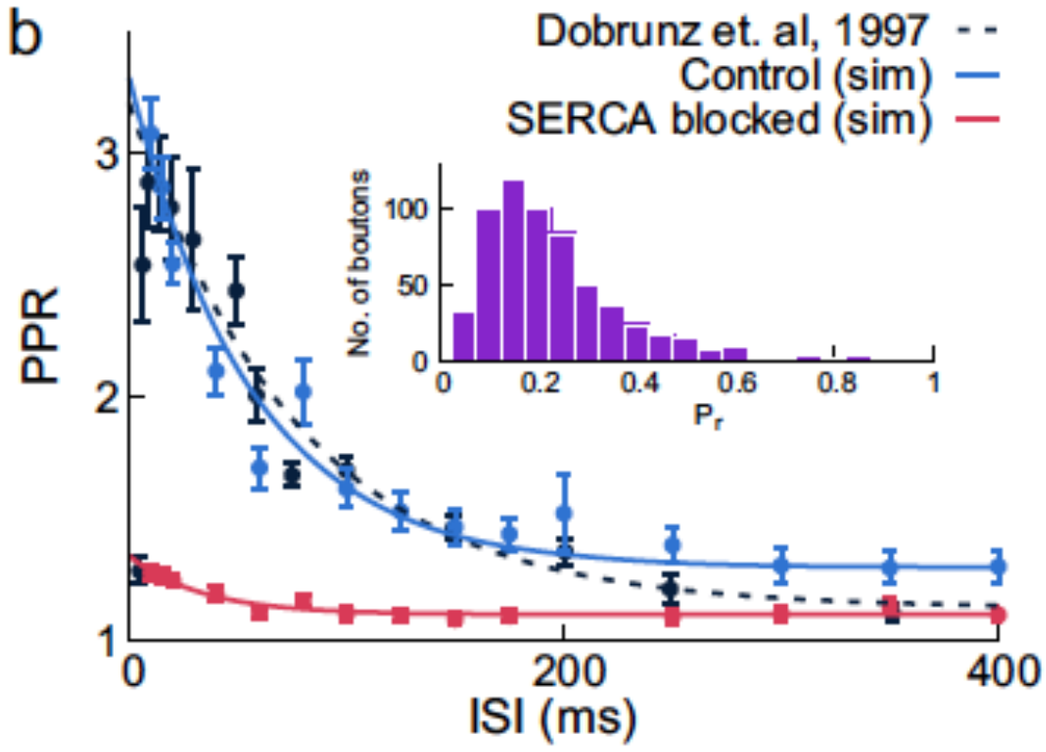
Activation of IP_3Rs on the ER and a conse
Ca^{2+} from the ER



Oscillatory response of Ca^{2+}

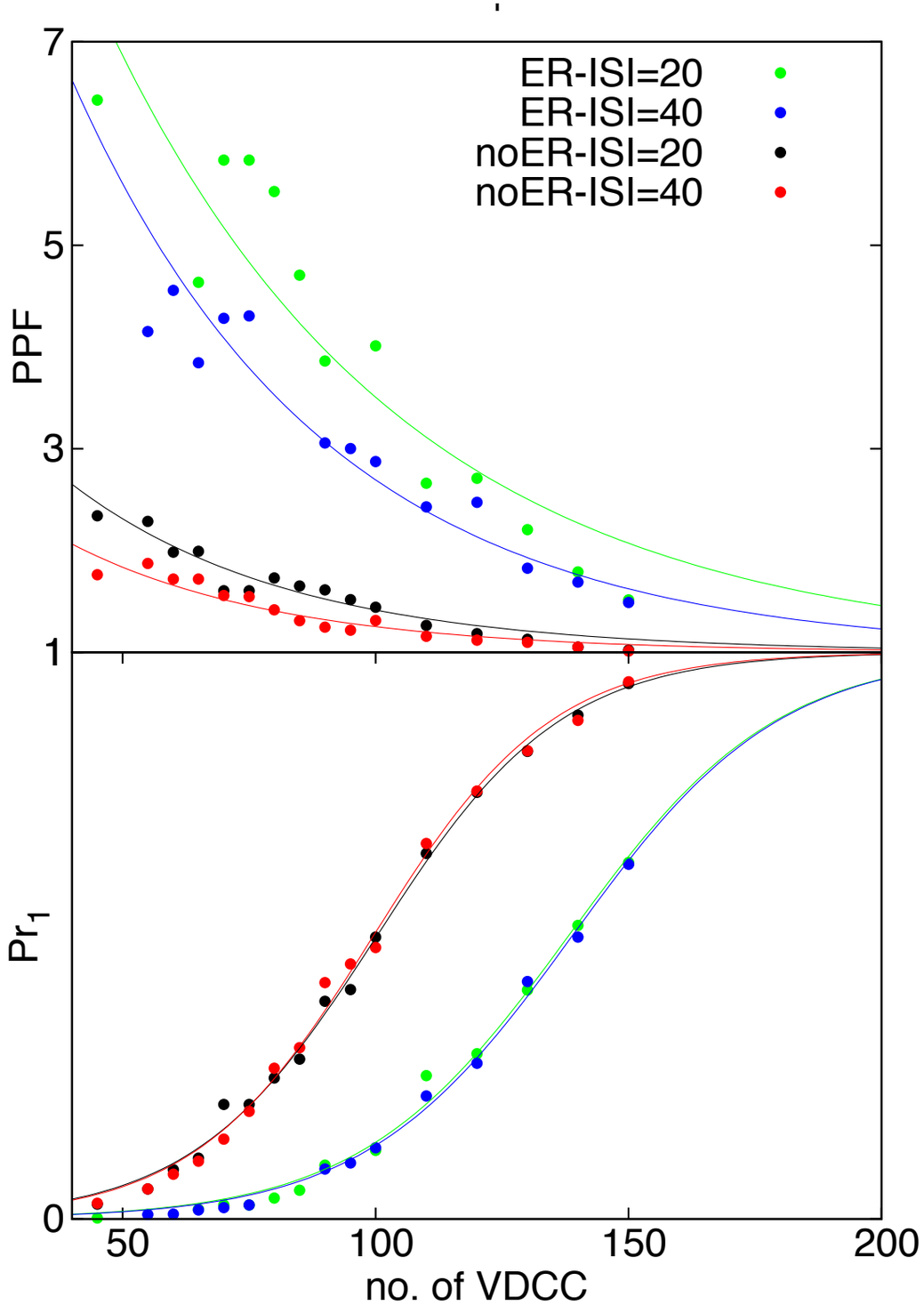
Presynaptic stores essential for normal STP

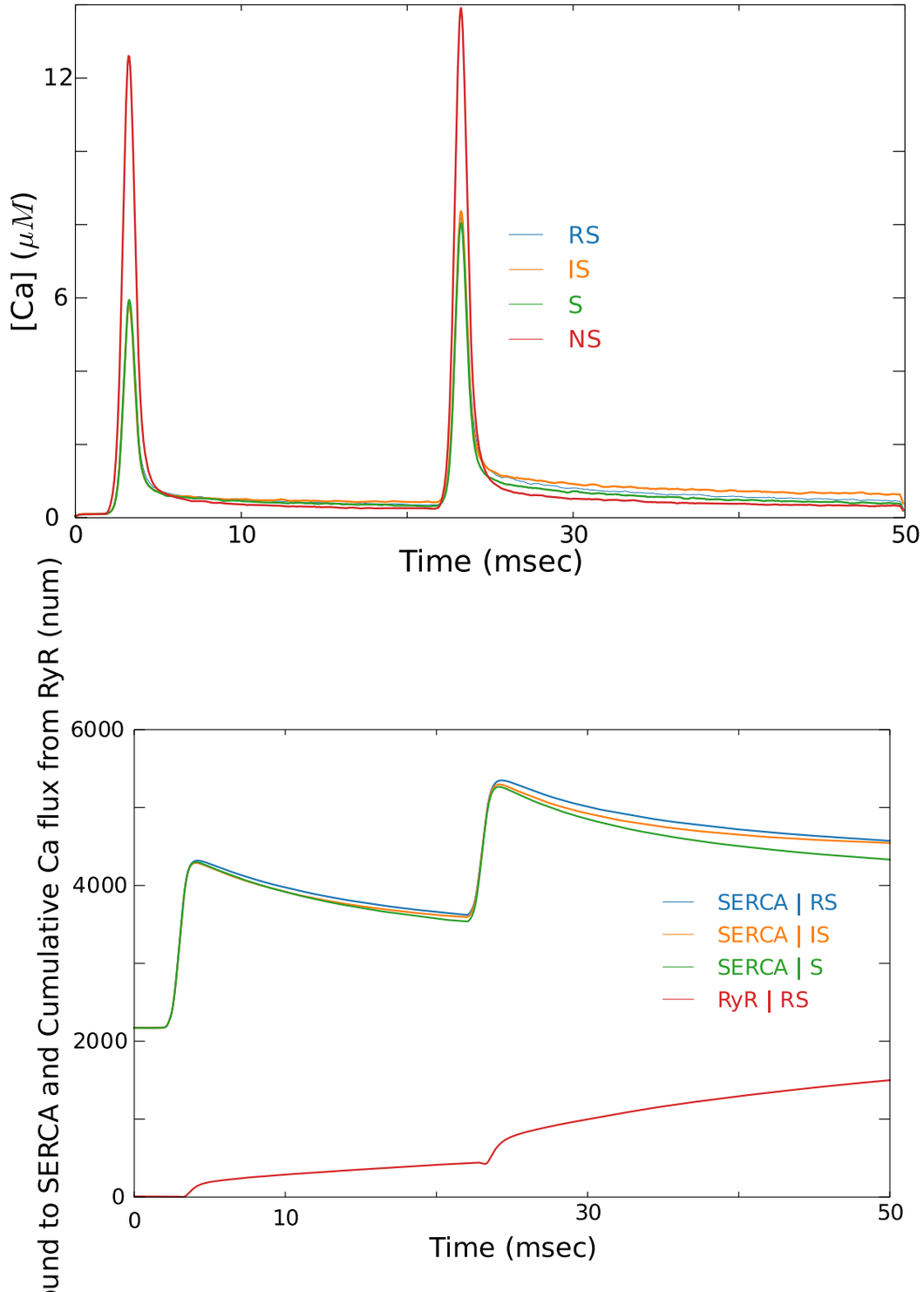




Singh et al. Nature Comm Bio 2021

Presynaptic ER Ca^{2+} stores machinery shifts the operating point to lower P_r and therefore higher PPF

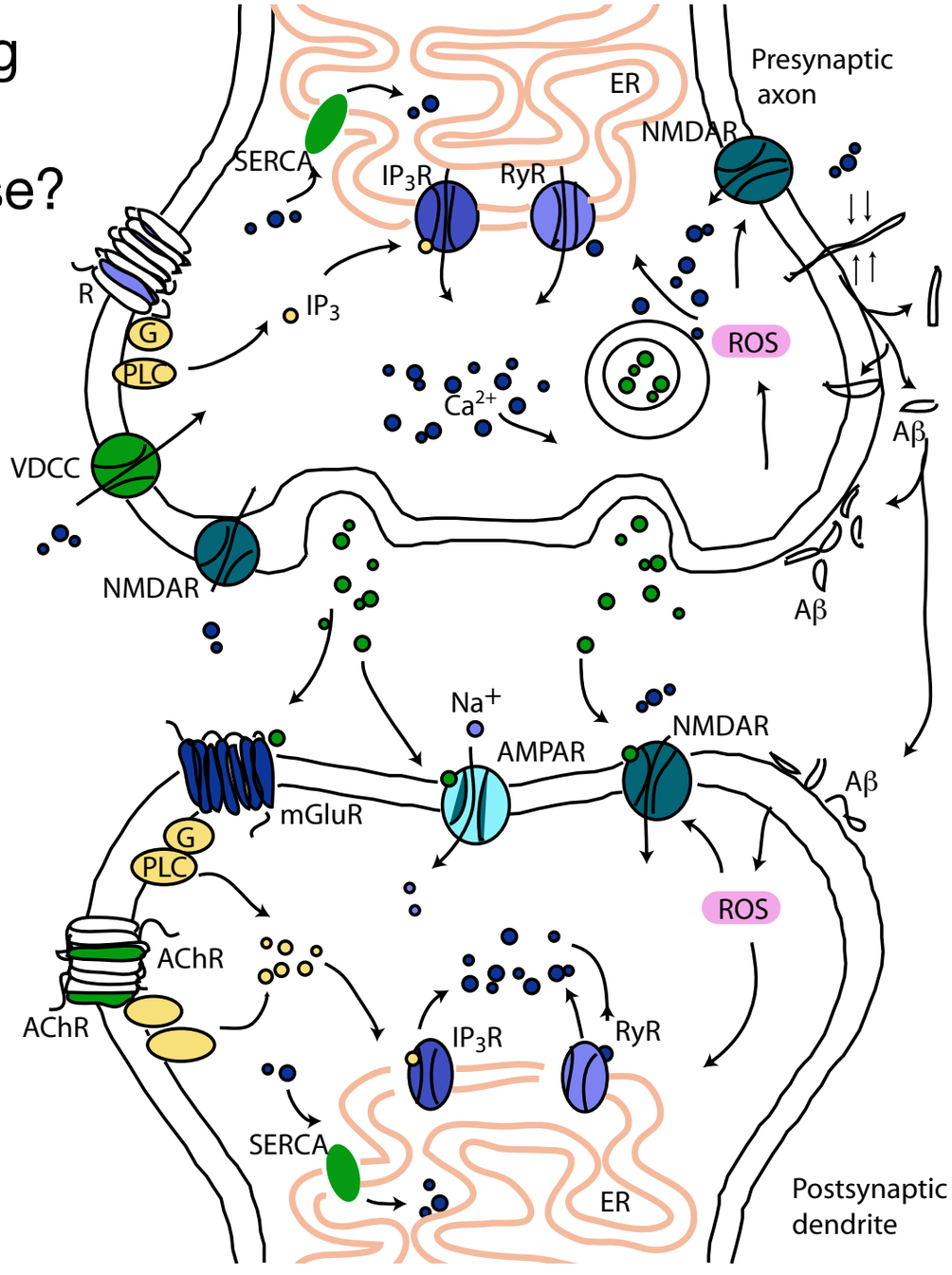




Calcium hypothesis of Alzheimer's Disease

What are the molecular signaling pathways underlying the disruption of synaptic transmission leading to cognitive deficits seen in inherited Alzheimer's Disease?

Ca2+ remodeling in PS1 mutant - (1) Increase in [Ca2+] in the ER (2) Increase/decrease in the expression of RyR (3) Increased open probability of IP3Rs (4) Down regulation of the calcium buffer Calbindin (5) ER leak channel is severely compromised (6)Reduced PPF in presynaptic PS1 mutants leading to aberrant LTP (7) Modified SERCA kinetics etc.



Calcium hypothesis of Alzheimer's

1. Q. Guo *et al.*, *Neuroreport* (1996). **2.** K.-H. Cheung *et al.*, *Sci Signal* (2010). **3.** G. E. Stutzmann *et al.*, *Ann N Y Acad Sci* (2007). **4.** G. E. Stutzmann, A. Caccamo, F. M. Laferla, I. Parker, *J of NeuroSci.* (2004). **5.** M. A. Leissring et al. *J of NeuroChem* (2008). **6.** G. E. Stutzmann *et al.*, *J of NeuroSci.* (2006). **7.** S. L. Chan, et al., *J Biol Chem* (2000). **8.** Q. Guo *et al.*, *Nat Med* , (1999). **9.** S. Chakroborty et al., *J Neurosci* (2009). **10.** H. Tu *et al.*, *Cell* (2006). **11.** D. Zhang *et al.*, *J of NeuroChem.* (2010). **12.** C. Zhang *et al.*, *Nature* (2009). **13.** H. Zhang et al. *J of NeuroSci.* (2010). **14.** M. P. Mattson, *Sci Signal* (2010). **15**. F. LaFerla, *Nat Rev Neurosci*., (2002).

Surabhi Sinha and Nishant Singh

Neuromuscular junction (NMJ)

Connection between axons of motor neurons of the spinal chord and skeletal muscle.

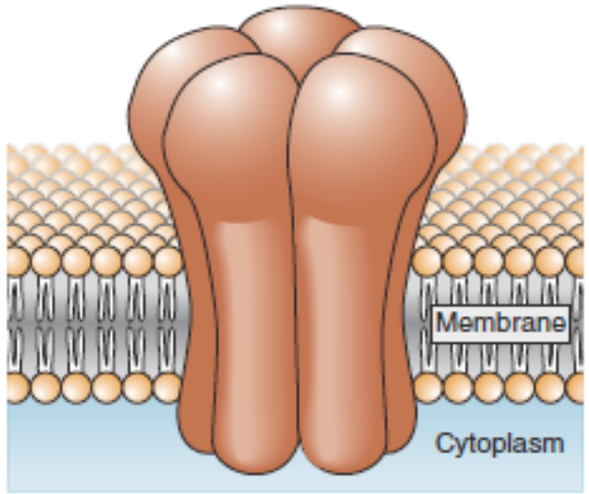
It is characterized by fast and reliable transmission. The reliability is manifested as large (1000s) number of Azs (almost redundant number of releases) in the largest synapse of the body.

The post-synaptic membrane, also called the motor end-plate, contains a series of shallow folds.

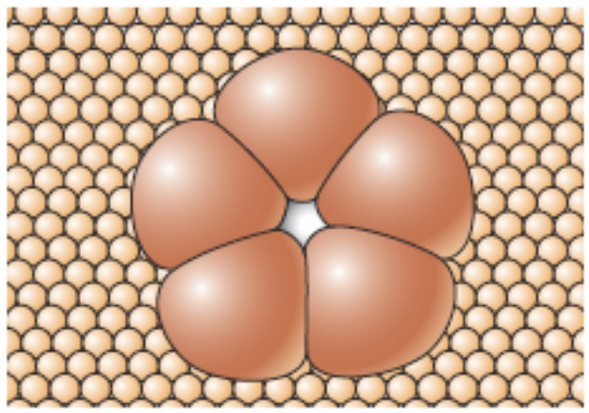
MCell Monte Carlo Simulation of a Miniature Endplate Current Using Realistic Endplate Morphology (Part 1)

MCell Monte Carlo Simulation of a Miniature Endplate Current Using Realistic Endplate Morphology (Part 2)

Neurotransmitter receptor and effector



(a)

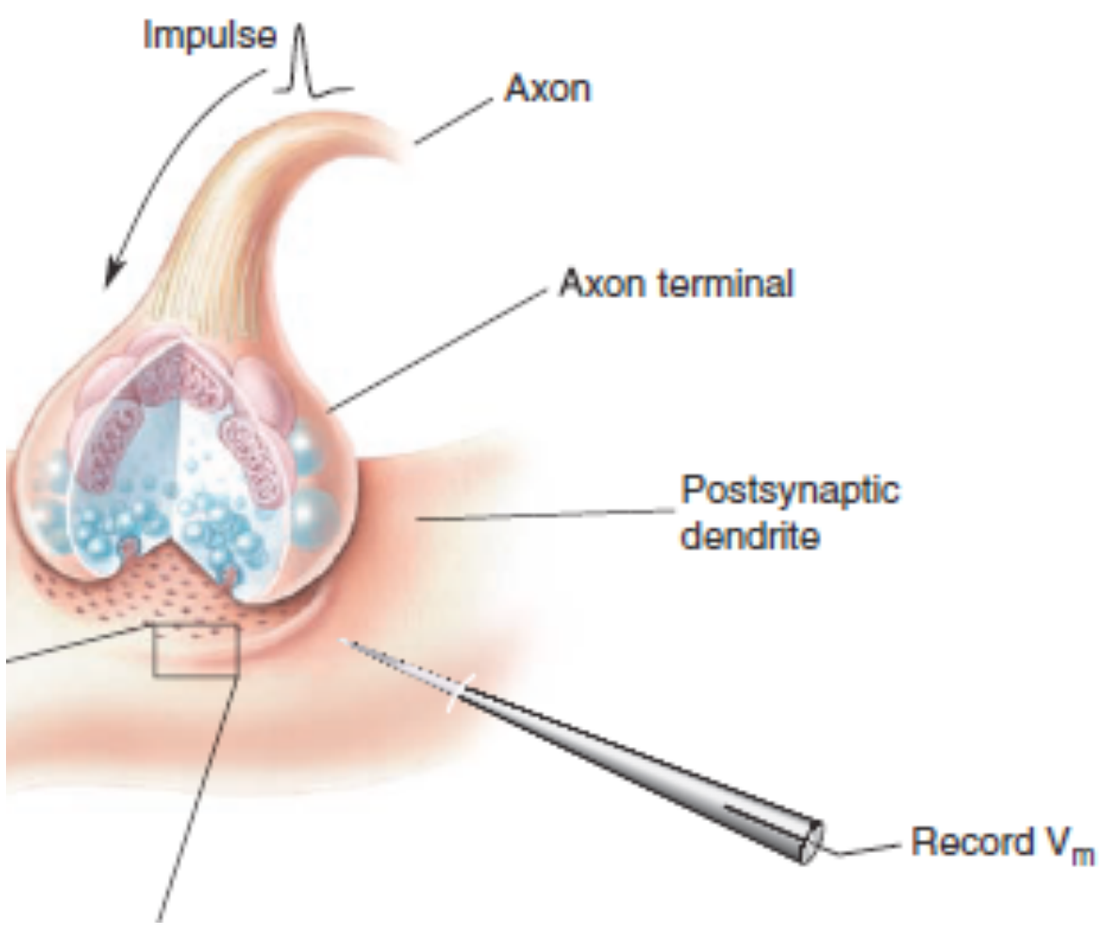


(b)

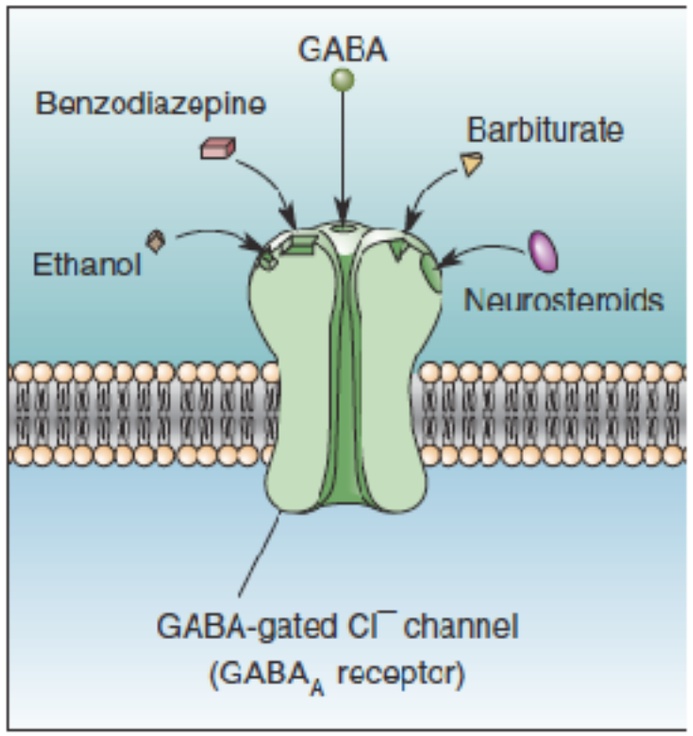
Ligand-gated and G-Protein coupled
Ionotropic and metabotropic

Ligand- gated ion channels are membrane-spanning proteins consisting of four or five subunits that come together to form a pore between them

Neurotransmitter binding causes a conformational change that opens a pore



Action of GABA (gamma-Aminobutyric acid)

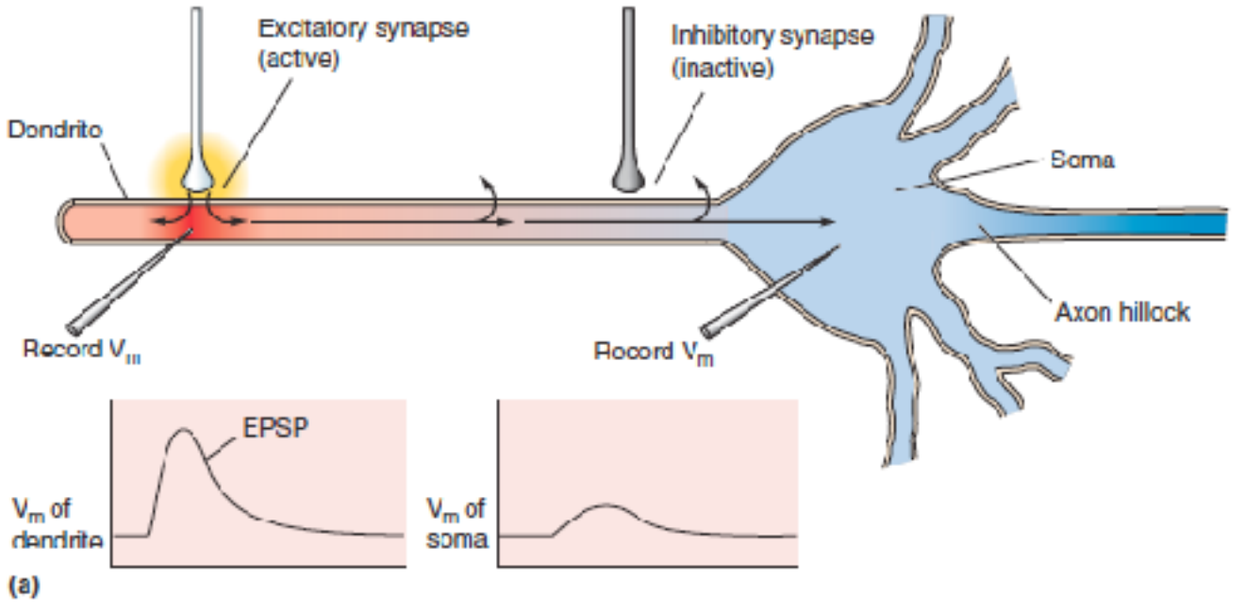


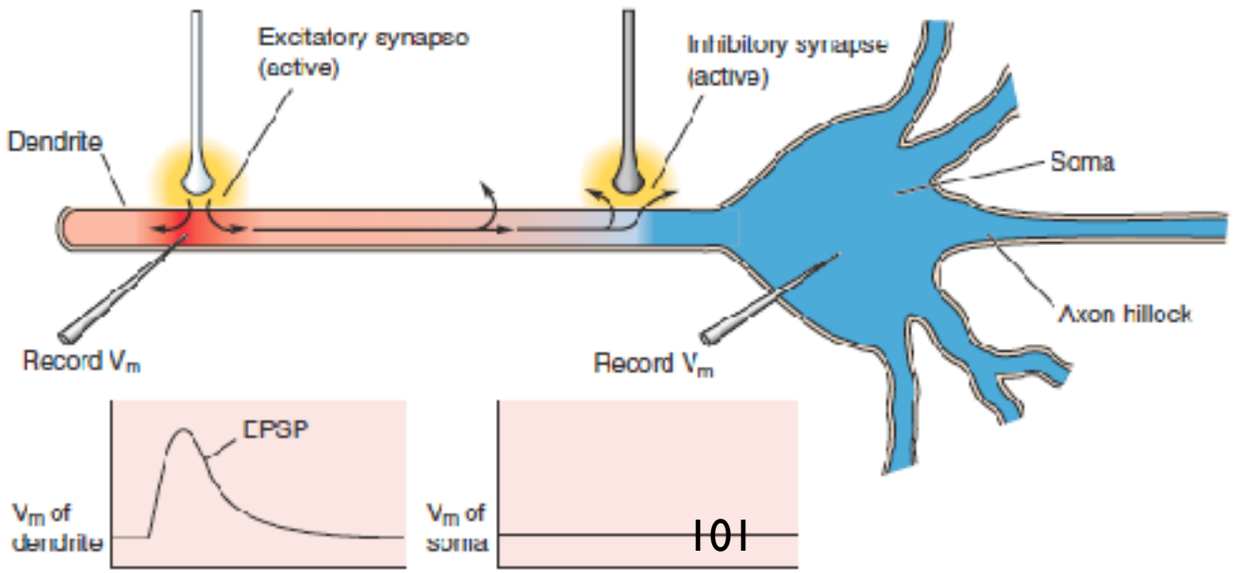
Inhibition

Takes away from threshold of AP

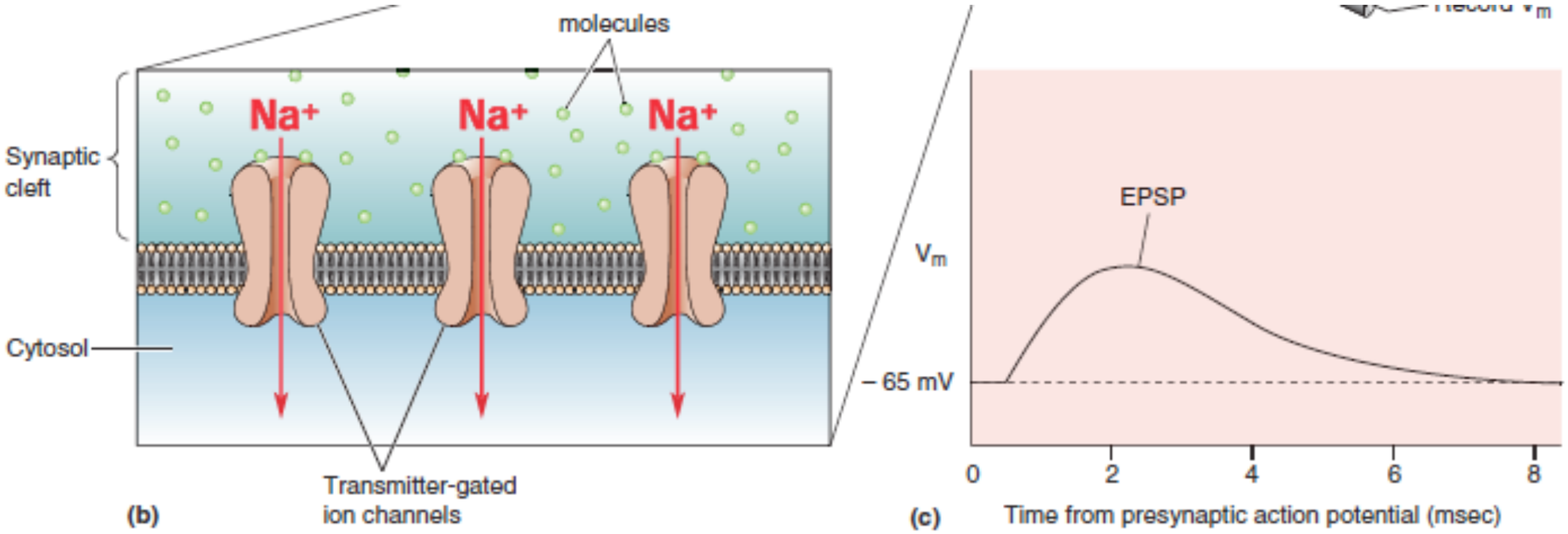
Important inhibitory transmitters:GABA and glycine

Aberrant glycine transmission: Hypereplexia:lack of habituation,
Aberrant GABA: Epilepsy, Schizophrenia
Strychnine:plant toxin, inhibits glycine transmission (spinal chord and brain stem)



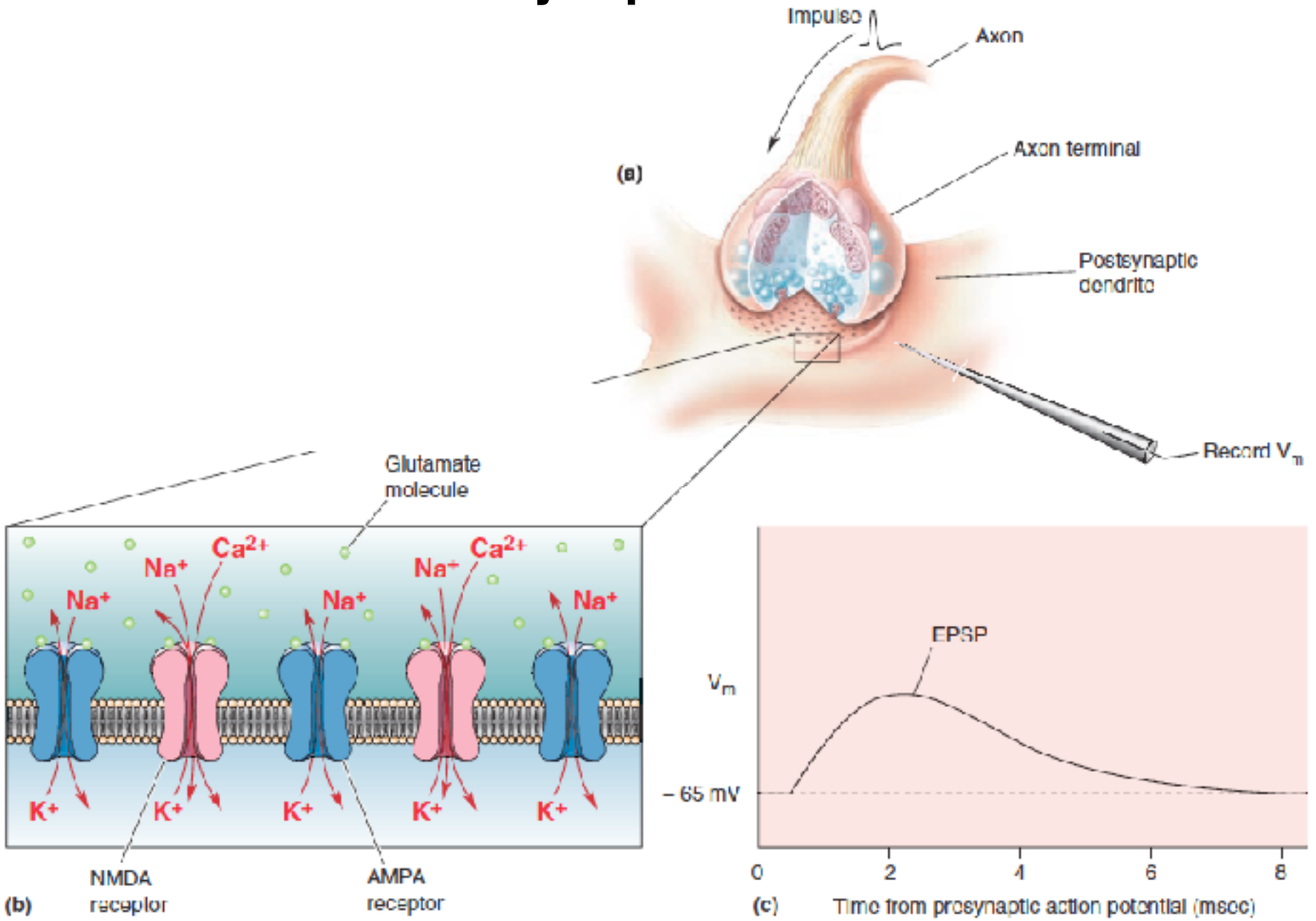


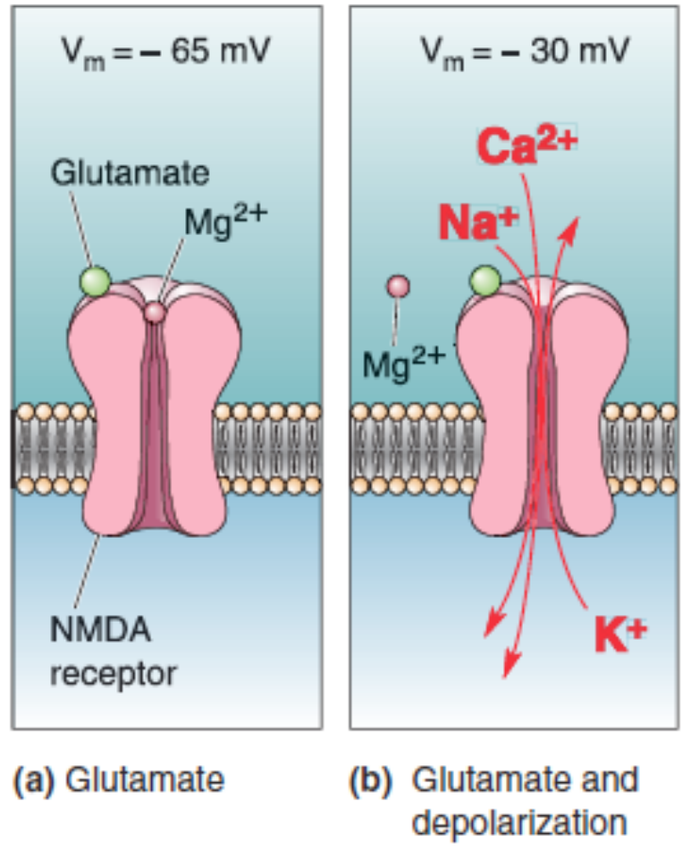
Glutamate mediated Excitation



Exploring the Brain (Textbook) BEAR et al.

The coexistence of NMDA and AMPA receptors in the postsynaptic membrane of a CNS synapse.



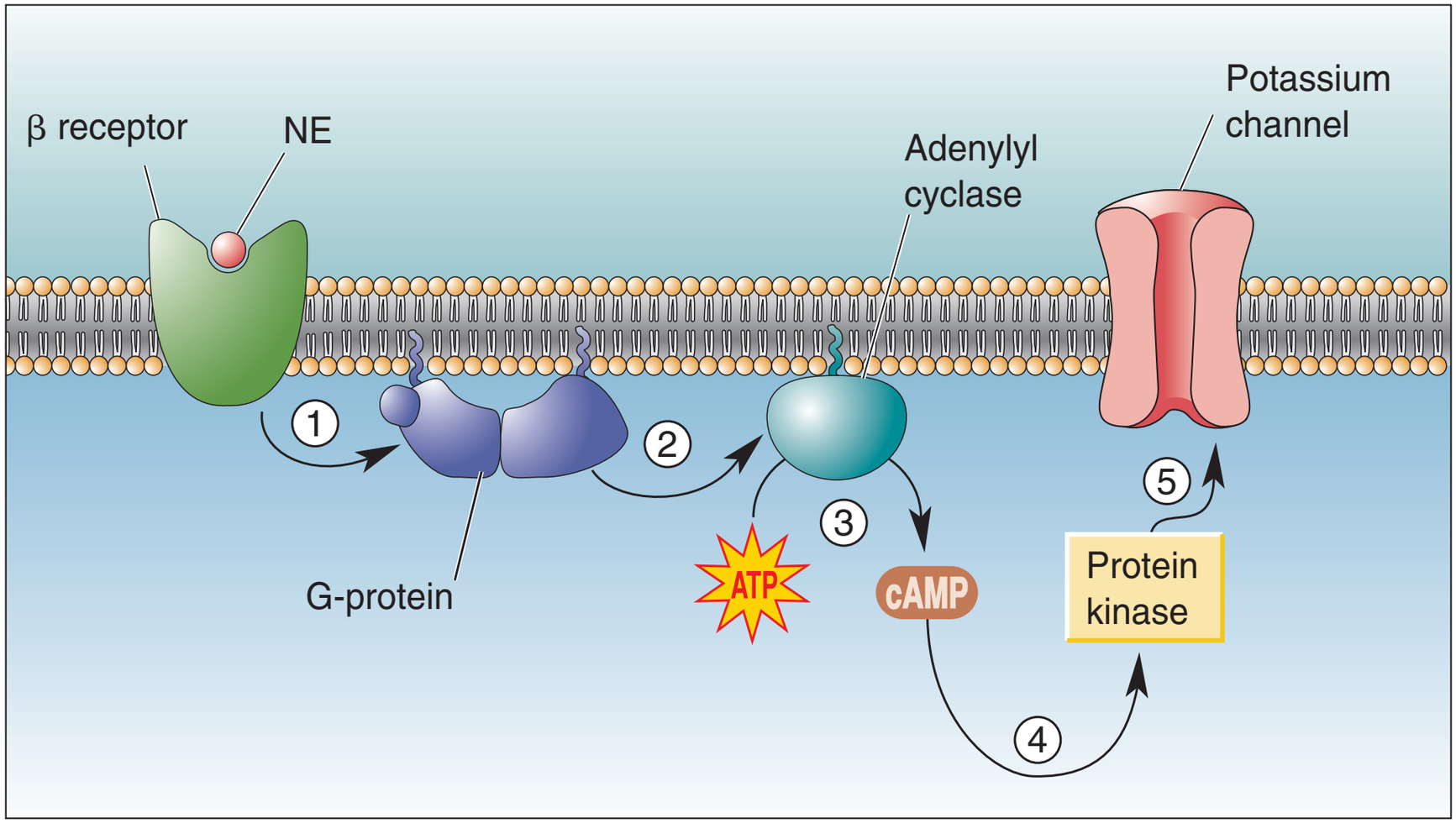


(a) Glutamate

(b) Glutamate and depolarization

Exploring the Brain (Textbook) BEAR et al.

G-Protein coupled receptors or metabotropic receptors



Modulation

Neuromodulators are a special kind of neurotransmitters that do not directly target single synapses.

Unlike regular neurotransmitters, there is no immediate uptake of neuromodulators by presynaptic transporters, indicating that they decay orders of magnitude more slowly in the extrasynaptic space compared to neurotransmitters.

The receptors of these molecules are widely expressed all over the central nervous system (CNS). They participate in what is termed as ‘Volume Transmission’ in which neuromodulators form a diffuse signal. This can change the overall activity level of the brain.

Synaptic Plasticity: Molecular Mechanisms of Learning and Memory

Hebb formulation (Donald Hebb, 1949): a synapse should be strengthened if a presynaptic neuron 'repeatedly or persistently takes part in firing' the postsynaptic one.

“When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is increased” (CAUSAL LINK)

“Cells that fire together,wire together.”

Link between plasticity and memory is difficult, strong correlations can be shown but causality is difficult 1) Synaptic changes are small and local 2) Learning involves both strengthening and weakening of synapses:No net change 3)Pharmacological blocks might not that specific 4)Compensatory mechanisms might take over

State of the art: We know a lot about about the molecular mechanisms and what happens when they are disrupted, have a general idea of which brain areas are involved but nothing in between

Synaptic Plastcity:Universal molecular mechanisms?

1) Events are represented first as changes in the electrical activity of the brain,
2) May lead to second messenger molecules and modifications of existing synaptic proteins.
3) These temporary changes are converted to permanent ones—and long-term memory—by altering the structure of the synapse by new protein synthesis
4) Assembly of new microcircuits.
5) Existing circuits may be disassembled.
6) Learning requires many of the same mechanisms that were used to refine brain circuitry during development.

Calcium: Universal feature

Its critical for neurotransmitter secretion and muscle contraction and it is involved in nearly every form of synaptic plasticity.

Because it is a charge-carrying ion on the one hand and a potent second messenger substance on the other, Ca has a unique ability to directly couple electrical activity with long-term changes in the brain.

Multiple memory systems exist,

The time scales vary from ms to years

Long-term changes require protein synthesis whereas short-term memory does not

A rose is a rose is rose?

Sources of calcium at the synapse
NMDA receptors
Voltage Dependent calcium channels
Endoplasmic reticulum (via RyR, IP3Rs)

Sinks of calcium at the synapse
Calcium binding proteins (Calbindin etc.)
SERCA pumps
PMCA Pumps
Mitochondria

How does the spatio-temporal characteristics and the source of the calcium signal determine the precise nature of the response?

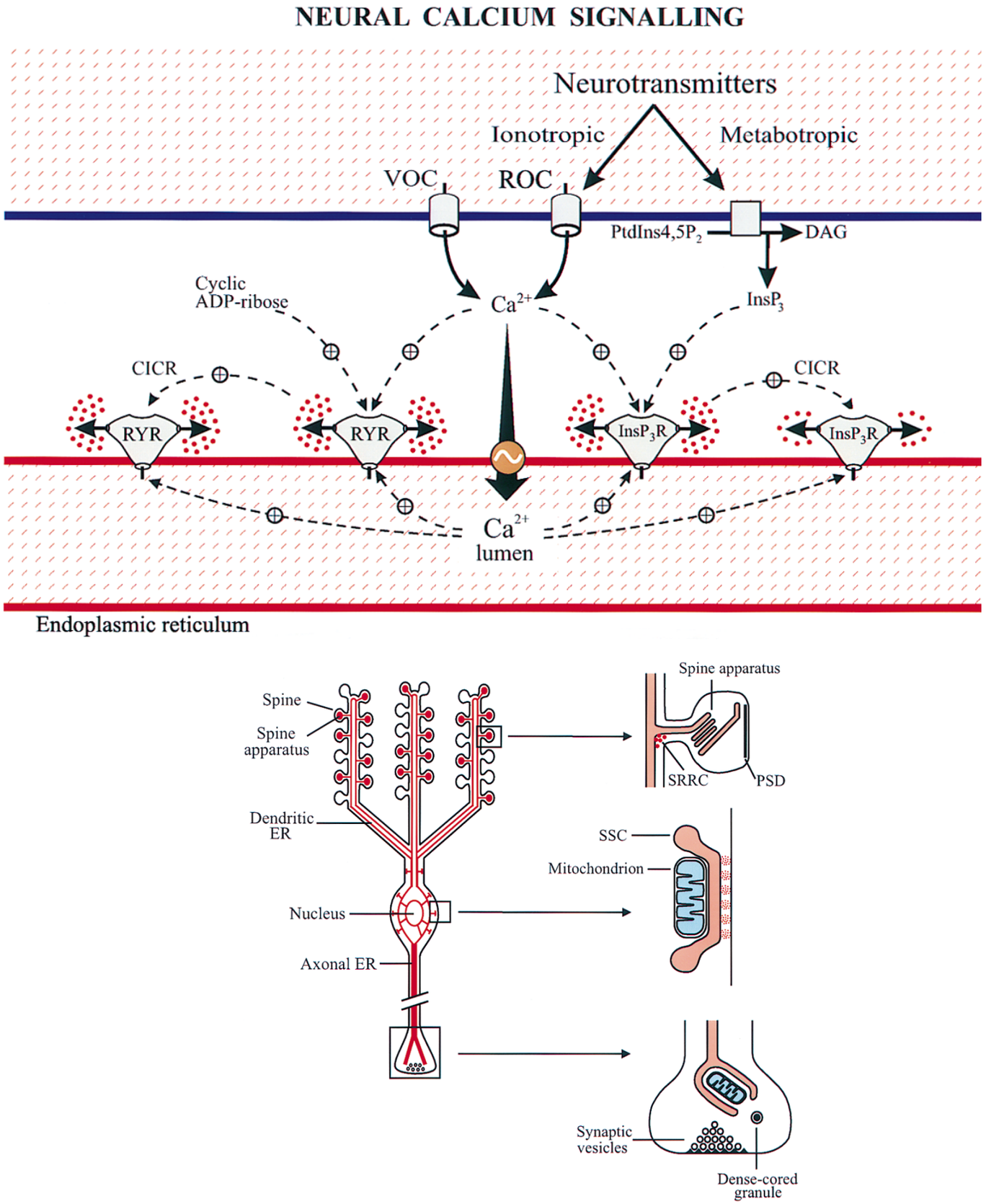
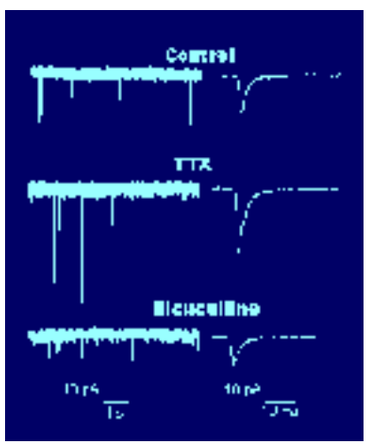
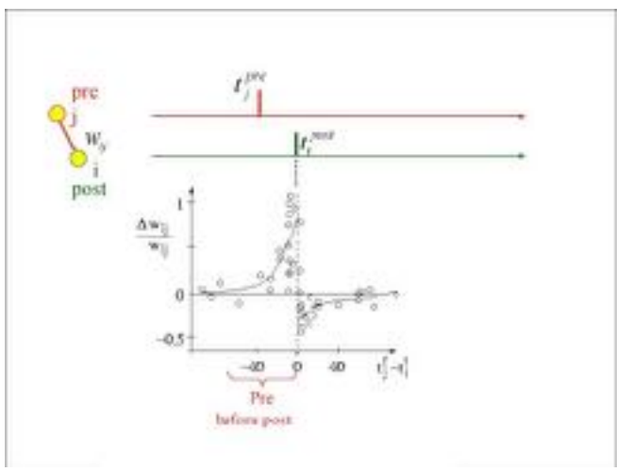


TABLE 13.1
Different Forms of Synaptic Plasticity

Phenomenon	Duration	Locus of induction
Short-term enhancement		
Paired-pulse facilitation (PPF)	100 msec	Pre
Augmentation	10 sec	Pre
Posttetanic potentiation (PTP)	1 min	Pre
Long-term enhancement		
Short-term potentiation (STP)	15 min	Post
Long-term potentiation (LTP)	>30 min	Pre and post
Depression		
Paired-pulse depression (PPD)	100 msec	Pre
Depletion	10 sec	Pre
Long-term depression (LTD)	>30 min	Pre and post

Spike time dependent plasticity (Mu-Ming Poo 1998)
Homeostatic Plasticity (1998, Gina Turrigiano)





Functions of Short-Term Synaptic Plasticity

High pass filters: Synapses with a low initial probability of release function as high-pass filters since they will facilitate during high-frequency action potential bursts while low-frequency bursts will not be transmitted with the same efficacy.

Low pass filters: Synapses with a high initial probability of release function as low-pass filters, since they will depress during high-frequency bursts but will reliably relay low-frequency activity

Thought to play important roles in short-term adaptations to sensory inputs, transient changes in behavioral states, and short-lasting forms of memory (working memory), Gain control, Directional selectivity, optimize information transmission

nature neuroscience

Synapses with short-term plasticity are optimal estimators of presynaptic membrane potentials

Jean-Pascal Pfister[1], Peter Dayan[2] & Máté Lengyel[1]

The trajectory of the somatic membrane potential of a cortical neuron exactly reflects the computations performed on its afferent inputs. However, the spikes of such a neuron are a very low-dimensional and discrete projection of this continually evolving signal. We explored the possibility that the neuron's efferent synapses perform the critical computational step of estimating the membrane potential trajectory from the spikes. We found that short-term changes in synaptic efficacy can be interpreted as implementing an optimal estimator of this trajectory. Short-term depression arose when presynaptic spiking was sufficiently intense as to reduce the uncertainty associated with the estimate; short-term facilitation reflected structural features of the statistics of the presynaptic neuron such as up and down states. Our analysis provides a unifying account of a powerful, but puzzling, form of plasticity.

Long-Term Synaptic Plasticity

It is the molecular and synaptic basis of long term storage of information in the brain.

Long term potentiation: Patterns of synaptic activity producing a long-lasting increase in synaptic strength

Long term depression Patterns of activity produce a long-lasting decrease in synaptic strength.

NMDA dependent Long Term Potentiation: Most studied
NMDA dependent Long Term Depression
Metaplasticity:Plasticity of plasticity
NMDA independent Long Term Potentiation
Presynaptic Long Term Potentiation
mGluR mediated Long Term Depression
Endocannabinoid-mediated LTD
Spike Time Dependent Plasticity
Homeostatic plasticity

State of the art on memory: memory engrams

The hypothetical material basis of learned information, the memory engram, was first conceived by Richard Semon (1859-1918) who theorized that learning induces persistent changes in specific brain cells that retain information and are subsequently reactivated upon appropriate retrieval conditions

CellPress

Neuron

Perspective

Memory Engram Cells Have Come of Age

Susumu Tonegawa,[1,2,*] Xu Liu,[1,2,3] Steve Ramirez,[1,*] and Roger Redondo[1,2]
[1]RIKEN–MIT Center for Neural Circuit Genetics at the Picower Institute for Learning and Memory, Department of Biology and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[2]Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[3]We dedicate this article to Xu Liu, who passed away in February, 2015
*Correspondence: tonegawa@mit.edu (S.T.), sramirez@mit.edu (S.R.)
http://dx.doi.org/10.1016/j.neuron.2015.08.002

The idea that memory is stored in the brain as physical alterations goes back at least as far as Plato, but further conceptualization of this idea had to wait until the 20th century when two guiding theories were presented: the "engram theory" of Richard Semon and Donald Hebb's "synaptic plasticity theory." While a large number of studies have been conducted since, each supporting some aspect of each of these theories, until recently integrative evidence for the existence of engram cells and circuits as defined by the theories was lacking. In the past few years, the combination of transgenics, optogenetics, and other technologies has allowed neuroscientists to begin identifying memory engram cells by detecting specific populations of cells activated during specific learning epochs and by engineering them not only to evoke recall of the original memory, but also to alter the content of the memory.

memory storage.

humans lacking large regions of the MTL showed dramatic

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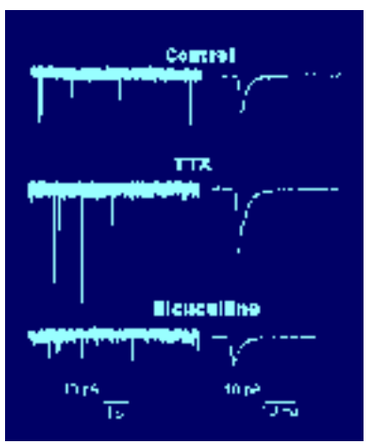

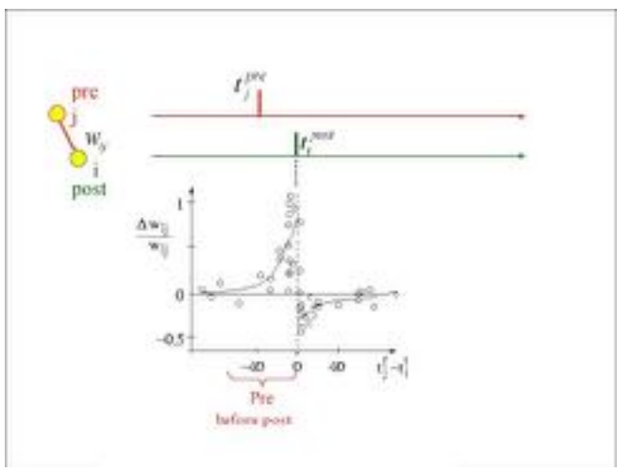

Short-Term Synaptic Plasticity

Thought to play important roles in short-term adaptations to sensory inputs, transient changes in behavioral states, and short-lasting forms of memory.

Most forms of short-term synaptic plasticity are triggered by short bursts of activity causing a transient accumulation of calcium in presynaptic nerve terminals: causes changes in the probability of neurotransmitter release

Paired-Pulse Facilitation and Depression

Facilitation and Depression Following Trains of Stimuli

Locus: Modulation of Transmission by Presynaptic Receptor and can be mediated by Glia

Short-Term Plasticity	Change in Nx release	Time course	Mechanism
Facilitation	Increase	10s of ms	Increased conc. Pre-synaptic Ca^{2+}
Depression	Decrease	100s of ms	Depleted vesicle store
Augmentation	Increase	Seconds	Increase Ca^{2+} binding for vesicle release (munc-13?)
Potentiation	Increase	10s seconds to minutes^{+}	Gene regulation

STP can act as filters with a wide range of properties:
Synapses with a low initial probability of release function as high-pass filters,
since they will facilitate during high-frequency action potential bursts while low-frequency bursts will not be transmitted with the same efficacy.

Synapses with a high initial probability of release function as low-pass filters, since they will depress during high-frequency bursts but will reliably relay low-frequency activity

nature neuroscience

ARTICLES

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Long-Term Synaptic Plasticity

NMDA dependent Long Term Potentiation: Most studied

NMDA independent Long Term Potentiation

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Homeostatic plasticity