Fundamentals of neuroscience

Course outline

1. **Part 1: Electrical Properties of the Neuron**

- LESSON 1 THE RESTING POTENTIAL
- LESSON 2 PASSIVE MEMBRANE PROPERTIES
- LESSON 3 ACTION POTENTIALS
- LESSON 4 ACTION POTENTIAL PROPAGATION

2. **Part 2: Networks and Neurons**

- LESSON 1 THE SYNAPSE
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3. **Part 3: The Brain**

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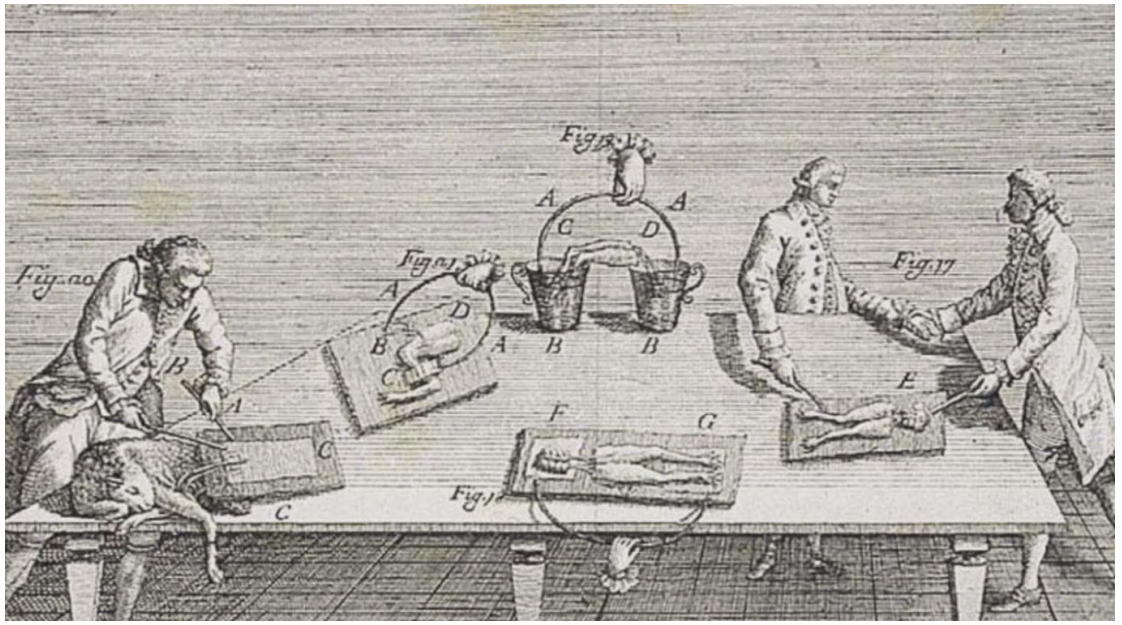
History of electricity

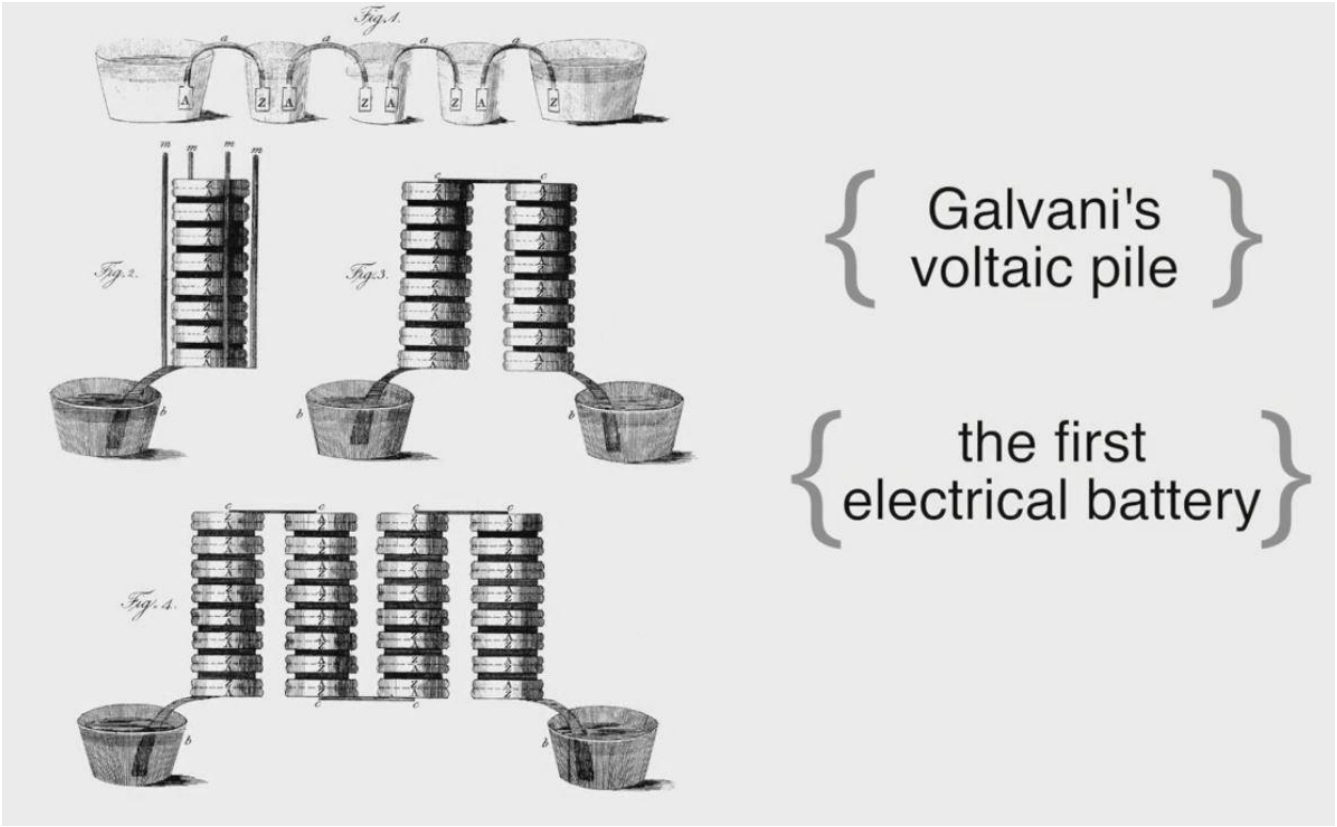
Luigi Galvani was a well-known physician, physicist and philosopher. (Italy)



In 1771, he was dissecting a frog when his assistant touched a nerve in the frogs leg with a metal scalpel that had picked up a static charge. The frogs leg moved!

Galvani thought he had discovered the key to life, an inherent electricity within animals which led to movement. He even posited the existence of an animal electric fluid, that gave rise to the effect.

Alessandro Volta, a physicist and contemporary of Galvani, repeated Galvani's experiments, but doubted the existence of an electric fluid intrinsic to animals.



Spurred on by Galvani's theories, Volta eventually went on to develop the first battery, proving that similar electricity could be generated outside of a living creature.

Volta, Galvani's rival, coined the term **galvanism** to refer to electrical phenomena living creatures, and Galvani's name appears as the root of many modern terms, such as **galvanic** and **galvanometer.**

While Galvani's notion of intrinsic animal electricity wasn't 100% on target, he was onto something -- **bioelectricity** plays a central role in the function of the nervous system.

Parts of nervous system

- There are over 1.3 million named and catalogued species on earth, and scientists estimate there are over 7 million more unnamed, unknown and undiscovered creatures sharing the planet with us.

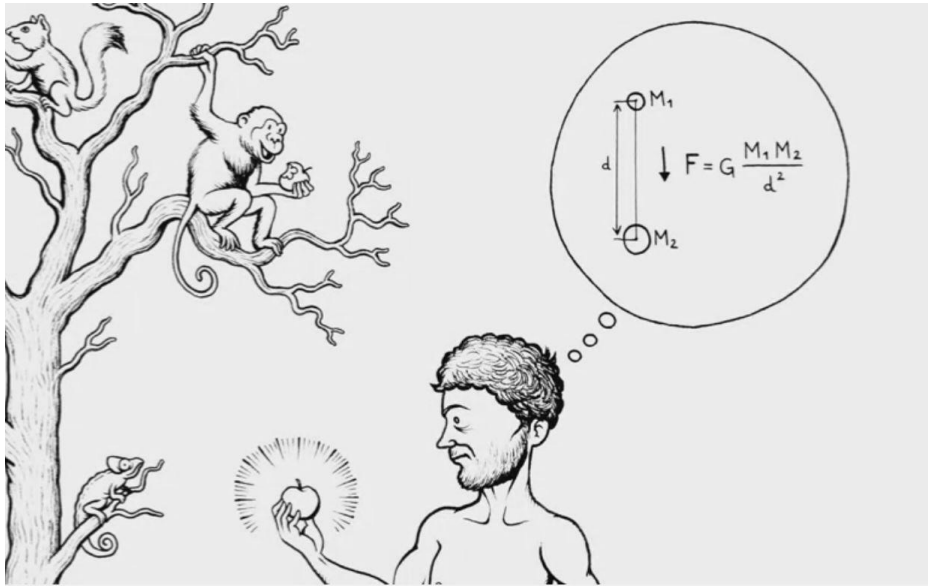
- What is it about humans that makes us distinct?

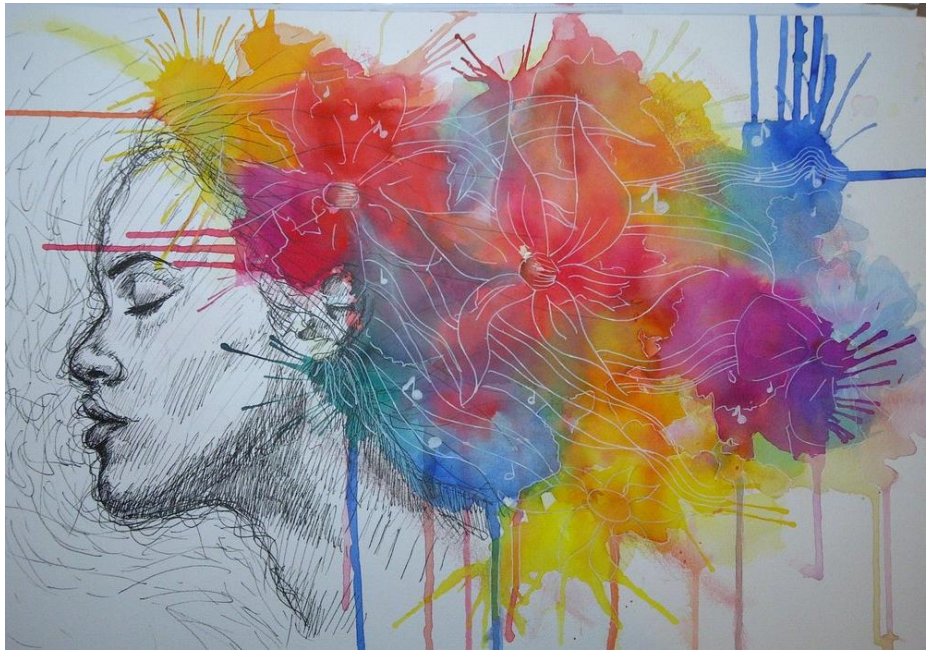
- Modern human behavior arguably emerged between 300 and 30 thousand years ago, when our ancestor's brains began to structurally and functionally resemble our own.

- It was then that humans began to think symbolically.

- Symbolic thought gave rise to language, art, music, religion, philosophy, science and complex technologies that allowed us to circumvent evolutionary and environment constraints.

- Our brains are the key to our evolutionary success.

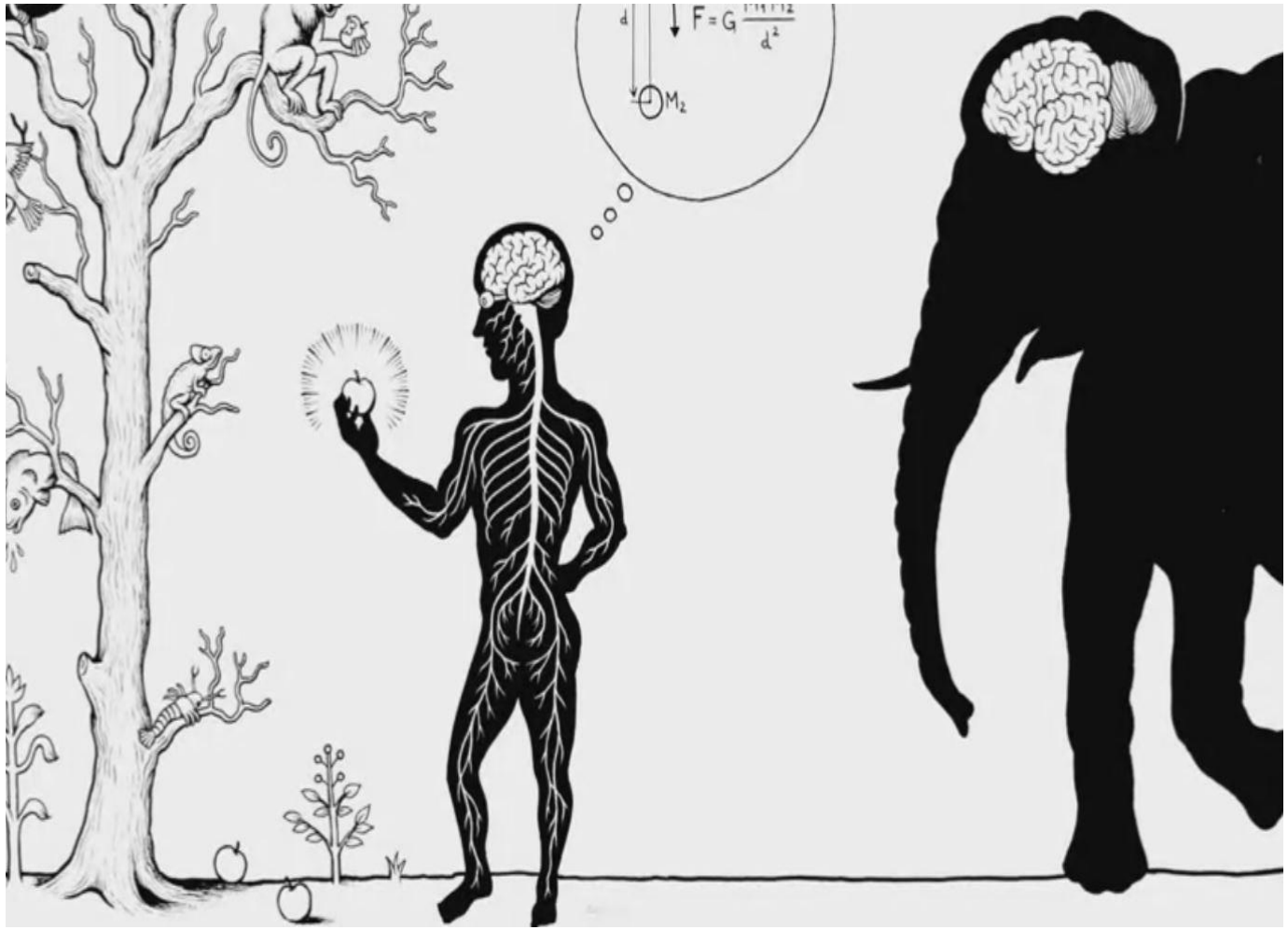




- Weighing in at only about 1.3 kg fully grown, our brain stores our every memory, generates every thought and feeling, and allows us to touch, see, and interact with our world.

- Our brains are among the largest in the animal kingdom, but elephants, whales and dolphins have even bigger brains. So clearly size isn't everything.

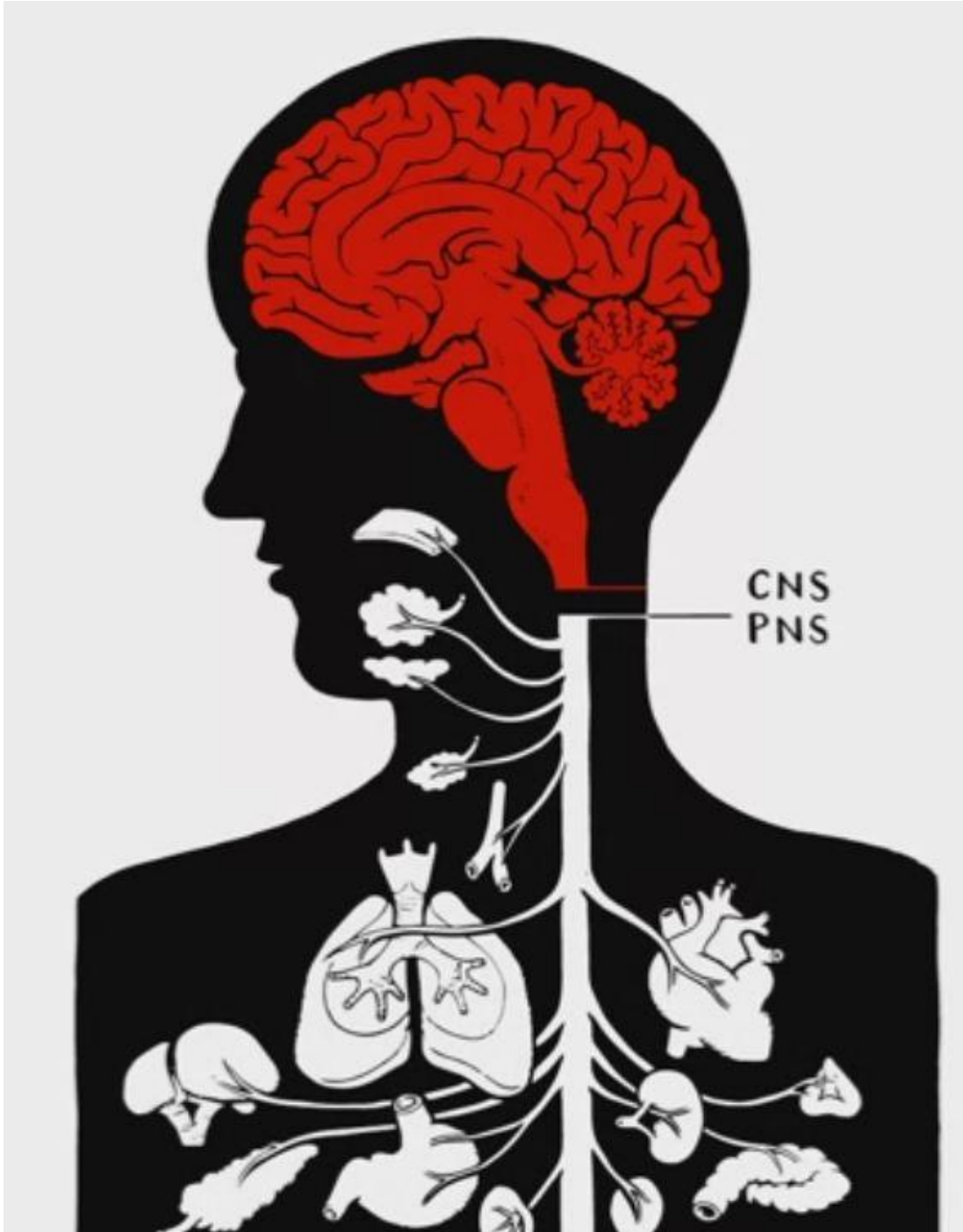
- The key to the human brain's unique capacities is not its size, but its inner wiring.



- The brain and spinal cord form the first great division, our central nervous system (or CNS).

- The second great division is the peripheral nervous system (or PNS).

- The brain sends messages via the spinal cord to the peripheral nerves throughout the body that control our skeletal muscles in our arms and legs, and internal organs.

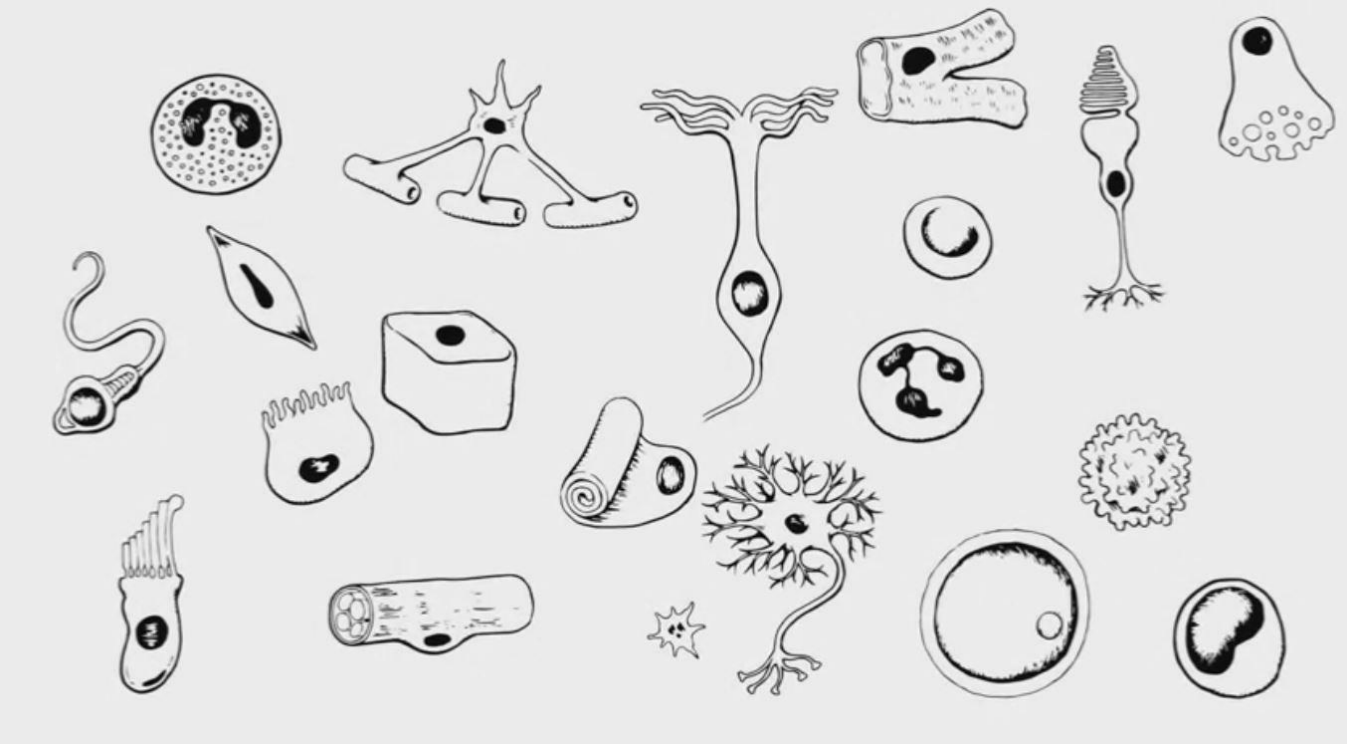


- Messages are carried throughout central and peripheral nervous system by specialized cells.

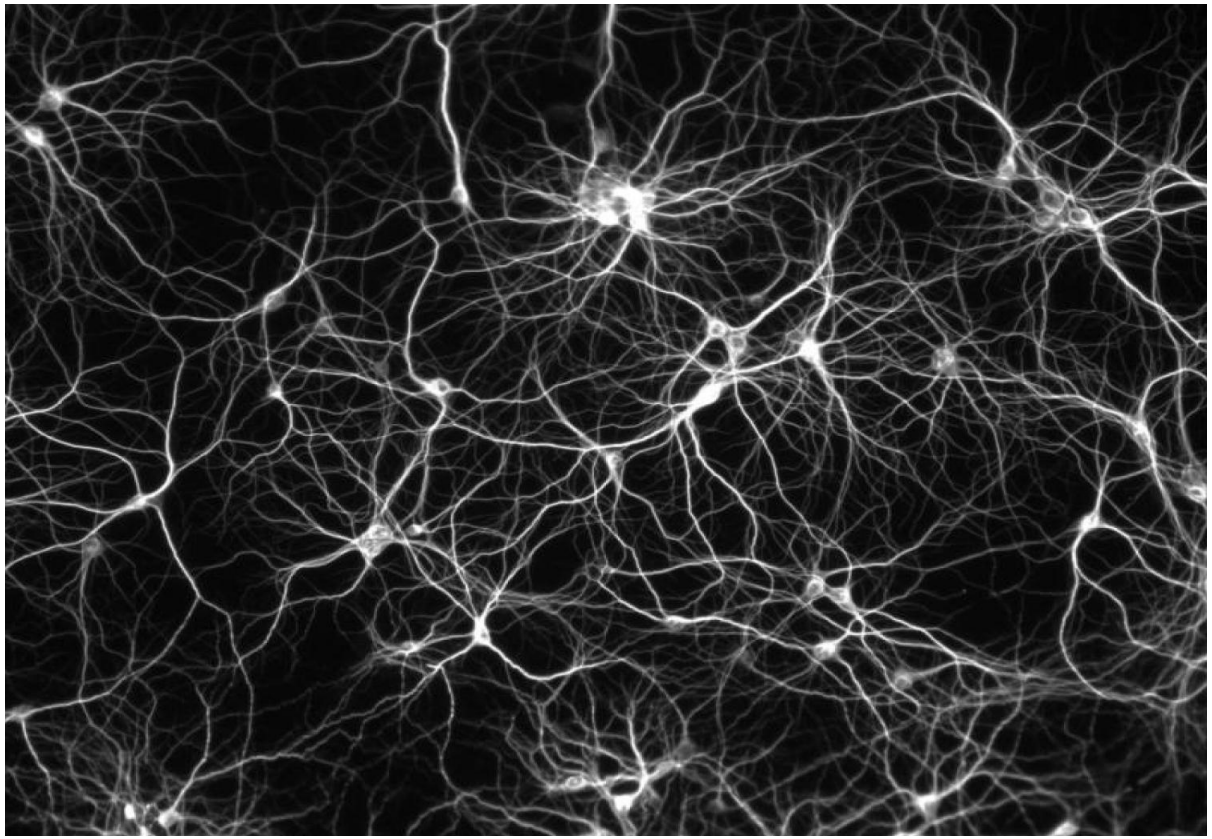
- Cells are the smallest structural and functional unit of a living organism, and the human body contains over 300 different types with highly specialized functions.

- Cells that can receive, process and transmit electrical impulses in our nervous system are called **Neurons**.

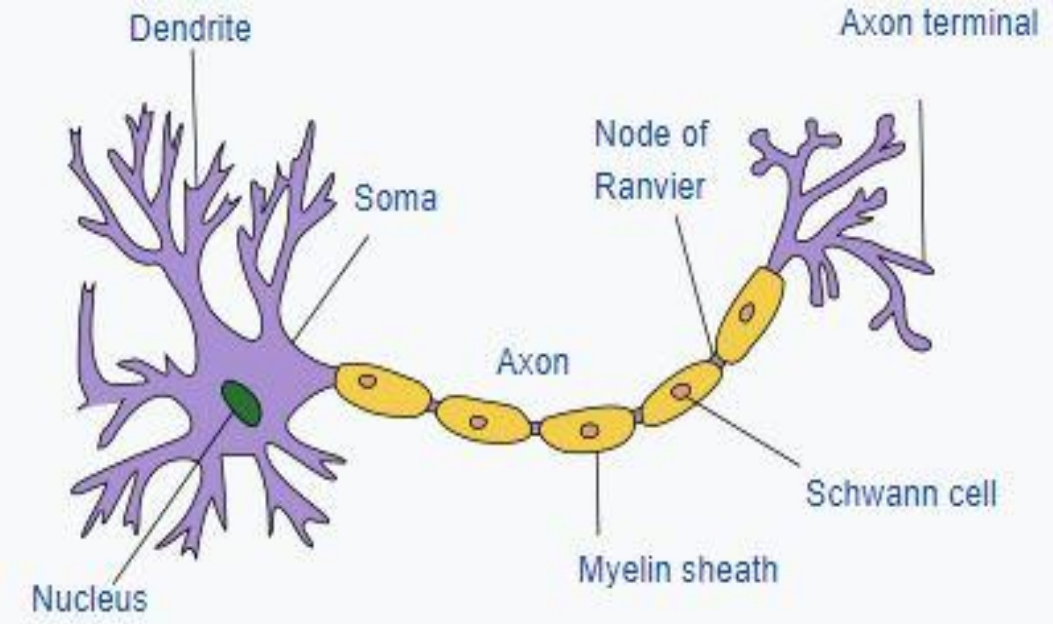
- Staggeringly complex, the brain is made up of some **100 billion neurons**, plus a myriad of other cell types.



Networks of neurons exchange information among dozens of brain areas specialized for different tasks, and researchers suspect that it is something about the organization and function of these networks that may hold the key to our uniquely human brain.



Neuron structure



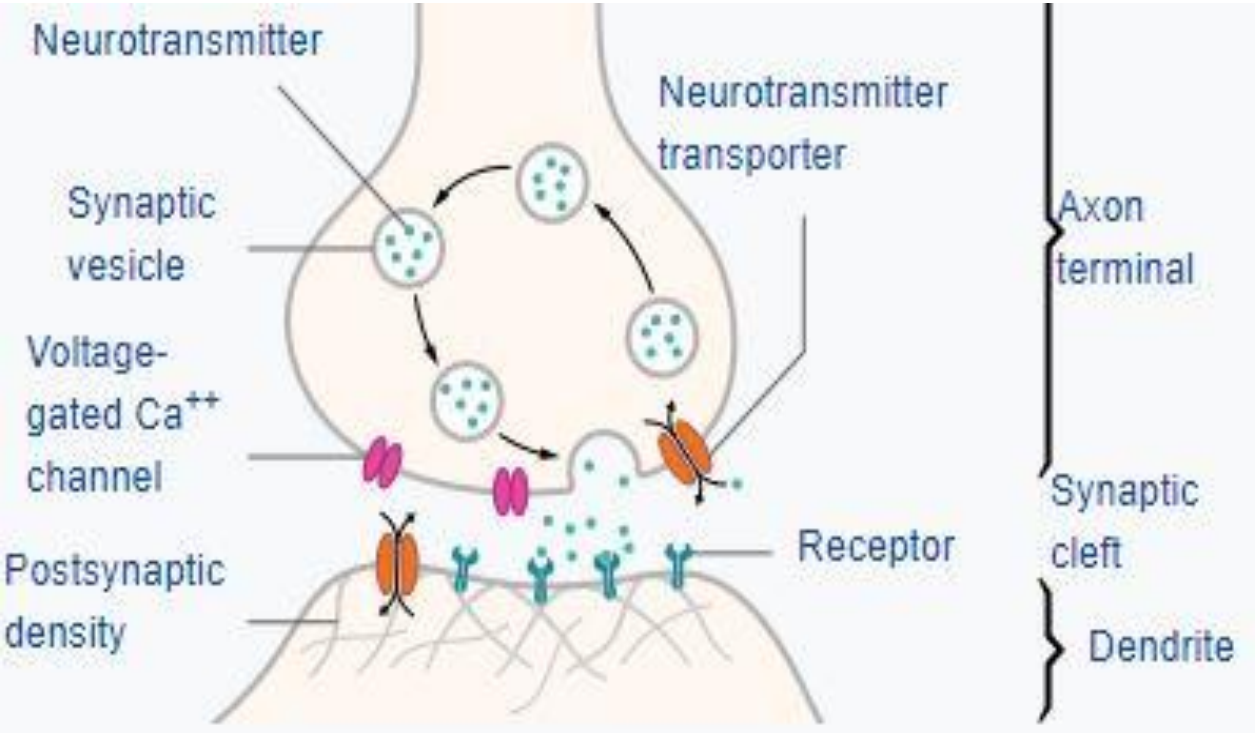
The **soma** is the body of the neuron. As it contains the nucleus, most protein synthesis occurs here.

The **dendrites** of a neuron are cellular extensions with many branches. This overall shape and structure is referred to metaphorically as a dendritic tree. This is where the majority of input to the neuron occurs via the dendritic spine.

The **axon** is a finer, cable-like projection that can extend tens, hundreds, or even tens of thousands of times the diameter of the soma in length. The axon primarily carries nerve signals away from the soma, and carries some types of information back to it.

The **axon terminal** is found at the end of the axon farthest from the soma and contains synapses.

Structure of typical chemical synapse



The word "synapse" – from the Greek *synapsis*, means "conjunction".

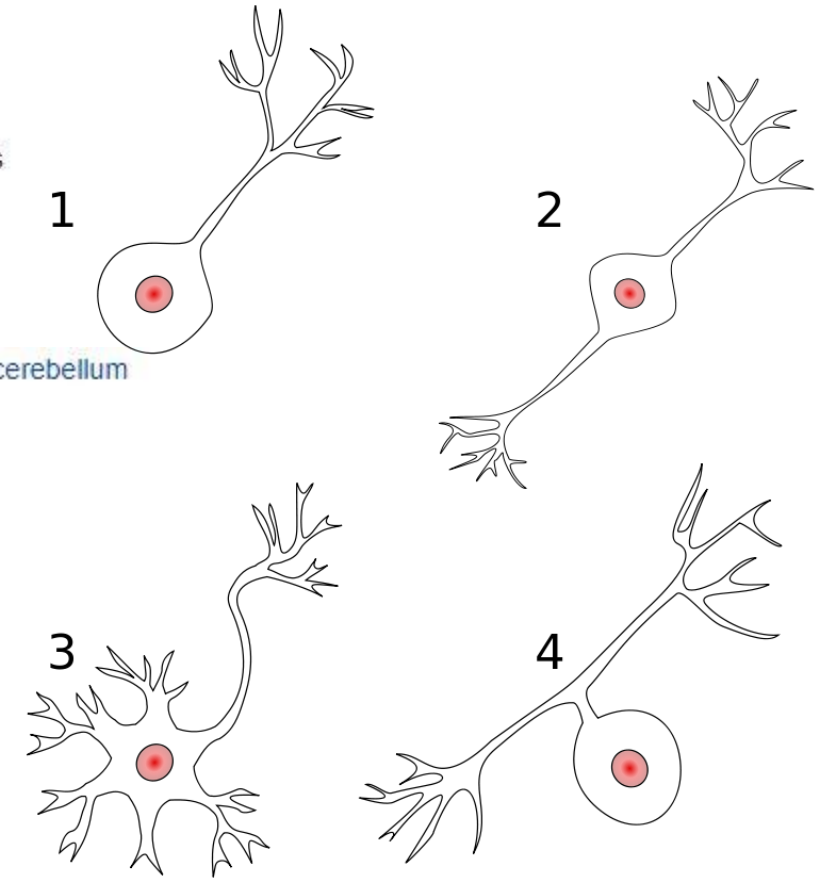
A **synapse** is a structure that permits a neuron (or nerve cell) to pass an electrical or chemical signal to another neuron or to the target effector cell.

Resting potential

Although there are many different kinds of neurons, the same basic electrical principles underlie their function.

- Unipolar: single process
- Bipolar: 1 axon and 1 dendrite
- Multipolar: 1 axon and 2 or more dendrites
  - Golgi I: neurons with projecting axonal processes; examples are pyramidal cells, Purkinje cells, and anterior horn cells
  - Golgi II: neurons whose axonal process projects locally; the best example is the granule cell
- Anaxonic: where the axon cannot be distinguished from the dendrite(s)
- Pseudounipolar: 1 process which then serves as both an axon and a dendrite

- Basket cells, interneurons that form a dense plexus of terminals around the soma of target cells, found in the cortex and cerebellum
- Betz cells, large motor neurons
- Lugaro cells, interneurons of the cerebellum
- Medium spiny neurons, most neurons in the corpus striatum
- Purkinje cells, huge neurons in the cerebellum, a type of Golgi I multipolar neuron
- Pyramidal cells, neurons with triangular soma, a type of Golgi I
- Renshaw cells, neurons with both ends linked to alpha motor neurons
- Unipolar brush cells, interneurons with unique dendrite ending in a brush-like tuft
- Granule cells, a type of Golgi II neuron
- Anterior horn cells, motoneurons located in the spinal cord
- Spindle cells, interneurons that connect widely separated areas of the brain



Lets see a small patch of membrane somewhere on the soma.

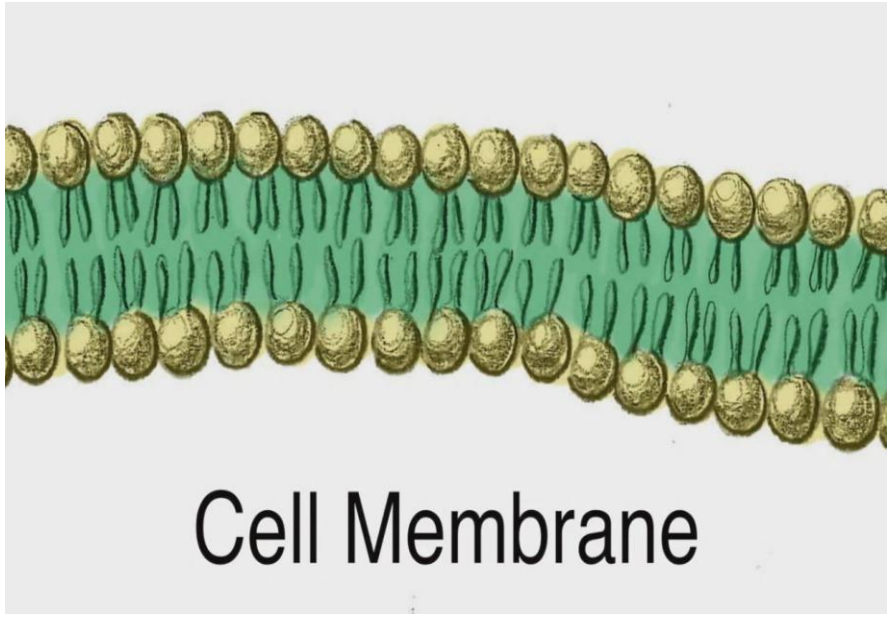
There's an awful lot of important stuff going on this humble little patch of membrane.

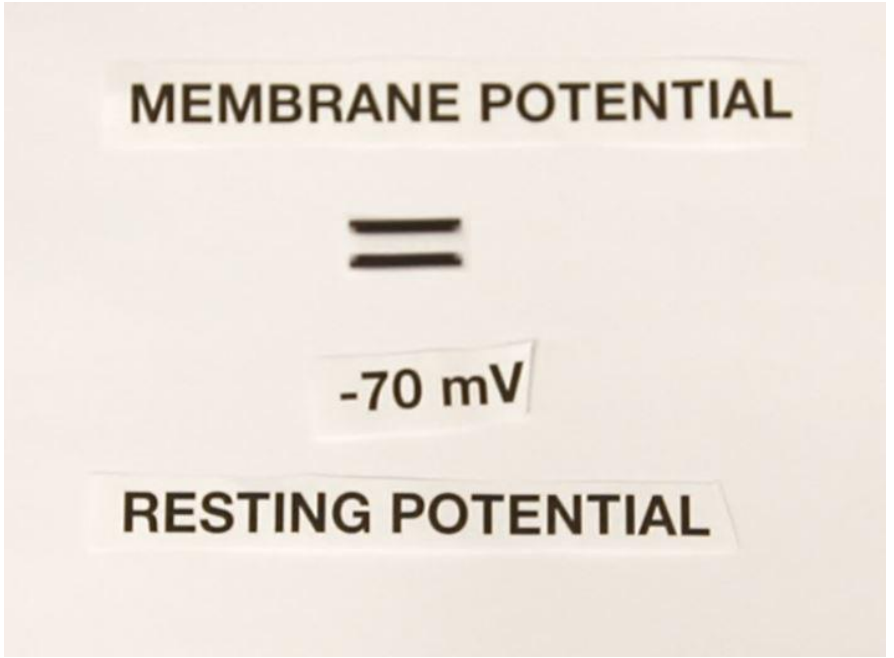
Even when the cell is at rest, its not electrically neutral.

If you measure the voltage -- the difference in electrical potential energy -- across this membrane, between the inside and outside of a living neuron, you will see a small but important voltage called the **membrane potential**. (-70 mV resting potential referencing 0 as outside of cell.)

You might be familiar with the idea of potential energy, or stored energy.

A battery, for instance, generates an electrical potential, or voltage, between its positive a negative terminals.





So, the neuron has small but not insignificant voltage across the cell membrane. How did it get this way?

Well, first, lets state what its not. Its not a battery like the double-A. Batteries like that generate voltages through electrochemical reactions that release electrons on one side of the battery and that use-up electrons on the other.

The key to understanding how neurons generate a resting potential lies in the stuff on either side of that cell membrane.

Both the inside and outside of the cell are basically made up of water with a host of stuff -- proteins, ions, sugars, dissolved in it. There are a whole host of charged ions and molecules floating in and around the cell, including Mg, H, HCO_3 (bicarbonate), HPO_4 (phosphate), SO_4 (sulfate), and many proteins.

We’ll be focusing for now on just a few key players, the charged ions Na sodium, K potassium, Ca(2) calcium, and Cl- chloride which are present in reasonably high concentrations and are important in generating a resting potential in the neuron.

Understanding Resting Potential

- If we want to understand the resting potential, we need to first introduce two basic phenomena in nature: **diffusion**, and **electrostatics**.

- Diffusion is the process by which particles spread-out, or mix, for instance, in a solution.

- This movement of the dye is governed by the thermal movement of individual dye molecules – they’re basically jiggling at an atomic scale, and bumping into each other. (Random motion)

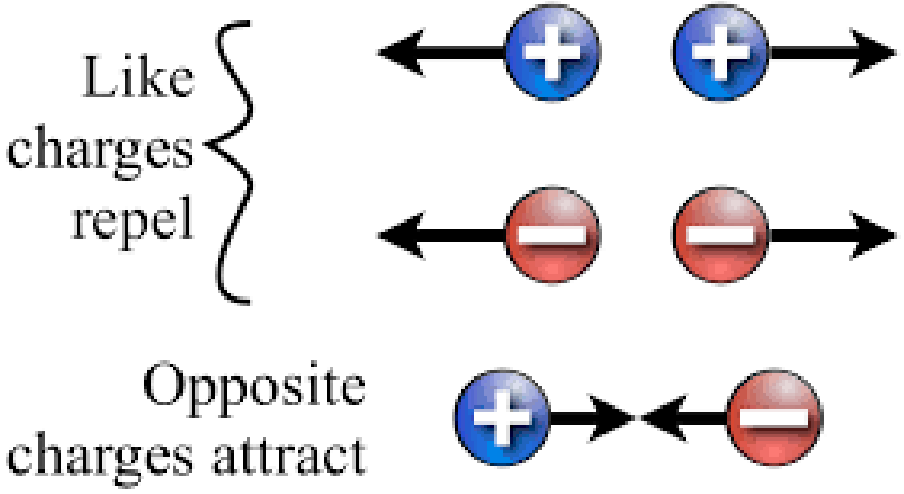
- In the aggregate, the process of diffusion causes particles to move from regions of high concentration, to regions where the concentration is lower.

- Even though its a purely random process, for all intents and purposes, we can think of diffusion as an inexorable force driving particles down a concentration gradient, from high to low.

- This process turns up all over biology, and is essential to life as we know it.

Electrostatic force

- Particles can have charge associated with them -- positive or negative. These charges serve as the basis of all electricity. Positive and negative charges attract one another, and like charges -- positive and positive, or negative and negative, repel.



Ion selectivity

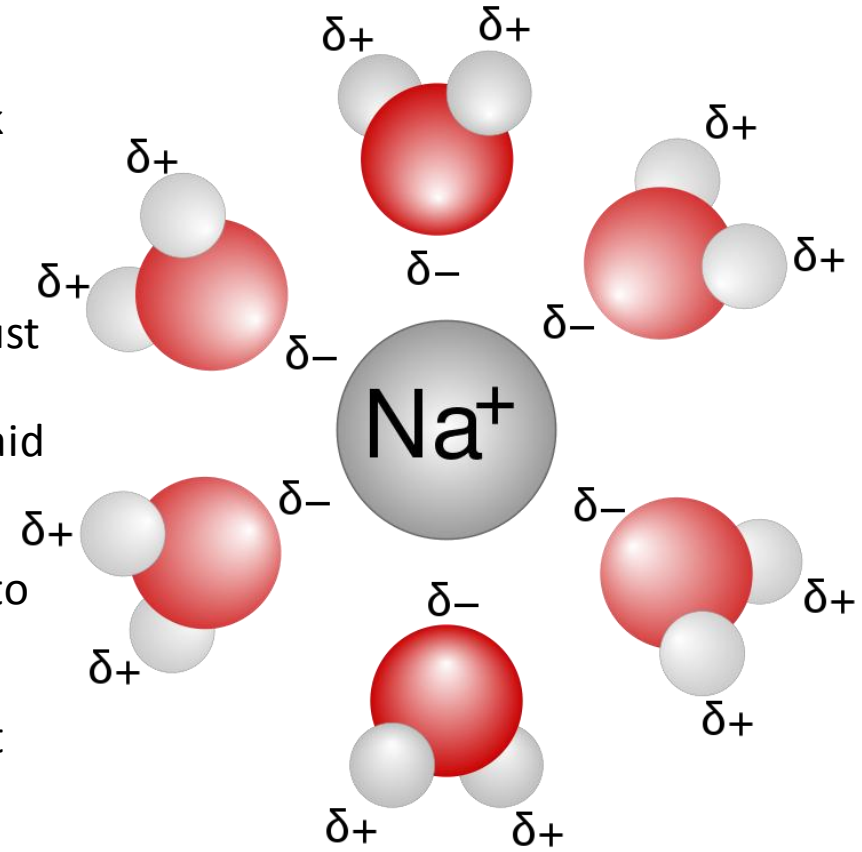
- Analogy : British and Americans in inside and outside bar.
- In our analogy, it's governed by
- a) the desire of the male Brits to balance their numbers, [diffusion]
- b) the uncomfortable feeling that they feel when there are two many male sailors in one room. [electrostatics]
- c) and the relative ease with which each type of male sailor can move between the two rooms. The British can move easily because of the British bouncer, but none of the other sailors are allowed to pass through.

- In a nutshell, the equilibrium potential is when the electrostatic forces caused by having a charge imbalance exactly balances out the force of diffusion, that drives those same ions from where they exist in a high concentration, to where they exist in a low concentration.

- In our analogy, the resting potential is the exact level of gender imbalance that just balances out the sailor's desire to even out their numbers.

How does it happen in the cell?

- Since this ion selectivity is so important, it's worth a short detour to talk about how on Earth nature achieves a channel that can let potassium pass through, but which blocks sodium.
- So, we need to somehow sort them based on their size.
- Now, these things are tiny. Absurdly tiny. The ionic radius of sodium is just 116 picometers and a potassium ion is just 152 picometers.
- The solution is nuanced and kind of cool. Do you remember when we said that positive and negative charges attract?
- Well, if we have positively charged ions diffusing around in water, they don't travel alone. The water -- H2O -- while net-neutral, has a polarity to it. The oxygen bit tends to be more negative, and the hydrogens tend to be more positive.
- So when we have a cation in solution, the water molecules are happiest when they point their negative ends towards the cation, and their positive ends away. The result is a sort of shell of water molecules surrounding the cation.
- We call this shell a solvation shell.



- Everything at a molecular level is about driving towards the lowest energy configuration -- and the solvation shell for a particular cation is in its lowest energy configuration at a very particular spacing -- where the interactions between the negative ends of the oxygen and the cation, and the interference and electrostatic interactions between the water molecules just balance out.

- Its one characteristic spacing for a potassium ion, which has a particular size, and it’s in a different configuration for a sodium ion, which has a slightly different size.

- In solution, the water molecules are free to situate themselves wherever, so these solvation shells just form, and that’s that.

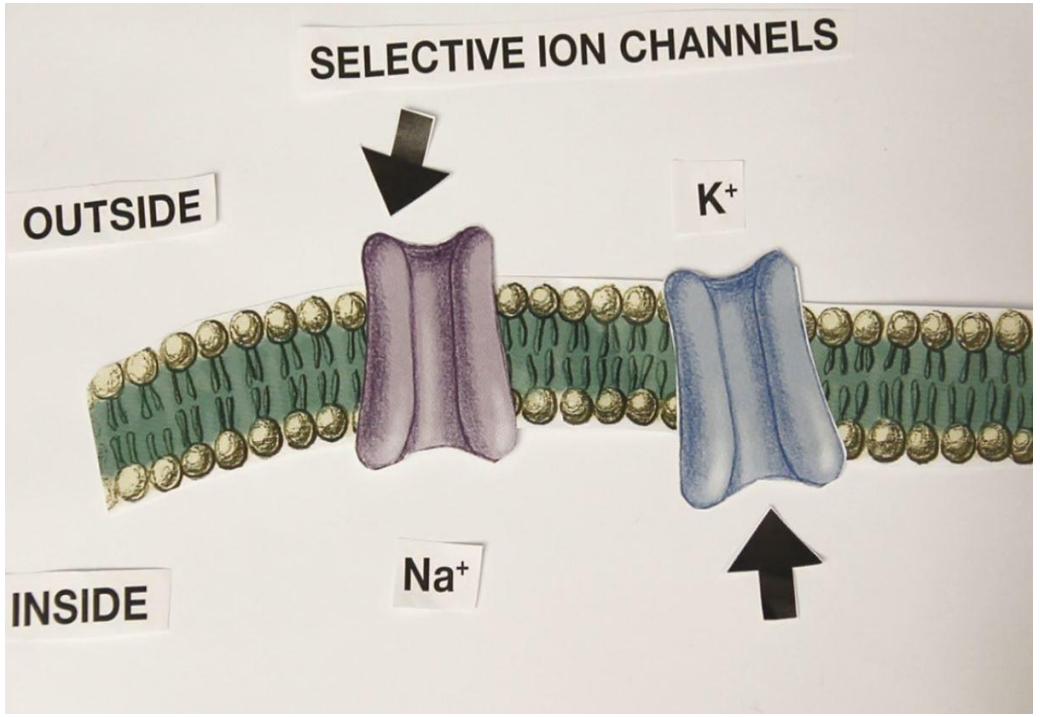
- But nature has arrived at a clever trick for leveraging this phenomenon to build selective ion channels.

- You see, the channel -- which is made of protein -- has a special mechanism in front of its pore called a selectivity filter. This molecular machine exists to do one thing: simulate the spacing of the solvation shell -- in a fixed configuration -- for its ion of interest.

- The result is that while potassium can happily exist in the space of the simulated solvation shell, and there it can diffuse through, the spacing is just a bit off for the sodium, making it energetically unfavorable for it to even go into the pore.

But how is the potential maintained?

- These selective ion channels are very important, because they selectively allow ions to flow DOWN their concentration gradients.
- These are the most basic of the ion channels: we call them leakage channels because they passively allow for certain ions to pass through.
- In a real neuron we have a lot of passive potassium selective channels, and fewer passive sodium channels and Cl- channels.
- Because the potassium permeability is much higher than the other channels, potassium dominates the resting potential, but any ion that can pass through the membrane even a little bit will contribute to the overall membrane potential.



- In nature the solution to maintaining this electrical gradient is the Sodium Potassium Pump, which continually moves three sodium ions out of the cell for every 2 potassium ions it pumps into the cell.

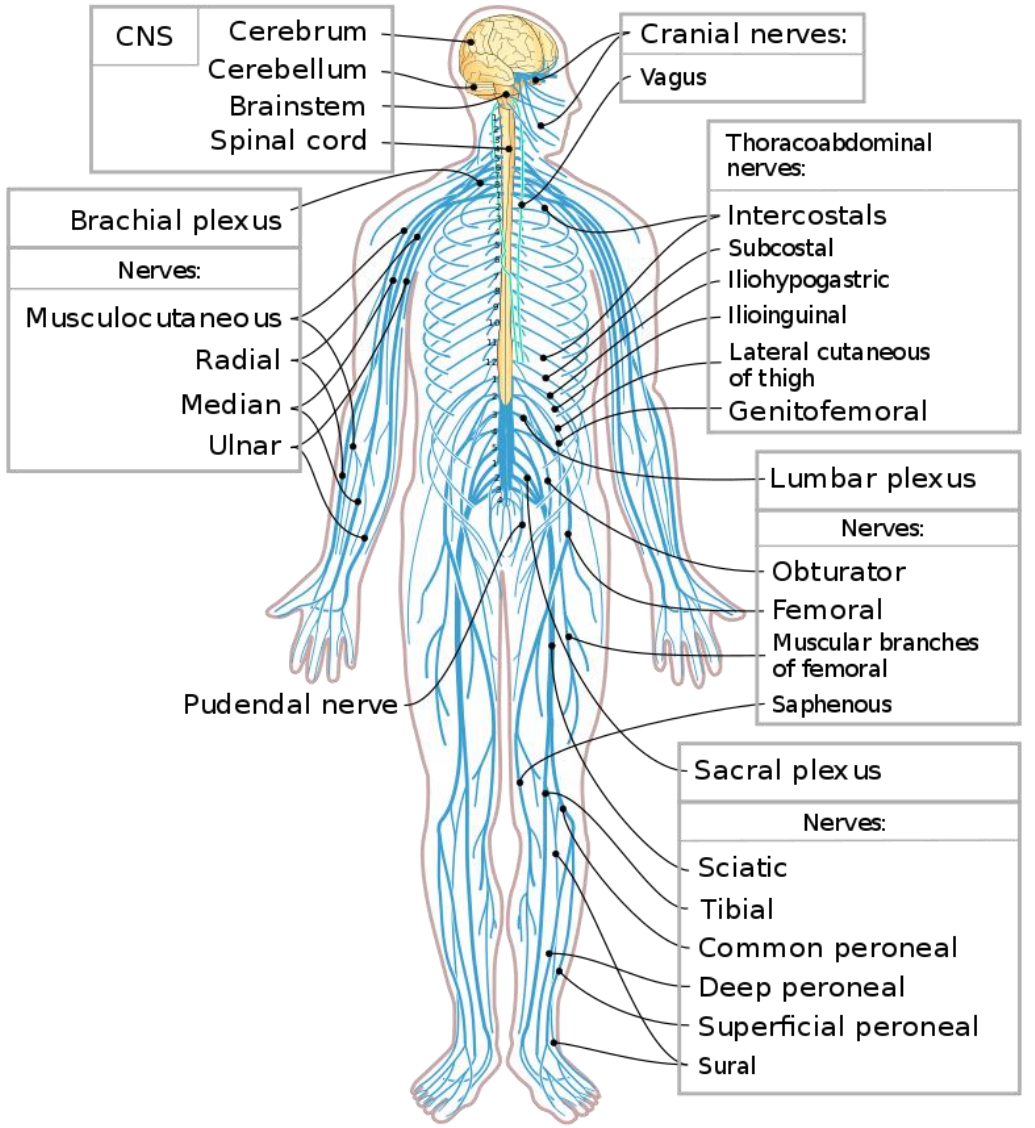
- This powerhouse uses ATP -- a key energy-carrying molecule in biology -- to drive its function and maintain an electrical gradient in neurons.

- The transport of Na out of the cell and K into the cell is so important to neural function that it consumes up to 70% of ATP required for overall brain function! That's a lot of energy, just to maintain the electrical gradient!

- To put that in perspective, something like a third of everything you eat in a day goes to powering this pump.

Changing membrane potential

- Everything we've been talking about so far is in terms of steady-states -- basically, what happens if you let the system run, in principle, forever, until everything settles into a state where there is no net change.
- Now, the function of the nervous system is all about sending signals. Signals from our senses, signals telling our muscles to move.
- We'll be sending those signals in neurons by transiently changing the membrane potential.
- The existence of a resting potential primes the system for action, but a signaling mechanism wouldn't be terribly useful if it never changed.
- We'll talk about the active mechanisms that allow us to change the membrane potential and how these give rise to neuronal signaling.



Resistance

- You've probably already noticed that there is strong connection between the properties of neurons we've talked about so far and the terminology and theory of electronics. (voltage across a membrane is similar to battery)

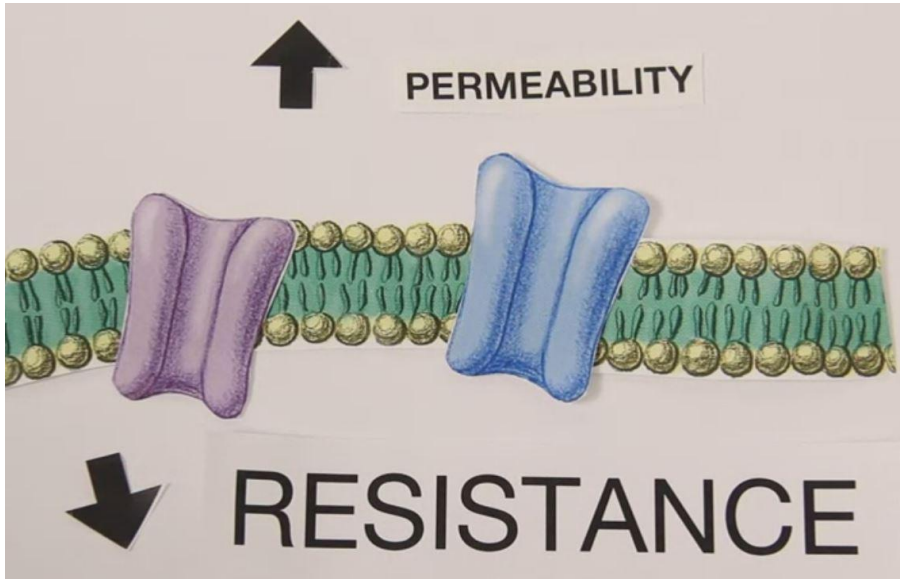
- Resistance is basically what it sounds like: a quantity that describes how much a conductor opposes the flow of charge through it.
- In the neuron, we've already encountered a variety of important resistances.

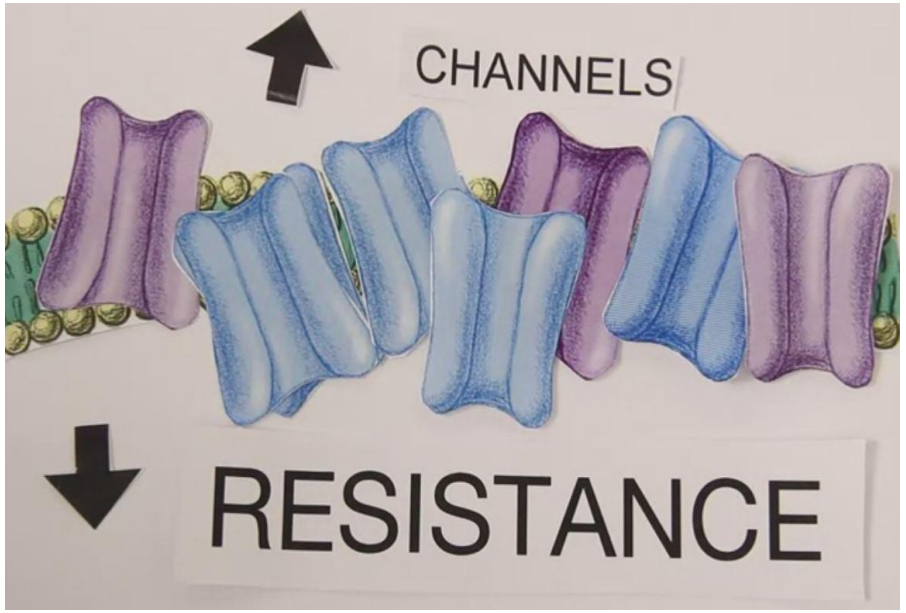
- Each type of ion channel, for instance, has an associated resistance.

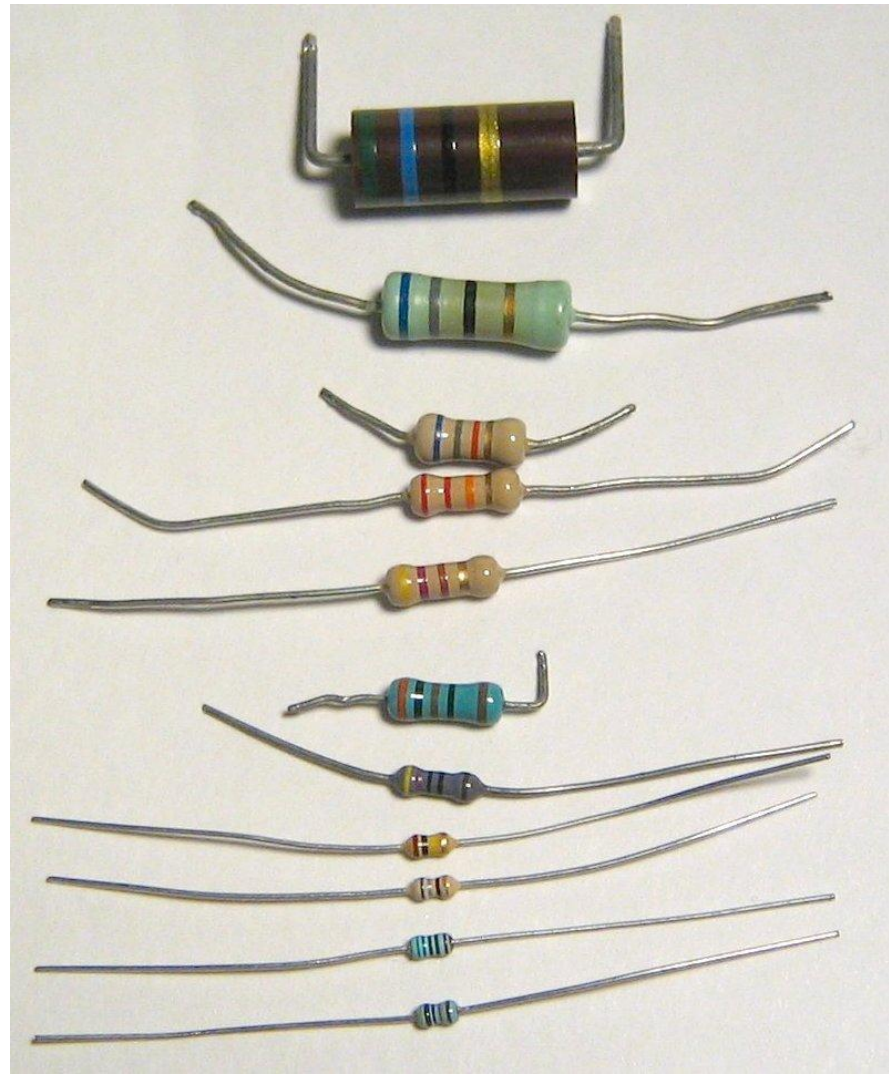
- The more permeable a channel is to ions, the lower it's resistance.

- Likewise, the more channels there are in a given patch of membrane, the lower the resistance.

- Typically, when we talk about resistance in neuronal membranes, we measure them in Ohms per square millimeter.





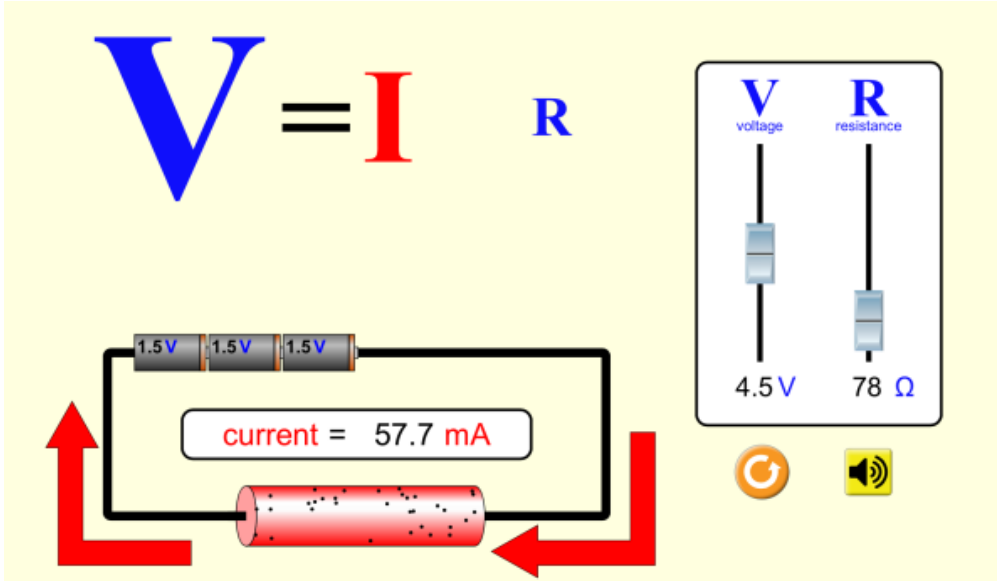


Capacitance

- So, we know that in the cell, we have two conductive regions of fluid, separated by an insulating membrane, with a voltage across either side of the membrane.
- In electrical circuits, a capacitor is a circuit element that can store electrical charge, and usually consists of two conductors separated by an insulating region called a dielectric.
- When a voltage is applied across a capacitor in an electronic circuit, charges line up on the two plates opposite each other across the insulator, opposing the applied voltage.
- This charge accumulation continues until the plates are effectively saturated, at which point the voltage across the capacitor is equal to the applied voltage.
- If we step back to the original voltage, the capacitor slowly discharges, going back to the original voltage. Again, the capacitor is slowing down the change.

Ohms law

- There is a relative ratio of permeabilities of potassium, sodium and chloride at rest. If these individual permeabilities changed, for example, as more ion-selective channels open or close, the ratio would change and charges would start moving.
- These moving charges are a current, which can be described using Ohm's Law.
- Ohm's law tells us the relationship between resistance, current and voltage.
- Ohm's law tells us that **I=V/R** where V is voltage, I is current measured in amperes, and R is resistance measured in ohms.
- So why do we care?
- The key concept to take away from Ohm's law is that voltage is proportional to current. As voltage increases, so does the current, if the resistance stays the same!

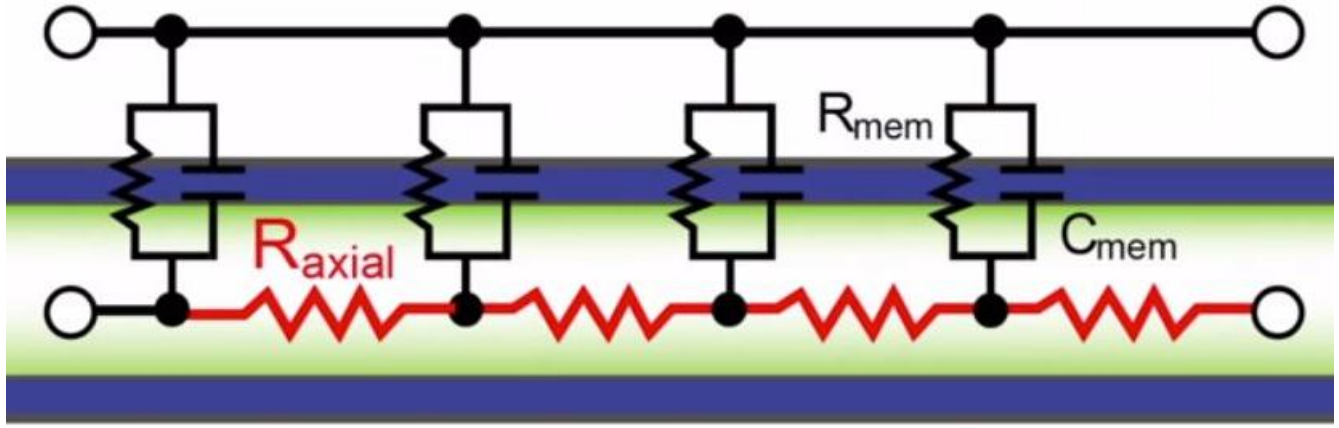


- Let's bring everything we know together and take a look at the big picture.

- The membrane acts like a capacitor, but remember the membrane is actually cylindrical, so we have many capacitors in parallel.

- Channels act like resistors, altering the conductance and permeability of ions, and allowing current to leak OUT of the cell, so we can think of resistance here along the membrane in parallel.

- Additionally, we also have resistance to current flow AXIALLY, along the neuron, so we additionally have resistance in series.



Membrane potential equation (Millman equation) (also called the Chord Conductance Equation)

- The membrane potential is the **weighted average** of each contributing ion's equilibrium potential. The size of each weight is the relative conductance of each ion. In the normal case, where three ions contribute to the membrane potential:

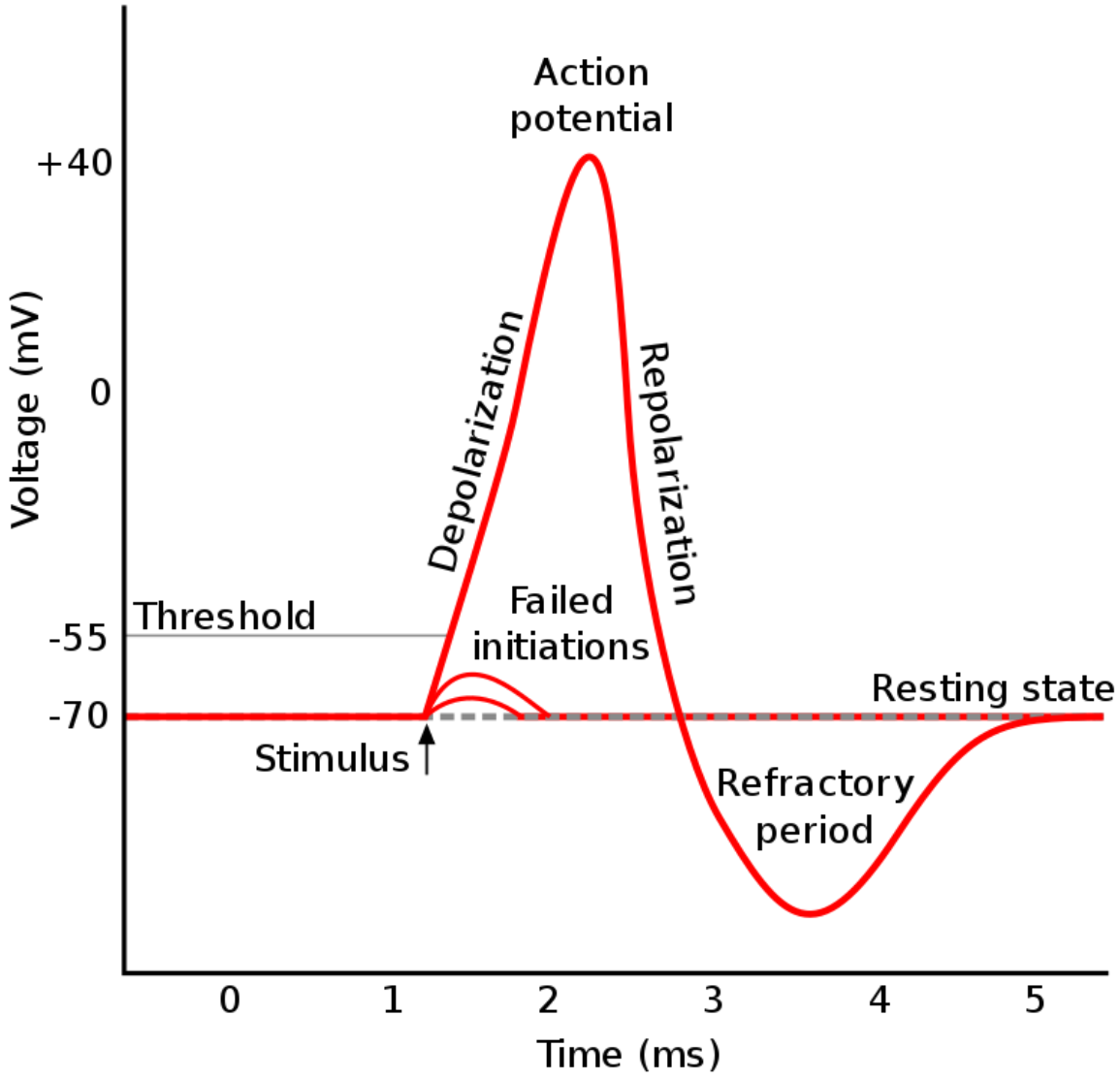
$$E_m = \frac{g_{K^+}}{g_{tot}} E_{K^+} + \frac{g_{Na^+}}{g_{tot}} E_{Na^+} + \frac{g_{Cl^-}}{g_{tot}} E_{Cl^-},$$

where

- E_m is the membrane potential, measured in volts
- E_X is the equilibrium potential for ion X, also in volts
- g_X/g_{tot} is the relative conductance of ion X, which is dimensionless
- g_{tot} is the total conductance of all permeant ions in arbitrary units (e.g. siemens for electrical conductance), in this case $g_{K^+} + g_{Na^+} + g_{Cl^-}$

Action Potential

In physiology, an **action potential** occurs when the membrane potential of a specific cell location rapidly rises and falls: this depolarization then causes adjacent locations to similarly depolarize. Action potentials occur in several types of animal cells, called excitable cells, which include neurons, muscle cells, endocrine cells, glomus cells, and in some **plant** cells.



Action Potential propagation

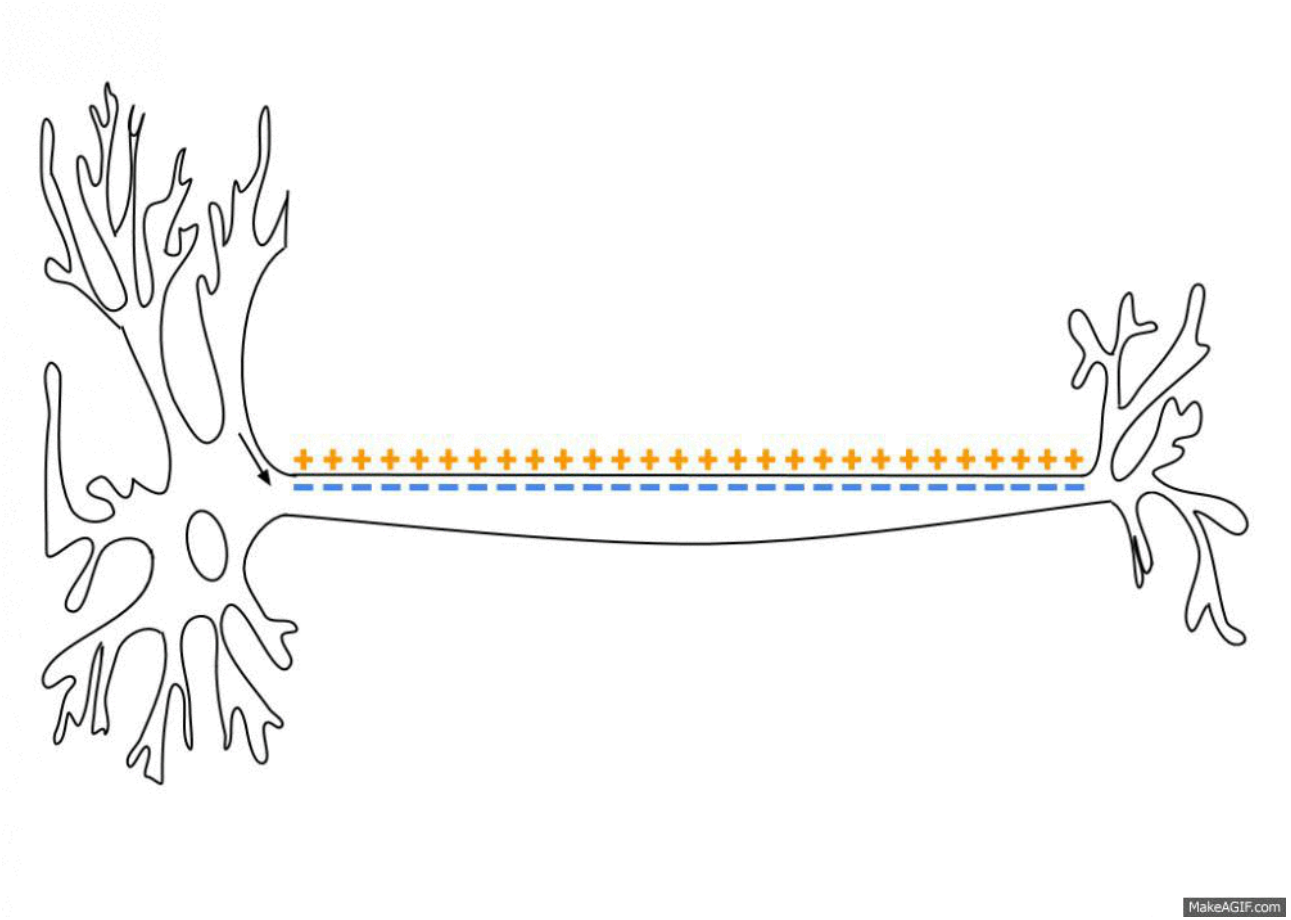
- The nervous system must be able to send signals over fairly large distances, and nature doesn't have the luxury of using a material as conductive as copper. The connectivity of cytoplasm is about 10 million times less than that of copper. In an axon, the losses over distances are even greater because of the leakage of current out of the cell and capacitor affects across the membrane. So we can't just fire an action potential with an amplitude of around 100 millivolts to cell body and expect it to propagate all the way to the end of a meter-long axon.

- So we have two options. First, we could increase the amplitude of the action potential to be much larger so the signal gets there in spite of the resistive and capacitive losses. However, at around -70 millivolts resting potential, neurons are already almost at their breaking point. Seventy millivolts isn't a huge voltage, but the membrane is only a few nanometers thick. This means that there's a huge electric field across the membrane itself, around 10 million volts per meter. Even at its ordinary resting potential, the membrane isn't far off from its so-called breakdown voltage. So raising the membrane potential isn't an option.

- The other option is the one that nature takes. We must repeatedly regenerate our signal to get it down the axon. The result is a situation where, rather than moving a molecule down the axon or moving electrons down a wire, we instead move the state of depolarization down the axon.

- If you examine a wave moving in water, something is clearly moving from one side to the other. But what is it? If you look at the water molecules in the water, they're certainly moving. But there isn't any net movement of the water molecules from the left side to the right. For the most part, the water molecules are moving up and down, perpendicular to the direction the wave is propagating. So the water itself isn't moving from left to right. The thing that's propagating through the water is the state of the wave. Action potential propagation works much the same way.

As an action potential (nerve impulse) travels down an axon there is a change in polarity across the membrane of the axon. In response to a signal from another neuron, sodium- (Na^+) and potassium- (K^+) gated ion channels open and close as the membrane reaches its threshold potential. Na^+ channels open at the beginning of the action potential, and Na^+ moves into the axon, causing depolarization. Repolarization occurs when the K^+ channels open and K^+ moves out of the axon, creating a change in polarity between the outside of the cell and the inside. The impulse travels down the axon in one direction only, to the axon terminal where it signals other neurons.



Why Action Potential for signals?

- In our own bodies we have the diffusion of signaling molecules within and between individual cells. Facilitating a transport of molecules across membranes and within themselves, and we have the transport of hormones throughout the body by the circulatory system.

- Trees and plants move signaling molecules over vast distances using a combination of diffusion, capillary action, and transpiration. And single celled organisms react and adapt to their environments, largely through the action of diffusion based molecular signaling cascades.

- However, in the nervous system, the signals that ultimately mediate our senses and our actions and reactions to the environment rely on another paradigm to get from here to there. Electrical signaling. Why did nature evolve yet another mechanism for signaling?

- Let's try and get an intuitive understanding of the physiological problem that we are facing. Suppose we have a tape measure, measuring from the distance from the spine out to the arm. And approximate the distance, which a signal in a neuron that controls the muscle fiber in the arm has to travel. It's about a meter. Say we want to pick up a cup of coffee.

- If we were to rely on diffusion to carry the signal across this distance, it would take the signal about a year to arrive. And by that time, our coffee would not only be cold, but it would have completely evaporated. So why use an action potential in a nervous system at all? Because we need to act fast.

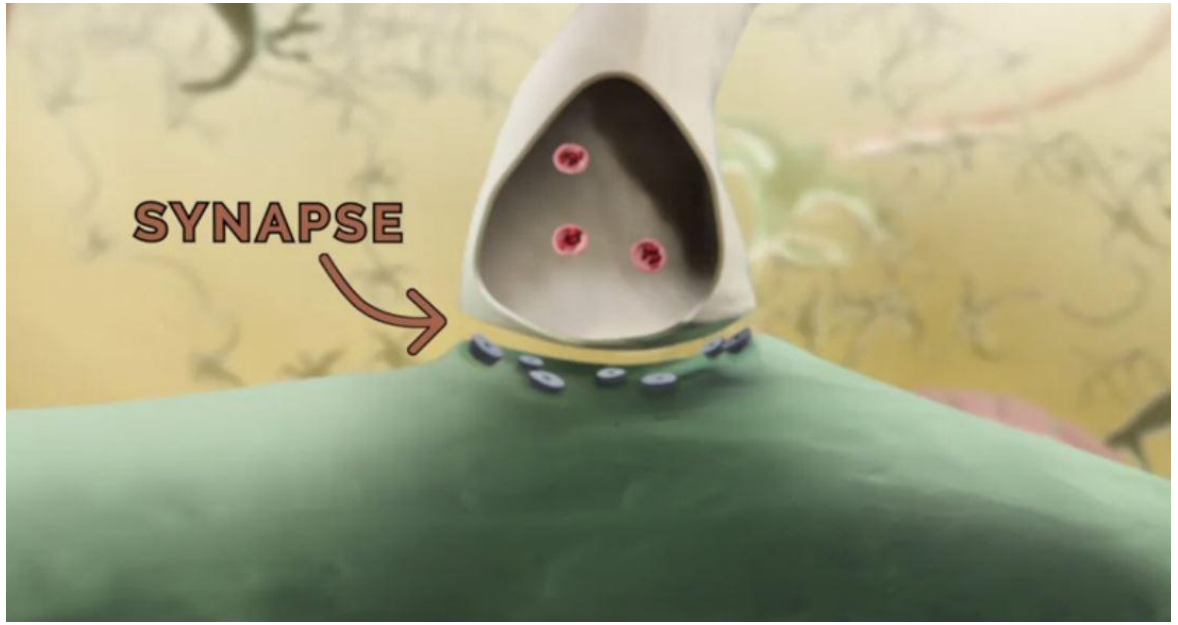
Summary till now

- We learned how electrical forces and diffusion give rise to membrane potentials and we learned how cells can generate and propagate signals called action potentials or spikes along the membrane.

- Understanding the properties of the neuronal membrane is essential, but understanding just these properties isn't sufficient to give us insight into collective behavior of the billions of connected neurons in our brains.

Synapses

- A signal received by a dendrite is passed to the cell body.
- If there is a sufficient depolarization of the cell body membrane to initiate an action potential, then an action potential is sent down the axon.
- The axon then carries the propagating action potential to another neuron.
- So what actually happens at the boundary between two neurons, between the axon of one neuron and the dendrite of another?
- This interface is called a Synapse.



Types of Synapses

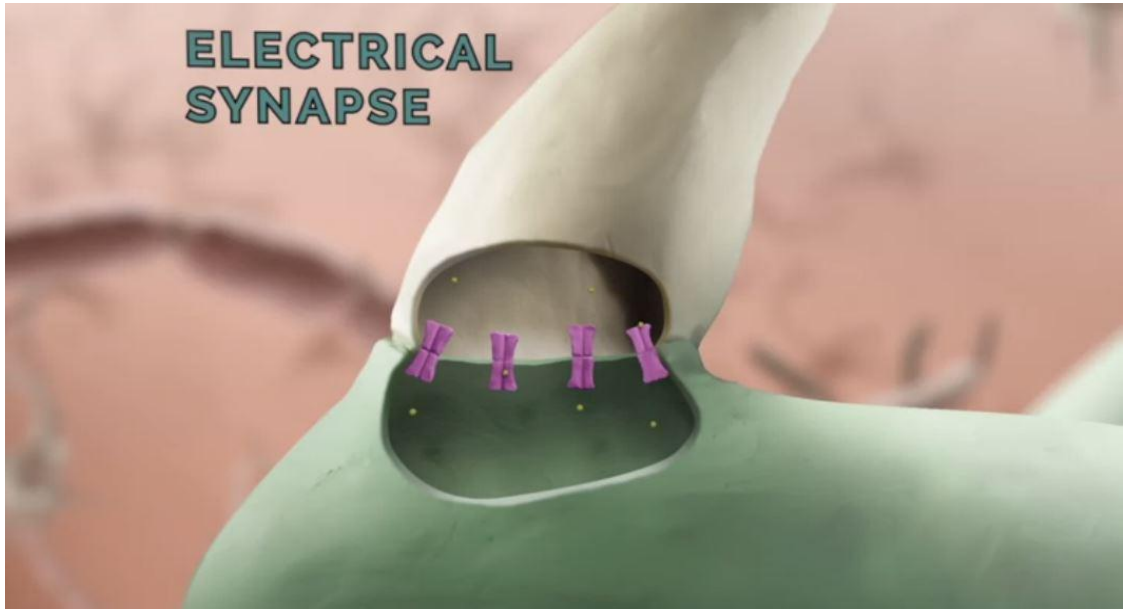
- There are two general types of synapses : **Electrical synapses** and **Chemical synapses.**

- Electrical synapses are less common in our own nervous systems, but they're simpler to think about. Electrical synapses are basically pores between two cell that allow ions to pass through.

- In an electrical synapse, there is a physical pore that allows ions to flow through, creating an intracellular current from the upstream neuron to the downstream neuron.

- The depolarization in the downstream neuron caused by this current, if it reaches threshold, can then cause a propagation of the action potential down the downstream neuron.

- There are lots of reasons that nature might need synapses like this from time to time – they're fast, and they allow cells to couple together with a high degree of synchronicity.



- But most neurons are connected together by a much more complicated structure called a Chemical synapse.

- In a chemical synapse, rather than simply passing along an electrical signal from one cell to another, the action potential travels to the end of the axon and causes a chemical to be released into a very small space between the two neurons called the **synaptic cleft**. (20-40 nm in size. That's about a thousandth of the width of a human hair.)

- It needs to be this small, since the signaling molecules must transverse this gap by diffusion.

- This chemical is taken up by the downstream neuron, on the other side of the cleft.

- In a chemical synapse, the two cells are electrically separate entities -- an action potential in one cell doesn't directly spread into the other cell.

- Instead, a chemical signal is released by the pre-synaptic or upstream cell, and then it is received by the post-synaptic, or downstream cell.

- Only after this signal is received can it possibly cause the downstream, post-synaptic neuron to fire.

- As you might imagine, with all of this extracellular signaling, chemical synapses are much slower than electrical synapses.

- But while they lack in speed, chemical synapses have a number of essential advantages over electrical synapses, and these advantages make them the dominant kind of synapse in the mammalian nervous system.

- One key advantage of chemical signaling is diversity.

- Electrical synapses essentially have one type of signal -- voltage -- that they use to transmit information. They can relay a signal, more or less unaltered, but that's about it.

- On the other hand, there is a huge diversity in signaling possible in chemical synapses.

- Some chemical signals tell the post-synaptic neuron to increase or decrease their **likelihood of firing**. These chemicals are called **Neurotransmitters**. These include molecules like acetylcholine and glutamate.

- Acetylcholine is the neurotransmitter used to control all voluntary muscle movements.

- Other chemicals, such as serotonin, dopamine, adrenaline can have different, more complicated, longer-term effects on neurons in circuits.

- These substances are broadly known as **Neuromodulators**, since they modulate the activity of neurons.

- Another key property of the chemical synapse is that it enforces directionality.

- In contrast to electrical synapses which pass signals in both directions, in a chemical synapse, chemicals are released from one side of the synapses and these signals are received by the post-synaptic cell.

- Except in special cases, this arrangement ensures that signals flow just one way.

- Finally, another key advantage of the chemical synapse is that it decouples the arrival of an incoming action potential from the generation of an action potential in the downstream neuron.

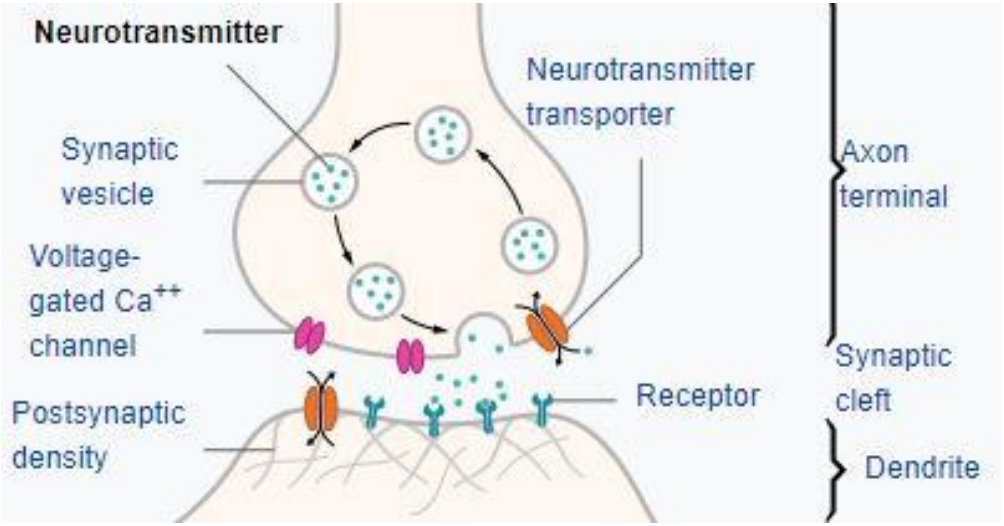
- While an action potential arriving at an electrical synapse will generally pass into the post-synaptic cell and cause a new action potential, the arrival of an action potential at a chemical synapse doesn't guarantee that a spike will occur in the post-synaptic cell.

- Instead, it's not uncommon for downstream neurons to require multiple incoming spikes arriving from multiple sources or close in time in order to reach threshold in the post-synaptic cell.

- This notion of summation across time and space is an incredibly important to the computational properties of neuronal circuits.

Neurotransmitters

- Neurotransmitters play an important role in neural communication. They are chemical messengers that carry messages between nerve cells (neurons) and other cells in your body, influencing everything from mood to involuntary movements. This process is generally referred to as **neurotransmission** or synaptic transmission.
- Specifically, **excitatory neurotransmitters** have excitatory effects on the neuron. This means they increase the likelihood that the neuron will fire a signal called an action potential in the receiving neuron.
- Neurotransmitters can act in predictable ways, but they can be affected by drugs, disease, and interaction with other chemical messengers.



What neurotransmitters do?

- Neurotransmitters affect neurons in one of three ways: they can be excitatory, inhibitory, or modulatory. An excitatory transmitter generates a signal called an action potential in the receiving neuron. An inhibitory transmitter prevents it. Neuromodulators regulate groups of neurons.
- **Excitatory neurotransmitters** have excitatory effects on the neuron. This means they increase the likelihood that the neuron will fire an action potential.
- **Inhibitory neurotransmitters** have inhibitory effects on the neuron. This means they decrease the likelihood that the neuron will fire an action.
- **Modulatory neurotransmitters** can affect a number of neurons at the same time and influence the effects of other chemical messengers.

Some neurotransmitters, such as dopamine, depending on the receptors present, create both excitatory and inhibitory effects.

Disorders linked to Neurotransmitters

- **Alzheimer's disease** has been linked to a lack of acetylcholine and glutamate Trusted Source in certain regions of the brain.
- **Schizophrenia** has been linked to excessive amounts of dopamine in the mesolimbic pathway of the brain.
- **Parkinson's disease** has been linked to too little dopamine in the brain's motor areas.
- **Mood disorders** such as manic depression, anxiety, and impaired sleep cycle have been linked to noradrenaline and other neurotransmitters.

Neuromodulator vs Neurotransmitter

- A neuromodulator is a type of neurotransmitter.

  The three main things distinguish neuromodulators as a subclass:
  They are released "diffusely" via "volume transmission", that is, the neurotransmitter is generally released into the neural tissue and not at a specific synapse, so it functions more as a chemical broadcast signal to a (possibly small) brain region rather than being targeted at particular neurons.

- They generally use a different type of neuroreceptor. The targeted, synaptically-released neurotransmitters use fast-acting "ionic" neuroreceptors that transmit positive (+) and negative (-) electrical signals into the target neuron. Neuromodulators, however, use so-called "metabotropic" or "G-protein" neuroreceptors. These are slow-acting receptors that tune and modulate the functioning of the neuron over longer periods.

- There are specific neurotransmitters that have been categorized as neuromodulators because they almost always work in the way described by #1 and #2. Those are: dopamine, serotonin , noradrenaline, and histamine . These neurotransmitters tune the functioning of neural circuits in neural tissue rather than sending signals directly into particular neurons.

Small circuits

- Let's briefly review what we've learned about individual neurons, both structurally and functionally. Neurons are the individual cellular unit in the nervous system. They receive input signals on their dendrites, integrate input information in the cell body (or soma), and determine whether or not to send an output signal through their axon to the presynaptic terminal.

- This is the fundamental principle of information processing in the nervous system.

- Like a bridge in the middle of nowhere without an entry or exit ramp, a single neuron cannot receive information and it cannot send it onwards in any useful way. In other words, each neuron within a circuit has to compare many levels and types of synaptic input, process the information centrally, and then decide if it should send an action potential.

- For this decision-making process, it matters first and foremost, what types of input a neuron receives: is it excitatory, or inhibitory?

- Second, it matters where along the dendrite this input occurs, since the farther away from the cell body, the higher the likelihood that the signal attenuates, or loses in strength, on its way to the soma.

- Third, it matters when and at what frequency inputs occur. The more closely together two excitatory inputs occur at the same synapse, the higher the likelihood that a neuron will reach threshold and fire an action potential.

- Lastly, if an excitatory input is interrupted on its way to the soma by an incoming inhibitory input, that signal will die and the soma will not fire an action potential.

- Our nervous system, and particularly the brain, works because neurons do not live and act in isolation, but rather they are highly interconnected in circuits.

- Very much like individual neurons, circuits come in many sizes (small or large), types (sensory or motor, peripheral or central circuits) and have specific functions.

- For example, specific circuits exist for fear perception or short- and long-term memory storage.

- Functionally, an ensemble of neurons (like a brain), does something very similar to what each individual neuron does : It listens, integrates incoming information, and then takes action - or not.

- And just like individual neurons, circuits are highly regulated by the types of synaptic inputs they receive.

- A single neuron can receive many types of input information, both excitatory and inhibitory, from other neurons.

- It has been shown experimentally that distinct regions of a neuron -- particularly along the dendrites, soma and axon initial segment -- are highly specialized for either excitatory or inhibitory input, but seldom both.

- For example, excitatory input is thought to occur mainly on dendritic spines... while inhibitory input tends to occur on dendritic shafts, the cell body, and on the axon initial segment.

- A single neuron can be innervated by up to thousands of incoming excitatory and inhibitory synapses.

- How do all of these inputs combine together to produce a coherent response?

- Why do neurons receive more than one kind of input? What rules govern information processing in multi-neuronal systems?

- Fundamentally, each individual neuron has to filter and integrate a barrage of incoming input and decide whether or not to send on a message down its axon.

Convergence and Divergence

- Convergence is when multiple, potentially disparate inputs come together to synapse onto a single downstream neuron.
- At a high level, convergence is quite intuitive. Our brains are constantly bringing together scraps of ambiguous information and synthesizing them into a coherent whole.
- Example : Recognizing face in a party
- Divergence example :When in forest, we sense that something possibly dangerous is in the grass, a cascade of neuronal activity is set into action.
- Sending a signal to just one neuron or muscle won't do. The entire body must be alerted. Heart rate rises. Breathing hastens. Pupils dilate. Muscles tense in preparation to run.
- In a few brief moments, we've pivoted from a collection of disconnected sensory impressions, converged these signals onto neurons that generate a feeling of fear, which in turn sends signals that diverge to nearly every part of our body to produce specific, coordinated action.

- So, every feeling that you get is just a network of neurons firing (love, hate, anger, sadness, happiness, etc).

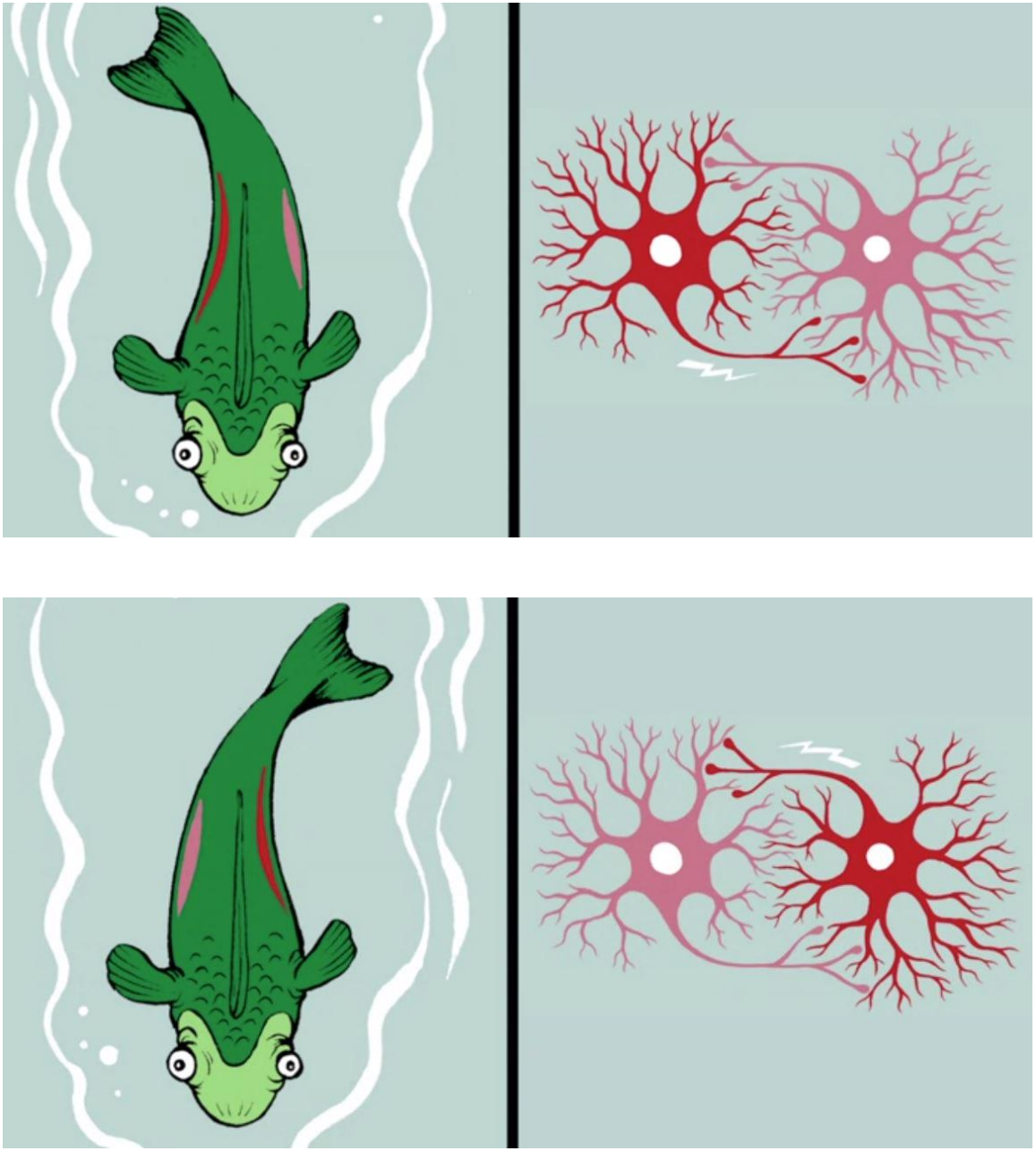
- So, on a side note, what people call love is just a chemical reaction that compels animals to breed.

  It hits hard and then it slowly fades leaving you stranded in a failing relationship.

  So, Break the cycle. Rise above. Focus on science.

Recurrence

- Recurrence describes the situation where some chain of connected neurons eventually loops back onto itself. Another word sometimes used here is feedback.
- In the simplest case, neuron A might connect to neuron B, but then B also sends its axon back to A.
- One common small circuit motif that often relies on recurrence is the so-called Central pattern generator, or CPG.
- In a nutshell, CPGs are neuronal networks that can produce rhythmic patterned outputs, even in the absence of ongoing sensory input, and they are found throughout nature, from tiny invertebrates to humans, controlling everything from the rhythmic muscle activity that govern swimming in molluscs, to the rhythmic contractions of our own digestive tract.
- RBM



Summary

- We explored the inner workings of chemical synapses to look at how networks of interconnected neurons give rise to behavior.

- We also looked at the role of defective synaptic physiology in neurological and psychiatric disorders, and we saw how synapses can be targeted by various psychoactive drugs and poisons.

- Finally we wrapped up by looking at how synapse can change with time, in response to external stimuli, playing a foundational role in how we learn and remember.

Takeaway

- The brain learns with an efficiency that none of our machine learning methods can match.
- Our supervised learning systems require large numbers of example.
- Our reinforcement learning systems require millions of trials which is why they work only for games and not in real world.
- That’s why we don’t have robots as agile as that of a cat or a rat.
- That’s why we don’t have dialog systems that have common sense.
- What is missing? – Learning paradigms that build (predictive) models of the world through observation and action.