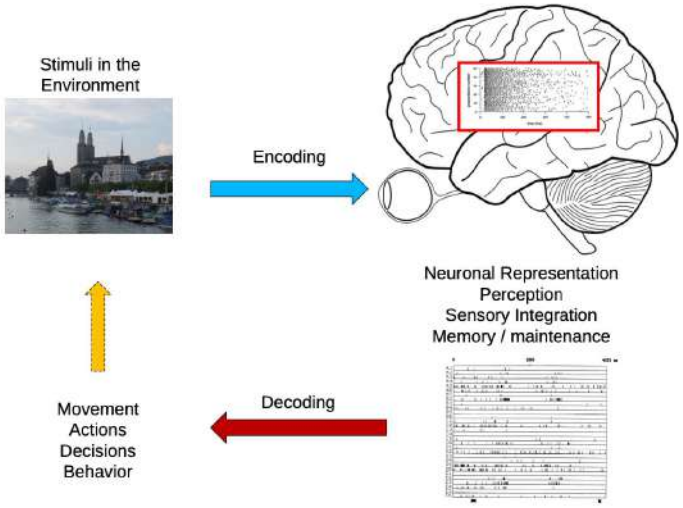
Introduction to Neuroinformatics

Lecture 1 - Introduction

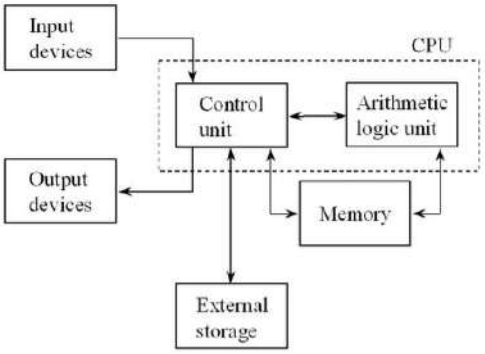
Brain

- 1.5 kg
- 1.1 - 1.2 l volume
- Not the biggest amongst animals
- Amount of neurons is a good indicator
- Humans ca. 83 Mia Neurons
-

Why do we have a brain according to Daniel Wolpert



Von Neumann (1903 - 1957) Architecture



How is a brain different/similar to a computer?

Similar	Different
• Process information • Logical operations • Memory • Use electrical (digital) signaling • Can learn from inputs • Consume energy • ...	• Massive parallelism • Separation of memory and processing • Constantly adapting • Chemical signaling • Unreliable units • Analog computation • Robust to damage • Very energy efficient • ...

Neurogrid

- Emulation of 1 Mio. neurons, 6 billion synapses, in mixed analog and digital hardware

Edge-Intelligence

- We are now entering the era of “edge intelligence” in which dedicated cognitive “chiplets” will be used to provide intelligence to a multitude of edge-computing devices

Neuromorphic Engineering and Computing

- Understand the principles of computation of cortical circuits for building neuromorphic agents.
- Develop neuromorphic electronic circuits that support neural computational primitive with synaptic plasticity and adaptation mechanisms.
- Build neural processing systems that can be interfaced to sensors and robotic platforms and interact with the environment in real time.

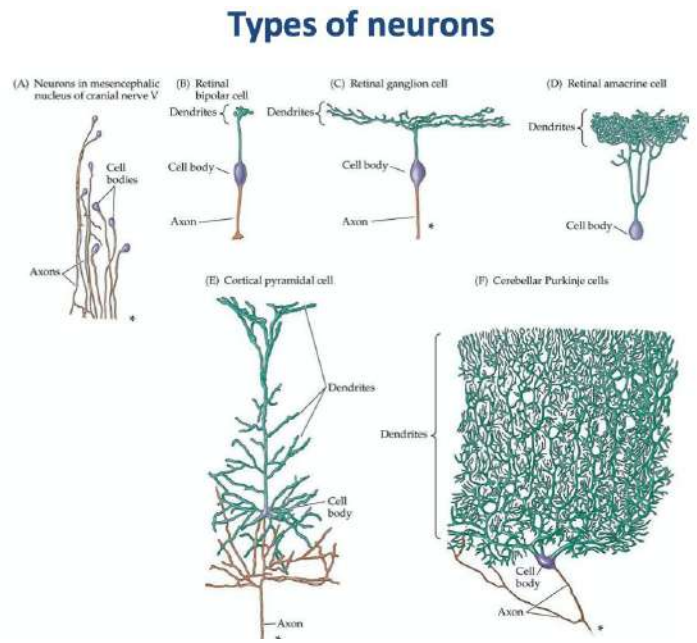
SUMMARY

- Brains as information processors
- What's special about the human brain?
- Key differences between brains and computers
- Artificial intelligence often modeled after nervous systems
- Today's largest computing systems exceed the capacity of brains, but need far more power
- Complexity of nervous systems is not matched in computer simulations

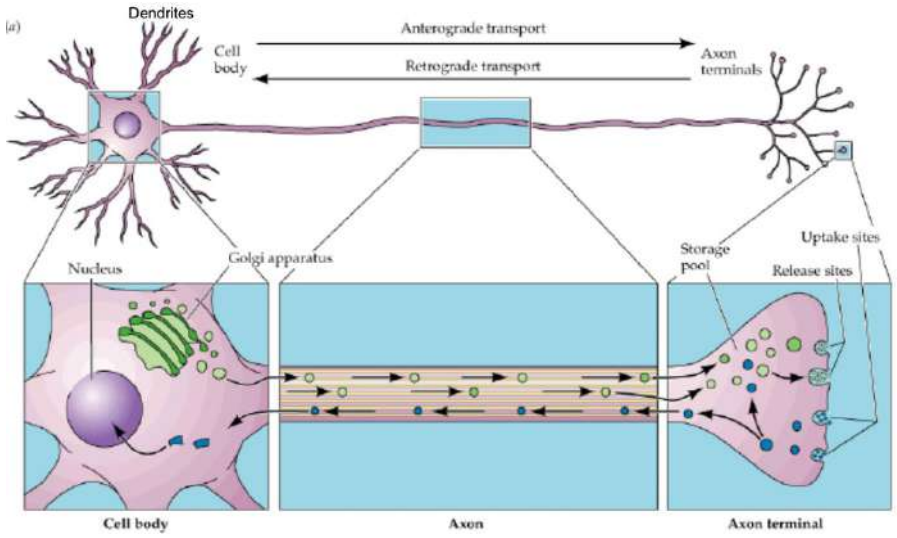
Lecture 2 - Nervous system organization

Neurons

- Basic building block of the brain
- With Golgi silver Coloring method first images of a neuron could be taken
- Different Cell Types differ in **morphology** (form & size), **physiology** (actions potential graph) and **molecular signature** (type of molecules)



The simplified Schematic neuron



- Nucleus stores all the DNA
- Golgi Apparatus is for the RNA Translation into Proteins
- Certain substances are transported back from the Axon terminal to the cell body

Key Components

Axon

- **Axon hillock** - starting point of the Axon, where the Action Potential is initiated
- Can be described by a cable equation - allows you to calculate electric current

Dendrites

- Complex trees of processes
- Place where the presynaptic neuron is contacting the postsynaptic neuron
    - Contact Point is usually on the dendrites

Synapse

- Is the interface between two neurons

Synaptic Cleft

- Small **10 nanometer** wide synaptic cleft

Presynaptic Neuron

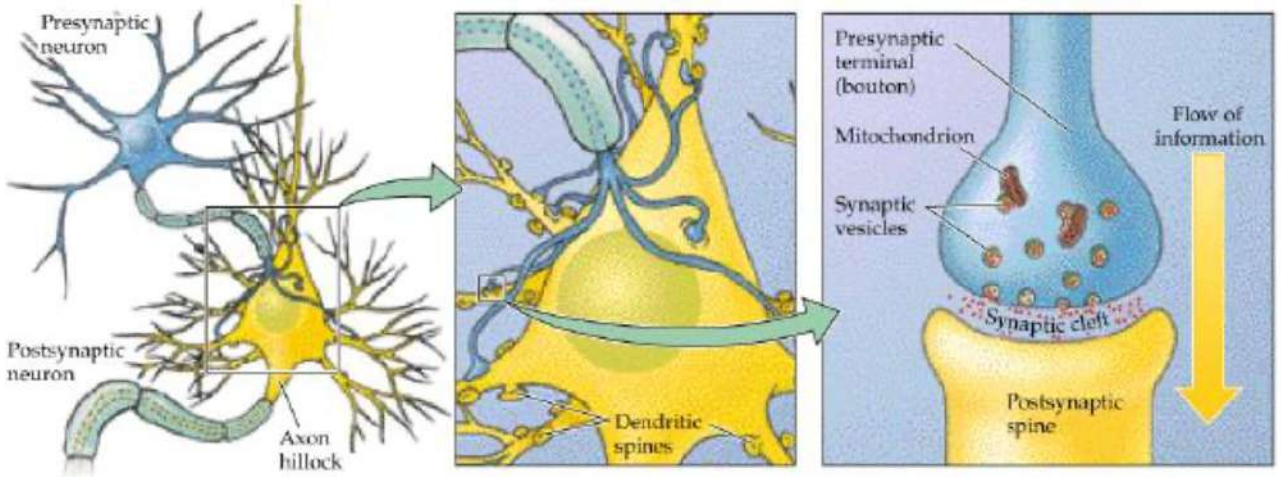
- You have neurotransmitter filled vesicles these are **liposomes**
- On the generation of an action potential these liposomes merge with the membrane and release the cargo into the cleft and elicit activity in the postsynaptic part

Boutons - another word for the presynaptic terminal shaped a bit like a bouton

Cleft Dendritic spines

Postsynaptic membrane - membrane of the postsynaptic spine e.g. on the other side of the synaptic cleft

Transmitter - a chemical messenger that transmits a message from a nerve cell across the synaptic cleft to a target cell (muscle, nerve, ...=), e.g. Neurotransmitter



Axon

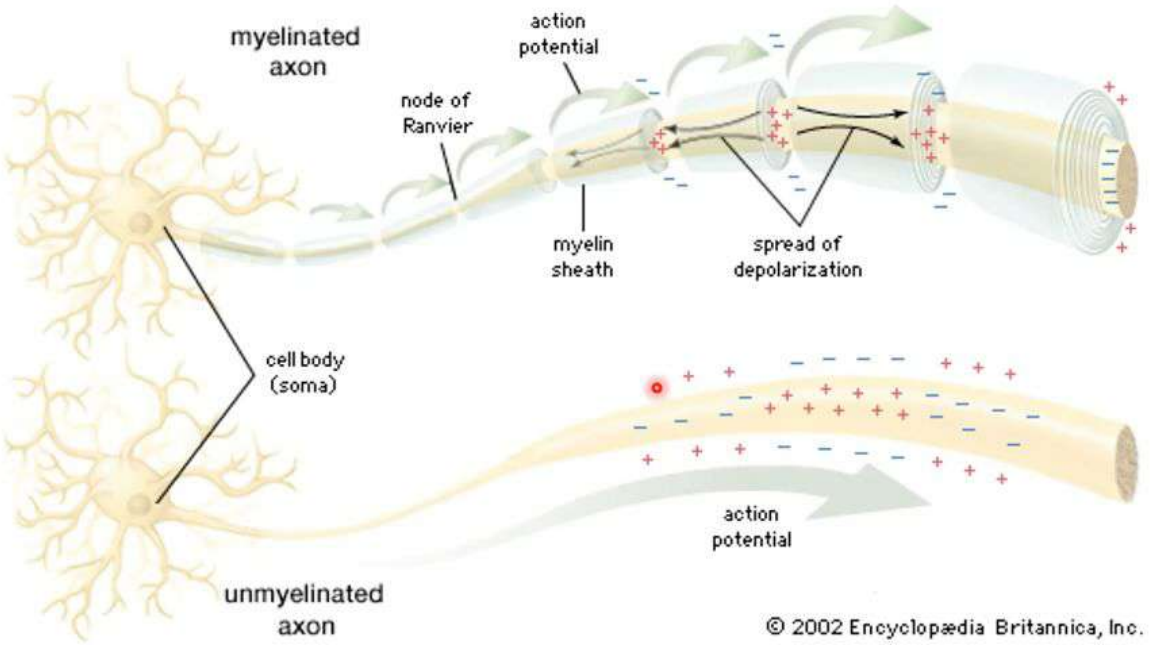
There are two modes for an axon to propagate an action potential

Unmyelinated Axon

- Easier one
- Large diameter axon with low resistance

Myelinated Axon

- Axon with insulation, these are gliacells
- They are interleaved with contact points
    - It's not one continuous pipe
- Saltatory Conduction - hopping one step at a time



Vesicles

- Small filled bubbles with neurotransmitter
- Once the action potential reaches the presynaptic part, voltage gated Calcium Channels releases Calcium as a messenger
- Calcium Concentration is very important
- Calcium triggers fusion of vesicles with the membrane and then release their cargo in to the cleft
- It then diffuses to the postsynaptic membrane

Flow of Neurotransmitter

1. In the cell body (nucleus) there is a synthesis of enzymes.
2. They are slowly transported along the axon
3. In the presynaptic terminal happens Synthesis and packaging of the neurotransmitter
4. Neurotransmitter are synthesized from simple precursors (amino acids)
5. The Vesicles membrane mergers with the presynaptic membrane and releases the neurotransmitter into the cleft
6. Precursors outside of the synapse are transported into the terminal to be used for future synthesis.

Neurotransmitter

- Decides how two cell interact

Postsynaptic receptor

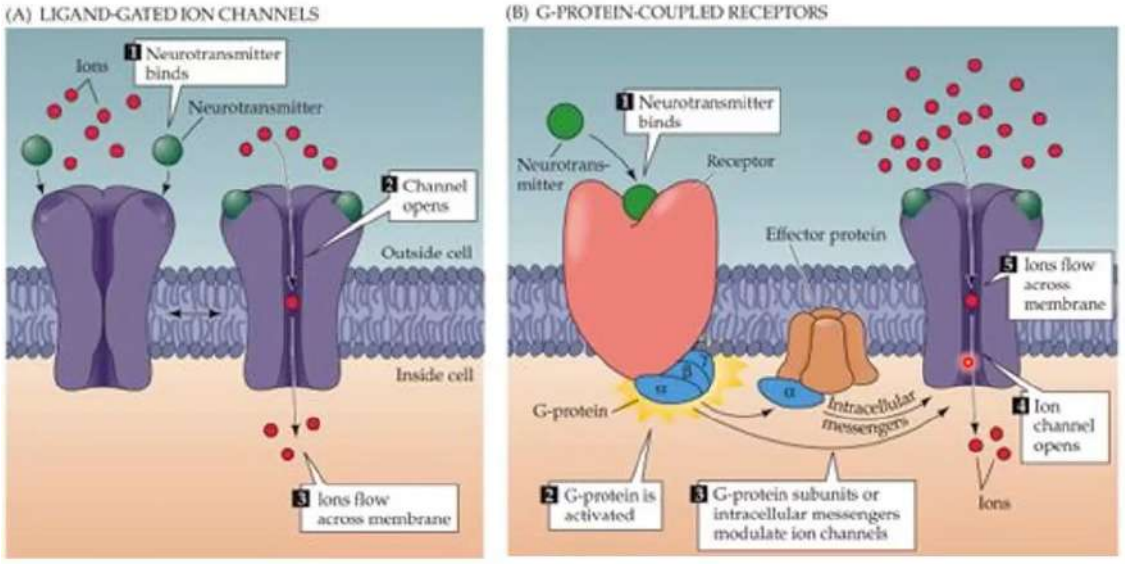
There are 2 types:

Ligand-gated Ion Channel

- Neurotransmitter diffuses, and binds to receptor, upon binding to the receptor the receptor channel opens and flow can occur for the specified type
- Very fast

G-Protein-Coupled Receptors

- Neurotransmitter diffuses and binds to receptor, triggers whole cascade
- Rather slow



Sequence of Events

- Neurotransmitter release
- Transmitter binding to the receptor
- Ion channels open or close
- Conductance change causes current flow of ions of charge
- Postsynaptic potential (passively) changes
- Postsynaptic cells either excited or inhibited
- Summation determines whether or not an action potential occurs

Neural Networks

Central Nervous System

- Brain & Spine

Peripheral nervous

- **Somatic Nervous -** voluntary muscles
- **Autonomic Nervous system** - involuntary muscles
    - Sympathetic - flight or fight response
    - Parathimpatheic - rest and digest system

Major Divisions of the brain

Telencephalon

- Far brain
- Silver cortex
- Hippocampus, ganglia, …

Diencephalon

- Talamus
- Hypothalamus
- Relay station

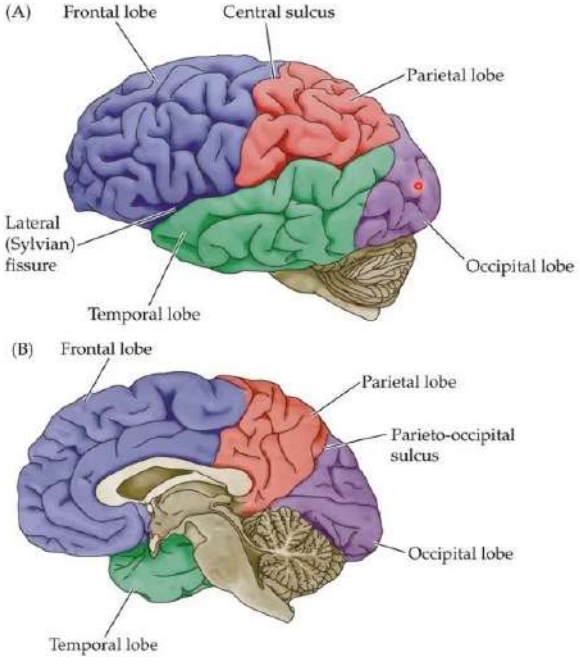
Mesencephalon

- Midbrain
- Inferior/superior curriculum

Metencephalon

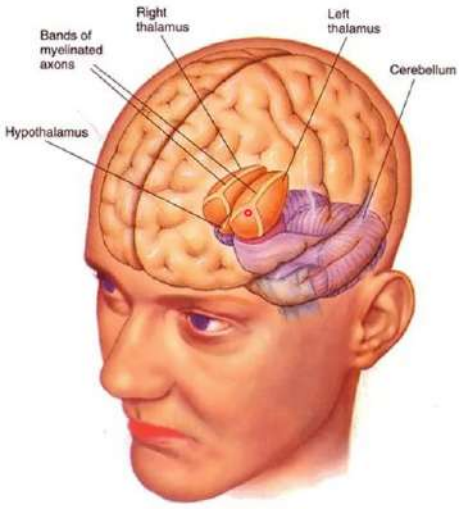
- Cerebellum - small brain (movement)
- Lot of cranial nerves leave the brain here

Lobes of cerebral cortex



Hypothalamus & Thalamus

- Thalamus gatekeeper / gate to the cortex



Upper Brain Stem: Diencephalon

- Thalamus
  - Structure
    - Relatively large
    - Two symmetric large nuclei
    - All thalamic nuclei receive ascending and descending input
    - Many projections
  - Function
    - Relay station
    - domain-specific information processing

- Hypothalamus
  - Structure
    - Very small
    - Contains an important collection of nuclei
  - Function
    - Controls autonomic mechanisms
    - Link to endocrine system

Most receptor potentials are depolarizing (excitatory), but interestingly, a receptor potential can also be hyperpolarizing (inhibitory) as in the retina.

So, the action potentials are all-or-none, but their frequency is graded.

Neurotransmitter release is quantal, so you could also consider neurotransmitter as digital: number of released vesicles

An analog sensor is more sensitive, can more easily be adaptive. In contrast, transmission over large distances is better with a periodically regenerated digital signal.

Sodium is more concentrated outside the cell, potassium inside. Therefore, when the membrane potential is between the two reversal potentials (EK, ENa) as is the case here, positively charged Na+ ions flow inward.

Typically, there is an excess of negative charge on the inside surface of the cell membrane, and a balancing positive charge on its outside surface. In this arrangement, the cell membrane creates a capacitance Cm.

Via αn and βn, the gating variable n is voltage and time dependent. Note that n∞ is voltage, but not time dependent.

Vrest is the resting potential of the cell (in other exercises denoted as the reversal potential of the leakage current EL)

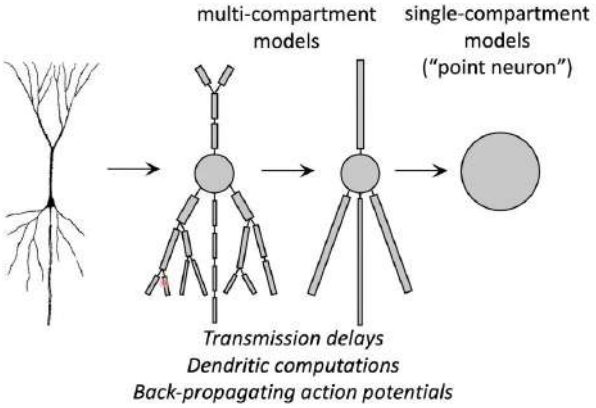
Lecture 3 - Membrane Potential

Why study single neurons?

- The computational unit of the brain
    - Constraints network computations
- Emulate in neuromorphic hardware
- Basis of experimental methods

We approach understanding neural computations not through **biologically realistic simulations** but **simplified and abstract** simulations.

You must choose your level of abstraction based on your task

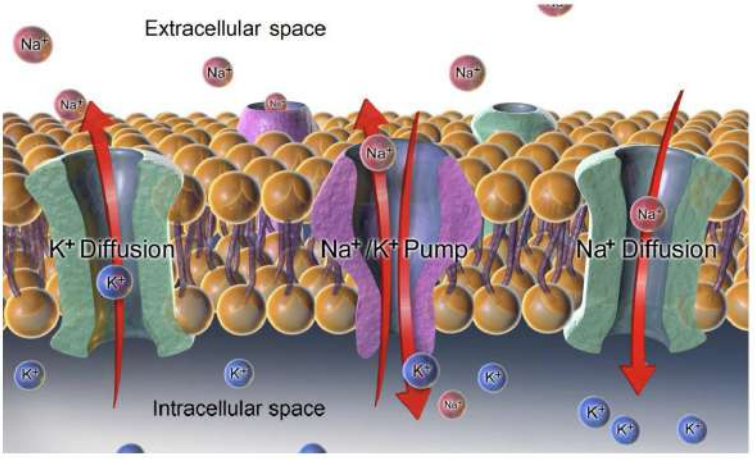


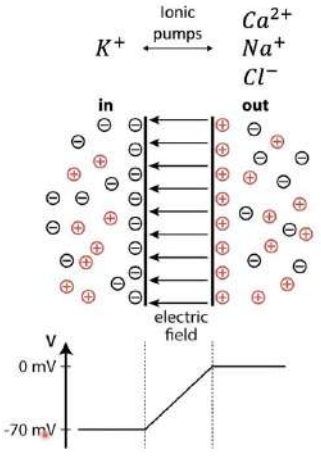
The resting potential

- Intracellular space V = - 70 mV (hyperpolarized)
- Extracellular space V = 0mV

The basic components

- The **Cell Membrane**
    - Separates in vs. out
    - **Electrical insulator**
    - Electrical capacitor (**stores charge**)
- **Concentration Gradients** in vs. out (due to ionic pumps)
- Selective **ionic Channels**
    - Sodium Na+ from inside to outside
    - Potassium K+ from outside to inside
- There are selective channels for example Sodium



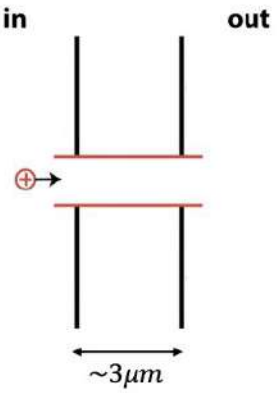


The Cell Membrane in Stats

1 μm^3 of cytoplasm:

- 10^10 H2O molecules
- 10^8 ions
- 10^7 small molecules (amino acids)
- 10^5 large molecules (proteins)

Ion Channels



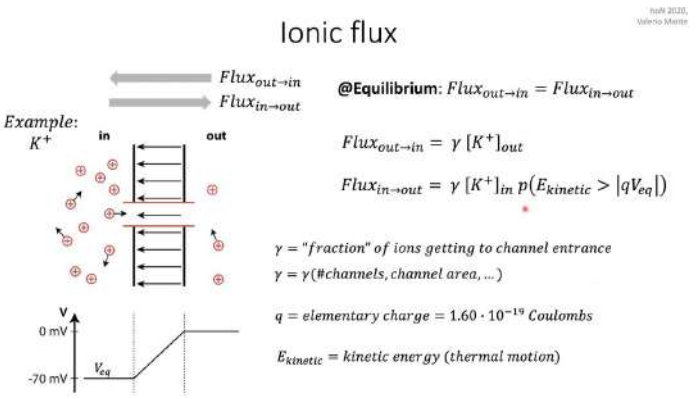
- They are **selective**
    - For every 10^4 correct Ions it only lets 1 wrong Ion pass
- **g** stands for conductance
- **Conductance** is the opposite of resistance - how easy it is for an electric current to flow through something
- Channels have a **large** conductance ~= 10^4 times the Membrane's conductance
- **Conductance** in this case**:** Given a certain potential difference from the inside and outside **how many Ions will flow through the channel/membrane in a unit of time**

Computing Neuron Behaviour

Many computations in the neurons result from:

- Channel selectivity for specific ion type
- Neurons are able to compute by changing the conductance gCH
- Time-dependence of gCH due to:
    - Neurotransmitters (by the synapses)
    - Voltage (for AP)
    - Second messengers (e.g. Ca2+)

- We would like to obtain an equation that tells ***what the Resting Potential is and what parameters affect it***



Gamma Factor

We summarize all effects (fractions of ions getting to channel entrance, conductance of channels, #channels) in parameter Gamma. We assume that Gamma is the same in and outside.

Lack of Electrical Field

There is no electric field outside or inside because we're not in a vacuum. We're in a conductor (water) filled with ions. Inside the conductor you don't have an electric field. **The only electric field is along the membrane.**

Flux Out->In:

- Once a particle reaches the begging of a channel it starts feeling the potential
- "Gets attracted" over to the other side / Slides down

Flux In->Out:

- When the positive particle gets to the channel it needs to **overcome the potential difference** because it is positively charged and the potential outside is larger.
- With enough **thermal/kinetic energy** they can go outside.
- P is the probability of the ions having enough kinetic energy
- $p(E_{kinetic} > |qV_{eq}|)$
  - q is the charge of one positive electron
  - Veq is the equilibrium Voltage

The Boltzmann Factor

What is the probability $p(E_{kinetic} > |qV_{eq}|)$? It can be described by the "Boltzmann factor"

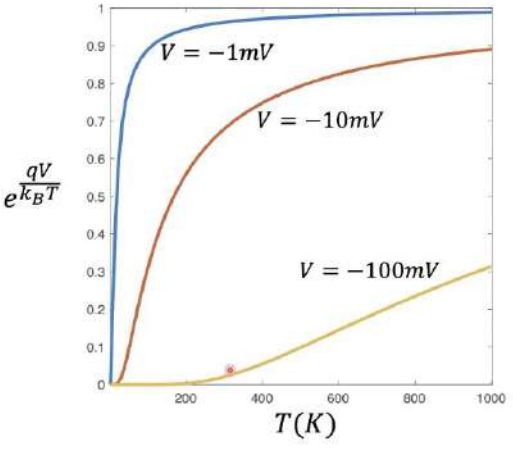
$$p(E_{kinetic} > |qV_{eq}|) = e^{\frac{qV_{eq}}{k_B T}} = e^{\frac{-E}{k_B T}}$$

$E = Energy$

$k_B = Boltzmann\ constant = 1.38 \cdot 10^{-23}\ J\ K^{-1}$

$T = Temperature\ (K)$

- In our case the energy we want to overcome is charge * equilibrium potential
- If the temperature is zero no particles crosses to the outside
- If you increase the temperature all particles make it



- We want **no dependence** to gamma.
- $Flux_{out \to in} = Flux_{in \to out}$
  - $Flux_{out \to in} = \gamma [K^+]_{out}$
  - $Flux_{in \to out} = \gamma [K^+]_{in} e^{\frac{qV_{eq}}{k_B T}}$
- If we solve for Veq we get this
  - $V_{eq} = \frac{k_B T}{q} \ln\left(\frac{[K^+]_{out}}{[K^+]_{in}}\right)$

This gives us the **Nernst equation:**

Nernst equation (single ion-type):

$$V_{eq} = \frac{k_B T}{zq} \ln\left(\frac{[X]_{out}}{[X]_{in}}\right)$$

$z = ionic\ charge\ (signed)$

- If we **wait for infinity** we get the Equilibrium voltage (steady state)

Effects

- **Temperature** increases/decreases => Veq increases/decreases
  - (increase or decrease depends on the sign of the voltage)
  - More kinetic energy, more particles making it across, possibility to maintain a larger potential difference
- increases => Veq decreases
  - Twice the charge requires twice the energy to make it across

Signs

If you change the sign(z) => change the sign(V)

- **You don't need to have a negatively charged ion to create a negatively charged inside**

Ionic Charge:

- Chloride -1
- Potassium +1
- Calcium +2

Questions:

- What if there's more potassium outside/inside
- What if it's a negatively charged ion that can be enriched inside or outside?

Checking our assumptions

Does our Neuron have enough ions to even create an equilibrium at -70mV?

Membrane capacitance - how much charge can be stored

$$\text{Membrane capacitance: } C_m = c_m \cdot A \qquad c_m \cong \frac{10nF}{mm^2}, A \cong 0.01 - 0.1\ mm^2$$
$$c_m = specific\ capacitance$$
$$A = area \qquad \Rightarrow C_m \cong 0.1 - 1\ nF\ (F = Farad)$$

How many ions are needed for an equilibrium at -70mV?

The total charge is $Q_m = C_m V_{eq} \cong 7 \cdot 10^{-11}\ C$

Therefore we need $\#ions = \frac{Q_m}{q} \cong 10^9\ (q = 1.60 \cdot 10^{-19}\ C)$ many ions.

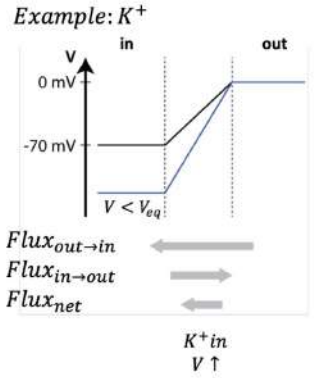
One neuron contains 10^14 ions - so we're safe with our assumption as we only need 10^9.

But volume grows faster than area so for smaller neural segments this might not be the case.

EXAMPLE 1 ion Potassium

CASE 1

What would happen if the potential inside was smaller than the equilibrium potential?

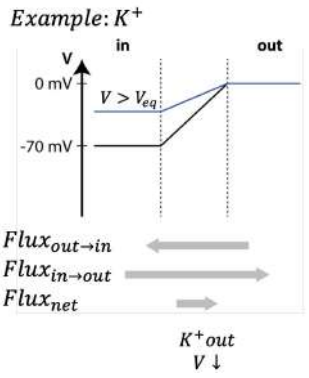


- Flux OUT ->IN - stays the same
  - Due to it not being affected by the equilibrium potential
- Flux IN -> OUT - is smaller
  - Because of the larger potential difference you have less ions with sufficient energy to make it across
- Flux Net - OUT->IN
  - We have Potassium flowing from the outside to the inside

We are now bringing positive charge inside and increasing the potential back up.

CASE 2

What would happen if the potential inside was bigger than the equilibrium potential?



- Flux OUT ->IN - stays the same
  - Due to it not being affected by the equilibrium potential
- Flux IN -> OUT - is bigger
  - Because of the smaller potential difference you have more ions with sufficient energy to make it across
- Flux Net - IN->OUT
  - We have Potassium flowing from the inside to the outside

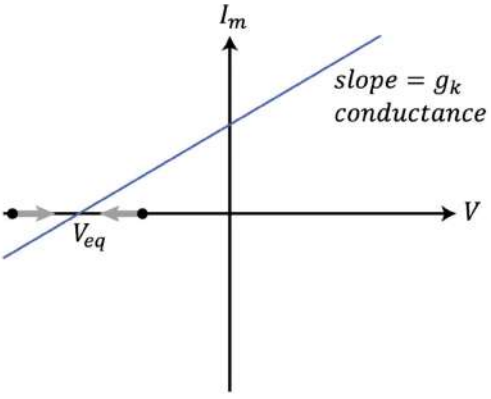
We are now bringing positive charge outside and increasing the potential back down.

Either way this **Veq** is **stable** and will be **bounced back to**.

Why is it called **reversal potential**?
Because at the specific voltage the **sign of the current reverses**!

Ohm's Law:

- Current = Voltage / Resistance
- Current = Voltage * Conductance



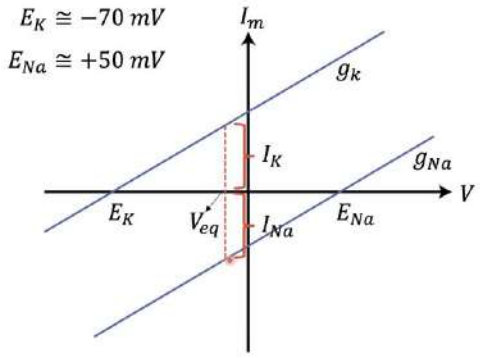
$Reversal\ potential:\ E_K = V_{eq}(K^+)$

$Ohm's\ law:\ I_m = g_k(V - E_K)$

Example 2 ions Potassium & Sodium
We consider Potassium & Sodium. Each of them have their own channels.

Sodium has a positive reversal potential. It's also positively charged but the concentration is larger outside than inside. Which flips the sign of the equilibrium potential.

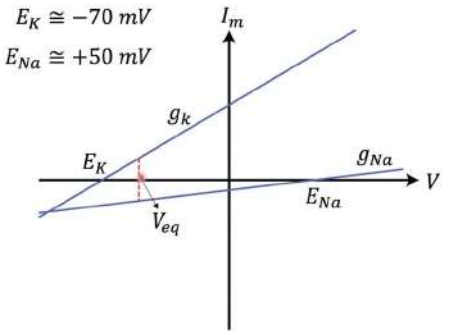
A potential will be reached where the current of the potassium channel is exactly opposite of the current of the sodium channel. They cancel out. Things won't change but there still is a net current flowing at all time. Requires pumps to be maintained.



Resting potential is the reversal potential of a particular ion type. Resting potential of a neuron is very close to the reversal potential of potassium.

Changing of the Conductance
By **opening** or **closing channels** the **slope gets steeper/gentler** and a **new equilibrium point** is determined.

Different channel types are associated with a specific reversal potential.



Channel types are associated with a specific reversal.

With only one channel type /ion type you reach the equilibrium potential and have a net flux of zero. **With two or more the net flux isn't zero and constant pumps need to b**e maintained.

Many single neuron computations based on this process:
If you open a channel with an reversal potential E and it dominates then the Equilibrium Potential will be pulled towards the reversal potential E.

Goldman-Hodgkin-Katz Equation

GHK equation (mixed ion-type):

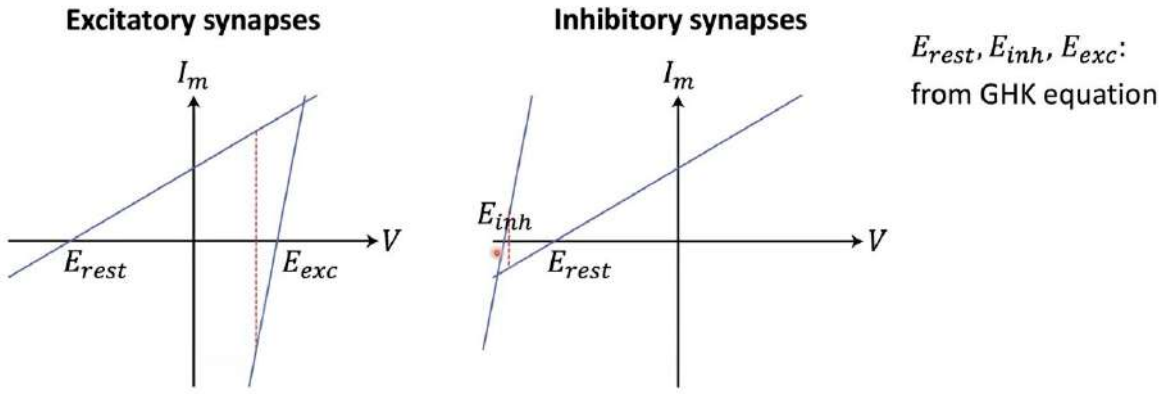
$$V_{eq} = \frac{k_B T}{q} \ln\left(\frac{P_K[K]_{out} + P_{Na}[Na]_{out} + P_{Cl}[Cl]_{in}}{P_K[K]_{in} + P_{Na}[Na]_{in} + P_{Cl}[Cl]_{out}}\right) \qquad P_X = permeability(X)$$

- Sign operator was incorporated in choosing whether in or out should be the denominator.
- Similar to Nernst Equation

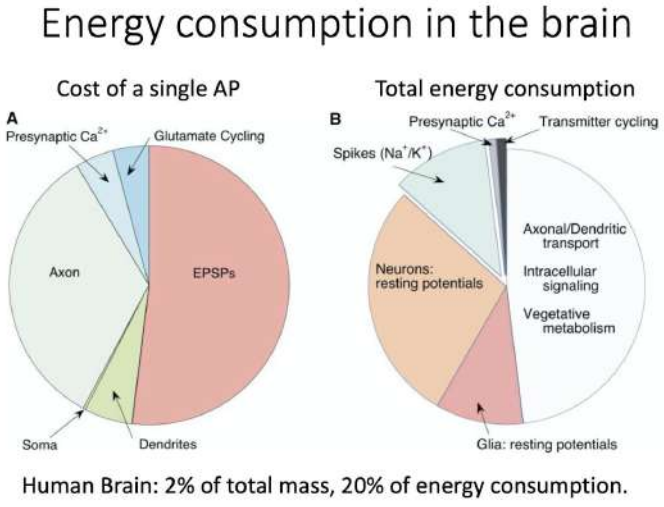
We have types of channels that are always open at -60 -70mV equaling the potential of the neuron, called **Leak Channels**. **Their Reversal potential is the resting potential of the neuron**.

Channels that have a positive reversal potential that is positive that **depolarize** the neuron are called **excitatory channels**.

Channels that have a strong negative reversal potential that polarizes the neuron are called **inhibitory channels**.



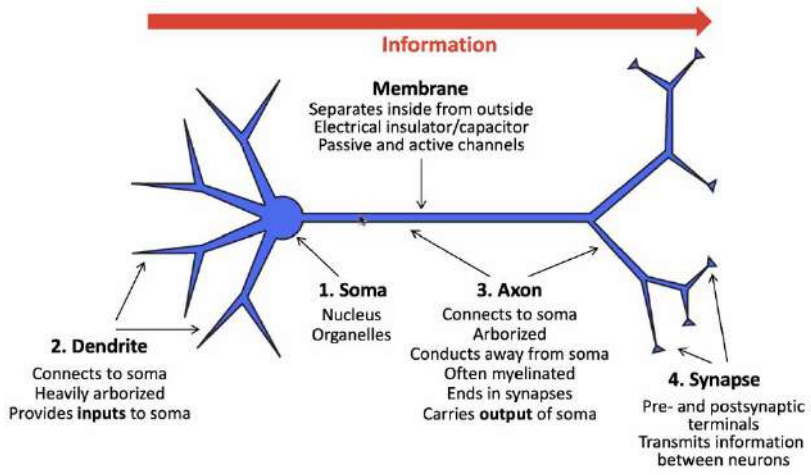
Energy Usage



Human Brain: 2% of total mass, 20% of energy consumption.

Lecture 4 - Passive membrane properties

The **passive membrane** is how current flows through neurons (non active part)



Ohmic conductances

The relationship that captures the current through the channels is a function of voltage, these linear relationships which are ohms law

Channels

- There are different channels that open based on neurotransmitter, voltage, … they are time dependent
- What differentiates these channels are the ions that flow through them thus comes the reversal potential associated to them.
- **AMPA/NMDA** are the main channels

Type	Ions	E	
AMPA/NMDA	Mixed cation	0 mV	Excitatory
GABA A	Cl^-	-65 mV	Inhibitory
GABA B	K^+	-90 mV	Inhibitory
AP V-dep.	Na^+	55 mV	Depolarizing
AP V-dep.	K^+	-90 mV	Hyperpolarizing

Synaptic Currents

1. Action Potential comes down an axon of a neuron and reaches the presynaptic terminal
2. Cascade of events leading to depolarization/polarization
    a. Leading to Current flowing OUTSIDE->INSIDE - excitatory
    b. Leading to Current flowing INSIDE -> OUTSIDE - inhibitory

- Action Potential comes down in the presynaptic part and creates a cascade of events leading to the depolarization / current into or out depending on inhibitory and excitatory synapses
- The current will flow down other branches of the dendrites and leak out into the extracellular space.

What happens when you inject a current?
How quickly does it change the potential?
How much does it change it and how does it change it over space?

This information leads to how many synapses do we need to activate at any given time to make a neuron generate an action potential

---

Cable equation
What happens in dendrite is like signal propagation in a conductive cable.

We want to find an expression for: $V = V(x, t)$

- x: length of a cable
- t: time

First we look at a single compartment level neuron - sphere that has the same that has all the same potential (no x).

Single compartment model

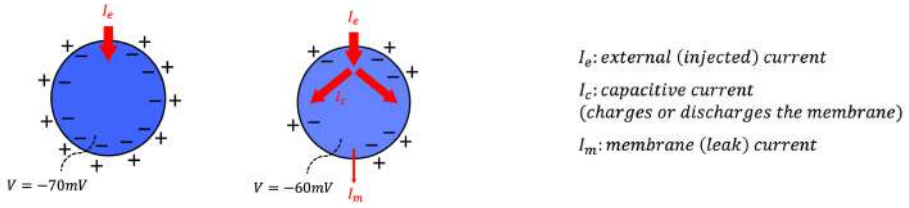
$$V = V(t)$$

- Sphere of membrane
- Has the same potential (x is not part of the equation)
- **Isopotential** there is just one potential
- We just observe what happens to the potential as a function of time

*We will prove this using the **conservation of electrical charge***

What happens to the potential as we inject current over time?

- Our neuron has a resting potential of -70mV
- There is an excess of negative charge inside of the membrane
- What happens if we inject a current into this model neuron from the outside, e.g. an **electrode**
- This current that we inject let's say positive charge **Ie** will bind with some of the negative charge
    - Reduce the potential (e.g. -60mV)
    - Now that resting potential is distrubed there is a net current **Im** flowing out/in through the membrane
- If we keep injecting current we continue changing the potential more
- Until there is an equilibrium until all the current we inject will just flow out.
- **Im** depends on **Ie**



Deriving V(t)

Due to the conservation of charge the current we inject can only go to 2 places

$$I_e = I_c + I_m$$

The membranes current is the voltage minus the reversal potential of the open channel times the conductance of gm of the channels

Membrane current (Ohm's law):

$I_m = g_m(V - E_m)$

Membranes capacity - capacity describes how much charge you can load onto the membrane given a potential difference between the inside and outside

*(As long as **Im** (leak current) isn't the **Ie** (injected current) you will raise the the potential of the neuron)*

Membrane capactitance:

$C_m = \frac{Q_m}{V}$ $\quad \frac{d}{dt}$

$C_m V = Q_m \rightarrow C_m \frac{dV}{dt} = \frac{dQ_m}{dt} = I_c$

- We assume capacitance of membrane **Cm** is **constant**
- Charge on the capacitance **Qm** is not constant and is time dependent so is **V**
- The amount of charge over time is **Ic** the **capacitive current**

If we pluck these values in we receive the following:

$$I_e - I_m = I_c$$

$$I_e - \frac{1}{R_m}(V - E_m) = C_m \frac{dV}{dt}$$

$$R_m I_e - (V - E_m) = R_m C_m \frac{dV}{dt}$$

$$\boxed{R_m I_e - (V - E_m) = \tau_m \frac{dV}{dt}}$$

$$R_m = \frac{1}{g_m} = \text{“input resistance”}$$

$$\tau_m = R_m C_m = \text{“membrane time constant”}$$

- **tauM** characterizes the neuron - how quickly the potential inside a neuron can change

Steady-State Solution

Once we start injecting current the potential increases and arrives at a steady level at **V**inf

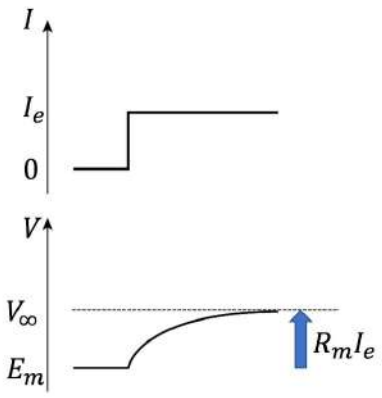
$$R_m I_e - (V - E_m) = \tau_m \frac{dV}{dt}$$

$$\textbf{Steady state}: V = V(t = \infty) = V_\infty$$

$$\Rightarrow \frac{dV}{dt} = 0$$

$$R_m I_e - (V_\infty - E_m) = 0$$

$$\boxed{V_\infty = R_m I_e + E_m}$$



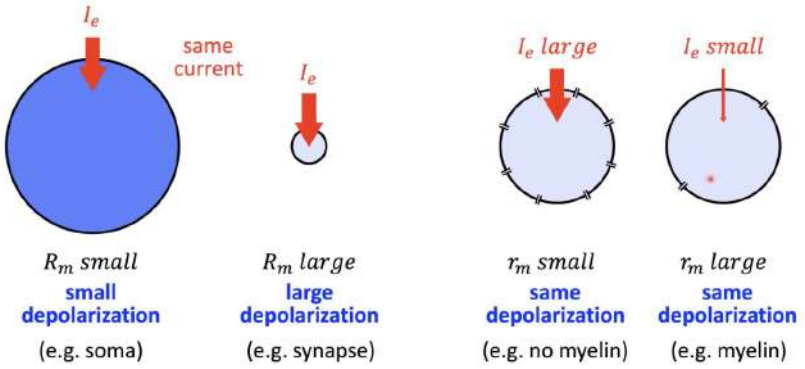
- If you wait till **V**inf the derivative of the potential is zero
- In the equation you set that to zero

- The potential we reach asymptotically if we inject a current and leave it on $V_\infty = R_m I_e + E_m$
- It scales if you double the current you'll reach double the potential.

Input Resistance

If you have two neurons with same current but they have different sizes:

$V_\infty = R_m I_e + E_m$ $\quad R_m = \frac{r_m}{Area}$ $\quad r_m = specific\ resistance$



The total resistance of the membrane **Rm** is dependent on the **area**

Once can think about neural structures as isopotential regions.

In myelinated axons you need smaller charges to depolarize due to the rm being smaller due to the myelinated isolation!

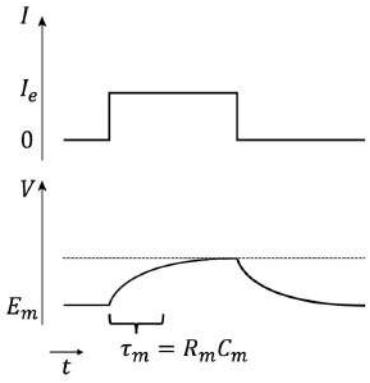
General Solution Formula

$$R_m I_e - (V - E_m) = \tau_m \frac{dV}{dt}$$

$$V(t) = V_\infty + (V(0) - V_\infty) \cdot e^{-\frac{t}{\tau_m}}$$

$V(0) = V(t = 0) = initial\ condition$

$V_\infty = R_m I_e + E_m$



- **Ie** is fixed
- **V0** is the potential at time zero
- How quickly the potential raises it dependent on the **Time constant ™**
- *Choose V0 and Vinf depending on the task if it's a 01 or 10 transition*

Time constant τ_m :

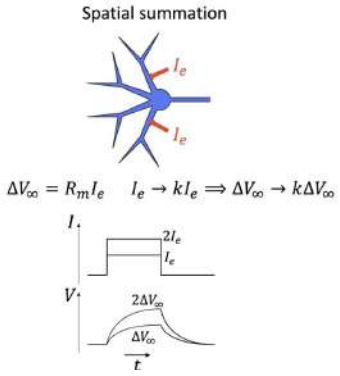
1. Typically: $\tau_m \approx 10 - 100$ms
2. The time-scale of change in the cell (slow compared to a computer)
3. The short-term "memory" of the cell (short compared to an organism)
4. Activity "forgotten" after τ_m
5. Longer memory: other mechanisms (e.g. plasticity, ...)

Spatial and temporal summation

- Both are **extreme cases**

Spatial summation

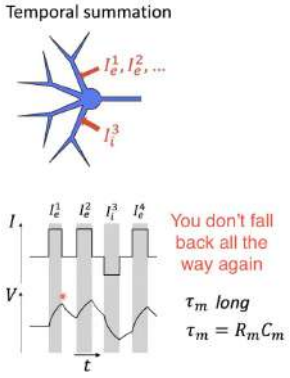
What if I inject currents in different places at the same time such that they reach the soma at the same time?



- If I scale my **Ie** by some factor k it scale **V**inf accordingly
- Inputs sum up in the soma

Temporal summation

Having synapse that is repeatedly active over a time interval

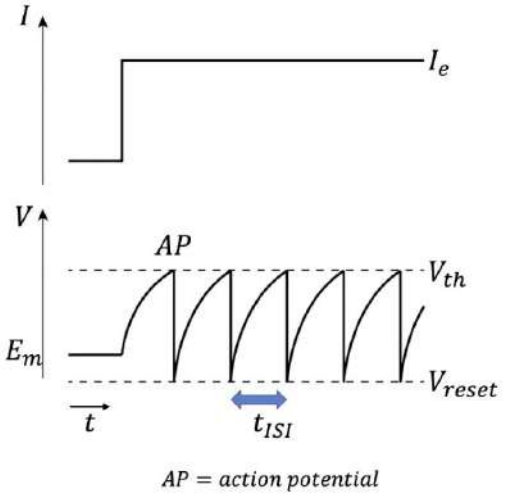


- You scale your **V**inf but **You don’t fall back all the way again**
- Inputs don’t come at the same time but they can still sum up

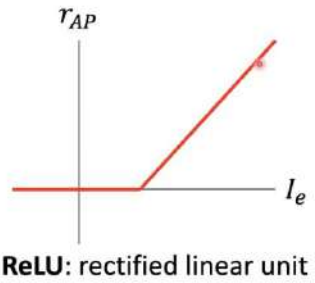
Integrate and fire neuron

Temporal or spatial summation only happens till a certain threshold is reached where it creates an Action Potential

The integrate and fire neuron tries to capture the non linear process model when the voltage reaches the threshold



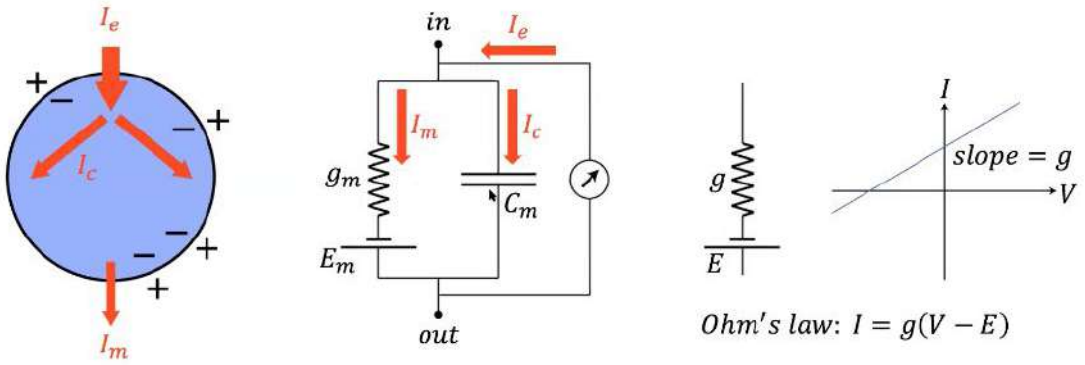
$$r_{AP} = \frac{1}{t_{ISI}} \approx \left[\frac{E_m - V_{th} + R_m I_e}{\tau_m (V_{th} - V_{reset})}\right]_+$$



ReLU: rectified linear unit

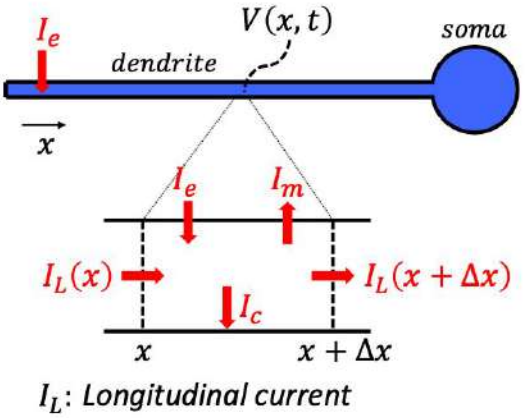
- As soon as potential reaches level an **Action Potential** is generated
- Potential is **reset** to some value via reset
- The left side is a scenario when a constant current is being injected.
- With the equations we derived we can compute the rate of action potentials
    - Bracket with + means we're only taking positive values
- Non linear relationship between the output of the neuron as a function of the total summed input of input
- **Ie** is the total amount of current reaching the **soma**
    - If the current is too small you don't get any AP => Vinf < Vth
    - Once you reach the threshold by increasing the current you reach a linear relationship between **rAP** and **Ie**

Equivalence among circuits



Deriving the cable equation

Finding a dependency to space as well.



Conservation of charge:

$$I_L(x+\Delta x) = I_L(x) + I_e - I_m - I_c$$

$$\frac{\partial}{\partial x}V(x+\Delta x) \quad \frac{\partial}{\partial x}V(x) \quad \frac{\partial}{\partial t}V$$

$$\frac{\partial^2}{\partial x^2}V(x)$$

- If we inject current in a cable we want to know how the **potential changes across the cable**

- We look at a very small section of the cable
- What are all the currents that can flow into or out of the cable section
    - **Ie** External Current
    - **Ic** Capacitive current stays in section of cable
    - **Im** Leak Current flows out
    - **IL** Incoming Current (left) (**Longitudinal current**)
    - **IL delta** Outgoing Current (right) (**Longitudinal current**)

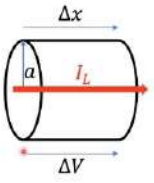
*Due to conservation of charge we can calculate **IL delta**:*

$$I_L(x+\Delta x) = I_L(x) + I_e - I_m - I_c$$

Longitudinal Resistance

Resistance of piece of cable

- It increases with length linearly
- Inversely Proportional to the area (“putting cables in parallel instead of series”)
- **rl** constance of how conductive a material is



R_L: ***Longitudinal resistance***

$$R_L = \frac{r_L}{Area}\Delta x = \frac{r_L}{\pi a^2}\Delta x$$

Ohm's law: $\Delta V = R_L I_L \qquad \Delta V = \frac{r_L}{\pi a^2}\Delta x \cdot I_L$

$$\Delta x \to 0 \quad \boxed{\frac{dV}{dx}(x) = -\frac{r_L}{\pi a^2} I_L(x)}$$

Define $\Delta V < 0$ for positive current from $x \to x + \Delta x$

Using Ohm's law:

- Potential across this distance is Resistance * Current
- If you divide by x you get the derivative **Voltage** as a function of x

Convention Direction of Current

- Added a minus sign in front of the resistance
- If you define a positive current flowing form x => x+delta
  - You'd have a drop in potential from x => x+delta
- We define the change in potential as < 0 when flowing from x => x+delta

Cable Equation

- You end up with a second derivative

Conservation of charge:

$$\underbrace{I_L(x+\Delta x)}_{\frac{\partial}{\partial x}V(x+\Delta x)} = \underbrace{I_L(x)}_{\frac{\partial}{\partial x}V(x)} + I_e - I_m - \underbrace{I_c}_{\frac{\partial}{\partial t}V}$$

$$\frac{\partial}{\partial x}V(x+\Delta x) - \frac{\partial}{\partial x}V(x) = \frac{\partial^2}{\partial x^2}V(x)$$

Cable equation:

$$\boxed{c_m \frac{\partial}{\partial t}V = \frac{1}{2ar_L}\frac{\partial}{\partial x}\left(a^2 \frac{\partial}{\partial x}V\right) - i_m + i_e}$$

- Radius a need not be constant, i.e. $a = a(x)$
- i_m could be very complicated, e.g. $i_m \approx \sum g_i\,(V - E_i)$ and $g_i(V)$
- In general: no analytic solution
- Consider simple cases or simulate

Current density: $i = \frac{I}{Area}$

$$R_m = \frac{r_m}{Area} \qquad C_m = c_m \cdot Area$$

$$I_e = 2\pi a \cdot \Delta x \cdot i_e$$
$$I_m = 2\pi a \cdot \Delta x \cdot i_m$$
$$I_c = 2\pi a \cdot \Delta x \cdot c_m \frac{\partial}{\partial t}V$$
$$I_L = -\frac{\pi a^2}{r_L}\frac{\partial}{\partial x}V$$

- Partial differential equation
- Express Current and Resistance as a function of area

Linear cable equation

Linear cable equation:

$$c_m \frac{\partial}{\partial t} v = \frac{a}{2r_L} \frac{\partial^2}{\partial x^2} v - \frac{v}{r_m} + i_e$$

A simpler case with the following assumptions:

a = constant

Define $v = V - E_m$

$i_m = \frac{v}{r_m}$

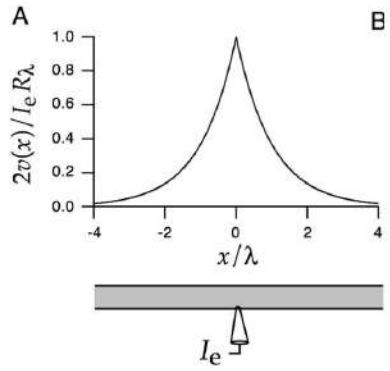
$$\tau_m \frac{\partial}{\partial t} v = \lambda^2 \frac{\partial^2}{\partial x^2} v - v + r_m i_e$$

Membrane time constant: $\tau_m = r_m \cdot c_m$

Membrane length constant: $\lambda = \sqrt{\frac{a r_m}{2 r_L}}$ *(electrotonic length)*

- **TauM** defines how quickly voltage can change overtime in a neuron
- Delta defines how quickly things can change in space

Case 1: Infinite cable & constant current



B

$$v(x) = \frac{I_e R_\lambda}{2} \exp\left(-\frac{|x|}{\lambda}\right) \qquad R_\lambda = \frac{r_m}{2\pi a \lambda} = \frac{r_L \lambda}{\pi a^2} \qquad \lambda = \sqrt{\frac{a r_m}{2 r_L}}$$

If I_e injected @ $x = 0$ in dendrite (e.g. through synapse):

- $V(x)$ decays exponentially with distance
- $V(x)$ reduced to ~0.37 of max @ $x = \lambda$

Dendrites have "effective" lengths in the order of λ, and thus:

- $V(x)$ attenuates strongly between distal dendrites and soma

How can a neuron increase λ ?

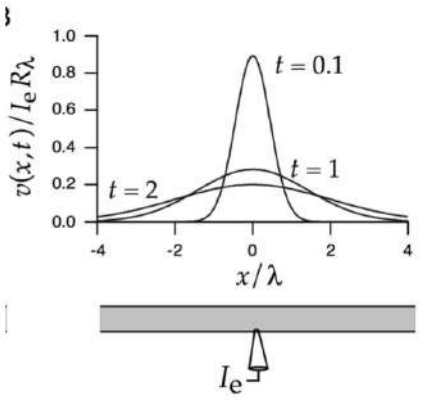
- $r_m \uparrow$: less leak i_m through the membrane (e.g. myelin)
- $a \uparrow$: larger cable (e.g. squid giant axon)
- $r_L \downarrow$: lower intracellular resistance (hard)

- **YAxis** Potential as a function of x normalized to max one
- **XAxis** x expressed in lambda (you've moved one lambda away from current injection)
- Injecting current **Ie** and leaving it on
- Lambda is for how many lambdas am I away from where the current was injected
    - X = 1 is 1 lambda away from where the current was injected at 0
- Exponential decay

Implications

- Dendrites effective length are in the order of lambda
- How can a neuron increase lambda?

Case 2: Infinite cable & current pulse

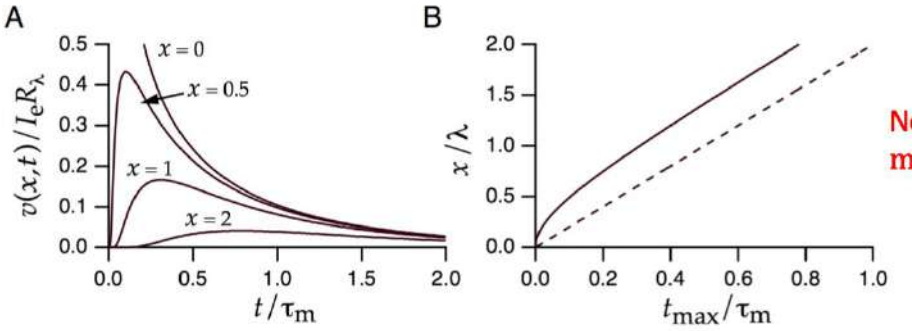


$$v(x,t) = \frac{I_e R_\lambda}{\sqrt{4\pi\lambda^2 t/\tau_m}} \exp\left(-\frac{\tau_m x^2}{4\lambda^2 t}\right) \exp\left(-\frac{t}{\tau_m}\right)$$

At each time t, $V(x,t)$ is a Gaussian

- Width $\sim \lambda\sqrt{\frac{t}{\tau_m}}$
- Area $\sim exp\left(-\frac{t}{\tau_m}\right)$: some charge lost through i_m

- Synapse that briefly opens and closes again
- Injecting a current pulse and not leaving it on
- Profile of voltage as a function of location of the current injection but we also have a curve as a function of time



Note: it's not a wave!
max V always @ $x = 0$

Time of peak & temporal spread of V depends on x

- Use to infer distance of EPSP from soma recordings
- Effective speed of the the "bump":

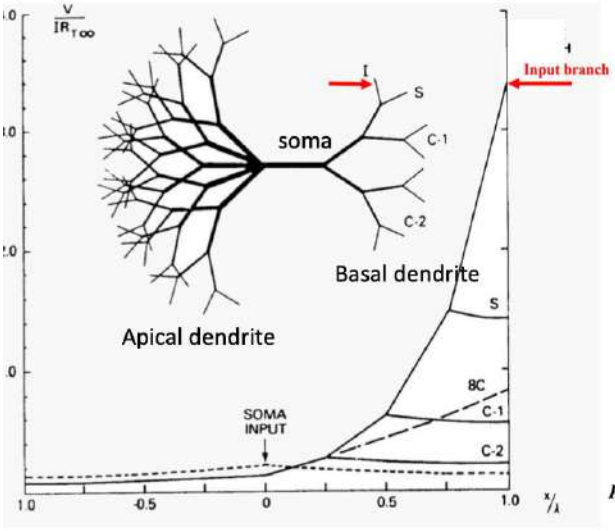
$$V_{bump} \approx 2\frac{\lambda}{\tau_m}$$

- $\lambda\uparrow \Rightarrow$ Potential spreads far $\Rightarrow V_{bump}\uparrow$
- $\tau_m\downarrow \Rightarrow$ Potential changes fast $\Rightarrow V_{bump}\uparrow$

Used in axons (unmyelinated and myelinated)

- Replot same Data, potential as a function of time at different locations with respect of location where we injected the current
- Max is always at x = 0
- Method used to infer the distance of Excitatory Postsynaptic Potentials in soma recordings
- You can find a speed of the bump that is almost linear
- Graph on the right: time to find pump function

Passive currents in a branching neuron



- ~ exponential decay from dendrite to soma
- a changes @ branches $\Longrightarrow$ slope changes
- Most current flows to soma $\Longrightarrow V \sim$ *const* up branches
- Smaller V if current injected @ synapse (input resistance)
- $\Delta V_{soma}(I_e$@synapse$) \sim \frac{1}{2}\Delta V_{soma}(I_e$@soma$)$: efficient

Rall and Rinzel, 1973

- Most currents flow to the Soma
- Transmission is quite efficient
- Dash line if the current had been injected in the soma

Potential Differences are 0.2 - 0.4 mV in CNS because there is this very strong exponential decay happening

- Soma is a big space

Resting at -70 mV, Threshold at -60 -> we need 25 inputs to fire (if linearly)

Lecture 5 - Action Potential

Equivalent Circuits

$$\frac{dV}{dt} = 0 \rightarrow V_\infty = \frac{I_e}{g_m + g_s} + \frac{g_m E_m + g_s E_s}{g_m + g_s}$$

Three special cases of this equation:

There is no external current injected. We only look at the effect of opening Synapse.

$$I_e = 0 \rightarrow V_\infty = \frac{g_m E_m + g_s E_s}{g_m + g_s} \quad \text{(compare to GHK)}$$

If **Es** is **excitatory** then it is higher than Em (resting potential)

- Vinf will be pulled to Es
- $I_e = 0, g_s \gg g_m \rightarrow V_\infty \approx E_s$

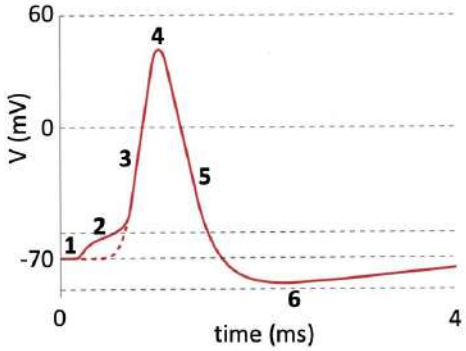
If **Es** is **inhibitory** then it is lower or similar to Em

If **Es** is excitatory and there is injected current what is its effect on Vinf if synapses are open at the same time?

- Still pulled to Es
- External current bounded by the synaptic conductance and therefore has less effect
- **Shunting Inhibition**
- By opening a synapse that hasn't a sufficient potential to reach an AP it can reduce the impact of other synapses (incoming currents)
- Chloride conductances can have an inhibitory effect due to their reversal potential being close to the resting potential

Axon Basics

- What happens if the voltage reaches a threshold at the axon hill
    - Strong depolarization
    - Travels down the axon like a wave
        - Self regenerating
    - When it reaches the presynaptic terminals it releases neurotransmitter



- Occurs in axons: travels away from soma
- Lasts 1-2 ms
- All-or-none: $I_e \uparrow \Longrightarrow AP$ occurs sooner, but same shape
- Stimulus intensity encoded as AP rate (r_{AP})
- Several phases:
    1. No input: $V = V_{rest}$
    2. Current $I_e \Longrightarrow V - V_\infty \sim exp(-t/\tau)$
    3. $V \Longrightarrow$ rapid increase in V
    4. Peak @ $V > 0$
    5. Rapid decrease in V
    6. Overshoot: $V < V_{rest}$

- Ideal starting state of a resting potential
- 2. Voltage has exponential approach to V_infinity
- 4. Peaks at a potential higher than 0
- Overshoot aka Undershoot

Action Potential generated by special conductances channels whose opening is **voltage** and **time dependent** these channels **only exist in the axon.**

Hypothesis
If we have some conductance in the neurons the voltage would be driven to the reversal potential of that channel.

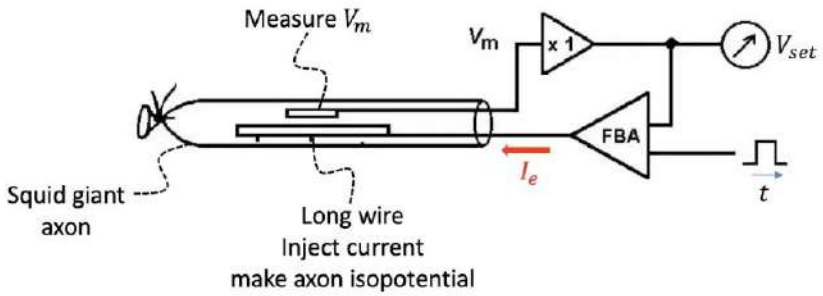
Rising phase of AP could be the rising of conductivity of $g_{Na} \uparrow$ or $g_{Ca} \uparrow$

Falling phase of AP could be the falling of conductivity of $g_{Na} \downarrow$ or $g_{Ca} \downarrow$ or $g_K \uparrow$ or $g_{Cl} \uparrow$

To test our hypothesis would need to measure the conductances for these channels with a **Voltage Clamp.**

Voltage Clamp

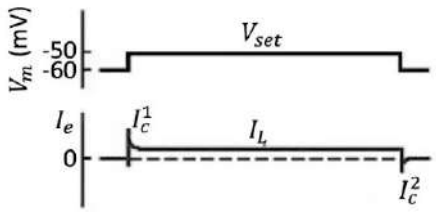
Squids have giant axons. (For a faster reaction you can make the wire area bigger.)



What is a **voltage clamp**?

- Fast feedback system by Hodgkin and Huxley
- They **fixed** the **voltage** inside of the Axon by **injecting current**.
- They inject a long wire to inject current and make the **axon isopotential** (potential is the same everywhere).
- We are studying static APs.???
- They measured some Potential in the axon and compared to the one they tried to achieve
- They then tinker to inject more or less current to achieve the desired Voltage to match the voltage in the axon
- Set desired **voltage V**, measure and adjust **current I**

Voltage clamp experiment



I_c^1: Depolarize membrane (add + charge inside)

I_L: Compensate for leak current (V ≠ V_{rest})

I_c^2: Repolarize membrane (remove charge added with I_c^1)

Initially or voltage is set to -60mV but then set to -50mV

- A current charges into the membrane
- We are not at the resting potential anymore
- Now there is a net current flowing out of the cell
- **II** leak current remains constant due to us setting the voltage to constant -50mV
- When going back to rest we need to remove charges from the cell

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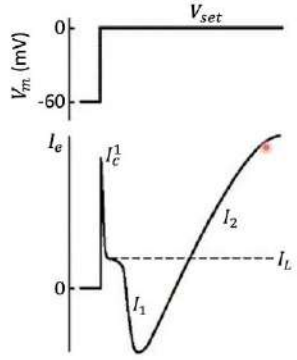
Voltage clamp experiment with higher potential



I_c^1: As above, but more charge added

I_1: Axon wants to depolarize
⟹ need to inject negative I_e to keep $V = V_{set}$

I_2: Axon wants to hyperpolarize
⟹ need to inject positive I_e to keep $V = V_{set}$

Clamping the voltage to a higher potential 0mV.

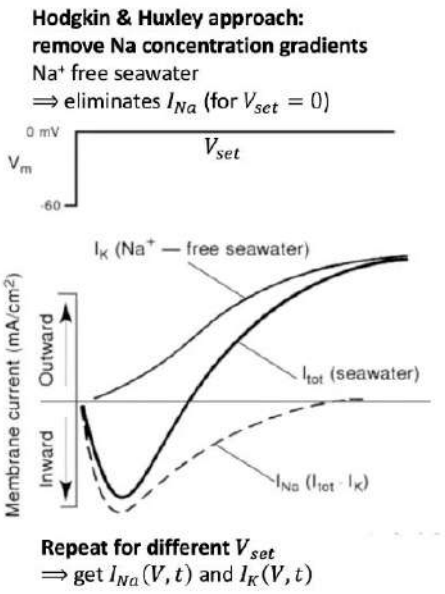
- We'd need a bigger positive charge flowing in
- One would expect just a larger leak current to hold the potential at 0mV
- But we have to reduce the current we inject and then inject negative charge to stay at 0mV
- Neuron/Axon is trying to depolarize itself
- Then the sign reverses and Neuron/Axon tries to hyperpolarize and we need to inject positive charge.

Hypothesis there are two currents one that depolarizes and one that hyperpolarizes.

Hypothesis: $I_1 \approx I_{Na}$, $E_{Na} \approx 50mV$ and $I_2 \approx I_K$, $E_K \approx -80mV$
with conductances that are both voltage and time dependent.

Note: no direct comparison of I_e to V_{AP}, because here V is clamped!

Identifying the currents



- Get rid of Sodium by using Sodium free water
    - We need to inject positive current to prevent form hyperpolarizing
    - Difference between two curves must be the current due to Sodium Channel
    - We Can do this for other currents as a function of voltage and time
- Later experiments with solutions containing things blocking the sodium currents entirely

From current to conductance through Ohm's law

Vary V_{set} to obtain $I_{Na}(V,t)$ & $I_K(V,t)$

Use Ohm's law to obtain $g_{Na}(V,t)$ & $g_K(V,t)$:

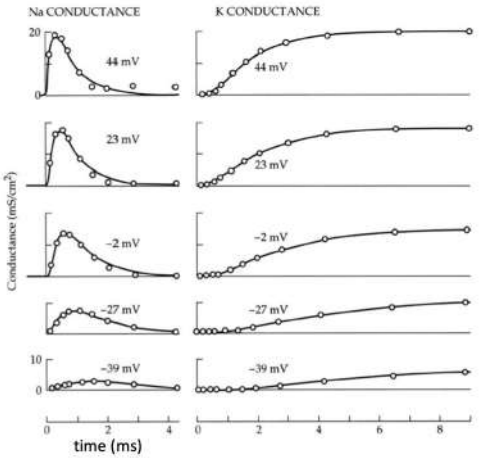
$I_{Na} = g_{Na}(V - E_{Na})$

$I_K = g_K(V - E_K)$

Result:

g_{Na}: fast activation
fast inactivation

g_K: slow activation
no inactivation



- If you depolarize a bit over the resting potential but still negative channels open and close
- If you depolarize more **over 0** then **channels open faster open more and close more quickly**
- Their conductance depends on voltage and time
- The higher the voltage the higher their dynamics
- Potassium **stay open** more the higher the voltage is set, overall they are **slower**

g_{Na}: fast activation
fast inactivation

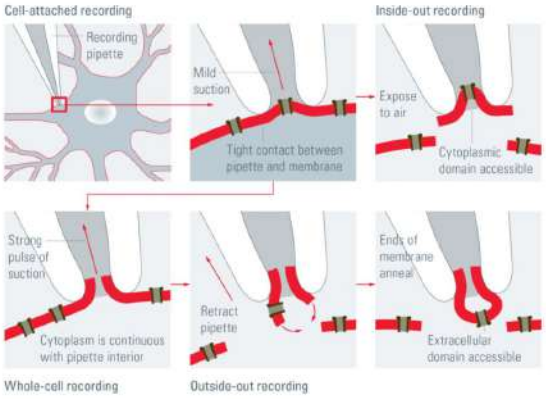
g_K: slow activation
no inactivation

How to explain voltage and time dependence in sodium and potassium conductance?

1. Single channels have variable (continuous) permeability
2. Single channels are either open or closed whereby probability(open) = function of (Voltage)

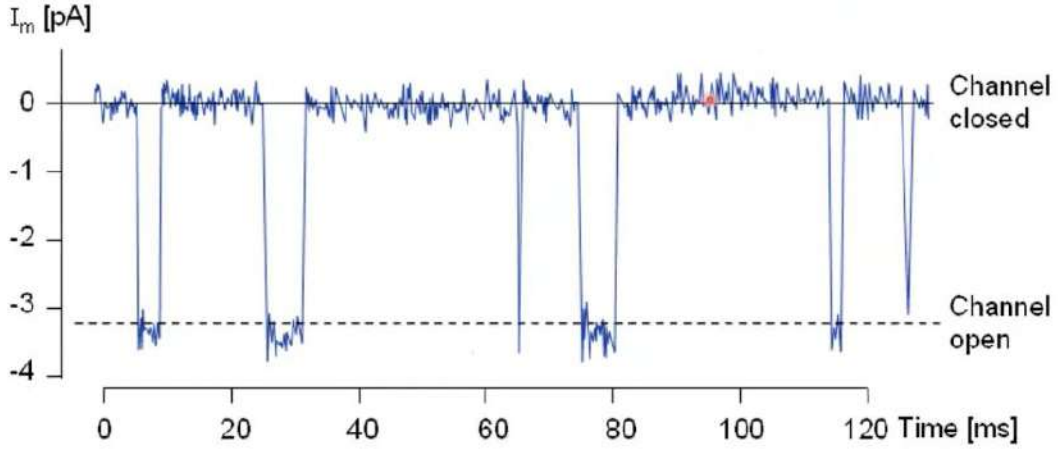
=> 2 Is correct by doing patch clamping of a single channel

Patch Clamp



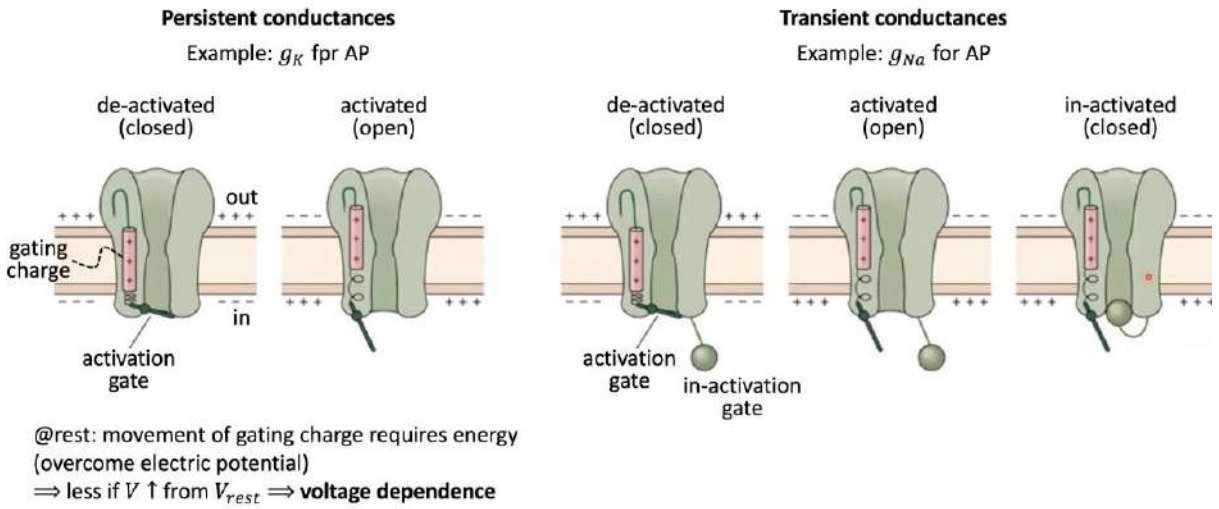
- You can get real close to the membrane of a neuron
- Isolate a single patch of membrane with a single channel
- Then only look at the conductance of this one channel
- There are other variants
- Main experiment is where you can measure conductance through a single channel

Analysis of a single channel



- Function of time
- Channel is only in 2 states, **closed** & **open**
- Almost random transitions (thermal motion)

Persistent and transient conductances



@rest: movement of gating charge requires energy (overcome electric potential)
$\Longrightarrow$ less if $V \uparrow$ from V_{rest} $\Longrightarrow$ **voltage dependence**

- Two kind of conductances
- **Energy** is involved in moving this gate

Persistent Conductance

- Potassium is a persistent conductance
- Can be closed or open
- Proteins form channel through the membrane where ions flow through
- Part of channel has charge associated with it
- Charged part (**gating charge**) of channel connected to activation gate
- Gate can be closed or open
- Energy involved moving the gating to charge to then open/close the gate

For persistent conductance, assume:
k identical/independent events are necessary to open a single channel:

$$P_K = n^k = \underbrace{n}_{\text{first}} \cdot n \cdot \cdots \cdot n \cdot \underbrace{n}_{\text{last}}$$

n: gating/activation variable = p(open) for single subunit
k: number of channel subunits (k=4 for g_K)

Transient Conductances

- Sodium has a transient conductances
- Has an additional **in-activation** gate - can be opened or closed
- Can close the channel even if activation channel is open/membrane is polarized

Hodgkin and **Huxley** formulated a formula for the overall conductance of a channel

$$g_i = \bar{g}_i \cdot P_i$$

g_i: overall conductance of type i channels
$\bar{g}_i$: maximum conductance of type i channels
P_i: probability (fraction) of type i channel open

- gi_ is a constance

Voltage and time dependent of the conductance has been pushed into *n*. All these values are used in the fitted voltage clamp data => they found out that they correctly predicted there to be 4 subunits for potassium.

Gating variables: time-dependence
We want to describe how this *n* changes with voltage and time

Time dependence described as follows:

Assume open→closed and closed→open transitions as follows:

$$\underbrace{\Delta n}_{\text{change in fraction open channels in } \Delta t} = \underbrace{\alpha_n \cdot (1-n) \cdot \Delta t}_{\substack{\text{closed}\to\text{open} \\ \text{in } \Delta t \\ \Delta n > 0}} - \underbrace{\beta_n \cdot n \cdot \Delta t}_{\substack{\text{open}\to\text{closed} \\ \text{in } \Delta t \\ \Delta n < 0}}$$

α_n: rate of opening
$(1-n)$: fraction closed
β_n: rate of closing
n: fraction open

What is the net change in the fraction of open channels during *deltat*?

For any given time interval *deltat* we have 2 contributions
- Number of closed channel that will open during *deltat*
- Number of open channels that will close during *deltat*

Derivative Formula

$$\frac{d}{dt} n(t) = \alpha_n(V) \cdot \big(1 - n(t)\big) - \beta_n(V) \cdot n(t)$$

- Moved voltage dependence in to *alphan* and *betan* (they are not time dependent)

We'll approach the asymptotic level with an exponential increase governed by the time constant *taun*

n_infinity(V) which subunits are open at point infinity for a certain voltage
- an_(V) > Bn(V) => n_infinity(V) = 1, more likely for closed subunits to transition to open
- an_(V) < Bn(V) => n_infinity(V) = 0, more likely for open subunits to transition to close

Solution:

$$\tau_n(V) \frac{d}{dt} n(t) = n_\infty(V) - n(t)$$

With time constant:

$$\tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)}$$

Faster transitions → faster change in n

And asymptotic level:

$$n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}$$

is between 0 and 1

$$\alpha_n(V) \gg \beta_n(V) \Longrightarrow n_\infty(V) \approx 1$$
$$\alpha_n(V) \ll \beta_n(V) \Longrightarrow n_\infty(V) \approx 0$$

Persistent and transient conductances

K^+conductance (persistent):

$P_K = n^4$

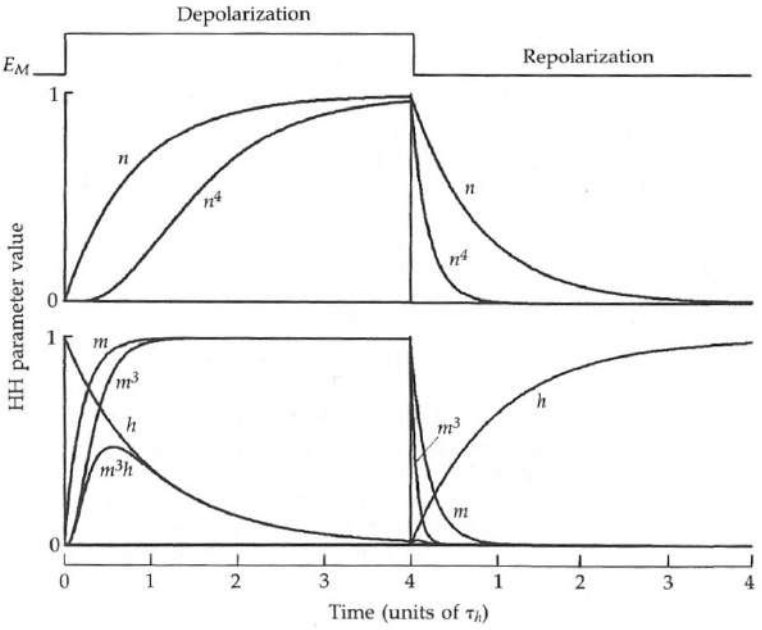
n: activation variable
p(activation-gate open)

Na^+conductance (transient):

$P_{Na} = m^3 \cdot h$

m: activation variable
p(activation-gate open)

h: in-activation variable
p(inactivation-gate open)

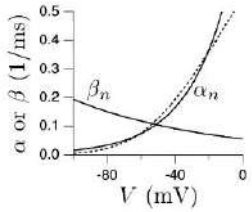


- **Pk** directly affects how conductance changes over time. n^4 vs n.
- **h** Inactivation gate - ball at receptor & activation gate affects P_Na
- If m or h is closed (is zero) the channel is closed
- **h** tends to close with the depolarization
- We first get a rapid increase of the conductance then it flattens

Gating-variables: voltage-dependence
What are these alpha and beta n values?

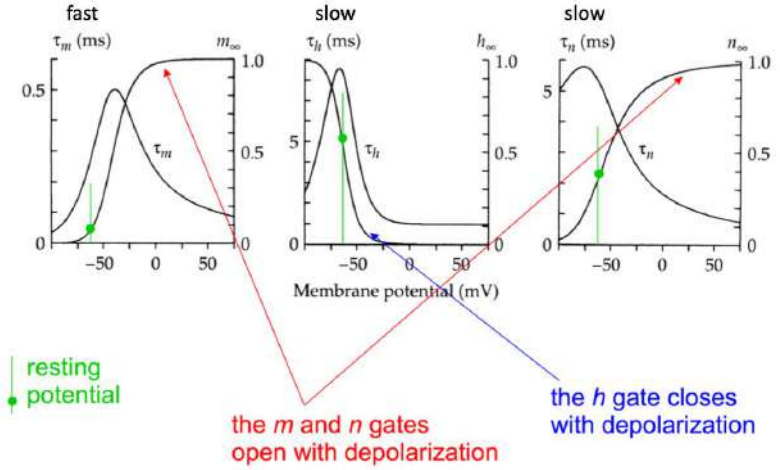
Determine $\alpha_n(V)$ and $\beta_n(V)$

In practice: fitted to voltage-clamp data
(approximately exponentials)



But: can be understood with thermodynamic arguments,
as gating-charge overcoming voltage-dependent energy barrier (Boltzmann factor)
See Dayan and Abbott book

Rate of channel increases with voltage and closing rate decrease as voltage is increased



- What is the time constant associated with the opening and closing of channels

Plot 1 & 2 - Sodium

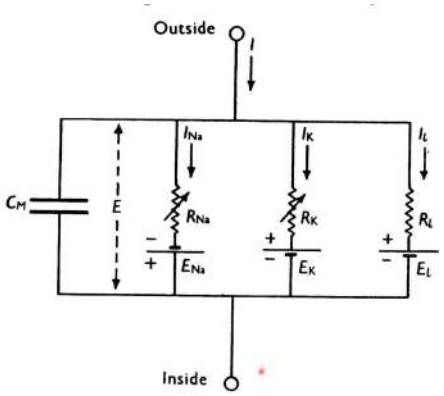
- Time constants are much smaller than in potassium example

Plot 3 - Potassium

voltage increased proportion of the activation variable increases from close to 0 to close to 1 and the time constant actually decreases. Conductance tends to change faster as the potential increases

Some Potassium & Sodium channels are somewhat open when at the resting potential. Why don't they trigger an action potential?

Circuit Equivalence



- Arrow indicates they have variable conductance.

Action Potential Prediction

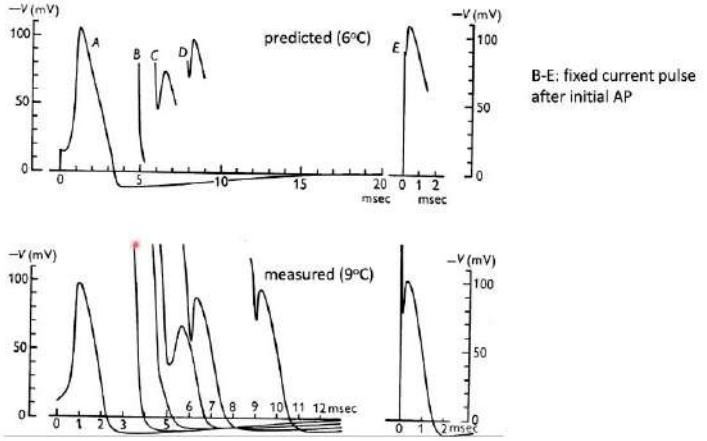
- We predicted that you get sodium channels open very quickly activation gate open h ilw inactivation get isn't yet open
- Then inactivation gate closes and at the same time the potassium channels are opening
- This leads to the potential decreasing in the end

- AP is positive feedback loop
    - Increasing potential
    - Opens channels
    - That create a current
    - That depolarizes the cell even more
    - Increases the potential more
    - ….

What determines the threshold of AP Generation

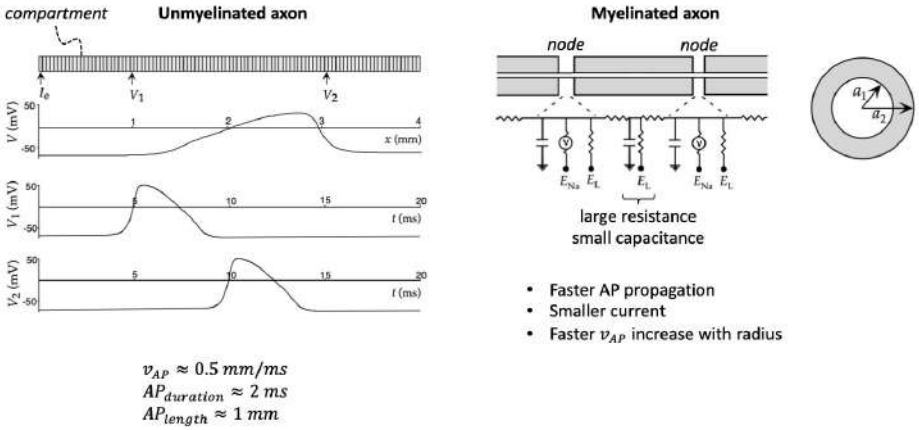
- **Channels already opened at rest**
- Why does it not trigger an AP
- **Because there is still a leak current that tries to depolarize the neuron**
- **The two voltages trying to get the voltage back to its resting potential (leak and potassium current) are larger than sodium current**
- **@v threshold: leak + potassium = sodium current**

Refractory Period



- Very briefly after first AP you can't release a second AP - refractory period

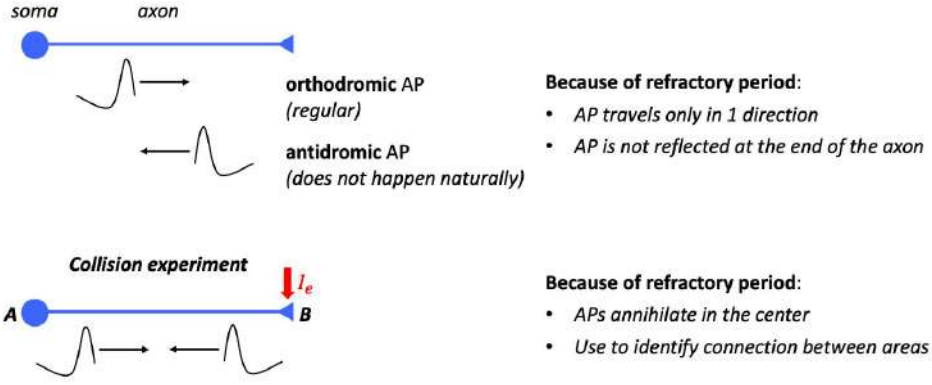
Action potential propagation



At myelinated regions you have

- Large resistance
- Small capacitance
- Faster AP propagation
- Smaller current
- Faster V_AP increase with radius

AP-collision



Why only AP in the axon?

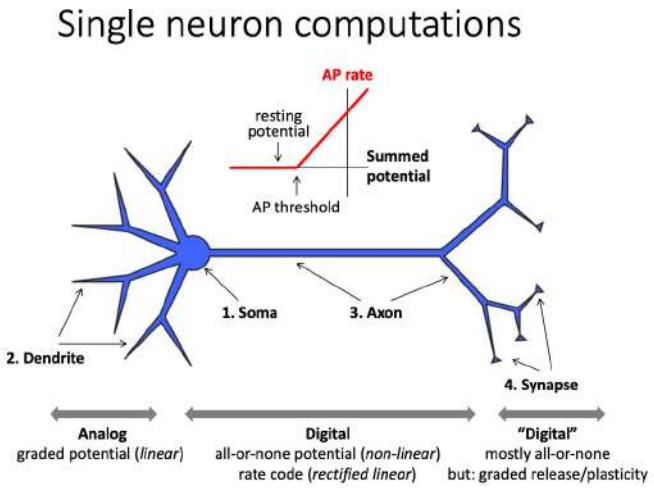
Because potassium & sodium conductances are missing outside the axon

- **Conductances only exist in axon**

However: in some cell types few g_{Na} & g_K also in dendrites
$\Longrightarrow$ insufficient on initiate AP
$\Longrightarrow$ sufficient to propagate AP for some distance (**back-propagating AP**)

Why is AP all-or-none?

Why that shape?

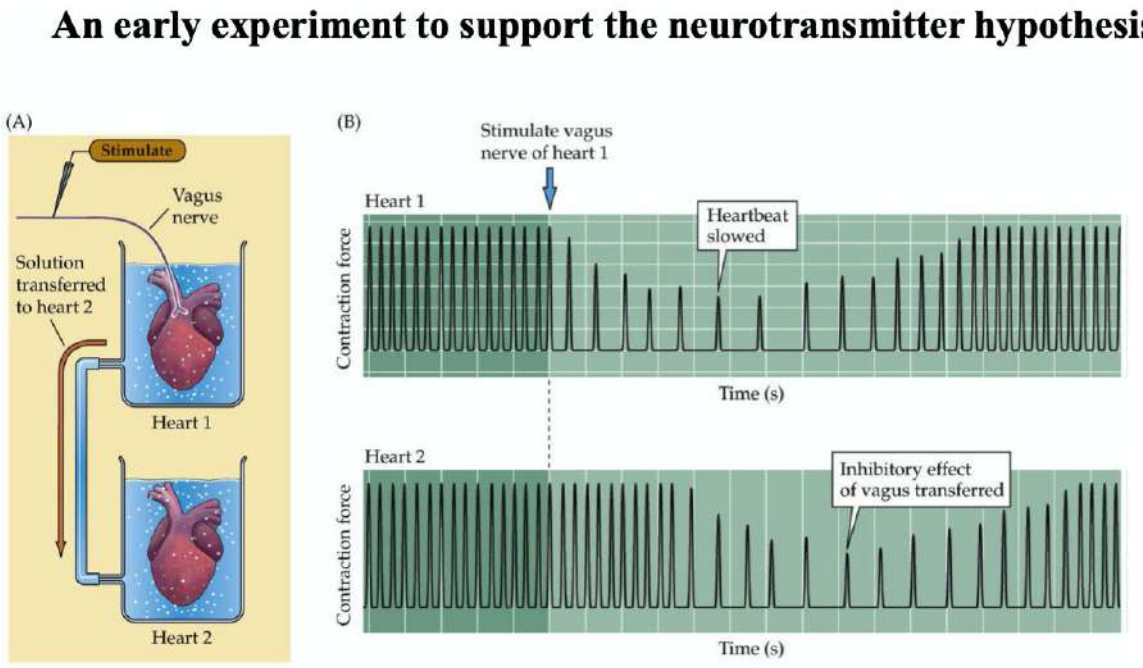


Lecture 6 - Synapses 1

- Discovery through **Cajal's golgi staining method**, there's a connection between cells

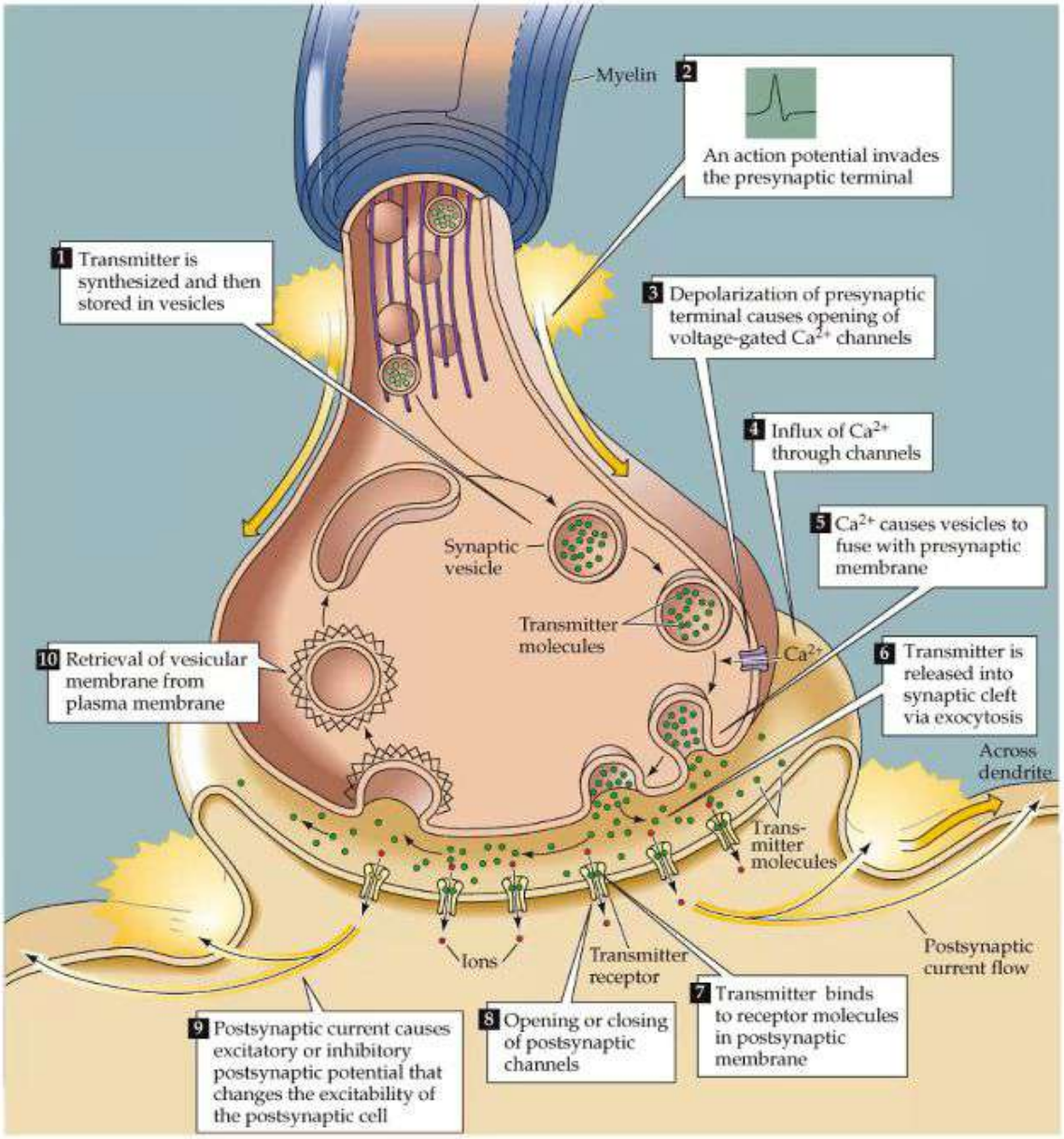
Soup vs Spark

- Is synaptic transmission mediated chemically or by direct electrical transfer of charge?
- Some experts thought aspects were too fast to be mediated chemically.
- There was some good evidence from the Neuromuscular Junction (nerve fiber that reach the muscle fiber) for chemical transmission



Otto Lowie, showed through the vagus nerve, it induces and inhibits the heart rate.

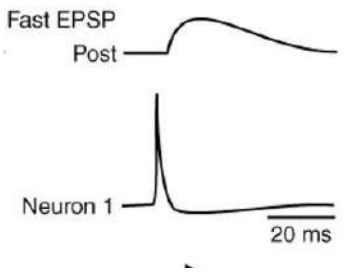
- Once you stimulate the nerve, slow down and strong reduction of heart beat intensity
- He had two hearts in the same container but only stimulated one
- But the other non stimulated hear showed an inhibitory effect as well which must have transferred chemically
- (Heart can beat without any outside input)



- They require many steps -> not very fast
- There are approx. 150 - 200 vesicles per terminal bouton.

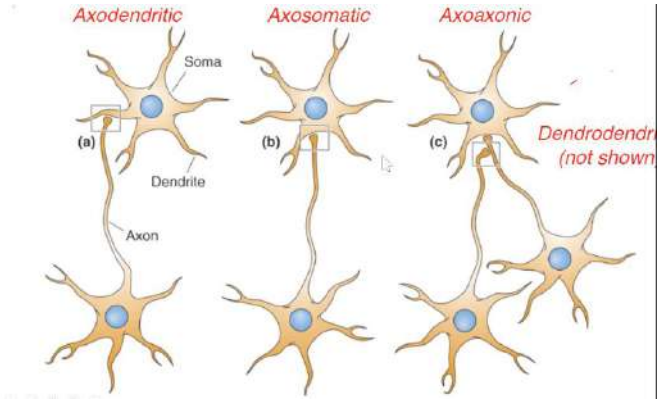
Chemical transmission

- Definition: Communication between cells which involves the rapid release and diffusion of a substance to another cell where it binds to a receptor (at a localized site) resulting in a change in the postsynaptic cells properties.
- Contrary to electrical transmission multiple steps are required to release transmitter chemicals and for them to act on postsynaptic receptors, resulting in a time delay (can be as short as 0.2 msec, from Ca2+ entry to secretion).
- **Directional**,select localization of release machinery to presynaptic terminals and receptors to postsynaptic specializations.
- Highly modulatable as it has many steps presynaptic terminal and at the postsynaptic sites.



- There is a small delay from the neuron being stimulated and the AP generation in the post synaptic Cell

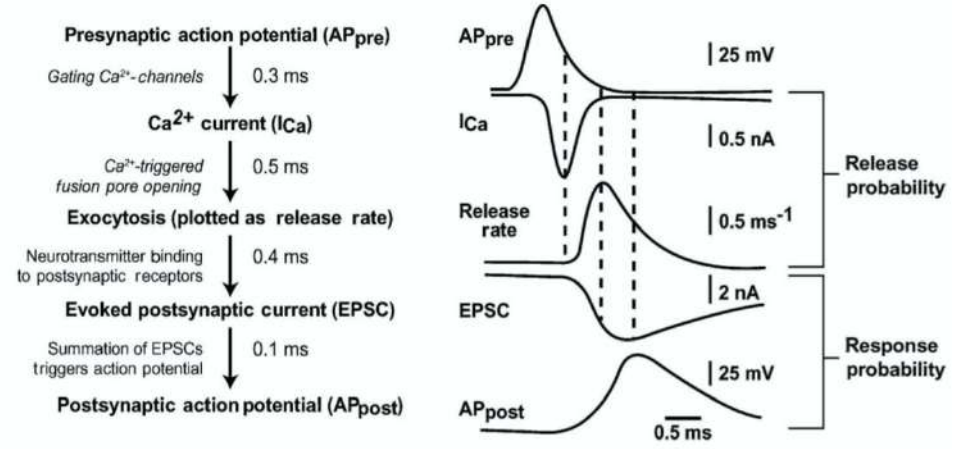
Types of Synapses

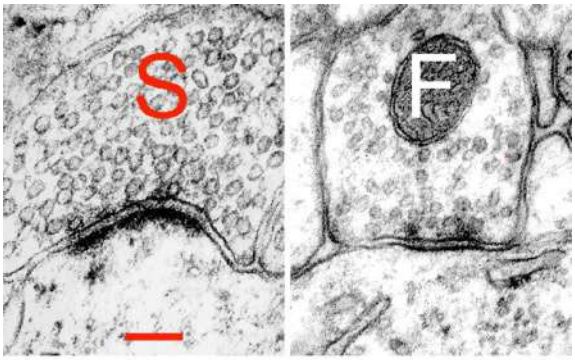


Steps to chemical synaptic transmission.

- First need to bring the presynaptic neuron to threshold at axon hillock.
- Conduction down axon, length, R*C dependent.
- Opening of voltage gated Ca channels.
- Diffusion and action of Ca at release machinery.
- Exocytosis and diffusion of transmitter in cleft.
- Activation of postsynaptic receptors.

Timings

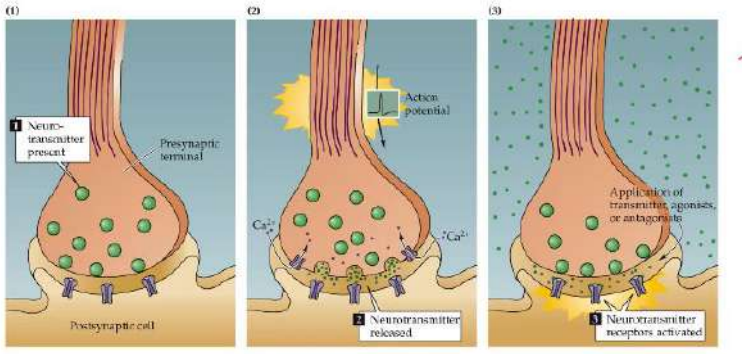




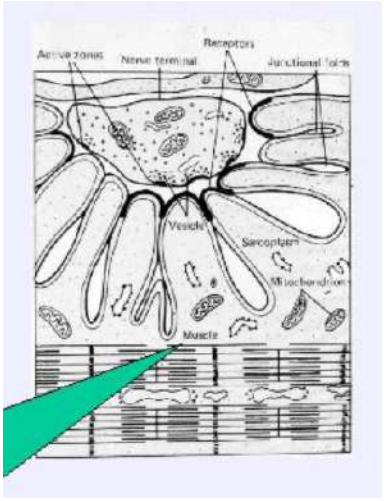
Type I Excitatory Type II Inhibitory

Criteria that define a neurotransmitter:

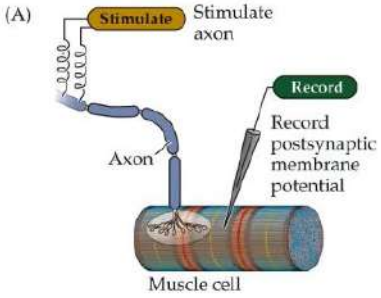
1. Must be present at presynaptic terminal
2. Must be released by depolarization, Ca++-dependent
3. Specific receptors must be present

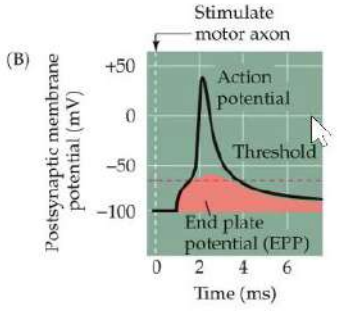


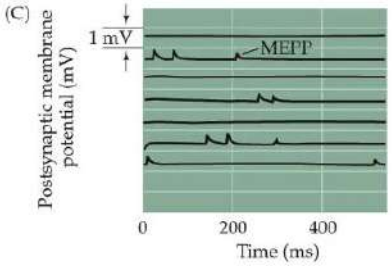
The neuromuscular junction

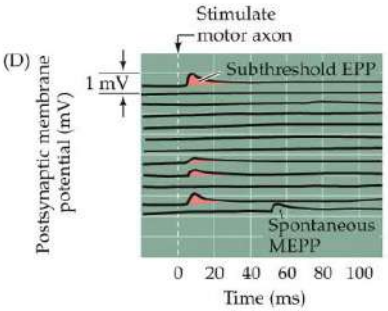


- Nerve Fiber aka Free nerve terminal that comes in contact with the muscle cell.
- Here most experiments for chemical transmission experiments







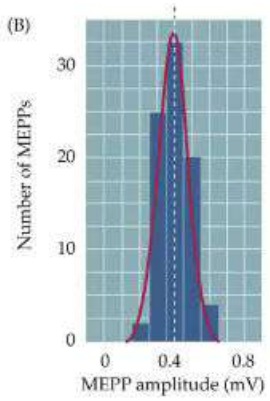


- If you stimulate you create an endplate potential
  - Potential in the muscle cell
  - If it reaches a certain threshold it triggers an AP and that will lead to number of reactions/contractions of muscle fiber
- Sometimes the Psmp fluctuate independently of a stimulation, miniature end plate potential
  - They happen spontaneous little polarisation
- It’s possible to stimulate the motor axon and nothings happens

Standard Katz (Quantal) Model of Synaptic Transmission

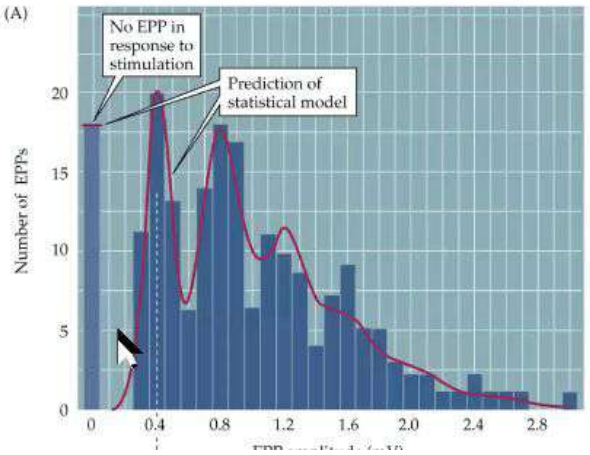
- One packet of neurotransmitter = 1 quantum
- AP transiently increases in the probability of releasing NX quanta
- Several quanta are available to be released
- Each quantum gives approximately the same postsynaptic response called the "**Quantal Amplitude**"
- The average number of quanta released, m = np
    - Where n=the number quanta available for release
    - P = their average release probability

When you don't stimulate



When you stimulate

- sometimes 1 quantum released sometimes 2,... with decreased probability



Quantal Release of Neurotransmitters

If the probability of a single unit responding is 'p', and if each unit has an independent and equal 'p', then the mean number of units responding to each stimulus is given by: 'np' is the total number of available

Probability that x-units successfully contribute is given by the binomial distribution. This is a statistical process.

$$P(success = x) = \binom{n}{x} p^{x} (1-p)^{\text{n-x}}$$

Electrical microscopy studies reveal that a MEPP could be caused by a single vesicle. It reveals a correlation between fusion of vesicles with plasma membrane and the size of postsynaptic response.

CNS synapses and quanta.

- At CNS synapses with only a single release site, changing the probability of release (i.e. changing calcium concentration) does not affect the amplitude of the response (as only zero or one vesicle is released in theory).
- At CNS synapses with multiple release sites, changing release probability can change the postsynaptic response amplitude as more transmitter is released (graded quantal levels).
- At the NMJ a single nerve can elicit a postsynaptic AP given multiquantal release, while at the CNS synapse (with low numbers of release sites) multiple synapses must cooperate, **forcing a network.**

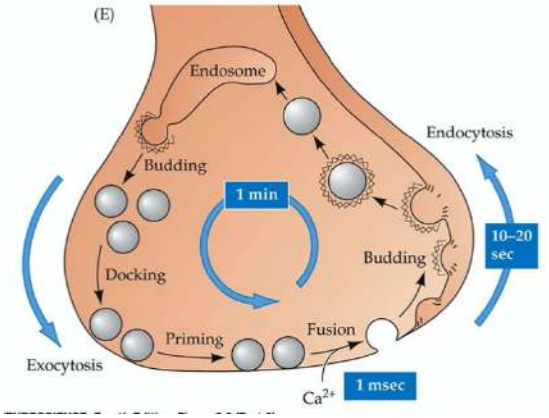
CNS synapses and miniature release.

- Miniature release is produced in the absence of action potential stimulation.
- Thought to reflect the release of single vesicles or transmitter quanta.
- Can be stimulated by calcium entry, but may not necessarily require calcium for release.
- Commonly studied to gain insight into changes in receptors or release probability during synaptic plasticity experiments, although can be difficult to interpret.

Docked Synaptic vesicles

- The readily releasable vesicles a synapse has available
- Vesicles need to dock before being used to eject neurotransmitters into the cleft
- High stimulus frequency can lead to a limited number of vesicles
- This influences the transmission
- Not having enough vesicles ready is called synaptic depression
- Calcium influx is sufficient for neurotransmitter release

The synaptic vesicle cycle

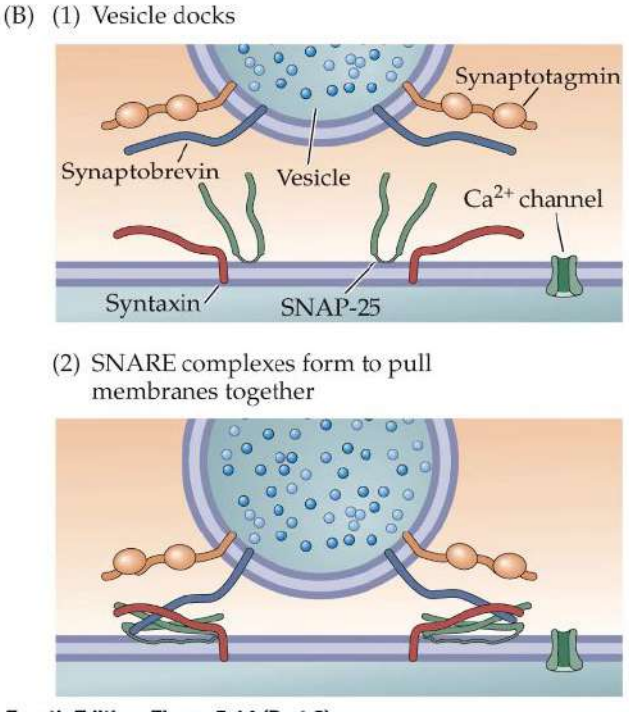


Synaptic vesicle release consists of three principal steps:

1. Docking
   Docked vesicles lie close to plasma membrane (within 30 nm)
2. Priming
   Primed vesicles can be induced to fuse with the plasma membrane by sustained depolarization, high K+ , elevated Ca++ , hypertonic sucrose treatment
3. Fusion
   Vesicles fuse with the plasma membrane to release transmitter. Physiologically this occurs near calcium channels, but can be induced experimentally over larger area (see 'priming'). The 'active zone' is the site of physiological release, and can sometimes be recognized as an electron-dense structure.

Vesicle release requires many proteins on the vesicle and plasma membrane.

A docked vesicle can be primed by the action of the snare complex, it makes the vesicle ready to fire. It's a trigger mechanism to quickly release the neurotransmitters.

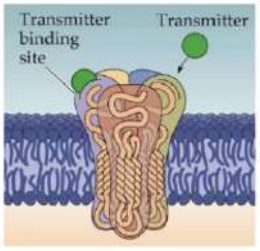


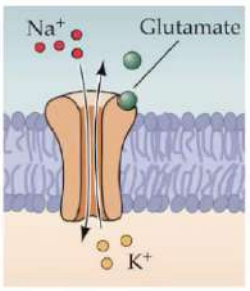
Lecture 7 - Synapse 2

Post-synaptic Receptors

Ionotropic Receptors

- Contains a ligand-binding site
- A normally-closed ion channel that opens after binding with the neurotransmitter
- Contribute to fast changes in the membrane potential, fast mechanism
- Glutamate is one example that acts on this type of receptor, ions start flowing

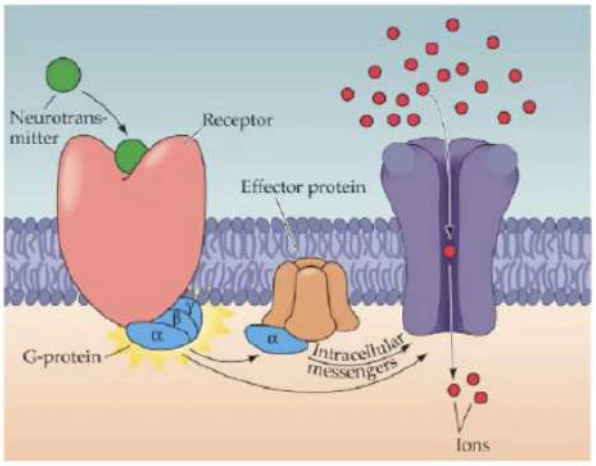




Metabotropic Receptors

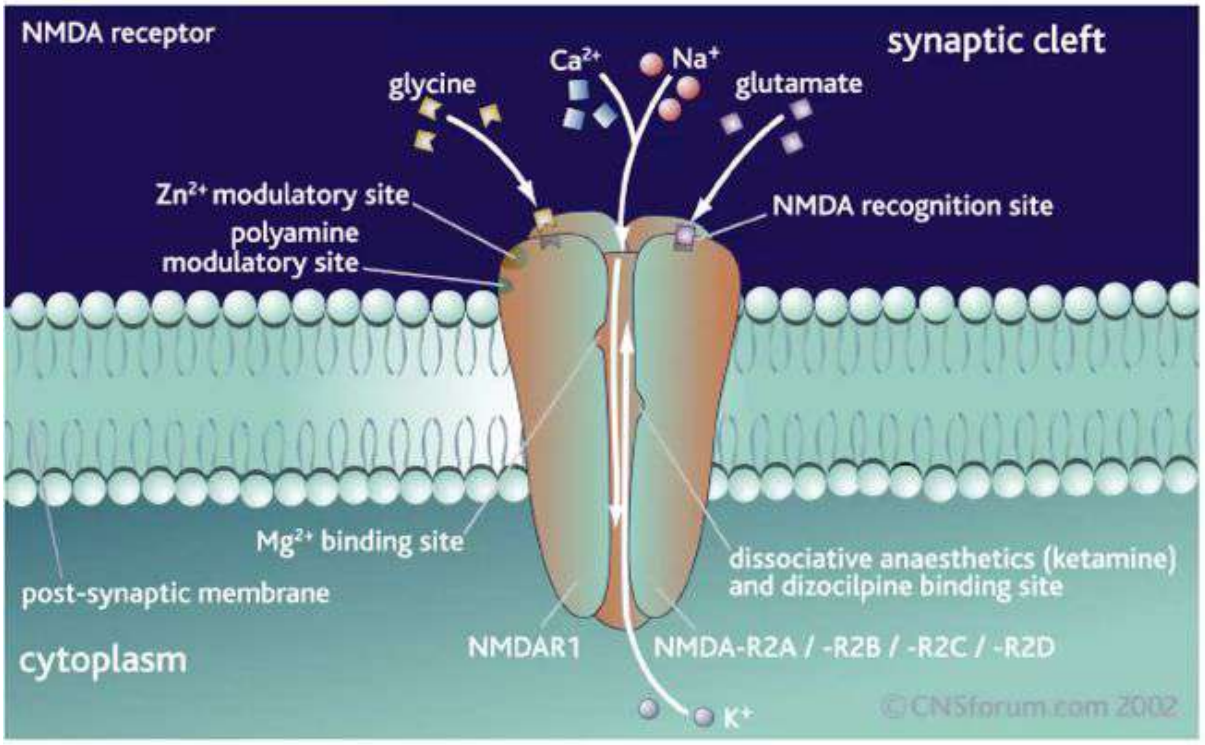
These are more complicated in their function. Cascade of biochemical reactions that relay on g-proteins.

- They are coupled with a G-protein receptor
- Secondary messenger involved
- Slow postsynaptic process **(plays a role in a synaptic plasticity)**
- Neurotransmitter will bind to a receptor (that isn't a channel) and triggers a reaction of intracellular messengers and as a result there is a channel that will change its configuration and ions will flow in and out of the cell



NMDA Receptor

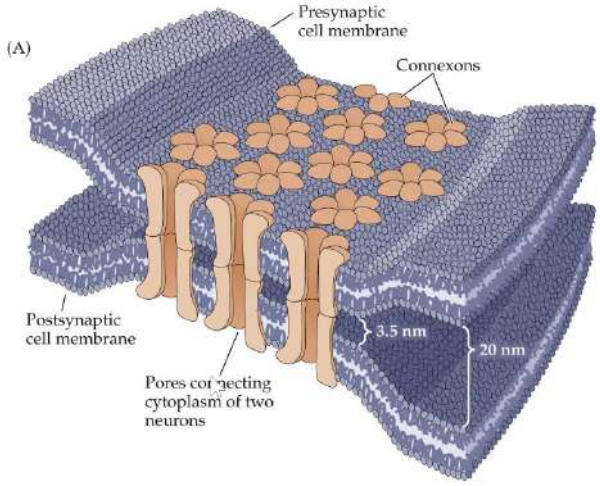
- Heavily studied
- Important receptor that allows synaptic plasticity.
- Receptors for glycine, zink…
- Receptor is voltage dependent

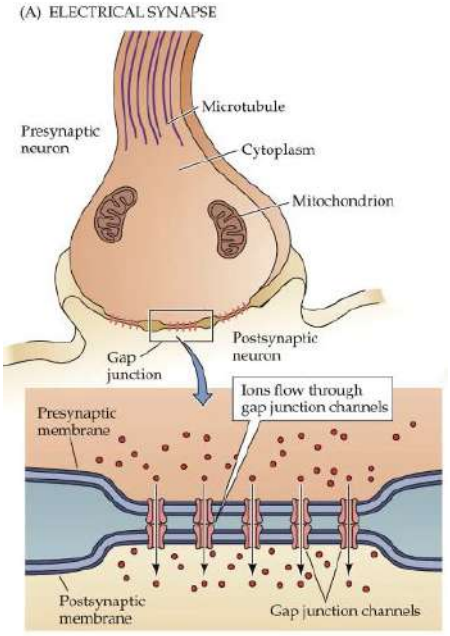

NMDA receptor
synaptic cleft
glycine
Ca2+
Na+
glutamate
Zn2+ modulatory site
polyamine
modulatory site
NMDA recognition site
Mg2+ binding site
post-synaptic membrane
dissociative anaesthetics (ketamine)
and dizocilpine binding site
cytoplasm
NMDAR1
NMDA-R2A / -R2B / -R2C / -R2D
K+
©CNSforum.com 2002

Kinds of Synapses

Electrical:

- Bidirectional
- Can be found in the retina, neocortex, hippocampus
- Gap Junction schematics





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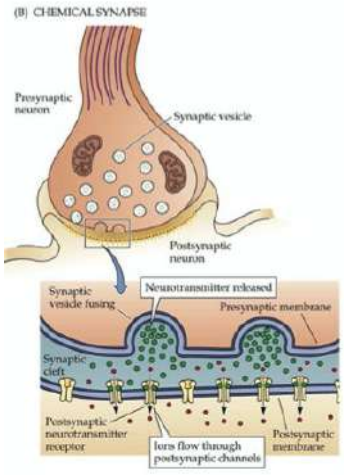
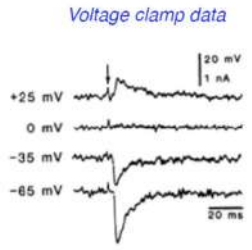


- Advantage
  - Very fast
  - Sometimes it is useful to **synchronise** the activity of neurons

Chemical:

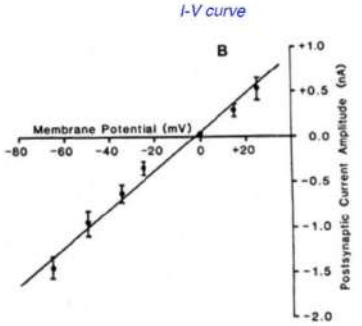
Electrical Synapse	**Chemical Synapse**
Simple primitive system	Highly developed structure
Often symmetrical, bidirectional	Polarized, structurally and functionally
Gap junction (connections)	Pre: active zone Post: postsynaptic density
Very fast, no synaptic delay	Slower, synaptic delay (~0.5 ms)
Ca2+-independent	Transmitter release requires Ca2+ influx
temperature-insensitive	temperature-sensitive

Large synapse	Thousands of small synapse
Limited functions, **usually excitatory**	Versatile: excitatory and inhibitory
Synchronized activity	Specificity: point to point communication



Modeling Synapses

Voltage clamping the synapse. Isolate the system and measure the effect of the postsynaptic potential when the whole synapse was kept at a constant voltage.

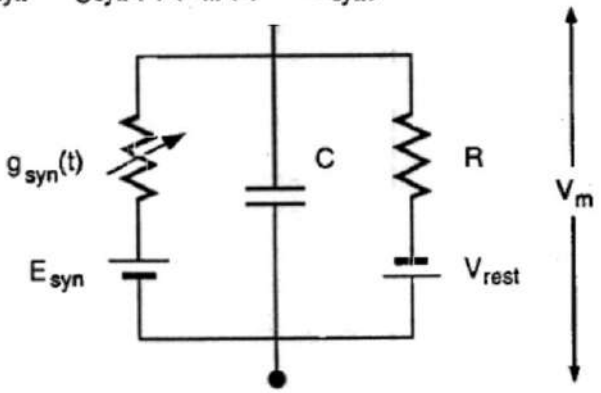


One can see the amplitude of the postsynaptic current as a function of the membrane potential this voltage clamp is set. It's linear. The linearity shows us that this is an electrical law. **Ohm's Law**.

Membrane Equation

Koch, Biophysics of Computatio

$$I_{syn} = g_{syn}(t)(V_m(t) - E_{syn})$$



Modified membrane patch equation with a synapse:

$$C\frac{dV_m}{dt} + g_{syn}(t)(V_m - E_{syn}) + \frac{V_m - V_{rest}}{R} = 0$$

- Added the synapse that introduces current over time.
- New term shows the variation in the conductance of the cell of the postsynaptic membrane depending on the activity of the particular synapse.

Another Formulation:

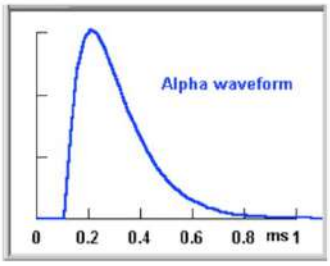
$$\tau\frac{dV_m}{dt} = -(1 + Rg_{syn}(t))V_m + Rg_{syn}(t)E_{syn} + V_{rest}$$

$$[\tau = RC]$$

Alpha Function

Synaptic input is usually approximated by an ‘alpha function’ of the form

$$g_{syn}(t) = g_{peak} \cdot t \cdot \exp\left(\frac{-t}{t_{peak}}\right)$$



- This has been measured experimentally
- good approximation of the currents you would measure that are elicited in the postsynaptic membrane potential

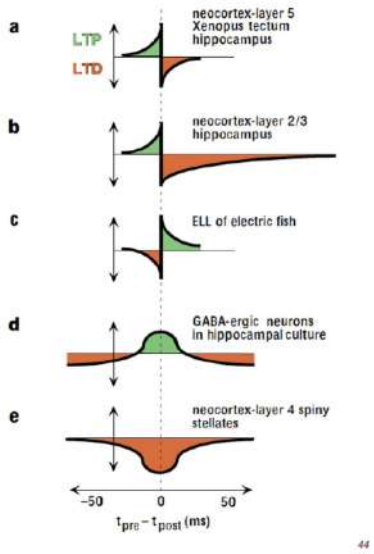
Hebb's Law

Synapses can change their efficacy and the changes are regulated by the activity of the pre and postsynaptic neuron.

Neurons that fire together wire together

Spike time dependent plasticity

How does the synapse between two neurons change based on the activity of a pre and postsynaptic neuron.



- Graph shows relationship of neuron 1 and neuron 2
- You either have potentiation or depression.
- Y axis - unit of synaptic strength
- X axis - time
- Content of plot: What are the changes you observe in the synapse
- Depression can help to reduce redundancy of information

You observe that the presynaptic neuron tends to fire 10ms before the postsynaptic neuron and that it potentiates (green area under the curve) so the synaptic connection strengthens.

a. When the presynaptic neuron is active before the postsynaptic neuron, you have potentiation and the synapse becomes stronger. Briefly before the postsynaptic neuron becomes active you have max potentiation in the presynaptic neuron. If the postsynaptic neuron is active before the presynaptic neuron you have depression.
b. Similar to A in potentiation but timing over which depression occurs is much longer
c. Exact opposite post firing before pre leads to potentiation and pre firing before post leads to depression
d. -
e. Only depression, depresses if neurons are active together. Useful if you want to decorrelate activity in a population of neurons. To reduce redundancy it makes sense to decorrelate neurons. => More information can be carried by a neuron population.

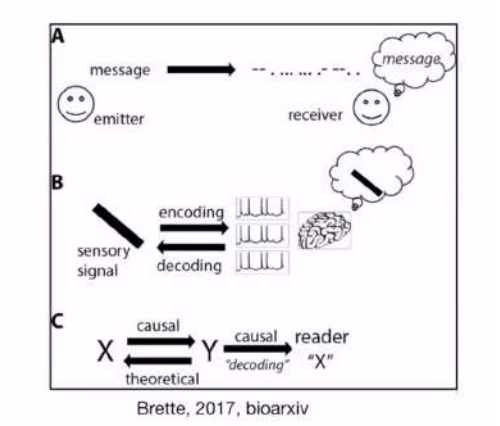
Lecture 8 - Neural Code

What is it that neurons use the encode Information?

- Is it more temporal where a specific time of a spike is important
- Or is it a rate code and the firing frequency of the neurons are important

How do populations of neurons encode information?

Coding/Encoding Metaphor



Brette, 2017, bioarxiv

There is a **direction** for **encoding and decoding**

Considering three elements (correspondence, representation, causality)):

1. The technical sense of a **code** is a **correspondence between two domains**, e.g. visual signals and spike trains. We call this relation a code to mean that spike trains specify the visual signals, as in a cipher: one can theoretically reconstruct the original message (visual signals) from the encoded message (spike trains) with some accuracy, a process called **decoding**.

2. **Not all cases** of **correlations** in **nature** are considered instances of **coding**. Climate scientists, for example, rarely ask how rain encodes atmospheric pressure. (Correlation != Causal)

3. Finally, we would not say that visual signals encode retinal spike trains, even though this would comply with the technical sense. The reason is the communication metaphor implicitly assumes a causal relation between the original message and the encoded message; here, spike trains result from visual signals by a causal process (transduction).

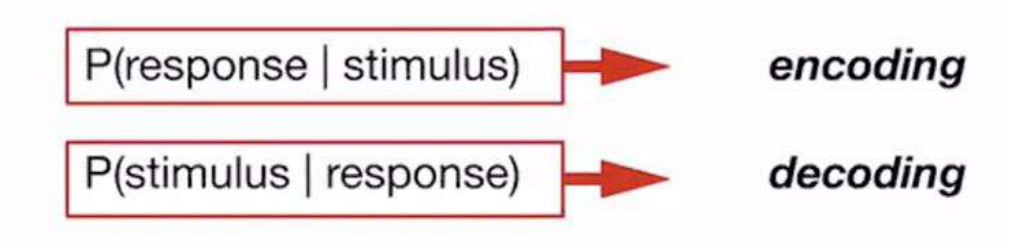
Encoding: How does a stimulus cause a pattern of responses?

- Building an **approximate mechanistic model of the world**.
- Our brain has internalized all the stimulus in its own code
- Builds **internal model of the information of the world**

Decoding: What do the responses tell us about the stimulus?

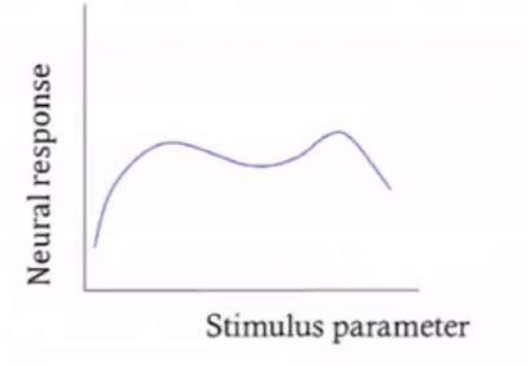
- How can we reconstruct the stimulus?
- How can we reconstruct the world stimulus for the activity we're measuring

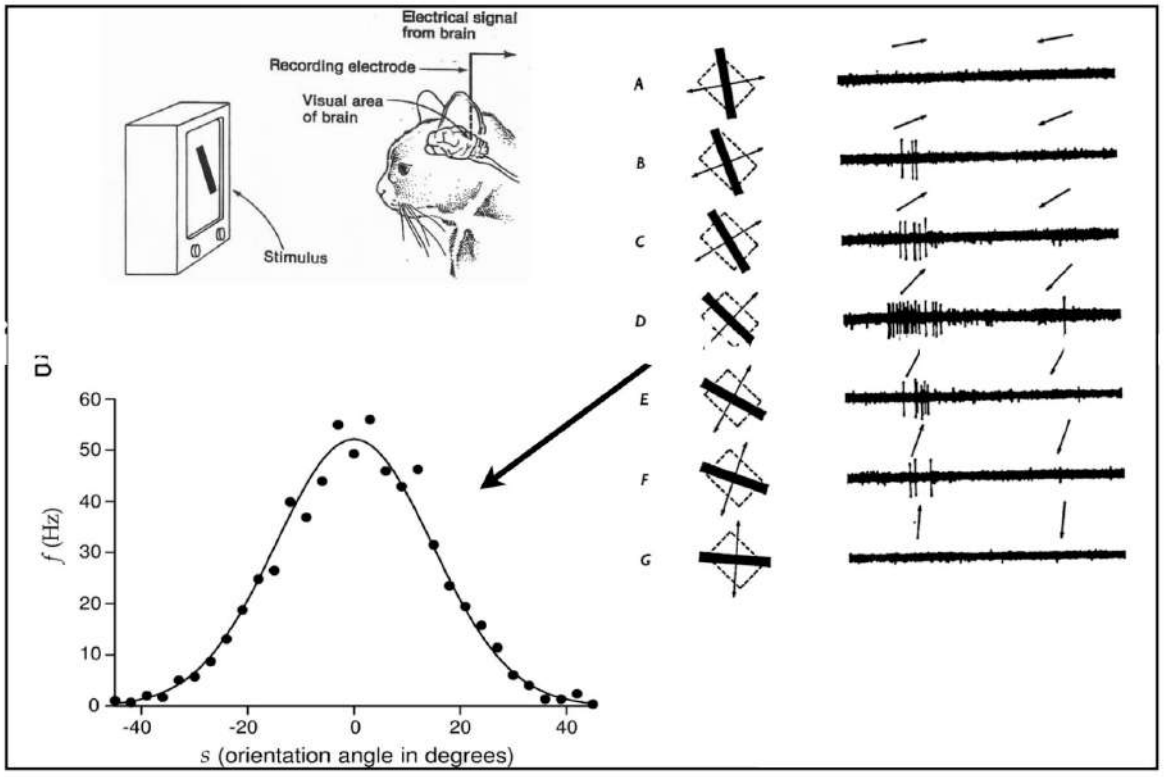
It's about finding the probability



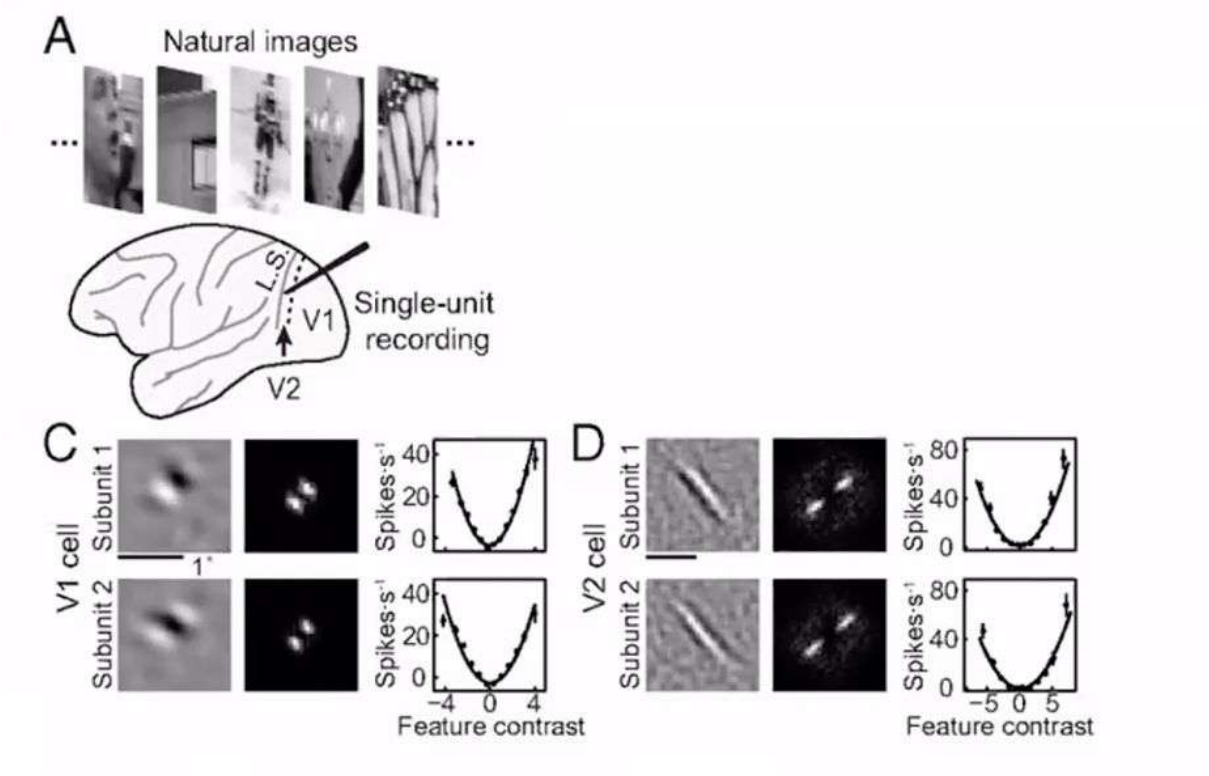
What is the relation of a stimulus and a response in the brain?

- Neural responses: firing frequency, peak amplitude,...
- Stimulus parameters: with variation of the stimulus you get variation in the neural response





- They found orientation and direction in selective neurons
- In the Tuning Curve it can be seen that 0 is the preferred angle of this neuron
- Neuron encodes with spike rate the direction of the edge filter moving across the cats view
- This is very consistent with primate visual cortex



- Edge Classifier in the Brain

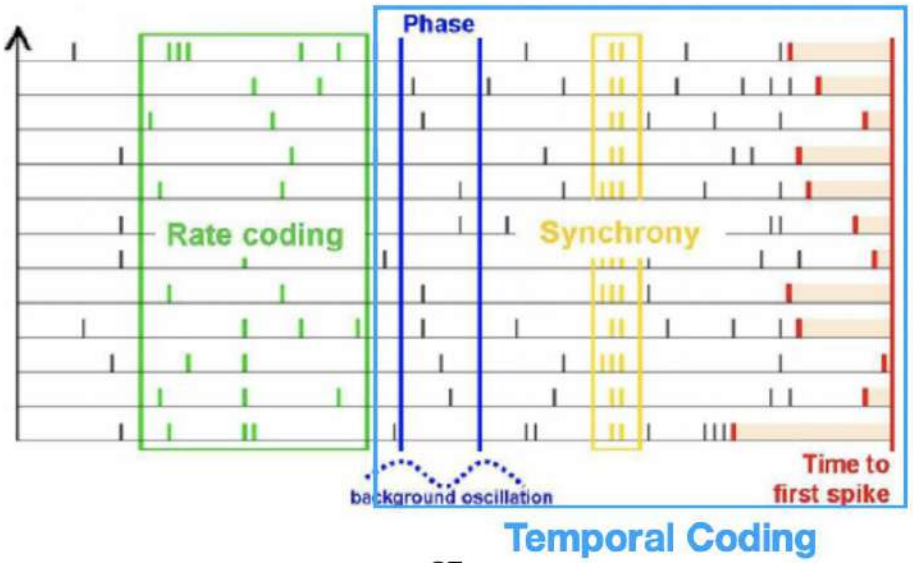
MIT Study in higher order cortex hierarchies what type of feature do this higher order visual cortex cells encode? What do they maximally correspond to?

- They created a 8 level deep learning model
- Created Visuals that maximally excite level 4 neurons
- Showed it to a monkey and found neurons firing (Human Level 4 Part found in the brain)

Rate Coding refers to information being carried by the firing rate. It is often argued, or assumed, **that firing rate captures essentially all relevant information.**

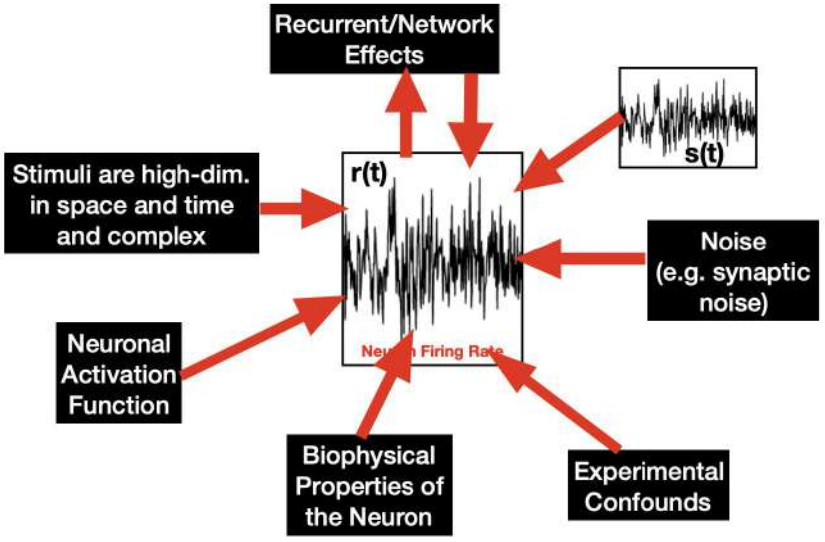
- Gaussian rate

Temporal Coding may refer to several quite different ideas: (i) Much of the information may be transmitted by a neuron during certain small intervals of time, (ii) synchronous, or what one could call quasi-synchronous, firing of neurons within and across ensembles may carry important information, (iii) the precise timing, or pattern, of spikes may carry information.

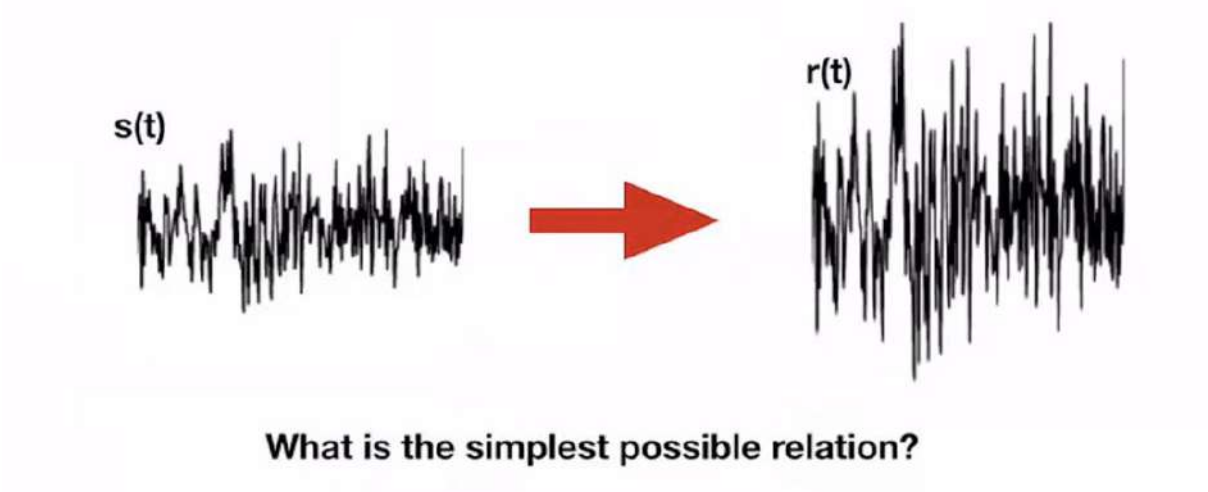


- Neuron that responds as first or at last, which neuron is the most tuned (**Time to first spike**)
- You need at least two neurons, how close in time are the spikes (**Synchrony**)
- There is background oscillation in neurons usually mediated through inhibition where the membrane potential of hippocampus neurons constantly fluctuate and depending on where the cell in this oscillation phase spikes encodes a position of the rat for example (**Phase**)

How to investigate the Stimulus Encoding of a Neuron?



- **Stimulus**
- **Noise** due to synaptic failure the stimulus may not reach the neuron
- **Experimental Confounds** some tone going on, unexpected factors introduce variability
- **Biophysical Properties of the Neuron** determine how a neuron can react to a stimulus presented, Calcium depletion
- **Neuronal Activation Function** waiting for Spike threshold reaching
- **Stimuli** are often high dimensional. We don't really know what features are being responded to.
- **Recurrent/Network Effects** neuron is part of a network, neighbours change, ….



Simplest relation is a linear filter

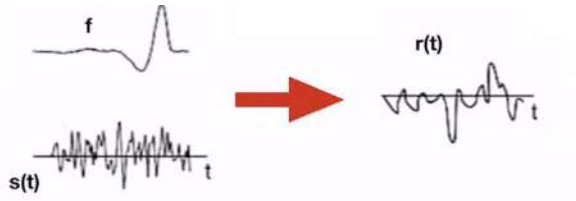
Linear Filter

$$r(t) = f\,s(t) \qquad [f\,s(t-\tau)]$$

$$\text{Linear Filter:} \quad r(t) = \sum_{k=0}^{n} s_{t-k}\, f_k$$

- F would be a filter and Tao our delay
- R of t is basically the sum over all the stimuli that we have multiply over a linear factor
-

Linear Temporal Filter

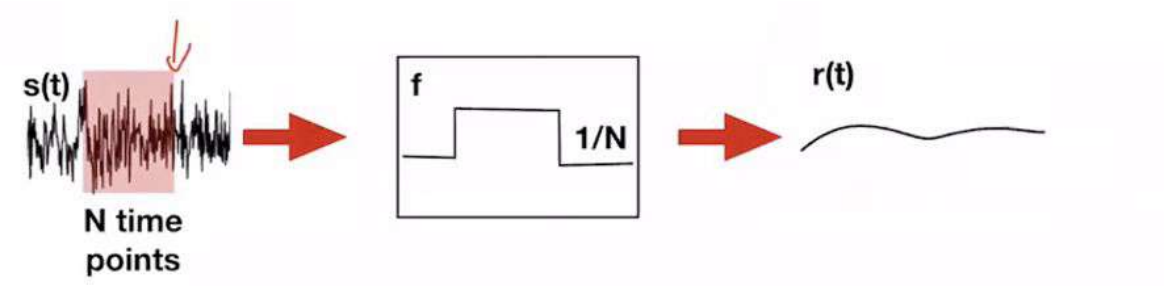


$$\text{Linear Temporal Filter:} \quad r(t) = \sum_{k=0}^{n} s_{t-k}\, f_k$$

$$r(t) = \int_{-\infty}^{t} d\tau\, s(t-\tau) f(\tau)$$

- We combine the stimulus over time with the filter function giving us r over t
- You can Sum or integrate over all time points

Example of the Running AVG Filter



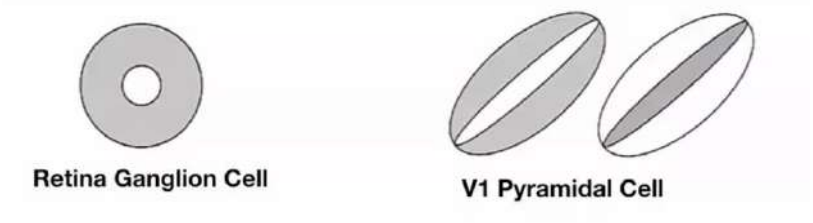
- Taking one times point
- Normalizing by 1 over n the values
- Plotting the result as output rate r(t)

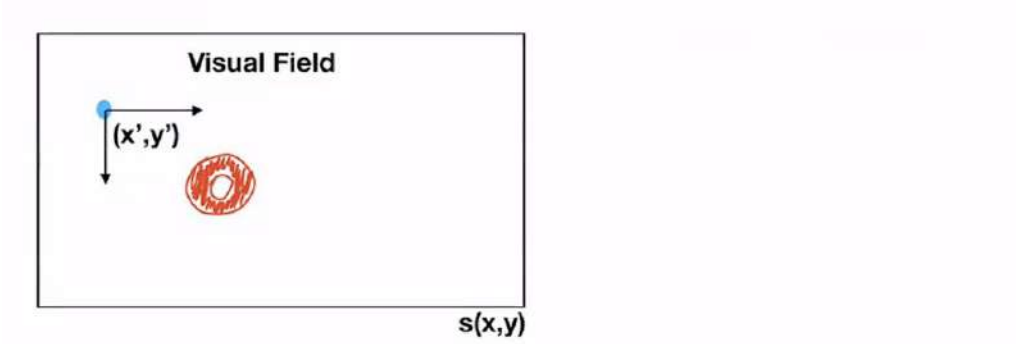
Example of the Leaky AVG Filter

- Take one point in time
- Convolve this with a decay (the idea of linear average filter) points that are a long time ago are weighted less and less, points that just had happen count more

Spatial Filters

Spatial filters show for example for a field of view which pixels should be weighed more.

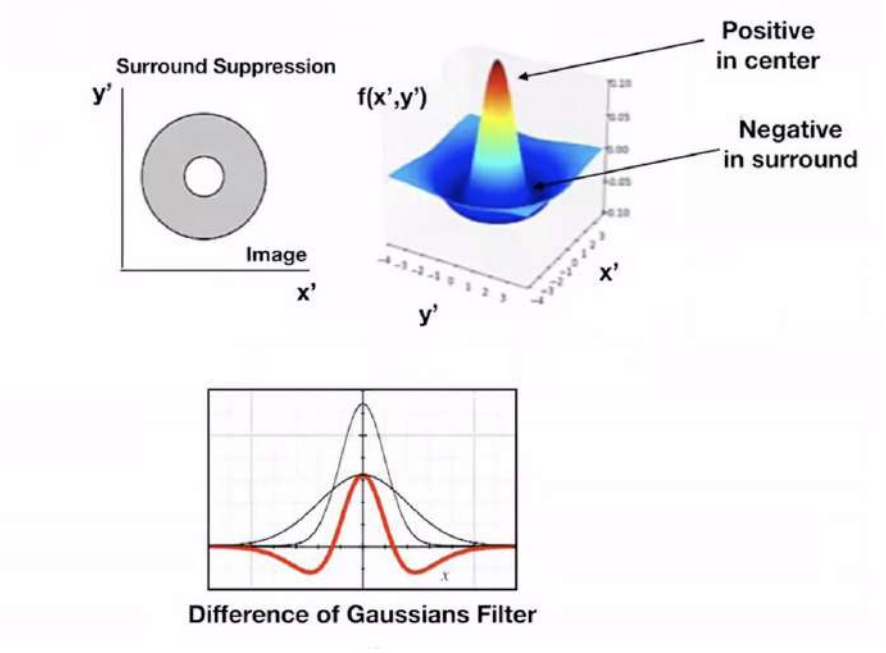




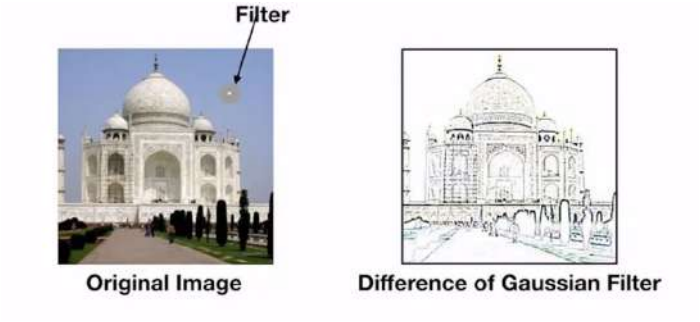
$$r(t) = \sum_{x=n,y=n}^{n} s_{x-x',y-y'} f_{x',y'}$$

$$r(t) = \int_{-\infty}^{\infty} dx'dy' \, s(x-x', y-y') f(x', y')$$

Positive weightening of the pixels in the center, negative weightening in surround
We integrate over space



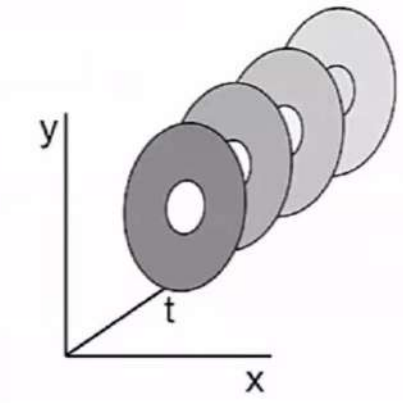
Difference of Gaussians Filter



Original Image

Difference of Gaussian Filter

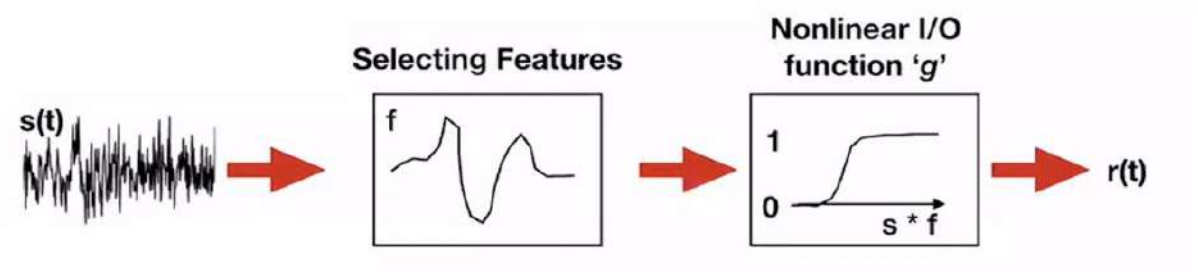
Combining Spatial and Temporal Filtering



$$r_{x,y}(t) = \iiint dx'dy'd\tau\, f(x',y',\tau)\, s(x-x',y-x',t-\tau)$$

Combining Filtering with a Nonlinearity

- Can spike rates be negative? No
- What happens if the stimulus becomes stronger and stronger? Can firing rates increase indefinitely? They shouldn't



- Nonlinear input output function (sigmoid)
- Y Axis is the output
- X Axis is the Filter Multiplied with a Stimulus integrating over time and space

Linear Filter + Nonlinearity:

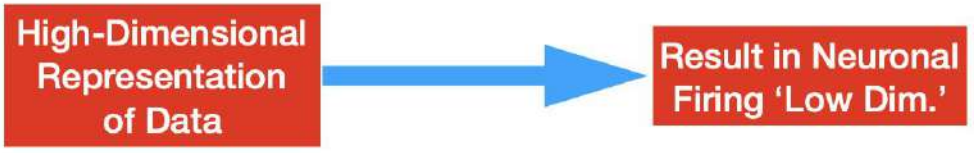
$$r(t) = g\left(\int s(t-\tau)\, f(\tau)\, d\tau\right)$$

- We have a linear filter a non linearity g

Problem is that we usually don't know the temporal feature of the nonlinear I/O function g

- For Temporal Time Points we can take each time segment and make it a feature

How do we accomplish this?

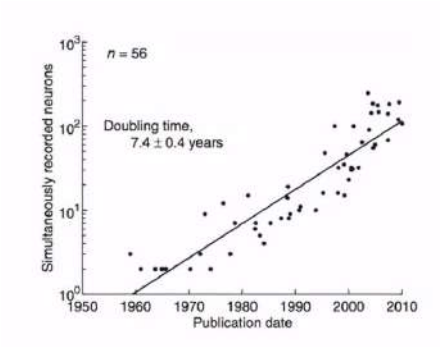


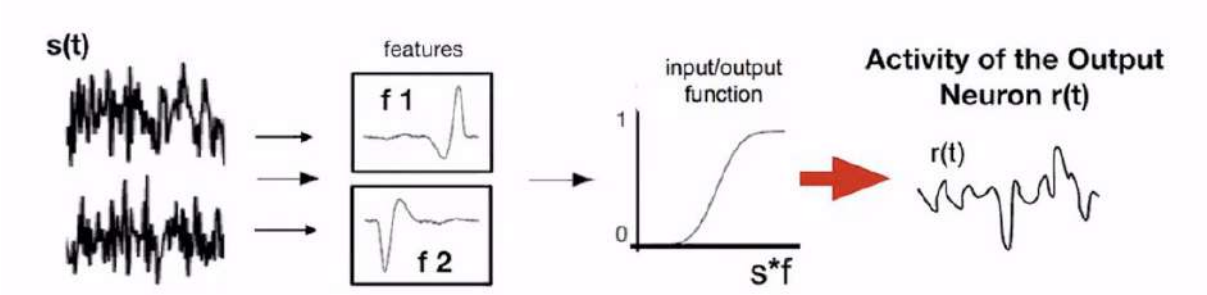
$$r(t) = \sum_{x=n,y=n}^{n} s_{x-x',y-y'}\, f_{x',y'}$$

Population vs. Single Neuron Coding

Methods to measure neurons:

- NeuralPixel Probe Electrodes 100s of neurons



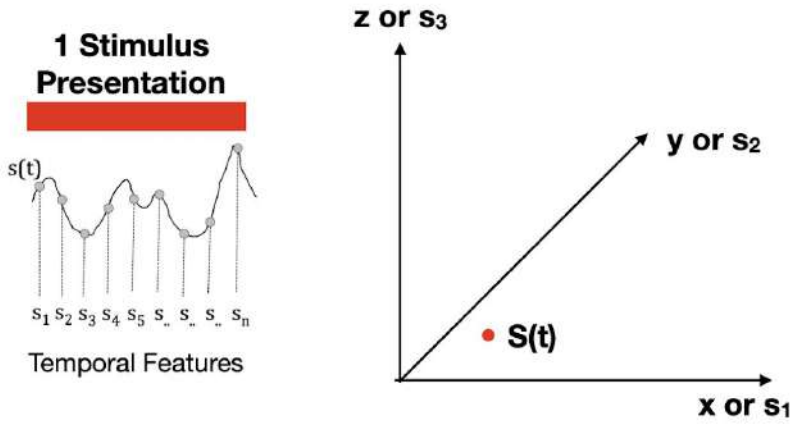


- Two stimuli
- Two features
- Filter functions
- Input into IO function
- Results in output activity

Population coding refers to information available from ensembles that goes beyond simple summation of individual signals. It is often associated with the method of Georgopolus et al (1986) but many analysts have also asked what an ideal observer could learn from a population of neurons.

All neurons encode exactly the same? Don’t analyze more neurons

All neurons encode differently? Look at more neurons



Now we want to repeatedly sample the responses to a variety of stimuli so that we can characterize what feature combination triggers a spike or a behavior.

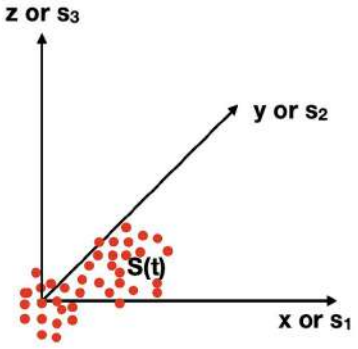
$$P(\text{response} \mid \text{stimulus}) = P(\text{response} \mid s_1, s_2, s_3, \ldots, s_n)$$

We take our temporal varying stimulus and divide into temporal features and plot each feature into high dimensional space.

What we want is the probability of a response given a certain stimulus.

We repeat and plot.

Finding the mean Population Response Vector.



What do we do next? Two possibilities.
1. We don't know the important features. We don't have any labels for the stimuli. → Unsupervised/clustering Approaches
2. We have labels for all stimuli classes. We know the features of interest. → Supervised Approaches

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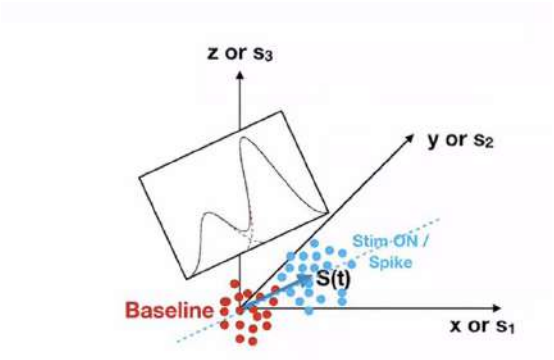
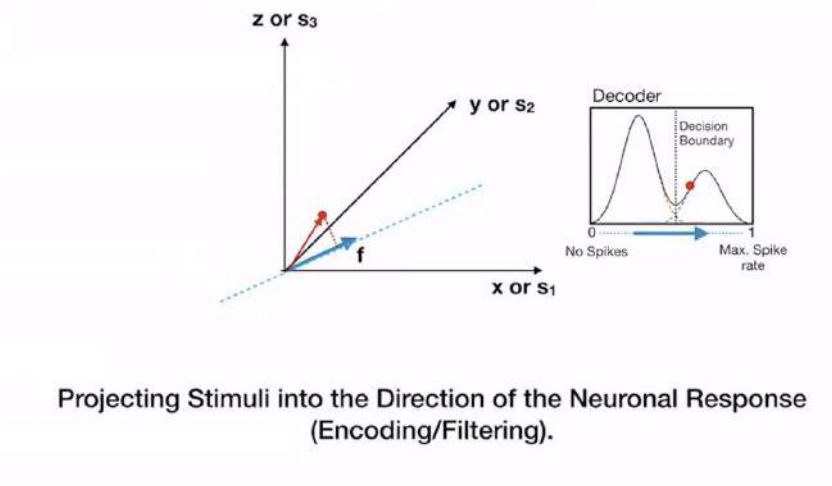
With supervision:



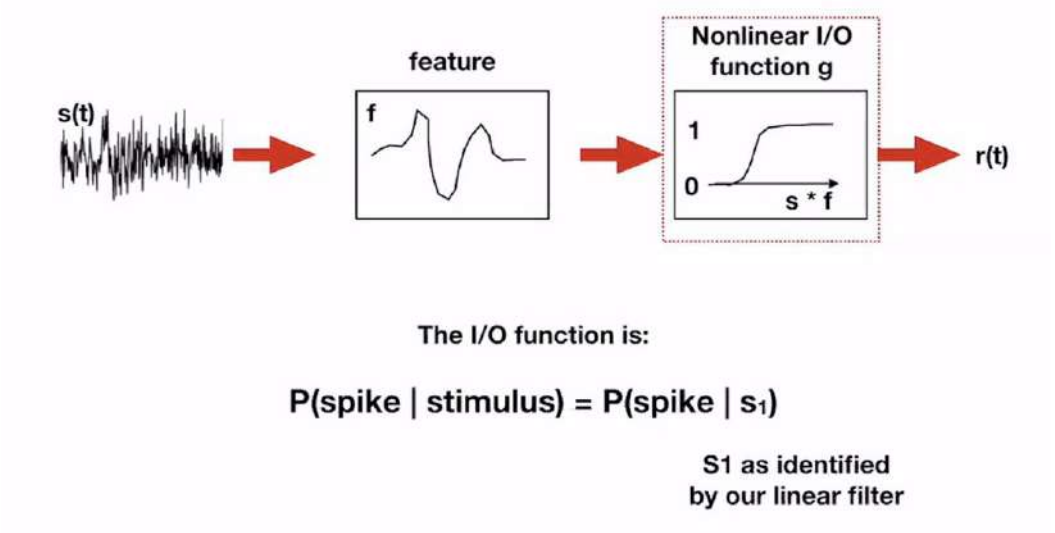
- Draw an arrow through these two means, taking this multidimensional response into one dimension. Here we get this bimodal distribution.
- Define a decision boundary, left hill f.ex. No spike right hill spike.

Then it's easy to test based on our model



Projecting Stimuli into the Direction of the Neuronal Response (Encoding/Filtering).

Finding the I/O Function for a single neuron

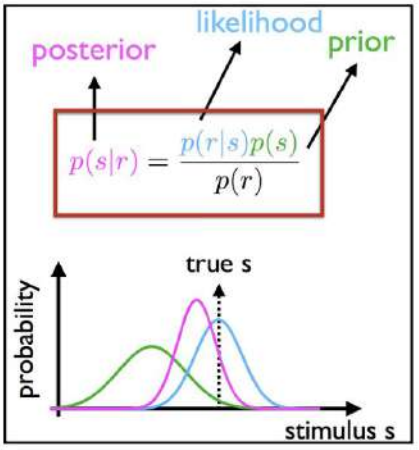


The I/O function is:

$$P(\text{spike} \mid \text{stimulus}) = P(\text{spike} \mid s_1)$$

S1 as identified by our linear filter

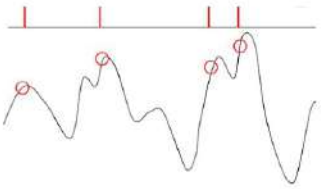
The I/O function can be found from data using the Bayes' rule:

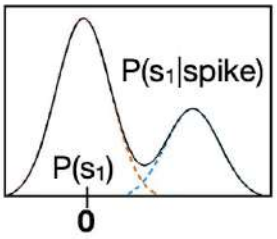


$$P(\text{spike}|s_1) = \frac{P(s_1|\text{spike})P(\text{spike})}{P(s_1)}$$

$P(s_1)$

$P(s_1|\text{spike})$





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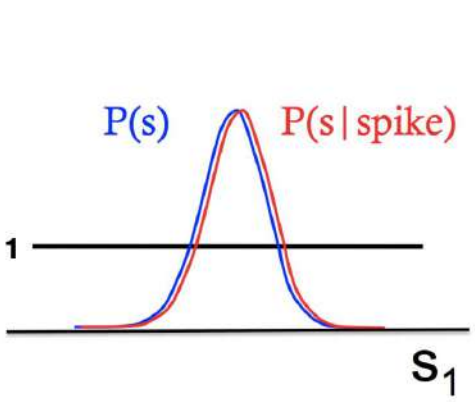
Posterior - p(spike|s1) - probability of stimulus given the response
Likelihood - p(s1|spike) - probability of the tneral occurs
p(r) - probability of the response

We measure the spikes and we measure the probability of s1 to occur. WE can then combine the times we had a spike and the matching p(s1).

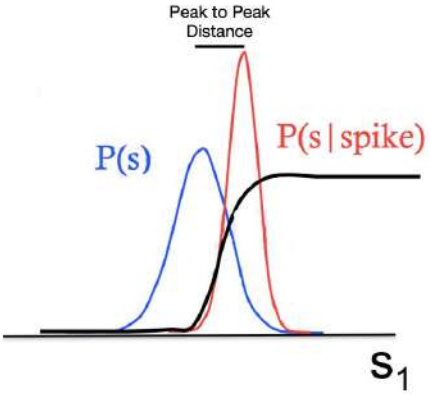
First peak would be the probability of the stimulus
Second peak the probability of the stimulus given a spike

Y Axis is the probability
X Axis is the stimulus s1?

$$P(spike|s_1) = P(s_1|spike)\ P(spike) / P(s_1)$$



Spikes are unrelated to stimulus.

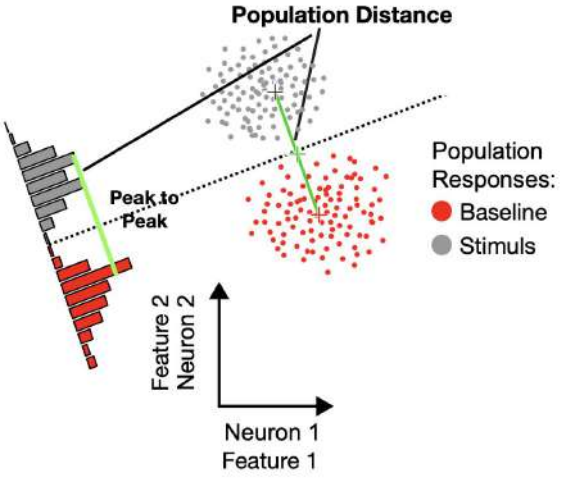


Spikes are selective!

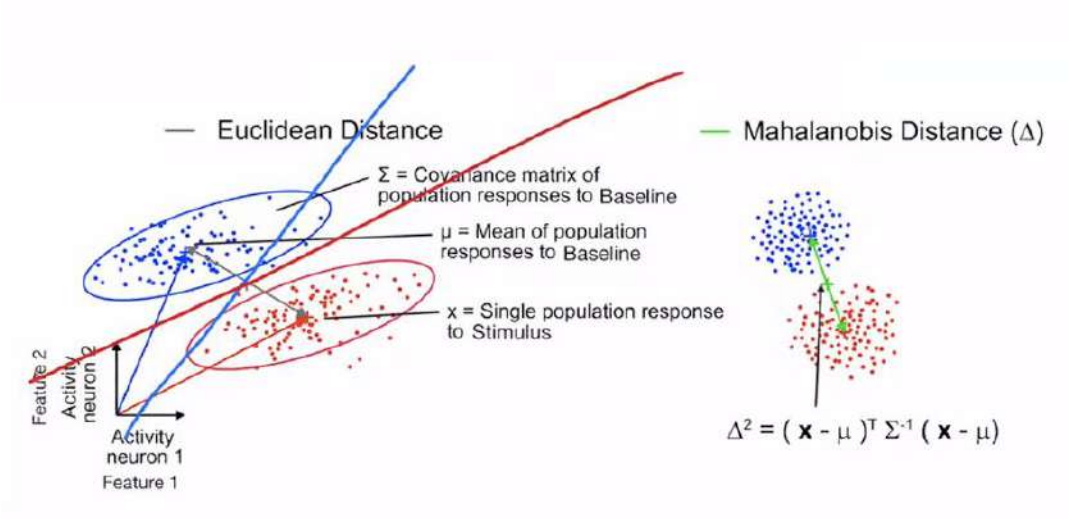
- Spike doesn't influence the stimulus to occur
- If peaks are shifted the distance of the peaks determines how selective is the cell / the spiking w.r.t the stimulus

How to classify differences in populations

- Two neurons
- Repeat stimulus
- How similar are they
- Connect their means project into 1 dimension and calculate the peak to peak distance
    - Equivalent to calculating the euclidean distance between the populations
    - Linear classifiers use the euclicidan distance



- Variability of population data can have a difference variance in the dataspace dimensions
- Doesn't take into account the variability of this population data (temporal/neuron/space/… - features) can have a different variance in the different data space dimensions



We want the red decision boundary but get the blue one when using the euclidean distance.

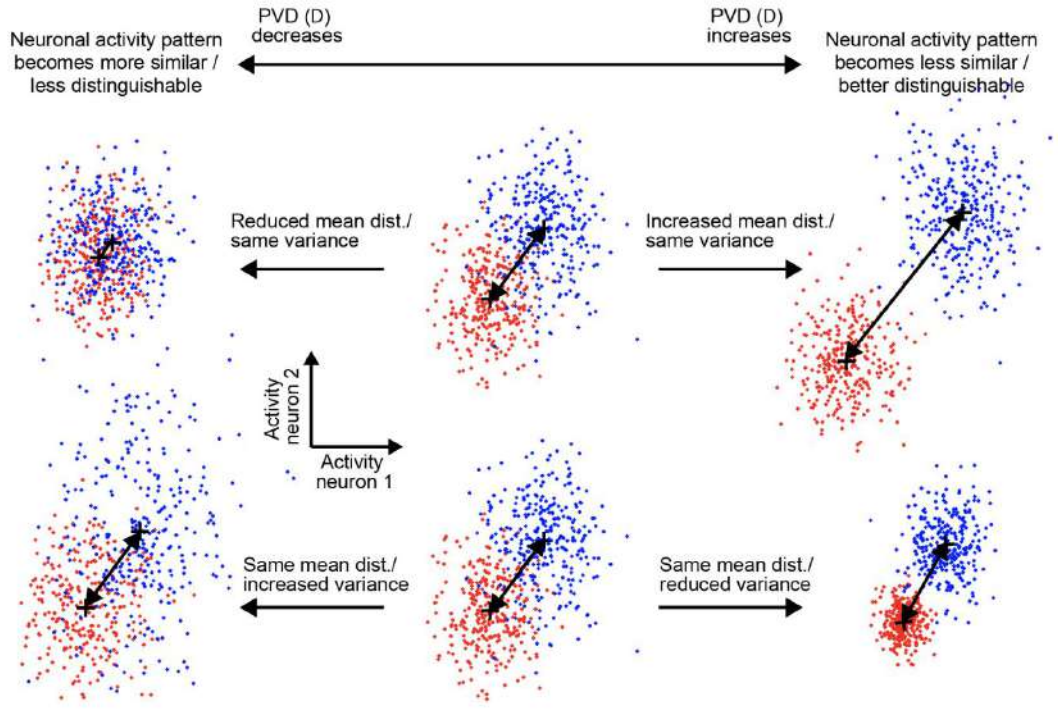
Mahalanobis Distance

- Normalizes variability
- It multiplies with the inverse of the covers matrix
- We transform our data into a subspace of unity variance
    - Nice round population clouds
    - Easy to take difference between the means and train classifier

Population Distance Metrics

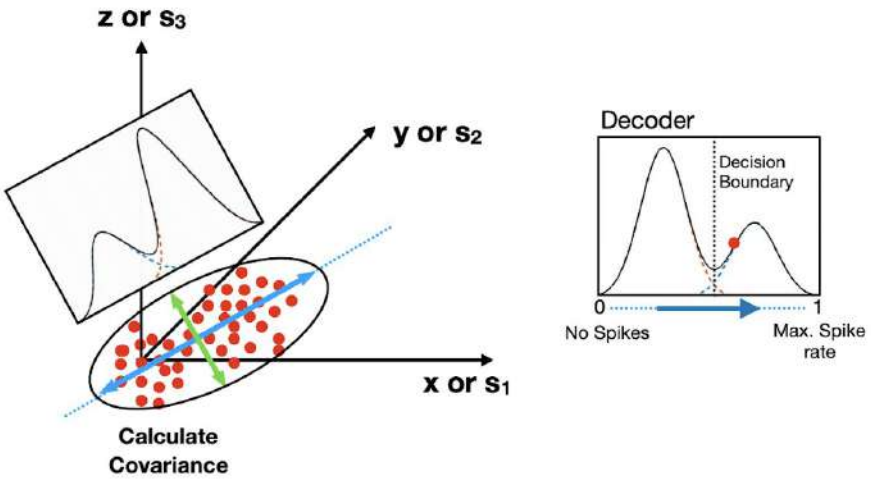
Two things are important:

- Difference in the means of 2 population responses (top row)
- Depends on variability of the stimulus (lower row)



Unsupervised Clustering via PCA

PCA: Principal Component Analysis



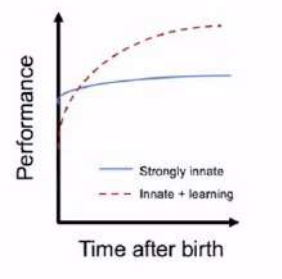
- Unsupervised: No label for spiking
- You could look at **direction of maximum variability**
- Projection along those lines => may find a bimodal distribution and train a classifier on it.

Lecture 9 - Learning and Plasticity

- In humans connections are mostly learned
- Learned information isn't stored in the genome
    - To be able to adapt to changes in the environment
- To store the entire brain and its connections it would take up too much space:

> The human brain has about 10^{11} neurons, and more than 10^3 synapses per neuron. Specifying a connection target requires about $\log_2 10^{11} = 35$ bits/synapse. Thus it would take about 3.5×10^{15} bits (~400 TB) to specify all 10^{14} connections in the brain.
>
> However, the human genome only has about 3×10^9 nucleotides, so it cannot encode more than ~1 GB of information (Wei et al., 2013).
>
> **Conclusion:** Even if every nucleotide of the human genome were devoted to efficiently specifying brain connections, the information capacity is orders of magnitude too small to encode all synaptic connections.

- Learning is a very strong evolutionary developed survival strategy.



- Performance (how well do you do in life)
- Blue - start well but pretty same
- Red - rules & learning resulting in more performance

- Intelligent Behaviour emerges with Learning

Learning (in ML Training) - The acquisition/storage of knowledge/information or the formation of a memory through experience.

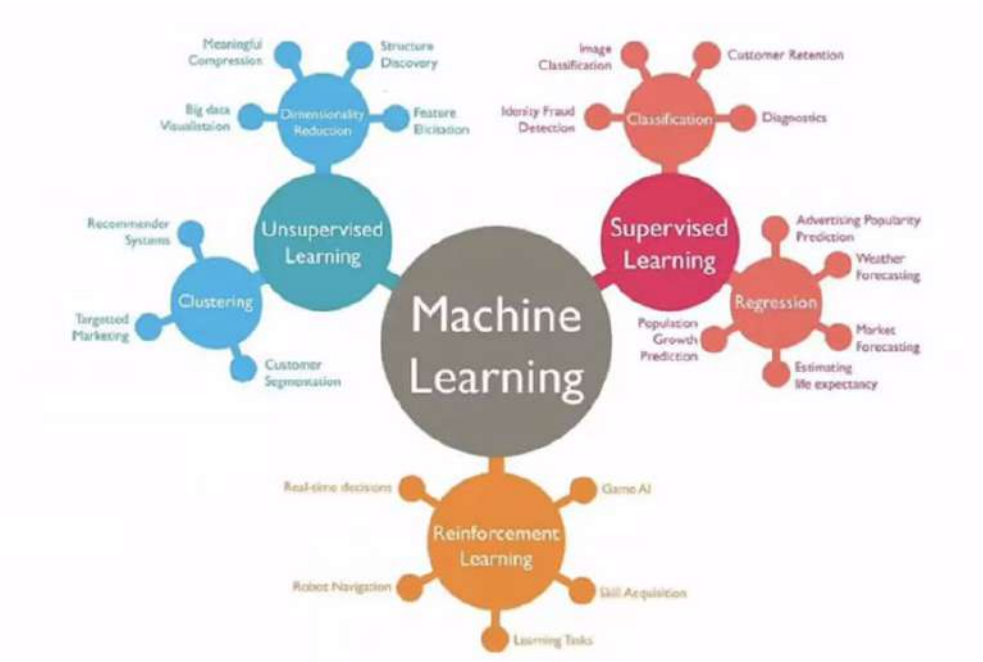
Memory – Stored information that can be recalled at a later stage in time.

- Learning results in memory - which itself has a further outcome - a change in future behaviour.
- Learning does not always imply a conscious attempt to learn. Simple observation can lead to the creation of a new memory.

Plasticity - The biological implementation of learning. Plasticity allows us to form a memory.

- There is an observable decrease of errors with increased learning

Learning in Computer Science



- Unsupervised Learning - you have no labels
- Reinforcement Learning - you're an agent who scores and learns

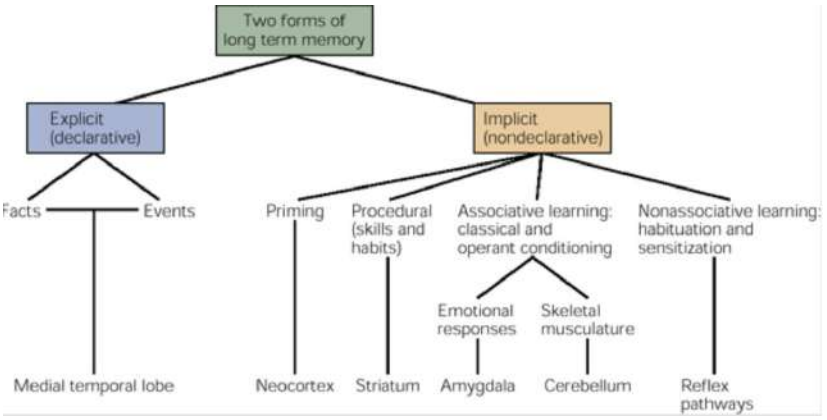
Learning in Neuro-Science

- Pavlovian Conditioning
  - Learning to associate reward and punishment with something
- Instrumental Conditioning
  - Learning to associate reward and punishment with something by doing an action (similar to reinforcement learning)
- Reward/Aversive Learning
  - Orthogonal to Pavlovian and Instrumental Conditioning
- Social Learning
  - Learning from parents for example
- Perceptual Learning - discriminate multiple stimulus
- Motor Learning - mouse runs a parcour

Types of Memories we have (Psychology)

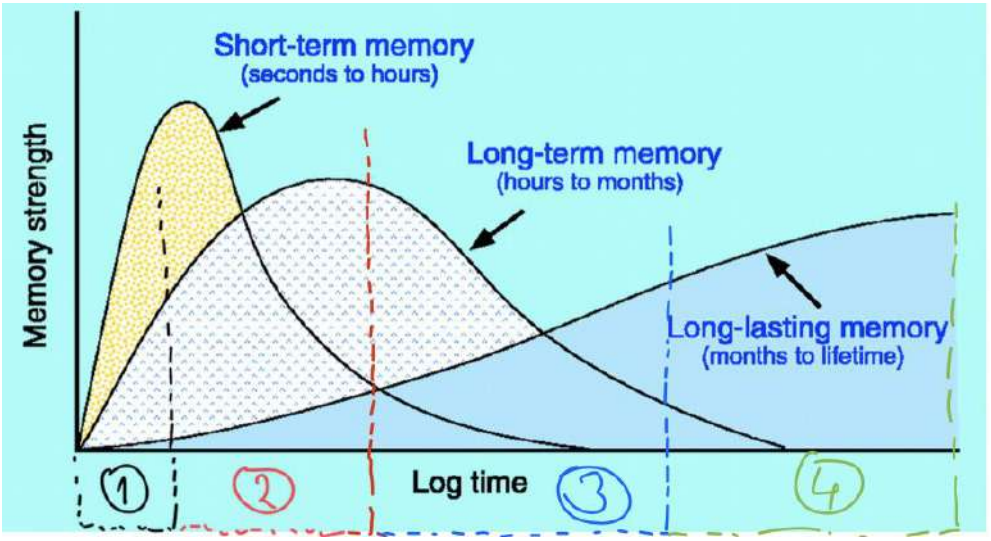
Memory is fundamental to the discipline of psychiatry and neuroscience.
Our memory stores:

- Our personal experiences
- Emotions
- Preferences/dislikes
- Motor skills
- World knowledge
- Language
- Cognitive Memories
- Spatial Memories



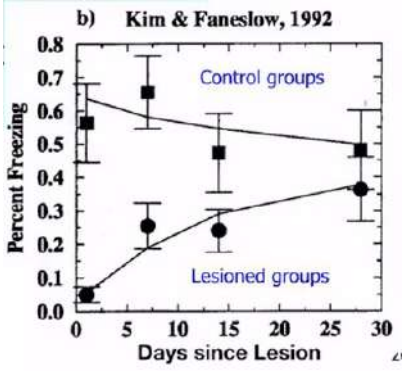
Fundamentally, we are derived from 'learning' experiences that have been stored in our nervous system.

Relevant Temporal Scales for Learning



1. Short term memory (seconds)
2. LTM - Long Term Memory (minutes)
3. Very LTM (hours-days)
4. Long Lasting Memory (months - lifetime)

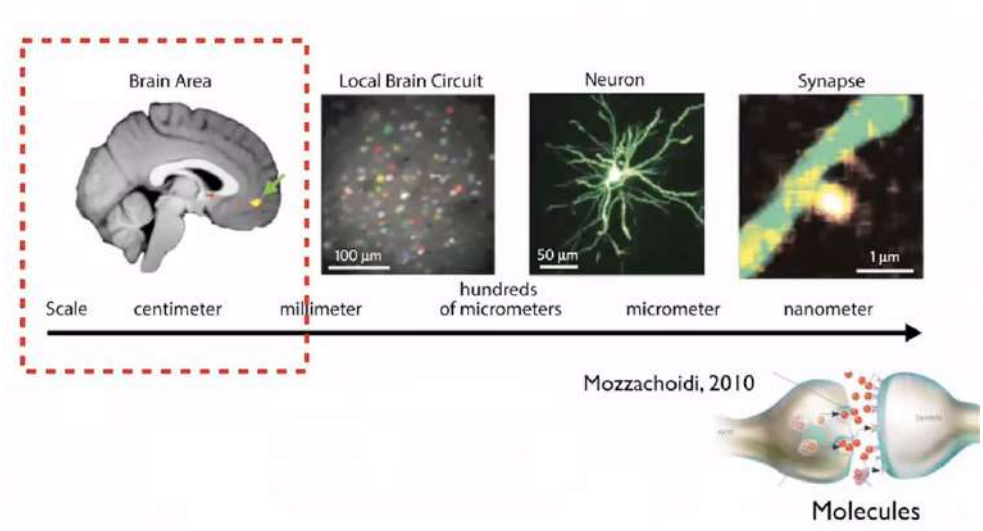
- Different brain areas are relating to these different time scales.
- Rodents learned some tasks
- Y Axis is the learned behaviour, X is time
- Hippocampus is mostly involved in short to long-term memory processing



Substrates of neural plasticity

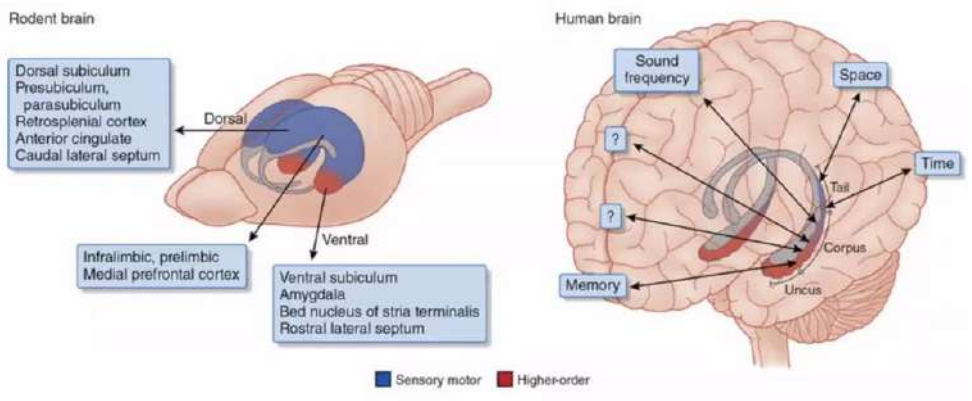
Network and Systems Plasticity

Different layers of plasticity:



- Brain Area - hippocampus
    - When learning something seeing some areas being more active
- Local Brain Circuit - Network of neurons
    - How do they change their population activity
- Single Neuron
    - How they change their synaptic strength with other neurons when learning
- Synapse
    - Which Protein ion channels really change when undergoing learning

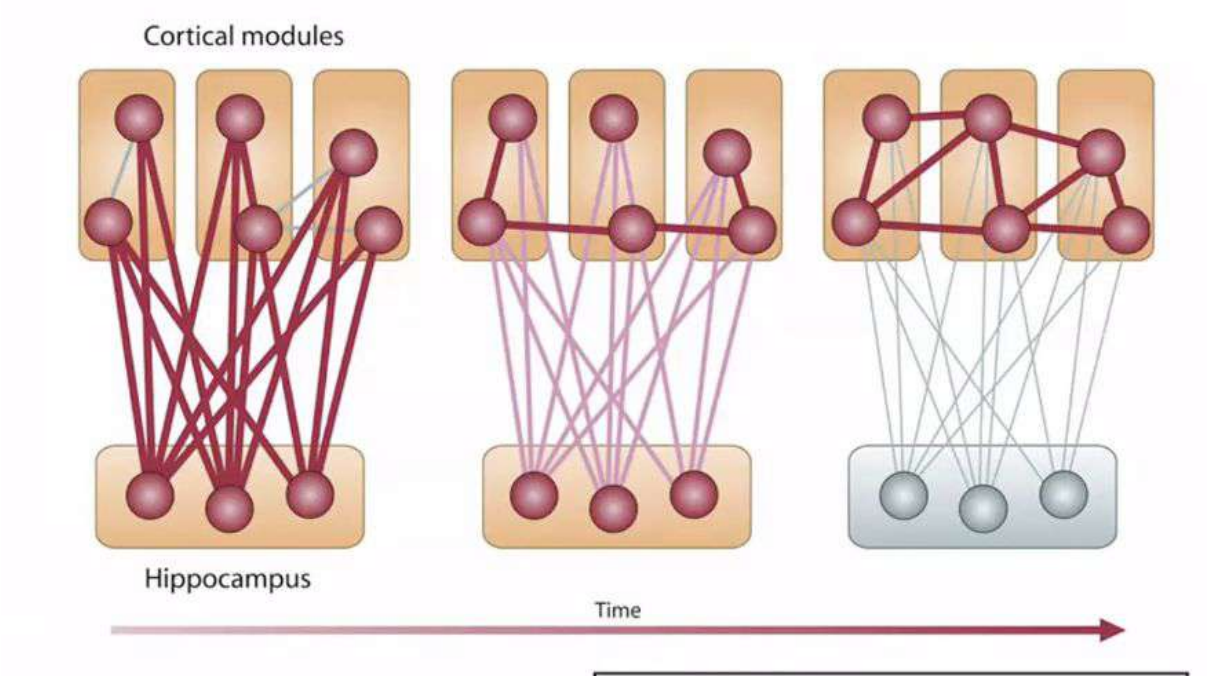
Brain Area Level



Conclusions of Patient H.M's Hippocampus removal:

- The Hippocampus is not a permanent storage area for explicit knowledge.
- The hippocampus is involved [with other cortical areas] in consolidation, a longer term process taking months to years (note retrograde amnesia in hippocampus lesion patients for up to 3 yrs).
- Consolidation is understood to involve biological changes taking place in those other areas of cortex,
- Once this has fully taken place, the hippocampus is not required for retrieval.

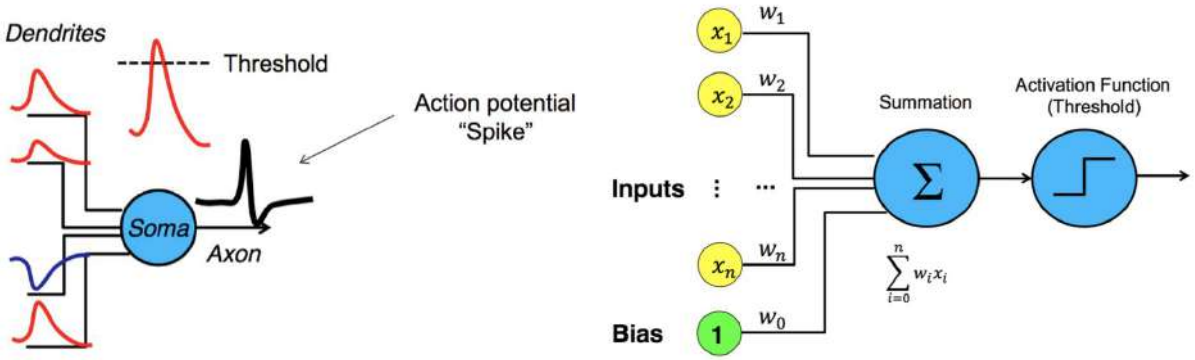
How memory is consolidated over time:



- First across Hippocampus connections things are learned till they are on their own.

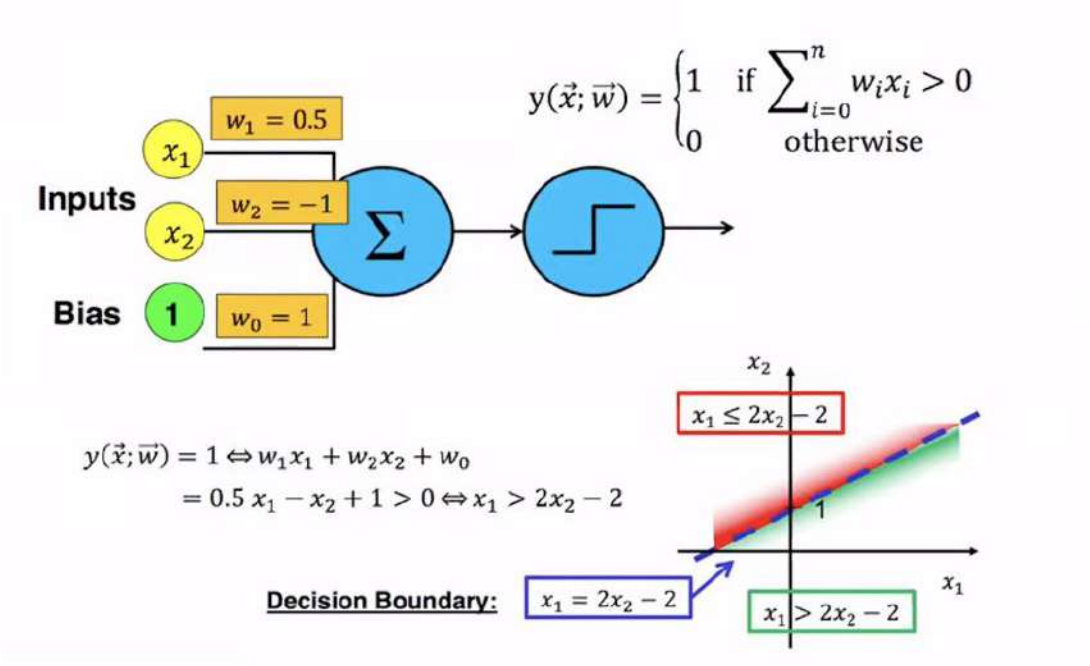
Cellular Plasticity, the Perceptron

Brain might implement hidden layer deep learning hierarchy



- Weight - how big is the synapse / size
- Threshold function - here step function

Doing this the perceptron is implementing a linear classifier
Example:



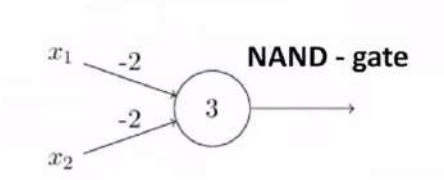
Perceptron Learning Algorithm

Algorithm: Perceptron Learning Algorithm

```
P ← inputs with label 1;
N ← inputs with label 0;
Initialize w randomly;
while !convergence do
    Pick random x ∈ P ∪ N ;
    if x ∈ P and w.x < 0 then
        w = w + x ;
    end
    if x ∈ N and w.x ≥ 0 then
        w = w − x ;
    end
end
//the algorithm converges when all the
 inputs are classified correctly
```

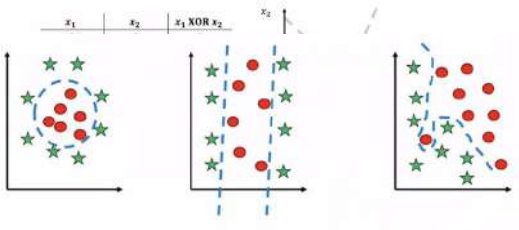
- What's the convergence in this algorithm?

Which logical Function does this perceptron realize?



Can all logical operations be implemented by a McCulloch-Pitts Neuron?

- No for example the XOR
- Non Linear Dataspaces can't be separated
- Can be overcome by chaining perceptrons together



The Perceptron Summary

- McCulloch-Pitts implements a linear decision boundary (separating hyperplane)
- The weights and bias define the decision boundary

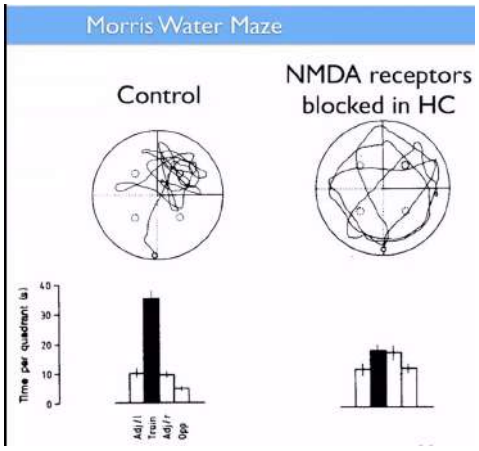
- They can implement many logical operations (And, Or, Not)
- They can't implement XOR (not linearly separable)
- They can be trained on labeled datasets (supervised learning)

If we put the perceptron in a deep network and we train it in a similar manner to backpropagation by backpropagating the error through the hierarchies then we can learn much more complex decision boundaries.

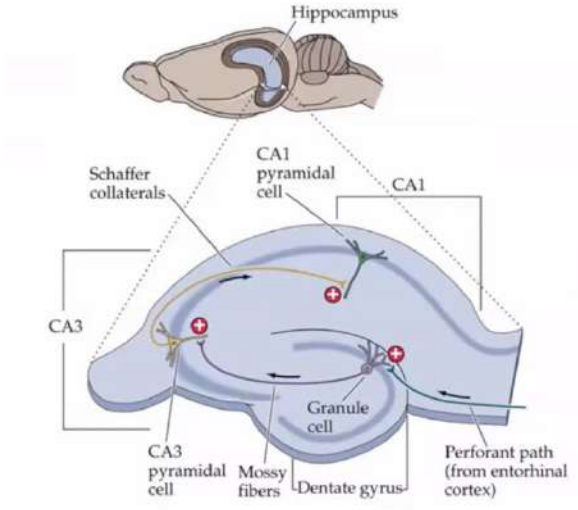
What is the function of the bias?
In a deep network you want different neurons to learn different things. Without bias every neuron would learn the exact same thing. Mostly initialized randomly in networks. Make a neuron more reactive to input A instead of input B.

A single neuron is as powerful as a 3 layer neural network. Synaptic inputs are integrated in the dendrites and a dendritic spike is triggered. Result of dendritic spike is variably strongly propagated to the soma, soma triggers another spike. Not just a perceptron.

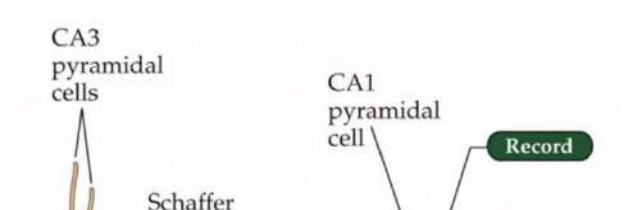
Hippocampus Spatial Representation



Cross Slicing Hippocampus Testing in Vitro



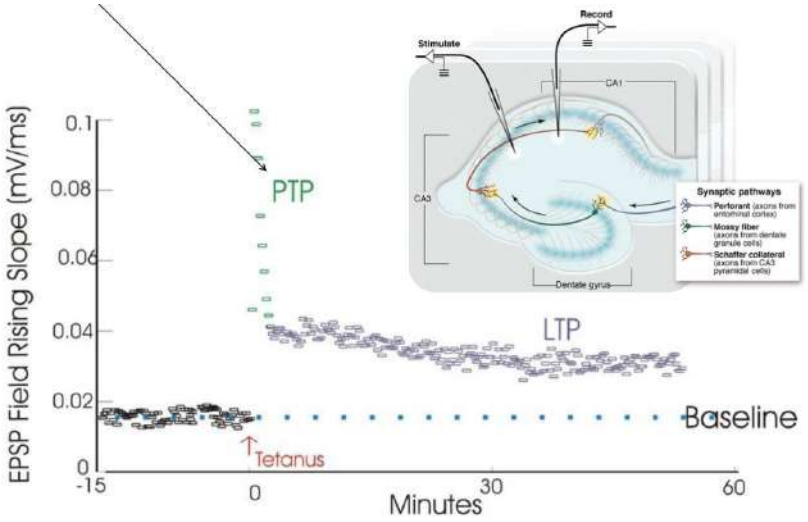
Most studied synapse CA3-> CA1



Find out how the postsynaptic potentials change

There can be a summation if the inputs are within 25ms from each other.

Paired activations of a synapse onto a CA 1 neuron. “Residual Ca2+” in the terminal for 10 to 100 ms after the first stimulus increases the probability of release.



EPSP Field Rising Slope - How strong is the signal coming in.

Minute -15 - 0: You give individual pulses - nothing happens

Minute 0. Tetanus Pulse has very strong repeated stimulations at a 100Hz. PTP due to residual Ca

After strong tetanic stimulation the EPSP in the postsynaptic cell has potentiated over the next 60 minutes.

- Our synapse has grown. **More ampa receptors. More vesicles.**

Stimulation frequencies that produce LTP usually range from ~50 to 200 Hz.

Depression
If you choose a low frequency from 1 to 10 Hz. You find a depression.

EPSC amplitude is the postsynaptic current which gets smaller and smaller if you do the low frequency tetanic stimulation.

There is some threshold where the neuron switches from Excitatory to Depression.

Frequency-dependent Long-term Potentiation (LTP)

- This term involves many mechanisms, all of which result in strengthening of the synapse for varying periods of time following tetanic stimulation.
- The mechanisms for LTP lasting 30 min to a few hours do not require new protein synthesis.
- **The mechanisms for LTP lasting longer than a few hours do require protein synthesis.**

Frequency-dependent Long-term Depression (LTD)

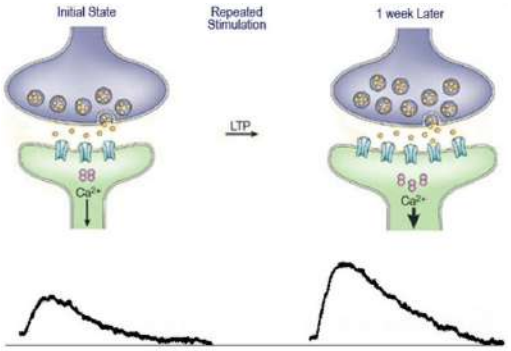
- This term also involves many mechanisms
- LTD, like LTP is thought to be used for sculpting circuits to store information

Spike-timing dependent synaptic plasticity (STDP) is thought to arise from the same set of mechanisms as LTP and LTD.

Synaptic plasticity, the Hebbian Synapse

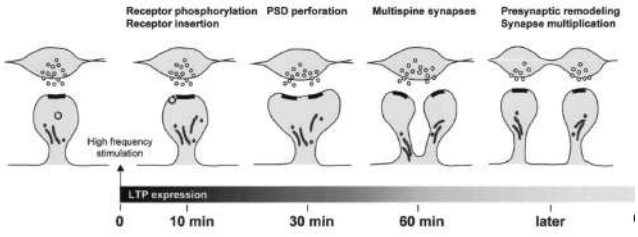
1. AP arriving at PreSyn.
2. Causes voltage gated calcium channels cause calcium influx in presynaptic part
3. Calcium Concentration leads to Vesicles full of Neurotransmitter Glutamate to go to the membrane and be dumped into the synaptic cleft.
4. Neurotransmitter bind to AMPA Receptors
5. Post voltage deflection (EPSP)

Cascade of Things with many possible bottlenecks. To strengthen synaptic plasticity you need to work on many of these.



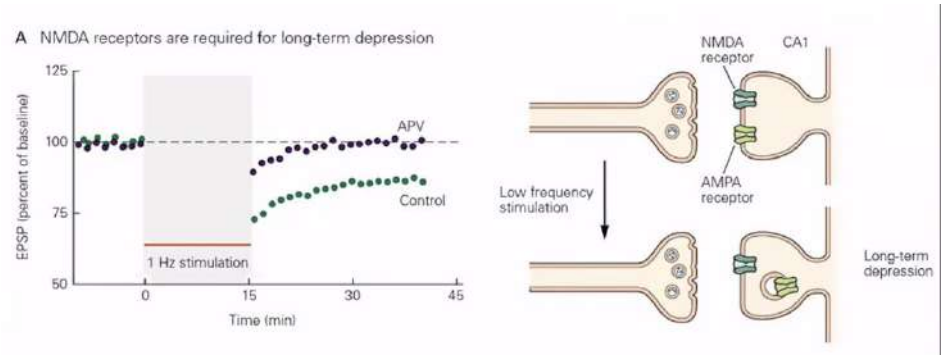
Number of new Ampa Receptors scales linearly with the size of the synapse.

1. Synaptic density size changes (Long term).
2. AMPA/NMDA ratio changes (Long term).
3. Number of spines changes (very Long term).



- There are more ion channels than AMPA Receptors
- NMDA is a channel that also binds Glutamate, lets through sodium and calcium
- After a certain time spines split up
- Presynaptic boutons split at some point

NMDA Receptors are required for long-term depression

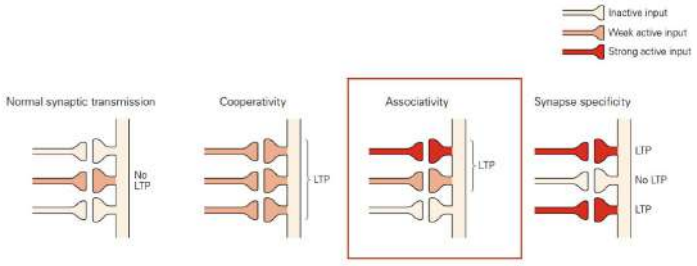


- APV is a NMDA Receptor Blocker
- Depression effect is partially blocked
- NMDA receptor also let through calcium which now isn't escaping the cleft

The role of Calcium in LTP/LTD

1. Calcium flows **through the activated NMDA** receptor.
2. One of its targets is calcium/calmodulin-regulated Protein Kinase to which it binds to.
    a. Special type of binding when calcium is only at a certain low level
    b. Low levels -> CamK3 and Calcineurin
    c. High levels -> CamK2 and CamK4
3. Level and timing of Ca2+ rise in spine determines LTD or LTP
4. Low frequency synaptic firing produces LTD; high frequency synaptic firing produces LTP

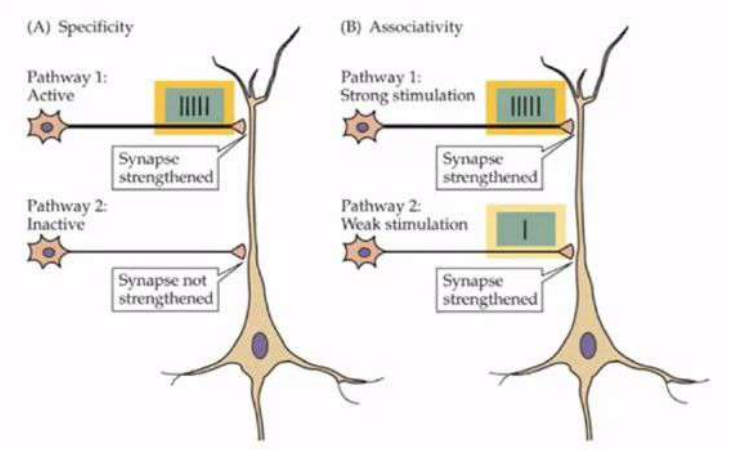
LTP and LTD are 'input synapse specific'



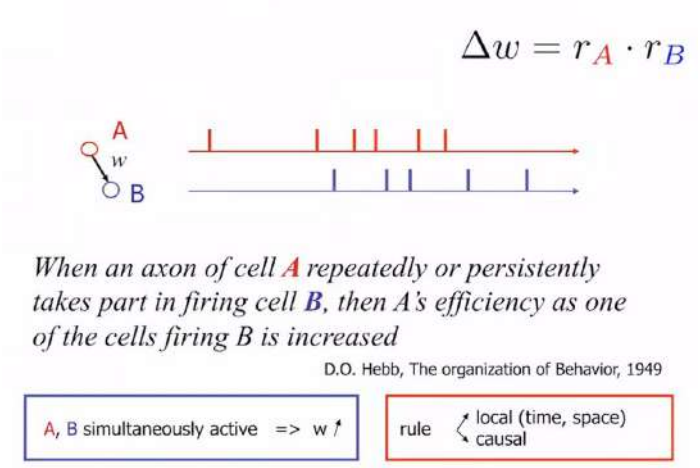
1. Cooperativity (induction threshold)
2. Input/synapse specificity
3. Enables associative learning

Hebb's Idea

Cells that fire together wire together.



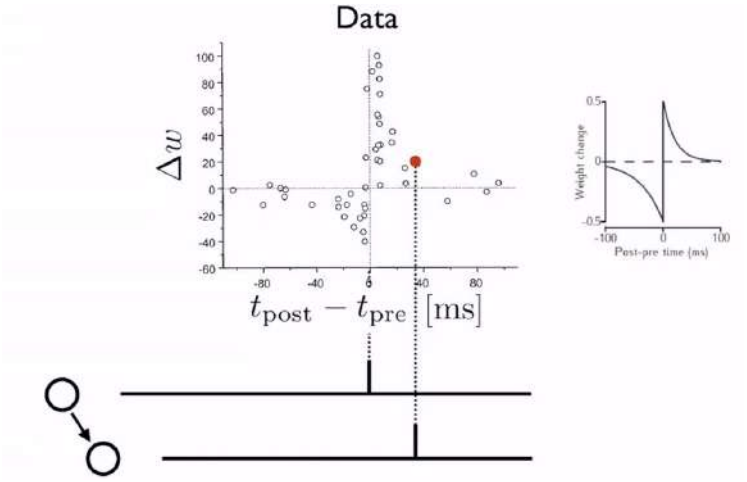
Hebb's Postulate



- Firing rate of neuron a times firing rate of neuron b

Experimental Verification

Spike-Timing dependent Plasticity

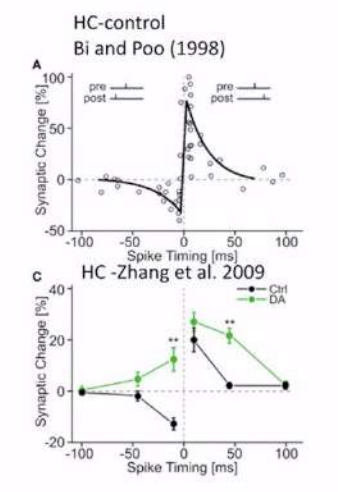


When you measure 2 neurons

- Delta w as percent change of ETSP
- Excite the first Neuron
- Then the second Neuron spikes
- Measure difference of presynaptic spike and postsynaptic spike
- If the difference is positive -> presynaptic neuron has fired first
    - Positive increase in the weight
- If negative we depress

Neuromodulators effects on STDP

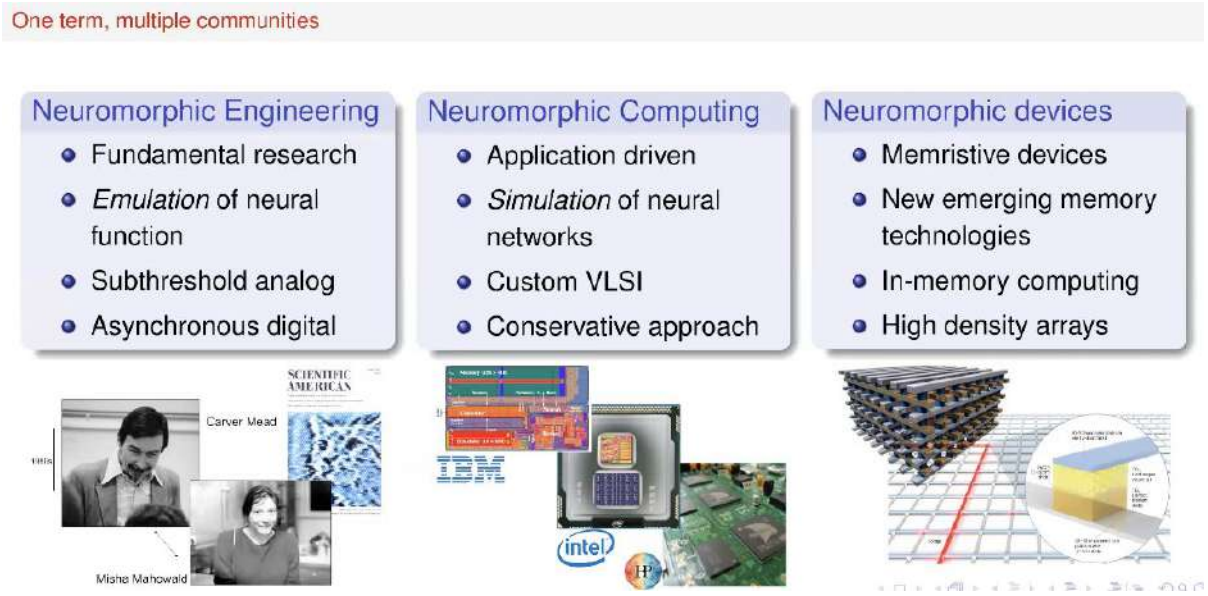
Dopamin, serotonin, neuroperefrin can effect this curve



Dopamine changes causal firing learning to correlated firing learning

Lecture 14

VLSI Very large scale integration systems



INI understanding the principles of computation in the brain

Goal

- Exploit device physics to directly **emulate the biophysics of neural systems**
- Let **time represent itself**

Building systems where memory and computation are colocalized

Exploiting Physical space

- Standard computer von Neumann spearetes computation and memory
- Transport of memory to CPU and write to Memory from CPU burns **Energy**
- In the brain everything is colocalized - no long distance travel
- Neurons only fire when they need to (sparsely in space and time)
- One can represent variables with a small number of neurons
- Neuron implementation done through **passive circuits** (no energy supply needed)
    - Input signals actually power the capacitors/transistors
    - Work in continuous time
- In electronics **active circuits** require energy supply to keep things active

We let time represent itself

- For interacting with environment systems time constant should match the time of the signal we're processing
- **Building** Matched Filters - Matching the circuit time constants with the input signal dynamics

Having matched filters with passive circuits and analog signals we have **low power & low bandwidth**

Largest bill for companies is electricity bill => we want lower power computing (e.g. the brain)

Transistor
Ionic currents flowing through the cell membrane are exponential with the voltage.

N type
Whether you have regions you have more electrons are lack of electrons

More electrons N-Fet

More holes P-Fet

Transistor Subthreshold Equations

- Physics of both equations are the same
- nFet charge flowing through is electrons => positive gate voltage => negative source => negative drain
    - Reference voltage is zero => Vg - 0, Vs - 0, Vd - 0
- pFet => negative gate voltage => positive source voltage => positive drain voltage
    - Reference voltage is vdd (the power supply) => we write it out

- In0 Ip0 current that flows through the device even when you have zero gate voltage - **dark current**
- Kappa depends on physics of device
- UT at room temp -25mV

n-FET

$$I = I_{n0} e^{\kappa_n V_g / U_T} \left(e^{-V_s/U_T} - e^{-V_d/U_T} \right)$$

p-FET

$$I = I_{p0} e^{\kappa_p (V_{dd} - V_g)/U_T} \left(e^{-(V_{dd} - V_s)/U_T} - e^{-(V_{dd} - V_d)/U_T} \right)$$

where

- I_{n0} and I_{p0} denote the nFET/pFET current-scaling parameter
- κ_n and κ_p denote the nFET/pFET subthreshold slope factor
- U_T the thermal voltage
- V_g the gate voltage, V_s the source voltage, and V_d the drain voltage.

The current is defined to be positive if it flows from the drain to the source.

Diffusion and saturation of Transistors
Whenever you change the **drain** to **source** voltage you have different concentrations of charge whether electrons or holes depending on the type of device => allows charge to flow through.

The larger the gate voltage the higher these concentrations => increasing the amount of current that is flowing through exponentially