NRSC lectures Monday and Tuesday
syllabus: action potential propagation, action potential integration, &
  synaptic transmission

Monday: review of driving force, ect..
new discussion passive properties of membrane
  action potentials vs local potentials
action potential propagation (spread, refractory limits, conduction)
  nerve muscle synapses
    EPSPs / IPSPs

Tuesday:
  why we care about cable theory,
  more integration
  synaptic release of neurotransmitter
review from day-1; review from day-2
practical examples to illustrate ALL concepts (e.g., test prep)
Review of basic concepts

Experiment 1

Cell

- Concentration Gradient

membrane

\[ \text{NaCl} \]

10 mM in

100 mM out
Measure membrane potential

- Concentration Gradient

\[ V = ?? \]
Measure membrane potential

- **Concentration Gradient**
- membrane is equally permeable to both Na and Cl

\[ V = ?? \]
Membrane is **selectively** permeable to Sodium
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Membrane is **selectively** permeable to Sodium

- **Excess of positive ions**: Na
- **Concentration Gradient**
- **Potential difference**
- **Excess of negative ions**: Cl

The diagram illustrates the flow of ions through the membrane, with Na ions moving from an area of higher concentration to one of lower concentration, and Cl ions moving in the opposite direction. This process is driven by the concentration gradient and the resulting potential difference.
Membrane potential

- Concentration Gradient across the membrane
- Membrane is selectively permeable to ions

$V = \frac{RT \log [\text{out}]}{F} \frac{[\text{in}]}{[\text{in}]}

V_{Na} = +58 \text{ mV}

V_{Cl} = -58 \text{ mV}
Membranes as capacitors

- Internal conducting solution (ions)
- External conducting solution (ions)
- Thin insulating layer (membrane, 4nm)
Membranes as Resistors

Internal conducting solution (ions)

External conducting solution (ions)

Ion channels
Voltage-gated, NT-gated etc.
Electrical model of the cell membrane

Ion channel
RESISTOR

Membrane
CAPACITOR
Capacitor

\[ Q \quad + \quad A = \text{Area} \quad Q \]

\[ d = \text{distance of plate separation} \]

**Capacitance**

\[ C = \frac{Q}{V} \quad \text{Coulomb/Volt or Farads (F)} \]

\[ C = \varepsilon_0 \frac{A}{d} \quad \varepsilon_0 \quad \text{electrostatic permittivity} \]

\[ \uparrow_A = \uparrow_C \quad \uparrow_d = \downarrow_C \]
Capacitor

- Rubber membrane
- Water pressure
- Release of pressure
- Small Capacitance
- Capacitors in parallel add larger Capacitance
Resistance

\[ R = \frac{V}{I} \quad \text{Ohms (Ω)} \]

\[ R = \rho \frac{l}{A} \]

\[ \uparrow l = \uparrow R \quad \uparrow A = \downarrow R \]

Ohm’s law

For the same current, a larger \( R \) produces larger \( V \)
Resistors

For ion channels is better to think in terms of conductance

\[ R_1 = \frac{1}{g_1} \]

As the # of Rs in parallel increases RT decreases!

\[ \frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} \]

More (open) channels in the membrane more conductance

\[ g_T = g_1 + g_2 \]

\[ R_T = R_1 + R_2 \]

Long, thin parts of a neuron have large resistance!
Some useful equations

**Current**

\[ I = \text{Coulombs/second Ampere(s)} \ (A) \]

**Ohm's law**

\[ V = IR \]

**Capacitance**

\[ C = \frac{Q}{V} \ 	ext{Coulombs/Volts} \ (F) \]

**Voltage across capacitor**

\[ V = \frac{Q}{C} \]

**Changing the voltage in a capacitor**

\[ \Delta V = \frac{\Delta Q}{C} \]

**We change the charge by passing current**

\[ I_c = \frac{\Delta Q}{\Delta t} \]

The change in \( V \) depends on the duration of \( I_c \)

\[ \Delta V = I_c \cdot \Delta t / C \]
Also remember...

Current likes to flow through the path with less resistance

\[ R = 100 \ \Omega \]

\[ I_T = I_1 + I_2 \]

And
Electrical model of the cell membrane

Ionic membrane current $I_i$

Membrane current $I_m$

Capacitive membrane current $I_c$

$I_m = I_i + I_c$
Effects of passing current on circuits containing $R$ and $C$

(A) $i$ $V = iR$

(B) $i$ $V = q/C$

(C) $i$ $i_R + i_C = i$

$V$ changes **instantaneously** with $I$

$V$ changes **linearly in time** with $I$

$V$ changes **exponentially** with a time constant = $RC$
RC circuits

For a rising exponential

\[ V = V_0 \left(1 - e^{-\frac{t}{RC}}\right) \]
Experiment 2

Passing current and recording the membrane potential from a paramecium

Negative current makes the membrane potential more negative hyperpolarization

Positive current makes the membrane potential more positive depolarization

"electrotonic potential"
Linear relationship between current and voltage

\[ V = I \times R_{\text{in}} \]

Input Resistance \( R_{\text{in}} = 100 \ \text{M} \Omega \)
Specific membrane resistance

cross section of a cell

To compare cell with different sizes

The specific membrane resistance (resistance per area)

\[ R_M = \Omega * \text{cm}^2 \]

depends on the # of channels per cm\(^2\)

More channels make \( R_M \) smaller

For a spherical cell

\[ R_{in} = R_M / 4\pi a^2 \quad a = \text{radius} \]

\( R_{in} \) determines how much the cell depolarizes in response to a steady current
Example

Same \( R_m = 2000 \ \Omega \cdot \text{cm}^2 \)

Cell diameter is 50 \( \mu \text{m} \)

\[ a = 25 \ \mu\text{m} = 25 \times 10^{-4} \text{cm} \]

\[ R_{in} = \frac{R_m}{4\pi a^2} \]

\[ R_{in} = \frac{2000 \ \Omega \cdot \text{cm}^2}{4\pi (25 \times 10^{-4} \text{cm})^2} \]

\[ R_{in} = 25 \ \text{M\Omega} \]

Cell diameter is 5 \( \mu \text{m} \)

Your numbers here...

\[ R_{in} = 637 \ \text{M\Omega} \]

\( R_{in} \) is larger in a smaller cell
Specific membrane capacitance of biological membranes

\[ C_M = 1 \ \mu\text{F/cm}^2 \]

For a cell at -80 mV how many ions is this?

\[ C_M = \frac{Q}{V} \]

\[ Q = 10^6 \ \text{C/V}*0.08 \ \text{V} \]

\[ Q = 8\times10^{-8} \ \text{C/cm}^2 \]

Faraday constant \( \approx 10^5 \ \text{Coulombs/mole} \)

Avogadro’s number = \( 6.02\times10^{23} \ \text{mole}^{-1} \)

Then this is \( 4.8\times10^{11} \ \text{ions/cm}^2 \) Is this a lot???
Let's assume the cell is 50 μm in diameter

\[ a = 25 \text{ μm} = 25 \times 10^{-4} \text{ cm} \]

The surface of the sphere is \[ A = 4\pi a^2 \]

\[ A = 7.85 \times 10^{-5} \text{ cm}^2 \]

4.8 \times 10^{11} ions in 1 cm² So total is 4 \times 10^7 ions

The volume of this cell is 6.55 \times 10^{-8} \text{ cm}^3

Then this number of ions is \( \sim 10^{-6} \text{ M} \)

If KCl inside is 120 mM this means that only
\( \sim 1/120,000 \) ions is in excess!
different cells require different amounts of charge

Large cell
large capacitance

Small cell
small capacitance

"C_m" is the same (same membrane)

For a spherical cell, the input capacitance

\[ C_{in} = C_m \times 4\pi a^2 \quad a = \text{radius} \]

More charge (current) is required to change the voltage across a large cell
In summary

\[ R_{in} = \frac{R_M}{4\pi a^2} \]
\[ C_{in} = C_M \times 4\pi a^2 \]
\[ \tau = R_{in} \times C_M \]

The product of input Capacitance and Resistance (\(\tau\)) determines the time it takes change the potential.

Notice that \(\tau\) is not affected by “a”
why do we care about time constants?

Figure 7-7 Membrane time constants and temporal summation. A, High membrane resistance results in a long time constant; the membrane capacitance may not be completely charged (dashed line) at the end of a relatively brief conductance change. B, Low membrane resistance results in a short time constant. Neurons or neuronal processes with long time constants (C) display more temporal summation than neurons with short time constants (D).

answer is ......
why do we care about time constants?

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Real Neurons

How are signals affected by the passive properties of the membrane?
Experiment 3

Local potentials are graded

resting potential

Almost no potential change is observed, why?
Current in axons and dendrites

Section of axon or dendrite of determined length (x). In this case 1 cm.

\( r_a \) axial resistance \((\Omega/cm)\)

\( r_m \) membrane resistance \((\Omega*cm)\)
Axial resistance increases with distance ($x$)

Total axial resistance

\[ r_x = r_a \times x \quad (x = 4) \]

(remember $RT = R1 + R2$)

Near the site of injection, the current flows $V_o$ through $r_m$ (less resistance)

Then $V_o = I_m \times r_m$
Axial resistance increases with distance \( (x) \)

Total axial resistance

\[ r_x = r_a \times x \quad (x = 4) \]

(remember RT = R1 + R2)

Near the site of injection, the current flows \( V_o \) through \( r_m \) (less resistance)

Then \( V_o = I_m \times r_m \)

the greater (longer) the length of cytoplasm, the greater the resistance. The larger (wider) the cytoplasmic core, the lower the resistance.
What is the value of $V$ at increasing distances from the site of current injection?

$$V = V_0 e^{-x/\lambda}$$

$\lambda$ is the length constant

$$\lambda = \sqrt{r_m/r_a} \text{ (cm)}$$

Increasing $r_m$ increases $\lambda$

Decreasing $r_a$ increases $\lambda$

i.e. $V$ is closer to $V_0$
For 1 cm of cytoplasm (dendrites or axon)

\[ \rho (\Omega \text{cm}) \] resistive property of 1 cm\(^3\) of cytoplasm (dendrites or axon)

\[ r_a = \frac{\rho}{(\pi a^2)} \]

\[ r_m = \frac{R_m}{(2\pi a)} \]

\[ \lambda = \sqrt{\frac{r_m}{r_a}} \]

\[ \lambda = \sqrt{\frac{2\rho}{R_m a}} \] If \( R_m \) and \( \rho \) are constant

\[ \lambda = \sqrt{K a} \] The length constant is proportional to the square root of the radius of the process

For neurons is usually 0.1 to 1 mm
Effect of length constant

Potential decays exponentially with distance. This exponential is the ‘membrane length constant.’ the longer the length constant, the further the spread of potential.

For a dendrite or axon with the same diameter as the length constant increases the potential decreases less with distance.
Effect of diameter

For a dendrite or axon with increasing diameters the length constant increases and the potential decreases less with distance.
The passive properties of membranes and axon diameter affect the speed of conduction of action potentials.

The speed of conduction of action potentials is inversely related to \( r_a \times C_m \).

The speed of conduction is increased by increasing the diameter of the axon which decreases \( r_a \).

The giant axon of the squid is 1 mm!
Myelination, the alternative to increasing the diameter of the axon.

Glial cell wrap around axons many times (20-160 times) this like adding 320 membranes (in series). This increases $R_m$ and decreases $C_m$

Increasing $R_m$ --> increases length constant
why do we care about length constants?

Spatial summation. Multiple simultaneous voltage changes (in this example, synaptic potentials) add to one another, to a degree determined by their relative proximity to one another and by various length constants. Summation may be sufficient to bring the neuron's trigger zone to threshold.
Figure 7-8 Passive spread of voltage changes in neuronal processes. A, Progressively less of a steady current entering a neuronal process at one location remains as the distance from the point of entry increases. Hence the voltage change declines exponentially with distance from the point of entry. B, Influence of the diameter of a neuronal process on its length constant. Membrane area (and conductance) increases directly with the diameter, whereas cross-sectional area (and conductance) increases with its square. Hence doubling the diameter doubles the membrane conductance but quadruples the longitudinal conductance. C, Effects of membrane capacitance on the longitudinal spread of voltage changes. The final value of the voltage change at any given point is dictated by membrane and longitudinal (not indicated) resistances. However, the rate of reaching this final value becomes progressively slower with distance, as more and more capacitance is added.
how are action potential & local potentials different?

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<th>slow potentials</th>
<th>spikes</th>
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## How are action potential & local potentials different?

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<td>unidirectional</td>
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- **Amplitude**: Slow potentials are graded, usually 1–2 mV, while spikes are all or none; 100 mV.
- **Duration**: Slow potentials are graded according to stimulus, while spikes have a duration of 1–2 ms.
- **Polarity**: Slow potentials can be + or −, whereas spikes are always (+) depolarizing.
- **Threshold**: Slow potentials have none (graded), whereas spikes have a threshold of 10–20 mV above RMP.
- **Summation**: Slow potentials have temporal/spatial summation, while spikes do not have any summation.
- **Conduction**: Slow potentials are decremental/passive, while spikes are nondecremental, active.
- **Propagation Direction**: Slow potentials can propagate in all directions, whereas spikes are unidirectional.
action potential propagation: refractory periods limit upper firing rates

Continuos depolarization or injection of current causes:

- repetitive spikes; proportional increase
- #/pattern of spikes is regulated by composition of ion channels in postsynaptic membrane
- in (A)see single spike; (c) see burst of spikes
- 2nd spike can not be generated during the refractory period. why? what is the mechanism?
- the refractory period (falling phase) sets limits on upper firing rates during falling phase; (1-2 ms; upper limit 1 KHz)
- refractory periods ensure spikes go 1 direction
- spikes are initiated in trigger zone, in axon near cell body. ....then spread antidromically (and passively) back into soma ......and then propagate orthodromically down axon
Abnormal voltage-gated Na⁺ channels in a patient with periodic paralysis.

Patch-clamp recordings of the current flowing through single channels of normal muscle membranes (A) and those of the patient (B).

Depolarizations from 120 to 40 mv indicate that the patient’s channels do not inactivate rapidly.

Averages were used to calculate the probability of channels being open (POPEN) over time.

**Conclusion:** The continued, reduced, probability of the patient’s channels being open corresponds to a small but constant inward Na⁺ current that depolarizes the fiber. (From Cannon SC: Trends Neurosci 19:3, 1996.)
action potential propagation: in an unmyelinated axon

A, Initiation of a spike in the axonal trigger zone close to the cell body causes the spread of depolarizing current in both directions—into the electrically inexcitable cell body and into adjacent, electrically excitable parts of the axon....VGCC density too low to reach threshold.

B, The action potential waveform spreads passively into the cell body and dendrites, becoming progressively later, slower, and smaller. However, there was enough VGCC, so in contrast, each successive part of the axon reaches threshold and generates its own action potential, so the spike becomes progressively later but not slower or smaller.

C, Thin axons have relatively short length constants, so a shorter length of axon is depolarized to threshold at any given time (i.e., conduction velocity is relatively slow).

D, Thick axons have relatively long length constants (lambda), so a greater length of axon is depolarized to threshold at any given time (i.e., conduction velocity is relatively rapid).

....remember conduction velocity is directly related to the length constant....longer length constant further spread
Action potential propagation: another example experiment

A, An action potential artificially induced partway along an axon would encounter excitable membrane in both directions. So can propagate both orthodromically and antidromically.

**How? I thought spikes were unidirectional?**

usually....action potentials begin under normal physiological conditions is flanked on one side by inexcitable membrane (the cell body) and on the other side by excitable membrane (the rest of the axon), propagation normally proceeds only in the orthodromic direction.

**Answer:**

B, A “normal” action potential “frozen” in time as it propagates orthodromically.

A small number of Na+ ions rush in at the site of action potential generation and depolarize membrane segments in both directions. However, the trailing zones of absolutely and relatively refractory membrane ensure that the action potential continues to propagate only orthodromically.

**Note** current enters the axon as Na+ ions, but leaves as K+ ions. **Note** current is *not* flowing in loops through axonal membranes by the same ions. rather ions that enter at one site repel ions of like charge, in succession.
finished with action potential propagation.

beginning nerve muscle synapses
nerve muscle synapses
Ordinarily each action potential in the motor axon causes enough Ach release to evoke an action potential in the muscle fiber. However, if the preparation is bathed in a low Ca²⁺ solution or is treated with curare, the subthreshold excitatory postsynaptic potential (EPSP; aka end-plate potential or EPP) is revealed. The amplitude of the EPP decreases, and its time course increases, with distance from the end-plate as dictated by the passive properties of the muscle fiber membrane (from Fatt and Katz, 1951).
The endplate current that underlies this excitatory postsynaptic potential (EPSP) is defined as:

\[ I_{EPSP} = g_{EPSP} \times (V_m - E_{EPSP}) \]

where \( I \) is the end-plate current, \( g \) is the conductance of the acetylcholine-gated channels, \( V_m \) is the membrane potential and \( E_{EPSP} \) is the driving force that results from the concentration gradients that results from the ions conducted through the acetylcholine channels.

The EPSC is inward at potentials more negative than \( E_{rev} \). This is because the driving force \((V_m - E_{rev})\) is a negative number.

At potentials more positive than \( E_{rev} \), the EPSC is outward (upward deflection) because the driving force \((V_m - E_{rev})\) is positive.
At the neuromuscular junction, the $E_{EPSP} = 0 \text{ mV}$, the $E_K = -100 \text{ mV}$, and the $E_{Na^+} = +55 \text{ mV}$
nerve muscle synapses

The end-plate current varies linearly with postsynaptic membrane potential, except for extreme hyper- or depolarizing holding potentials. Thus, the synaptic conductance is not voltage-dependent. The reversal potential provides information about ion selectivity (from Takeuchi and Takeuchi, 1960).
nerve muscle synapses

With two electrodes it is possible to record the postsynaptic membrane potential and inject constant current to change it. The postsynaptic membrane potential is not really "clamped". Thus, the voltage amplitude of the EPP can be recorded following motor axon stimulation. EPP amplitude is sensitive to membrane potential.

It is also possible to do a voltage-clamp experiment. A feedback amplifier is used to inject the current required to hold the muscle fiber membrane potential at different command values. The end-plate current can be measured following nerve stimulation. The end-plate current varies with postsynaptic membrane potential.
reversal potentials and threshold potentials determine EPSP/IPSP

(+) Glu receptor -> $G_{Na^+}$ and $G_{K^+}$. 
--> membrane toward $E_{\text{rev}} \sim 0 \text{ mV}$, which is more (+) than > threshold (-40 mV).

A depolarizing shift pushes cell toward an action potential. This is an EPSP

(+) GABA-A receptor 
can be depolarizing if the shift $E_{\text{rev}}$ is toward threshold

This is a depolarizing IPSP

RMP: -60 mV; spike threshold: -40 mV.

(+) GABA-A receptor 
--> $G_{Cl^-}$ 
--> membrane toward $E_{\text{rev}} \sim -70 \text{ mV}$, --> moves membrane further from threshold (-40 mV).

hyper-polarizing shift away from an action potential. This is an EPSP
review on reversal potentials and threshold

comments on cable theory (Rall)