

Introduction to Neuroinformatics

Summary of the lectures 2014

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1 Neuroinformatics

1.1 Introduction

- Human brain on average: 1.5kg weight, 1.2l volume.
- The brain mainly is there to receive stimuli from the environment, encode it, do sensory integration and finally decode to make movements, actions and decisions.

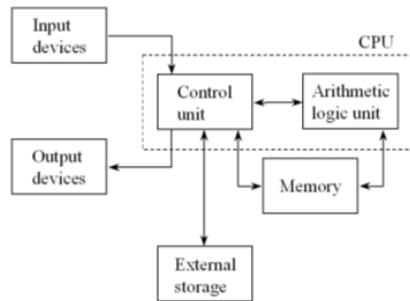


Figure 1: Turing Machine / CPU

Differences between a brain and a computer:

- Massive parallelism
- Constantly adapting
- Chemical signaling
- Unreliable units
- Analog computation
- Robust to damage
- Very energy efficient

Similarities between a brain and a computer:

- Process information
- Logical operations
- Memory
- Use electrical (digital) signaling
- Can learn from inputs
- Consume energy

Other facts

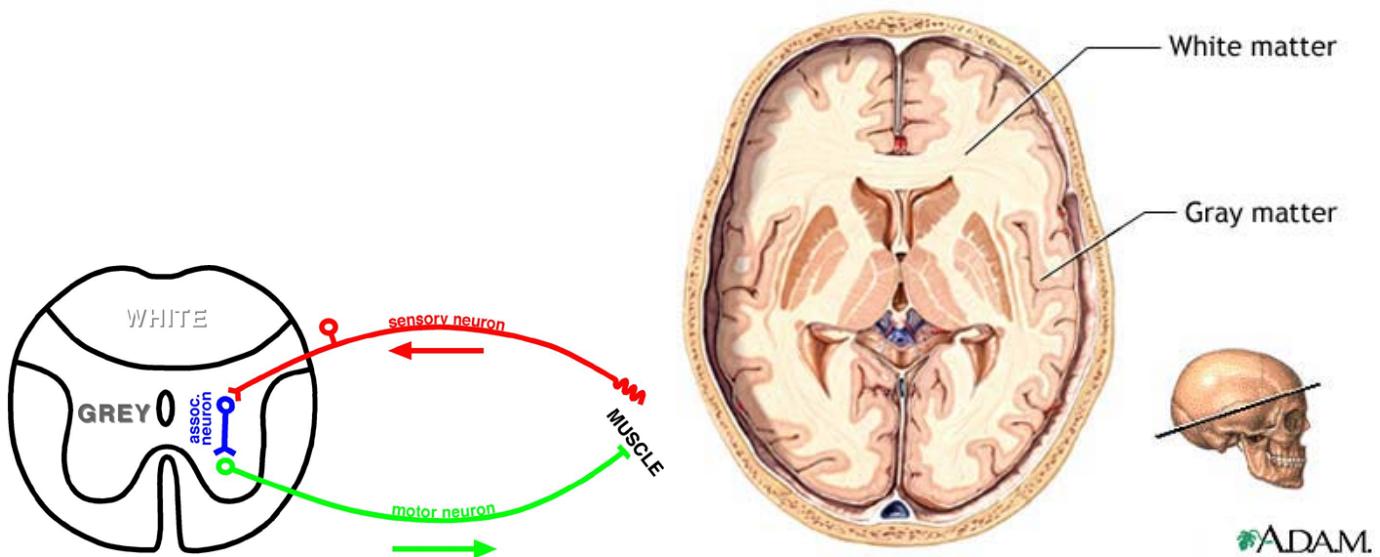
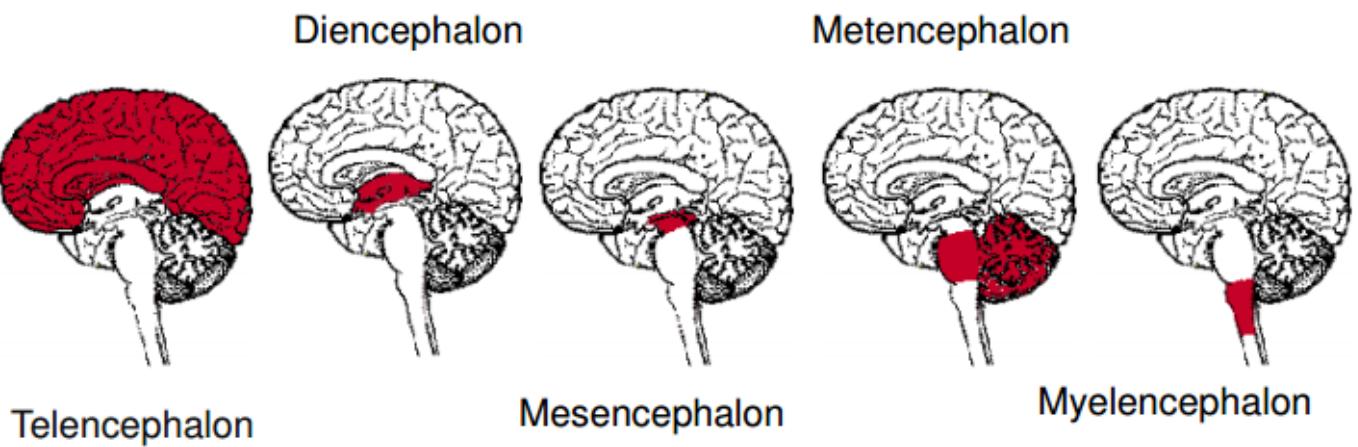
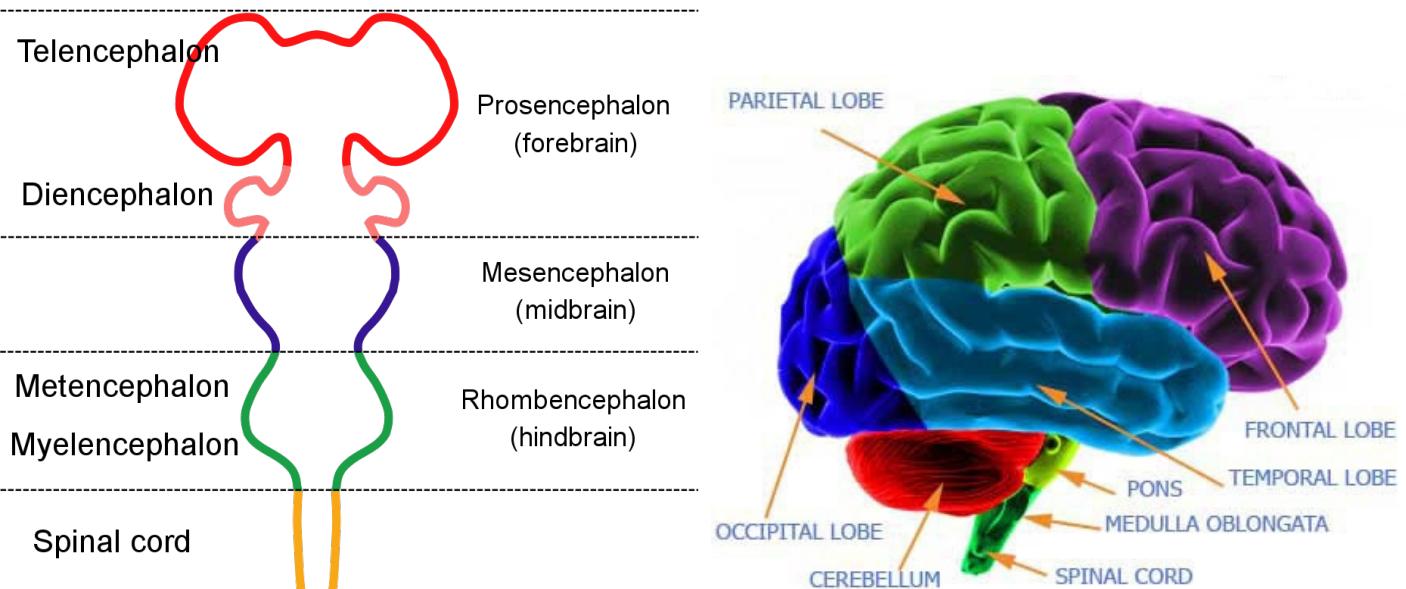
- An 83000-Processor supercomputer can only match 1% of the human brain.
- C. Elegans (worm) has 302 nerve cells, a frog 16M, a cat 1B and a human 85B.
- Human brain project aims to simulate the entire human brain on computers.
- More efficient simulations of brain behavior by Neurogrid or IBM TrueNorth.
- Number of neurons in human brain: $\sim 10^{11}$, synapses: $\sim 10^{15}$.

2 Nervous System Organization

2.1 Anatomy

- Central nervous system (CNS): Brain and spinal cord.
- Peripheral nervous system (PNS): Somatic, autonomic (sympathetic and parasympathetic) NS.
- Brain cuts: Horizontal plane cut, coronal/frontal cut and sagittal cut (between eyes). Cross-section through spinal cord, for example.
- The skull protects, meninges envelope the CNS and has 3 layers, the dura mater, arachnoid mater and pia mater. Primary function is protection.
- The cortex is the layer directly under the surface of the brain.

- There are 4 lobes in each hemisphere. Lobes are separated by fissures in the cortex.



2.2 Building elements of the brain

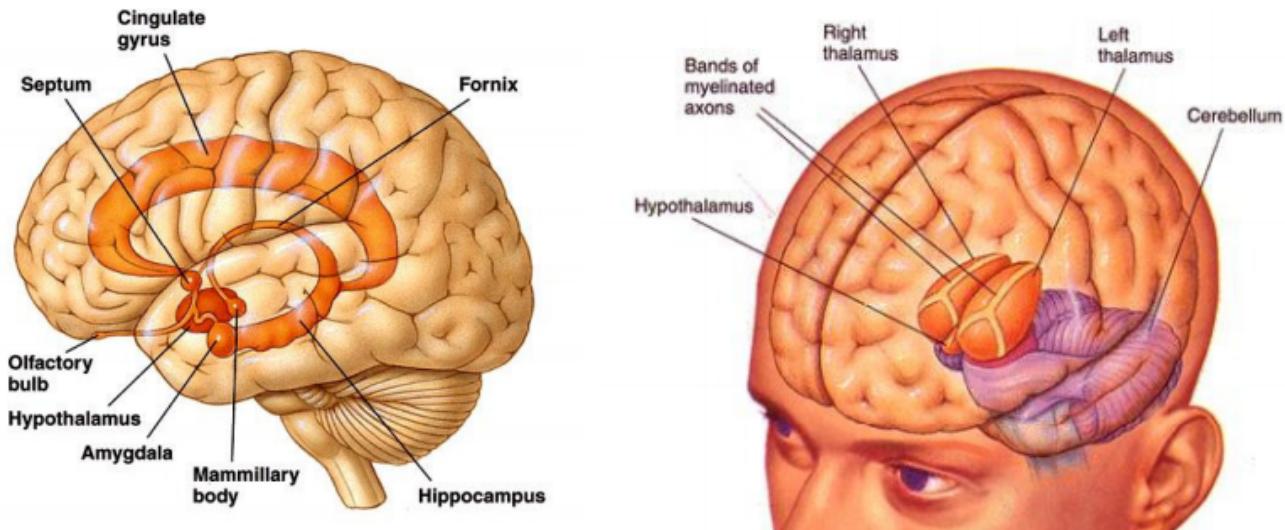
- Forebrain (Prosencephalon): Cortex, thalamus, hippocampus, basal ganglia, corpus callosum.
- Midbrain (Mesencephalon): Tectum, tegmentum.
- Hindbrain (Rhombencephalon): Cerebellum, pons, medulla oblongata.

- White matter: Glia cells, myelinated axons.
- Grey matter: Neurons (soma).
- Neocortex: Six-layered cortex that forms the surface of most of the cerebral hemispheres.
- Corpus callosum: Midline fiber bundle, connects the two cerebral hemispheres.
- Gyrus: Ridges of the cortex, with valleys (sulci).

2.2.1 The limbic system

- Structure: On medial and basal surfaces of cerebral hemispheres.
- Includes cingulate gyrus, parahippocampal gyrus, hippocampal formation, fornix, amygdala, septum, mamillary bodies
- Function: Emotional expression, memory acquisition, fear conditioning, violence and aggression.

► Location of Major Limbic System Structures



2.2.2 Hypothalamus and thalamus

- Structure: Relatively large, two symmetric large nuclei, many projections.
- Function: Relay station, domain-specific information processing.
- The upper brain stem is the diencephalon.
- The hypothalamus is very small and controls autonomic mechanisms.

2.2.3 Basal ganglia

- Structure: Collection of nuclei embedded deep within the cortex.
- Partially surrounds the thalamus.
- Sensory projections to the cerebrum
- Function: Regulate voluntary movement.
- Movement disorders like Parkinson's.

2.2.4 Cerebellum

- Structure: “little brain”, has layered appearance and symmetry.
- Two hemispheres are connected by the vermis.
- Function: Coordinated motor behavior, posture adjustments and stores memories for simple learned motor responses.

2.2.5 Reticular Formation

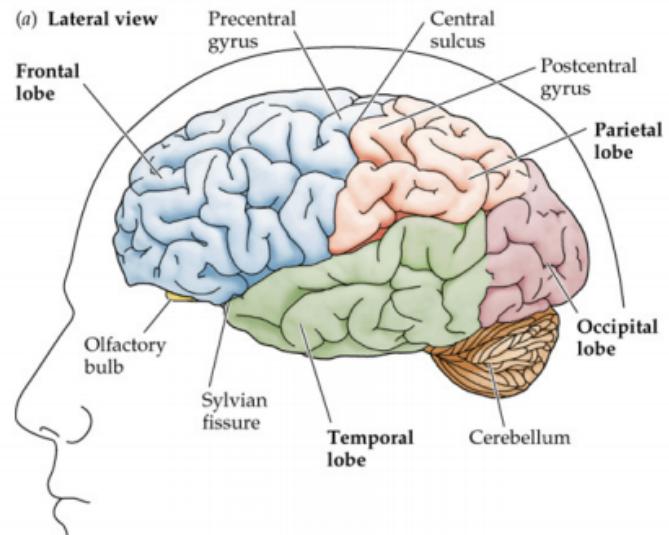
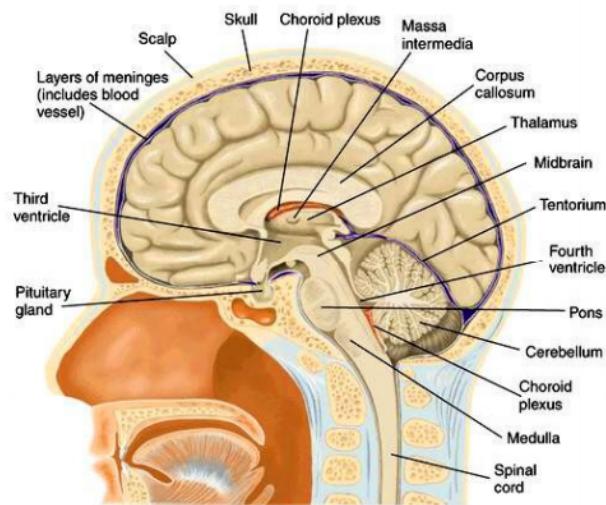
- Structure: Diffuse arrangement of ascending and descending neurons.

- Function: Arousal, selective attention, respiration.

2.2.6 Connections

- The Basal ganglia projects to the cerebral cortex (via thalamus).
- The cerebellum projects to the cerebral cortex (via thalamus).
- The cerebral cortex projects to basal ganglia, cerebellum and motor neurons (and interneurons) via pons.

► Midsagittal View of the Brain and Part of the Spinal Cord



2.3 Nervous system in numbers

- 1 mm³ of white matter is 9 m of axons.
- 1 mm³ of grey matter is 50'000 neurons.
- In 1 mm³ about 100'000 cells.
- The cortex has six layers.

2.4 Basic structure of the neuron

2.4.1 Components

- Cell body
- Nucleus
- Dendrite: Input component.
- Axon: Output component, makes contact to other neurons.
- Myelin: Wraps around axons, makes white matter white.
- Boutons: At the ends of the axons, connects neurons.
- Soma: Body of a cell without its extensions.
- Afferent: Neurons that carry nerve impulses from receptors to the CNS.
- Efferent: Neurons that carry information away from the CNS.
- Projection neuron: Neuron with long axons that project to distant targets.

2.4.2 Axon transport

- Golgi apparatus sits at the cell body.
- Transport of vesicles to the axon terminal (anterograde).
- Transport of empty vesicles back to the cell body (retrograde).

2.4.3 Synapse

- Boutons: connection point.
- Cleft: Little gap between presynaptic and postsynaptic neuron.
- Dendritic spines: Dendritic part of the synapse.
- Transmitter: Gets released by the presynaptic neuron, in vesicles.
- Vesicles: Transport the transmitter inside the cell.
- Receptors: Binding site for the transmitter.

2.5 Muscle reflex and antagonistis

2.5.1 Reciprocal innervation of antagonistic muscles

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 involved (but gets informed).

2.5.2 Elicitation of a stretch reflex

- 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.
- The burst triggers a burst of firing in the thigh muscle motor neurons, causing contraction.

3 Membrane Potential

3.1 Introduction

- System can be described at different levels.
- CNS, Systems, Maps, Networks, Neurons, Synapses and Molecules.

3.2 Membrane structure

- The membrane bilayer is creating the energy barrier.
- Ions can not just flow through. Channels and pumps are needed.
- ECS: Extra cellular solution.
- ICS: Intra cellular solution.
- Membrane is built of two types of molecules, charged hydrophilic dipole head-group (outside) and an uncharged, hydrophobic hydrocarbon tail.
- It is a phospholipid bilayer.

3.3 Neurons

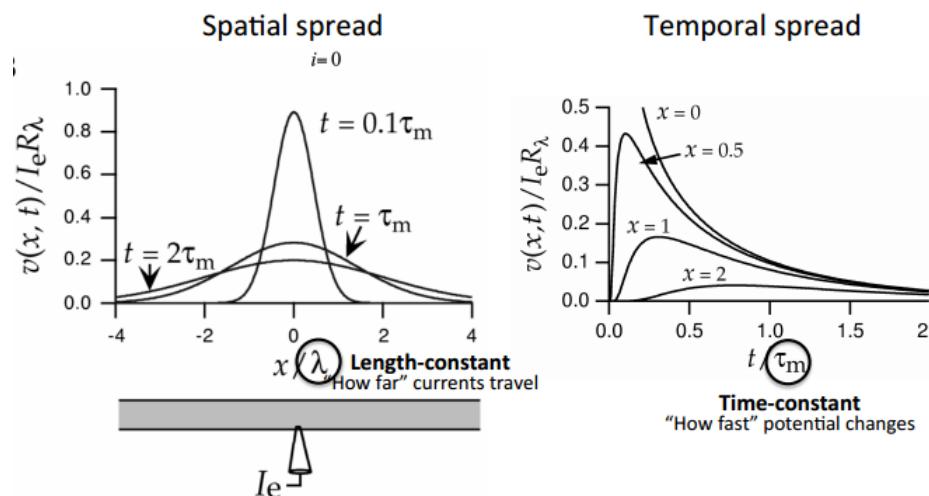
- Membrane: Separates inside from outside.
- Soma: Cell body, contains nucleus and organelles.
- Dendrites: Connect to soma, provide inputs to soma.
- Axons: Connects to soma, conducts away from soma. Often myelinated and ends in synapses. Carries output.
- Synapse: Pre- and postsynaptic terminals, transmit information between neurons.
- In the order of magnitude, there are about 10'000 synapses per neuron.

3.4 Hyperpolarization

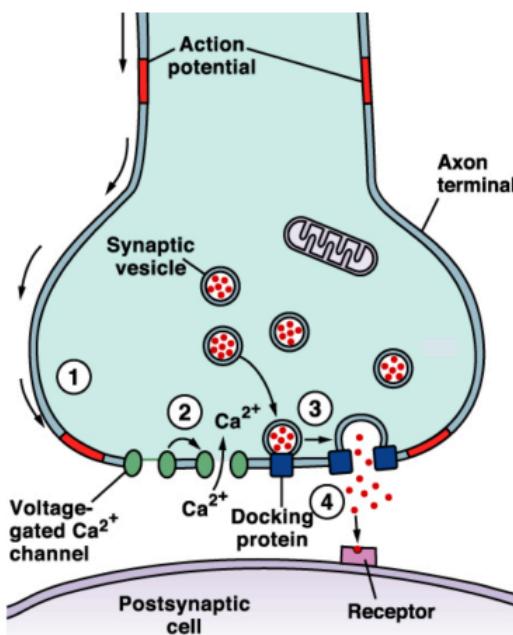
- The extracellular space has potential $V = 0 \text{ mV}$.
- The intracellular space has resting potential $V = -70 \text{ mV}$.

3.5 Inputs to neurons, excitatory

- Inputs to neurons over synapses.
- Depolarization, about $V = 30 \text{ mV}$ presynaptic.
- Excitatory current is positive charge, which comes from the extra- to intra-cellular space.
- The signal is analog and graded.
- On the way to the soma, the intra-cellular current gets reduced by leak current (positive charge) that leaves the intra-cellular space.
- From the large depolarization ($V = 0 \text{ mV}$), about $V = -69.5 \text{ mV}$ is the value at the soma.
- EPSP (excitatory postsynaptic potential) 0.2 to 0.4 mV .
- Spatial and temporal spread of the signal.
- τ_m defines how fast potentials changes.
- λ defines how far currents travel.



3.6 Chemical synapses



- Digital transmission, but can have failures, and graded release.
- There can even be synapses directly on the soma or axon.

3.7 Inhibitory post-synaptic potential

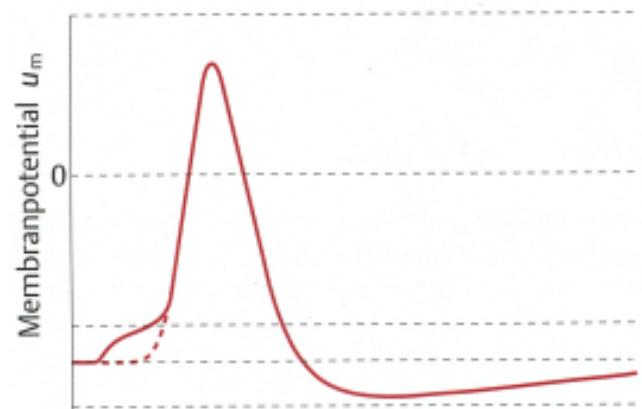
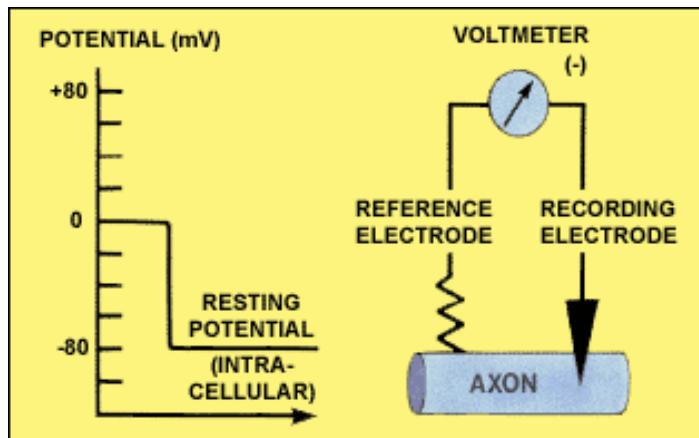
- Depolarization, about $V = 30 \text{ mV}$ presynaptic.
- A large hyperpolarization, $V = -90 \text{ mV}$ at postsynaptic dendrite.
- Small hyperpolarization at soma, $V = -70.2 \text{ mV}$.

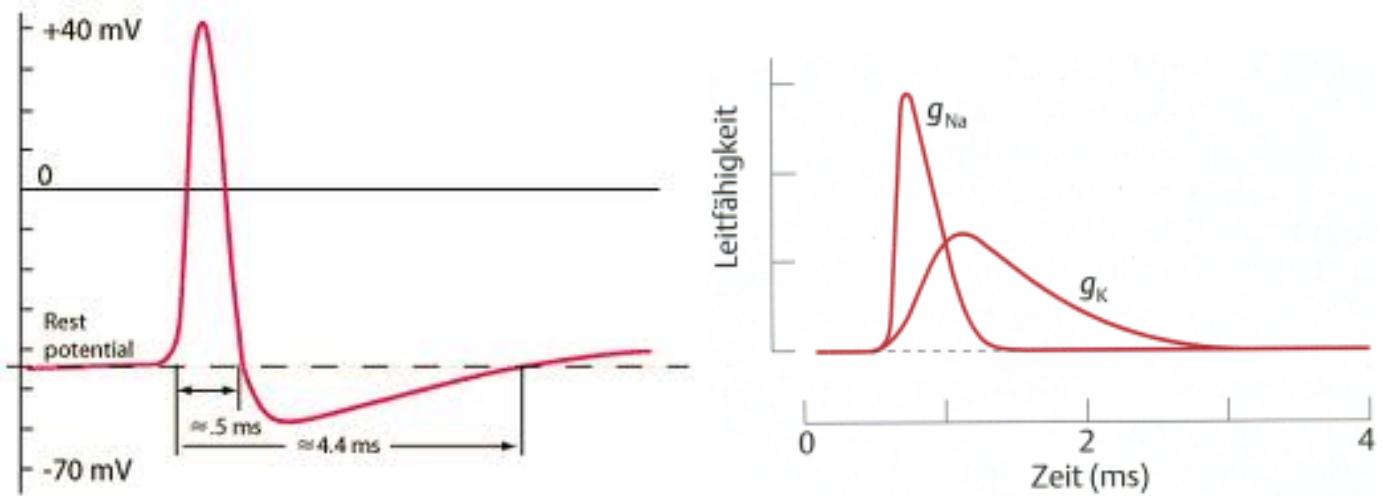
3.8 Summation of Inputs

- Temporal summation, one input after another.
- Spatial summation, inputs from different dendrite branches.
- Summing up, the threshold is crossed.
- Typically 20 to 30 Inputs are needed to go above threshold.
- The action potential gets triggered at the beginning of the axon.
- The threshold is about -60 mV .

3.9 Action potential

- Has an active regenerative process.
- The duration is about 1 to 2 ms.
- All-or-none (digital).
- Amplitude gets converted into rate.
- Components: Depolarization, overshoot ($> 0 \text{ mV}$), repolarization/hyperpolarization and a refractory period (back to -70 mV).
- Peak about 0.5 ms long, 4.4 ms refractory period.





3.10 Axon

- Myelin sheet is often wrapped around the axon.
- This makes the white-matter white.
- Myelin is an electrical insulator which grants faster propagation.
- Less energy is needed with myelinated axons.
- The current goes through the node of ranvier (myelin sheath gaps).

3.11 Ionic currents and equilibrium

3.11.1 Receptors:

- Excitatory: AMPA/NDMA, mixed cation, $V(\text{drive}) = 0 \text{ mV}$
- Inhibitory: GABA A, chloride (Cl^-), $V(\text{drive}) = -65 \text{ mV}$
- Inhibitory: GABA B, potassium (K^+), $V(\text{drive}) = -90 \text{ mV}$

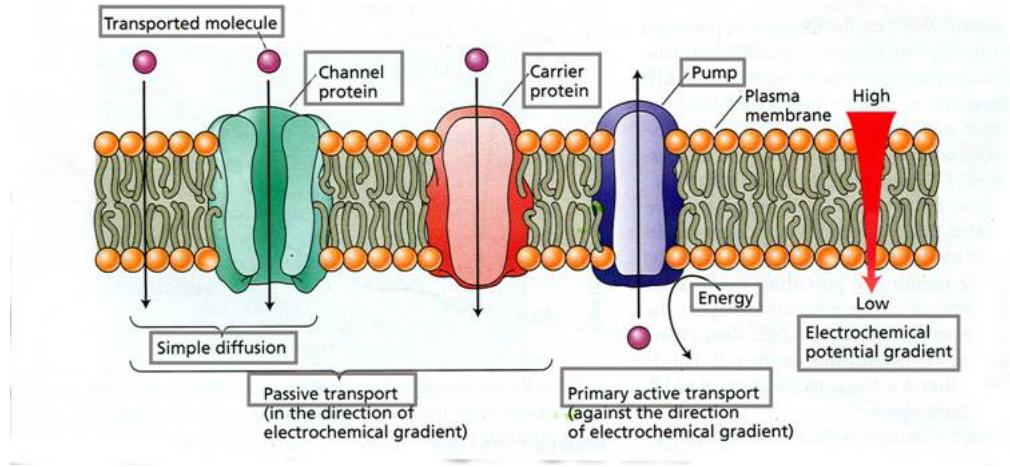
3.11.2 Action potential:

- Sodium (Na^+): $V(\text{drive}) = 55 \text{ mV}$
- Potassium (K^+): $V(\text{drive}) = -90 \text{ mV}$

3.11.3 Ion equilibrium

Charge carrier (giant squid axon):

Ion type	Cytoplasm (mM)	Extracellular (mM)	Equilibrium potential (mV)
K^+	400	20	-75
Na^+	50	440	+55
Cl^-	52	560	-60
Ca^{2+}	0.0001	10	
Organic anions	385	-	



3.12 Nernst-Equation

3.12.1 Acting forces

- Ion concentration gradient (diffusion).
- Electric potential (electrostatic force).
- Both forces are in equilibrium in resting/passive state.
- Equilibrium potential can be computed with the Nernst equation.
- Neurons have K^+ , Na^+ and Cl^- channels.
- K^+ permeability is greater than Na^+ permeability.
- Active Na^+-K^+ pump creates an ion gradient. The exchange is 2 K^+ against 3 Na^+ ions.

3.12.2 General equation

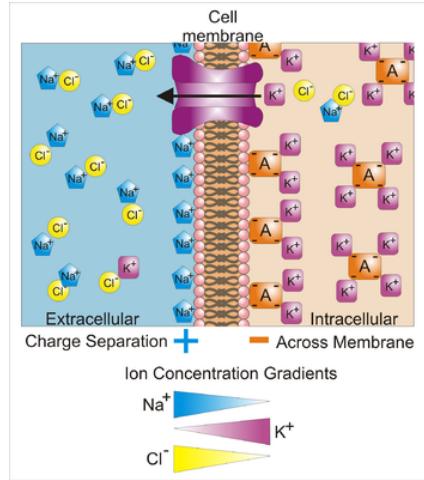
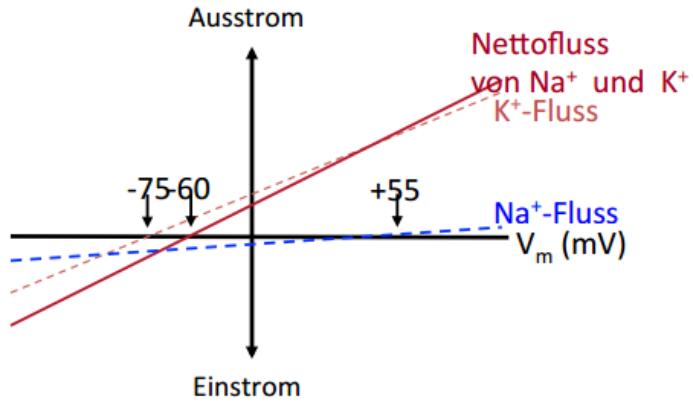
$$E_{ion} = \frac{RT}{zF} \cdot \ln\left(\frac{[Ion]_{extracellular}}{[Ion]_{intracellular}}\right)$$

- R: Universal gas constant ($8.3144 \frac{J}{mol \cdot K}$).
- T: Absolute temperature (kelvin).
- F: Faraday constant ($96500 \frac{C}{mol}$).
- z: Number of electrons involved (1 for K^+ , 2 for Ca^{2+}).
- One mole has $6.022 \cdot 10^{23}$ ions, solution is one molar when its concentration is $1 \frac{mol}{l}$.

3.12.3 Simplified equation

- Take the temperature as $37^\circ C$ or $25^\circ C$.
- Replace \ln with \log_{10} , gives a factor 2.3.
- This gives a factor 60 respectively 58 for $\frac{RT}{F}$.

$$E_{ion} = \frac{58}{z} \cdot \log_{10}\left(\frac{[Ion]_{extracellular}}{[Ion]_{intracellular}}\right)$$



3.13 Goldmann-Equation

- Nernst does not consider multiple ions and permeability.
- Goldmann describes membrane potential, with multiple ions and permeability.
- Assumes ion flux obeys Nernst/Planck equation.
- Assumes ions move across membrane independently, without interaction.
- Equilibrium: $P_K : P_{Na} : P_{Cl}$ is $1 : 0.04 : 0.45$.
- Action potential: $P_K : P_{Na} : P_{Cl}$ is $1 : 20 : 0.45$.
- V_m : Membrane potential.
- P : Membrane permeability.
- $[A^x]$: Ion concentration.

$$V_m = \frac{RT}{F} \ln \left(\frac{P_K [K^+]_{out} + P_{Na} [Na^+]_{out} + P_{Cl} [Cl^-]_{in}}{P_K [K^+]_{in} + P_{Na} [Na^+]_{in} + P_{Cl} [Cl^-]_{out}} \right)$$

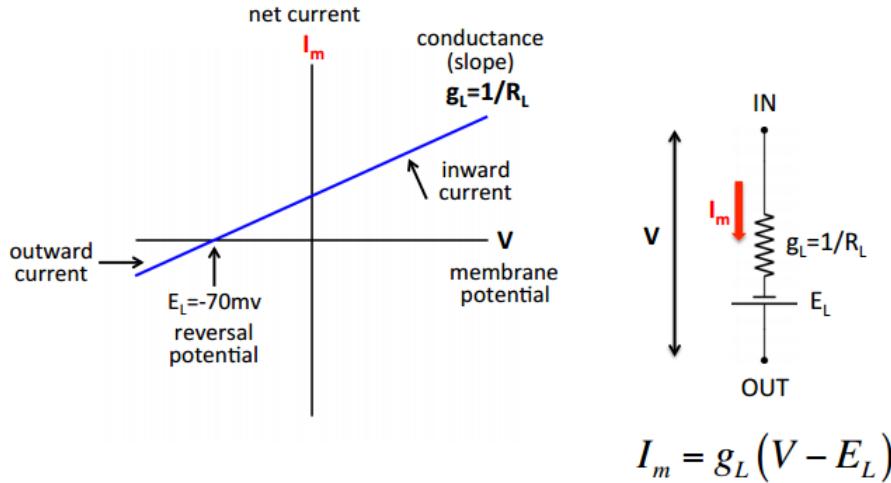
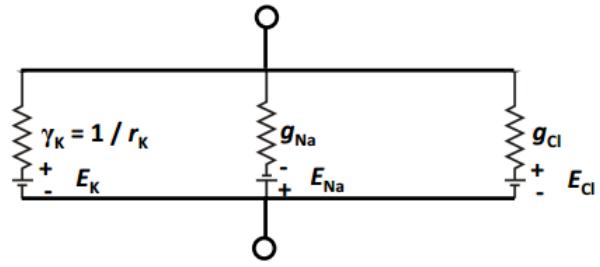
4 Passive (Cable) Membrane Properties

4.1 Basic electronics

- Ohm's Law: $V = I \cdot R$
- Kirchoff's Current Law (KCL): The sum of all currents entering and leaving any node in a circuit is zero.
- Kirchoff's Voltage Law (KVL): The sum of all voltages around a closed loop is equal to zero.

4.2 Ion channel replacement circuit

- Ion channel is equal to resistance.
- Ion gradient is equal to battery.
- Cell membrane is equal to capacitor.
- Conductivity $S = \frac{1}{R}$.
- Ion resistance is $R = V/I$.
- Ion conductivity is $\gamma = g_L = I/V$.
- Outward current for an ion is $I_m = g_L(V - E_L)$.
- If the concentration of an ion on one side is raised (with a corresponding molecule of opposite charge) and the membrane is permeable for this ion, then the side which has a higher concentration gets more negative, because the ions go to the other side, leaving behind uncompensated negative charges.



$$I_m = g_L(V - E_L)$$

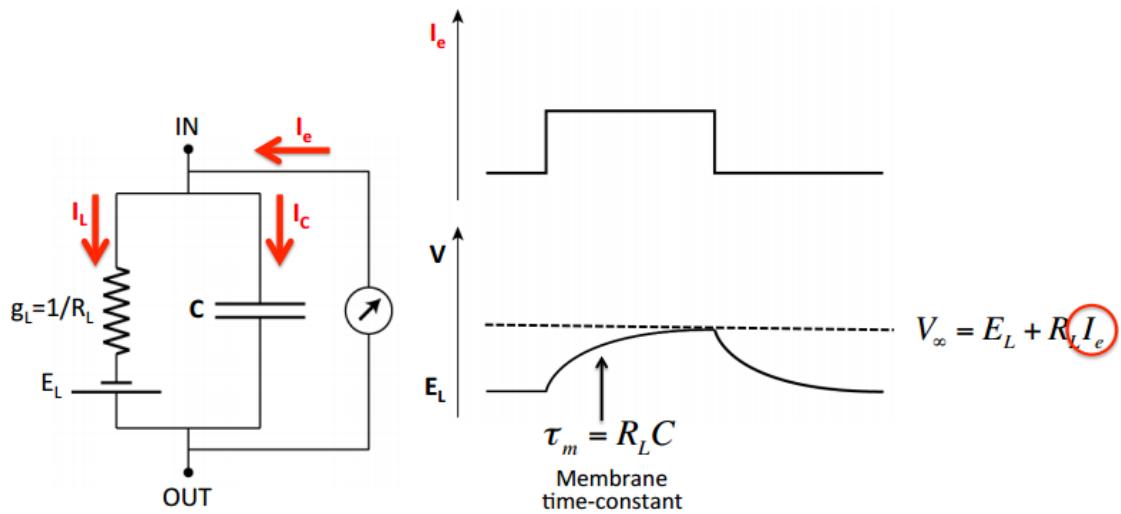
4.3 Single-compartment model

4.3.1 Assumptions, configuration

- Assume isopotential and a sphere of membrane.
- I_e is an injected current.
- I_C is the capacitive current, discharging the membrane.
- There is also a leak current $I_L = g_L(V - E_L)$.

4.3.2 Membrane as electrical circuit

- $I_e = I_L + I_C$ and $I_L = g_L(V - E_L)$
- $C \frac{dV}{dt} = I_C$
- $V(t) = V_\infty + (V(0) - V_\infty)e^{-\frac{t}{\tau_m}}$
- $V_\infty = E_L + R_L I_e$
- Membrane time-constant: $\tau_m = R_L C$
- Larger current due to spatial summation.
- Less depolarization with small resistance (larger area).

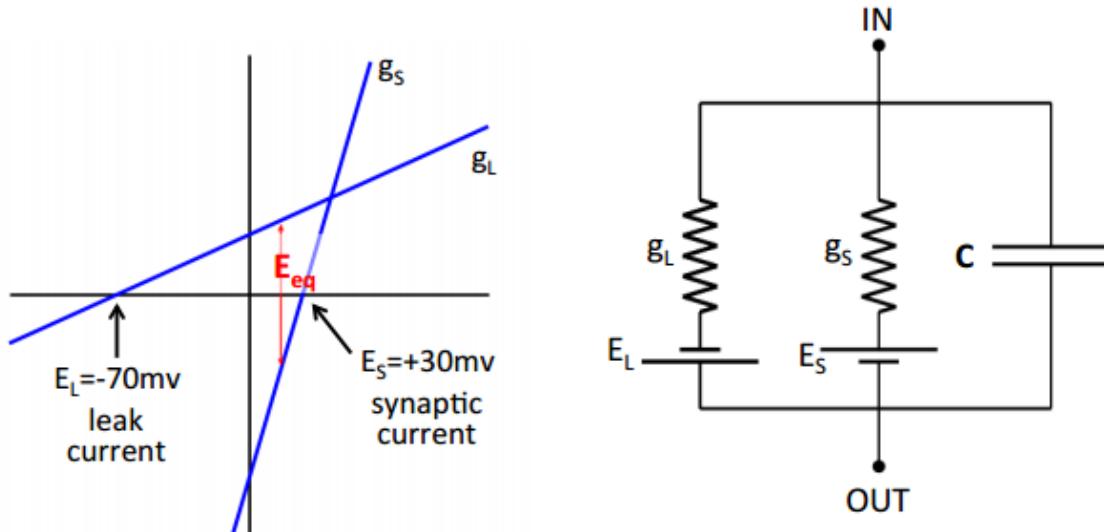


4.3.3 Input resistance

- A is the surface area of the membrane.
- $R_L = \frac{r_L}{A}$

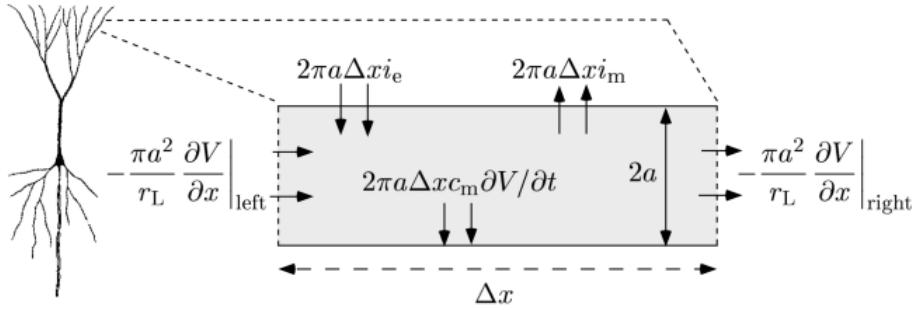
4.4 Two ionic currents

- Equilibrium at $I_L = I_S$
- $V_\infty = \frac{g_L E_L + g_S E_S}{g_L + g_S}$
- $\tau_m = \frac{C}{g_L + g_S}$

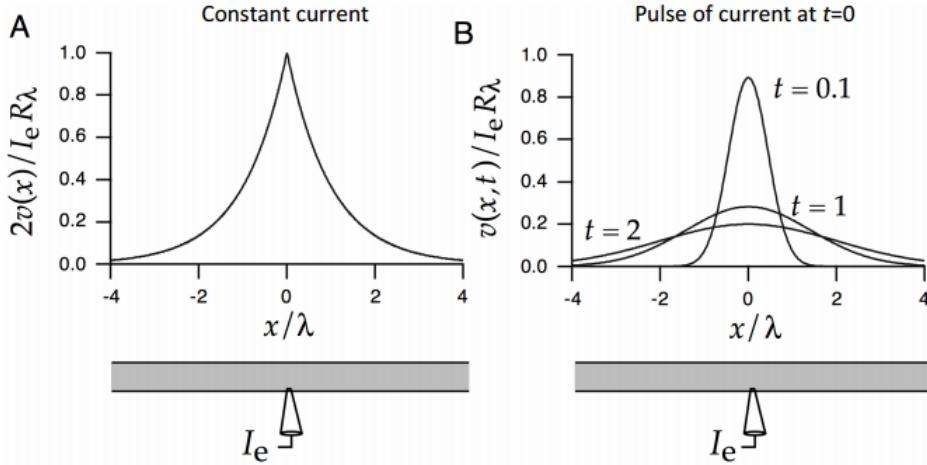


4.5 The cable equation

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



4.5.1 Infinite cable



- $v(x) = \frac{I_e R_\lambda}{2} \exp(-\frac{|x|}{\lambda})$
- $R_\lambda = \frac{r_m}{2\pi a \lambda} = \frac{r_L \lambda}{\pi a^2}$
- $\lambda = \sqrt{\frac{a r_m}{2 r_L}}$ sets the scale for the spatial variation in the membrane potential.
- λ is the electronic length, or how far the signal travels.
- $\tau_m = r_m c_m$ sets the scale for the temporal variation in the membrane potential.
- $v(x, t) = \frac{I_e R_\lambda}{\sqrt{4\pi \lambda^2 t / \tau_m}} \exp(-\frac{\tau_m x^2}{4\lambda^2 t}) \exp(-\frac{t}{\tau_m})$
- a is the radius of the axon, about $2 \mu m$
- r_m is the specific membrane resistance, about $1 M\Omega \cdot mm^2$
- $v = V - V_{rest}$
- r_L is the longitudinal resistance, about $1 k\Omega \cdot mm$
- I_e is the injected current.
- It follows, that increasing R_m also increases λ . With better isolation, signals travel further.
- Increasing the diameter also increases λ .

4.6 Level of approximation

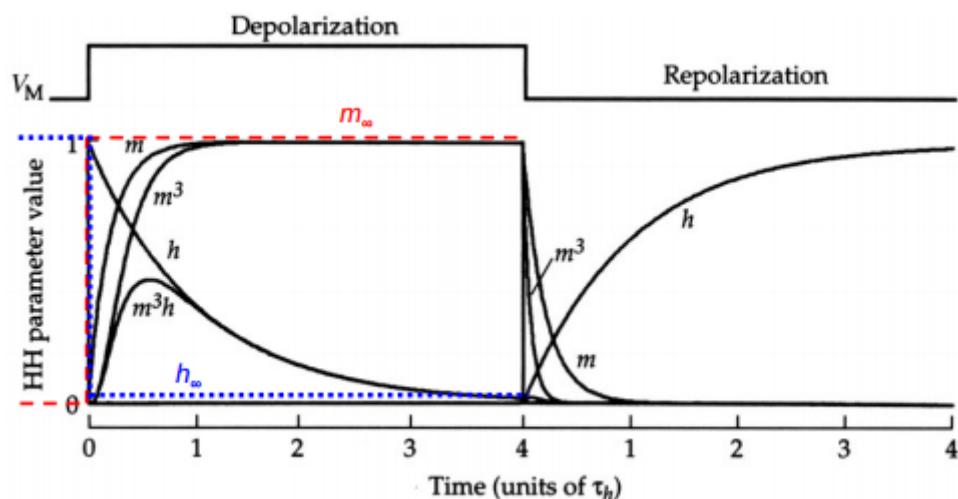
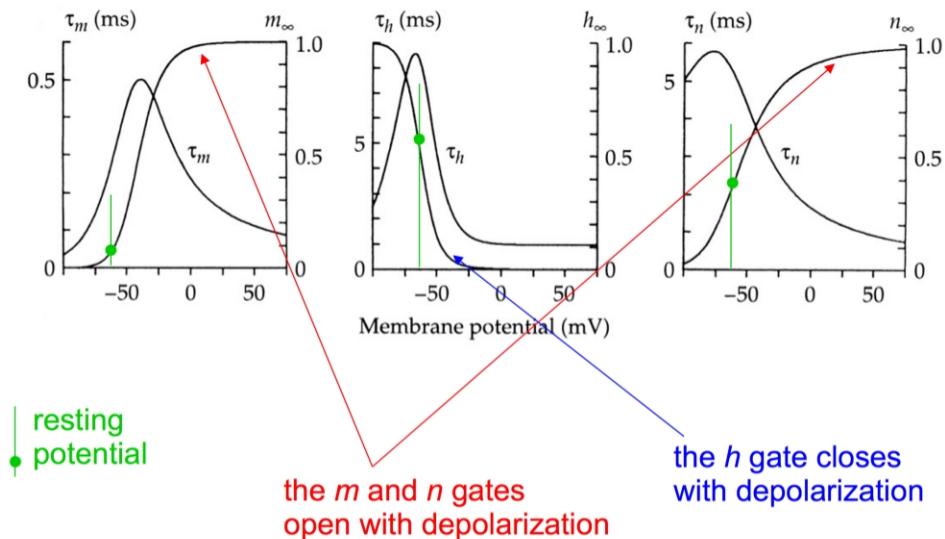
- A neuron can be represented by a variable number of discrete compartments.
- Compartments represent a region, each with a single membrane potential.
- The connections between compartments have resistive couplings.

4.7 Hodgkin-Huxley Equations

- Model that describes how action potentials in neurons are initiated and propagated.
- n and m are probabilities for a gate to be open.
- h is the probability that an open channel is not blocked.
- The gating variables have a voltage dependence.
- \bar{g} values are the maximum conductance possible.

- There is no inactivation for potassium, only for sodium.
- The membrane does not get locked at positive values.
- \bar{g}_L stands for some generic leak.
- The functions $n_\infty(V)$, $m_\infty(V)$ and $h_\infty(V)$ determine whether gates serve to activate channels (with depolarization) or inactivate the channel (close with depolarization). τ_m , τ_h and τ_n are time constants.

$$C \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_L (V - V_L) + I_{inj} = 0$$



5 Action Potential

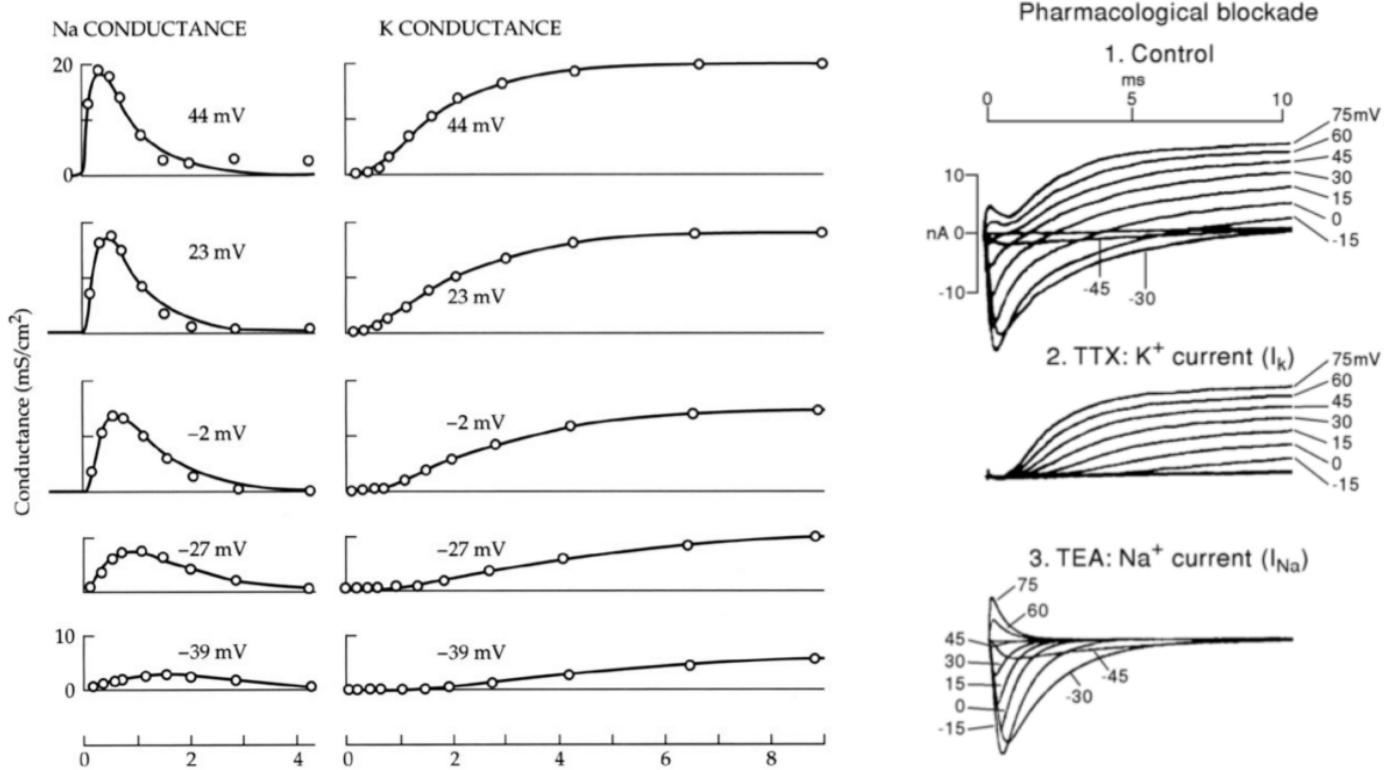
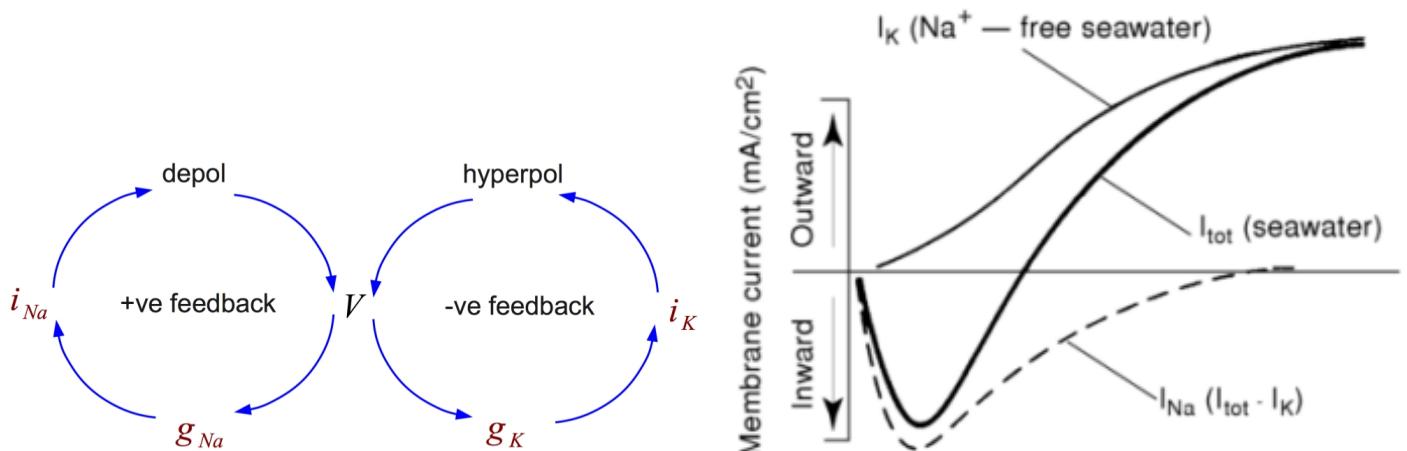
- Refraction period ensures maximum frequency.
- Action potential is about 1 to 10 m/s fast.
- It would take 100 years to go through all axons of the human brain in a serial fashion.

5.1 Equilibrium voltage

- When $I_m = 0$ and $\frac{dv}{dt} = 0$ then
- $V = \frac{g_K E_K + g_{Na} E_{Na} + g_{Cl} E_{Cl}}{g_K + g_{Na} + g_{Cl}}$
- $I_m = I_{cap} + I_K + I_{Na} + I_L$

5.2 Voltage clamp experiment

- Command voltage is set by the experimenter, the feedback circuit holds the voltage constant.
- The voltage clamp allows the membrane voltage to be manipulated independently of ionic currents, allowing the current-voltage relationships of membrane channels to be studied.
- With negative feedback circuit, the Na^+ current is auto-catalytic. An increase in the voltage increases conductance, which increases the Na^+ current, which increases the voltage again.
- Voltage and time dependent conductances for g_{Na}, g_K :
 - g_{Na} increases quickly, but then inactivation kicks in and it decreases again.
 - g_K increases more slowly, and only decreases once the voltage has decreased.
- The threshold for action potential initiation is where the inward Na^+ current exactly balances the outward K^+ current.



6 Synapse

6.1 Introduction

- First mentioned by Sherrington (1873).

- Otto Loewi experimented with the vagus nerve.
 - Stimulating the vagus nerve slows down the heart beat, has an inhibitory function.
 - Ringers solution is a mixture of chemicals in which the heart can continue beating.
 - When switching the solution with one that has been used with an activated vagus nerve, the heart will slow down.
- It was found that the “Vagusstoff” is acetylcholine (ACh).
- The synapses are receptive for nicotine, muscarine and acetylcholine, because of ACh-receptors. This makes certain substances very addictive.
- Residual acetylcholine has to be cleared and removed immediately. This happens with acetylcholine esterase enzymes.

6.2 Synapse properties

- Only vesicles which are already on the presynaptic membrane (docked) will be released after the AP, not all of them.
- One single synapse produces only a small potential. More are needed for an actual action potential.
- Release of neurotransmitters is calcium dependent.
- Probabilistic release of neurotransmitter.
 - In the CNS, most of the time only one vesicle is released with probability 0.2 to 0.4.
 - An amplitude histogram shows poisson distribution, which gives the probability of firing.
 - The action potential (probability of firing of synapses, probability of postsynaptic receptors to bind neurotransmitter) give the plasticity (overall probability of passing action potential to postsynaptic neuritic changes).
- Single activated synapse is usually not enough. EPSP is about 0.1 mV .
- The current-voltage lines have bio-measured sigmoid-curves, because channels open with a probability.

6.3 Synaptic mechanism

1. Synthesis: Building blocks of transmitter substance gets to the terminal where neurotransmitter is synthesized and packed into vesicles.
2. Release: In response to an AP, the transmitter is released, across the membrane, by exocytosis. The presynapse has voltage-gated Ca^{2+} channels, which will cause an inflow and trigger vesicle fusion (exocytosis).
3. Receptor activation: The transmitter crosses the synaptic cleft and binds to a receptor.
4. Inactivation: The transmitter is taken back or inactivated in the synaptic cleft.

6.4 Receptor types

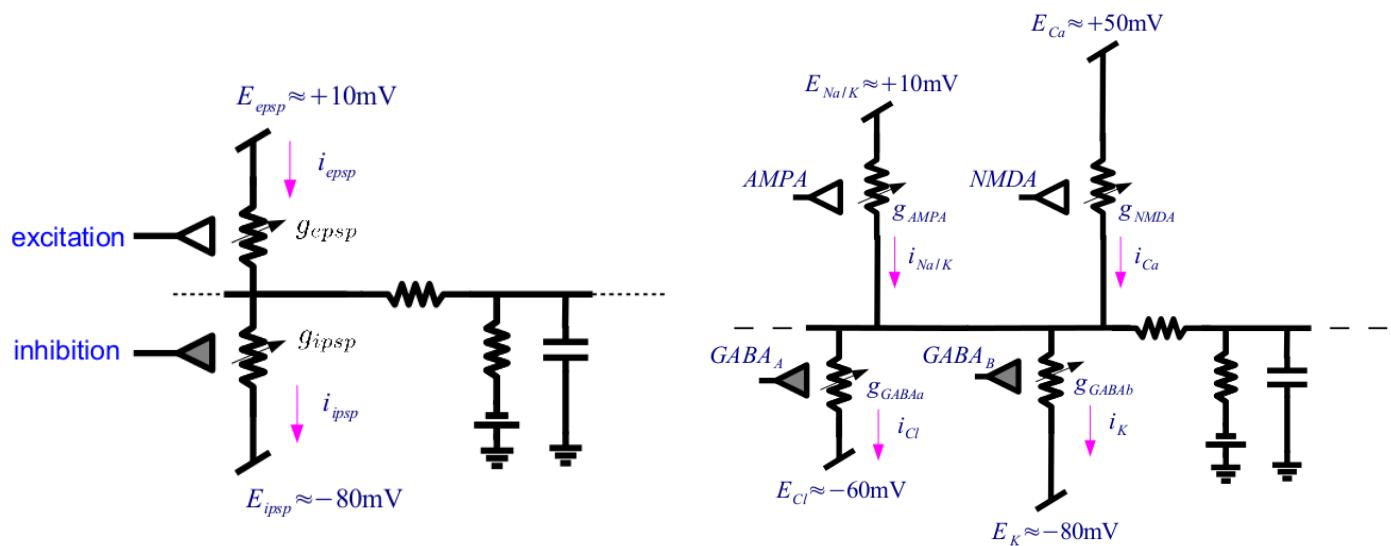
Ionotropic receptor	Metabotropic receptor
Binding site + channel combined	Binding site not associated with channel
Second messenger independent	G-protein or second messenger involved
Short latency action	Longer latency
Rapid response (10 to 50 ms)	Slow responses
Postsynaptic, in general	Pre- and postsynaptic

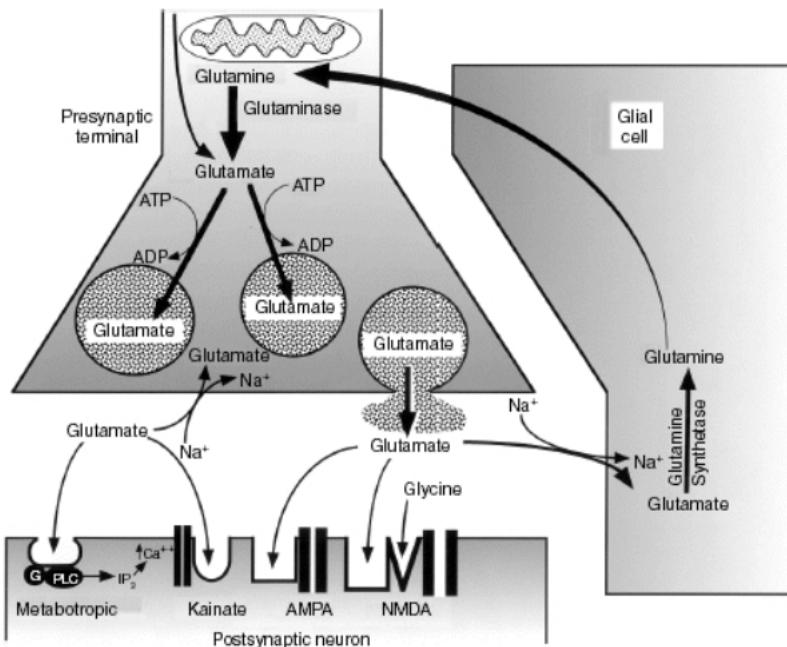
6.5 Synapse types

Electrical synapse	Chemical synapse
Simple primitive system	Highly developed structure
Often symmetrical, bidirectional	Polarized, structurally and functionally
Gap junction (connexins)	Pre: active zone, post: postsynaptic density
Very fast, no synaptic delay	Slower, synaptic delay (0.5 ms)
Ca^{2+} -independent	Transmitter release requires Ca^{2+} influx
Large synapse	Thousands of small synapses
Limited functions, usually excitatory	Versatile: Excitatory and inhibitory
Synchronized activity	Specific: point to point communication

6.6 Receptor overview

Receptor	Transmitter	Ions	Approx. E_{rev}	Agonist
AMPA	glutamate	Na, K, Ca	+0 mV	AMPA
NMDA	glutamate	Na, K, Ca	+0 mV	NDMA
mGLU	glutamate	G-coupled		
$GABA_A$	gaba	Cl	-65 mV	muscimol
$GABA_B$	gaba	K	-90 mV	





6.7 Glutamate receptors

- Glutamate enables both synapses, but NMDA is voltage dependent, while AMPA is not.
- The receptors end up being conductive for Na^+ and K^+ , as well as Ca^{2+} . 10 times more for Ca^{2+} than the others.
- $E_S = 0\text{ mV}$
- Ca^{2+} inflow causes a calcium cascade: Phosphorylation (PO_4) of the channel proteins opens channels even more.

6.7.1 NMDA

- Voltage dependent.
- The channel is blocked by Mg^+ below voltages of -40 mV .
- The block gets pushed out with more positive voltage.

6.7.2 AMPA

- Voltage independent.

6.8 GABA

- GABA-A is for Cl^- , ionotropic (fast), -65 mV
- GABA-B is for K^+ , metabotropic (slow), -90 mV

6.9 Neuromodulators

- Neurotransmitter that is not reabsorbed by the pre-synaptic neuron or broken down into a metabolite.
- These end up a longer time in the cerebrospinal fluid, modulating the activity of several other neurons in the brain.
- For example norepinephrine, dopamine, serotonin.

7 Plasticity and Learning

7.1 Learning and Memory

- Learning is the acquisition of new information or knowledge.
- Memory is the retention of learned information.
- The brain has a more complex configuration than given by genes.
- There is lots of room for learning (and also need).
- Only brain area responsibility and cortex thickness (6 layers) are genetically fixed. But even that can sometimes change later on.

7.1.1 Types of Memory

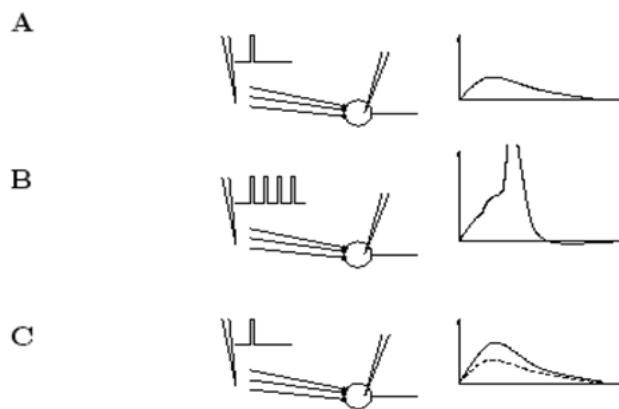
- Declarative memory (facts, events)
- Non-declarative memory
- Procedural memory (skill, habits)
- Emotional responses

7.1.2 Connections to Synapses

- Neurons communicate via AP and are interconnected via synapses.
- Information is represented by distributed activity.
- Learning and memory is based on changes in synaptic connections.
- Synapses get formed, retracted.
- Synapse efficacies/plasticity can change.

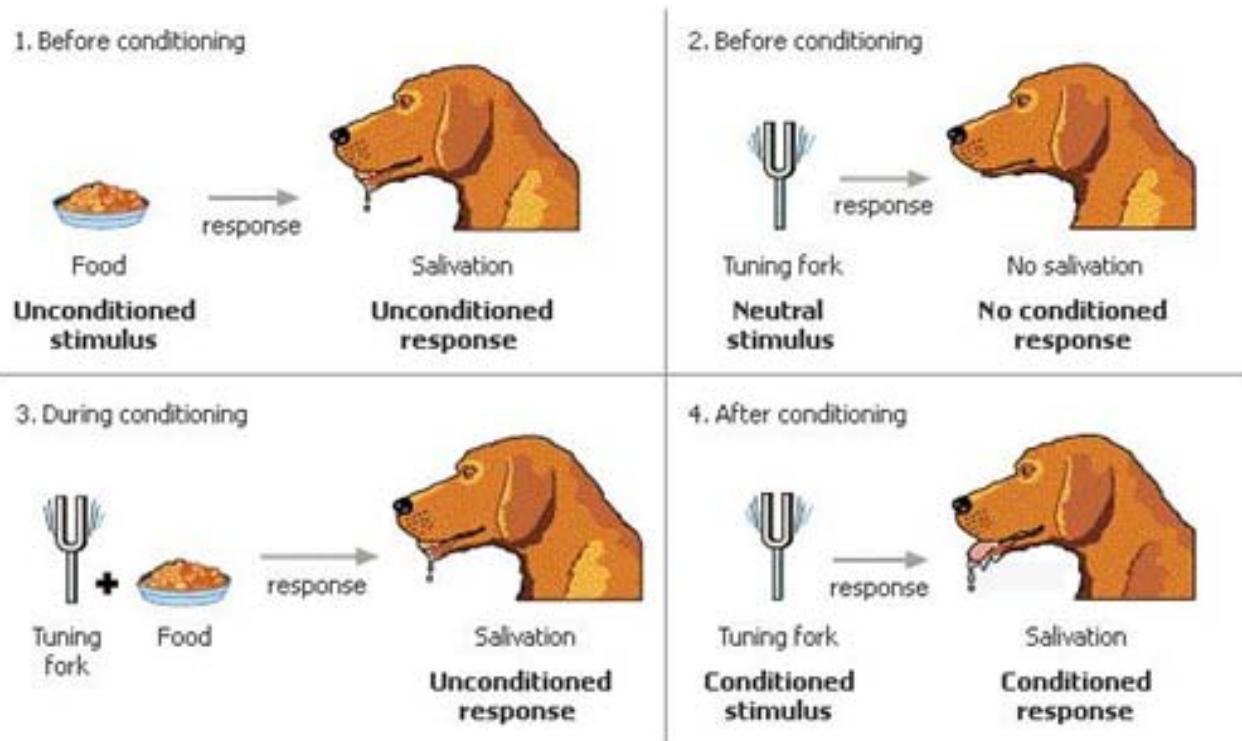
7.2 Plasticity

- Modification of postsynaptic potentials (PSPs) evoked by presynaptic spikes.
- 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 than initially.



7.2.1 Parameters that define synapse strengths

- Neurotransmitter and receptor type
- Position of synapse
- Availability of vesicles
- Re-uptake of transmitters
- Neuromodulators, such as dopamine
- Postsynaptic cellular processes (such as more or less receptors)
- Pre/postsynaptic firing



7.2.2 Models of Synaptic Plasticity

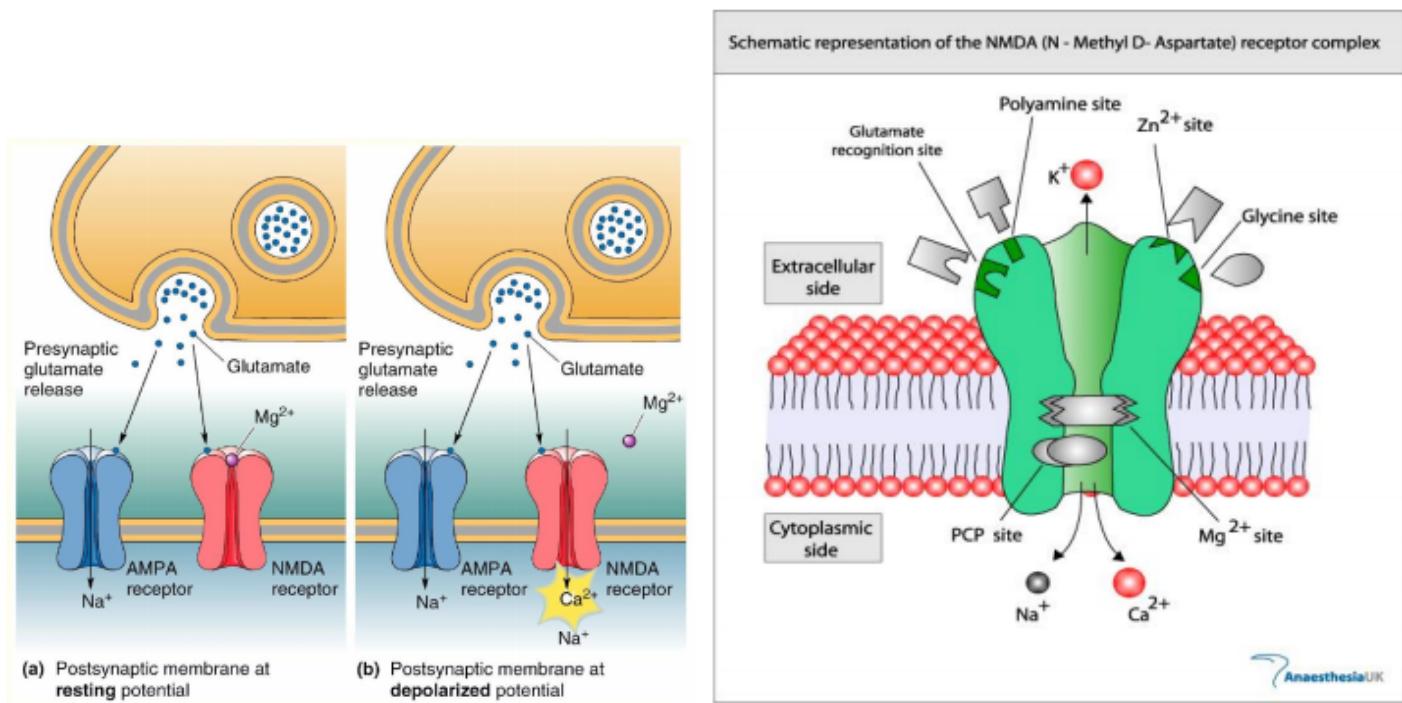
- There is also non synaptic plasticity, such as dendrite strength, excitability of neurons, isolation of axons.
- Phenomenological models show input-output relationships between activity and plasticity.
- Biophysical models tell what processes are involved.
- Hebb's Postulate: "When an axon of cell A is near enough to excite cell B or 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"

7.3 Pavlovian Conditioning

7.4 Hebbian Learning

- Learning based on correlations between pre- and postsynaptic firing.
- Uses only variables locally available at the synapse.
- Expressed in a rate-based model: $\Delta w_{ij} \propto v_i \cdot v_j$.
- Only weight increases, potentiation modeled.
- It will lead to instability because of positive feedback loops.
- Other rules can be added for weight reduction (depression) and normalization (Oja, BCM).
- Hebb's postulate implies constraints for synaptic learning:
 - Direction of information flow (forward).
 - Global effects arise from local learning.
 - Variables are action potentials, synapse weights (efficacy) and neuromodulator/calcium concentration (locally).

7.5 NMDA Synapse

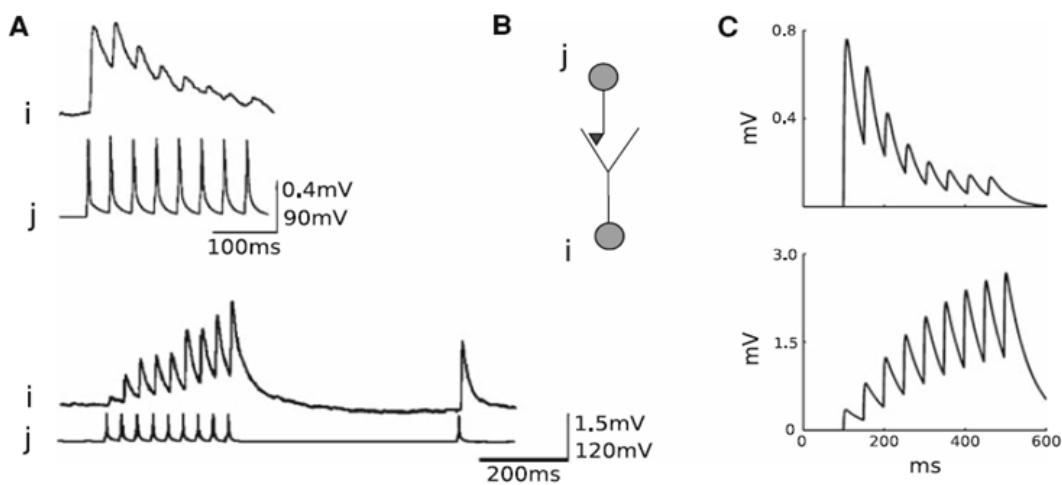


- Can act as a coincidence detector for pre- and postsynaptic firing.
Backpropagating action potentials.
Depolarization from other synapses.
- Calcium influx is crucial for plasticity.
- Strong NMDA receptor activation gives potentiation.
- Weak NMDA receptor activation gives depression.

7.5.1 Potentiation with NMDA

- Phosphorylation of AMPA receptors makes the synapse stronger.
- Synthesis of new AMPA (but not NMDA) receptors.
- Transport of AMPA receptors to membrane.
- Release probability or quantity of the presynapse can be improved.

7.6 Short-term plasticity (STP)



- A neuron j fires several times, neuron i fires as well and the spike size is increased (the higher the spike, the more efficient the neuron), but decreases after a short time (caused by loss of vesicles).
- Effect goes away in order of milliseconds to seconds.
- Short term depression is a safety mechanism.

7.7 Long-term potentiation (LTP)

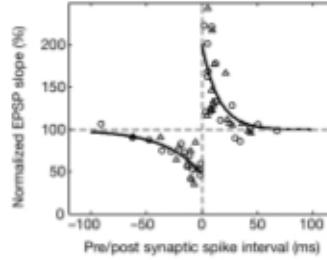
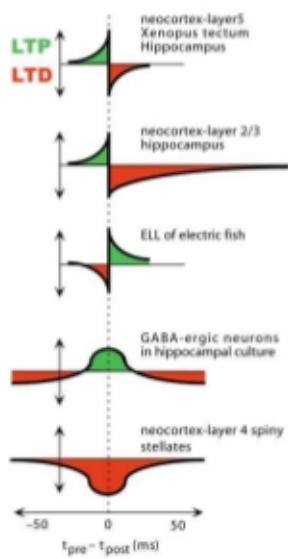
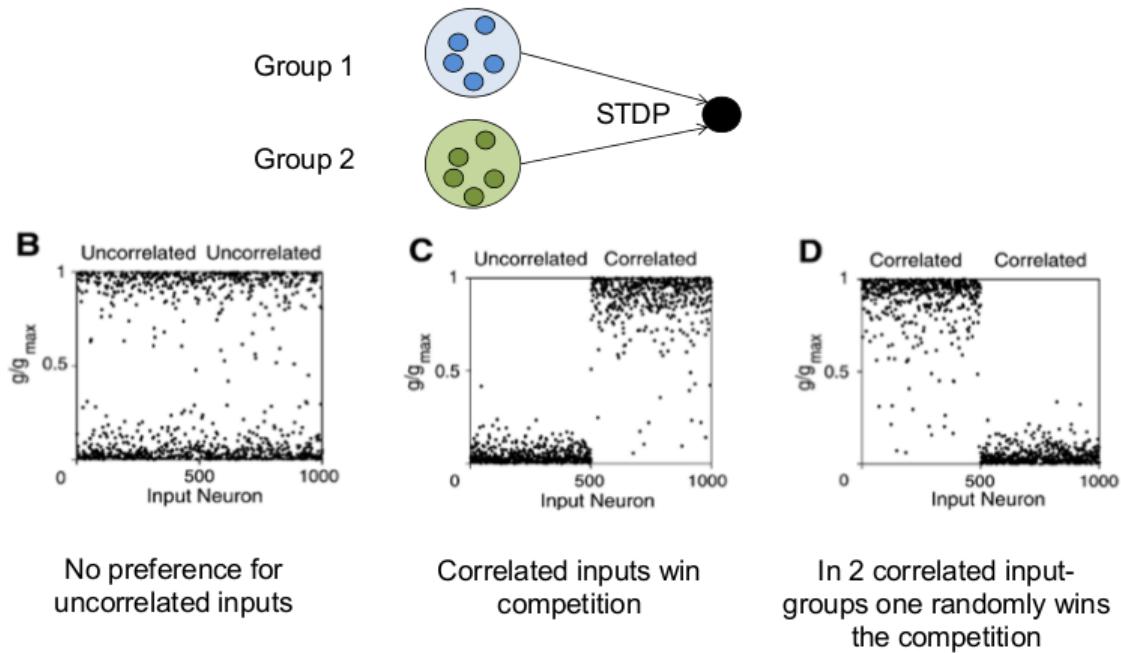
- The hippocampus is involved in transferring from short to long term memory.
- Tetanus stimulus, strong, high frequent stimulation are required.
- A pre- and postsynaptic depolarization at the same time is needed.
- Voltage clamp during tetanus prevents LTP from happening.
- LTP is cooperative, many weak synapse stimulations give also some effect.
- LTP needs a simultaneous depolarization beyond a threshold.
- LTP is input specific and can enhance the synaptic effectiveness of a synapse without affecting other synapses in the same cell. This increases the storage capacity of individual neurons.
- LTP is associative, weak stimulation in pathways coupled with strong simulation in other pathways can induce LTP.
- Stimuli must be delivered at high frequency, because the post-synaptic cell must be depolarized past a certain threshold for LTP.
- LTP has a transient early phase (1 – 3 hours), followed by a consolidate later phase (≥ 24 hours). The early phase doesn't need new protein synthesis. The later phase needs protein and RNA synthesis for new presynaptic active zones and postsynaptic receptors.

7.8 Long-term depression (LTD)

- Weakening of the synapse.

7.9 Spike-timing dependent Plasticity (STDP)

- Not only correlation but also timing of spikes is important.
- NMDA receptors and backpropagating action potential creates this timing-dependence of plasticity.
- Sign of plasticity is determined by local calcium concentration.
- Postsynaptic spike travels back to the dendritic tree and activates voltage-dependent Ca channels.
- Presynaptic activity can allow Ca influx through NMDA channels, if the postsynaptic part is sufficiently depolarized.
- If pre-spike is soon afterwards followed by post-spike, NMDA-R activity is supralinearly enhanced by depolarization due to backpropagating spike.



- ① If a pre-synaptic spike arrives at the synaptic terminal before a post-synaptic spike is emitted, within a critical time window, the synaptic efficacy is increased.
- ② If the post-synaptic spike is emitted soon before the pre-synaptic one arrives, the synaptic efficacy is decreased.

7.9.1 Functional consequences of STDP

- Rate normalization, temporal coding, reduced latency, prediction and conditioning.
- Only one direction can get stronger, no positive feedback can occur.
- STDP can become a simple temporal pattern detector and already fire on the beginning of such a pattern.
- Stimulation frequency has an effect on STDP.
- Dopamine can extend the LTP timing window or even convert LTD to LTP. Dopamine floats around the cells.
- LTP is blocked by AP5. Behavioral success and LTP are correlated.

7.10 Factors that influence plasticity

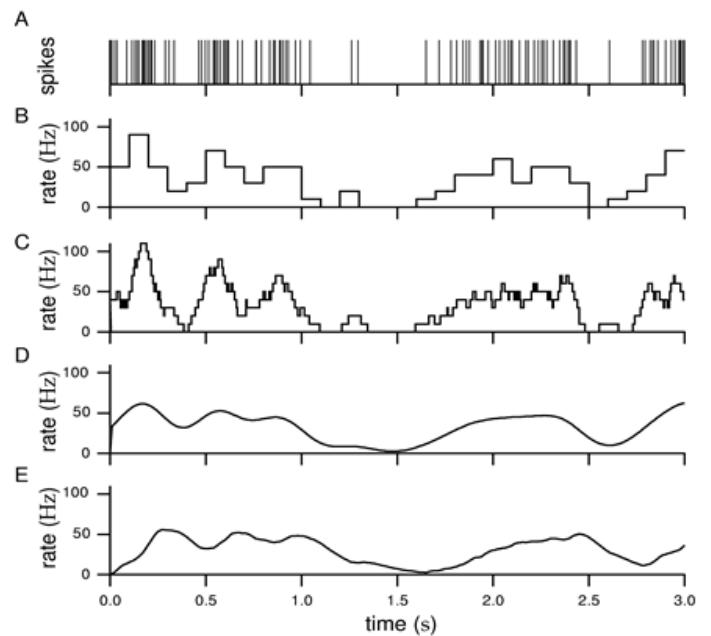
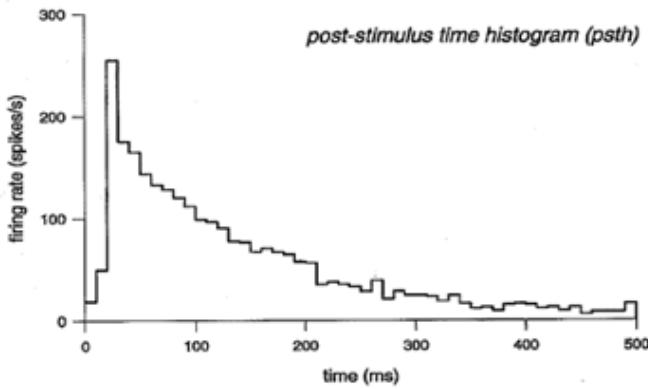
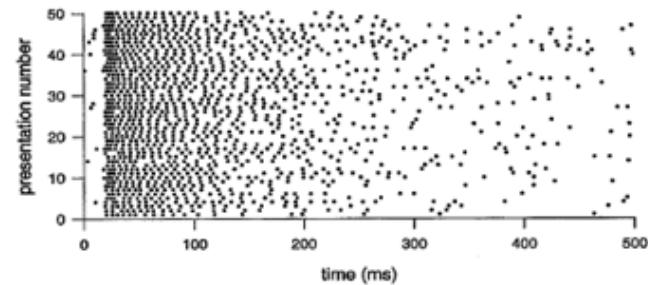
- Different plasticity in different brain areas.
- Diversity of neuron and synapse types.
- Large number of control parameters for plasticity experiments.
- Influence of neuromodulators, calcium, drugs, proteins.

- Long term vs. short term effects.
- Unlikely that a single model explains all plasticity effects found in biology.

8 Rate / Event Coding

8.1 Neural Coding

- Information is encoded by firing of single neurons and firing of populations of neurons.
- A neuron encodes information, fires to stimuli.
- Firing rate and spike timing encodes information.
- Spatial/temporal resolution of different measurement techniques tell us about the neural code.
- It is an issue to record from many neurons simultaneously.
- There is not much information in the slope of a spike.



- Raster plot with spikes and histogram. Stimulus takes place at $t = 0$.
- Use bins (about 100 ms in time) with a sliding window and a gauss filter and causal filter.
- Problematic are intermediate stages, probability of firing, background activity and varying membrane potentials.
- Causal filter is $w(\tau) = [\alpha^2 \tau \exp(-\alpha\tau)]$
- Typically neurons fire between 1 Hz and 200 Hz - often around 40 Hz.

8.2 Neuronal Rate Codes

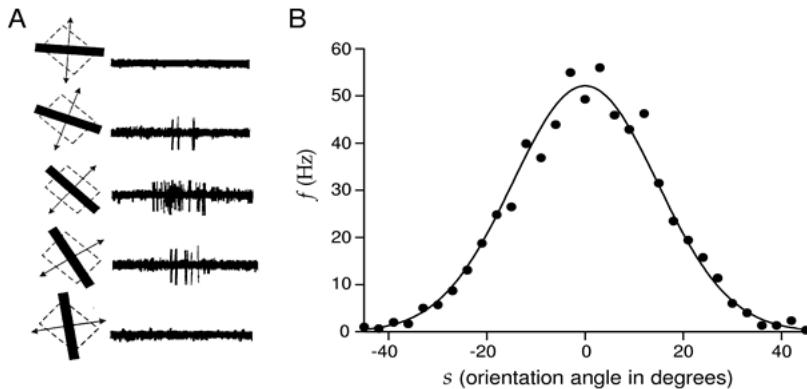
- Rate = average over time, single neuron, single run.
- $v = \frac{n_{sp}}{T}$
- Definition of the mean firing rate via a temporal average.
- Neuronal gain function (curve). The output spike rate is given as a function of the total somatic input current I_0 .
- Easy to understand, but no timing effects and misleading as more than one stimulus might be encoded.
- It takes time to compute a temporal average and behavioral response time is shorter than integration time.

8.3 Peri-Stimulus Time Histogram (PSTH)

- $\rho = \frac{1}{\Delta t} \frac{1}{K} n_K(t; t + \Delta t)$ where K is the number of trials.
- Spike density is an average over several runs of the experiment.

8.4 Tuning Curves

- Tuning curves show average firing rate response to varying stimulus parameters.



8.5 Orientation Maps

- Nearby neurons have similar preferred orientations.
- Orientation-selective neurons (in the primary visual cortex of cats).
- Orientation column and pinwheels.

8.6 Poisson Spike Trains

- Mathematical model to describe and generate spike trains.
- Poission distribution for the number of spikes in interval T with firing rate r .
- $P_T(n) = \frac{(rT)^n}{n!} \exp(-rT)$
- Homogeneous: Constant rate.
- Inhomogeneous: Variable rate.
- Approximation: Probability of a spike occurring in short interval of length Δt : $r(t) \cdot \Delta t$

8.7 What a single neuron can encode

- Places (on entering a particular region).
- Grids (regularly arranged triangular grid of locations).
- Head-direction, compass-like.
- Single cells that respond to only one person.

8.8 Population Rates

- Rate = average over pool of equivalent neurons (several neurons, single run).
- Activity $A = \frac{1}{\Delta t} \frac{n_{act}(t; t + \Delta t)}{N}$
- A postsynaptic neuron receives spike input from a population m with activity A_m . The population activity is defined as the fraction of neurons that are active in a short interval $[t, t + \Delta t]$ divided by Δt .

8.9 Population Codes

- Different cells encode different ranges of the stimulus.
- Averaging over a population often meaningless.

- Allows accurate reconstruction of the signal, also interpolated between peaks.
- Sparse coding: Only few cells are activated.
- Retina as an example: Different cells for different light wavelengths.

8.9.1 Population Vector Code

- Population of neurons with different preferred arm movement directions.
- Encoded direction (arrow) corresponds to vectorial addition, weighted by firing rate.
- Interesting for brain-computer interfaces.

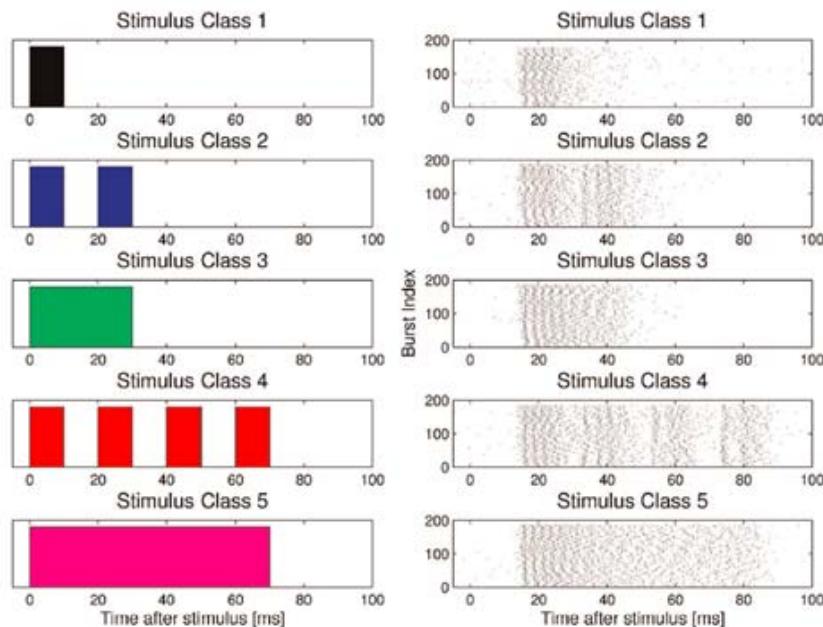
8.10 Neuronal Event Codes

8.10.1 Time-to-first Spike Codes

- High rate implies fast firing.
- Can implement competition among different input cells.
- Can be extended to rank-order codes (firing sequence of different neurons).
- Is very fast and efficient, has evidence in auditory, visual and somatosensory systems.
- Susceptible to noise, requires a reference signal.

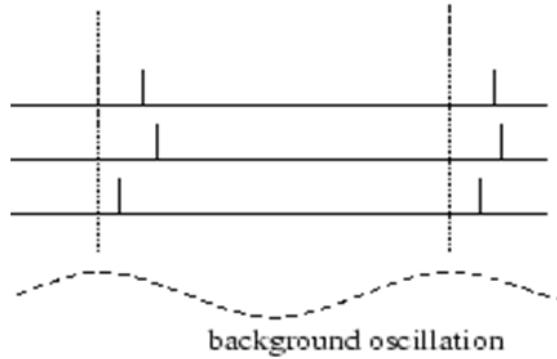
8.10.2 Burst- and Temporal Codes

- Bush-cricket auditory neurons in natural environment.
- Preserve very high coding precision in extreme noise.



8.10.3 Oscillations and Phase Coding

- Phase: The neurons fire at different phases with respect to the background oscillation.
- Phase could code relevant information.



8.10.4 Coding by Synchrony

- Synchrony can encode information.
- Neurons can fire (nearly) synchronous.

8.11 Local Field Potential (LFP)

- Low-pass filtered extracellular recording.
- Reflects the integration of membrane currents in a local region.
- Dominated by dendritic synaptic activity.
- Might encode different properties of the stimulus than single cell firing.
- Spike sorting: Assigning spikes to different neurons from extracellular signal (spike shapes are unique for each neuron).

8.12 fMRI

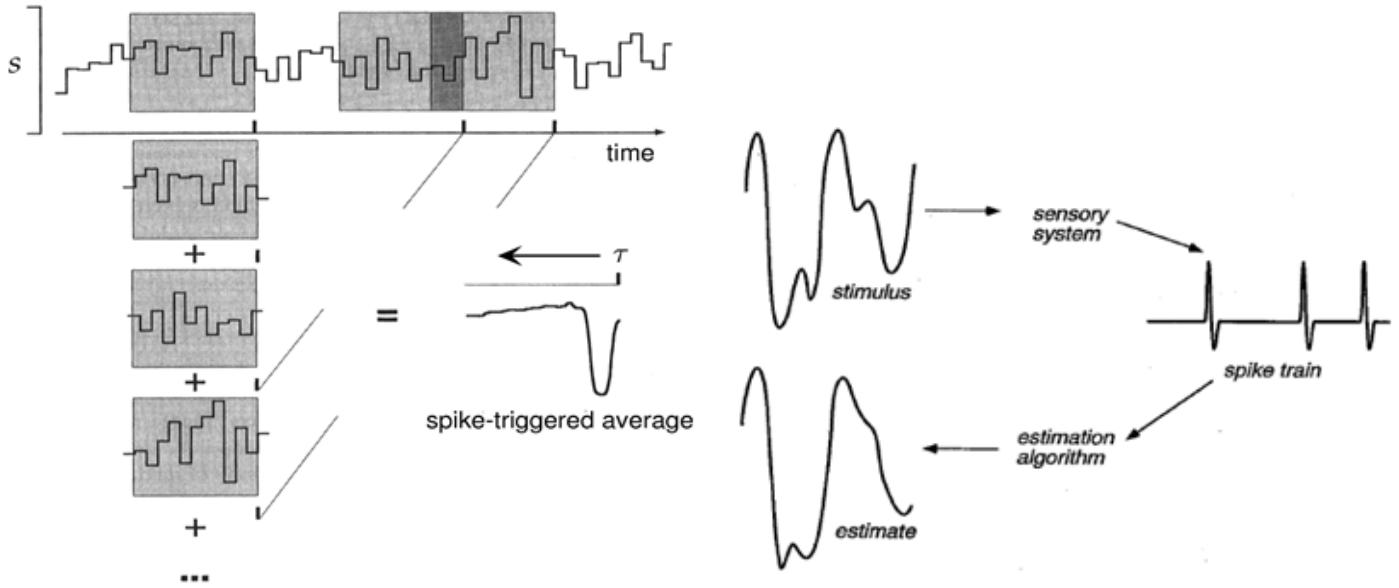
- Functional magnetoc resonance imaging.
- Non-invasive technique for monitoring brain function.
- Based on BOLD (blood oxygenation level dependent signal change). Haemodynamic response function (HRF).
- Slow temporal resolution.

8.13 Binding Problem

- Occurs frequently: Visual processing (what, where).
- Potential mechanism: Temporal synchrony, hierarchical coding, population coding.

8.14 Averages

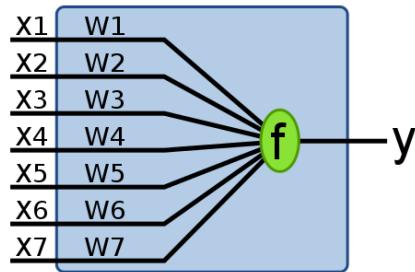
- Spike triggered average: Average over stimulus in short time window before spike.
- Sensory neurons typically respond stronger to rapid changes in stimulus properties.



8.15 Stimulus Reconstruction

- Allows an observer to reconstruct the stimulus from spike trains.
- Probability and information theory is the mathematical background.
- Whole stimulus reconstruction may not be relevant.
- Evolution may have shaped us to encode particular features better than others, for example faces.
- Cells may respond to only particular aspects of stimulus.
- Cells may respond to multiple aspects of stimulus.
- Artificial stimuli used for studies may be predictable.

9 Perceptron Learning Algorithm



- Model represents a neuron as a number of inputs X and one Output Y . Weights W determine influence of the inputs. f is a function determining the Output, usually $\sum_i (w_i \cdot x_i) \geq \theta$.
- Two states: Active or inactive.
- Usually bias is added so that $w_0 + \sum_i (w_i \cdot x_i) \geq 0$ activates the neuron.
- This model can create AND/OR/NOT-Gates. Not the XOR/XNOR-Gate however.

9.0.1 XOR impossibility with Perceptrons

- It is required that $w_0 < 0$, $w_2 + w_0 \geq 0$, $w_1 + w_0 \geq 0$ and $w_1 + w_2 + w_0 < 0$.
- This causes a contradiction because $2w_0 + w_1 + w_2 < 0$ and $2w_0 + w_1 + w_2 \geq 0$ when adding up the constraints.
- XOR is not a linear combination of the inputs.

9.1 Logic gates

- A table with N inputs has 2^N rows. The number of function outputs is then $2^{(2^N)}$.

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

9.2 McCulloch-Pitts Neuron / Perceptron

Similarities to real neurons:

- Both can be active or inactive.
- The input/output is directed.
- The activation of a neuron is dependent on a weighted function of other neurons.

Differences to real neurons:

- Real neurons exist in continuous time, whereas McCulloch-Pitts neurons operate in discrete time.
- Real neurons have degrees of activation, not just on/off.
- The activation as a function of the inputs of real neuron is typically not linear or threshold linear.

9.3 Perceptron Learning Algorithm

- Choose random initial weights.
- Calculate output for given input.
- If the output is not the expected value, then $e = d - c$, where d is the desired output and c the current output.
- Change the weight of inputs and bias by $\Delta w_i = e \cdot \alpha \cdot x_i$. For the bias, always use $x = 1$.

10 Hopfield Networks

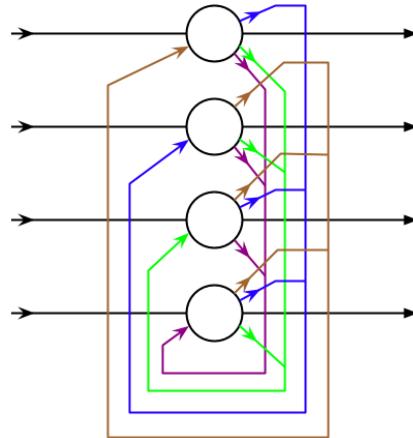
- Every node is connected to every other node but not to itself.
- Connection weights are symmetric.
- $\sum x_i w_i < 0$ is disabled, $\sum x_i w_i \geq 0$ is enabled.
- Entire Network is in some state at any time. Set of active units of the entire network is important.
- Some states are stable and some are not. While in an unstable state, updating the network leads to a state change.
- Stable state is a local minimum. This does however not have to happen.
- Bias is an unit that is always on.
- Weight of a connection is correlated to frequency of firing together (Hebbian learning).

10.1 Hopfield and Memory

- A hopfield network is an associative type of memory. Information is stored in the stable states as local minima.
- It is important that information is distinct.
- Associative memory has room for error but is still recognizable. Convergence to nearby stable states.
- Only helpful if reliable input.
- If some units are retrievable and all others are set randomly, the correct units will eventually set wrong units right.

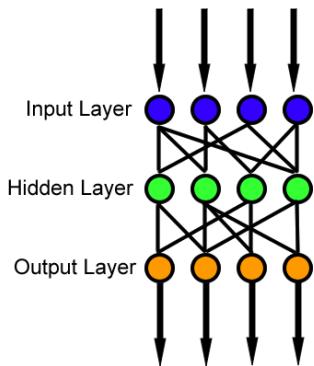
10.2 Updates and State Dynamics

- Nodes can be updated synchronously or asynchronously.
- State: Set of units that are active.
- Dynamics: Units update their activity level.
- When a node is updated, weights are considered from all other active nodes, like with a perceptron.
- Asynchronous updates (greedy algorithm) converge to a stable state (sequential), but the converged state can depend on update order.
- Asynchronous is either in max-clique state if activity is in $\{0, 1\}$ or min-cut if activities are in $\{-1, 1\}$.
- Synchronous, parallel updates either also go to a stable state, just like asynchronous, or can get stuck in a pair of patterns (flipping or cyclic).



11 Feed-Forward Networks

- Multiple layers of neurons with a certain number of inputs and outputs.
- Every layer of nodes feeds the next layer with inputs.
- There is an input and an output layer with hidden layers in between.



11.1 Backpropagation and Error function

- The inputs and desired outputs are given as $S = \{(x, d)^1, \dots, (x, d)^l\}$.
- The error function is given as $E(S) = \sum_i \frac{1}{2} \|y(x^i) - d^i\|^2$.
- The output is a non-linear transformation $y = f(a)$.
- $f(a)$ is the activation function, which is usually a sigmoid function.
- The error function for a single training sample is $E(S) = \frac{1}{2}(f(x_1 w_1 + x_2 w_2 + w_0) - d)^2$.
- The output of a simple network is for example $y(x_1, x_2, x_3) = f(x_1 w_{21} + f(x_2 w_{11} + x_3 w_{12} + w_{10}) w_{22} + w_{20})$.
- $\frac{\partial E(w_1, w_2, w_0)}{\partial w_1} = (f(x_1 w_1 + x_2 w_2 + w_0) - d) \cdot f'(x_1 w_1 + x_2 w_2 + w_0) \cdot x_1$.

- $\frac{\partial E(w_1, w_2, w_0)}{\partial w_2} = (f(x_1w_1 + x_2w_2 + w_0) - d) \cdot f'(x_1w_1 + x_2w_2 + w_0) \cdot x_2$.
- $\frac{\partial E(w_1, w_2, w_0)}{\partial w_0} = (f(x_1w_1 + x_2w_2 + w_0) - d) \cdot f'(x_1w_1 + x_2w_2 + w_0)$.
- The error terms travel backwards through the network and get multiplied with the derivative of the activation function of that input. Multiple error terms can just be added up.
- The partial derivative of the error E term in relation to the weight w to be adjusted can be added to the weight in order to learn. An additional weighting factor can be added.

12 Signal Propagation in a Network

12.1 Avalanche Model

- For example needed with sensory neurons, as small signals have to be amplified in order to be detectable by the superior areas.
- No recurrent connections or risk of positive feedback with risk of explosion.
- $(pn)^2$ active neurons per layer. p is a probability and n is the number of neurons that every next layer has more than the previous ones. One neuron from the last layer is connected with n from the next one.

12.2 Synfire Chain

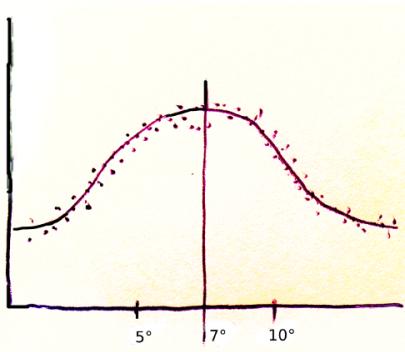
- The synfire chain is a feedforward structure.
- Synchrony is the most important factor for the transmission of the signal.
- Noise is important: The chain is usually embedded in a larger network to transmit information. Introducing noise avoids that large-scale synchronization of neuronal firing contaminates the whole network.

12.3 Divergence, convergence

- A connection is said to be converging if a neuron receives input from several other neurons.
- A connection is said to be diverging if a neuron projects to several other neurons.

13 Interacting Neural Populations

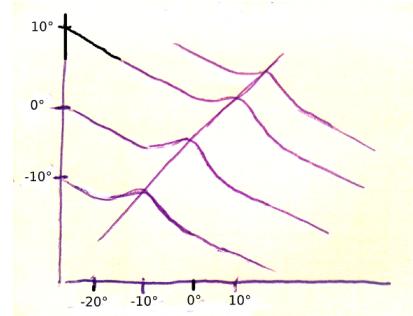
- Neurons can represent information through population codes.
- Neurons are tuned to preferred stimuli.
- Information is represented by the pattern of activity in a neural population.
- Each neuron has a preferred input, for example orientation, that it responds to. The neuron is tuned to that value.
- Not every neuron shows clear tuning curves.
- Neurons usually do not only respond to their preferred stimulus, but also with decaying strength to close ones.



(a) Tuning curve of one cell



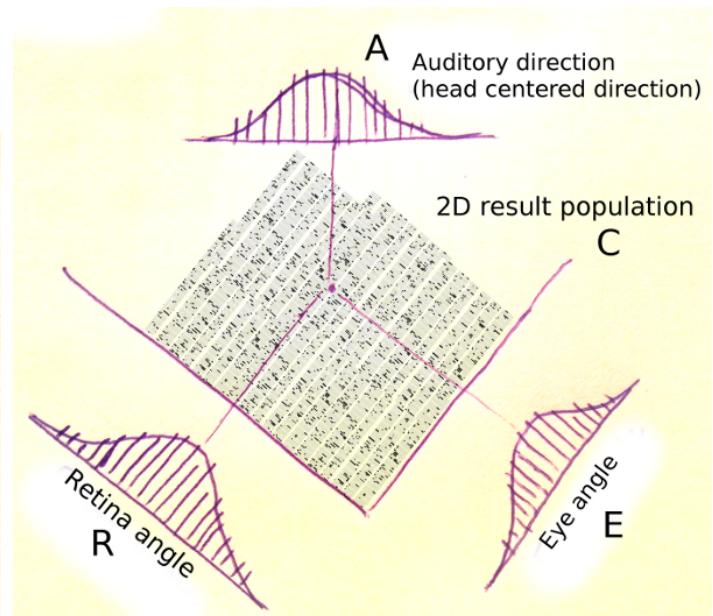
(b) Cells ordered by response to 20°



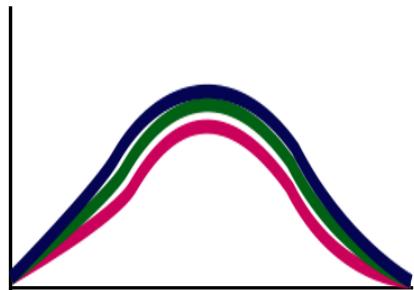
(c) 3D visualization of cell's response to different degrees



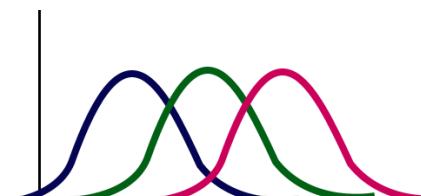
(a) Monkey holding gaze fixed on point 10° and light falling in from 20°



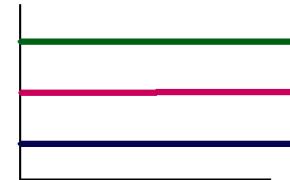
(b) Visualization of Retina angle ordering cell set R, Eye angle ordering set E, 2D result population C and auditory direction set A.



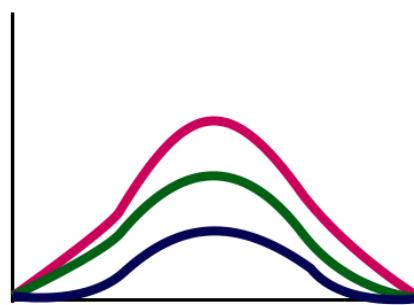
(a) Cell $A \in R$



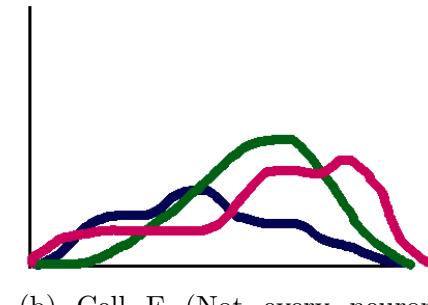
(b) Cell $B \in A$



(c) Cell $C \in E$



(a) Cell $D \in C$



(b) Cell E (Not every neuron shows clear tuning curves)

14 Neuromorphic VLSI

14.1 VLSI

- Very large scale integration technology allows to fabricate chips and memory.
- VLSI are usually digital, high power, not fault tolerant or robust, and clocked (synchronous), not massively parallel.
- Neuromorphic VLSI contain analog/digital circuits that exploit the physics of silicon to reproduce the bio-physics of neural circuits.

- The goals are to understand biological neural systems using standard CMOS VLSI technology as a tool.
- Known properties of biological systems can be exploited to design devices for engineering applications.

14.2 Neuron circuits

- Reproduce physics of neural computation using subthreshold analog circuits and asynchronous digital circuits.
- Build autonomous learning behaving systems that can interact with the environment in real-time.
- Best exploit for current and future VLSI technologies.
- Suited for nano and emerging technologies.
- Ideal tools for real- and accelerated-time modeling of neural systems.
- Compact, low-power sensory processing devices.
- Can interface directly with living systems.

14.3 Circuits

14.3.1 n-FET subthreshold

- I_0 current-scaling parameter.
- κ_n subthreshold slope factor.
- U_T the thermal voltage.
- V_g the gate voltage, V_s the source voltage, V_d the drain voltage.
- The current is defined to be positive if it flows from the drain to the source.
- $I_{ds} = I_0 e^{\kappa_n V_g / U_T} (e^{-V_s / U_T} - e^{-V_d / U_T})$
- If $V_{ds} > 4U_T$ it becomes $I_{ds} = I_0 e^{\kappa_n V_g / U_T - V_s / U_T}$

14.3.2 p-FET subthreshold

- In traditional CMOS circuits, all n-FETs have the common bulk potential V_b connected to ground (GND) and all p-FETs have a common bulk potential connected to the power supply rail (V_{dd}).
- $I_{ds} = I_0 e^{\kappa_p (V_{dd} - V_g) / U_T} (e^{-(V_{dd} - V_s) / U_T} - e^{-(V_{dd} - V_d) / U_T})$

14.3.3 Current Mirror

- Two MOSFETs of the same size.
- $I_{out} = e^{(V_{s1} - V_{s2}) / U_T} I_{in}$

14.3.4 Differential-pair

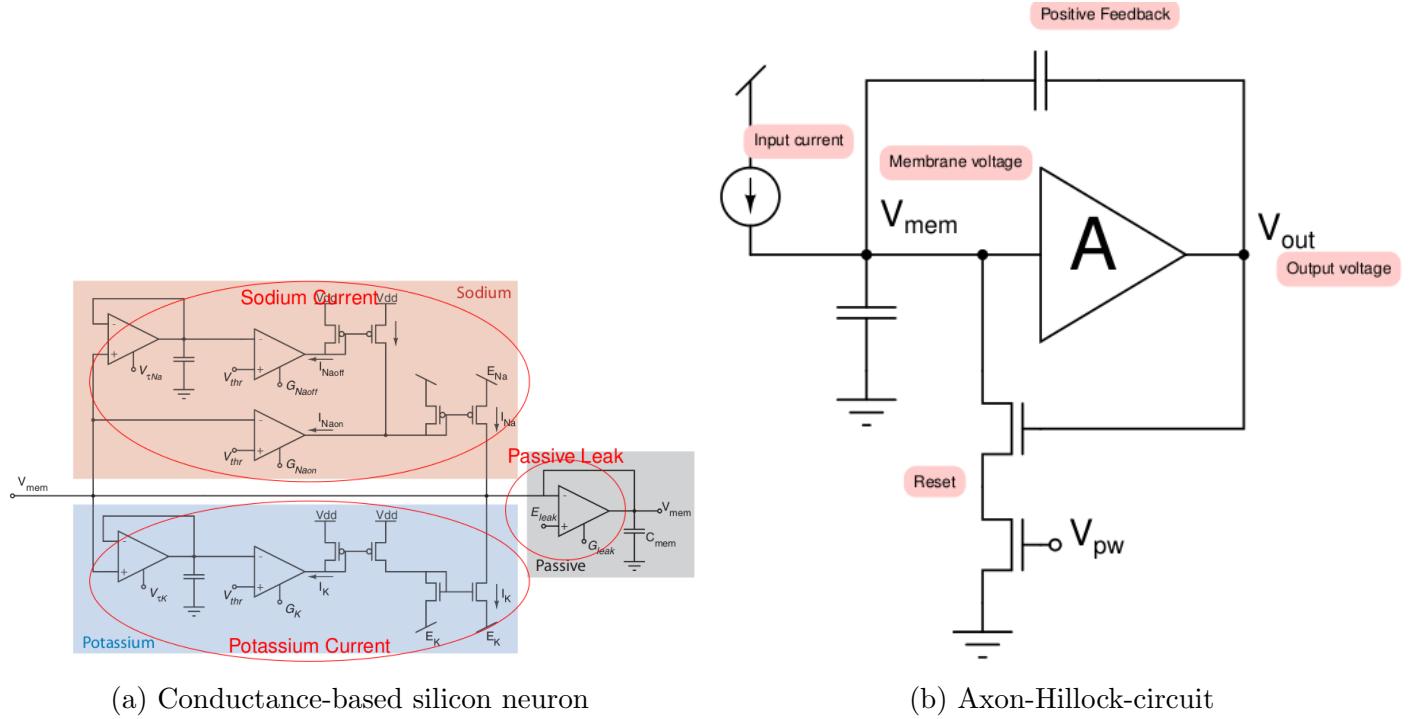
- $I_b = I_1 + I_2 = I_0 e^{\kappa V_b / U_T}$
- $I_1 = I_b \frac{e^{\kappa V_1 / U_T}}{e^{\kappa V_1 / U_T} + e^{\kappa V_2 / U_T}}$
- $I_2 = I_b \frac{e^{\kappa V_2 / U_T}}{e^{\kappa V_1 / U_T} + e^{\kappa V_2 / U_T}}$

14.3.5 Transconductance Amplifier

- $I_{out} = I_b \tanh\left(\frac{\kappa}{2U_T}(V_1 - V_2)\right)$

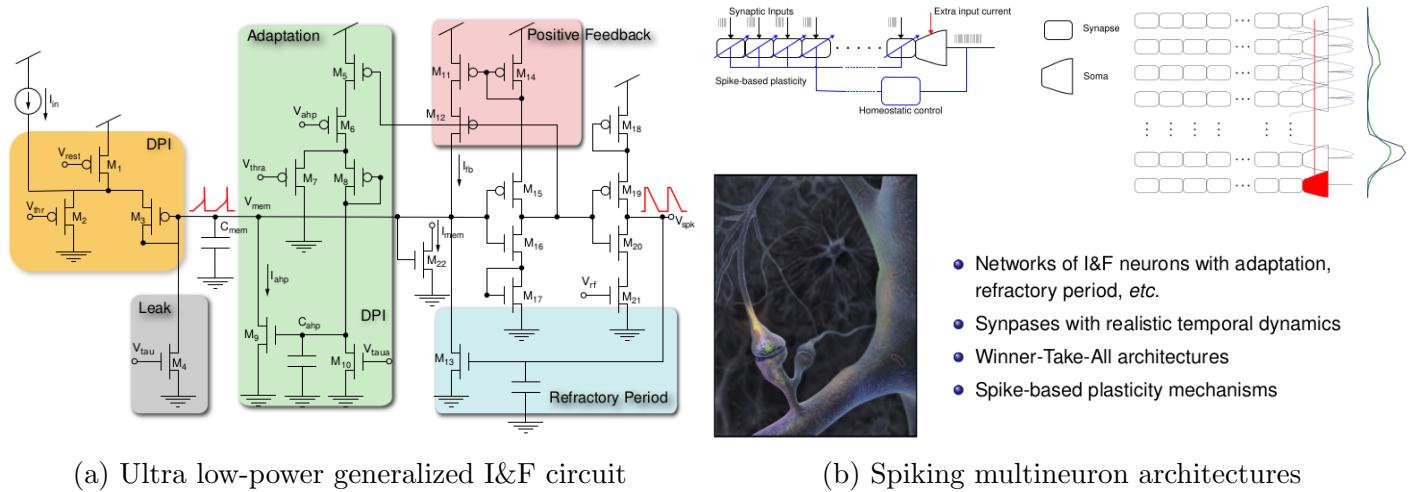
14.4 Remarkable circuits

- McCulloch and Pitts artificial neuron model (first).
- Mahowald and Douglas conductance-based silicon neuron, similar to real cortical neurons.
- Integrate and fire model (I&F).



(a) Conductance-based silicon neuron

(b) Axon-Hillock-circuit



(a) Ultra low-power generalized I&F circuit

(b) Spiking multineuron architectures

- Networks of I&F neurons with adaptation, refractory period, etc.
- Synapses with realistic temporal dynamics
- Winner-Take-All architectures
- Spike-based plasticity mechanisms