INI summary

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Contents

A quick side note on the notation of reversal potentials. For some reason, certain sources are kinda like just using V_i and E_i interchangeably. So I did the same, so if you ever see V_R, E_s, E_{Na}, etc. it's all just the reversal potential for a channel or membrane expressed as the subscript.

1. Neuroinformatics

1.1. Introduction

1.1.1. Information processing in the brain

Occurs at many different levels, from the highest to the lowest.

1. behavior
2. system and pathways
3. circuits
4. neurons
5. microcircuits

6. synapses
7. membrane potential

1.1.2. Differences and similarities between brain

brain	brain and computer
• massively parallel • constantly adapting • unreliable units • analog computation • robust to damage • very energy-efficient • memory fixed in place	• can process information • uses logical operations • has memory • uses electrical (digital) signaling (e.g. AP) • can learn from inputs • consumes energy

1.1.3. Task difficulty | brain vs computer

- Human capabilities in comparison to a computer change with time.
- Some things are easy for humans that are hard for computers and vv.

1.1.4. Neuron structure

component	function
membrane	Separates inside from outside
dendrites	Provide inputs / connect to soma
axons	Connects to soma and conducts away from it. Often myelinated and ends in synapses.
synapse	Pre- and postsynaptic terminals, transmit information between neurons

2. Nervous System Organization

2.1. Broad Anatomy

Central nervous system | **CNS** : Includes brain and spinal cord

Peripheral nervous system | **PNS**: somatic (voluntary muscle) and autonomic (involuntary) NS
- sympathetic NS: “fight-or-flight”, is driven by adrenaline
- parasympathetic NS: “rest-and-digest”, normal functioning

Cranial nerves: connection between senses and brain

Brain cuts: separate brain regions
- horizontal plane: superior/inferior (up/down)
- coronal/frontal plane: anterior/posterior (front/back)
- sagittal plane: left/right

Outer brain layers:
1. Skull
2. Meninges - surround CNS with 3 layers

Lobes: 4 in each hemisphere and separated by fissures
- frontal
- temporal
- parietal
- occipital

2.1.1. Brain anatomy

Layers

1. Skull: protects the brain, provides fixed points
2. Meninges: protect the brain against infection
   - dura mater
   - arachnoid mater
   - pia mater - follows brain surface/curvature

Cerebral Spinal Fluid (**CSF**) - protection so the brain does not touch bones and does not damage itself

2.1.2. Brain building elements

Development: happens from the *neural plate*

Forebrain (Prosencephalon)	Cortex, Thalamus, Hippocampus, Basal Ganglia, Corpus Callosum
Midbrain (Mesencephalon)	Tectum, Tegmentum
Hindbrain (Rhombencephalon)	Cerebellum, Pons, Medulla oblongata
White matter	Glial Cells, Myelinated axons
Neocortex	Surface of cerebral hemispheres
Corpus callosum	Midline fiber (connects hemispheres)

2.1.3. Limbic system

Region of the brain related to emotion

location	on the medial and basal surface of the cerebral hemisphere
components	cingulate gyrus, parahippocampal gyrus, hippocampal formation, fornix, amygdala, septum, mamillary bodies
function	emotional expression, memory acquisition, fear conditioning, violence and aggression

note - The amygdala is particularly important for fear conditioning

2.1.4. Hypothalamus and thalamus

hypothalamus	**thalamus**
• controls emotion • regulates body temperature and other autonomic mechanisms	• "gatekeeper" between messages from the spinal cord and cerebral hemispheres

2.1.5. Basal ganglia

Related to movement control. Ensures correct movements are *initiated and maintained* while unattended movements are *suppressed*.

structure	caudate nucleus, putamen, globus pallidus, substantia nigra, subthalamic nucleus
location	embedded deep in the cortex as a collection of nuclei
projections	cerebrum
function	regulated to voluntary movement

note - involved in movement disorders like Parkinson's

2.1.6. Cerebellum

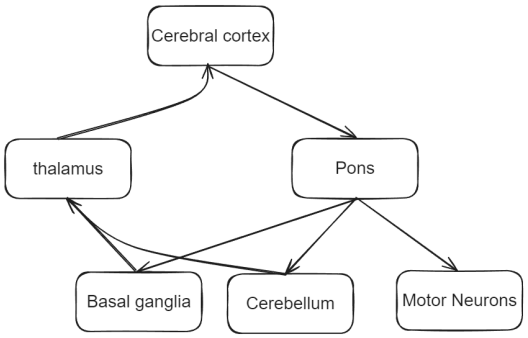
Ensures movements take place in a smooth and controlled way.

structure	little brain with layered appearance and symmetry, connection between hemispheres via vermis
function	coordinated motor behavior, posture adjustment, stores memories for simple learned motor behaviors

2.1.7. Reticular formation

structure	diffuse arrangement of ascending and descending neurons
function	arousal, selective attention, respiration

2.1.8. Connections

notes	connection diagram
Cortex layers • 6 in total Connection types • feedforward : superficial → deep layers • feedback : deep → superficial layers	

2.2. Basic Neuron structure

2.2.1. Types of neurons

There are *different types of neurons* but they all follow the same basic structure, this being

- cell body, axon, and axon terminal

2.2.2. Neuron components and key terminology

component	definition
nucleus	“”
dendrite	input component
axon	output component, makes contact with other neurons
myelin	wraps around axons, makes white matter white
boutons/terminal	at the end of neurons, connects neurons
soma	cell body without it’s extensions (axon/dendrites)

term	definition
afferent neuron	neurons that carry nerve impulse from receptor → CNS
efferent neuron	neurons that carry nerve impulse from CNS → receptor

2.2.3. Axon transport types

The movement of vesicles that store the NT can be classified into two types.

anterograde	transport of vesicles → axon terminal
retrograde	transport of empty vesicles back → cell body

2.2.4. Synapse

Conversion between electrical (AP) to chemical (NT) signal takes place in the synapse.

part	**function**
boutons/terminal	connection point
cleft	gap between presynaptic and postsynaptic neuron
dendritic spines	dendritic part of synapes/just the dendrites
transmitter (**NT**)	released by presyn. neuron, via exocytosis out of vesicle
receptors	binding site for transmitter

2.2.5. NT release sequence

1. AP arrives opening Ca^{2+} channels
2. Increase in Ca^{2+} leads to vesicle binding to presyn. membrane.
3. The vesicle undergoes exocytosis and NT release into the synaptic cleft.
4. NT bind with postsyn. receptors.
5. Opening or closing of ion channels.
6. Change in the conductance → current flow
7. Flow of current → change in postsyn. potential
8. Inhibition or Excitation of postsyn. cell
9. Summation of all signals determines if AP or not

2.2.6. Post-synaptic receptors

ligand-gated ion channel (**LGIC**)	allow ions to pass through in response to binding with a chemical messenger (e.g. NT)
g-protien coupled receptors (**GPRC**)	allow ions to pass through in response to binding with chemical messenger via a signaling protein

2.3. Muscle reflex and antagonists

2.3.1. Reciprocal intervention of antagonistic muscles

Muscles work in *antagonistic* pairs with one generally contracting and the other relaxing.

Steps

1. A tack produces a burst of firing (sensory neurons, for example on the finger).
2. The burst excites excitatory spinal interneurons, which then excite the motor neurons of a muscle.
3. The burst also excites inhibitory spinal interneurons that inhibit antagonist muscle motor neurons.
4. One muscle gets contracted, the other relaxed, allowing for a rapid flexion. No brain is involved (but gets informed).

2.3.2. Strech reflex

Stretch reflex is the contraction of a muscle in response to its passive stretching.

Steps

1. When hitting the knee tendon with a hammer, the spindles of the thigh muscle get stretched and this elicits a burst of firing in the spindle afferents.
2. The burst triggers a burst of firing in the thigh muscle motor neurons, causing contraction

3. Membrane potential basic case

Setup

- Membrane barrier
- Cell filled with + and - ions
- Channels permeable/selective to one type of ion, e.g. +
- $[X]$ - conc. of ion

Process

- Assuming $[X]_{\text{in}} \neq [X]_{\text{out}}$
- Diffusion leads to an outward flow of positively charged ions
- Electrostatic gradient caused by outward diffusion increases the inner attractive charge
- As $t \to \infty$ we have $[X^+]_{\text{in}} > [X^+]_{\text{out}}$ because the concentration gradient force and the electric potential force are at equilibrium with an excess charge on the surface of the cell membrane

3.1. Membrane properties

membrane	phosolipid bilayer which creates an energy barrier
ion movement	ions cannot just flow through, channels are needed
ECS	extra-cellular solution
ICS	intra-cellular solution
membrane outside	uncharged, hydrophilic, dipole head-group
membrane inside	hydrophobic hydrocarbon tail

3.1.1. Resting and outside potential

Neurons have their membrane potential mostly determined by K^+

extracellular potential	generally $\approx 0\text{mV}$
intracellular potential	generally $\approx -70\text{mV}$

3.2. Properties excitatory neuron input

There are some key properties of an excitatory input to a neuron

input	happens of synapses
depolarization	generally occurs at around 30mV from the present. membrane
excitatory current	positive charge which comes from extra-to intra-cellular space
signal properties	analog and graded
leak current	on the way from dendrite $\to$ soma the intracellular current is reduced
ESPS	excitatory post-synaptic potential
signal spread	the signal has a spatial and temporal spread in the postsyn. cell
temporal spread	the time-constant τ_m defines how fast the potential changes
spatial spread	the length-constant λ defines how far the current travels

3.3. Chemical synapses

digital transmission	can have failures, is a graded release
synapses	there can be synapses directly on the soma

3.4. Inhibitory post-synaptic potential

There are 3 key properties of IPSP's

location	**activity**
presynaptic cell	depolarization, $V = 30\text{mv}$
postsynaptic dendrite	hyperpolarization $V = -90\text{mV}$
postsynaptic soma	smaller hyperpolarization $V = -70.2\text{mV}$

3.5. Summation of Inputs

There are two main types of input summation *temporal summation* and *spatial summation.*

temporal summation	summing one input after another
spatial summation	summing inputs coming from different dendritic branches

Also, there are some key points to remember in regard to the summation of inputs

- typically 20 - 30 inputs are needed to go above the threshold
- AP triggered at the beginning of the axon
- threshold value is $\approx 60\text{mV}$

3.6. Action Potential

process	AP's function via an active regeneration process, that is, they propagate via regeneration
duration	1 - 2ms
all-or-none	AP's either cross the threshold and fire or they don't
amplitude $\rightarrow$ rate	amplitude is converted to rate
components	depolarization/hyperpolarization, repolarization/hyperpolarization

3.7. Axon

myelin sheath	myelin sheath often wrapped around axon
white matter	made white by the myelin sheath
electrical insulator	myelin sheath acts as an electrical insulator which grants faster propagation
less energy	mylendated axons require less energy
node of ranvier	these are the gaps between the myelin sheath

3.8. Key receptors

type	**name**	**ion**	**driving force**
excitatory	AMPA/NMDA	mixed cation	0mV
inhibitory	GABA A	chloride (Cl)	–65mV
inhibitory	GABA B	potassium (K)	–90mV

3.9. Acting forces

There are various points to consider with the acting forces on the membrane potential

diffusion	caused by an ion concentration gradient and represents the gradient force

electrostatic force	caused by the potential difference across the membrane due to different concentrations of + and - ions
equilibrium potential	reached as $t \to \infty$ when both acting forces balance out, computed with nernst equation
channels	most neurons have Na^+, K^+ and Cl^- channels

3.9.1. Nernst equation

The Nernst equation expresses the voltage equilibrium V_{eq} given some simple conditions for a membrane model. The variables of the equation are

- κ_B - Boltzmann constant
- Z - charge of the ion
- T - absolute temperature (kelvin)
- qZ - charge of the ion including the sign
- V_{eq} - voltage equilibrium

The actual equation is expressed as follows

$$V_{eq} = \frac{\kappa_B T}{qZ} \times \ln\left(\frac{[Ion]_{extracellular}}{[Ion]_{intracellular}}\right) \tag{1}$$

Observations

$\uparrow T$	increase in V_{eq} because more thermal energy means less resistance to cross barrier
Δq	changes the sign of V_{eq}
$\uparrow Z$	decreases in V_{eq} due to greater resistance to cross barrier

There is also a concentration dependence, for V_{eq} which has the following two implications

$$\begin{aligned} [X]_{out} > [X]_{in} &\to V > 0 \text{ and } Z > 0 \\ [X]_{in} > [X]_{out} &\to V < 0 \text{ and } Z < 0 \end{aligned} \tag{2}$$

You can verify these two cases by just looking at their effect on the log term.

3.9.2. Membrane capacitance

Membrane capacitance generally denoted by the letter C expresses a membrane's capability to store a particular electric charge.

The capacitance of a membrane can be expressed by the following equation

$$C_m = \frac{c_m}{A} \tag{3}$$

- c_m - specific membrance capacitance
- A - area

3.9.3. Goldman-Equation

Equation used to calculate the voltage equilibrium taking into account permeability and multiple channel types.

*skipping for brevity

4. Passive (Cable) Membrane Properties

4.1. Biophysics of membrane

3 main factors give rise to the resting/reversal potential.

- A membrane to separate the inside from out and act as an insulator/capacitor.
- Ionic pumps with a different concentration gradient $[\text{ion}]_{\text{in}} \neq [\text{ion}]_{\text{out}}$
- Selective ion channels

4.2. Basic electronics

Ohms Law	$V = I \times R$; implies $R = \frac{1}{I}V, I = \frac{1}{R}V$
KCL Kirchoffs Current Law	Sum of currents entering and leaving any node in a circuit is 0
KVL Kirchoffs Voltage Law	Sum of all voltages around a closed loop is 0
Current	$I = \frac{1}{R}V$; alternatively $I = \frac{dQ}{dt}$ AKA rate of charge through a surface
Capacitance C	$C = \frac{1}{V}Q$; implies $CV = Q \rightarrow C\frac{dV}{dt} = \frac{dQ}{dt} = I$

4.3. Single-compartment model

4.3.1. Assumptions, configuration

- spherical membrane
- injected current I_e
- leaky/resistive current I_R
- capacitive current I_C

4.3.2. Important relationships

1	$I_C = I_e - I_R$	So the current that exists across the membrane is just the difference between the incoming injected current and the outgoing leaky current
2	$I_R = g_m(V - V_R)$	The leaky current is the inverse conductance of the membrane g_m times the difference in the current potential from the reversal/resting potential

4.3.3. Different time points

We can make some observations about this SCM at different points in time

$t = 0$	The external current arrives, and there is some leak current
$t > 0$	$I_e > I_R$ meaning that the injected current is larger than the leaky current
$t = \infty$	$I_e = I_R$ meaning that we cell is fully charged also implying that $I_C = 0$

4.3.4. Solving the equation

We can express the injected current as follows using the equations from the basic relationships and rules

$$
\begin{aligned}
I_e &= I_R + I_C \\
I_e &= g_m(V - V_R) + C\frac{dV}{dt} \\
I_e &= \frac{V - V_R}{R} + C\frac{dV}{dt}
\end{aligned}
\tag{4}
$$

Then introducing a time constant $\tau_m = RC$ we can rewrite the derivation of I_e as

$$
\tau_m \frac{dV}{dt} = V_R - V + RI_e \tag{5}
$$

Then to solve for $V(t)$ we simply integrate both sides which gives

$$
V(t) = V_R + RI_e\left(1 - \exp\left(-\frac{t}{\tau_m}\right)\right) \tag{6}
$$

4.3.5. Case $t \to \infty$

For the case as $t \to \infty$ we end up with $V(\infty) = V_R + RI_e$

The reason for this is that after a certain point, the charge on the capacitor no longer changes so all charge must flow through the resistor. Also, the exponential term goes to 0.

Observations

- If either $\uparrow R$ or $\uparrow I$ that implies a higher $V(\infty)$
- Since $R = \frac{r}{\text{area}}$ a smaller neuron will have more resistance for the same amount of current I_e
- A myelinated neuron has less resistance and thus needs less current input to achieve the same voltage change

4.3.6. Interspike firing rate

For a constant input current I_e if we assume the threshold is next reached at time t_{isi}, then solving for the inverse, so $r_{\text{isi}} = \frac{1}{t_{\text{isi}}}$ can give us the *interspike firing rate*. Its a formalization of the idea that when we achieve a threshold an action potential is a generation, a reset occurs, and then it repeats.

$$
\begin{aligned}
r_{\text{isi}} &= \frac{1}{t_{\text{isi}}} = \left[\tau_m \ln\left(\frac{RI_e + V_R}{RI_e + E_L - V_{\text{th}}}\right)\right]^{-1} \\
r_{\text{isi}} &\approx \left[\frac{V_R - V_{\text{th}} + RI_e}{\tau_m(V_{\text{th}} - V_R)}\right]
\end{aligned}
\tag{7}
$$

4.3.7. Adding a synapse

In the case we add another synapse s there are two main cases to consider

$g_s \gg g_m$	for $t \to \infty$ we have $V(t) = V_{Rs} + \frac{1}{g_s} I_e$ implies a reduced effect of I_e AKA shunting inhibition
$g_s \ll g_m$	for $t \to \infty$ we have $V_{\text{eq}} = V_R$ so just that the equilibrium will be the cells normal resting potential

4.4. The cable equation

*TODO - will add

4.5. Levels of approximation

The types of approximations you make when you model neuronal dynamics are important

discrete compartments	A neuron can be represented by a variable number of discrete compartments
compartments	represent a region, each with a single membrane potential
connections	resistive couplings exist for connections between compartments
isopotential	the basic model containing only a single compartment

5. Action Potential

The action potential (**AP**) has some essential properties

location	occurs only in axons
movement	travels down the axon
refractory period	ensures maximum frequency of the AP
speed	about $1 \rightarrow 10$m/s fast

The steps including the behavior at each step can be described as follows

name	**voltage**	**what happens**
resting potential	$V = V_R$	the neuron is at rest
threshold reached	$\uparrow I_e \rightarrow \uparrow V$	if the injected current I_e is large enough such that $V = V_{\text{th}}$ then the threshold is reached
depolarization	$V \geq V_{\text{th}}$	in the case the potential difference reaches the threshold depolarization happens, that is, an action potential is generated
overshoot	$V > 0 (\approx 30\text{mV})$	an overshoot happens
hyperpolarization and undershoot	$V < V_R$	the membrane potential temporarily dips below the resting potential V_R

A key observation is that during AP generation we see channels opening and pulling V towards the resting potential V_R. The main hypothesis for why this happens is elaborated in the *voltage clamp experiment*.

5.1. Voltage clamp

The hypothesis that motivated the voltage clamp experiment had the following reasoning

1. An increase in conductance means a decrease in resistance (literally just $g = \frac{1}{R}$)
2. Decrease in resistance means easier flow of ions through channels
3. Easier flow of ions means faster change of V
4. Faster change of V means approach V_R faster

The actual experiment can be described as follows

1. Set voltage to a value V_{set}
2. Voltage clamp automatically adjusts the membrane potential to maintain V_{set}
3. Measure injected current I_e required to keep $V_{\text{measured}} = V_{\text{set}}$

5.1.1. case: small V

In the case of a small voltage being set the measured current follows the below pattern

1. Initial current to depolarize the membrane
2. Continous constant charge to account for leak current during maintenance
3. Repolarization to remove the charge added in step 1

5.1.2. case: large V

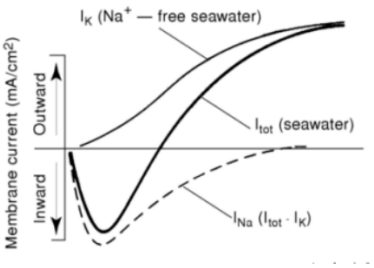
In the case of a large voltage being set our current-time graph exhibits the following properties

1. Initial current to get to V_{set}
2. Cell wants to now depolarize so we have to inject a negative current as a means to maintain V
3. The cell wants to now hyperpolarize so we need to inject a positive current

The key thing to take away from this is that in the case of a large V the characteristic shape of the injected current is an initial spike, then a negative dip, and then a positive dip, akin to an inverted action potential curve.

5.1.3. Separating the currents

Something specifically to look at is the effects of separate types of currents to maintain V_{set}.

By repeating the experiment for many different V_{set} we can express the channel-specific currents in terms of a given voltage. That is we can create a model for $I_{\text{Na}}(V,t)$ and $I_K(V,t)$	

Key observations

- Since we know the combined current change I_{tot} (in the diagram) we can express the channel-specific current for I_{Na} or conversely for I_K as the difference of curves from the combined current.

5.1.4. Deriving the conductances

Since we now have models to represent the currents for different channels we can use ohms law to derive the corresponding conductances g_K and g_{Na}. If we express the reversal potential for a specific channel as E_{channel}

$$\begin{aligned} I_K &= g_K(V - E_K) \\ \Rightarrow g_K(V,t) &= \frac{I_K(V,t)}{V - E_K} \end{aligned} \tag{8}$$

Likewise, we can derive an expression for the conductance g_{Na}

$$g_{\text{Na}}(V,t) = \frac{I_{\text{Na}}(V,t)}{V - E_{\text{Na}}} \tag{9}$$

5.1.5. Graphing the conductances

We can then graph the conductances for different V over some time scale t

Na conductance

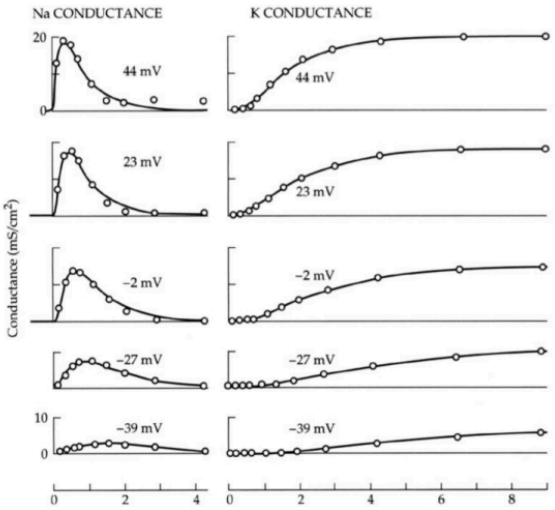
fast activation → inactivation

1. The sodium channels open quickly causing a spike
2. The sodium channels close quickly which leads to the inactivation *ensuring AP propagation*

K conductance

slow activation → no inactivation

1. The potassium channels open slowly which leads to the slow activation
2. The potassium channels stay open to *help with repolarization*



5.1.6. Voltage and time dependence

The reason why the conductances are voltage and time-dependent is because the single channels have the state of either being opened or closed where the ratio between these two states is a function of voltage and time.

5.2. Patch clamp

This is a technique where we record a current I through a single channel. From this experiment, there are two key observations about the types of conductances for channels.

persistent conductance	channels which do not inactivate and thus conduct ions across the membranes persistently, (e.g. K channels)
transient conductance	channels which inactivate and thus only transiently/temporarily conduct ions across the membrane, (e.g. Na channels)

5.2.1. Modelling persistent conductance

To model persistent conductances we can use the expression

$$g_i = \overline{g}_i \times P_i \tag{10}$$

Where

- g_i is the overall conductance of a channel of type i
- $\overline{g}_i$ is the maximal conductance if all the channels were open
- P_i is the probability of the channel to be open (or the fraction of open channels)

The probability P_i can be expressed as the product of the probability of the subunits being open, that is

$$P_i = p(e_1) \times ... \times p(e_n) = p(e_i)^n \tag{11}$$

Where

- $p(e_i)$ is the probability of a subunit gate i being open, so event e_i being true, $p(e_i)$ can also just be expressed as the *gating variable* n

Key observation

Since $p(e_i)$ is a voltage and time-dependent event the conductance itself must then also be a function of both voltage and time.

5.2.2. Time dependence of gating variable n

Intuitively we can think of n just expressing the fraction of open channels, we can express the rate of change of this fraction in open and closed channels as follows

$$\Delta n = \underbrace{\alpha_n(1-n) \times \Delta t}_{\text{closed} \to \text{open in } \Delta t} - \underbrace{\beta_n \times n \times \Delta t}_{\text{open} \to \text{closed in } \Delta t} \tag{12}$$

An alternative but equivalent notation would be to express this as the proper derivative concerning voltage and time

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V) \times n \tag{13}$$

Where
- $\alpha_n(V)$ here is the rate at which gates go from closed $\to$ open
- $\beta_n(V)$ here is the rate at which gates from from open $\to$ closed

Key observations
- $\Delta n > 0$ implies more transitions from closed $\to$ open
- $\Delta n < 0$ implies more transitions from open $\to$ closed

Another useful form of eq (13) is the following

$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n \tag{14}$$

Where
- $\tau_n(v) = (\alpha_n(V) + \beta_n(V))^{-1}$
- $n_\infty = \alpha_n(V) \times \tau_n(V)$

Key observations
- $\tau_n(V)$ intuitively can be thought of by the fact that the rate of fractional change is inversely proportional to the rates of closing + opening
- for a fixed voltage V, n approaches the limiting value $n_\infty(V)$
- $n_\infty \in [0, 1]$, so for $\alpha_n(V) \gg \beta_n(V) \to n_\infty(V) = 1$ and conversly $\alpha_n(V) \ll \beta_n(V) \to n_\infty(V) = 0$

5.2.3. Transient conductances

In the case of transient conductances where the channels *can* inactivate we express P_i as

$$P_i = m^3 \times h \times n \tag{15}$$

Where
- m^3 is the activation variable
- h is the inactivation variable

Key observations
- m is fast, that is, we generally have a fast activation
- h and n are slow, so we have a slower inactivation
- m and h have *opposite* V-dependence

5.3. Hodgkin-Huxley Model

The HH model describes how AP in neurons is initiated and propagated.

The model parameters are *fit to the conductances* $g_{\text{Na}}(V,T)$ and $g_K(V,t)$ from the voltage clamp experiment.

The key parameters and their meanings can be summarized as follows

h	probability that an open channel is not blocked
n, m	probabilities for gates to be open
$\overline{g}$	maximum conductance
$\overline{g}_L$	generic leak

Some key points regarding the model

- The gating variables m and n have a voltage dependence
- There is no inactivation for potassium, only for sodium (transient vs persistent conductance)
- The membrane does not get locked at positive values

5.3.1. Model expression

It's just the single-compartment model but with the single resistive current now being expanded into three ion currents along with their gating variables.

Abstractly we can express this as

$$I_e = \left(\sum_k I_k\right) + I_C \tag{16}$$

In the case of the HH model, we can expand Equation 16 as

$$\begin{aligned} I_e &= (m^3 I_{\text{Na}} + n^4 I_K + I_L) + I_C \\ I_e &= (m^3 g_{\text{Na}}(V - E_{\text{Na}}) + n^4 g_K(V - E_K) + g_L(V - E)) + I_C \end{aligned} \tag{17}$$

Equation 17 can also be written in the following equivalent form if we expand I_C using the relation

$$\begin{aligned} I_C &= \frac{dQ}{dt} = C\frac{dV}{dt} \\ \Rightarrow 0 &= C\frac{du}{dt} + \sum_k I_k - I_e \end{aligned} \tag{18}$$

Something that I think Equation 18 demonstrates quite nicely is that it's just KCL again.

5.3.2. Model predictions

AP threshold

We know that n_{inf}, m_{inf}, and h_{inf} are all > 0 when we are at V_R. This implies that $g_{\text{Na}} > 0$ at V_R.

The main reason why we *don't* have an AP at V_R even though we are conducting ions, that is we are creating a potential difference is because the currents in the opposing direction. In this case, the potassium current and leaky current, are larger than the sodium current.

$$I_L + I_K > I_{\text{Na}} \quad \text{at } V_R \tag{19}$$

To reach the threshold potential V_{th} we need to balance the the magnitude of the currents to trigger the reversal potential leading to the depolarization and the resulting AP.

$$|I_L + I_K| = |I_{\text{Na}}| \tag{20}$$

Refractory period

It requires a larger current injection to generate a new action potential after one has just fired because g_K is still active and g_{Na} is inactive.

AP propagation in unmyelinated axon

In the myelinated part of the axon has small capacitance and large resistance but in the nodes of Ranvier we have AP regeneration, which compared to unmyelinated leads to :
- faster anterograde AP propagation
- smaller current
- faster V_{AP} increase with axon radius

AP propagation in one direction

The reason why the AP generally only propagates from soma to axon terminal is that during hyperpolarization g_{Na} is inactivated which makes it hard for an AP to move in the opposite direction.

Another reason is that because g_{Na} is missing in dendrites AP generally does not propagate there. In a few cells where there is some conductance of Na its generally insufficient to generate an AP but can propagate it to the dendrite to some extent.

orthodromic	propagation of the AP from the soma $\rightarrow$ axon terminal
antidromic	propagation in the opposite direction
collision experiment	generate an orthodromic and antidromic AP and have them collide and annihilate each other
axon backpropagation	the propagation of APs from the soma back to the dendrite in the presence of some g_{Na}

6. Neural Coding

The main goal of neural coding is to elucidate "the representation and transformation of information in the nervous system". This includes 5 main concepts

concept	**definition**
correspondence	a *code* is the correspondence between two domains, e.g. visual signals encoded via a spike train
representation	not all cases of correlation are considered an instance of coding
causality	spike trains encode a visual signal but visual signals do not encode a spike train due to the causal relationship that visual signals are what *cause* spike trains, not the other way around
encoding	how does a stimulus cause a pattern of response, building an approximate mechanistic model of the world
decoding	what do responses tell us about the stimulus, how can we reconstruct the stimulus

There are also some general notes about neural coding

information encoding	information is encoded in the firing rate and spike timings of neurons
spatial/temporal resolution	spatial/temporal resolution of different measurement techniques tell us about the neural code
many neuron recordings	it's hard to record from many neurons simultaneously
slope of spike	does not contain much valuable information
recording responses	by recording responses from the stimuli we can see how the brain encodes it in the form of spike trains for example

6.1. Neuronal Rate Codes

Rate coding refers to information being carried by the firing rate. The argument is that the firing rate captures essentially all relevant information.

rate v	the rate is the average number of spikes n_{sp} over some time T, $v = \frac{n_{\text{sp}}}{T}$
tuning curve	curve with impulses/s on the y-axis and some property of a stimulus on the x-axis usually following a bell curve where the center represents the optimal tuning for the stimulus to generate the max firing rate
problems with rate	easy to understand but potentially misleading as more than one stimulus might be encoded in a specific rate
temporal average	takes time to compute the temporal average rate for a stimulus, and the behavioral response time might be shorter than the integration time

6.2. Neuronal Temporal Codes

Temporal coding can refer to several different ideas of information encoding all relating to time

small time intervals	information is carried/transmitted during small time intervals
quasi-synchronous	information is carried through the firing of neurons within or across an ensemble (group)
precise timing/pattern	information is carried through a precise timing or pattern of spikes

6.3. Sound localization via Interaural Time Difference (IDT)

One method of binaural sound localization the brain uses is the interaural time difference, this means that we compute an angle from which sound is coming from based on the differences in the time it takes for a sound to arrive in one ear vs the other.

6.4. Peri-Stimulus Time Histogram (PSTH)

PSTH are histograms of the times at which neurons fire. They visualize the rate and timing of neuronal spikes discharged by an external event or stimulus.

The spike density ρ is an average over several runs of the experiment and can be expressed as follows.

$$\rho = \frac{1}{\Delta t} \times \frac{1}{K} \times n_K(t; t + \Delta t) \tag{21}$$

Where
- K is the number of trails
- n_K is the total number of spikes observed in the time window Δt

6.5. Orientation Maps

There are some key things to remember regarding orientation maps

nearby neurons	nearby neurons have similar preferred orientations
orientation-selective neurons	there are some neurons selective for specific orientations
orientation columns and pinweels	certain types of organized groups (columnar, pinwheel) of neurons all respond to similar orientations

6.6. Poisson Spike Train

The Poisson spike train is a *mathematical model* to describe and generate spike trains. It can be expressed by the following equation

$$P_T(n) = \frac{rT}{n!}\exp(-rT) \tag{22}$$

Where
- n is a sequence of spikes
- $r = r(t)$ represents the firing rate for a homogeneous Poisson process
- $P_T(n)$ is the probability that any sequence of n spikes will occur in a trial duration of T

homogeneous	constant rate spike train
inhonogeneous	variable rate spike train
approximation	we can create an approximation for the probability of a spike occurring in the short interval of length Δt: $r(t) \times \Delta t$

6.7. Single neuron encoding

A single neuron can encode 4 main things

places	when entering a particular region for example
grids	regularly arranged triangular grids of locations
head-direction	so like compass headings
people	some neurons respond to specific people

6.8. Population rates

Here the rate is the average over a poll of equivalent neurons. We define the activity A as

$$A = \frac{1}{\Delta t}\frac{1}{N}n_{\text{act}(t;t+\Delta t)} \tag{23}$$

A postsynaptic neuron receives a spike input from a population m with activity A_m. The population activity is the fraction of neurons that are active in a short interval $[t, t + \Delta t]$ divided by t.

6.9. Population codes

Population coding refers to when different cells encode different ranges of the stimulus. Some key properties of this are :

meaningless averages	averages over the population are often meaningless
accurate reconstruction	population codes allow accurate reconstruction of the signal
sparse coding	only a few cells are activated
retina	different cells are used to encode different light wavelengths, AKA population coding
encoding behavior	a neuronal population encodes behavior whereas a single neuron encodes a stimulus

6.9.1. Population Vector Code

Population vector coding refers to the population coding of neurons for a specific direction. Where the direction encoded as a vector corresponds with the sum of the preferred directions of the ensemble of neurons.

6.9.2. Measuring population activity in vivo

There are two main ways of measuring the activity of neuron populations in a live brain (in vivo).

calcium imaging	since calcium is needed for vesicle exocytosis for NT release we use calcium indicators to correlate this release with some population acitvity
functional Magnetic Resonance Imaging (**fMRI**)	measures brain activity by detecting changes associated with the blood flow

6.9.3. Multiple stimuli

In the case of multiple stimuli, we can repeatedly sample responses to a variety of stimuli so that we can characterize what feature combinations trigger a spike behavior.

$$P(\text{response} \mid \text{stimulus}) = P(\text{response} \mid s_1, s_2, ..., s_n) \tag{24}$$

To then identify what characteristic triggers a behavior we can use one of two approaches

- no labels - in the case of no labels we can use an unsupervised/clustering approach
- yes labels - in the case of having labels we can use a supervised approach

6.10. Neuronal Event Codes

6.10.1. Time-to-first spike Codes

Transmit information to the destination on the arrival of the first spike. Some properties of this are as follows

high rate	high rate implies a fast firing
competition	ttf can be implemented in the form of a competition between different input cells
rank-order codes	ttf can be extended to rank-order codes
fast and efficient	has evidence in auditory, visual, and somatosensory systems
susceptible to noise	this susceptibility means it requires a reference signal

6.10.2. Bust- and Temporal Codes

Just refers to coding which uses time as a reference somehow. It preserves a high coding precision in extreme noise.

A famous example of neurons that temporally code information are Bush-cricket auditory neurons.

6.10.3. Oscillations and Phase Codes

Here neurons fire at different phases concerning some constant *background* oscillation. The phase is hypothesized to code the relevant information.

6.10.4. Synchronous Codes

Here neurons fire at the same time, so synchronously to encode some type of information.

6.11. Local Field Potential (LFP)

Local field potentials (LFP) are transient electrical signals generated in nerves and other tissues by the summed and synchronous electrical activity of the individual cells (e.g. neurons) in that tissue. The 3 main properties of LFPs are

extracellular	signals are generated by transient imbalances in ion concentrations in the spaces outside the cells, that result from cellular electrical activity
local	signals are recorded by an electrode placed near the generating cells. As a result of the Inverse-square law, such electrodes can only 'see' potentials in spatially limited radius
potentials	signals are generated by the voltage that results from charge separation in the extracellular space
field	extracellular charge separations essentially create a local electric field

6.12. functional Magnetic Resonance Imaging

fMRI is a *non-invasive* technique for monitoring brain function. It's based on BOLD (blood oxygenation level-dependent signal change). It also has a slow temporal resolution.

6.13. Binding Problem

The "binding problem" is about how items that are encoded by different brain circuits can be combined for perception, decision, and action.

Some potential mechanisms proposed for how this works is through the aforementioned *temporal synchrony, hierarchical coding, and population coding.*

6.14. Spike-triggered averaging

Spike-triggered averaging is a tool for characterizing the response properties of a neuron using the spikes emitted in response to a time-varying stimulus.

Sensory neurons typically respond strongly to *rapid changes* in stimulus properties.

6.15. Stimulus Reconstruction

This is the process of reconstructing the stimulus from a given spike train.

mathematical basis	based on probability theory and information theory
whole reconstruction	may not be relevant to reconstructing the correct stimulus
human evolution	may have shaped us to encode particular features better than others, for example, faces

particular response	cells may respond to only particular aspects of a stimulus
multiple responses	cells may respond to multiple aspects of a stimulus
artificial stimulus	may be predictable

7. Synapse

7.1. Introduction

Some basic facts about the synapse to be considered

ACh receptors	these make the synapses receptive to nicotine, muscarine, and acetylcholine which leads to certain substances being very addictive
acetylcholine esterase enzyme	enyzme which clears and removes residual acetylcholine

7.2. Chemical transmission

Chemical transmission between cells involves the rapid release and diffusion of a substance (e.g. NT) to another cell where it binds to a receptor (e.g. ligand-gated) at a localized site resulting in a change in the postsynaptic cell properties (e.g. AP generation)

In the context of the synapse, there are a few key components involved in chemical transmission

synaptic cleft	space between presyn. and postsyn. membrane, 20 to 40nm
vesicles	undergo Ca^{2+} induced exocytosis to release contained NT into cleft
neurotransmitters	the substance which goes from the presyn. cell to the postsyn. cell, > 1000 / vesicle
Ca^{2+} dependence	depolarization in the presyn. axon terminal releases Ca^{2+} which leads to the binding of vesicles on the presyn. membrane $\rightarrow$ exocytosis $\rightarrow$ NT release which implies Ca^{2+} dependence

7.3. Steps of NT transmission

I swear this was already mentioned at least twice before but idk, here we go.

Before anything with have the synthesis where the building blocks of NT's are sent to the terminal for NT's synthesis and vesicle packing.

1. AP is generated and reaches the axon terminal in the presynaptic cell
2. This triggers the voltage-gated Ca^{2+} channels
3. Diffusion and action of Ca^{2+} at the release machinery
4. Exocitosys and diffusion of NT in the cleft, and binding to some receptor either ionotropic or metabotropic.
5. Activation of post-synaptic cell and NT is taken back/inactivated in the synaptic cleft

Model of synaptic transmission

Neurotransmitter is released in discrete packages (quanta).

quantal size	the size of an individual quanta, so how many NTs in the quanta
quantal content	the number of quanta released
quantum	one package of neurotransmitter

quantal amplitude	the response generated by the release of a quantum
number released m	several quanta are generally able to be released, the average number is given by $m = np$ where n is the number available for release and p is the release probability

7.3.1. Synapse properties

There are some key properties for synapses to be aware of

vesicle docking	only vesicles which are already docked with the presyn. membrane will be released after the AP, not all of them
single synapse	a single synapse only produces a small potential, more are needed to reach V_{th}
calcium dependency	release of NT is dependent on calcium
bio-measured sigmoid curves	the current-voltage channels have bio-measured sigmoid curves because they open with a probability
types of synapses	axodendritic, axosomatic, axoaxonic, dendrodendritic

7.3.2. Receptor types

Receptors can be classified into ionotropic and metabotropic.

ionotropic receptors	**metabotropic receptors**
positive binding site	binding site not associated with a channel
no second messanger	G-protien or second messenger involved
short latency action	longer latency
rapid response (10 to 50ms)	pre- and postsynatpic

7.3.3. Synapse types

Synapses can be classified into electrical or chemical

electrical synapse	**chemical synapse**
simple primitive system	highly developed structure
often symmetrical, bidirectional	polarized, structurally and functionally
gap junction (connexins)	pre: active zone, post: postsyn. density
very fast, no synaptic delay	slower, some synaptic delay
Ca^{2+} independent	Ca^{2+} dependent
large synapse	thousands of small synapses
limited functions, usually excitatory	versatile: excitatory and inhibitory
synchronized activity	specific: point-to-point communication

7.3.4. Glutamate receptors

Receptors for the transmitter glutamate enable both synapses but NMDA is voltage-dependent, while AMPA is not.

7.3.5. GABA receptors

receptor	**ion**	**type**	V

GABA-A	Cl^-	ionotropic	−65mV
GABA-B	K^+	metabotropic	−90mV

7.3.6. Neuromodulator

Neuromodulatory is NT's which are not reabsorbed by the presyn. neuron or broken down into metabolites.

location	end up a longer time in the CSF
function	modulate the activity of several other neurons in the brain (e.g. norepinephrine, dopamine, serotonin)

7.4. Electrical transmission

Electrical synapses are built for speed. Electrical coupling is a way to synchronize neurons with one another. In electrical synapses, the postsynaptic neuron starts to change its membrane potential almost instantaneously with the presynaptic neuron.

A basic example of electrical synapses is the synapse from the Rod photoreceptor through to the ganglion cell.

8. Synapse model

We can model the synapse by simply including the synaptic current I_S in Equation 5

$$\begin{aligned} \tau_m \frac{dV}{dt} &= E_L - V - I_S + RI_e \\ \tau_m \frac{dV}{dt} &= E_L - V - r_m g_s (V - E_S) + RI_e \end{aligned} \tag{25}$$

Where

- r_m is the specific membrane resistance term left over from the simplification of Equation 5
- E_L is just the membrane reversal potential, so $E_L = V_R$, just notation difference
- g_s is the synaptic conductance which can be expanded to $\overline{g}_s P_s$
  - $\overline{g}_s$ is the total synaptic conductance
  - P_s is the open channel probability

Key observations | E_s and E_{th}

$E_s > E_{\text{th}}$	Excitatory signal
$E_s < E_{\text{th}}$	Inhibitory signal
$E_s \approx E_{\text{th}}$	Shunting / mutual inhibition

8.1. Multiple synaptic input

To generalize Equation 25 we can simply sum the different synaptic conductances for multiple inputs

$$\tau_m \frac{dV}{dt} = E_L - V - r_m \underbrace{\sum_{i=0}^{n} \left[g_{s,i} (V - E_{s,i}) \right]}_{\text{sum of synaptic inputs in parallel}} + RI_e \tag{26}$$

There are two main things to consider

$g_s(t) \approx g_s$	synaptic inputs generally vary slowly, that is, little time dependence
$V \ll E_s$	the membrane potential V is generally lower than the reversal potential

8.2. Alpha function

For simplicity's sake, synaptic input is usually modeled by an "alpha function" in the form.

$$g_s(t) = g_{\text{peak}} \times t \exp\left(\frac{-t}{t_{\text{peak}}}\right) \tag{27}$$

9. Neuroplasticity and Learning

Neuroplasticity is the ability of the neural networks in the brain to change through growth and reorganization its a key component in learning.

9.1. Learning and Memory

learning	acquisition/storage of new information or knowledge (or formation of memory through experience)
memory	stored information that can be recalled at a later stage
learning $\leftrightarrow$ memory	learning results in memory and change in future behavior
unconcious learning	learning does not inherently imply a conscious attempt to learn, e.g. learning through passive observation
placticity and learning	placticity is the biological implementation of learning, it allows for the formation of memories
genetics	only fix a few parameters in the brain

9.2. Memory types and timeframes

9.2.1. memory types

Memory can be broken down into declarative/explicit and non-declarative/implicit memories which can be further broken down into subtypes.

memory type	**memory $\rightarrow$ location**
declarative/explicit	• medial temporal lobe $\rightarrow$ facts and events
non-declarative/ implicit	• neocortex $\rightarrow$ priming • procedural memory (skills, habits) $\rightarrow$ striatum • associative emotional responses $\rightarrow$ amygdala • associative skeletal musculature $\rightarrow$ cerebellum • nonassociative (habituation, sensitization) $\rightarrow$ reflex pathways

9.2.2. memory timeframes

In the context of time memories can be broken down into short-term memory (**STM**) long-term memory (**LTM**) and long-lasting memory (**LLM**)

memory length type	**time-scale**
short-term memory	seconds to hours
long-term memory	hours to months

long-lasting memory	months to lifetime

9.3. Memory and the synapse

information representation	information is represented by the distributed activity of neurons
learning and memory	learning and memory is based on the changes in the synaptic connections
efficacies/placticity	neuron efficacies and plasticity can change

9.4. Plasticity

Plasticity can occur on different levels, namely: brain area, cellular level, and synapse level.

9.4.1. Networks and system plasticity

The hippocampus can be used as a *model system* to study learning and memory. An instance of this is with the patient **HM**.

Context: The amygdala, hippocampal gyrus, and anterior two-thirds of the hippocampus were removed.

unaffected	**affected**
• STM and LTM for events before the surgery	• could no longer transfer memory from STM → LTM • could no longer consolidate new declarative memories

Conclusion The hippocampus is *not* a permanent area of storage it's involved in *consolidation but not retrieval.*

9.4.2. Cellular plasticity

Some general notes on cellular plasticity in regards to its location, functioning, and how it's measured.

location	occurs in the local brain circuitry
weights of NN	at cellular level plasticity is akin to the training weights of a neural network
perceptron	• also known as McCulloch and Pitts neuron • implements a *linear decision boundary* • defined by weights and a bias term • can implement ***linearly separable*** *logical operations* • can be trained on a labeled dataset
hippocampus and spatial memory	• The hippocampus has cells related to spatial memory • e.g. place cells, grid cells, etc.
Morris water maze	• the mouse is trained to look for platforms in water • after training → mouse can find platform • experiment: block NMDA receptor in the hippocampus • outcome: The mouse does not recognize the right place to look for the platform

measuring neuronal plasticity in hippocampus	• commonly studies synapse: CA3 → CA1 • experiment: stimulate neurons at CA3 and record effects at CA1

9.5. Synapse plasticity

Plasticity in the synapse has 3 main effects in regards to how the synapse changes

size	the physical size of the synapse changes
AMPA/NMDA	the ratio of AMPA/NMDA changes
spines	the number of dendritic spines change

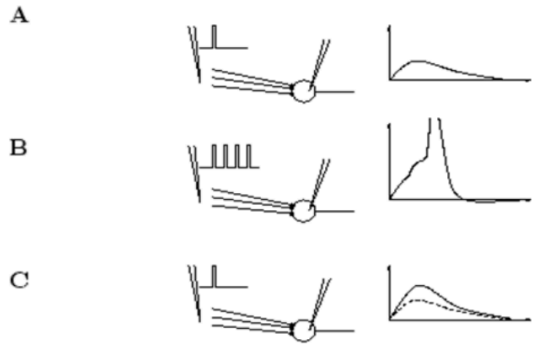
Some additional notes

- There is also *nonsynaptic plasticity* such as dendrite strength, the excitability of neurons, isolation of axons
- Hebbian theory is a neuropsychological theory claiming that an increase in synaptic efficacy arises from a presynaptic cell's repeated and persistent stimulation of a postsynaptic cell. Hebb's postulate states this as follows :

> … When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.
>
> — Hebb

9.5.1. Testing synaptic plasticity

We can observe synaptic plasticity through the modification of postsynaptic potentials (**PSPs**) evoked by presynaptic spikes.

explanations	**diagram**
• A: Postsynaptic response triggered by a weak test pulse • B: Strong stimulation triggers postsynaptic firing • C: A later test pulse evokes a larger postsynaptic response	

9.5.2. Parameters that define synapse strength

Synapse strength is the average amount of current or voltage excursion produced in the postsynaptic neuron by an action potential in the presynaptic neuron. The higher the average the stronger the synapse. The parameters that define this are.

parameter	**note**
Neurotransmitter and receptor type	""

Position of the synapse	e.g. dendrite or soma
Availability of vesicles	more vesicles means more NT to release
Neuromodulators	e.g. dopamine
Postsynaptic cellular processes	e.g. more or fewer receptors on the posts cell
Pre/postsynaptic firing	“”

9.5.3. Models of synaptic plasticity

model type	**description**
Phenomenological models	show input-output relationships between activity and plasticity
Biophyical models	tell us what processes are involved in synaptic plasticity

9.5.4. NMDA synapse

NMDA is often described to act as a *coincidence detector*.

Example: An arbitrary NMDA receptor only becomes activated if some neuron A and another B both become activated (fire).

Two main aspects influence plasticity

AP backpropagation	AP backpropagation is necessary for the release of Brain-Derived Neurotrophic Factor (BDNF). BDNF is an essential component for inducing synaptic plasticity and development.
depolarization from other synapse	Depolarization can influence the likelihood of an AP occurring and by extension can affect synaptic plasticity, as we saw when testing the plasticity for example.

In the context of NMDA calcium is of particular importance to plasticity. Specifically calcium influx which is modulated by *activated NMDA receptors*.

The key aspects of Calcium that affect Long Term Potentiation (LTP) and Long Term Depression (LTD)

low-frequency firing (5Hz)	produces LTD
high frequency firing (50 $\rightarrow$ 100Hz)	produces LTP

strong NMDA receptors	activation gives potentiation
weak NMDA receptors	activation gives depression

9.5.5. Potentiation

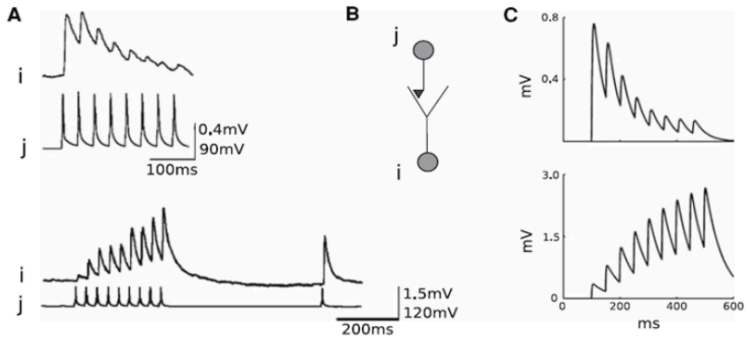
There are a few main contributors to potentiation (synapse strengthening),

AMPA Phosphorylation	phosphorylation of AMPA receptors makes the synapse stronger, in other words, it contributes to potentiation
AMPA Synthesis	a cell may increase the production of AMPA receptors, in response to some synaptic activity, this in turn leads to further potentiation

AMAP Transport (to the membrane)	the trafficking of AMPA receptors to the membrane increases the number of receptors available for binding which enhances the synaptic strength
Release probability/ quantity	an improvement in the release quantity or probability of NTs for example can lead to a greater synaptic strength

9.5.6. Short-term plasticity (STM)

Short-term plasticity as the name implies is a short period of higher synaptic plasticity followed by a decrease in activity after this short time window.

description	**diagram**
A neuron j fires several times, in response a neuron i's spike is increased (synaptic plasticity). But, due to the loss of vesicles and by implication the loss of NT's we have a decrease in the spike size after a short amount of time.	

9.5.7. Long-term potentiation (LTP)

Long-term potentiation is the strengthening of the synapse for varying (longer) periods following tetanic (high-frequency sequence) stimulation. Some key properties to be aware of

duration and protein synthesis	• LTP for 30min $\rightarrow$ few hours does *not* require protien synthesis • LTP > few hours *does* require protien synthesis
hippocampus involvement	the hippocampus plays a crucial role in transferring information from short-term to long-term memory, and LTP is the assumed mechanism that enables this
stimulation requirement	• high-frequence sequence (tetanic) stimulation required for LTP • both pre-and postsynaptic depolarization at the same time is necessary
voltage clamp and LTP	the use of a voltage clamp during tetanus prevents the occurrence of LTP
cooperative nature	LTP is cooperative, many weak synapse stimulations can also have some effect
depolarization threshold	LTP requires simultaneous depolarization beyond a certain threshold
input specificity	LTP is input-specific and enhances the synaptic effectiveness of a particular synapse without affecting othes in the same cell, increasing individual neuron storage capacity
associativity	LTP is associative, weak stimulation in one pathway coupled with strong stimulation in another can induce LTP
LTP phases	1. transient early phase (1 - 3h): no protein synthesis 2. consolidated later phase ($\geq$ 24h): necessitates protein and RNA synthesis for new presyn. active zones and postsyn. receptors.

9.5.8. Long-term depression (LTD)

Long-term depression (LTD) is an activity-dependent reduction in the efficacy of neuronal synapses lasting hours or longer following a long patterned stimulus.

The most common neurotransmitter involved in LTD is L-glutamate acts on NMDA receptors thus necessitating them for LTD.

9.5.9. Spike-timing-dependent plasticity (STDP)

Spike-timing-dependent plasticity considers not only the correlation between spikes but also the actual timing of spikes.

role of NMDA and backpropagating APs

- timing-dependence of plasticity in STDP is facilitated by NMDA receptors and backpropagating APs
- NMDA play role in integrating temporal aspects of synaptic activity

sign of plasticity

- the sign of plasticity is determined by the local calcium concentration of the synaptic environment

backpropagation of postsynaptic spikes

- postsynaptic spikes travel back to the dendritic tree, activating voltage-dependent calcium channels
- backpropagation essential for the integration of temporal information in plasticity

presynaptic activity and NMDA channels

- presynaptic activity can lead to calcium influx through NMDA channels, particularly when postsyn. part is adequately depolarized

supralinear enhancement with pre- and post-spikes

- if a presyn. spike is closely followed by a postsyn. spike, the activity of NMDA receptors is supralinearly enhanced
- enhancement is usually a result of depolarization due to backpropagating postsyn. spike

9.5.9.1. Functional consequences of STDP

key consequences	rate normalization, temporal coding, reduced latency, prediction and conditioning
directional strength	only one direction can get stronger, no positive feedback can occur
temporal pattern	STDP can become a simple temporal pattern detector and fire on the beginning of such a pattern
stimulation frequency	has an effect on STDP
dopamine effects	can extend LTP timing window or even convert LTD to LTP, floats around the cells
AP5	LTP is blocked by AP5, behavioral success and LTP are correlated

9.5.10. Factors that influence plasticity

brain area plasticity	different plasticities in different brain areas
neuron/synapse diversity	diversity of neurons and synapse types
control parameters	there are a large number of control parameters for plasticity experiments
other influences	neuromodulators, calcium, drugs, proteins etc.
long/short term	there are long term and short term effects

model limitations	its unlikely that a single model explains all plasticity effects found in biology

9.6. Hebbian Learning

When an axon of cell A repeatedly/persistently takes part in firing cell B, then A's efficiency as one of the cells firing B is increase.

A quote to summarize Hebbian learning is "neurons that fire together, wire together", i.e. Spike Time Dependent Plasticity.

Some aspects of Hebbian learning are as follows :

learning	based on correlations between presynaptic and postsynaptic firing
synapse variables	uses only variables locally available at the synapse
rate-based model	its expressed in a rate-based model $\Delta w_{ij} \propto v_i \times v_j$
potentiation model	only weight increases are modeled for the potentiation
positive feedback loops	there is some instability due to positive feedback loops
other rules	additional rules can be added for weight reduction (depression) and normalization (Oja, BCM)

Hebb's postulate implies some constraints for synaptic learning

1. The direction of information flow is forward
2. Global effects arise from local learning
3. Variables are: APs, synaptic weights (efficacy), and neuromodulators/calcium concentration (locally)

9.7. Pavlovian Conditioning

Pavlovian conditioning refers to the behavioral and physiological changes brought about by experiencing a predictive relationship between a neutral stimulus and a consequent biologically significant event.

10. Neuromorphic VLSI

10.1. Very Large Scale Integration (VLSI)

VLSI is a process of designing integrated circuits (ICs) and memory on a very small scale by integrating a very large number of transistors.

characteristics	VLSI circuits are typically digital, high-powdered, not fault-tolerant and synchronous (clocked), and not massively parallel
limitation	the failure of a single transistor can lead to the failure of the entire computer system
paradigm shift	there was a paradigm shift in computing when researchers looked at the brain for inspiration, e.g. bees' brains are smaller, consume less power, and offer real-time interaction with the environment

10.2. Neuromorphic

Neuromorphic is fundamentally used to describe VSLI systems containing electronic analog/digital circuits that exploit the physics of silicon to reproduce the bio-physics of neural circuits present in the nervous system.

The two main goals of neuromorphic research are :

We want to *understand* the biological neural systems using standard CMOS VLSI technologies as a tool.

We want to *use* the known properties of biological systems to design devices for engineering applications.

Neuromorphic research can be split into *neuromorphic computing* and *neuromorphic engineering*.

neromorphic computing	**neuromorphic engineering**
neuromorphic computing uses dedicated VLSI hardware and high-performance computing, it is *application-driven* and uses conservative approaches	neuromorphic engineering is *research-driven* , and deeply rooted in biology, it aims to emulate neural function in a subthreshold analog and asynchronously digital

10.3. Neuron circuits

Some of the key goals of neuronal circuits are

reproduce neural computation physics	we want to use subthreshold analog circuits and asynchronously digital circuits to replicate the physics of neural computation
autonomouse learning/ behaving systems	we want to create autonomous learning systems capable of real-time interaction with the environment
optimal exploitation of VLSI technologies	the design of neural circuits is suited to harness both the capability of current VLSI but also future VLSI technologies
adaptability to emerging tech	the design of neural circuits is suited for nano and other emerging technologies

Some potential applications of neuron circuits are

application	**description**
tool for real-time and accelerated-time modeling	neuron circuits can serve as a tool for both real-time and accelerated-time modeling of neuron systems, which can further help with understanding
compact low-power processing device	neuron circuits can create low-power sensory processing devices, aligning with the general demand for energy-efficient solutions to this problem
interface with living systems	neuron circuits can interface with living systems, suggesting potential applications in biocompatible technologies and neural interfaces

10.4. Circuits

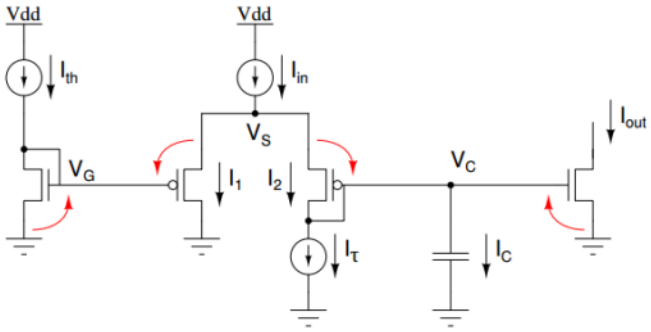
Transistors act as a type of switch, they can be broken down into analog and digital.

digital	operate only in minimum or maximum type fashion, no intermediate values
analog	also use intermediate results in their computations

In Complementary Metal-Oxide Semiconductors (CMOS) there are two types MOS Field-effect transistors (MOSFETs)

n-FET	**p-FET**
have a common bulk potential V_b connected to ground (GND)	have a common bulk potential connected to power supply rail V_{dd}

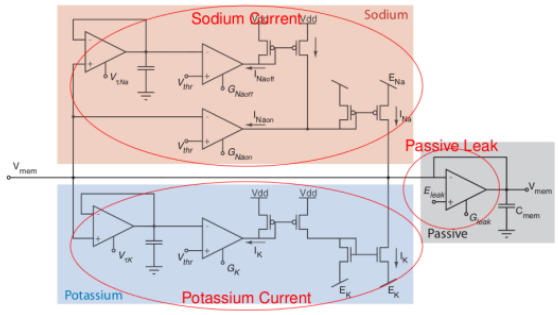
10.4.1. Differential-pair circuit

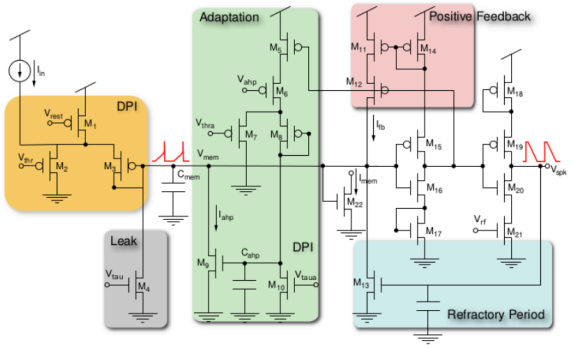


10.5. Remarkable circuits

The first of these circuits was the McCulloch and Pits artificial neuron, so the circuit represents the perceptron.

After this emerged two main classes of neuron models: conductance-based, integrated and fire models (I&F).

neuron model type	**diagram**
Conductance based models • Exemplified by Mahowald and Douglas silicon neuron • Mimics real cortical neurons with conductance properties	 (a) Conductance-based silicon neuron

Integrate and Fire models	 (a) Ultra low-power generalized I&F circuit

10.6. Spikes and Address Event Representation (AER)

Address Event Representation (AER) represents when a spike (action potential) arrives. At the time of a spike, the address where the spike occurred is broadcast.

10.7. Neuromorphic chips

10.7.1. DYNAP and ROLLS

There are two prominent neuromorphic chips this being the *DYNamic Neuromorphic Asynchronous Processor* (DYNAP) and *Reconfigurable On-Line Learning Spiking chip* (ROLLS)

chip	features
DYNAP	• analog and digital co-design • distributed SRAM and TCAM memory cells • on-chip inference and learning
ROLLS	• short-term plasticity (STM) • long-term plasticity (LTM) • homeostatic plasticity • configurable recurrent connectivity • and more...

10.7.2. Neuromorphic Cognitive Systems

Some systems in which the above chips are used in are

- Working memory and decision-making in autonomous real-time systems
- Context-dependent embedded systems and emerging technologies
- Brain-machine interface and prosthetics

11. Introduction to Perceptron Learning Algorithm

We are limited in understanding the brain because we most likely do not have the right abstraction to understand its higher-level processing fully. We can study neurons but this gives little insight into the overall functioning of the brain.

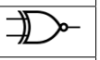
The McCulloch and Pitts neuron model also known as the linear threshold unit/gate or just perceptron models a single neuron with multiple inputs but only one output. As a network, it might give some insights into the modeling of higher-level brain functions.

11.1. Perceptron vs Biological Neuron

similarities	differences
• both can be active or inactive • the input and output is directed • activation is dependent on the weighted function of other neurons	• real neurons exist in continuous time, and perceptron exists in discrete time • real neurons have degrees of activation, not just on/off • activation as a function of inputs typically not linear or threshold linear

11.2. Basic Digital Logic

Gates are processing units. They are functions that evaluate inputs. The following is a table to show all the inputs for the gates and their corresponding outputs.

Input		Output						
A	B	AND	OR	NOT	XOR	NAND	NOR	XNOR
								
0	0	0	0	1	0	1	1	1
0	1	0	1	1	1	1	0	0
1	0	0	1	0	1	1	0	0
1	1	1	1	0	0	0	0	1

11.3. Linear Threshold (LT) unit/gates (perceptron)

A perceptron is a neuron model with a few main components

inputs	$\{i_1, i_2, ..., i_n\}$
weights	$\{w_1, w_2, ..., w_n\}$
summation term	$\sum_{k=1}^{n}(i_k \times w_k)$
threshold function	$f(x)$
output	$o \in \{0, 1\}$ where 0 is inactive and 1 is active

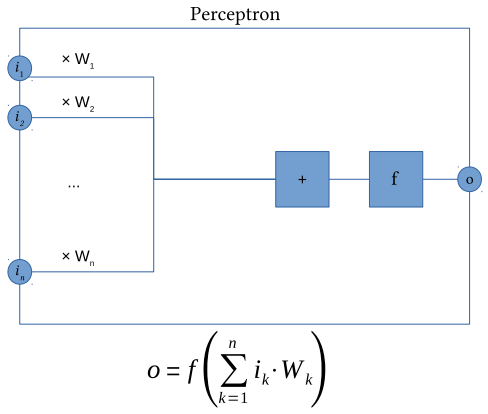


Figure 1: Perceptrong neuron model

If the input of all the neurons crosses a combined threshold θ then the neuron becomes active. Formally we can express this "active state" as in the threshold form

$$\sum_k (i_k \times w_k) \geq \theta \tag{28}$$

We can also use a bias term $i_0 = -\theta$ to rewrite Equation 28 as

$$i_0 + \sum_k (i_k \times w_k) \geq 0 \tag{29}$$

This model can implement the logic of AND/OR/NOT-gates

11.3.1. threshold function

We can create a simplified version of the above-described model using vector notation, first, we represent the threshold function $f(x) = \theta(x)$ as

$$\theta(x) := \begin{cases} 0 \text{ if } x < 0 \\ 1 \text{ if } x \geq 0 \end{cases} \tag{30}$$

The inputs we rewrite in vector form as such $\vec{i} = (i_1, i_2, ..., i_n)$ same for the weights $\vec{w} = (w_1, w_2, ..., w_n)$ which then allows us to rewrite the threshold function $f(x)$ as such

$$f(\vec{x}) = \theta\Big(\vec{w} \times \vec{i} + w_0\Big) \tag{31}$$

11.3.2. XOR impossibility with perceptrons

Following the truth table for XOR to compute it we must have that

- $w_0 < 0$
- $i_2 \times w_2 + w_0 \geq 0$
- $i_1 \times w_1 + w_0 \geq 0$
- $i_1 \times w_1 + i_2 \times w_2 + w_0 < 0$

This causes a contradiction when you add up the constraints because

$$x_1 w_1 + x_2 w_2 + 2w_0 < 0 \land x_1 w_1 + x_2 w_2 + 2w_0 \geq 0 \tag{32}$$

The reason for this is that XOR is *not* a linear combination of inputs, formally XOR is said to be not linearly separable.

XOR can still be modeled with multiple perceptrons the same way it can be represented with multiple gates.

11.4. Perceptron Learning Algorithm (PLA)

The perceptron algorithm is an algorithm in which we optimize the weights through iterative steps to converge on some approximation of a solution for the perceptrons.

11.4.1. Supervised error-correcting rules

Here we

1. start with an intial guess of the weights
2. we then compare the output in response to a particular input with the desired output
3. we change the weights such that we get closer to the desired output

11.4.2. Convergence

If a solution to a problem is linearly separable in the case of a single perceptron then PLA must converge, i.e. it will update the weights a finite number of times.

11.4.3. Algorithm steps

This is essentially just a longer version of what was described for the supervised error-correction rules

1. Choose random intial weights
2. Calculate outputs for a given input
3. If the output is not the expected value then calculate the error term e as $d - c$ where d is the desired output and c is the current output
4. Change the weights of the inputs and bias by $\Delta w_i = e \times \alpha \times i_i$ for the bias you can just use $w_0 = 1$

11.5. Converting real weights to integers

Because it generally is easier to work with integers than floats it makes sense to convert these, this can be done through an algorithm.

Here we ensure that the approximation doesn't lead to the issue of having a 0 sum
1. find the largest possible negative sum (close to 0)
2. increase the bias such that no sum is zero

Here we actually transform the weights to be integers
3. replace the weights with rational approximations more
4. scale up the weights to be integers (multiply by some constant)

12. Hopfield Network

Hopfield networks are a type of network that implements associative memory.

Memory works with pattern recognition, also known as *Content Addressable Memory* or *Associative Memory* .

The main parts of the Hopfield network are as follows

node state	a node can be either *active*, *inactive*, *bias*
bais node	a bias node is always active
neuron state x_i	each neuron has a state value x_i generally $\in \{1, 0\} \Leftrightarrow \{\text{active}, \text{inactive}\}$
edge weight w_i	each undirected edge has a weight w_i
inactive nodes with zero threshold	do not send inhibitory signals, and thus don't take part in the activation of other neurons

Hopfield networks give insights into how memory works by having
- highly interconnected network as opposed to just connected in one direction
- computes with no input-output but with *states*

Hopfield networks are dynamic and they move from one state to another untill they arrive at some stable state (also known as an *attractor*).

12.1. Updates and State Dynamics

The idea of the update algorithm is that we consider the sum of weights between active units Q and always increase Q.

- That is that we turn a node n active if $Q = \sum x_i w_i \geq \theta$.
- We do this for all nodes except the bias node.

This algorithm can be seen as a greedy algorithm to find the `MAX-CLIQUE`.

A key property of transitions

- active $\rightarrow$ inactive $\Rightarrow Q = Q_{\text{new}} \geq Q$ AKA Q stays the same or increases
- inactive $\rightarrow$ active $\Rightarrow Q = Q$ AKA Q stays the same

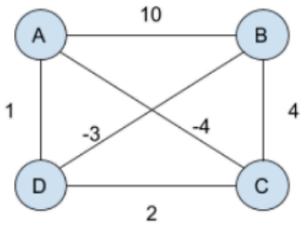
12.1.1. Asynchronous dynamics

In the asynchronous case we update one unit at a time, the two key things this implies

- the network *will* always converge to a stable state
- the network *will not* always converge to the same stable state, it depends on the update order

12.1.2. Example - asynchronous dynamics

First we can show the full picture of the network along with the state of each node over time



state	A	B	C	D
	1	0	0	1
time	1	1	0	1
updating C	1	1	1	1

Figure 2: (left) the hopfield network in the final state with all nodes active, (right) the state table for all the nodes at different time points

Lets consider the specific case of updating B so when we went from $x_B = 0 \rightarrow x_B = 1$.

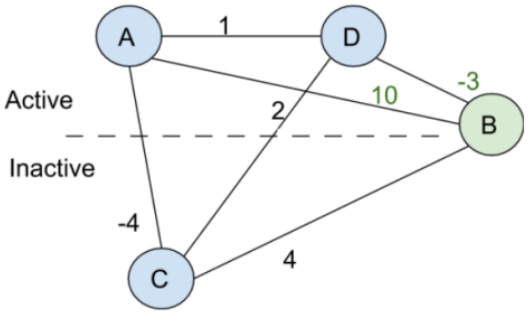


Figure 3: Evaluation of node B

Assuming $\theta = 0$ as our threshold we can compute Q as

$$Q = \sum_i x_i w_i = (10 - 3) = 7 \Rightarrow Q \geq 0 \Rightarrow Q \geq \theta \tag{33}$$

By Equation 33 we can clearly see B passes θ thus it can be brought into the active part.

12.1.3. Example - synchronous dynamics

In the synchronous case we update all nodes at the same time. The result of this is that it results in a deterministic system as it doesn't depend on the update order anymore. We can start by considering the basic network

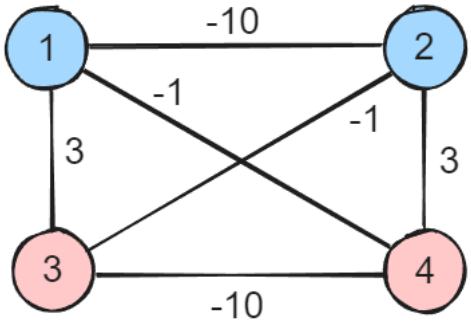
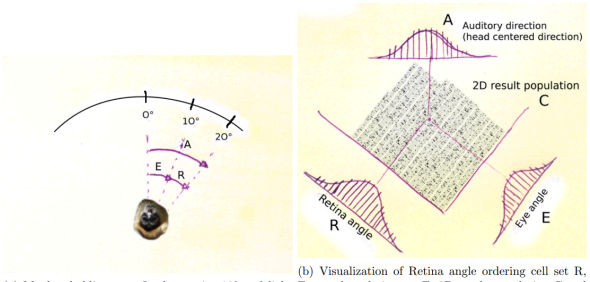


Figure 4: nodes 1 and 2 are active, next step nodes 3 and 4 will be active; network does not have a unique stable state, converges to cycle between two states

A trick for synchronous dynamics is to duplicate the units into two columns and only use non-zero weights between them



(a) Monkey holding gaze fixed on point 10° and light falling in from 20°

(b) Visualization of Retina angle ordering cell set R, Eye angle ordering set E, 2D result population C and auditory direction set A.

Figure 5: 1 and 2 active $\rightarrow$ 3, 4 active in col. 2 ; first column represents $t = 0$ second $t = 1$; with synchronous updates a hopfiled network converges to a cycle of length 2 or to a stable state

12.1.4. Summary

node updating	nodes can be updated synchronously or asynchronously
state	the set of units that are active, can be seen as the activity vector
dynamics	units updating their activity level
weights	when a node is updated weights are considered from all other active nodes, like with a perceptron
asynchronous updates	converge to a stable state, but which converged state can depend on update order
asynchronous states	`MAX-CLIQUE` if activity is $\in \{0, 1\}$ or `MIN-CUT` if activity $\in \{-1, 1\}$
synchronous updates	parallel updates either go to stable state or can get stuck in pair of patterns (flipping or cycle)

13. Feed-Forward Networks (FFN)

Feed-forward networks have a few basic properties to be aware of

layers	FFN generally have an input layer, some number of hidden layers and an output layer
information flow	information flows forward from the input $\rightarrow$ hidden $\rightarrow$ output layers
acyclic	a FFN is acyclic, that is, it contains no cycles
inptuts	the input from one layer is connected to all the inputs in the next layer

13.1. overview FFNs

One of the main reasons FFNs are so widely used is because they are good function approximators.

13.1.1. training

Evaluation in an FFN is straightforward the outputs are continuous functions of the inputs.

In the case of wrong outputs, we employ *training*.

training	the adjustments of the weights in response to some output for a given input
training data	input/output pairs (x_i, d_i) where x_i is the input and d_i is the desired value
error	the error E can be defined as, $E = \sum_k \left(f(x_k) - d_k\right)^2$ where $f(x)_k$ is the output of the network
reducing error	to reduce the error we can use gradient descent

13.1.2. differences to HN

Some differences to Hopfield networks

- we don't need continuous updates
- we don't reevaluate units

⇒ FFNS have the idea of a pipeline which is distinct from the brain

13.1.3. FFN Training algorithm

1. Give the network some input
2. Calculate all the values in the network to produce an output
3. Compare the output with the desired output. This gives us the error E.
4. Update the weights. For example, use gradient descent to optimize the parameters and minimize the error term.

13.2. Backpropagation and Error Function

Backpropagation is the process of calculating the derivatives, using the chain rule, from the last layer to the first layer. The process is akin to walking through the network backward.

13.3. Boltzmann Machines

Unit which uses a Boltzmann distribution in the sampling function. Units are similar to Hopfield Networks, however, they have a probability of being active.

13.3.1. Updating process

We set the value to zero or one probabilistically following a sampling function.

⇒ Boltzmann machines do not converge, they do not reach a stable state.

It can be seen as a system for sampling or random walking in the state space.

14. Interacting Neural Populations

To understand the brain, we need to understand its structure and functionality (processes). Different areas in the brain are highly connected.

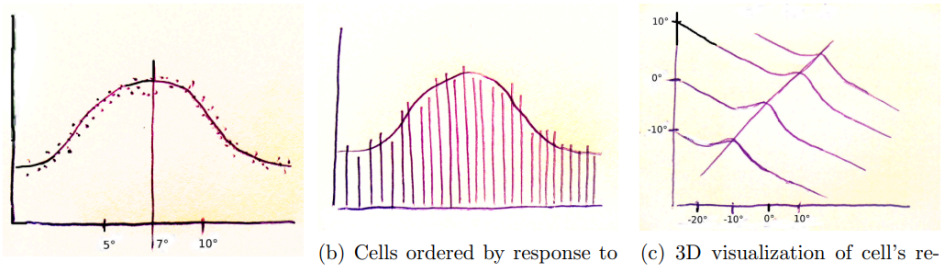
The brain similar to an FFN seems to be able to create general solutions for complex problems. Neurons can be broken down into their individual and collective functionality.

individual	collective
• neurons are tuned to a set of values for the parameters they care about • e.g. neuron can be tuned to a moving bar at a certain angle in its perceptive field, also velocity, position, bar width, etc.	• together neurons respond to **combinations** of properties, features, aspects of the situation, etc.

14.1. Population code

population coding	information being encoded by a group of neurons
neuron group	all the neurons in a particular area
encoding	the values are encoded by the pattern of activity

14.1.1. Example - simple population code



(a) Tuning curve of one cell

(b) Cells ordered by response to 20°

(c) 3D visualization of cell's response to different degrees

Figure 6 (a)
- x-axis: Parameter we are tuning for
- y-axis: Neuron activity/response, so typically the firing rate/response

Figure 6 (b) Here we are applying the tuning process to many neurons and sorting them in regards to the parameter we are looking for. In the case of example 20°

Figure 6 (c) Just a 3D visualization of Figure 6 (b)

14.2. Summary
- Neurons can represent information through population codes.
- Neurons are tuned to preferred stimuli
- Information is represented by the pattern of activity in the neural population
- Each neuron has a preferred input, e.g. orientation, that it responds to; neuron is tuned to that value
- Not every neuron shows a clear tuning curve
- Neurons usually do not only respond to their preferred stimulus but also with decaying strength to close ones
- Population coding has an easy to read out value
- Population coding is robust to noise
- Population coding requires a lot of units