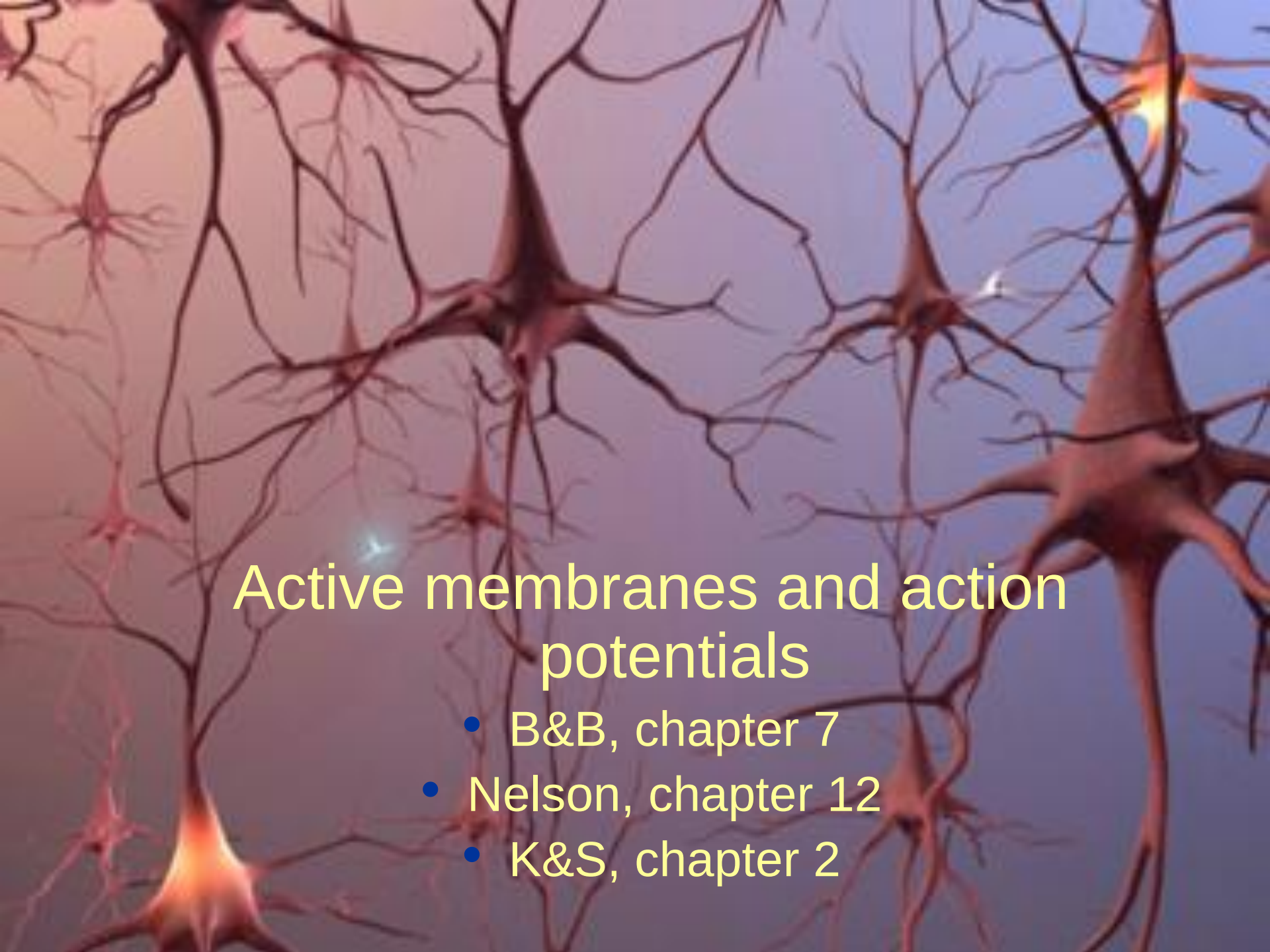
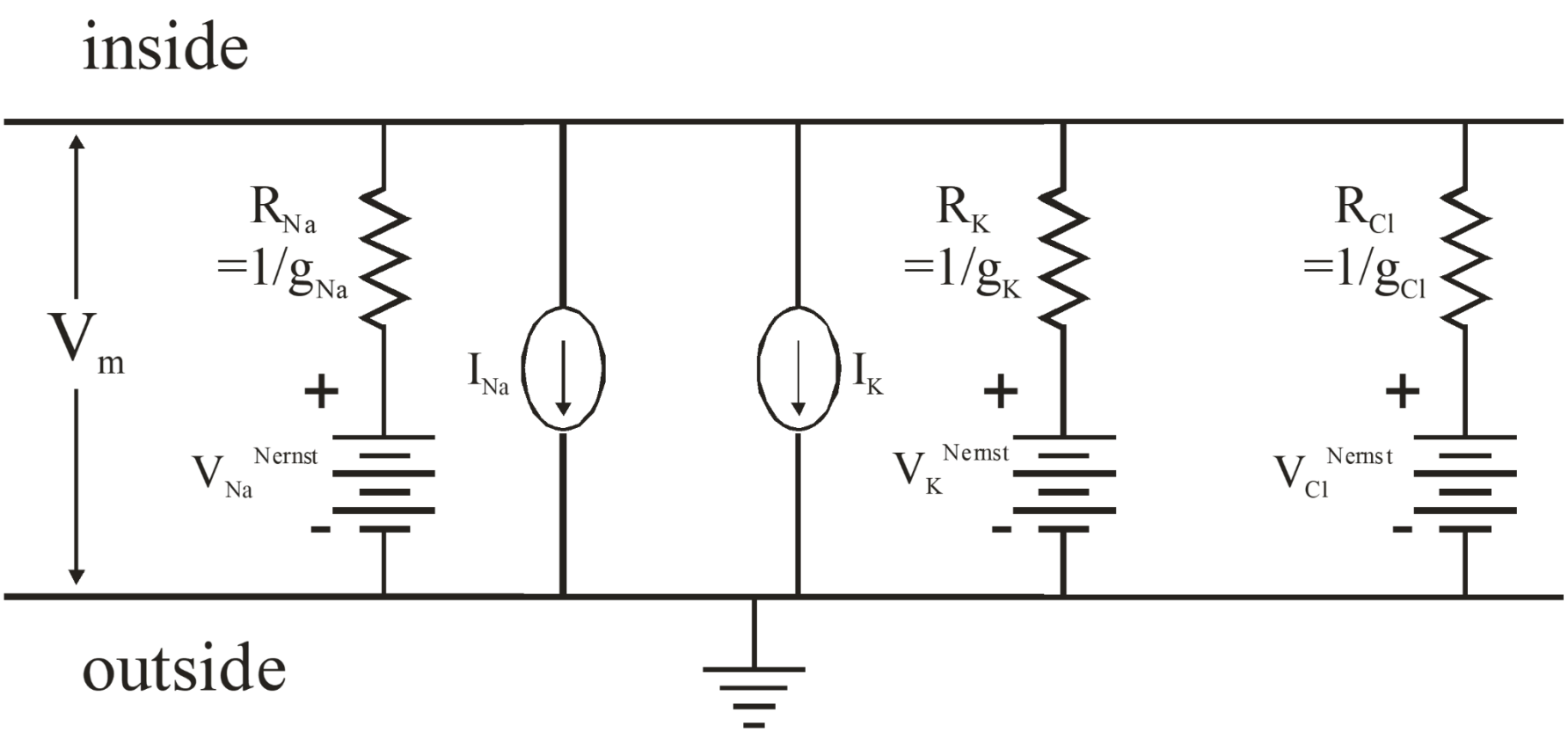


Active membranes and action potentials

- B&B, chapter 7
- Nelson, chapter 12
- K&S, chapter 2



$$V_i^{Nernst} = -\frac{k_B T}{n_i q} \ln\left(\frac{C_{i,int}}{C_{i,ext}}\right)$$

$$j_{q,i}^{ohmic} = n_i q j_i^{ohmic} = \left(\Delta V - V_i^{Nernst}\right) g_i$$

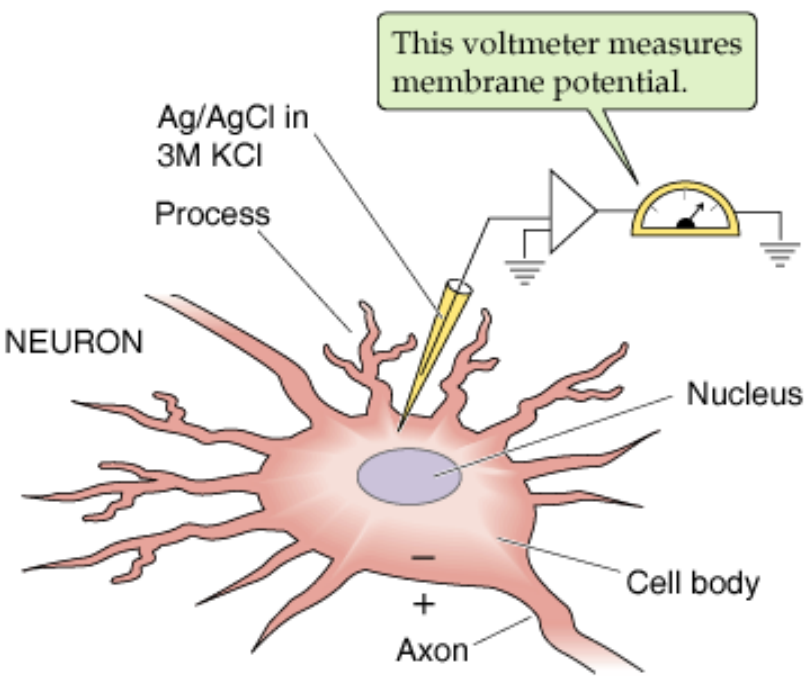
q = charge of electron, 1.6E-19 C

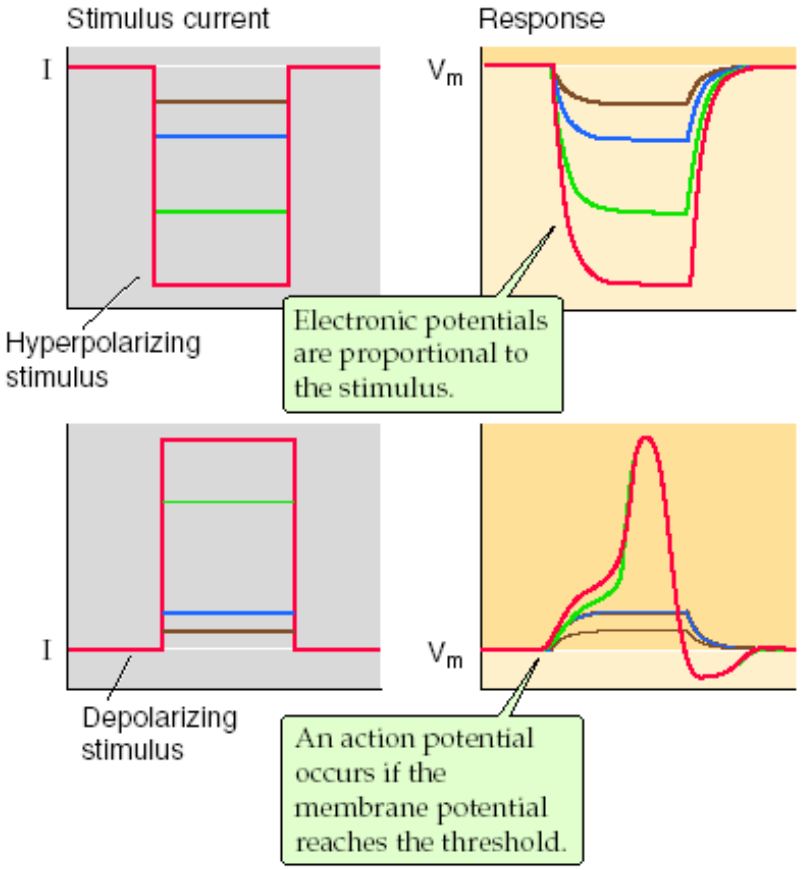
n_i= number of charges on ion

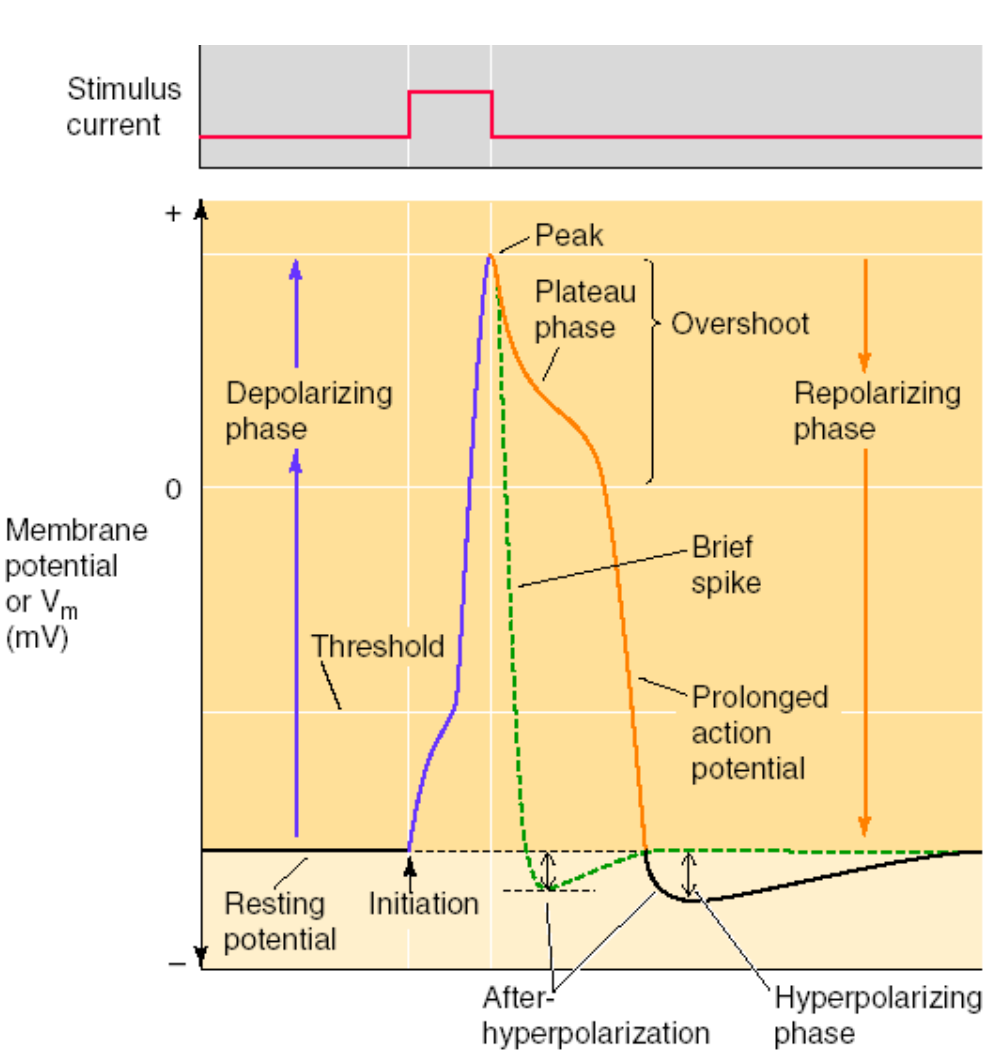
$j_{q,i}$ = current across membrane

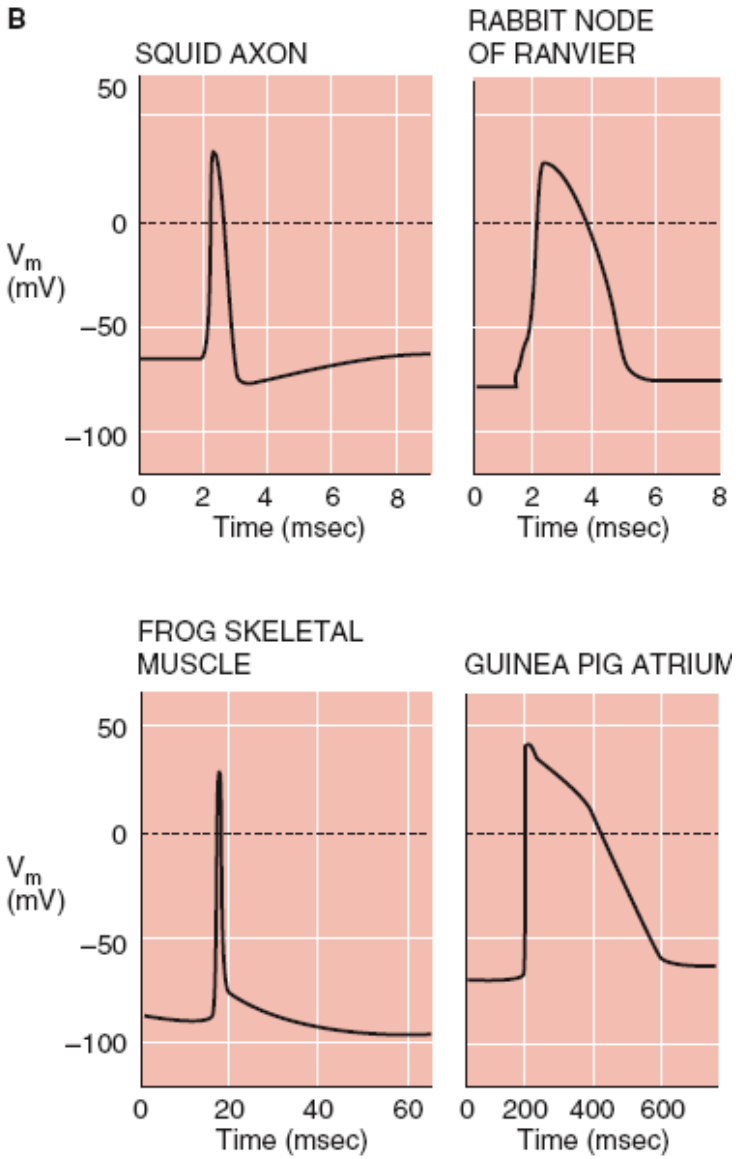
j_i = ion flow across membrane

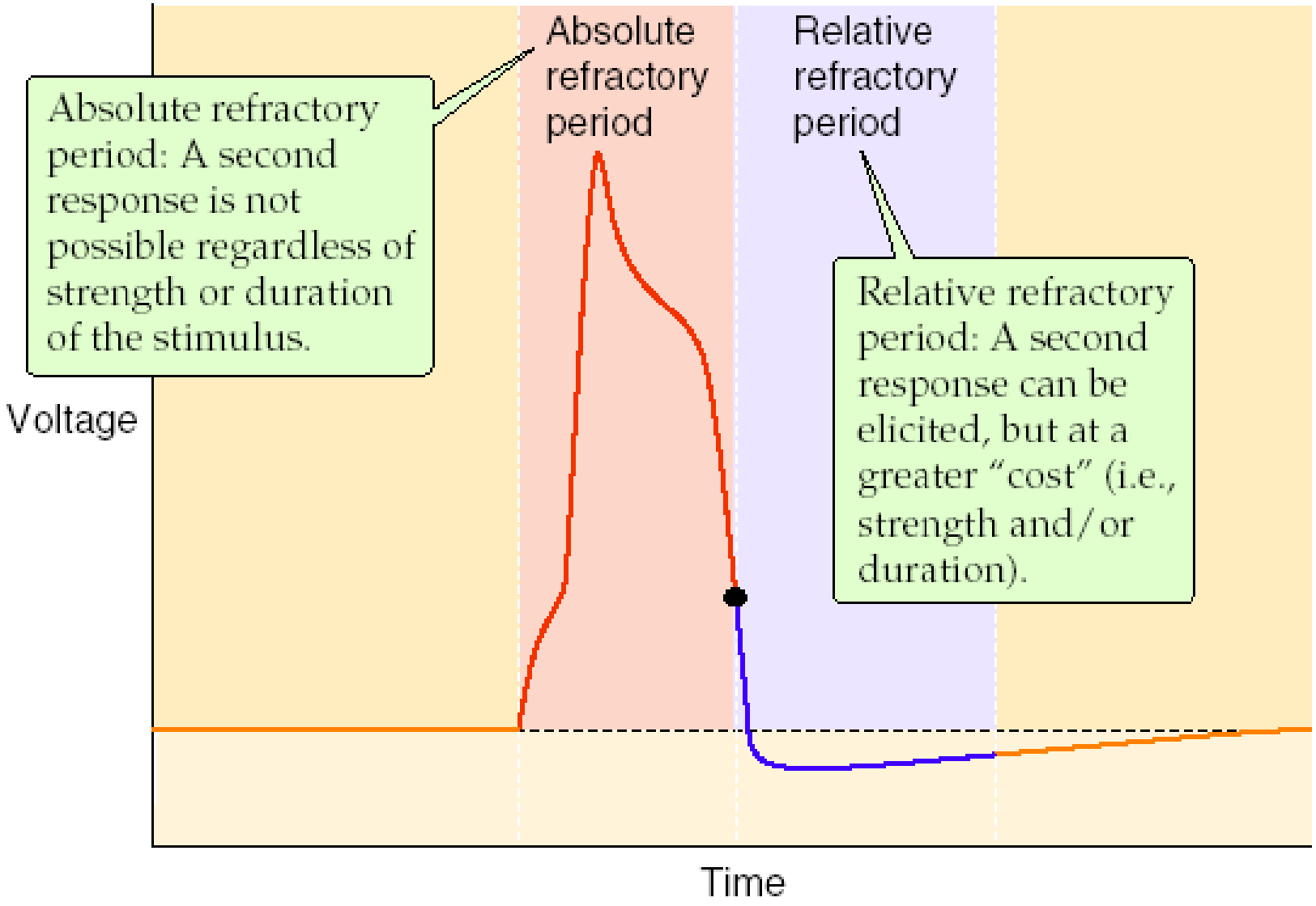
g_i = conductance for ion


This voltmeter measures membrane potential.
Ag/AgCl in 3M KCl
Process
NEURON
Nucleus
Cell body
Axon
−
+


Stimulus current
Response
I
V_m
Hyperpolarizing stimulus
Electronic potentials are proportional to the stimulus.
I
V_m
Depolarizing stimulus
An action potential occurs if the membrane potential reaches the threshold.


Stimulus current
+
0
–
Membrane potential or V_m (mV)
Peak
Plateau phase
Overshoot
Depolarizing phase
Repolarizing phase
Brief spike
Threshold
Prolonged action potential
Resting potential
Initiation
After-hyperpolarization
Hyperpolarizing phase

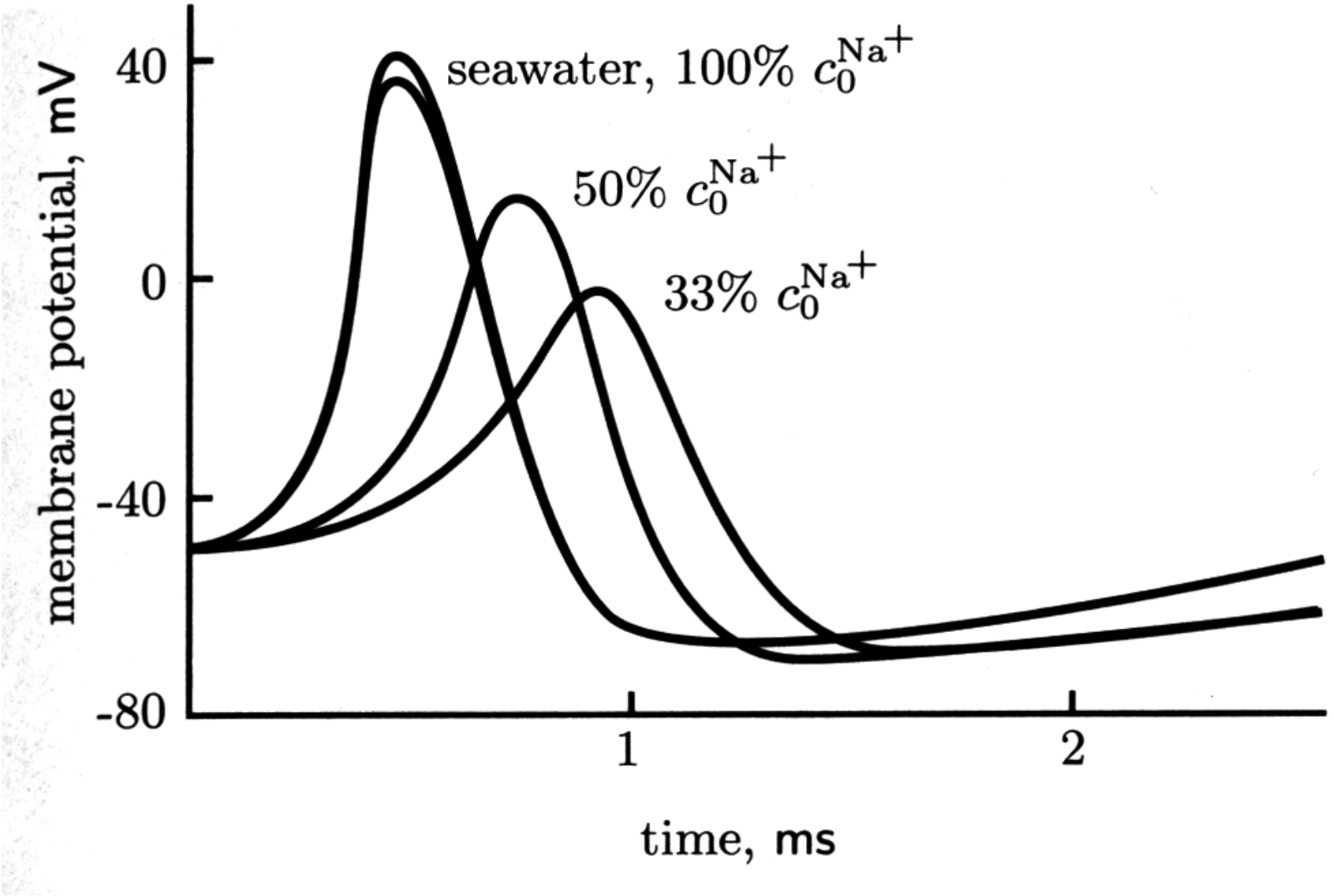

B
SQUID AXON
RABBIT NODE OF RANVIER
V_m (mV)
50
0
–50
–100
0 2 4 6 8
Time (msec)
FROG SKELETAL MUSCLE
GUINEA PIG ATRIUM
0 20 40 60
0 200 400 600
Time (msec)


Absolute refractory period
Relative refractory period
Absolute refractory period: A second response is not possible regardless of strength or duration of the stimulus.
Relative refractory period: A second response can be elicited, but at a greater "cost" (i.e., strength and/or duration).
Voltage
Time

Ion components of the action potential

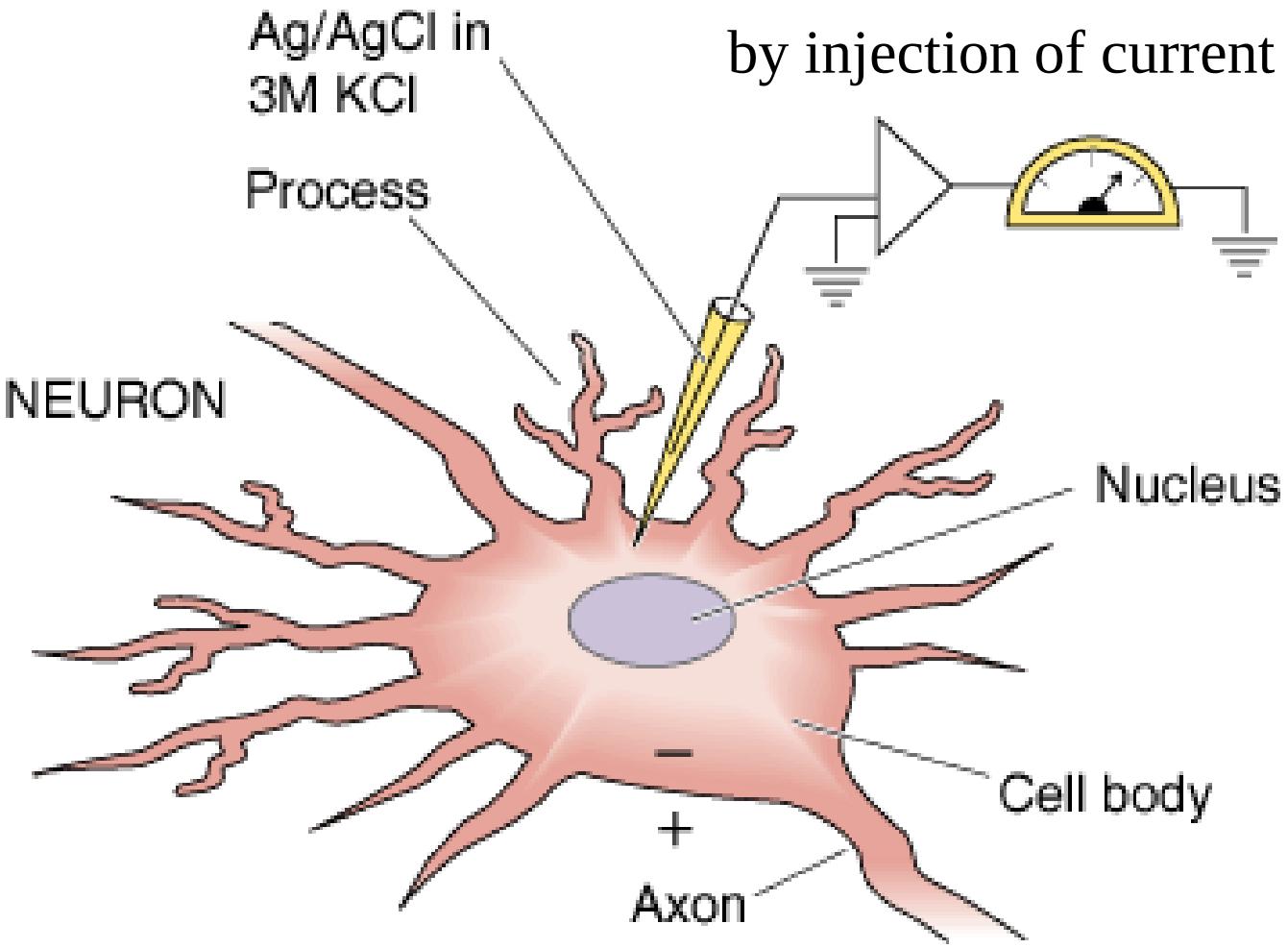
Ion	concentration (mM)		
	interstitial space	cell ("typical")	V^{nernst} (mV)
Na^+, mammalian cell	145	15	+59 (37C)
K^+, mammalian cell	4.5	120	-71 (37C)
Na^+, squid giant axon	440	50	+54 (15C)
K^+, squid giant axon	20	400	-75 (15C)

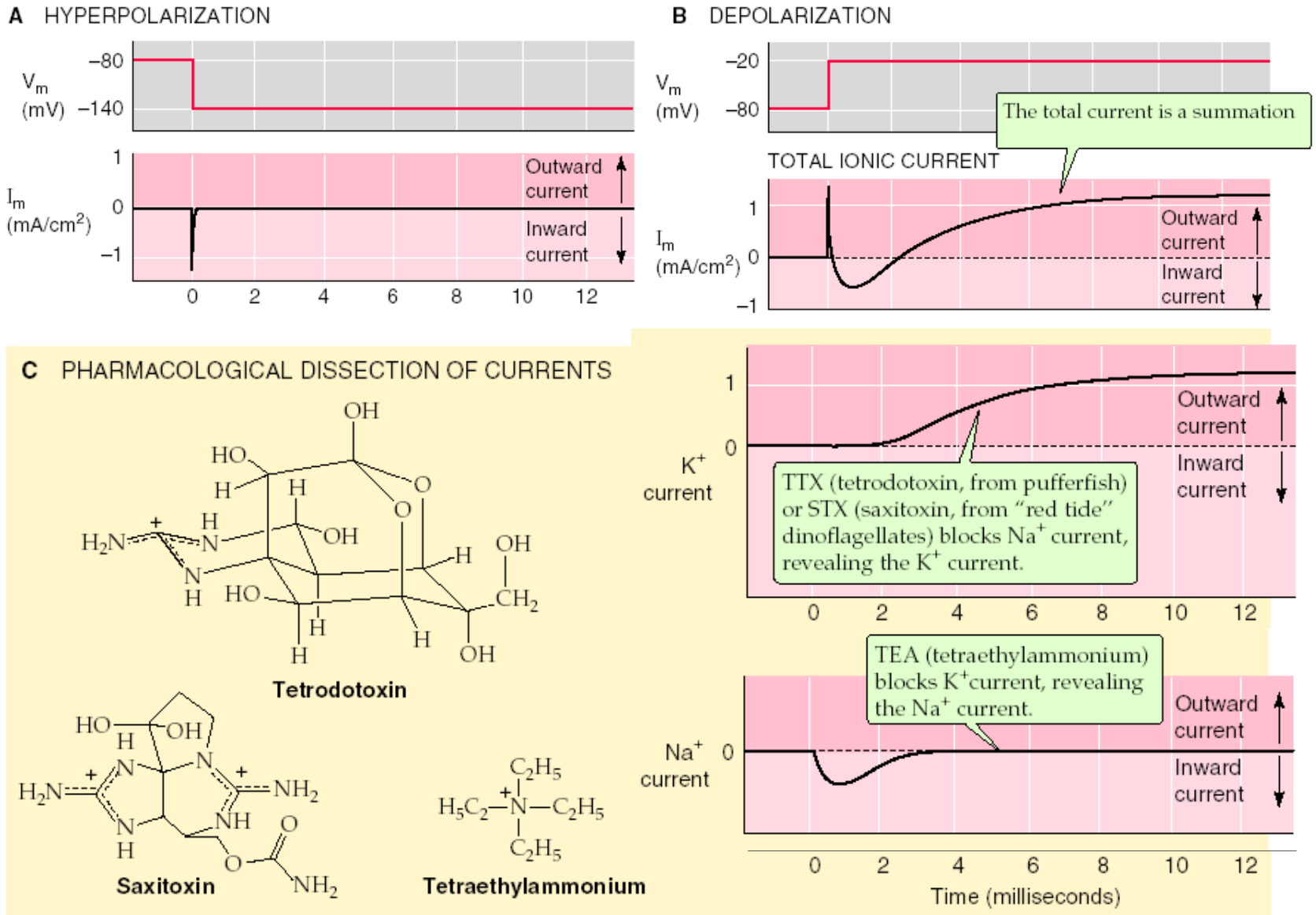
- Bernstein, **1902**. K^+ conductance is key to resting potential.
- late 1930's, Cole & Curtis, and demonstrated that action potentials are associated with increased membrane conduction.
- Later, Cole & Curtis, and simultaneously by Hodgin & Huxley, measured the transmembrane voltage, and found that it actually crossed zero, going to near +40mV, near that for Sodium
- 1940s, Hodgkin & Katz show that altering the external Na^+ concentration (bringing it down from seawater, but maintaining electroneutrality), altering action potential shape (graph on next slide).

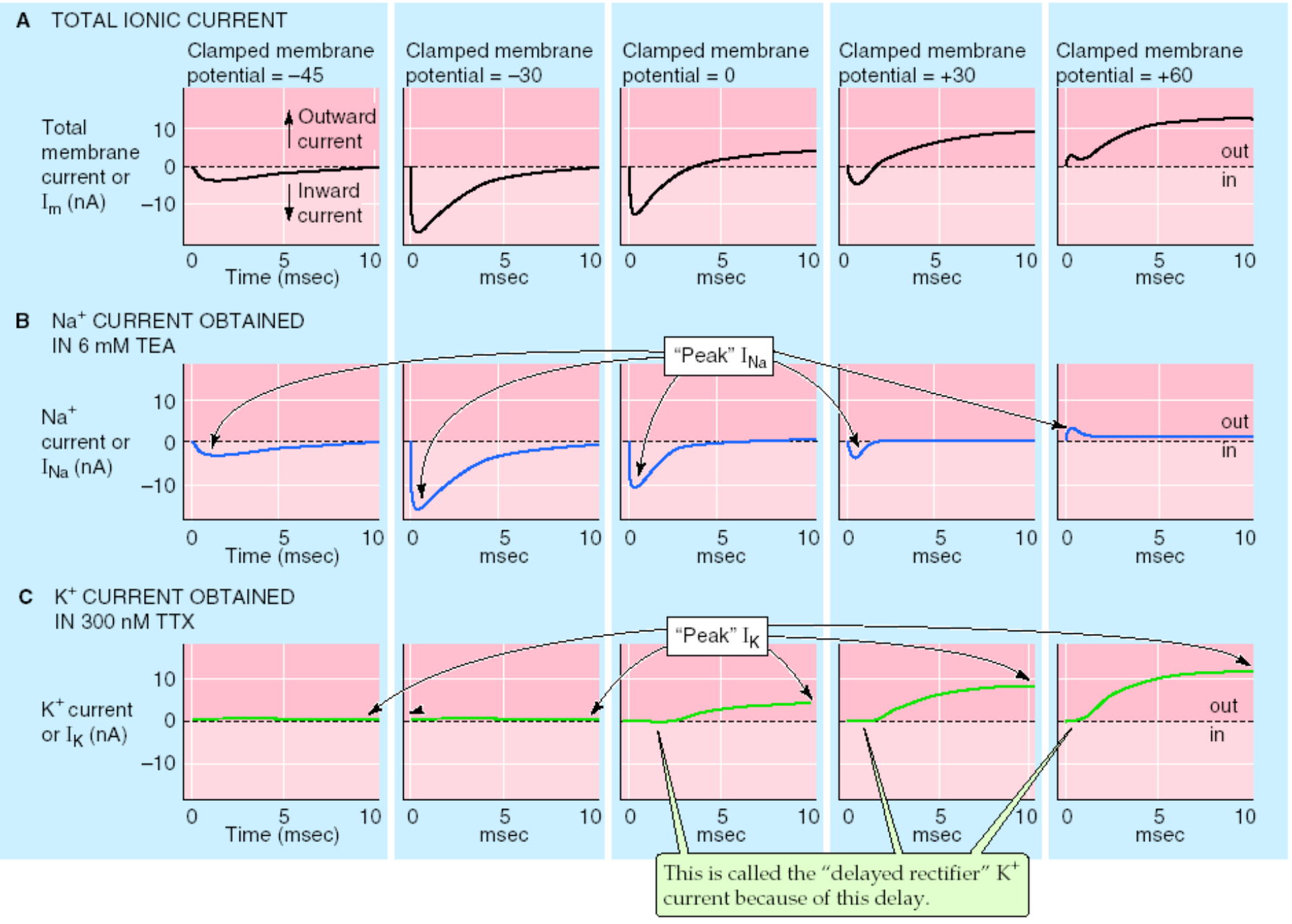

40
0
-40
-80
membrane potential, mV
seawater, 100% $c_0^{Na^+}$
50% $c_0^{Na^+}$
33% $c_0^{Na^+}$
1
2
time, ms

Voltage clamp

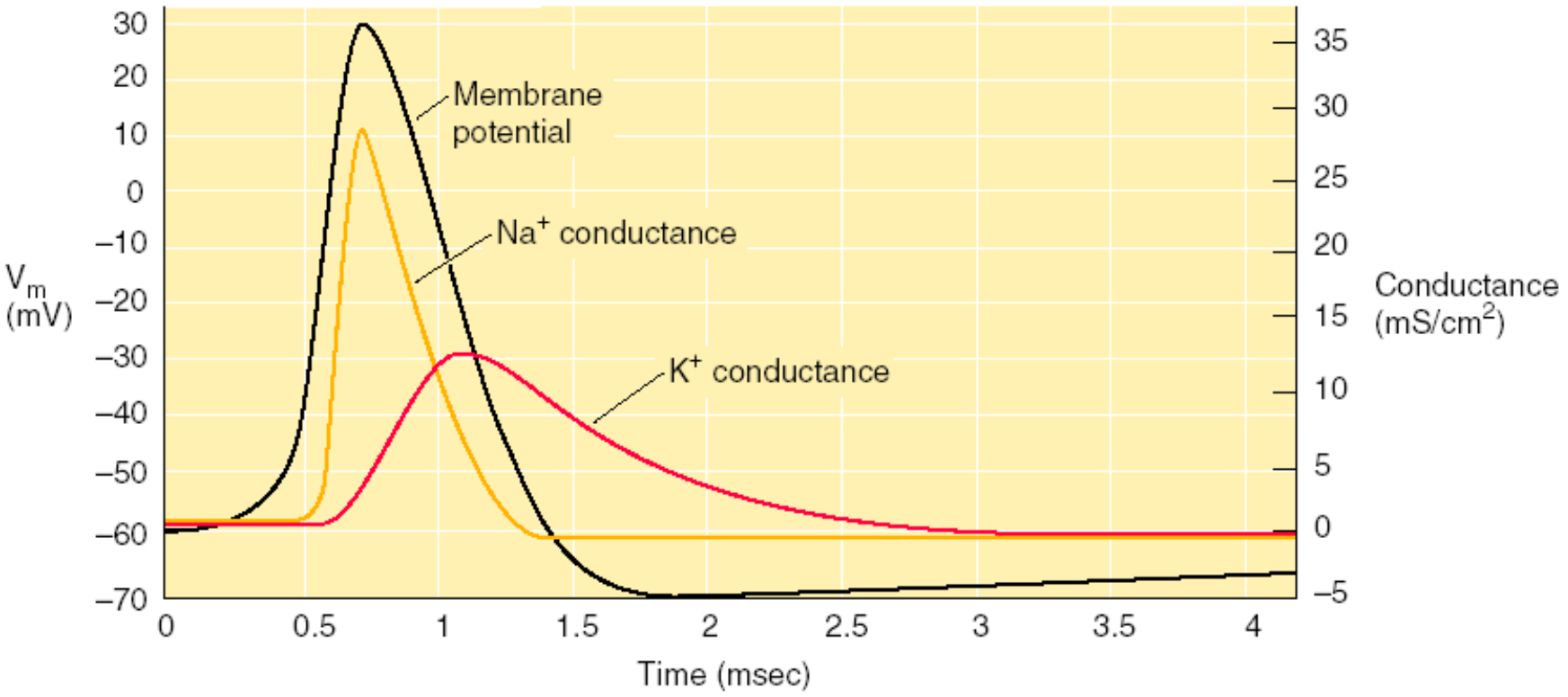
Additional electronics allow control over membrane voltage by injection of current




A HYPERPOLARIZATION
V_m (mV)
−80
−140
I_m (mA/cm^2)
1
0
−1
Outward current
Inward current
0 2 4 6 8 10 12
B DEPOLARIZATION
V_m (mV)
−20
−80
The total current is a summation
TOTAL IONIC CURRENT
I_m (mA/cm^2)
1
0
−1
Outward current
Inward current
C PHARMACOLOGICAL DISSECTION OF CURRENTS
Tetrodotoxin
Saxitoxin
Tetraethylammonium
K^+ current
1
0
Outward current
Inward current
TTX (tetrodotoxin, from pufferfish) or STX (saxitoxin, from "red tide" dinoflagellates) blocks Na^+ current, revealing the K^+ current.
0 2 4 6 8 10 12
TEA (tetraethylammonium) blocks K^+current, revealing the Na^+ current.
Na^+ current
0
Outward current
Inward current
0 2 4 6 8 10 12
Time (milliseconds)

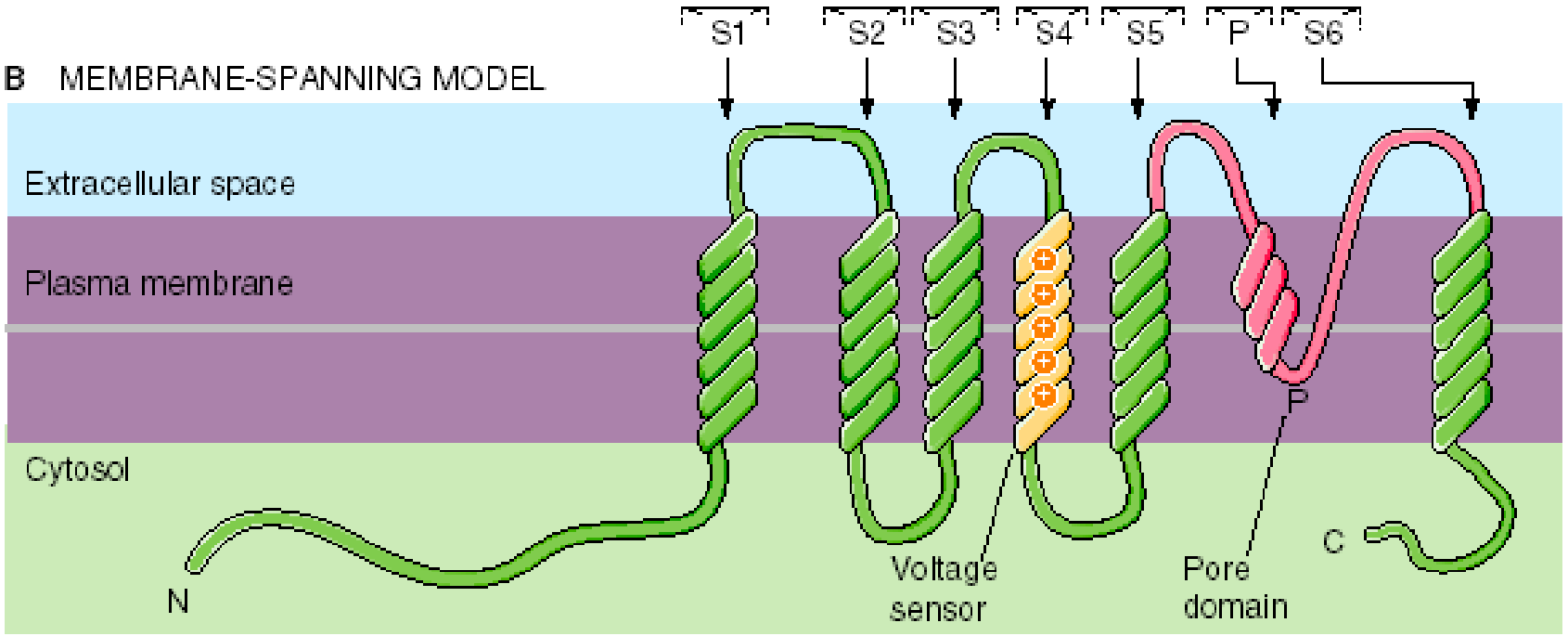

A TOTAL IONIC CURRENT
Clamped membrane potential = –45
Clamped membrane potential = –30
Clamped membrane potential = 0
Clamped membrane potential = +30
Clamped membrane potential = +60
Total membrane current or I_m (nA)
Outward current
Inward current
10
0
–10
0
5
10
Time (msec)
msec
out
in
B Na^+ CURRENT OBTAINED IN 6 mM TEA
"Peak" I_{Na}
Na^+ current or I_{Na} (nA)
C K^+ CURRENT OBTAINED IN 300 nM TTX
"Peak" I_K
K^+ current or I_K (nA)
This is called the "delayed rectifier" K^+ current because of this delay.

Hodgkin & Huxley model

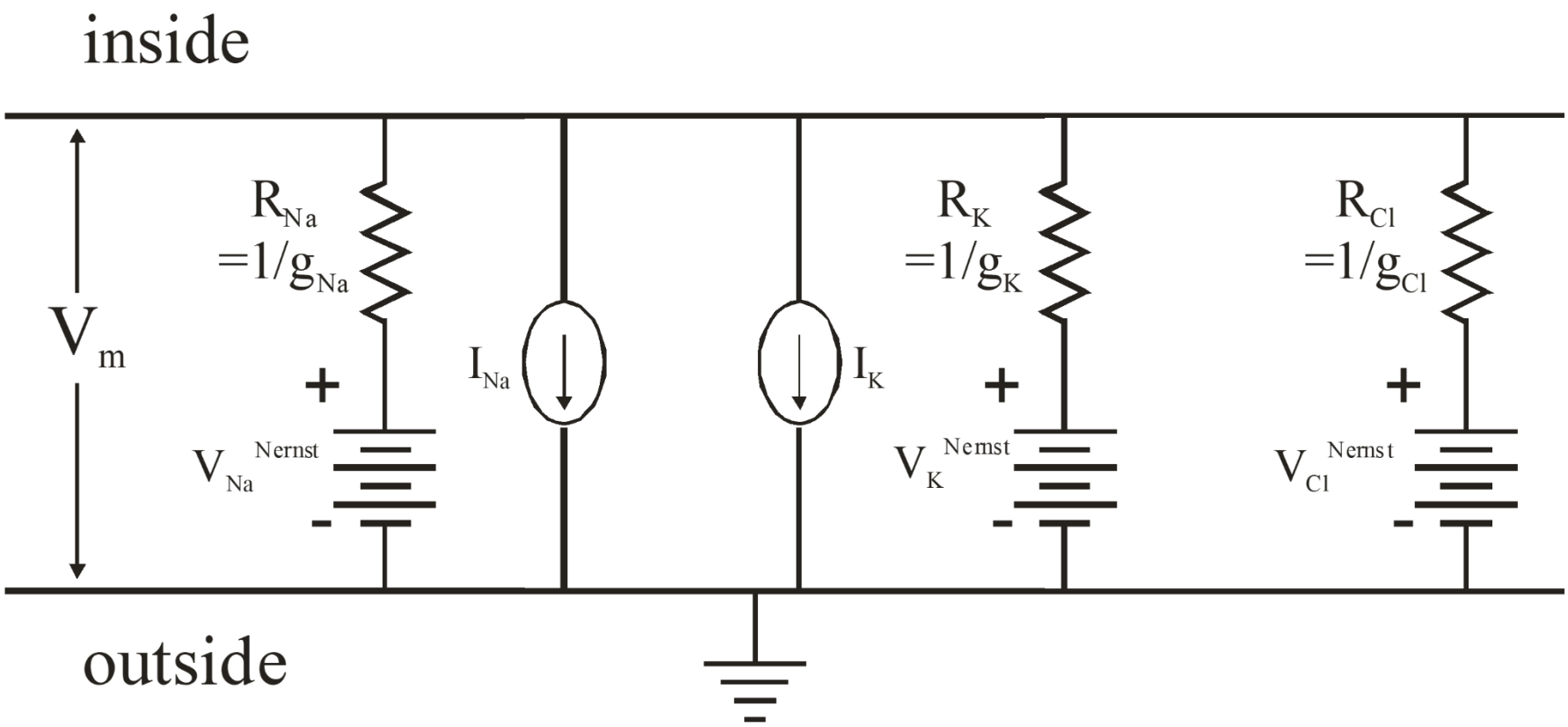


- Two channel systems, which add to conductance of the membrane
- Na^+ channel
  - voltage sensitive, fast opening, self-closing
- K^+ channel
  - voltage sensitive, slow opening v

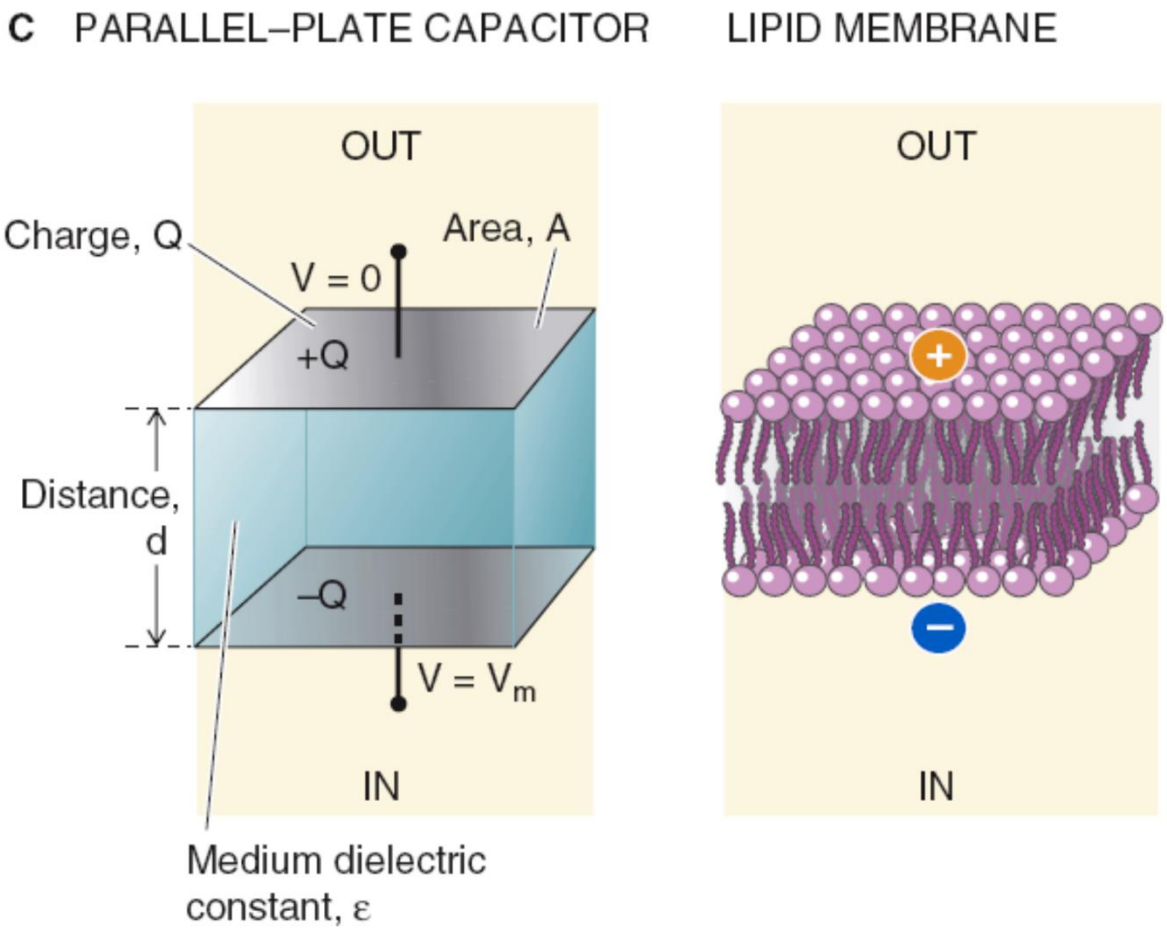
Voltage-sensitive channels



Time dependence of membrane voltage



Time dependence of membrane voltage



$C=\varepsilon_0*\varepsilon*A/d$, or $c=\varepsilon_0*\varepsilon/d$

ε_0 = permittivity constant of space

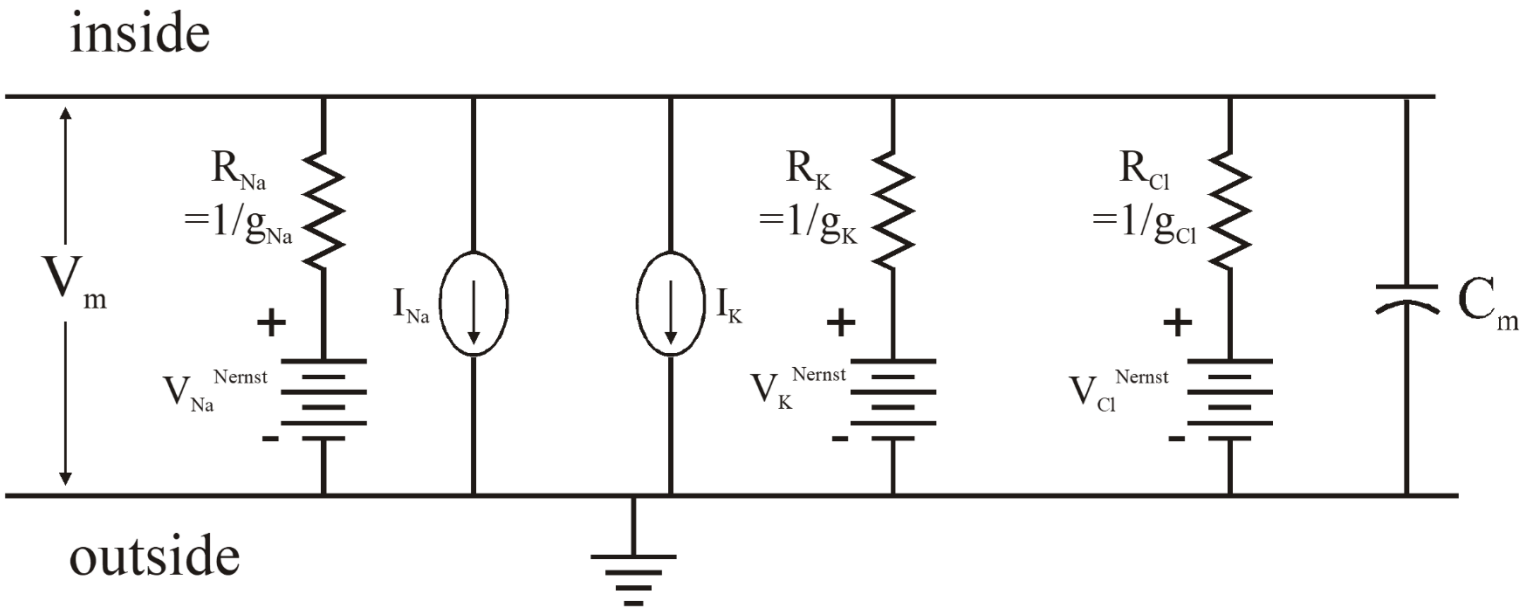
$\varepsilon_0 = 8.854 \times 10^{-12}\ C^2/(N*m^2)$

$\varepsilon_{lipid} = 5$

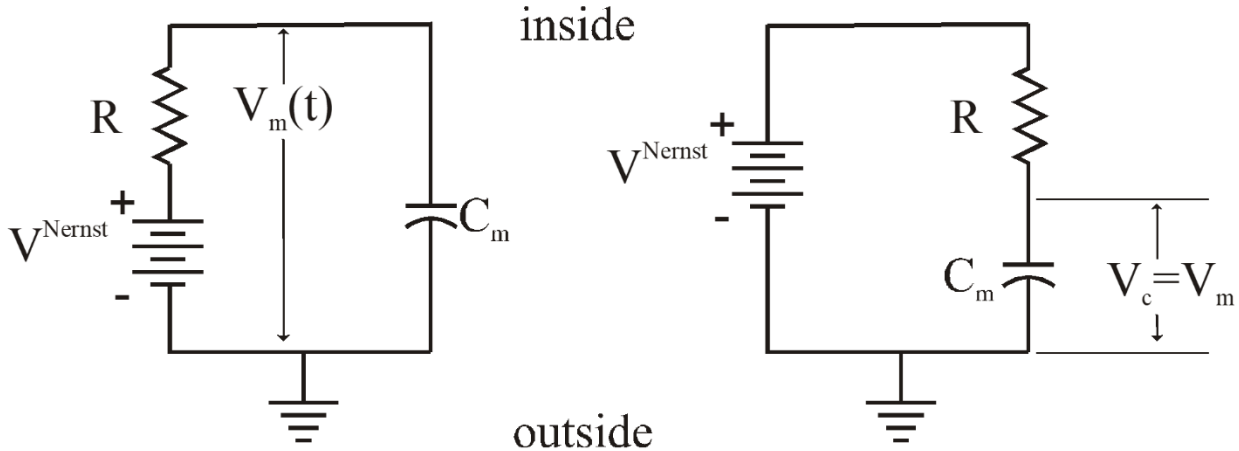
$d \sim 5$ nm

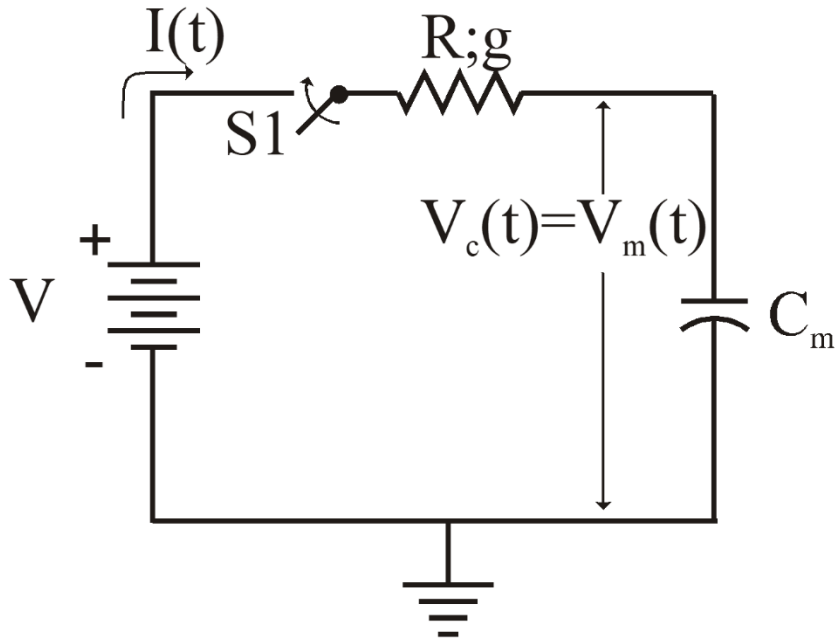
$C = 8.85 \times 10^{-2}\ F/m^2 \sim 1\ \mu F/cm^2$

Time dependence of membrane voltage



Reduce this circuit to





- at time 0, membrane voltage is V_0
- at time 0, the switch is closed, the potential "V" is applied
- How does this system respond?

$$I(t) = g\left[V - V_m(t)\right]; \text{resistor}$$

$$I(t) = C_m \frac{dV_m(t)}{dt}; \text{capacitor}$$

$$\frac{dV_m(t)}{dt} = \frac{g}{C_m}\left[V - V_m(t)\right]$$

And now, using $V'(t)=V_m(t)-V$,

$$\frac{dV'(t)}{dt} = -\frac{g}{C_m}V'(t)$$

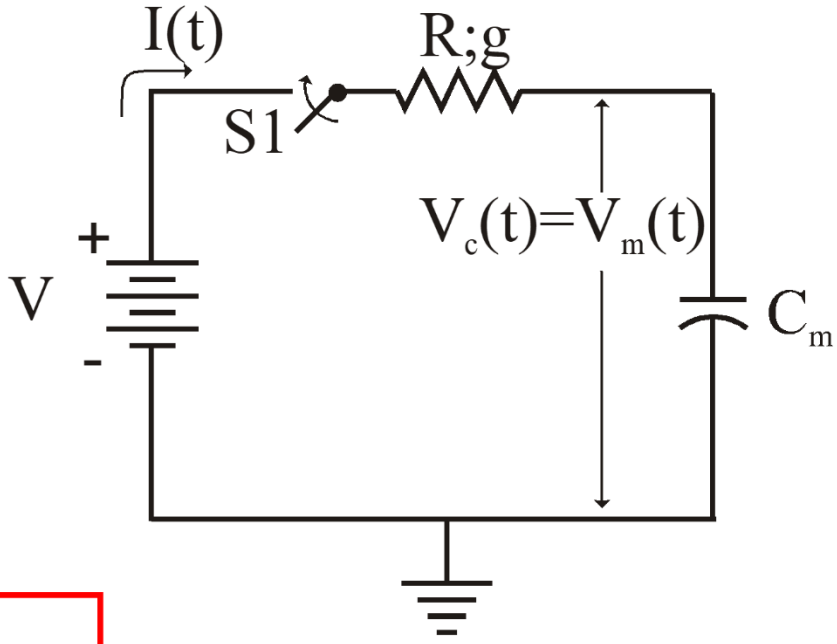
With a solution

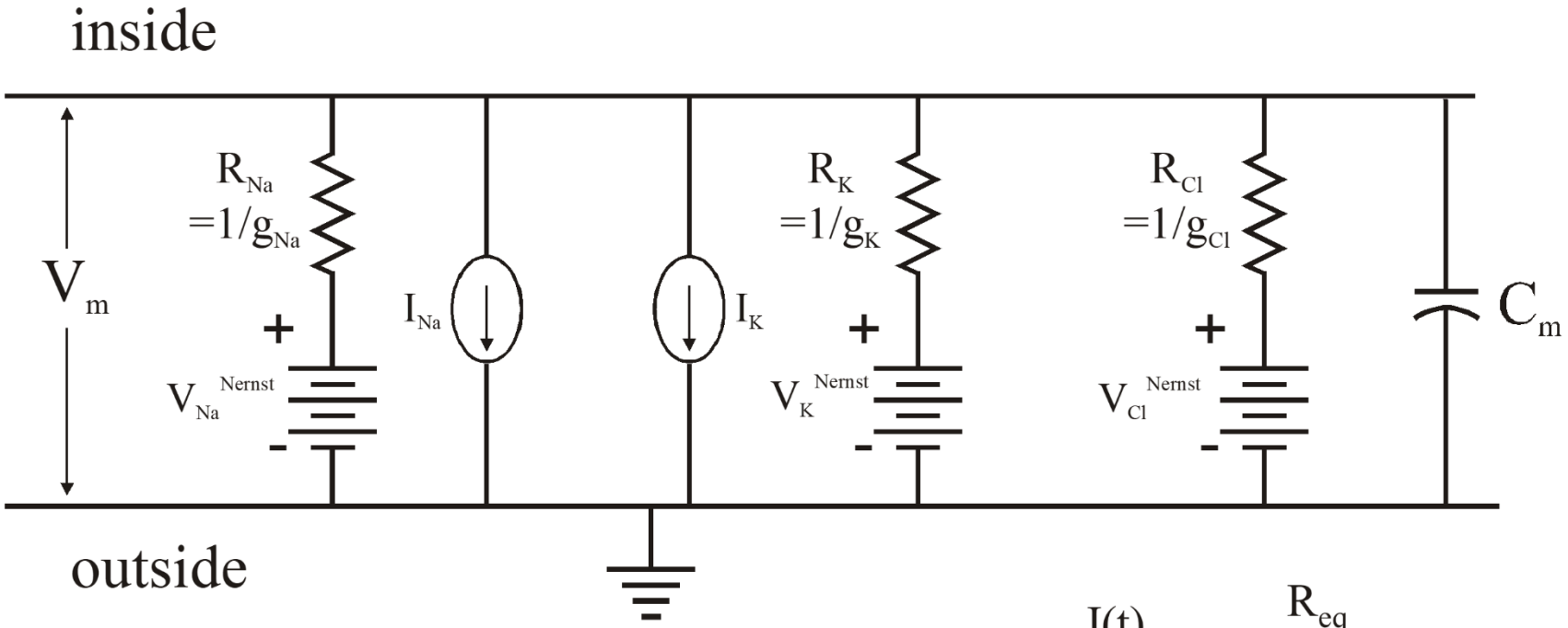
$$V'(t) = A\exp\left(-\frac{g}{C_m}t\right)$$

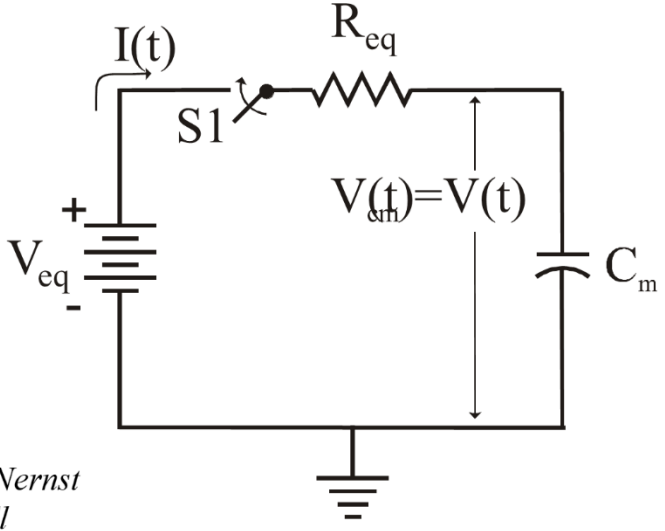
Using $V_m(0)=V_0$

$$V_m(t) = (V_0 - V) * \exp\left(-\frac{g}{C_m}t\right) + V$$

Time constant = $\tau = C_m/g$





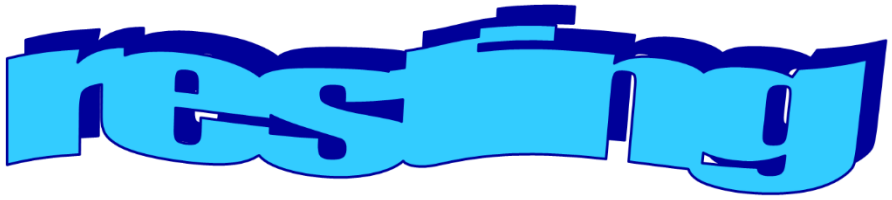


$$R_{eq} = \left(\frac{1}{R_{Na}} + \frac{1}{R_K} + \frac{1}{R_{Cl}} \right)^{-1}$$

$$V_{eq}^{Nernst} = \frac{-I_{Na} - I_K + g_{Na} V_{Na}^{Nernst} + g_K V_K^{Nernst} + g_{Cl} V_{Cl}^{Nernst}}{g_{Na} + g_K + g_{Cl}}$$

Ion	concentration (mM)		
	outside	inside	V^{nernst} (mV)
Na^+	440	50	+54
K^+	20	400	-75
Cl^-	560	52	-59

- Na^+ conductance, peak, action potential, squid axon: 27 mS/cm^2
- K^+ conductance, peak, action potential, squid axon: 12 mS/cm^2
- Na^+ conductance, resting, squid axon: 0.1 mS/cm^2 = 100 $\mu S/cm^2$
- K^+ conductance, resting, squid axon: 1.5 mS/cm^2
- Cl^- conductance, squid axon: .8 mS/cm^2



$$V_R = \frac{3V^{Nernst}_{K^+} g_{K^+} + 2V^{Nernst}_{Na^+} g_{Na^+}}{\left(2g_{Na^+} + 3g_{K^+}\right)}$$

$$\Delta V = -70 \text{ mV}$$

open Na+ channels

- g_{Na}= 27 mS/cm^2
- g_K=1.5 mS/cm^2
- g_{Cl}=0.8 mS/cm^2
- Pump-leak=> 44 mV

Consider a 500 μm diameter axon, take a 1 μm length

Area = π*500μm*1μm=1570μm^2

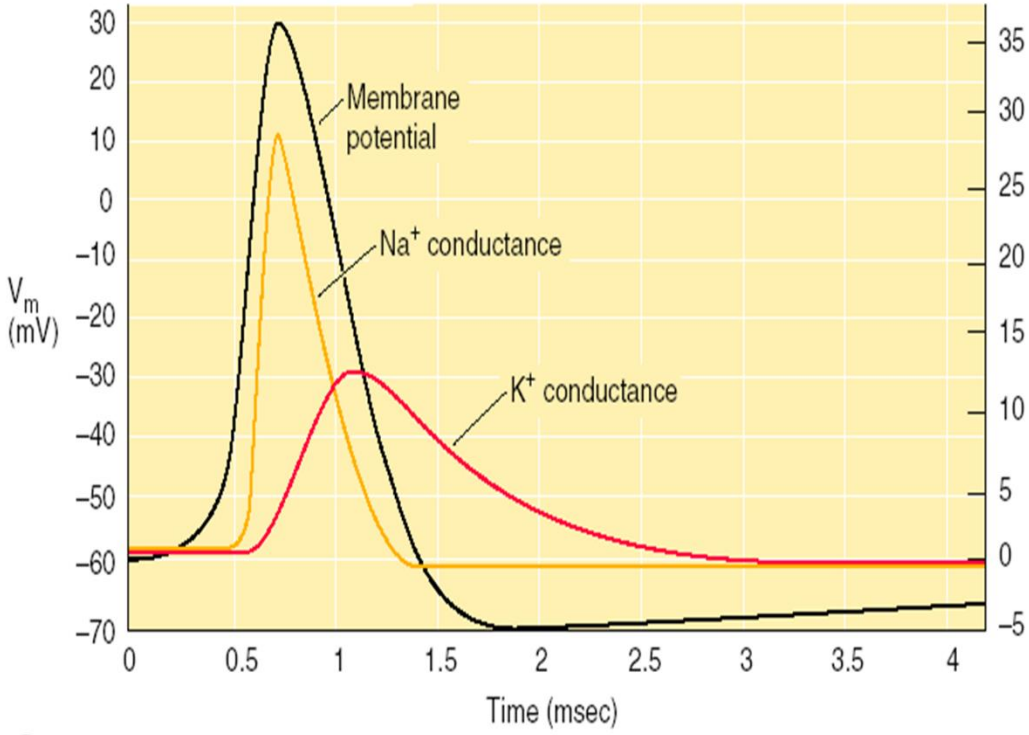
Capacitance = 1μF/cm^2 * 1570μm^2*(1E-8 cm^2/μm^2) = 1.6E-11 Farad

Resistance for this patch = 1/($g_{Na,AP}$*1570μm^2)=1/(4.2E-7S)=2.36 MΩ

Time constant = 3.7E-5 seconds ~ 35 μs.

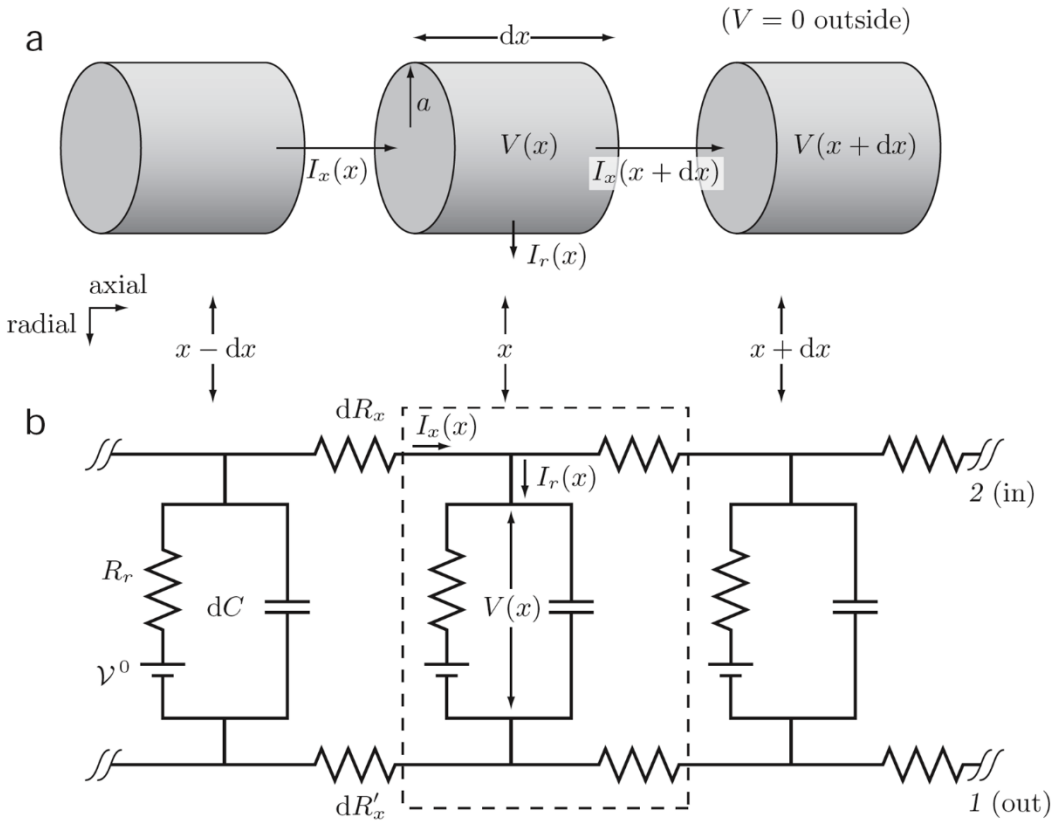
repolarization

- g_{Na}= 7 mS/cm^2
- g_K=12 mS/cm^2
- g_{Cl}=0.8 mS/cm^2

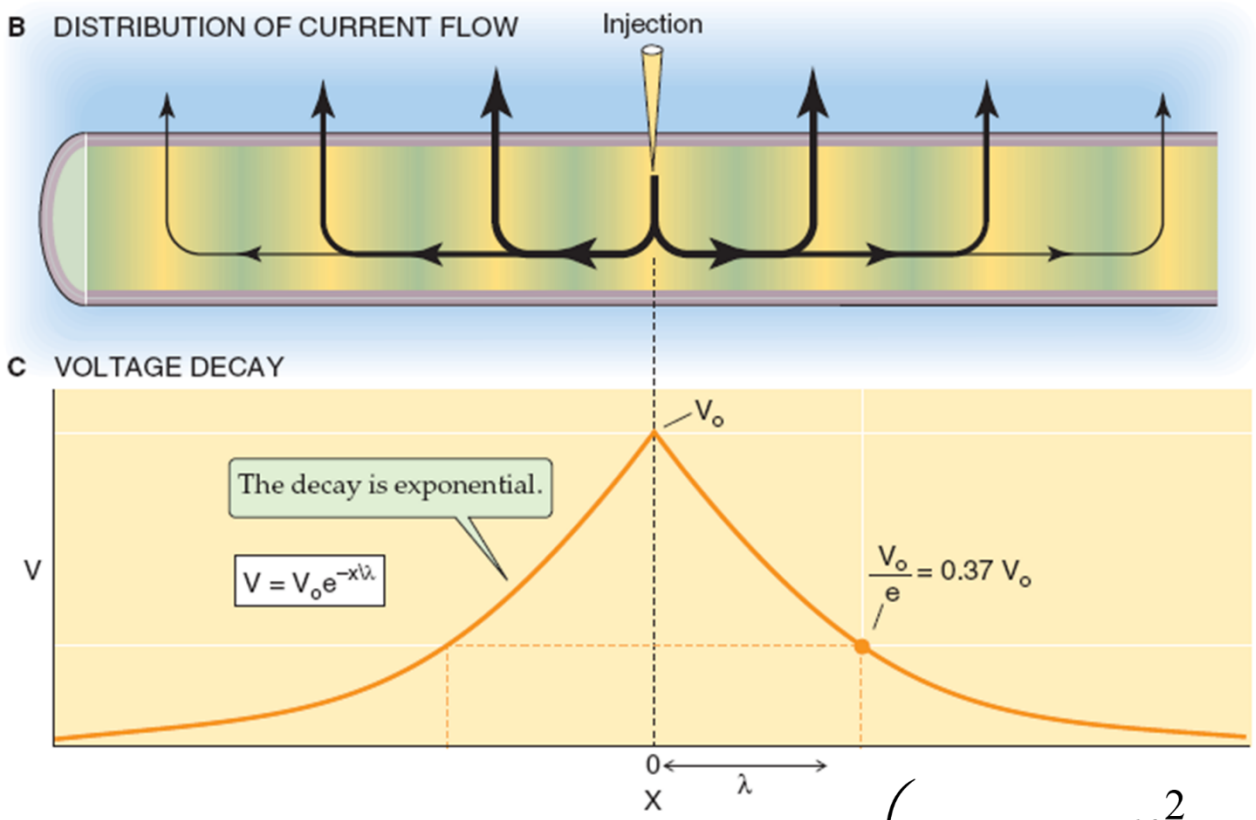


time constant = 53 μs

Cable equation – linear solution



- Treat axon membrane as chain of cylinders, each with radial and axial components
- Extend this concept to create a continuum of distributed resistors and capacitance
- Typically, solve for voltages and currents as function of position



$$v(x,t) = C * \exp(-t/\tau) * t^{-1/2} * \exp\left(-\frac{x^2}{(4 * t * \lambda^2/\tau)}\right)$$

$\tau = C_m * R_m$; time constant

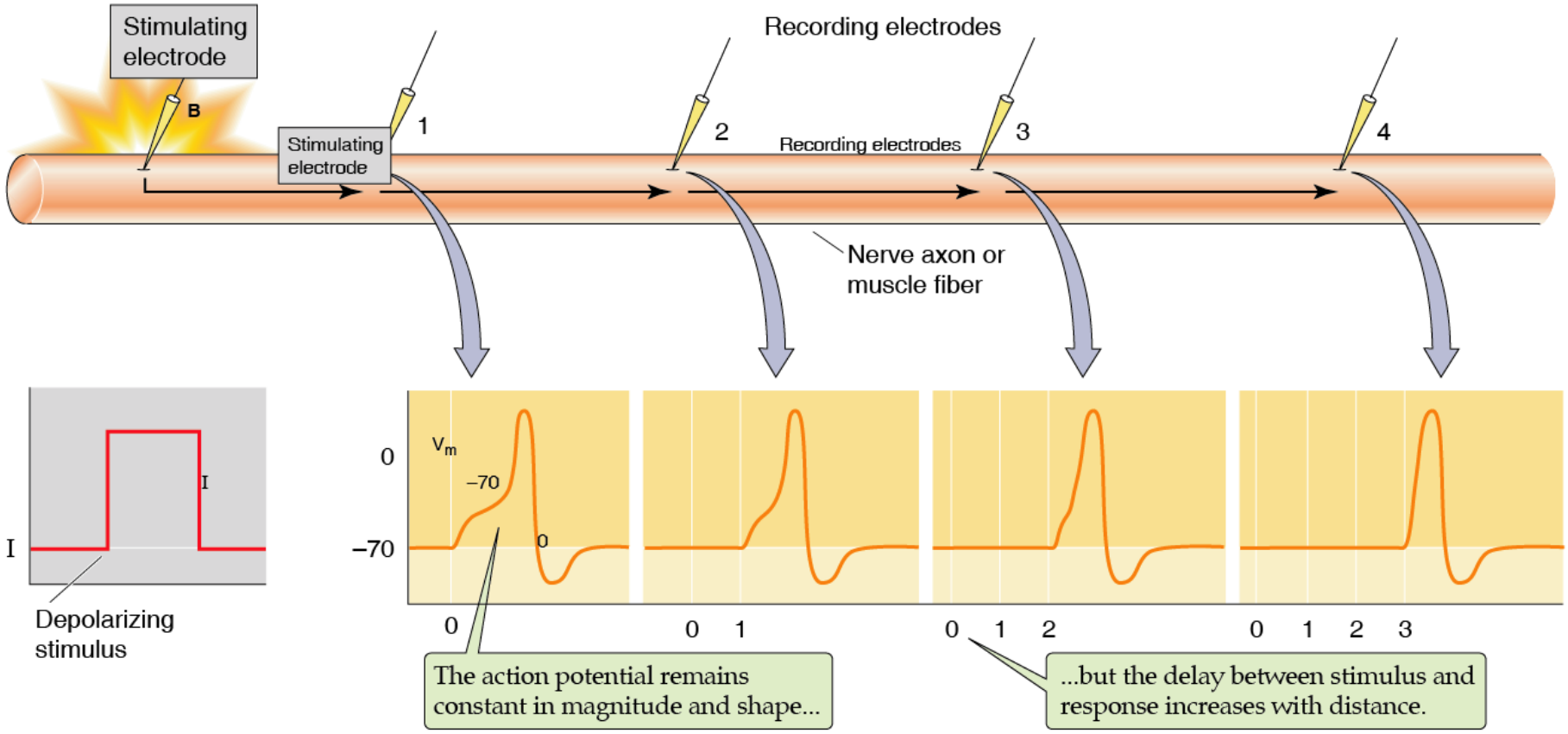
R_m = membrane resistance

λ = 0.1 mm to 10's of mm under typical conditions

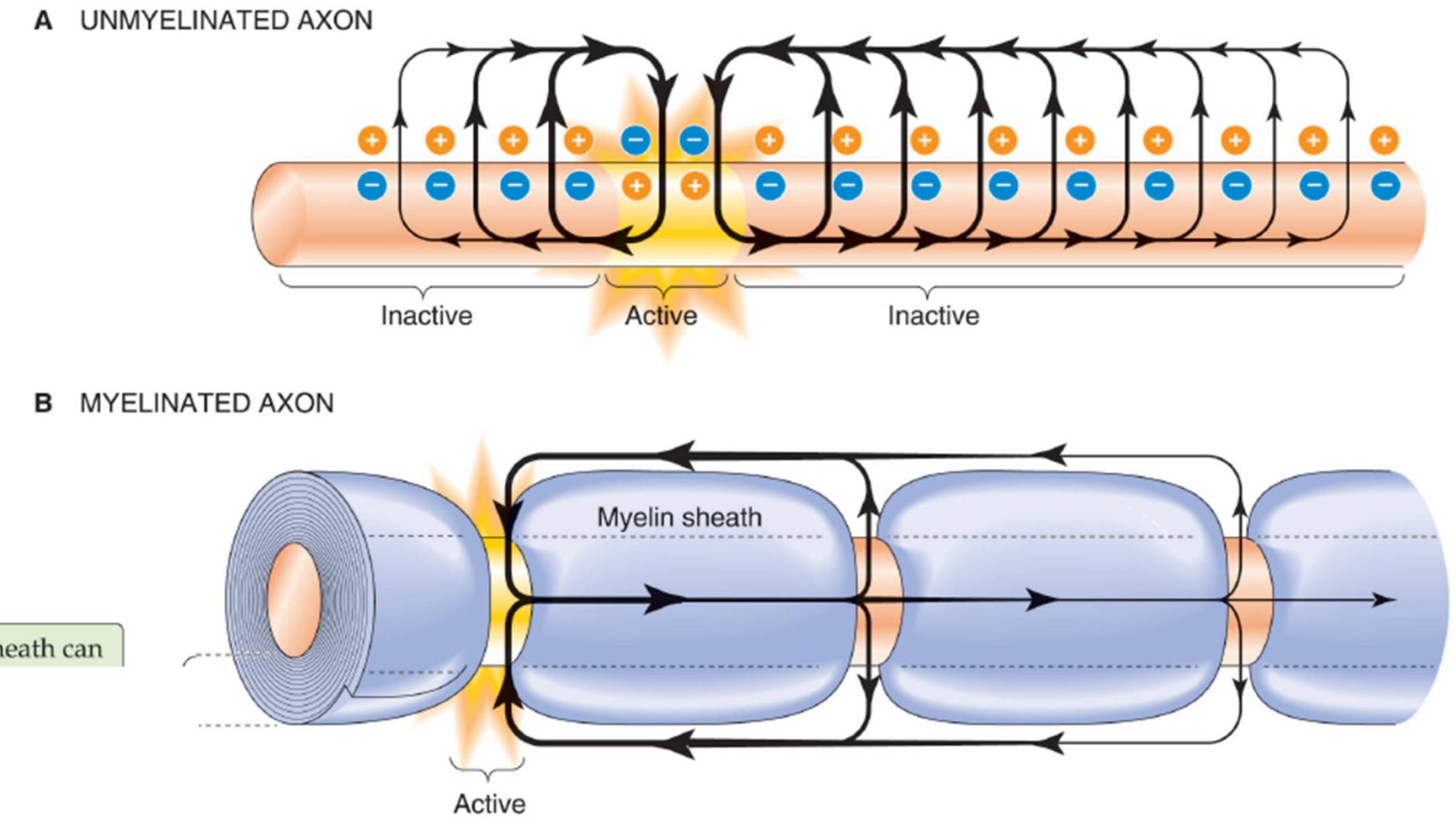
$\lambda = \text{sqrt}(a * R_m/(2 * R_i))$; length constant

R_i internal resistance, a = radius

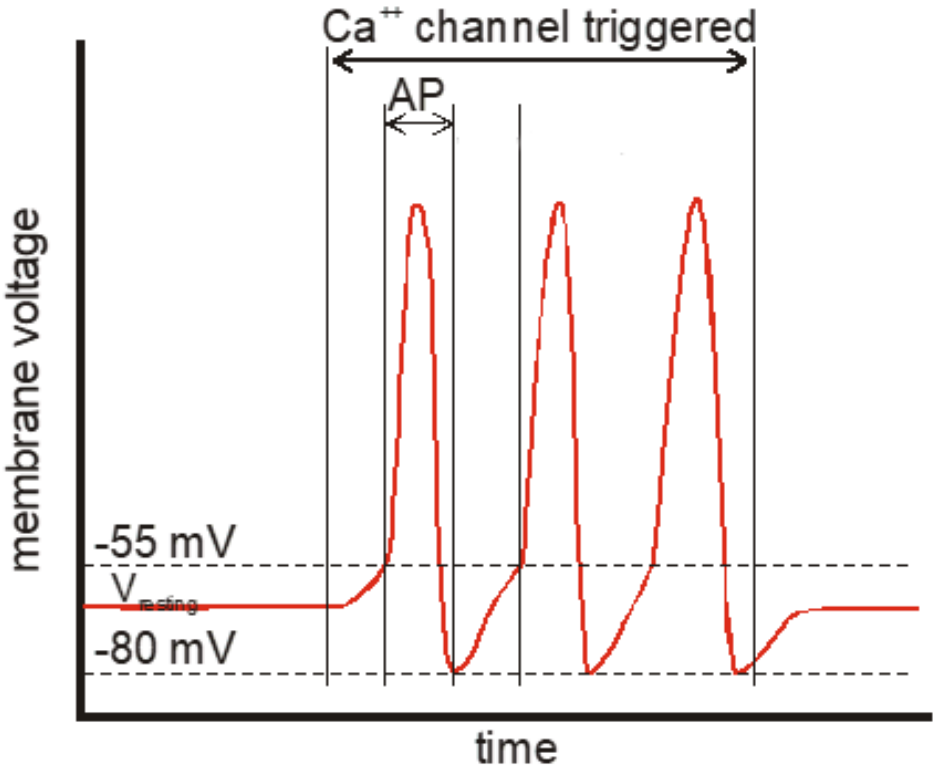
Traveling action potentials

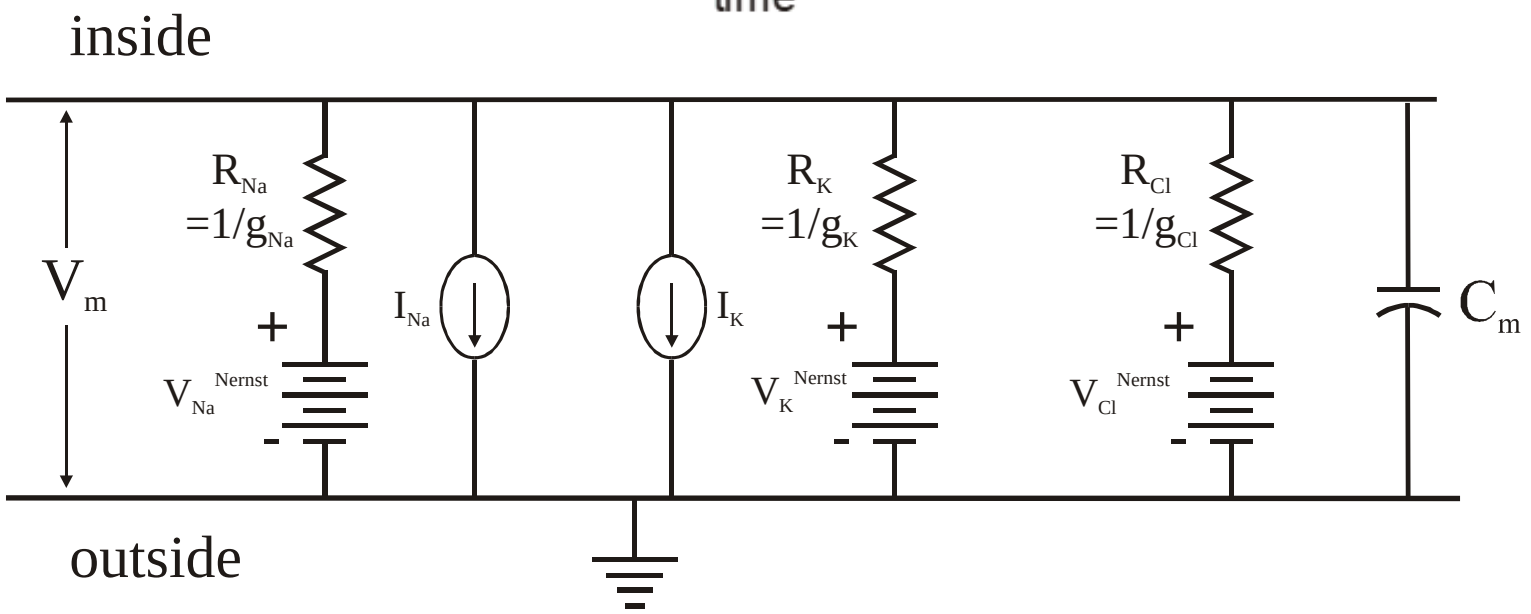


initiation of action potentials



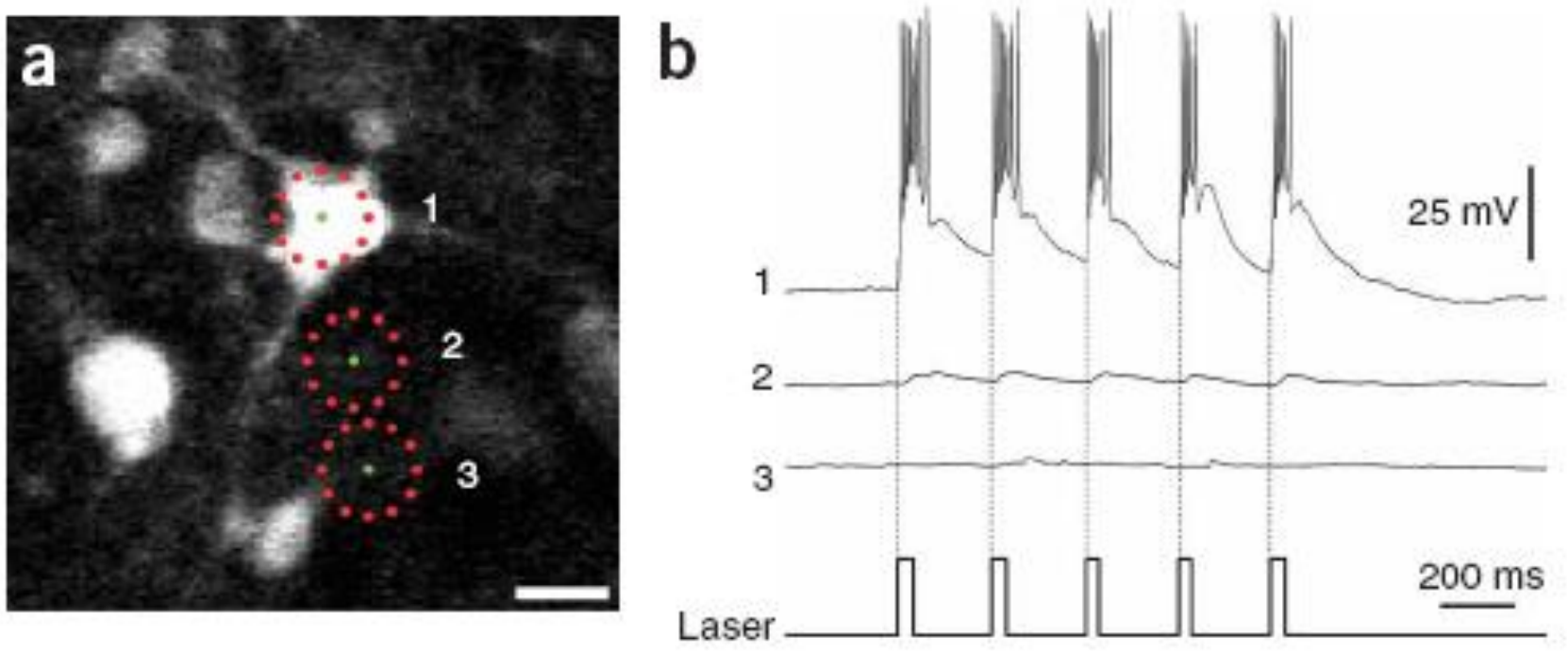
Myelination enhances transmission by reducing capacitance and increasing membrane resistance


Ca++ channel triggered
AP
membrane voltage
-55 mV
V resting
-80 mV
time


inside
V m
R Na
=1/g Na
I Na
I K
R K
=1/g K
R Cl
=1/g Cl
C m
V Na Nernst
V K Nernst
V Cl Nernst
outside

Optic-driven stimulation in slices

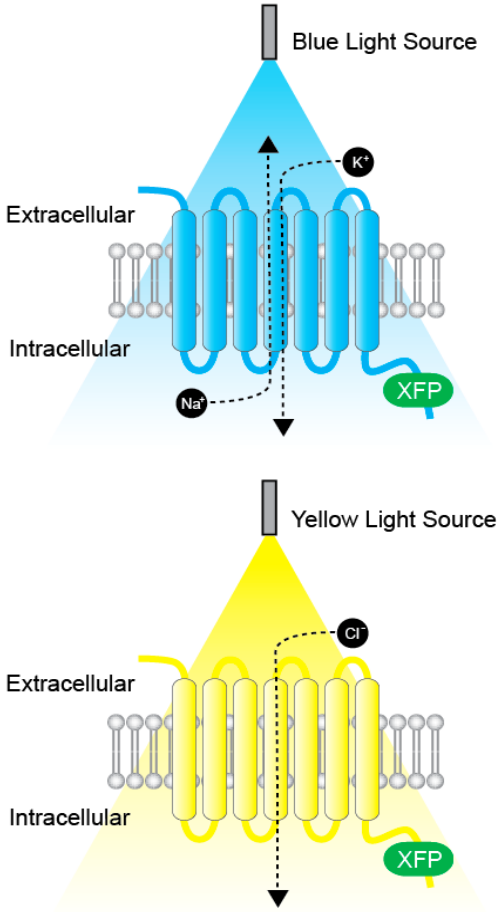
Nikolonko, Poskanzer, & Yuste, *Nat Methods*, 4:943 (2007)



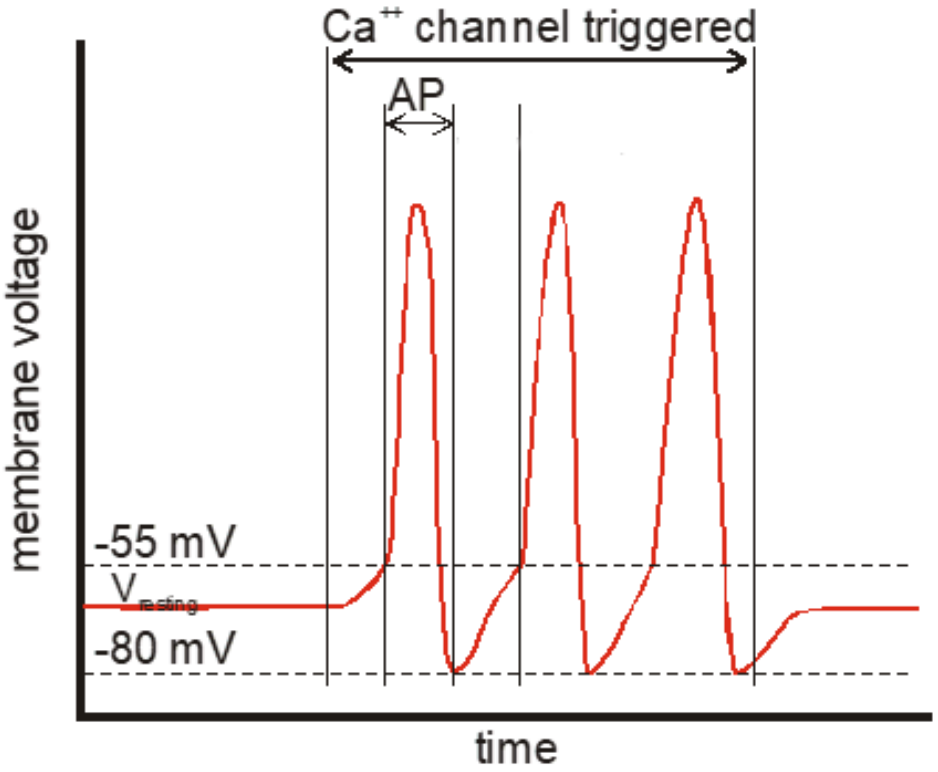
- Laser-induced uncaging of glutamate

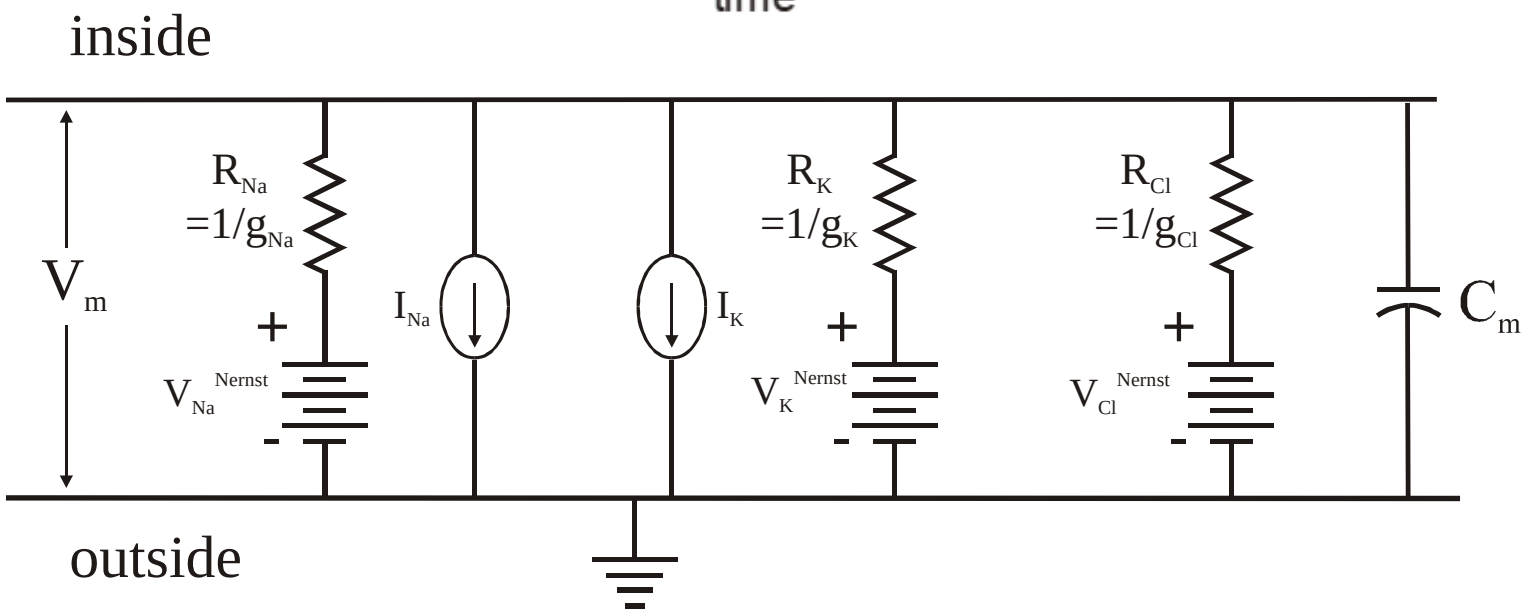
Optogenetics. Deisseroth, K., *Sci Am* **303**:48-55 (2010)

Channelrhodopsin-2
nonspecific cation channel, depolarize



Halorhodopsin
chloride pump, hyperpolarize


Ca++ channel triggered
AP
membrane voltage
-55 mV
V resting
-80 mV
time


inside
V m
R Na
=1/g Na
I Na
I K
R K
=1/g K
R Cl
=1/g Cl
C m
V Na Nernst
V K Nernst
V Cl Nernst
outside