

The Brain and Behavior

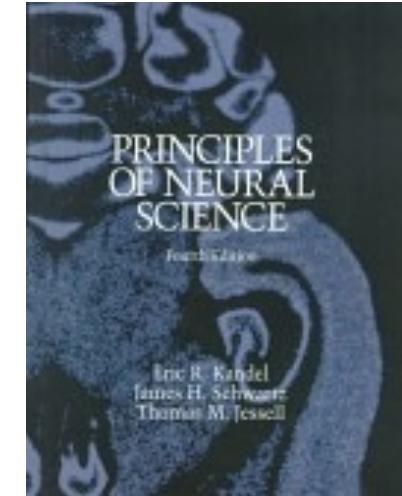
Carnegie Mellon

18-698 / 42-632
Neural Signal Processing
Spring 2022
Prof. Byron Yu

Roadmap

Introduction to neuroscience

- Chapter 1 – The brain and behavior
- Chapter 2 – Nerve cells and behavior



How are neural signals generated?

- Chapter 7 – Membrane potential
- Chapter 9 – Propagated signaling: the action potential

How do neurons communicate with each other?

- Chapter 10 – Overview of synaptic transmission
- Chapter 12 – Synaptic integration

Introduction to Neuroscience

- Reading assignment from *Principles of Neural Science* (PNS):
 - Chapter 1 – The brain and behavior
 - Chapter 2 – Nerve cells and behavior
- Neural science (neuroscience) – understand mental processes underlying perception, action, learning and memory.
- Are mental processes localized in the brain, or distributed?
- What is the relationship between anatomy, physiology & function?
- Should we study regions as a whole, or individual cells?
- Are mental processes hard wired?
- Role of genetics in nerve growth? Regulated by learning?
- How does experience alter brain processing of subsequent events?

Introduction Continued

- Neuroscience studies all of this and attempts to link molecules to mind.
- Human brain: highly-interconnected network of ~100 billion individual nerve cells.
 - Must learn how neurons are organized into signaling pathways and how they communicate.
 - So, let's get started...

A Brief History

- Galen (100s) – mental activity occurs in the brain, not the heart!
 - nerves convey fluid secreted by the brain.
- Galvani (1700s) – muscle and nerve cells produce electricity.
- Golgi and Ramon y Cajal (1800s) – saw a network of discrete cells, not a continuous mass/web, with compound microscope.
- DuBois-Reymond, Muller & Helmholtz (1800s) – electrical activity of one nerve cell affects activity of adjacent cell in predictable ways.
- Ramon y Cajal's *neuron doctrine* (1800s) – individual neurons are the elementary signaling elements of the nervous system.
- Bernard, Erlich & Langley (1800s) – drugs bind specifically to receptors on the cell surface (membrane) → chemical basis of communication between nerve cells.
- Harrison (1920s) – two processes that grow out of cell body: dendrites and the axon.

Phrenology

- Gall (1800s)
 - 1) All behavior emanates from the brain.
 - 2) Particular regions of cerebral cortex control specific functions (functional organization).
 - 3) Centers for each neural function grow with use (like a muscle).
- Growth → bumps on skull → psychology of bumps termed phrenology.

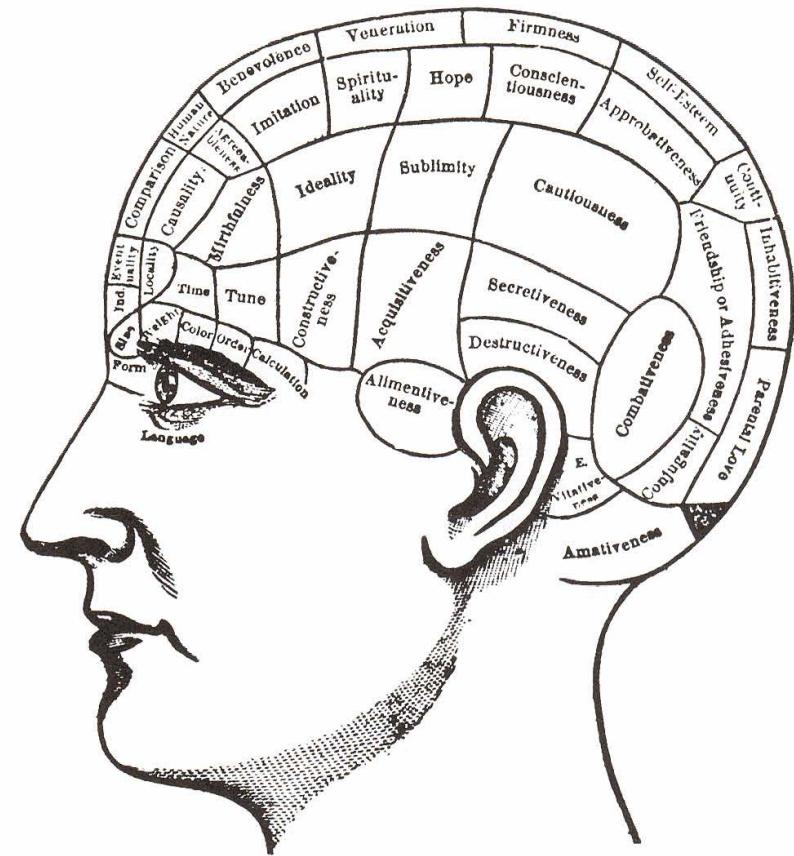


Figure 1-1 According to the nineteenth-century doctrine of phrenology, complex traits such as combativeness, spirituality, hope, and conscientiousness are controlled by specific areas in the brain, which expand as the traits develop. This enlargement of local areas of the brain was thought to produce characteristic bumps and ridges on the overlying skull, from which an individual's character could be determined. This map, taken from a drawing of the early 1800s, purports to show 35 intellectual and emotional faculties in distinct areas of the skull and the cerebral cortex underneath.

Cellular Connectionism

- Wernicke, Sherrington & Ramon y Cajal (~1850) put forth a view of the brain termed *cellular connectionism*:
 - Individual neurons are the signaling units of the brain.
 - They are generally arranged in functional groups.
 - They connect to one another in a precise fashion.
- This is in opposition to a previous view termed *aggregate field*:
 - All brain regions participate in every mental operation.
 - Injury to a specific area of the brain affects all higher functions equally.

Brain has Distinct Functional Regions

- CNS is bilateral and symmetrical.
- Modern imaging techniques confirm that different regions are specialized for different functions.
- However, parallel distributed processing (functions served by more than one neural pathway) in operation.
- CNS has 7 major parts:
 - 1) skin, joints, muscles of limbs / trunk
 - 2) breathing, heart rate
 - 3) movement: 4 \leftrightarrow 7
 - 4) learning motor skills
 - 5) eye movements
 - 6) info gate keeper 7 $\leftarrow \rightarrow$ rest
 - 7) higher brain funtions: sensory, motor, memory, emotion

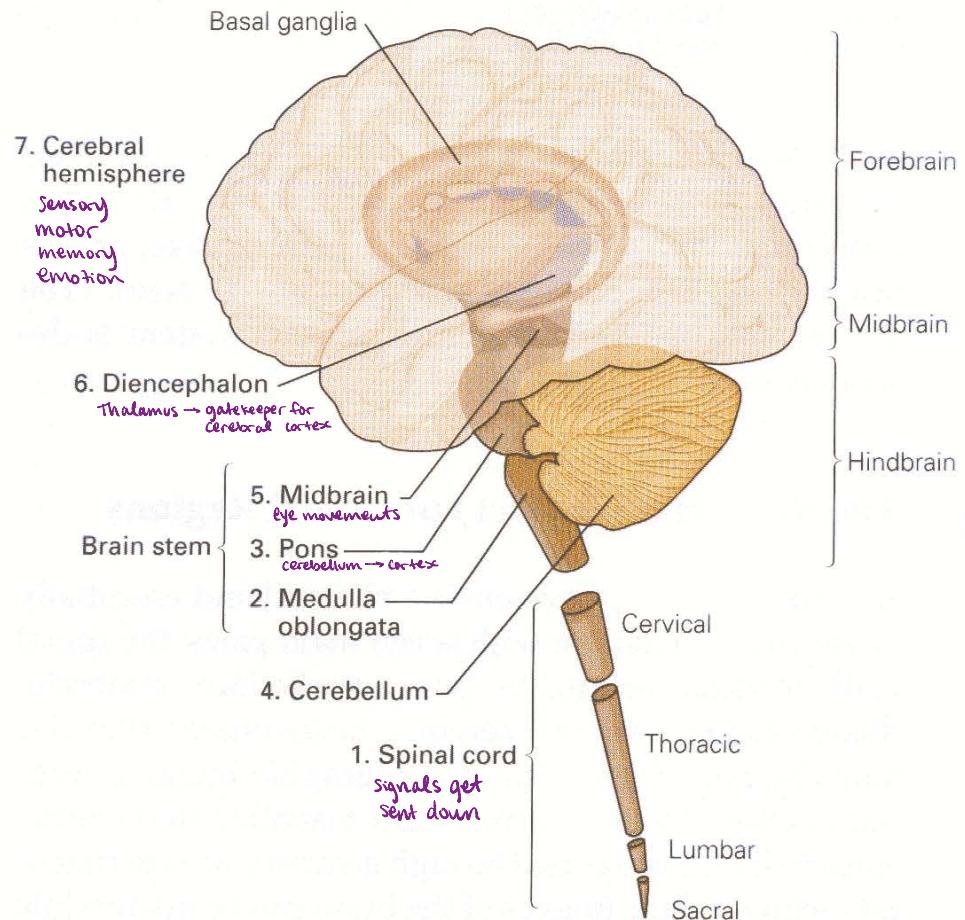


Figure 1-2A The central nervous system can be divided into seven main parts.

Major Divisions of the Brain

- Easy to see the major divisions anatomically (left) or with modern non-invasive imaging such as MRI.

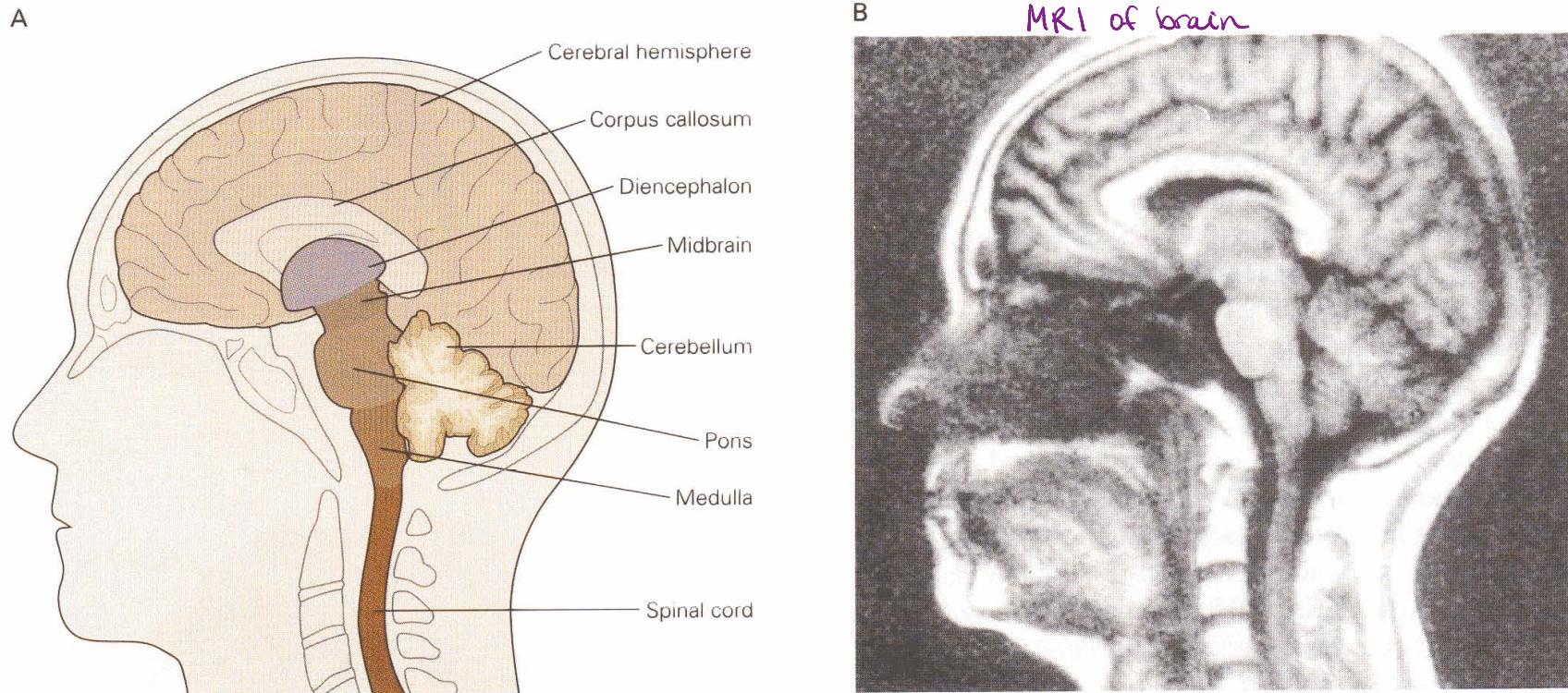


Figure 1-3 The main divisions are clearly visible when the brain is cut down the midline between the two hemispheres.

A. This schematic drawing shows the position of major structures of the brain in relation to external landmarks. Students of

brain anatomy quickly learn to distinguish the major internal landmarks, such as the corpus callosum, a large bundle of nerve fibers that connects the left and right hemispheres.

B. The major brain divisions drawn in A are also evident here in a magnetic resonance image of a living human brain.

Cerebral Cortex

- Brain operations responsible for our cognitive abilities occur in the cerebral cortex.
- Cerebral cortex – “furrowed gray matter” covering the two cerebral hemispheres.
- Folds increase surface area: gyri (crests) and sulci (grooves)
- Four anatomically distinct lobes:
 - Frontal – planning future action and the control of movement
 - Parietal – somatic sensation, relationship between body and space
 - Temporal – hearing, learning, memory and emotion
 - Occipital – vision

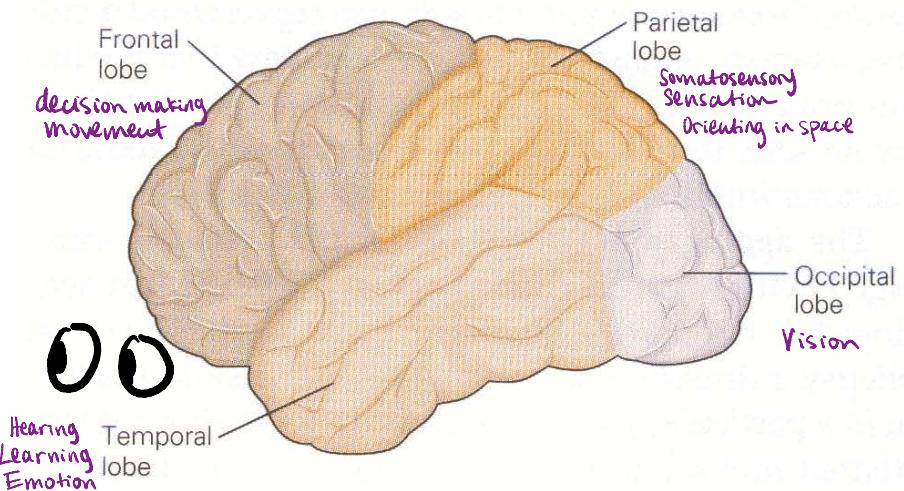


Figure 1-2B The four lobes of the cerebral cortex.

← anterior posterior →
(front) (back)

Two Important Features of Cerebral Cortex

- Each hemisphere is concerned primarily with sensory and motor processing of the contralateral (opposite) side of the body.

E.g., electrically stimulate left motor cortex → right arm movement (Fritsch & Hitzig, 1870s).

- The hemispheres are similar in appearance, but are not completely symmetrical in structure or in function.

E.g., language centers in left hemisphere (aphasia patients, Broca, 1860s).

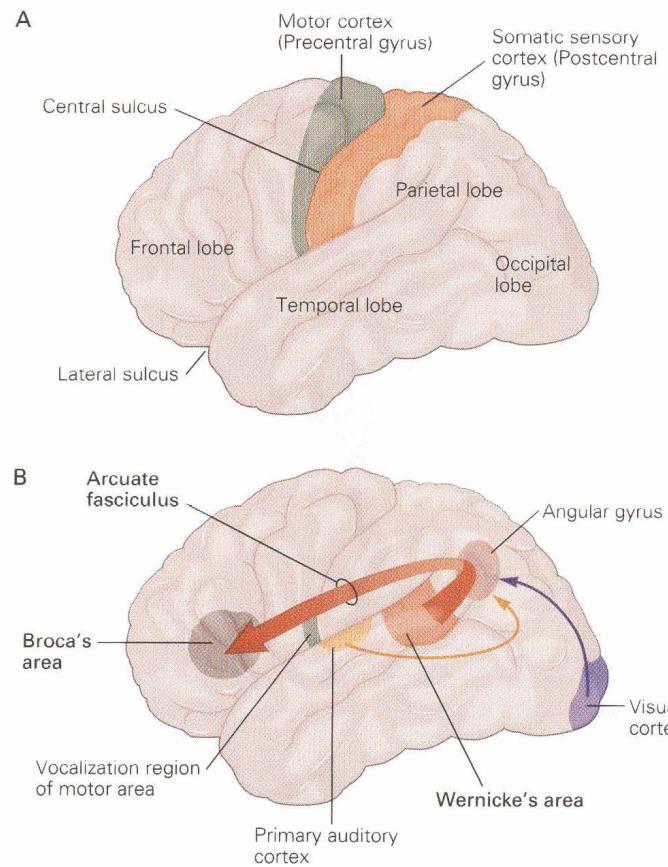


Figure 1-4 The major areas of the cerebral cortex are shown in this lateral view of the left hemisphere.

A. Outline of the left hemisphere.

B. Areas involved in language. **Wernicke's area** processes the auditory input for language and is important to the understanding of speech. It lies near the primary auditory cortex and the angular gyrus, which combines auditory input with information from other senses. **Broca's area** controls the production of intelligible speech. It lies near the region of the motor area that controls the mouth and tongue movements that form words. Wernicke's area communicates with Broca's area by a bidirectional pathway, part of which is made up of the **arcuate fasciculus**. (Adapted from Geschwind 1979.)

Brodmann's Areas

- Brodmann (~1900) distinguished *functional areas* of the cortex based on variations in the *structure of cells* and in the *arrangement of these cells* into layers.
- 52 anatomically and functionally distinct areas in human cerebral cortex.
- Still widely used today (e.g., motor cortex is area 4).

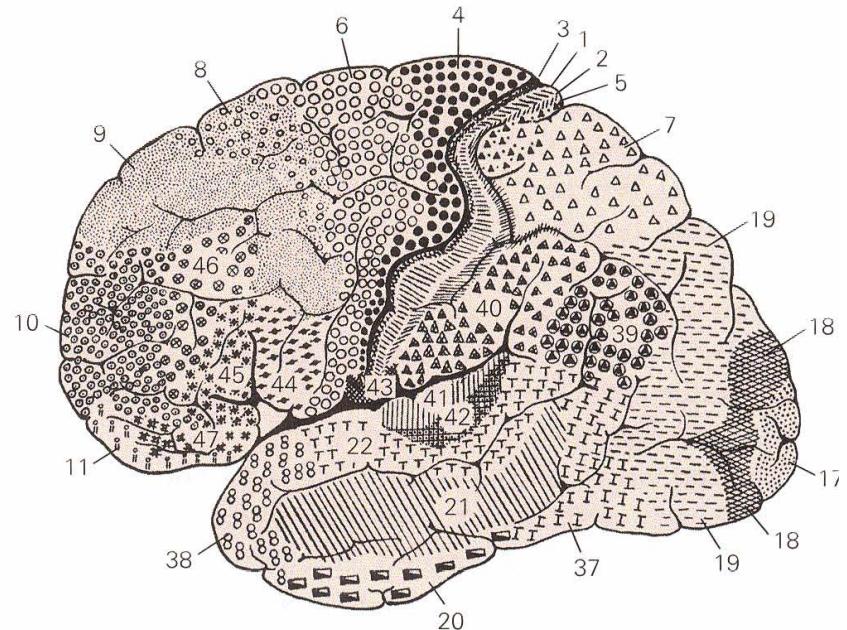


Figure 1-5 In the early part of the twentieth century Korbinian Brodmann divided the human cerebral cortex into 52 discrete areas on the basis of distinctive nerve cell structures and characteristic arrangements of cell layers. Brodmann's scheme of the cortex is still widely used today and is continually updated. In this drawing each area is represented by its own symbol and is assigned a unique number. Several areas defined by Brodmann have been found to control specific brain functions. For instance, area 4, the motor cortex, is responsible for voluntary movement. Areas 1, 2, and 3 comprise the primary somatosensory cortex, which receives information on bodily sensation. Area 17 is the primary visual cortex, which receives signals from the eyes and relays them to other areas for further deciphering. Areas 41 and 42 comprise the primary auditory cortex. Areas not visible from the outer surface of the cortex are not shown in this drawing.

Functional Localization in Language

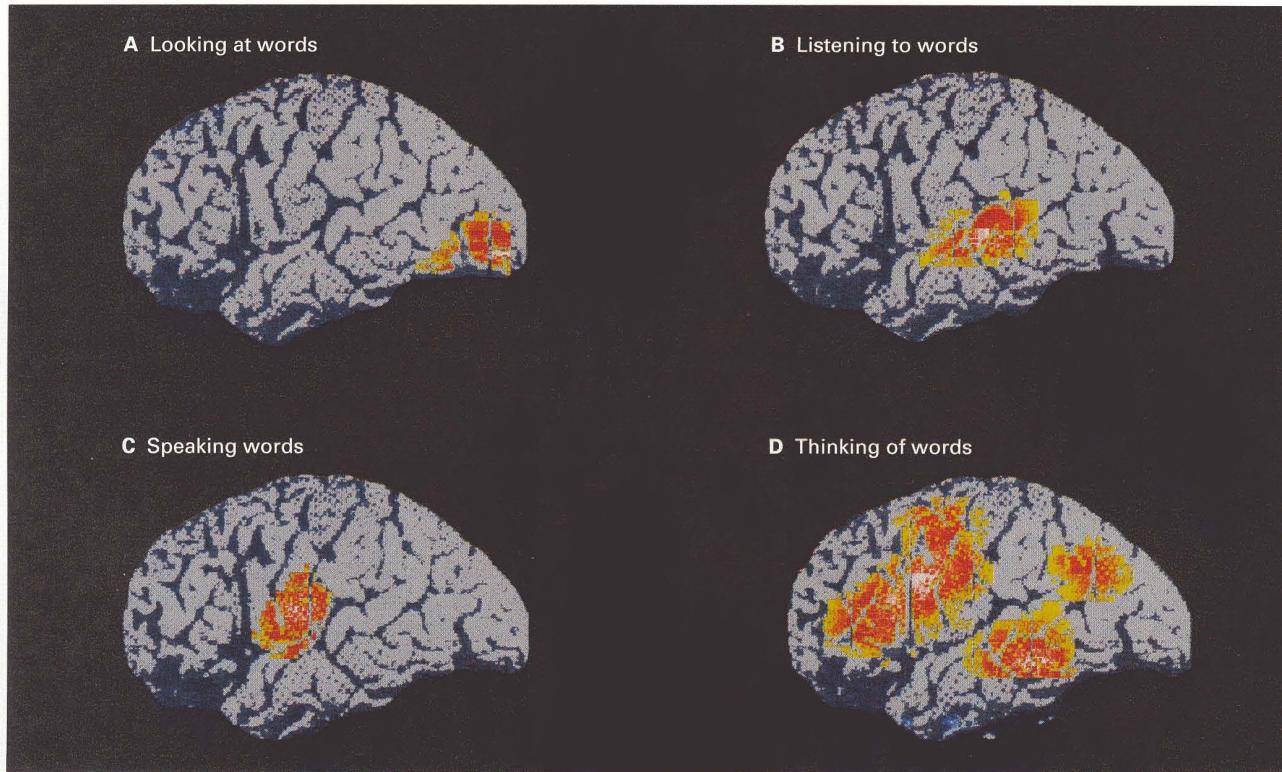


Figure 1-6 Specific regions of the cortex involved in the recognition of a spoken or written word can be identified with PET scanning. Each of the four images of the human brain shown here (from the left side of the cortex) actually represents the averaged brain activity of several normal subjects. (In these PET images white represents the areas of highest activity, red and yellow quite high activity, and blue and gray the areas of minimal activity.) The “input” component of language (reading or hearing a word) activates the regions of the brain shown in A and B. The motor “output” component of language (speech or thought) activates the regions shown in C and D. (Courtesy of Cathy Price.)

- A. The reading of a single word produces a response both in the primary visual cortex and in the visual association cortex (see Figure 1-5).
- B. Hearing a word activates an entirely different set of areas in the temporal cortex and at the junction of the temporal-

parietal cortex. (To control for irrelevant differences, the same list of words was used in both the reading and listening tests.) A and B show that the brain uses several discrete pathways for processing language and does not transform visual signals for processing in the auditory pathway.

C. Subjects were asked to repeat a word presented either through earphones or on a screen. Speaking a word activates the supplementary motor area of the medial frontal cortex. Broca’s area is activated whether the word is presented orally or visually. Thus both visual and auditory pathways converge on Broca’s area, the common site for the motor articulation of speech.

D. Subjects were asked to respond to the word “brain” with an appropriate verb (for example, “to think”). This type of thinking activates the frontal cortex as well as Broca’s and Wernicke’s areas. These areas play a role in all cognition and abstract representation.

PNS Chapter 2

Nerve Cells and Behavior

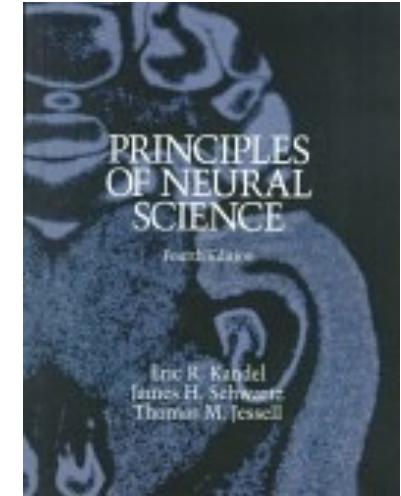
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Neurons

- Nerve cells (**neurons**) are the basic unit of the brain.
- Neurons are relatively simple in their morphology.
- Approximately 10^{11} neurons in the human brain.
- About 1000 different types, but all have same basic architecture.
- Thus “complexity” arises primarily from precise anatomical circuits, not neuron specialization.
- Neurons with basically similar properties produce quite different actions because of their connections with each other.

Neurons Continued

- We will now focus on four basic features of the nervous system:
 - 1) Mechanisms by which neurons produce signals.
 - 2) Patterns of connections between neurons.
 - 3) Relationship of different patterns of interconnection to different type of behavior.
 - 4) Means by which neurons and their connections are modified by experience.

Nervous System has Two Cell Classes

- Nerve cells (neurons) and glial cells (glia).
- Glia are support cells, and outnumber neurons 10-50:1.
- Glia are not directly involved in information processing.
- Glia do:
 - 1) Support neurons by providing structure.
 - 2) Produce myelin used to electrically insulate neural axons (*oligodendrocytes & Schwann cells*).
 - 3) Scavenge to remove debris after injury or cell death.
 - 4) Sop up previously-released chemical transmitters.
 - 5) Help guide axon growth during development.
 - 6) Help regulate properties of presynaptic terminal.
 - 7) Help form blood-brain barrier (*astrocytes*).
 - 8) Release growth factors and nourish neurons.

Glia

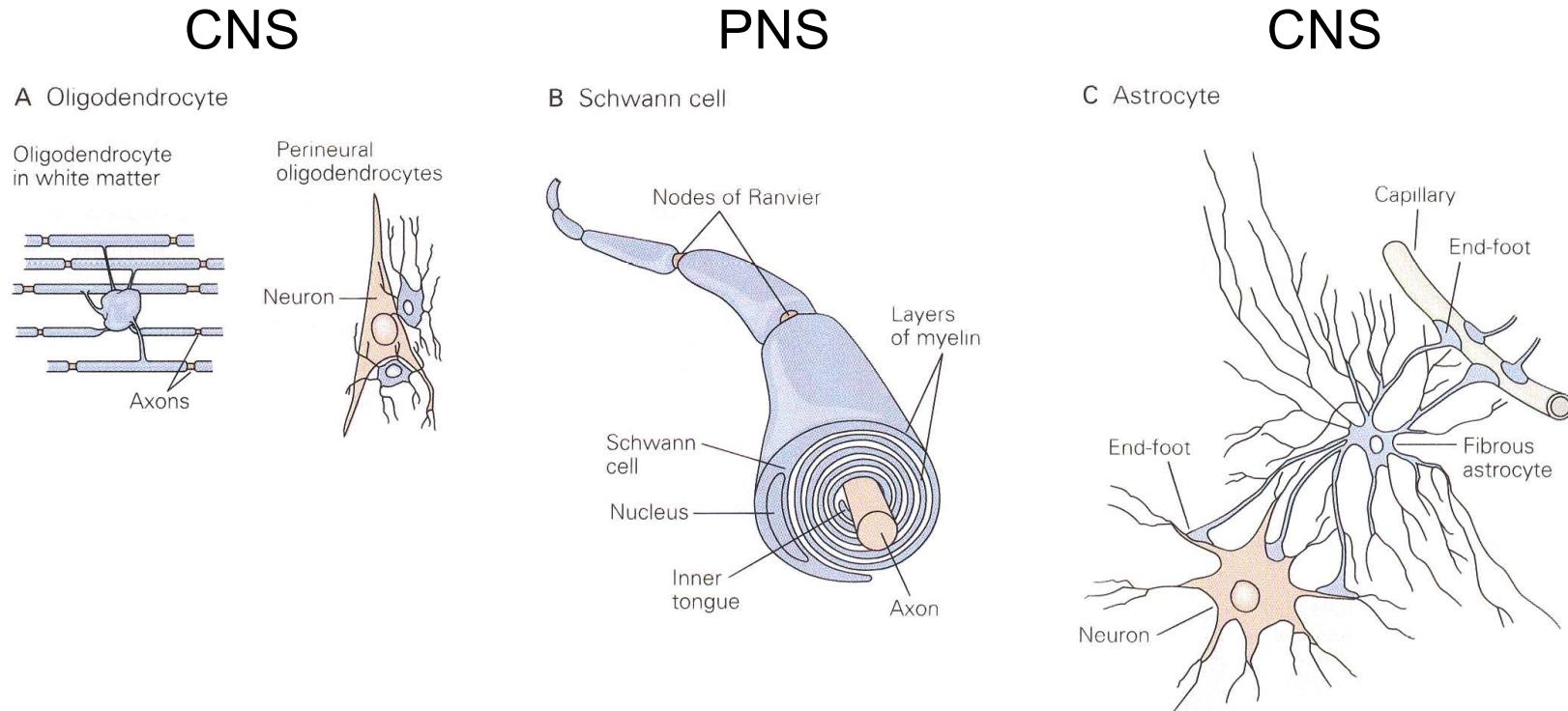


Figure 2-1 The principal types of glial cells in the central nervous system are astrocytes and oligodendrocytes and in the peripheral nervous system, Schwann cells.

A. Oligodendrocytes are small cells with relatively few processes. In white matter (left) they provide the myelin, and in gray matter (right) perineurial oligodendrocytes surround and support the cell bodies of neurons. A single oligodendrocyte can wrap its membranous processes around many axons, insulating them with a myelin sheath.

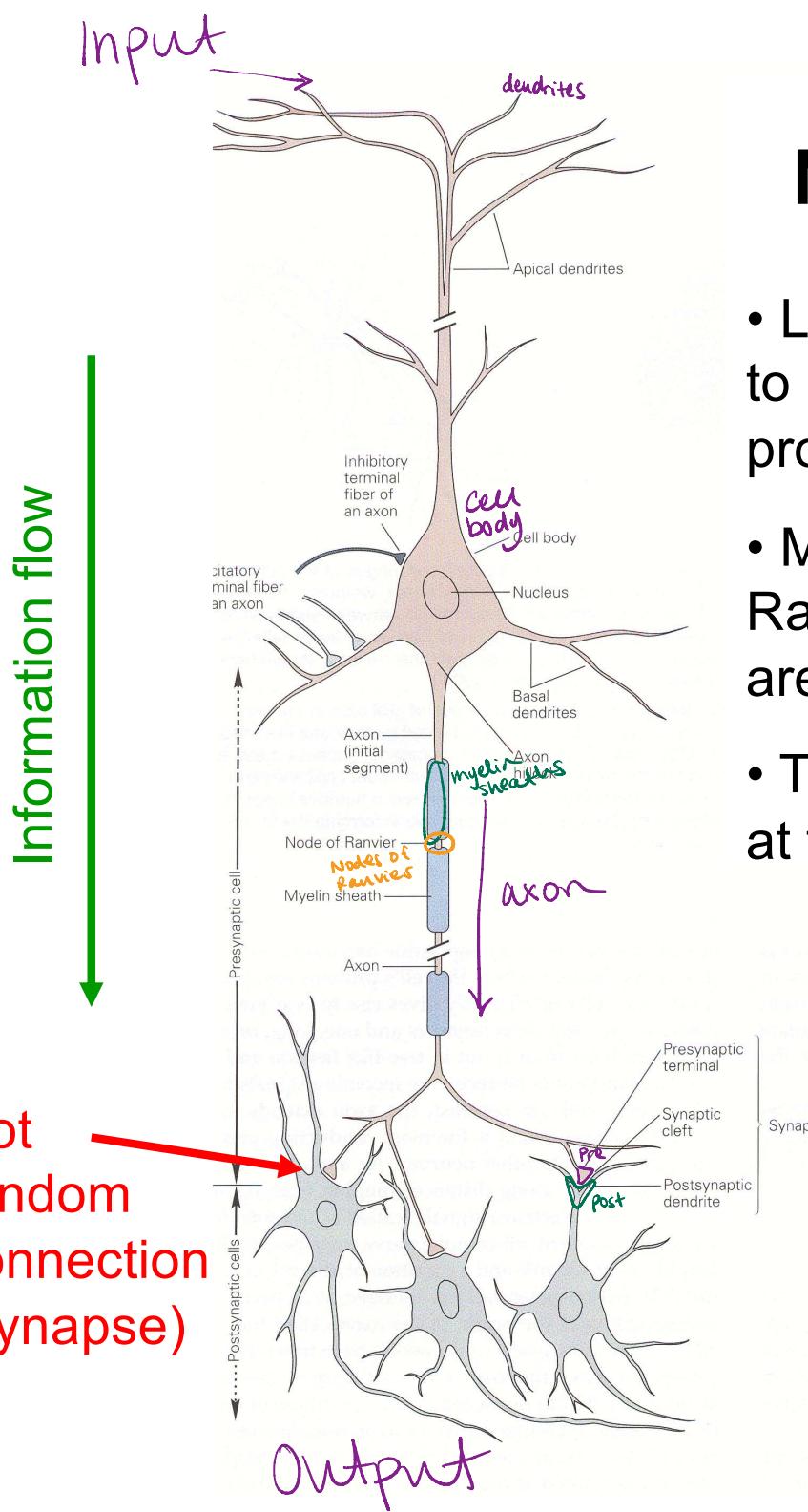
B. Schwann cells furnish the myelin sheaths that insulate axons in the peripheral nervous system. Each of several Schwann cells, positioned along the length of a single axon, forms a segment of myelin sheath about 1 mm long. The

sheath assumes its form as the inner tongue of the Schwann cell turns around the axon several times, wrapping it in concentric layers of membrane. The intervals between segments of myelin are known as the nodes of Ranvier. In living cells the layers of myelin are more compact than what is shown here. (Adapted from Alberts et al. 1994.)

C. Astrocytes, the most numerous of glial cells in the central nervous system, are characterized by their star-like shape and the broad end-feet on their processes. Because these end-feet put the astrocyte into contact with both capillaries and neurons, astrocytes are thought to have a nutritive function. Astrocytes also play an important role in forming the blood-brain barrier.

Neurons

- Neurons are the main signaling units of the nervous system.
- Neurons have four regions:
 - 1) **Cell body** (soma) – metabolic center, with nucleus, etc.
 - 2) **Dendrites** – tree like structure for receiving incoming signals.
 - 3) **Axon** – single, long, tubular structure for sending outgoing signals.
 - 4) **Presynaptic terminals** – sites of communication to next neurons.
- Axons convey signals to other neurons:
 - Conveys electrical signals long distances (0.1mm – 3 m).
 - Conveys **action potentials** (~100 mV, ~1 ms pulses). *"all or nothing"*
 - Action potentials initiate at the axon hillock.
 - Propagate w/o distortion or failure at 1-100 m/s.
 - Actively regenerated while propagating; shape preserved.



Neurons

- Large axons are wrapped in fatty myelin to increase the speed of action potential propagation.
- Myelin sheath interrupted at Nodes of Ranvier; it is here that action potentials are regenerated.
- Two neurons communicate, chemically, at the **synapse** (w/o physically touching).

Figure 2-2 Structure of a neuron. Most neurons in the vertebrate nervous system have several main features in common. The cell body contains the nucleus, the storehouse of genetic information, and gives rise to two types of cell processes, axons and dendrites. Axons, the transmitting element of neurons, can vary greatly in length; some can extend more than 3 m within the body. Most axons in the central nervous system are very thin (between 0.2 and 20 μm in diameter) compared with the diameter of the cell body (50 μm or more). Many axons are insulated by a fatty sheath of myelin that is interrupted at regular intervals by the nodes of Ranvier. The action potential, the cell's conducting signal, is initiated either at the axon hillock, the initial segment of the axon, or in some cases slightly farther down the axon at the first node of Ranvier. Branches of the axon of one neuron (the presynaptic neuron) transmit signals to another neuron (the postsynaptic cell) at a site called the synapse. The branches of a single axon may form synapses with as many as 1000 other neurons. Whereas the axon is the output element of the neuron, the dendrites (apical and basal) are input elements of the neuron. Together with the cell body, they receive synaptic contacts from other neurons.

Action Potentials

- Signals by which brain receives, analyzes and conveys information.
- Action potentials are highly stereotyped throughout nervous system.
- Action potentials convey all information about vision, audition, odors, etc...
- Information not conveyed by shape.
- Information conveyed by the pathway down which the signal travels and pattern of action potentials.

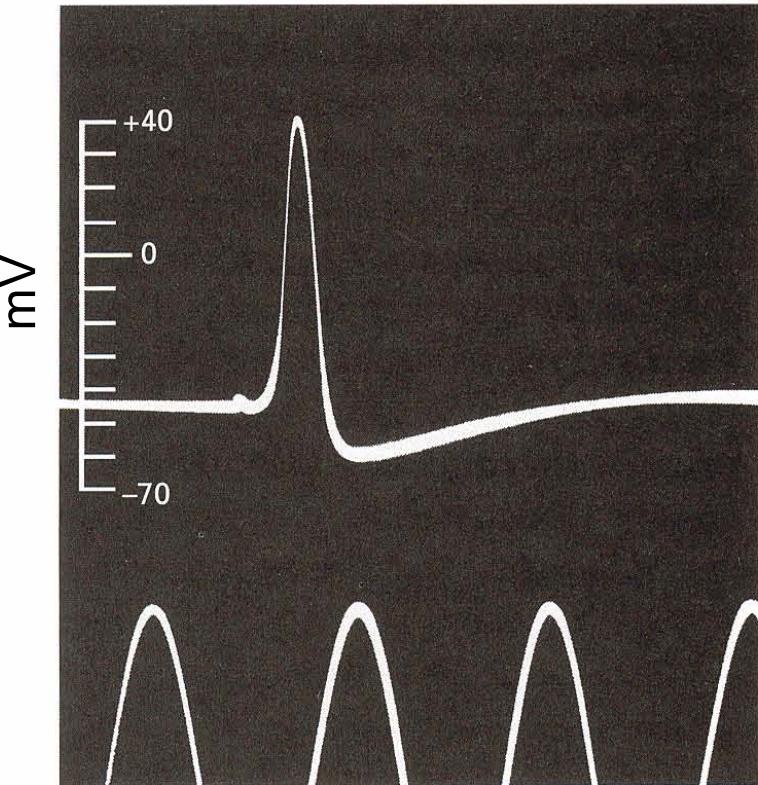


Figure 2-3 This historic tracing is the first published intracellular recording of an action potential. It was obtained in 1939 by Hodgkin and Huxley from the squid giant axon, using glass capillary electrodes filled with sea water. Time marker is 500 Hz. The vertical scale indicates the potential of the internal electrode in millivolts, the sea water outside being taken as zero potential. (From Hodgkin and Huxley 1939.)

Two principles advanced by Ramon y Cajal

- Principle of dynamic polarization:

Electrical signals within a nerve cell flow only in one direction.

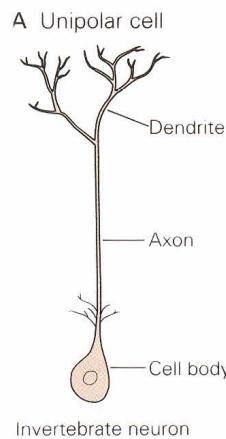
- Principle of connectional specificity:

Neurons do not connect indiscriminately to form random networks. Instead, neurons make specific connections with certain target neurons but not others.

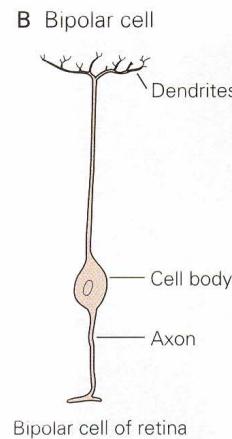
Neural Shape Varies Considerably

Figure 2-4 Neurons can be classified as unipolar, bipolar, or multipolar according to the number of processes that originate from the cell body.

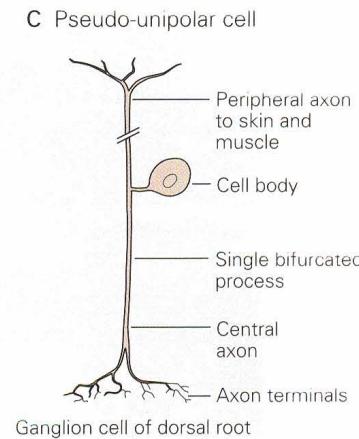
A. Unipolar cells have a single process, with different segments serving as receptive surfaces or releasing terminals. Unipolar cells are characteristic of the invertebrate nervous system.



B. Bipolar cells have two processes that are functionally specialized: the dendrite carries information to the cell, and the axon transmits information to other cells.

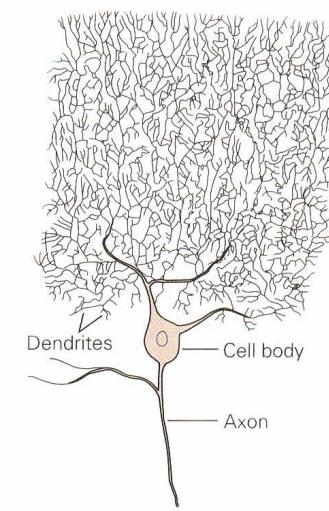
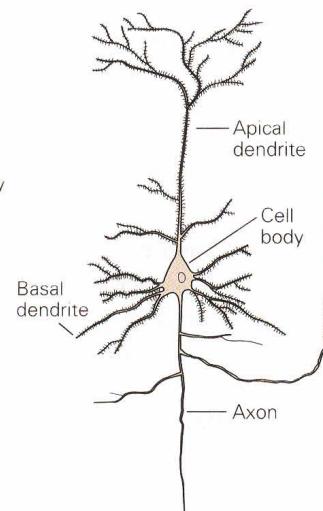
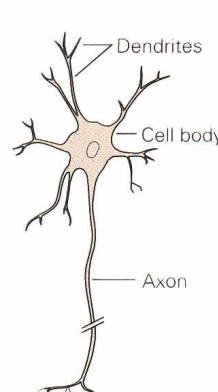


C. Certain neurons that carry sensory information, such as information about touch or stretch, to the spinal cord belong to a subclass of bipolar cells designated as pseudo-unipolar. As such cells develop, the two processes of the embryonic bipolar cell become fused and emerge from the cell body as a single process. This outgrowth then splits into two processes, both of which function as axons, one going to peripheral skin or muscle, the other going to the central spinal cord.



D. Multipolar cells have an axon and many dendrites. They are the most common type of neuron in the mammalian nervous system. Three examples illustrate the large diversity of these cells. Spinal motor neurons (left) innervate skeletal muscle fibers. Pyramidal cells (middle) have a roughly triangular cell body; dendrites emerge from both the apex (the apical dendrite) and the base (the basal dendrites). Pyramidal cells are found in the hippocampus and throughout the cerebral cortex. Purkinje cells of the cerebellum (right) are characterized by the rich and extensive dendritic tree in one plane. Such a structure permits enormous synaptic input. (Adapted from Ramón y Cajal 1933.)

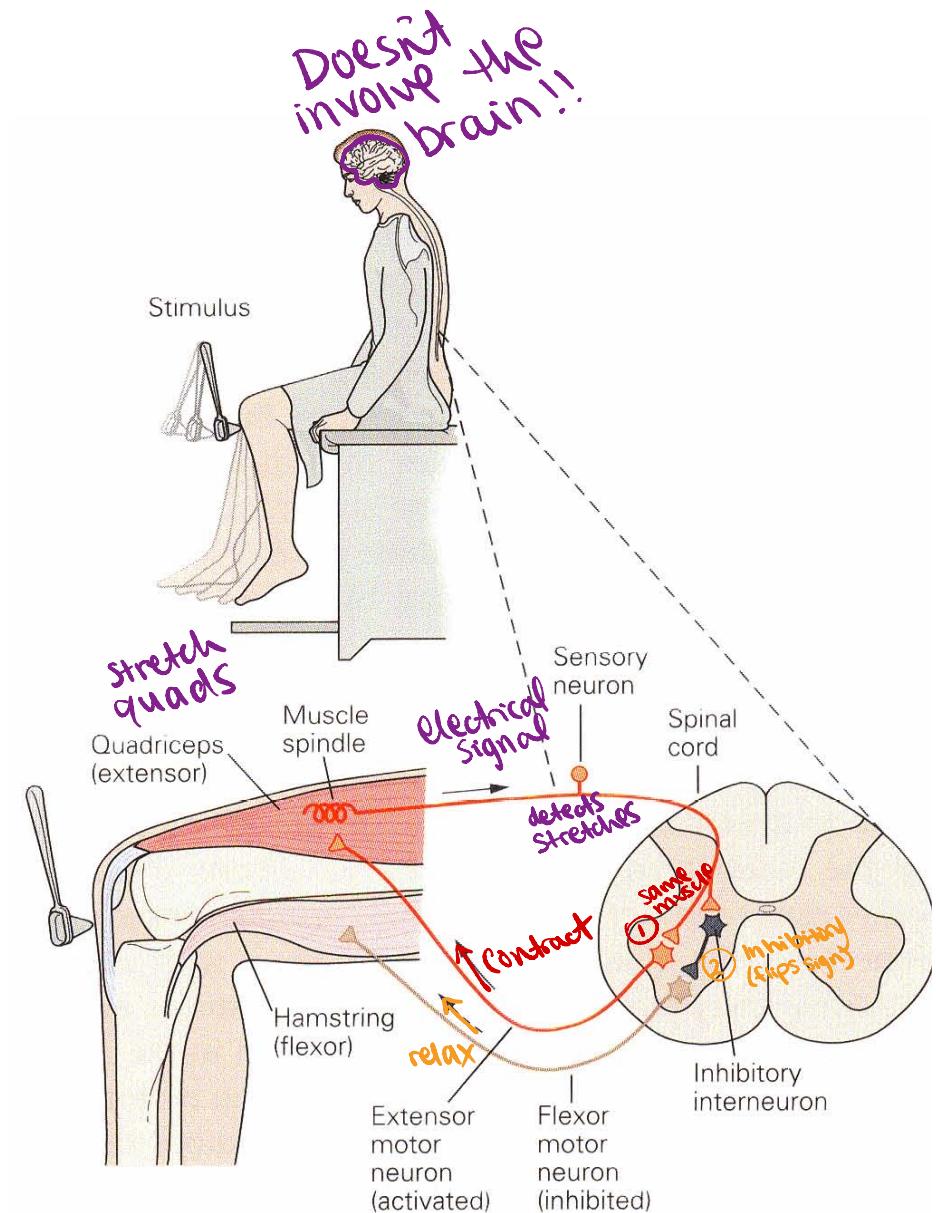
D. Three types of multipolar cells



input
↓
cell body
↓
output

Knee-Jerk Spinal Reflex Circuit

- Different classes of neurons (sensory, motor or interneuronal) have different morphologies to best serve their functionality.
- All behavioral & computational functions are carried out by sets of interconnected neurons.
- In this example, a single sensory event triggers a cascade of signals in the spinal cord that result in extension of the leg.
- Signals are also sent to higher brain structures for further processing, but does not necessarily require that cortex "get involved" → **distributed processing**.



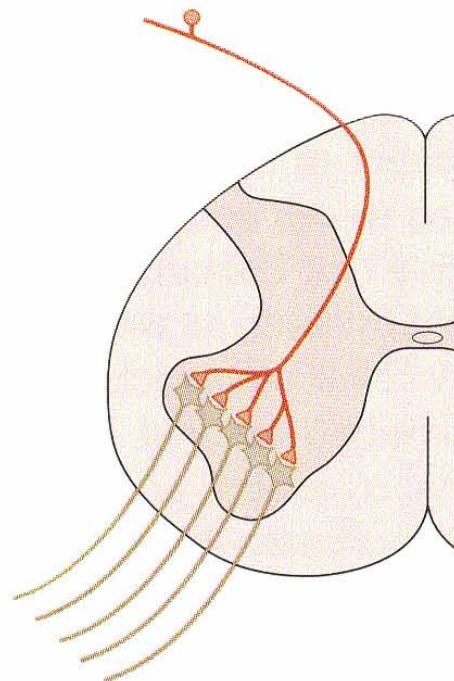
Divergence (fan-out) & Convergence (fan-in)

one neuron talks
to many neurons

many neurons talk
to same neuron

- The previous circuit was greatly (overly) simplified.
- Sensory neurons often **diverge** – allows a single sensory neuron to exert wide and diverse influence.
- Motor neurons often receive **converging** inputs – allows a single motor neuron to integrate diverse information from many sources.

A Divergence



B Convergence

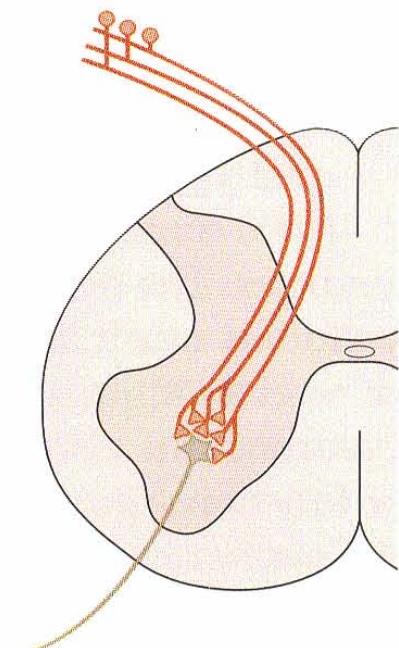


Figure 2-6 Diverging and converging neuronal connections are a key organizational feature of the brain.

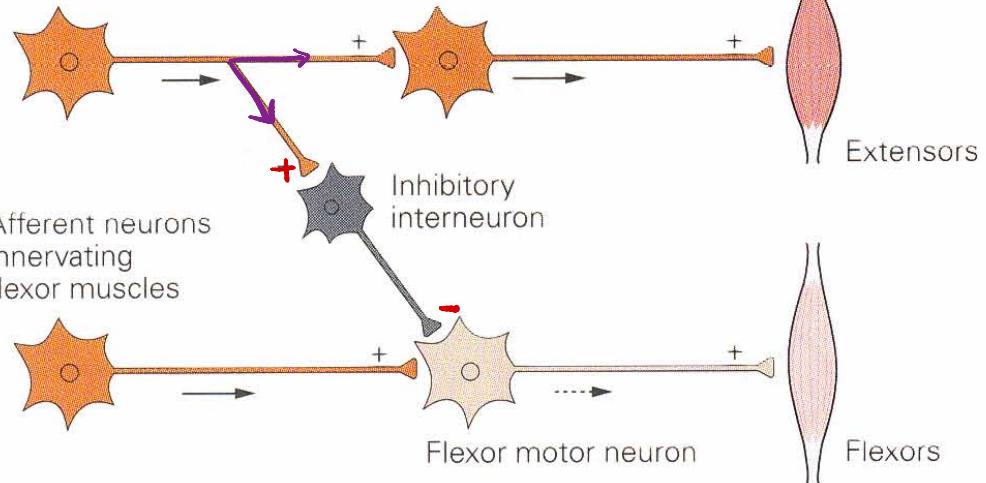
- A. In the sensory systems receptor neurons at the input stage usually branch out and make multiple, divergent connections with neurons that represent the second stage of processing. Subsequent connections diverge even more.

Feed-forward & Feedback Inhibition

- The previous two circuits were still greatly (overly) simplified.
- Reciprocal feed-forward inhibition** assures that extensor and flexor muscles are not simultaneously strongly activated.
- Negative feedback inhibition** helps regulate drive signal.
- The BIG PICTURE here is that neural circuits can be quite complex and sophisticated.
- Intriguing to consider how they were “designed” and “built” – beyond the scope of this course.

A Feed-forward inhibition

Afferent neurons
innervating
extensor muscles



Afferent neurons
innervating
flexor muscles



Extensor motor neuron

Inhibitory
interneuron

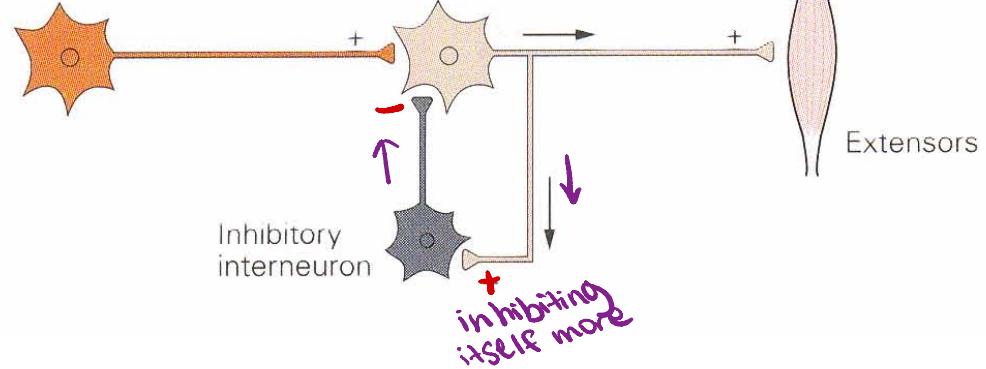
Flexor motor neuron

Extensors

Flexors

B Feedback inhibition

Afferent neuron
innervating
extensor muscles



Inhibitory
interneuron

+
inhibiting
itself more

Extensor
motor neuron

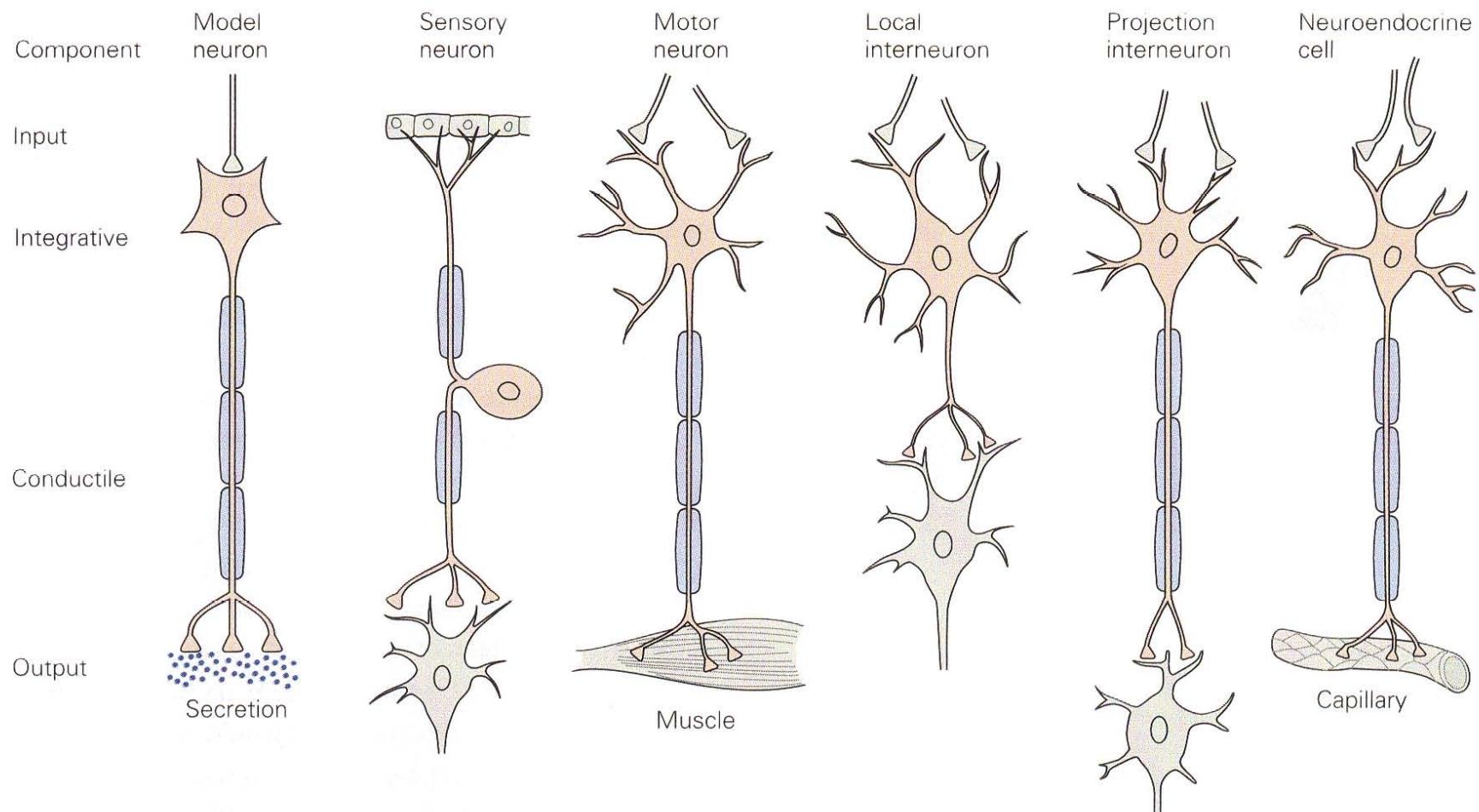
Extensors

Signaling Organization

- Almost all neurons have **input, integrating-triggering, conductive** and **output** signals.

receiving multiple inputs
and integrating them

info down axon



Resting Membrane Potential

- Neurons maintain a difference in electrical potential across the cell membrane.
- Roughly -65 mV (outside arbitrarily defined as 0 V / ground).
- Potential difference created by:
 - Unequal distribution of charged ions (e.g., Na^+ and K^+) inside/outside of cell membrane.
 - **Selective membrane permeability to K^+ .**
- Mechanism:
 - **Membrane protein pumps Na^+ out and K^+ in.**
 - **Ion channels let K^+ leak out.**

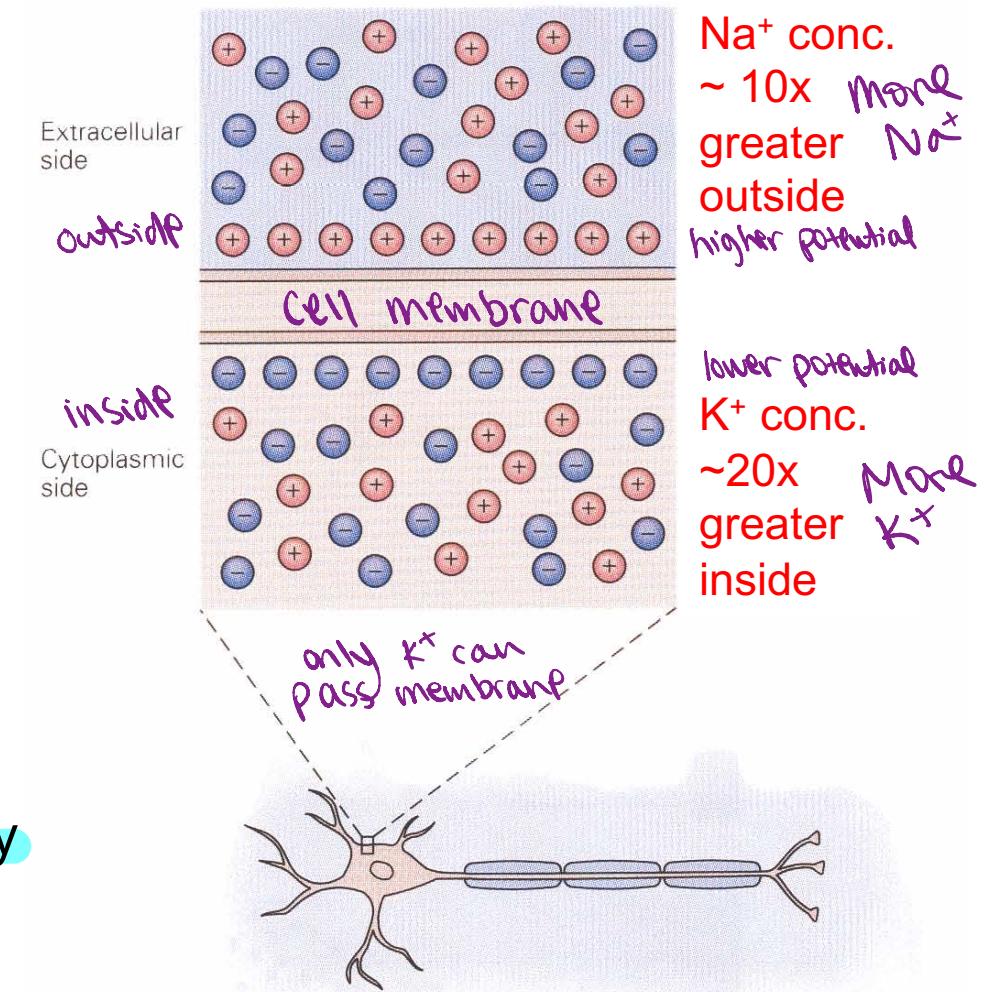


Figure 2-9 The membrane potential of a cell results from a difference in the net electrical charge on either side of its membrane. When a neuron is at rest there is an excess of positive charge outside the cell and an excess of negative charge inside it.

A 2nd Look at Action Potentials

- Neurons are **excitable cells** – can rapidly change membrane potential.
- Rapid change can serve as a signaling mechanism – **action potential**.
- Slight decrease in membrane potential (e.g., $-65 \text{ mV} \rightarrow -55 \text{ mV}$) makes membrane much more permeable to Na^+ than K^+ .
- This further reduces membrane potential and further increases Na^+ over K^+ permeability.
- This **positive feedback** loop creates sharp ($<< 1 \text{ ms}$) depolarization event (**rising edge of the action potential**).
- Action potentials are “all or nothing” and are actively propagated along axon.

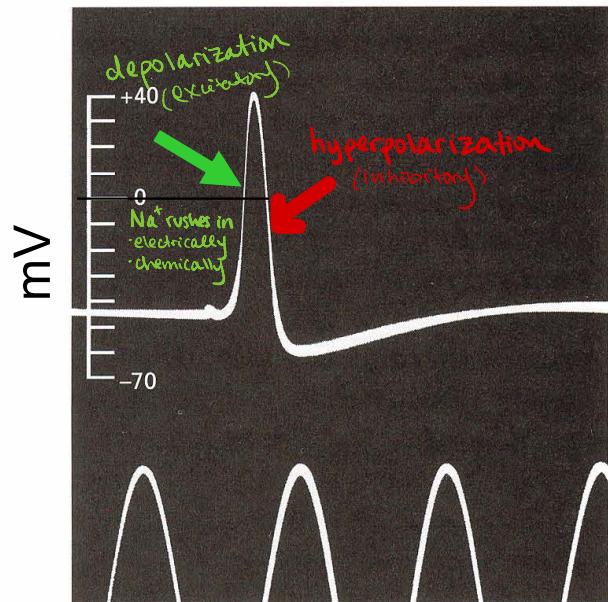


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Depolarization and Hyperpolarization

- Axonal action potentials are long range.
- Receptor and synaptic potentials are more local, short range. These signals decay on the order of millimeters.
- Both types result from a change in the membrane potential; the baseline (-65 mV) potential is the reference level.
- A reduction (e.g., -65 mV → -55 mV) termed **depolarization**. This makes action potentials more likely, and is thus **excitatory**.
- An increase (e.g., -65 mV → -75 mV) termed **hyperpolarization**. This makes action potentials less likely, and is thus **inhibitory**.

Putting it All Together

1) Receptor potential is graded and local; 1st representation of stretch.
• “Analog like”

2) Action potentials are all or nothing and long range;
2nd representation.
• “Digital like”

3) Neurotransmitter release to communicate to next neuron is statistical; 3rd representation.
• “Probabilistic like”

4) Synaptic potential is graded and local...

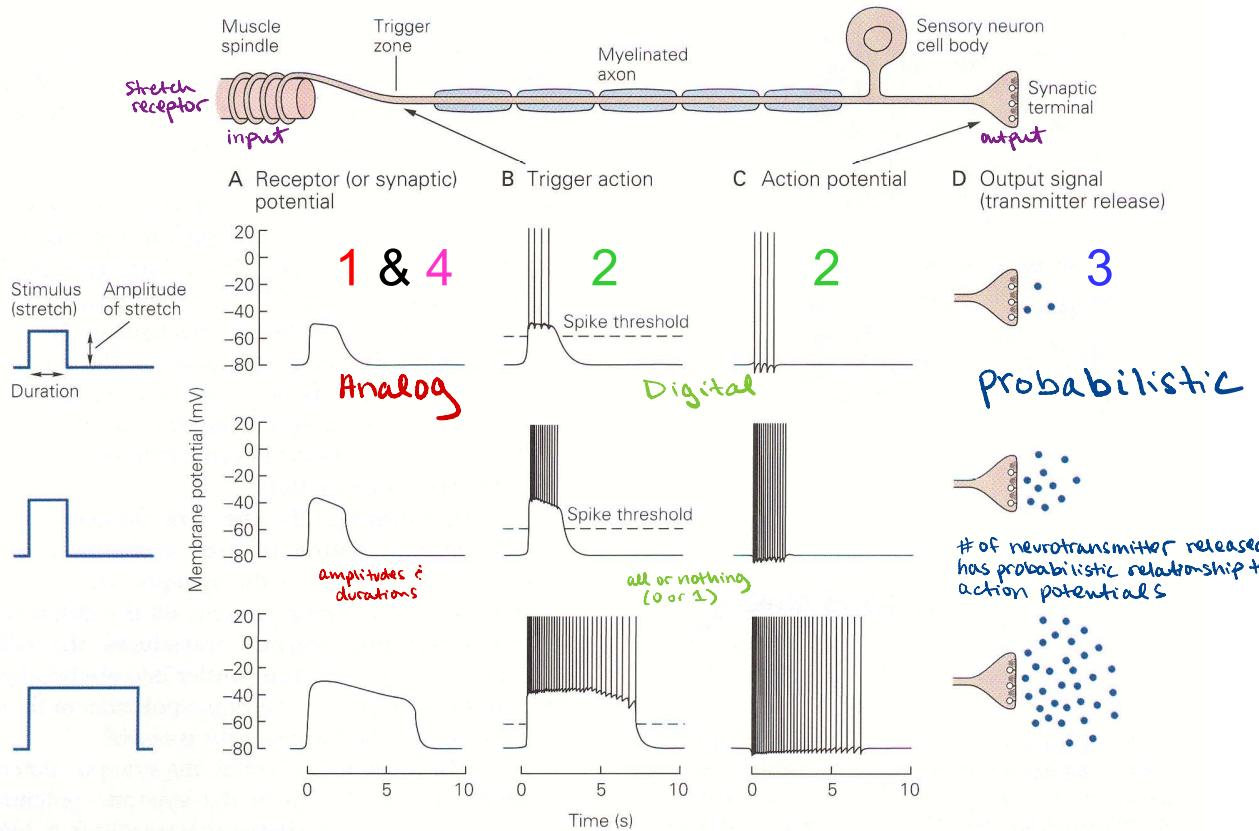


Figure 2-10 A sensory neuron transforms a physical stimulus (in our example, a stretch) into electrical activity in the cell. Each of the neuron's four signaling components produces a characteristic signal.

A. The **input signal** (a receptor or synaptic potential) is graded in amplitude and duration, proportional to the amplitude and duration of the stimulus.

B. The **trigger zone integrates the input signal**—the receptor potential in sensory neurons, or synaptic potential in motor neurons—into a trigger action that produces action potentials that will be propagated along the axon. An action potential is generated only if the input signal is greater than a certain **spike threshold**. Once the input signal surpasses this threshold, any further increase in amplitude of the input signal increases the **frequency** with which the action potentials are generated, not

their amplitude. The **duration** of the input signal determines the number of action potentials. Thus, the graded nature of input signals is translated into a frequency code of action potentials at the trigger zone.

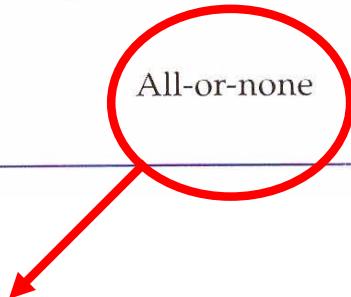
C. **Action potentials are all-or-none.** Every action potential has the same amplitude and duration, and thus the same waveform on an oscilloscope. Since action potentials are conducted without fail along the full length of the axon to the synaptic terminals, the information in the signal is represented only by the frequency and number of spikes, not by the amplitude.

D. When the action potential reaches the synaptic terminal, the cell releases a chemical neurotransmitter that serves as the output signal. The total number of action potentials in a given period of time determines exactly how much neurotransmitter will be released by the cell.

Passive & Active Signal Summary

Table 2-1 Comparison of Local (Passive) and Propagated Signals

Signal type	Amplitude (mV)	Duration	Summation	Effect of signal	Type of propagation
Local (passive) signals					
Receptor potentials	Small (0.1–10)	Brief (5–100 ms)	Graded	Hyperpolarizing or depolarizing	Passive
Synaptic potentials	Small (0.1–10)	Brief to long (5 ms to 20 min)	Graded	Hyperpolarizing or depolarizing	Passive
Propagated (active) signals					
Action potentials	Large (70–110)	Brief (1–10 ms)	All-or-none	Depolarizing	Active



- Since all or none, action potentials are essentially identical in shape.
- Information can not be coded / conveyed in the shape of the pulse.
- Information is coded / conveyed in the frequency emission.

Question

Q: If signals are stereotyped, how is the message that carries visual information distinguished from one that sends motor commands to the arm?

A: The message of an action potential is determined by the **neural pathway** that carries it.

Knee-Jerk Spinal Reflex Circuit – Revisited

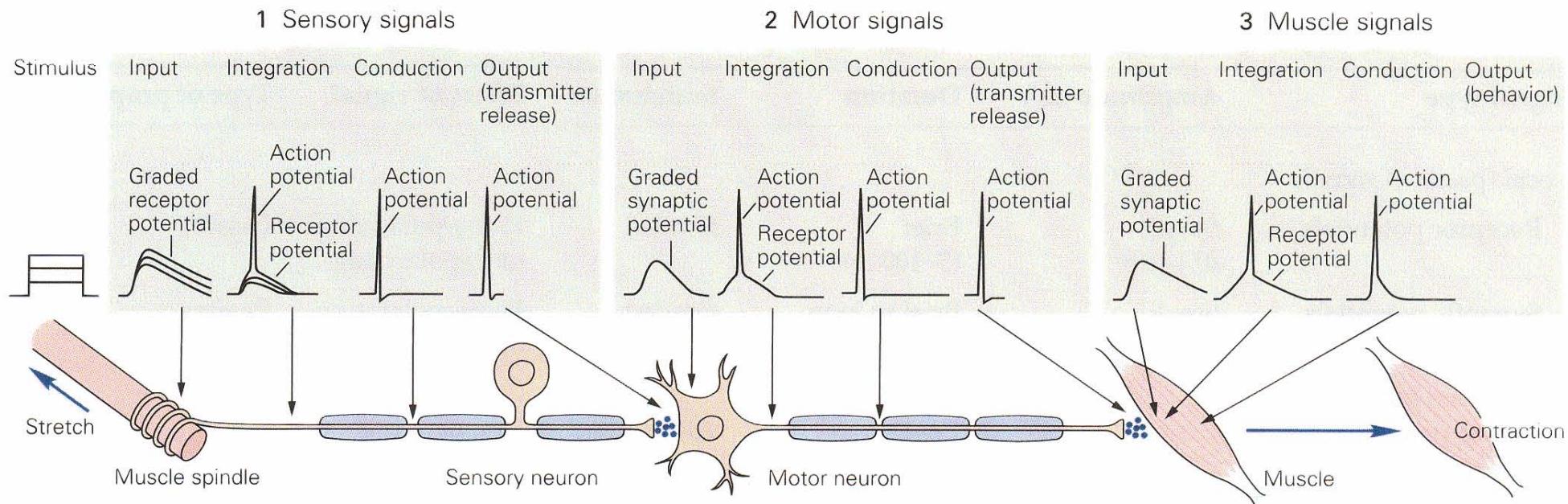


Figure 2-11 The sequence of signals that produces a reflex action.

1. The stretching of a muscle produces a receptor potential in the terminal fibers of the sensory neuron (the dorsal root ganglion cell). The amplitude of the receptor potential is proportional to the intensity of the stretch. This potential then spreads passively to the integrative segment, or trigger zone, at the first node of Ranvier. There, if the receptor potential is sufficiently large, it triggers an action potential, which then propagates actively and without change along the axon to the terminal region. At the terminal the action potential leads to an output signal: the release of a chemical neurotransmitter. The

transmitter diffuses across the synaptic cleft and interacts with receptor molecules on the external membranes of the motor neurons that innervate the stretched muscle. 2. This interaction initiates a synaptic potential in the motor cell. The synaptic potential then spreads passively to the trigger zone of the motor neuron axon, where it initiates an action potential that propagates actively to the terminal of the motor neuron. The action potential releases transmitter at the nerve-muscle synapse. 3. The binding of the neurotransmitter with receptors in the muscle triggers a synaptic potential in the muscle. This signal produces an action potential in the muscle, causing contraction of the muscle fiber.

PNS Chapter 7

Membrane Potential

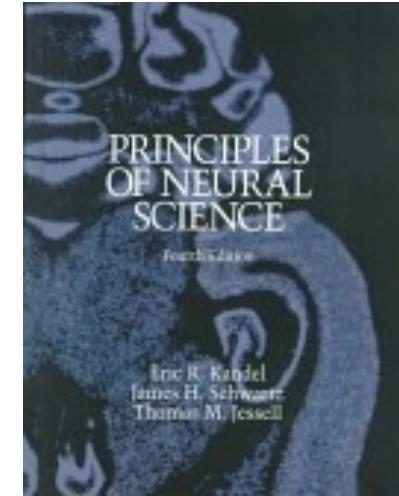
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Roadmap

Introduction to neuroscience

- Chapter 1 – The brain and behavior
- Chapter 2 – Nerve cells and behavior



How are neural signals generated?

- Chapter 7 – Membrane potential ←
- Chapter 9 – Propagated signaling: the action potential

How do neurons communicate with each other?

- Chapter 10 – Overview of synaptic transmission
- Chapter 12 – Synaptic integration

Membrane Potential

- Reading assignment from *Principles of Neural Science* (PNS):
 - Chapter 7 – Membrane Potential
 - Chapter 9 – Propagated Signaling: The Action Potential (up to p.158)
- Information carried within & between neurons w/ electrical & chemical signals.
- Transient electrical signals (action potentials) critical for transmitting time-sensitive data rapidly and over long distances.
- Action potentials produced by temporary changes in current flow in/out of cell.
- This in turn changes the electrical potential across the cell membrane – the **membrane potential**.
- Current flow controlled by ion channels in membrane.

Resting and Gated Ion Channels

Resting channels

- Normally open.
- Not influenced by membrane potential.
- Important for maintaining resting membrane potential.

Gated channels

- Normally closed.
- Probability of opening is a function of external factors.
- External factors: mechanical (pressure or stretch) forces, changes in membrane potential, or ligand (chemical transmitter) binding

Separation of Charges Across Membrane

- At rest, excess of + charge outside of cell membrane; - charge inside.
- Membrane maintains this separation by blocking diffusion.
- Membrane potential definition:

$$V_m = V_{in} - V_{out}$$

- Resting membrane potential (V_r) = V_m when gated channels are closed.
- V_r typically = -60 mV to -70 mV.
- Electric current carriers are positive (cations) and negative (anions) ions.
- Direction of current flow defined as direction of net movement of + charge.

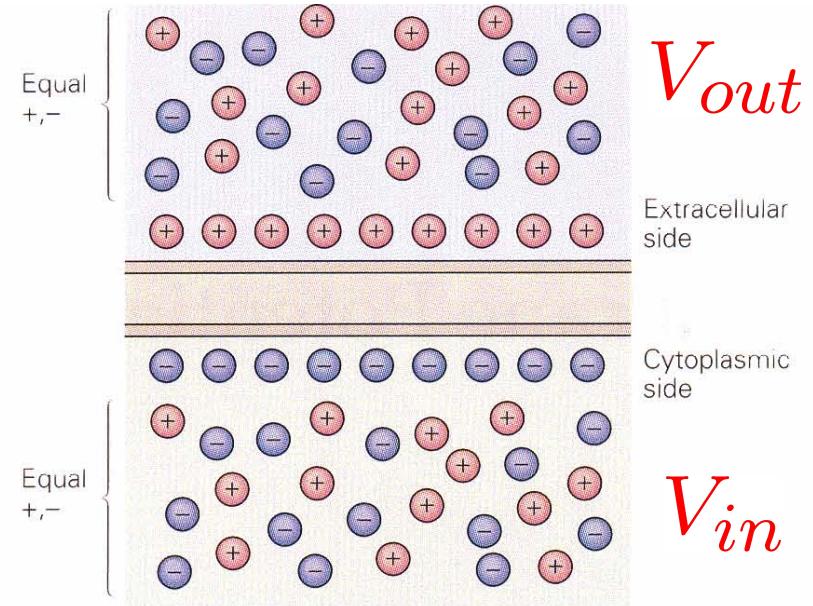


Figure 7-1 The membrane potential results from a separation of positive and negative charges across the cell membrane. The excess of positive charges (red circles) outside the membrane and negative charges (blue circles) inside the membrane of a nerve cell at rest represents a small fraction of the total number of ions inside and outside the cell.

Recording the Membrane Potential

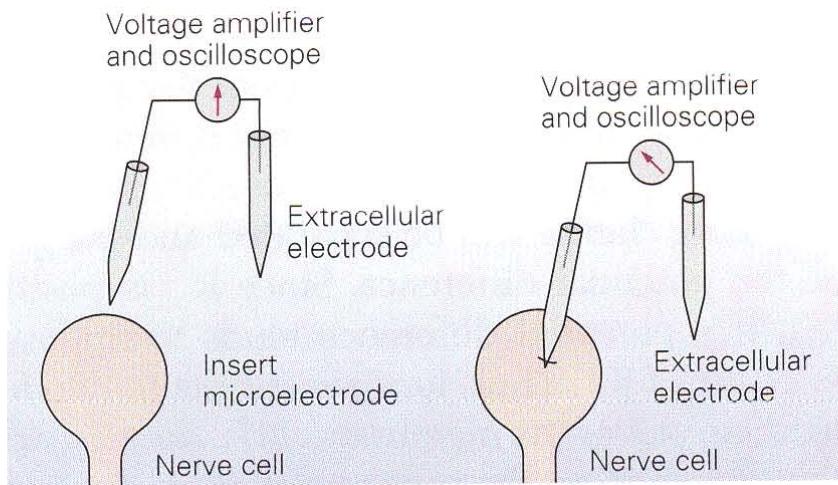


Figure 7-2A The recording setup.

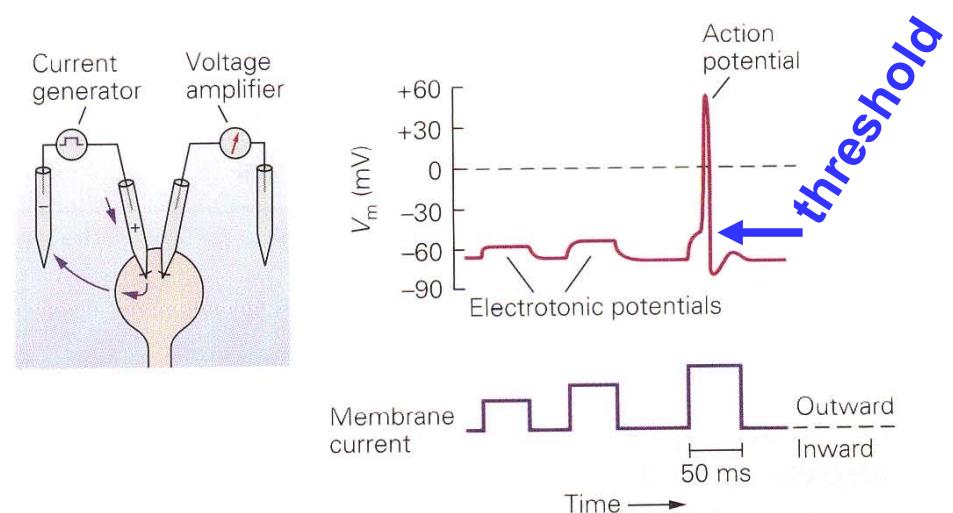


Figure 7-2C Depolarization.

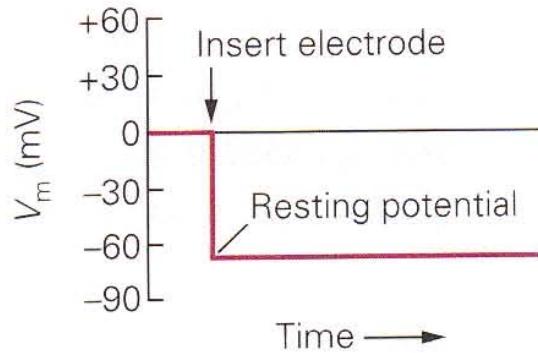


Figure 7-2B Oscilloscope display.

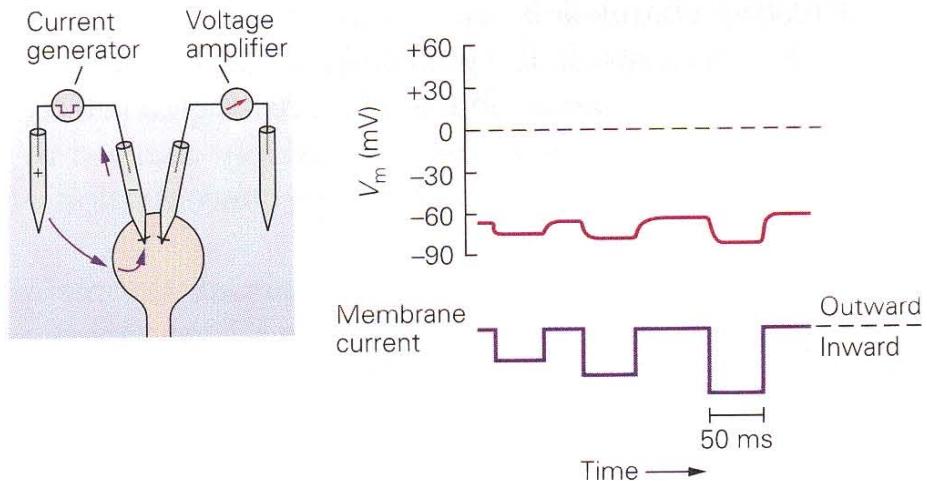


Figure 7-2D Hyperpolarization.

Resting Potential Determined by Resting Ion Channels

- No ion species is distributed equally inside/outside membrane.
- Table shows giant squid axon concentrations; ionic concentrations in vertebrates are 2-3x lower, but concentration gradients similar.

Table 7-1 Distribution of the Major Ions Across a Neuronal Membrane at Rest: the Giant Axon of the Squid

Species of ion	Concentration in cytoplasm (mM)	Concentration in extracellular fluid (mM)	Equilibrium potential ¹ (mV)
K ⁺	400	20	-75
Na ⁺	50	440	+55
Cl ⁻	52	560	-60
A ⁻ (organic anions)	385	—	—

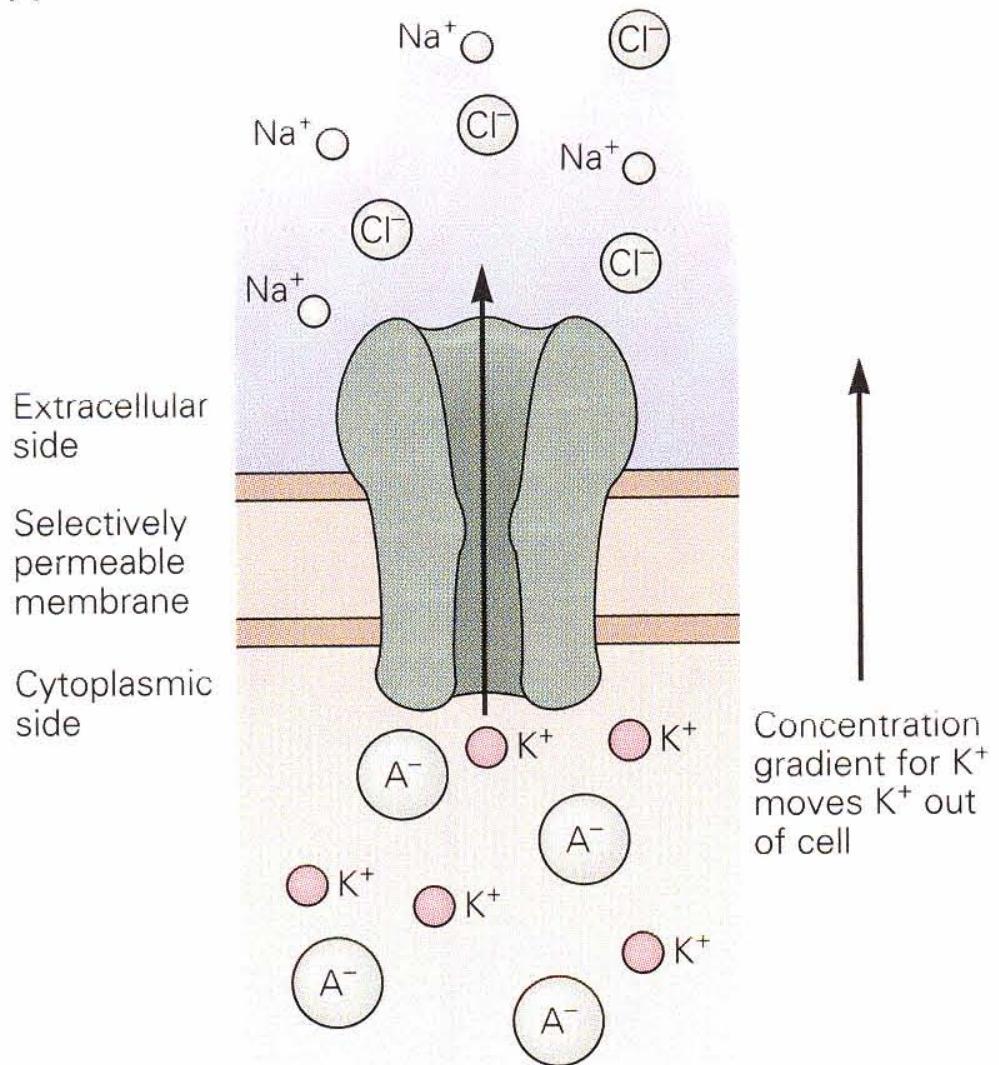
¹The membrane potential at which there is no net flux of the ion species across the cell membrane.

Concentration Gradients & Resting Potential

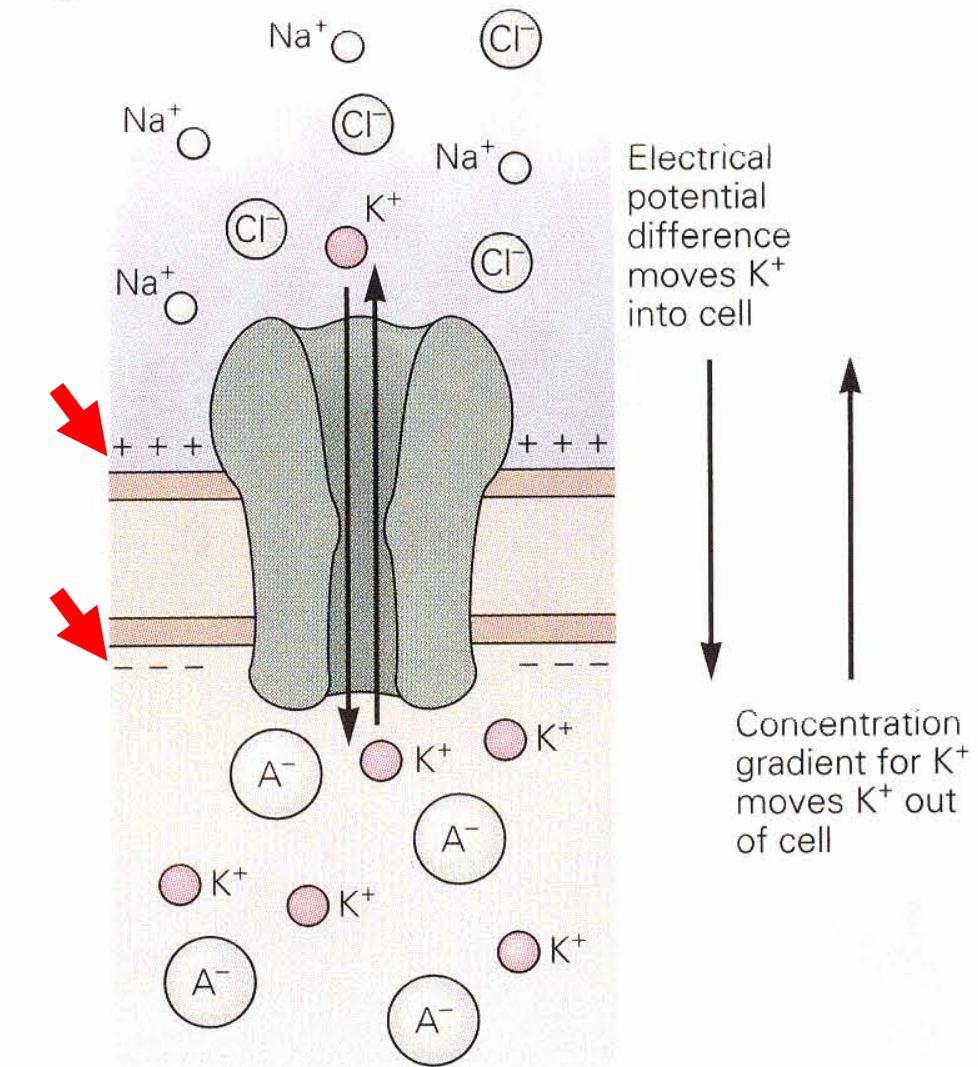
- For simplicity, we first consider glia.
- Simply because glial membranes are permeable to only K^+ , not to all species present (we'll consider this case next).
- A high concentration of K^+ and A^- exists **inside** the cell.
- A high concentration of Na^+ and Cl^- exists **outside** the cell.
- Intuitively, species that can not transport through the ion channels must stay put (inside or outside of cell).
- Intuitively, species (i.e., K^+) that can transport through the ion channels can potentially do so – but there must be a driving force.

Sketch of Drift and Diffusion Currents

A



B



Concentration Gradients & Resting Potential

- 1) K⁺ **diffuse** inside→outside cell, down concentration gradient, creating **diffusion current**.
- 2) Thus, outside accumulates a slight excess of + charge (K⁺) and inside accumulates a slight excess of - charge (lack of K⁺).
- 3) Excess charges attract, forming sheet charges along membrane.
- 4) Sheet charges create electric (E) field, pointing from outside→in (+→-).
- 5) E-field applies force (**drift**) on K⁺ ions in direction of E-field (outside→in). This creates **drift current**.
- 6) At equilibrium (no net current flow), a specific E-field exists such that **drift current** is equal and opposite **diffusion current**.

Concentration Gradients & Resting Potential

- The potential difference across the membrane associated with this specific E-field is termed the equilibrium potential (E_K).
- As per previous table, $E_K = -75 \text{ mV}$.
Note: don't be confused, here E is a voltage not an electric field.
- Equilibrium potential for arbitrary ion X given by Nernst equation:

$$E_x = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}$$

with R (gas constant), T (temperature in Kelvin), z (valence of the ion), F (Faraday constant) and $[X]_o$ and $[X]_i$ are chemical concentrations outside and inside of cell.

Calculating Resting Potential

- Since $RT/F = 25 \text{ mV}$ at room temperature (25° C), we can write:

$$E_x = \frac{25mV}{z} \ln \frac{[X]_o}{[X]_i}$$

- Or, including a factor of 2.3 to convert $\ln \rightarrow \log$:

$$E_x = \frac{58mV}{z} \log \frac{[X]_o}{[X]_i}$$

- And, with $z = 1$ for K^+ :

$$E_x = 58mV \log \frac{[20]}{[400]} = -75mV$$

Calculating Resting Potential

- Nernst Equation can be used to find the equilibrium (resting) potential of any ion that is present on both sides of a membrane permeable to that ion.
- See previous table (repeated here for convenience) for equilibrium potentials associated with each ion present in the giant squid axon:

Table 7-1 Distribution of the Major Ions Across a Neuronal Membrane at Rest: the Giant Axon of the Squid

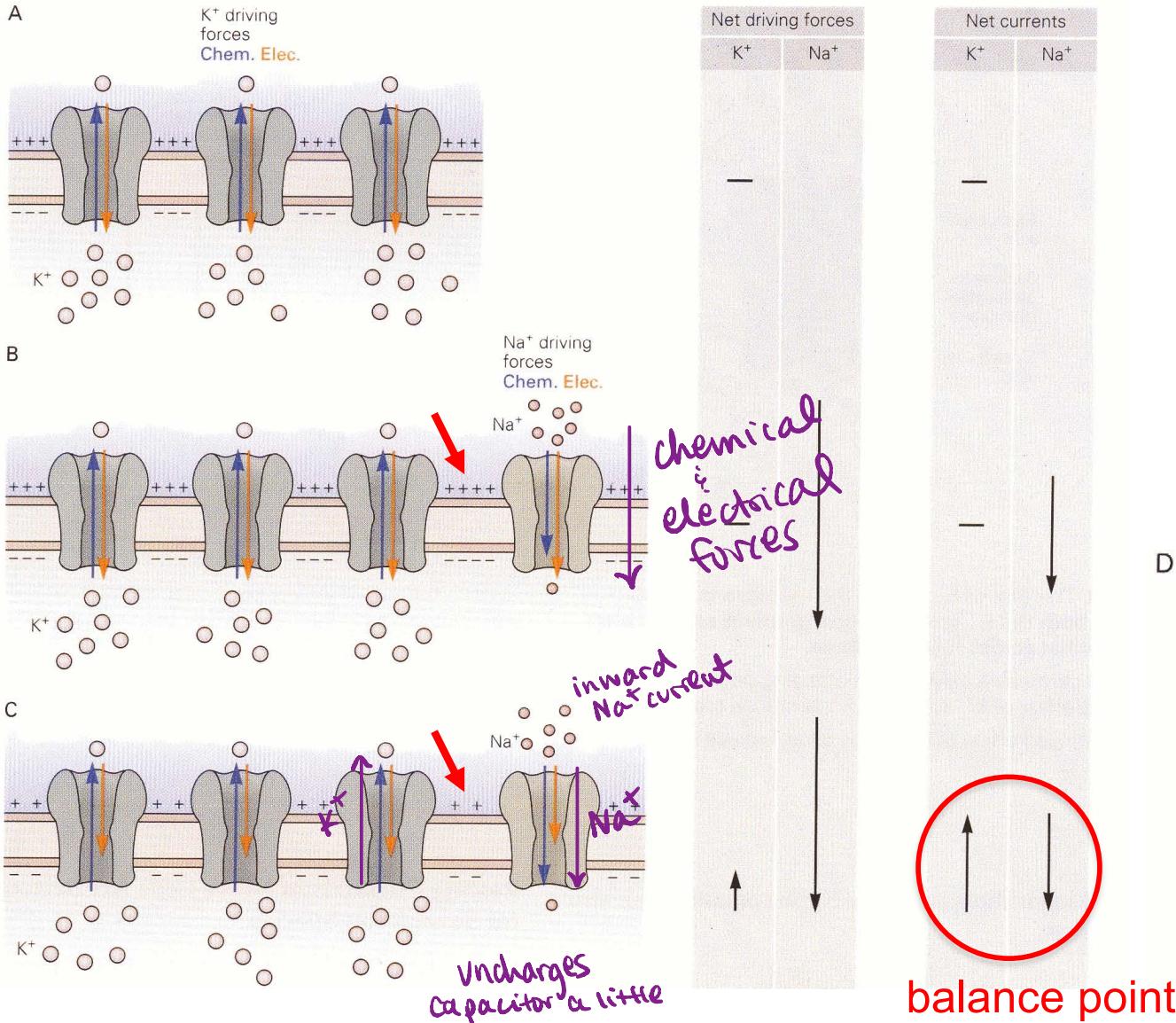
Species of ion	Concentration in cytoplasm (mM)	Concentration in extracellular fluid (mM)	Equilibrium potential ¹ (mV)
K ⁺	400	20	-75
Na ⁺	50	440	+55
Cl ⁻	52	560	-60
A ⁻ (organic anions)	385	—	—

¹The membrane potential at which there is no net flux of the ion species across the cell membrane.

Concentration Gradients & Resting Potential

- Having considered simple glia, we now turn to neurons.
- Neurons at rest are permeable to Na^+ and Cl^- ions, in addition to K^+ ions.
- A^- ions unable to permeate; thus set aside.
- When multiple ion species can permeate membrane, a new resting potential is established such that net current flow is zero (steady state).

Understanding Resting Potential w/ 2 Species



- Why isn't Na⁺ flux huge?
- Can these equal and opposite K⁺ and Na⁺ continue indefinitely?

Why isn't Na⁺ influx huge?

- Ion flux is the product of electrochemical driving force and membrane conductance to that ion:

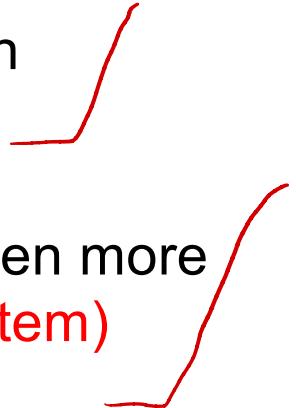
ion flux = (electrical driving force + chemical driving force) x
membrane conductance

- There are relatively few resting Na⁺ channels (compared w/ resting K⁺ channels) so the conductance to Na⁺ is quite low.

$\text{Na}^+ - \text{K}^+$ Pump

- Now assume that the resting potential has been achieved.
- Passive movement of K^+ out of cell = passive movement of Na^+ into cell.
- But these concentrations gradients will eventually run down, thereby reducing the resting membrane potential!
- Need $\text{Na}^+ - \text{K}^+$ pump.
- Moves Na^+ and K^+ **against** their net electrochemical gradients.
Moves Na^+ out of cell; moves K^+ into cell.
- Pump requires energy (ATP hydrolysis).
- Continuous passive influx of Na^+ and efflux of K^+ through resting channels is counterbalanced by $\text{Na}^+ - \text{K}^+$ pump.
- Pump: membrane-spanning protein

Another Quick Peek at Action Potentials

- Though we will study action potentials in depth soon enough, a quick peek is warranted now.
- If the membrane is depolarized past the “threshold voltage”, then voltage-gated Na^+ channels open rapidly.
- Thus Na^+ influx exceeds K^+ efflux → further depolarization → even more voltage-gated Na^+ channels open → ... (positive feedback system)
- Takes V_R very close to $E_{\text{Na}} = + 55 \text{ mV}$ because permeability to Na^+ is predominant.
- Why does membrane ever repolarize, to end action potential?
 - Voltage-gated Na^+ channels gradually *inactivate*.
 - Voltage-gated K^+ channels are slow, but eventually open.

Goldman Equation: V_R w/ Multiple Species

- Membrane conductance (1/resistance) is a convenient measure of how readily an ion crosses the membrane.
- Permeability (P , units of cm/s) is another convenient measure; similar to a diffusion constant.
- Membrane potential is easy to calculate w/ Goldman Equation:

$$V_m = \frac{RT}{F} \ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$

- Species with highest concentration and permeability dominates – consider limit cases:

At rest, permeability of K^+ dominates.

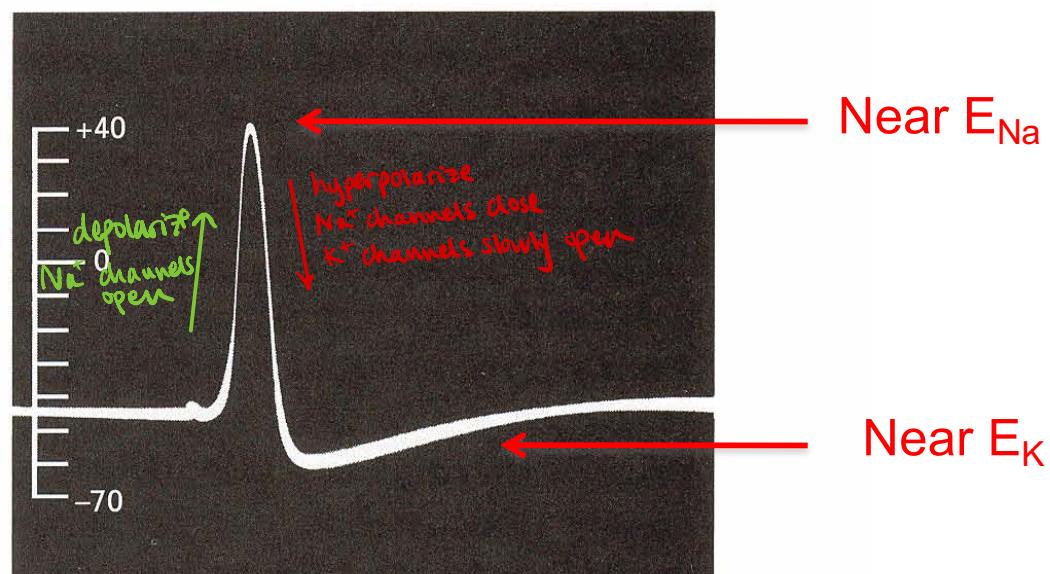
At peak of action potential, permeability of Na^+ dominates.

Dynamic range of action potential waveform

Table 7-1 Distribution of the Major Ions Across a Neuronal Membrane at Rest: the Giant Axon of the Squid

Species of ion	Concentration in cytoplasm (mM)	Concentration in extracellular fluid (mM)	Equilibrium potential ¹ (mV)
K ⁺	400	20	-75
Na ⁺	50	440	+55
Cl ⁻	52	560	-60
A ⁻ (organic anions)	385	—	—

¹The membrane potential at which there is no net flux of the ion species across the cell membrane.



Rest of Chapter 7

- We've covered topics in Chapter 7 up to, but not including, the section titled, "The Functional Properties of the Neuron Can Be Represented in an Electrical Equivalent Circuit".
- If you've had a circuits course, it turns out that a neuron can be thought of as an electrical circuit, where:
 - Resistors – represent the ion channels.
 - Voltage sources – represent concentration gradients of relevant ions.
 - Capacitors – capacity of membrane to store charge.
 - Current sources – $\text{Na}^+ \text{-K}^+$ pump.
- Feel free to read if you are interested in learning more.

Propagated Signaling: The Action Potential

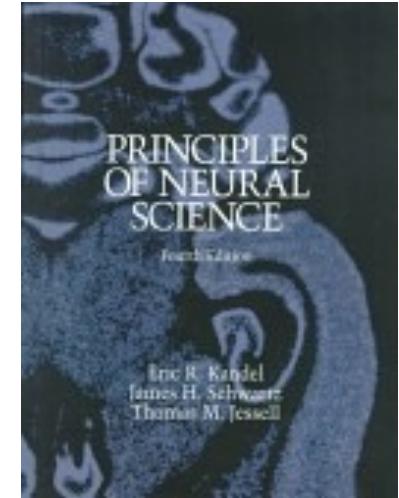
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How are neural signals generated?

- Chapter 7 – Membrane potential
- Chapter 9 – Propagated signaling: the action potential 

How do neurons communicate with each other?

- Chapter 10 – Overview of synaptic transmission
- Chapter 12 – Synaptic integration

Action Potentials

- Reading assignment from *Principles of Neural Science* (PNS):
 - Chapter 9 – Propagated Signaling: The Action Potential (up to p.158)
- Neurons can carry information long distances b/c of action potentials.
- Action potentials (APs or “spikes”) – regenerative electrical signal whose amplitude does not attenuate as it moves down the axon.
 - Chap. 7 – APs arise from sequential changes in membrane’s selectivity for Na^+ and K^+ .
 - Chap. 9 – here we consider voltage-gated ion channels, which are critical for generating and propagating APs.

Geyser eruption: an explosive, all-or-nothing event



Geyser Strokkur, Iceland

- There are no half-eruptions. It's all or nothing.
- One eruption cannot directly follow another (minimum 5 minute gap) because it takes time for pressure to build.

APs and Ion Flow Through Voltage-Gated Channels

- How are APs generated?
- Ion conductance *HIGH* during AP.
- 1st evidence that AP result from change in ion flux through membrane channels.

- But which ions?

- Big clue: if extracellular $[Na^+]$ *LOW*, then AP amplitude *LOW*.
- Thus Na^+ responsible for rising edge of AP.
- Hodgkin's & Katz's data also pointed to K^+ involved w/ falling edge of AP.
- To test these hypotheses, need to measure Na^+ and K^+ conductance as a function of membrane potential (V_m).
- Problem: V_m cannot be held steady.
- Solution: The Voltage Clamp.

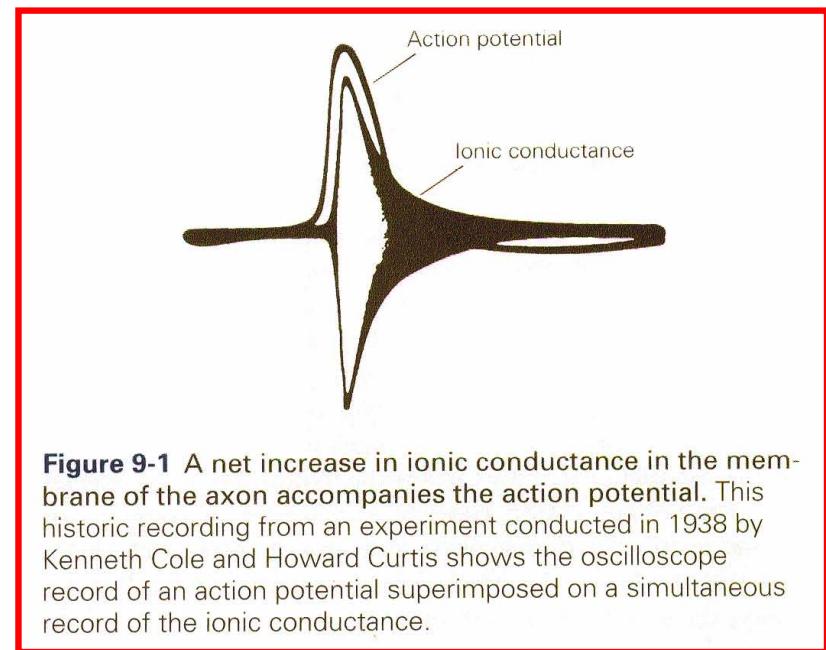
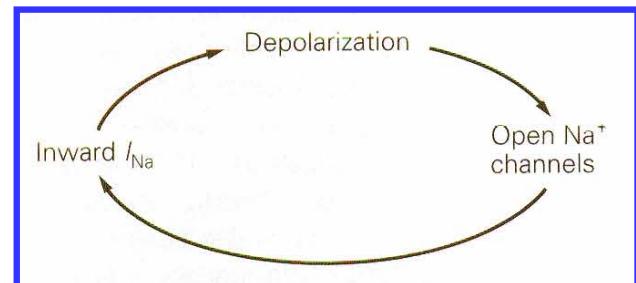


Figure 9-1 A net increase in ionic conductance in the membrane of the axon accompanies the action potential. This historic recording from an experiment conducted in 1938 by Kenneth Cole and Howard Curtis shows the oscilloscope record of an action potential superimposed on a simultaneous record of the ionic conductance.

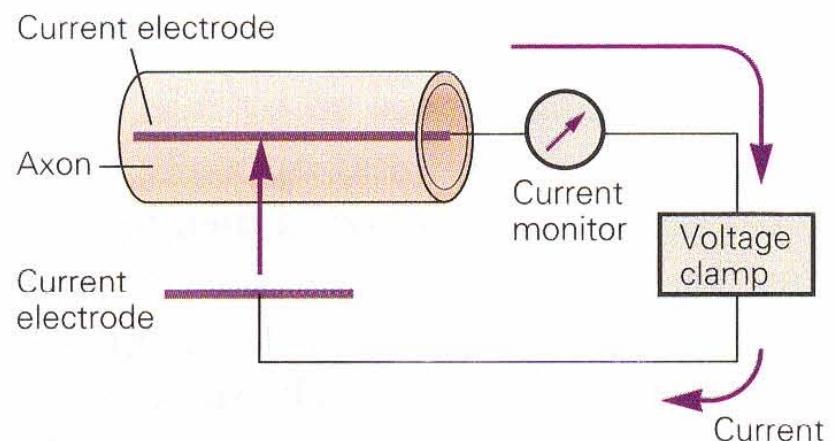


The Voltage Clamp

Basic idea:

- 1) Voltage clamp fixes the membrane potential by passing current into or out of neuron, thereby preventing the charge separation across the membrane from changing.
- 2) Because the membrane potential is fixed, so is the ionic conductance.
- 3) The amount of current needed for 1) allows one to compute the ionic conductance:

$$\text{Conductance} = \text{Current} / \text{Voltage}$$



The Voltage Clamp

- Hodgkin & Huxley used voltage clamp to provide 1st complete description of ionic mechanisms underlying APs.
- A brief aside – How important was this work?
 - The Nobel Prize in Physiology or Medicine 1963, Hodgkin
 - The Nobel Prize in Physiology or Medicine 1963, Huxley
 - The Nobel Prize in Physiology or Medicine 1970, Katz

Channel Conductance Kinetics

- Na^+ and K^+ conductance **similarities**:
 - Depolarizing V_m steps → channels open (larger g).
 - Larger depolarizing steps → probability and rate of opening increases (g rises faster).
- Na^+ and K^+ conductance **differences**:
 - Rates of opening: $\text{Na}^+ > \text{K}^+$.
 - Responses to prolonged depolarization: Na^+ opens and closes (*inactivation*); K^+ stays open.

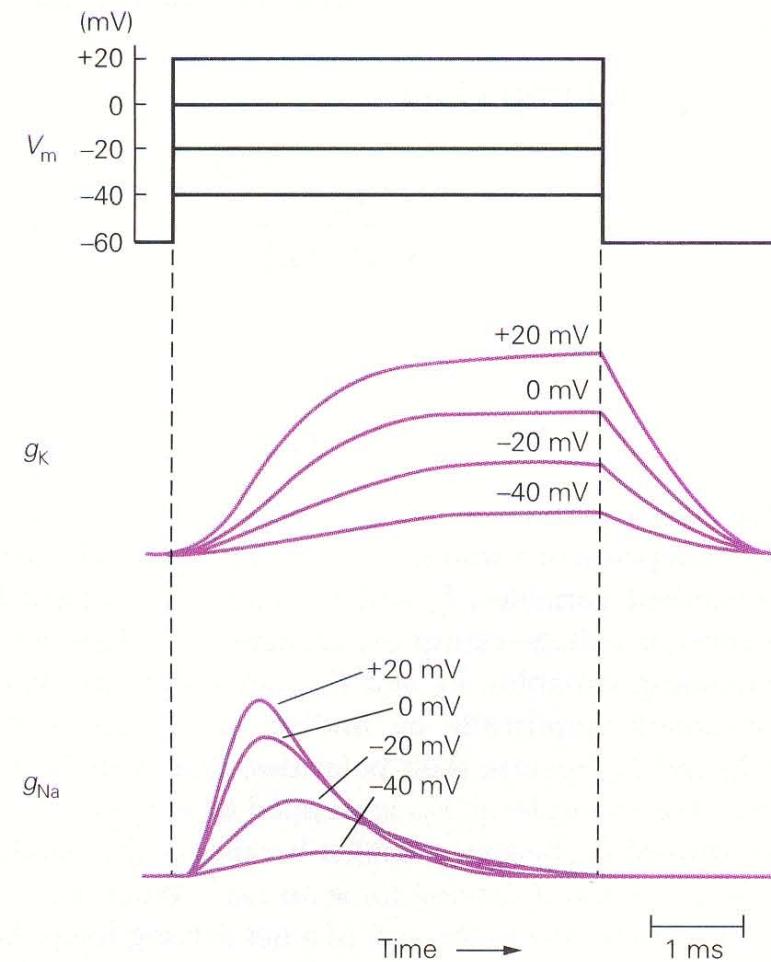


Figure 9-6 Voltage-clamp experiments show that Na^+ channels turn on and off more rapidly than K^+ channels over a wide range of membrane potentials. The increases and decreases in the Na^+ and K^+ conductances (g_{Na} and g_K) shown here reflect the shifting of thousands of voltage-gated channels between the open and closed states.

Short-term vs. Long-term Depolarization

a) Short-term depolarization

allows Na^+ and K^+ channels to return to their resting states.

b) Long-term depolarization

cause Na^+ channels to enter *inactive state*.

K^+ channels remain open.

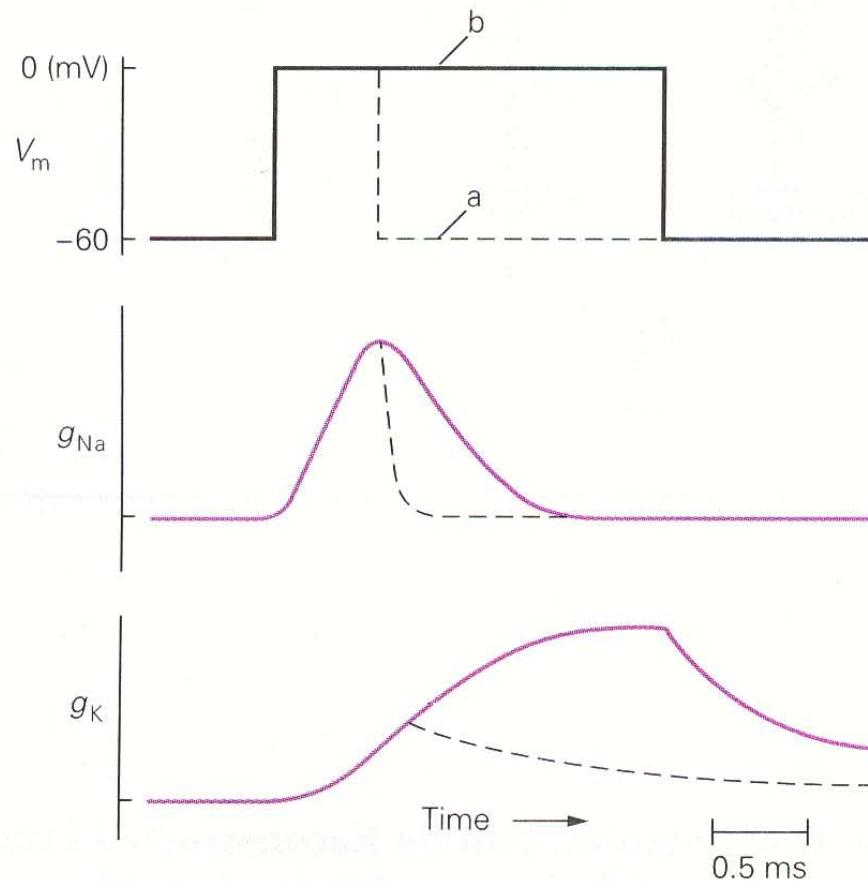


Figure 9-7 Sodium and potassium channels respond differently to long-term depolarization. If the membrane is repolarized after a brief depolarization (line a), both g_{Na} and g_K return to their initial values. If depolarization is maintained (line b), the Na^+ channels close (or inactivate) before the depolarization is terminated, whereas the K^+ channels remain open and g_K increases throughout the depolarization.

Na^+ Channel Inactivation Timecourse

- Once inactivated, Na^+ channels must be repolarized for a few ms in order to return to the resting state.
- If the membrane is depolarized prematurely, g_{Na} will not increase appreciably (channel still inactivated).
- Inactivation timecourse underlies the *refractory period*.

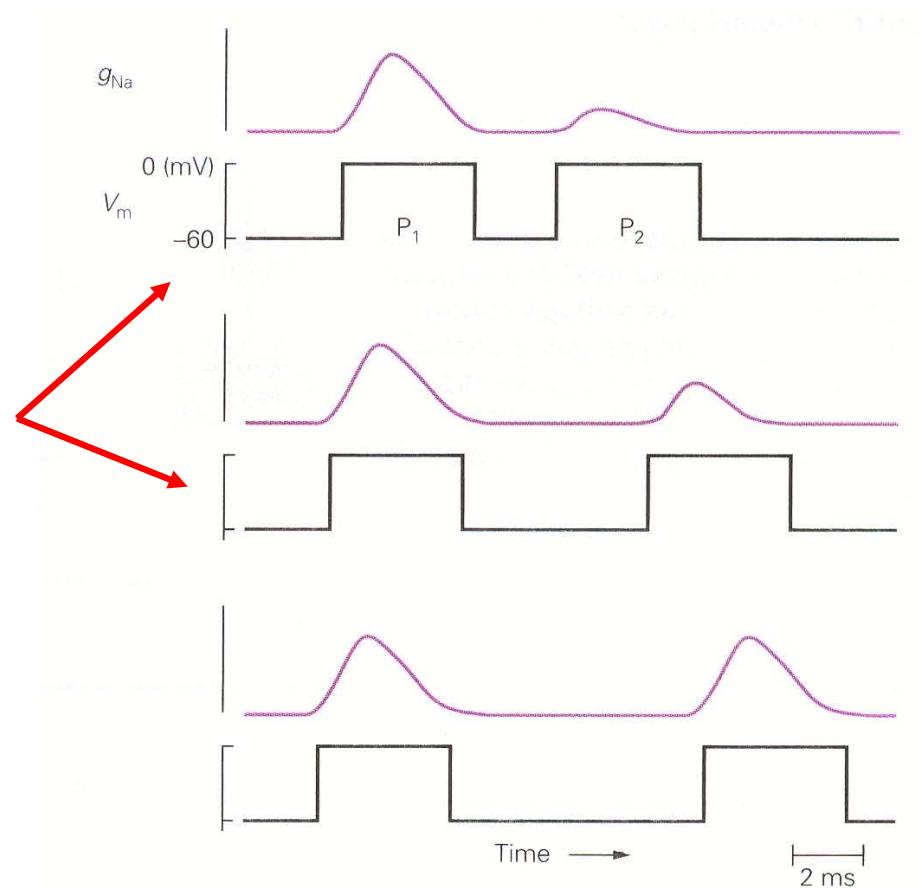


Figure 9-8 Sodium channels remain inactivated for a few milliseconds after the end of a depolarization. Therefore if the interval between two depolarizing pulses (P₁ and P₂) is brief, the second pulse produces a smaller increase in g_{Na} because many of the Na^+ channels are inactivated. The longer the interval between pulses, the greater the increase in g_{Na} , because a greater fraction of channels will have recovered from inactivation and returned to the resting state when the second pulse begins. The time course of recovery from inactivation contributes to the time course of the refractory period.

Activation Gate (fast) and Inactivation Gate (slow)

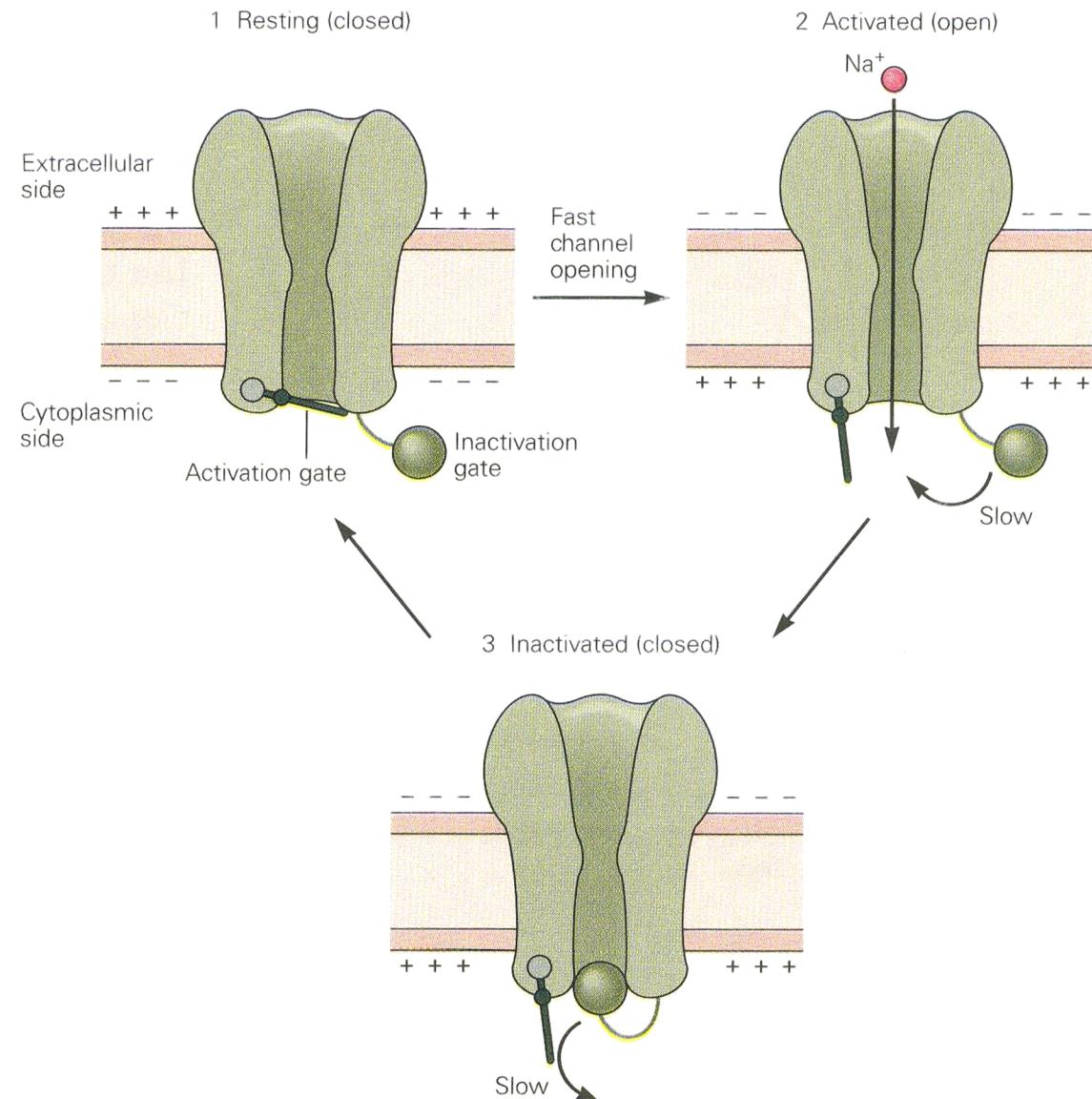


Figure 9-9 Voltage-gated Na^+ channels have two gates, which respond in opposite ways to depolarization. In the resting (closed) state the activation gate is closed and the inactivation gate is open (1). Upon depolarization a rapid opening of the activation gate allows Na^+ to flow through the channel (2). As the inactivation gates close, the Na^+ channels enter the inactivated (closed) state (3). Upon repolarization, first the activation gate closes, then the inactivation gate opens as the channel returns to the resting state (1).

Hodgkin-Huxley Measurements & Model Explain APs

- 1) Depolarization event.
- 2) Na^+ channels open fast ($g_{\text{Na}} \uparrow P$).
- 3) Inward Na^+ current.
- 4) Further depolarization.
- 5) Further Na^+ channels open.
- 6) Positive feedback continues...
- 7) $V_m \rightarrow E_{\text{Na}}$.
- 8) Na^+ channels inactivate ($g_{\text{Na}} \downarrow W$).
- 9) K^+ channels start opening ($g_{\text{K}} \uparrow P$).
- 10) Outward current decreases V_m .
- 11) $V_m \rightarrow E_{\text{K}}$. Hyperpolarizes beyond resting potential (*after potential*).
- 12) Absolute refractory period (due to Na^+ inactivation).
- 13) Relative refractory period (due to increased opening of K^+).

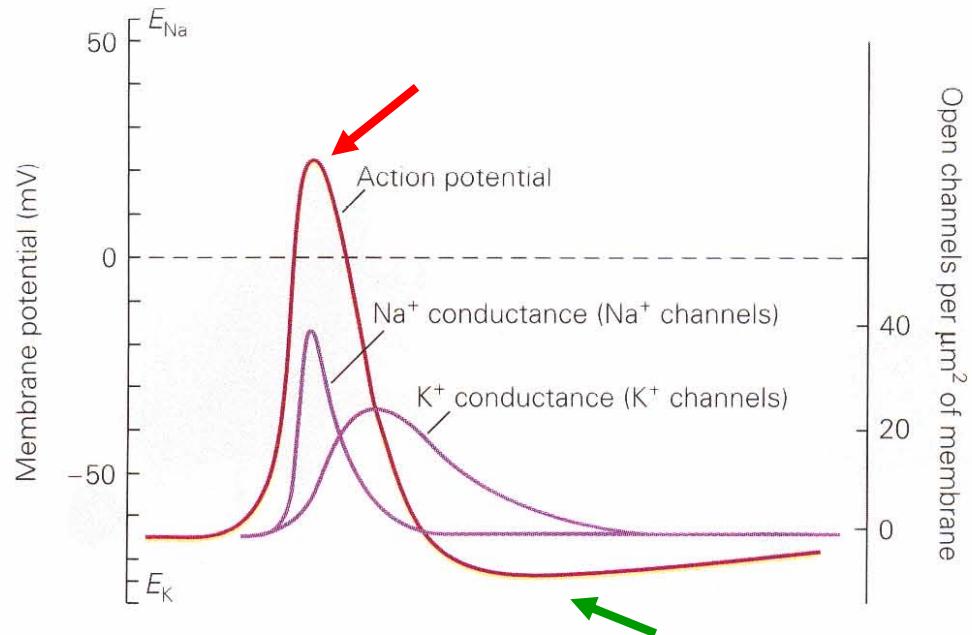
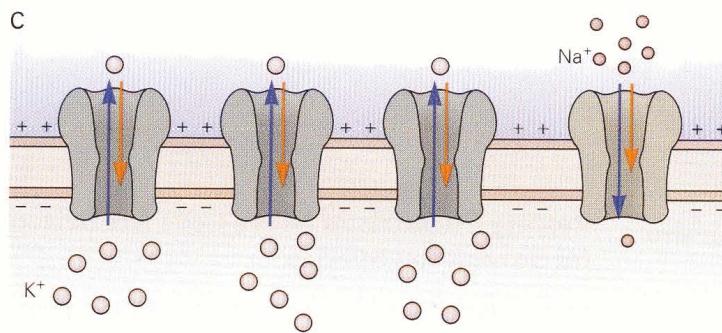


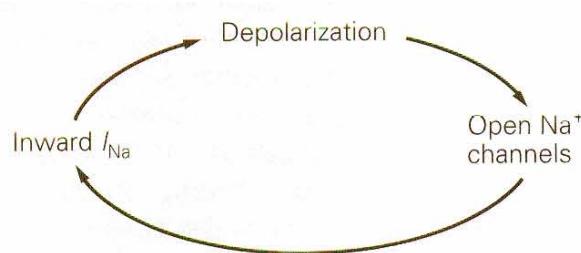
Figure 9-10 The sequential opening of voltage-gated Na^+ and K^+ channels generates the action potential. One of Hodgkin and Huxley's great achievements was to separate the total conductance change during an action potential, first detected by Cole and Curtis (see Figure 9-1) into separate components attributable to the opening of Na^+ and K^+ channels. The shape of the action potential and the underlying conductance changes can be calculated from the properties of the voltage-gated Na^+ and K^+ channels.

All-or-nothing behavior of APs

Before V_m crosses a particular value (threshold), outward I_K resists depolarizing effect of inward I_{Na} .



Threshold is the membrane voltage at which inward I_{Na} exceeds outward I_K . At this point, **positive feedback** takes over



and the rest of the AP waveform unfolds.

Rest of Chapter 9

- We've covered topics in Chapter 9 up to, but not including, the section titled, "Variation in the Properties of Voltage-Gated Ion Channels Increase the Signaling Capabilities of Neurons."
- We will not cover this section or beyond.
- Feel free to read if you are interested in learning more.

PNS Chapters 10 and 12

Synaptic Transmission and Integration

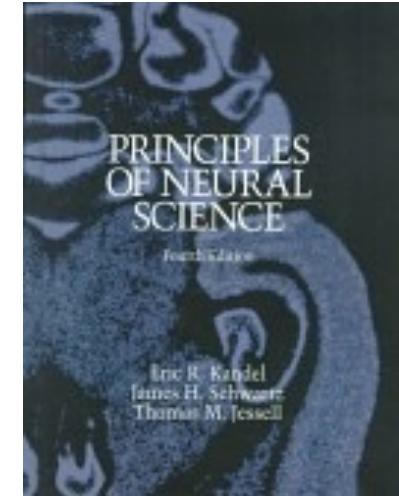
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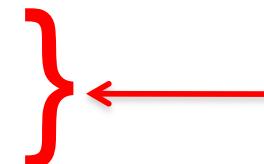


How are neural signals generated?

- Chapter 7 – Membrane potential
- Chapter 9 – Propagated signaling: the action potential

How do neurons communicate with each other?

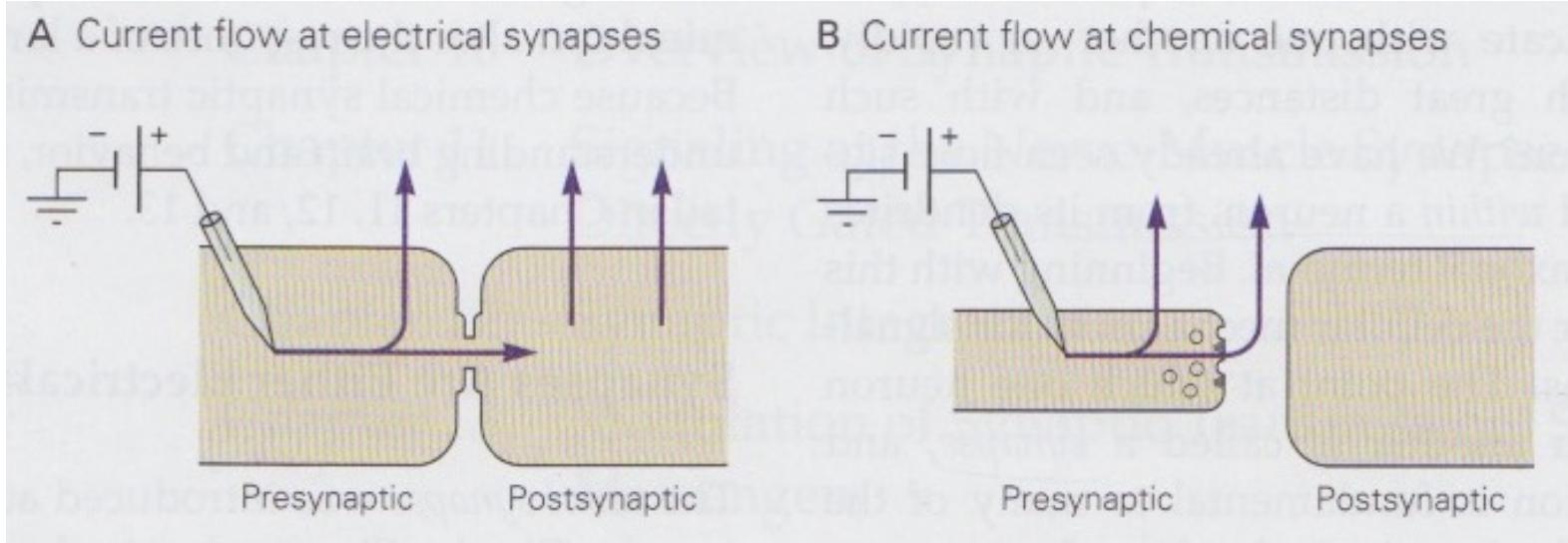
- Chapter 10 – Overview of synaptic transmission
- Chapter 12 – Synaptic integration



Synaptic Transmission

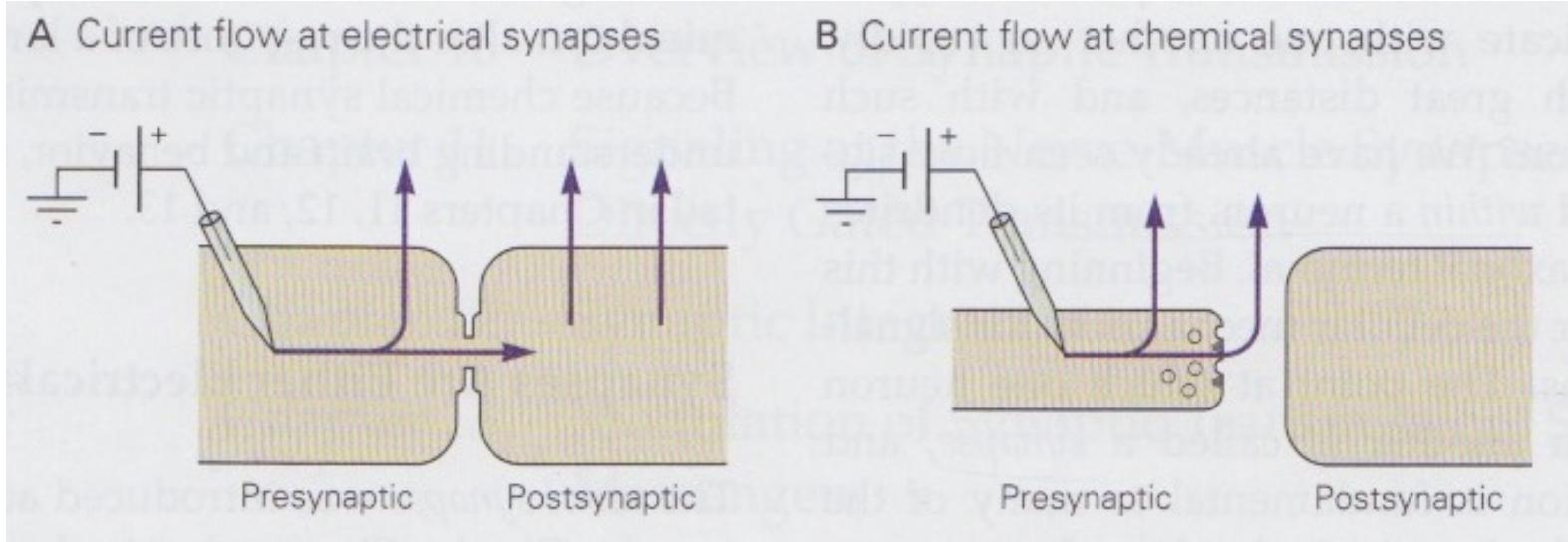
- We will only cover excerpts from Chapters 10 and 12 of *Principles of Neural Science* (PNS).
- You are only responsible for text corresponding to figures shown in these lecture notes.
- The point at which one neuron communicates with another is called a **synapse**.
- The average neuron forms about 10^3 synaptic connections and receives $> 10^3$ synaptic connections.
- With $>10^{11}$ neurons in the brain, $>10^{14}$ synaptic connections are formed in a single brain – more than the number of stars in our galaxy!
- **Plasticity** – the change in strength of synaptic transmission – is crucial to memory and other higher brain functions.

Electrical vs. Chemical Synapses



- **Electrical synapses** – specialized ion channels (“gap junction channels”) that connect the pre- and postsynaptic cells provide a low-resistance pathway for electrical current to flow between the two cells.
- **Chemical synapses** – action potential in the presynaptic neuron leads to the release of a chemical substance (“neurotransmitter”) that in turn initiates current flow in the postsynaptic cell.

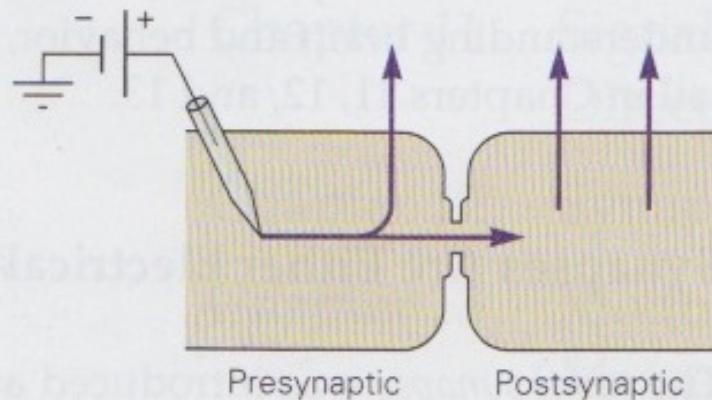
Electrical vs. Chemical Synapses



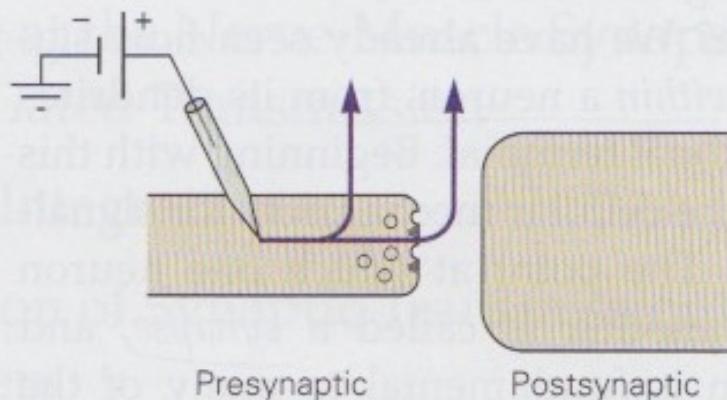
- Electrical synapses – any amount of current (even subthreshold) in the presynaptic cell triggers a response in the postsynaptic cell.
- Chemical synapses – the presynaptic current *must* reach threshold for an action potential before the cell can release neurotransmitter and affect the postsynaptic cell.

Electrical vs. Chemical Synapses

A Current flow at electrical synapses

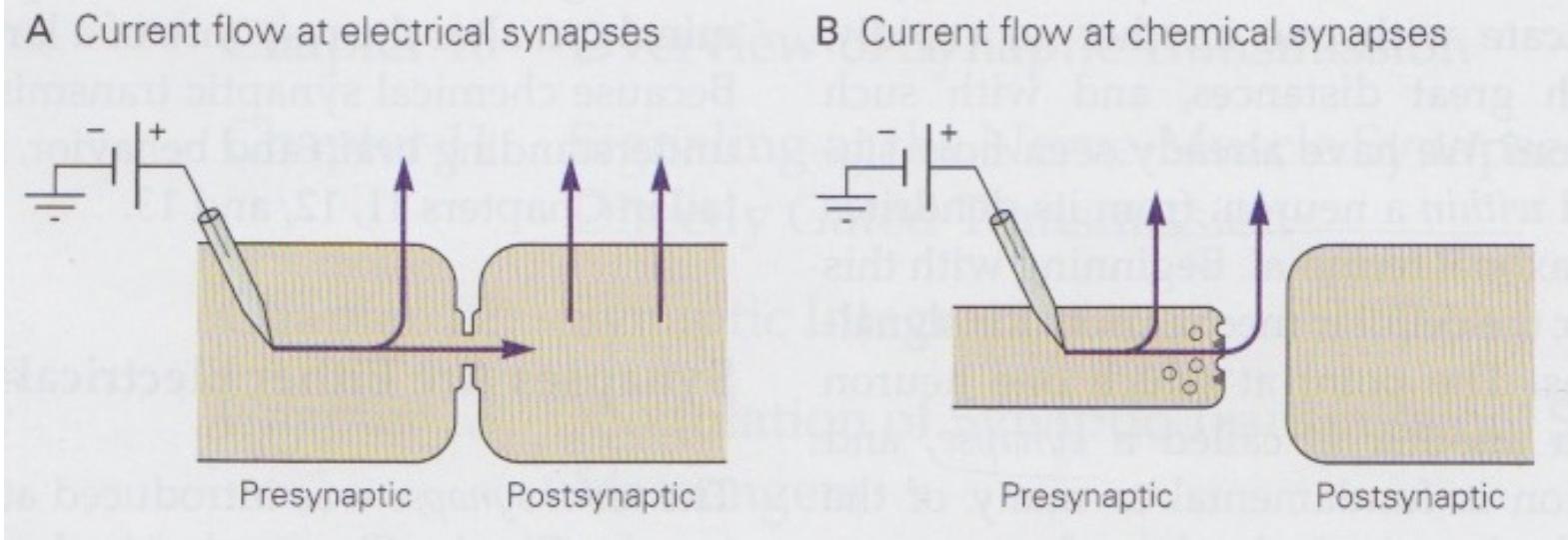


B Current flow at chemical synapses



- Electrical synapses – largely excitatory
- Chemical synapses – can be excitatory or inhibitory

Electrical vs. Chemical Synapses



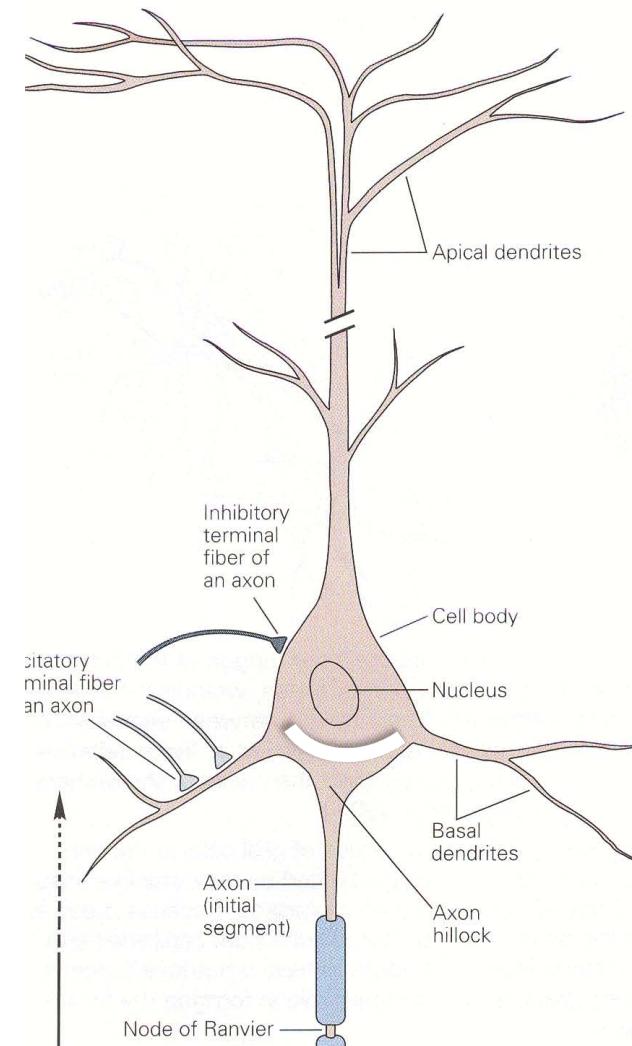
Type of synapse	Distance between pre- and postsynaptic cell membranes	Cytoplasmic continuity between pre- and postsynaptic cells	Ultrastructural components	Agent of transmission	Synaptic delay	Direction of transmission
Electrical	3.5 nm	Yes	Gap-junction channels	Ion current	Virtually absent	Usually bidirectional
Chemical	20–40 nm	No	Presynaptic vesicles and active zones; postsynaptic receptors	Chemical transmitter	Significant: at least 0.3 ms, usually 1–5 ms or longer	Unidirectional

Electrical vs. Chemical Synapses

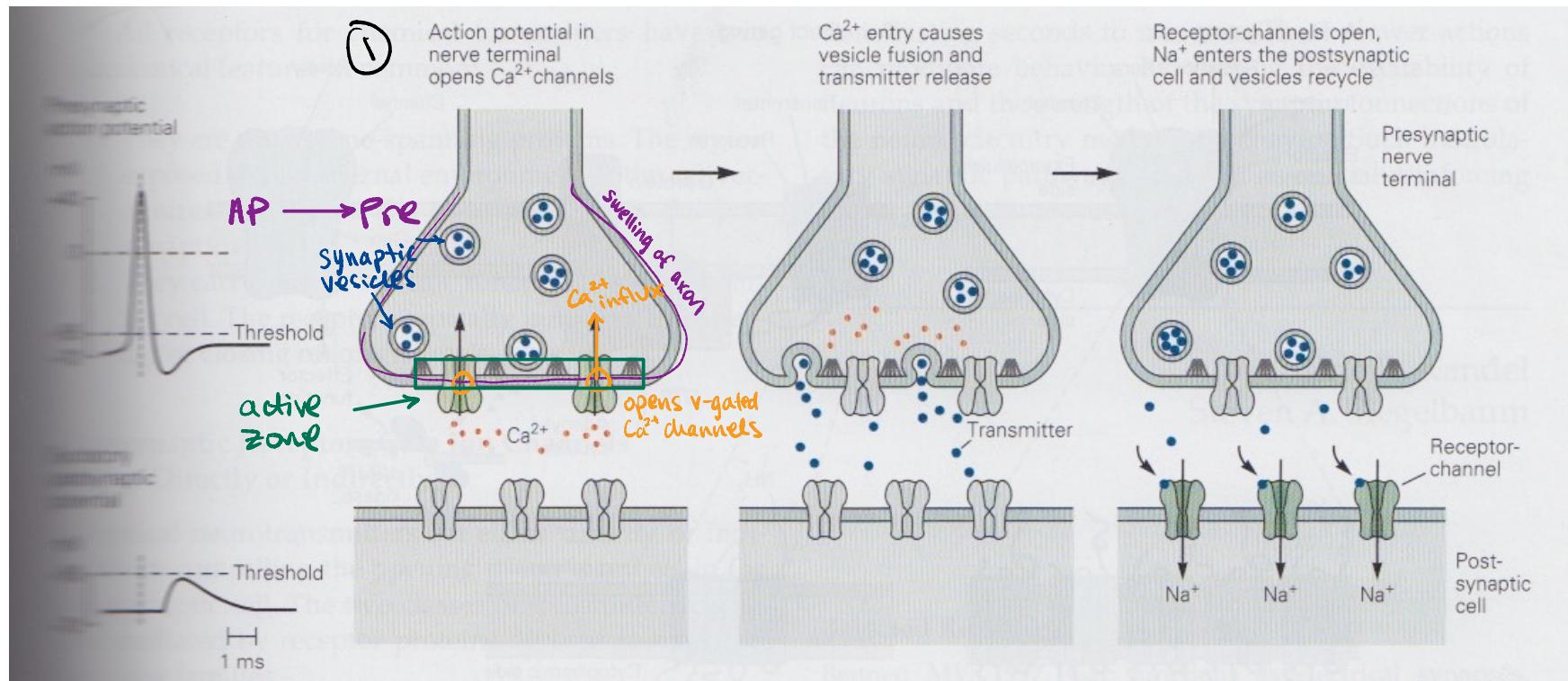
- Most synapses are chemical.
- Chemical synapses are capable of more variable signaling than electrical synapses (vis-à-vis excitatory / inhibitory effects, synaptic plasticity, signal amplification).
- Chemical synapses are central to most brain functions we know and love.
- Thus, we will focus on chemical synapses.
- If you want to learn more about electrical synapses, you can read about it in PNS Chapter 10 (p. 177-182), but it's beyond the scope of this course.

Calcium is Essential For More than Just Healthy Bones

got milk?

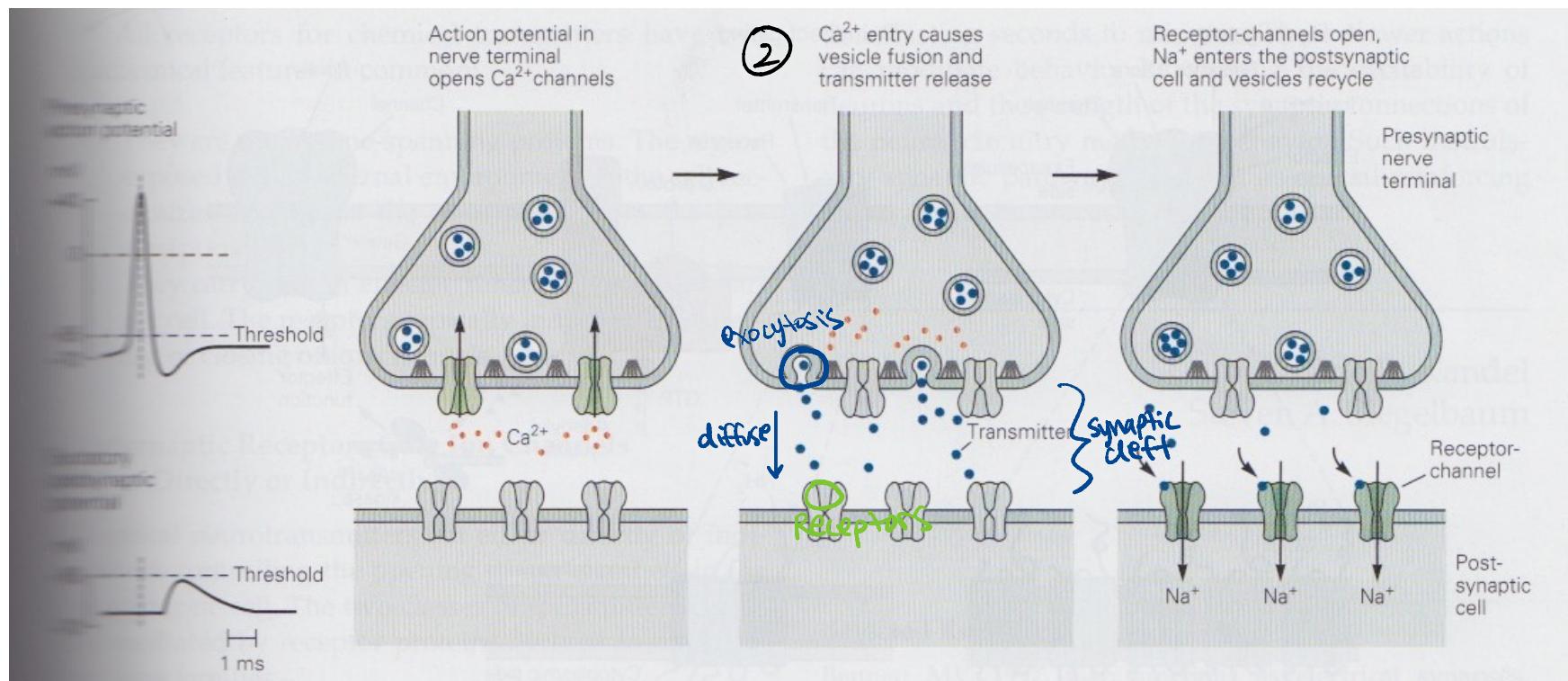


Synaptic Transmission at Chemical Synapses



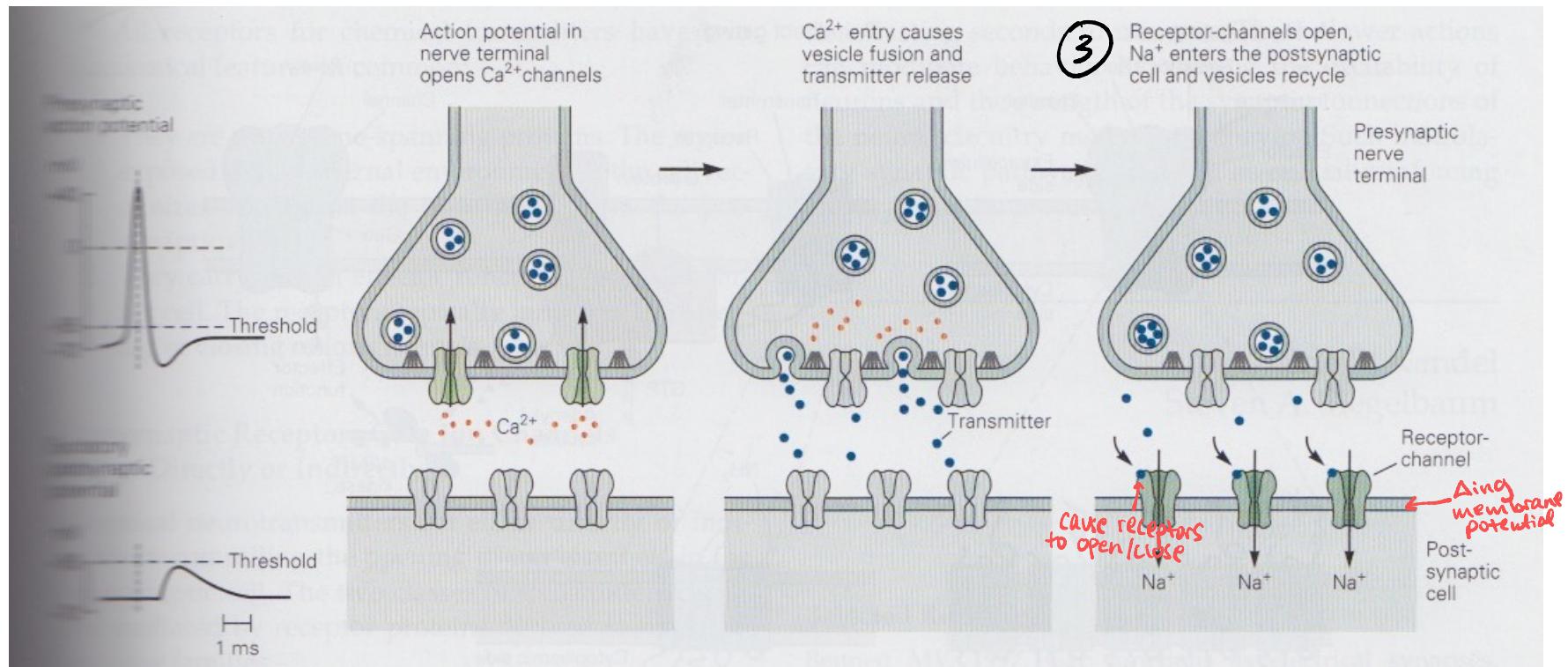
- 1) Action potential arriving at **presynaptic terminal** (swelling of axon) causes voltage-gated Ca^{2+} channels at the **active zone** (membrane specialized for releasing neurotransmitter) to open.
- 1) Influx of Ca^{2+} causes **synaptic vesicles** containing **neurotransmitter** to fuse with the presynaptic cell membrane.

Synaptic Transmission at Chemical Synapses



- 3) Vesicles release their contents into the **synaptic cleft** (a process termed “**exocytosis**”).
- 4) Released neurotransmitter molecules diffuse across synaptic cleft and bind to specific receptors on post-synaptic membrane.

Synaptic Transmission at Chemical Synapses



- 5) Receptors cause ion channels to open (or close), thereby changing the membrane potential of the post-synaptic cell.
- 6) If membrane of post-synaptic cell crosses threshold, then the action potential is propagated.

Chemical Synapses Can Amplify Signals

- The action of **one** synaptic vesicle can open **thousands** of ion channels in the postsynaptic cell!
- Reason: one vesicle contains several thousand molecules of neurotransmitter, but only a couple molecules are typically needed to open an ion channel.
- Thus, even a small presynaptic terminal (with weak electrical current) can depolarize a large postsynaptic cell.

Neurotransmitter release is probabilistic

- Transmitter released in discrete packages called *quanta* (one vesicle contains one quantum of transmitter).
- Each quantum produces a postsynaptic potential of a fixed size, called the *quantal synaptic potential*.
- **Probability** that a loaded vesicle will dock at a release site and release a quantum of transmitter is directly dependent on the amount of Ca^{2+} influx into the presynaptic terminal.
- Alterations in Ca^{2+} concentration affect the average number of quanta that are released in response to a presynaptic action potential, *not* the size of a quantum.
- The effectiveness of chemical synapses can be modified by Ca^{2+} concentration => synaptic plasticity

• opening | closing of channels
• Release of neurotransmitters } not deterministic

Chemical Synapses Can Mediate Either Excitatory or Inhibitory Effects on Postsynaptic Cells

- There are many kinds of neurotransmitters (e.g., acetylcholine, dopamine, glutamate).
- There are many types of postsynaptic receptors (some gate ion channels directly, others indirectly).
- Whether the effect of a chemical synapse is excitatory or inhibitory depends *not* on the neurotransmitter, but on the receptor.

Synaptic integration

- Everything that we've talked about so far involves just one synapse.
- But, a typical neuron receives $> 10^3$ synaptic connections.
- These synaptic connections may be excitatory or inhibitory.
- Some connections are strong, some are weak.
- How does a neuron integrate its inputs to “decide” whether or not to emit an action potential?

Threshold varies within a cell

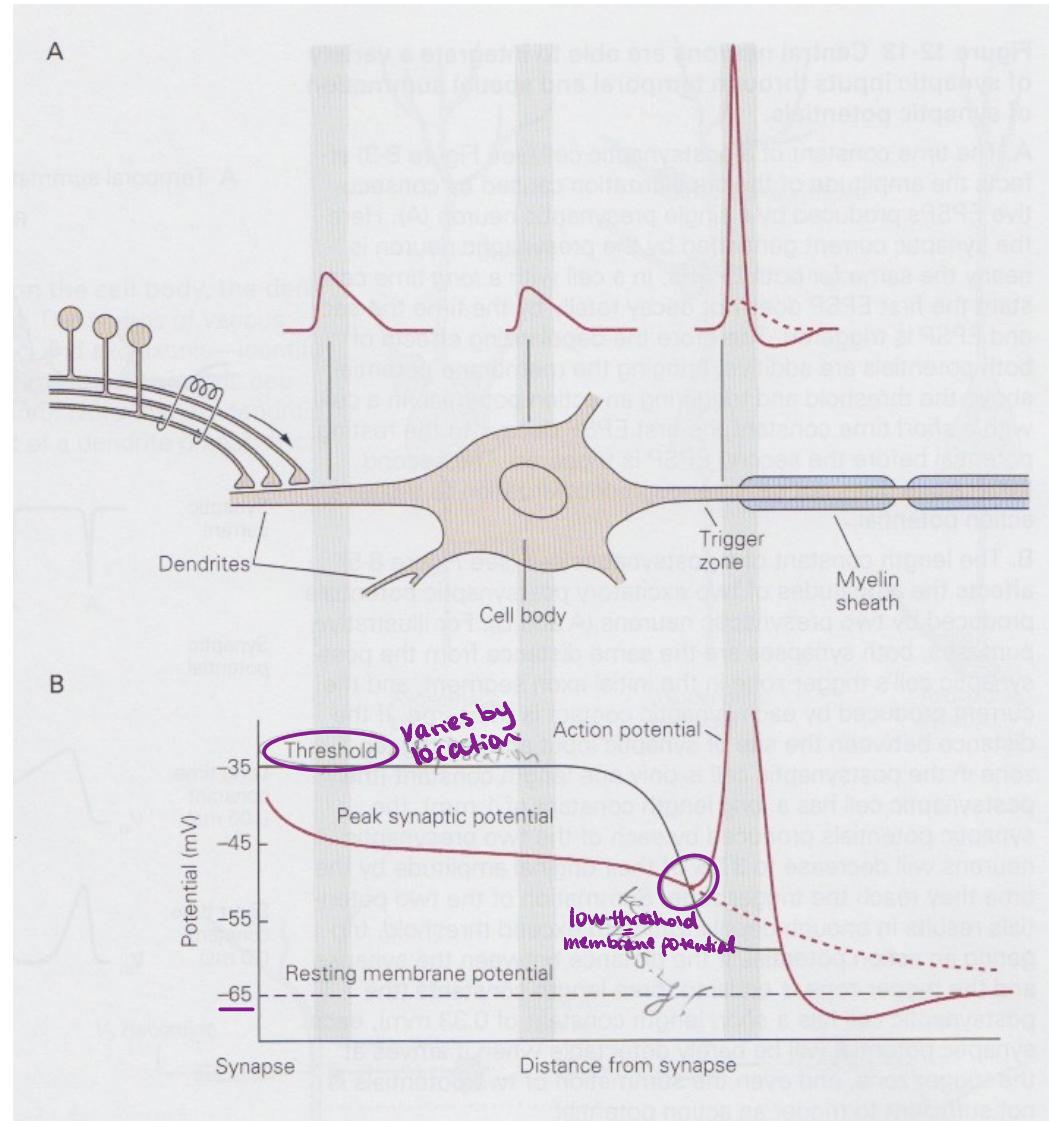
- Recall: an action potential is generated when the membrane potential exceeds threshold.
- Threshold is lower at the axon hillock than at cell body or dendrites.
- Reason: The **axon hillock** has a high density of voltage-dependent Na^+ channels. For each increment of membrane depolarization, more inward current flows at the axon hillock than elsewhere in the cell.

Axon hillock:

- ↑ concentration of voltage-gated Na^+ channels
- ↓ threshold for action potential

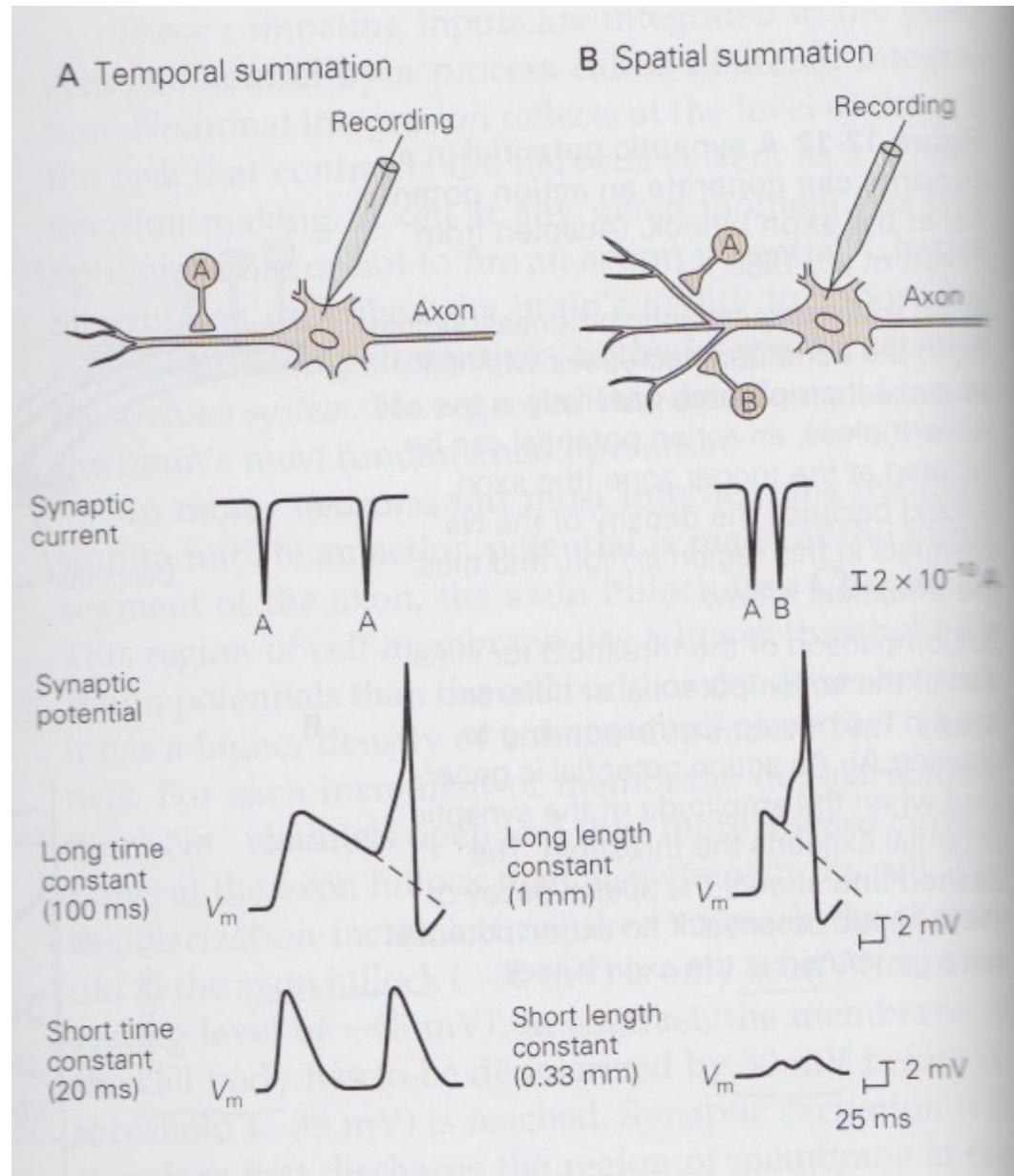
Action potential typically generated at axon hillock

- Difference between threshold and resting membrane potential is 10 mV at axon hillock, compared to 30 mV in cell body.
- Peak synaptic potential drops with distance from synapse.
- Key crossing point:** neuron fires an action potential.
- Membrane potential at axon hillock serves as the readout for the integrative action of a neuron.



Temporal summation

- Consecutive synaptic potentials are added together in the postsynaptic cell.
- Larger time constant => more likely that two consecutive inputs will summate to cross threshold.
- Time constant depends on density of resting ion channels, their conductance, membrane properties.



Spatial summation

- Inputs from presynaptic neurons acting at different sites on postsynaptic neuron are added together.
- **Larger length constant => signals do not rapidly decay with distance, thus 2 different inputs are more likely to bring postsynaptic neuron to threshold.**
- Length constant depends on size of axons and dendrites, resistive properties of cytoplasm, density of resting ion channels, their conductance.

