Propagation & Integration: Passive electrical properties

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Earlier lectures examined potentials, calculated using the Goldman equation, caused by ions moving across a membrane. These concepts work for steady state (unchanging) voltages, but do not explain what happens with dynamic changes in membrane during action potentials or synaptic potentials—when the voltage is changing constantly. The goal of this lecture is to understand how passive electrical properties and membrane geometry—2 elements that should be constant between different neurons—influence the spread of potential.

Sources: ALL Lecture notes, slides and cartoons are compiled from the following: Neuroscience (Purves et al); Fundamental Neuroscience (Zigmond et al), Principles of Neural Science (Kandel et al.), Synaptic Organization of the brain (Shepard); Ion channels of excitable membranes (Hille), Human physiology (CNS clinic), membrane properties—Araneda (Columbia), the human brain (nolte)

key concept: There are 3 passive electrical properties important for signaling: (1) resting membrane resistance, (2) membrane capacitance, (3) intracellular axial resistance along membrane.

These elements provide return for current flow through the membrane. They control the time course and amplitude of synaptic potentials, generated by synaptic currents. Together these factors regulate whether an item will reach threshold (time course and amplitude) and the speed that the action potential travels.

Input resistance ($R_{in}$) controls the magnitude of the passive change in the membrane potential

Injecting negative current increases the charge separation across membrane, making the membrane more hyperpolarized. Interactions between the current and voltage create resistance. The neurons input resistance is $R_{in}$.

The $R_{in}$ determines how the cell responds to steady-state injections of current ($I$). The magnitude (but not the time-course) of the resulting depolarization ($\Delta V$) follows ohms law:

$$\Delta V = I \times R_{in}$$

Key concept: Cells with higher input resistances, display greater changes in membrane voltage. However, the larger the neuron, the greater the membrane surface area and the lower the input resistance ($R_{in}$) .... because there are more resisting channels conducting ions.

Often we want to compare 2 types of brain neurons with different sizes. How? We calculate the specific membrane resistance, $R_m$ (Ω cm$^2$).

Membrane capacitance prolongs time courses

So, the magnitude (not the time-course) is related to the membrane voltage of a cell.
Key concept: the rise and decay in the potential are slower than the current. This property is due to the membrane capacitance.

To understand why capacitance slows voltage responses, remember that voltage across a capacitor is proportional to the charge on the capacitor: \( \Delta V = \frac{Q}{C} \), where \( \Delta V \) (change in charge); \( Q \) (charge; coulombs); \( C \) (capacitance; faradays)

Charge (\( \Delta Q \)) is the flow of current across the capacitor \( I_c \). Current is the flow of charge per unit time \( I_c = \frac{\Delta Q}{\Delta t} \). The change in the voltage across a capacitor as a function of current and the time that the current flows (\( \Delta t \)):

\[
\Delta V = I_c \Delta t / C
\]

Capacitance is directly proportional to the area of plates of the capacitor. Larger plates correspond to more charge.

Key concept: The capacitance depends not only on size, but also on the insulation (i.e., myelin) and the distance between the two plates.

Somas vary in size. In contrast, biological membranes (lipid bilayers) are similar. They are separated by 4 nm, creating a capacitance of 1 \( \mu F/cm^2 \). For spherical soma, the total input capacitance is the capacitance per unit area multiplied by the area of the cell: \( C_m = C_m (4 \pi a^2) \).

Key concept: Because capacitance increases with the size of cell, more charge (e.g., more current) is required to produce the same change in the membrane potential in a large cell than in a smaller cell. That is, smaller cells display greater changes in potential in response to the same current.

Capacitance increases as long as current is applied. The current carried by ions is the ionic membrane current (\( I_i \)). The ion current that changes the net charge on the membrane is the capacitive membrane currents (\( I_c \)). An outward current adds positive charge to the inside of the membrane by removing an equal number of positive charges from the outside of the membrane. So the total current crossing the membrane (\( I_m \)) is: \( I_m = I_i + I_c \)

Key concept: Capacitance slows the rate at which the membrane potential changes in response to a current pulse.

If the membrane had only capacitive properties, then the membrane potential would change linearly with time. Because the membrane has both capacitive and resistive properties (in parallel), the actual change in membrane potential is a composite of both 2 features. That is, the initial slope reflects the relation between \( V_m \) and time (purely capacitive elements), whereas the final slope and amplitude reflect a resistive element.

Key concept: The membrane time constant, \( \tau \), is an experimental value that helps predicts whether 2 inputs will summate.

\( \tau \) is the product of the input resistance and capacitance of the membrane (\( \tau = R_m C_m \)); it is not effected by the area (\( a \)). It is the time it takes the membrane potential to rise about 63% of steady
state. This constant (τ) is discussed below in relation to temporal summation. Bottom line—the larger the τ, the more likely 2 inputs will summate.

**Membrane and axoplasmic resistance influence the efficiency of signal conduction**

The points above are relevant to somata—distance isn’t discussed, because the soma is assumed (incorrectly) to be a sphere with equidistance on all sides.

So, consider instead non-spherical dendrites. Synaptic potentials that originate in dendrites are conducted along the dendrite toward the cell body and trigger zone. The cytoplasm in the dendrite offers resistance, because it has a small cross-sectional area and the ions inside interact in a small space.

**Key concept:** the greater (longer) the length of cytoplasm, the greater the resistance. The larger (wider) the cytoplasmic core, the lower the resistance.

In dendrites, propagation of a subthreshold voltage signal decreases in amplitude with increasing distance. This is because most of the current flows across the membrane close to the injection site. That is, current “flows downhill.” This is because: (1) current follows the least resistance and (2) the total axial resistance, \( r_a \), increases with distance from the site of injection.

**Key concept:** Potential decays exponentially with distance. This exponential is the membrane length constant, \( \lambda \). The longer the length constant, the further the spread of potential.

Examples to illustrate this concept include: (1) Insulation increases conduction—producing a greater length constant (\( \lambda \)); (2) A decrease in the resistance of inner core (lower \( r_a \)) increases the length constant (\( \lambda \)); (3) Increasing the membrane diameter increases the length constant (\( \lambda \)).

So thick dendrites may have longer length constants (\( \lambda \)), than narrow axons. The length constant (\( \lambda \)) is an experimental measure of efficiency of passive spread along the neuron, *electronic conduction*.

The efficiency of electrotonic conduction is important because it impacts neuronal function in two ways:

1. **Spatial summation**—the process by which synaptic potentials generated in different parts of the neuron add together at the trigger zone. Greater length constant (\( \lambda \)) = more summation.

2. **Propagation of action potentials**—after threshold, action potentials spread electrotonically down the axon allowing successive regions of membrane reach threshold. Greater length constant (\( \lambda \)) = greater spread and the speed of the local-circuit current and therefore action potentials propagate more rapidly.

**The larger the axon, the more easily it’s excited**

**Key concept:** Axons with the largest diameter (lowest axial resistance) are the most excitable (e.g., lowest threshold for extracellular current).
The propagation velocity of action potentials is regulated by passive membrane properties and the axon diameter

Passive spread of a depolarizing current is not instantaneous. Electrotonic conduction is a rate-limiting factor in the propagation of the spikes. The larger the axoplasmic resistance, the smaller the current flow and the longer it takes to change the charge on the membrane.

Likewise, the larger the membrane capacitance, the more charge must be deposited on the membrane to change the potential. Consequently, current must flow for a longer time to produce a given depolarization.

Fast propagation of spikes is important. Two mechanisms have evolved to increase speed:

1. Conduction velocity—increased by increasing core diameter of the axon (e.g., squid gain axon with a diameter of 1 mm). Increasing diameter = decreasing \( r_a c_m \).
2. Myelination—increases the thickness of the axon membrane. Increasing thickness decreases membrane capacitance (\( C_m \)). Myelination yields proportionally greater decreases in \( r_a c_m \) than does the same increase in the diameter axon core.

Action potentials: triggered by interactions between myelinated and non-myelinated membrane segments

Often spikes propagating through myelinated axons started back in non-myelinated segments called axon hillocks. Inward current flowing through the hillock discharges the capacitance of the myelinated axon ahead of it. The thickness of the myelin makes the axon capacitance small. However, the amount of current flowing through the axon-core is not sufficient to discharge capacitance along the entire length of the myelinated axon.

The action is prevented from dying out by periodic bare patches of membrane, enriched with VGCC’s that generate an intense depolarizing Na+ current in response to a passive spread of depolarization.

Between nodes, spikes move quickly because of the low capacitance of the myelin sheath, and slow down as it moves across the high-capacitance bare regions. This jumping movement, saltatory conduction, was discussed in your earlier lecture (Kara).

Review:
I. Nerve muscle synapses—an example of postsynaptic potentials

The nerve muscle synapses is an excellent system to study signaling between presynaptic terminals and postsynaptic synapses. Muscle cells are big enough to place multiple recording electrodes are usually innervated by only one presynaptic axon.

The motor nerve innervates the muscle at a membrane called the end-plate. The axon releases the neurotransmitter acetylcholine onto receptors located on the muscle from presynaptic terminals (also called presynaptic boutons).

The presynaptic bouton contains a specialized section of membrane called the active zone. Active zones contain acetylcholine neurotransmitter packaged into synaptic vesicles and specialized machinery (voltage gated calcium channels) to release the vesicles.

Key concept: depolarization of the endplate produces an endplate potential (EPP). As it propagates into muscle, EPP amplitude declines and the time course increases—this should sound like the passive spread of potential.
Ion channels at the endplate are permeable to sodium and potassium
Activation of acetylcholine receptors produces this response by opening of channels permeable to sodium and potassium. Remember from earlier lectures that current flow through a membrane conductance is given by the product of the membrane conductance and the electrochemical driving force on the ions conducted through the channels.

**Na**⁺ and **K**⁺ move in opposite directions through the same channel.

*Key concept:* The polarity and the magnitude of the EPSC depends on the electrochemical driving force.

The *reversal potential* is an experimental value. With it, you can determine which ion conductances underlie an unknown potential.

**3 things to remember:**
1. If the postsynaptic membrane potential is more negative than the resting potential, the amplitude of the EPSC is large.
2. When the membrane potential is less negative than the resting potential, the EPSC is smaller.
3. At the potential where the EPSC goes to zero (~ 0 mV for the neuromuscular junction) this is by definition the *reversal potential*.
4. If the potential continues to become less negative, the polarity will reverse in direction (polarity change).

*Key concept:* *reversal potential* is the membrane potential at which a given neurotransmitters causes no net current flow of ions.

Another example of the reversal potential.

**Pretend** that endplate receptors were only permeable to Na⁺ (*Fig. A*). How are these results different if the receptors were permeable to both Na⁺ and K⁺ (*Fig. B*).

**Answer:**
1. If only Na⁺ flux caused EPSPs, the reversal potential would be at +55 mV (*the E* Na⁺). In reality the EPSP reverses around 0 mV (*Fig. b*).
2. If only Na⁺ flux caused EPSPs, then at *E* Na⁺ there would show zero conductance. In reality, there is a large current at +55 mV (*fig. b*)
3. So, more than one ion must be moving

*Key concept:* neurotransmitters function by pulling the postsynaptic potential toward the *E* rev for that particular ion channel.

II. Excitatory and inhibitory postsynaptic potentials

Post synaptic events in response to neurotransmitter binding usually involve a depolarizing or a hyperpolarizing change.

**EPSPs**

Excitatory receptors at synapses open Na⁺ and K⁺ channels. This increases membrane permeability (in both directions). Each ion follows its chemical gradient. Typically the inward Na⁺ current is greater than the outward K⁺ gradient causing the postsynaptic membrane to depolarize. The resulting potential (EPSC) brings the cell from its resting state closer to threshold. Single EPSPs, a local response, decay quickly. Remember that normal permeability has K⁺ diffusing outward more readily than Na⁺ diffuses inward, thus the repolarizing the membrane to the resting state quickly.
IPSPs
This is essentially the opposite that of the excitatory synapse. The ions involved are usually K+ and Cl-. Remember from the earlier Kara lectures that because of their ionic gradient, K+ flows outward and Cl- flows inward.

**Key concept:** An EPSP has a reversal potential more positive than action potential threshold. IPSPs have reversal thresholds more negative than action potential threshold.

III- Summation
As mentioned, most EPSPs short lasting (15 ms), local potentials. Alone these potentials are too slow and small to produce an action potential. *Spatial summation* is a summated EPSP resulting from the simultaneous activation of many synapses onto that neuron. If enough of them fire at the same time local EPSPs summate to produce an electrotonic potential that depolarizes the hillock through the instantaneous spread of electronic current. If threshold is not reached, no action potential will be seen. *Temporal summation* is similar except it uses timing (rather spatial inputs) to shift the potential toward threshold.

Remember that local responses are graded; action potential are not.

**Key concept:** The amplitude of the EPSPs reflects the number of synapses firing or the timing/frequency of activation of input onto the neuron membrane.

Tomorrow
Synaptic transmission (presynaptic release) and review.
In 1967, Rall proposed a theoretical model for current spread and synaptic potentials in dendrites and the expected voltage changes recorded at the soma. Before this, dendrites were believed not to play a significant role at the cell body. Rall changed this perception and showed that:

1. Distal excitatory synapses do contribute to the depolarizing charge propagating to soma.
2. However, it is the location of the dendritic input that dictates the time course of the somatic EPSP.
3. Different locations experience different amounts of filtering of high frequencies because of the different distribution of capacitances along the dendrite.

Rall’s observations forced a reexamination that neurons were isopotential spheres and that somatic EPSP of different shapes reflected activation of different mechanisms or different receptors. Rall’s work showed that identical synaptic conductances generate different time courses because different electronic distances, $\chi$ (in units of the space constant, $\lambda$).

**Key concept:** The farther away the synapse, the slower the EPSP rises and the broader the signal is at the soma. So, if recording at the soma, **distal events** are smaller and broader; **proximal events** are bigger and thinner.

**New tool: kinetics**

Change in the kinetics of the EPSP (rise time, decay constants) became a tool to determine (with somatic recordings) where in the dendrites a synapse was activated.

In particular, it was demonstrated that excitatory and inhibitory synapses in dendrites do not sum linearly with each other.

A dendritic tree with only passive membrane does not sum synaptic potentials linearly. This is because a synaptic input is by definition a conductance change, which when activated, perturbs (shunts) the dendritic membrane. The closer 2 synapses are together, the more they shunt each other.

In vivo the simultaneous activation of several inputs reduces input resistance and membrane time constant, which increases the cable length. So, models that stimulate linear synaptic integration with current injection do not represent accurately what happens in the neuron. This later formed the basis for the recognition of ‘shunting inhibition.”

In 1969, Rall examined a passive isopotential soma coupled to an electrically passive dendritic tree.

In later years, it became apparent that dendrites are not isopotential; leading to the likely situation that different part of the dendritic tree may behave electrically (and chemically) different from each other. This work lead to a revolutionary (at the time) prediction that mitral and granule cells interact with each other via dendrodendritic synapses. This remains an outstanding example of how a theoretical model can predict an unknown anatomical connection and physiological action. In one sense, this work again was a surprising turn, because it indicated that dendrites were not simply postsynaptic elements.
Passive regulation of synaptic potentials

Passive dendrites are bad at propagating voltage signals from dendrites to soma for several reasons. (1) The $R_m$ is usually low, allowing current loss along the dendritic tree (distance-dependent decline in the amplitude of the voltage signal).

(2) The $C_m$ acts as a low-pass filter, which primarily decreases fast synaptic voltage responses.

(3) Shape: dendrites become narrower with distance, meaning that voltage-decreases are asymmetrical. That is, voltages prefer to propagate away from (not toward) soma.

The net result of passive properties is a reduction in the amplitude and slow time-course of distal events, as they propagate from dendrites to soma.

Key point—Rule-1: The farther the input from the soma, the larger and faster the local response is to a given synaptic input (Fig. 1A-D). This is because membranes of distal dendrites are narrower—meaning they possess (i) higher impedances and (ii) lower $C_m$. This increases the size and time course of the local voltage response. In contrast, synaptic responses near the soma are filtered by the large $C_m$, which decreases the amplitude and slows the time course.

Interactions of multiple excitatory responses

Single synaptic responses are usually an insufficient depolarization to trigger a spike. Spikes usually require summation of multiple EPSPs. Interactions between EPSPs are regulated by the same passive properties noted above.

Rule-2: The degree of potentiation depends upon the temporal and spatial overlap of EPSPs. Two inputs active in close proximity with overlapping timing will produce a sublinear summation, due to a reduction in driving force. In contrast, synaptic inputs separated temporally and spatially produce near-linear summation (Fig. 1E-G).

Key concept: Postsynaptic potentials decay several times slower than conductance changes. Conductance changes are more spatially restricted than voltage responses.

Interactions between Excitatory & Inhibitory responses

The same passive properties regulate interactions between excitatory and inhibitory responses. Recall that because the reversal potential is close to the resting membrane potential, GABA can depolarize or hyperpolarize. GABA diminishes the probability of spikes, by diminishing the likelihood of concurrent EPSCs by clamping the membrane potential below spike potential threshold necessary for a spike.

This 'shunting inhibition' is more effective than general postsynaptic hyperpolarization for several reasons:

(1) temporal precision: inhibits spike generation only during the few milliseconds the channel is open.

(2) conductance changes are more spatially restricted than voltage responses, meaning that GABA-A can influence discrete parts of the dendritic tree.

(3) depolarizing responses to GABA can be inhibitory or excitatory,
Summary:

(1) Synaptic events function as conductance changes, rather than voltage sources.

(2) Their interaction is regulated by the dendritic morphology.

(3) Events, if spatially or temporally isolated, summate linearly. That is, in passive systems, excitatory inputs distributed in time or along the dendrite have a greater impact on spike generation, than concurrent inputs to a single location.