Chapter 2

Lessons From Neuroscience

Neural Networks: A Classroom Approach

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From Shakespeare…

Art thou not, fatal vision, sensible
To feeling as to sight? or art thou but
A dagger of the mind, a false creation,
Proceeding from the heat oppressed brain?

Macbeth, II, i, 36-39

The Human Brain

- A formidably complex structure.
- Comprises a network of roughly a hundred billion neurons.
- Each neuron has about 10,000 synapses on an average, and therefore, the total number of connections is a phenomenal one thousand trillion—1000,000,000,000,000 or 10^{15}.
- A cubic millimeter of brain contains on an average nearly a billion synapses.

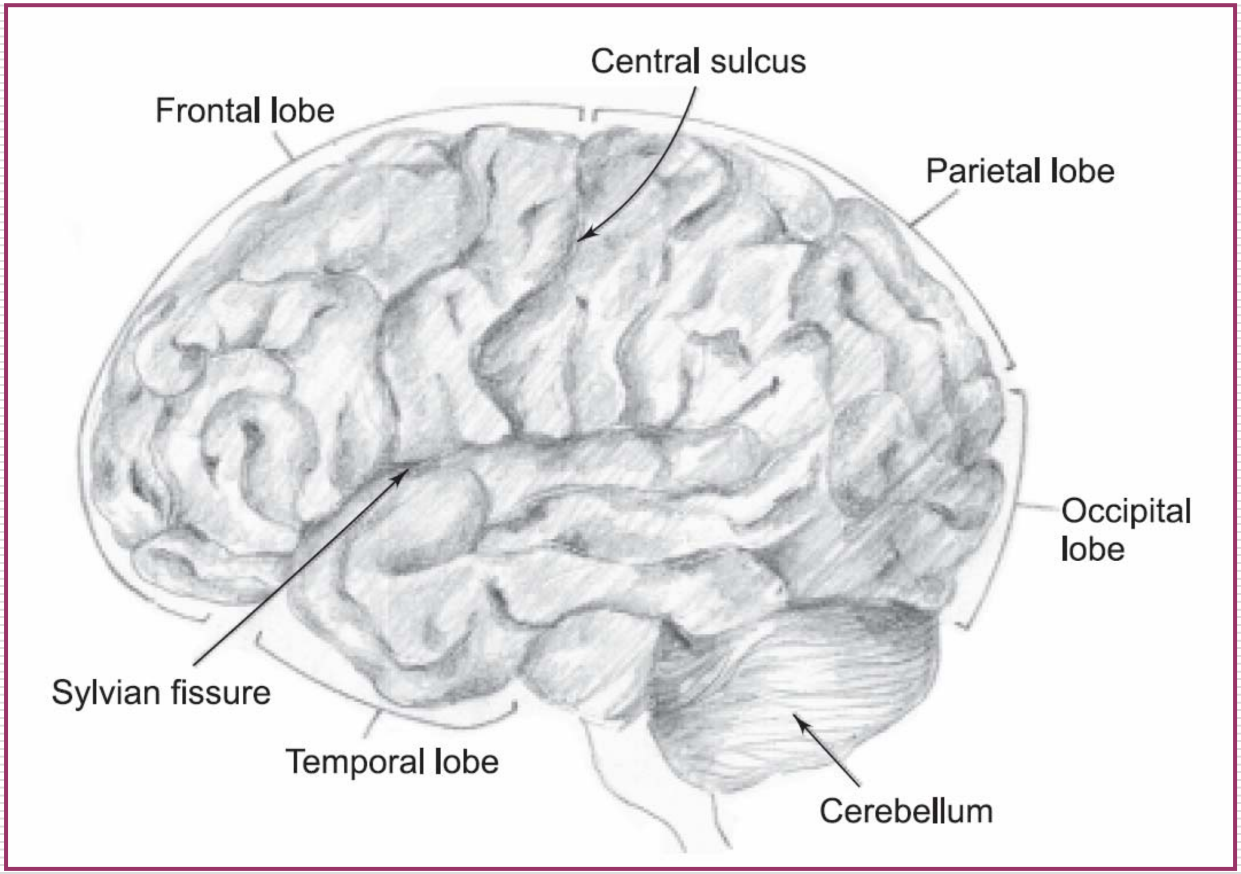
What do these numbers mean to us?

- Here are a few numbers for you to consider:
  - The sun turned on some 5 billion years ago.
  - The universe has some 100 billion galaxies, each with about 100 billion stars.
  - A lifetime averaging 80 years amounts to some 2.5 billion seconds.

Modern Technologies Bring Forth New Insights

- Staining techniques help identify cells and their interconnections.
- Optical recording techniques help study the firing patterns of populations of neurons in brain slices.
- A high level picture obtained from imaging and other techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI), computer aided tomography (CAT), and electroencephalography (EEG).
- Confocal microscopy for three-dimensional views of a neuron.
- Radioactive tracing allows axonal connections to be mapped.
- Intra- and extracellular recordings obtained using microelectrodes and patch clamping.
- Voltage and concentration sensitive dyes change their colour with the varying cell potential or the concentration of calcium ions.

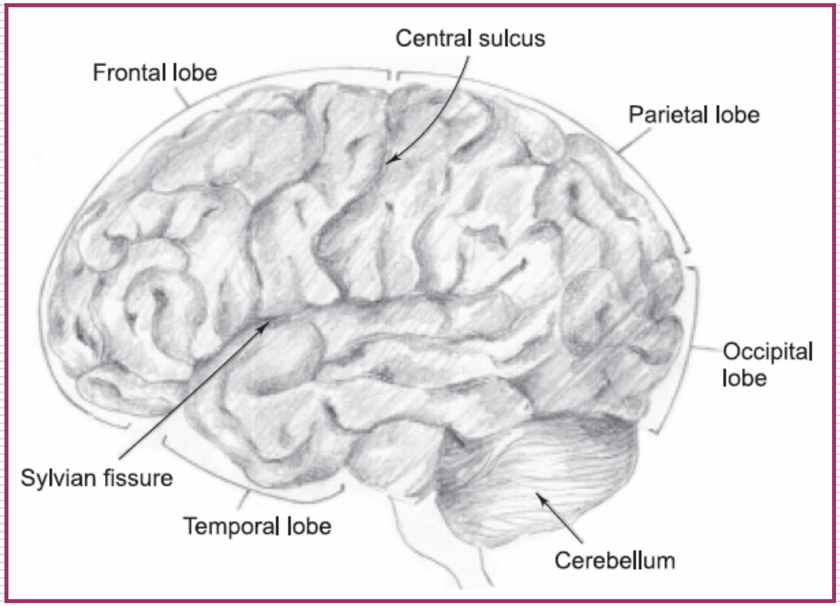
Cerebrum



Central sulcus
Frontal lobe
Parietal lobe
Occipital lobe
Sylvian fissure
Temporal lobe
Cerebellum

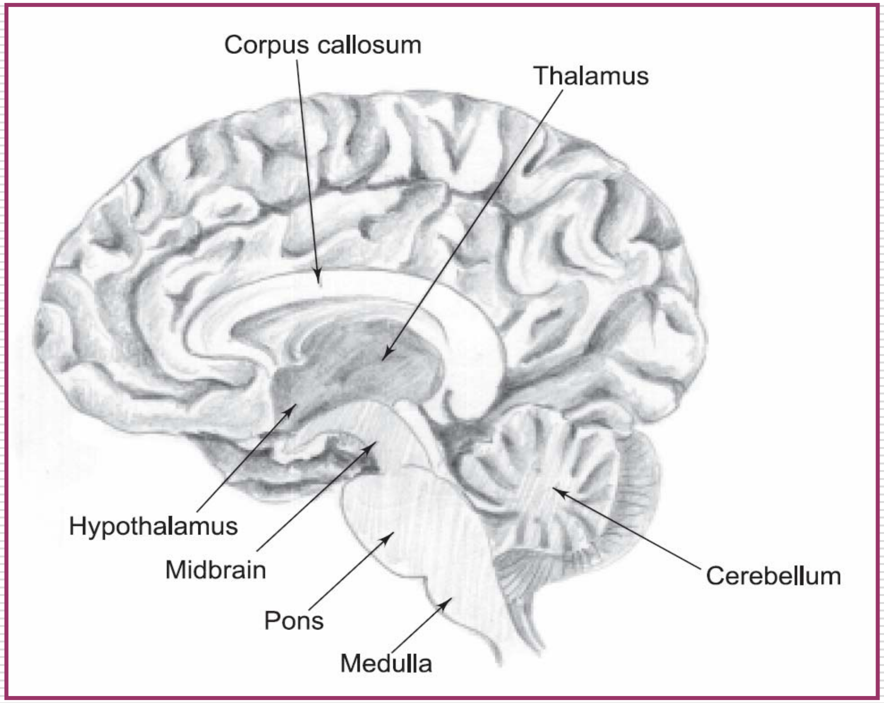
Cerebrum

- Weighs about three and a half pounds.
- Outside surface has a wrinkled texture and is divided into *gyri* (ridges) and *sulci* (valleys).
- There is a small projection at the back which is called the *cerebellum*.
- Thin outer surface layers of grey matter and larger inner regions of white matter: *cerebral cortex* and *cerebellar cortex*.
- Cortex of the cerebral hemispheres is 3–4 mm thick.
- **Wrinkling ensures that the cortical area is many times larger than that of the skull.**

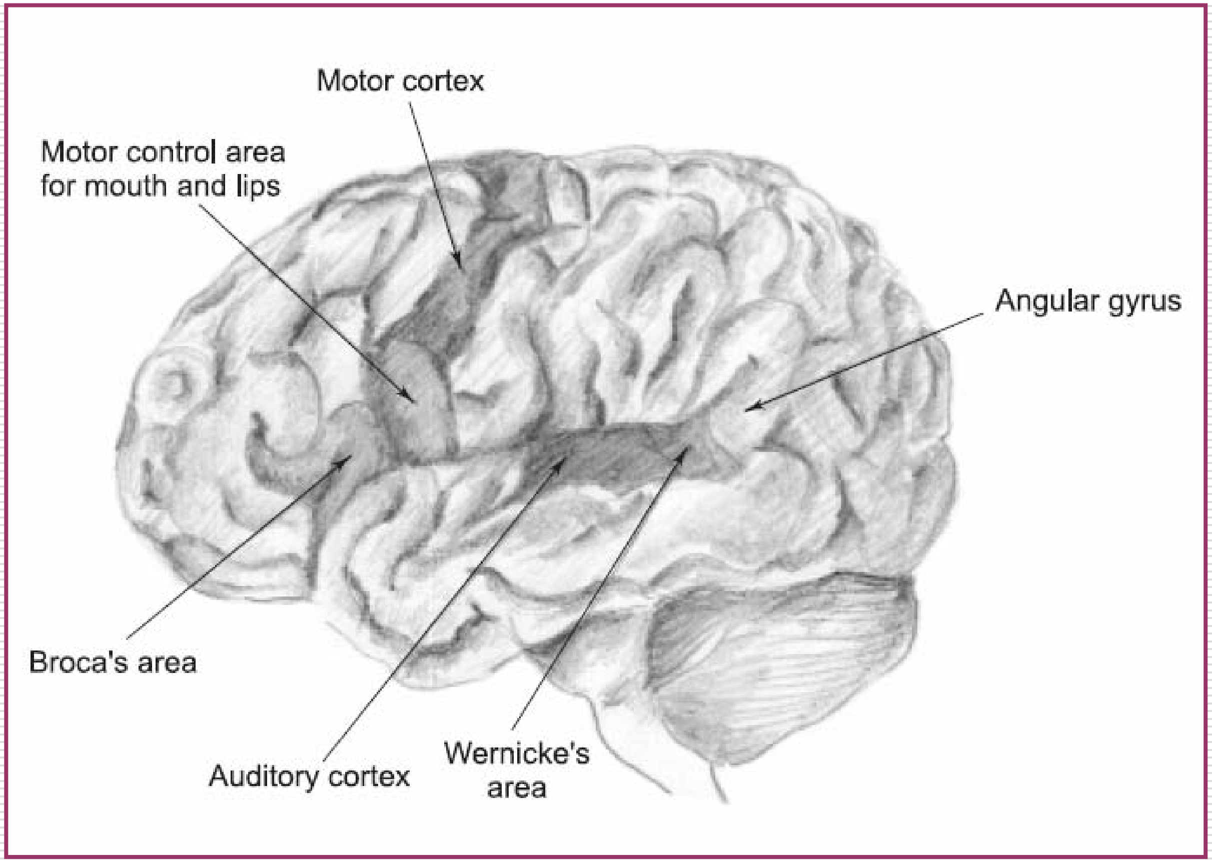


Cross-sectional View Of The Human Brain

- Pons: responsible for conveying information about movement from the cerebrum to the cerebellum.
- Medulla oblongata: controls vital autonomic functions such as breathing, heart rate and digestion.
- Thalamus: a switching centre which processes information from the central nervous system before transmitting it to the cerebral cortex.
- Hypothalamus: regulates the endocrine system and autonomic function.
- Hippocampus: participates in aspects of memory storage.
- Corpus callosum: a bundle of fibers that go from one hemisphere to the other thereby permitting inter-hemisphere communication.



Localization Of Language: Broca's And Wernicke's Areas



Cerebellum: Hind brain

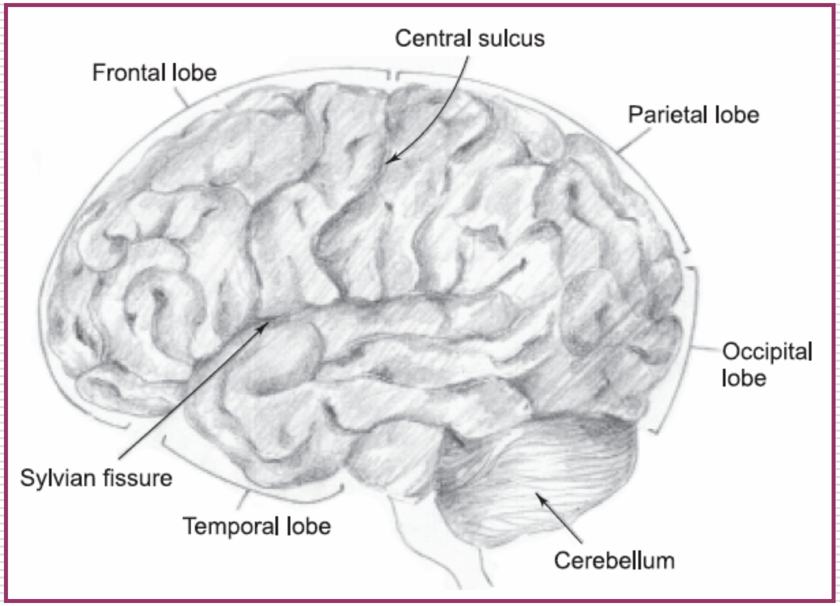
- Function is similar to that of the spinal cord.
- Coordinates movements of the head, mediates sensorimotor reflexes and controls the fine-grained coordination of muscle timing and activation.
- Remarkable both in regularity and simplicity. Sections anywhere are indistinguishable from one another despite differences in function.
- Contains only five types of cells.
- The largest cells are the 15 million or so Purkinje cells:
  - Very large dendritic trees which can receive input signals from almost 80,000 presynaptic neurons.
  - Extends in two dimensions.
  - Inhibitory in nature.
- Electrical stimulation of the cerebellum in humans never results in conscious experience.

Thalamus: Switching Centre

- Located at the head of the brain stem.
- Comprises different nuclei that receive sensory information about sensation, audition and vision.
- Responsible for the conduction of sensory and motor information from the CNS to sensory and motor areas of the cerebral cortex.
- Mediates motor information from the cerebellum to the cerebral cortex.
- Thalamic nuclei define corresponding cortical areas based on regions to which they project.
- Simple in its design:
  - Afferent fibers from different sense organs synapse directly on principal cells.
  - Principal cells project axons to different cortical regions.
- The thalamus acts like a synaptic relay for information that reaches the cerebral cortex.

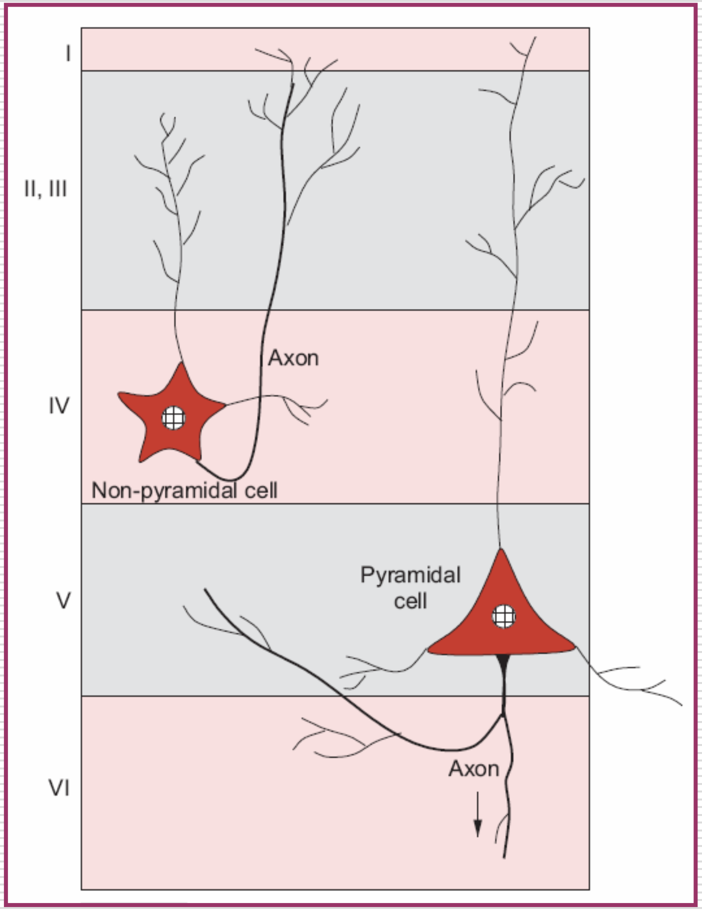
Neocortex

- Appears as a thick convoluted sheet 2–4 mm thick.
- Covers the two cerebral hemispheres.
- Forms the largest structure of the human brain.
- Total brain weight: about 1400 grams in human beings.
- Grey matter of each cortical hemisphere weighs about 250 grams.
- Forms a continuous sheet of neural tissue with an area of approximately 2200 sq. cms.
- Continuity of the tissue is important for its function.



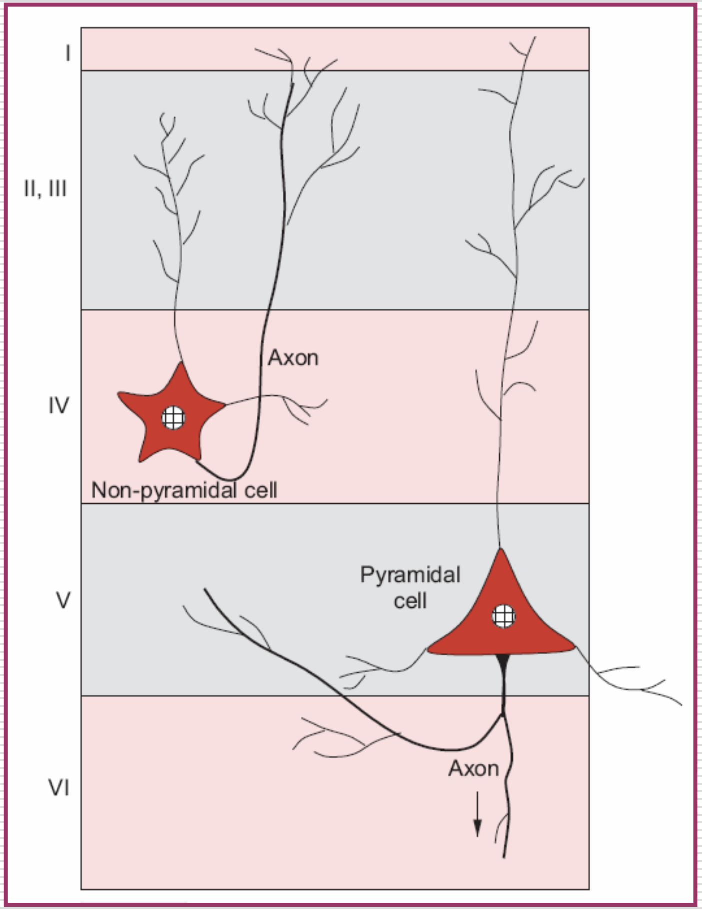
Layers of Neocortex

- Layer 1 at the top
  - Provides a means for interconnecting different cortical regions.
  - Has an extensive network of connections with many different kinds of synapses.
  - Has very few neuron cell bodies.
- Most of the output to other cortical regions comes from Layers 2 and 3 which respectively contain small and large pyramidal cells.



Layers of Neocortex

- Inputs from the thalamus are concentrated in **Layer 4** non-pyramidal cells.
- The largest pyramidal cells whose axons leave the cortex for sub-cortical destinations (such as the basal ganglia, brain stem and spinal cord), are largely concentrated in **Layer 5**.
- **Layer 6** also contains pyramidal cells that send axons back to the thalamus.
- The white matter residing just below the cortex is composed of axons that carry messages to and from the cortical regions.



Pyramidal Cells

- The pyramidal cells are the most important.
- Have dendrites covered with spines that make synaptic contacts thought to be involved in learning.
- Transmit signals down a column.
- Since the pyramidal cells account for almost 75 per cent of the cells in the cortex, one can say that the cortex comprises a network of pyramidal cells.

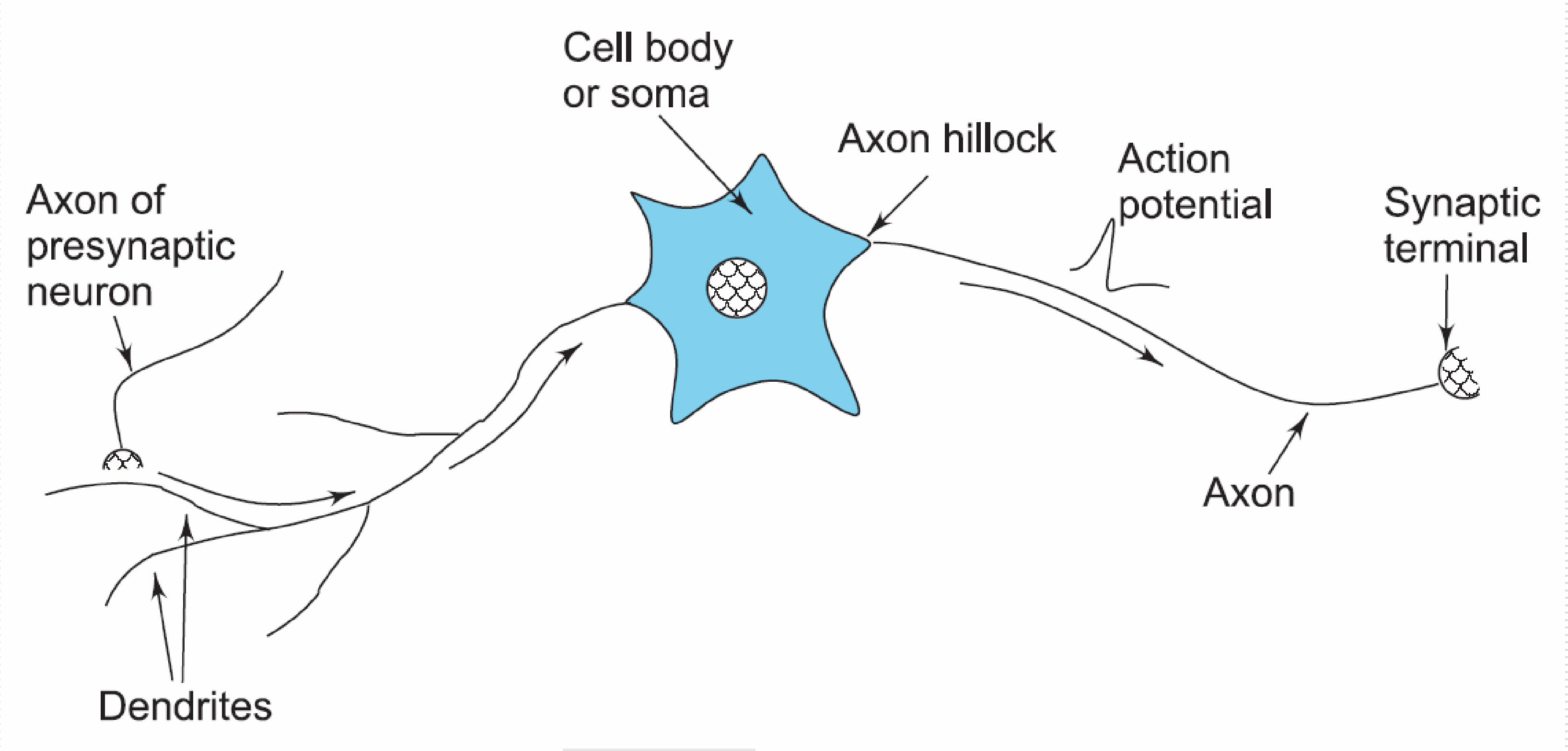
Non-Pyramidal Cells

- The Martinotti cell concentrated in lower layers which transmits signals upward through the cortex to Layer 1.
- The stellate cell
  - Has dendrites radiating in all directions around it.
  - Axon branches in the region of the cell body.
  - Believed to be involved primarily in local interactions.
  - Have the densest axonal trees whereas pyramidal cells have the loosest and largest.
- Whereas pyramidal cells are excitatory, stellate cells are inhibitory, and serve to modulate their firing, which would otherwise be uncontrolled.

The Cortex Communicates Primarily With Itself

- Most of the fibers in the cortex originate from within the cortex, and these are many more than those which enter the cortex from other structures or leave the cortex to go to other brain areas.
- In other words, almost 99 per cent of the axons leaving the grey matter area re-enter it without synapsing else where.

Biological Neurons



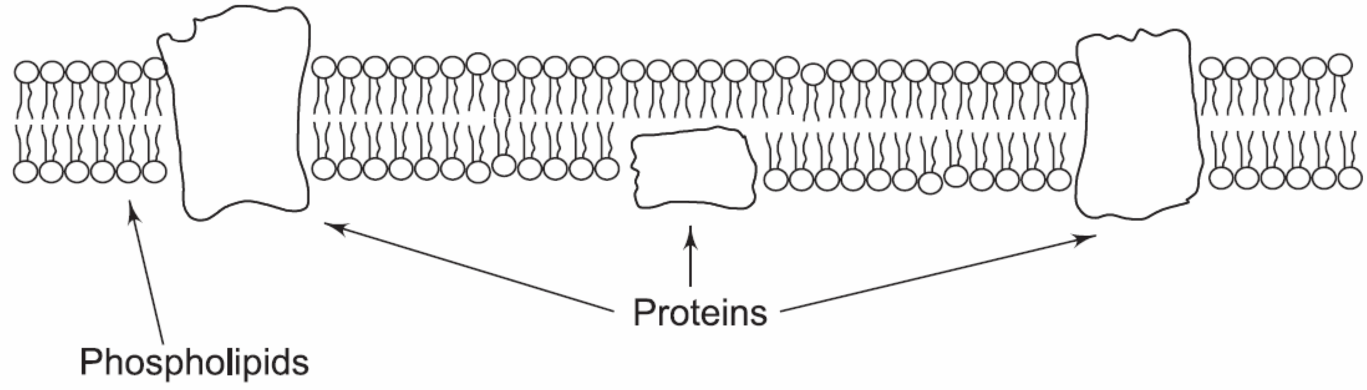
Parts of a Neuron

- Soma or cell body
  - It contains the cell's nucleus and other vital components called *organelles* which perform specialized tasks.
- A set of dendrites
  - It forms a tree-like structure that spreads out from the cell. The neuron receives its input electrical signals along these.
- A single axon
  - It is a tubular extension from the cell soma that may repeatedly branch to form an axonal tree, it carries an electrical signal called action potential away from the soma to another neuron for processing.
- The dendrites and axon together are sometimes called processes of the cell.
- Axons and dendrites are the main communication links of a neuron.

Glial Cells

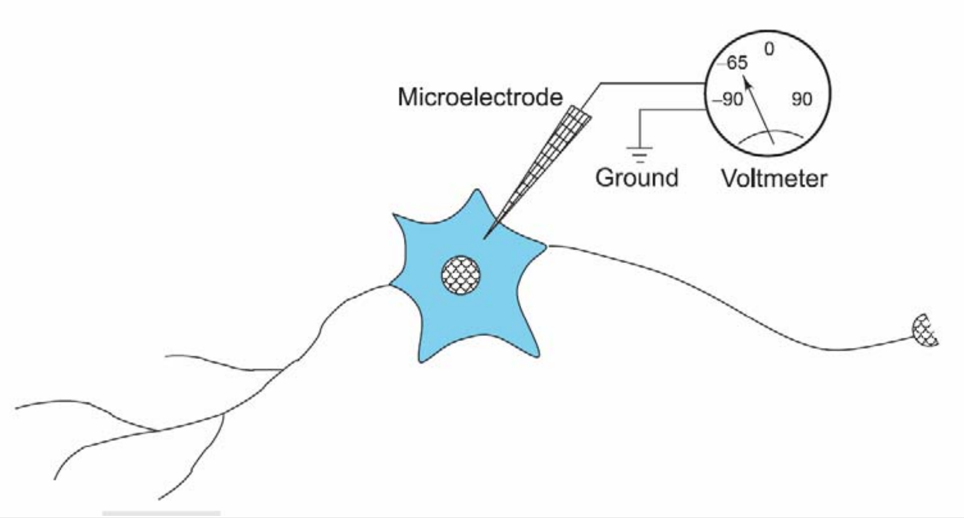
- Glial cells account for about nine-tenths of the cells in the brain.
- Three varieties, each with a specialized role.
  - Star shaped astroglia surround the neurons and isolate them from the smallest blood vessels of the brain called capillaries.
    - Form an interface with the capillary walls called the blood-brain barrier.
    - Selectively absorb nutrients from the blood and transfer them to the neurons.
    - Provide physical support and electrical isolation for neurons which minimizes inter-neuron crosstalk.
  - Microglia are small cells that move continuously between neurons and glia to clean up debris.
  - Oligodendroglia send out membranous processes that wrap themselves tightly around axons, forming a dense layer of spiraling membranes called a myelin sheath.

Cell Membrane



- Encloses neurons in a two-layered structure about 90 Å thick (a dimension that can only be resolved using electron microscopes).
- The cytosol within the cell is effectively isolated from the extra-cellular fluid by the phospholipid bilayer membrane which consists of phospholipid molecules.
- Each molecule has a
  - hydrophilic (water loving) head.
  - hydrophobic (water avoiding) tail made of a hydrocarbon chain.
- These molecules self-organize into a stable surface.

Resting Potential



- Arises due to a difference in ion concentrations inside and outside the cell.
- Observed through recordings from an electrode placed inside a cell is about –65 mV with respect to the external medium.

Concentrations Of Ions Within And Outside The Neuronal Membrane

Ion	Concentration inside (mM)	Concentration outside (mM)
Sodium ([Na^+])	15	150
Potassium ([K^+])	100	5
Chloride ([Cl^-])	13	150

- Ions diffuse into and out of the cell because of the concentration gradient.

Example: K^+ Equilibrium Potential

Excess within the cell and diffuses out

↓

Leaves behind unbalanced negative charges within the cell

↓

Makes the interior increasingly negative exterior increasingly positive

↓

Sets up an electric field which opposes the movement of the ions

↓

Eventually leads to equilibrium (no net movement across membrane)- electrical force due charge imbalance balances diffusive force

↓

Equilibrium potential

Nernst Equation

- Given the charge of an ion and its concentrations inside and outside the cell, the Nernst equation predicts the potential difference.
- Assuming the ion in question is in a state of equilibrium where it neither flows into nor out of the cell.

$$E_X = \frac{RT}{ZF} \ln \frac{[X]_o}{[X]_i}$$

R is the ideal gas constant,
T is the temperature in Kelvin,
Z is the charge on the ion *X*,
F is the Faraday constant, and
$[X]_o$, $[X]_i$ are the concentrations of *X* outside and inside the cell respectively.

Equilibrium Potentials For Some Important Ions

- Assuming the temperature to be the body temperature, i.e. 37°C
  - For an ion with $Z = +1$, $RT/ZF = 26.72$ mV
  - For an ion with $Z = -1$, $RT/ZF = -26.72$ mV.
- Then, the equilibrium membrane potentials for the three ions can be calculated as:
  - Chloride
    - $E_{Cl} = -26.72 \times \ln 150/13 = -65.34$ mV
  - Sodium
    - $E_{Na} = 26.72 \times \ln 150/15 = 61.52$ mV
  - Potassium
    - $E_K = 26.72 \times \ln 5/100 = -80.04$ mV

How Does The Cell Maintain Its Resting Potential At -65 Mv?

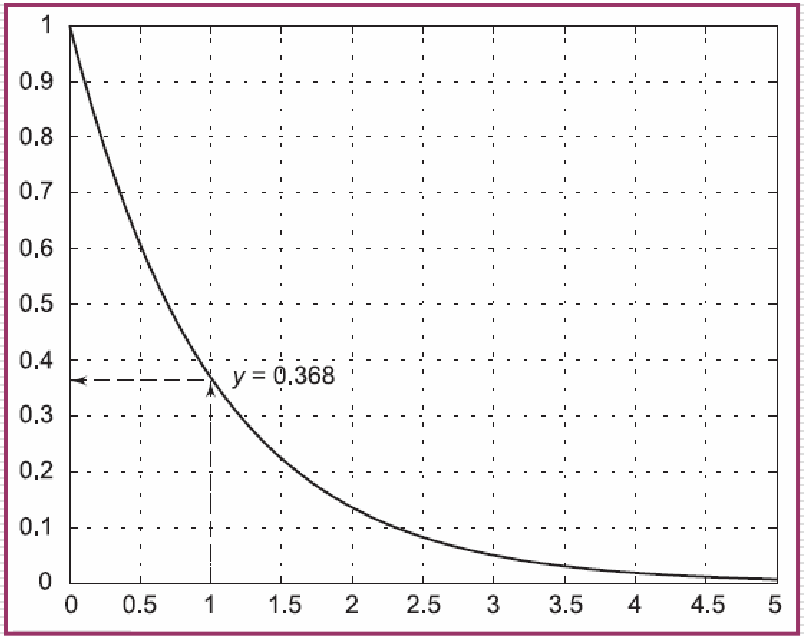
- Microscopic sodium-potassium pumps actively pump sodium out of the cell and potassium into the cell in order to maintain a high sodium ion concentration outside the cell and high potassium concentration within the cell.
- The pump consists of a single protein molecule, or a complex of protein subunits, with a molecular weight of 275,000 D.
- Each unit of the pump exchanges some 200 sodium ions for 130 potassium ions every second.
- About a million such pumps at a density of 100 to 200 per square micron of membrane surface.
- At rest, about 40 per cent of the cell's metabolic energy expenditure is for pumping ions in and out.

Graded Potentials Spread in Space and Time

- External signals impinging on the neuron at synapses create disturbances in the cell potential called graded potentials.
- If an impinging signal decreases the internal potential below the resting potential then the neuron is hyperpolarized.
- If the external disturbance increases the potential above the resting potential, then the neuron is said to be hypopolarized or depolarized.

Space Constant

- Graded potentials spread in space, and decay exponentially with distance.
- The distance over which the potential decays to 36.8% of its initial value is called the space constant.
- The space constant is different on every part of the neuron, since it depends upon:
  - The shape of the membrane.
  - The number of the ion channels.
  - The nature of the membrane proteins.
  - Since the amount of fluid inside the membrane of the dendrite is responsible for conduction of electricity, the space constant also depends on the diameter of the dendrite.



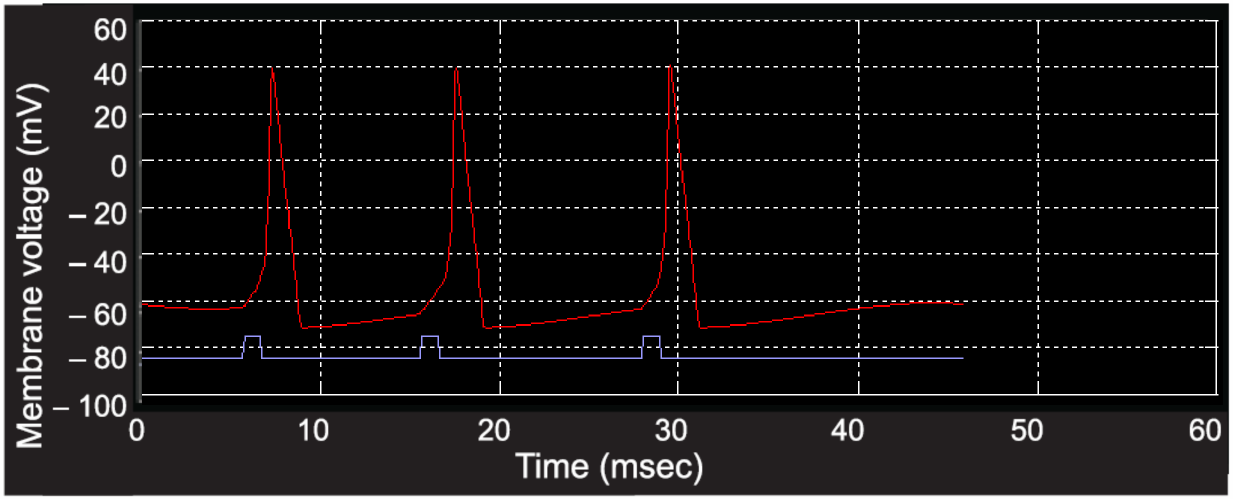
Time Constant

- When an external stimulus disturbs the ionic balance of ions in a resting membrane, it takes a finite time for the diffusion and pumping of ions to restore the resting potential.
- Graded potentials are thus sustained for sometime before they decay back to the equilibrium values.
- The time constant quantifies the rate at which the decay to the resting value takes place.
- For a typical neuron the time constant is about 4-10 ms.
- Thus, when a stimulus is applied to a dendrite, the membrane potential is restored to the rest value in a small fraction of a second.
- Graded potentials are electrical potentials and are conducted through the neuron almost at the speed of light.

Cell Soma Temporally Integrates Impinging Signals

- Synapses: points of contact where neurons constantly receive inputs from other neurons along their dendrites.
- Postsynaptic potentials (PSPs): inputs which are in the form of small electrical disturbances.
- Hundreds or thousands of tiny PSPs occur asynchronously in space and time at various points along dendrites of a neuron.
- Each PSP is an increasing/decreasing voltage pulse that decays in space and time.
- These small disturbances are superimposed upon each other at the cell soma.
- Therefore the soma potential reflects a temporal integration of these potentials.
- The soma potential varies continuously in time sometimes increasing and sometimes decreasing back towards the resting value.

Action Potentials



- At the point where the axon of the neuron meets the cell body, the axon expands into a structure called the axon hillock.
- Here, ion channels exist in considerably high density and are highly sensitive to small perturbations in the integrated soma potential.
- Ion channels constantly monitor the soma potential in such a way that when the cell potential exceeds a threshold value of about –40 mV, the neuron fires an action potential that is transmitted down its axon towards a synaptic terminal.

A Historical Digression

- The celebrated experiments of Hodgkin and Huxley conducted during the 1940s, earned them the Nobel Prize in 1963.
- Provided the first concrete evidence for the ionic basis of the action potential.
- Towards the late 1940s researchers realized that the action potential involved electrical events carried by ions.
- It was also known that sodium was responsible for the peak of the action potential because the peak's amplitude got reduced if the external medium contained a reduced concentration of sodium ions (predicted by the Nernst equation).

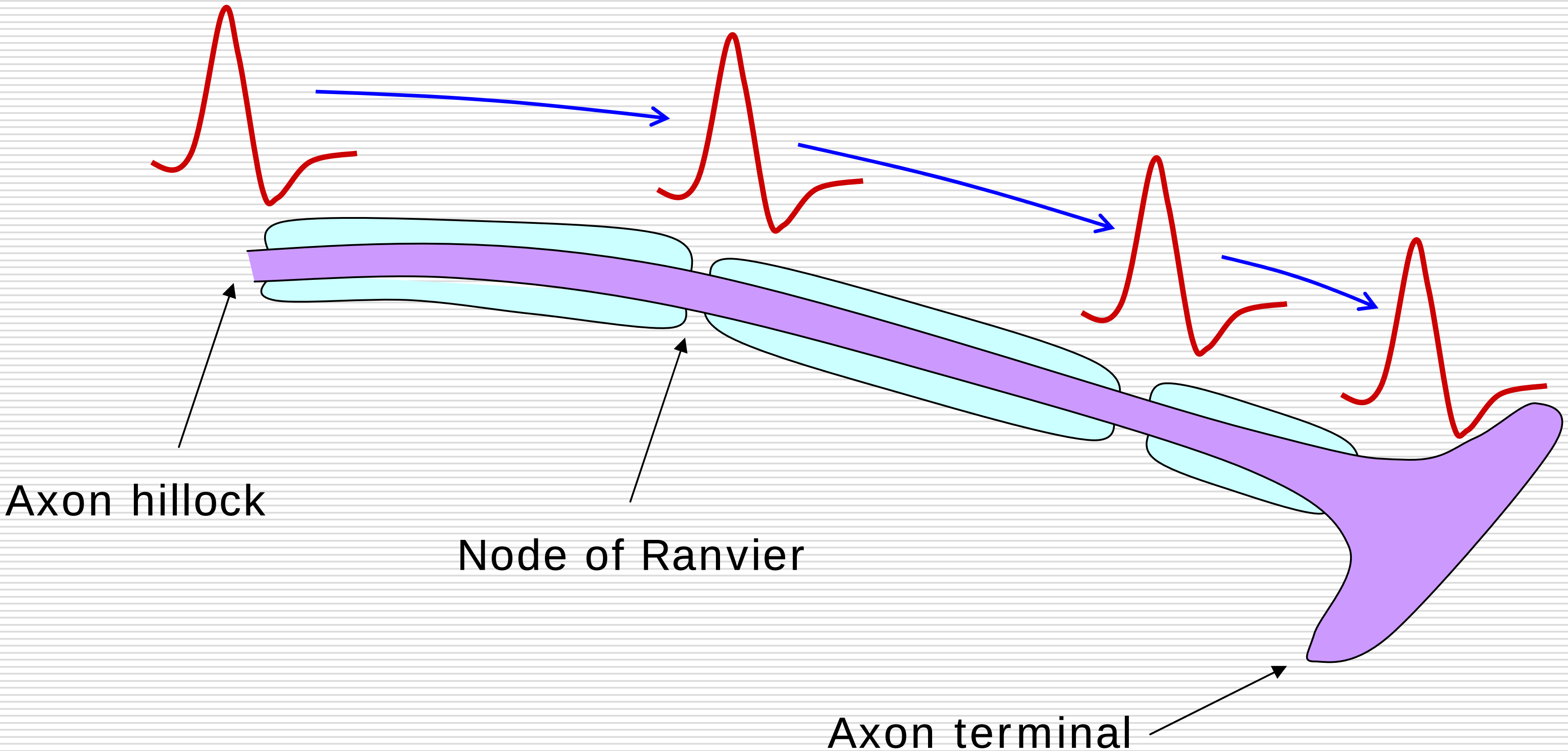
The Voltage Clamp

- In the experiment, an electrode was inserted in the squid giant axon and connected to a circuit which would maintain the membrane voltage fixed at a predefined value by automatically adjusting the injected current via negative feedback.
- The amount of external current required to hold the voltage constant thus provided a measure of the current flowing across the membrane.

Refractory Periods

- No matter how strong the applied external stimulus is made, an action potential cannot be re-generated during the action potential itself.
- This period of inexcitability lasts for some 1–2 ms and is called the absolute refractory period.
- During the undershoot when the potassium channels are closing, it is more difficult than usual to excite the axon since the membrane potential is still hyperpolarized.
- This period is called the relative refractory period, because the axon is excitable but requires a larger stimulus than normal.
- The absolute and relative refractory periods naturally impose a biological limit on the maximum frequency of firing of action potentials.
- No neuron can respond at rates much over 1000 spikes/sec (1000 Hz), and even this is possible only for a fraction of a second with very strong stimuli.

Propagation of Action Potentials

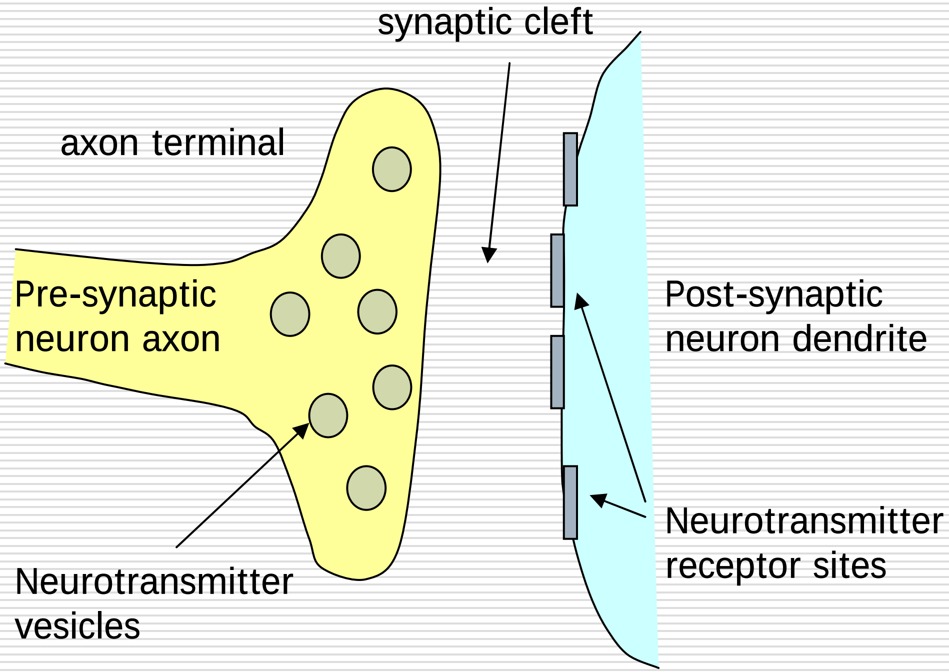


Sequence of Events in Propagation

- As the action potential waveform rises towards its peak at the axon hillock, the potential along considerable length of axonal membrane adjacent to the axon hillock is also pushed above the threshold.
- Membrane is exposed at Nodes of Ranvier where sodium channels open due to the adjacent disturbance.
- Initiates the entire sequence of events that generate an action potential.
- The action potential jumps from node to node: saltatory conduction.
- Continually renewed in full strength as it passes physically down the axon.
- This design obviates the need for biological amplifiers irrespective of the length of the axon.

Chemical Synapses

- The transmission process across a synapse requires a two-step transduction process:
- From electrical action potential to chemical transmitter substance which is released into the synaptic cleft.
- From chemical transmitter back to an electrical signal post-synaptic potential.



Synaptic Transmission: Phase 1

Action potential hits axon terminal

Depolarizes the terminal

Influx of Ca++ increases concentration

Vesicles filled with ACh move towards the presynaptic terminal

Neurotransmitter vesicles fuse with the membrane wall

Ach is released into the synaptic cleft

Synaptic Transmission: Phase 2

Neurotransmitter (ACh) released in the synaptic cleft diffuses across 200Å thick extra cellular medium in 50ms.

↓

Ach interacts with specialized receptor sites at post synaptic membrane

↓

Ach is a key that opens channel on the post synaptic membrane

↓

Channels in the post synaptic membrane specifically allow the passage of Na or K ions resulting in depolarization or hyperpolarization of the postsynaptic cell.

↓

Creates either an excitatory or inhibitory post synaptic potential