FYS388

Summary of example exam questions.

Electrical properties of neurons

1.1 The neuronal membrane

A lipid bi-layer with ion-channels. The lipids tails are hydrophobic and therefore align against each-other. The membrane is $\sim 10\ nm\ (= 10 \times 10^{-9} m)$ thick.

1.1.1 Resting membrane potential

The potential difference between the inside and the outside of a neuron cell where the ion-flow (in terms of charge) is in a steady state. I.e., the potential where the influx and efflux of ions are constant.

The resting potential is around -60 and -70 mV. The membrane is *polarized* (negative).

1.1.2 Depolarization

If the membrane potential becomes less negative (i.e., more positive) we say that the cell is depolarized.

1.1.3 Hyper-polarization

If the opposite happens, i.e., the cell becomes more negative, we say that the cell is hyper-polarized.

1.2 Ions setting up the neuronal membrane potential and mediating electrical signals

The potassium ions (K+) greatly influence the membrane potential. There is generally a big concentration of K^+-ions inside the cell, leading to a concentration gradient. This gradient "force" potassium-ions out of the cell. There are however also ion-pumps (in addition to the ion-channels) which actively pump K^+-ions back into the cell. When the net efflux/influx of ions is stable, the resting potential is reached.

1.3 Ion channels

An ion channel is a pathway into or out of the cell for ions. There are different ion channels corresponding to different ions. That is; there is no universal channel, but one for K^+ and one for Na^+ etc.

1.3.1 Active ion channels

The active ionic channels are dependent on some external input. For instance a change in voltage (voltage-gated ion channels). Active channels therefore open/close depending on various factors, and is what causes a neuron to spike.

1.3.2 Passive ion channels

Passive ionic channels, in contrast to active channels, are always open. This lets ions freely move across the membrane (with respect to gradients etc.) without need for a specific triggering. The passive channels are what cause the resting-potential of the cell, i.e., when the ion flow in and out of the cell is in equilibrium.

1.4 Ion pumps

An ionic pump is a protein which actively transport ions against their gradient. For instance, the Na+/K+ (sodium-potassium) -pump, which insert potassium and remove sodium from the cell even though their concentration gradients are the other way around. The ion pumps require ATP (energy) in order to achieve this.

1.4.1 Pump setting up the membrane potential

The sodium-potassium (Na+/K+) -pump is an important factor in obtaining the resting-potential for a neuron. Potassium (K+) ions naturally move out of the cell (as they are abundant within the cell). Sodium (Na+) the opposite. The sodium-potassium pump moves three Na+ for every two K+ (3Na+ ¡-¿ 2K+), therefore making the outside less polarized (negative) compared to the inside of the cell.

1.4.2 Electrogenic pump

An electrogenic pump is a pump which creates (or moves against) the equilibrium electric potential. For instance, the sodium-potassium (3Na+ / 2K+) -pump is an electrogenic pump because the removed charge is unequal to the inserted charge.

1.5 The Nernst-Planck equation

The Nernst-Planck equation describes the flux of ions across the membrane of a neuron. It combines both the effect of electric fields and diffusion. The flux of ion X is given by

$$J_X = J_{X,\text{diffusion}} + J_{X,\text{drift}}$$

$$= -D_X \left(\frac{d[X]}{dx} + \frac{z_X F[X]}{RT} \frac{dV}{dx} \right)$$

Where D_X is the diffusion coefficient for ion X, $[X]$ the concentration of ion X ($d[X]/dx$ the concentration gradient), z_X the valence of the ion, F Faraday's constant, R the gas constant, T the temperature and V the potential (and therefore dV/dx the electric field).

1.6 Nernst potential

The Nernst potential for an ion is the potential at which the ion is in equilibrium. I.e., the potential across a membrane that balances the ion's concentration gradient, resulting in net zero movement across the membrane.

1.7 Derivation of Nernst potential from the Nernst-Planck equation

Because we want net zero movement we set $J_X = 0$, and solve for the potential.

$$J_X = -D_X \left(\frac{d[X]}{dx} + \frac{z_X F[X]}{RT} \frac{dV}{dx} \right)$$

$$0 = -D_X \left(\frac{d[X]}{dx} + \frac{z_X F[X]}{RT} \frac{dV}{dx} \right)$$

$$= \frac{d[X]}{dx} + \frac{z_X F[X]}{RT} \frac{dV}{dx}$$

$$-\frac{z_X F[X]}{RT} \frac{dV}{dx} = \frac{d[X]}{dx}$$

$$-\frac{z_X F}{RT} \frac{dV}{dx} = \frac{1}{[X]} \frac{d[X]}{dx}$$

$$-\frac{z_X F}{RT} dV = \frac{1}{[X]} d[X]$$

$$-\frac{z_X F}{RT} \int_0^{E_m} dV = \int_{[X]_{\text{in}}}^{[X]_{\text{out}}} \frac{1}{[X]} d[X]$$

$$-\frac{z_X F}{RT} E_m = \ln \frac{[X]\text{out}}{[X]\text{in}}$$

$$E_m = -\frac{RT}{z_X F} \ln \frac{[X]\text{out}}{[X]\text{in}}$$

□

1.8 The principle of electroneutrality

Electroneutrality means that there is no potential difference. A neuron in the resting state is therefore not electroneutral, as it has a potential difference of around -70 mV.

1.8.1 Is a large deviation from electroneutrality needed to set up the resting membrane potential?

No. The resting membrane potential is typically around -70 mV for neurons. This relates to quite a small difference in the charge present inside and outside of the cell. The reason for this potential difference is due to the passive ionic channels and active transportation (such as sodium-potassium pumps).

1.9 The Goldman-Hodgkin-Katz (GHK) model

The Goldman-Hodgkin-Katz model is used for investigating the diffusion of ions through the membrane of a neuron.

1.9.1 Current equation

$$I_X = P_X z_X^2 \frac{F^2 V}{RT} \left(\frac{[X]_{\text{in}} - [X]_{\text{out}} e^{-z_X FV/RT}}{1 - e^{-z_X FV/RT}} \right)$$

1.9.2 Voltage equation

Given the GHK equation for current, and the equilibrium criterion ($\sum I = 0$) we get

$$E_m = \frac{RT}{F} \ln \left(\frac{\sum_X^{\text{ions}} P_X [X]_{\text{out (if + else in)}}}{\sum_X^{\text{ions}} P_X [X]_{\text{in (if + else out)}}} \right)$$

where P_X is the permeability (of ion X), z_X the valence, F Faraday's constant and V the membrane potential.

1.9.3 Approximations assumed in the GHK model

- **Independence** of ions diffusing across the membrane. I.e., no interaction.
- **Constant electric field** is assumed across the membrane.

1.9.4 The GHK model can account for inward and outward rectification of ion currents. What is meant by this?

This means that the model focuses on the ionic conductance both into and out of the cell, i.e., that the conductance of the membrane is different for inwards and outwards currents.

1.9.5 Inward rectification

When an ionic channel is more conductive in the inwards direction. This leads to "rectifying" the current, by sending in more of that ion than what is moving out.

1.9.6 Outward rectification

The opposite, when a channel allows more current to flow outwards than into, is called outward rectification. This process is usually caused by voltage-gated calcium and potassium channels – leading to the re-polarization phase of the action potential.

1.10 Quasi-ohmic relation between membrane potential and ionic current

Ohmic relationships are linear: $\Delta V = IR$. For this to be satisfied, this proportionality must be constant over all values of voltage; and the resistant remain constant over this voltage-change. When we call something "quasi-ohmic", we mean that this linearity holds for small changes in the voltage, but that the relationship is more dynamic (opposed to the firm linear relationship).

1.10.1 Voltage-dependence

Many ion channels are voltage-gated, meaning their probability of being open or closed is a function of the membrane potential. This means that the "resistance" they offer to ion flow is not constant but changes with the voltage, which deviates from ohmic behavior.

1.10.2 Rectification

Some ion channels preferentially allow ions to pass more easily in one direction than the other. This directional flow cannot be described by a simple linear relationship because it depends on both the voltage and the direction of ion flow.

In a "quasi-ohmic" approximation, the behavior of ion channels is simplified to a linear I-V relationship over small voltage ranges or under specific conditions, which makes modeling more tractable while still capturing the essential features of ion flow for those conditions. However, this simplification can break down when the voltage or other conditions change significantly, revealing the complex, non-linear behavior of the channels.

1.11 Capacitive current

The capacitive current is a current (charge flow) across the membrane that does not move through ion channels. This current charges/discharges the membranes capacitance – making the membrane have the same properties as a capacitor. The membrane can in other terms hold and separate charge on either side of the lipid bi-layer.

1.11.1 Mathematical expression

When modelling the membrane, it is modelled as a capacitor:

$$I_c = C_m \frac{dV}{dt}$$

where I_c is the capacitive current, C_m the capacitance and $\frac{dV}{dt}$ the rate of voltage change across the membrane.

1.12 Derivation of the reversal potential (Em) for a neuron with several quasi-ohmic ion channels

$$\begin{aligned} I_m &= I_x + I_y + I_z \\ &= g_x(V - E_x) + g_y(V - E_y) + g_z(V - E_z) \\ &= (g_x + g_y + g_z)\left(V - \frac{g_x E_x + g_y E_y + g_z E_z}{g_x + g_y + g_z}\right) \\ &= g_m(V - E_m) \end{aligned}$$

where

$$g_m = \frac{1}{R_m} = g_x + g_y + g_z \qquad \text{and} \qquad E_m = \frac{g_x E_x + g_y E_y + g_z E_z}{g_x + g_y + g_z}$$

□

1.13 Derivation of a differential equation for a simple "RC-circuit" neuron

For a RC-neuron we have the capacitive and ionic currents

$$I_{\text{capacitive}} = C_m \frac{dV}{dt}$$

$$I_{\text{ionic}} = \frac{V - E_m}{R_m}$$

When looking at the whole cell, with a surface area a, through an electrode (using Kirchhoff's current law) we get

$$I_{\text{electrode}} = a \times I_{\text{capacitive}} + a \times I_{\text{ionic}}$$

$$a \times I_{\text{capacitive}} = -a \times I_{\text{ionic}} + I_{\text{electrode}}$$

$$C_m \frac{dV}{dt} = \frac{E_m - V}{R_m} + \frac{I_{\text{electrode}}}{a}$$

□

1.14 During and after injection solutions to differential equation

$$\begin{aligned} \text{DURING} \quad & A + B(1 - e^{-t/\tau}) \\ \text{AFTER} \quad & A + Be^{-t/\tau} \end{aligned}$$

1.15 Solving for the membrane potential receiving constant current starting at an initial time and determining the constants A, B, and C

$$\frac{dV}{dt} = \frac{E_m - V}{C_m R_m} + \frac{I_{\text{electrode}}}{C_m a}$$

$$V(t) = A + B(1 - \exp\left(-\frac{t}{C_m R_m}\right))$$

When solving the differential equation we can see that $C = \tau = C_m R_m$, which is the time constant. A and B can further be found by solving the equation at $t = 0$ and $t = \infty$.

$$\begin{aligned} V(t=0) &= A + B(1 - \exp\left(-\frac{0}{C_m R_m}\right)) \\ &= A + B(1 - 1) \\ &= A \end{aligned}$$

□

$$\begin{aligned} V(t=\infty) &= A + B(1 - \exp\left(-\frac{\infty}{C_m R_m}\right)) \\ &= A + B(1 - 0) \\ &= V(0) + B \end{aligned}$$

Which means that $V(0) = A = E_m$ is the resting potential of the cell. □

1.16 What is the limiting value of V when t goes to infinity?

1.16.1 During current injection

When the cell is receiving constant current, the voltage goes towards a new "resting" potential.

$$\begin{aligned} V(0) &= E_m \\ V(t=\infty) &= V(0) + B \\ V(\infty) &= E_m + B \\ V(\infty) &= E_m + I_{\text{electrode}} R_m / a \end{aligned}$$

This new potential is the previous resting potential plus an additional potential difference.

1.16.2 After current injection

After the current has been injected, the voltage goes back towards the resting potential.

$$V(\infty) = E_m$$

1.17 At a time "e", the current is turned off, determine the constants A', B', and C'

Rewriting the equation, but now for a discharging capacitor, we get

$$V(t) = A' + B' \exp\left(-\frac{t - t_e}{C'}\right)$$

Solving this at the boundary conditions, we get

$$\begin{aligned} V(0) &= A' + B' \exp\left(-\frac{0 - t_e}{C_m R_m}\right) \\ &= A' + B' \exp\left(\frac{t_e}{C_m R_m}\right) \end{aligned}$$

□

$$\begin{aligned} V(\infty) &= A' + B' \exp\left(-\frac{\infty - t_e}{C_m R_m}\right) \\ &= A' \end{aligned}$$

□

where A' then is the resting potential E_m of the cell, C' the same as before, and B' an unknown that depends on the membrane potential at t_e.

1.18 The membrane time constant τ_m

The time constant is

$$\tau_m = C_m R_m$$

which characterises how quickly the membrane potential of the neuron responds to input.

1.19 Input resistance

The input resistance is a measure of how much the membrane potential of a neuron changes in response to current input.

$$R_m = \frac{\Delta V}{\Delta I}$$

Hodgkin-Huxley model

2.1 Hodgkin and Huxley's development of their model of action potential propagation

The Hodgkin-Huxley model of action potential propagation is a complex mathematical explanation of how action potentials propagate down the axon. The equations captures the complex interactions between the ion channels.

The reason for their model being as important as it is, was that it provided the first quantitative description of action potentials in neurons.

2.1.1 Squid giant axon

The squid giant axon is as the name describes, a giant axon. This means that it is easy to investigate through measurements (compared to smaller-scaled axons). Therefore, because of practical reasons, they chose to focus on this.

2.1.2 Outline the scientific approach Hodgkin and Huxley used to develop their model

Their model relied greatly on experimental data, and they were able to approximate this data through their equations.

They recorded intracellular activity using a voltage clamp to analyse current flow based on different voltages. By modifying the extracellular concentration of sodium (Na+), they inferred the contributions of sodium and potassium ions to the current. They then fitted the results to a mathematical model which included this ion-selective voltage-dependent channels controlled by multiple gating particles.

The Hodgkin-Huxley-model provides a comprehensive understanding of how action potentials occur, and their dynamics along the axon.

2.2 Clamps

2.2.1 Current clamp

A current clamp is a method for "clamping" the current inside a neuron. That is, to hold the current at a constant value. This is then used to measure the changes in membrane potentials over different currents.

An electrode is inserted into the cell, which is used to inject a specific amount of current. By doing this, a neurons threshold current can for instance be determined.

2.2.2 Space clamp

A space clamp is used to hold the membrane potential constant (across the whole neuron). This eliminates the spatial variations in membrane potentials, simplifying the study of ion channels and membrane properties.
An electrode is inserted inside the cell and one outside. Current is injected into the cell in order to keep a constant potential difference between the two electrodes.

2.3 Ion channel currents included in the model

The Hodgkin-Huxley-model included the following ionic channels:

- **Na+** Sodium
- **K+** Potassium
- **L** Leakage (Cl- and others)

2.4 Action potential generation

$$I_{\text{capacitive}} = C_m \frac{dV}{dt}$$

$$I_L = \bar{g}_L (V - E_L)$$

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

$$I_K = g_K(V,t)(V - E_K)$$

We can rewrite $g_x = \bar{g}_x p_x(V,t)$, where $p_x(V,t)$ is the (probability of the channel being open for single cells and) fraction of open channels (for the cell).

The currents for potassium and sodium channels need to be fitted to experiments.

2.4.1 Potassium K+

Hodgkin and Huxley based the following equations on experimental data. They found that four gates for the K+ channel was a good fit (n^4).

$$I_K = \bar{g}_K n^4 (V - E_K)$$
$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n$$

$$\alpha_n(V) = 0.01 \frac{V + 55}{1 - e^{-(V+55)/10}}$$
$$\beta_n(V) = 0.125 e^{-(V+65)/80}$$

where V is in mV.

2.4.2 How were the model parameters describing the potassium current determined?

Through trial and error. The parameters were found by fitting the model to experimental curves.

2.4.3 Sodium Na+

The sodium channels (unlike potassium ones) peaks and then decays to zero over time. The model therefore both has an activation variable m (as n for K+), and an inactivation variable h.

$$
\begin{aligned}
I_{\text{Na}} &= \bar{g}_{\text{Na}} m^3 h (V - E_{\text{Na}}) \\
\frac{dm}{dt} &= \alpha_m (1 - m) - \beta_m m \\
\frac{dh}{dt} &= \alpha_h (1 - h) - \beta_h h
\end{aligned}
$$

$$
\begin{aligned}
\alpha_m(V) &= 0.1 \frac{V + 40}{1 - e^{-(V+40)/10}} \\
\beta_m(V) &= 4e^{-(V+65)/18} \\
\alpha_h(V) &= 0.07e^{-(V+65)/20} \\
\beta_h(V) &= \frac{1}{1 + e^{-(V+35}/10}
\end{aligned}
$$

2.4.4 How does the model for the sodium current differ from the model for the potassium current?

The potassium channels conductance increases over time until it stabilizes at a steady state value for $t = \infty$. The sodium channel, however, peaks and then decays to zero. Therefore, two parameters m and h are needed. These parameters control the activation and inactivation of the channel.

2.4.5 Inactivation variable

The inactivation variable is the h. This is found in the sodium modelling, and describes the probability that the inactivation process has **not** occurred. I.e. that the sodium channel is open.

2.5 Full Hodgkin-Huxley model

$$
C_m \frac{dV}{dt} = -\bar{g}_L (V - E_L) - \bar{g}_K n^4 (V - E_K) - \bar{g}_{\text{Na}} m^3 h (V - E_{\text{Na}}) + I_{\text{stim}}
$$

Where

$$
\begin{aligned}
C_m &= 1.0 \frac{\mu F}{\text{cm}^2} \\
E_{\text{Na}} &= 50\,\text{mV} & E_K &= -77\,\text{mV} & E_L &= -54.4\,\text{mV} \\
g_{\text{Na}} &= 120 \frac{\text{mS}}{\text{cm}^2} & g_K &= 36 \frac{\text{mS}}{\text{cm}^2} & g_L &= 0.3 \frac{\text{mS}}{\text{cm}^2}
\end{aligned}
$$

2.6 Gating particle

Each ion channel is controlled by one or more gating particles. These gating particles can be in an *open* or *closed* position, and determines whether the ion channel is open or not. For the channel to be open, **all** gating particles must be open.

2.6.1 How is the dynamics of the gating particles modeled in the Hodgkin-Huxley model?

If a channel has z gating particles, the probability of the channel being open is n^z for potassium channels and m^z for sodium channels. Based on experimental data, Hodgkin and Huxley found n^4 and m^3 to be good fits.

2.7 Ions carrying the leak current

The leak current is a passive current across the neuron's membrane independent of the action potential mechanisms. This current is mainly chloride (Cl-).

2.8 Refractory periods

2.8.1 Absolute refractory period

The time during and immediately after an action potential. This is when a neuron is completely incapable of initiating another action potential, regardless of stimulus.

This period corresponds to the time when the sodium channels are either open or in the inactivated state (when h is low).

2.8.2 Relative refractory period

The period following the absolute refractory period. The neuron can in this stage initiate another action potential, but requires a stronger stimulus than usual.

This period corresponds to the phase when sodium channels are returning to their resting state, and the membrane potential is being re-polarized (and hyper-polarized). h begins to recover.

2.8.3 How does the Hodgkin-Huxley model account for the refractory period of neurons?

The refractory periods are encapsulated in the inactivity variable h.

2.9 Temperature-dependent ion-channel dynamics

The movements of particles are highly dependent on temperature, which affects the rate of reactions. The temperature therefore also affect how quickly channels open and close when stimulated, as well as the ion mobility.

2.9.1 What is a Q10 factor?

Quantifies the effect of a $10°C$ increase in temperature on the rate of biochemical process or reaction.

$$\text{Q10} \begin{cases} < 1 & \text{decrease in rate with increasing temperature} \\ = 1 & \text{no temperature dependence} \\ > 1 & \text{increase in rate with increasing temperature} \end{cases}$$

With ion channels, a Q10-factor is typically greater than 1.

Multi-compartmental modelling and cable equation

3.1 Isopotentiality

An isopotential neuron is when the membrane potential is constant across the whole neuron. I.e. that there are no significant voltage differences across the membrane for the whole neuron.

3.1.1 When is isopotentiality a good approximation?

Whether or not to model a neuron isopotentially is dependent on the study and the neuron in question.

Generally, one can assume neurons to be isopotential when they are small and/or compact. This means that the cell body is small enough that electrical signals can spread without leaking across the whole neuron.

Also, if a neuron displays low levels of synaptic activity or if synaptic inputs are uniformly distributed across its membrane, the changes in the potential can be modeled as isopotential.

One can also approximate bigger neurons as isopotential. This makes modeling for instance networks a lot less computationally expensive.

3.2 Cable theory

3.2.1 How can non-isopotential neurons be modeled?

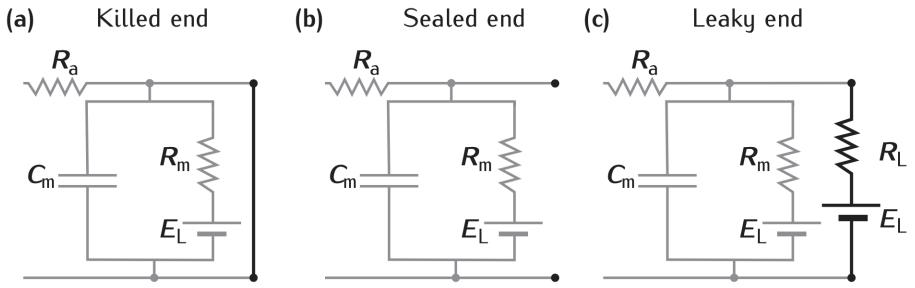
By dividing a neuron into various compartments (e.g., one for the soma and one for the axon), each individual compartment can be isopotential, but differ between each other.

3.2.2 The principles behind multi-compartmental modeling

Neurons are modeled as an electrical cable, divided into compartments, and is used to simulate the electrical properties of neurons. These compartments each represents a small section of the neuron's structure, and together form the whole neuron.

3.2.3 Boundary conditions

The boundary conditions are crucial for accurately simulating the electrical properties of neurons. Specifically the ends of the cable, which is either the dendrites or the axon.



(a) **Killed(open)-end** Models the boundary as open-circuited. This means that the ends have no potential; $\delta V/\delta x = 0$ at the end of the cable. No current flows out of this end. This means that the cable (neuron) does not actively connect to other cells or structures.

(b) **Sealed-end** Models the boundary as an insulator. Like the killed end, no current flows out of this end, but the potential is nonzero.

(c) **Leaky-end** Somewhere in-between a killed- and sealed-end, allowing some current to leak out.

3.3 Derivation of the cable equation from the fundamental equation for multi-compartmental modeling

$$I_j^M = I_j^{\text{cap}} + I_j^{\text{ion}} + I_j^{\text{stim}} = \pi \times d \times l \times C_m \frac{dV_j}{dt} + \pi dl \frac{V_j - E_m}{R_m} + I_j^{\text{stim}}$$

$$\pi \times d \times l \times C_m \frac{dV_j}{dt} = \pi dl \frac{E_m - V_j}{R_m} + \pi d^2 \left(\frac{V_{j+1} - V_j}{4R_a l} - \frac{V_j - V_{j-1}}{4R_a l} \right) - I_j^{\text{stim}}$$

$$C_m \frac{dV_j}{dt} = \frac{E_m - V_j}{R_m} + \frac{d}{4R_a} \left(\frac{V_{j+1} - V_j}{l^2} - \frac{V_j - V_{j-1}}{l^2} \right) - \frac{I_j^{\text{stim}}}{\pi dl}$$

□

3.4 Derivation of the steady-state solution for a semi-infinite cable with a constant current injected in one end

$$C_m \frac{\partial V(x,t)}{\partial t} = \frac{E_m - V(x,t)}{R_m} + \frac{d}{4R_a} \left[\frac{1}{\partial x} \left(\frac{V(x+\partial x,t) - V(x,t)}{\partial x} - \frac{V(x,t) - V(x-\partial x,t)}{\partial x} \right) \right] + \frac{I_e(x,t)}{\pi d}$$

Where the term inside the square brackets goes towards $\partial^2 V/\partial x^2$ when $\partial x \to 0$:

$$\frac{\partial^2 V(x,t)}{\partial x^2} = \lim_{\partial x \to 0} \frac{1}{\partial x} \left(\frac{V(x+\partial x,t) - V(x,t)}{\partial x} - \frac{V(x,t) - V(x-\partial x,t)}{\partial x} \right)$$

With this inserted into the original equation we get:

$$C_m \frac{\partial V(x,t)}{\partial t} = \frac{E_m - V(x,t)}{R_m} + \frac{d}{4R_a}\frac{\partial^2 V(x,t)}{\partial x^2} + \frac{I_e(x,t)}{\pi d}$$

Which can be rewritten to:

$$\tau_m \frac{\partial V(x,t)}{\partial t} = E_m - V(x,t) + \frac{dR_m}{4R_a}\frac{\partial^2 V(x,t)}{\partial x^2} + \frac{I_e(x,t)R_m}{\pi d}$$

$$= E_m - V(x,t) + \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} + \frac{I_e(x,t)R_m}{\pi d}$$

□

3.4.1 The length constant lambda λ

In the equation above, τ_m is the membrane time constant ($R_m C_m$), and lambda

$$\lambda = \sqrt{\frac{dR_m}{4R_a}} = \sqrt{\frac{r_m}{r_i}} \quad \begin{matrix} \leftarrow \text{MEMBRANE} \\ \leftarrow \text{INTERNAL} \end{matrix}$$

the electronic length constant (for a cylindrical cable), which is a typical length scale. In the equation, $r_m = dR_m$ is the membrane resistance per unit length, and $r_i = 4R_a$ the internal (axial) resistance per unit length.

That is, the balance between the membrane resistance and the internal resistance of the neuron. It's value therefore provides a measure of how far an electric signal can travel along the dendrite/axon before it decays significantly.

3.5 Derivation of the input resistance for a semi-infinite cable with a constant current injected in one end from the steady-state solution

In the steady-state condition, the temporal derivative of membrane potential ($\partial V/\partial t$) is zero, which simplifies the equation significantly.

When looking at a semi-infinite cable, we can make some simplifications. Assuming we have a current I_e injected at one end of a semi-infinite cable, we get

$$\frac{\partial V}{\partial t} = E_m - V + \lambda^2 \frac{\partial^2 V}{\partial x^2} \quad (+ \text{ current at } x = 0)$$

$$0 = \frac{d^2 \hat{V}}{dx^2} - \frac{1}{\lambda^2} \qquad (\hat{V} = V - E_M \quad \rightarrow \quad \frac{\partial \hat{V}}{\partial x} = \frac{\partial V}{\partial x})$$

$$0 = \frac{\partial^2 \hat{V}}{\partial x^2} - \frac{1}{\lambda^2}\hat{V}$$

Solving this differential equation yields

$$\hat{V}(x) = \hat{V}(0)e^{-x/\lambda} \qquad (e^{-x/\lambda} \text{ diverges as } x \to \infty)$$

$$V(x) = E_m + (V(0) - E_m)e^{-x/\lambda}$$

$$R_\infty = \frac{\Delta V}{I_e} = \frac{V(0) - E_m}{I_e} \qquad \text{INPUT RESISTANCE}$$

□

Synapses

A synapse is a connection between two neurons. More specifically, the connection between one neuron's axon and another dendrite. The synaptic cleft, i.e., the gap between one neuron's axon and the other's dendrite, is a physical space of around $20 - 30\ nm$ ($n = 10^{-9}$) which the neurotransmitter (chemical substance) diffuses across. This is a slow process (compared to electrical signals), but the gap is small enough for the information (neurotransmitter) to diffuse across efficiently.

4.1 Chemical synapse

Most common. A neurotransmitter is released from the presynaptic neuron which then bind to the receptors in the postsynaptic neuron, initiating a response.

4.2 Electrical synapse

Electrical synapses the ionic current to directly move between neurons. This is faster than the chemical synapses. The electrical synapse, omitting the neurotransmitter, makes the response less controlled.

4.3 Postsynaptic receptors

In a chemical synapse, a neurotransmitter is sent between the neurons. The most common postsynaptic receptors are *ionotropic* and *metabotropic*.

4.3.1 Ionotropic receptors

These receptors are directly linked to ion channels, which open in response to neurotransmitter binding - allowing ions to flow across the membrane.

- **AMPA & NMDA** are responsive to neurotransmitter *glutamate*.
- **$\mathbf{GABA_A}$** are responsive to neurotransmitter *GABA*, and are typically inhibitory (reducing neuronal excitability).

4.3.2 Metabotropic receptors

These receptors are indirectly linked to ion channels through proteins and second messengers. The play a part in a variety of cellular processes and have longer-lasting effects compared to ionotropic receptors. **$\mathbf{GABA_B}$** is an example of a metabotropic receptor, which is involved in slow inhibitory processes.

4.4 Electrical response at the postsynaptic side of a chemical synapse

Through the familiar equation below, the current can be modelled by the conductivity of the postsynaptic receptor times the voltage difference of the membrane potential and the synapse.

$$I_{\text{syn}}(t) = g_{\text{syn}}(t)(V(t) - E_{\text{syn}}) \qquad \text{for } t \geq t_s$$

4.4.1 Functions for the postsynaptic conductance following the presynaptic arrival of an action potential

i. exponential decay $\quad g_{\text{syn}}(t) = \bar{g}_{\text{syn}} e^{-(t-t_s)/\tau} \Theta(t - t_s)$

ii. α-function $\quad g_{\text{syn}}(t) = \bar{g}_{\text{syn}} \frac{t - t_s}{\tau} e^{-(t-t_s)/\tau} \Theta(t - t_s)$

iii. β-function $\quad g_{\text{syn}}(t) = \bar{g}_{\text{syn}} \frac{\tau_1 \tau_2}{\tau_1 - \tau_2} \left(e^{-(t-t_s)/\tau_1} - e^{-(t-t_s)/\tau_2} \right) \Theta(t - t_s)$

Where $\Theta(t)$ is the (Heaviside) unit step function $\Theta(t \geq 0) = 1$, $\Theta(t < 0) = 0$.

4.5 Synaptic plasticity

The synapses can change strength in response to activity. This often connected to learning and memory. Synaptic plasticity can be induced by various stimuli.

When the strength of a synapse decreases, this is referred to as **synaptic depression**. In contrast, **synaptic facilitation** is when the strength of a synapse increases.

4.5.1 Long-term potentiation (LTP)

If neurons frequently get activated "together", their synaptic strength may increase. This is where "cells that fire together, wire together" comes from. This increased efficiency can be due to various molecular structure changes;

i. Increased number of neurotransmitter receptors.

ii. Enhanced release of neurotransmitters.

iii. Morphological changes (in dentritic spines).

iv. Intracellular signaling pathways (calcium-inflow (Ca2+) due to activation of NMDA receptors).

4.5.2 Spike-timing dependent plasticity (STDP)

A more specific synaptic plasticity is the spike-timing dependent plasticity. This depends on the precise timing of pre- and post-synaptic spikes. The main idea is that the order and timing of neuronal firing are crucial.

If a pre-synaptic neuron fires just before a post-synaptic neuron ($\sim 20ms$ after), the synapse is strengthened. The reason for this is that the pre-synaptic neuron is seen as contributing to the firing of the post-synaptic neuron. In contrast, if the post-synaptic neuron fires first, the synapse is weakened.

4.6 Modelling spike-timing dependent plasticity

$$\Delta w_{ij} = \begin{cases} A_{\text{LTP}} e^{-\Delta t/\tau_{\text{LTP}}} & \text{if } \Delta \geq 0 \\ -A_{\text{LTD}} e^{-\Delta t/\tau_{\text{LTD}}} & \text{if } \Delta t < 0 \end{cases}$$

Where *LTP* is long-term potentiation and *LTD* long-term depression, and

$$\begin{aligned} t_i &= t_{\text{pre}} \qquad \text{time of presynaptic spike} \\ t_j &= t_{\text{post}} \qquad \text{time of postsynaptic spike} \end{aligned}$$

$$\begin{aligned} \Delta t &= t_i - t_j \\ &= t_{\text{pre}} - t_{\text{post}} \end{aligned}$$

4.7 Modelling electrical synapses

Two axons connected by a gap junction can be modelled by ohmic connections,

$$\begin{aligned} I_1 &= g_c(V_2 - V_1) \\ I_2 &= -I_1 = g_c(V_1 - V_2) \end{aligned}$$

Active ion channels

Ionic channels in neurons can either be active or passive. *Active* ion channels are dependent on either voltage levels or molecular bindings, while *passive* channels always are "open".

5.1 Voltage- and ligand-gated ion channels

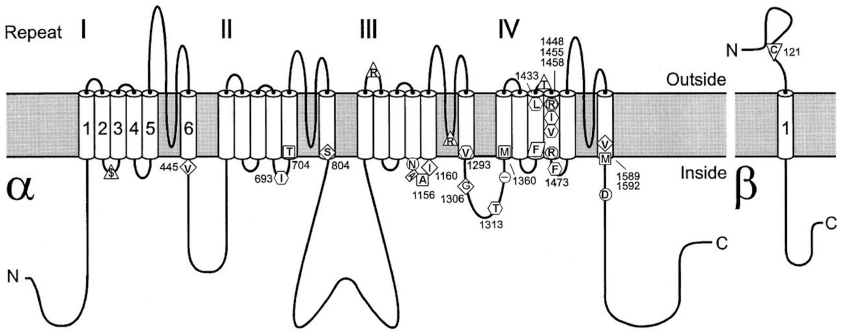
As the names explain; voltage-gated ion channels depend on the membrane voltage of the neuron, and the ligand-gated ion channels on chemical (molecular) bindings such as a neurotransmitter.

5.1.1 Voltage-gated ion channel structure

Voltage-gated channels are **crucial** for the generation (and propagation) of action potentials. These channels open or close in response to neuronal membrane potential changes. In humans, there are a ~ 100 different types of voltage-gated ion channels.

Composed of several sub-units forming a pore (channel) through which ions can pass when open.

Most studied (Na+, K+ and Ca2+) channels typically have *four homologous domains (I-IV), each with six trans-membrane segment (S1-S6).*



5.2 Nomenclature (naming) schemes for ion channels

- **IUPHAR** Chemical symbol of principal permeating ion (e.g., K, Na, Cl and so on).
- **Gene** Set by committee.
- ***Ad hoc*** (Sometimes) used when gene combinations not known (e.g., I_A and I_h).

5.3 Experimental techniques for investigating ion channels

- **Single channel recordings**

  Technique involving recording the activity of individual ion channels. It's highly detailed, and allows for observing the opening and closing of single channels. These recordings are done using a *patch-clamp electrode*. This method involves inserting an electrode which "isolates" a patch of the membrane.

- **Channel blockers**

  Specific blockers are used to isolate certain types of ion channels. This helps the studying of other ionic channels (by removing specific channels from the mix – making it easier to investigate the wanted channels).

  - **TTX (tetrodotoxin)** Blocks sodium (Na+) channels. Sodium channels are essential for action potentials, and by blocking these, one can study how sodium currents contribute to neural activity.
  - **TEA (tetraethylammonium)** Blocks some potassium (K+) channels. Potassium channels are key for repolarizing the neuron after action potentials, and by blocking these, one can study how potassium plays a role in neuronal excitability and signal transmission.

- **Channel isolation by mRNA transfection**

  By injecting mRNA into cells that normally do not express ion channels ("empty" cells), one introduces said ionic channels. By doing this, one can investigate the effects and properties of certain ion channels in isolation.

- **Gating current**

  Current from gate opening itself can be measured (when ions are nonpresent in the surrounding solution).

5.4 Structure of gating-particle models for ion channel currents

Gating-particle models assume that the opening and closing (i.e., gating) of ion channels are controlled by the movement of charged particles within the channel structure.

Ion currents modelled in the Hodgkin-Huxley way by means of *activating* (a) and *inactivating* particles (b). Their dynamics is described by:

$$I(t) = \bar{g} a^x b^y (V - E)$$

For potassium and sodium current, this is:

$$I_K = \bar{g}_K a^4 b^0 (V - E_K) \qquad I_{Na} = \bar{g}_{Na} a^3 b^1 (V - E_{Na})$$

In *thermodynamic models* the form of the rate coefficients are derived from "transition state theory".

$$x_\infty = \frac{1}{1 + e^{-(V - V_{1/2})/\alpha}}$$

$$\tau_x = \tau_x(V; V_{1/2}, \delta)$$

■

Intracellular signaling and calcium

6.1 Calcium concentration importance (in contrast to that of sodium, potassium and chloride)

When neurons spike, it's the calcium (Ca2+) concentration that determine neurotransmitter release. While sodium (Na+), potassium (K+) and chloride (Cl-) ions are important for action potential propagation, it's often just their current that is interesting (and therefore what's modelled). While for the synapse, its the calcium concentration that it vital.

The intracellular concentration of calcium being $\sim 10^{-3}$ magnitudes smaller than other ions, calcium currents will affect the intracellular concentrations significantly. The reversal potential (Nernst potential) for calcium is

$$E_{Ca} = \frac{RT}{Z_{Ca}F} \ln \frac{[Ca]_{\text{out}}}{[Ca]_{\text{in}}}$$

6.2 Diffusion

Diffusion is a slow process, that doesnt move molecules very far. It's therefore important for short-distance transport inside cells (and less so for larger distances).

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right)$$

$$= D\nabla^2 c$$

where D is the diffusion coefficient (constant) describing how fast the substance diffuses, and $\nabla^2 c$ indicating that the net movement is from high to low concentration.

Solution of diffusion equation with N molecules (e.g., Ca) starting at $t = 0$:

$$c(\vec{r}, t) = \frac{N}{(4\pi D t)^{3/2}} e^{-r^2/(4Dt)}$$

$$= \frac{N}{(\sqrt{2\pi}\sigma(t))^3} e^{-r^2/(2\sigma(t)^2)}$$

□

with a Gaussian distribution with time-dependent standard deviation $\sigma(t) = \sqrt{2Dt}$.

6.2.1 Concentration profile over time of N molecules released at a point

Knowing that molecules move from high-concentration areas to low-concentration areas, we know that the initial high concentration (N) at the point will diffuse radially outwards over time.

Assuming a D of $2 \times 10^{-10} m/s$, we can plug in different times to get an idea of how far the molecules diffuse;

$$\text{Diffusion } \sigma(t) \sim \sqrt{2Dt}$$

$1\mu s$	$r_{\text{diffusion}} \sim 0.02\mu m$
$10ms$	$r_{\text{diffusion}} \sim 2\mu m$
$1s$	$r_{\text{diffusion}} \sim 20\mu m$
$100s$	$r_{\text{diffusion}} \sim 200\mu m$

6.3 Dynamics of calcium concentration

$$\frac{\partial [Ca^{2+}]}{\partial t} = J_{\text{diff}} - J_{\text{buff}} + J_{\text{cc}} - J_{\text{pump}} - J_{\text{up}} + J_{\text{rel}} - J_{\text{leak}}$$

J_{diff} Diffusion flux.

J_{buff} Calcium buffering. Interactions (and bindings) to other molecules in the intracellular space.

J_{cc} Ionic calcium current (electric) I_{cc}.

J_{pump} Membrane-bound pumps contributing to maintaining low resting-level calcium concentrations (by pumping against gradient). E.g., Ca-Na-pumps or Ca-ATPase-pumps (PMCA):

$$J_{\text{pump}} = V_{\text{pump}} \frac{[Ca^{2+}]}{K_{\text{pump}} + [Ca^{2+}]}$$

J_{up} Calcium uptake into intracellular stores like the *endoplasmic reticulum* (ER) via Ca-ATPase-pumps (SERCA):

$$J_{\text{up}} = V_{\text{up}} \frac{[Ca^{2+}]^2}{K_{\text{up}}^2 + [Ca^{2+}]^2}$$

2 because two ions are bound and transported per ATP molecule.

J_{rel} Calcium release from intracellular stores like the ER. Either

$$J_{\text{rel}} = V_{\text{rel}} R([Ca^{2+}]) \left([Ca^{2+}]_{\text{store}} - [Ca^{2+}]\right)$$

or

$$R([Ca^{2+}]) = \frac{[Ca^{2+}]^n}{K_{\text{rel}}^n + [Ca^{2+}]^n}$$

where n is a suitable Hill coefficient.

J_{leak} Leakage.

Brain tissue

The brain consists of two cell types; **neurons** and **glial** cells. The glial cells support and protect the neurons, and come in various types.

40% Glial cells

7.0.1 Astrocytes

Maintain chemical balance in the extracellular space. They are star-like (*astro*), and can store ions. In this way, they are able to suck excess ions to stabilize concentration gradients (i.e., move ions into one "leg" and out another).

7.0.2 Myelin

Works as an insulator around axons. The main types are **oligodendrocytes** and **Schwann cells**.

7.1 20% Extracellular space (ECS)

The space (volume) around cells is filled with a fluid. This fluid serves as a medium for the exchange of ions, neurotransmitters and other molecules between cells.

The fraction of the ECS in brain tissue is estimated to be $\sim 20\%$. Neurons and glial cells take up $\sim 40\%$ each.

7.1.1 Extracellular concentrations of ions and the activity of neurons

The ionic concentrations of the ECS are essential for the electrical activity of neurons. The ions contribute to both the resting potentials and action potentials of neurons. Therefore, changes in the extracellular concentrations significantly affects neuron excitability and synaptic transmissions.

In standard theory (i.e., cable equation and Hodgkin-Huxley model) the extracellular ion concentrations were assumed to be constant, and grounded ($V_e = 0$).

7.2 Extracellular diffusion

Diffusion of molecules in the ECS follows the same physical laws as "standard" diffusion, and is therefore bound by the same equations.

7.2.1 Tortuosity $\lambda \approx 1.6$

When modelling extracellular diffusion, a *tortuosity*-parameter is introduced. This parameter (λ) represents hindrances and obstacles to "free diffusion", and is estimated to be around 1.6.

In addition, the volume fraction of ECS (20%) is also taken into account; $\alpha = 0.2$. That is, diffusion can only occur in 20% of the total tissue volume.

The flux density is given by Fick's law in 3D, $\vec{J}_{X,diff} = -D_X^* \nabla[X]$, where X is the ion. The continuity equation therefore becomes

$$\begin{aligned} \frac{\partial[X]}{\partial t} &= -\nabla \vec{J}_{X,diff} + \frac{s_X}{\alpha} \\ &= D_X^* \nabla^2[X] + \frac{s_X}{\alpha} \qquad\qquad D_X^* = \frac{D_X}{\lambda^2} \end{aligned}$$

□

where s_X is a source term (ions added per tissue volume), scaled by the volume fraction α.

7.3 Volume conductor theory

Biological tissue is considered as volume conductors, and therefore follow specific physical laws.

7.3.1 Electrical conductivity

The electrical conductivity of the ECS is a measure of how efficiently the electrical signal is propagated (i.e., drifts).

The flux density of ion X due to 3D electrical drift is given by

$$\vec{J}_{X,drift} = -\frac{FD_X^*}{RT} z_X [X] \nabla V_e$$

where V_e denotes the ECS potential.

The current associated with ion X is proportional to the flux;

$$\vec{I}_{X,drift} = F z_x \vec{J}_{X,drift}$$

And the total current density (for all ion-types) is therefore the sum of these:

$$\begin{aligned}
\vec{I} &= \sum_X \vec{I}_{X,drift} \\
&= -\frac{F^2}{RT} \left(\sum_X D_X^* z_X^2 [X] \right) \nabla V_e \\
&= \sigma \vec{E}_e \\
&= -\sigma \nabla V_e
\end{aligned}$$

□

where the conductivity is defined as

$$\sigma = \frac{F}{RT} \sum_X D_X^* z_X^2 [X]$$

7.3.2 The extracellular potential from a point current source when sigma is isotropic and constant

Since V_e only changes in the radial direction, we can rewrite the current as

$$\vec{I} = -\sigma \nabla V_e \quad \Rightarrow \quad I(r) = -\sigma \frac{dV_e}{dr}$$

and insert this into $i_e = 4\pi r^2 I(r)$ we get

$$\begin{aligned} \frac{dV_e}{dr} &= \frac{-i_e}{4\pi\sigma r^2} \qquad \text{defining } V_e(\infty) = 0 \\ V_e(r) &= \frac{i_e}{4\pi\sigma r} \end{aligned}$$

which expands to

$$V_e(\vec{r}) = \sum_k \frac{i_{e,k}}{4\pi\sigma|\vec{r} - \vec{r}_k|}$$

□

for several point sources.

Instead of working with point sources, we introduce a current-source density

$$\begin{aligned} c(\vec{r}, t) &= \nabla \vec{I} \\ &= -\sigma \nabla^2 V_e \qquad \text{where} \qquad \int\int\int_{\text{volume}} c dV = i_e \end{aligned}$$

7.4 Ephaptic coupling

When neurons activate they cause fluctuations in V_e, which in turn affects membrane potentials and neighbouring neurons (as well as the "source" neuron itself).

7.5 Electrodiffusion

The dynamics of an ECS concentration is governed by both diffusion and electrical drift of ions, i.e., it's of electrodiffusive nature.

Electrodiffusion is modelled by the Nernst-Plancks continuity equation with the flux-density containing both a diffusive- and drift-term.

$$\begin{aligned} \frac{\partial [X]_e}{\partial t} &= -\nabla \vec{J}_{X,diff} + \frac{s_X}{\alpha} \\ &= -D_X^* \nabla^2 [X]_e - \frac{F D_X^*}{RT} z_X [X]_e \nabla V_e \end{aligned}$$

□

To solve the equation (numerically), V_e must be defined. The two ways this may be done are:

7.5.1 (i) Poisson-Nernst-Planck (PNP) framework

In the Poisson-Nernst-Planck framework, the extracellular charge density ρ_e is expressed as a function of extracellular ion concentrations $[X]_e$, while ϵ is the permittivity of the medium.

$$\nabla^2 V_e = -\frac{\rho_e}{\epsilon} \qquad \text{where} \qquad \rho_e = F \sum_X z_X [X]_e$$

7.5.2 (ii) Electroneutral frameworks (e.g., Kirchhoff-Nernst-Planck (KNP))

An alternative to *PNP* rather derive V_e from the constraint that the bulk solution should remain electroneutral.

$$\frac{\partial \rho_e}{\partial t} = \begin{cases} 0 & \text{everywhere without membrane} \\ -c_{\text{cap}} \propto -\frac{dV_m}{dt} & \text{where there is membrane} \end{cases}$$

7.6 Debye length

The electric field around a point charge in vacuum is $E_r \sim \frac{1}{\epsilon r^2}$. However, with ions present, shielding occurs. In brain tissue, any net charge will therefore reside in thin layers around the membrane.

- $\rho_e \neq 0$ on the membrane surface
- ρ_e decays exponentially as a function of distance from membrane surface.

The length scale of this decay, the **Debye length**, is about $1nm$, so that ρ_e is close to zero outside this.

Modeling what you can measure

When trying to understand the brain, experiments are vital. There is a variety of techniques used in order to try and fit mathematical models to real-life data. Neurons are, however, quite small and hard to measure - in addition to being inside the brain. Therefore, various non-intrusive methods has been engineered in order to measure electrical activity in the cortex.

8.1 Experimental techniques used to measure cortical activity

The most common method to measure extracellular activity is to measure the electric potentials. A typical experiment consists of measuring the potential difference between two electrodes – one tip inserted and one as a reference. These experimets have various names depending on where the recording electrode is placed.

- **LFP (local field potential)**

  Inside cortex. Measures the potential in the extracellular space, and reflects the synchronized activity of a population of neurons. High spatial resolution.

- **MUA (multi-unit activity)**

  Inside cortex. Measures the spikes from multiple neurons near the electrode (unlike LFP which measures slow potential-fluctuations). High temporal resolution.

- **ECoG (electrocorticography)**

  On top of cortex.

- **EEG (electroencephalography)**

  On scalp. Non-intrucive.

8.2 Volume-conductor theory

Volume-conductor theory assumes the brain is split into two domains;

- A continuous extracellular (EC) domain. I.e., outside cells.
- A non-continuous intracellular (IC) domain. I.e., inside cells.

8.3 Point-neuron and computation of extracellular potentials

Due to their simplicity, point-neuron-models **cannot** be used to compute extracellular potentials. They are simply too simple, in terms of lacking a spatial structure. The extracellular potential is highly dependent on the more intricate nature of neurons and their interaction with their surroundings. Point-neurons, just representing neurons as a single point, is, however, great for studying network configurations and dynamics.

8.4 Two-compartmental neuron model

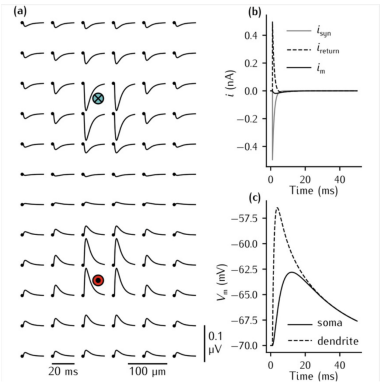
Compartmental models, do, however, make it possible to model the extracellular potentials. The simplest being two compartments.

8.4.1 Extracellular potential set up by a two-compartment neuron model

$$V_e(\vec{r}_{el}, t) = \frac{I_e(t)}{4\pi\sigma|\vec{r}_{el} - \vec{r}_{dend}|} - \frac{I_e(t)}{4\pi\sigma|\vec{r}_{el} - \vec{r}_{soma}|}$$

Where σ is the electrical conductivity

A two-compartmental model with input at the soma, will produce the following LFP-grid.



For a general multicompartmental model (of N compartments), the equation above generalizes.

$$V_e(\vec{r}, t) = \frac{1}{4\pi\sigma}\sum_{n}^{N}\frac{I_n(t)}{|\vec{r} - \vec{r}_n|}$$

$$\sum_{n}^{N} I_n(t) = 0$$

Simplified neuron models

Modelling networks of neurons is extremely computationally costly. It is therefore a goal to make these models as simple as possible (without loosing too much functionality), in order to simulate and study large networks.

9.1 Spike propagation down the axon

> Since spike propagation can be viewed as a current moving through a wire, it is often not needed a detailed model of this behaviour – and just include the time-delay of the propagation instead.

9.2 Two-compartmental models

> A simplification that can be made is to reduce the numbers of modelled compartments – the simplest being the two-compartmental model. This retains the most important dynamics, whilst simplifying the modelling greatly.

9.2.1 The Pinsky-Rinzel model

> The Pinsky-Rinzel model is a reduced two-compartmental model which captures the main functions of a complex CA3 hippocampal pyrimidal neuron. The model includes various ionic currents such as calcium (Ca2+), a calcium-dependent potassium (K+) current, and a sodium (Na+) - potassium (K+) current.
>
> The model incorporates the dynamics of the intracellular calcium concentration, which is important in simulating bursting potentials seen in hippocampal neurons.

9.3 Integrate-and-fire neuron

> The integrate-and-fire neuronal models, as the name explains, accumulates charge/potential, and fires when above a threshold.

9.3.1 The sub-threshold membrane dynamics

> $$C_m \frac{dV}{dt} = -\frac{V - E_m}{R_m} + I$$
>
> $$\tau_m \frac{dV}{dt} = -V + E_m + R_m I$$
>
> Where the neuron fires when $V \to E_m + \Theta$, before reset to E_m.

9.3.2 f-I curve with an absolute refractory period

> $$f(I) = \frac{1}{\tau_r - \tau_m(1 - \Theta/R_m I)}$$
>
> Where τ_r is the absolute refractory period.

9.3.3 Conductance-based synapse

$$I_{\text{syn}}(t) = g_{\text{syn}}(t)(V(t) - E_{\text{syn}})$$
$$g_{\text{syn}}(t) = \bar{g}_{\text{syn}} e^{-(t-t_s)/\tau_{\text{syn}}} \Theta(t - t_s)$$

9.3.4 Current-based synapse

$$I_{\text{syn}}(t) = \bar{I}_{\text{syn}} e^{-(t-t_s)/\tau_{\text{syn}}} \Theta(t - t_s)$$

9.3.5 AMPA and GABA receptors

As E_{syn} for AMPA $\sim 0mV$, $V - E_{\text{syn}}$ is quite constant, and current-based synapse is a good approximation.

E_{syn} for GABA is typically close to E_m, therefore a conductance-based synapse is a good approximation.

9.4 Poissonian spike train

A spiking pattern following a Poissonian distribution is classified a a Poissonian spike train. That is, the probability of firing in action potential per time unit is constant.

$$P(\text{spike}) = \frac{\text{action potential}}{\text{time}} = \not{C}$$

Which is characterised by exponentially decaying interspike interval distribution. This idea comes from a balance in excitation and inhibition, while the firing follows a stochastic (random) pattern.

9.5 Balanced excitation and inhibition

When a neuron on average gets an equal amount of excitatory and inhibitory inputs, it's in balance.

This balance leads to stable network dynamics, independent of external input. The network, in other terms, is able to adapt the convey the same amount of information across immense and low stimuli, as the balance and firing-rate is constant.

9.6 The Stein model

Integrate-and-fire neuron receiving infinitely short current pulses (δ-function pulses) with a Poisson distribution is the idea of the Stein model. For these models, the balanced input of excitatory and inhibitory gives a greater variability (compared to excitatory-only input).

The Stein model can give analytical results for mean firing rate ν for Poisson-input.

9.7 Integrate-and-fire models

9.7.1 Leaky integrate-and-fire LIF

$$C_m \frac{dV}{dt} = I - \frac{V - E_m}{R_m}$$

9.7.2 Quadratic integrate-and-fire QIF

$$C_m \frac{dV}{dt} = I - \frac{(V - E_m)(V_{\text{thresh}} - V)}{R_m(V_{\text{thresh}} - E_m)}$$

9.7.3 Exponential integrate-and-fire EIF

$$C_m \frac{dV}{dt} = I - \left(\frac{V - E_m}{R_m} - \frac{\Delta_T}{R_m} e^{(V - V_T)/\Delta_T} \right)$$

9.8 Noise and the dynamics of integrate-and-fire neurons

Noise can be added either to the input current or the threshold potential.

- **Diffusive** Noisy input current.
- **Escape** Noisy threshold Θ.

Added noise leads to asynchronous firing of neurons. The firing rate is, in other terms, modified stochastically, where the firing rate is the average firing of a *single neuron* or the average across a *population* for a time window.

9.9 Firing-rate function

The firing-rate function tells what the steady-state firing rate is given a constant input current.

Piece-wise linear	$f(I) = k(I - \Theta)$	for $I \geq \Theta$, else 0
Sigmoid	$f(I) = \bar{f}/(1 + e^{-k(I-\Theta)})$	
Step	$f(I) = \bar{f}$	for $I \geq \Theta$, else 0
Static feed-forward	$I_j = \sum_i w_{ij} f_i$	where $f_j = f(I_j)$
Dynamic	$\tau_{\text{syn}} \frac{dI_j}{dt} = -I_j + \sum_i w_{ij} f_i$	where $f_j = f(I_j)$

9.10 Networks

9.10.1 Feed-forward

In feed-forward networks, information moves in one direction (forwards). This means that there is no feed-back connections between neurons.

In feed-forward networks, the current flow is in one direction, and a function of the neurons respective weights. Seen in the equation above.

9.10.2 Recurrent (dynamic)

Opposite that, recurrent networks has connections in a loop, allowing for information-flow between neurons (through the network).

Recurrent networks are more complex. The dynamics being more complex, also allows for the historic (spiking) information to be retained, affecting future spikes, as the firing rate is a function of the previous spikes in addition to new. Recurrent networks therefore allow for generating and responding to temporal patterns in a way that feed-forward networks cannot.

Neuronal networks

10.1 Down-scaling

When modelling networks, they are usually too big to be modelled with great detail. Therefore, scaling down larger networks is an important aspect when imitating and modelling real-life networks. It is in these cases important to keep track of the ratio of excitatory and inhibitory neurons, and that neurons receive the correct amount of inhibitory inputs per excitatory input.

When scaling down networks, inhibitory synaptic connections need to be dealt with. There are two options to achieve this:

DOWN-SCALING BY A FACTOR OF 10

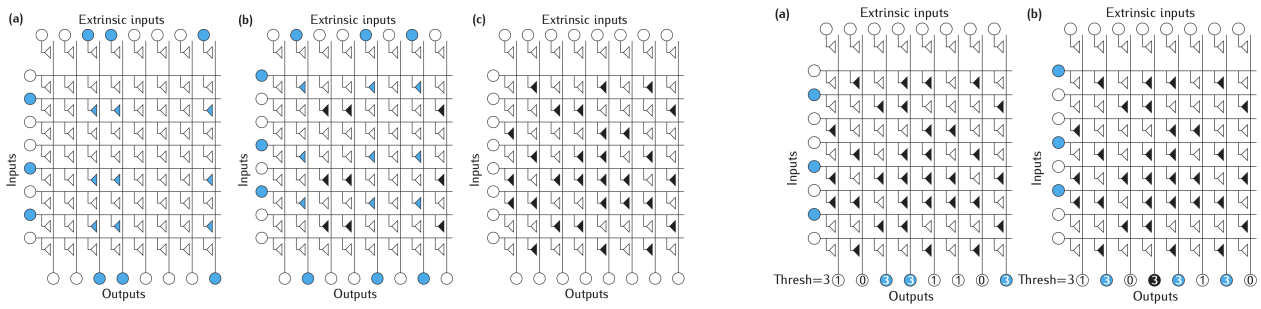
1. Up-scale synaptic conductance from inhibitory neurons by a factor of 10.
2. Create 10 times the number of synaptic contacts per neuron.

10.2 Associative memory

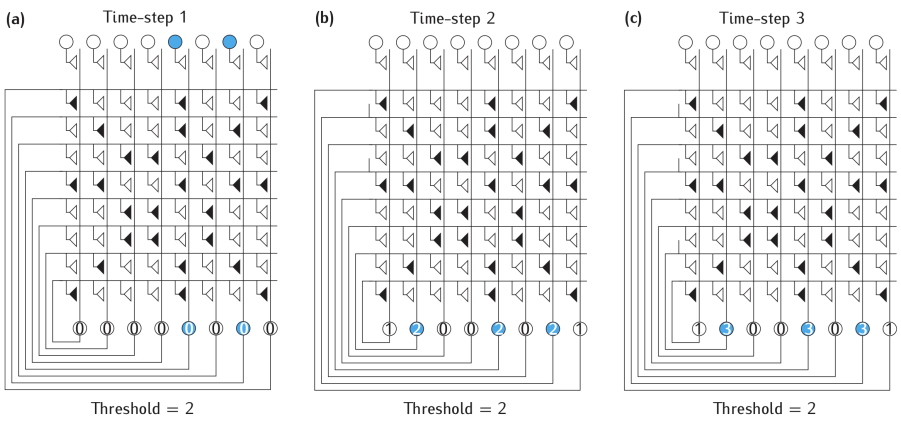
Networks of neurons are able to learn. This learning is achieved by strengthening synaptic connections between neurons who fire in turn (Hebbian learning), for a given input. These associations can be re-created if weighted input for these neurons reaches a threshold, e.g., five of nine neurons forming the memory fires, leading to the full memory (all nine neurons) being activated.

10.3 Storing and recall of memories in associative networks

Storing and recalling memories in a feed-forward network (with extrinsic input for storing memories, i.e., setting up weights):



Recalling memories in a recurrent network, step-by-step, with a threshold of two neurons for recollection:



10.4 Amit and Brunel network

Recurrent network of excitatory and inhibitory integrate-and-fire neurons. Here, N_E is the amount of excitatory neurons and N_I the number of inhibitory neurons.

$$\frac{dV_j}{dt} = -\frac{V_j}{\tau_j} + I_j^{\text{rec}} + I_j^{\text{ext}}$$

where $$I_j^{\text{rec}}(t) = \sum_{i \in E,k}^{N_E} c_{ij} w_{ij} \delta(t - \tau_{ij} - t_i^k) - \sum_{i \in I,k}^{N_I} c_{ij} w_{ij} \delta(t - \tau_{ij} - t_i^k)$$

Where c_{ij} is a random binary variable 0 or 1 denoting whether the connection exists, w_{ij} a randomly drawn Gaussian weight, τ_{ij} a randomly drawn delay $[0.5, 1.5]ms$ and I_j^{ext} the Poisson input.