Theoretical neuroscience notes

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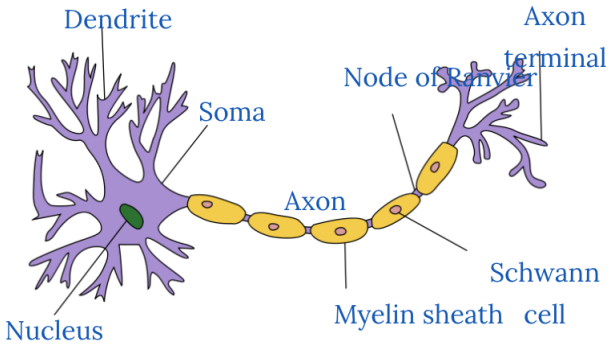
1 Biology primer - neurons

This section introduces the biology of a neuron and the models we will use throughout the course.

1.1 Idealised model of a neuron



The typical model of a neuron comprises a cell body (soma), dendrites and a single axon. Action potentials travel from incoming connections at dendrites to outgoing connections at axon terminals. The junction between one neuron's axon and the next neuron's dendrite is called a synapse.

Dendrites are short and heavily branched, with lengths not exceeding ∼1mm. Axons can be much longer (from several mm up to ∼1m).

In this course we will view the neuron with a few different models:

- To consider general electrical properties and action potentials, we ignore the structure shown above and imagine the neuron to be a leaky bag of charged ions. Ion channels and ion pumps regulate the voltage gradients and we analyse the time dynamics of cell voltage.
- To consider the propagation of incoming action potentials, we consider dendrites as long thin cables and apply standard cable theory analysis.
- To consider the propagation of outgoing action potentials, we add myelinated sections to the cable model and combine the cable electrical properties with the behaviour of ion channels.

1.2 Leaky bag model

The cell membrane holds a bunch of charged ions inside the neuron, which is what gives a neuron its voltage (often called 'membrane potential'). Outside the cell membrane there is also a solution of ions, with different concentrations. The membrane itself is impermeable to these ions. Voltage is regulated by the action of ion channels and ion pumps which are embedded in the cell membrane and allow ions to move in and out of the cell.

The **main ions** we consider are sodium (Na^+), chlorine (Cl^-), potassium (K^+) and calcium (Ca^{++}). Of these, calcium isn't heavily involved in action potentials, so we often ignore it.

Ion channels passively allow the flow of ions between the inside and outside of the cell, as determined by ion concentrations and voltage gradients. The flow is limited, with the channels acting like resistors impeding ion flow. Channels can be opened or closed in response to voltage or the binding of a particular molecule. Ion channels tend to be very selective - they will only allow a specific ion to pass through.

Ion pumps actively move ions between the inside and outside of the cell, to maintain ionic gradients. This requires energy and allows ions to be moved against their concentration gradient.

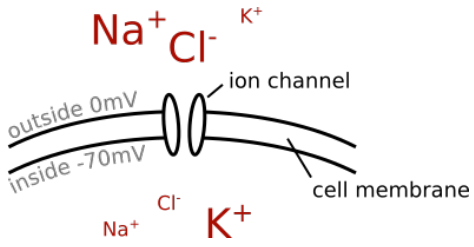


Figure 1: Typical concentration of ions

Sodium and chlorine are much higher outside the cell than inside (∼100mM vs. 5-10mM). Chlorine is the reverse.

Ionic pumps maintain a *resting potential* of -70 mV difference by expelling Na+ out and allowing K+ ions in.

When an ion channel is open, it selectively allows a particular type of ion to move in the direction specified by both (a) the potential gradient and (b) the concentration gradient.

Each type of ion has a *reversal potential* which is the potential at which ions are at an overall equilibrium (and hence would not flow through an open ion channel). For example, Na^+ is higher concentration outside the cell membrane, so the concentration gradient would push it inside. For the voltage to counteract this, we need a *positive* voltage inside (to repel the positive ions).

The reversal potentials we care about are:

- K^+: -77 mV
- Na^+: $+50$ mV

The reversal potential may also be referred to as the "equilibrium potential" or the "Nernst potential".

2 Electrical analysis

This section describes the electrical equations describing the time-varying voltage behaviour of neurons.

2.1 Equations governing voltage

All we need to start to analyse voltage in the cell is two well-known equations from physics:

$$Q = CV; \qquad V = IR \tag{1}$$

The first governs the flow of charge across a capacitor. The capacitor in question is the membrane of the cell - a layer of high resistance between two conductors (ionic solutions on either side). The capacitance of a neuron's cell membrane is of the order of $10nF/mm^2$.

Before using this equation we will differentiate both sides, to give:

$$Q = CV \qquad \implies \frac{dQ}{dt}(= -I) = C\frac{dV}{dt} \implies \frac{dV}{dt} = -\frac{I}{C} \tag{2}$$

In the above equation I is the ***outward*** current.

The second equation describes the current flow across ion channels, but needs adjusting slightly for our model of the neuron. In normal circumstances, zero potential difference would imply zero current. In our case, however, there is always a concentration gradient acting as well as a voltage gradient. We define the *reversal potential* ϵ as the potential difference required to perfectly offset the concentration gradients and result in zero current. Our equation becomes the following:

$$I = \frac{V - \epsilon}{R} = g(V - \epsilon) = \sum_{all\ channels} g_{channel}(V - \epsilon_{channel}) \tag{3}$$

In the above equation, V describes voltage *inside* the cell, and g is the *conductance* of a channel.

2.2 Passive neuron, no external input

Let us assume that the conductance of each channel is constant (this is what we mean by passive). We can combine equations 2 and 3 to give a full differential equation describing the time-varying voltage:

$$\frac{dV}{dt} = -\frac{\sum_x g_x(V - \epsilon_x)}{C} \tag{4}$$

We can simplify this with regard to the sum over different channels, by splitting up the $V - \epsilon_x$ term and dividing everything by $\frac{\sum_x g_x}{C}$:

$$\frac{dV}{dt} = -\frac{\sum_x g_x V}{C} + \frac{\sum_x g_x \epsilon_x}{C} \tag{5}$$

$$\frac{C}{\sum_x g_x}\frac{dV}{dt} = -V + \frac{\sum_x g_x \epsilon_x}{\sum_x g_x} \tag{6}$$

Now let us define $\tau_m = \frac{C}{\sum_x g_x}$ is the membrane time constant ($\sim 10ms$ in practise) and $\epsilon_L = \frac{\sum_x g_x \epsilon_x}{\sum_x g_x}$ is the combined leak potential:

$$\tau\frac{dV}{dt} = -(V - \epsilon_L) \tag{7}$$

This is an easy first order ODE which has the following solution: (see Appendix for derivation)

$$V(t) = \epsilon_L + (V(0) - \epsilon_L)e^{-t/\tau} \tag{8}$$

This can be seen to be an exponential decay toward the steady state value ϵ_L.

2.3 Passive neuron, with generic external input

In practise, we wish to know how a neuron responds to external inputs, which can come either from synaptic inputs (voltage spikes from preceding neurons) or from an experimenter injecting current. Let's add the external input to the last equation, and re-arrange with the same substitutions as before:

$$\frac{dV}{dt} = -\frac{\sum_x g_x(V - \epsilon_x)}{C} + \frac{I_{ext}(t)}{C} \tag{9}$$

$$\tau \frac{dV}{dt} = -(V - \epsilon_L) + \frac{I_{ext}(t)}{\sum_x g_x} \tag{10}$$

$$= -(V - \epsilon_L) + V_{ext}(t) \tag{11}$$

To solve this ODE (for a general input V_{ext}), we rearrange one more time to make it look like a classical linear ODE with a forcing function, to which we can apply the integrating factor approach. We solve for $u = (V - \epsilon_L)$ rather than V directly, and take an integrating factor of $e^{t/\tau}$ (see appendix for a more detailed derivation)

$$\frac{\mathrm{d}u}{\mathrm{d}t} + \frac{1}{\tau_m} u = \frac{1}{\tau_m} V_{ext}(t) \tag{12}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(e^{t/\tau} u(t)\right) = e^{t/\tau} \frac{1}{\tau_m} V_{ext}(t) \tag{13}$$

$$e^{t/\tau} u(t) = \int_{t_0}^{t} e^{t'/\tau} \frac{1}{\tau_m} V_{ext}(t') dt' \tag{14}$$

$$u(t) = \frac{1}{\tau_m} \int_{t_0}^{t} e^{-\frac{(t-t')}{\tau}} V_{ext}(t') dt' \tag{15}$$

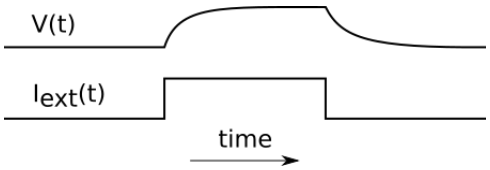
This can be seen to just be an exponential filter applied to the external input. Conclusion: passive neurons integrate external inputs with a quickly-forgetting ($\tau_m \sim 10ms$) filter.

2.4 Passive neuron, with specific external input

If you know the form of the time-varying external input, then you can get a closed-form solution to the membrane potential by evaluating the integral above.

An example of the response is given in Figure 2.

Figure 2: Time course of membrane potential for step input



3 Active channels

So far we have assumed the channel conductances each remain fixed. In reality, there are some passive channels with fixed conductance, but the really interesting dynamics occur because of the presence of channels whose conductance varies with respect to external voltage or chemical binding.

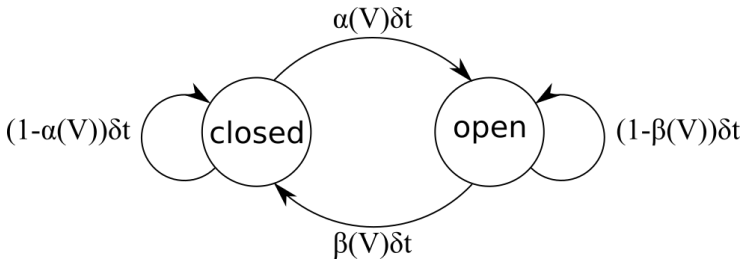
We think of active ion channels as passageways connecting the inside and outside of a neuron, with gates that are controlled via biomolecular mechanics. Gates may be opened in response to changes in voltage, to the binding of a particular biomolecule (neurotransmitter) or ion (typically calcium). They can also be opened by mechanical forces, but we do not consider this in this course.

While we're just considering the neuron as a leaky bag of ions, the gates that control conductance of ion channels tend to be controlled by voltage. Later when we look at what happens at the synapse we'll see other forms of gating.

3.1 Biology - gating

The simplest model of an ion channel is a 'ball-on-stick' analogy. Imagine a charged particle on the end of a stick - this may be positively or negatively charged. This forms a gate, which can be open or closed when the 'ball' (ion) is attracted or repelled by the potential difference. When it is open, ions can flow through. Opening and closing of the gate is a stochastic process which depends on voltage. The probability of transitioning from a closed to an open state (and vice versa) is a function of voltage, and we consider it independent of past history (in reality it has a small refractory period). We can therefore model its behaviour as a Markov model:

Figure 3: Markov model for gating



This model is only valid as $\delta t \to 0$ since for longer timesteps it would be possible to transition multiple times.

In a more general case, there may be many more states, where a state represents a certain conformation of biomolecules.

To derive the dynamics of the system, let us fix voltage so that α and β are constants. Let $m(t)$ be the probability that channel is already open at time t. What is the probability that the channel is open at time $t + \delta t$?

$$\begin{aligned} m(t+\delta t) &= P_{open} * P(o \to o) + P_{closed} * P(c \to o) && (16)\\ &= m(t)(1-\beta\delta t) + (1-m(t))\alpha\delta t && (17)\\ &= m(t) - \beta\delta t m(t) + \alpha\delta t - m(t)\alpha\delta t && (18)\\ &= m(t) + [\alpha - (\alpha+\beta)m(t)]\,\delta t && (19)\\ \frac{m(t+\delta t) - m(t)}{\delta t} &= \frac{\mathrm{d}m}{\mathrm{d}t} = \alpha - (\alpha+\beta)m(t) && (20) \end{aligned}$$

Adding back in the voltage dependence of α, β we rearrange to look like a simple differential equation:

$$\begin{aligned} \frac{1}{\alpha(V)+\beta(V)}\frac{\mathrm{d}m}{\mathrm{d}t} &= \frac{\alpha(V)}{\alpha(V)+\beta(V)} - m(t) && (21)\\ \tau_m(V)\frac{\mathrm{d}m}{\mathrm{d}t} &= m_\infty(V) - m(t) && (22) \end{aligned}$$

The above gives the chance of an individual channel being open. To figure out overall channel conductance, we need to consider the number of open channels. For $N >> 1$, we have:

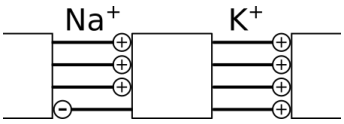
- Expected number of channels open = Nm
- Standard deviation $\propto \sqrt{N}$

The overall conductance is therefore proportional to m.

3.2 Channels with multiple sub-units

In reality, the 'ball-on-stick' analogy is pretty reasonable, but real ion channels have subunits which each act like individual balls on sticks - and the channel is only open if all subunits are open.

Figure 4: Gating for sodium and potassium channels



For sodium the state of the positive subunits are represented with a gating variable $m(V)$ and the negative subunit has the gating variable $h(V)$ (which has the opposite relationship to voltage since it has a negative ion). Luckily the time constants for h and m are different, so we get interesting dynamics rather than the opposite subunits working just against each other. In order for the ion channel to be open, all 4 subunits must be open. This means that conductance is proportional to m^3h. For potassium we have four equal balls, so conductance is proportional to n^4.

We are now in a position to add these dynamic ion channels to the equation governing voltage that we derived in Equation 10. Note that the passive channels are still present (represented by g_p), but we're adding extra terms for dynamic potassium and sodium channels:

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = -(V - \epsilon_L) - \frac{\overline{g}_{Na}}{\sum_p g_p} m^3 h (V - \epsilon_{Na}) - \frac{\overline{g}_K}{\sum_p g_p} n^4 (V - \epsilon_K) + V_{ext}(t) \tag{23}$$

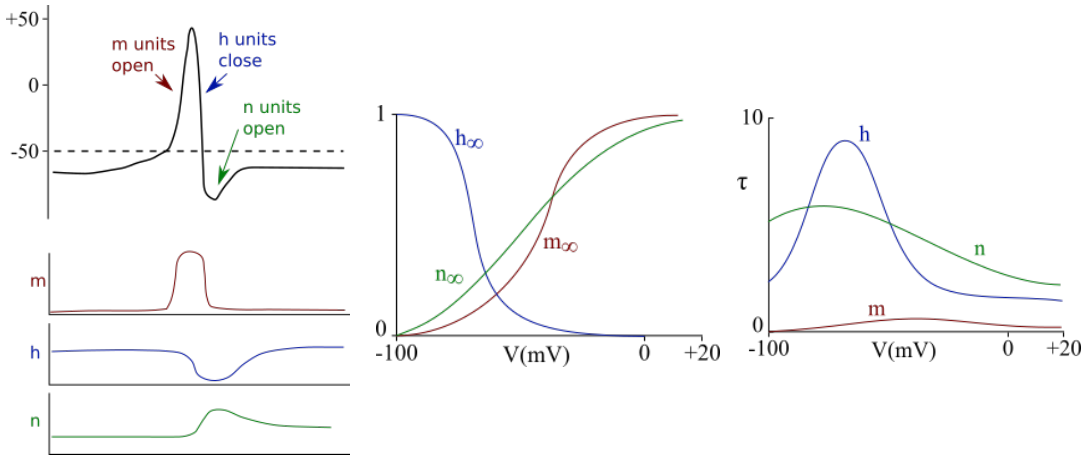
$$= -(V - \epsilon_L) - \rho_{Na} m^3 h (V - \epsilon_{Na}) - \rho_K n^4 (V - \epsilon_K) + V_{ext}(t) \tag{24}$$

We also have three more differential equations describing the gating dynamics:

$$\tau_x(V) \frac{\mathrm{d}x}{\mathrm{d}t} = x_\infty - x \qquad for\ x := [m,\ h,\ n] \tag{25}$$

Overall we now have a set of ODEs in four dimensions. Let's take a look in more detail at the different gate dynamics. The steady-state gating variables are shown in Figure 5, along with the corresponding time constants which tell you how quickly the steady state values are reached upon a change in voltage (low time constant = fast).

Note in particular that m is "very fast" (we often consider it instantaneous) and also that m is much faster than h. This means when voltage increases, the (positive) m subunits open (increasing the voltage and therefore opening more), and then the h subunits close after a delay. This gives an initial runaway increase in voltage, shortly followed by a rapid drop. Let's take a look at the time course for a spike, and see what happens to the different gating units.



(a) Gating during action potential (b) Steady-state gating (c) Gating time constants

Figure 5: Gating behaviour

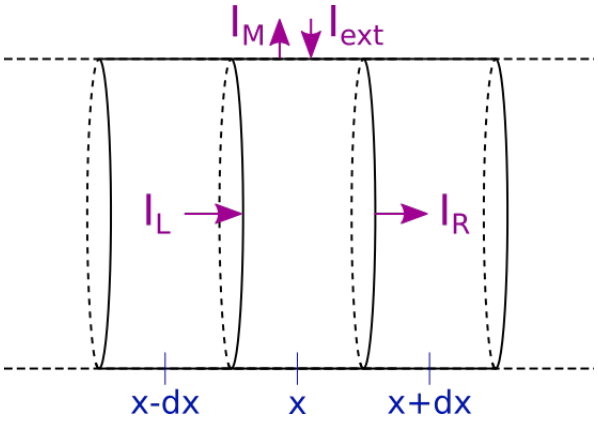
4 Analysis of dendrites

When we analyse dendrites, we treat them as a long homogeneous cable into which current may be injected somewhere in the middle (by an experimenter, or an incoming synapse). For this we use standard cable theory.

4.1 The setup

We split the cable into infinitesimal slices, and analyse one slice in the context of it's neighbours. In particular, we look at the currents flowing in and out of this slice.

- I_{ext} is the current injected into the neuron at position x.
- I_M is the leakage current crossing the membrane (through intrinsic channels).
- I_L and I_R are axial currents coming from/going to neighbouring slices.



4.2 Filling in some maths

We begin with the classic $C\frac{\mathrm{d}V}{\mathrm{d}t} = -I$, where C is the membrane capacitance, and I is comprised of the 4 components identified above.

$$\begin{aligned} C_m \frac{\mathrm{d}V}{\mathrm{d}t} &= I_L - I_R - i_m + I_{ext} \\ &= \frac{V(x-dx) - V(x)}{R_{axial}} - \frac{V(x) - V(x+dx)}{R_{axial}} - i_m + I_{ext} \end{aligned}$$

The two voltages $V(x \pm dx)$ can be replaced by second order Taylor series expansions.

$$\begin{aligned} C_m \frac{\mathrm{d}V}{\mathrm{d}t} &= \frac{[V(x) - dx\frac{\partial V}{\partial x} + \frac{1}{2}dx^2\frac{\partial^2 V}{\partial x^2}] - V(x)}{R_{axial}} - \frac{V(x) - [V(x) + dx\frac{\partial V}{\partial x} + \frac{1}{2}dx^2\frac{\partial^2 V}{\partial x^2}]}{R_{axial}} - i_m + I_{ext} \\ &= \frac{dx^2\frac{\partial^2 V}{\partial x^2}}{R_{axial}} - i_m + I_{ext} \end{aligned}$$

4.3 Filling in material properties

We now need to know how capacitance and resistance scale with dx. This requires some basic physics. The axial resistance of a cable goes *up* with length, and *down* with (cross-sectional) area. This gives us our first equation. We denote the diameter of the dendrite by a.

$$R_{axial} = \frac{\rho l}{A} = \frac{r_L l}{A} = \frac{r_L dx}{\pi a^2}$$

The capacitance of the membrane goes up with the area of membrane involved, which is the circumferential area of the slice, $dx * (2\pi a)$.

$$C_m = c_m A = 2c_m \pi a dx$$

Let's substitute these into our differential equation:

$$\begin{aligned}
\frac{\mathrm{d}V}{\mathrm{d}t} &= \frac{dx^2 \frac{\partial^2 V}{\partial x^2}}{R_{axial}} - i_m + I_{ext} \\
2c_m \pi a dx \frac{\mathrm{d}V}{\mathrm{d}t} &= dx^2 \frac{\partial^2 V}{\partial x^2} \frac{\pi a^2}{r_L dx} - i_m + I_{ext} \\
c_m \frac{\mathrm{d}V}{\mathrm{d}t} &= \frac{dx^2}{2\pi a dx} \frac{\partial^2 V}{\partial x^2} \frac{\pi a^2}{r_L dx} - \frac{i_m}{2\pi a dx} + \frac{I_{ext}}{2\pi a dx} \\
c_m \frac{\mathrm{d}V}{\mathrm{d}t} &= \frac{a}{2r_L} \frac{\partial^2 V}{\partial x^2} - i_m + i_{ext}
\end{aligned}$$

where i_m and i_{ext} are current densities.

We now multiply both sides by the membrane's intrinsic resistance, r_m.

$$\begin{aligned}
r_m c_m \frac{\mathrm{d}V}{\mathrm{d}t} &= \frac{r_m a}{2r_L} \frac{\partial^2 V}{\partial x^2} - r_m i_m + r_m i_{ext} \\
\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} &= \lambda^2 \frac{\partial^2 V}{\partial x^2} - r_m i_m + r_m i_{ext}
\end{aligned}$$

In the last step we define the *electrotonic length* λ, which we will later see sets the scale of spatial variation in membrane potential. Finally, we note that the leak current density is given by $i_m = (R - E_L)/r_m$ and thus $r_m i_m = (V - E_L)$.

4.3.1 The passive cable equation

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = \lambda^2 \frac{\partial^2 V}{\partial x^2} - (V - E_L) + r_m i_{ext}$$

If we wanted to include the behaviour of active channels, we'd need to add the Hodgkin-Huxley model to the $r_m i_m$ term.

4.4 Analysis - steady state voltage with constant input

4.5 Input summation in dendrites

In general we might assume that inputs sum linearly, but there are also situation in which we might observe sub- or supra-linear summation. Here we discuss some possible causes...

4.5.1 Sub-linear behaviour

- The voltage change at one synapse reduces the driving force across the membrane at a nearby synapse, reducing the current.
- The opening of synaptic channels decreases the neuron's input resistance, leading to shunting of synaptic current.

4.5.2 Supra-linear behaviour

- Dendritic (NMDA-mediated) action potentials can occur if the PSP is high enough.

4.5.3 Either sub- or supra-linear

- The opening/closing of voltage-dependent gates may change local dynamics.

5 Synapses and plasticity

5.1 Synaptic transmission

Synaptic transmission consists in a cascade of effects initiated by an incoming action potential:
presynaptically:

- Action potential arrives at pre-synaptic terminal
- Voltage-gated Ca^{2+} channels are opened
- Internal $[Ca^{2+}]$ goes up
- With probability $P_{release}$, vesicles fuse with the cell membrane and release their neurotransmitters

post-synaptically:

- With probability p_j, neurotransmitter binds to receptors on the post-synaptic cell membrane, opening type-j channels
- If resulting current is sufficiently high, an action potential may occur

This gives the following expression for synaptic current, in which we assume that no more than one vesicle is involved, which is often a reasonable assumption according to PEL.

$$i_{syn} = -\xi_{syn} \sum_j p_j \bar{g}_j (V - E_j)$$

where $\xi_{syn} = 1$ with probability P_{rel}, otherwise 0; $\bar{g}_j$ gives the conductance of the j-channels, and E_j is the reversal potential of the type-j ion channels.

There's a bunch of maths to do with this, but ultimately we end up with a *complete* model for a neuron, where p_{ij} has it's own time dynamics:

$$\tau_m \frac{\mathrm{d}V_i}{\mathrm{d}t} = -(V_i - E_L) - \text{H-H currents} - \sum_j p_{ij} \bar{g}_{ij} (V_i - E_j)$$

This is pretty much everything you need to describe what happens in the brain at a given point in time, but the more interesting question is how are the parameters regulated? This is where plasticity comes in. The two parameters we consider are $P_{release}$ and synaptic conductances $\bar{g}_{ij}$. $P_{release}$ can be modified on a short (and long) timescale; where $\bar{g}_{ij}$ is only modified on a longer timescale.

5.2 Short term plasticity - modulating release probability

The probability of the release of a vesicle is dependent on two factors:

- Recent incoming action potentials: a release is **more likely** if there is still spare calcium hanging around from recent incoming spikes.
- Recent releases of vesicles: a new release is **less likely** if a vesicle has just been released (in response to an incoming spike) - this is because there are a limited number of vesicles, they take time to replenish themselves, and some vesicles are just less likely to release their contents.

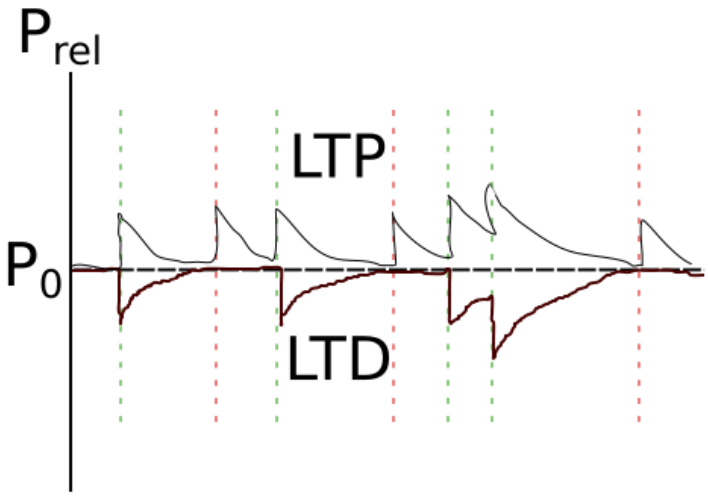
These two things obviously interact: a recent incoming action potential increases the likelihood of a recent vesicle release.

We analyse these dynamics with two versions of a differential equation, with different time constants for LTP vs LTD. In both cases we see a exponential return to steady state release probabilities.

$$\tau \frac{\mathrm{d}P_{rel}}{\mathrm{d}t} = P_0 - P_{rel} + \sum_{\text{spikes j}} \delta(t - t_j) \begin{cases} -\xi_j (1 - f_D) P_{rel} & \text{LTD} \\ f_F (1 - P_{rel}) & \text{LTP} \end{cases}$$

where f_D and f_P are experimentally-determined constants $\in [0, 1]$.

This gives the following exponential behaviour where incoming spikes or outgoing vesicle release triggers deviations from the baseline followed by exponential decay. Green vertical lines show spikes with vesicle release; red lines shown spikes without vesicle release.



5.3 Long term plasticity - modulating conductances

We have many computational models for long-term plasticity but few biological explanations. One of the few postulated mechanisms is the unblocking of NMDA receptors via back-propagating action potentials. To understand this story, we need to piece together a few biological facts.

- **Glutamate** is a very common excitatory neurotransmitter
- Glutamate quickly opens **AMPA** channels which are permeable to sodium and potassium (sometimes calcium but we ignore that).
- Glutamate more slowly opens **NMDA** channels, which are permeable to calcium (as well as sodium and potassium, but they are less important to our story)
- Once calcium ions have been let into the post-synaptic neuron, they can trigger the **insertion** or **deletion** of AMPA channels.
- **Magnesium** ions (Mg^{2+}) block NMDA channels, preventing them from opening.

The combination of these behaviours means that:

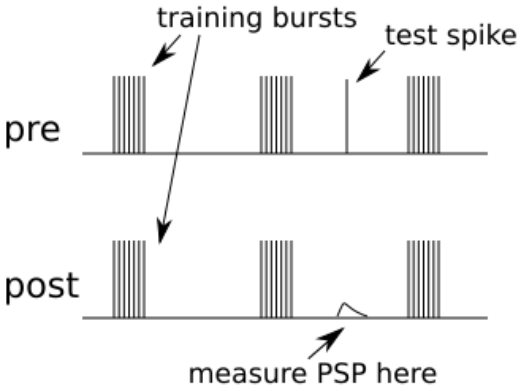
- AMPA channels are responsible for the quick transmission of action potentials; having more or fewer AMPA channels changes the strength of the synaptic connection.
- NMDA channels are responsible for changing the weights of the synaptic connection.
- NMDA channels can **only** be opened when (a) there is glutamate within the synaptic cleft following a pre-synaptic action potential; **and** the post-synaptic neuron is depolarised enough to remove the blocking Mg^{2+} ions from the NMDA channels.
- Depolarisation in the post-synaptic neuron occur via back-propagating action potentials travelling back along the dendrite.

This is great, since it explains Hebbian LTP and LTD - changes are only made when inputs (pre-synaptic spikes) and outputs (post-synaptic spikes) co-occur.

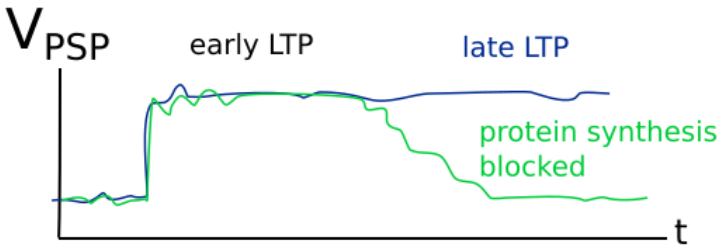
5.4 Some experimental results

5.4.1 Experimental setup

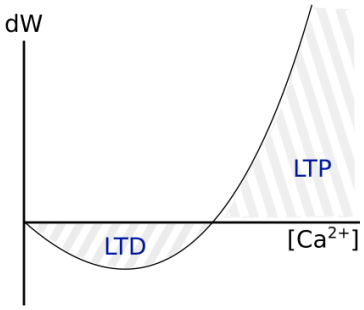
To inspect potentiation and depression in vitro (in brain slices), you find two neurons which are connected, and inject current into both the pre-synaptic and post-synaptic neurons. You can then pair up spiking at each end. Typically spikes are sent simultaneously for brief bursts around 100Hz for about a second at a time. In gaps between the bursts, a single spike is sent to the pre-synaptic neuron and the resulting potential of the post-synaptic neuron (PSP) is measured.



Early and late LTP: If the correlated input bursts are high frequency then potentiation occurs rapidly, and is maintained for days. If protein synthesis is blocked, then after a few hours the potentials return to their previous levels. We refer to the first stage (which is independent of protein synthesis) as *early LTP* and the later stage (which requires protein synthesis) as *late LTP*.



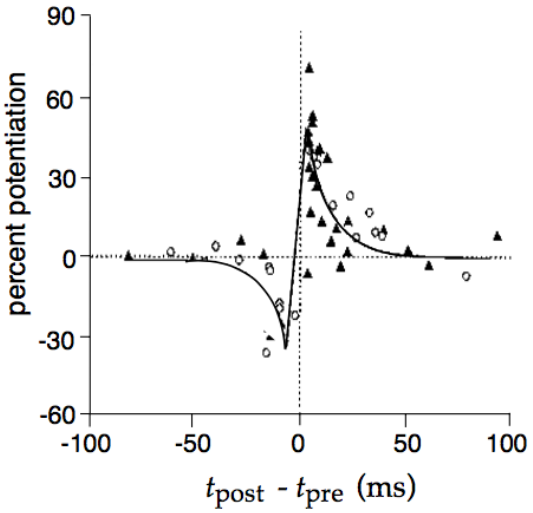
LTD: Long-term depression occurs when pre- and post-synaptic spikes are coincident, but with a lower frequency. The relationship between calcium influx (which is higher when high frequency pulses are sent) and weight changes are given in the following graph.



This looks suspiciously like a threshold rule for Hebbian plasticity. If the second intersection can slide left and right, we get something like the BCM rule.

5.5 Spike Timing Dependent Plasticity

If instead of sending coincident spike bursts you send carefully-timed individual spikes, you can see that depression and potentiation depend on the exact timing of incoming and outgoing spikes. If the post-synaptic neuron spikes shortly after the pre-synaptic spike, potentiation occurs. If the post-synaptic spike happens first, then depression occurs. The classic experiment was originally carried out in cultured cells, but has also been replicated in (young) animals. The following figure is from Dayan and Abbott.



Appendix

ODEs

Separable ODES

For the simple first-order linear ODE:

$$\tau \frac{dv}{dt} = v_\infty - v(t)$$

Let $z = v - v_\infty$, our equation becomes:

$$\tau \frac{dz}{dt} = -z(t)$$

Rearrange to separate dz, dt:

$$\frac{1}{z} dz = -\frac{1}{\tau} dt$$

Integrate both sides for $t = [0, t]$:

$$\int_{z(0)}^{z(t)} \frac{1}{z} dz = \int_0^T -\frac{1}{\tau} dt$$

$$log(\frac{z(t)}{z(0)}) = -\frac{t}{\tau}$$

Rearrange to get $z(t)$:

$$z(t) = z(0)e^{-\frac{t}{\tau}} \tag{26}$$

And substitute back in $z = v - v_\infty$:

$$v(t) = v_\infty + (v(0) - v_\infty)e^{-\frac{t}{\tau}} \tag{27}$$

First order ODEs with forcing function

[integrating factor]

For a simple example, we use the ODE for a passive neuron that is used in Dayan and Abbott's integrate-and-fire model. Note that this example could (with the right substitution) be turned into a separable ODE, but we consider it to have a constant forcing function $R_m I_e$. If the method is unclear, revise integrating factors.

The original ODE is as follows:

$$\tau_m \frac{\partial V}{\partial t} = E_L - V_0 - R_m I_e$$

We make a substitution, $u(t) = V(t) - E_L$ and rearrange to look like the standard integrating factor ODE:

$$\frac{\partial V}{\partial t} + \frac{1}{\tau_m} u(t) = \frac{R_m I_e}{\tau_m} \qquad \textit{compare to:} \qquad \frac{\partial y}{\partial x} + p(x)y(x) = q(x)$$

Now we multiply both sides by the integrating factor $v(x) = e^{\int p(x)dx}$ or $v(t) = e^{\int 1/\tau_m dt} = e^{t/\tau_m}$, and note that the left-hand side looks like (as we expect) the product rule.

$$\begin{aligned} \frac{\partial V}{\partial t} e^{t/\tau_m} + \frac{1}{\tau_m} u(t) e^{t/\tau_m} &= \frac{R_m I_e}{\tau_m} e^{t/\tau_m} \\ \frac{\partial}{\partial t}\left[u(t) e^{t/\tau_m}\right] &= \frac{R_m I_e}{\tau_m} e^{t/\tau_m} \end{aligned}$$

Now we can re-arrange and integrate the RHS, **not forgetting the constant of integration**:

$$\begin{aligned} \frac{\partial}{\partial t}\left[u(t) e^{t/\tau_m}\right] &= \frac{R_m I_e}{\tau_m} e^{t/\tau_m} \\ &= \frac{R_m I_e}{\tau_m} \int e^{t/\tau_m} dt \\ &= \frac{R_m I_e}{\tau_m} \left[\tau_m e^{t/\tau_m} + C_1\right] \\ u(t) &= e^{-t/\tau_m} \frac{R_m I_e}{\tau_m} \left[\tau_m e^{t/\tau_m} + C_1\right] \\ &= R_m I_e + C_2 e^{-t/\tau_m} \end{aligned}$$

We solve for the constant C_2 by considering the initial condition, $u(0) = V(0) - E_L$:

$$\begin{aligned} u(0) = V(0) - E_L = R_m I_e + C_2 \implies C_2 &= V(0) - E_L - R_m I_e \\ \implies u(t) &= R_m I_e + \left[V(0) - E_L - R_m I_e\right] e^{-t/\tau_m} \\ V(t) &= E_L + R_m I_e + \left[V(0) - E_L - R_m I_e\right] e^{-t/\tau_m} \end{aligned}$$

If the forcing function is a function of time rather than a constant, then the integral will be more complicated, but the process is the same.

Second order ODE

$$\begin{aligned} \lambda^2 \frac{\partial u}{\partial x} - u &= r_m i_{ext} \delta(x) \\ u(x) &= c_1 e^{-\frac{x}{\lambda}} + c_2 e^{\frac{x}{\lambda}} \end{aligned}$$