

## **YO! Physiologer dudes**

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Many of my friends have found these notes useful in their study for Physiology 1A.

But before you take a look at them and start cramming as if your life depends on it, take a moment to meet the God that created a universe that is so complex and worthy of study, yet knows you and I personally:

*Psalm 139:13-14 - "For you created my inmost being; you knit me together in my mother's womb. I praise you because I am fearfully and wonderfully made; your works are wonderful, I know that full well."*

Check it out sonnnnnn!: <http://www.matthiasmedia.com.au/2wtl/>



# 1 Lecture 1

## 1.1 Describe very generally an example of a single cell function

Outer hair cells act as **acoustic pre-amplifiers**.

- Deflection of inner ear hair-cell stereocilia opens mechanically gated cation channels.
- This allows an influx of cations from the endolymph into the cell.
- This depolarises the cell, resulting in an action potential.
- In response to the action potential, the protein prestin in the outer hair cell contracts, driving oscillations of the cell's length at the same frequency as the sound resulting in pre-amplification.

## 1.2 Appreciate cells are basic fundamental units, define what is meant by excitable cells, giving some examples and appreciate that single cells use chemical and electrical signalling

Every organ is made of cells; the basic fundamental unit. Some of these cells are **excitable** including:

- Nerve cells (neurons)
- Muscle cells (skeletal, cardiac, smooth)
- Endocrine cells (pancreatic  $\beta$  cells)

**Excitable cells:**

- Possess a voltage across their cell membrane due to an uneven distribution of charge on either side (polarised).
- To vary this voltage, they alter the distribution of charge on either side of the membrane by moving ions across it. (All cells also need to import energy substrates and export wastes across the membrane).
- Do not act in isolation, but communicate these changes to other cells via electrical and/or chemical signalling.

## 1.3 Schematically draw a cell membrane and identify the functional components of a typical membrane phospholipid and give an example

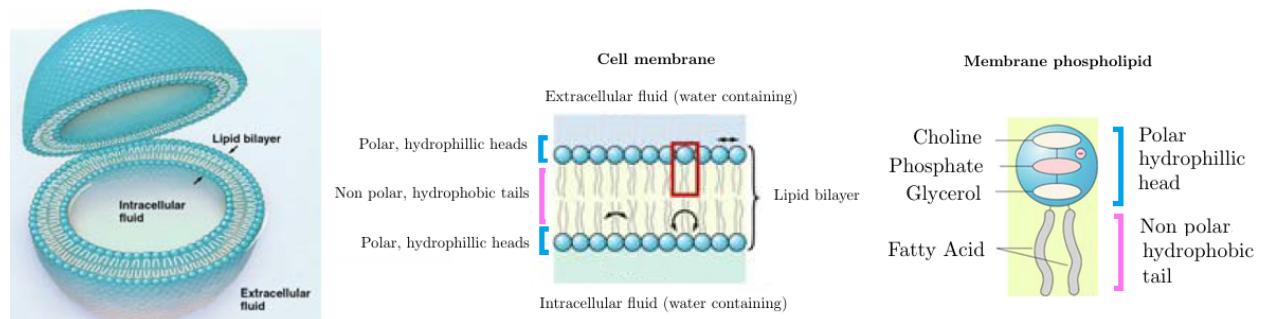


Figure 1: Schematic diagram of the cell membrane and phospholipid (phosphatidylcholine).

- There are different types of membrane lipids.
  - A specific example of a membrane phospholipid is presented in Figure 1, **phosphatidylcholine**.
  - It is a phospholipid with a choline group attached to its head.
  - Figure 2 provides a more detailed schematic of phosphatidylcholine.

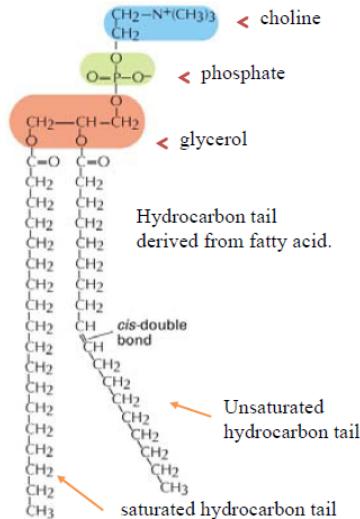


Figure 2: Schematic diagram of phosphatidylcholine.

- Furthermore, the cell membrane also contains embedded proteins that impart the ability to move substances in and out of the cell.
  - Figure 3 demonstrates the different types of membrane proteins.

- Integral membrane proteins (1-2) spanning the lipid bilayer
  - Lipid anchored membrane proteins (3-4)
  - Peripheral membrane protein (5-6)

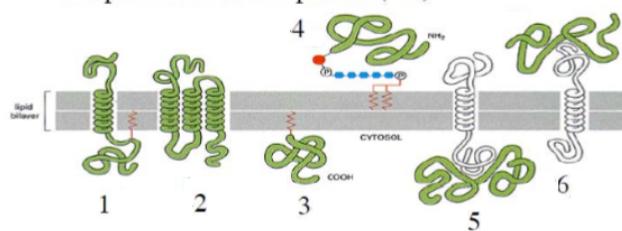


Figure 3: Different types of membrane proteins.

## 1.4 Know the terms polar and non-polar and how it relates to membranes and ions

**Polarity** arises from charge and geometric **asymmetry**. Charge asymmetry is caused by a difference in the electronegativities of the atoms of the molecule and thus an unequal sharing of the electrons in its bonds. This causes a polar molecule to possess a slight electrical dipole moment. One end of the molecule has a partial positive charge, whilst the other has a partial negative charge.

**Non-polarity** arises from the equal sharing of electrons in bonds or because the geometric **symmetry** causes the vector sum of the bond dipoles to cancel out despite the bonds being polar.

The cell membrane consists of phospholipids which mainly constitute its bilayer as well as other membrane lipids to a lesser extent.

- **Phospholipids** consist of a negatively charged phosphate group at its head, making it polar and hydrophilic, and two adjacent uncharged, non polar, hydrophobic, hydrocarbon fatty acid tails.
- Thus, when phospholipids are immersed in water, they spontaneously self assemble into a bilayer. This is the most energetically favourable configuration due to the preferred interaction between phospholipid sections of like polarity.
- The hydrophobic tails form bonds with each other via dispersion forces, whilst the hydrophilic heads form hydrogen bonds with water, resulting in a stabilised lipid bilayer structure.

In order to establish a membrane potential in the first place, it is necessary to have two distinct aqueous compartments on either side of the membrane.

- 1.1 says that an action potential can be triggered by varying the membrane potential.
- 1.2 says that cells vary this membrane potential by altering the distribution of charge on either side (by moving ions across it).

Therefore, if the movement of ions across the cell membrane is critical for excitable cell function, we must know:

1. The properties of these ions in solution (addressed here)
  2. How these ions move across the cell membrane (addressed in Lecture 2)
- Anions and cations present in a solid form crystals.
  - A crystal of NaCl consists of  $Na^+$  and  $Cl^-$  held together in a lattice by electrical forces of attraction because of their opposite charges. These are called ionic bonds.
  - When ionic solids dissolve in water, the ionic bonds are disrupted by electrical attractions between the ions and the polar water molecules.  $Na^+$  is surrounded by the partial negative charges from the oxygen ends of the water molecules, whilst the negatively charged  $Cl^-$  is surrounded by the partial positive charges from the hydrogen ends.
  - This continues until every individual ion is surrounded by a hydration shell and dispersed in solution.

However we know that the hydrated ions are charged. Therefore, whilst the ion and its hydration shell can interact with the polar hydrophilic phospholipid heads, they cannot interact with the hydrophobic tails and cannot dissolve or cross the bilayer.

*So how do they cross the membrane?*

## 1.5 Relate the basic components of an electrical circuit to a potential difference across the cell membrane

A **capacitor** consists of two conducting materials separated by an insulator. In the case of a cell, the extracellular and intracellular fluids are the conductors, and the cell membrane is the insulator. Because charge cannot flow across the insulator, it builds up at the interface generating a potential difference (i.e. a resting membrane potential). This makes it possible to have different amounts of charge inside and outside of the cell.

Simplifying this even further and omitting discussion of a capacitor, we can relate the components of biological electricity with those of a hardwired electrical circuit.

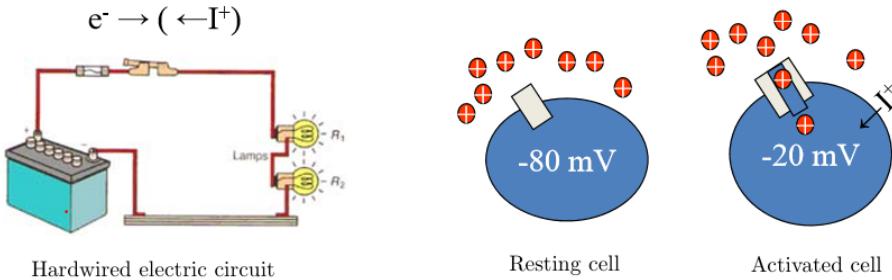


Figure 4: A comparison of hardwired and biological electricity.

- **Battery EMF  $\Rightarrow$  Electrochemical driving force**

Similar to a battery EMF, the different amounts of charge inside and outside the cell result in an electrochemical driving force.

- **Open circuit  $\Rightarrow$  Membrane which ions cannot cross**

- **Switch  $\Rightarrow$  Ion channel**

When the switch is open, there exists an open circuit in the hardwire circuit that current cannot cross. Similarly, ions cannot cross the cell membrane unless ion channels facilitate their transfer.

- **Response: Emission of light  $\Rightarrow$  Depolarisation**

As current flows through filaments the response constitutes the emission of heat and light as the filament glows due to its high resistance. The response of cations crossing into the membrane is a **depolarisation**.

## 2 Lecture 2

### 2.1 Distinguish between active and passive membrane transport

In response to the question posed in 1.4, there exist three broad methods in which substances move across the membrane.

#### 1. Passive diffusion

Particle movement down a **concentration gradient** across the membrane through Brownian motion.  
**No energy input.**

- Simple diffusion
- Facilitated diffusion

#### 2. Active transport

Particle movement up a concentration gradient across the membrane through an **energy input**.

- Primary active
- Secondary active
  - Carrier protein
  - Ion channel protein

#### 3. Incorporation into a lipid vesicle

- Exocytosis
- Endocytosis

### 2.2 Distinguish simple and facilitated diffusion, and facilitated diffusion via channels and carriers

### 2.3 Briefly describe an example of a facilitated diffusion transport process including physiological relevance and protein involved

#### 2.3.1 Fick's Law

Before we discuss the two modes of passive diffusion, we first introduce **Fick's law**; a mathematical description of diffusion.

$$J = DA \frac{dc}{dx} = DKA \frac{dc}{dx} \quad (1)$$

Where:

- $J$  = flow rate of solute
- $A$  = area of interface
- $\frac{dc}{dx}$  = solute concentration gradient across a membrane of width  $x$
- $D$  = Diffusion coefficient
- $K$  = Partition coefficient

**Note:** For membrane diffusion, the partition coefficient  $K$  (a value from 0-1, 0 meaning insolubility and 1 meaning maximum solubility) is necessary to take into account how easily a substance can dissolve in the lipid bilayer.

### 2.3.2 Simple diffusion

- Simple diffusion is the movement of particles across the membrane down a concentration gradient that does not require an energy input or proteins to facilitate this movement.
- Only **blood gases** such as  $O_2$ ,  $CO_2$ ,  $N_2$  and **small lipid soluble non polar (hydrophobic) molecules** such as **steroids** and **fatty acids** can simply diffuse across the membrane because they can dissolve in the lipid bilayer.
- Furthermore, simple diffusion does not have specificity, competition nor does it reach saturation.

### 2.3.3 Facilitated Diffusion

- **Polar (hydrophilic)** or **lipid insoluble molecules** cannot cross the membrane because they cannot dissolve in the lipid bilayer.
- Thus, their movement into and out of the cell is facilitated by **membrane transport proteins**.
- Facilitated diffusion compared to simple diffusion has **specificity**, **competition** and reaches a **saturation point**.

There are two categories of membrane transport proteins:

1. **Carrier proteins** (glucose transport into cells after a meal)
2. **Channel proteins** ( $Na^+$ ,  $K^+$  movement during an action potential, aquaporins).

### 2.3.4 Carrier proteins for glucose transportation into the cell - a vital facilitated diffusion process

**Carrier proteins** operate according to the **occluded access model**.

- Carrier membrane proteins contain an amino acid structure binding site that specifically matches a larger solute such as glucose.
- The carrier undergoes a conformational change to outward open, "rocking back" to expose the binding site at which glucose binds.
- The transporter then undergoes a conformational change to occluded that traps the glucose inside the middle of the protein.
- The carrier undergoes another conformational change to inward open, "rocking" in the other direction, allowing glucose to "hop" off onto the inside of the cell.

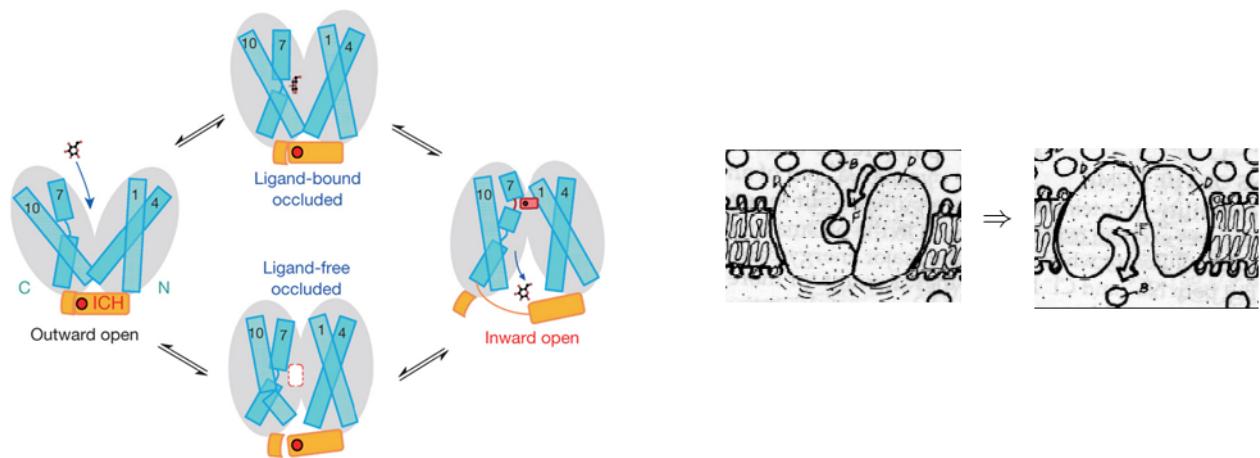


Figure 5: The occluded access model.

## Physiological relevance

- ATP is the major source of energy for all major chemical reactions that fuel the body.
- To produce ATP, glucose must first be transported into the cell where it undergoes cytoplasmic glycolysis and the Kreb's cycle/oxidative phosphorylation in the mitochondria.
- Glucose however is a hydrophilic, polar molecule and cannot cross the membrane via simple diffusion.
- GLUT4 specifically** facilitates the transport of glucose across the membrane via facilitated diffusion.
- The binding site of these transporters perfectly fits D-glucose (which we use for energy), as well as L-glucose to a lesser extent). This gives rise to **competition** in binding to the protein.
- Furthermore, if the extracellular concentration of glucose is so high that all of the carrier proteins are **saturated**, its flux reaches a maximum.
- The body compensates for this saturation by releasing the hormone insulin. Insulin binds to insulin membrane receptors, signalling glucose transporters to be inserted in to the membrane, increasing the glucose intake capacity.

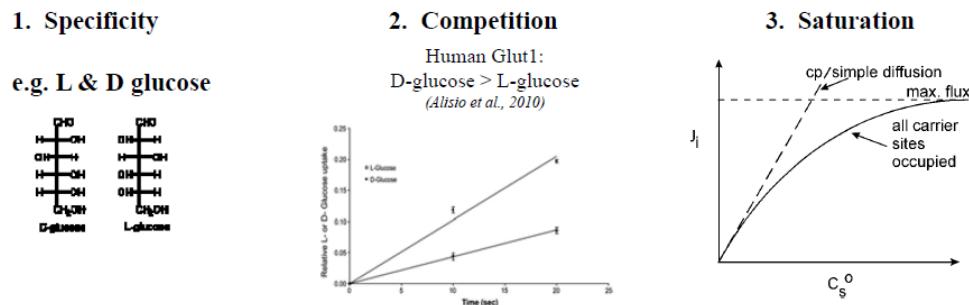


Figure 6: The principles of selectivity, competition and saturation.

## 2.4 Define ion channels and their basic properties of gating and selectivity

**Ion channel proteins** are membrane proteins with aqueous pores that allow the diffusion of ions.

- Ion channels are **selective**; they only let ions of a certain size and/or charge pass through.
- When ions cross the membrane, they redistribute the charge. For example if a cation is travelling across the membrane, the inside of the cell becomes increasingly positive. Because like charges repel, the electrostatic repulsion actively opposes the chemical gradient. Thus the motion of these ions is not just dependent on a chemical gradient, but an **electro-chemical gradient**.
- Ion channels can either be **pores/non gated** (always open) **gated**.

There are **4** main modes of **gating** as seen in Figure 7.

- Voltage-gated** - open and close in response to the membrane potential. - e.g.  $Na^+/K^+$  channels involved in action potentials.
- Ligand-gated (extracellular ligand)** - e.g. a neurotransmitter chemical (the ligand) released at the synapses can trigger opening.
- Ligand-gated (intracellular ligand)** - e.g. a change in phosphorylation due to metabotropic receptors can open/close different  $K^+$  channels; an intracellular 2nd messenger like cyclic AMP can open channels in sensory cells.
- Mechanically gated** - e.g. mechanosensitive channels in sensory nerve endings that detect touch.

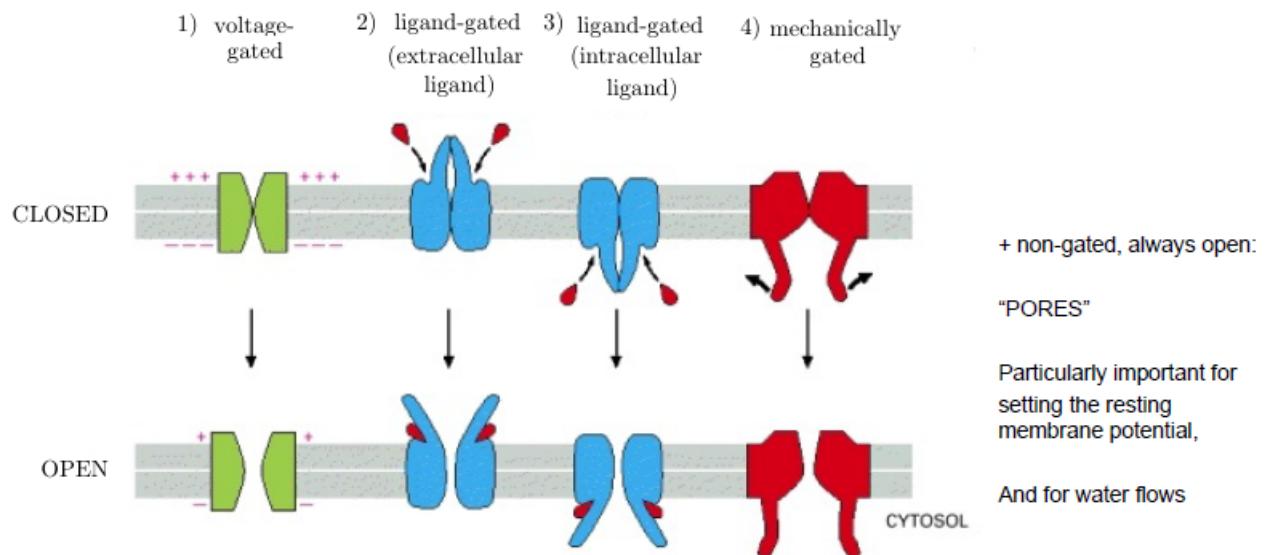


Figure 7: The four different types of gating.

### 3 Lecture 3

#### 3.1 Recognise osmosis as water diffusion and relate tonicity and water flux across cell membranes.

- **Osmosis** is the net movement of water across a semipermeable membrane from an area of lower solute concentration to that of a higher solute concentration. Because water cannot directly cross the membrane, it diffuses into the cell via **aquaporins**.
- **Tonicity** is the ability of an extracellular solution to make water move into or out of a cell by osmosis.
- A solution's tonicity is related to its **osmolarity**; the total concentration of solutes in a solution.
- When solutions of different osmolarities are separated by a membrane permeable to water, but not to solute, water will move from the side with lower osmolarity to the side with higher osmolarity.
- The terms **hypotonic**, **isotonic**, and **hypertonic** are used to compare the osmolarity of a cell to the osmolarity of the extracellular fluid around it. When we use these terms, we are only considering solutes that cannot cross the membrane.
  - If the extracellular fluid has lower osmolarity than the intracellular fluid, it is **hypotonic**, and the net flow of water will be **into** the cell.
  - If the extracellular fluid has a higher osmolarity than the intracellular fluid, it is **hypertonic**, and the net flow of water will be **out** of the cell.
  - If the extracellular fluid and intracellular fluid have the same osmolarity, it is **isotonic**, and there is **no net movement** of water.

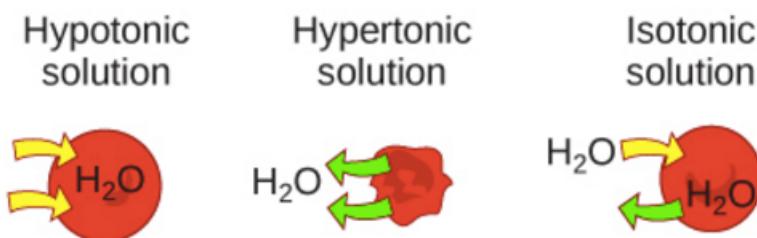


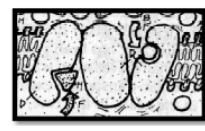
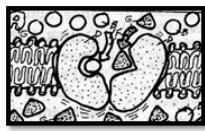
Figure 8: The net movement of water when a cell is placed in a hypo, hyper, and isotonic solution.

#### 3.2 Define primary and secondary active transport, and counter-transport and co-transport, and give examples of each.

As opposed to passive diffusion, **active transport** uses energy.

- **Primary active transport** utilises ATP hydrolysis to fuel **direct** uphill solute flux. An example is the  $Na^+-K^+$  ATPase.
- **Secondary active transport** involves a membrane transport protein (antiporter or symporter) coupling the movement of an ion down its electrochemical gradient (initially generated by primary active transport) with the uphill flux of another molecule or ion against its electrochemical gradient.
  - **Counter-transport** is where the driven ion/molecule moves in the **opposite direction** as the driving ion. An example of this is the  $Na^+-Ca^{2+}$  exchanger/antiporter.  $Ca^{2+}$  is a double-edged sword; it is a very important signalling molecule inside the cell but leads to cytotoxicity in excess concentrations. The  $Na^+-Ca^{2+}$  exchanger uses the electrochemical gradient generated by the  $Na^+-K^+$  ATPase.  $Ca^{2+}$  and  $Na^+$  bind at sites on the protein which then rocks and moves  $Ca^{2+}$  uphill extracellularly and  $Na^+$  downhill intracellularly in opposite directions.

- **Co-transport** is where the driven ion/molecule moves in the **same direction** as the driving ion. An example of this is the **sodium-glucose transporter**. Following a meal, we want to store glucose as glycogen in the muscle/liver cells. However, via facilitated diffusion, the concentration of glucose may reach a level that exceeds the blood glucose. Therefore we cannot use facilitated diffusion to move anymore glucose into the cell. Again, the symport uses the electrochemical gradient generated by the  $Na^+-K^+$  ATPase. Glucose and  $Na^+$  bind at sites on the protein which then rocks and moves both ions into the cell.



Co-transport

Counter-transport

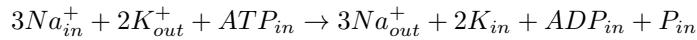
Figure 9: Symport and antiporter.

## SUMMARY

	Passive processes			Active processes		
	Simple Diffusion	Facilitated Diffusion		Primary Active Transport	Secondary Active Transport	
		Carrier	Channel		Co-transport*	Counter transport*
Alternate name	Lipid diffusion	Diffusion carrier	Channels or pores	Pump	Uniporter	Exchanger
Energy used	Nil	Nil	Nil	Yes, direct	Yes, indirect,	Yes, indirect,
Chemical nature of transported substance	Non-polar / lipid soluble molecules	Ions or other polar substances	Ions or other polar substances	Ions or other polar substances	Ions or other polar substances	Ions or other polar substances
Permeation pathway / mechanism	Via the lipid	Via membrane protein	Via membrane protein	Via membrane protein	Via membrane protein	Via membrane protein
Driving force for solute movement	Chemical (concentration gradient)	Chemical (concentration gradient)	Electro-chemical (concentration gradient & electrical force)	ATP hydrolysis fuels uphill solute flux	Electrochemical gradient of all solutes, extent depends on stoichiometry	Electrochemical gradient of all solutes, extent depends on stoichiometry
Example of substances transported	O <sub>2</sub> , CO <sub>2</sub> , steroids	Glucose, amino acids	Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> , Ca <sup>2+</sup> , H <sub>2</sub> O	Na <sup>+</sup> , K <sup>+</sup> , Ca <sup>2+</sup> , H <sup>+</sup>	Glucose, amino acids, Cl <sup>-</sup> ,	Ca <sup>2+</sup> , H <sup>+</sup>
Example of transporter	Not applicable	GLUT4 glucose transporter	Voltage-dependent Na <sup>+</sup> channel	Na <sup>+</sup> / K <sup>+</sup> / ATPase (Na <sup>+</sup> pump)	GLUT1 glucose transporter	Na <sup>+</sup> /Ca <sup>2+</sup> exchanger
Example of physiological function	Oxygen flow from blood to cells	Glucose movement into cells following a meal	Generation and propagation of the action potential	Establish and maintain physiological [Na <sup>+</sup> ] and [K <sup>+</sup> ]	Store glucose into liver cells	Intracellular [Ca <sup>2+</sup> ] homeostasis

### 3.3 Know the basic cellular function of the $\text{Na}^+$ pump and the ions that it transports, including the directions and quantities

Present in nearly every cell and crucial to its physiological processes, the  $\text{Na}^+-\text{K}^+$  ATPase **actively** transports 3  $\text{Na}^+$  out of the cell and 2  $\text{K}^+$  ions into the cell through the cell membrane. This is facilitated by the hydrolysis of 1 ATP molecule per cycle.



The  $\text{Na}^+-\text{K}^+$  ATPase:

1. Is a direct coupling between ATP and transport
2. Establishes  $\text{Na}^+$  and  $\text{K}^+$  gradients.
3. Provides energy for secondary transport and electrical signalling.

### 3.4 Briefly describe exocytosis and endocytosis using physiological examples

- **Exocytosis** is a form of bulk transport in which materials are transported from the inside to the outside of the cell in membrane-bound vesicles that fuse with the plasma membrane.
  - An example is the communication between the pre- and post-synaptic nerve cells via the release of lipid vesicles containing signalling molecules such as neurotransmitters/hormones. The vesicles are docked to the pre-synaptic cell membrane and release their contents when triggered by a rise in intracellular  $\text{Ca}^{2+}$ . The neurotransmitter vesicles are then recycled via endocytosis.

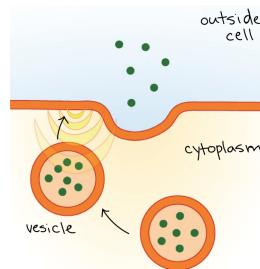


Figure 10: Exocytosis.

- **Endocytosis** is a general term for the various types of active transport that move particles into a cell by enclosing them in a vesicle made out of plasma membrane. The plasma membrane invaginates a target particle, forming a pocket around it. The pocket then pinches off with the help of specialised proteins, leaving the particle trapped in a vesicle or vacuole inside the cell.

Endocytosis can be further subdivided into:

1. **Pinocytosis:** The sampling of surrounding fluid and intake of small amounts of extracellular fluid containing nutrients and other molecules.

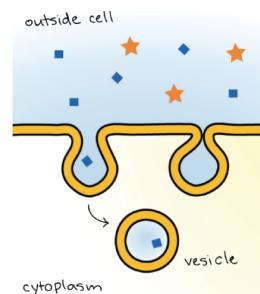


Figure 11: Pinocytosis.

2. **Phagocytosis:** The intake of large particles such as cells or cellular debris. An example of this is microglial phagocytosis of debris from infections and dying nerve cells in disease.

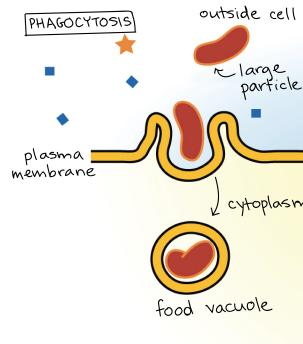


Figure 12: Phagocytosis.

3. **Receptor mediated endocytosis:** The capture of specific target molecules using transmembrane receptor proteins called coat proteins. Once receptors bind to their specific target molecules, their attached molecules are taken into the cell in a vesicle. The coat proteins give the vesicle its rounded shape and help it bud off from the membrane. This process brings in useful substances relatively rare in the extracellular fluid however pathogens use the same endocytosis pathways to gain entry.

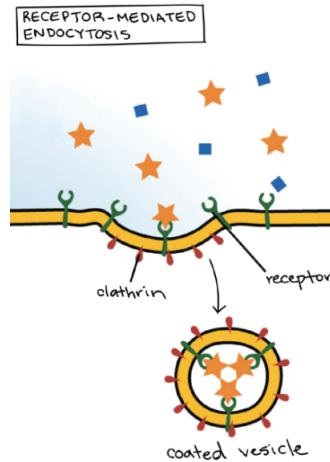


Figure 13: Receptor mediated endocytosis.

### 3.5 Understand the forces that dictate how an ion moves across the cell membrane, including being able to describe electrochemical equilibrium and to predict how an ion moves at a given membrane potential and concentration gradient, or at a given equilibrium potential.

### 3.6 Know the Nernst equation and be able to use it (if given the values of the constants) to calculate equilibrium potentials

Ions are subjected to two forces which **mutually influence** the direction of its movement.

- A **chemical** force that arises from a concentration gradient.
- An **electric** force that attracts ions of opposite charge and repels ions of like charge.

#### 3.6.1 Electrochemical equilibrium

The membrane potential of a resting neuron is primarily determined by the movement of  $K^+$ . Let us develop an intuition for membrane potentials and electrochemical equilibrium by considering a case in which only  $K^+$  can cross the membrane.

- Firstly, the  $Na^+-K^+$  ATPase has generated a concentration gradient. Hence, there is a high intracellular concentration of  $KCl$  and a high extracellular concentration of  $NaCl$ .
- In this hypothetical state, no membrane potential exists because each  $K^+$  and  $Na^+$  are grouped with their respective anions  $Cl^-$ .
- If  $K^+$  selective channels are opened,  $K^+$  will move down its concentration gradient, from the inside to the outside of the cell. Because  $Cl^-$  cannot travel with  $K^+$ , the inside of the cell becomes negative relative to the outside, generating a potential difference across the membrane.
- Eventually the inside of the cell becomes negative enough that it now starts to influence the  $K^+$  to move back in. You'll come to an equilibrium where the voltage inside the cell will be negative enough to counterbalance the chemical force that wants to push the potassium out.
- Eventually, the potential difference across the cell membrane builds up to a high enough level that the electrical force driving  $K^+$  back into the cell is equal to the chemical force driving  $K^+$  out of the cell. At this point, the system is at equilibrium.
- The **equilibrium potential** is the membrane potential that exactly balances the concentration gradient for an ion.
- The higher steeper the concentration gradient, the higher the equilibrium potential required to balance that concentration gradient. Normally only a **couple** of ions are required to generate it.

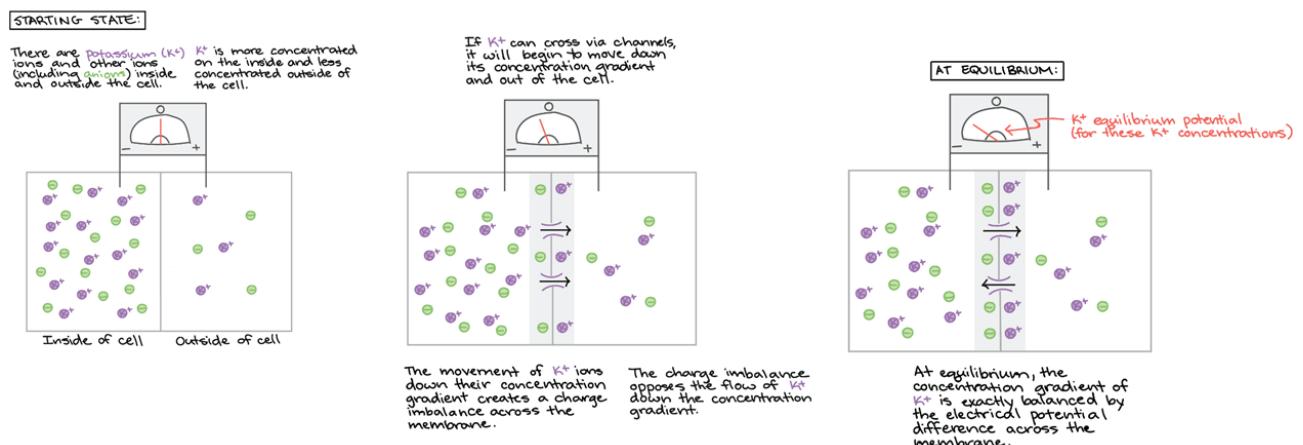


Figure 14: Membrane and equilibrium potentials.

### 3.6.2 Nernst equation

We determine the equilibrium potential using the **Nerst equation**.

$$V_m = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i} \quad (2)$$

- $V_m$  = membrane potential
- $R$  = ideal gas constant = 8.3145 V Cmol/K
- $T$  = absolute temperature (K)
- $F$  = Faraday's constant = 96,485 C/mol
- $z$  = valency of ion  $X$
- $[X]$  = ion concentration inside (i) or outside (o) cell

### 3.6.3 Predicting the direction of ion movement

- When an ion is not at equilibrium, an electrochemical driving force  $V_{DF}$  acts on the ion, causing its net movement down its own electrochemical gradient.
- The driving force is given by,

$$V_{DF} = V_m - E_x \quad (3)$$

where  $E_x$  is the equilibrium potential.

- The magnitude of the driving force indicates how far the membrane potential is from equilibrium.
- The polarity of the driving force can be used to predict the direction of ion flow across the membrane into or out of the cell as seen in Table 1.

Ionic species	Sign of driving force ( $V_{DF} = V_m - V_{eq.}$ )	Direction of ion flow
Cation	+	Outward
	0	No net flow
	-	Inward
Anion	+	Inward
	0	No net flow
	-	Outward

Table 1: Relationship between driving force polarity and direction of ion movement

## 4 Lecture 4

### 4.1 Describe how the resting membrane potential is generated and how changes in membrane potential occur (in terms of ion flows)

- The resting membrane potential is generated by the uneven distribution of **ions** between the inside and outside of the cell, and by the different permeability of the membrane to different types of ions.
- In most neurons,  $K^+$  and organic anions are present at higher concentrations inside the cell.
- $Na^+$  and  $Cl^-$  by contrast are present at higher concentrations outside the cell.
- This means there are stable concentration gradients across the membrane for all of the most abundant ion types.
- In contrast to the example discussed when addressing equilibrium potentials, if a system only permeable to  $Na^+$  was considered,  $Na^+$  would travel down its concentration gradient, leaving  $Cl^-$  behind, making the inside of the cell positive relative to the outside. Because of this, the  $Na^+$  equilibrium potential will be positive.
- However most resting neurons are also permeable to  $Na^+$  which is main reason why the resting membrane potential is different from the  $K^+$  equilibrium potential.
  - $Na^+$  tries to drag the membrane potential towards its positive equilibrium potential.
  - $K^+$  tries to drag the membrane potential towards its negative equilibrium potential.
- Because of this tug of war, the resting membrane potential exists between the equilibrium potentials of these ions. However it will be **closer** to the equilibrium potential of the ion type with **higher permeability**.
- In a neuron, the resting membrane potential is closer to the  $K^+$  equilibrium potential because the resting membrane is much more permeable to  $K^+$  than  $Na^+$ .
  - If more  $K^+$  channels were opened, the membrane would **hyperpolarise** toward the  $K^+$  equilibrium potential.
  - If more  $Na^+$  channels were opened, the membrane would **depolarise** toward the  $Na^+$  equilibrium potential.
- Changing the number of open ion channels provides a way to control the cell's membrane potential and a great way to produce electrical signals.
- **Note:** At the resting membrane potential, you reach a state that is not negative enough to prevent  $K^+$  efflux, but not positive enough to prevent  $Na^+$  influx. Thus we reach a steady state **not** equilibrium, but there would still be a force on  $Na^+$  and  $K^+$ , albeit no net movement of charge across the membrane because there is a small force (higher permeability) for  $K^+$  efflux but a strong force (lower permeability) for  $Na^+$  influx.

### 4.2 Define depolarisation, hyperpolarisation, electrochemical equilibrium

- **Depolarisation:** Membrane potential more positive than its resting potential.
- **Hyperpolarisation:** Membrane potential more negative than its resting potential.
- **Electrochemical equilibrium:** The point at which the membrane potential exactly balances the concentration gradient of an ion.

#### 4.3 Know the basic cellular physiology mechanisms (6 steps) of how pancreatic $\beta$ cells secrete insulin and the role of specific membrane transport processes and ion fluxes in this process

- The pancreas releases enzymes that aid digestion (exocrine) and synthesises and secretes hormones related to blood glucose homeostasis including **insulin** in the islets of Langerhans of the pancreatic  $\beta$  cells (endocrine).
- Before we discuss the 6 main steps, we begin with a hypothetical  $\beta$  cell in which the  $Na^+-K^+$  ATPase has generated concentration gradients of  $Na^+$  and  $K^+$ .
- The law of electroneutrality states that these cations do not exist in isolation but are paired with anion partners. Here, these anions are simplified to all be  $Cl^-$ . In this state there is no separation of charge and thus no membrane potential.

**Steps:**

- A negative resting  $V_m$  due to  $K^+$  leak:** If  $K^+$  selective ion channels are opened,  $K^+$  will efflux down its concentration gradient, leaving behind its  $Cl^-$  partners. This leads to the inside of the cell being more negative than the outside, generating a negative resting membrane potential of approximately  $V_m = -60\text{mV}$ .
- Glucose transport:** Following a meal, glucose moves into the cell via GLUT4 facilitated diffusion transporters where it is metabolised in the mitochondria to produce ATP.
- ATP sensitive  $K^+$  channels close:** The  $K^+$  channels through which the efflux is occurring are ATP sensitive and some close when the intracellular concentration of ATP rises.
- Depolarisation:** Because less  $K^+$  efflux occurs, the cell is depolarised from  $-60$  to  $-30\text{ mV}$ .
- Voltage gated  $Ca^{2+}$  selective channels open causing  $Ca^{2+}$  influx:** The depolarisation triggers the opening of voltage gated  $Ca^{2+}$  selective channels causing  $Ca^{2+}$  to influx down its electrochemical gradient.
- $Ca^{2+}$  influx triggers exocytosis:** The  $Ca^{2+}$  influx triggers insulin exocytosis by causing insulin vesicles docked at the membrane to fuse with it and release the insulin into the blood.

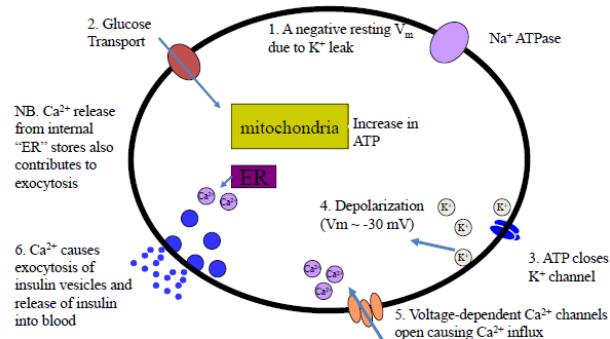


Figure 15: Summary of glucose homeostasis via insulin.

- In reality, there are many other ion channels and transporters involved and communicate to each other to elicit bursts of action potentials and  $Ca^{2+}$  in response to glucose.

## 5 Lecture 5

- 5.1 Define the concepts of voltage-dependent gating, activation and inactivation
- 5.2 Understand the physiological mechanisms of the action potential including:
  - 5.2.1 Draw and label the nerve AP correctly and identify the major phases
  - 5.2.2 Describe the ionic currents that mediate the depolarisation and repolarisation
  - 5.2.3 Describe the ion channels that mediate the above ionic currents, and link the different conformation states of these channels (i.e. their gates) to the different phases of the AP

Before we address the phases of the action potential and their underlying currents, we introduce the ion channels which facilitate this process.

### Voltage gated $K^+$ channel protein

- The voltage-dependent  $K^+$  channel protein consists of 4 polypeptide subunits (tetramer).
- Each subunit consists of 6 transmembrane  $\alpha$  helices.
- The protein also has a pore forming region as well as a region of basic amino acids such as arginine and lysine that have fixed positive charges in their structure. This forms a region that has a high density of charges; the voltage sensor that keeps the gate closed until it is stimulated above a threshold.

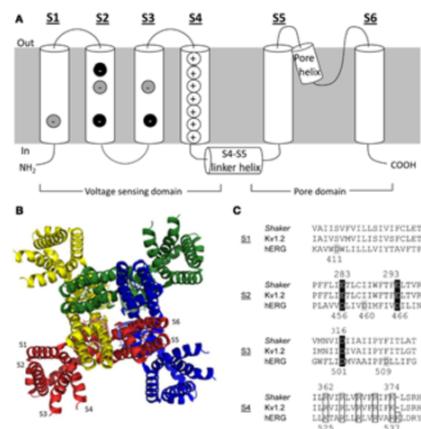


Figure 16: Voltage gated  $K^+$  channel.

### Voltage gated $Na^+$ channel protein

- The voltage gated  $Na^+$  channel protein has two gates; an **activation** and **inactivation** gate with the same voltage sensor.

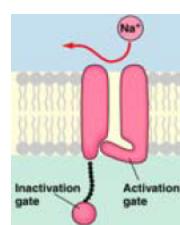


Figure 17: Voltage gated  $Na^+$  channel.

## Stages of the action potential

1. **Stimulus:** A stimulus of positive current is injected into the cell causing a depolarisation from its resting quiescent voltage of  $-70$  mV.
  - If this depolarisation is large enough to exceed or equal the voltage threshold, then an action potential is initiated.
  - If the depolarisation doesn't reach the threshold, no response occurs (all or nothing).
2. **Rapid depolarisation:** If the stimulus current was of sufficient magnitude to exceed or equal the threshold, the voltage sensor triggers the activation gate of the voltage gated  $Na^+$  proteins to open, causing an  $Na^+$  influx. This causes a rapid depolarisation of the cell to  $+40$  mV.
3. **Slow repolarisation:** A slow repolarisation is then caused by the slow closing of the inactivation gates of the  $Na^+$  channels which are incapable of opening until the cell has returned to the resting membrane potential. As the membrane permeability to  $Na^+$  declines, the slow voltage gated  $K^+$  channels open producing a  $K^+$  efflux. This expulsion acts to restore the negative resting membrane potential of the cell.
4. **After-hyperpolarisation:** Due to a period of increased  $K^+$  permeability, there is an excessive  $K^+$  efflux before the activation gates of the  $K^+$  channels slowly close. This results in hyperpolarisation. The  $Na^+$  channels begin to reset. The cell cannot fire during this refractory period.

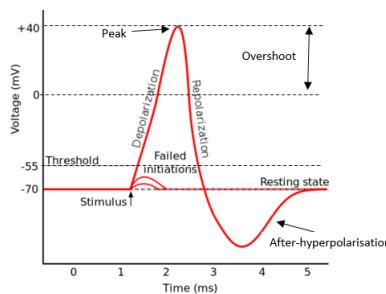


Figure 18: Diagram of a nerve action potential.

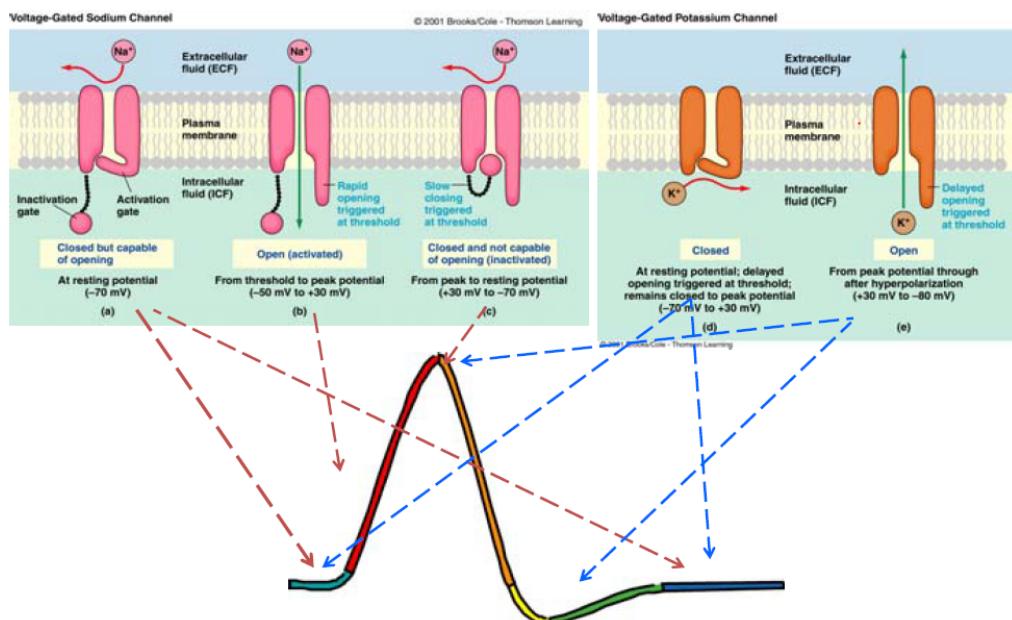


Figure 19: Summary of action potential generation.

**Note:** Ventricular APs are much slower because you don't want it contracting 300 times a second. It has a plateau region of  $Ca^{2+}$  influx balanced by  $K^+$  efflux and then repolarises.

#### 5.2.4 Describe the role of passive and active propagation in how the AP travels along an axon

- An action potential is generated in a specialised region of high  $Na^+$  channel density which in a sense lowers the threshold called the **axon hillock**.
- The signal must then be communicated to other cells by travelling along the axon and reaching the synaptic regions.

##### Passive propagation

1. Some positive current enters at a point, causing a depolarisation at that point (e.g. starting at the axon hillock).
2. The point of depolarization is more positive with respect to the resting membrane potential. This initiates a spread of current along the length of the axon that passively depolarizes adjacent sections of the axon.
3. However, some of this local current leaks out across the cell membrane (via leak or other channels), and hence the depolarisation gets smaller and smaller as it moves along the axon.

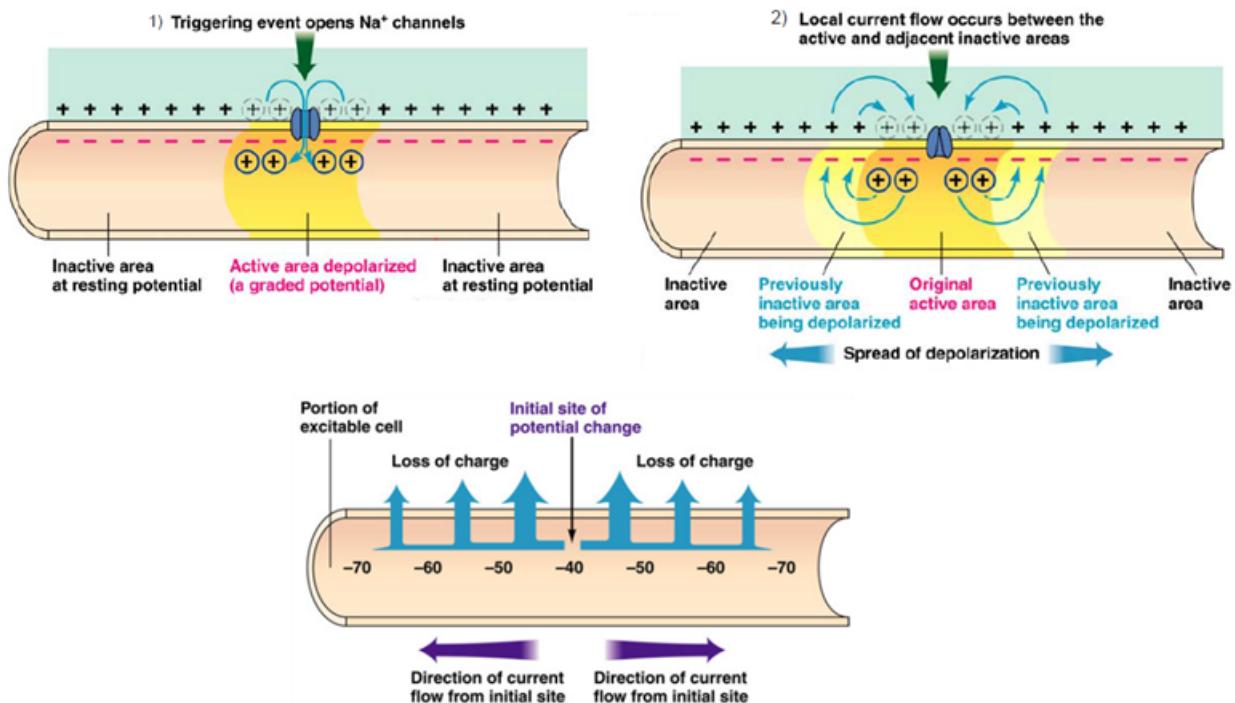


Figure 20: Passive propagation

##### Active propagation

- Active propagation enables the voltage to propagate for longer distances without failing. Along the axon, there are voltage gated  $Na^+$  channels that open when a threshold voltage is reached. Passive propagation facilitates the threshold to be reached by adjacent sections, leading to a depolarisation which cyclically propagates down through the axon as seen in Figure 21.

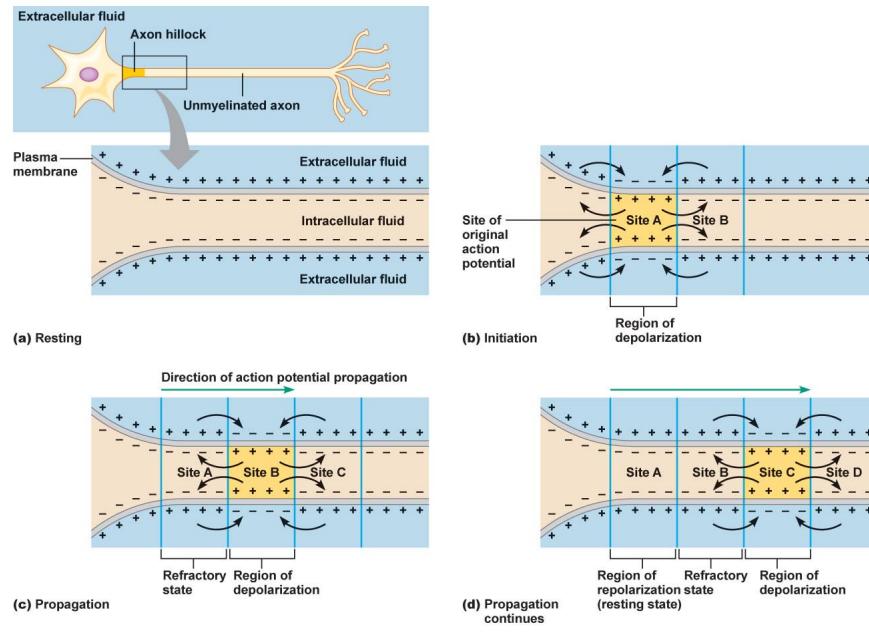


Figure 21: Action potential propagation

### 5.2.5 Appreciate what myelin is and how it affects AP propagation

- Some central/peripheral axons are myelinated. These insulation wraps enable the passive depolarisations to spread much further and hence increase conduction velocity.
- The need for ionic fluxes along the entire axon is reduced, so also increases efficiency.
- The jumping nature of the spread of depolarisation is called **saltatory conduction**. Voltage-dependent  $Na^+$  channels and transmembrane ionic influx occurs only at the **Nodes of Ranvier**, located between the myelin sheaths.

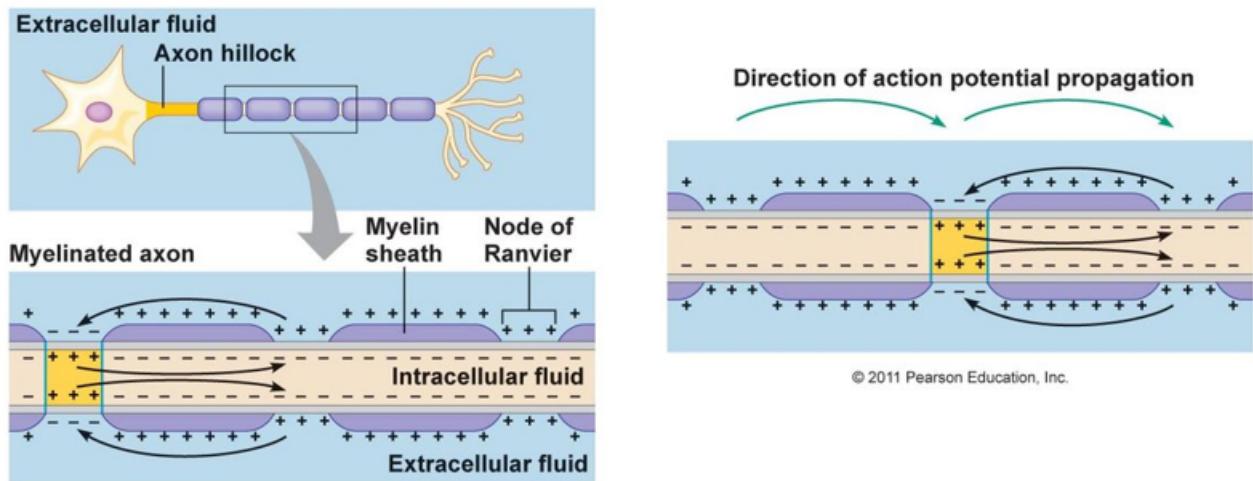


Figure 22: Saltatory conduction

### 5.3 Describe the cellular basis of electrical communication between cells and its broad function

Cells do not act in isolation. There are two broad types of cell communication.

#### Electrical communication

- Instead of wires, adjacent cells communicate via **connexons**; groups of multiple connexins.
- Because of these channels, adjacent cells have the same  $V_m$ .
- If the membrane potential of one cell changes, the  $V_m$  of the adjacent cells also changes allowing the simultaneous firing of an action potential as opposed to independent generation.
- The broad function is synchronisation which is especially important in the **peristalsis of the GI tract**.
- If these channels are found at the synapses, they are called **electrical synapses**.

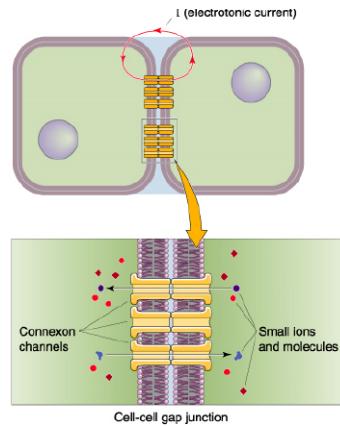


Figure 23: Electrical communication via connexons

#### Chemical communication

- Addressed in next lecture.

## 6 Lecture 6

### 6.1 State the similarities and differences between autocrine, paracrine and endocrine signaling

In general, in chemical communication, all cells synthesise and release chemicals that travel to target sites in order to elicit a response. The main differences are described below.

#### 1. Autocrine signalling

- A cell releases a ligand that binds to receptors on its **own** surface or receptors inside the cell.
- Important during development in helping cells take on and reinforce their correct identities and is thus thought to play a key role in metastasis.

#### 2. Paracrine signalling

- Cells communicate through the release of ligands that diffuse to other cells between small inter-cellular spaces.
- Ligands degrade quickly; used to elicit quick response.
- Used to locally coordinate activities with neighbour cells.
- Impact development by telling neighbouring cells what cellular identity to take on.

#### 3. Endocrine signalling

- Specialised cells in the endocrine glands synthesise and release signals which use the circulatory system to travel to distant parts of the body called **hormones**.
- Hormones are the master regulators of development and physiology.
- Slow but long lasting response.

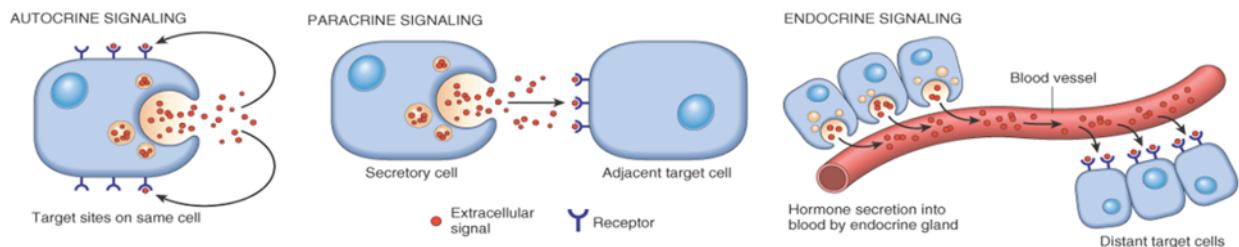


Figure 24: Chemical signalling modes.

### 6.2 Know the 8 steps involved in synaptic transmission at the neuromuscular junction in correct sequence

- The neuromuscular junction is where motor neurons talk to muscle cells.
- The axon terminal is the end of an axon where a neuron casts a signal away. It gets larger at the end and tapers back off.
- Muscle cells sit adjacent to these axon terminals across the synaptic cleft.
- These cells have "in foldings" which maximise the surface area and thus space for cation selective channels that facilitate the transmission of signals into the muscle cell.

### Steps in synaptic transmission

1. An action potential travelling along the motor nerve causes a depolarisation in the pre-synaptic motor nerve terminal.
2. The depolarisation activates voltage gated  $Ca^{2+}$  channels sitting in the membrane resulting in a  $Ca^{2+}$  influx into the terminal.
3. At the axon terminal are docked vesicles containing a neurotransmitter called acetylcholine (ACh). The  $Ca^{2+}$  influx signals the exocytosis of ACh and its diffusion across the synaptic cleft.
4. ACh binds to cation selective nicotinic ACh receptors at the specialised post-synaptic region known as the end plate. This facilitates the influx of  $Na^+$  and  $K^+$  to a lesser extent. There is a weaker force for  $K^+$  efflux and a strong force for  $Na^+$  influx.
5. The net inflow of  $Na^+$  causes a depolarisation of the post-synaptic membrane and a small end-plate potential (EPP). Many smaller EPPs summate and spread beyond the endplate.
6. The depolarisation of the muscle membrane potential cross the voltage threshold and causes a muscle action potential.
7. Meanwhile, nicotinic ACh receptors close, and ACh is decomposed into choline and acetate by the enzyme acetylcholinesterase found at the endplate.
8. Choline is recycled back into the nerve terminal where it can be used to resynthesise ACh.

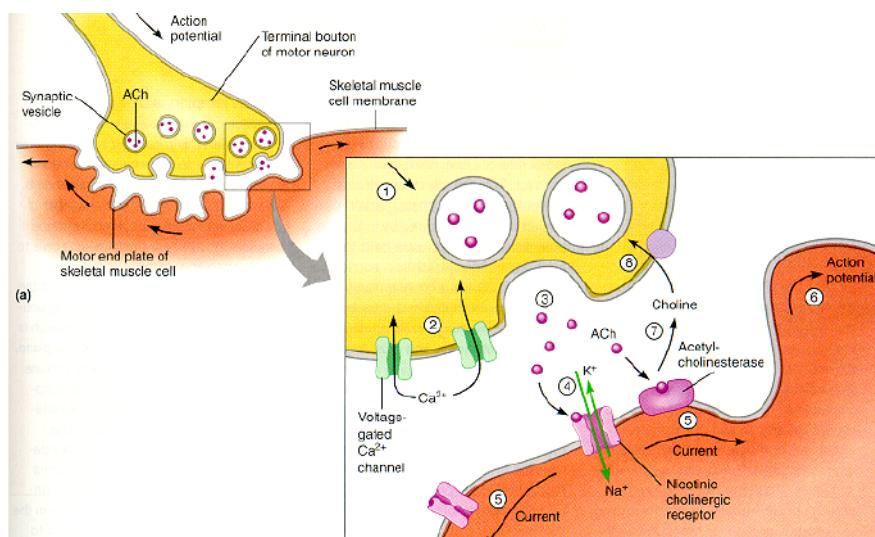


Figure 25: Synaptic transmission.

### 6.3 Compare and contrast the broad features of signaling via ionotropic and metabotropic receptors, with an example of each

There are two broad classes of receptor proteins that are activated by neurotransmitters:

- **Ionotropic receptors:**

- Membrane spanning ligand activated ion channels.
- This may have an excitatory or an inhibitory effect depending on the ions that pass through the channel and their concentrations inside and outside the cell.
- Produce rapid physiological responses.
- Current stops as soon as neurotransmitter is no longer bound to its receptors.

- Neurotransmitter is removed from the synapse very quickly thanks to enzymes that break it down or neighbouring cells that take it up.
- **Example: Nicotinic ACh receptors** at the neuromuscular junction open in response to ACh binding causing a depolarisation of the target cell.

- **Metabotropic receptors:**

- The receptor is not itself an ion channel.
- Activating this receptor via the binding of a ligand activates a second messenger which elicits a response whether this may be opening or closing ion channels indirectly.
- Because it involves more steps, signalling is much slower than with ionotropic receptors.
- Some have excitatory effects when activated (more likely to fire an action potential) while others have inhibitory effects.
- Signalling through metabotropic receptors can also have effects on that postsynaptic cell that don't involve ion channels at all. Broad scope; amplification, cross modulation.
- **Example: Muscarinic ACh receptors** in the heart muscle trigger signalling pathways in the target cell that inhibit firing of an action potential.

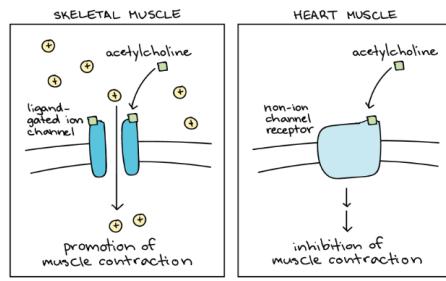


Figure 26: Ionotropic nicotinic receptor and the metabotropic muscarinic receptor.

Below are some neurotransmitters and their receptors types.

Excitatory postsynaptic potential (EPSP, depolarisation)			
Table 1 Ligand-gated ion channel neurotransmitter receptors	Neurotransmitter	Receptor type	Channel selectivity
Same gene family (i.e. common structure & mechanisms)	Acetylcholine	Nicotinic (peripheral) Nicotinic (neuronal)	$\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$ $\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$
	Adenosine triphosphate	P2X1-7	$\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$
	Glutamate	NMDA AMPA Kainate	$\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$ $\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$ $\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$
	$\gamma$ -Aminobutyric acid (GABA)	GABA <sub>A</sub> GABA <sub>C</sub>	$\text{Cl}^-$ $\text{Cl}^-$
	Glycine	GlyR	$\text{Cl}^-$
	5-Hydroxytryptamine	5-HT <sub>3</sub>	$\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$

AMPA,  $\alpha$ -amino-3-hydroxy-5-methylisoxazolepropionate; NMDA,  $N$ -methyl-d-aspartate.

**Inhibitory Postsynaptic Potentials  
(IPSPs, hyperpolarisation)**

Figure 27: Common neurotransmitters and their receptors.

#### 6.4 Describe an example of how an EPSP and an IPSP may be generated at a synapse, including the ion(s), receptor and chemical involved.

- Postsynaptic depolarisations make it easier to reach threshold and generate an action potential and thus a **excitatory postsynaptic response (EPSP)**.

Example:  $Na^+$  influx through glutamate-gated cation channels.

- Postsynaptic hyperpolarisations make it harder to reach threshold and is thus an **inhibitory postsynaptic response (IPSP)**.

Example:  $Cl^-$  influx through GABA-gated anion channels.

#### 6.5 Appreciate that a nerve cell must integrate or summate EPSPs and IPSPs and describe how EPSPs and IPSPs affect the ability of nerve cells to generate action potentials

- A neuron may receive up to 1000 single synaptic inputs each with a small EPSP, IPSP and conductance shunt.
- The nerve cell has to decide if it will change its firing rate to become more excited or inhibited.
- It makes this decision by summing these small inputs into a total input and decide overall whether it wants to become more depolarised or hyperpolarised by changing its firing.
- The cell soma summates these signals in time (inputs happening at the same time) and space (inputs from different locations).
- The whole brain function is basically a balance between excitation and inhibition .e.g. the tricep needs to relax when the bicep contracts.

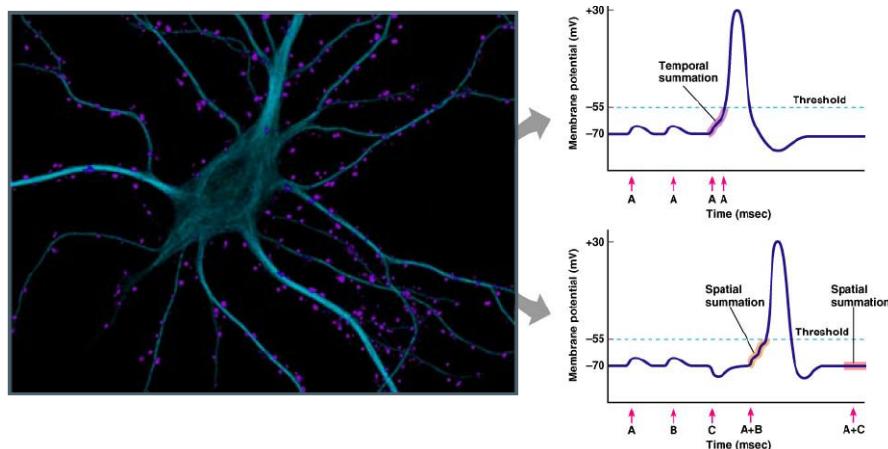


Figure 28: EPSP and IPSP summation

#### 6.6 List the different ways that chemical signalling is terminated and be able to describe an example of one of these

1. **Uptake transporters:** Some neurotransmitters have specific transport proteins that recycle them back into the axon terminals that released them .e.g. GABA via symporters.
2. **Enzyme breakdown:** .e.g. ACh broken down by AChE at the neuromuscular junction.
3. **Densensitisation/internalisation:** The receptor itself may become less sensitive or change its concentration or location in the membrane.
4. **Diffusion or flow:** The chemical leaves the receptor, e.g. a hormone carried away by blood, transmitter diffusing away from a synapse.