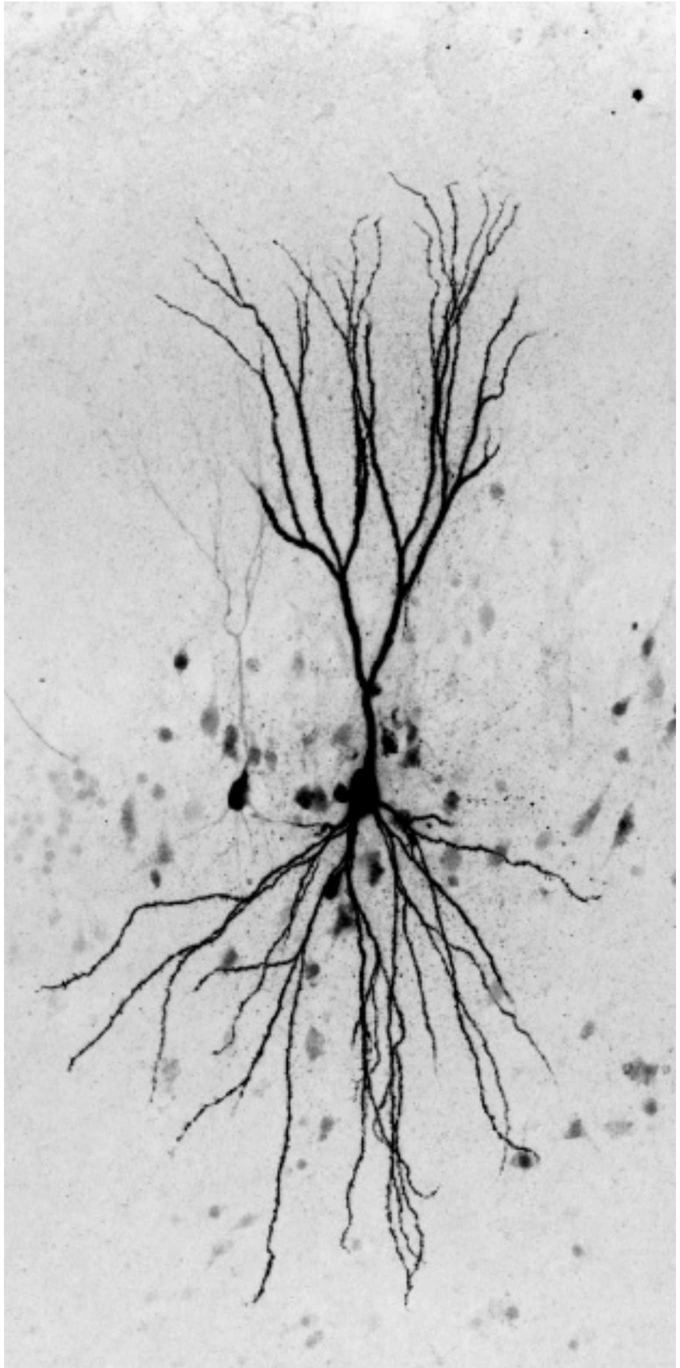


SHP Neuroscience

Lecture 2

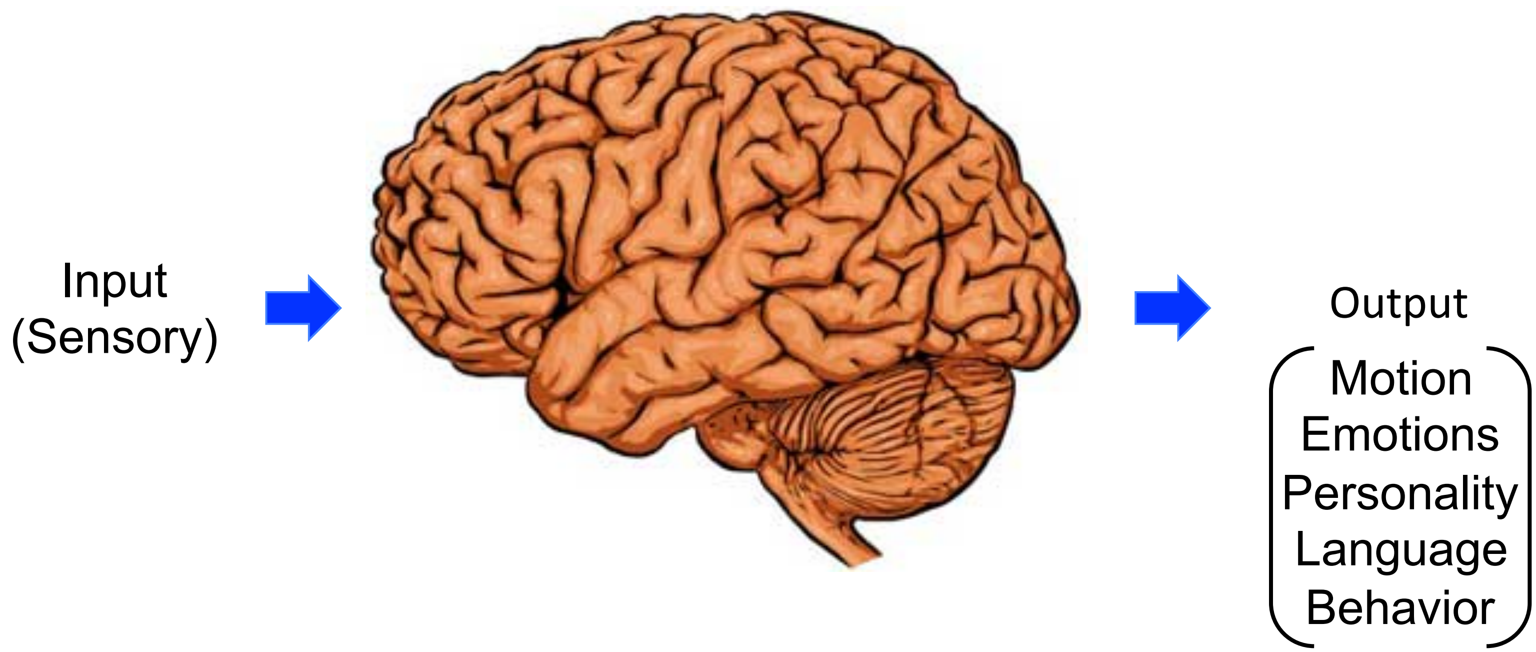
Electrical Properties of Neurons

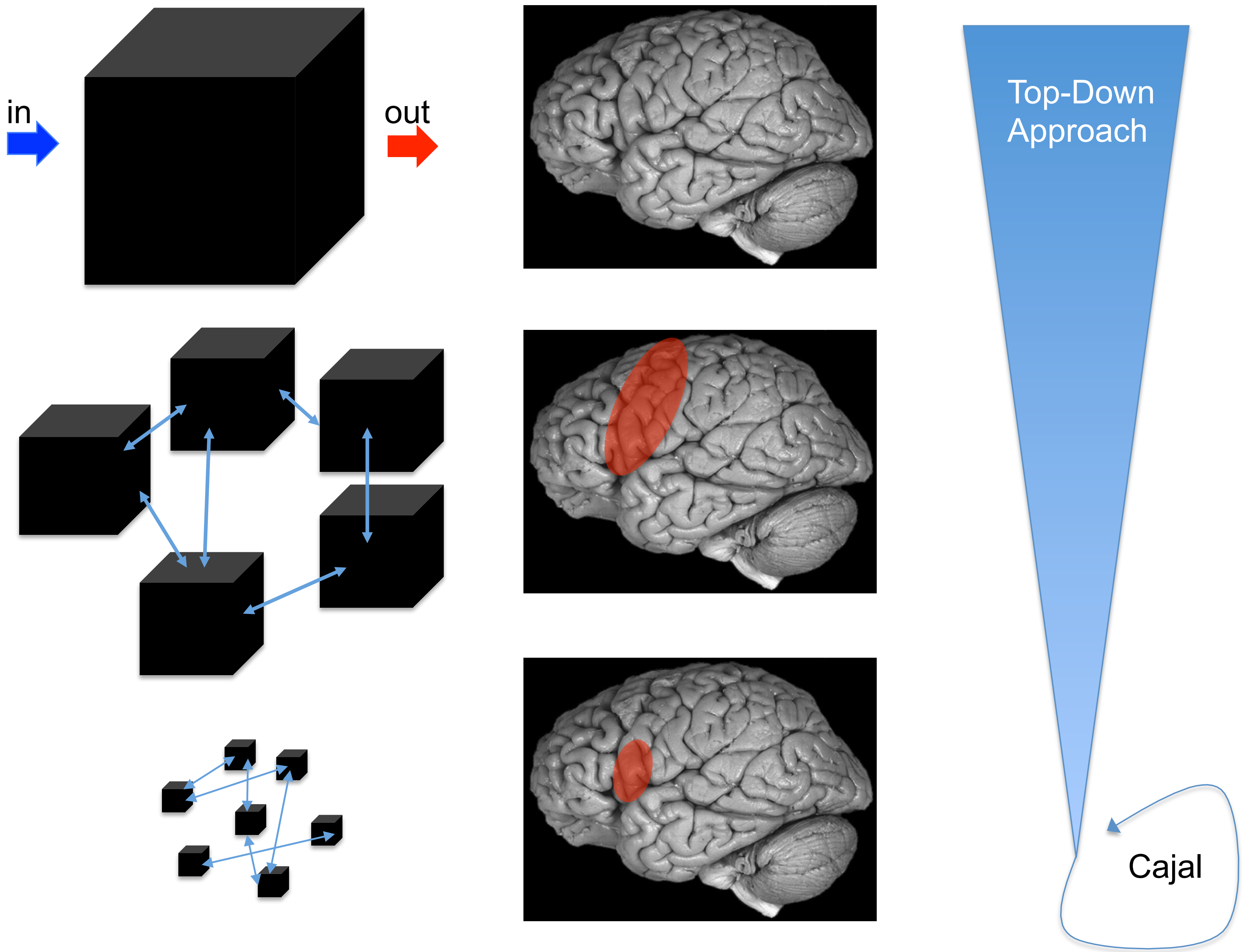
Neurons

Electrochemical gradients

Action potentials

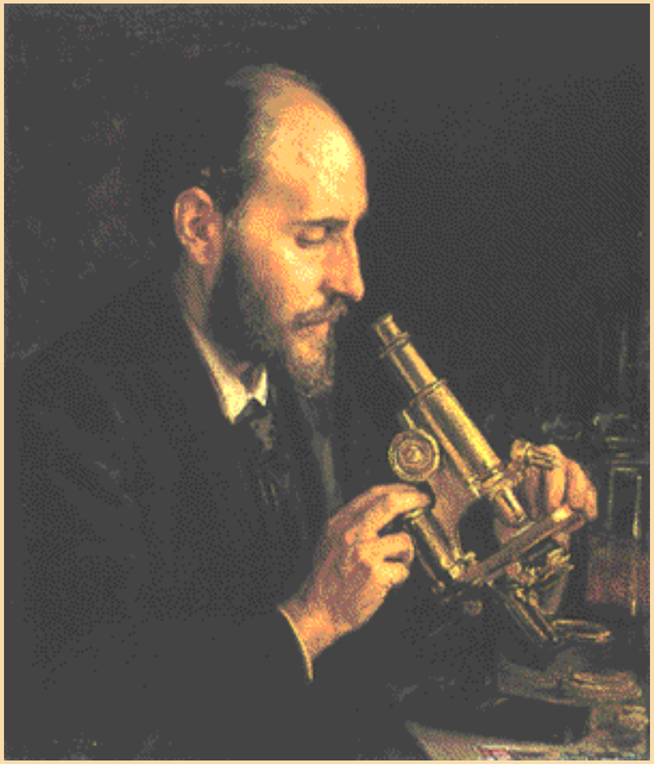
Ion channels

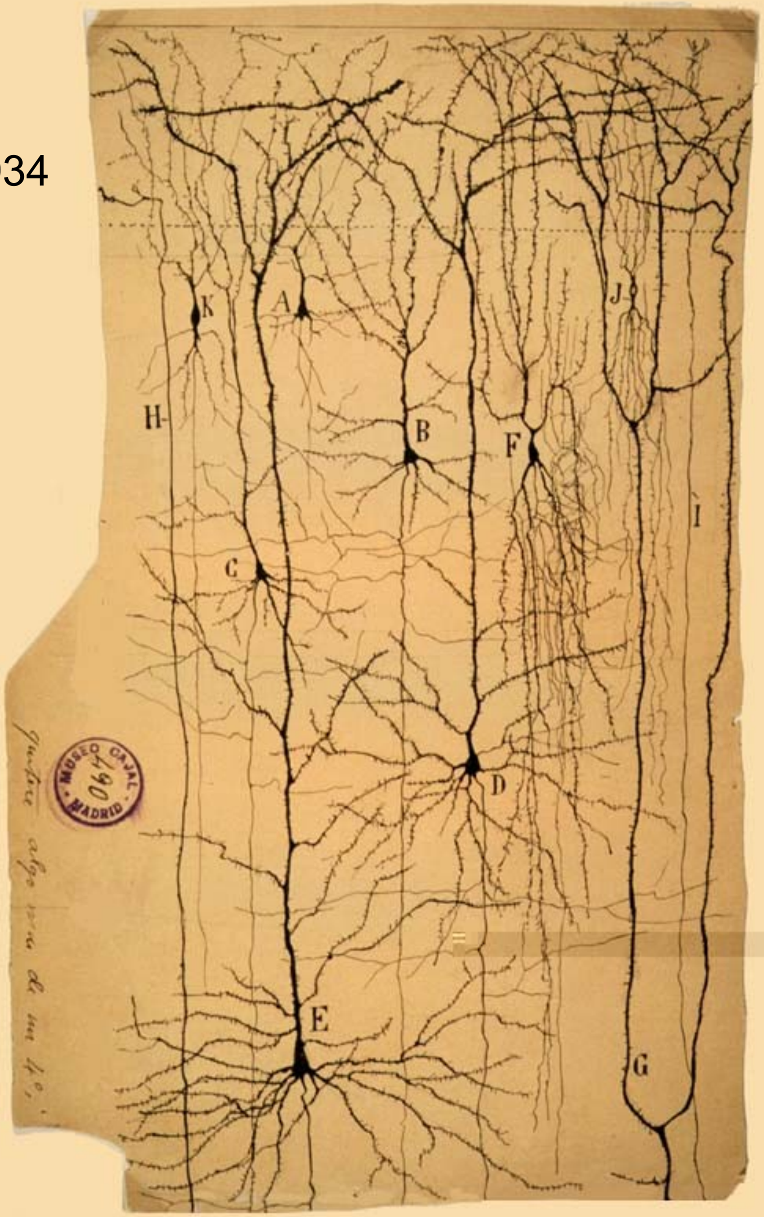

Input
(Sensory)
Output
Motion
Emotions
Personality
Language
Behavior


in
out
Top-Down
Approach
Cajal

Modern Neuroscience Begins

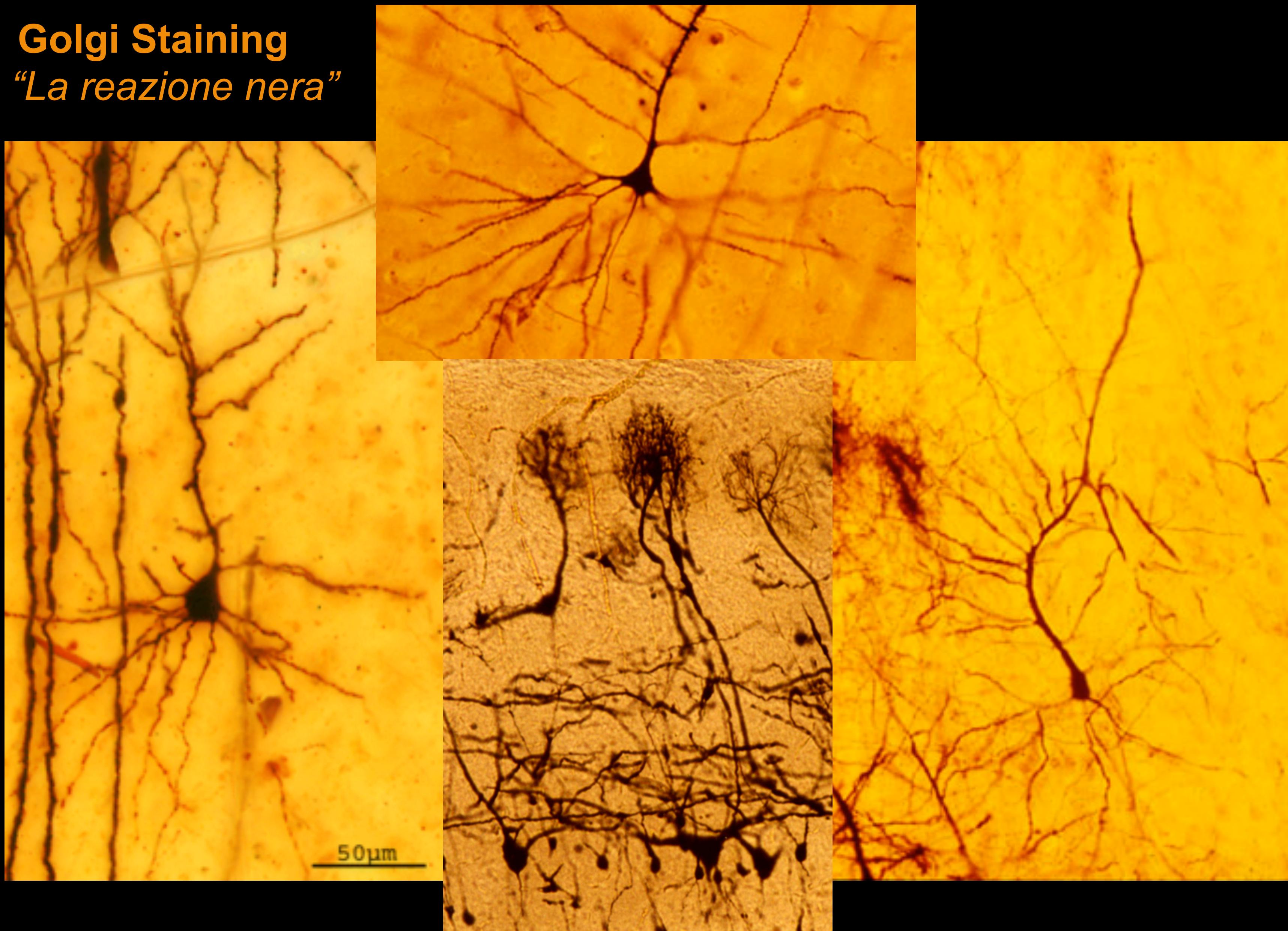
Santiago Ramon y Cajal, 1852-1934

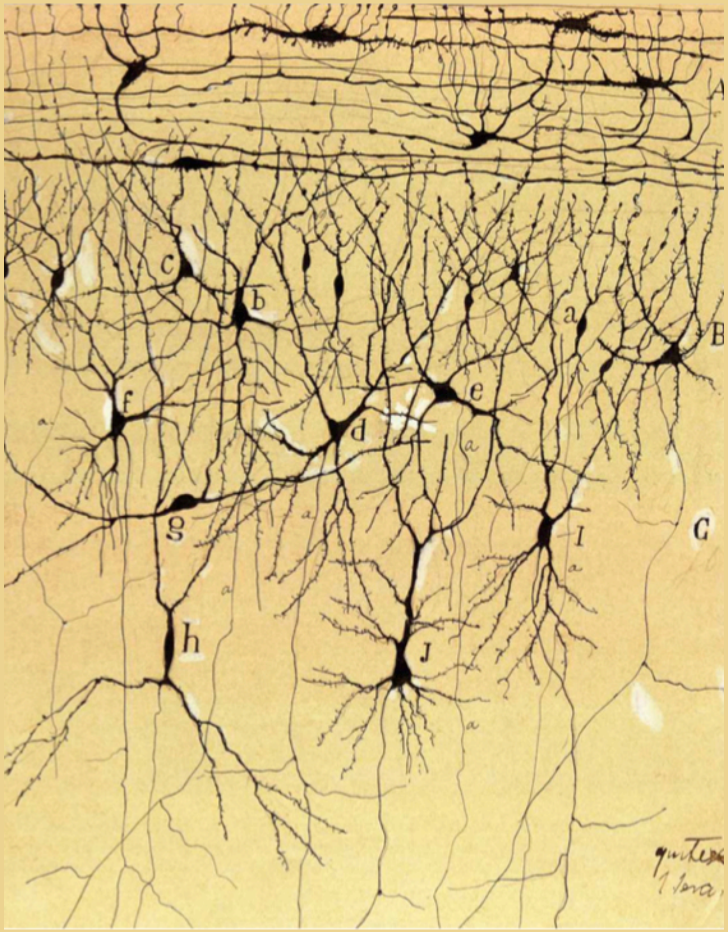


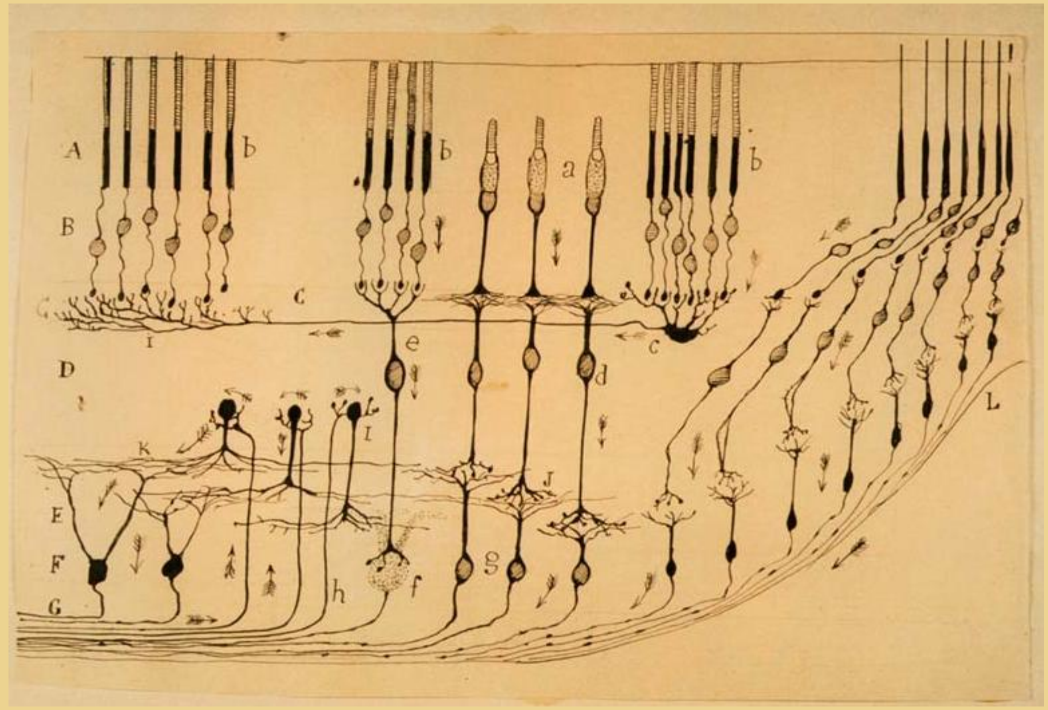


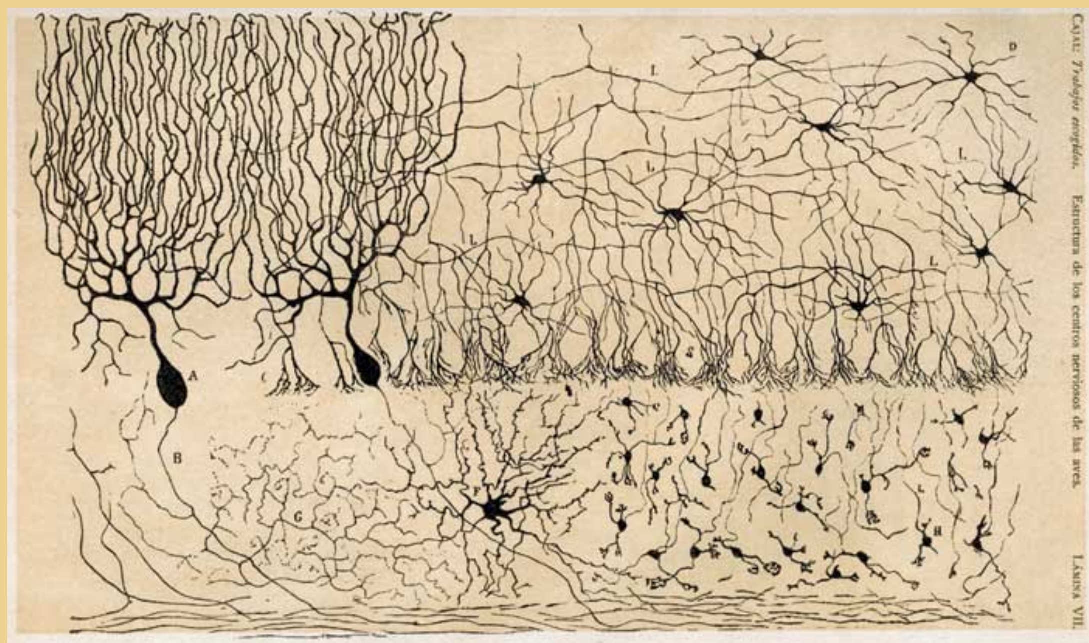
Golgi Staining

“La reazione nera”








CAJAL: Trabajos escogidos.
Estructura de los centros nerviosos de las aves.
LÁMINA VII.

Foundations of neural signaling

① **Neuron doctrine**

② Ionic hypothesis

③ Chemical synaptic transmission

The Neuron Doctrine

The neuron is the basic cellular component of brain circuits

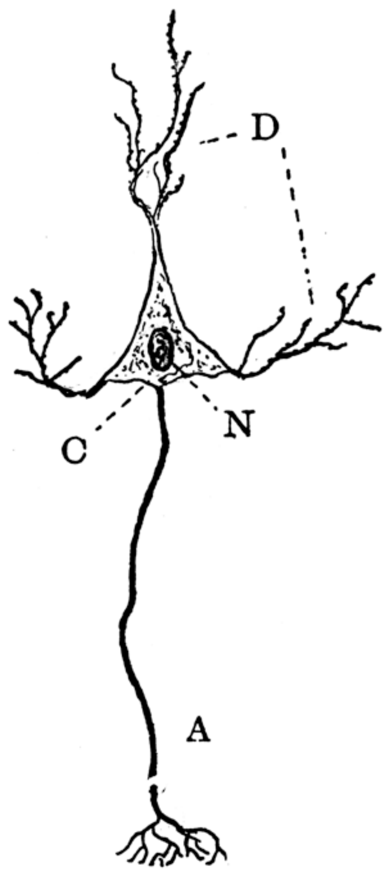
↓ *later*

The neuron is the basic information processing unit

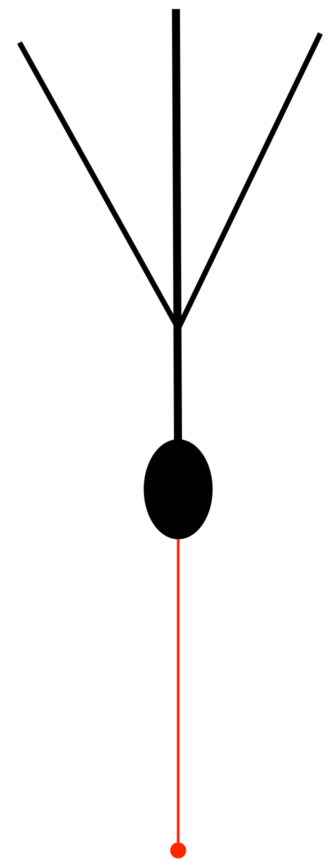
The Law of Dynamic Polarization

"The transmission of nervous movement occurs from protoplasmic branches [dendrites] and the soma to the nervous expansion [axonal process]"

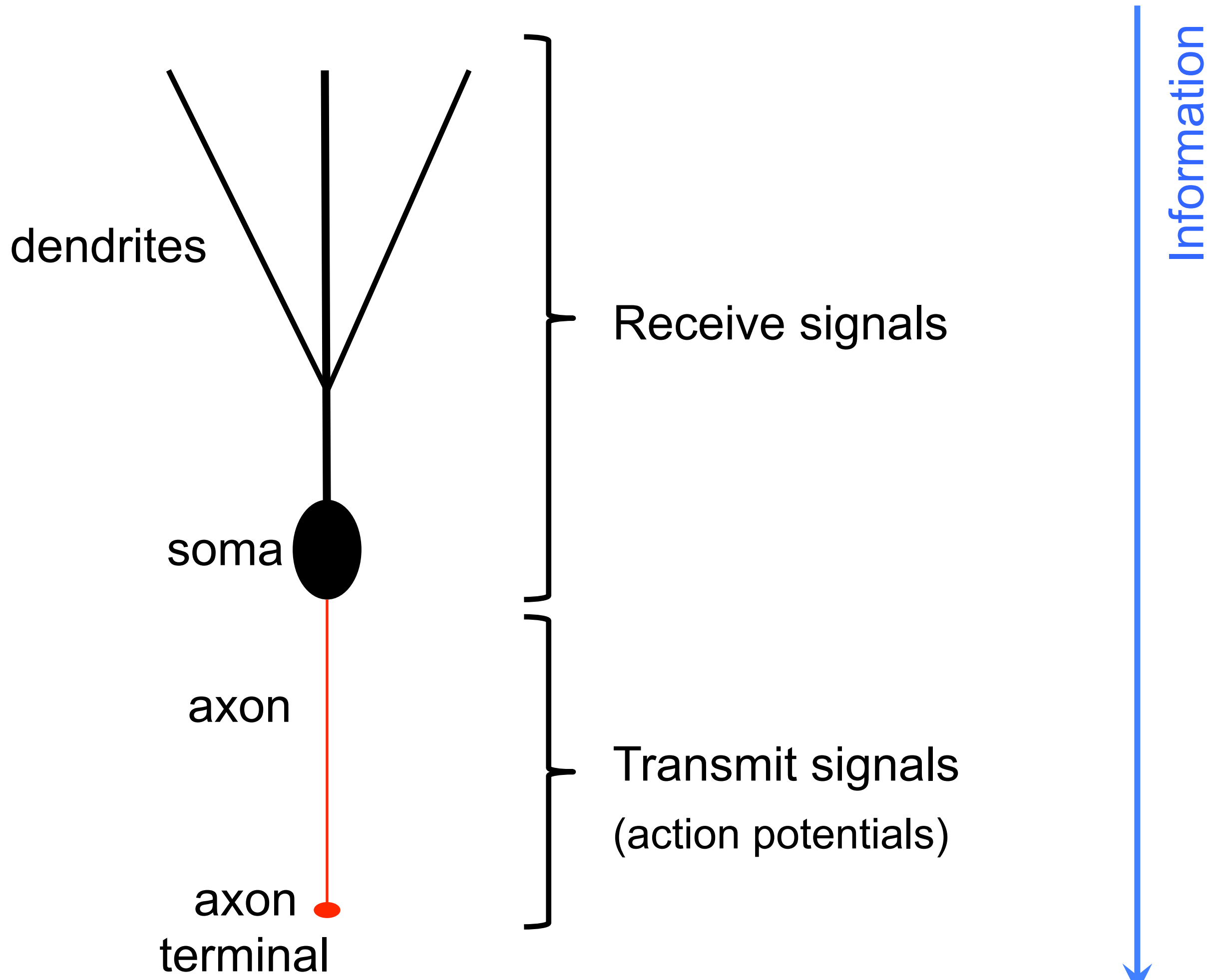
- Cajal, 1891

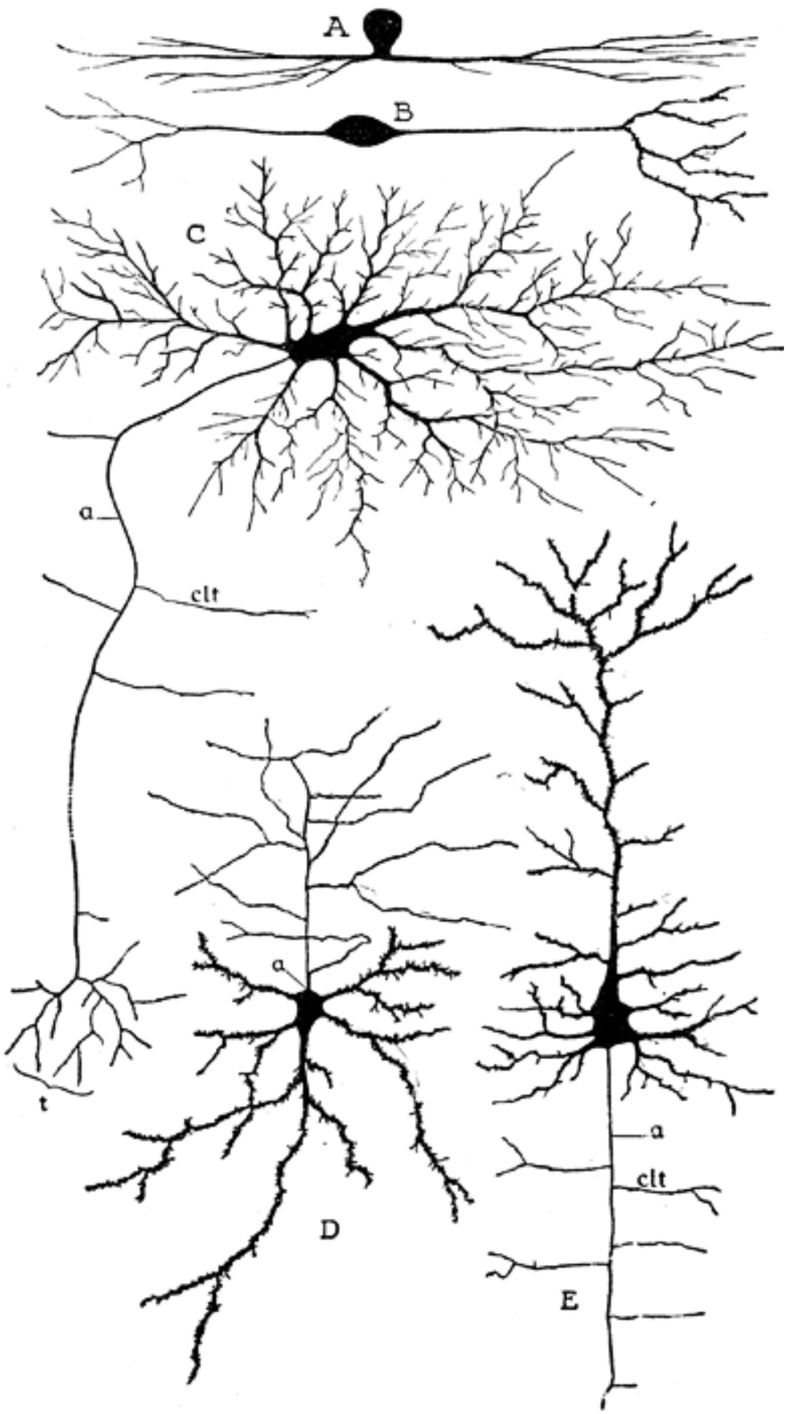


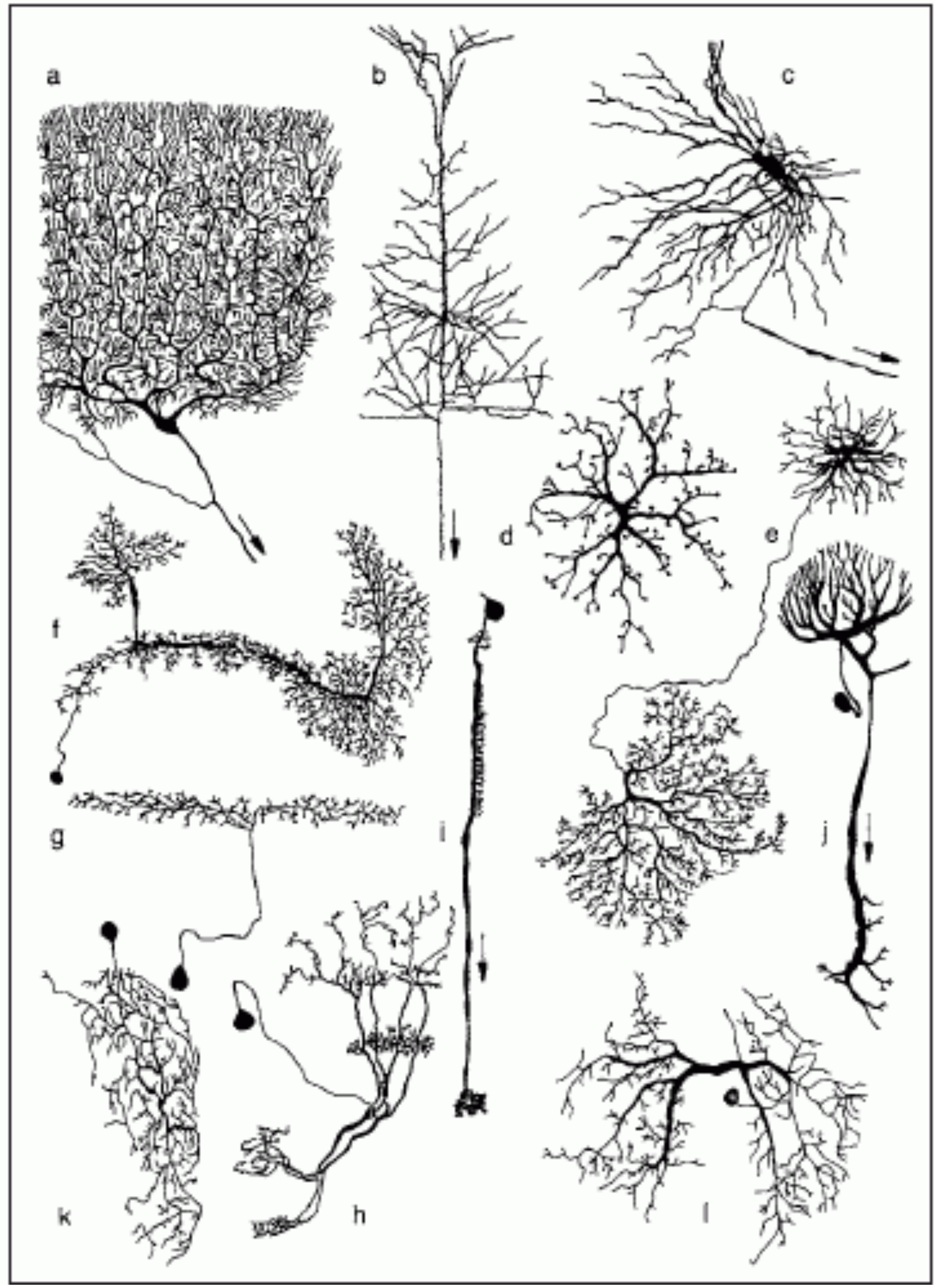
Motor neuron



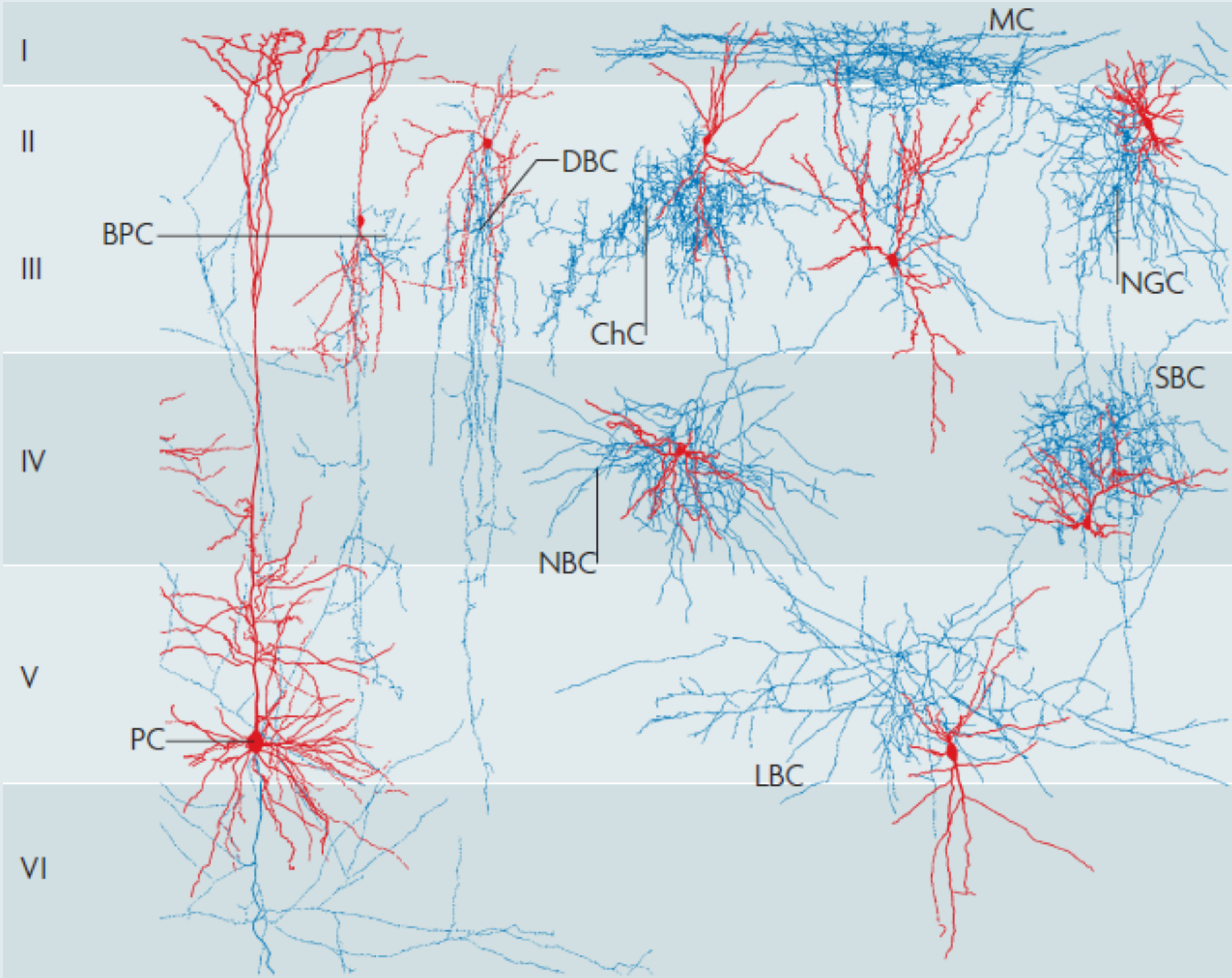
The Law of Dynamic Polarization




A
B
C
a
clt
t
a
D
a
clt
E


a
b
c
d
e
f
g
i
j
k
h
l

Dendrites and axons can be quite complex



ZJ Huang et al. 2007

Foundations of neural signaling

① **Neuron doctrine**

② Ionic hypothesis

③ Chemical synaptic transmission

Foundations of neural signaling

① Neuron doctrine

② **Ionic hypothesis**

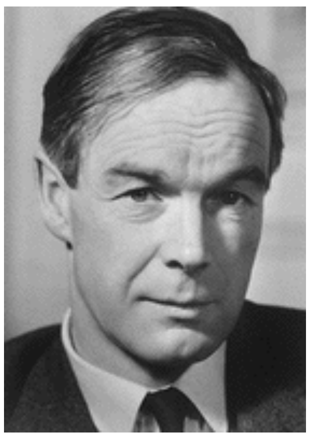
③ Chemical synaptic transmission

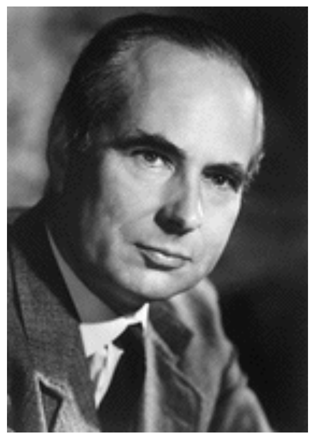
The Ionic Hypothesis

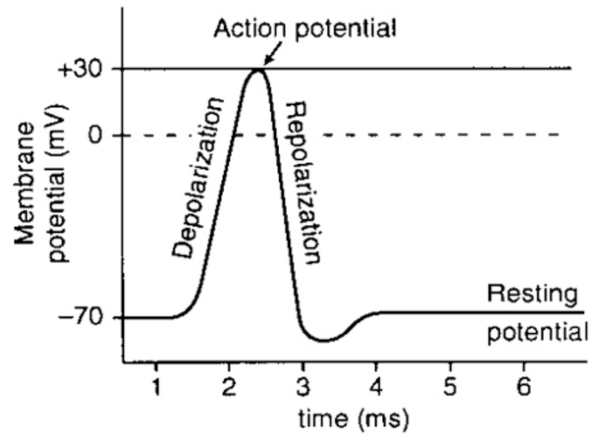
"Nerve signals" are **action potentials**

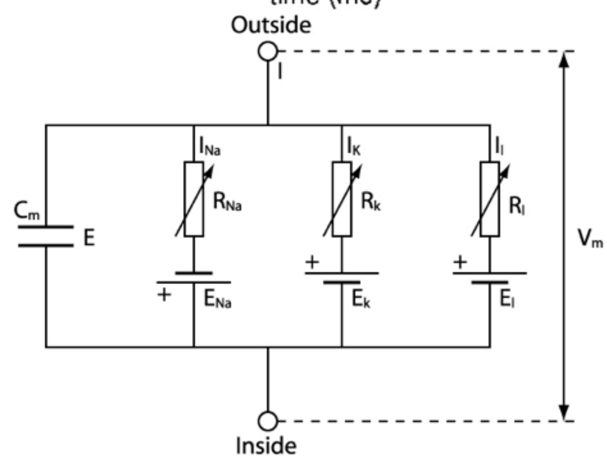
action potentials due to controlled flow of **ions** across the neuron membrane

ions are charged particles, such as **Na^+ K^+ Ca^{2+} Cl^-**


Alan Hodgkin


Andrew Huxley





Foundations of neural signaling

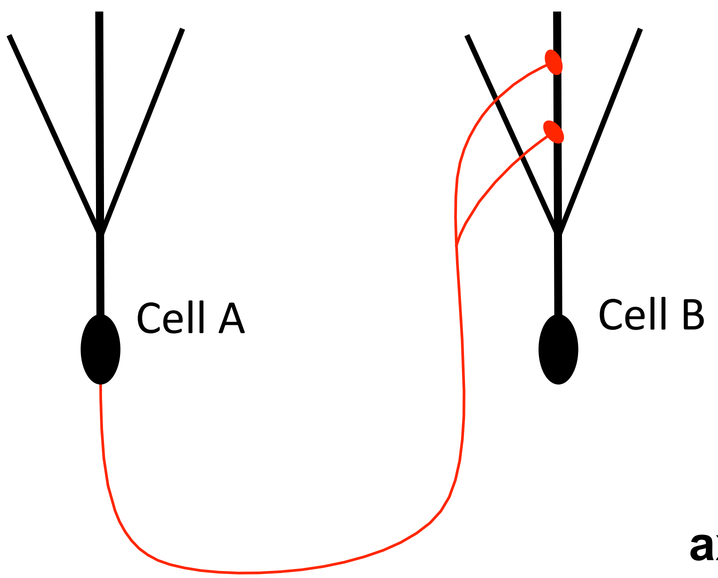
① Neuron doctrine

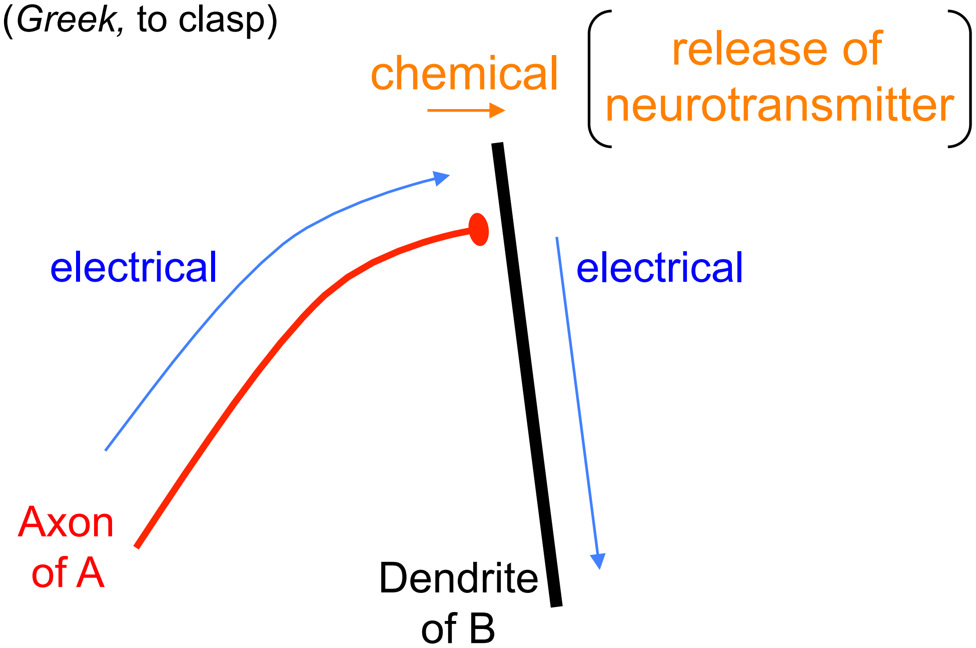
② Ionic hypothesis

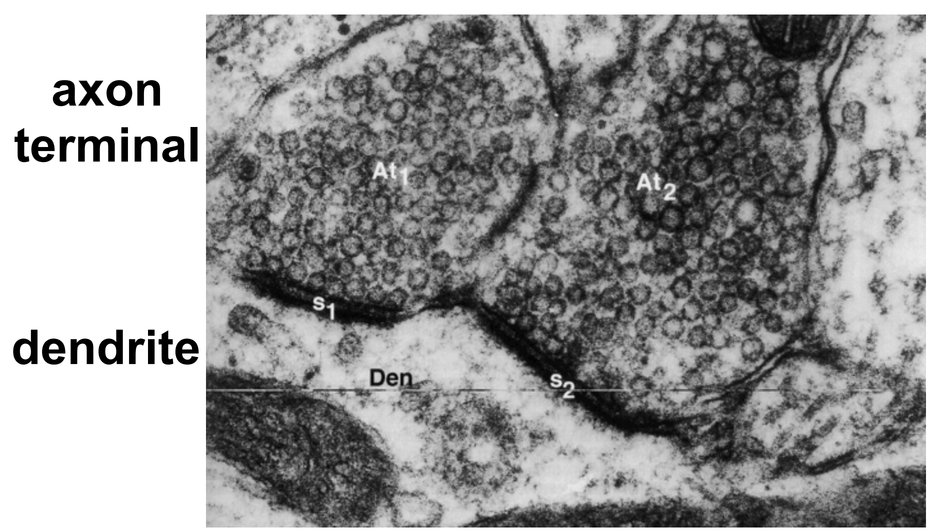
③ Chemical synaptic transmission

Chemical synaptic transmission

Charles Sherrington, 1897 **synapse** (*Greek,* to clasp)



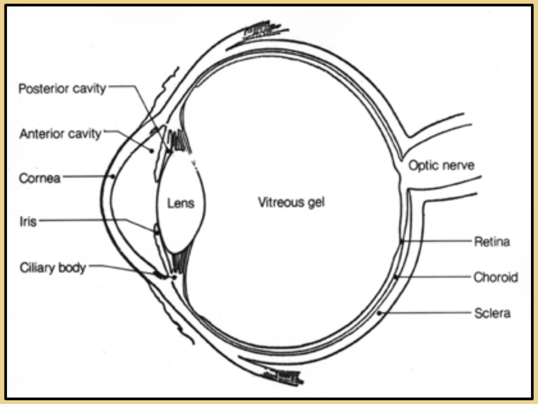


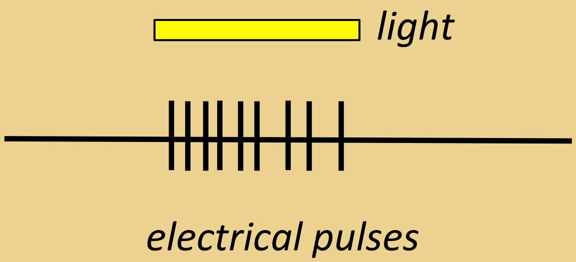


Action Potentials

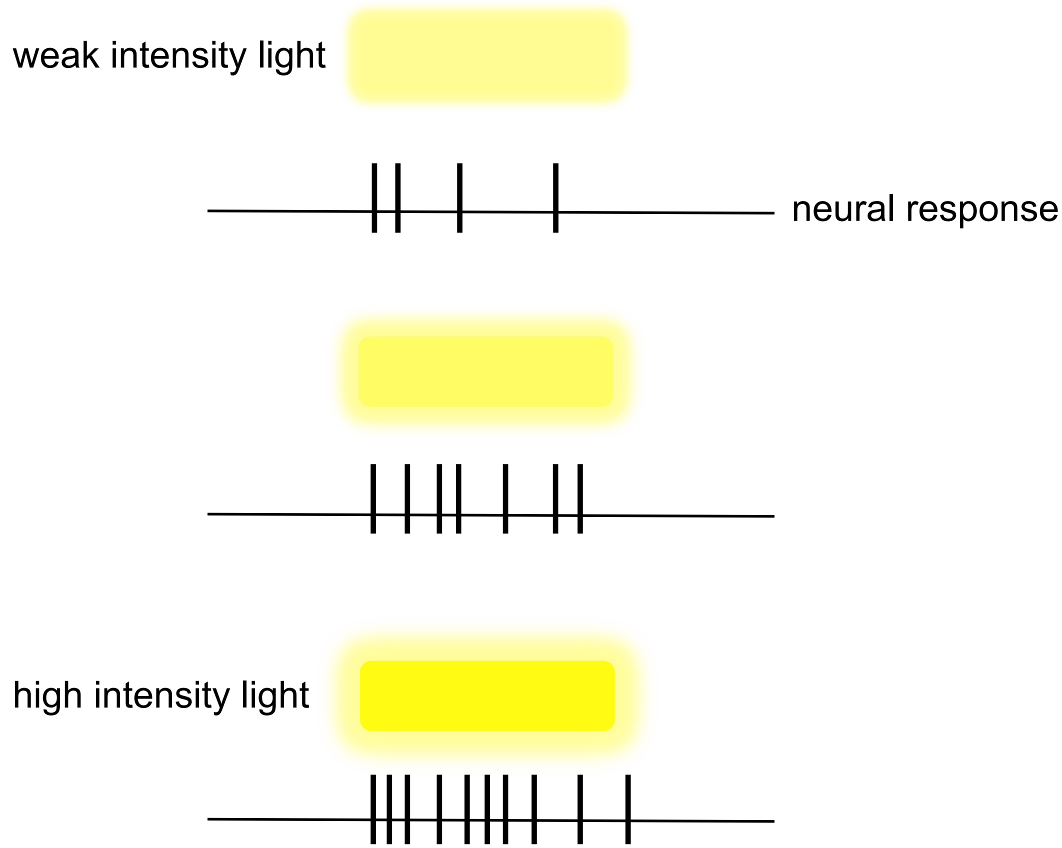
"I had arranged electrodes on the optic nerve of a toad in connection with some experiments on the retina. The room was nearly dark and I was puzzled to hear repeated noises in the loudspeaker attached to the amplifier, noises indicating that a great deal of impulse activity was going on. It was not until I compared the noises with my own movements around the room that I realized I was in the field of vision of the toad's eye and that it was signaling what I was doing."

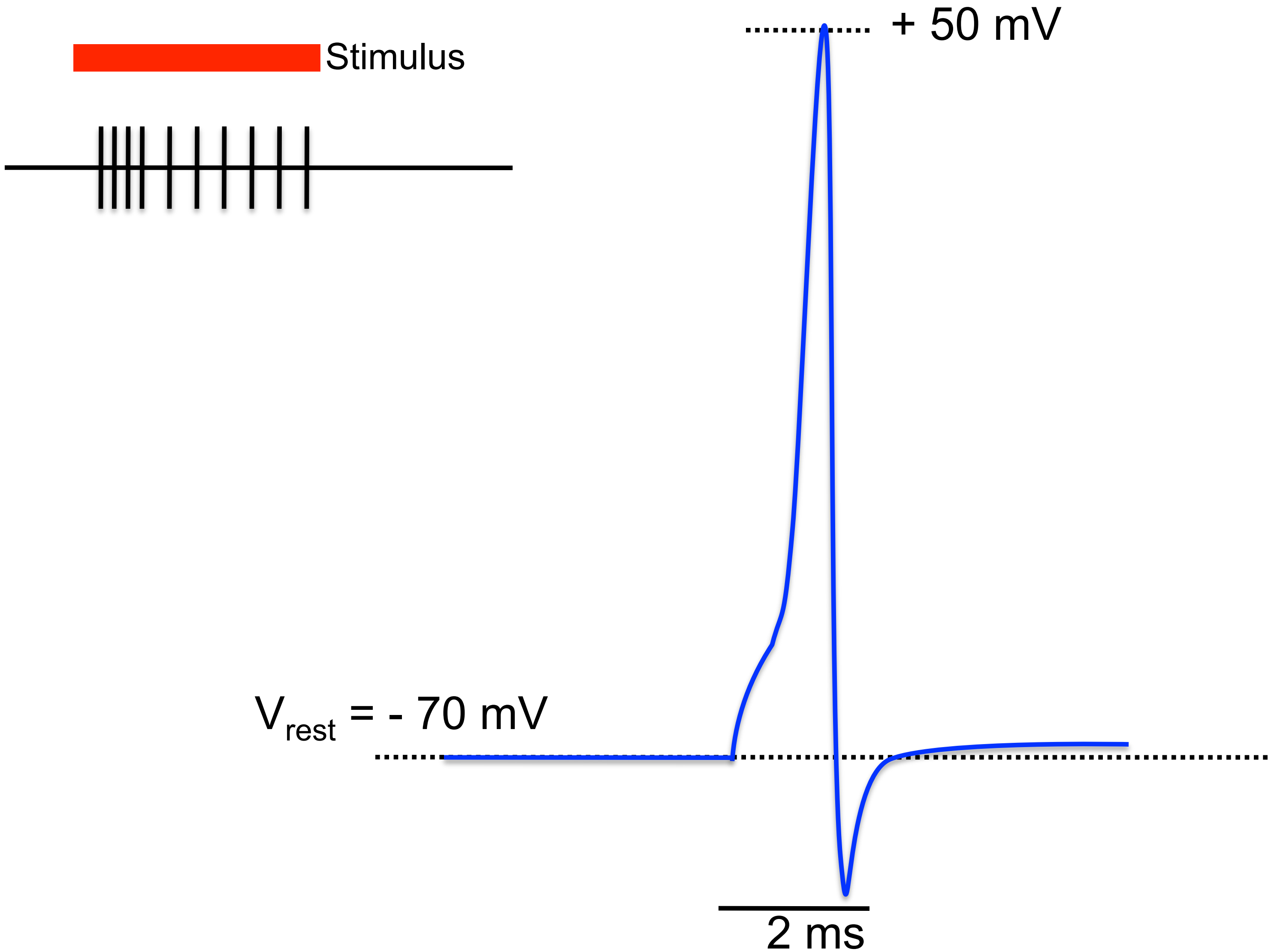
- Edgar Douglas Adrian, 1928





The First "Neural Code"





Action potential = spike = nerve impulse = “firing”

Building blocks

Diffusion

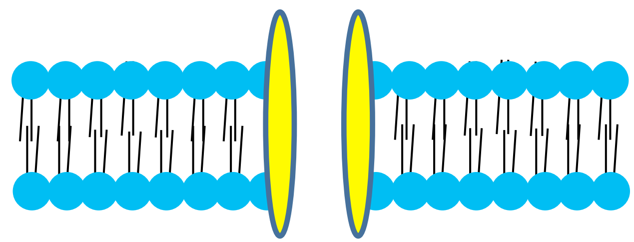
Ions… charged particles

Na^{+} K^{+}

Ca^{2+} Cl^{-}

Cell membrane + Ion channels

…a selectively permeable barrier



Ohm's Law

$$V = IR$$

V : voltage
I : current
R : resistance

$$V = R\frac{\Delta charge}{\Delta t}$$

What is charge?

What is current?

What is voltage?

Ohm's Law

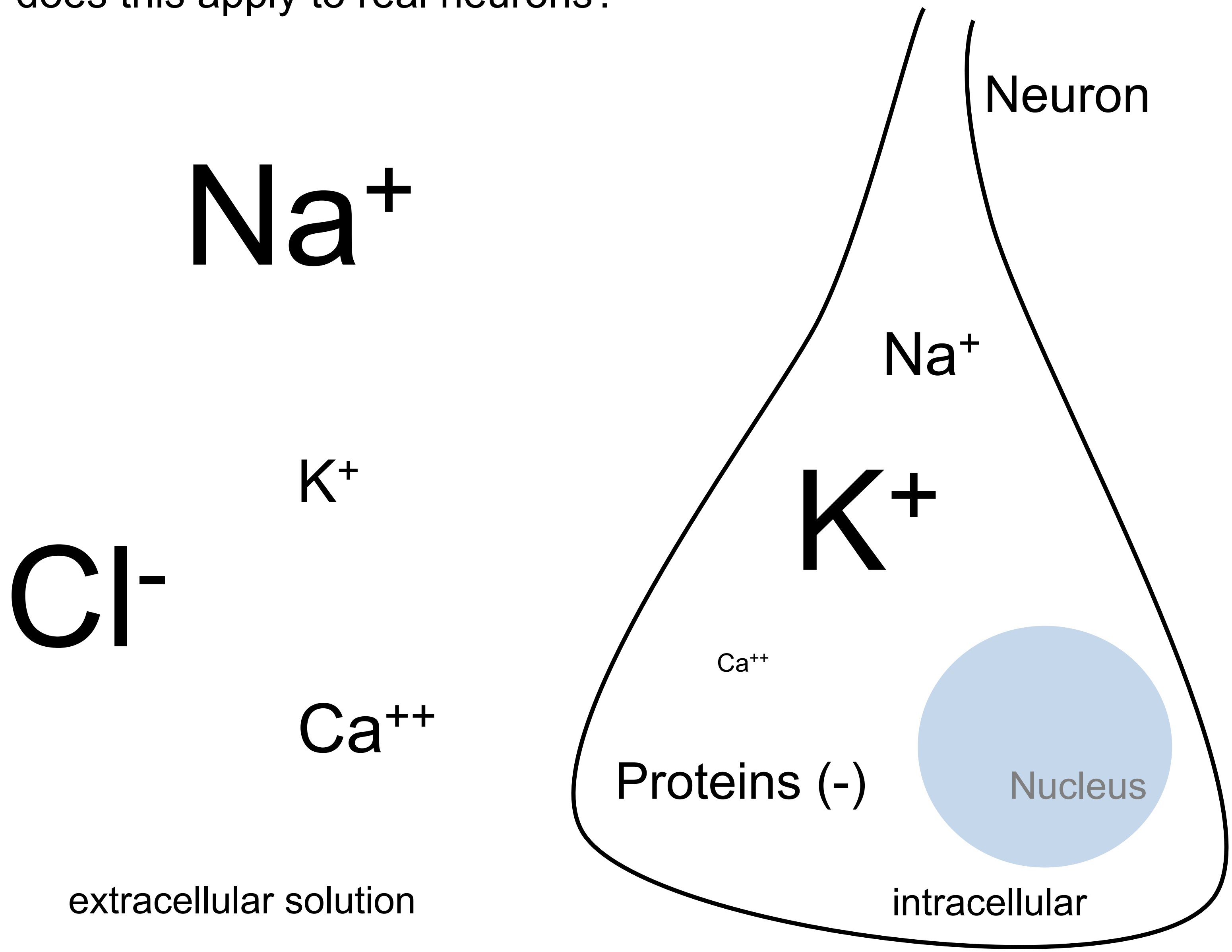
$$V = IR$$

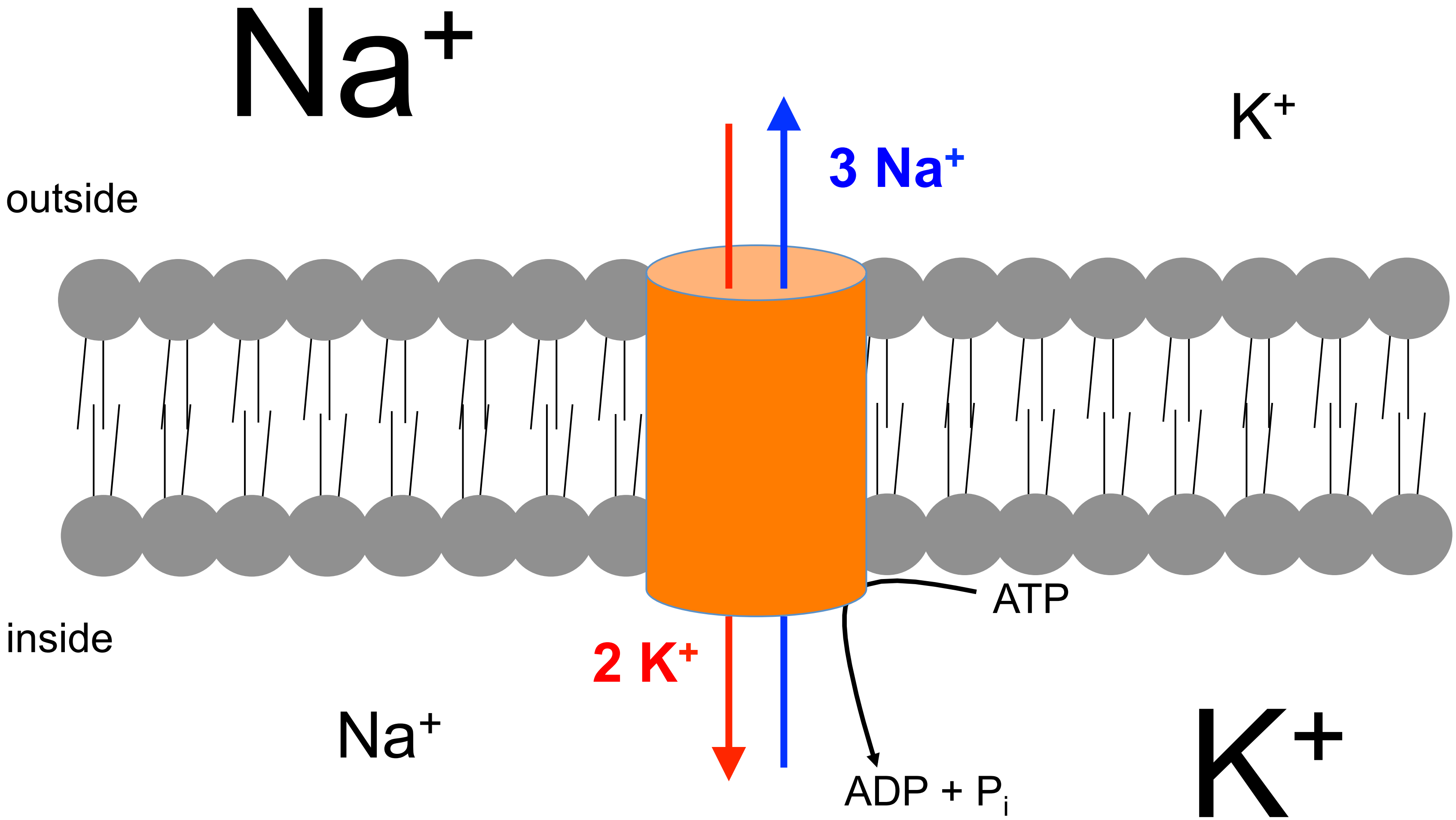
V : voltage
I : current
R : resistance

or, if you prefer: $I = GV$ where **G** = 1/R = conductance

so, current that flows will be proportional to number of openings in the membrane (conductance)

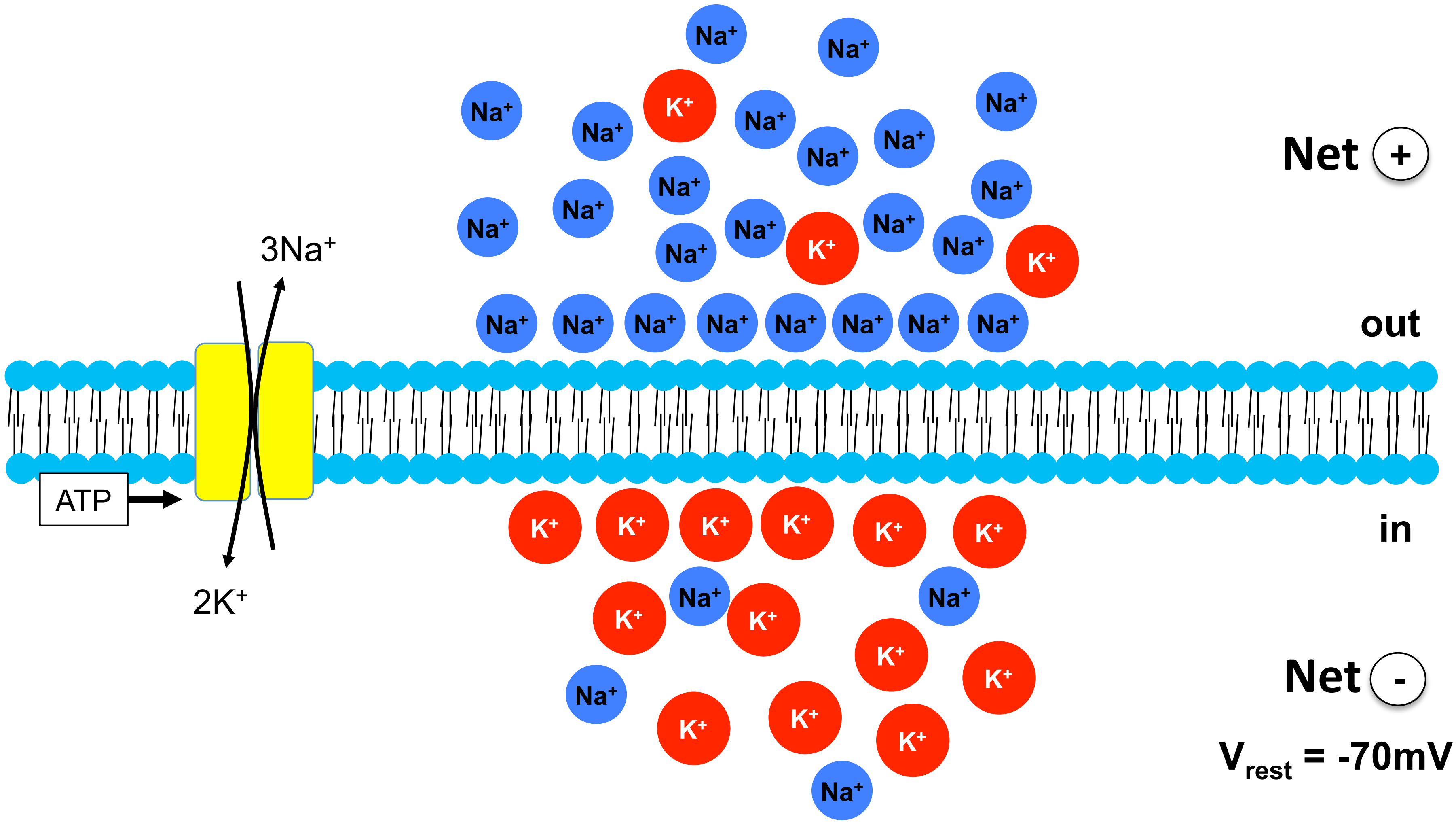
How does this apply to real neurons?



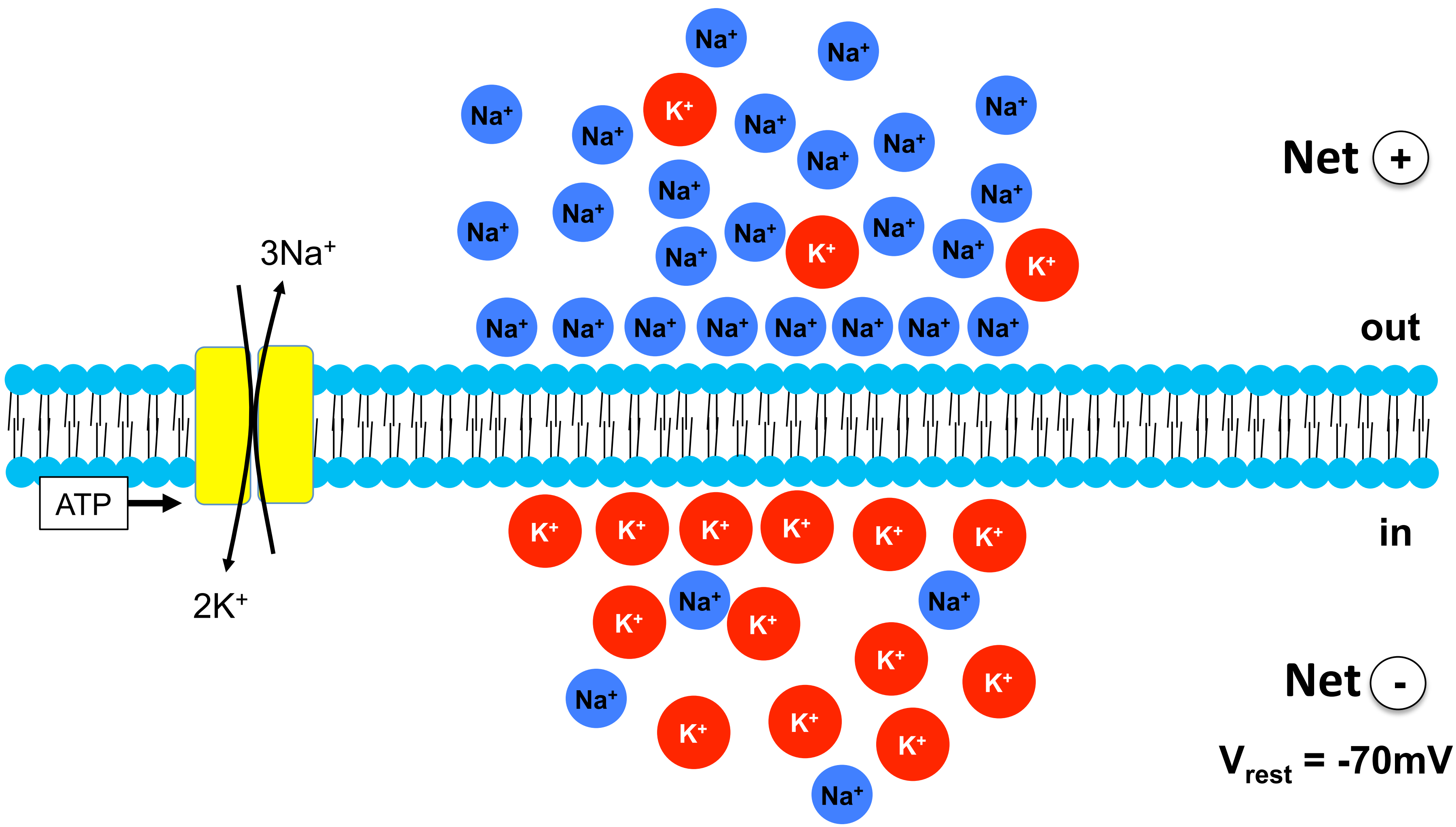


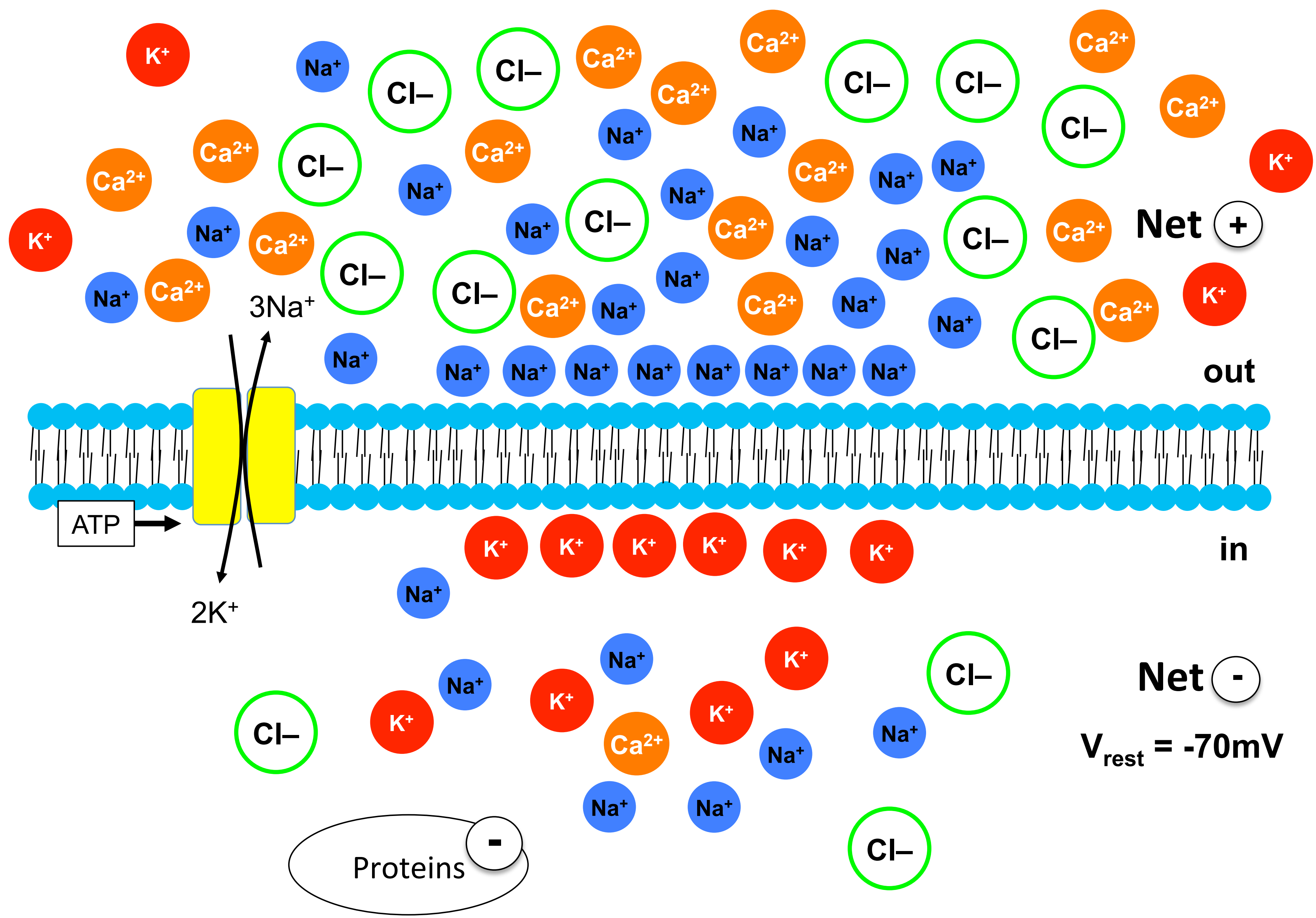
Na+
K+
3 Na+
outside
inside
2 K+
ATP
Na+
K+
ADP + Pi

Resting Potential



Which way would ions move if the membrane became permeable?





K+
Na+
Cl–
Ca2+
3Na+
2K+
ATP
Net +
out
in
Net -
V rest = -70mV
Proteins
-

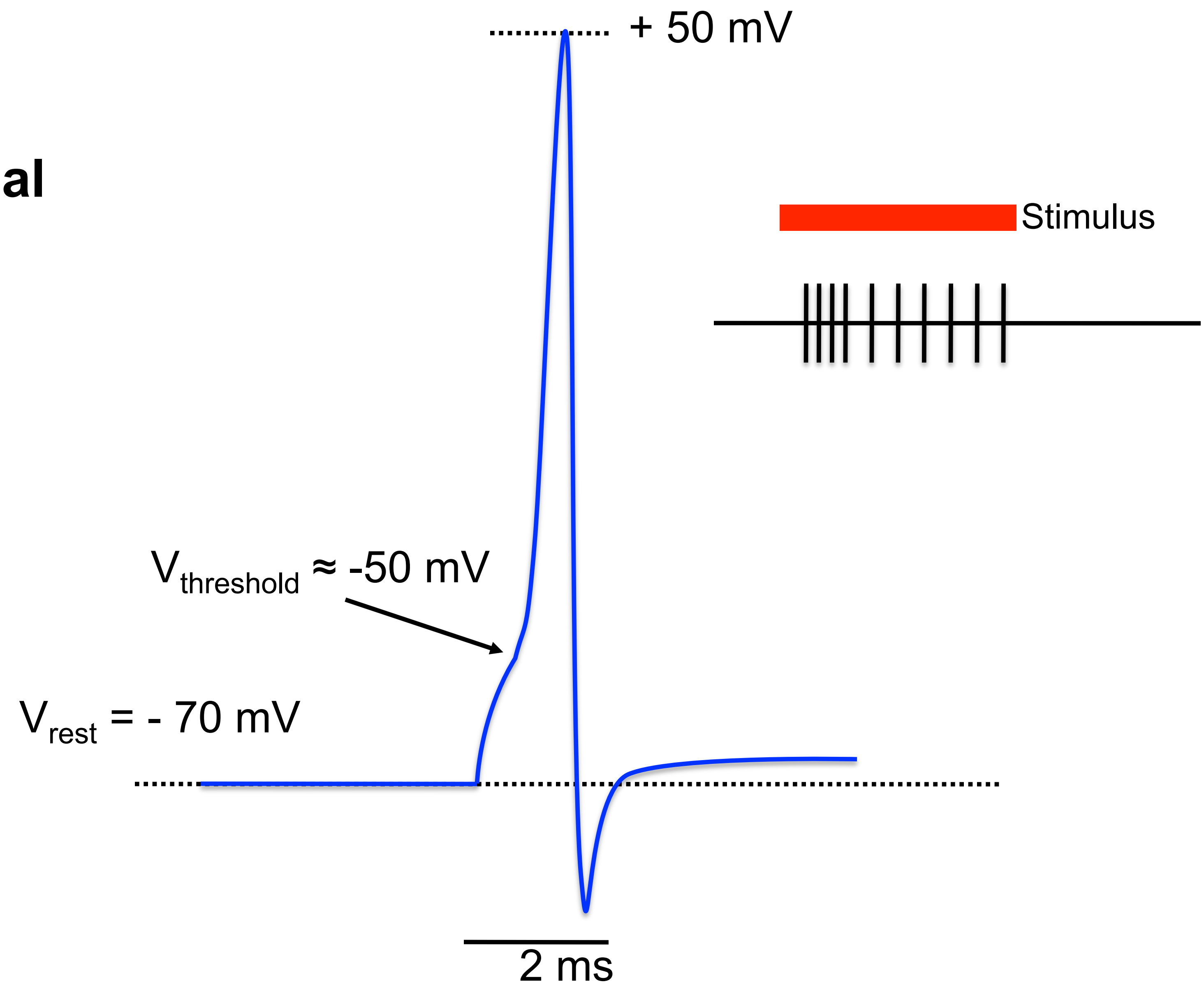
Resting Potential

Action of Na^{+}/K^{+} ATPase pump creates a concentration and charge difference

Typically -60 to -70 mV in healthy neurons

Neuron can use this stored energy for signaling

The Action Potential



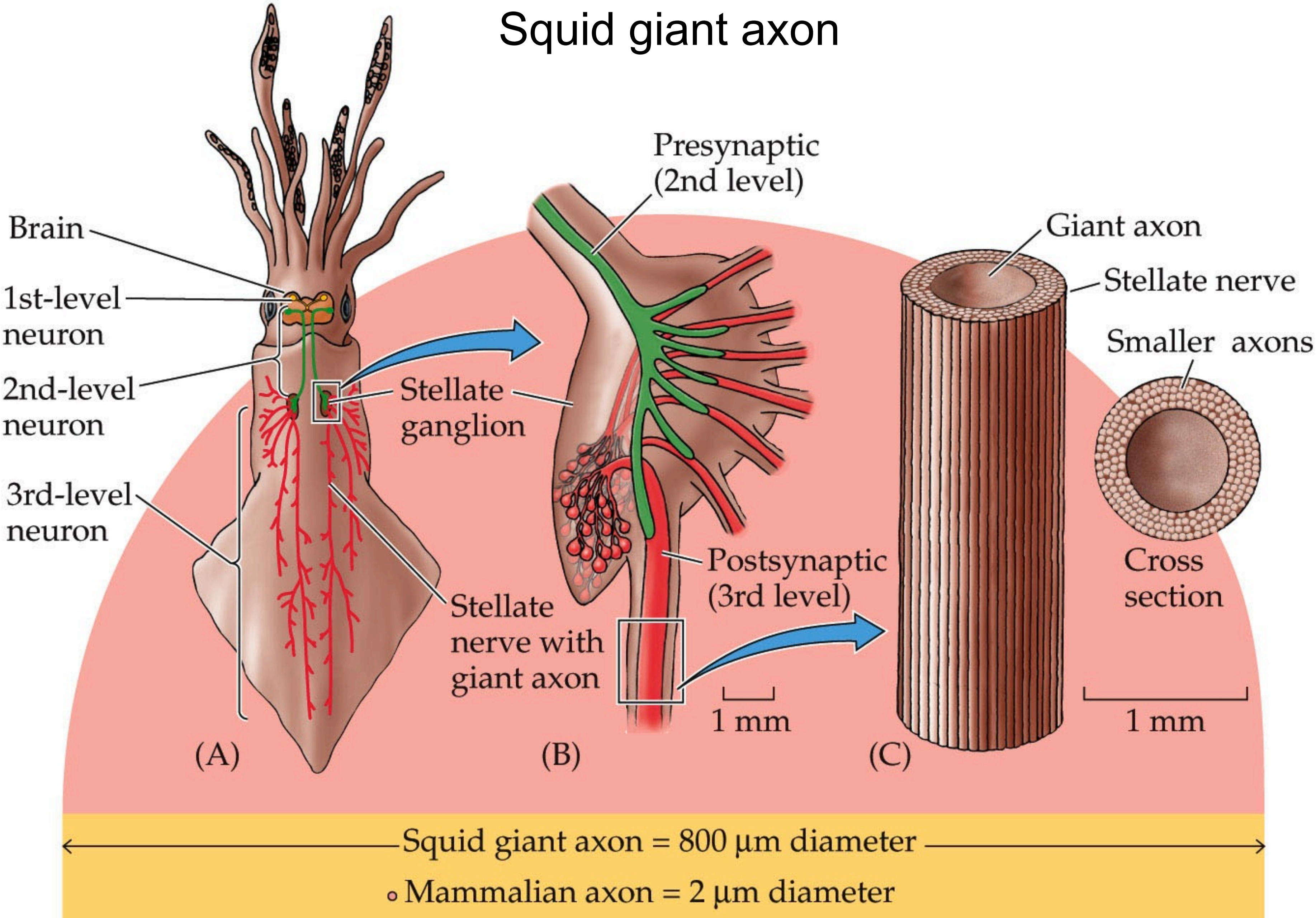
History of the Action Potential

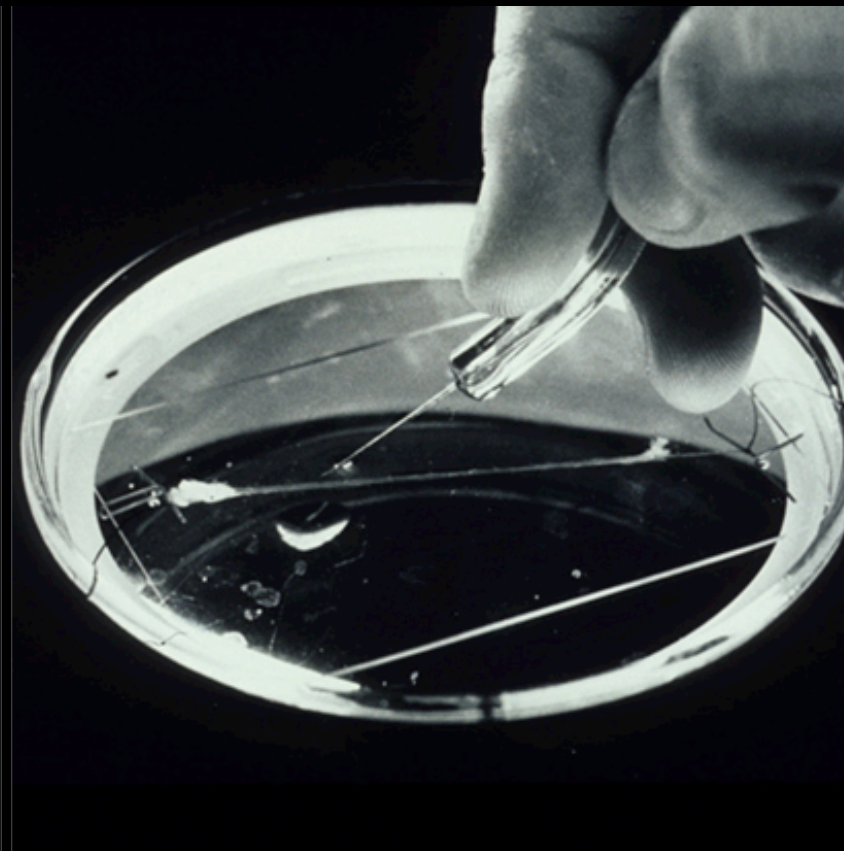
…a gradual understanding

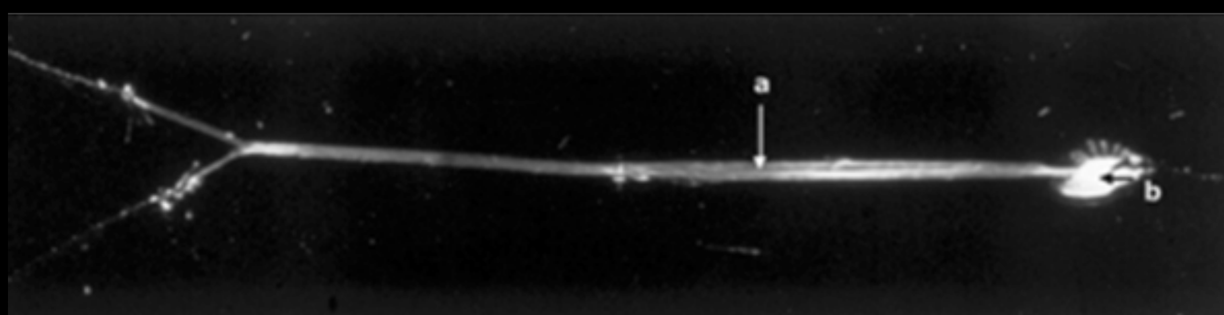
1791	**Luigi Galvani** electrical stimulation of frog's legs
1844	**Carlo Matteucci** cell membranes have a voltage and can produce a direct current
1849	**Hermann von Helmholtz** measured speed of nerve conduction
1850	**Emil DuBois-Reymond** measured the first action potential
1902	**Julius Bernstein** proposed that action potentials due to membrane permeability changes
1928	**Edgar Douglas Adrian** action potentials are "all-or-none" phenomena
1949	**Kenneth Cole** invents voltage clamp method
1952	**Hodgkin & Huxley** reveal ionic mechanisms underlying the action potential

How did they first study the action potential?

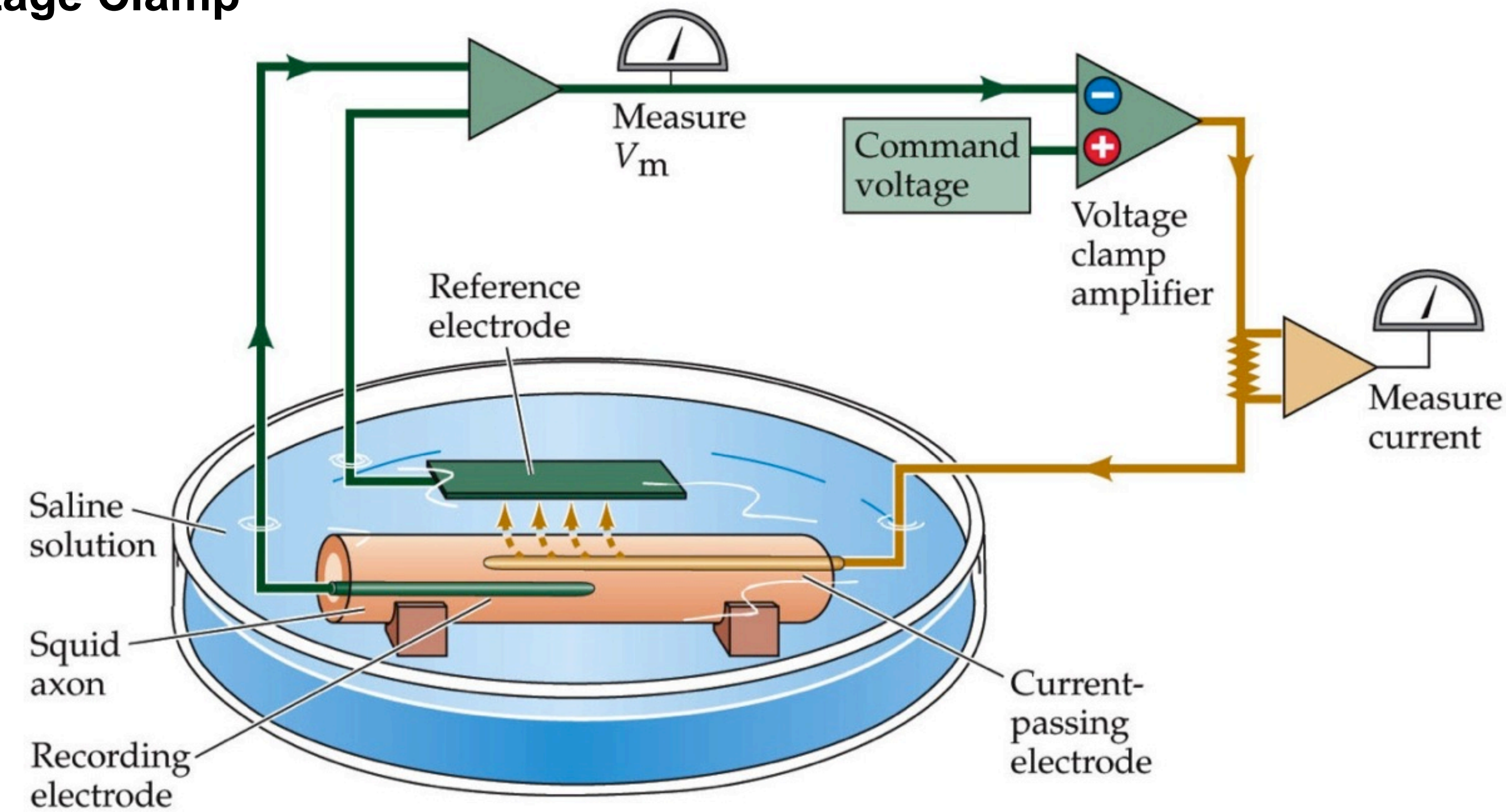
Squid giant axon





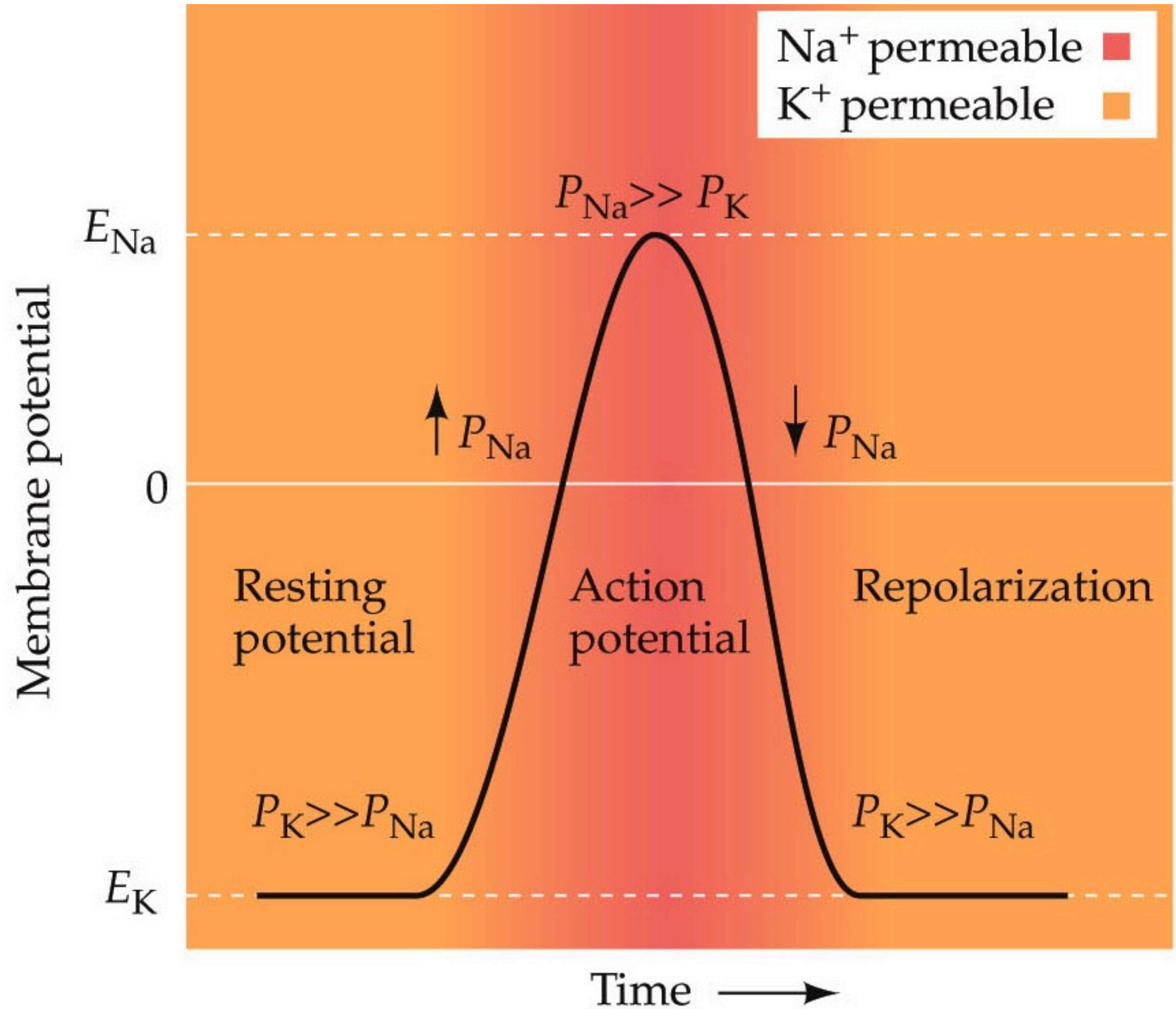

a
b

Voltage Clamp

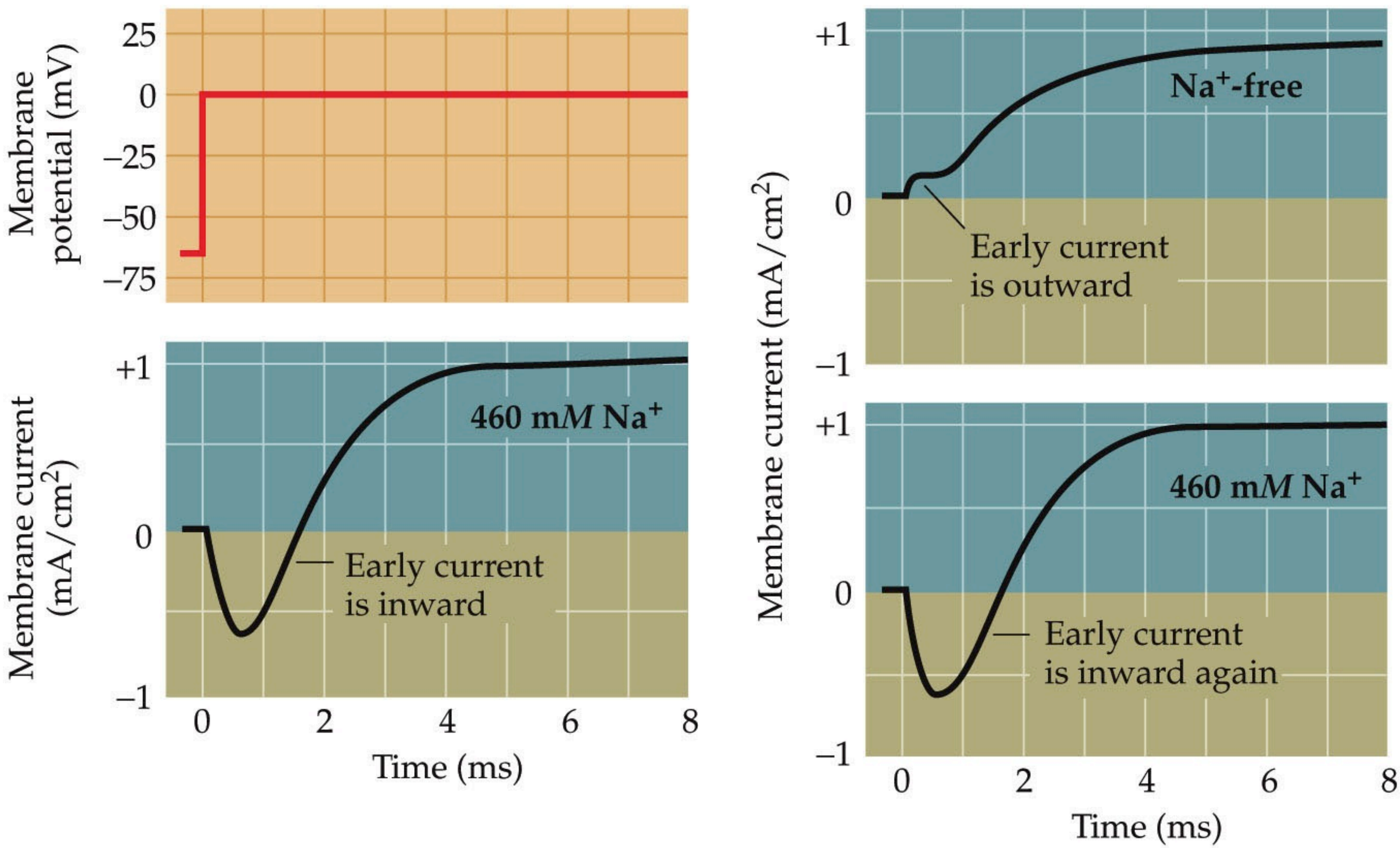


Method to measure amount of current (charge flow) at different voltages

The Squids Giant Axons

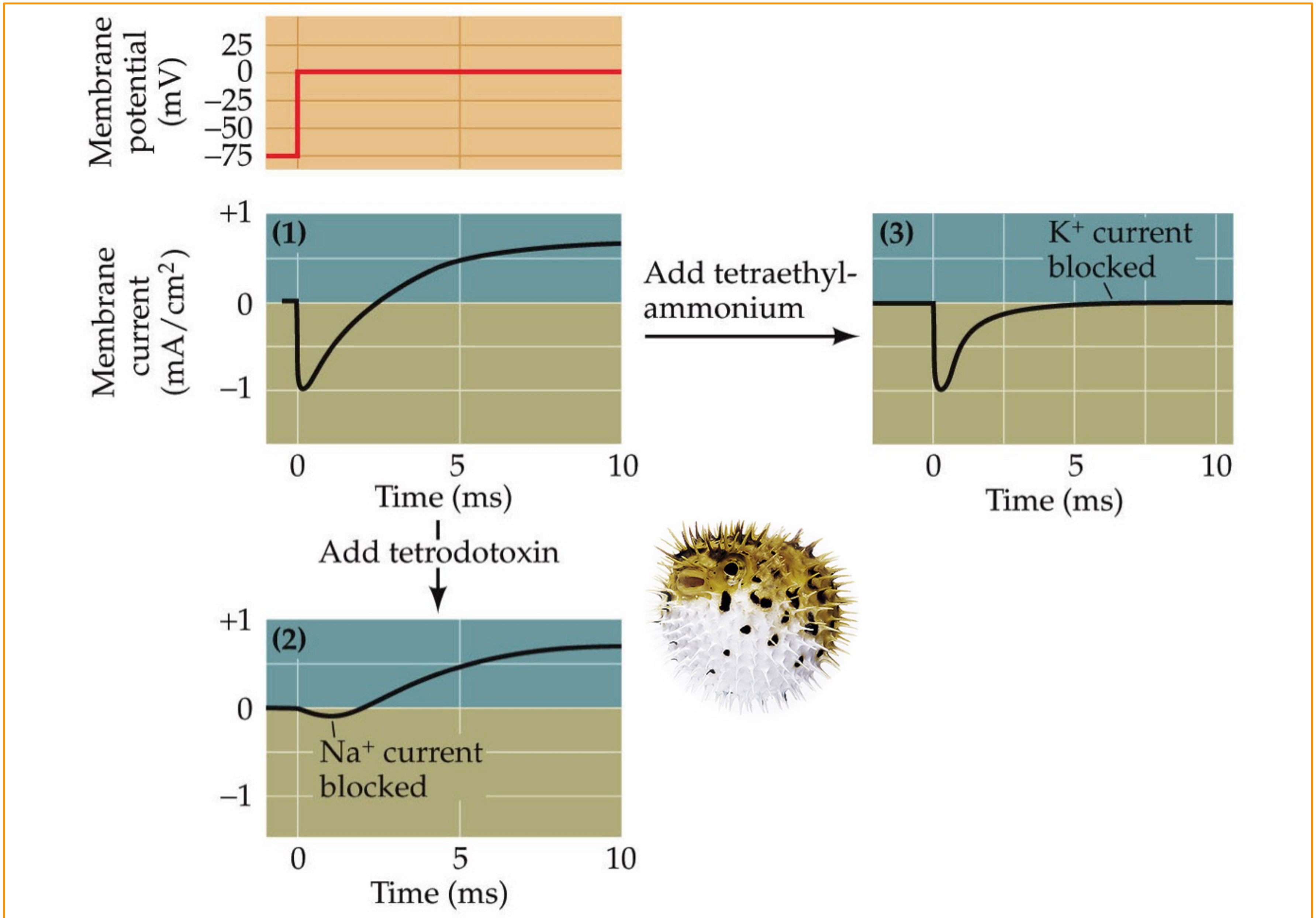


Na+ permeable
K+ permeable
$P_{Na} >> P_K$
E_{Na}
Membrane potential
↑ P_{Na}
↓ P_{Na}
0
Resting potential
Action potential
Repolarization
$P_K >> P_{Na}$
$P_K >> P_{Na}$
E_K
Time



Membrane potential (mV)
25
0
–25
–50
–75
Membrane current (mA/cm²)
+1
0
–1
460 mM Na+
Early current is inward
0
2
4
6
8
Time (ms)
Membrane current (mA/cm²)
+1
0
–1
Na+-free
Early current is outward
460 mM Na+
Early current is inward again
0
2
4
6
8
Time (ms)

Drugs that Block Action Potentials have Specific Effects on Na^+ and K^+ Currents



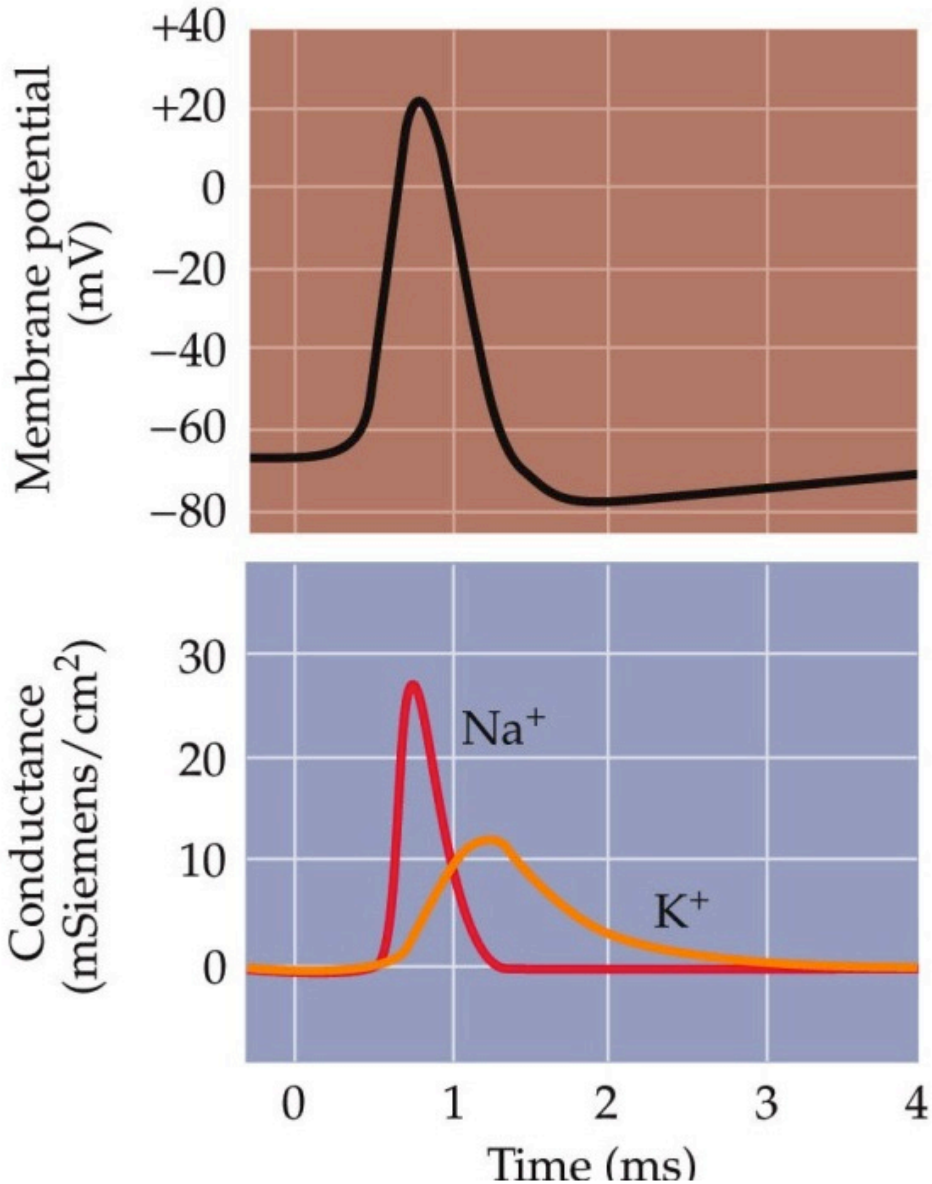
Toxins that impair action potentials

tetrodotoxin
blocks Na^+ channels

dendrotoxins
block K^+ channels

conotoxins
block Na^+ and K^+ channels

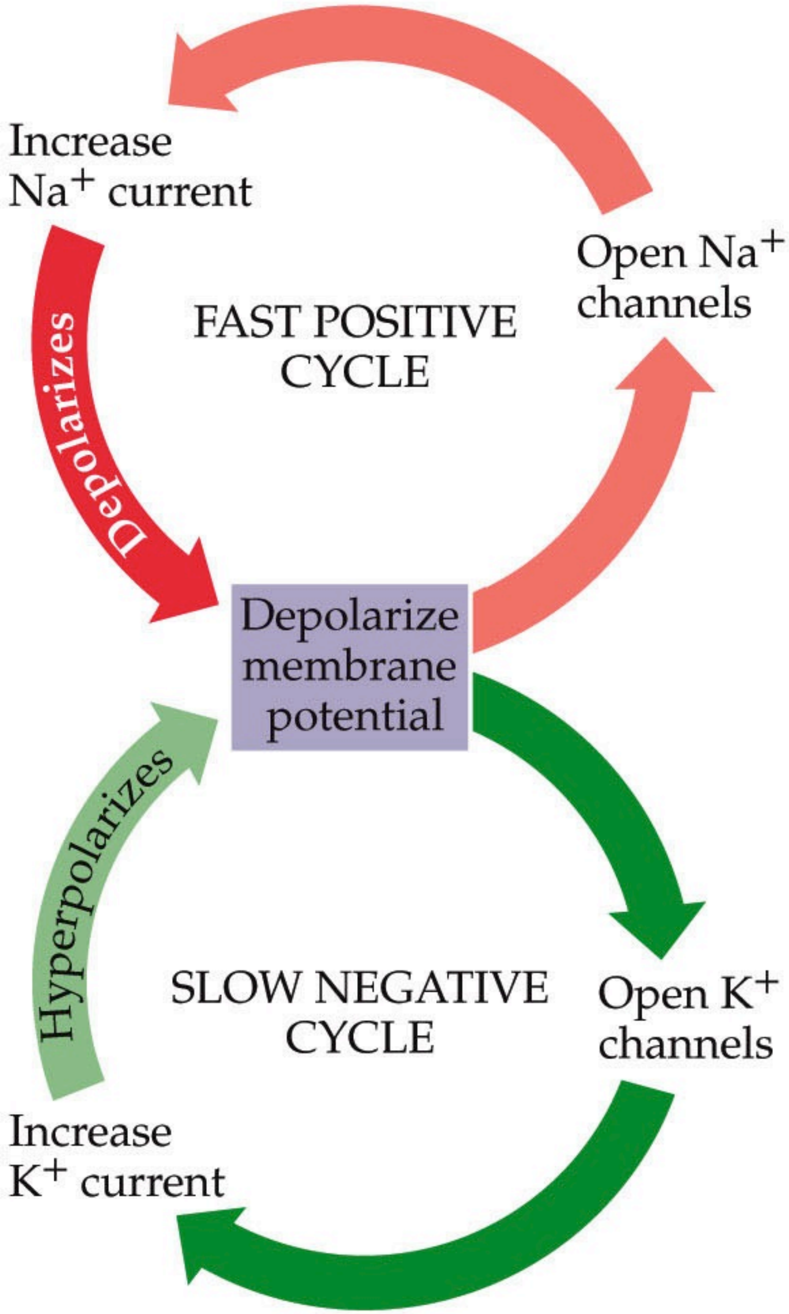
birtoxin
alters Na^+ channel gating



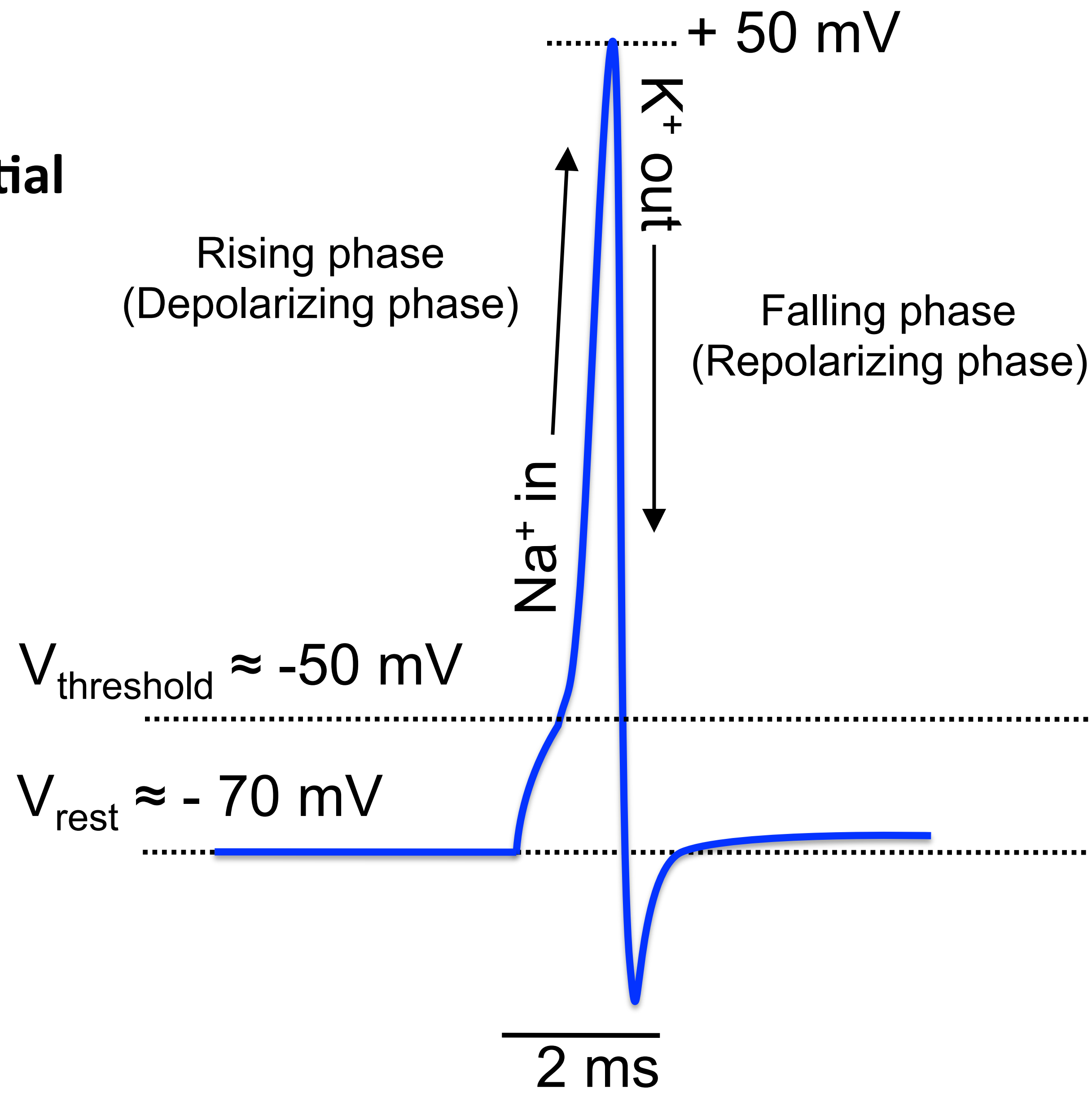
Action Potential

Contributing Currents

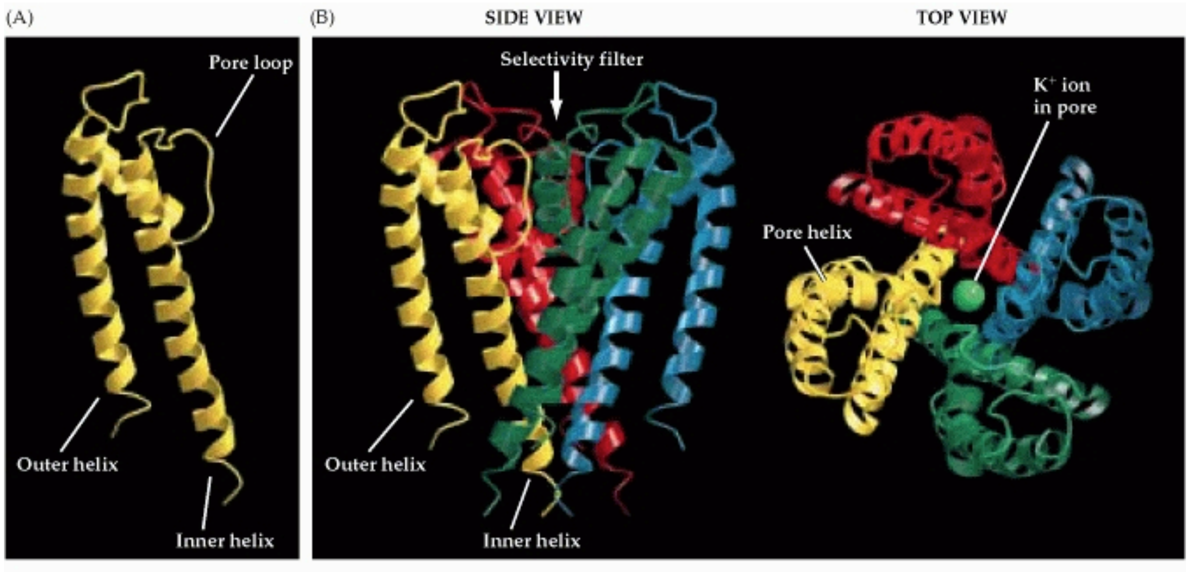
Fast, early Na^+ current
Slower, longer-lasting K^+ current

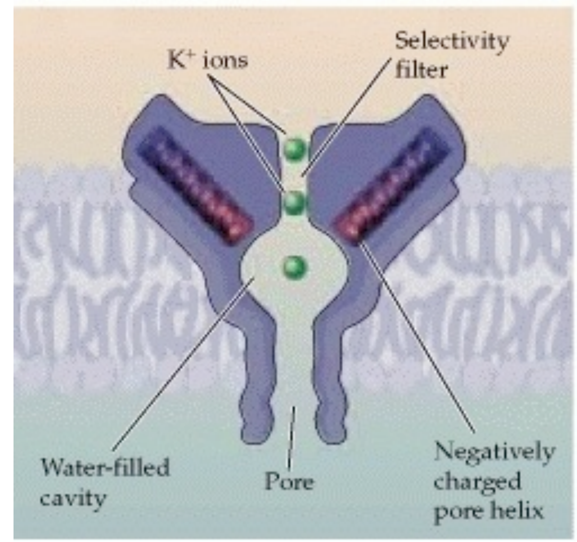

Increase
Na+ current
Open Na+
channels
Depolarizes
FAST POSITIVE
CYCLE
Depolarize
membrane
potential
Hyperpolarizes
SLOW NEGATIVE
CYCLE
Open K+
channels
Increase
K+ current

The Action Potential



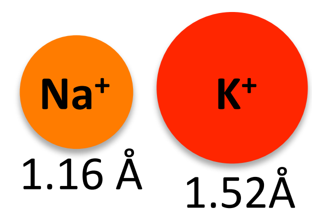
Ion Channels Evolution as the perfect nano-engineer…





① Conduction: moving hydrophilic ions through a hydrophobic membrane

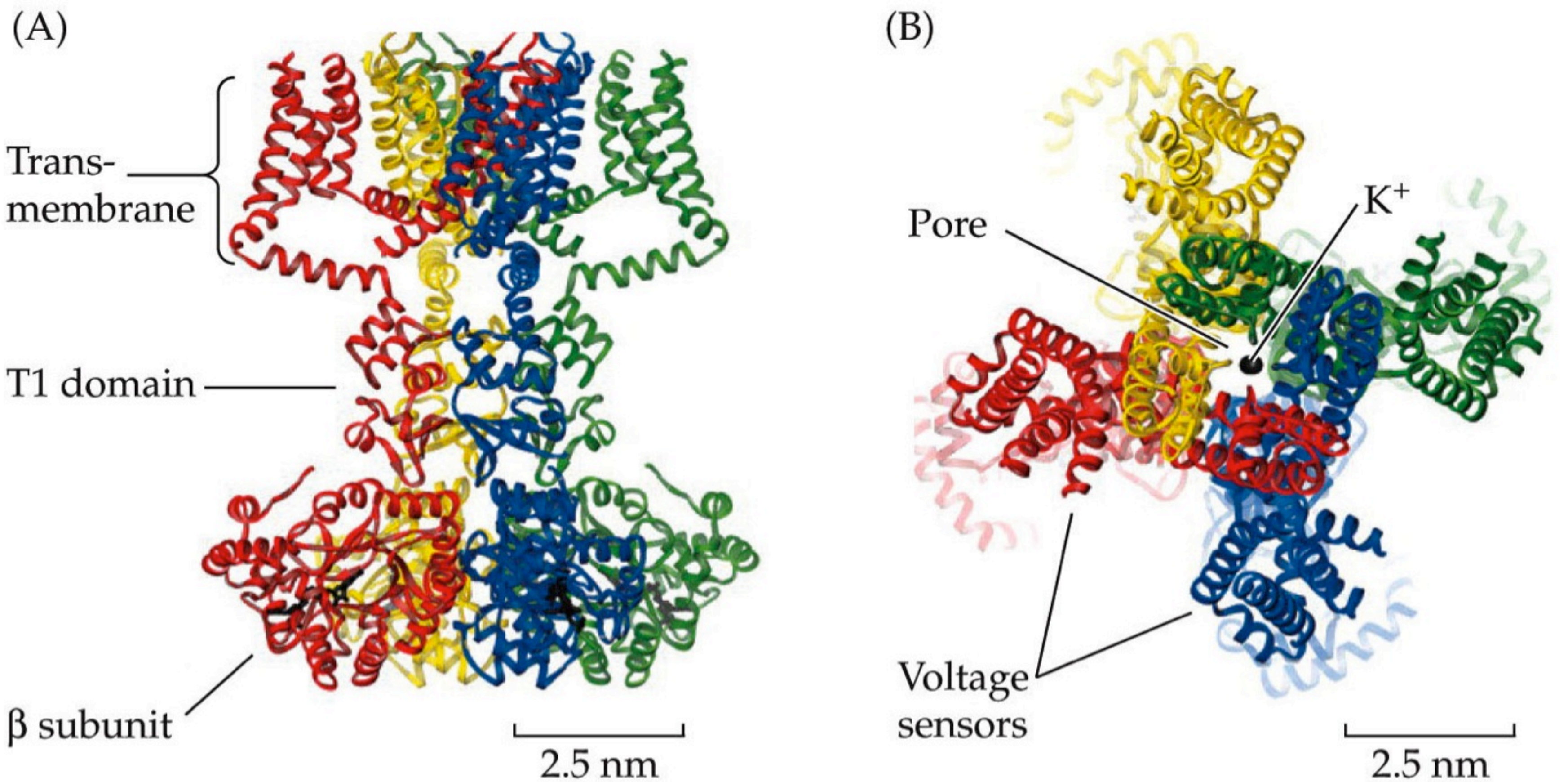
② Selection: restrict movement to a single ionic species!

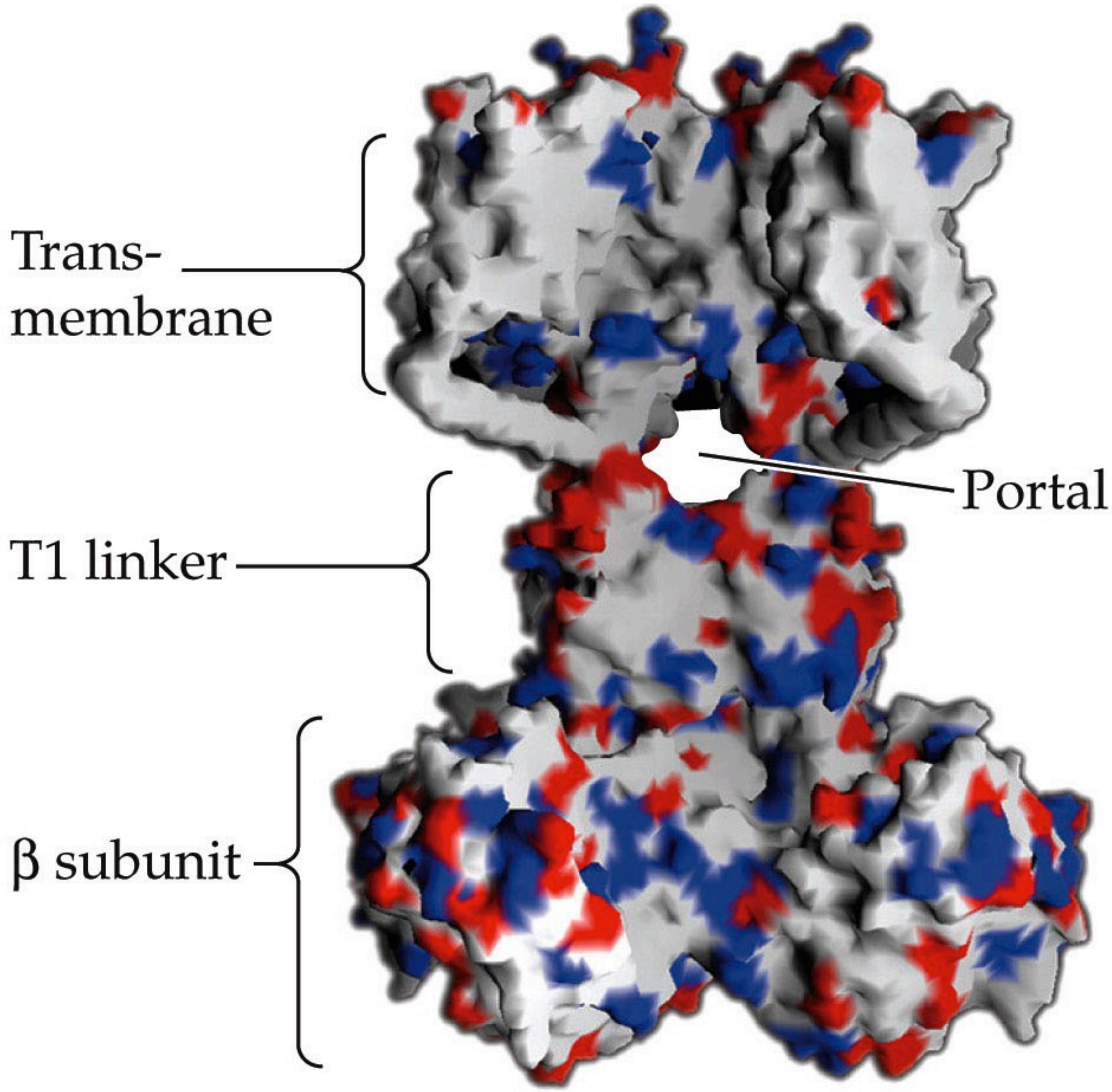


③ Gating: direct sensors of the environment

i.e. voltage

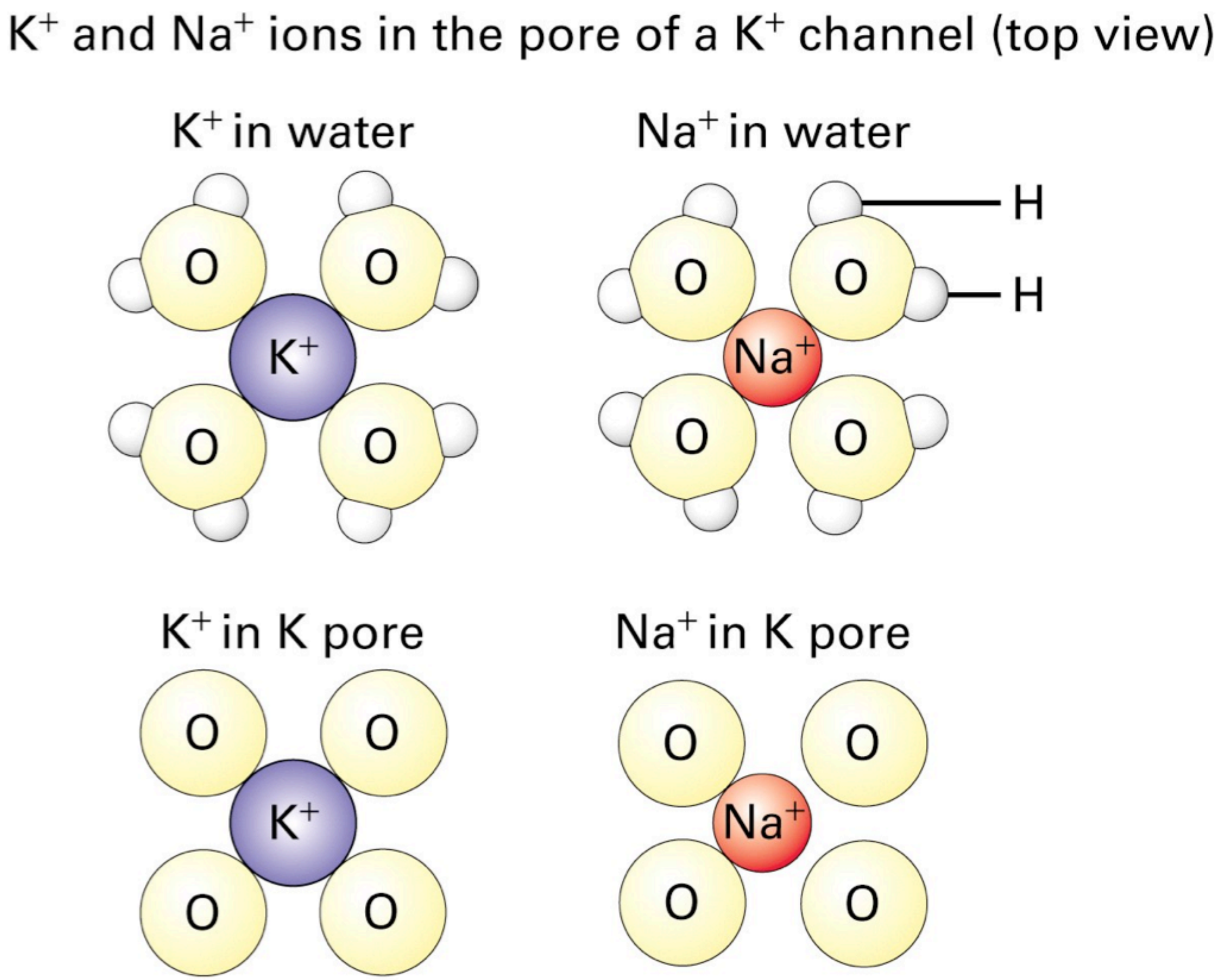
X-ray Crystallography - Structure of K^+ Channel





Trans-
membrane
Portal
T1 linker
β subunit

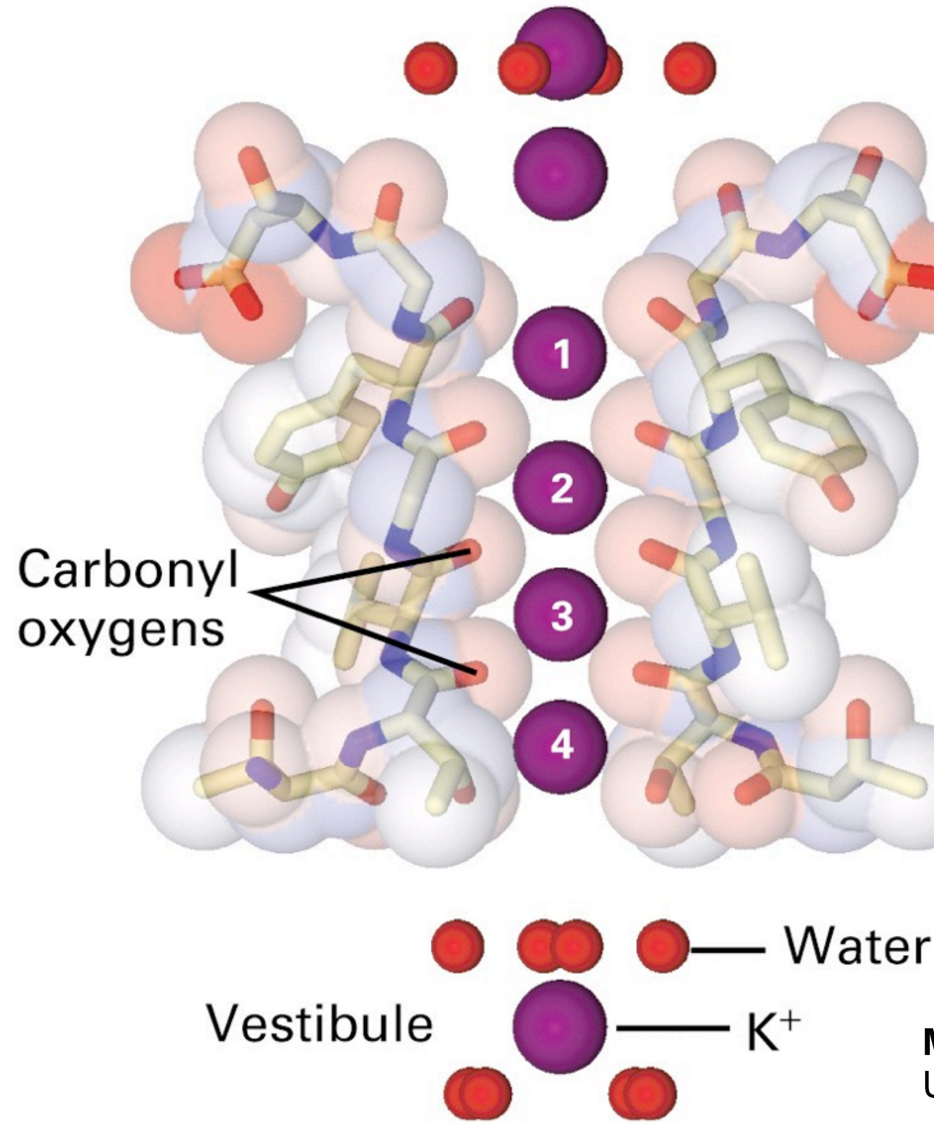
1 Conduction



Manuela Gardner
University of British Columbia

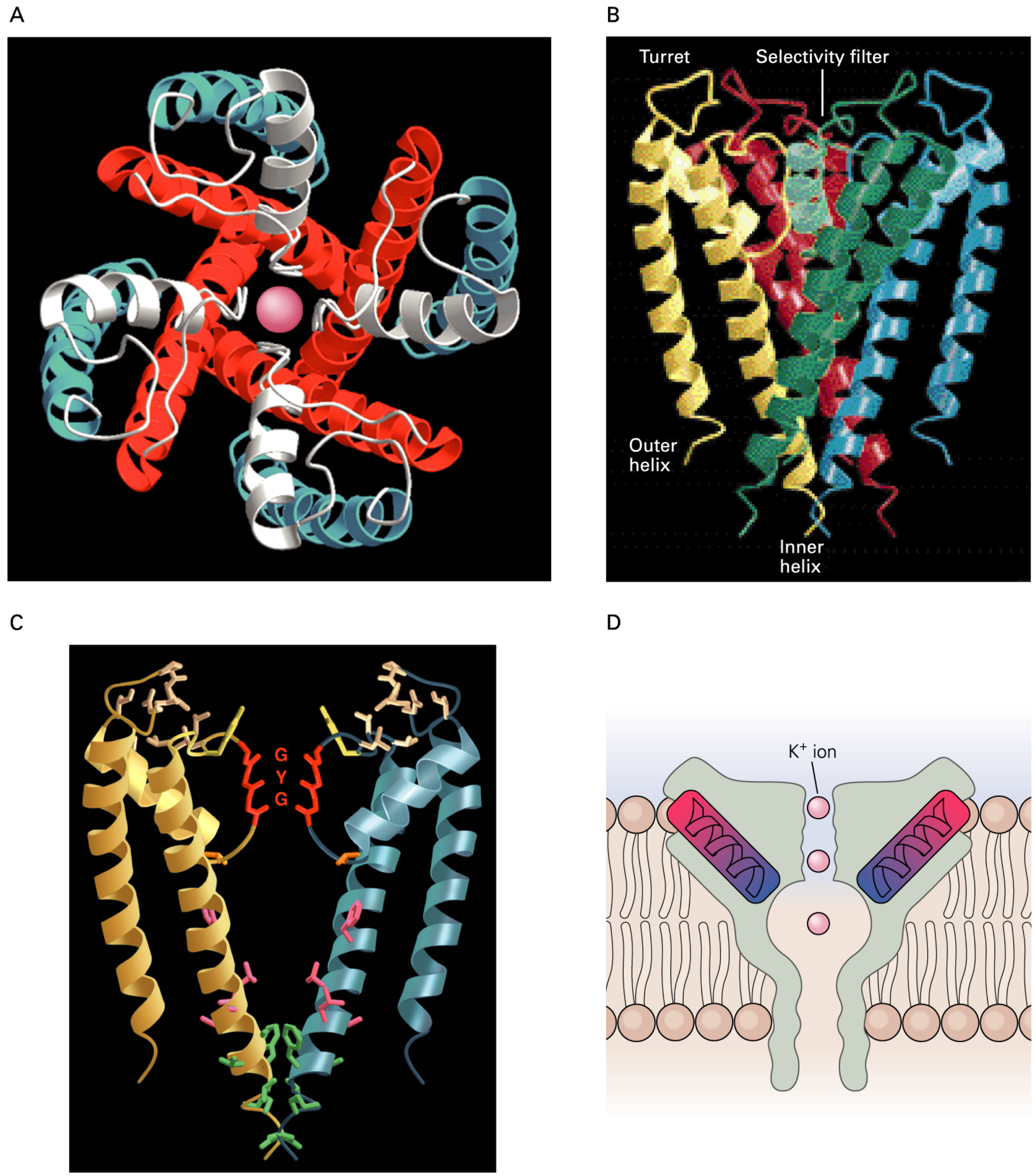
① Conduction

K⁺ ions in the pore of a K⁺ channel (side view)

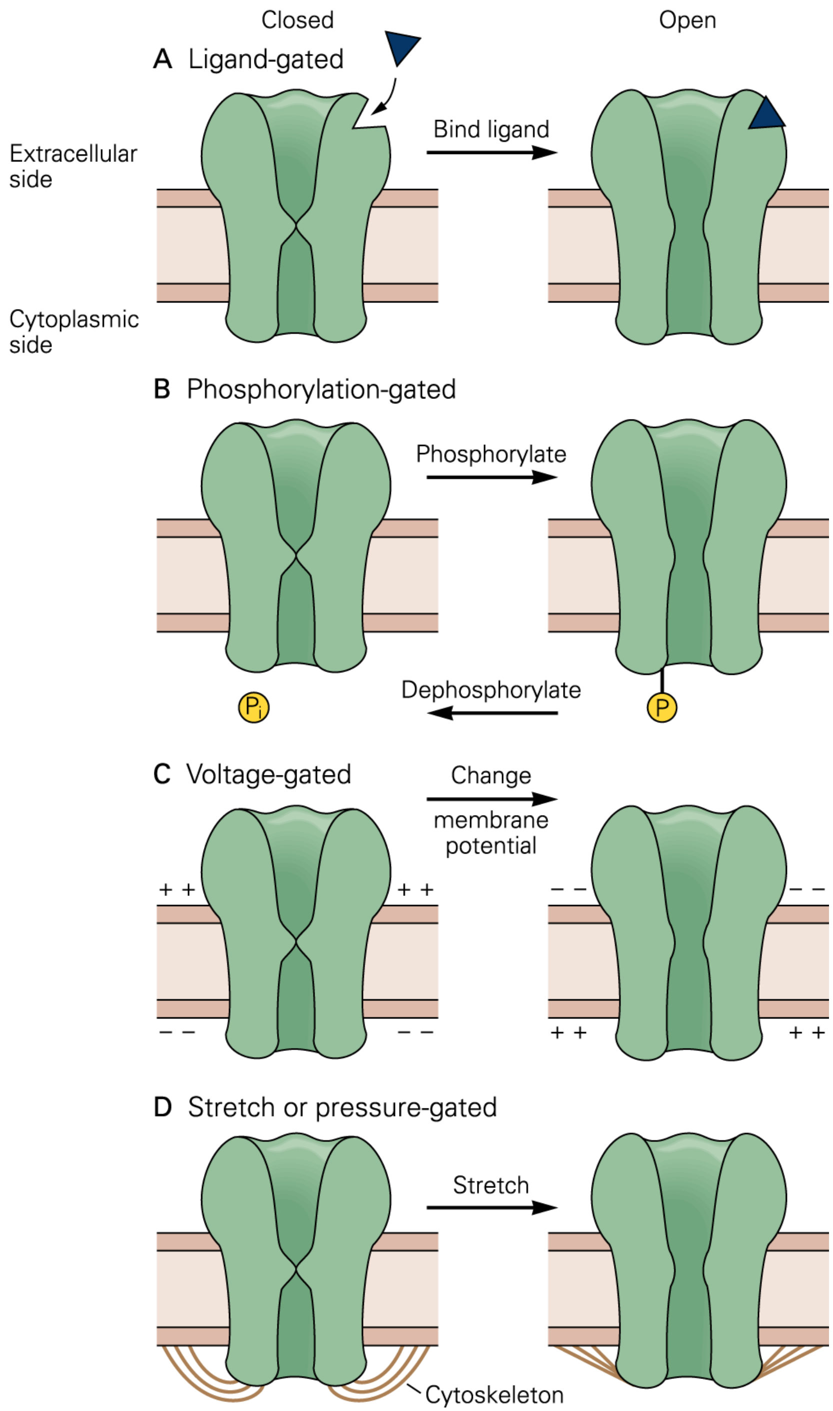


Manuela Gardner
University of British Columbia

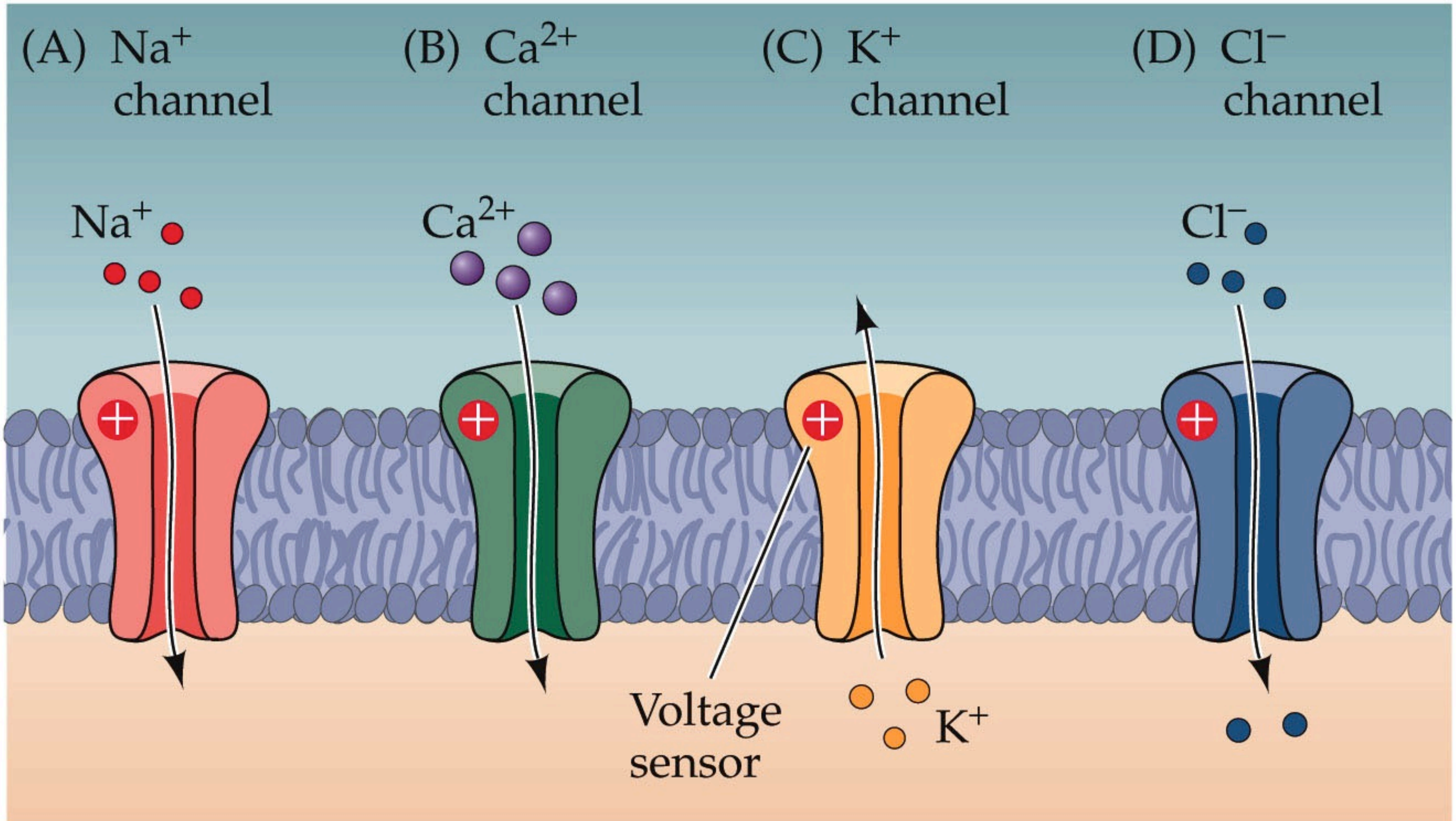
2 Selectivity



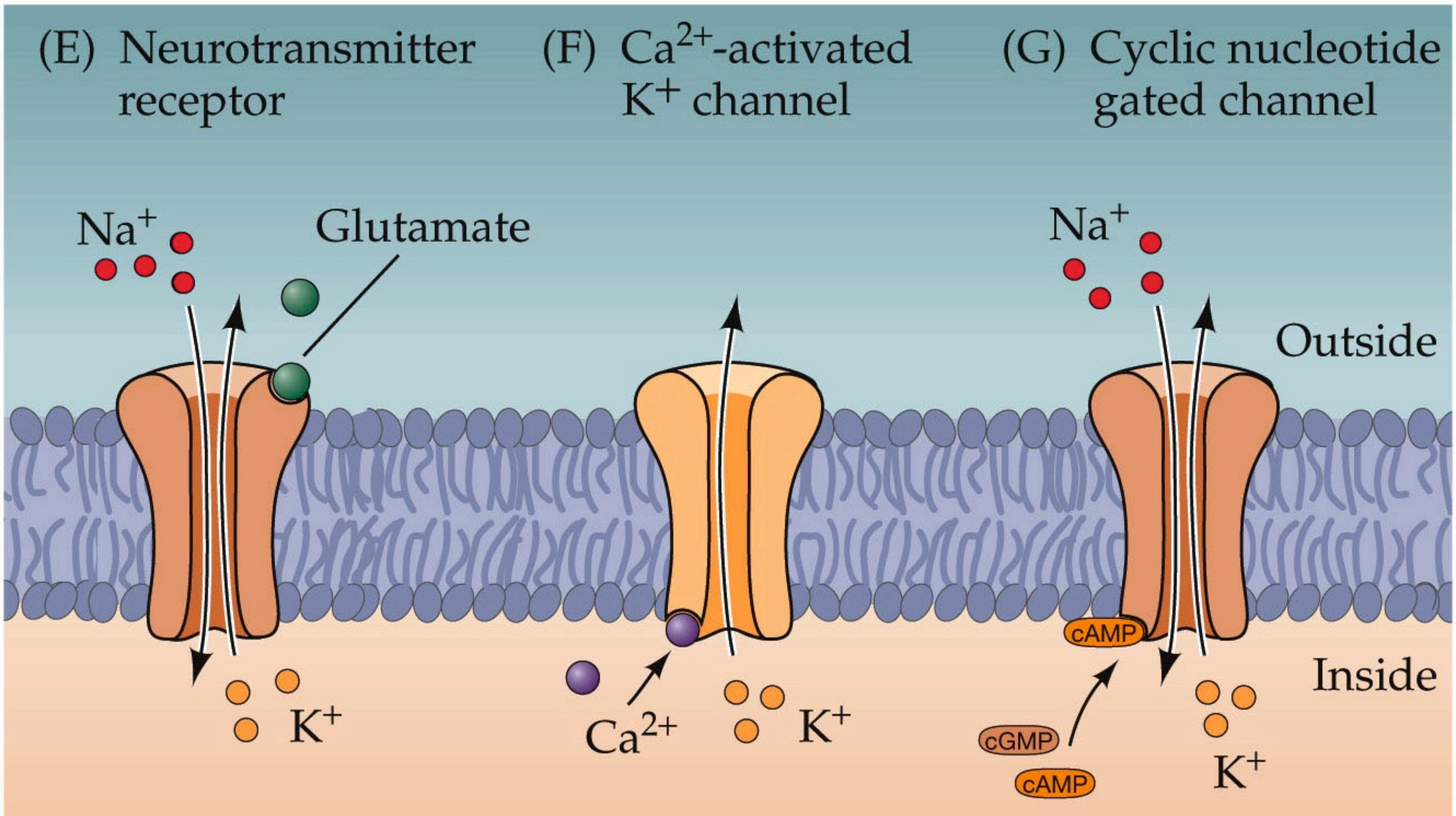
3 Gating


Closed
Open
A Ligand-gated
Bind ligand
Extracellular side
Cytoplasmic side
B Phosphorylation-gated
Phosphorylate
Dephosphorylate
P_i
P
C Voltage-gated
Change membrane potential
+ +
– –
D Stretch or pressure-gated
Stretch
Cytoskeleton

Voltage Gated Channels

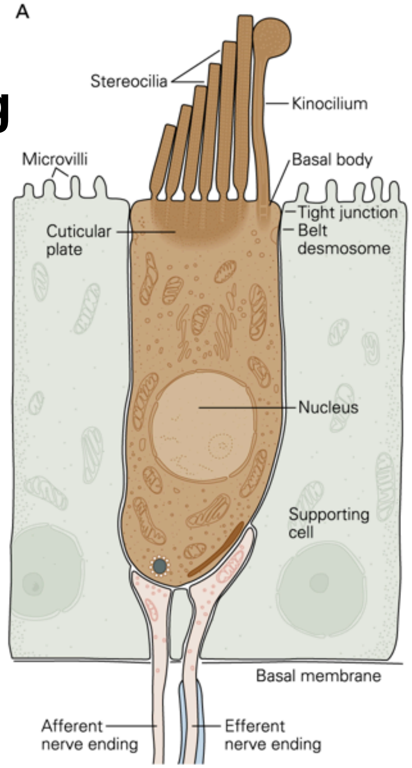


Ligand Gated Channels

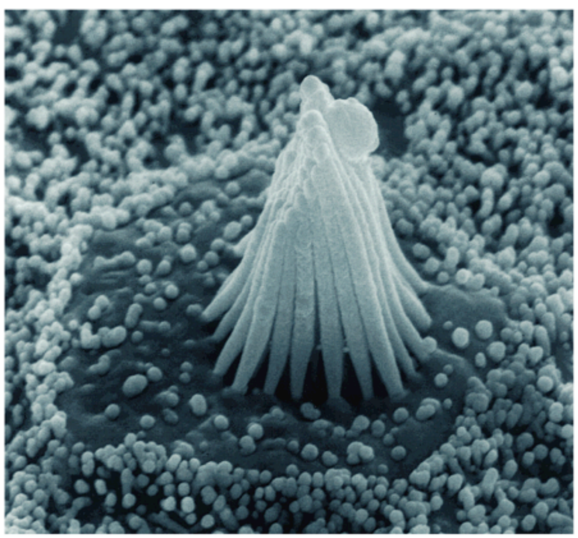


3 Gating

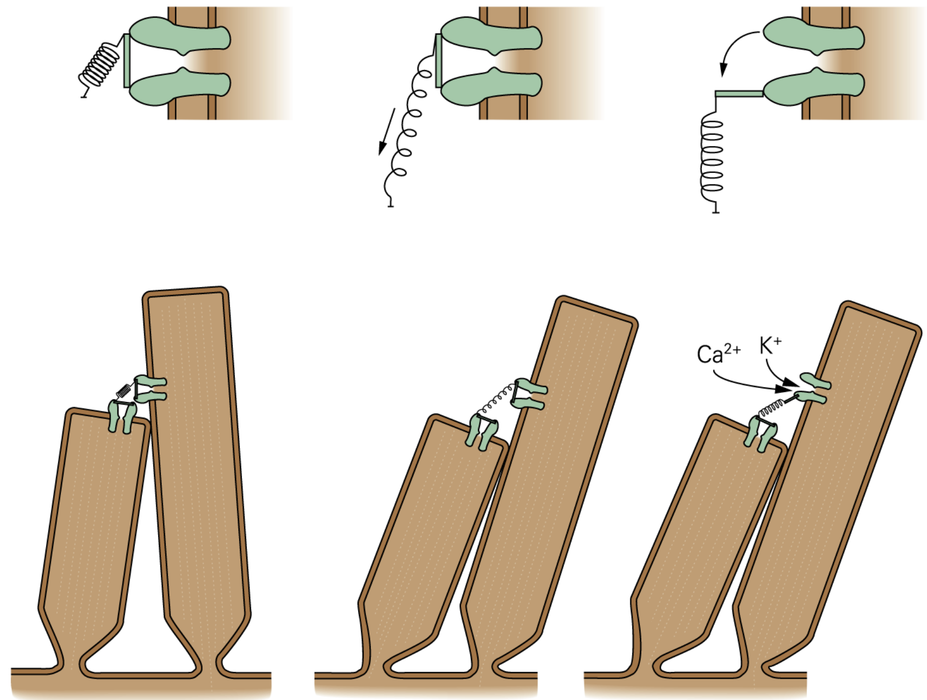
A



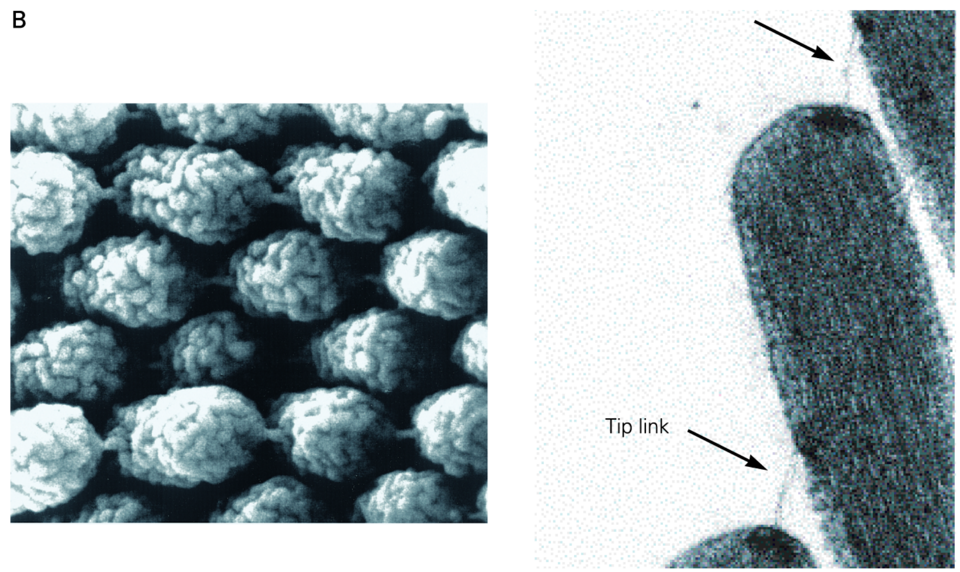
B



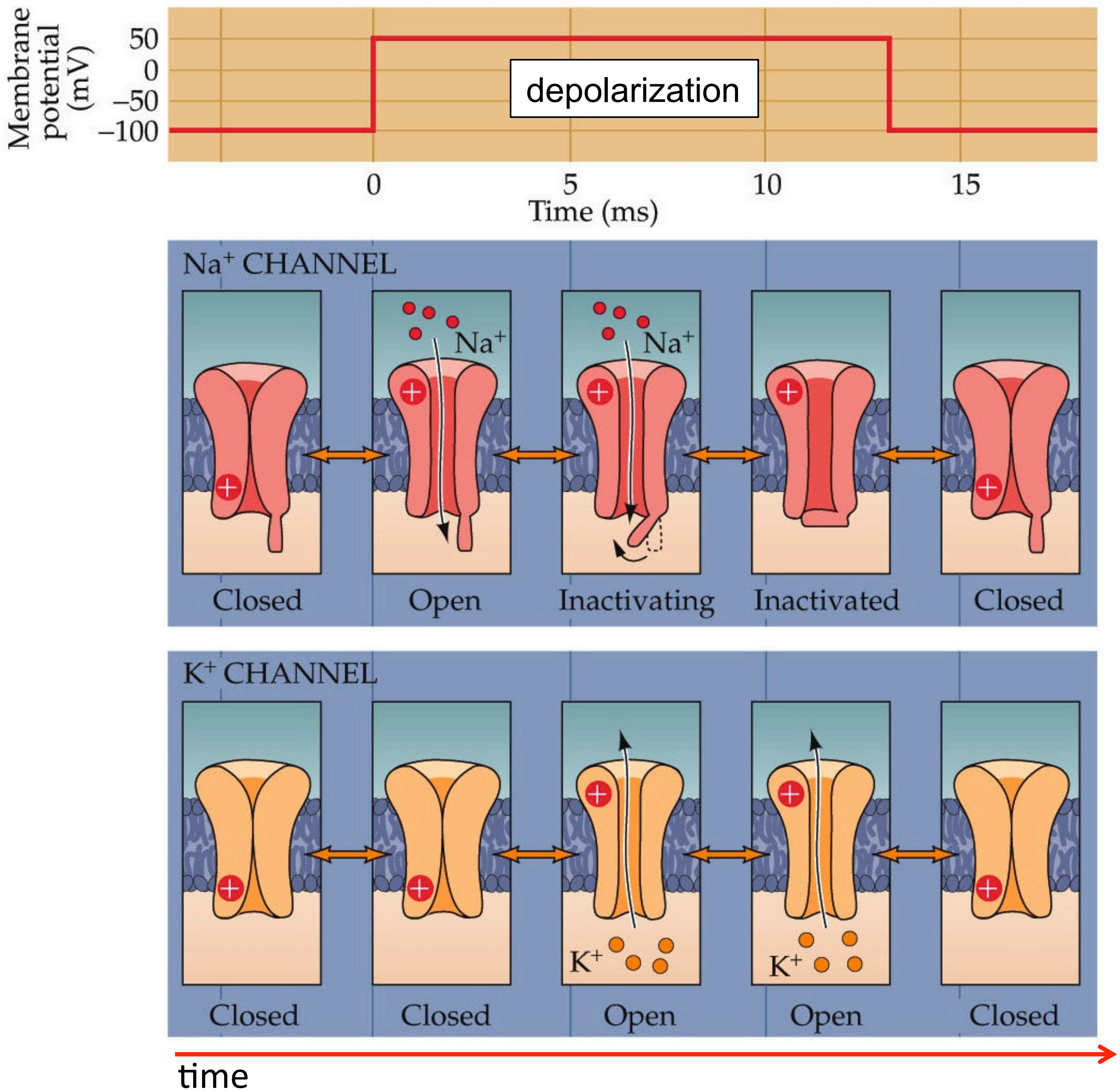
A



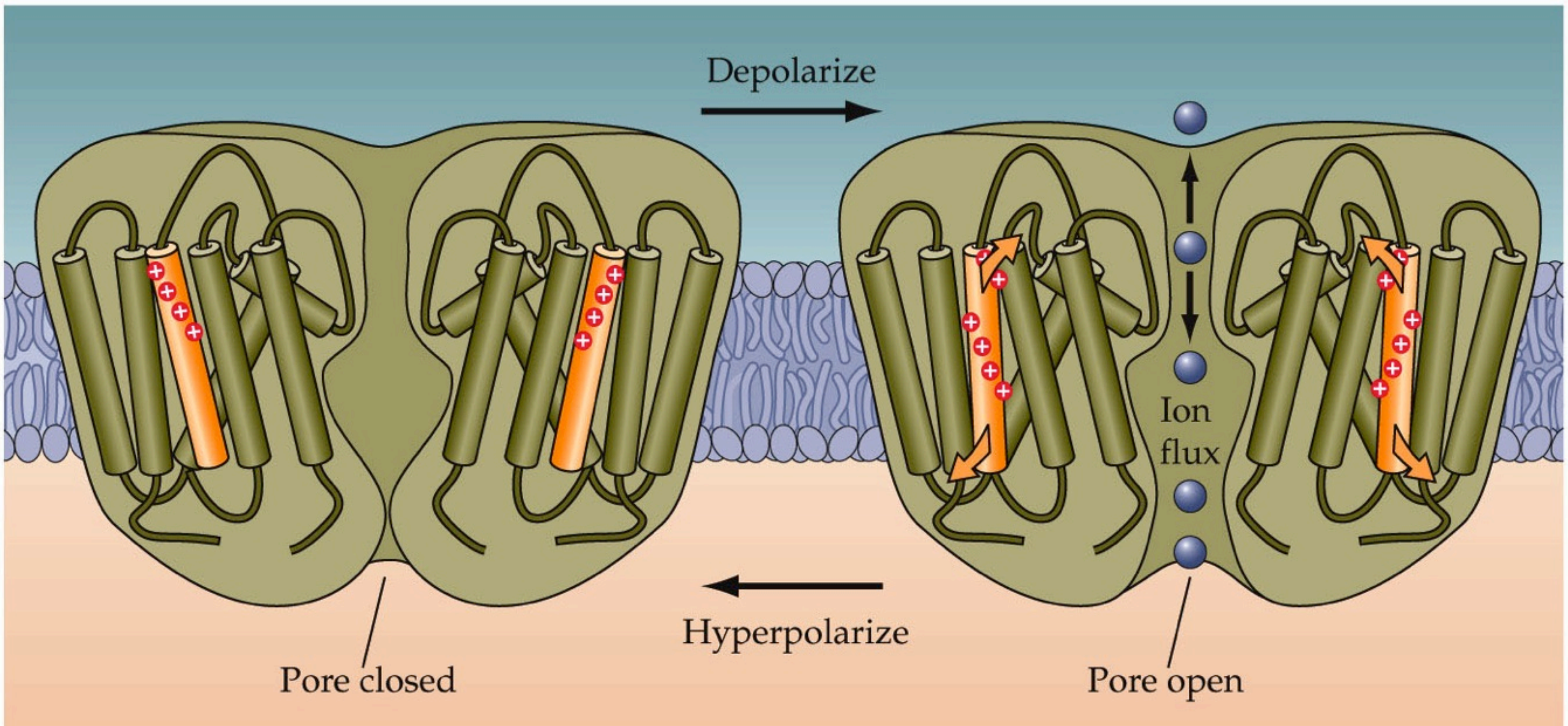
B

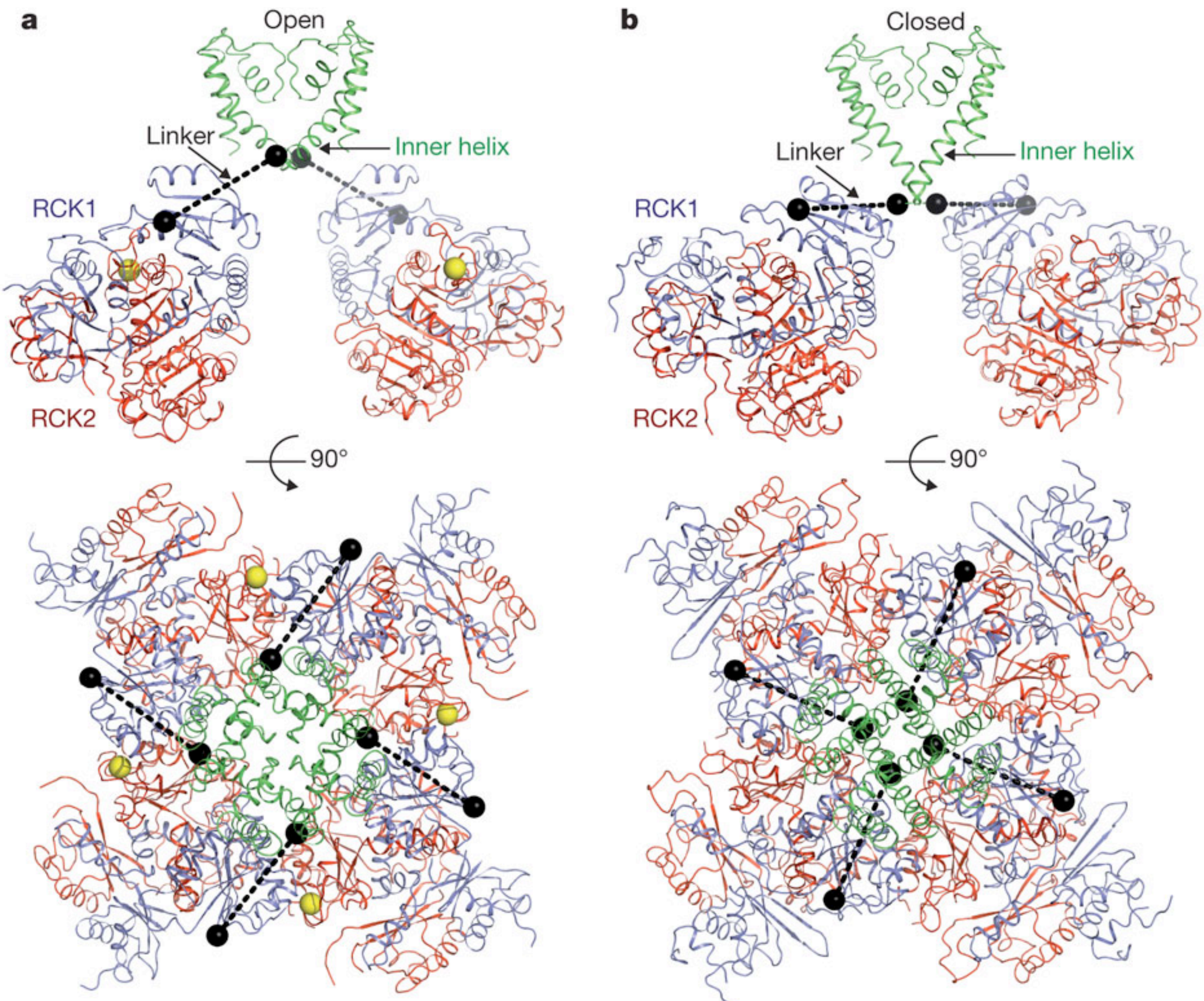


Action Potentials

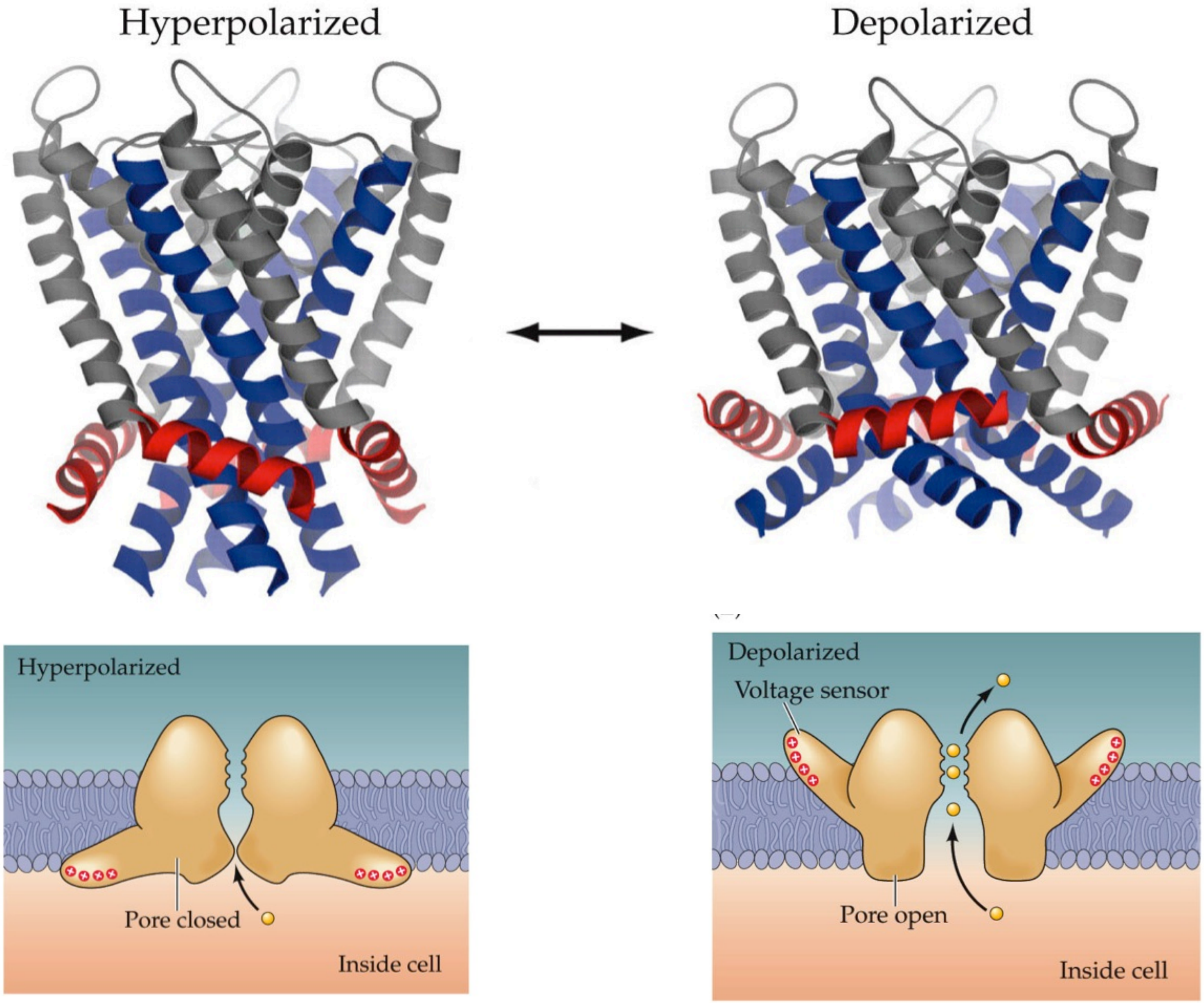


Voltage Gating of Channels



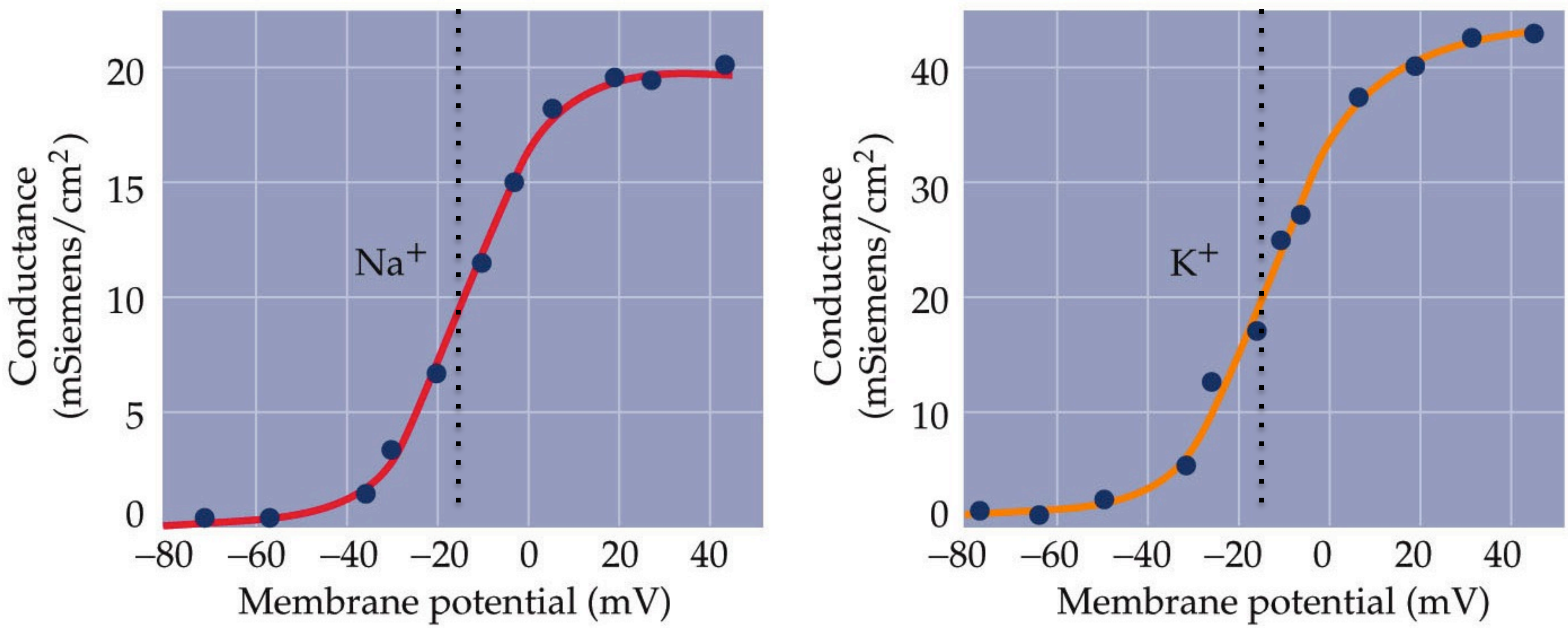


Yuan *et al.* 2012



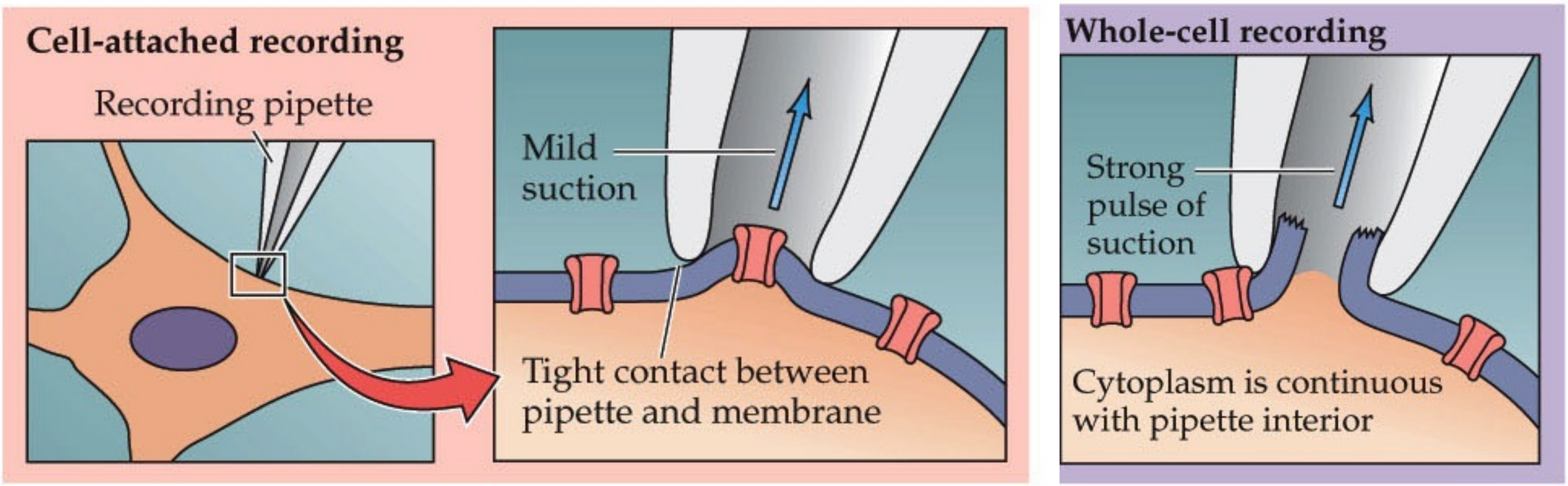
Hyperpolarized
Depolarized
Hyperpolarized
Pore closed
Inside cell
Depolarized
Voltage sensor
Pore open
Inside cell

Na^+ and K^+ Channels Have Roughly Same Voltage-dependence…

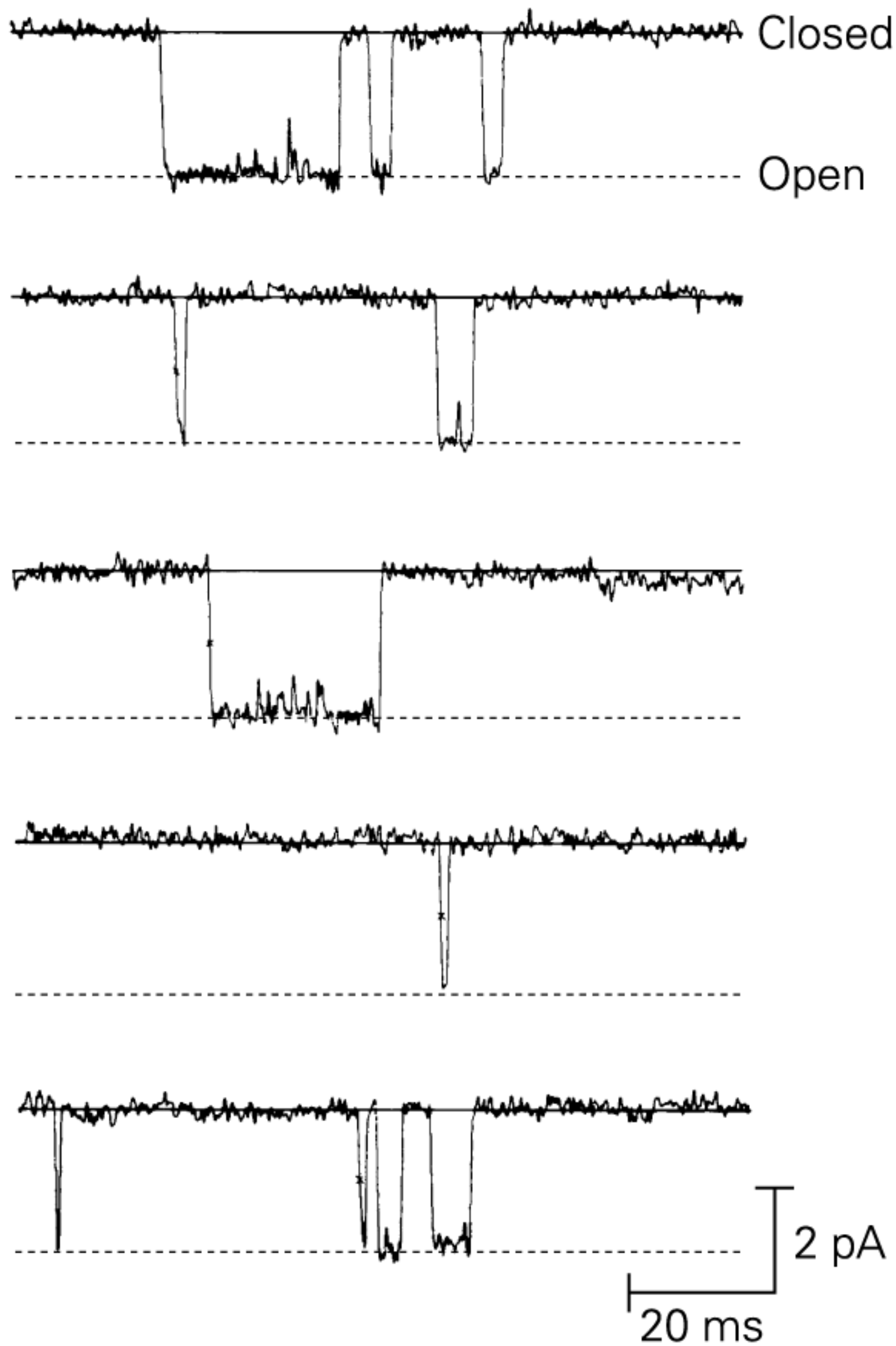


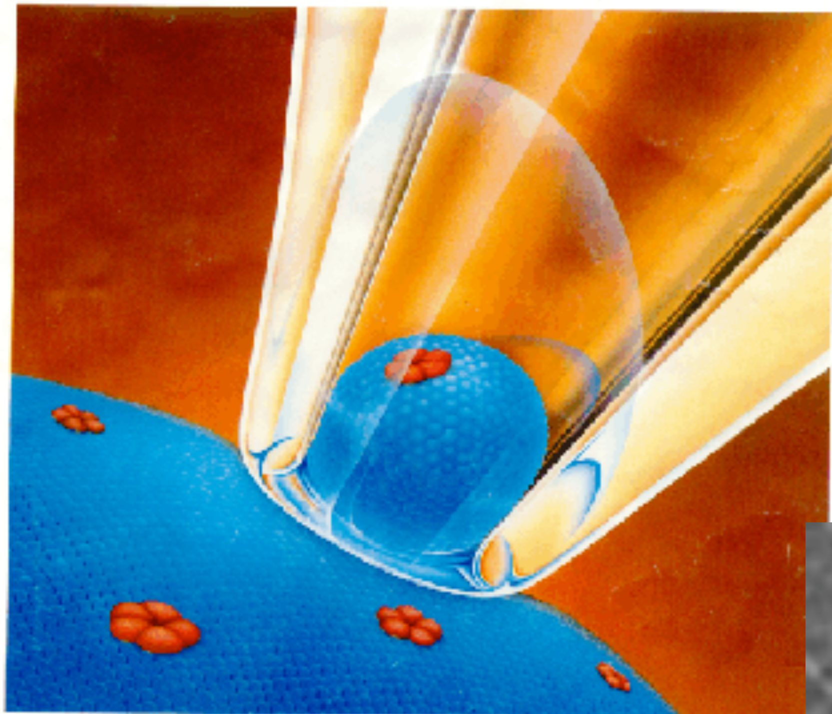
…but K^+ channels open more slowly

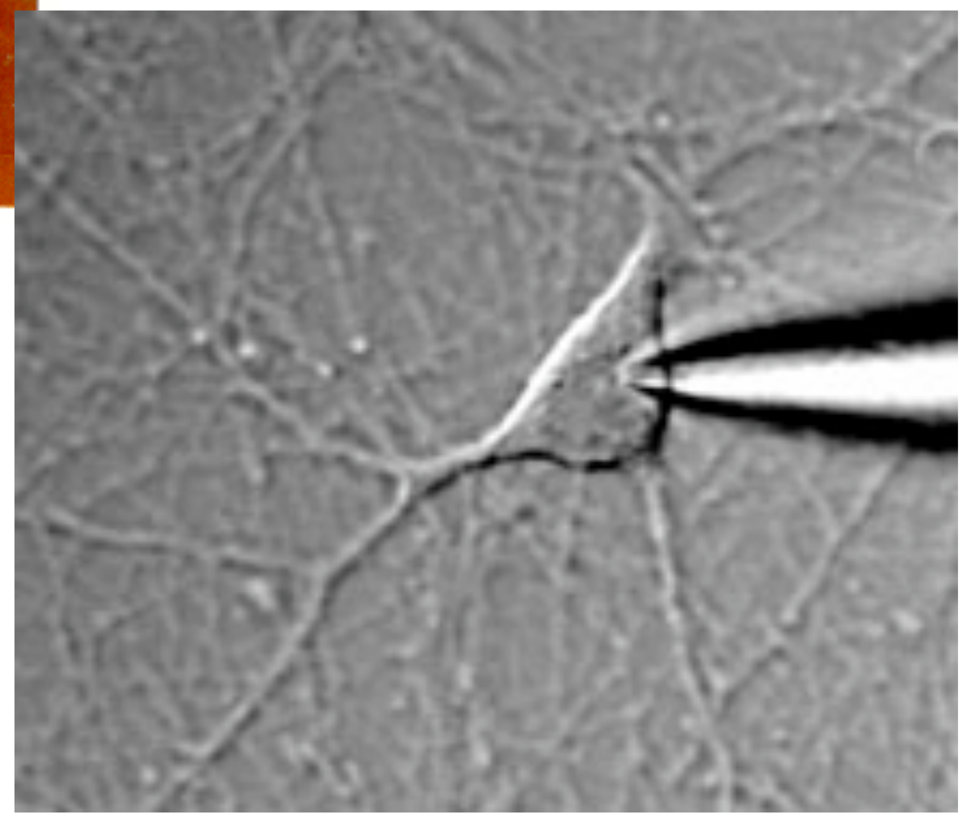
Patch Clamp Methods

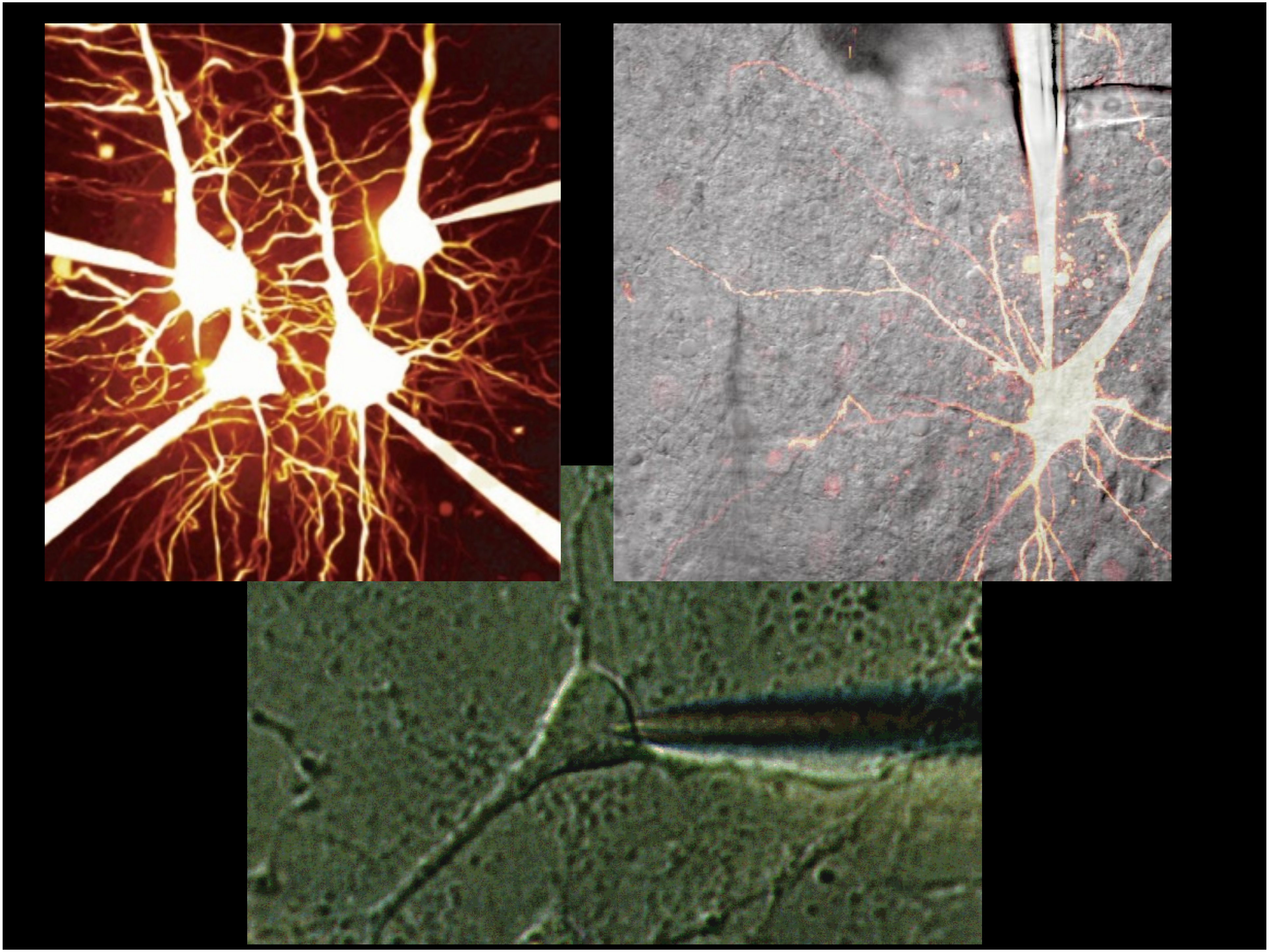


Single Ion Channel Currents

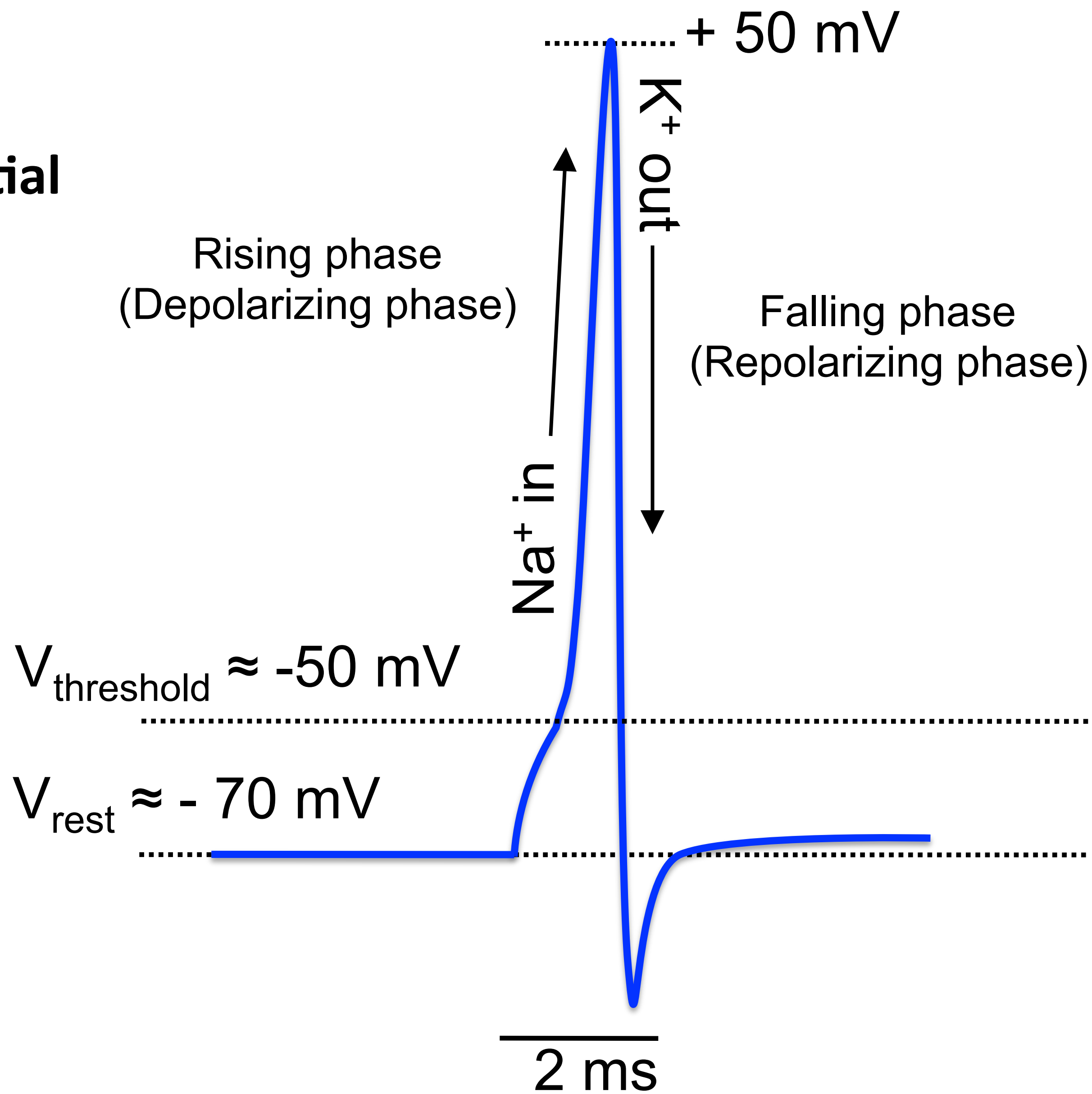




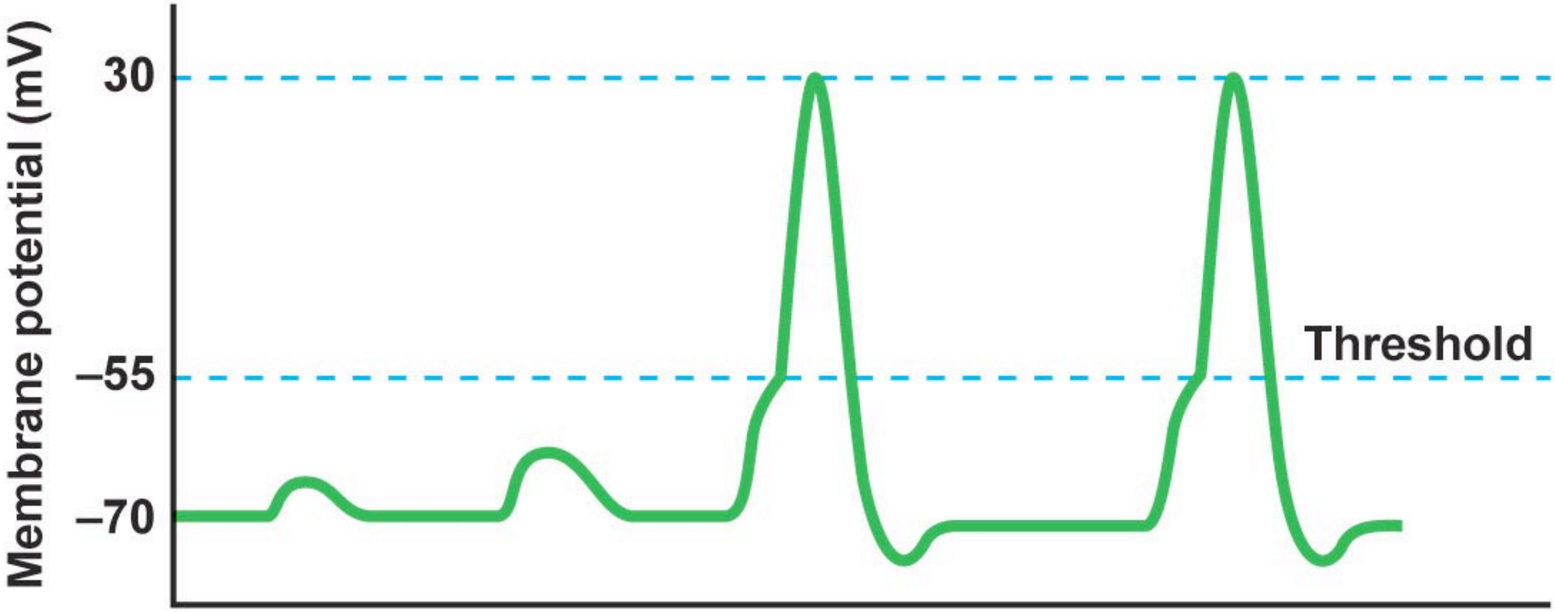




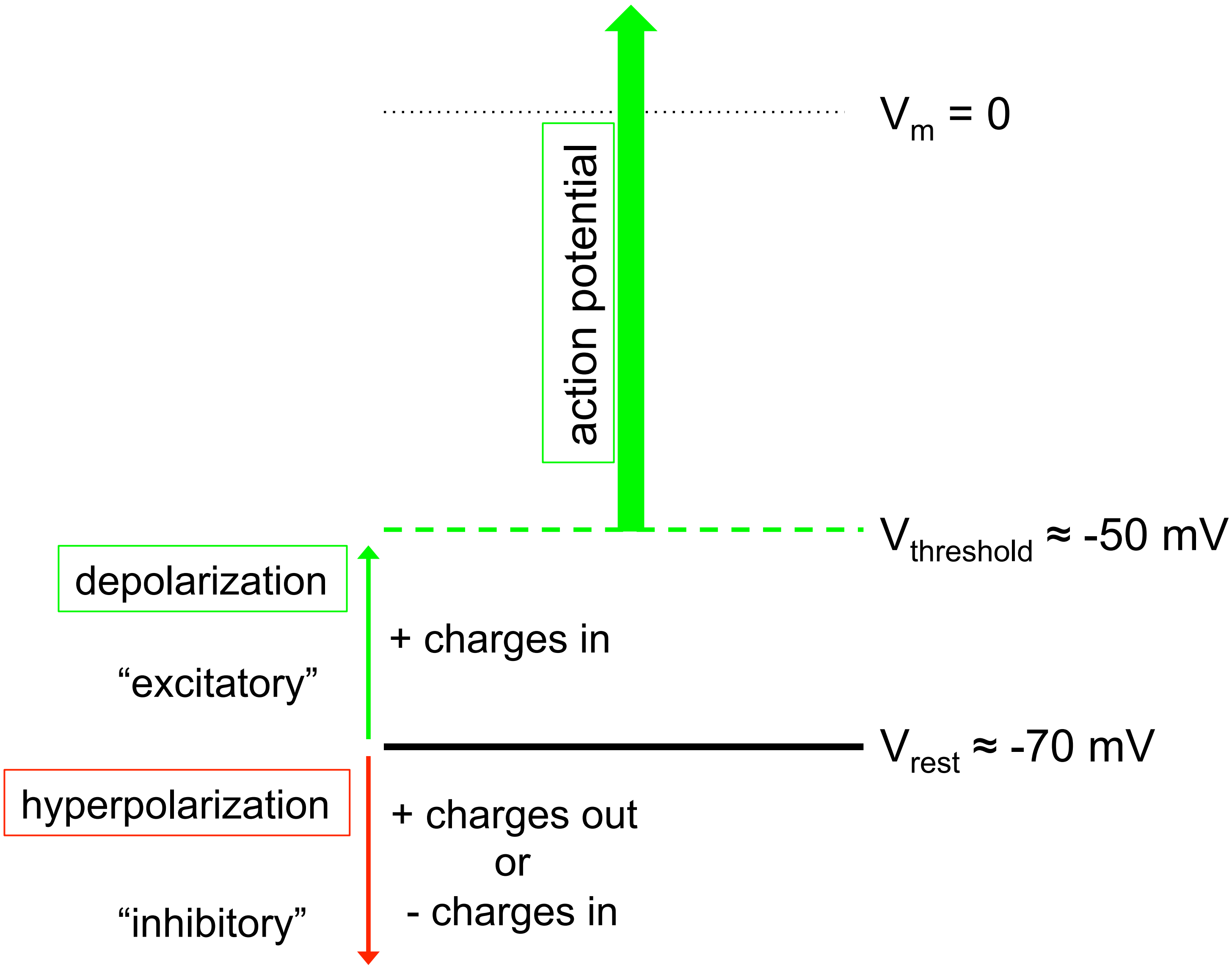
The Action Potential



Threshold

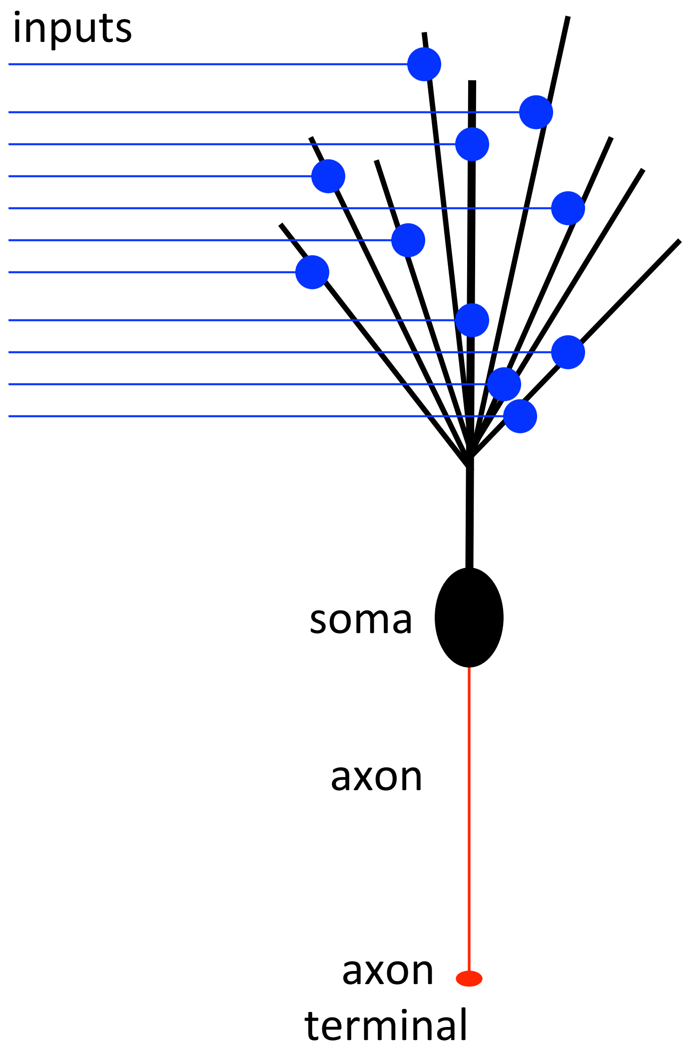


Point when Na^+ charge that enters is sufficient to change voltage enough to cause opening of more Na-channels


$V_m = 0$
action potential
$V_{threshold} \approx -50$ mV
depolarization
+ charges in
“excitatory”
$V_{rest} \approx -70$ mV
hyperpolarization
+ charges out
or
- charges in
“inhibitory”

excitatory = ***depolarizing*** = **closer to firing action potential**

inhibitory = ***hyperpolarizing*** = **further from firing action potential**

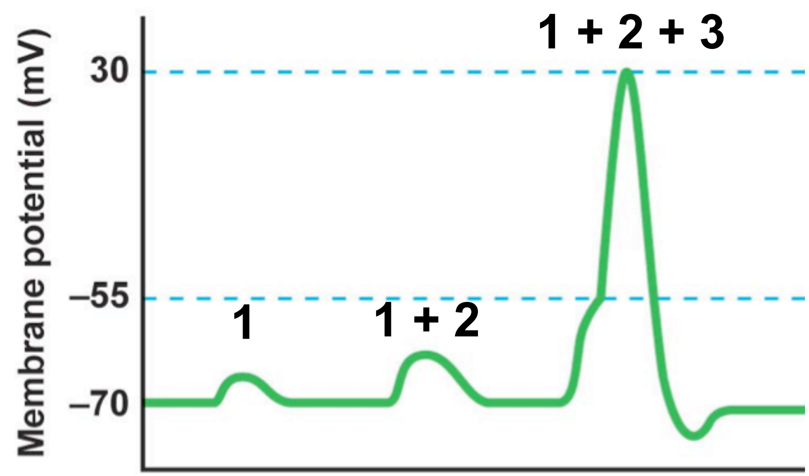


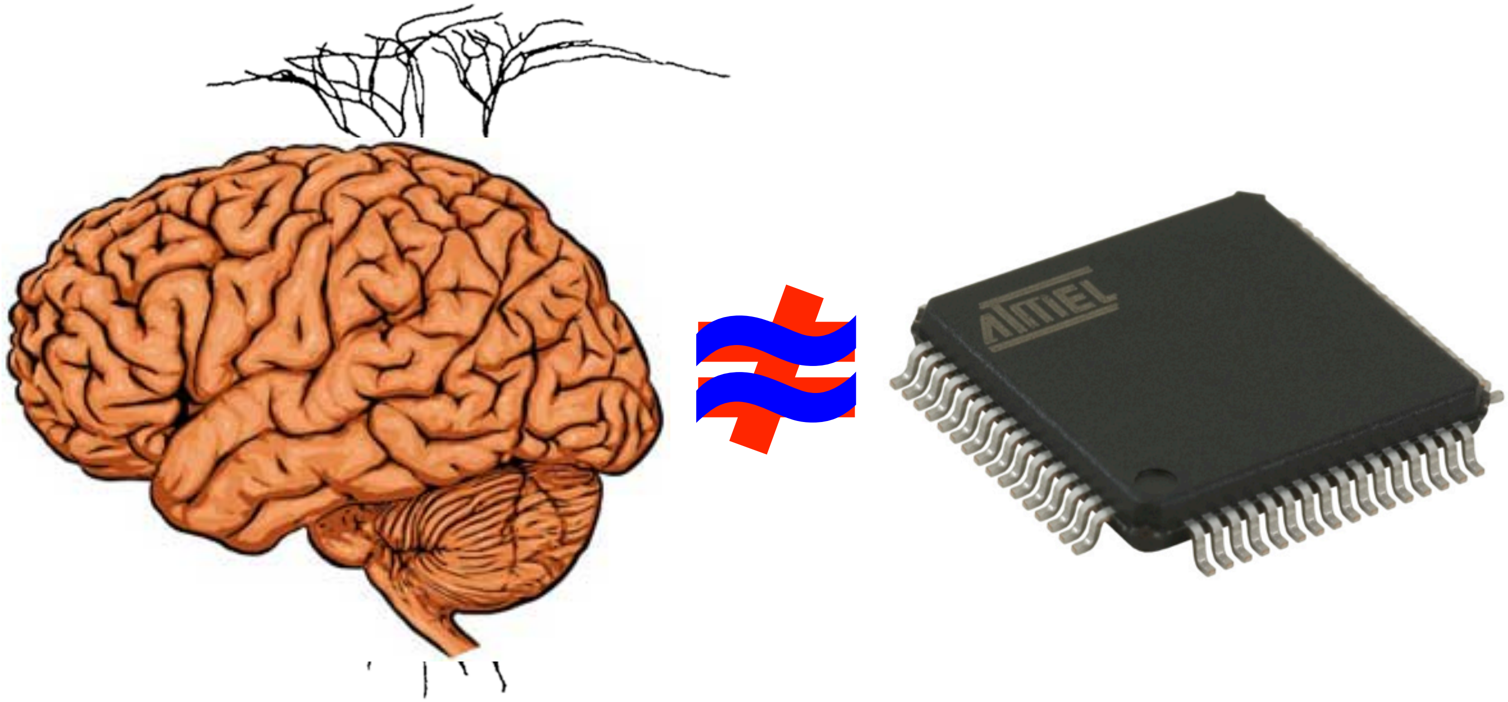
simple computation by a neuron:

$$\text{if} \quad \sum_{\text{inputs}} > V_{\text{threshold}}$$

then,

fire action potential





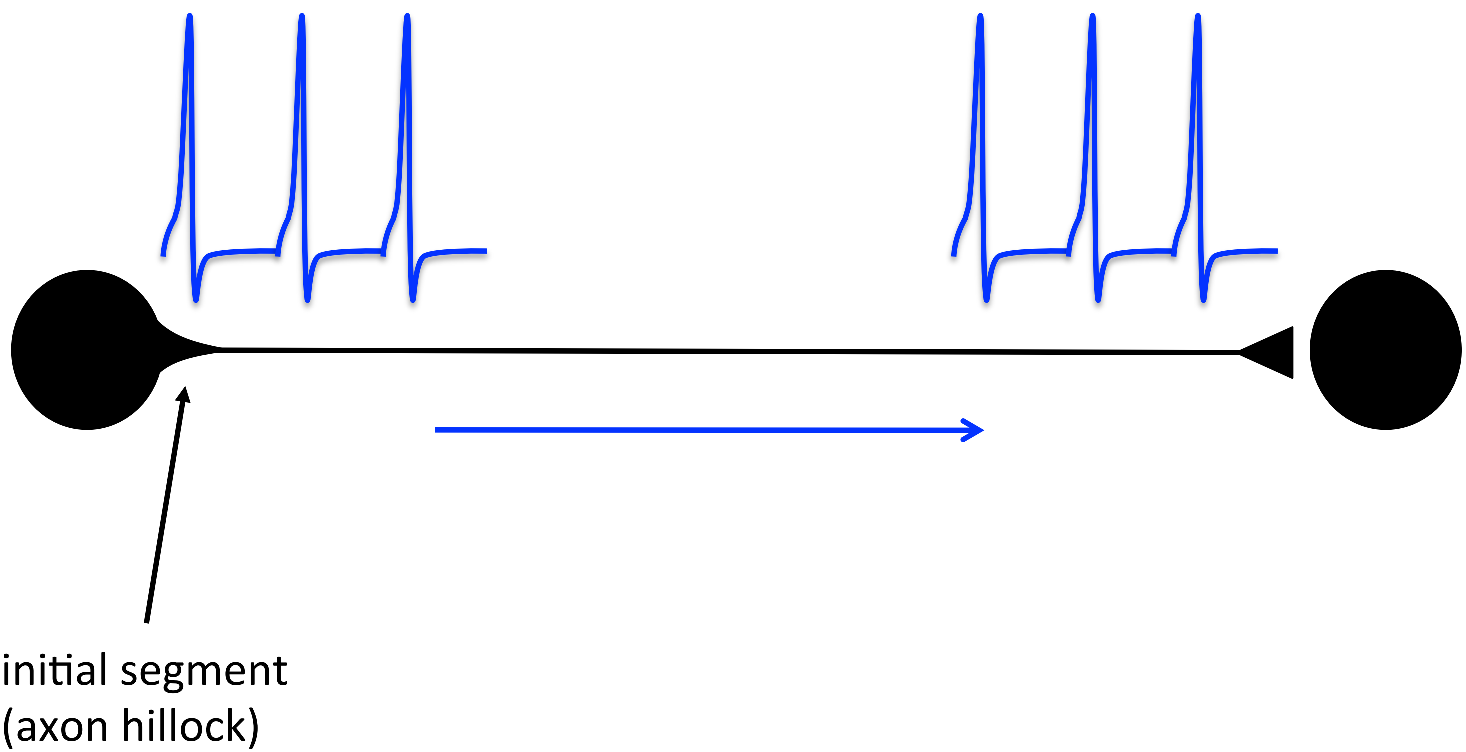
Individual neurons can perform computations

Networks of neurons can perform even more powerful computations

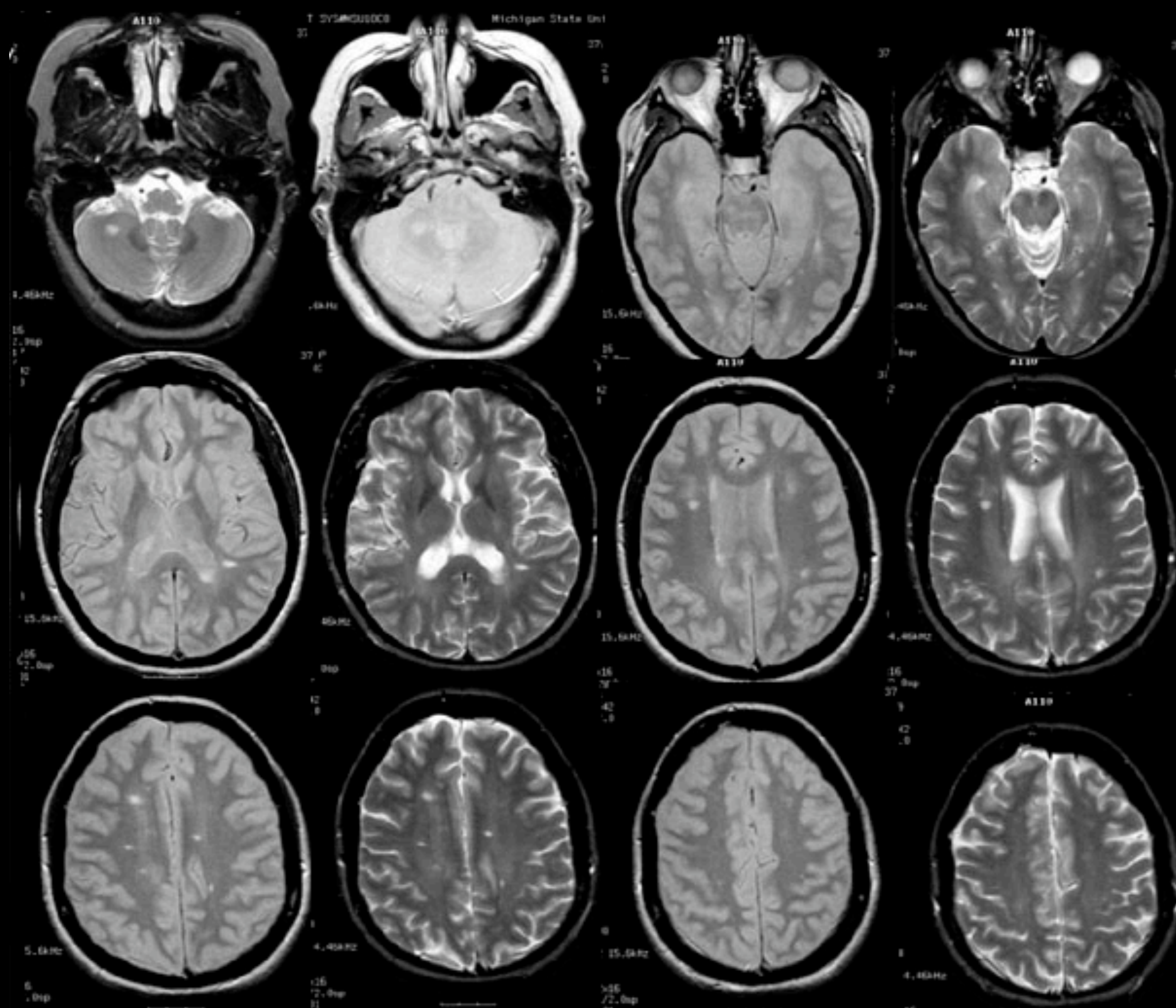
Remember: 10^{11} Neurons
10^{3} Synapses/Neuron

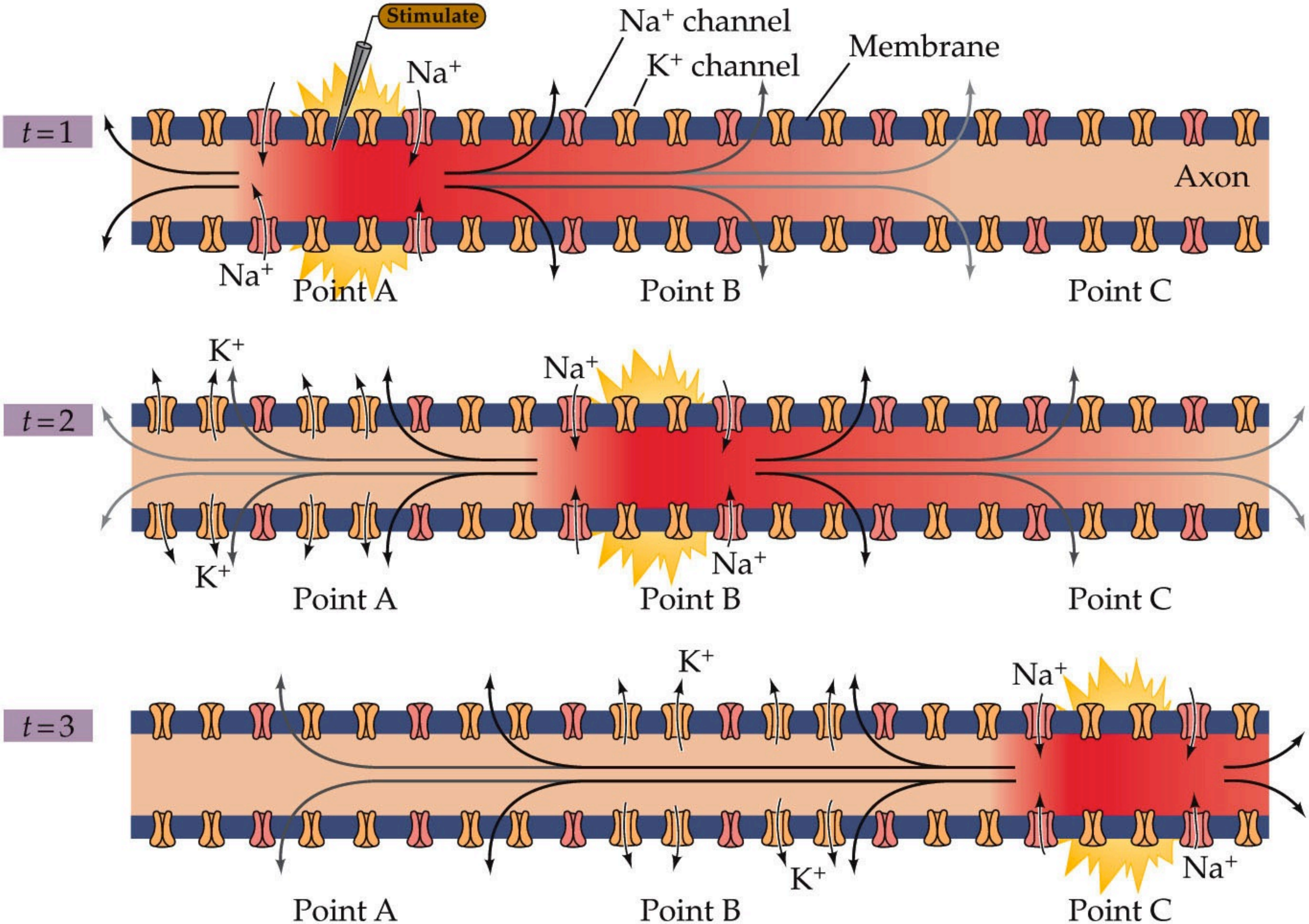
Action potentials:

- "all-or-none" (always the same size)
- rapid (spike and return to baseline in < 2ms)
- start in initial segment
- propagate to axon terminals (initiate synaptic signaling!)

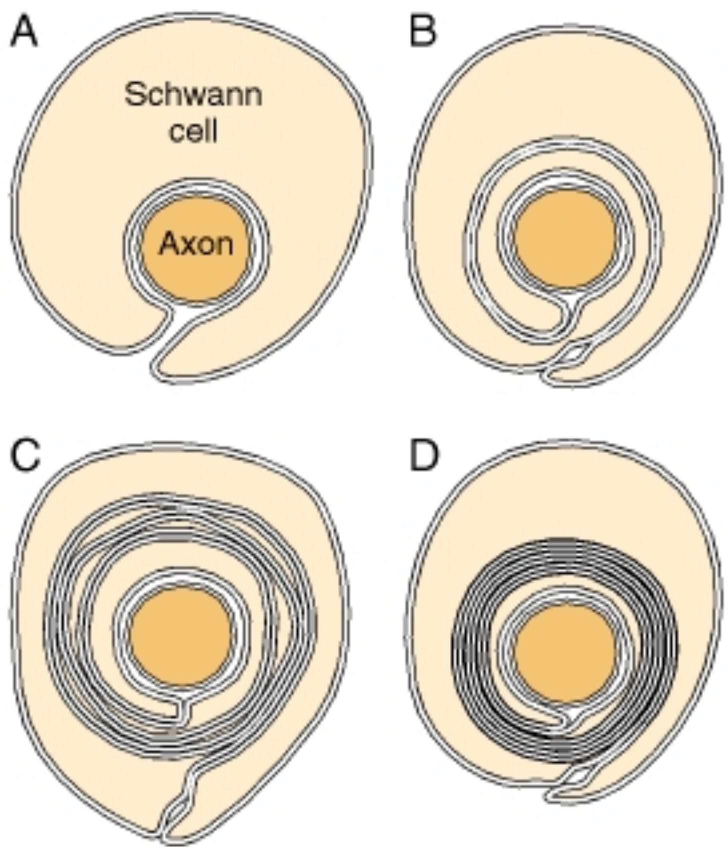


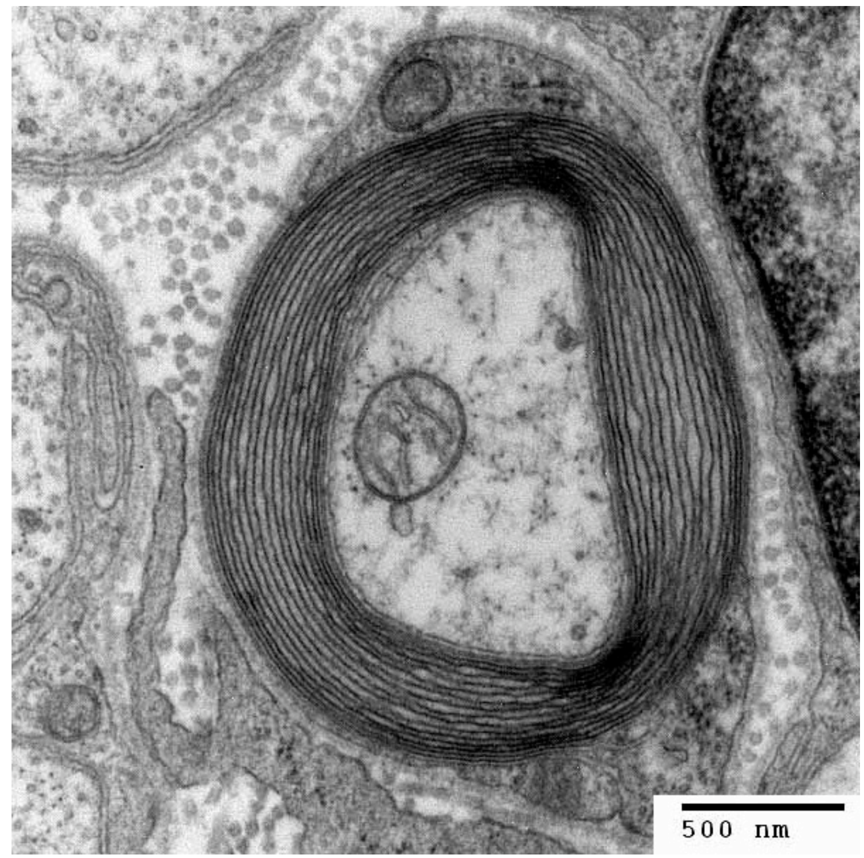
Action Potential Propagation and Myelination




Stimulate
Na+ channel
K+ channel
Membrane
Na+
Axon
t = 1
t = 2
t = 3
K+
Point A
Point B
Point C

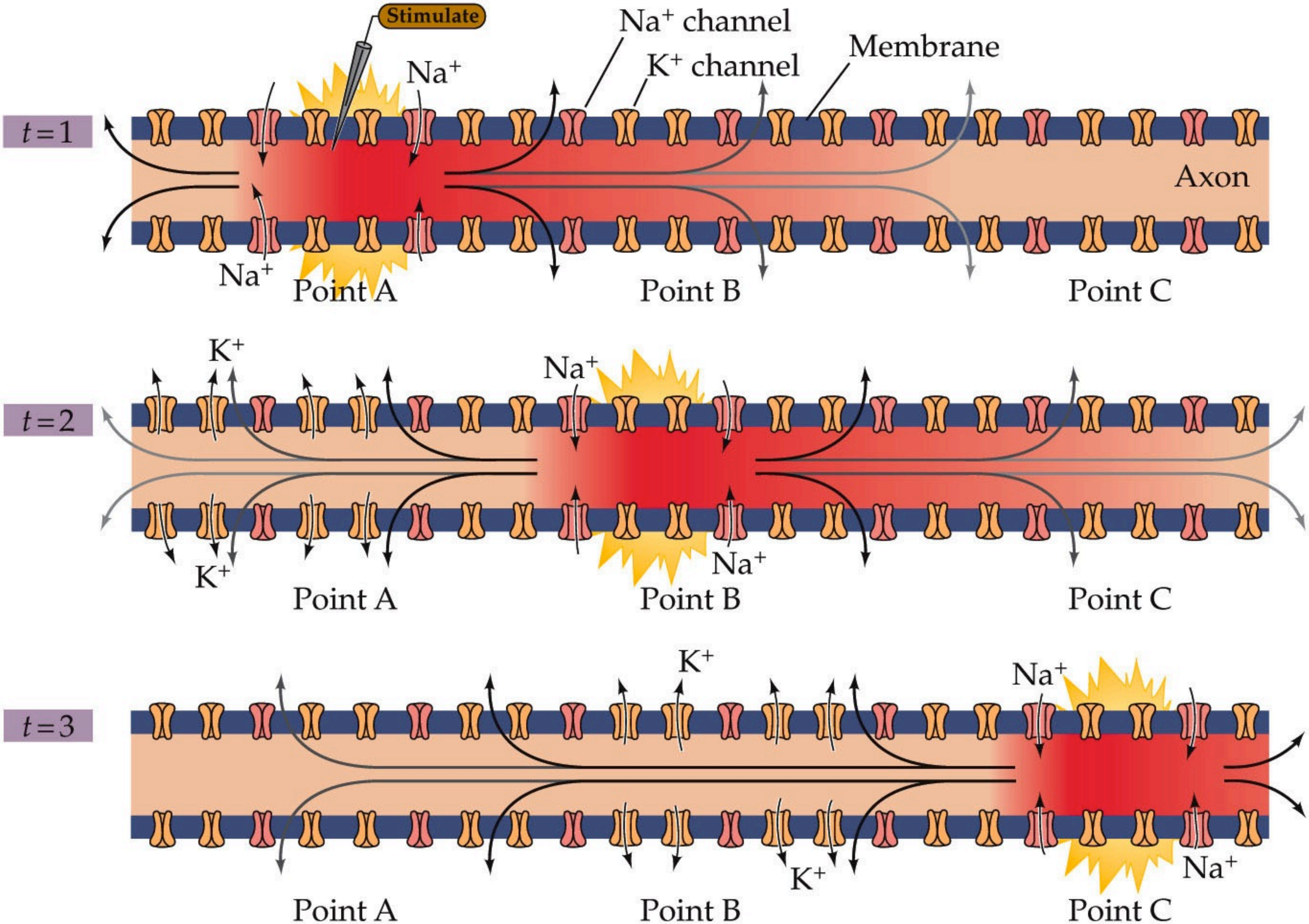
Myelination

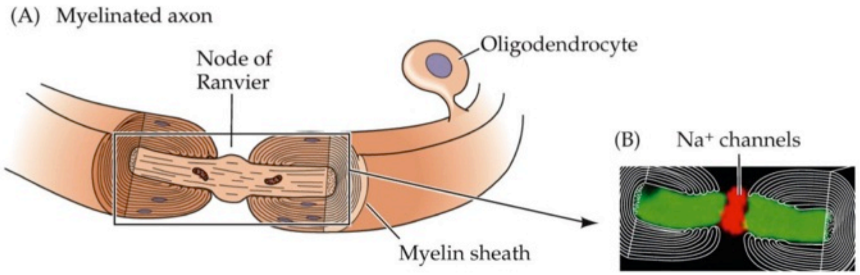


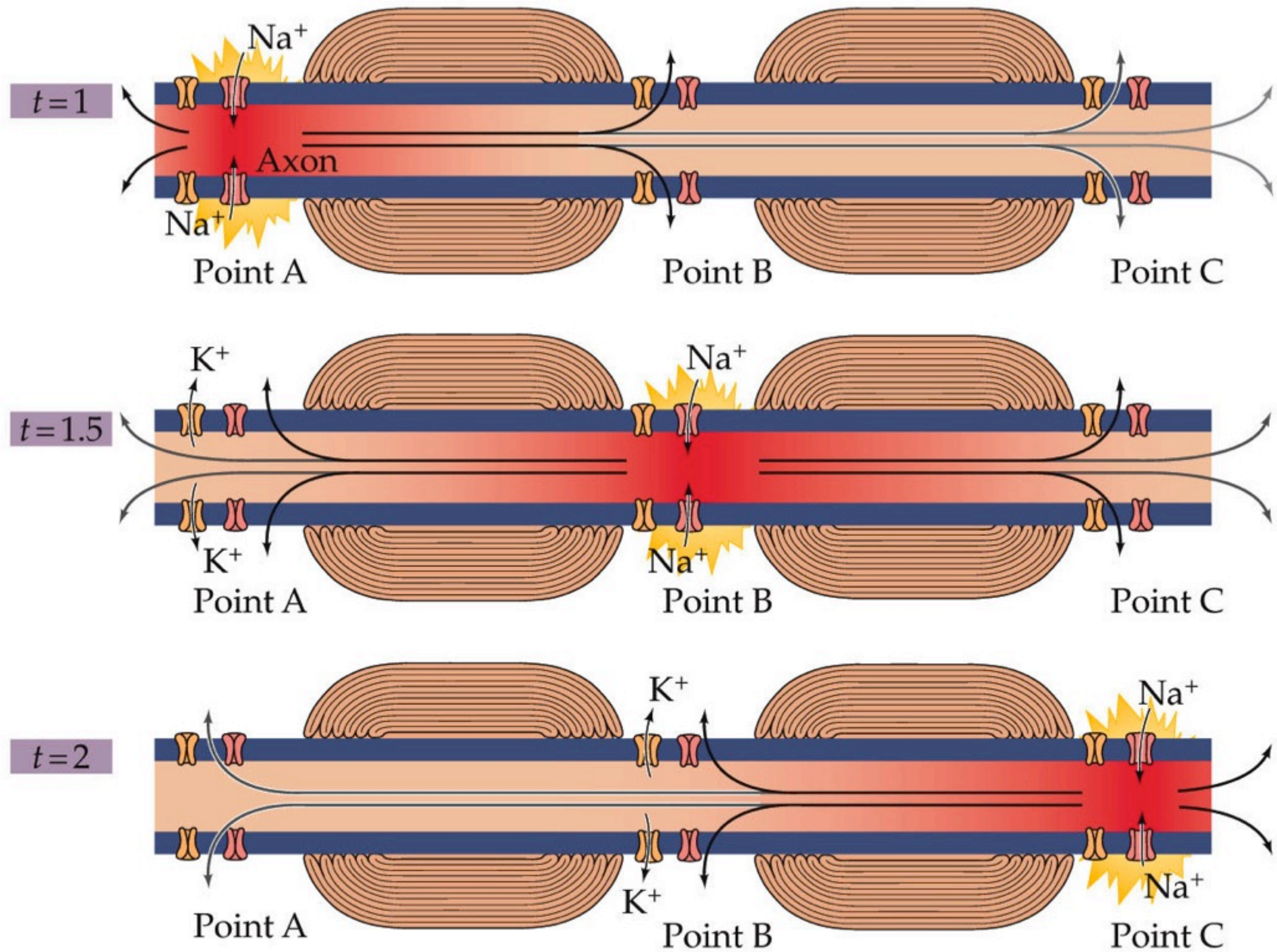


White matter = myelin (axon tracts)

Gray matter = neurons and dendrites

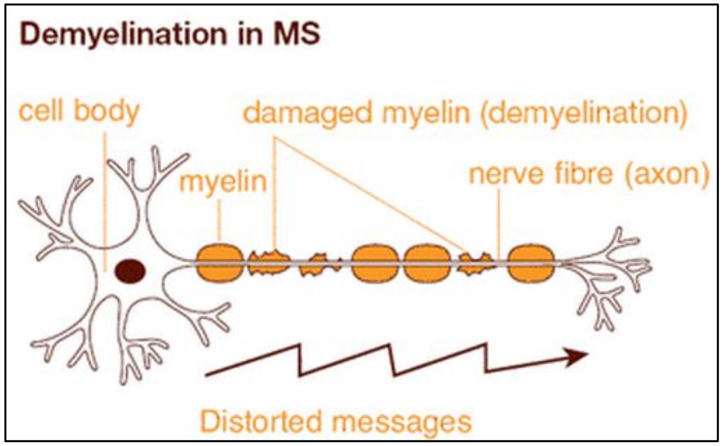

Stimulate
Na+ channel
K+ channel
Membrane
Na+
Axon
Na+
t = 1
Point A
Point B
Point C
t = 2
K+
Na+
K+
Na+
Point A
Point B
Point C
t = 3
K+
Na+
K+
Na+
Point A
Point B
Point C


(A) Myelinated axon
Node of Ranvier
Oligodendrocyte
Myelin sheath
(B) Na^+ channels


$t = 1$
Na^+
Axon
Na^+
Point A
Point B
Point C
$t = 1.5$
K^+
Na^+
K^+
Na^+
Point A
Point B
Point C
$t = 2$
K^+
Na^+
K^+
Na^+
Point A
Point B
Point C

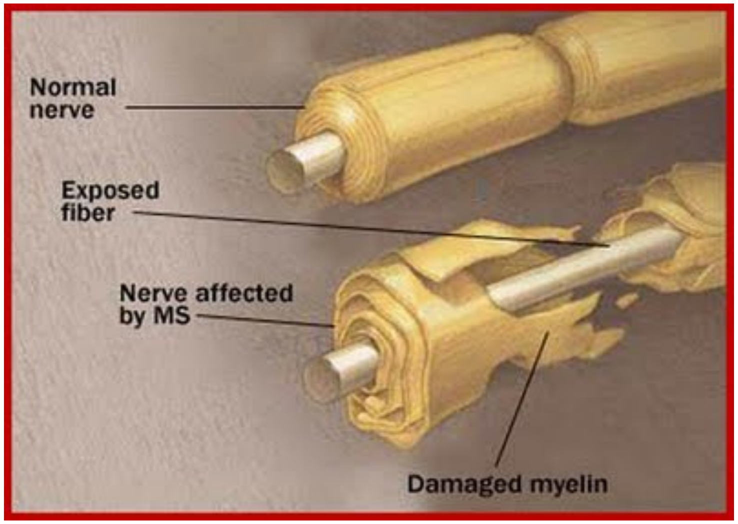
Demyelinating diseases of the CNS:

multiple sclerosis
Vitamin B12 deficiency
Tabes Dorsalis
transverse myelitis
Devic's disease
progressive multifocal leukoencephalopathy
Optic neuritis
Leukodystrophies



Demyelinating diseases of the PNS

Guillain-Barré syndrome
anti-MAG peripheral neuropathy
Charcot-Marie-Tooth Disease
Copper deficiency



Next week:

Synapses and chemical neurotransmission (neurotransmitters!)