# PSL300 membrane notes

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# 1 Membrane Potentials

Review points:

1. The cell membrane is not rubber bag; it's composed of a phospholipid bilayer

2. Lipid soluble molecules and gases diffuse through readily

3. Water soluble molecules cannot cross without help

4. Impermeable to organic anions (proteins)

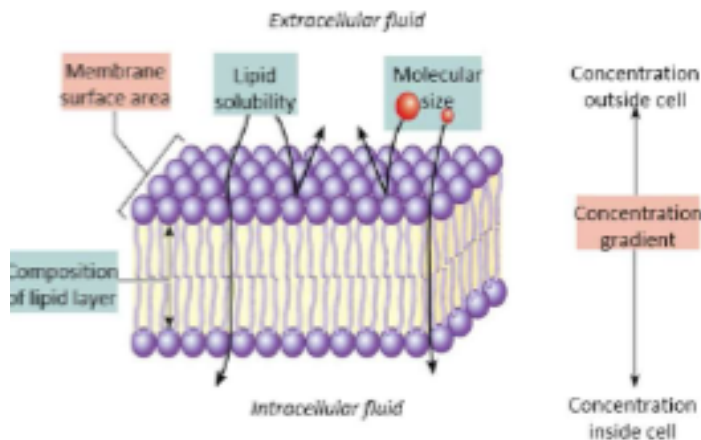5. Permeability depends on **molecular size, lipid solubility, and charge**



Figure 1: Cell membrane (from lecture slides)

If a substance can cross through membrane by any means, it is permeable.

> **Definition 1: Concentration Gradient**
>
> Concentration gradient (shorthand: [] gradient) is the difference of concentration of a molecule on the outside of the cell membrane vs inside. Going "down" the concentration gradient means going from high to low concentration (the entropically favourable thing).

## 1.1 Simple Diffusion

Small lipid soluble molecules and gases ($O_2$, $CO_2$, ethanol, etc.) either pass directly through phospholipid bilayer or through pores. This involves Brownian motion (outside scope of the course). Movement of substance is down it's concentration gradient. Relative rate of diffusion is roughly proportional to concentration gradient. No energy input (ATP) required.
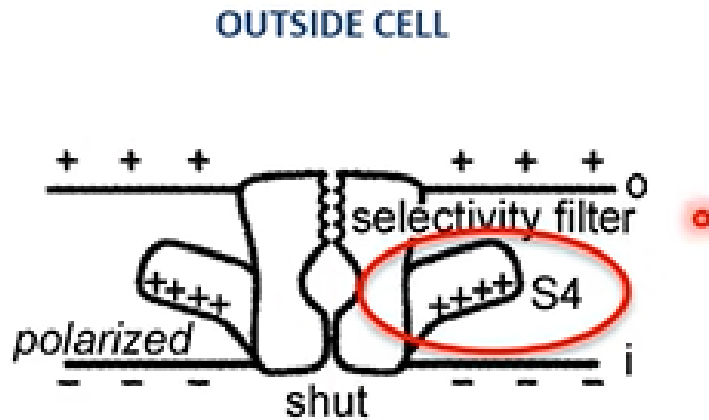
**OUTSIDE CELL**

Figure 2: S4 wings (from lecture slides). The "natural" position is up and open, but polarization causes them to clamp down and shut the gate

## 1.2 Facilitated diffusion

Needs assistance of carrier proteins (kind of like drawbridges, embedded in the membrane, but proteins themselves don't cross). Moves polar (sugar, amino acids, etc.) molecules across cell membrane down the concentration gradient. Energy comes from concentration gradient of solute. There are only so many carrier proteins, so it's not a continuous process. The outside side of the protein opens, the molecule enters, then opening closes, then the intracellular gate opens.

## 1.3 Active transport

Transport against concentration gradient. requires energy from ATP. Substance binds to protein carrier. Most common example is Na+/K+ ion pumps.

## 1.4 Secondary Active Transport

Rides the coattails of primary active transportation; involves sequential binding of substance. SAT is powered by chemical energy in substance diffusing down it's gradient (stored creates a delta, like a capacitor) and this is used to "push" some other substance against its concentration gradient.

## 1.5 Channels

Channels in a membrane; 4-5 protein subunits create central pore, lets specific ions diffuse through. Pores are always open, not selective, but channels are usually gated and very selective. Can be either ligand gated channel, or voltage gated channel.

### 1.5.1 Ligand gated channels

Cell membrane receptors part of body chemical signalling system. Binding of receptor with ligand triggers events at membrane, such as activation of enzyme.

### 1.5.2 Voltage gated channel

Some membrane channels are sensitive to potential difference across membrane (e.g. depolarization). Usually has negative voltage inside. Voltage sensing mechanism is in 4th transmembrane domain of protein, S4 segment (positively charged wings).

# 2 Endo/exocytosis

**Definition 2: Endocytosis**

Endocytosis: inward pinching of membrane to create vesicle (pouch holding membrane) to capture protein from outside to inside.

# 3 Membrane potential (MP)

MP is the potential difference across cell. A *negative* MP means that the inside of the cell is more negative than the outside. All cells generate MP; if non negative potential on the inside and the MP is 0, the cell is probably dead. For a neuron, the MP is typically around -70 mV. An MP requires 2 conditions.

1. To create a concentration gradient, we need an enzyme ion pump. Ions move down that concentration gradient.

2. We also need a semi permeable membrane to allow certain ion species to diffuse more (or at different rates).

All cell membrane have Na+/K+ pumps. Breaks down (hydrolyses) ATP so that energy is used to move ions against it's concentration gradient. For each ATP, 3 Na+ ions are pumped out, 2 K+ ions pumped in. Pump alone creates potential difference of -10mV. Consumes 1/3 of energy needs of body. But in neurons, this process consumes 2/3rds of total energy.

## 3.1 Resting membrane potential

Due to existence of semi permeable membrane. K diffuses out of cell, down concentration gradient. Cations accumulate on the outside of the membrane, leaving net negativity inside membrane. At rest, the membrane is very permeable to potassium until *electrochemical equilibrium* (when chemical force outwards (gradient) matches electromagnetic force inwards (positive charge); equal and opposite. then it closes. Membrane potential at equilibrium is determined by concentration gradient.

## 3.2 Nernst equation

In an ideal situation, (only potassium ions move, can never really happen) You get -90mV for equilibrium potential of K (what ptassium wants the membrane to be (if potasium channels were open and nothing else). Typical neuron is -70 to -80 mV since Na and Cl ions are diffusing a bit. The actual membrane potential is calculated from expanded nernst equation (Goldman equation):

$$E_m = RT/Fln(\text{outside concentration/inside concetration} \tag{1}$$

At rest, potassium ion is the biggest contributor. If the membrane were more permeable to sodium, can use nernst equation. We know at rest, sodium channels are not very open. What if they're too open? The membrane becomes more positive on inside. Sodium then diffuses along a concentration gradient until membrane becomes positive on inside (when it reaches equilibrium, sodium has an MP of about +60 mV (should be positive)). The actual membrane potential is closer to -70 mV because the membrane more permeable (35-45x more) to potassium than sodium.

## 3.3 CL ions

No pump, but due to existence of negatively charged proteins in the molecule that can't get out except via exocytosis, Cl ions are concentrated on outside. Creates relatively small concentration gradient.

## 3.4 Sodium channels (add graphics later, clunky)

To generate action potential (signal), membrane increases conductance by opening a channel only permeable to Na+ ion (voltage gated). In normal resting MP, channel is shut. To open channels, we need to make the inside of the membrane a little more positive. This will move the wings upwards to allow passage of sodium from the outside to the inside. The wings are closed at -70mV, but if something causes the MP to depolarize to about -55mV, the gate opens. That number is called the threshold potential. After that number, things happen very quickly, since it's a positive feedback loop. There is an inactivation gate (kinda like a drain plug or a ball and chain) on the inside of the membrane that closes the channel half a millisecond after depolarization. Without the inactivation gate, the MP should get to +60 mV (sodium equilibrium potential). Activation gate opens at threshold, and is still open when the **inactivation** gate is closed. The inactivation gate is time and voltage dependent. Closed until MP goes *below* (more negative) activation potential. Action potential is an impulse, short lived change. Can only

produce AP in membrane that has enough voltage gated Na channels, which are called "excitable" membranes. When channels open, MP becomes closer to voltage equilibrium potential (60 mV) but it never reaches because it closes 0.5 milliseconds after. MP reaches maybe +30 mV. Only left with potassium leakages as main current. We know we have more potassium inside than outside.

Types of stimuli:

1. < 15 mv: Subthreshold stimulus, opens some sodium channels, but not enough to overcome potassium outflow.

2. ~15 mV: Threshold stimulus just enough to start AP

3. > 15 mV Suprathreshold, more than enough, but still same level of MP reached. All or nothing principle (APs are binary, like an on/off switch.

Information is encoded in changes in frequency of action potentials. 10 millisecond threshold stimulus, can maybe generate 1 action potential.

## 3.5 Refractory period (RP)

> **Definition 5: Absolute refractory period**
>
> In the absolute RP, none of the channels are reconfigured, so no action potential is generated no matter what. The maximum frequency is governed by this.

> **Definition 6: Relative refractory period**
>
> In the relative RP, some of the channels are reconfigured. This lasts about 2-5ms. We could generate another AP, but it's less likely since there are fewer open channels.

> **Example 1: Lethal injection**
>
> We could block a membrane from producing APs by making it permanently depolarized. If we kept the MP at +30 mV for example, the sodium channels become permanently inactivated. This kills cells and thus people. If you added KCL, you remove the concentration gradient. Potassium is no longer leaving the cell, so the membrane remains depolarized.

## 3.6 After-hyperpolarization

K+ voltage gated channels open up after coming back down below threshold. But with the existence of extra channels, becomes more negative, and overshoots the original -70 mV. This happens after the generation of AP. Might repolarize to somewhere like -80 mV.

# 4 Impulse conduction

In an AP. local reversal in potential temporarily goes from - to + on inside. This propagates from wherever it originates to rest of cell in **all directions**. One AP creates current, which creates AP in an adjacent patch of cells, etc. Most cells are not excitable bc they lack voltage gated Na channels, but will still conduct passive current, just won't generate AP. Most cells also won't carry a signal any distance, without an axon. An axon is like a wire that carries AP to other location. Only neurons with long axons and muscle cells generate APs. Tissue is poor conductor, we lose about half of the potential difference. Due to capacitive property of tissue, the wave becomes more triangular with rounded top rather than square (less magnitude too)

## 4.1 Cable properties

> **Definition 7: Length Constant**
>
> $\lambda$, the length constant measures how fast potential difference decays to zero as a function of zero. Lambda increases with increasing diameter, since there is less internal resistance. Lambda is also increased with increasing membrane resistance, since less current leaked out, current forced down membrane (**NOTE:** *internal* resistance is lower, but the walls have higher resistance, so less leakage.)

$$\lambda = \sqrt{\frac{R_m}{(R_i + R_o)}}$$

, but since $R_i >> R_o$, we can ignore that term. $R_i$ is internal resistance (decreases with increasing radius), $R_m$ is membrane resistance. $R_o$ is extracellular fluid resistance. $\lambda$ is the distance you can travel until voltage drops around 37% of original. We want to increase that as much as possible so that current goes further. Changing axon diameter is kinda very hard to do physically, so it's more practical to increase membrane resistance (myelination).

> **Definition 8: Glial Cells**
>
> Glial cells are kinda like a glue for the system. Specialized glial cells (Schwann in the peripheral nervous system, oligodendrocytes in the central nervous system) wrap around an axon, a myelin sheath of 50-100 layers. Reduces leakage outside membrane. increases lambda by maybe 25x.

Only a minority of axons are myelinated. Schwann cells wrap around one axon, squeezes out cytoplasm. Oligodendroctye is like an octopus, wraps around bunch of axons individually.

> **Definition 9: Node of Ranvier**
>
> The gap between adjacent glial cells is called the node of Ranvier. This is only place where AP can be generated, because it's the only place where voltage gated channels can exist (otherwise you run into the myelination).

Saltatory conduction (jumping) between nodes. In myelinated portion, there is no AP, it just passively passes current. One node can generate enough PD for 5-10 nodes, it will all be in different phases though (preceding nodes lead). The only relevant node is the last node down the line, becomes depolarizing force for next 10 or so nodes. If some nodes are damaged, the process still can work, need to destroy fair length of membrane to stop an AP.

> **Example 2: Multiple Sclerosis**
>
> You can get MS if myelination is damaged. Signal gets leaked more, difficulty sending signals to/from brain.

## 4.2 Unmyelinated axons

There is lots of leakage in those. both Na and K channels are mixed and have some insulation. Schwann cell/oligodendroctye engulf axons (5-30 axons) without winding: called a remak bundle. This improves membrane resistance. AP will be conducted until the end of the axon. Still generates depolarizing current. An AP **cannot** "turn around" because of the refractory period (the preceding cell is probably still in absolute refractory period), and it eventually dies out. It can only go one direction.

# 5 Synapses

Functional association of neuron or effector organs.

1. Electrical synapse, kinda like twisting two wires together. They're about 35 angstrom apart. Transmitted from one cell to the next. bidirectional and Bridged by connexin proteins.

2. Chemical synapse. most common. transmitted (dopamine, etc) through snaptic cleft (gap) is about 200 angstrom wide. very specialized space due to existence of post synaptic membrane. contain specific protein receptors which bind that transmitter molecule.

Axons end in Boutons filled with vesicles (tiny organelles containing neurotransmitters, released into ECF). The trigger for exocytosis is calcium ions. Bouton membrane contains VG calcium channels, which open when depolarized by AP currents. AP depolarizes membrane, reaches threshold for opening VG CA channels (approx -50mV). These then diffuse into bouton, triggering reactions which result in vesicle exocytosis (kiss and run type = transient. Or full fusion = all transmitters released). Vesicles are lined up with membrane, calcium makes it fuse with membrane, makes it release contents into membrane.
Chemical synapses are a processing station. vesicle release is **probabilistic**. 1 AP has 10-90% chance of releasing 1 vesicle.

## 5.1 Post synaptic receptors

What happens at the post synaptic cell does not depend on transmitter itself, but rather the receptor.

### 5.1.1 Ionotropic receptors

Simplest: ligand binding opens an ion channel. Change in post synaptic membrane potential (PSP). 20-40 ms (as long as a transmitter is present). Ion channel may be specific for cations, (Na+, K+, known as E(xcitory) PSP (depolarizing) or may be specific for Cl or K:I(nhibiotry) PSP).

Binding and channel opening is in one machinery (quicker). Ligands for ionotropic receptors include **(Acetylcholine, glutamate, GABA, glycine.**. GABA is commonly generated IPSP, becomes a muscle relaxant. Treats anxiety, etc. reduces communication to brain.

### 5.1.2 Metabotropic receptors

Binding of ligand activates enzyme that is usually G protein coupled. Either increased production or destruction of second messengers (cAMP, cGMP, or lnP3) This then activates other enzymes. If we phosphorlate membrane proteins (i.e. ion channels, result in modulation of ion currents). Metabotropic takes time. Might not have effect on MP. Slower EPSP and IPSP, has to go through all enzyme activity first.

> **Example 3: Beta receptor**
>
> Beta receptor: metabolic receptor NA. binding activates adenyll cyclase via G protein alteration. AC increases production of cAMP (2nd messenger). cAMP then activates kinases which phosphorylate membrane Ca channel. increases Ca influx.

Possible ligands for metabotropic receptors

1. ACh

2. peptides

3. catecholamines

4. serotonin

5. purines

6. gases

PSPs are generated in inexcitable part of membrane (neuronal dendrites and cell bodies). Since there are not enough Na channels, this cannot initiate AP. Instead, we have a graded potential, which are lower the further away they are from the stimulus (synapse). Action potential **only in trigger zone**. EPSP must spread through membrane, hoping by the time we reach trigger zone, we still have enough depolarization. Need lots of EPSPs to depolarize. Can sum graded potentials (PSPs). Types of graded potentials:

1. **Spatial Summation:**10-30 synchronous EPSPs in each dendritic tree, from different synapses.

2. **Temporal Summation** few active synapses, each generate a lot of EPSPs. Magnitudes add together. Have to overlap in time though. can sum from same synapse. (staircase sorta effect). need high frequency of input.

In real life, it's always a mixture of both types.

## 5.2 IPSPs

Preferentially located on soma, halfway between EPSP generation and trigger zone. This is so that it can try to shunt/kill depolarizing EPSP current out of cell. IPSPs work by making membrane more negative. IPSP opens CL channel, equilibrium potential (EP) for CL is very close to -70 mV, so opening channel brings MP back when depolarized. IPSP are more important than EPSPs because they shape information, more precise and specific.

## 5.3 Spike train

Powerful post synaptic input, lasts up to 500 ms. We want a lot of APs to generate spike train, we need to hyperpolarize membrane, otherwise never generate spike train.

# 6 Receptor potential

Change in MP due to receipt of signal from exterior sensory cue. Energy in environment reacts with proteins, will cause depolarization (similar to EPSP). Receptor proteins will change shape, can either directly open ion channel. or activate enzyme with G protein coupling, leading to lots of 2nd messengers, **amplifying** signal.
Chemical stimulus. activates G protein, activates adjacent enzyme (could be adynyl cyclase in olfactory for example), produces second messenger (cAMP), activates kinases, directly interacts with ion channels.

## 6.1 Transmission of signal

Located at axon terminal, first patch of excitable membrane at branch point, receptor potential will have to travel and generate summation. This generates receptor potential (graded), which then spreads into trigger zone.

Or, sensory cell releases vesicles when depolarized impulses generated in post synaptic neuron. If DP current produces **no** AP, current travels through membrane, at other end, depolarizes membrane, Influx of Ca+ ions and triggers exocytosis vesicles, sensory cell releases vesicles and doesn't produce AP.

### 6.1.1 Taste receptor

small cell, no AP, only RP. Depolarizing current opens Ca voltage gated pore. 2nd order neurons create AP, because otherwise the brain wont get any signal.

## 6.2 Adaptation

If you were continuously pinched, you don't feel a constant level of pain, i.e. the original voltage is not sustained, and drops over time.

There are two types of adaption:

1. **Slow:** There is always some receptor potential sustained as long as you maintain stimulus. A square wave just becomes almost a triangle, slowly decays. Gives you information about magnitude.

2. **Fast:** rapidly adapting, potential elicited by change in stimulus energy, decays to zero when constant. interested in velocity of stimulus (vibratory, or slope of magnitude).

Pain does not adapt very well.

### 6.2.1 Habituation

Response to successive stimuli, (get used to) less and less voltage.

## 6.3 Coding of stimulus intensity

Greater stimuli intensity means greater receptor depolarization (graded potential) which either increases AP frequency, or more transmitter is released. Also, the greater the depolarization, the faster membrane will recover from hyperpolarization. There exists a "ceiling" for each neuron (how much voltage information it can transfer). If we want to code above ceiling, we recruit additional neurons with a higher threshold, greater stimulus. (different types of receptors).

## 6.4 Modality (labelled line strategy)

Instead of having a receptor for every colour of the rainbow, you can **population code** RGB, The receptive field is the physical territory which you can activate a particular sensory neuron. Receptive fields are smaller in more sensitive areas (fingertips) and larger in less sensitive areas (back, up to $1 - 2cm^2$

# 7 Blood brain barrier (BBB)

The brain and spinal cord are protected. We cannot have a neurotransmitter floating around for no reason. BBB is two fold entity. Between blood vessels and interstitial fluid and also between blood vessels and cerebral spinal fluid(CSF). fills cavities/ventricles in brain. But between intersitial fluid and CSF, there is basically free diffusion, since they are chemically very similar. MSG cannot cross BBB, but it can activate glutamate receptors outside brain and PNS. Pituitary gland connected directly to hypothalamus, BBB purposely broken to allow release of hormones. in "circumventricular organs" third ventricle. BBB is broken is so neurons can sense specific chemical concentration. BBB is broken in areas that interact with endocrine system.

## 7.1 Brain encasings

1. skull (duh)

2. **Duramater:** very tough membrane, sac containing brain and spinal cord

3. arachnoid membrane (delicate tissue)

4. subarachnoid space (filled with CSF, brain floats to protect from mechanical stress.

5. pia matter (lies right on top of brain, tetherd to arachnoid by trabeculae)

Make up cranial or nervous meninges. membranes surrounding csf can bend. endothelial lining of general blood vessels contain large gaps through which molecules pass. in brain, cells are tightly bound, so there are no gaps.

## 7.2   ventricles

Ventricles are filled with CSF. Large curving Lateral Ventricle (LV) (first (right) and second (left) ventricles) areinside each hemisphere, paired across midline. LV empties into 3rd ventricle (middle, deep under cerebral hemisphere). 3rd ventricle communicates via "aqueduct of sylvius" to 4th ventricle. from 4th ventricle, we have canal, connecting to spinal cord. all ventricles have CSF, all connected.

CSF moves around through central canal, to outer parts of brain, then exits at top of brain (large venous sinus). 1/2 of CSF drains through arachnoid villi. Out pouching of arachnoid tissue, through duramater into venous sinu, then drains into venous.

## 7.3   Choroid plexus

CSF is produced from plasma by choroid plexus (lines all of the ventricles) CSF itself is bathing medium of brain, highly regulated ionic content, few macromolecules. eventually drains back into general blood circulation. Occurs without a pump, and allows a cleansing mechanism. Some CSF is produced in brain capillaries. CP is made up of epithlial cells connected by tight junctions. produces 550 ml a day of CSF. CSF fills ventricles and subarachnoid space, has same osmolarity and [Na] as blood. A lot lower K, Ca, and Mg, concentration. avg person has about 215 ML of csf. cranial csf is 140 ml (25 ml in ventricles, 115 ml in subarachnoid space, 75 ml in spinal. most csf is a cushion. replaced about 3 times a day. spinal tap - collects CSF.

## 7.4   Astrocytes

another type of glial cell. look like stars. they are end feet of flial cells. bridge between neurons and blood vessels. atrocytes are efficient at glycolysis, produces lactate as end product. Astroctyes lactch onto blood vessels. Can also help removing neurotransmitters, provide energy substrate. can regulate local blood flow. good spot to signal BV when to dilate/constrict. When lots of activity is happening, send signal upstream, to get more nutrients, etc. in response to glutamate being released (neurotransmitter), can be detected by MgluR receptor (in astroctye) Binds to glutamate, triggers calcium release within astroctye. Wave of calcium travels to through astroctye to feet (touching blood vessel). triggers release of protogrladin. (PGE2), causes vasodilation, increases blood flow.