

ICL Neuroscience and Physiology

Ian Poon

October 2024

Woah! First time not using MIT OCW materials? Well yeah...there are no notes for MIT 7.20 Physiology.

Contents

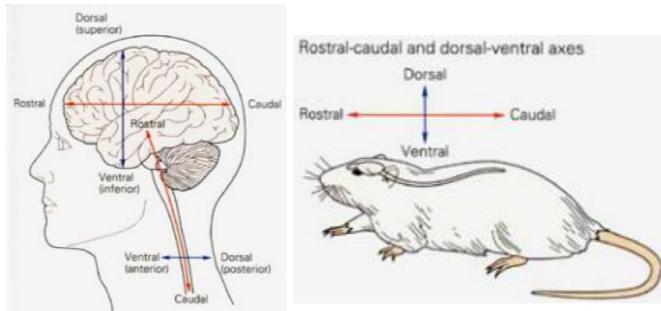
1	Introduction to Neuroscience	4
2	neurons and bioelectric signals	5
3	signal propagation,transmission and integration.....	15
3.1	Voltage-Clamp Experiments – Hodgkin and Huxley.....	19
3.2	Calculation of Conductances.....	21
3.3	Voltage Gated Ion Channels.....	21
3.4	overview of action potential.....	22
3.5	Patch Clamp Experiments.....	23
3.6	synaptic transmission.....	24
3.7	Electrical Synapses.....	25
3.8	Chemical Synapses.....	26
3.9	direct and indirect gating.....	28
3.10	Synaptic Integration.....	29
4	General Principles of Sensing	30
4.1	stimulus intensity	34
4.2	Stimulus Location	35
4.3	Lateral Inhibition	36
5	The Auditory System	37
5.1	The Basilar Membrane: Frequency Analysis	39
5.2	The organ of Corti: Mecanoelectrical Transduction	40
5.3	Central Auditory Pathways	41
5.4	The Cochlea Nuclei	43
5.5	Delay-Line Mechanism.....	43
5.6	Cochlea Implants	44
6	The Vestibular System	44
7	the visual system	46
7.1	Photoreceptors	48

7.2 Low-Level Visual Processing	52
7.3 Higher Level Visual Processing	54
8 The Somatosensory System.....	57
8.1 Morphology of Mechanoreceptors.....	57
8.2 Transmission to CNS.....	58
8.3 Action of Mechanoreceptors	58
8.4 Ascending Pathways.....	60
8.5 The Somatosensory Cortex.....	62
8.6 Higher Order Processing	62
9 Simple Reflexes.....	64
9.1 Contextual Dependency.....	64
9.2 Spinal Reflexes.....	64
9.3 Local Spinal Circuitry	67
9.4 The Golgi Tendon Organ.....	73
10 Eye Movements	74
10.1 Functions	74
10.2 Neuronal Control Systems	74
10.3 The Ocular Motor Plant.....	75
10.4 Brain Areas and Cranial Nerves.....	75
10.5 Extraocular Motor Neuron Encoding	76
10.6 The Vestibular-Ocular Reflex	76
10.7 Saccadic Eye Movements	78
10.8 Head-Eye Coordination.....	79
11 Premotor and Motor Cortices	81
11.1 The Spinal Cord.....	81
11.2 Ascending Pathways.....	81
11.3 Cortical Processing	82
11.4 Descending Pathways.....	83
11.5 Transcranial Magnetic Stimulation	83
11.6 Spike-Triggered Averaging	84
11.7 Neural Plasticity.....	85
11.8 The Premotor Cortex	85
11.9 Population Vector – Encoding Limb Movement Direction	85
11.10 Visuomotor Transformations	85
11.11 Major Control Pathways	86
11.12 Ventral Premotor Area and Mirror Neurons	86
12 Cerebellum and Motor Learning	86
12.1 The Cerebellum	86
12.2 Calibration of the VOR.....	89
12.3 Neural Plasticity: Long Term Potentiation	90

12.4 Role of Cerebellum in Motor Learning	92
12.5 Conceptual Model for Fine-Tuning Motor Action.....	93
13 The Skeletal System	94
13.1 Long Bone Structure.....	95
13.2 Bone Growth	97
13.3 Bone Remodelling and Repair	99
13.4 Calcium Regulation	100
13.5 Bone Marrow Function	100
13.6 Anatomy of Various Bones	101
13.7 Joints.....	102
14 Skeletal muscle	102
14.1 The Muscle Fibre and Myofibrils	103
14.2 Sliding Filament Theory of Muscular Contraction.....	104
14.3 Energy for Muscle Activity.....	107
14.4 Control of Contraction	108
14.5 Neuromuscular Junctions.....	109
14.6 Contraction Terminology	110
14.7 Sarcomere length, tension and contraction	111
14.8 Types of Muscle Fibres.....	111
14.9 Training and Atrophy	112
15 Cardiac Muscle	112
15.1 Function.....	112
15.2 Morphology	112
15.3 Contraction	113
15.4 Smooth Muscle Cells.....	114
15.5 Structure.....	114
15.6 Control.....	115
15.7 Contraction	115
15.8 Summary of Muscle Types.....	117
16 Introduction to the Endocrine System	117
16.1 Scope of Endocrine System	117
16.2 Fundamentals	118
16.3 Types of Hormones	119
16.4 Regulation of Hormone Concentration.....	120
16.5 Categories of Endocrine Disorders.....	121
17 The Hypothalamic-Pituitary Axis and Growth	121
17.1 Control of Growth.....	124

1 Introduction to Neuroscience

Anatomical Spatial Definitions

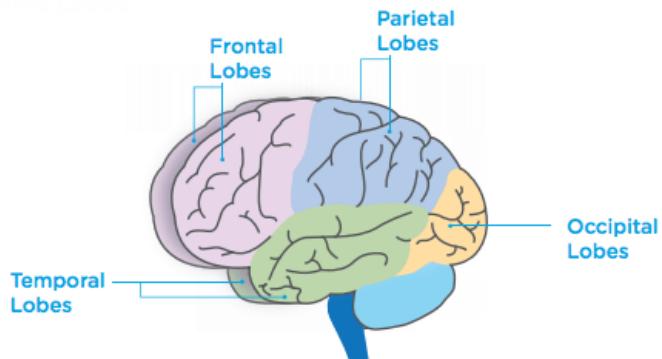


Definition 1 (Terms for anatomical position)

Rostra-cadula and dorsal ventral axes(1st four terms) and last 2 you should be familiar from similar terminology in heart vessels if you recall(superior,inferior arteries/veins)

- **rostral**(Latin rostrum 'beak, nose'): towards the nose
- **caudal**(Latin cauda 'tail'): towards the tail
- **dorsal**(Latin dorsum 'back'): towards the back
- **ventral**(Latin venter 'belly'): towards the belly
- **superior**: upper
- **inferior**: lower

Major Lobes



Fact 2

Etymology

- Latin *parietālis*, from *pariēs* ("wall").
- Latin from *occiput* ("the back of the head, occiput") + *-ālis* ("-al", adjectival suffix)

The rest is just standard english

- "Frontal": front obviously
- "Temporal": Of or situated in the temples of the head

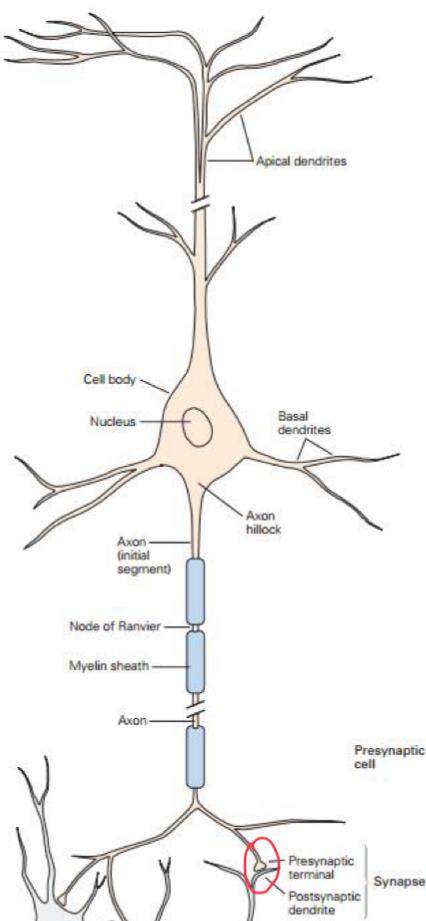
2 neurons and bioelectric signals

functional organisation of a neuron

Definition 3

Typical neurons have four morphological regions

- **cell body**(soma): metabolic centre
- **dendrites**: input region
- **axon**: signal propagation
- **synaptic terminals**: signal transmission



the soma

- Contains the nucleus, GA and other organelles
- branches out into two kinds of processes
 - several short dendrites
 - one long tubular axon
- the soma integrates the signals received and may change activity of the cells causing generation of an AP

Dendrites

- branch out in a tree like pattern
- main apparatus for receiving incoming signals from other nerve cells

Axon

- axon extends some distance from the soma and carries signals to other neurons
 - AP is initiated in a special trigger region near beginning of axon called the **initial segment**

- propagation is at speeds of 1 to 100m/s
- AP remains an 100mV as it is an **all-or-nothing** response generated at regular intervals
- information conveyed by the AP is determined by the pathway and frequency
- ranges from 0.1mm to 2m
- large axons are wrapped in **myelin sheath** interrupted by the **nodes of ranvier**

synapses

- near its end the axon divides into fine branches that contact other neurons at specialized zones of communication known as synapses
 - the nerve cell transmitting a signal is called the presynaptic cell
 - the cell receiving the signal is the postsynaptic cell
- the presynaptic cell transmits signals from specialized enlarged regions of its axon branches called presynaptic terminals or nerve terminals
 - the presynaptic and postsynaptic cells are separated by a very narrow space called the **synaptic cleft**
 - most presynaptic terminals end on the postsynaptic neuron's dendrites; but the terminals may also terminate on the cell body or less often at the beginning or end of the axon of the receiving cell

Cell membrane properties and potentials

Information is carried within neurons and from neurons to their target cells by electrical and chemical signals.

Definition 4

Transient electrical signals refer to

- receptor potentials
- synaptic potentials
- action potentials

which are produced by temporary changes in the electric current into and out of the cell which then drives the electrical potential across the cell membrane away from its resting value

Question 5. Why is there an electric potential across the cell membrane in the first place?

- the neuron's cell membrane has thin clouds of +ve and -ve ions spread over its inner and outer surface
(at rest the extracellular surface has an excess of +ve charge while the cytoplasmic surface has an excess of -ve charge)
- separation is maintained by the lipid bilayer of membrane which serves as a barrier to the diffusion of ions
so the cell membrane acts as a **resistor** to the flow of ions
- the charge separation gives rise to a voltage across the membrane called the **membrane potential** (V_m)
 - it is calculated by $V_m = V_{in} - V_{out}$
 - we call the membrane potential of a cell at rest the **resting membrane potential** (V_r) where by convention $V_{out} = 0$ so $V_r = V_{in}$ which is usually in the range of $-60mV$ to $-70mV$

Definition 6

The direction of current is conventionally defined by the net movement of +ve charge that is

- cations move in the direction of electric current
- anions move in the opposite direction

and at rest there is no net charge movement

Definition 7

Depolarisation refers to the reduction of charge separation(less -ve V_m). Conversely **polarisation** refers to the increase of charge separation(more -ve V_m)

Definition 8

changes in V_m that do not lead to opening of gates of ion channels are called **passive responses** and the corresponding changed potentials are called **electrotonic potentials**

Ion concentrations and selective permeability

Certain ion species are differently concentrated on either side of the membrane

Table 6-1 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	none	none

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

Example 9

Consider that at overall resting membrane potential,

1. Potassium is about 20 times higher concentrated *within the cell* than outside
2. Sodium is about 9 times higher concentrated *outside the cell* than within the cell

But altogether is balanced(as implied by *resting* membrane potential) due to the organic anions

The flow of ions through their specific ion channels are governed by

1. concentration gradient which provides the "chemical driving force" driving ions across the membrane
2. as cations leave the cell, spare negative charges inside the cell accumulate at the inner surface of the cell membrane. This results in an electrical gradient which then results in an opposing "electrical driving force"

So equilibrium occurs when these 2 forces cancel. Formally we have

Fact 10

For a general charge particle x the chemical driving force A is found by

$$W_A = RT \ln \frac{[X_o]}{X_i}$$

where R is the gas constant $8.31Jm^{-1}K^{-1}$ and the electrical driving force B is found by

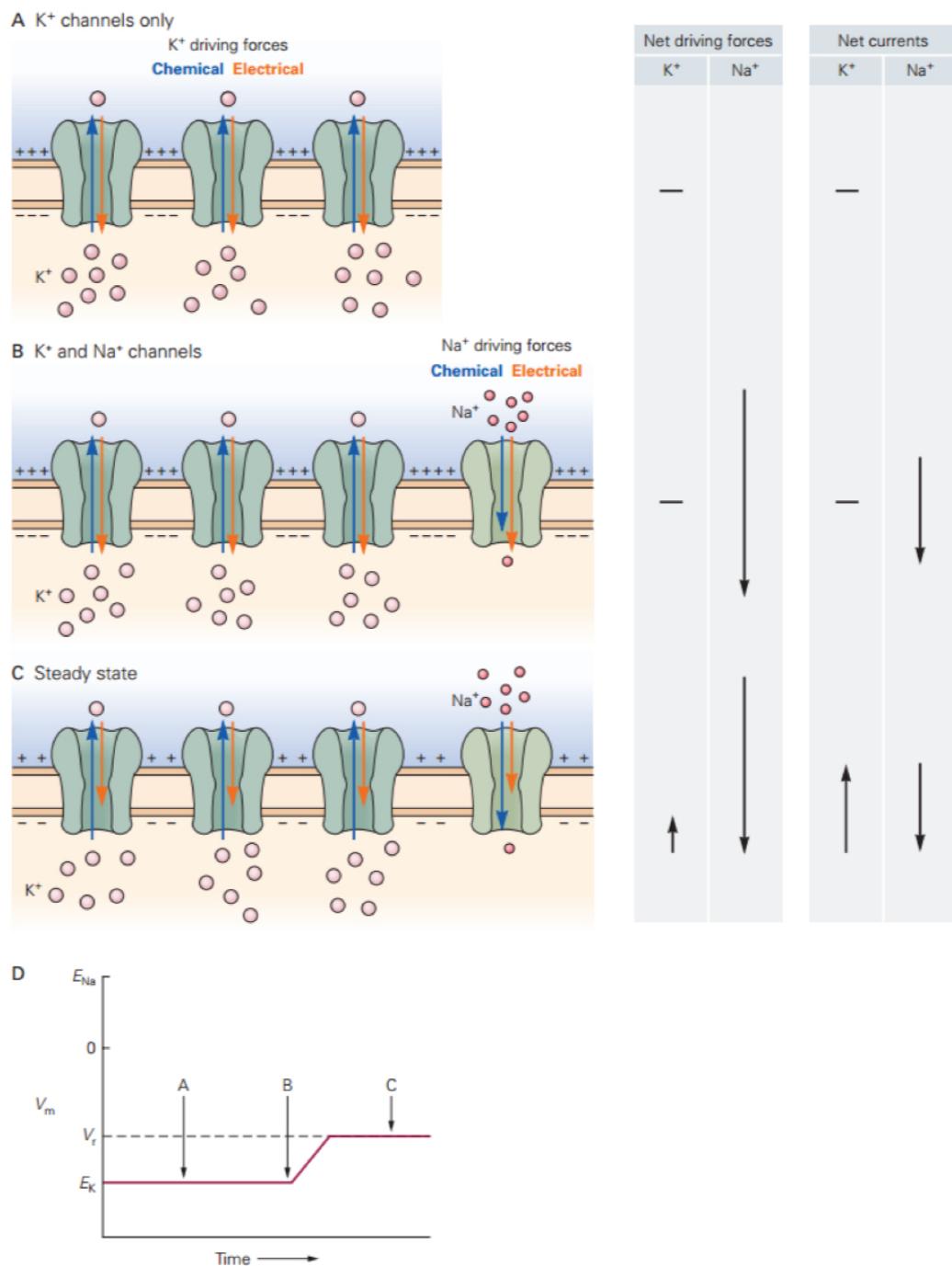
$$W_B = E_x z F$$

where z is the valence of ion while F is the faraday constant $96500Cmol^{-1}$

Equating the 2 driving forces to cancel them out we have the **Nernst equation**

$$E_x = \frac{RT}{zF} \ln \frac{X_o}{X_i}$$

resting potential of a neuron



Question 11. Account for the resting potential of the neuron

- nerve cells at rest are permeable to Na^+ , Cl^- and K^+ at rest
- there are many more resting K^+ channels than Na^+ channels so V_r does not deviate much from $E_K = -75mV$ to the $E_{Na} = +55mV$

Let us examine what is happening in the above figure

- (a) in a resting cell in which only K^+ channels are present K^+ ions are in equilibrium and $V_m = E_K$.
- As mentioned previously in 9 at resting potential the concentration of K^+ ions within the cell is much higher than the outside hence the figure makes sense
- (b) Adding a few Na^+ channels to the resting membrane allows Na^+ to diffuse into the cell
- and this influx begins to depolarize the membrane
 - both* the chemical(recall that concentration of Na^+ outside is much greater at resting state) and electrical driving forces(just like the case of K^+ , the ions are drawn due to the negative electric potential across the membrane) for Na^+ are inward
- (c) steady state reached eventually
- according to 10 as E_r becomes less $-ve$, the electrical driving force that drives K^+ into the cell is weaker
 - that means there is now a net flow of K^+ out of the cell
 - eventually the efflux K^+ counteracts the influx of Na^+ (you will see why later when you learn about pumps)
 - which is reflected by the equal net currents of K^+ and Na^+
 - also a relatively small net driving force drives a current equal and opposite to the Na^+ current which is driven by a much larger net driving force for Na^+ because there are much more K^+ channels and hence higher aggregate conductance. This is because:

$$\text{ion flux} = \text{electrical force} + \text{chemical driving force} \times \text{membrane conductance}$$

We will explore this further later

The goldman equation and permeability of different ion species

Theorem 12

For ions the membrane can be thought as as imposing a specific resistance r or conductance $g = \frac{1}{r}$. Then the associated permeability P_x of a species is related to the contributions of all ions to the membrane potentials via the **goldman equation** which states

$$V_m = \frac{RT}{F} \ln \frac{P_K[K^+]_0 + P_{Na}[Na^+]_0 + P_{Cl}[Cl^-]_0}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_i}$$

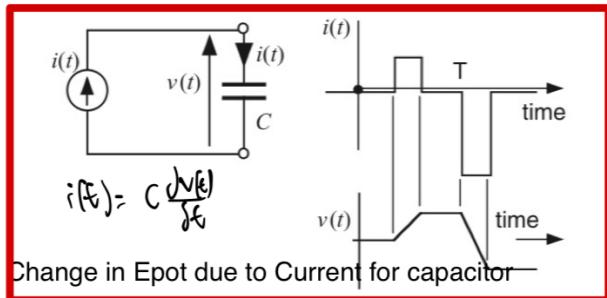
The goldman equation is convenient for describing the membrane potential as it allows for adding of ion species the membrane is permeable for. Note that the ion with the highest permeability will dominate V_m

Electrical equivalent circuits

Fact 13

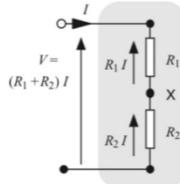
A mathematical model of the cell membrane called an **equivalent circuit** represents all of the important electrical properties of the neuron by a circuit consisting of conductors or resistors, batteries and capacitors

If necessary here is a recap of some basic circuit concepts learned in year 1 that will be used in the following discussions.



(1) KVL

$$V = R_1 I + R_2 I = (R_1 + R_2) I \quad (3.8)$$



Can also use KCL(out)

KCL @ A (IN)

Figure 3.20

$$\frac{(-15 - V_A)}{5} + 2 + \frac{(V_B - V_A)}{4} = 0 \quad (4.6)$$

We then express KCL for node B though arbitrarily choosing to sum currents flowing out of B:

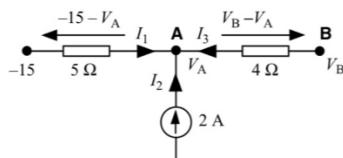


Figure 4.8 Illustration of the application of KCL at node A of the circuit of Figure 4.7

Derivation of the equivalent resistance of two resistors connected in series



Reference arrow conventions. May choose any direction as long as I and V are opposite in direction. Cannot choose for power sources tho already fixed. The longer line refers to the higher potential end. Note the V arrow points from lower to higher potential

(2) For KVL: Choice of reference directions are arbitrary as long as you sum them in a consistent manner like so

anti-clockwise

$$V_1 - V_A - V_2 + V_3 = 0$$

.....

clockwise

$$V_1 + V_2 + V_3 - V_4 = 0$$

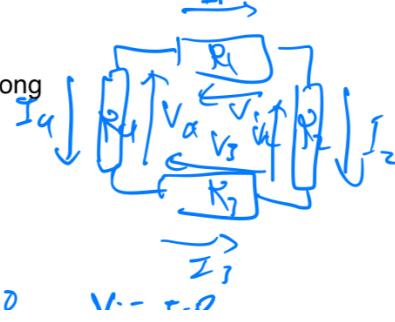


Figure 2: Quick Year 1 Circuits Recap

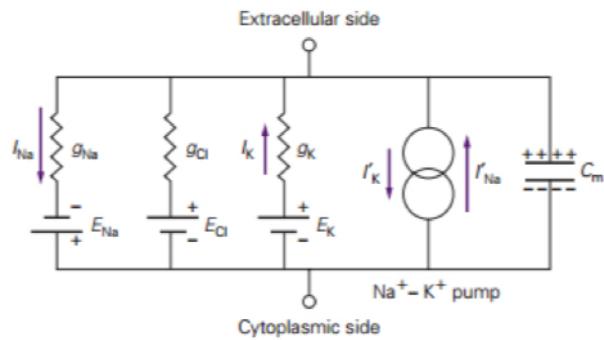
components

- The lipid bilayer models capacitance
- the ion channels models conductance/resistance
- The ion equilibrium potentials model batteries

Example 14

The **K^+ equivalent circuit** is represented as a resistor or conductor of ionic current with a single current conductance of γ_K

the sodium potassium pump



Note that the net inward current for Na is given by

$$I_{Na} - I'_{Na}$$

while the net outward current for K is given by

$$I'_K - I_K$$

which in steady conditions are equal in magnitude.

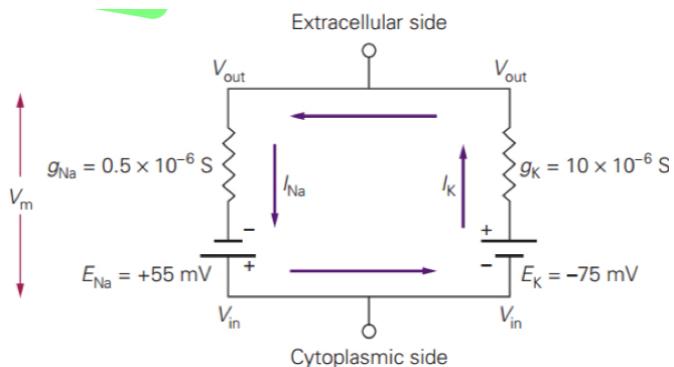
Fact 15

The $Na^+ - K^+$ pump exchanges 3 sodium ions for every 2 potassium ions. It is responsible for the steady state of the neuron as described in 2 as it maintains the original ions concentration gradients

This means I'_{Na} is 50% greater than I'_K . Therefore under steady conditions it follows that I_{Na} must also be 50% greater than I_K .

calculating membrane potential using equivalent circuits

In order to model 2 as the equivalent circuit below



we make the following assumptions

1. Initially ignore the Cl^- channels and begin with only K^+ and Na^+ channels

2. also ignore the small influence of the $\text{Na}^+ - \text{K}^+$ pump
3. consider that in steady state V_m is not changing so ignore membrane capacitance and its delaying effects on the changes in V_m

Remark 16. As seen from the diagram the value of conductance g_K is about 20 times higher than conductance g_{Na} . This has been mentioned before in our description of 2 which says that it is due to much more resting K^+ channels than Na^+ channels

Now let us calculate the values of the current and potentials in our circuits. In equilibrium resting conditions it follows that there is no net current across the membrane so therefore

$$I_{\text{Na}} + I_K = 0$$

See the chosen reference direction for V_m is such that it points from V_{out} to V_{in} since recall 5 by definition $V_m = V_{\text{in}} - V_{\text{out}}$. So taking

$$V_m = E_{\text{Na}} + \frac{I_{\text{Na}}}{g_{\text{Na}}}$$

which is $\xrightarrow{V_m} - \xrightarrow{E_{\text{Na}}} = \xrightarrow{\frac{I_{\text{Na}}}{g_{\text{Na}}}}$ and so we have

$$I_{\text{Na}} = g_{\text{Na}} \times (V_m - E_{\text{Na}})$$

Similarly taking

$$V_m = E_K + \frac{I_K}{g_K}$$

which is $\xrightarrow{V_m} - \xleftarrow{E_K} = \xrightarrow{\frac{I_K}{g_K}}$ and so we have

$$I_K = g_K \times (V_m - E_K)$$

Remark 17. Notice that from these equations we see that if V_m is more positive than $E_K = -75\text{mV}$ the driving force is positive and the current is outward. Because then we get some positive I_K and the I_K arrow points outward

Fact 18

Reminder that I points in the opposite direction of V for any component. Noticing the chosen reference direction for I_{Na} is in the opposite direction of the calculated direction from above it follows that $I_{\text{Na}} < 0$. Similarly since I_K is aligned with the calculated directions it follows that $I_K > 0$

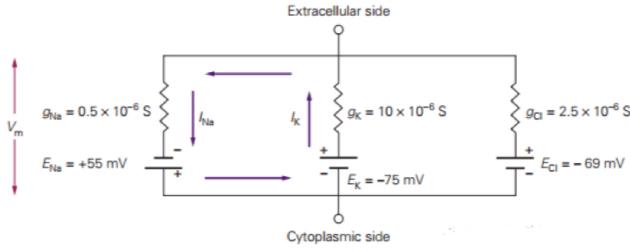
Combining the 2 equations above we have

$$-g_{\text{Na}} \times (V_m - E_{\text{Na}}) = g_K \times (V_m - E_K)$$

so

$$V_m = \frac{(E_{\text{Na}} \times g_{\text{Na}}) + (E_K \times g_K)}{g_{\text{Na}} + g_K}$$

We may easily add a branch for Cl^- too via the same steps



Explicitly starting from no net current at resting conditions again

$$I_{Na} + I_K + I_{Cl} = 0$$

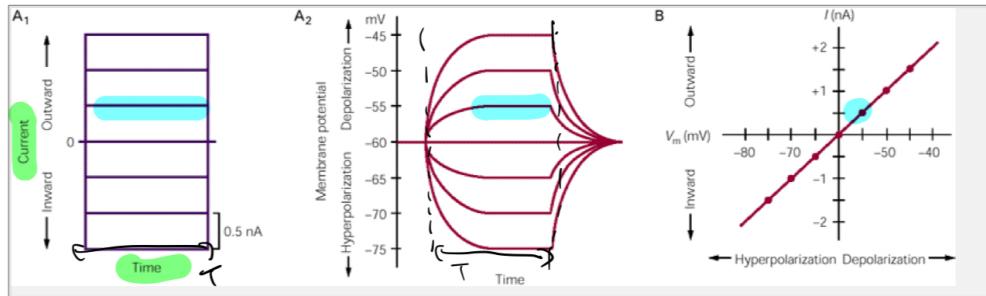
in which following the same steps above we get

$$V_m = \frac{(E_{Na} \times g_{Na}) + (E_K \times g_K) + (E_{Cl} \times g_{Cl})}{g_{Na} + g_K + g_{Cl}}$$

Remark 19. This equation is similar to that of the Goldman equation in that contributions of E_i to V_m are weighted by some quantity, in this case it is conductance instead of permeability. Similarly the one ion with the greatest conductance dominates and V_m will approach that ion's equilibrium Nernst potential

3 signal propagation, transmission and integration

the membrane current voltage relationship



First let's examine what is happening here. A_1, A_2 depicts a series of outward and inward current pulses being injected into a neuron.

- A_1 : depicts the current injections, with symmetrical positive (outward) and negative (inward) pulses over time.
- A_2 : illustrates how the membrane potential (V_m) changes in response to these current pulses, producing symmetrical depolarization (positive shifts) and hyperpolarization (negative shifts) proportional to the input current.

As for B , it is a plot of I-V (Current-Voltage) relationship by comparing the steady-state voltage (V_m) to the injected current. The linear slope of this relationship defines the neuron's input resistance (R_{in}). For example, a 10 mV voltage change per 1 nA of current corresponds to an input resistance of 10 MΩ (Ohm's law: $\Delta V = I \times R$).

Definition 20

To compare membrane properties of neurons of differing sizes electrophysiologists often use the resistance of a unit area of membrane known as the **specific membrane resistance** R_m measured in $\Omega \text{ cm}^2$.

Example 21

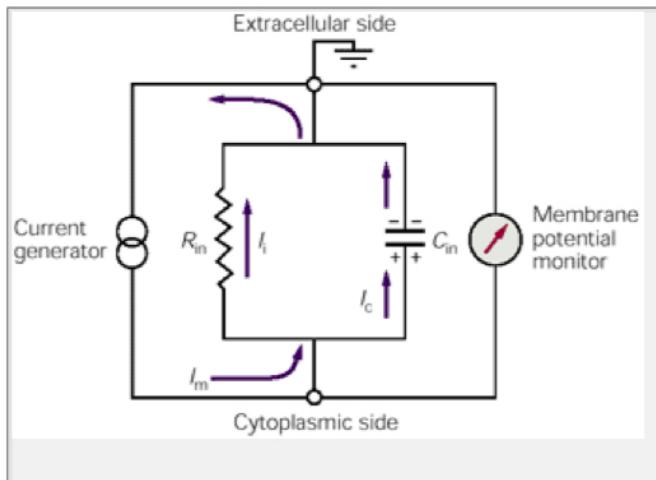
For a spherical neuron, the total input resistance R_{in}

$$R_{in} = R_m / 4\pi a^2$$

where a is the radius of the neuron

Rate of membrane Potential Changes

Consider



Proposition 22

With this circuit model, assume the membrane potential starts off at $0mV$ (voltage across the resistor and capacitor are both $0mV$ too). At $t = 0$ a depolarizing current of magnitude I_m is injected into the membrane. Then the change in potential from $0mV$ with respect to time as the current is applied is given by

$$\Delta V_m(t) = I_m R_{in} (1 - e^{-t/\tau})$$

where $\tau = R_{in} C_{in}$ which is defined to be the **membrane time constant**

Proof. The membrane potential change over time is modeled using an RC circuit, where the total membrane current is given by:

$$I_m = I_i + I_c \quad (1)$$

where:

- I_i is the ionic current through the membrane resistance R_{in} ,

- I_c is the capacitive current due to the membrane capacitance C_m .

Applying Ohm's law:

$$I_i = \frac{V_m}{R_{in}}, \quad I_c = C_m \frac{dV_m}{dt}. \quad (2)$$

Substituting these into the total current equation:

$$I_m = \frac{V_m}{R_{in}} + C_m \frac{dV_m}{dt}. \quad (3)$$

Rearranging:

$$C_m \frac{dV_m}{dt} + \frac{V_m}{R_{in}} = I_m. \quad (4)$$

Defining the membrane time constant:

$$\tau = R_{in}C_m, \quad (5)$$

we rewrite the equation as:

$$\frac{dV_m}{dt} + \frac{V_m}{\tau} = \frac{I_m R_{in}}{\tau}. \quad (6)$$

Using the integrating factor $e^{t/\tau}$, we multiply both sides:

$$e^{t/\tau} \frac{dV_m}{dt} + \frac{V_m}{\tau} e^{t/\tau} = \frac{I_m R_{in}}{\tau} e^{t/\tau}. \quad (7)$$

Recognizing the left-hand side as a derivative:

$$\frac{d}{dt} (V_m e^{t/\tau}) = \frac{I_m R_{in}}{\tau} e^{t/\tau}. \quad (8)$$

Integrating:

$$V_m e^{t/\tau} = \int \frac{I_m R_{in}}{\tau} e^{t/\tau} dt. \quad (9)$$

Since $I_m R_{in}/\tau$ is constant:

$$V_m e^{t/\tau} = I_m R_{in} e^{t/\tau} + C. \quad (10)$$

Dividing by $e^{t/\tau}$:

$$V_m(t) = I_m R_{in} + C e^{-t/\tau}. \quad (11)$$

Applying the initial condition $V_m(0) = 0$:

$$0 = I_m R_{in} + C \Rightarrow C = -I_m R_{in}. \quad (12)$$

Thus, the final solution is:

$$V_m(t) = I_m R_{in} \left(1 - e^{-t/\tau}\right). \quad (13)$$

This equation describes the time-dependent change in membrane potential, where $\tau = R_{in}C_m$ is the membrane

time constant that determines the speed of the response. □

Spatial Voltage Spread Along Axons

Previously we considered only 1 local membrane patch over time. Now we consider the entire cell spatially at a given time.

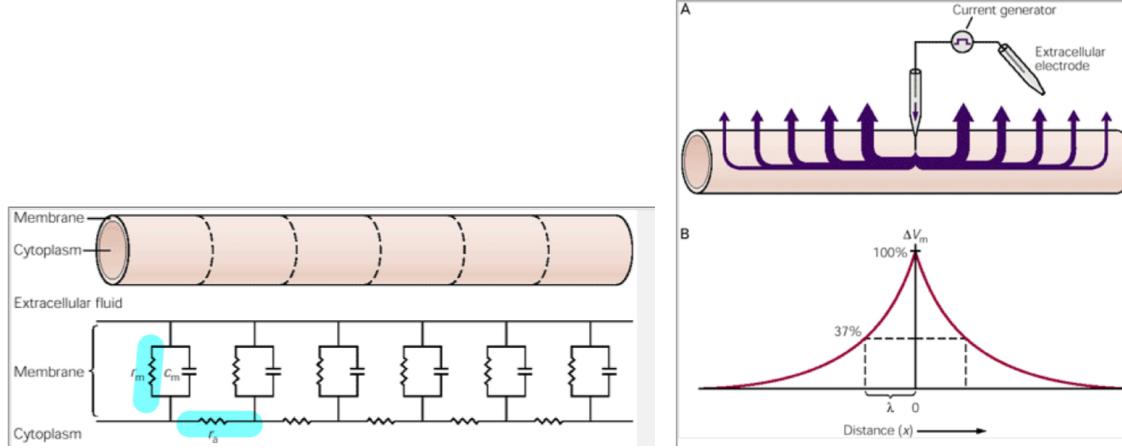


Figure 3: (a) The 1st image describes the equivalent circuit model of a membrane spatially. Essentially it is 3 put side by side. Note that r_a represents the axial resistance while r_m represents the membrane resistance.(b) the voltage change spatially as modelled by an exponential decrease with distance from point of application at $x = 0$

Specifically we found it was

$$\Delta V(x) = \Delta V_0 e^{-x/\lambda} \quad (14)$$

where we have defined the **length constant** $\lambda = \sqrt{r_m/r_a}$. Note that λ indicates the distance from the initial voltage change at which the membrane potential drops to 37%

Propagation of AP along Axon

somehow cells with greater length constants λ spread more quickly. Hopefully we find out why later

Increasing conduction speed

AP propagation can be sped up by increasing λ by increasing r_m which can be achieved by

- patches of additional insulation called **myelin sheaths** along the axon

The Action Potential

The action potential is a key process in neuronal signaling and has four important properties:

- **Threshold for initiation:** Depolarization must reach a threshold ($\sim -50 mV$) for an action potential (AP) to occur.
- **All-or-nothing event:** Once the threshold is reached, the AP occurs fully, regardless of the stimulus strength.

- **Self-regenerative:** The AP can propagate over long distances without losing strength.
- **Refractory period:** Limits the frequency of signals by preventing immediate reactivation.

The AP is generated by the movement of **ions through voltage-gated channels**:

- Na^+ influx is responsible for the **rising phase** of the AP:
 - Depolarization past the threshold increases Na^+ permeability (P_{Na}), overwhelming the dominant resting K^+ permeability (P_K).
 - This shifts the **membrane potential** (V_m) toward the Na^+ equilibrium potential (E_{Na}).
- The **falling phase** occurs due to a later increase in K^+ permeability (P_K), allowing K^+ to leave the cell.

3.1 Voltage-Clamp Experiments – Hodgkin and Huxley

The **voltage-clamp technique** was developed to study Na^+ and K^+ conductance in neurons.

Problem 23

Measuring ion conductance as a function of membrane potential (V_m) is difficult due to strong interdependence between:

- Membrane potential,
- Voltage-gated Na^+ and K^+ channels (VGCS),
- Positive feedback in AP generation.

Question 24. explain what is meant by the positive feedback loop in AP generation

1. When a neuron depolarizes and reaches the **threshold potential** ($\sim -50 \text{ mV}$), voltage-gated Na^+ channels (Na^+ -VGCS) begin to open.
2. As **more Na^+ enters** the cell, the membrane potential (V_m) becomes even more **positive**, moving towards the Na^+ equilibrium potential (E_{Na}).
3. This depolarization **triggers more Na^+ channels to open**, increasing Na^+ conductance (g_{Na}).
4. The cycle continues until peak depolarization is reached (around $+40 \text{ mV}$), at which point Na^+ channels start inactivating and K^+ channels open to repolarize the membrane.

Question 25. explain why This Makes V_m Measurement Difficult

Clearly this feedback loop will make measurement of g_K , g_{Na} difficult in real time as V_m will change rapidly due to the positive feedback loop described above

Question 26. explain How Voltage-Clamp Solves This Problem

- The **voltage-clamp technique** breaks this interdependence by **holding V_m constant**.
- It does this by injecting current equal and opposite to the ion currents flowing through the membrane.
- Since V_m is clamped at a fixed value we can take precise measurement of g_{Na} and g_K without interference from feedback loops.

- therefore we are able to find g_{Na} , g_K as a function of V_m as desired

Let us now see how it is done.

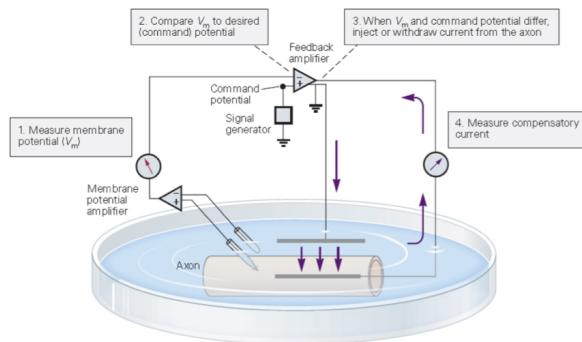


Figure 4: negative feedback mechanism of voltage clamp(makes sense as you want to cancel out the positive feedback loop)

1. **Measure V_m** using intracellular and extracellular electrodes.
2. **Compare V_m to a desired "command" potential** using a feedback amplifier.
3. **If there is a difference, inject or withdraw current** to maintain V_m at the command potential.
4. **Measure the compensatory current**, which reflects the current flowing across the membrane.

Fact 27

Essentially the Voltage Clamp works via a Negative Feedback Mechanism

- The command potential (chosen by the experimenter) is fed into the amplifier.
- The amplifier subtracts the membrane potential from the command potential and amplifies the difference.
- The amplifier's output drives a current that alters the membrane voltage, minimizing the difference between V_m and the command potential.

Fact 28 (Usage considerations)

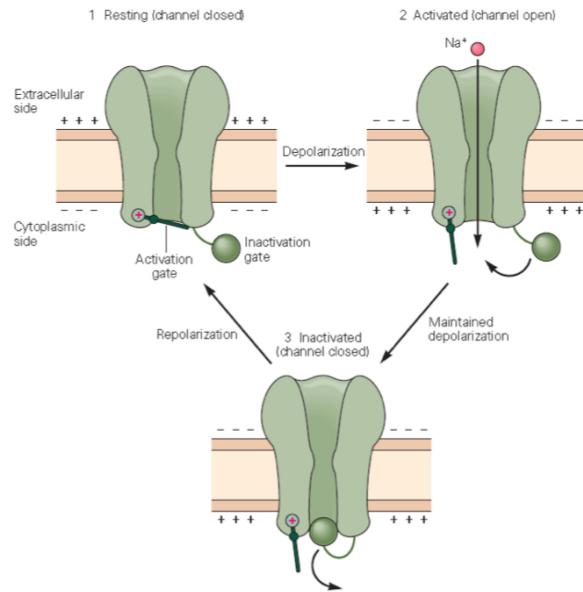
To ensure accurate measurement, the membrane potential must be uniform along the axon's inner surface. This is achieved by:

- Using a highly conductive internal current electrode.
- Short-circuiting axial resistance to near zero.
- Eliminating variations in electrical potential along the axon core.

This method allowed Hodgkin and Huxley to quantify ionic currents and revolutionized our understanding of action potentials.

3.2 Calculation of Conductances

3.3 Voltage Gated Ion Channels



Let us see what is going on here

Resting State (Closed, Activatable)

At the resting membrane potential (V_m), the sodium channels are in a closed but activatable state:

- The **activation gate** is closed, preventing Na⁺ entry.
- The **inactivation gate** is open, allowing the channel to be ready for activation.

Activation (Open)

When the membrane potential reaches the threshold level:

- The **activation gate opens**, allowing Na⁺ influx.
- This influx of Na⁺ leads to further **depolarization** due to positive feedback.
- More voltage-gated sodium channels are opened, amplifying the depolarization process.

Inactivation (Closed, Inactivatable)

Shortly after activation:

- The channel undergoes **inactivation** through the closing of the **inactivation gate**.
- This follows the **ball-and-chain hypothesis**, where a blocking mechanism prevents Na⁺ flow.
- Even though the activation gate remains open, Na⁺ conduction stops.
- The channel is now in a refractory state and must reset before it can be reactivated.

Repolarization and Resetting

Once the membrane repolarizes:

- The activation gate closes, and the inactivation gate reopens.
- The channel returns to its **resting state**, ready for the next depolarization event.

Fact 29

So in summary, the voltage-gated Na^+ channel cycles through three distinct states:

1. **Closed (activatable)** – The channel is closed but can be activated when the membrane depolarizes.
2. **Open** – The activation gate is open, allowing Na^+ to enter the cell.
3. **Closed (inactivatable)** – The inactivation gate prevents Na^+ influx, even though the activation gate remains open.

3.4 overview of action potential

The action potential (AP) is a fundamental electrical event in excitable cells such as neurons and muscle fibers. It involves a rapid sequence of depolarization and repolarization, driven by the dynamics of voltage-gated ion channels.

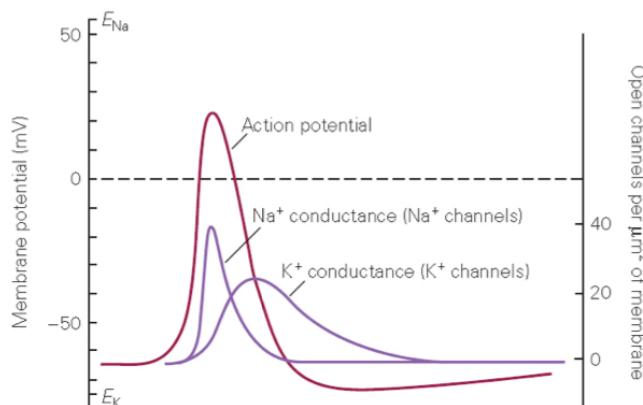


Figure 7–10 The sequential opening of voltage-gated Na^+ and K^+ channels generates the action potential. One of

Depolarization Phase

Depolarization occurs when the membrane potential exceeds a threshold value (approximately -50 mV), leading to:

- An increase in Na^+ conductance (g_{Na}) as voltage-gated Na^+ channels (Na^+ -VGCS) open.
- Inward Na^+ current, which further depolarizes the membrane.
- A **discharge of membrane capacitance**, contributing to further depolarization.
- Positive feedback, where increased Na^+ influx opens more Na^+ -VGCSs.
- The process continues until the membrane potential (V_m) approaches the Na^+ equilibrium potential (E_{Na}), defining the rising phase of the AP.

Repolarization Phase

As depolarization reaches its peak:

- Na^+ -VGCS become inactivated.
- Voltage-gated K^+ channels (K^+ -VGCS) open with a delay (delayed rectifier).
- Na^+ conductance (g_{Na}) decreases, and K^+ conductance (g_{K}) increases.
- Outward K^+ current dominates, driving the membrane potential back toward the resting level.

Hyperpolarization and Refractory Periods

After repolarization:

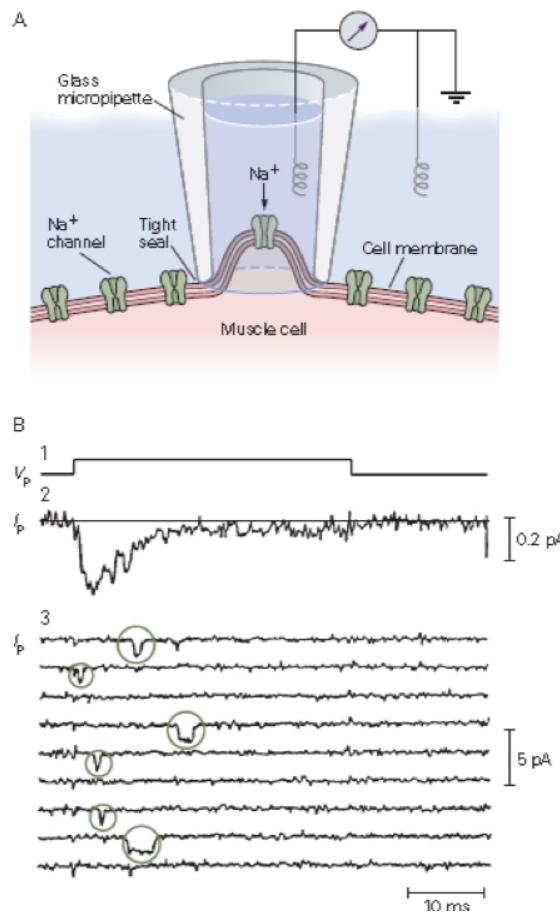
- The membrane potential temporarily hyperpolarizes past the resting potential.
- K^+ -VGCS take time to close, so g_{K} remains higher than its resting value.
- The membrane potential moves closer to the K^+ equilibrium potential (E_{K}).

This phase includes:

- The **absolute refractory period**, where no new AP can be fired due to Na^+ -VGC inactivation.
- The **relative refractory period**, during which some Na^+ -VGCS recover, allowing an AP to be triggered by a stimulus greater than the threshold.

3.5 Patch Clamp Experiments

Patch clamp techniques allow the study of ion channels at the single-channel level using a specialized glass micropipette.



Principles of the Patch Clamp Technique

- A glass micropipette with a tight seal isolates a small membrane patch.
- This enables the recording of ionic currents through individual ion channels.
- It provides insights into the properties of ion-channel molecules.

Findings from Patch Clamp Experiments

- Voltage-gated ion channels exhibit two fundamental states: open and closed.
- Depolarization triggers channel opening in an **all-or-none** fashion:
 - Channels exhibit brief current pulses of fixed amplitude but variable duration.

- Channels inactivate rapidly after opening.
- Averaging over many individual channels produces

results consistent with traditional voltage-clamp experiments.

3.6 synaptic transmission

Definition 30

Synaptic transmission is the process by which one neuron communicates with another at a structure called a **synapse**.

This transmission is essential for neural function, and each neuron typically forms thousands of synaptic connections.

Types of Synapses

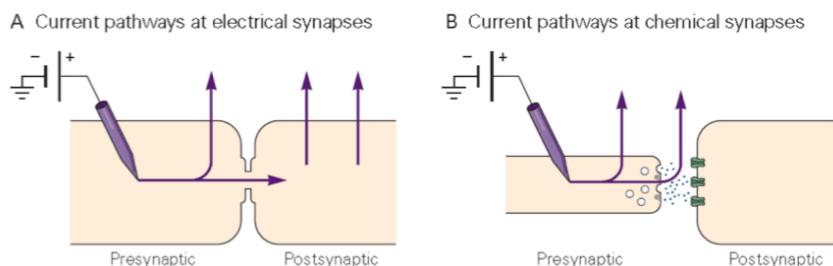
Neurons use two primary forms of synaptic transmission: **electrical** and **chemical**. The effectiveness of each synapse can be modified by cellular activity. Let us first compare their functionality

Question 31. *What is the difference in functionality of the electrical and chemical synapses?*

- **Electrical synapses** transmit rapid and stereotyped depolarizing signals.
- **Chemical synapses** allow for more complex signaling, including:
 - The generation of diverse behavioral responses.
 - The mediation of excitatory or inhibitory effects in the postsynaptic neuron.
 - Electrical changes of varying durations.
 - Amplification of neuronal signals.

Now we compare their physical structures

Question 32. *What differences in physical structures of electrical and chemical synapses*



(A) Electrical Synapses

Electrical synapses provide direct cytoplasmic continuity between the presynaptic and postsynaptic neurons through **gap-junction channels**. These channels create a low-resistance, high-conductance pathway for electrical current.

- The separation between pre- and postsynaptic membranes is approximately **4 nm**.
- These synapses allow **bidirectional** transmission of ion currents.
- The transmission delay is **virtually absent**, ensuring rapid signal propagation.

(B)Chemical Synapses

Chemical synapses rely on the release of neurotransmitters to transmit signals between neurons.

- The separation between pre- and postsynaptic membranes ranges from **20-40 nm**.
- There is **no cytoplasmic continuity** between the two neurons.
- Chemical synapses include specialized structures such as:
 - **Presynaptic vesicles**, which store neurotransmitters.
 - **Active zones**, where neurotransmitter release occurs.
 - **Postsynaptic receptors**, which mediate signal reception.
- Transmission occurs in a **unidirectional** manner.
- There is a **synaptic delay**, typically ranging from 0.3 ms to several milliseconds.

Remark 33. *Intuitively you can see the properties above make sense when you consider their functionalities. For example you have low separation between pre and post synaptic membranes for faster transmission speeds for electrical but you have more complex signal mediating components for chemical.*

Summary: Comparison of Electrical and Chemical Synapses

A summary of key differences between electrical and chemical synapses is presented below:

Type of Synapse	Distance (nm)	Cytoplasmic Continuity	Components	Transmission Agent	Direction
Electrical	4	Yes	Gap-junction channels	Ion current	Bidirectional
Chemical	20-40	No	Vesicles, receptors	Neurotransmitters	Unidirectional

3.7 Electrical Synapses

Now let us look at electrical synapses in more detail.

Electrical synapses are specialized junctions where ionic currents flow directly between neurons through gap junction channels. These synapses enable rapid and reliable transmission of electrical signals, allowing synchronized activity in neuronal networks.

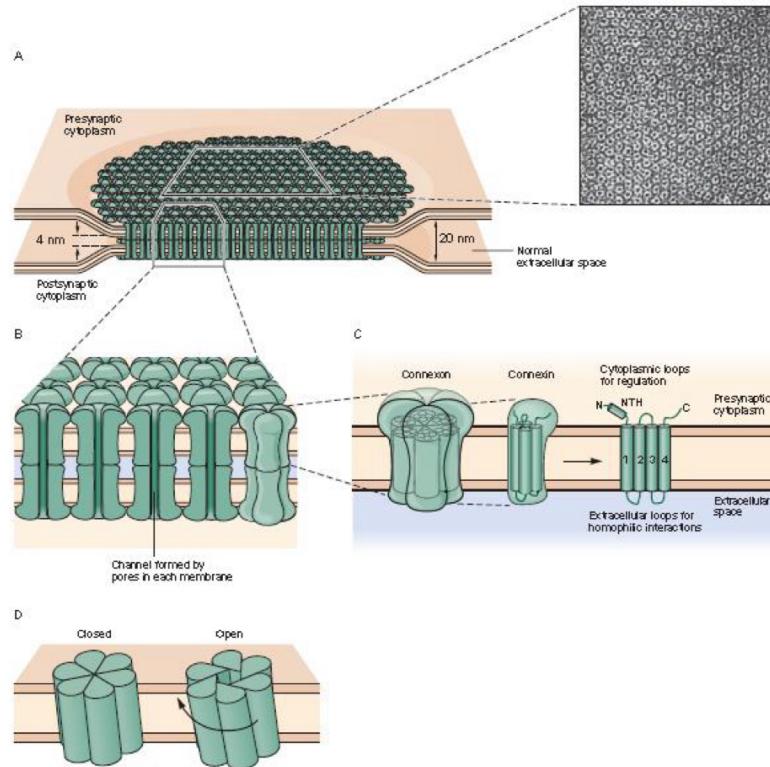
Generation of Postsynaptic Currents

Voltage-gated ion channels in the presynaptic neuron generate ionic currents that depolarize the postsynaptic cell. Key factors influencing this process include:

- The presynaptic terminal must be **large** enough to contain many ion channels to generate the necessary current.
- The postsynaptic cell must be **smaller**, resulting in a higher input resistance (R_{in}) and a greater voltage change (ΔV).

Propagation of Electrical Signals

- Electrical synapses allow both **depolarizing and hyperpolarizing** currents to be transmitted.
- This transmission is similar to the **passive propagation** of sub-threshold electrical signals along an axon (electrotonic transmission).
- Some synapses contain voltage-gated channels (VGCS) that permit **unidirectional** transmission, known as **rectifying synapses**.



Structure of Gap Junctions

Transmission at electrical synapses occurs through a region called the **gap junction**, characterized by:

- A separation of only **20 nm** between presynaptic and postsynaptic membranes, much smaller than the usual inter-neuronal distance.
- **Gap junction channels** bridge the space between neurons, facilitating ion flow.
- These channels are:
 - **Arranged in arrays** to create multiple conductive pathways.
 - Capable of conducting **ion currents** directly.
 - Subject to **conformational changes** that regulate conductance.

3.8 Chemical Synapses

Now let us look at chemical synapses in more detail

Chemical synapses are junctions between neurons where neurotransmitters mediate signal transmission. Unlike electrical synapses, chemical synapses do not have direct structural continuity between pre- and post-synaptic neurons. The transmission relies on the diffusion of neurotransmitters across a synaptic cleft, which is wider than a normal intercellular space (approximately 20-40 nm).

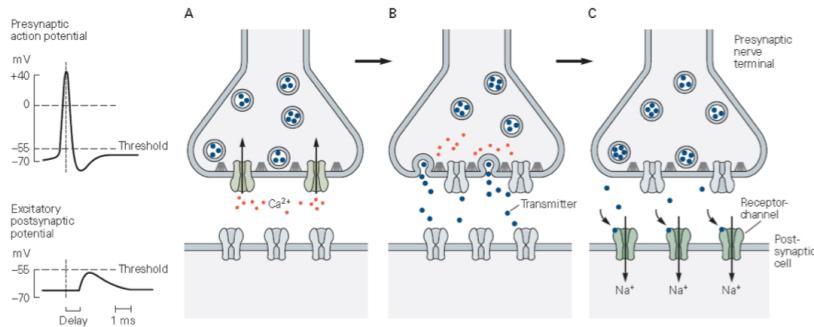


Figure 8-8 Synaptic transmission at chemical synapses involves several steps. The complex process of chemical

B. The Ca^{2+} channel opening produces a high concentration of intracellular Ca^{2+} near the active zone, causing vesicles contain

Mechanism of Neurotransmitter Release

Question 34. briefly describe the storage and release mechanism of neurotransmitters in chemical synapses

- Neurotransmitters are stored in synaptic vesicles within the presynaptic terminal.
- These vesicles contain thousands of neurotransmitter molecules
(the circle with dots inside in the figure above)
- Specialized clustered regions known as *active zones* are responsible for vesicle docking and release
(the grey filaments in the figure above)

Role of Calcium in Neurotransmitter Release

Question 35. what role does Calcium play in Neurotransmitter Release in chemical synapses

- When an action potential reaches the presynaptic terminal, voltage-gated calcium channels (Ca^{2+} -VGCS) open.
- The influx of Ca^{2+} into the presynaptic terminal triggers the fusion of synaptic vesicles with the membrane.
- This fusion leads to exocytosis, releasing neurotransmitters into the synaptic cleft.

Neurotransmitter Diffusion and Postsynaptic Response

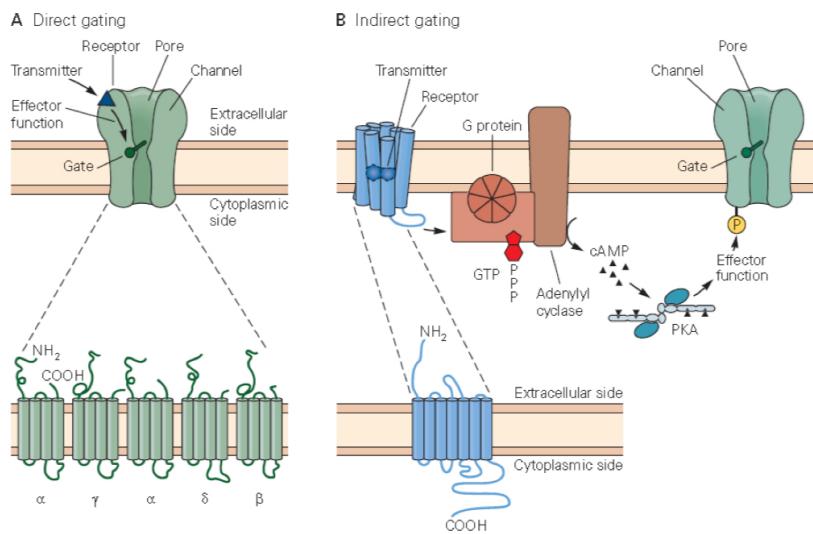
- The released neurotransmitters diffuse across the synaptic cleft.
- They bind to specific receptors on the postsynaptic membrane.
- This binding leads to the opening of ion channels, altering membrane potential and conductance.
- The postsynaptic response can be excitatory or inhibitory depending on the type of neurotransmitter and receptor interaction.

Delay and Amplification

- The process of neurotransmitter diffusion and receptor activation introduces a synaptic delay, typically greater than 0.3 ms.
- amplification occurs because each synaptic vesicle contains thousands of neurotransmitter molecules, ensuring a significant impact on the postsynaptic neuron.

3.9 direct and indirect gating

Neurotransmitters regulate the activity of ion channels in the postsynaptic cell by either direct (ionotropic) or indirect (metabotropic) mechanisms. These two classes of transmitter actions are mediated by receptor proteins that originate from distinct gene families.



Direct Gating (Ionotropic Receptors)

Question 36. describe what happens during direct gating starting from when neurotransmitters arrive at the postsynaptic cell

nu → α helical region → ion channel open

- In direct gating, neurotransmitters bind to receptors that are an integral part of ion channels.
- These ligand-gated channels are composed of multiple subunits, typically five, with each subunit containing four membrane-spanning α -helical regions.
- The binding of a neurotransmitter induces a conformational change that directly opens the ion channel.
- This allows ion flow across the postsynaptic membrane, leading to changes in membrane potential and neuronal excitability.

Indirect Gating (Metabotropic Receptors)

Question 37. describe what happens during indirect gating starting from when neurotransmitters arrive at the postsynaptic cell

nu → α helical region → GTP → Adenyl cyclase → **cAMP** → PKA phosphate → ion channel open

- Indirect gating involves neurotransmitter receptors that are separate from the ion channels they regulate.
- These receptors belong to a family of proteins with a single subunit containing seven transmembrane α -helical regions.
- Upon neurotransmitter binding, these receptors activate a guanosine triphosphate (GTP)-binding protein, commonly known as a *G-protein*.
- The activated G-protein triggers a **second-messenger cascade** that modulates ion channel activity.
- One major pathway involves the activation of adenyl cyclase, which converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP).
- cAMP, in turn, activates protein kinase A (PKA), which phosphorylates the ion channel, leading to a change in function.

Comparison of Direct and Indirect Gating

- **Speed:** Ionotropic receptors act faster because they directly open ion channels, whereas metabotropic receptors involve multiple steps, introducing a delay.
- **Duration:** The effects of ionotropic receptors are short-lived, whereas metabotropic receptor activation leads to longer-lasting changes due to second-messenger signaling.
- **Regulatory Complexity:** Indirect gating allows for signal amplification and modulation, making it important for complex neural processes.

3.10 Synaptic Integration

Neurons receive both excitatory and inhibitory inputs from multiple sources and respond through ionotropic and metabotropic receptors. These diverse inputs must be integrated to determine the overall effect on neuronal activity.

Excitatory and Inhibitory Synapses

- In the central nervous system (CNS), synapses can be classified into two major morphological types:
 - **Type 1: Glutamatergic Synapses**
 - * Typically excitatory.
 - * Located on dendrites.
 - **Type 2: GABAergic Synapses**
 - * Typically inhibitory.
 - * Located on the soma (cell body).

Postsynaptic Integration

- Neurons integrate multiple synaptic inputs to produce a single output.
- A single presynaptic potential is usually not sufficient to depolarize a postsynaptic neuron to the action potential (AP) threshold.
- The net effect of synaptic inputs depends on various factors, including:
 - The location, size, and shape of the synapse.
 - The proximity and relative strength of synergistic or antagonistic synapses.
 - The resting membrane potential of the postsynaptic neuron.
- This process is known as **neuronal integration**.

AP Generation at the Spike Initiation Zone

- The axon hillock (trigger zone) at the somatic base of the axon has a lower threshold for AP generation due to a higher density of voltage-gated Na^+ channels.
- Neuronal integration depends on the summation of synaptic potentials spreading toward the trigger zone.
- The process is influenced by two passive membrane properties:
 - **Membrane Time Constant, τ**
 - * Determines the time course of synaptic potentials, influencing **temporal summation**.
 - * A larger τ increases the likelihood that consecutive signals will summate to bring the membrane potential (V_m) to threshold.
 - **Length Constant, λ**
 - * Determines the extent of local depolarization by passive spreading, influencing **spatial summation**.
 - * A longer λ leads to a more minimal decrement of the signal over distance.

4 General Principles of Sensing

A sensory system is a component of the nervous system (NS) that enables the detection and processing of external and internal stimuli. It consists of:

- Sensory receptors that receive stimuli from the environment.
- Neural pathways that transmit information from receptors to the central nervous system (CNS).
- Brain regions that process sensory information.

Sensory information can be processed consciously or subconsciously. When a person becomes aware of sensory input, this is termed **perception**.

Sensory Processing Steps

Fact 38

Sensory information is processed in several key steps:

- **Transduction:** Conversion of stimulus energy into receptor potentials and then action potentials (APs) in afferent neurons.
- **Coding:** The pattern of APs in neurons serves as a code that conveys details about the stimulus:
 - Intensity
 - Location
 - Specific type of energy
- **CNS Processing:** Primary areas of the CNS receive sensory input and communicate with the brain for further processing.
 - This can result in reflex responses, perception, storage, and other neural activities.

Sensory Receptors

Sensory receptors are located at the peripheral ends of afferent neurons and transduce environmental information into graded potentials. These graded potentials, if strong enough, initiate APs that are transmitted to the CNS.

Definition 39

The term **receptor** can refer to either:

- The sensory receptor itself.
- The receptor proteins present on sensory membranes.

- Most sensory receptors are highly sensitive to their specific type of stimulus.

- **Types of Sensory Receptors:**

- **Mechanoreceptors** – respond to mechanical forces (e.g., touch, pressure).
- **Thermoreceptors** – detect temperature changes.
- **Photoreceptors** – specialized for detecting light.
- **Chemoreceptors** – respond to chemical stimuli.
- **Nociceptors** – detect pain.

Receptor Potential

The transduction process involves the opening and closing of ion channels, leading to:

- A change in membrane potential (V_m), generating a graded potential known as the **receptor potential** (RP).
- The receptor potential's magnitude depends on stimulus intensity.
- Unlike action potentials, RPs do not follow an all-or-none principle but vary in size.

Action Potential Generation

- APs are **not generated** in the receptor region.
- Instead, local currents flow to a trigger zone along the axon where voltage-gated channels (VGCS) are located.
- If the receptor potential is sufficient to reach the threshold at the trigger zone, an AP is initiated.
- **Firing Frequency:**
 - The frequency of APs increases as receptor potential magnitude increases.
 - However, the magnitude of each AP remains constant.
 - the magnitude of receptor potential is controlled by stimulus strength, rate of change of stimulus strength, temporal summation of RP and adaptation

Adaptation

Definition 40

Adaptation refers to the decrease in receptor sensitivity over time despite a constant stimulus. This results in a reduction of action potential (AP) frequency in afferent neurons.

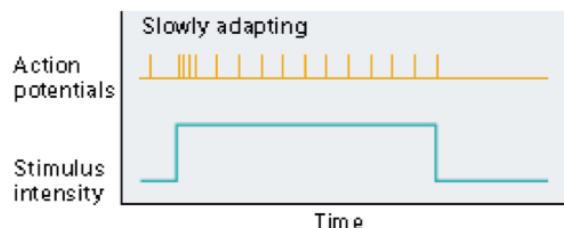
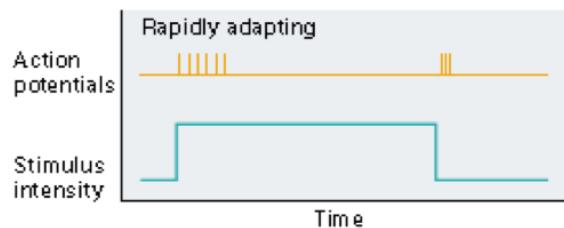


FIGURE 9–15

Rapidly and slowly adapting receptors. The top line in each graph indicates the action-potential firing of the afferent nerve fiber from the receptor, and the bottom line, application of the stimulus.

- **Slowly Adapting Receptors:**

- Maintain a persistent or slowly decaying receptor potential (RP) during a constant stimulus.

- **Rapidly Adapting Receptors:**

- Generate a receptor potential and AP at the onset of the stimulus but quickly stop responding.

Primary Sensory Coding

Sensory coding is the conversion of stimulus energy into a signal that transmits relevant sensory information to the central nervous system (CNS).

- This coding conveys information about:
 - Type of energy.
 - Intensity of the stimulus.
 - Location on the body where the stimulus is detected.

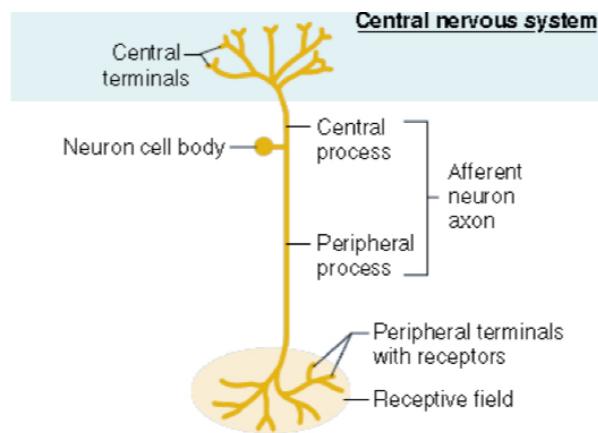


FIGURE 9-4
Sensory unit and receptive field.

Definition 41

A single afferent neuron, along with all of its receptor endings, constitutes a **sensory unit**.

The peripheral end of the neuron often branches into multiple terminals, each associated with a receptor.

Remark 42. So to be clear the sensory unit is not the same as the receptor. The neuron is connected to many receptors which together form the sensory unit

Definition 43

Receptive Field: The area of the body that, when stimulated, activates a particular neuron.

Receptive fields of different sensory units often overlap, ensuring that single activation rarely occurs in isolation.

Stimulus Type

Definition 44

The type of stimulus, also known as **modality**, is determined by the specific sensory receptor that it activates.

Each receptor type is adapted to respond to a specific type of stimulus due to its biochemical properties.

Example 45

Example: Skin receptors lack the molecular components required to detect light. See the different types of receptors mentioned above

So how does this translate to the sensory unit(i.e how are these specialized receptor connected to each neuron)? Well intuitively it turns out each single afferent neuron is connected usually to a single type of receptor, thus making it specialized to detect *one* specific type of stimulus/modality.

Question 46. *Nevertheless these specialized neurons each with their receptive field consisting of one specific special type of receptors, are not necessarily activated separately. How so?*

- Adjacent sensory units may respond to different modalities.
- Due to overlapping receptive fields, a single stimulus can generate multiple sensations.

Example 47

Example: An ice cube touching the skin can produce sensations of both **touch** and **temperature**.

4.1 stimulus intensity

The intensity of a stimulus is conveyed through the frequency of action potentials (APs) generated by sensory neurons.

- A larger stimulus results in:
 - A larger receptor potential.
 - A higher frequency of APs.
- As the strength of a local stimulus increases, receptors on adjacent branches of an afferent neuron become activated.
 - The summation of local currents leads to a greater AP frequency.

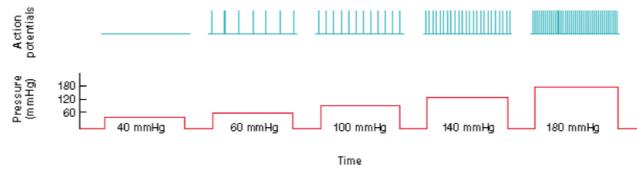


FIGURE 9-9

Action potentials from an afferent fiber leading from the pressure receptors of a single sensory unit as the receptors are subjected to pressures of different magnitudes.

Definition 48

Stronger stimuli activate a greater area, leading to activation of similar receptors on other afferent neurons. This process is known as **recruitment**.

4.2 Stimulus Location

The nervous system encodes the location of a stimulus based on which sensory receptors are activated and the neural pathways involved.

- Stimulus location is determined by:
 - The site of the stimulated receptor.
 - The specific neural pathway through which information travels.
 - These specific pathways are known as **labelled lines**.

Definition 49

Acuity refers to how well a stimulus can be distinguished from adjacent stimuli.

- It depends on the amount of convergence in ascending neural pathways.
- Greater convergence results in lower acuity.

Acuity also depends on:

- **Receptive Field Size:** Smaller receptive fields allow for better stimulus localization.
- **Sensory Unit Density:** Higher receptor density enhances localization.
- **Receptive Field Overlap:** Overlapping receptive fields help refine stimulus location.

Fact 50 (Key Observational relationship between density and position)

Afferent neurons respond most vigorously to stimuli applied at the center of their receptor fields.

- This is due to higher receptor density at the center.
- More receptors are activated, leading to an increased AP frequency.

You will learn later that this is a consequence of **lateral inhibition**

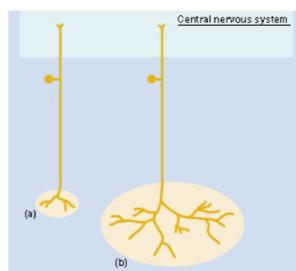


FIGURE 9-10
The information from neuron a indicates the stimulus location more precisely than does that from neuron b because a's receptive field is smaller.

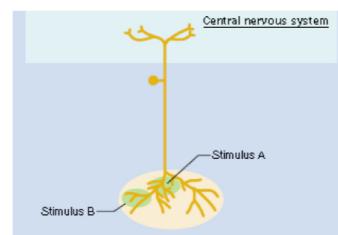


FIGURE 9-11
Two stimulus points, A and B, in the receptive field of a single afferent neuron. The density of nerve endings around area A is greater than around B, and the frequency of action potentials in response to a stimulus in area A will be greater than the response to a similar stimulus in B.

Figure 5: Fig 9-10: (a) more precise than (b) due to smaller receptive field. Fig 9-11: Frequency AP at point A greater since closer to center where nerve endings tensor

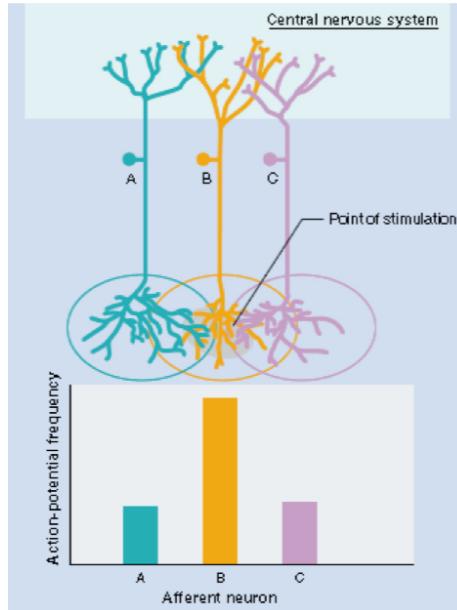


FIGURE 9–12

A stimulus point falls within the overlapping receptive fields of three afferent neurons. Note the difference in receptor response (that is, the action-potential frequency in the three neurons) due to the difference in receptor distribution under the stimulus (low receptor density in A and C, high in B).

Figure 6: See effect of overlap. The AP frequency graph should make sense as clearly the point of stimulation is closest to the center of B

Effect of Receptive Field Overlap:

- Overlapping receptive fields mean multiple sensory units are triggered.
- Neurons at the periphery of the stimulus fire at lower frequencies than those at the center.
- This helps enhance both localization and stimulus intensity perception.

4.3 Lateral Inhibition

Lateral inhibition is a neural mechanism that enhances the localization of sensory stimuli by increasing contrast. It plays a crucial role in sensory systems such as vision and touch.

Mechanism of Lateral Inhibition

Lateral inhibition works by suppressing signals from neurons at the edges of a stimulus while maintaining strong signals from the center. This selective inhibition enhances the perception of important stimuli and reduces background noise.

- Neurons at the stimulus edges are more inhibited than those at the center.
- This contrast enhancement helps in focusing on relevant information.
- It usually occurs at an early stage in sensory pathways.

Applications of Lateral Inhibition

Lateral inhibition is crucial in systems that require high spatial resolution and precision.

- **Vision:** In the retina, lateral inhibition enhances visual acuity by sharpening image contrast.
- **Touch:** In mechanoreceptors of the skin, lateral inhibition helps in detecting fine details such as the exact point of contact.

5 The Auditory System

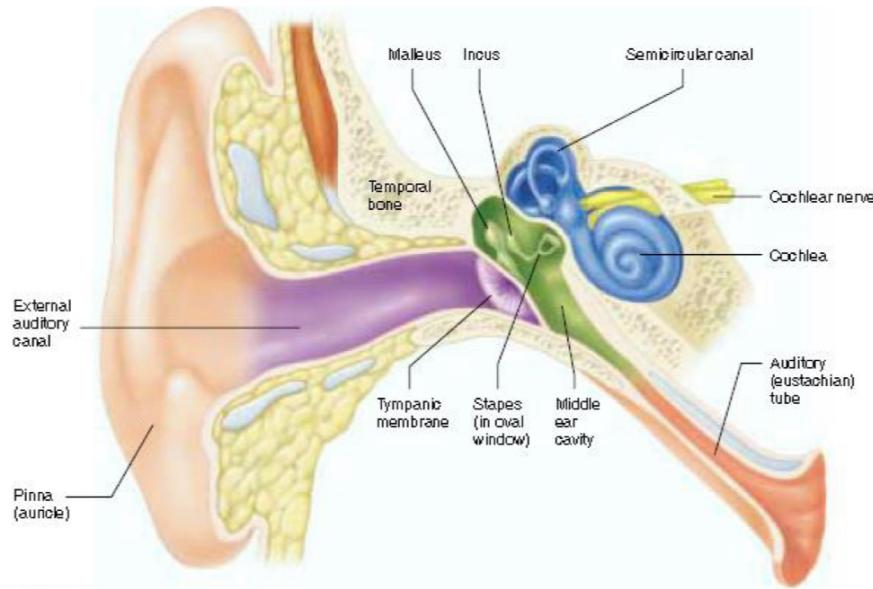


Figure 7: Violet: outer ear. Green: middle ear. Blue: inner ear.

The auditory system is responsible for hearing and involves the physics of sound and the physiology of the external, middle, and inner ear. It also includes the neural pathways that process acoustic information in the brain.

Nature of Sound

Sound is produced by the disturbance of air molecules, creating waves that travel through the medium. These waves have specific characteristics:

- Sound waves consist of alternating zones of **compression** (high-pressure regions) and **rarefaction** (low-pressure regions).
- The amplitude of a sound wave is determined by the pressure difference between the compression and rarefaction zones.
- The **frequency** of vibration determines the pitch of the sound we perceive.

The External and Middle Ear

Hearing begins when sound waves enter the external auditory canal.

- The **pinna (auricle)** and auditory canal help amplify and direct sound toward the eardrum.
- Sound waves cause the **tympanic membrane** (eardrum) to vibrate:

- It **vibrates** at the same frequency as the incoming sound waves.
- Moves inward during compression and returns to its original position during rarefaction.
- The extent of movement depends on the amplitude of the sound wave.
- The **middle ear cavity** is an air-filled space in the temporal bone, connected to the pharynx by the **auditory (Eustachian) tube**, which equalizes pressure.
- **Vibrations** from the tympanic membrane are transmitted to the **ossicles** (three small bones in the middle ear: **malleus, incus, and stapes**):

Question 51. *Explain the function of ossicles with regard to sound energy transfer*

- These bones maximize the efficiency of sound energy transfer
- liquid having a higher density than air has a higher acoustic impedance
- They transfer **Vibrations** to the **oval window**, a smaller membrane that increases the force per unit area by 15-20 times to negate the impedance difference, achieving impedance matching
- which by analogy of maximum power transfer theorem for electrical circuits is where power transfer is maximized when impedance is matched

Remark 52. *The effect of using a smaller membrane area to amplify is essentially the analogous to increasing the number of coils in a step up transformer. Explore more in MIT Waves 8.03*

Question 53. *Describe the pathway in which sound **vibrations** take when they first enter the external auditory channel*

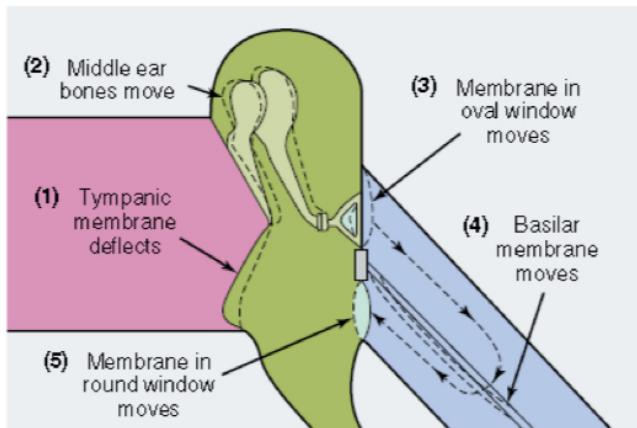


FIGURE 9-37

Transmission of sound vibrations through the middle and inner ear. 

Figure 8: notice the blue region is the inner ear since below you will learn that the Scala vestibuli(top) is closed by the oval window while the Scala tympani(bottom) is closed by the round window. The basilar membrane is located in the middle between these 2 scalae

The Inner Ear and the Cochlea

The inner ear converts sound vibrations into neural signals.

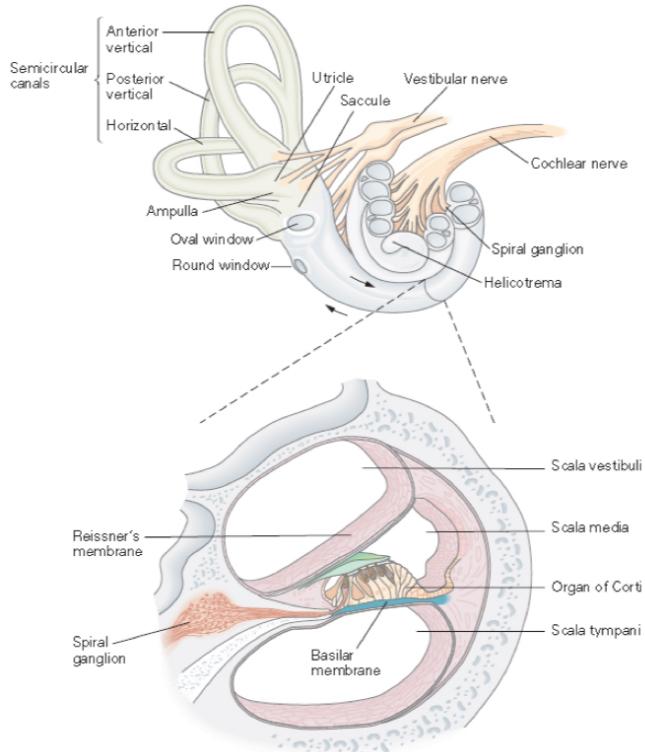


Figure 9: structure of cochlea

- The primary structure of the inner ear is the **cochlea**, a spiral-shaped, fluid-filled structure in the temporal bone.
- The cochlea consists of three fluid-filled chambers:

Question 54. describe the relative locations of these fluid filled chambers of the cochlea using 9. Also describe which chamber contains which window that leads to the middle ear

- **Scala vestibuli:** The upper chamber, which begins at the **oval window**.
- **Scala tympani:** The lower chamber, which ends at the **round window**.
- **Cochlear duct:** The middle chamber, containing the **scala media**, which houses the sensory organ for hearing.
- The **basilar membrane** separates the cochlear duct and supports the **organ of Corti**, which contains the auditory receptor cells.

5.1 The Basilar Membrane: Frequency Analysis

The basilar membrane plays a crucial role in the auditory system by responding to different sound frequencies. Pressure differences across the cochlear duct induce vibrations in the basilar membrane, enabling the analysis of sound frequencies. The extent of displacement at specific regions of the basilar membrane depends on the frequency of the sound source.

Frequency Dependence of Basilar Membrane Displacement

The location of maximum displacement along the basilar membrane varies according to the frequency of the sound:

- **Low-frequency sounds:** At the distal end (apex) of the basilar membrane, which is broad and flaccid, the sensitivity to low-frequency oscillations is higher.
- **High-frequency sounds:** At the proximal end, near the tympanum, the membrane is stiffer and more responsive to high-frequency sounds.
- **Logarithmic transition:** The transition from high-frequency to low-frequency sensitivity along the membrane follows a logarithmic scale.

Tonotopic Map and Signal Processing

The basilar membrane exhibits a **tonotopic map**, where neighboring frequency values correspond to neighboring locations along the membrane. This property aids in efficient signal processing:

- A **tonotopic map** ensures that neighboring values in stimulus space are encoded by neighboring **sensory units**.
- This organization facilitates processes such as lateral inhibition, which enhances frequency discrimination.

5.2 The organ of Corti: Mecanoelectrical Transduction

The organ of Corti, located within the cochlea of the inner ear, is the primary receptor organ (recall it contains all the auditory receptor cells) responsible for converting mechanical sound vibrations into electrical neural signals. This process is crucial for auditory perception.

Question 55. *What is the key structural composition and function of the organ of Corti?*

Structure and Function

The organ of Corti contains approximately 16,000 hair cells, which serve as the sensory receptors for sound. These hair cells are innervated by about 30,000 afferent nerve fibers (all with specialized auditory receptors) that transmit auditory information to the brain.

Question 56. *What other structural features allow the organ of Corti to differentiate between high and low frequencies*

Tonotopic Organization

Remark 57. *Consider the ethymology. Tono - sound, topic(eg. topology) - spatial arrangement.*

The hair cells within the organ of Corti are arranged in a **tonotopic** manner (i.e spatial arrangement of cells each most sensitive to a distinct frequency):

- At any given position along the basilar membrane, hair cells exhibit maximum sensitivity to a specific frequency.
- These frequency sensitivities are **logarithmically mapped**, with low frequencies detected at the cochlear apex and high frequencies at the base.

Region	Location	Sound Frequency Sensitivity
Base	Near the oval window , close to the middle ear.	High frequencies (20,000 Hz)
Apex	Innermost tip , deepest part of the cochlear spiral.	Low frequencies (20 Hz)

Table 1: Tonotopic Organization of the Cochlea

The Hair Cells

Hair cells in the cochlea serve as mechanoreceptors for auditory transduction. They contain **stereocilia** and a single **kinocilium** protruding from one end.

- Hair cells transform pressure waves into receptor potentials.
- They remain in contact with the overhanging **tectorial membrane**.

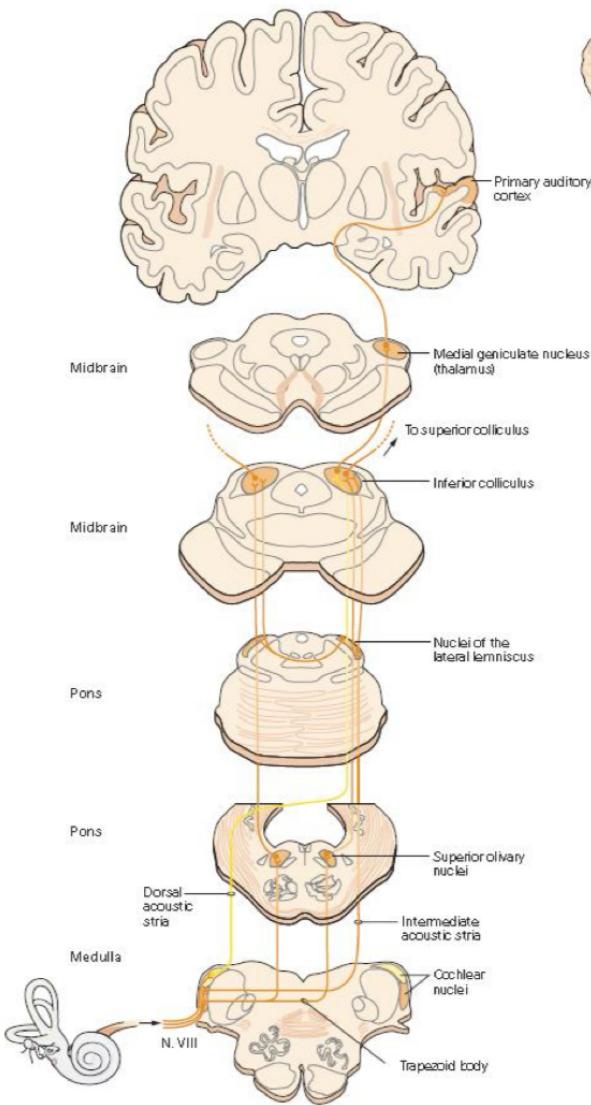
Mechanism of Activation:

- As the basilar membrane displaces, hair cells move relative to the tectorial membrane, causing shear forces on the stereocilia.
- This shearing opens ion channels gated by **spring-like structures**.
- Depending on the direction of movement, ion channels open for **Ca²⁺** or **K⁺**.
- Voltage-gated channels (VGCs) further contribute to the receptor potential (RP) response.

5.3 Central Auditory Pathways

Once auditory signals are transduced by hair cells, the information follows specific pathways to reach the auditory cortex.

- Signals from the cochlea are transmitted to the **cochlear nucleus** in the medulla.
 - Conveyed by the central processes of cochlear ganglion cells.
- Information is relayed to various neurons in the cortex, maintaining **tonotopic arrangements**.



Major Auditory Pathways:

- The **dorsal acoustic stria** carries information from the dorsal cochlear nucleus.
 - Projections run through the **pons** and connect to the **inferior colliculus** in the midbrain.
- Information then travels to the **medial geniculate nucleus** and subsequently to the **primary auditory cortex**.
- The **intermediate acoustic stria** links the cochlear nucleus with the **lateral lemniscus** in the pons.
 - From here, signals are sent to the **inferior colliculus**.
- The **trapezoid body** transmits information to the **superior olive**, where the first **binaural interactions** occur, aiding in sound localization.
 - A second binaural relay station is found in the **nucleus of the lateral lemniscus** in the pons.

5.4 The Cochlea Nuclei

- The afferent nerve fibres from cochlear ganglion cells are bundled in the cochlear or auditory component of the eighth cranial nerve (N. VIII) and terminate exclusively in the cochlear nuclei
 - The cochlear nerve fibres terminate in these nuclei in a tonotopic organisation
 - * Fibres that carry information from the apical end of cochlea terminate ventrally in the ventral and dorsal cochlear nuclei.
 - * The ones from the basal end terminate dorsally.
 - Each fibre innervates several different types of neurones that have distinct projection patterns up to higher centres
 - * Auditory pathway is split into at least four parallel ascending pathways.
 - * These extract different features from the acoustic information.

Types of Neurons in the Cochlear Nuclei

Stellate Cells

- Encode sound frequency.
- Each cell responds to a characteristic frequency.
- Depolarising current injections induce regularly spaced spikes.

Bushy Cells

- Single spike upon current injection.
- Encode sound onset and horizontal sound localisation.

Fusiform Cells

- Vertical sound localisation.

Octopus Cells

- May be involved in recognition of sound patterns.

5.5 Delay-Line Mechanism

- Coincidence detection with respect to the two ears is used to generate a map of interaural time differences.
 - The spatio-temporal correlation of signals is used to extract localisation information in the horizontal plane.
- Acoustic signal from the right ear (ipsilateral input) is sent to a 1D spatial array of interneurons.
 - These also receive an input from the contralateral ear.
 - An interneuron generates an output signal if both inputs coincide.
- Which interneuron fires encodes where the source of the sound is.
 - Relies on the fact that electrical signals travel at finite speeds.

- To obtain simultaneous arrival of a signal elicited by sound first picked up in the left ear, with a signal induced by the same sound source in the right ear, the left ear signal is made to travel along a long "delay line" which compensates for the later arrival of the right ear signal.
- Very short membrane time constants, otherwise also nearly coincident inputs would result in their activation.

5.6 Cochlea Implants

- Intense stimulation of the hair cells may cause permanent damage as the stereocilia lose their ability to return to the neutral position.
 - This results in sensorineural hearing loss.
- Cochlear implants bypass the hair cells by frequency/position-dependent direct extracellular stimulation of afferent fibres.
 - Requires sound processing and tonotopic arrangement of electrodes.

6 The Vestibular System

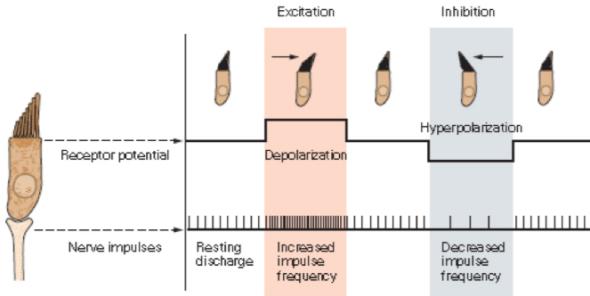
- A mechanosensory system that monitors linear and angular accelerations of the head and the body.
 - Signals from the vestibular system are used for balance, posture, and eye reflexes.

Anatomical Structure

- There are two primary functional systems:
 - The **utricle** and **saccule** (otolith organs) detect linear acceleration.
 - The three **semi-circular canals** detect angular acceleration.
- These five components are bony, hollow structures filled with endolymph.

Measuring Head Tilt

- Hair cells in the utricle measure head tilt.
- Relative motion between the otolithic membrane and hair cells results in receptor activation.
 - Deflection of stereocilia in the preferred direction of a hair cell results in its depolarisation and an increase in afferent fibre spike rate.
 - Deflection in the opposite direction results in hyperpolarisation and a decrease in spike rate.
 - Stimulation in orthogonal directions has little effect on spike rate.
- Modelled by a cosine-shaped function.



Population Coding

- Hair cells are arranged in a way so that different hair cells measure head tilt in different directions.
 - Using an entire population of cells to encode a continuous parameter is a general principle used in the nervous system (NS).

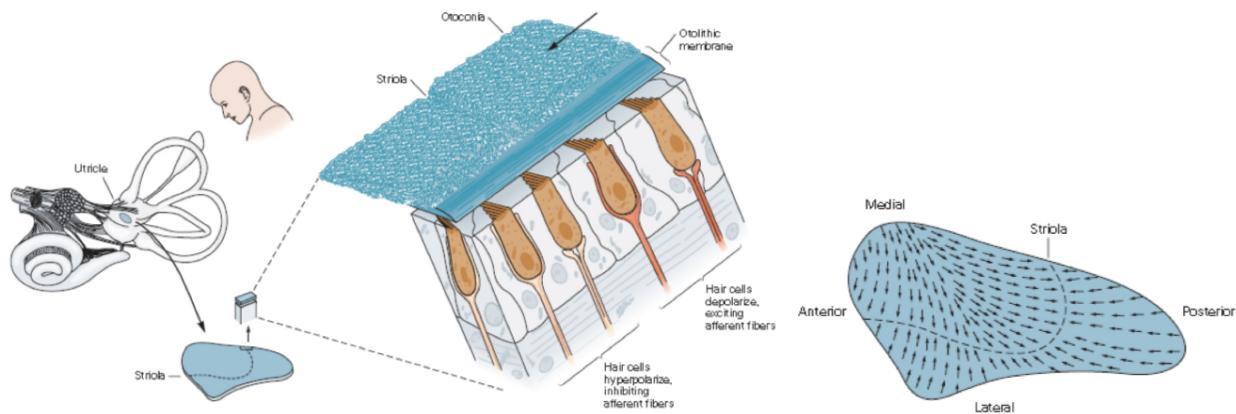


Figure 10: bottom: represents the spatial map of "preferred directions" of the hair cells

Head and Body Rotations

- In the ampullae of the semicircular canals, during head rotations, the inertia of the fluid within the canals forces a deflection of the stereocilia of the hair cells.
 - The measuring axes of the canals build an almost orthogonal system.
 - The signals of the horizontal canals as well as the signals of anterior/posterior canals may be combined to refine the information about angular rotations.

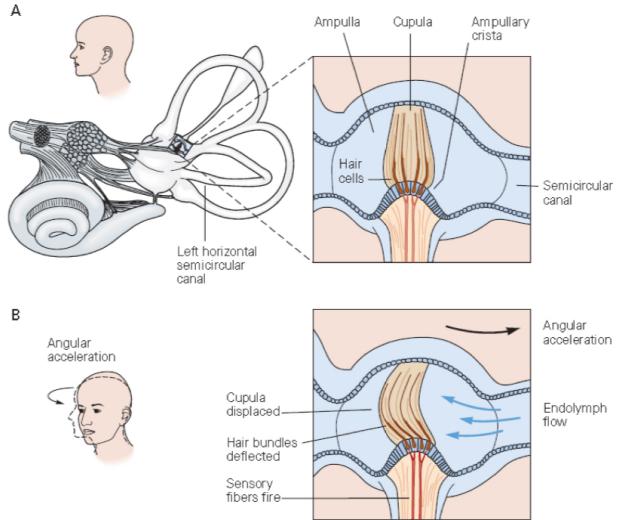


Figure 11: Remember as kids when you spin around on some play wheel you noticed covering your ears made you less dizzy

Vestibular-Ocular Reflexes

- To avoid motion blur, the lateral eye muscles contract to counter-rotate the eyes.
- Such alignment of sensor and actuator axes can be of tremendous help when response speed is important.
 - Which in stabilization reflexes usually is the case.

This brings us to the next section

7 the visual system

- Provides long and short-range sensory information about the layout of surroundings.
 - Converts photons into electrical signals.
 - Processes the signals using several pathways:
 - * Analyses visual scenes, identifies objects and faces.
 - * Provides info about threats.
 - * Estimates self-motion and motion of external objects.

Anatomy of the Visual System

- The optical apparatus is suited to focus light onto the photoreceptors in the retina.
 - By adjusting the curvature of the lens, visual objects located at different distances are focused onto the retina.

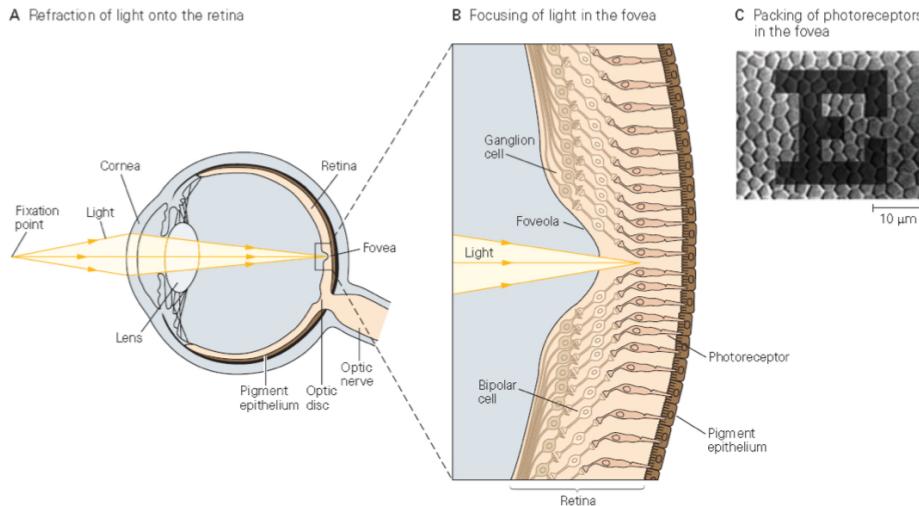


Figure 26–1 The eye projects the visual scene onto the retina's photoreceptors.

- A. Light from an object in the visual field is refracted by the cornea and lens and focused onto the retina.
- B. In the fovea, corresponding to the very center of gaze, the proximal neurons of the retina are shifted aside so light has direct access to the photoreceptors.

C. A letter from the eye chart for normal visual acuity is projected onto the densely packed photoreceptors in the fovea. Although less sharply focused than shown here as a result of diffraction by the eye's optics, the smallest discernible strokes of the letter are approximately one cone diameter in width. (Adapted, with permission, from Curcio and Hendrickson 1982.)

Figure 12:

- The retina consists of a multilayer of cells:

- **Photoreceptor cells (PRCs):**

- * Outermost layer.
- * Absorb light and convert it to a neural signal (phototransduction).

- **Bipolar cells:**

- * Receive synaptic signals from PRCs.

- **Retinal Ganglion cells:**

- * Innermost layer.
- * Input from bipolar cells.
- * Output from retina, with axons forming the optic nerve.

- **Horizontal cells:**

- * Provide lateral connections.

- The area of the retina near the optical axis, the fovea, is where vision is the sharpest.

- Corresponds to the centre of gaze when we look at something.
- Density of photoreceptors, bipolar cells, and ganglion cells is highest at the fovea.
- In the centre of the fovea, the foveola, cellular layers are pushed aside to allow more immediate access to PRCs.

7.1 Photoreceptors

- All PRCs have a common structure with four functional regions:
 - Outer segment: At distal surface of the retina.
 - Inner segment: Located proximally.
 - Cell body.
 - Synaptic terminal.
- The two types of photoreceptors, rods and cones, are distinguished by their morphology.

A Morphology of photoreceptors

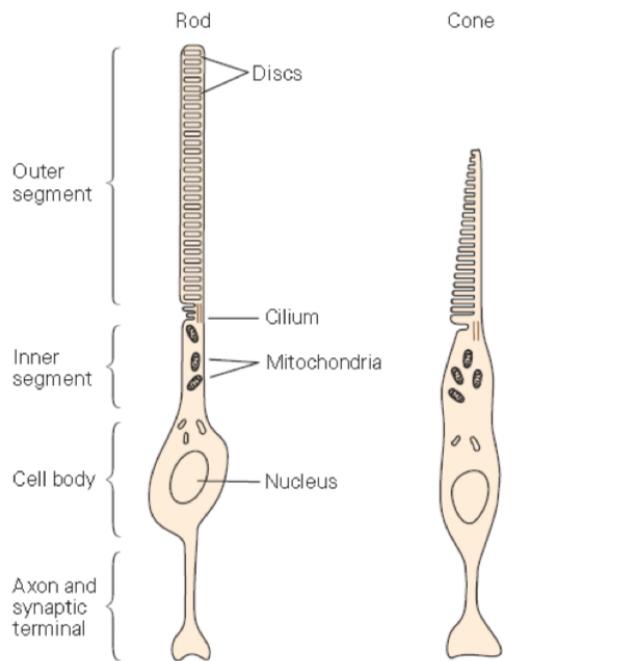


Figure 26–5 Rod and cone photoreceptors have similar structures.

Question 58. list the key differences between Rods and Cones. Hint: consider physical geometry, sensitivity, number and location

Rods

- Long, cylindrical outer segment within which the stacks of discs are separated from the plasma membrane.
- Highly sensitive, even to a single photon, so dominate vision at low light levels.
 - Saturate at higher light levels.
- Only a single type present in primates.
- 100 million in the human retina.
 - None in the fovea.
 - * We can't see what we are directly looking at during the night.

Cones

- Shorter, tapered outer segment, and the discs are continuous with the outer membrane.
- Much less sensitive to light.
 - Make no contribution to night vision.
- Considerably faster response.
- Primates have three types:
 - L, M, and S cones.
- 6 million in the human retina.
 - Concentrated in the fovea.
 - S-cones make up 10% but are absent in the fovea.
- Thus, the fovea is specialised for daytime vision.

The Photocascade

- Again, the membrane potential of a RPC is controlled by conductances of K^+ and Na^+ ions whose transmembrane gradients are maintained by pumps.
 - In the dark, Na^+ ions flow into the photoreceptor through nonselective cation channels that are activated by the second messenger cGMP.
 - Absorption of a photon triggers a biochemical cascade that lowers the concentration of cGMP, closing the gated channels and hyperpolarising the cell to the K^+ potential.

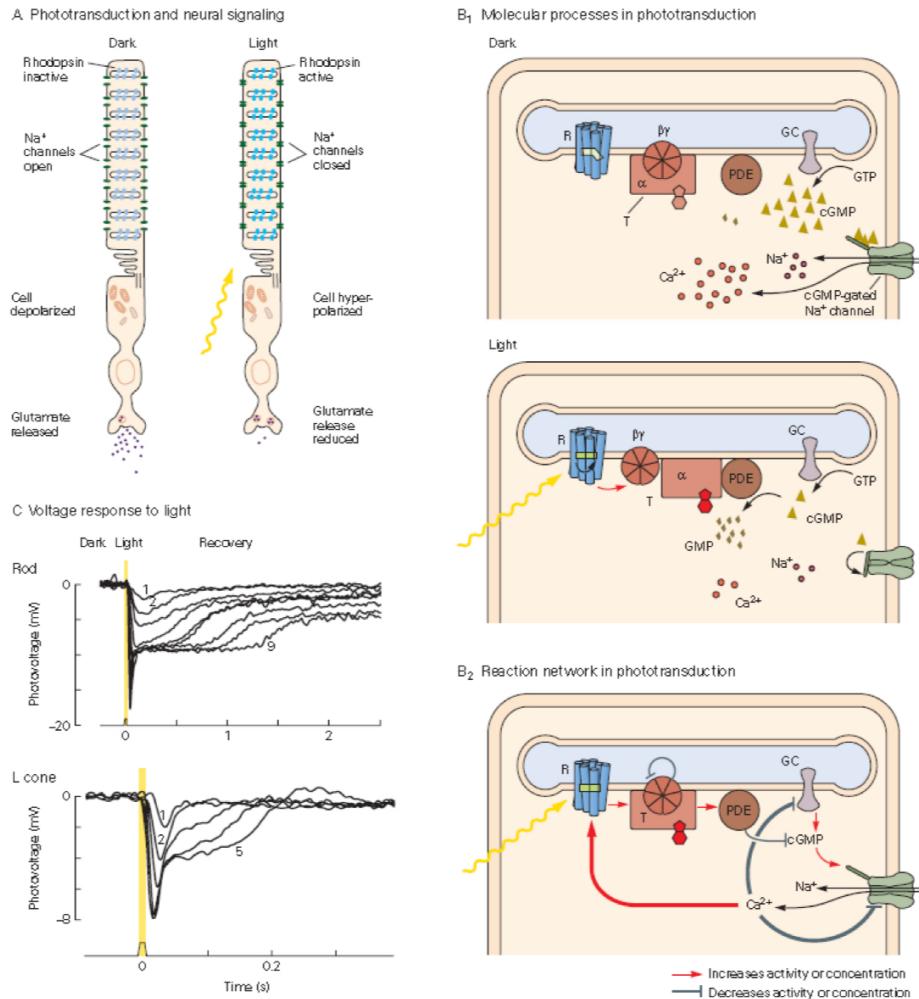


Figure 13: B: T refers to transducin(the G-protein for rods). For (C) notice cones are less sensitive than rods as mentioned

The mechanism above will now be described in detail. Red is the essential information the rest are for context/background.

Rhodopsin Activation

- Rhodopsin is the visual pigment in rod cells.
 - Opsin component embedded in the disc membrane.
 - Retinal is the light-absorbing moiety.
 - * 11-cis isomer covalently linked to a lysine residue of Opsin.
 - * Absorption of a photon causes it to flip from 11-cis to the all-trans configuration.

Phosphodiesterase Activation through G-protein

- The activated rhodopsin diffuses within the disc membrane where it encounters a G-protein (transducin in rods).
 - Inactive form binds GDP, but interaction with rhodopsin promotes binding of GTP instead.

- * This causes the alpha subunit of transducin to become activated(active subunit of transducin).
- The active transducin subunit $T\alpha$ -GTP complexes with cGMP phosphodiesterase(PDE), increasing its activity.
 - Enzyme hydrolyses cGMP \rightarrow 5'-GMP
 - hence lowering cGMP concentration

Reduction of Inward Current

Note that the inward current refers to Na^+ while the outward current refers to the outward current

- The concentration of cGMP controls the activity of the cGMP-gated Na^+ channels in the plasma membrane of the outer segment.
 - With now Lowered cGMP from previously the cGMPT Na^+ channels close, reducing the inward current into the outer segment.

The Dark-Current

- Dark current refers to the continuous inward *and* outward current in darkness. In the dark
 - PRC membrane potential ~ -40 mV.
 - Cell's synaptic terminal continually releases neurotransmitter glutamate.
- No Na^+ current flow(since cGMPT Na^+ channels close as discussed above) in the presence of light. So in the light
 - PRC membrane potential is now about that of potassium equilibrium potential ~ -70 mV(since essentially now only K^+ can pass through the cell) so it is essentially now hyperpolarized
 - Hyperpolarisation slows the release of glutamate from the photoreceptor terminal and so initiates a neural signal.

Fact 59

To summarize

Dark

- **Rhodopsin (R)** is inactive.
- **Transducin (T)** (a G protein) remains in its inactive state.
- **Phosphodiesterase (PDE)** enzyme is inactive.
- **Guanylate cyclase (GC)** is producing cGMP.
- **High levels of cGMP** keep the **cGMP-gated sodium (Na^+) channels** open.
- **Sodium (Na^+) and Calcium (Ca^{2+}) ions enter** the cell, keeping it **depolarized**.
- The depolarization **continuously releases the neurotransmitter glutamate**, which inhibits the downstream bipolar cells.

Light

- **Photon (light) activates rhodopsin (R)**, converting it into **metarhodopsin II**, which interacts with **transducin (T)**.
- **Transducin (T) activates** by exchanging **GDP for GTP** on its **α -subunit**.
- The activated **α -subunit of transducin** binds to **phosphodiesterase (PDE)**, activating it.
- **PDE breaks down cGMP into GMP**, reducing cGMP levels.
- **Low cGMP levels** cause the **cGMP-gated Na^+ channels** to close.
- **No Na^+ or Ca^{2+} influx**, leading to **hyperpolarization** of the rod cell.
- **Reduced neurotransmitter (glutamate) release** signals the presence of light to the **bipolar and ganglion cells**, which ultimately send the visual signal to the brain.

7.2 Low-Level Visual Processing

We now move on to processing. we start with how the bipolar and ganglion cells react to reduced glutamate.

- The photoreceptor layer produces a simple representation of the visual scene.
 - Neurons in bright regions are hyperpolarised, and those in dark regions are depolarised.
- The retinal circuit must edit the information before it is conveyed to the brain.
 - This can be seen physically as the optic nerve has 1% as many axons as there are receptor cells.

Retinal Signal Processing

- The retina hosts several interconnected cell types:
 - **Local Interneurons** – generate graded membrane potentials.
 - * **Horizontal cells** – collect signals from several neighbouring photoreceptor cells (PRCs).
 - * **Bipolar cells** – send signals to amacrine or ganglion cells.
 - * **Amacrine cells** – horizontal processing layer.
 - **Retinal ganglion cells** – axons form the optic nerve and send action potentials (AP) to the brain.

Remark 60. note that horizontal cells are located between the ganglion and bipolar cells in 12(not explicitly labelled there). Or just refer to the diagram below

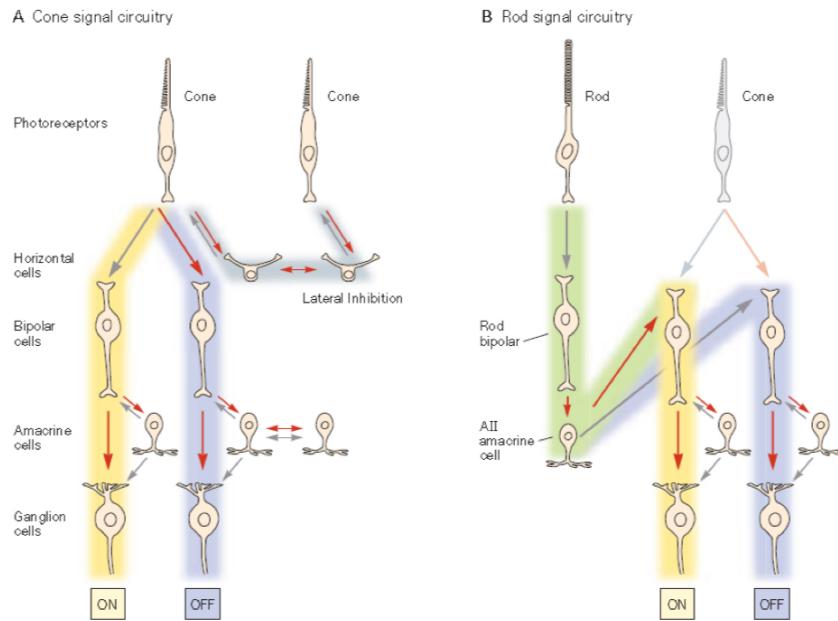


Figure 14: Caption

Receptive Fields of Retinal Ganglion Cells

- Retinal ganglion cells (RGCs) have **receptive fields** that are physically represented by a compact area on the retina.
 - Comprises of a **centre** region and a **surround** region.
 - These two regions produce antagonistic responses.
- RGCs come in 2 types: the "on" or "off" type

To see how this works consider

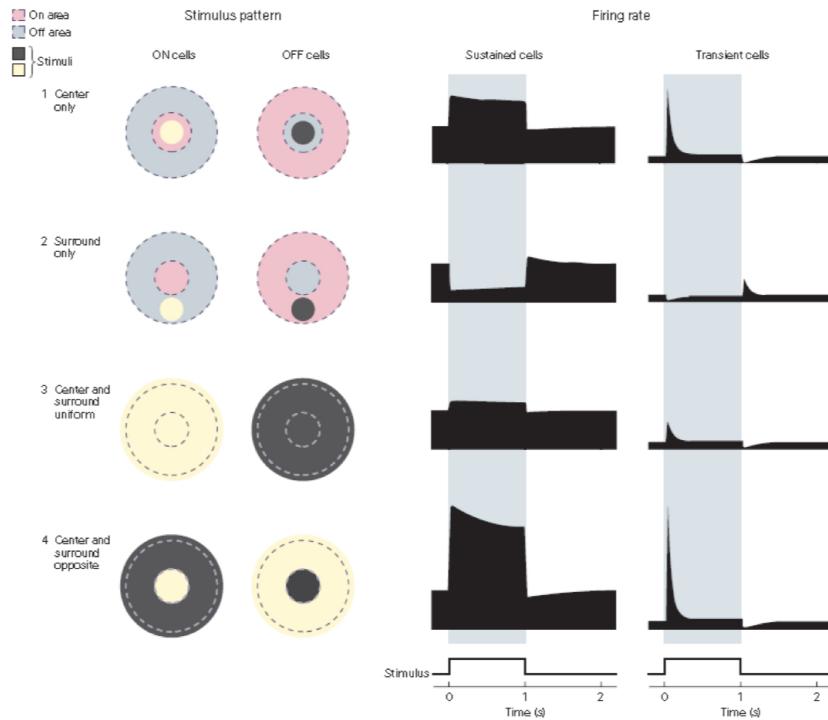


Figure 15: the dark box refers to darkness stimuli while the yellow box refers to the light stimuli

Question 61. explain the effect on firing rate, when light is incident on the surround and centre of an On RGC respectively

On RGCs

- Increased firing rate when light is incident on the centre of the receptive field.
- Decreased firing rate when light is incident on the surround of the receptive field.
- If both parts of the receptive field are covered, a weaker response occurs.

Question 62. explain the effect on firing rate, when light is incident on the surround and centre of an Off RGC respectively

Off RGCs

- Decreased firing rate when light is incident on the centre of the receptive field.
- Increased firing rate when light is incident on the surround of the receptive field.

Or equivalently if center dark stimuli (then increase fire rate) or surround dark stimuli (then decrease fire rate)

7.3 Higher Level Visual Processing

Having accounted for signals from the RGCs we now explore what happens next to them

Question 63. what the three visual pathways signals transmitted from the RGCs? what is the broad purpose of each pathway?

RGCs transmit signals to the brain through three visual pathways:

Pretectum	Superior colliculus	Lateral geniculate nucleus (LGN)
Pupillary reflex.	Control of eye movements.	Visual perception.

Let us talk a bit more about the LGN.

The Lateral Geniculate Nucleus

- The LGN acts as the primary relay for the visual system.
 - Part of the thalamus.
 - Processes light intensity and colour information in separate pathways.
 - These are retinotopically organised.
 - Outputs to the primary visual cortex.

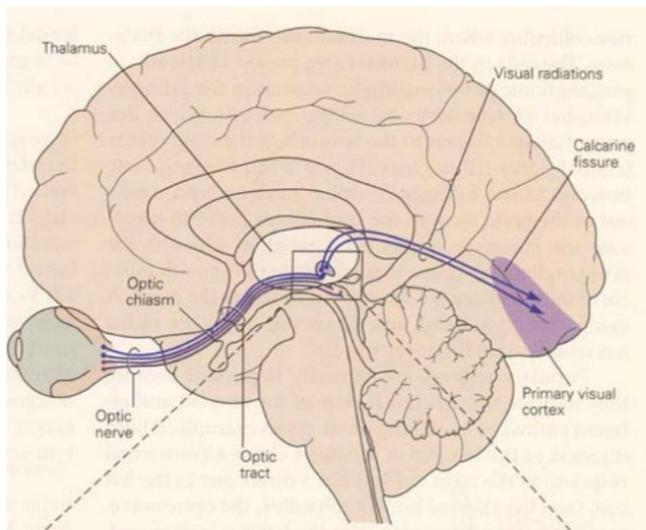


Figure 16: LGN pathway

Simple Cells of the Primary Visual Cortex

- Simple cells are located in the primary visual cortex.
 - Orientation-selective neurones.
 - Have receptive fields divided into ON and OFF sub-regions.

Question 64. how do the receptive fields of simple cells in the primary visual cortex differ from those of RGCs?

- Larger than those of RGCs.
 - Respond optimally if a light bar of specific orientation enters the ON region.

• Characteristic response to a moving bar.

- Discharge briskly when a bar of light leaves an OFF region and enters ON(i.e transient cell responses)
- Highly selective for the position of a line or edge in space.
- Receptive field organisation of simple cells may be explained by convergent synaptic connections.
 - Individual simple cells may receive inputs from three LGN cells whose receptive fields are arranged in space.
 - The receptive fields are summed to create an orientation-selective receptive field.

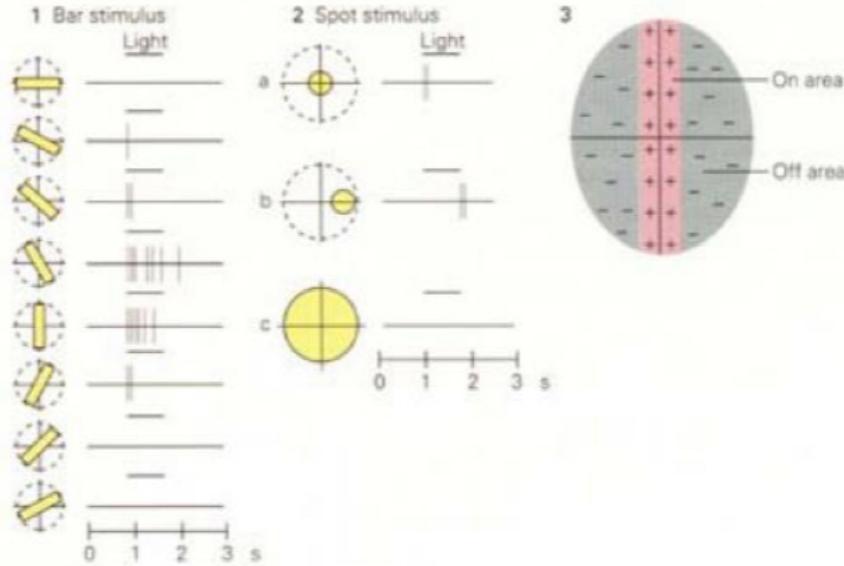


Figure 17: The lines(spikes) on the time scale represent APs. So APs closer together represent higher frequency. Above we are clearly using transient cells here where essentially there is short burst of spikes at the onset of stimulus which then decreases in frequency over time even as stimulus sustained. i.e transient responds to changes in stimulus and recall frequency of AP represent response strength . Naturally those spikes with higher frequency last longer since with higher initial signal response strength.

We now explain the differences in responses as in the above figure to different stimulus below.

Bar Orientation	Alignment with ON/OFF Regions in (3)	Response Strength
Bar perpendicular to ON/OFF regions (horizontal orientation)	The bar equally activates both ON and OFF areas , canceling out excitation and inhibition.	Weak or No Response
Slightly tilted bar	Some ON and OFF areas are activated differently, but not perfectly aligned . Partial response.	Moderate Response
Bar aligned with ON/OFF regions (preferred orientation, vertical or near-vertical)	The bar maximally aligns with ON/OFF areas, creating strong contrast between excitatory and inhibitory zones.	Strongest Response (Maximal Firing Rate)
Opposite tilt	The bar still interacts with ON/OFF regions, but less optimally. Partial response.	Moderate Response
Bar parallel to ON/OFF boundaries	The bar does not differentiate ON and OFF regions well , leading to weak contrast.	Weak or No Response

Table 2: Effect of Bar Orientation on V1 Neuron Response Based on ON/OFF Receptive Fields

Condition	Spike Spacing Pattern	Why?
Spot in ON Region (a)	Spikes appear earlier and more closely spaced at stimulus onset	ON response is immediate and excitatory , leading to an early and strong firing .
Spot in OFF Region (b)	Spikes appear later and more widely spaced at first but then become closer	OFF response is delayed , and firing builds up over time as light is removed.
Large Spot Covering ON and OFF Regions (c)	No spikes or very sparse spikes	ON and OFF responses cancel out , leading to no significant firing.

Table 3: Spike Spacing Differences in ON vs. OFF Responses to spot stimulus

8 The Somatosensory System

- Haptic sensors that provide close-range sensory information
 - Key in planning and executing motor action
 - Comprised of several receptor types and ascending pathways

8.1 Morphology of Mechanoreceptors

- Various types of cutaneous and subcutaneous receptors mediate the sensations of touch, texture, and pain

- Each type of receptor has different morphologies and purposes

Remark 65. Note: *morphology: ethymology - "morph" refers to shape, size and anatomical features in the context of biology*

Nociceptors

- These sense pain and are located at different depths in the skin
- Bare nerve endings giving rise to myelinated A_α , A_β , A_δ or un-myelinated C fibres

Pressure/Touch Receptors

Example 66

There are several types of these:

- Merkel disk receptors
- Pacinian corpuscles
- Ruffini endings
- Meissner's corpuscles

Except for some bare nerve endings, most of the mechanoreceptors are innervated by myelinated axons which convey information to the spinal cord as action potentials (APs)

8.2 Transmission to CNS

- Information from cutaneous mechanoreceptors is sent to the spinal cord
 - Cell bodies of these afferent fibres are located in the dorsal root ganglia
 - Axons enter the spinal cord through the dorsal roots
- Axons bifurcate in the dorsal horn of the spinal cord
 - Send information to neighbouring segments of the spinal cord and to the higher brain centres.

8.3 Action of Mechanoreceptors

- Mechanoreceptors sense physical deformation of the tissue in which they reside.
- Mechanical distension, such as pressure/stretch, is transduced into electrical energy:
 - Through the physical action of the stimulus on cation channels in the membrane.
 - Deformation of receptor protein opens stretch-sensitive ion channels, increasing Na^+ and Ca^{2+} conductances that depolarize the receptor neuron.

Adaptation

- Mechanoreceptors adapt to stimuli so that a larger range can be encoded.
 - Slowly adapting (SA) receptors respond to a step stimulus by a strong transient increase in spike rate that decreases slowly while the stimulus stays constant.
 - Rapidly adapting (RA) receptors respond with a similar initial behavior, but the decrease happens much quicker so that the spike rate may not differ from the OFF state.
- Prevents output saturation of the neuron's dynamic response range.
 - Neurons can only generate a finite number of spikes/second, approximately ~ 500 spikes/s.
 - Only 500 different states can be encoded by instantaneous spike rate.
 - * Solved by having sensory and neural processing systems adapt dynamic range using some kind of gain control mechanism.

Mechanisms for Adaptation

- Changes in morphology are temporary and return to the original state even if the signal is still present.
- Opening of ion channels counteracting depolarization and preventing action potential (AP) from being reached in the axon.

Mechanoreceptors in the skin are specialized sensory receptors that detect mechanical stimuli such as pressure, vibration, and skin stretch. These receptors are categorized into four main types based on their adaptation properties and depth in the skin.

Types of Mechanoreceptors

Other than adaption speed, mechanoreceptors can also be categorized by how deep in the skin layer it is: type (1) being shallow type (2)

Question 67. Name 4 key mechanoreceptors found in the human hand and briefly state their type(adaption,depth) for each.

- **Type 1 (Superficial receptors):** Have small, localized receptive fields.
 - **SA1 (Slowly Adapting Type 1):** Merkel cells, located at the tip of epidermal sweat ridges, respond best to edges and points.
 - **RA1 (Rapidly Adapting Type 1):** Meissner corpuscles, found in dermal papillae close to the skin surface, respond to lateral motion.
- **Type 2 (Deep receptors):** Have larger receptive fields.
 - **SA2 (Slowly Adapting Type 2):** Ruffini endings, located in the dermis(deep tissue), respond to skin stretch.
 - **RA2 (Rapidly Adapting Type 2):** Pacinian corpuscles, found in deep dermal layers, respond to vibration.

Receptive Fields and Tactile Sensitivity

Question 68. compare the receptive fields of mechanoreceptor type 1 and 2

- Mechanoreceptors have receptive fields mapped onto the skin.
- Type 1 fibers have small, highly localized receptive fields with multiple sensitivity hotspots.
- Type 2 fibers have larger receptive fields and gather information from a broader area.
- The density of receptors in the fingertips leads to smaller receptive fields and higher spatial resolution.

Touch and Mechanoreceptors in the Hand

In summary

- The hand contains all four types of mechanoreceptors.
- Each receptor has a distinct response based on morphology, depth, and innervation patterns.
- Superficial mechanoreceptors (Meissner corpuscles and Merkel cells) have smaller receptive fields compared to deep receptors (Pacinian corpuscles and Ruffini endings).
- RA fibers adapt rapidly to stimulation, while SA fibers adapt more slowly.

8.4 Ascending Pathways

- Sensory information is conveyed to the thalamus and the cortex.
- The two systems run parallel through the medulla, pons, and midbrain.

Question 69. Describe the differences between the dorsal column-medial lemniscal and anterolateral system (Hint where do each of them cross the midline? What kind of signal do each of them transmit and to where?)

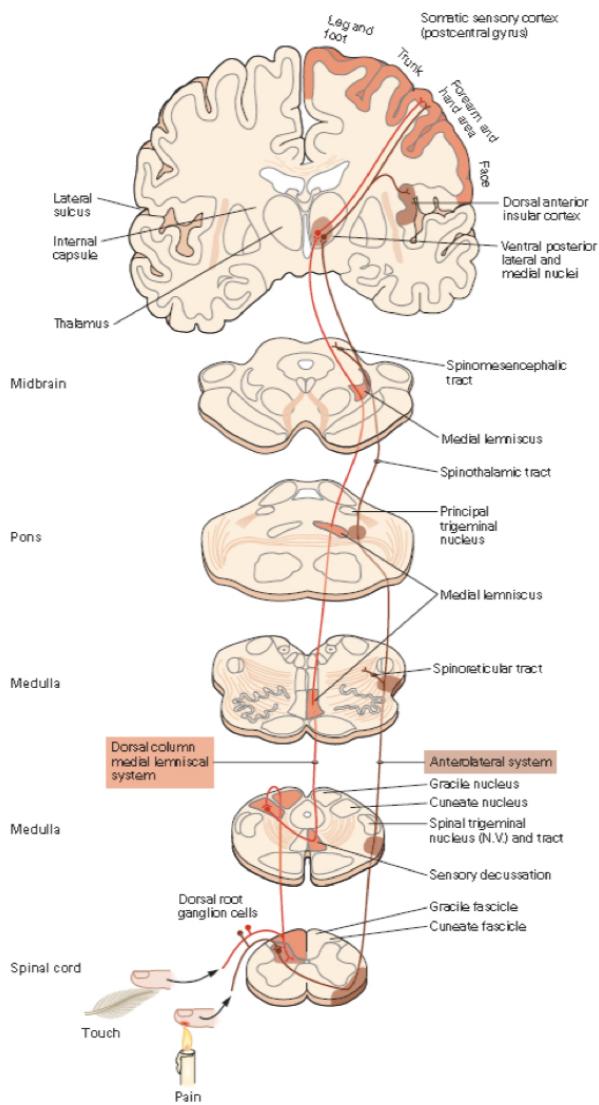


Figure 18: The somatosensory cortex is labeled in orange at the top as you can see

The Dorsal Column-Medial Lemniscal System

- Responsible for touch and proprioception.
- Information is transmitted to the primary somatosensory cortex.
- Ascends ipsilaterally (same side of body) and crosses the midline in the medulla.

The Anterolateral System

- Processes pain signals directed to the dorsal anterior insular cortex, anterior cingulate gyrus, and primary somatosensory cortex.
- Crossing the midline occurs immediately in the same spinal segment where the afferent fibers enter the spinal cord.

Remark 70. The midline refers to the imaginary vertical line that runs down the center of the body, dividing it into left and right halves. In the nervous system, the term "crossing the midline" refers to when nerve fibers decussate (cross from one side to the other)

8.5 The Somatosensory Cortex

- Each area of the somatosensory cortex receives input from a specific receptor type:
 - **1** - Rapidly adapting skin mechanoreceptors.
 - **2** - Pressure and joint position from deep tissues, along with information on complex touch of the skin.
 - **3a** - Information from deep tissue in muscles and stretch receptors.
 - **3b** - Input from both slowly and rapidly adapting skin receptors.
- The cortex is organized in columns that extend through all six layers:
 - Defined by their specific sensory inputs.
 - In area 3b, neighboring columns receive input from different mechanoreceptors whose receptive fields have significant overlap but exhibit different adaptation properties.

8.6 Higher Order Processing

Fact 71

First-order neurons send information to second-order neurons. The information is combined and/or processed in different ways to extract specific features of a stimulus. Processing is most commonly achieved through a convergent connectivity scheme. Beyond connectivity, connections could be classified as either excitably/inhibitory or by receptive field location.

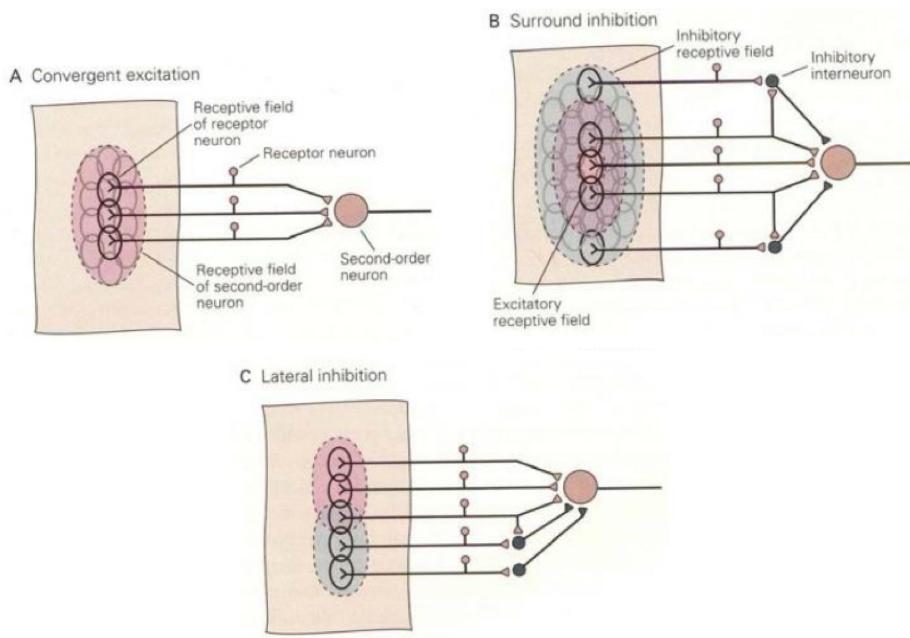


Figure 19: Note that A,B,C all follow a convergent connectivity scheme

(A)Convergent Excitation

- Larger receptive field of the second-order neuron compared to first-order neurons.

- Increases signal-to-noise ratio.
- Reduces spatial resolution.
- The receptive field can be orientation selective.

(B) Surround Inhibition

- Only the central primary receptor neuron provides a purely excitatory signal to the second-order neuron.
- Most peripheral receptors mediate inhibitory signals to the second-order neuron via inhibitory interneurons.
- Intermediate neurons both inhibit and excite the second-order neuron.
- Such receptive fields resemble a "Mexican hat" and help indicate the precise location of a small stimulus.

(C)Lateral Inhibition

- A row of inhibitory signals is integrated.
- Helps in identifying contrast edges in the spatial domain.

Feature Detection in Area 2

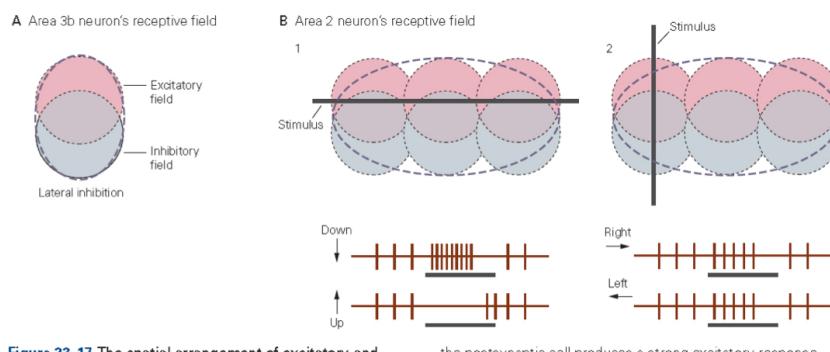


Figure 20: Caption

- The spatial arrangement of excitatory and inhibitory inputs to a cortical neuron determines the encoding of stimulus features.
- In area 3b of the primary somatosensory cortex, neurons have overlapping excitatory and inhibitory zones in their receptive fields.

• Motion Sensitivity:

- Convergence of three presynaptic neurons with the same excitatory and inhibitory zones allows for direction and orientation selectivity.
- Downward motion of a horizontal bar across the receptive field produces a strong excitatory response.
- Upward motion is strongly inhibited due to entering inhibitory fields first.
- The neuron responds poorly to upward motion because inhibition outlasts the stimulus.

- Motion of a vertical bar across the receptive field evokes a weak response since it simultaneously crosses excitatory and inhibitory zones.
- Motion to the left and right is not distinguished in this case.

9 Simple Reflexes

- Simple reflexes help maintain balance and prevent injuries.
- Proprioceptors play an essential role in these circuits:
 - They provide information about the current state of the motor system in terms of joint angles and muscle tension.
- Reflexes can be modified by supraspinal brain areas:
 - Stereotyped responses are influenced by the current state of the system.

9.1 Contextual Dependency

- Reflex actions depend on the specific task being performed.
- The same stimulus can produce different responses based on the environment and task.

9.2 Spinal Reflexes

- These reflexes operate continuously without conscious awareness.
- They help maintain balance and mediate limb withdrawal from harmful stimuli.

Definition 72

The **flexion-withdrawal reflex** is a protective mechanism causing coordinated contraction of all flexor muscles in a limb.

This reflex circuit is confined to a single spinal segment and can persist even after spinal transection.

Example 73 (Stepping on a Sharp Object)

Imagine walking barefoot and accidentally stepping on a sharp nail. Pain receptors (nociceptors) in your foot detect the stimulus and send signals via A δ fibers to the spinal cord. This activates the motor neurons responsible for contracting the hip and knee flexor muscles, causing you to lift your foot away from the nail. Since this reflex occurs at the spinal cord level, it happens almost instantly without requiring brain involvement.

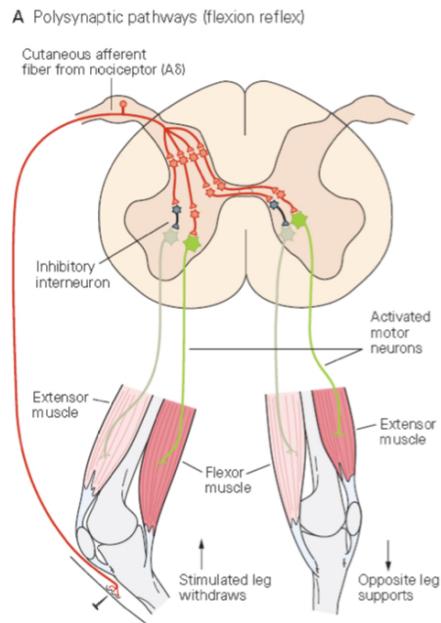


Figure 21: Flexion and cross-extension Reflex: the muscle of leg in pain withdraws while the muscle of the other leg extends to balance can be maintained on that leg

Flexion Reflex: Reciprocal Innervation of Ipsilateral Antagonistic Muscles

Question 74. *Describe flexion reflex that uses reciprocal innervation mechanism*

- When pain-sensitive A δ fibers are stimulated, signals are transmitted to the dorsal horn of the spinal cord.
- The signal is relayed to:
 - An excitatory neuron that activates the motor neuron controlling the flexor muscle ipsilateral to the pain source.
 - An excitatory interneuron that activates an inhibitory interneuron, preventing activation of the antagonist extensor muscle.
- This reciprocal innervation prevents co-contraction of antagonistic muscle pairs (in 21 that would be the extensor and flexor muscle)

Example 75 (Pulling Hand Away from a Hot Stove)

If you accidentally touch a hot stove, the flexion-withdrawal reflex ensures a rapid response. Sensory neurons detect the painful heat and activate excitatory interneurons in the spinal cord, which stimulate the motor neurons controlling the biceps brachii (flexor muscle). Simultaneously, inhibitory interneurons prevent activation of the triceps brachii (extensor muscle). This reciprocal innervation allows your hand to quickly withdraw from the stove without resistance from the antagonist muscle.

Crossed-Extension Reflex

Question 76. *what is crossed extension reflex. give an example where it is useful*

- The pain signal is also transmitted to:
 - An interneuron that activates a neuron crossing the midline, which excites the contralateral extensor muscle.
 - Another interneuron that inhibits the contralateral flexor motor neuron.
- This mechanism is crucial for providing support when withdrawing one limb.

Example 77 (Stepping on a Sharp Object While Walking)

When you step on a sharp object while walking, the injured leg must flex to withdraw from the stimulus (recall flexion reflex). However, this movement could cause loss of balance if the opposite leg does not compensate. The crossed-extension reflex ensures stability by sending signals across the spinal cord to activate extensor muscles in the contralateral leg. As a result, the uninjured leg stiffens, allowing you to remain upright while withdrawing the affected foot.

Stretch Reflex

- If the tendon of a muscle is stretched, the muscle itself will also stretch.
 - Muscle stretch is detected by **muscle spindles**.
 - Ia fibers from these spindles send action potentials (AP) to the dorsal horn of the spinal cord.
- The signal is then used to:
 - Activate the motor neuron of the homonymous muscle (where the activated spindle is located). note that we will learn later that this is a pathway in the servomechanism system
 - Activate synergistic muscles to facilitate flexion.
 - Inhibit antagonistic muscles to prevent counteraction.

Example 78 (Knee-Jerk Reflex (Patellar Reflex))

When a doctor taps the patellar tendon with a reflex hammer, the quadriceps muscle momentarily stretches. This stretch is detected by muscle spindles, which send signals via Ia sensory fibers to the spinal cord. In response, the spinal cord activates the motor neuron of the quadriceps, causing it to contract. Simultaneously, synergistic muscles such as the rectus femoris are activated to enhance the extension of the knee, while inhibitory signals prevent the hamstrings from counteracting the movement. As a result, the lower leg involuntarily kicks forward. This reflex is crucial for maintaining posture and balance.

Fact 79

Dorsal root cutting experiments show the involvement of muscle spindle afferent in reflexes

The force generated by the muscle in response to a stimulus is significantly greater before cutting the dorsal roots than after they have been severed.

B Monosynaptic pathways (stretch reflex)

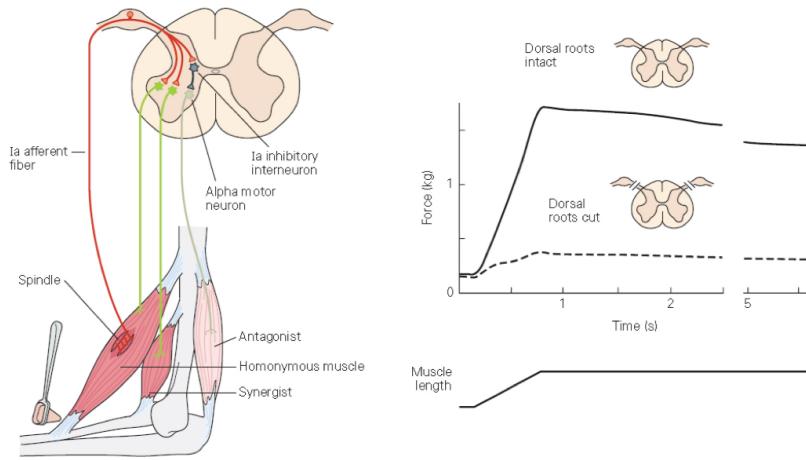


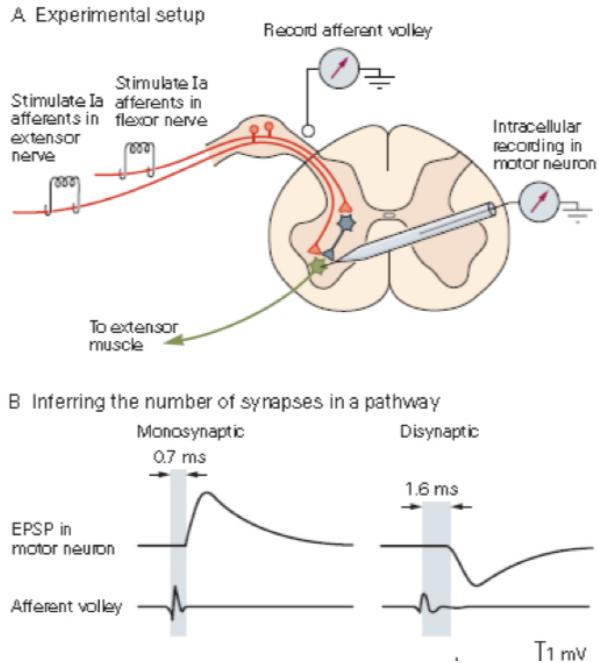
Figure 22: Stretch Reflex

we will discuss more on muscle spindles later

9.3 Local Spinal Circuitry

Monosynaptic and Disynaptic Pathways

- Synaptic latency between afferent stimulation and motor neuron response onset reflects the number of synapses involved.



- Experimentally:

- Intracellular electrodes measure excitatory postsynaptic potentials (EPSPs) in extensor motor neurons.

- Extracellular electrodes near the dorsal root record summed activity of afferent fibers.

Results Different latencies between afferent activity and motor neuron EPSPs:

- Ia afferents of extensors stimulate motor depolarization 0.7 ms after the volley.
- Ia afferents of flexors stimulate motor depolarization 1.6 ms after the volley.

Proposition 80

Since Signal transduction across a chemical synapse takes approximately 0.7 ms hence we infer that

- The extensor pathway is monosynaptic.
- The flexor pathway is disynaptic.

Role of Inhibitory Neurons

We consider 2 types

Question 81. *what are 2 types of inhibitory neurons and what are their functions*

Ia Inhibitory Interneurons

- Inhibitory interneurons are present in almost all spinal circuits.
- Their function is to **prevent co-contraction of antagonistic muscles**.
- They also integrate excitatory and inhibitory inputs from descending corticospinal pathways:
 - This ensures muscles can be used for non-reflex purposes.
 - Achieved by corticospinal input causing stronger inhibition of Ia inhibitory interneurons.

Example 82

Example: Manipulating delicate objects where controlled co-contraction allows slow movement.

Renshaw Cells

- Renshaw cells form a negative feedback loop known as **recurrent inhibition**.
- They are activated by collaterals of motor neuron axons.
- These cells make inhibitory connections with motor neuron populations to regulate excitability:
 - **Includes inhibition of the same motor neuron that excites them.**
 - Also inhibits Ia inhibitory interneurons.
- This **mechanism stabilizes firing rates and controls motor neuron excitability through descending pathways**.
- **Prevents excessive activation that could lead to tetanus.**

Modulation of Spinal Reflexes

- Strength of spinal reflexes can be modified at different levels in the pathways:
 - α motor neuron level
 - Interneurons in polysynaptic pathways
 - Presynaptic terminals of afferent fibres
- These three sites receive inputs from neurones in motor centres in the brain stem, cerebral cortex, and other regions of the spinal cord:
 - Regulate strength of reflexes by changing the tonic (background) level of activity at the site.
 - Example: Increase in tonic activity moves membrane potential closer to threshold so that a smaller input will cause activation.
 - This is known as **gating**.

Proprioception

Definition 83

Afferent (Sensory) Neurons: Carry sensory information from the body to the central nervous system (CNS) (brain and spinal cord).

Direction: Afferent/Sensory = Arriving at the CNS.

Definition 84

Efferent (Motor) Neurons: Carry motor commands from the CNS to muscles or glands to produce movement or a response.

Direction: Efferent/Motor = Exiting the CNS.

The Muscle Spindle

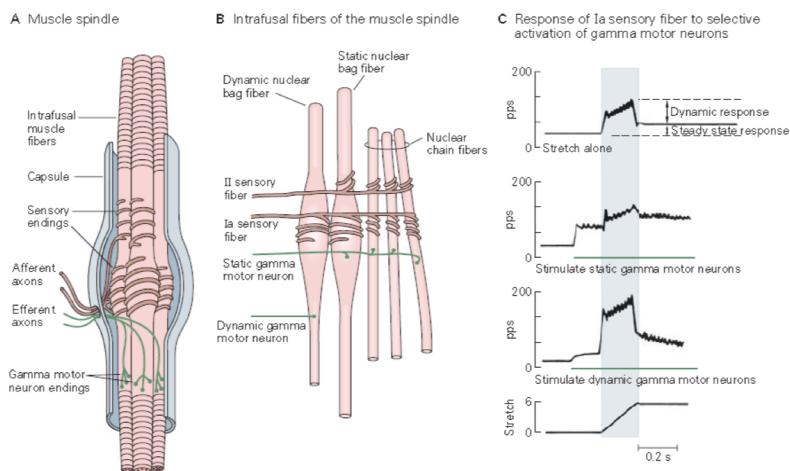


Figure 23: Caption

- Muscle spindles are small encapsulated *sensory receptors*:
 - Signal changes in the length of the muscle in which they reside.
 - Changes in length are associated with changes in angles of joints.
 - Used by CNS to sense relative body segment positions.
- Three main components of the muscle spindle:
 1. Intrafusal muscle fibres with central non-contractile regions. (nuclear chain, dynamic & static nuclear bag)
 2. Afferent sensory fibres that terminate in the non-contractile regions. (Ia - primary and II - secondary)
 3. Efferent γ -motor axons that terminate in the polar contractile regions. (static and dynamic)

Action

- When the intrafusal fibres of the muscle spindle are stretched, sensory nerve endings are stretched and increase their firing rate.
 - Channels mechanically opened by stiff fibres connecting them.
 - Muscle spindles are connected in parallel with the muscle (see fig below)
 - Stretching a muscle causes muscle spindle sensory ending activity to increase and vice-versa.

Muscle fibers can be classified into extrafusal and intrafusal based on their function and location within the muscle.

Feature	Extrafusal Fibers	Intrafusal Fibers
Function	Generate force and movement	Detect stretch and send sensory signals
Location	Bulk of skeletal muscle	Inside muscle spindles
Controlled by	Alpha (α) motor neurons	Gamma (γ) motor neurons
Sensory Role	No direct sensory function	Monitored by Ia sensory fibers

Table 4: Comparison of Extrafusal and Intrafusal Muscle Fibers

Innervation

- Extrafusal muscle fibres in the muscle are innervated by α motor neurons.
- Efferent intrafusal innervation by dynamic and static γ -motor neurons of the bag fibres in muscle spindle:
 - Activation of these afferent/motor (into CNS) fibres causes shortening of polar intrafusal regions (more taunt see figure below), stretching the central region and increasing the firing rate of the muscle spindle.
 - Hence essentially Gamma motor neurons adjust spindle sensitivity.
- The change in muscle length has two phases: dynamic and steady-state. Structural specialisations allow spindle afferents to signal each phase separately:
 - Single Ia axon spirals innervates all intrafusal fibres and serves as the primary sensory ending.
 - Variable number of type II axons innervate bag fibres, serving as secondary sensory endings.
 - Dynamic gamma motor neurons innervate dynamic bag fibres.
 - Static gamma motor neurons innervate static bag fibres.

Encoding

Muscle spindles are sensory receptors in muscles that detect changes in muscle length and velocity. They contain primary (Ia) and secondary (II) endings, which provide different types of information:

- Tonic discharge of primary and secondary endings signals steady-state **length**.
- Primary endings are also sensitive to **velocity** of stretch, encoding the rate of change in muscle length.
- The central nervous system can independently adjust the dynamic and static sensitivity of different sensory endings in muscle spindles:

The central nervous system (CNS) can regulate how sensitive these sensory endings are by controlling the activity of gamma motor neurons(which affects how taunt the muscle spindle is if you recall):

- Increases in the firing rate of **dynamic gamma motor neurons**
 - increase the **dynamic sensitivity** of primary sensory endings(recall velocity signals) but have no influence on secondary sensory endings(as expected if you read above).
- Increases in the firing rate of **static gamma motor neurons**
 - increase the **tonic level of activity** in both primary and secondary sensory endings(recall steady state length signals),This prevents primary endings from going silent when a muscle returns to its resting length.
 - decreasing the **dynamic sensitivity** of primary endings.

We now go into detail about two important regulation/modulation systems for the muscle spindle.

The Fusimotor System - Gamma Motor Neurones and Sensitivity

Activity of muscle spindles is modulated by changing gamma motor neurone activity.

When only α motor neurons of the extrafusal muscle fibre is stimulated,

- the extrafusal fibre contracts, unloading the spindle (see the figure).
- which makes the muscle spindle less taunt
- recall that the muscle spindle is stretch sensitive and reduces activity when slackened.
- therefore the Ia afferent/sensory(out of CNS) fibres pauses during this time

Now if γ is activated at the same time,

- the pause is eliminated as the contraction of intrafusal fibres keeps the spindle under tension.
- This maintains Ia fibres within the optimal range for signalling changes in length.
- $\alpha - \gamma$ coactivation stabilises the sensitivity of muscle spindles and is used in voluntary movements.

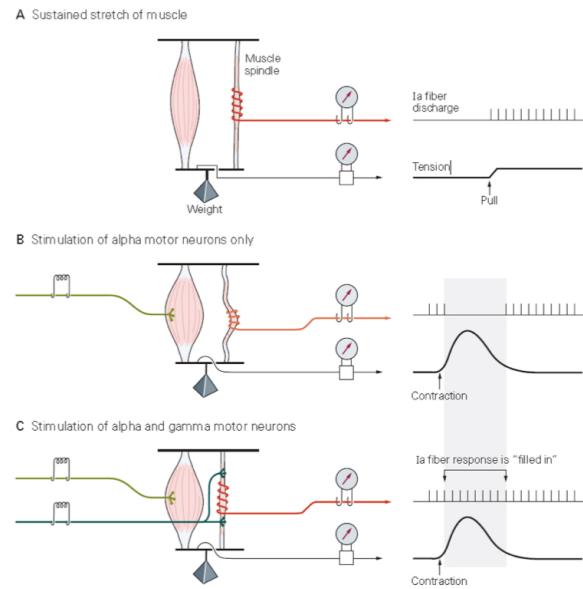


Figure 24: Recall the muscle spindle and the muscle are connected in parallel. Now when the plates are shortened (by shortening of extrafusal muscles), for the same length the muscle spindle becomes more slack. However if the muscle spindle itself contracts/shortens then it becomes more taunt instead

Servomechanism System - feedback loops

- Stretch-reflex pathways contribute to the regulation of motor neurones during voluntary movements and maintenance of posture because they form closed feedback loops.
 - Stretching a muscle increases activity in spindle sensory afferents (since connected in parallel the spindle gets stretched too)
 - Leading to muscle contraction and consequent shortening of the muscle. (see picture below Ia fibres connected to α motor neuron!)
 - Muscle shortening in turn leads to decreased activity in spindle afferents.
 - Reduction of muscle contraction and lengthening of the muscle.
- The reference value is set by descending signals that act on α and γ motor neurones.
 - If the shortening of the whole muscle is less than that required by a task, as when the load is greater than anticipated, the sensory fibres increase their firing rate because the contracting intrafusal fibres are stretched (loaded) by the relatively greater length of the whole muscle.
 - If shortening is greater than necessary, the sensory fibres decrease their firing rate because the intrafusal fibres are relatively slackened.

A Alpha-gamma co-activation reinforces alpha motor activity

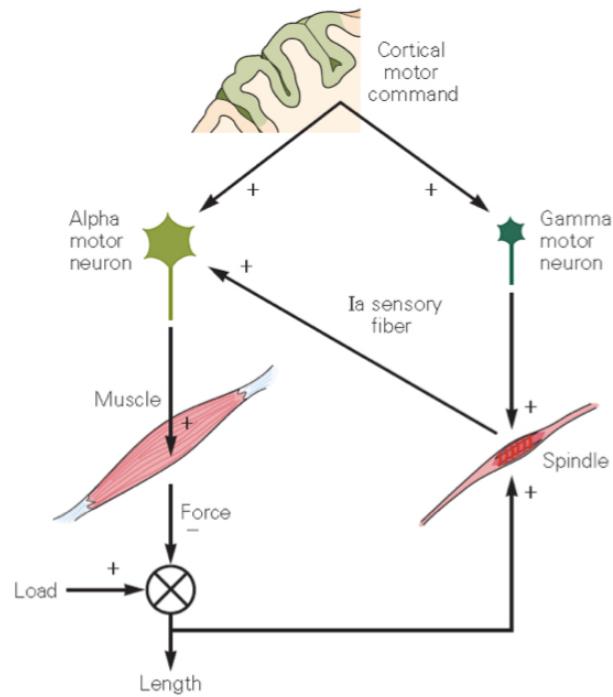


Figure 25: Recall in the stretch reflex section it was mentioned "Activate the motor neuron of the homonymous muscle (where the activated spindle is located)". That is precisely represented by the diagonal Ia sensory fiber path here.

9.4 The Golgi Tendon Organ

- Golgi tendon organs are most sensitive to changes in muscle tension.
 - Slender encapsulated structures.
 - Approx. 1mm long and 0.1 mm in diameter.
 - Located at the junction between skeletal muscle fibres and tendon.
- Each capsule encloses several braided collagen fibres connected in series to a group of muscle fibres.
 - Each tendon organ is innervated by a single Ib axon that branches into many fine endings inside the capsule.
 - These endings become intertwined with the collagen fascicles.
- Stretching the organ straightens the collagen fibres, compressing the Ib nerve endings and causing them to fire.
 - Even small stretches cause compression and firing.
- Contraction of the muscle fibres connected to the collagen fibre bundle containing the receptor is a particularly potent stimulus to a tendon organ.
 - The tendon organs are thus readily activated during normal movements.
- Close agreement between "firing frequency and force" is consistent with the view that the tendon organs continuously measure the force in a contracting muscle.

10 Eye Movements

- Eye movements are mostly induced in a reflex-like way.
 - Important to efficiently use vision for gathering information about the environment.
- Most eye movements are saccade-like – consisting of brief and rapid movements taking place at a millisecond time scale.
 - Micro-saccades – tiny retinal image shifts to counteract adaptation.
 - Larger saccades act to stabilize the retinal image in its default orientation.

10.1 Functions

- Eye movements help stabilize the gaze to facilitate the processing of visual information.
 - Reduce blurring due to relative motion between eyes and environment.
 - Keep a visual target with the fovea.
 - Maintain default orientation of the retinal image.
 - Voluntary eye movements – scan region of interest.

10.2 Neuronal Control Systems

- There are six systems that direct the fovea to a visual target and keep it there:
 1. **Saccadic** eye movements shift the fovea rapidly to a new target.
 2. **Smooth-pursuit** movements keep the image of a moving target on the fovea.
 3. **Vergence** movements move the eyes in opposite directions so the image is positioned on both foveae.
 4. **Vestibulo-ocular reflexes** hold images still on the retina during brief head movements.
 - Compensatory eye movements induced by the vestibular system.
 5. **Optokinetic** movements hold images stationary during sustained head rotation or translation.
 - Compensatory eye movements induced by the visual system.
 6. **Fixation** system holds the eye stationary during intent gaze through active suppression of eye muscles.
- These systems all share the same effector pathway of three bilateral groups of oculomotor neurons in the brain stem.

The Vestibular System

- The vestibular system is very efficient in detecting any fast changes in head and body orientation and in initiating correspondingly fast compensatory eye movements.
- The three measuring axes (semi-circular canals) of the vestibular system are orthogonally arranged, as are the pairs of eye muscles rotating the eyeball in the orbit.

- This arrangement, where the measuring axes of a sensory system and the pulling planes of the muscular system are arranged in Cartesian coordinates, helps to speed up the transformation of sensory signals into motor commands.

10.3 The Ocular Motor Plant

- The eye is a sphere that sits in a socket called the orbit.
 - Eye movements are rotations of the eye in this orbit.

Axes of Movement

- Eye movements are described as rotations around the horizontal, vertical, and torsional axes.
 - Horizontal rotation away from the nose is abduction, and rotation towards the nose is adduction.
 - Vertical movements are elevation and depression.
 - Torsional movements include intorsion (top of cornea to nose) and extorsion (rotation away from the nose).

Extraocular Muscles

- Each eye is rotated by six extraocular muscles arranged in three agonist-antagonist pairs.
 - Four rectus muscles (lateral, medial, superior, and inferior).
 - * Share a common origin at the apex of the orbit(at the back near the optic nerve).
 - * Insert on the surface of the eye, anterior to the eye's equator.
 - Two oblique muscles (superior and inferior).
 - * Originate on the medial wall of the orbit(the bone walls of the eye socket).

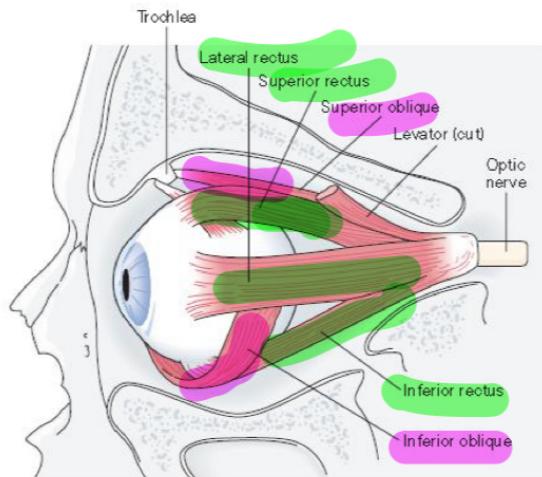


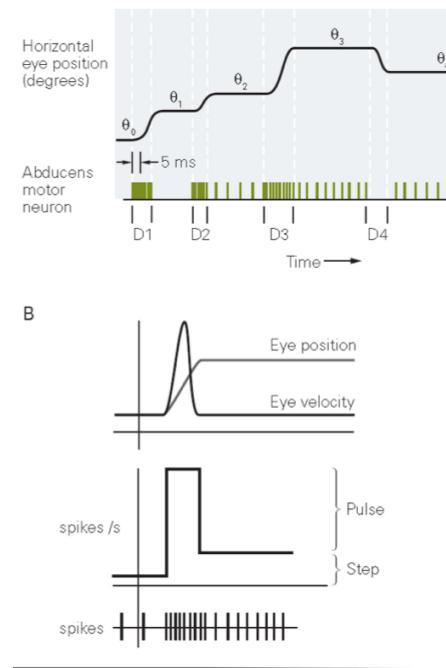
Figure 26: green:rectus,purple:oblique

10.4 Brain Areas and Cranial Nerves

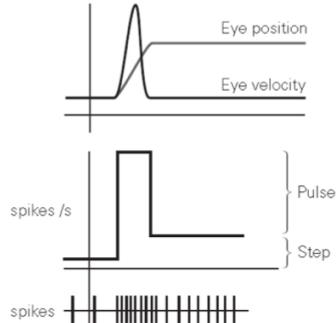
- The extraocular muscles are innervated by groups of motor neurons whose cell bodies are clustered in three nuclei in the brain stem.
 - The lateral rectus is innervated by the abducens nerve (cranial nerve VI), whose nucleus lies in the pons.
 - The superior oblique muscle is innervated by the trochlear nerve (cranial nerve IV), whose nucleus is in the midbrain.

- The medial, inferior, and superior recti, and inferior oblique are innervated by the oculomotor nerve (cranial nerve III), whose nucleus is in the midbrain.

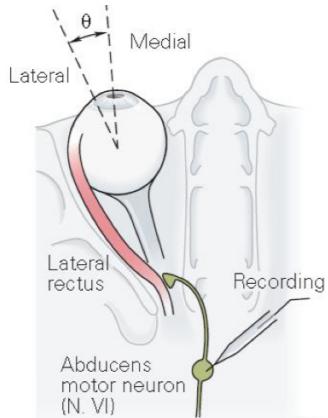
10.5 Extraocular Motor Neuron Encoding



B



- The activity of motor neurons driving the eye muscles reflects:
 - Eye position in orbit (tonic component).
 - Duration of saccades (duration of phasic component).
 - Eye velocity (spike rate of phasic component).
- Thus, neuronal spike rate may encode three different properties:
 - Duration is D_x , encoded by the duration of increased spike rate.
 - Velocity encoded by spike rate.
 - Current angular position θ , encoded by spike rate in between eye movements.



10.6 The Vestibular-Ocular Reflex

Fact 85

The vestibular-ocular reflex (VOR) is a critical mechanism that stabilizes vision by ensuring that the eyes move in the opposite direction of head movements. This allows for clear vision even when the head is in motion

Features

- Fast reflex (~14 ms compared to 60 ms for visually induced reflexes).
- Only 2-3 synapses involved in each pathway.
- The system is an open-loop feed-forward mechanism calibrated as the visual system cannot compete with the reaction time of the vestibular system.

Now to achieve its goal as stated in 85 it does it through

- Activating the necessary muscles for movement.
- Inhibiting the opposing muscles to prevent resistance.

Neuronal Pathways

- For horizontal eye movement compensations, afferent vestibular signals are sent to the vestibular nucleus.
 - Excitatory and inhibitory projections are formed to activate the lateral and medial rectus muscles in both eyes.
 - Excitatory projection neurons cross the midline and activate motor neurons on the right abducens nucleus and the left oculomotor nucleus, from where the left medial rectus is activated.
 - Co-contraction is avoided by inhibiting motor neurons which innervate the left lateral rectus and the right medial rectus.

Example 86

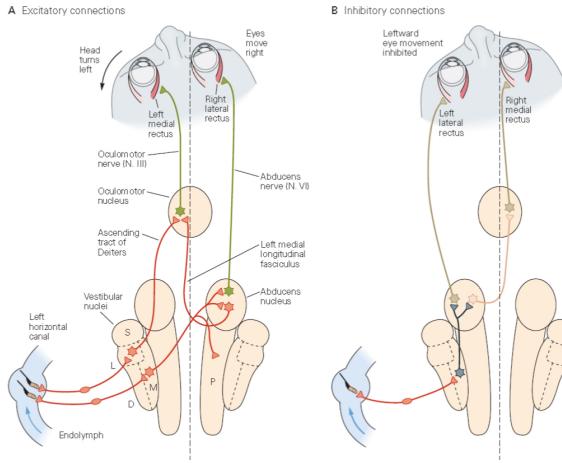
Excitatory Pathway (Activating the Correct Muscles)

1. The **right vestibular nucleus** sends excitatory signals.
2. These signals **cross the midline** and reach:
 - The **right abducens nucleus**, which activates the **right lateral rectus** (pulls the right eye outward).
 - The **left oculomotor nucleus**, which activates the **left medial rectus** (pulls the left eye inward).
3. This coordinated activation moves **both eyes to the left**.

Example 87

Inhibitory Pathway (Preventing Opposing Muscle Activation)

- At the same time, the system ensures that opposing muscles are **inhibited** to avoid co-contraction.
- The **left lateral rectus** and **right medial rectus** must be relaxed for smooth movement.
- This inhibition happens through **interneurons** in the **medial longitudinal fasciculus (MLF)**, which suppresses:
 - The **left lateral rectus** (opposite to the activated medial rectus).
 - The **right medial rectus** (opposite to the activated lateral rectus).



10.7 Saccadic Eye Movements

- We perform saccadic eye movements to analyze features in our visual environment.
 - The fovea is moved from one fixation point to another.
- Highly stereotyped, very fast (900 degrees per second).
 - Velocity determined only by the distance of the target from the fovea.
- We can change the amplitude and direction of saccades voluntarily but not their speed.
 - No time for visual feedback to modify the course of a saccade.
 - Corrections are made through successive saccades.

Cortical Pathways

The saccadic eye movements are controlled by a **saccade generator** located in the brainstem. This structure translates signals from higher cortical areas into specific muscle commands, allowing rapid shifts of gaze.

Several cortical areas contribute to determining whether a saccade should be executed and in which direction:

- The **posterior parietal cortex** (LIP) provides spatial attention and decision-making input.
- The **supplementary eye fields** (SEF) contribute to voluntary control of saccades.
- The **frontal eye fields** (FEF) play a crucial role in initiating and directing eye movements.

The **superior colliculus (SC)**, located in the midbrain, is a key structure for **visuomotor integration**. The FEF sends projections to the SC via two main pathways + 1 additional:

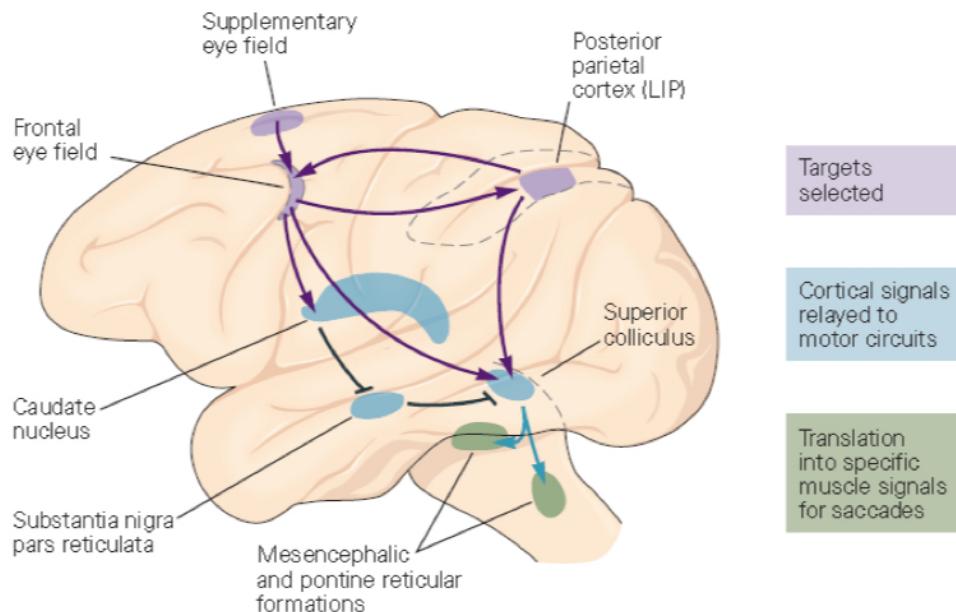
1. **Direct Excitatory Pathway (+)** The FEF sends direct excitatory signals to the SC, promoting the initiation of saccadic eye movements.
2. **Indirect Inhibitory Pathway (-) via the Caudate Nucleus** The FEF also influences the SC indirectly through the basal ganglia:
 - The **caudate nucleus** inhibits the **substantia nigra pars reticulata (SNr)**.

- The SNr normally inhibits the SC. By inhibiting the SNr, the caudate nucleus disinhibits (removes suppression from) the SC.
- This disinhibition allows the SC to execute saccadic eye movements.

3. Additional Input from the Posterior Parietal Cortex

- The posterior parietal cortex (LIP) also sends direct excitatory input to the superior colliculus, further influencing eye movement selection and execution.

A Monkey



Fact 88

Summary of Saccadic Eye Movement Pathways

- Higher cortical areas (**FEF, SEF, and LIP**) decide if and where to move the eyes.
- The **FEF projects to the SC** via:
 - A **direct excitatory pathway** that initiates eye movements.
 - An **indirect inhibitory pathway** through the **caudate nucleus**, which ultimately **removes inhibition from the SC**, enabling movement.
- The **SC integrates all inputs and sends commands to the saccade generator** in the brainstem, which executes the movement.

10.8 Head-Eye Coordination

Coordinated eye and head movements depend on the size of the gaze shift.

- Small gaze shift ⇒ In-sequence movements.

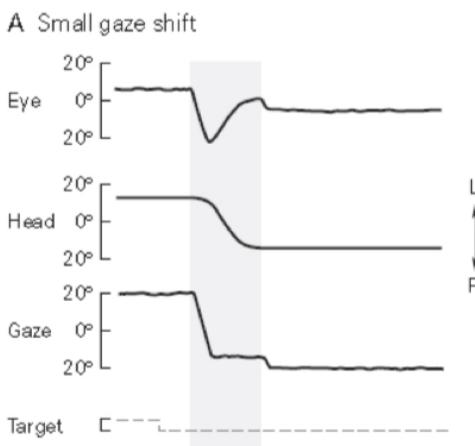
- Large gaze shift \Rightarrow Simultaneous movements.

Why?

- The eye muscles can move much faster (recall earlier) than the head and neck muscles.
- Small gaze shifts ($<20^\circ$): The eye alone can quickly reposition the gaze without needing head movement.
- Large gaze shifts ($>20^\circ$): The eye reaches its limit (orbital constraint), so the head must also move.

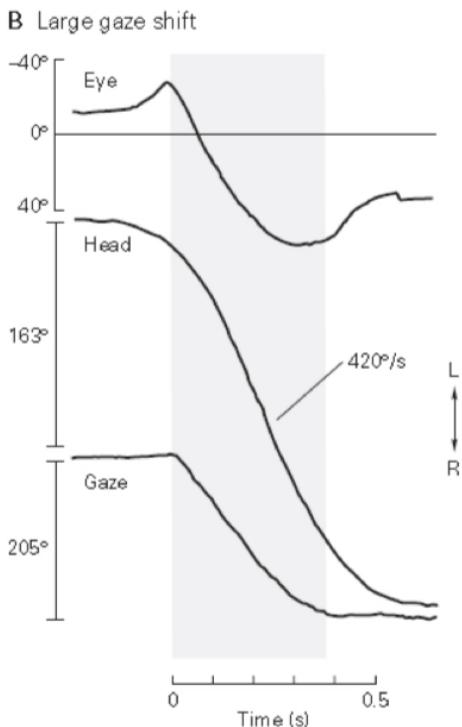
When interpreting the traces of both subfigures, remember that

- the gaze is always the sum of eye and head movements.
- in all cases, the gaze shift strategy is chosen so that the time during which there actually is relative motion between the eye and the environment (where gaze shift graph as non-zero gradient) is minimized – for a good reason:
 - During eye rotations, *efference copies* inhibit our visual perception.



Small Gaze Shifts

- For example, moving the position of a visual target.
- The eyes start moving first to bring the target into foveal vision.
- Once the primary visual axis is on target, the head starts moving.
 - Accompanied by eye movements in the opposite direction.
 - Results in stabilizing the target on the fovea.
- Small eye movement correction performed.



Large Gaze Shifts

- Simultaneous movement of eyes and head.
- The head starts moving towards the target.
- At first, the eyes counteract this movement to stabilize the gaze (cf. positional changes left to the shaded area).
- Then the eyes reverse the direction of motion and move in the same direction as the head (left edge of the grey area).
 - At this point in time, the gaze starts to shift (upper trace).
- Towards the end of the head movement, the eyes first remain still and then reverse direction, which

results in stabilizing the gaze again (upper trace).

11 Premotor and Motor Cortices

11.1 The Spinal Cord

- Sensory information enters the CNS through the dorsal roots.
- Activation of the muscles happens through the ventral roots.
- The central axons of the dorsal root ganglion cells form a neural map of the body surface when they terminate in the spinal cord.
 - This orderly somatotopic distribution of inputs from different portions of the body surface is maintained throughout the entire ascending somatosensory pathway.

11.2 Ascending Pathways

- Ascending pathways convey information to the brain from all modalities.
 - Relay structures (e.g., the thalamus) pass the information to cortical areas.
- Following integration, planning, and execution of motor action mainly take place in the premotor and motor cortices, respectively.
 - Population coding and **somatotopic maps** are key.

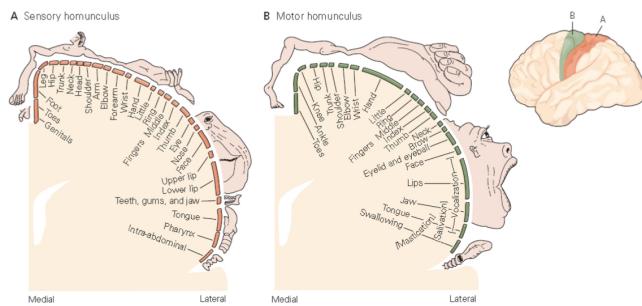
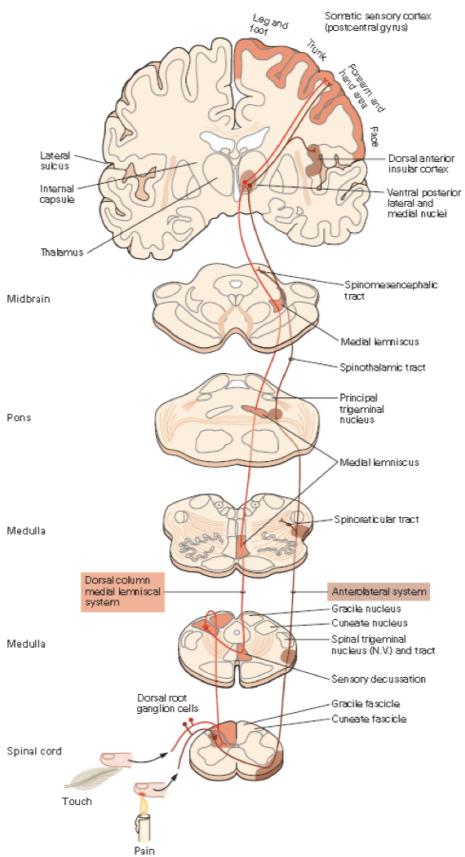


Figure 27: somatotopic map is the point-for-point correspondence of an area of the body to a specific point on the central nervous system

The major ascending pathway is:



1. Spinal cord

- (a) Dorsal root ganglion

2. Medulla

- (a) Sensory decussation
- (b) Medial lemniscus

3. Pons

- (a) Medial lemniscus

4. Midbrain

- (a) Medial lemniscus

5. Cerebral cortex

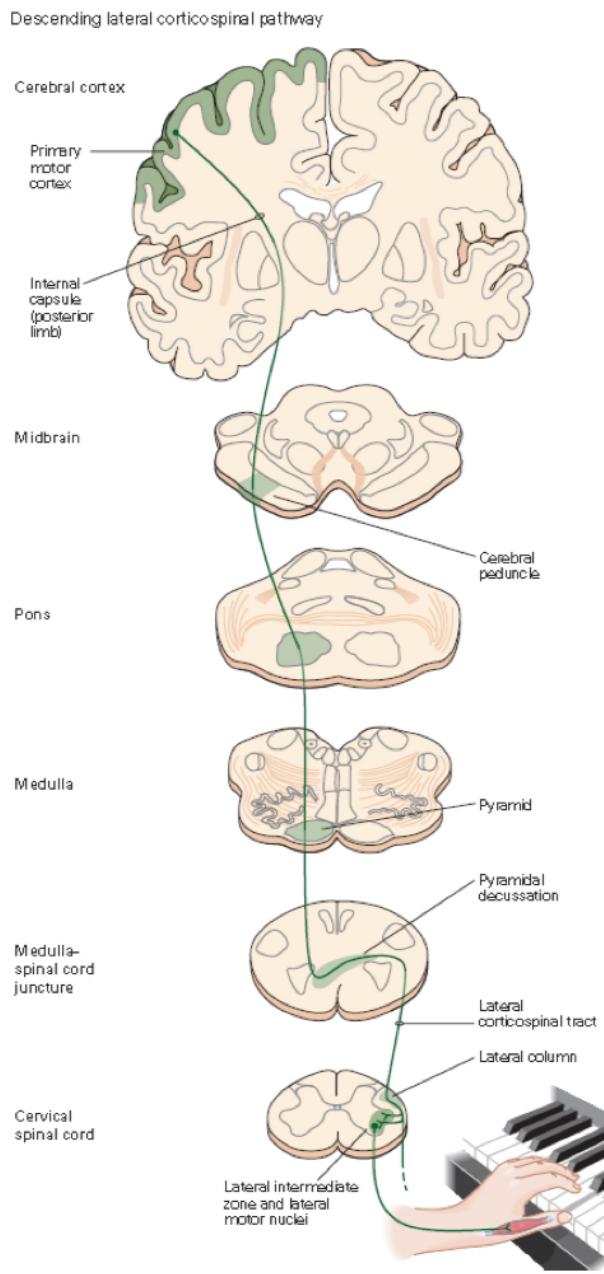
- (a) Thalamus
- (b) Somatosensory cortex

Figure 28: Caption

11.3 Cortical Processing

- Processing of sensory information at the cortical level occurs in several stages:
 - Primary sensory cortices
first stop for incoming sensory data.
 - Unimodal association cortices – single modality
process information from a single sensory modality
 - Multimodal association cortices – Combines sensory modalities
multiple sensory inputs are combined to create a more comprehensive perception.
- Information is processed in serial and parallel pathways from the dorsal root ganglia to the somatosensory cortex, to unimodal association areas, to multimodal association areas.

11.4 Descending Pathways



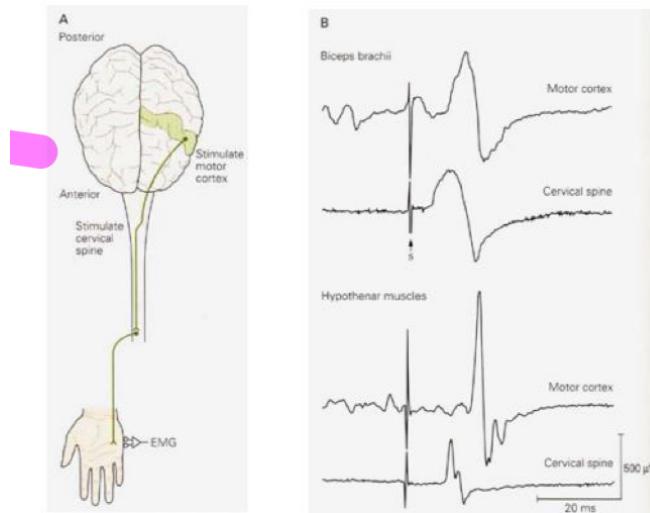
- Signals travel from the primary motor cortex via descending pathways to the spinal cord.
 - Axons of projection neurons (pyramidal tract neurons) originating from the motor cortex run all the way down to their respective spinal segments.
 - Pathway includes:
 - * Midbrain – cerebral peduncle
 - * Pons/medulla – pyramid
 - * Pyramid decussation
 - * Lateral corticospinal tract
 - * Lateral column
 - Connects to motor neurons in the ventral horn (lateral motor nuclei).
- Motor action **closes the behavioural “loop”** in that it results in a new set of sensory inputs, which is processed and finally modifies the behaviour again.
- There is **one synapse** between the motor cortex and the motor neurons in the spinal column(i.e directly sent there does no synapse anywhere in between)
 - Thus, modulation can only occur in the spinal cord or at the cortical level.
 - it cannot occur in the midbrain, pons, medulla

Figure 29: observe that the motor nuclei is at the bottom
the motor cortex is at the top

11.5 Transcranial Magnetic Stimulation

- Magnetic stimulation of the motor cortex and spinal cord induces EMG activity.
- TMS allows selective activation, **through the skull**(i.e non invasive activation), of projection neurons sending motor commands to the spinal motor neurons.

When Applied directly at the motor cortex level or at the spinal cord level such that in cases, the same projection neuron is activated.



- Stimulus causes an artifact in the EMG trace.
- In both cases, the stimulation at the motor cortex is followed by a deflection in the EMG after a longer delay compared to the delay observed for spinal stimulation.
- Reflects the different distances the signal travels from the stimulation site to the muscle.
- Cortical stimulation obviously takes longer to affect the muscles than spinal stimulation (since further than spinal)
- This method would be useful to diagnose at which level a spinal injury has occurred.

11.6 Spike-Triggered Averaging

- Also known as post-spike facilitation.
- Used to reveal the effect of **individual** cortical neurons on muscle activity.
- **Method:**
 - Spikes of a neuron in the motor cortex are recorded.
 - Simultaneously, the EMG of the wrist extensor is recorded.
 - The trace shows the cumulative EMG recording after the occurrence of a number of spikes.
 - * The cumulative average of EMG activity after 2000 spike-triggered EMG sections shows the effect of cortical neurons.
- **Findings:**
 - No facilitation occurs due to the spike from a single neuron
 - however large scale averaging of spike-triggered EMG recordings out to reduce Signal-to-noise ratios reveals the contribution of a single neuron to the EMG.
 - Small delay of 6ms between spike and deflection.

11.7 Neural Plasticity

- The somatotopic map in the motor cortex can be rearranged after damage.
 - Implications on recovering from brain lesions.

11.8 The Premotor Cortex

- Neurons in the premotor cortex are involved in planning movements.

Example 89

Monkey planning experiment

- Consider an experiment where a monkey has been trained to move its hand to an illuminated target only when a trigger signal is given.
 - Neuron recorded in the premotor cortex that spikes when movement to the left is needed.
 - Firing is suppressed when planning to move to the right.
- This occurs regardless of timing between illumination and trigger signal.
 - Stops firing after the trigger signal.

11.9 Population Vector – Encoding Limb Movement Direction

- Neurons in the motor cortex are broadly tuned to movements executed in their preferred directions.
 - Responds best in one direction but is inhibited in the other.
- Population of tuned neurons determines the direction of limb movement.
 - Black lines indicate activity of individual neurons.
 - Blue arrows give the population vector.
- The nervous system (NS) uses population vectors not only to encode the direction of movements at the motor level but also to encode sensory information.

11.10 Visuomotor Transformations

- Visually controlled reaching and grasping movements use different pathways, both of which originate in the primary visual cortex.
- **Reaching**
 - This pathway connects the primary visual cortex via the parieto-occipital extrastriate area (PO) with the dorsal premotor area (PMd).
 - Connections are:
 - * Direct

- * Through medial dorsal parietal (MDP) and medial intraparietal (MIP) areas.
- * Along this pathway, visual information in extrapersonal space is transformed into the direction of reaching movements.

- **Grasping**

- Projections of the primary visual cortex reach the dorsal extrastriate cortex (ES) and connect via the anterior intraparietal area (AIP) to the ventral premotor area (PMv).
- Conveys information about shape and other object properties into signals for planning appropriate grasping movements.

11.11 Major Control Pathways

- Major pathways involved in planning, execution, and control of voluntary movements.
 - Other sensory brain regions are omitted but contribute via the thalamus.
 - Motor commands are sent from the motor cortex via the pyramidal tract to the spinal cord.
 - Feedback loops involve the thalamus, the basal ganglia, the cerebellum, and other midbrain structures.
 - Fine-tuning of the pyramidal tract is achieved at the spinal cord level or via the basal ganglia, the cerebellum, and the thalamus, which project to the premotor and motor cortices.
 - The **final common pathway** at which motor commands can be modified is always at the motor neuron in the spinal cord.
- Descending pathways in green, feedback pathways in purple.

11.12 Ventral Premotor Area and Mirror Neurons

- Neurons in the PMv are active when the animal observes or performs a specific motor action.
 - For example, the same (mirror) neuron fires when a human/monkey is observed doing a motor action or if the monkey itself does it.
 - This has been interpreted as the neuron being involved with the abstract concept of the motor task.
 - **Control:** No activity for different motor actions.

12 Cerebellum and Motor Learning

12.1 The Cerebellum

- Comprises 10% of total brain volume but contains over 50% of the neurons.
- Attached to the pons of the brainstem.
- Highly folded cortex and accommodates half of the neurons of the entire brain.
- Cerebellum hemispheres are linked up by a structure called the vermis.

- Other structures are the primary fissure, the declive, the nodulus, and the lingula.
- The major neuron type is the Purkinje cell.

Functional Regions

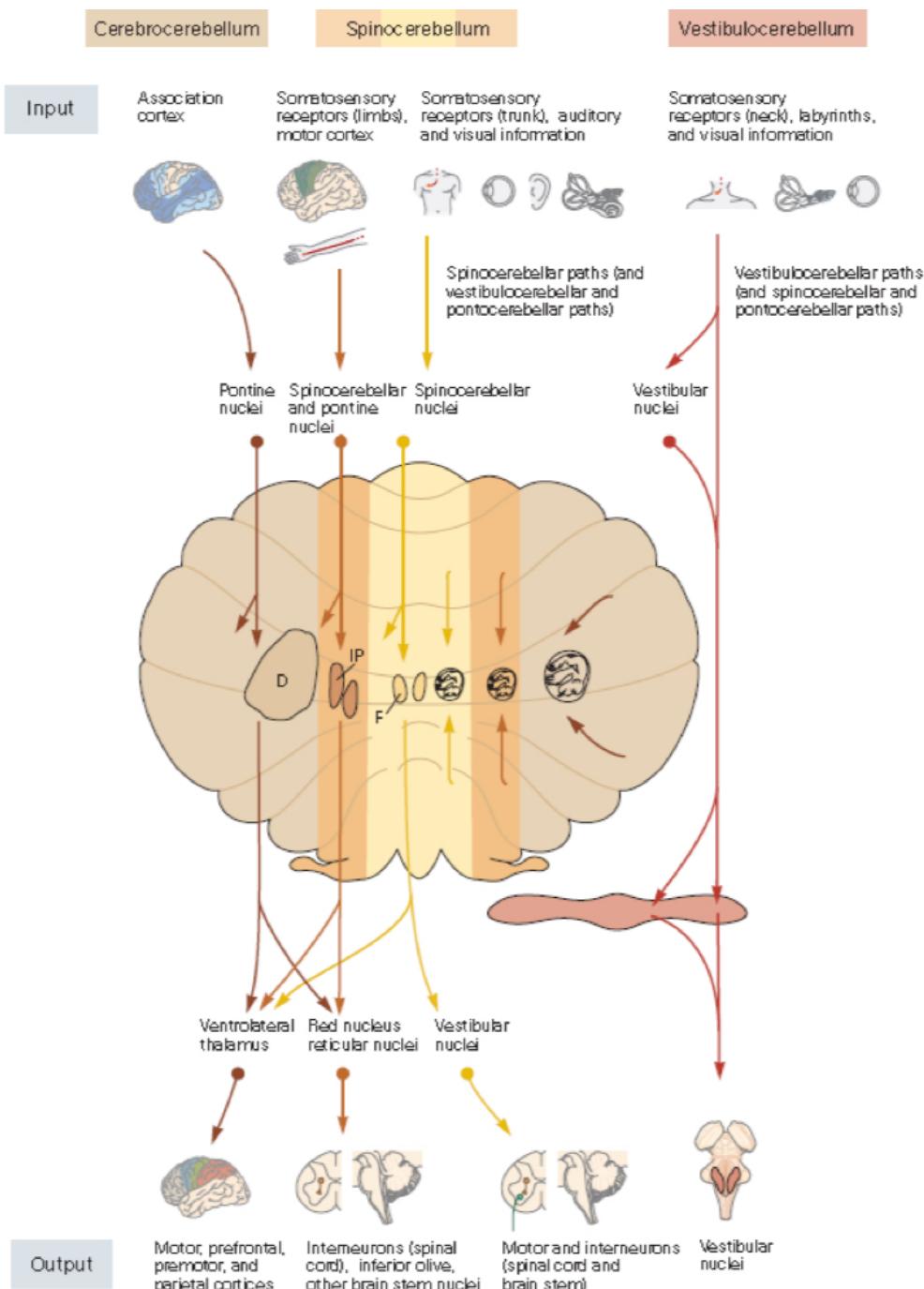


Figure 30: The three functional regions: (1)Cerebrocerebellum,(2)spinocerebellum,(3)vestibulocerebellum

Input-Output Organisation

- The figure shows the primary and secondary inputs to the cerebellum.

- Unspecific Purkinje cell input via mossy fibres.
- Specific Purkinje cell input via climbing fibres.

Mossy Fibres

- Originate from cell bodies in the spinal cord and brainstem and carry sensory information from the periphery as well as information from the cerebral cortex.
- Form excitatory synapses on the dendrites of granule cells in the granular layer.
 - Each granule cell receives inputs from just a few mossy fibres.
 - Granule cell axons distribute information widely from each mossy fibre to a large number of Purkinje cells.
- Mossy fibre input is highly convergent.
 - Each Purkinje neuron is contacted by axons from somewhere between 200,000 and 1 million granule cells.
- Encodes magnitude and duration of peripheral stimuli or centrally generated behaviours by controlling the firing rate of simple spikes in Purkinje cells.

Climbing Fibres

- Originate in the inferior olive nucleus and convey sensory information to the cerebellum from both the periphery and the cerebral cortex.
 - Each climbing fibre connects to 1 – 10 Purkinje neurons, but each Purkinje neuron receives input from a single fibre.
- Action potential in climbing fibre generates a protracted Ca^{2+} conductance in the soma and dendrites of the postsynaptic Purkinje cell.
 - Prolonged depolarisation with a complex spike.
- Seems specialised for event detection as firing rate carries little information.

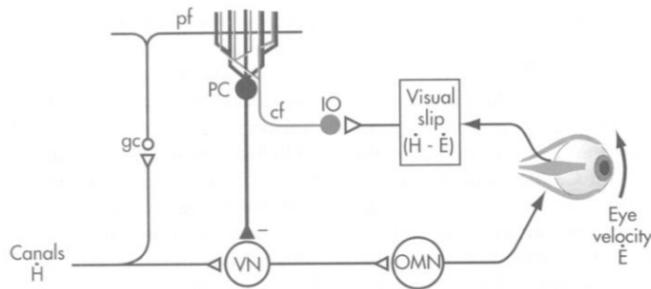
Lesions and Impairment

- Cerebellum lesions cause deficiencies in performing simple motor tasks.
 - Simple motor tasks need to be executed consciously.
 - Pre-programmed motor patterns can no longer run automatically.
- Cerebellum is involved in the fine-tuning of movements.
 - Cerebellum patients are still able to perform movements, but they have to concentrate hard to solve a given motor task.
 - Normally, a movement programme, if it has been learned before, is just initiated by a subject and then simply executed in an efficient (smooth) way under the control of the cerebellum.

Fractured Somatotopic Maps

- Several subdivisions of the cerebellum contain somatotopic maps.
 - Recordings from granule cells show that these maps differ from those in the motor and premotor cortices.
- The cerebellum maps are fractured and show multiple representations of the same body part in different locations.
 - E.g. parts around the mouth next to parts of the animal's paws.
- Indicates an arrangement which facilitates the control or fine-tuning of entire motor programmes that involve disjunct parts of the body.

12.2 Calibration of the VOR



- **Feedforward calibration of the VOR**
 - Cerebellum adjusts the efficiency of vestibular afferent signals.
 - Cerebellum adjusts the gain of the reflex by modulating the sensitivity of vestibular afferents.
 - Recall that closed-loop control does not work due to the mismatch between visual and vestibular reflex speeds.
 - Therefore, eye movements are feedforward calibrated.
- **Process**
 - Head movements in one direction activate semi-circular canals in the vestibular system and generate a signal that is relayed via the vestibular nucleus (VN) to the oculomotor nucleus (OMN).
 - Motor neurons drive the eye muscles which move the eye in the opposite direction with a velocity \dot{E} .
 - If there is visual slip between \dot{E} and head velocity \dot{H} , an error signal ($\dot{H} - \dot{E}$) is sent via climbing fibres from the inferior olive (IO) to the Purkinje cells (PC).
 - An afferent vestibular signal copy is conveyed to granule cells (gc) and thus to parallel fibres (pf), which arrive at Purkinje cell dendrites.
 - Purkinje cells inhibit the vestibular nucleus and allow adaptation of VOR by modulating signals sent to eye muscles.

12.3 Neural Plasticity: Long Term Potentiation

LTP is a key process underlying learning and memory. It involves the strengthening of synaptic connections through repeated stimulation, allowing neurons to communicate more effectively. This phenomenon is primarily mediated by NMDA (N-methyl-D-aspartate) glutamate receptors and other molecular mechanisms.

Role of NMDA and AMPA Receptors

- **Glutamate**, the major excitatory neurotransmitter in the CNS, plays a critical role in synaptic transmission.
- It binds to two key receptors:
 - **AMPA Receptors**: Ionotropic receptors that allow Na^+ and K^+ ions to pass when activated, leading to **fast excitatory synaptic transmission**.
 - **NMDA Receptors**: Normally blocked by Mg^{2+} ions, preventing ion flow.

Definition 90

In this context, sensitivity refers to for the same amount of stimulation(AP to CA3), the response(AP of CA1) is greater

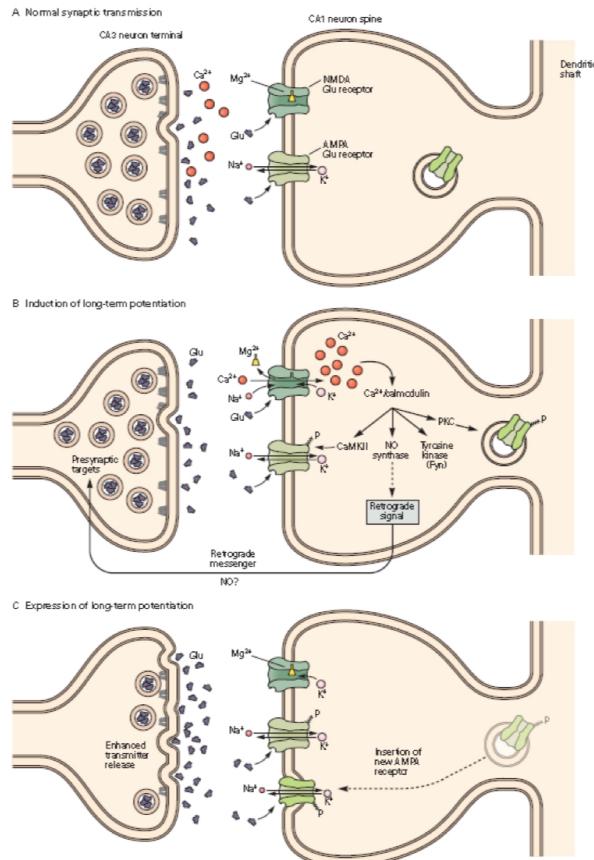
Phases of LTP

A. Normal Synaptic Transmission (Before LTP)

- When an action potential reaches the **CA3 neuron terminal**, glutamate is released into the synaptic cleft.
- Glutamate binds to **AMPA receptors**, allowing Na^+ influx and causing **a slight depolarization**.
- NMDA receptors **remain blocked** by Mg^{2+} , preventing Ca^{2+} entry.

B. Induction of LTP (Triggering Synaptic Strengthening)

- During **high-frequency stimulation**, repeated AMPA receptor activation causes sufficient **depolarization of the postsynaptic membrane**.
- This depolarization **removes the Mg^{2+} block** from NMDA receptors, allowing Ca^{2+} to enter.
- Increased Ca^{2+} **concentration** inside the spine activates key signaling pathways:
 - Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII)**: Phosphorylates AMPA receptors, increasing their sensitivity. Also activates some previously silent receptor channels
 - Protein Kinase C (PKC)** and **Tyrosine kinase (Fyn)**: Further modulate receptor function.
 - Metabotropic glutamate receptors (mGluRs)**: Trigger additional **calcium release from the endoplasmic reticulum (ER)**.



C. Expression of LTP (Long-Term Strengthening)

- Enhanced AMPA receptor function leads to:
 - More Na^+ entry**, causing a **stronger postsynaptic response**.
 - Insertion of new AMPA receptors** into the membrane, increasing synaptic efficiency.
- A **retrograde messenger**, likely **nitric oxide (NO)**, signals the **presynaptic neuron** to release **more glutamate**, strengthening communication.

Fact 91

In summary, Structural and Functional Effects of LTP:

- **Postsynaptic changes:**

- Increased sensitivity of AMPA receptors.
- Recruitment of silent synapses (previously inactive receptors become functional).

- **Presynaptic changes:**

- NO retrograde signaling increases neurotransmitter release.

- **Anatomical modifications:**

- Formation of **new synaptic spines** and **presynaptic terminals**, enhancing connectivity.

12.4 Role of Cerebellum in Motor Learning

- The cerebellum is involved in the acquisition, modification, and execution of motor programmes.

David Marr's Model (1970s)

- Assumed that motor programmes are learned in a sequence of steps.

- First requires conscious performance of movements involved in a certain motor task.
- After repeating the sequence of movements many times, eventually the cerebellum runs the motor program on its own.

- **Idea**

- Movements always generate sensory feedback.
- Sensory feedback, caused by a given movement, coincides with initiating the subsequent movement.
 - * This again causes sensory feedback that is associated with the next part of a movement sequence.
- A sequence of coincident sensory feedback and movements is created that includes the whole motor programme, always associating sensory feedback with the next consecutive part of the movement sequence.

Example 92

Execution: Playing a Scale

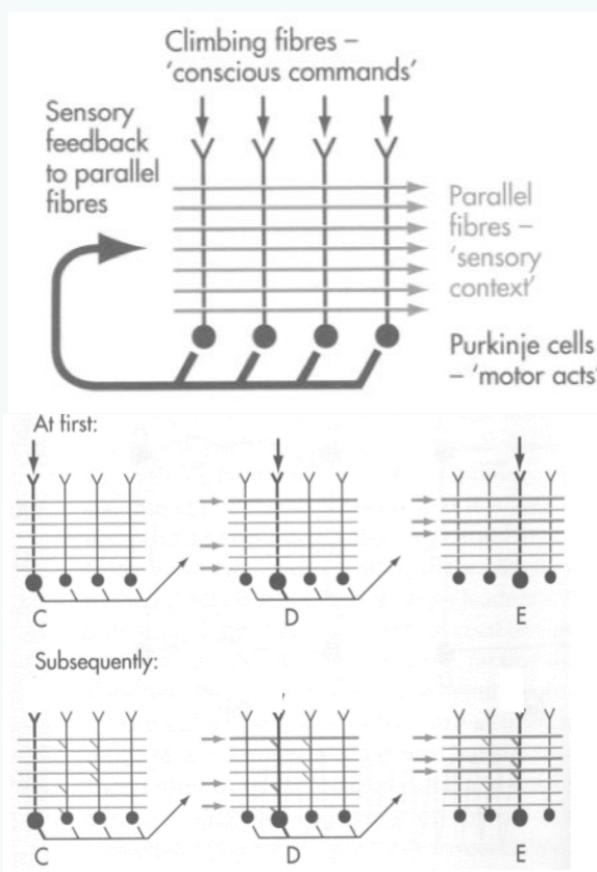


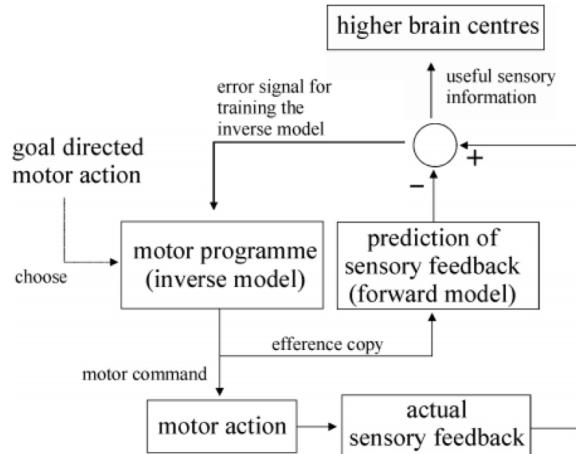
Figure 31: the playing of C,D,E becomes automatic now that the parallel fibres are strengthened. So say signal for C can automatically go to D then E without needing a new additional signal for each note

- Conscious command activates a particular Purkinje cell via the climbing fibre input, which in turn, causes one finger to play a C.
- The sensory feedback, mediated by the parallel fibre system, that may include mechanosensory, acoustic, and visual information, coincides with the activity of another Purkinje cell as we play the next note using a different finger.
- Again, by playing the note, the resulting sensory feedback will be associated with the activity in a third Purkinje cell, which initiates playing the third note.
 - Coincident activity of the Purkinje cell and parallel fibres increases the synaptic efficacy between those two cells.
- As the sequence is repeated, the synaptic transmission of the parallel fibres may become strong enough to activate the Purkinje cell even without the conscious command, and thus the next note will be played 'automatically'.
- A conscious command will only be required to start the execution of the entire sequence.

Modification of Motor Programmes

- Ballistic motor movements are pre-programmed and cannot be easily modified using feedback control once executed.
 - Analysis and modification can only occur after execution.
- Visual change (e.g. prism glasses) disrupts the motor programme as inputs do not align.
 - The programme eventually adapts as the person actively adjusts.
- This is due to neural plasticity.

12.5 Conceptual Model for Fine-Tuning Motor Action



- **Process**

- When we decide to perform a task, we choose one from a pool of available motor programmes, giving an "**inverse model**" for the appropriate motor action.
 - * This programme is executed and produces a generally predictable outcome.
- An efference copy of motor commands is sent to generate a prediction of sensory consequences.
 - * This is known as the "**forward model**".
- Motor action generates actual sensory feedback, which is subtracted from the forward model.
 - * Differences are used as an error signal for recalibration at higher brain centres.
- Physical implementation is unknown except in electric fish.

13 The Skeletal System

- Consists of bones, joints, cartilage, and ligaments.
- The adult body contains 206 bones.
- Axial skeleton – central bones (skull, vertebral column, rib cage).
- Appendicular skeleton – pelvic, pectoral girdle, and limbs.

Functions

1. Support soft tissue and provide sites of attachment for skeletal muscles.
2. Movement and posture.
3. Protection of internal tissue.
4. Storage of minerals – esp. Ca^{2+} and P.
5. Red bone marrow – in the skull, pelvis, and ribs, produces blood cells.
6. Yellow bone marrow – "chemical energy" stored as triglycerides.

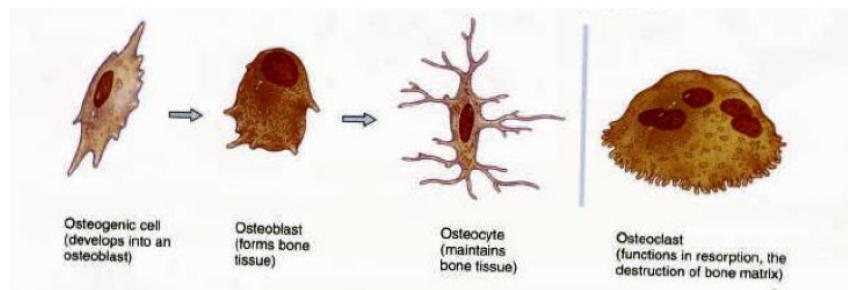
Composition and Types of Bone

- Bone contains 60% minerals and 40% collagen.

- Contains hydroxyapatite, $CaCO_3$, and some Mg , Na , K , fluoride, and sulfate.
- Allows it to be hard/stable without being brittle.

Flat	Long	Short	Irregular
Skull, ribs	Arms, legs	Wrist, ankle	Vertebra
Protection of soft tissue Sandwich design	Structural support	Large range of movement	Irregular shape with projections for attachment of muscles, tendons, and ligaments

Histology of Bone



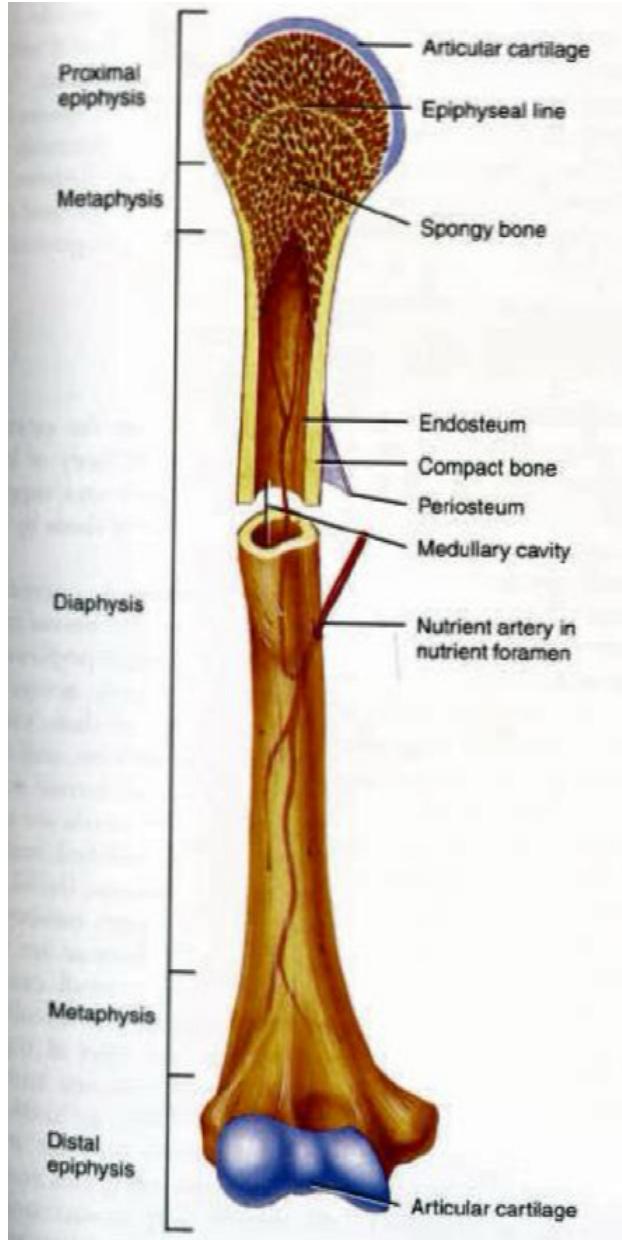
Question 93. what the functions of these 4 bone cells

- **Osteogenic (Osteoprogenitor) Cells**
 - Mitotic.
 - Found in the periosteum and endosteum.
- **Osteoblasts**
 - Non-mitotic.
 - Build bone.
 - Collagen → ossification(build bone tissue)
- **Osteocytes**
 - Non-mitotic.
 - Maintain bone.
- **Osteoclasts**
 - Fused monocytes(type of white blood cells).
 - Multinuclear.
 - Destroy bone using enzymes and (citric/lactic) acids.

13.1 Long Bone Structure

- Long bone is structured so that the ends consist of spongy bone, and the shaft (diaphysis) consists of compact bone.

Question 94. what are the 3 main components of the long bone giving their relative locations and functions



Compact Bone

- Hard, dense layer of bone.
- Osteocytes reside in lacunae, which contain protein fibres and mineral deposits.
- contains **Haversian system**: System of canals allows blood vessels to pass through the bone, ensuring circulation.

Spongy Bone

- Strong but light, reducing overall bone weight.
- Contains osteocytes.
- Many **trabeculae**, plate-like structures that follow stress lines in bone.
 - Act like braces and provide support to the bone.

Marrow

- Along the **diaphysis** (the shaft), compact bone surrounds a hollow centre called the **medullary cavity**.
- This cavity contains the bone marrow.
 - In the red marrow, a process called **haematopoiesis** forms blood cells.
 - Yellow marrow functions as fat storage.

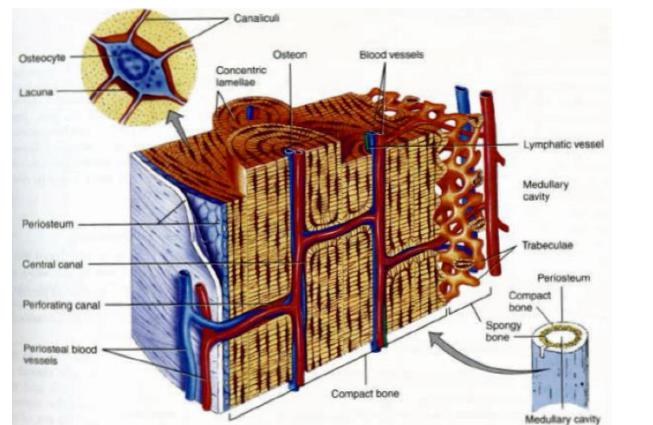


Figure 32: Cross section compact bone: harvesian system

Layers

- **Endosteum**

- Thin layer of connective tissue that lines the surface of bony tissue, forming the medullary cavity.
(i.e inner layer of compact bone see above figure)
- Reabsorbed when malnourished.

- **Periosteum**

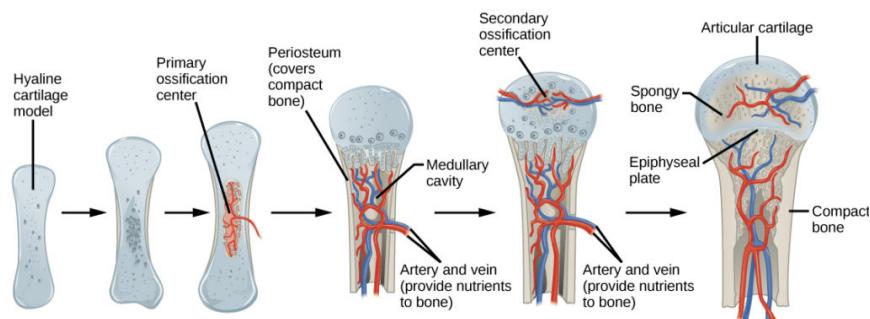
- Lines the outer surface of the bone.
(i.e outer layer of compact bone see above figure)
- Continuous with ligaments/tendons connecting to muscles.
- Blood vessels pass from the periosteum into the bone, providing nutrients, O_2 , removing waste, and transporting newly created blood cells out.

13.2 Bone Growth

Fact 95

Bones of children and young adults grow due to hormonal influence.

- Length increase – New bone matrix is continuously added to the outer surface of the bone by osteoblasts and removal from inside.
- End growth mechanism based on the epiphyseal plate.
 - Mass of osteoblasts which lay down collagen to which bone minerals are adsorbed.
- After a growth spurt, the epiphyseal plate degenerates, and the length of long bones becomes static.



1. Hyaline Cartilage Model

- **Starting Tissue:** A small “template” of hyaline cartilage forms the earliest version of the bone.
- **Purpose:** This cartilage model provides a shape and framework for subsequent bone development.

2. Primary Ossification Center (in the Diaphysis)

- **Bone Collar Formation:** Osteoblasts in the outer layer (periosteum) begin producing a thin layer of bone around the cartilage shaft, known as the “bone collar.”

- **Central Cartilage Degeneration:** As the bone collar cuts off some of the cartilage's nutrient supply, the cartilage cells (chondrocytes) in the center die, leaving cavities.
- **Invasion of Blood Vessels:** Blood vessels grow into these cavities, bringing osteoblasts and osteoclasts.
- **Osteoblast Activity:** Osteoblasts lay down new bone matrix, gradually converting the cartilage "model" into actual bone tissue.

3. Periosteum and Medullary Cavity

- **Periosteum:** The outer connective tissue membrane that develops around the diaphysis, housing osteogenic cells and nerves/blood vessels.
- **Medullary (Marrow) Cavity:** Osteoclasts (bone-resorbing cells) carve out a central cavity in the diaphysis, which will eventually house bone marrow.

4. Secondary Ossification Centers (in the Epiphyses)

- **Formation in Bone Ends:** Similar processes occur at the epiphyses (the ends of the bone), forming secondary ossification centers.
- **Spongy Bone Development:** In these areas, spongy (trabecular) bone forms, while hyaline cartilage remains on the outer surfaces to become articular cartilage (covering joint surfaces).

5. Role of the Epiphyseal (Growth) Plate

- **Location:** Between the primary ossification center (diaphysis) and each secondary center (epiphysis), a thin plate of hyaline cartilage remains. This is the epiphyseal plate or growth plate.
- **Mechanism of Growth:**
 - *Chondrocyte Proliferation:* Cartilage cells within the epiphyseal plate multiply and stack up, pushing the epiphysis away from the diaphysis, effectively lengthening the bone.
 - *Cartilage Replacement:* The older cartilage cells closer to the diaphysis begin to die, and osteoblasts replace this cartilage with bone tissue.
 - *Continuous Process:* As long as the plate remains active (open), the bone can continue to grow in length.

6. Maturation and Closure of the Epiphyseal Plate

- **Hormonal Influences:** During adolescence, hormones (e.g., estrogen, testosterone) accelerate both cartilage growth and bone replacement.
- However Sex hormones also trigger signaling pathways that push chondrocytes(responsible for cartilage growth) toward maturity and eventual death (hypertrophy), shortening the lifespan of the growth plate
- **Epiphyseal Fusion:** Eventually, the rate of cartilage growth slows, relative to bone formation continues, leading to the "closing" of the growth plates(thinning of cartilage layer as it is replaced by bone)
- **Epiphyseal Line:** Once fully ossified, the plate becomes a thin epiphyseal line—no further lengthwise growth is possible at this point.

Foetal Growth

- Bones in a foetus are first formed from cartilage.

- Mineral salts such as calcium are deposited, and the bone becomes calcified in the process of ossification.
 - Ossification starts in the middle of the bone(yep recall primary ossification centre)
 - Osteoblasts continue to calcify cartilage cells.
 - As a child grows, osteocytes (mature bone cells) replace the osteoblasts.

13.3 Bone Remodelling and Repair

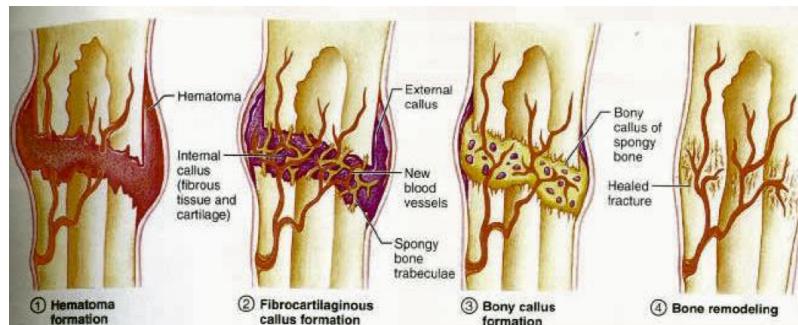
- All bones in the body are replaced every three years.
 - Bone is a living tissue with cells that age and die.
- Bone responds to stresses placed on it.
 - Weight-bearing exercises increase bone strength.
 - Disuse leads to osteoporosis.
 - Worst in aging women due to hormones.
- During remodelling, osteoclasts destroy bone while osteoblasts rebuild it.
 - 5% of the skeleton is recycled per week.

Requirements

Mineral/Ion	Use	Deficiency
Ca, P	Matrix	Soft bone
Mg	Osteoblast activity	Stunting
Vit. A	Osteoblast activity	Stunting
Vit. C	Matrix, collagen synthesis	Retarded growth and repair
Vit. D	↑ Ca absorption from gut	Retarded growth, soft bones, rickets, and osteomalacia

Pre-puberty	Puberty	Adults
<ul style="list-style-type: none"> Human growth hormone - anterior pituitary Insulin-like growth hormone – bone, liver Over secretion – gigantism Under secretion – dwarfism 	<ul style="list-style-type: none"> Oestrogens (ovaries), androgens (testes and adrenals) 	<ul style="list-style-type: none"> Insulin Thyroid hormones Human growth hormone - over secretion acromegaly

Bone Repair Mechanism



Question 96. describe this process

1. A hematoma (blood clot) forms, and the area swells up.
 - This happens very fast, nearly instantaneously.
2. Collagen fibres begin to connect the pieces of bone inside the internal callus.
 - New blood vessels grow into the area, which allows all the nutrients, proteins, and O_2 to enter the internal callus for repair and helps remove waste products.
 - This process lasts for hours to days.
3. Osteoblasts create spongy bone with trabeculae; this area of spongy bone is called a bony callus.
 - By now, the hematoma is reabsorbed, and the bone is solid.
 - This stage of the repair can last from several days to a few weeks.
4. Lastly, the new compact bone is formed.
 - Osteoclasts reabsorb the spongy bone, and a new medullary cavity is formed.

13.4 Calcium Regulation

- Calcium is needed for normal nerve, muscle, and cardiac function, blood clotting, enzymes, etc.(see more later in role of calcium)
- The Calcium concentration needs to be very tightly controlled because:
 - If the Calcium concentration is too high, it results in non-responsiveness of nerves and abnormal Ca deposits.
 - If the Calcium concentration is too low, it results in hyper-excitable nerves.

13.5 Bone Marrow Function

Red Marrow

- Haematopoiesis: Forms all blood cells except lymphocytes.
- In infants, nearly all marrow is red.

- Resides in the medullary cavity and spongy bones of long bones and in flat, short, and irregular bones.
- In adults, only in the spongy bones of long bones and in flat, short, and irregular bones.

Yellow Marrow

- Fat storage.
- Can turn into red marrow in case of extreme blood loss.
- In adults, it is located in the medullary cavity of long bones.

13.6 Anatomy of Various Bones

The Skull

- Sutures in baby heads are moveable to allow the head to deform during birth.
- The main function is to protect the brain.
- Foramen occur in bones where nerves must pass through the bone.

The Spinal Column

- Functions of the spine include articulation, protection, vertical support, and providing attachment points for muscles.
- Curvature helps to absorb shock and vibrations caused by walking.
- Intervertebral discs have the same function and allow the vertebrae to move against each other without friction.

Rib Cage

- Protects important inner organs like the heart and lungs and serves as attachment points for muscles.
 - E.g. intercostal muscles that allow us to breathe.

Pectoral and Pelvic Girdle

- Attachment points and support structures for the limbs.
- Hips are wider in females due to the requirements for birth.
- In adults, the shoulder blades and the hips are involved in haematopoiesis.

The Limbs

- Consist of long bones, with the hands and feet mainly composed of irregular bones.
- Limbs need to be sturdy and light.
 - Hollow centres of the shaft and sturdy.
 - Light spongy bone at the ends of the long bones.
 - Hard, solid, and sturdy compact bone that forms the outer wall of the shaft.

13.7 Joints

- Connections between bones.
 - Can be immobile or articulated.
 - Contain connective tissue or cartilage.

Types of Joints

- **Fibrous** – Held together by tough connective tissue.
 - Suture (seam, skull).
 - Syndesmosis (greater separations).
 - Gomphosis (nail or teeth).
- **Cartilaginous** – Fusion of cartilage on ends of bones.
 - Slightly moveable.
- **Synovial joint**
 - Highly moveable, low friction.
 - Articular cartilage held in place by ligaments.

14 Skeletal muscle

Introduction to Muscles

	Skeletal Muscle	Smooth Muscle	Cardiac Muscle
Overview	<ul style="list-style-type: none">• Attached to bones in legs, arms, and torso• Controlled by NS• Multinucleated, striated, and cylindrical	<ul style="list-style-type: none">• Found in hollow organs (e.g., intestines, stomach, bladder)• Involuntary contractions• Fibres are uninucleated, spindle-shaped, and form sheets	<ul style="list-style-type: none">• Found in heart wall• Cannot fatigue• Involuntary• Fibres are uninucleated, striated, cylindrical, and branched
Function	<ul style="list-style-type: none">• Holds skeleton together• Acts against gravity• Enables movement• Maintains body temperature	<ul style="list-style-type: none">• Digestion and waste removal• Controls blood flow	<ul style="list-style-type: none">• Pumps blood

Skeletal Muscle Anatomy

Transverse Section

- **Subcutaneous fat layer**

- Pathway for blood vessels and nerves before they divide and enter the muscles.

- **Fascia**

- Tough connective tissue layer holding all muscle elements together.

- **Muscle Structure**

- Muscle
 - Fascicle
 - Muscle fibre (the cell)
 - Myofibril – structural unit of cells
 - Sarcomere – active motor units

14.1 The Muscle Fibre and Myofibrils

Each fibre is surrounded by a cell surface membrane called the sarcolemma.

- Bits of the sarcolemma fold inwards across the fibre and stick into the sarcoplasm.
- These folds are called transverse (T) tubules.
- These help to spread electrical impulses throughout the sarcoplasm so they reach all the parts of the muscle fibre.

Muscle cell cytoplasm is known as the sarcoplasm and contains organelles including:

- Many mitochondria.
 - To provide the ATP needed for contraction.
- Extensive sarcoplasmic reticulum (a specialised ER).
 - This stores and releases the calcium ions needed for contraction.

- A number of myofibrils.

Myofibrils are the contractile elements.

- Each consists of smaller contractile units called sarcomeres.
- Two types of protein myofilaments – thin actin and thick myosin.

Sarcomere

Myofibrils contain bundles of thick and thin myofilaments that move past each other to make muscles contract.

Thick myofilaments are made up of myosin.

- Each molecule consists of a tail and two protruding heads that can bind to a site on actin.

Thin myofilaments are made up of actin.

- Mainly of two strands of F actin made up of G actin subunits.
- Tropomyosin (rod-shaped protein) molecules coil around this, reinforcing it.
- A troponin complex is attached to each tropomyosin molecule.
 - Troponin consists of three polypeptides:
 - * One that binds to actin.
 - * One that binds to tropomyosin.
 - * One that binds to Ca^{2+} .

A myofibril contains a pattern of alternating dark and light bands.

- Dark bands contain thick myosin filaments and some overlapping actin.
 - These are known as A-bands.
- Light bands contain thin actin filaments only.
 - These are called I-bands.

The ends of each sarcomere are marked with a Z-line.

The middle of each sarcomere/myosin is the M-line.

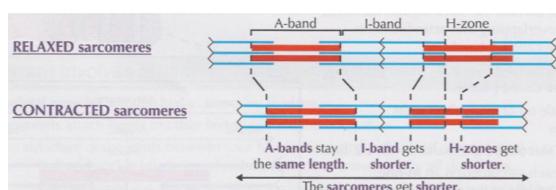
Around the M-line is the H-zone.

- The H-zone only contains myosin filaments.

Cross sections of myofibrils show the hexagonal organisation of actin and myosin filaments.

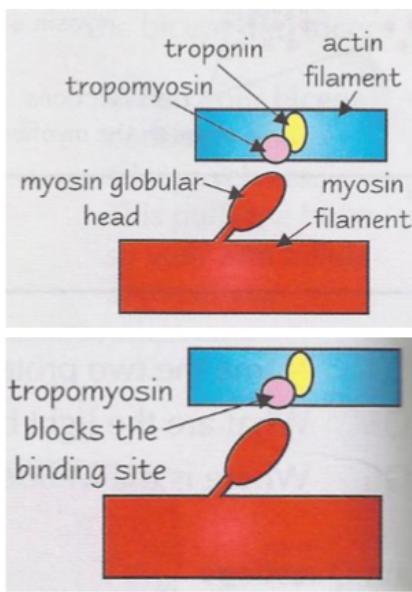
14.2 Sliding Filament Theory of Muscular Contraction

Muscle contraction is explained by the sliding filament theory.



- Myosin and actin filaments slide over one another to make the sarcomeres contract – the myofilaments themselves don't contract.
- The simultaneous contraction of lots of sarcomeres means the myofibrils and muscle fibres contract.
- Sarcomeres return to their original length as the muscle relaxes.

Binding Sites and Blocking



Myosin filaments have globular heads that are hinged, so they can move back and forth.

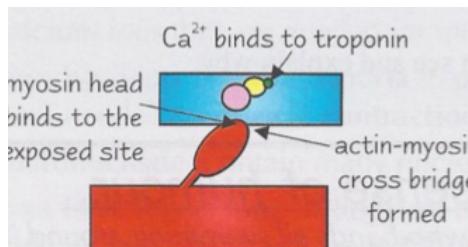
- Each myosin head has a binding site for actin and a binding site for ATP.
- Actin filaments have binding sites for myosin heads, called actin-myosin binding sites.
- Tropomyosin and troponin are found between actin filaments.
 - These help the myofilaments move past each other.

In resting (unstimulated) muscle, the actin-myosin binding site is blocked by tropomyosin, which is held there by troponin.

- So myofilaments can't slide past each other because the myosin heads can't bind to the actin-myosin binding site on the actin filaments.

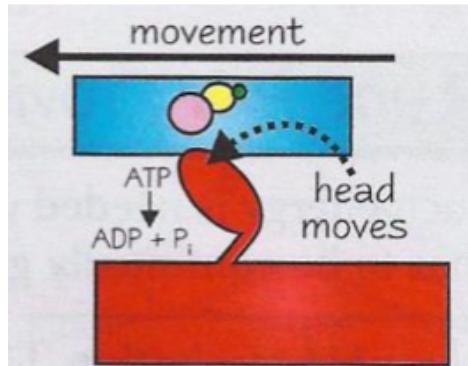
Contraction

1. The action potential triggers an influx of calcium ions



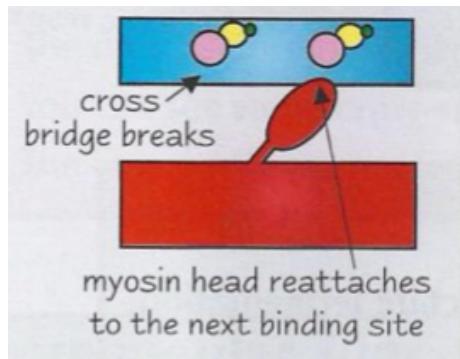
- When an action potential from a motor neurone stimulates a muscle cell, it depolarises the sarcolemma, causing depolarisation to spread down the T-tubules to the sarcoplasmic reticulum.
- This causes the SR to release stored calcium ions into the sarcoplasm.
- Calcium ions bind to troponin, causing it to change shape.
 - This pulls tropomyosin out of the actin-myosin binding site.
 - This exposes the binding site, which allows the myosin head to bind.
 - The bond formed when a myosin head binds to an actin filament is called an actin-myosin cross-bridge.

2. ATP provides the energy needed to move the myosin head in the power stroke



- Calcium ions activate ATPase, which breaks down $\text{ATP} \rightarrow \text{ADP} + \text{P}_i$ to provide the energy needed for muscle contraction.
- The energy released causes the myosin head group to bend, causing the actin filament to be pulled along and so overlap more with the myosin.
- This is the power stroke.

3. ATP is also used to break the cross bridge



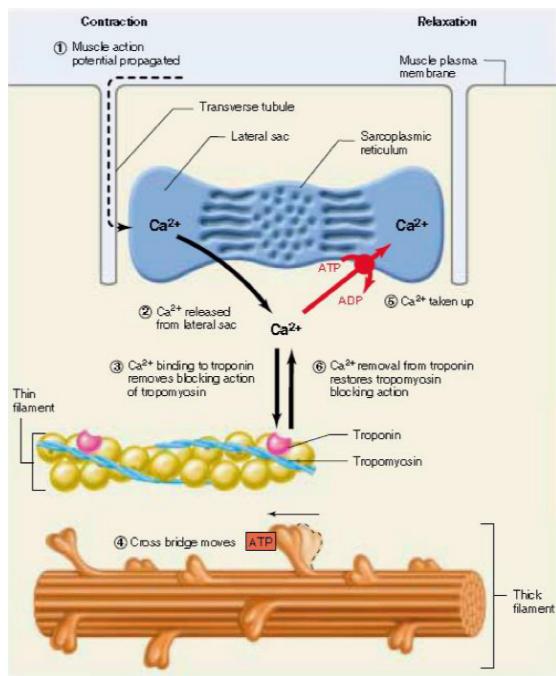
- ATP provides the energy to break the actin-myosin cross bridge, so the myosin head detaches from the actin filament after it has moved.
 - The head also bends back to its original position, becoming cocked.
- The myosin head then reattaches to a different binding site further along the actin filament.
 - A new actin-myosin cross bridge is formed and the cycle is repeated.
 - * Attach, move, detach, reattach to a new site.
- Many cross bridges form and break very rapidly, pulling the actin filament along.
 - This shortens the sarcomere, causing the muscle to contract.
- The cycle will continue as long as calcium ions are present and bound to troponin.

Termination

- When excitation stops, calcium ions leave binding sites on the troponin.

- They are moved by active transport back into the sarcoplasmic reticulum.
- The troponin molecules return to their original shape, pulling the attached tropomyosin molecules with them.
 - Tropomyosin molecules once again block the actin-myosin binding sites.
- Muscles aren't contracted as no myosin heads are attached to actin filaments, so there are no actin-myosin cross bridges.
- The actin filaments slide back to their relaxed position, which lengthens the sarcomere.

Role of Calcium



- Calcium is needed because it binds to troponin and moves the troponin-tropomyosin complex to expose the myosin binding sites on the actin fibres.
 - Without calcium, myosin cannot bind to actin.
- The membranes of the sarcoplasmic reticulum contain primary active-transport proteins, Ca-ATPases, that pump calcium ions from the cytosol back into the lumen of the reticulum.
 - Calcium is released from the reticulum upon arrival of an action potential in the T tubule, but the pumping of the released calcium back into the reticulum requires a much longer time.
 - Cytosolic calcium concentration remains elevated, and the contraction continues for some time after a single action potential.

14.3 Energy for Muscle Activity

A lot of ATP is required for muscle contraction, so it must be **continually generated to keep up with demand**.

- This happens by three main mechanisms.

Aerobic Respiration

Most ATP is **generated by oxidative phosphorylation** in the cell's mitochondria.

- Aerobic respiration needs **oxygen**, so it's good for long periods of low-intensity exercise.
- **Dependent on availability of oxygen and respiratory substrate**
 - Supply up-regulated for continuous activity.

Blood Supply Regulation

Large amounts of O_2 and glucose need to be delivered, while CO_2 , lactate, and other waste products need to be transported away during exercise.

- A large blood supply all the time would not be good.
 - Therefore, many blood vessels exist, but the arterioles are constricted at rest to reduce the blood supply.
- The muscular vasculature has highly developed metabolic autoregulatory activity.
 - Arteriolar dilatation occurs in the presence of low O_2 , high CO_2 , low pH, etc.

Anaerobic Respiration

Anaerobic respiration occurs in the muscle cell sarcoplasm via **glycolysis**.

- The process is quite quick.
- However, it **produces lactic acid, which is toxic**.
 - This can build up in muscles and cause fatigue.
- **Good for short periods of hard exercise (30-40 seconds)**
 - Builds up an oxygen debt that must be repaid.

ATP-Phosphocreatine (PCr) System

Transfer from creatine phosphate (PCr) in the sarcoplasm.

- **Phosphate group from PCr is transferred to ADP to form ATP very quickly** by the action of **creatine phosphotransferase**.

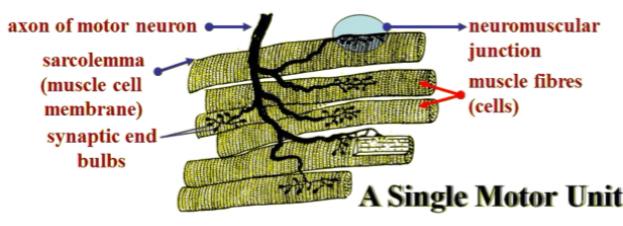
Sufficient PCr exists to support contraction for 15 seconds.

- Suitable for short bursts of vigorous exercise.

Anaerobic and doesn't produce lactate acid.

14.4 Control of Contraction

Muscle tissue is innervated by many motor neurons.



- Each motor neuron innervates a group of muscle fibres ranging from as few as 2 to as many as 2000 fibres.

A single motor neuron and the muscle fibres it stimulates make up a single motor unit.

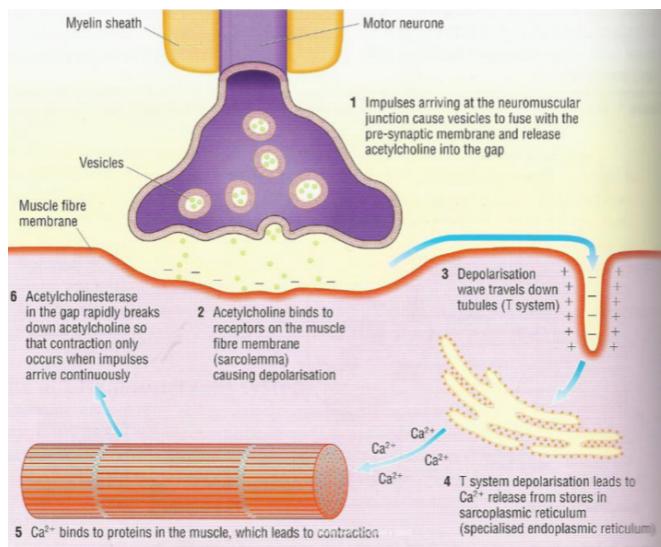
The area of contact between the synaptic end bulbs of a motor neuron and the sarcolemma is the neuromuscular junction.

Some muscular movement requires a stronger contraction than others.

- Many motor neurons stimulate a single muscle.
- Each motor neurone branches to many neuromuscular junctions.
- The brain can stimulate more motor units, so making more muscle fibres contract, which leads to a greater force of contraction.
- This is known as **graduation of response**.

14.5 Neuromuscular Junctions

The neuromuscular junction is the contact point between a motor neuron and a skeletal muscle cell.



Neuromuscular junctions are similar to synapses in how they work:

1. An arriving action potential (AP) causes voltage-gated calcium channels to open.
2. Calcium enters the synaptic knob and binds to acetylcholine vesicles, causing their exocytosis.
3. Acetylcholine then binds to receptors on the sarcolemma, causing depolarisation. (specifically it opens ligand-gated ion channels, allowing Na^+ to enter)
4. This triggers an AP that self-propagates across the sarcolemma surface in both directions.
5. The depolarisation spreads inwards through the transverse tubules, causing depolarisation of the sarcoplasmic reticulum and the release of calcium ions.
6. The Ca^{2+} binds to proteins in the muscle leading to contraction (recall the sliding filament theory earlier)
7. Following the generation and spread of the muscle AP, the enzyme acetylcholinesterase is activated.
 - This is located in clefts within the sarcolemma. Acetylcholinesterase splits the acetylcholine molecules into acetate and choline.
 - Acetate and choline molecules are reabsorbed by the synaptic knob where they are resynthesised into acetylcholine molecules.
 - Mitochondria in the synaptic knob provide the energy required for resynthesis of acetylcholine molecules.

8. No further contraction of the muscle fibre occurs until a new nerve impulse arrives at the neuromuscular junction.

Energy from ATP is used to pump calcium ions back into the sarcoplasmic reticulum.

Comparison with Synapses

	Neuromuscular Junction	Synapse
Postsynaptic membrane	Cell surface membrane/sarcolemma of a muscle	Cell surface membrane of a neuron
Neurotransmitter	Acetylcholine for skeletal muscle	May be acetylcholine, norepinephrine, glutamate or another transmitter
Different postsynaptic receptors		
Receptors	More postsynaptic receptors	Fewer postsynaptic receptors
Depolarisation	Depolarisation of postsynaptic membrane is stimulatory	Depolarisation of postsynaptic membrane may be stimulatory or inhibitory
Membrane Structure	Postsynaptic membrane has clefts containing AChE	Postsynaptic membrane is smooth
Neurotransmitter Breakdown	Neurotransmitter broken down by AChE	Neurotransmitter broken down by various means
In both, neurotransmitter is secreted, diffuses across a cleft, binds to receptors in the postsynaptic membrane and is finally broken down .		

14.6 Contraction Terminology

Isotonic and Isometric Contraction

Contraction does not always mean that the muscle shortens, it just means that a force is generated.

Isotonic contractions – result in movement.

- Concentric contraction – lifting a cup.
- Eccentric contraction – lowering a weight slowly and carefully.

In a concentric contraction, the muscle tension rises to meet the resistance then remains stable as the muscle shortens.

During eccentric contraction, the muscle lengthens as the resistance becomes greater than the force the muscle is producing.

Remark 97. *Although the muscle is lengthening, it is still named eccentric "contraction" in a sense the muscle is still actively trying to oppose the extension by producing contractile forces. Think of it as a spring.*

Isometric contractions – result in no movement (no length change of muscle).

- Holding a load in one position.

Periods and Response Times

After an action potential (AP) arrives:

- **Latent period:** excitation-contraction coupling.
- **Contraction period:** tension develops.

- **Relaxation period:** Ca^{2+} removed from sarcoplasm.

Muscles differ in their response time:

- Ocular muscle: specific, rapid eye movements; response very quickly with short movements.
- Gastrocnemius: Walking and running; responds rapidly and has a medium-long contraction.
- Soleus: Balance; shows slow onset, long-term movements.

Tetanus

Definition 98

In muscle physiology, tetanus refers to the sustained contraction of a muscle fiber (or entire muscle) due to high-frequency stimulation.

Active tension in a muscle varies with the rate of stimulation, from a single twitch to fused tetanus.

- Repetitive stimulation causes the summation of contraction force.
- Increasing the stimulation rate causes saturation, resulting in fused tetanus.
- Delay in cessation of stimulation and reduction of force to baseline due to time for Ca^{2+} reuptake.

14.7 Sarcomere length, tension and contraction

The length of the muscle at the start of a contraction influences the amount of tension the muscle can create.

- This has to do with the amount of overlap between Myosin and Actin as well as the elastic properties of Titin.
- With increased stretch of the muscle, the passive tension (Titin) increases.
- The passive elastic properties will keep a relaxed muscle at optimal length.

14.8 Types of Muscle Fibres

Slow Oxidative(Slow twitch)

- Small, red, much myoglobin (Mb) and many blood capillaries.
- Many mitochondria.
- Generate ATP mainly by aerobic metabolism, resistive to fatigue but slow.

Fast Glycolytic(Fast twitch)

- Largest, most powerful and fastest.
- Little Mb, few mitochondria, but much glycogen.
- Depend mainly on glycolysis, used mainly for intense activity of short duration, fatigue quickly.

Fast Oxidative-Glycolytic(mix)

- Intermediate muscles contain differing proportions, e.g., back (mainly slow), eyes (mainly fast), arms (mixed).
- Fixed in each individual.

14.9 Training and Atrophy

Muscle fibres get bigger (don't increase in number)

- **Aerobic** (e.g. jogging) – blood supply to muscle improves.
 - Mitochondria increase in size, and there is more Mb.
- **Anaerobic** (e.g. heavy weights) – stimulates hypertrophy of fibres, especially the fast glycolytic type.

Muscular atrophy occurs with disuse

- **Disuse atrophy** – muscle wasting, fibres decrease in size – reversible.
- **Denervation atrophy** – lack of neural impulses leads to loss of muscle and replacement with connective tissue
 - irreversible.
- Normally, muscles are continually being stimulated to a low extent, even at rest, so they are never completely flaccid – this only happens when the nerve supply is cut.

15 Cardiac Muscle

15.1 Function

The heart must beat continually on a timescale of about one beat per second.

- Doesn't need to sustain a contraction.
 - Cannot be prone to tetanus.
- Must be a delay between atrial and ventricular contractions.
- Involuntary control.
- Cannot be attached to bones.

15.2 Morphology

In the heart, cardiac cells are:

- Arranged in a circular spiral.
- Embedded in loose connective tissue (endomysium) containing nerves (not excitatory) and many capillaries – metabolic autoregulation.
- Attached to the fibrous skeleton of the heart.

Cardiac Muscle Fibre

Similar to skeletal muscle:

- T system has greater diameter/more surface area.
- SR is less dense, and the cisternae are less prominent.

Intercalated discs/desmosomes:

- Large contact area - cells bond strongly.

Gap junctions:

- **Electrical continuity**

- Action potential passes unhindered from cell to cell.
- The whole atrial or ventricular muscle (they are electrically isolated from one another) is a functional syncytium.
 - One stimulus will fire the whole of each.

Cardiac muscle has more (10x) and larger mitochondria than skeletal muscle.

Much more myoglobin (Mgb), showing its almost exclusive reliance on aerobic metabolism.

- Like skeletal muscle, it uses glucose and fatty acids as its main sources of ATP by oxidative processes.

15.3 Contraction

Some cardiac cells are self-excitatory and spontaneously trigger their own depolarisation.

- Influenced by hormones.

Similar contraction process as for skeletal muscle.

- Cardiac muscle differs in the sequence of events that cause calcium release from the sarcoplasmic reticulum.

In cardiac muscle:

- Action potential (AP) travels down T-tubules, opening voltage-gated calcium channels.
 - Calcium diffuses from extracellular fluid into cells, causing a small increase in cytosolic calcium concentration in the region of the T-tubules and adjacent to the sarcoplasmic reticulum (SR).
- Small increase in calcium concentration causes calcium to bind to receptors on the SR membrane.
 - These receptors contain intrinsic calcium channels.
- Activation of receptors opens calcium channels, allowing a large net diffusion of calcium from the interior of the SR to the cytosol.
 - Termed "**calcium-induced calcium release**" (**CICR**).

- **It is this calcium that mainly causes the contraction.**

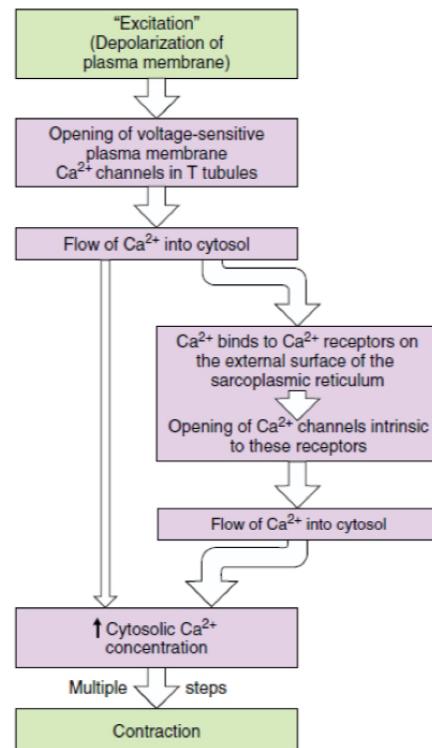


Figure 33: note that the SR pathway is main source of Ca^{2+} release. The direct path is insufficient

Thus, the movement of Ca^{2+} during the AP acts as a signal for contraction.

- Contraction ends when cytosolic calcium concentration is restored to its original extremely low value by active transport back into the SR.
- The small amount that entered during excitation is actively transported out into extracellular space.

In cardiac muscle, the release of calcium is not sufficient to saturate all troponin sites as mentioned in the above figure

- Therefore, increased release of calcium from the SR will achieve a greater strength of contraction.

Fact 99

Skeletal Muscle: T-tubule depolarization is sensed by the dihydropyridine (DHP) receptor, which is *mechanically* linked to the ryanodine receptor (RyR). This direct coupling allows the DHP receptor's conformational change to physically open RyR, releasing Ca^{2+} from the sarcoplasmic reticulum.

Fact 100

Cardiac Muscle: The L-type Ca^{2+} channel (also termed the DHP receptor) is *not* mechanically linked to RyR. Instead, a small influx of extracellular Ca^{2+} through this channel triggers a larger Ca^{2+} release from the sarcoplasmic reticulum via calcium-induced calcium release (CICR). Hence, cardiac muscle contraction *depends* on extracellular Ca^{2+} entry.

15.4 Smooth Muscle Cells

These are found in the walls of hollow internal structures.

- Blood vessels, airways of lungs, stomach, intestines, uterus, etc.

Example 101

Functions include:

- Contract blood vessels, Break up and move food through the GI tract.
- Move fluids, Eliminate wastes, Deliver babies.

Need to function well when being stretched. Smooth muscles form internal sphincters.

- Limit rate of movement through the piping (e.g., the gut or urinary tract).

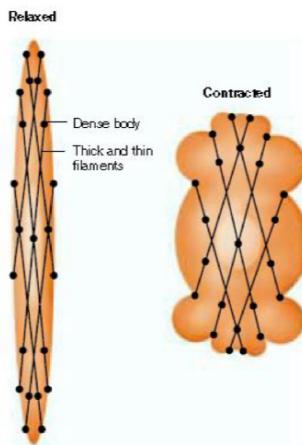
15.5 Structure

- Largely involuntary, uni-nucleate, non-striated (hence smooth), small ($2\text{-}10 \mu\text{m}$ diameter, $100\text{'s } \mu\text{m}$ long) and fusiform.
- Very often, there are two associated sheets arranged at right angles.
 - This arrangement is ideal for mixing and peristalsis.
- Often the cells in these sheets are connected by gap junctions and so act as functional syncytia.

15.6 Control

- The smooth muscle can be affected by neural impulses (e.g., sympathetic to arterioles), hormones (e.g., adrenaline to bronchioles), autorhythmicity, stretch, local factors like pO_2 , pCO_2 , etc.
 - They have a variety of receptors.
- The neural interactions are much less structured than in skeletal muscle.
 - There are large swellings (varicosities) that release neurotransmitters over a wide synaptic cleft in the region of the smooth muscle cells (diffuse junctions).

15.7 Contraction



- Sarcoplasmic reticulum (SR) is less developed, so contraction is slower and less powerful than in skeletal muscle.
- Smooth muscle lacks the regular sarcomere structure. Instead, Actin and myosin filaments are arranged diagonally (see figure above)
 - This allows Actin and myosin filaments to contract much more of their length than in skeletal or cardiac muscle.
 - Useful in the uterus, stomach, intestines, and bladder.
- Activity is $\sim 30x$ slower than skeletal muscle and has lower energy requirements (largely aerobic).
- Contractions can be maintained for long periods without fatigue.
- This is important as many of these muscle sheets have to maintain a continuous 'tone', e.g., in arterioles.
- Smooth muscles can build up tension and contract when stretched, which is very important for the bladder and uterus.

Remark 102. recall from year 1 that this is essentially the myogenic response which has important applications in pressure auto-regulation. also recall that this not the same as Frank Starling effect which is separate also stretch induced response for the cardiac muscle.

Process

1. Ca^{2+} binds to calmodulin, which activates a kinase on the Myosin molecule.
2. The activated Myosin now splits an ATP to make it capable of interacting with Actin.
3. The Actin polymers have Tropomyosin to support them but no Troponin, so their active sites are never hidden.
 - Hence, the activated Myosin can immediately interact and "pull".
4. Relaxation takes place when the Ca^{2+} level falls.
 - As for the other muscle types, by pumping out Ca^{2+} through the Sarcolemma.

Note that we have only described the main pathway in which Ca^{2+} triggers contraction. In reality there is also

Fact 103

Pathway 1: Direct Extracellular Ca^{2+} Entry (Primary Mechanism)

1. Depolarization of the membrane opens voltage-gated Ca^{2+} channels (L-type channels).
2. Extracellular Ca^{2+} enters the cytoplasm, increasing intracellular Ca^{2+} concentration.
3. Ca^{2+} binds to calmodulin, activating myosin light chain kinase (MLCK).
4. MLCK phosphorylates myosin, enabling contraction.

Fact 104

Pathway 2: Calcium-Induced Calcium Release (CICR) from the SR (Secondary Mechanism)

1. Extracellular Ca^{2+} influx through voltage-gated channels can also trigger SR Ca^{2+} release.
2. This happens through ryanodine receptors (RyR), similar to cardiac muscle but less pronounced.
3. The additional Ca^{2+} from the SR enhances contraction.

Fact 105

Pathway 3: IP_3 -Mediated Ca^{2+} Release from the SR (Hormonal and Neurotransmitter Control)

1. Hormones or neurotransmitters (e.g., norepinephrine, acetylcholine) bind to G-protein-coupled receptors (GPCRs).
2. This activates phospholipase C (PLC), which produces IP_3 (inositol triphosphate).
3. IP_3 binds to IP_3 receptors on the SR, causing Ca^{2+} release into the cytoplasm.
4. This contributes to contraction without the need for extracellular Ca^{2+} influx.

Pathway 3 is separate thing, we will discuss it more in endocrine system. Comparing pathway 1 and 2, we note that pathway 2 is more significant for smooth muscle cells because SR is not well as well developed in smooth muscle cells. In contrast if you recall 33, pathway 2 is the most significant source of Ca^{2+} that leads to contraction in cardiac cells. As for skeletal cells, none of these are even in the discussion. Recall from 99 AP is mechanically connected to SR release of Ca^{2+} internally. There is no dependence on extracellular Ca^{2+} for contraction unlike smooth and cardiac muscle.

15.8 Summary of Muscle Types

Characteristic	Skeletal	Cardiac	Smooth
Myosin and Actin	yes	yes	yes
Sarcomeres	yes	yes	no
T-tubules	yes	yes	no
SR	++++	++	+
Gap junctions	no	yes	few
Source of Ca^{2+}	SR	SR and extracellular	SR and extracellular
Site of Ca^{2+} regulation	Troponin	Troponin	Myosin
Speed of contraction	Fast-slow variable	Slow	Very slow
Effect of stimulation	Excitation	Excitation and inhibition	Excitation and inhibition
Effect of hormones	no	yes	yes
Effect of stretch	no	no	yes

Note that "effect of stretch" refers to the myogenic response as mentioned in 102. You should also recall that cardiac,smooth muscle can be influenced by hormones but not skeletal from year 1. We will explore this more in next section on the endocrine system

16 Introduction to the Endocrine System

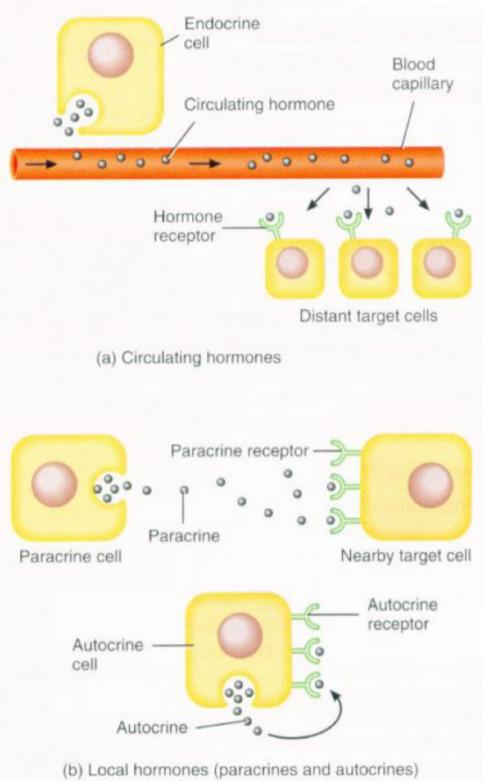
Hormones are chemical messengers that circulate in the bloodstream.

- Act as effectors on specific target cells or tissues.
 - They control and regulate processes like water/ion homeostasis, glucose levels, and growth.
- Produced in specific organs.
 - Mostly secreted from endocrine glands but also from the hypothalamus, placenta, etc.

16.1 Scope of Endocrine System

Unlike the nervous system (NS), the endocrine (EC) system acts to elicit activity at a distant location.

- Takes time to get to the site of action.
- Slow feedback loops for input/output regulation.
- Controls metabolic responses where constant small adjustments are required.



Modifications of the EC system include:

- **Neuroendocrine system:** Nerves release neurohormones into the blood.
- **Paracrine system:** A cell releases a substance to diffuse in the extracellular fluid to affect neighbouring cells.
- **Autocrine system:** A cell releases a substance into the extracellular fluid to affect its own function.

Endocrine vs. Exocrine

- Exocrine glands secrete their products into ducts which lead directly to external environments.
- Endocrine glands are ductless and secrete products directly into the bloodstream.

16.2 Fundamentals

- All hormones require a receptor at the target cell.
- They travel in the bloodstream.
- Hormones can be produced and stored or produced *de novo* on release.
- Hormones often work far away from where they are produced and have global and multiple effects.
- The same hormone can have different effects in different tissues.
- Hormonal effects are on very different time scales, from seconds to days.
- Hormones are very reactive and their concentration in the blood needs to be tightly regulated.

Scope of Effect

Hormones can act globally because they are transported in the bloodstream.

- Because they are everywhere, their effect on the target tissue needs to be tightly controlled.
 - This is done by specific receptors.
 - * The target organ expresses a specific receptor.
 - Different tissues or even different cells in one tissue can express different receptors! And their numbers can be regulated.
 - The receptor, not the hormone, determines the effect on the cell. The same hormone can have very different effects on different target tissues.

Hormone Effects on Cellular Processes

- Changes in membrane permeability/ion channels.
- Changes in protein synthesis.
- Changes in enzyme activity.
- Changes in genes.
- Induction of secretory activity.
- Stimulation of mitosis.

16.3 Types of Hormones

- Hormones can be classified as hydrophilic or hydrophobic.

Hydrophobic Hormones

- Soluble in fat but not in water.
- Require carrier molecules to travel in blood but easily get through the cell membrane.
- Examples include:
 - **Steroid hormones** – derived from cholesterol.
 - * Cortisol (adrenal cortex).
 - * Oestrogen (ovaries).
 - * Testosterone (testes).
 - **Thyroid hormones**.
 - * Thyroxine from tyrosine.

Action

- Hormone diffuses easily through the cell membrane
meets specific receptor in the cytoplasm or nucleus
- activates or modifies transcription
de-novo protein synthesis activated, slow process
- signal amplified from DNA to protein
hormone receptor complex is turned off by cellular enzymes

Hydrophilic Hormones

- Soluble in water but not in fat.
- Can travel in the bloodstream but cannot enter the cell.
- Examples include:

- **Amine hormones** – derived from modified amino acids.
 - * Adrenaline from tyrosine (adrenal medulla).
- **Peptide/protein hormones** – chains of amino acids.
 - * Insulin (pancreas).
- **Eicosanoid hormones** – derived from fatty acids.
 - * Prostaglandins (most cells).

Action

- No carrier molecule for transport in the blood.
- Cannot diffuse through the cell membrane.
- The hormone docks with a specific receptor on the cell membrane.
 - The receptor activates a second messenger cascade, creating specific and different effects in the cell.
 - Amplification of the signal occurs due to the second messenger cascade.

Adenylyl Cyclase-cAMP System

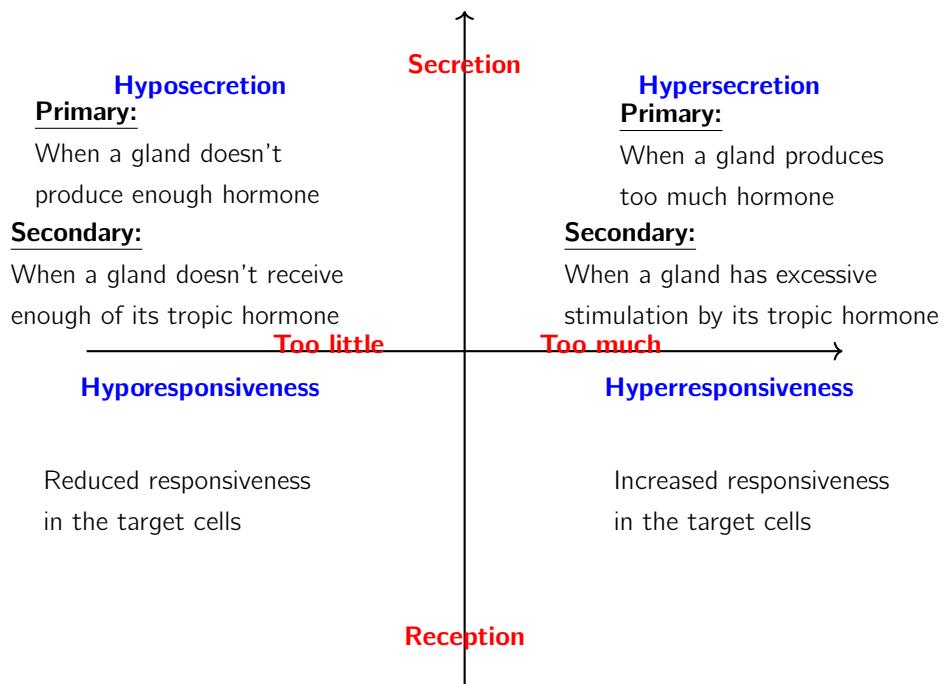
1. Hormone/Receptor binding - specificity.
2. *G(guanidine)-protein activation.*
3. Adenylyl cyclase activation to produce cAMP.
4. cAMP activates a cascade(s) of proteins to produce the required effect.
5. Amplification.

16.4 Regulation of Hormone Concentration

- Hormones are highly active.
 - Synthesis is tightly regulated.
 - Circulating levels are low (10^{-12} to 10^{-6} g/ml) but can vary depending on time of day, season, or stage of development.
- Hormone secretion can be continual, phasic, or episodic.
 - It is often in bursts.
 - Stimulation increases the frequency of the bursts.
- Individual hormone release can be influenced by positive or negative feedback.
 - The activity elicited by a hormone or its plasma concentration feeds back on its own release.
 - Most systems use negative feedback (e.g., Ca^{2+} and parathyroid) but a few are positive (e.g., during childbirth, oxytocin stimulates uterine contraction, which in turn stimulates more release of oxytocin).
- Inputs that control hormone secretion:

- Changes in plasma concentration of minerals or organic nutrients (e.g., insulin secretion in response to plasma glucose levels, Ca^{2+} homeostasis by PTH).
 - Neurotransmitter release from neurons impinging on endocrine cells (e.g., adrenal medulla system, hypothalamus, and anterior/posterior pituitary system).
 - Other hormones, which are called trophic hormones (e.g., gonadotropin-releasing hormone (GnRH) stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn stimulate the gonads).
- Control of hormone inactivation:
 - Due to their activity, hormones must be deactivated so their action is transient. Mechanisms for this include:
 - * Hormones are destroyed by the liver or enzymes in the blood and/or excreted.
 - * The receptor-hormone complex (often endocytosed) is destroyed by the cell.
 - Hormone release and inactivation can be regulated differently.

16.5 Categories of Endocrine Disorders



17 The Hypothalamic-Pituitary Axis and Growth

- The hypothalamus is the main link between the nervous and endocrine systems.
- The pituitary gland is connected to the hypothalamus by a stalk-like structure.
- The hypothalamus and the pituitary gland secrete a multitude of hormones.
 - Major regulators of growth, development, metabolism, and homeostasis.

The Pituitary Gland

Posterior Lobe (Neurohypophysis)

- The posterior pituitary is a neural extension of the hypothalamus.
- Hormones are synthesised in the cell bodies of neurons residing in the hypothalamus.
 - Axons of these neurons pass down to and terminate in the posterior pituitary gland.
 - Synthesised hormone is packaged into vesicles and moves down to the neuron terminals where it is stored.
- Upon stimulation of the neuron, action potentials (APs) will travel down the axons and the hormones will be released into the blood supply.
 - They can then act on their target tissues.
- The posterior pituitary gland releases two hormones that are delivered by separate neurosecretory cells with cell bodies in different parts of the hypothalamus.
 - **Oxytocin**
 - * Delivery of milk by the breast, stimulated by nursing.
 - * Contraction of uterine smooth muscles, stimulated by labour.
 - **Vasopressin (ADH)**
 - * Acts on smooth muscle of blood vessels, constricts blood vessels, and thus increases blood pressure.
 - * Acts within the kidney to reduce water loss through the urine and thus maintains blood volume.

Anterior Lobe (Adenohypophysis)

- Neurosecretory cells from specific nuclei in the hypothalamus end in the median eminence where the hypothalamo-pituitary portal blood supply originates.
 - Neurons secrete hypophysiotropic hormones into the hypothalamo-pituitary portal.
 - Blood flows from the median eminence towards the anterior pituitary where the hormones stimulate secretion of anterior pituitary hormones.
- Most of these hypophysiotropic hormones are the first hormone in a 3-hormone sequence:
 - A hypophysiotropic hormone controls the release of
 - An anterior pituitary gland hormone, which controls
 - A hormone from some other endocrine gland.
 - * This last hormone then acts on the target cells.

Hypophysiotropic Hormones

- These, as stated, act on the pituitary gland and are tropic hormones:
 - **Stimulating** or **inhibiting**
 - 1. **GHRH** Growth hormone-releasing hormone

- 2. SS Somatostatin
- 3. TRH Thyrotropin-releasing hormone
- 4. GnRH Gonadotropin-releasing hormone
- 5. DA Dopamine
- 6. CRH Corticotropin-releasing hormone

Anterior Pituitary Hormones

1. **Human growth hormone (hGH)** – growth and metabolism (GH's are not interchangeable between animals, this one is called *human* growth hormone, hGH)
 - GHRH Growth hormone-releasing hormone stimulating
 - SS Somatostatin inhibiting
2. **Thyroid-stimulating hormone (TSH)** – stimulates release of thyroid hormones.
 - TRH Thyrotropin-releasing hormone
3. **Follicle-stimulating hormone (FSH)** – production of sperm, oocytes, estrogens.
 - GnRH Gonadotropin-releasing hormone
4. **Luteinising hormone (LH)** – stimulates ovulation and release of testosterone, oestrogen, and progesterone.
 - GnRH Gonadotropin-releasing hormone
5. **Prolactin (PRL)** – involved in secretion of milk.
 - DA Dopamine
6. **Adrenocorticotrophic hormone (ACTH)** – influences secretions from the adrenal cortex.
 - CRH Corticotropin-releasing hormone
7. **Melanocyte-stimulating hormone (MSH)** – function not known, but excessive amounts cause excessive darkening of the skin.

All act via cAMP second messenger systems AND all are controlled by releasing/inhibiting hypothalamic hormones which are either stimulating (red) or inhibiting (blue).

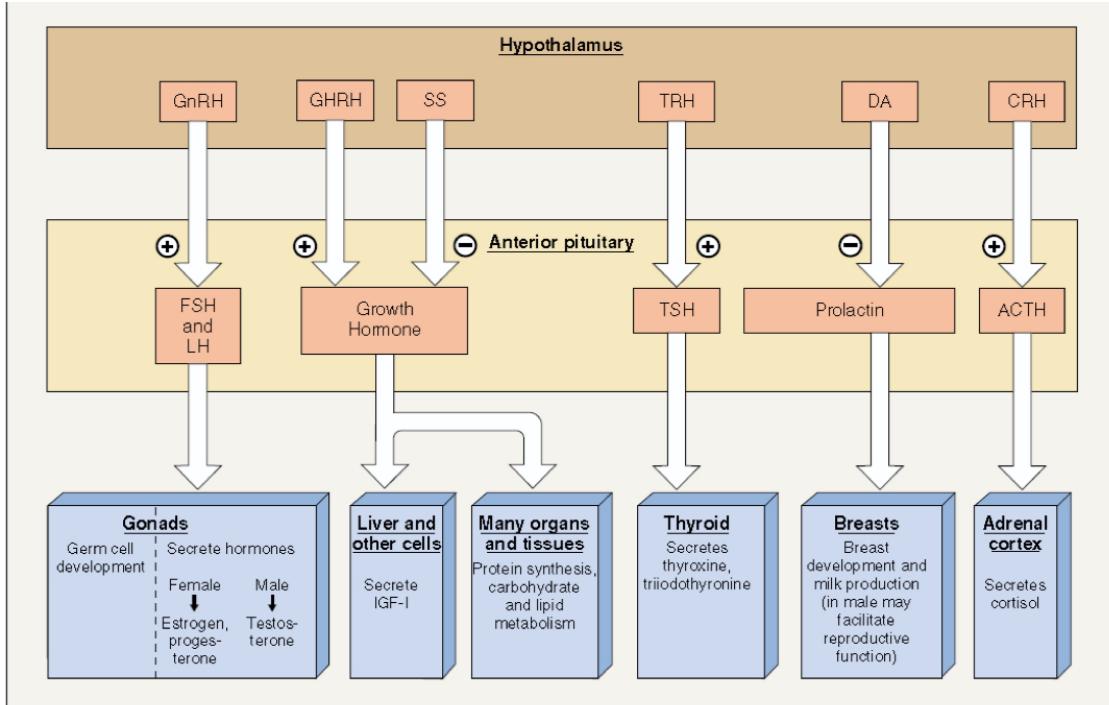


Figure 34: Summary hypothalamic anterior pituitary system

17.1 Control of Growth

- Several hormones are important for growth:
 - Hypothalamus: GHRH and GHIH (SS)
 - Anterior pituitary: GH (aka somatotrophin)
 - Insulin-like growth factors 1 and 2
 - Thyroid hormones T_3 and T_4
 - Insulin
 - Testosterone and estradiol
 - Range of peptide growth factors
 - * Paracrine/autocrine pathways to stimulate cell division and differentiation

Human Growth Hormone (hGH)

- hGH released every few hours
 - Controlled by GHRH and GHIH/SS
- Plasma concentration usually a few 10^{-9} g/ml
 - Increases when exercising
- Not involved in fetal growth

Table 5: Major Hormones Influencing Growth

Hormone	Principal Actions
Growth hormone	Major stimulus of postnatal growth: Induces precursor cells to differentiate and secrete insulin-like growth factor 1 (IGF-I), which stimulates cell division Stimulates secretion of IGF-I by liver Stimulates protein synthesis
Insulin	Stimulates fetal growth Stimulates postnatal growth by stimulating secretion of IGF-I Stimulates protein synthesis
Thyroid hormones	Permissive for growth hormone's secretion and actions Permissive for development of the central nervous system
Testosterone	Stimulates growth at puberty, in large part by stimulating the secretion of growth hormone Causes eventual epiphyseal closure Stimulates protein synthesis in male
Estrogen	Stimulates the secretion of growth hormone at puberty Causes eventual epiphyseal closure
Cortisol	Inhibits growth Stimulates protein catabolism

- In adolescents responsible for growth rate
 - Especially in spurts and especially of the skeleton and skeletal muscles
 - Levels decrease after adolescence
- In adults, it maintains the skeleton (remodeling) and musculature as well as promoting tissue repair

Table 6: Major Effects of Growth Hormone

#	Effect
1.	Promotes growth: Induces precursor cells in bone and other tissues to differentiate and secrete insulin-like growth factor 1 (IGF-I), which stimulates cell division. Also stimulates secretion of IGF-I by liver.
2.	Stimulates protein synthesis, predominantly in muscle.
3.	Anti-insulin effects: <ul style="list-style-type: none"> • Renders adipocytes more responsive to lipolytic stimuli • Stimulates gluconeogenesis • Reduces the ability of insulin to stimulate glucose uptake