Chemical synapses

Spikes, the voltage pulses that carry signals from neuron to neuron, are notably stereotypical; there aren't big spikes and small spikes, to a good approximation, there are just spikes. However, the effect one neuron has on the other can vary considerably, not just from neuron to neuron, but from time to time. This variablity can occur because of chemical synapses, the complicated biochemical machinery responsible for connect the axon of one neuron to the dendrite of another.

Chemical synapses are not the only synapses, there are also *gap junctions*. If an axon is connected to a dendrite by a gap junction there is a small hole directly connecting the inside of one neuron through to the inside of the other, usually this means that the axon of one neuron is connected to the dentrite of the other, though axon to axon gap junctions are also found. For an axon to dentrite gap junction this means that when a spike travelling along the axon reaches the gap junction some of the charged ions diffuse through the gap changing the charge in the dendrite. In some simple animals like jelly fish most or all of the synapses are gap junctions. There are gap junctions in the mammalian brain, for example gap junctions are thought to be responsible for the dynamics which supports very rapid oscillations in the hippocampus, however, most of the synapses in the mammalian brain are chemical synapses. We will see that this allows a more variable effect of a pre-synaptic spike on the voltage of the post-synaptic dendrite.

In a chemical synapse the pre-synaptic spike does not affect the post-synaptic voltage directly, instead it causes a cascade of bio-electrodynamics events which ultimately causes a transient change in conductance of the post-synaptic membrane.

Roughly, the synapse consists of a protuberance in the axon called the *terminal bouton*, the terminal bouton is held by astrocytes, supporting non-neuronal brain cells, so that it is separated by a tiny gap, called the *synaptic cleft* from a protuberance in the dendrite called the *dendritic spine*; depending on the neurons involved this protuberance might be a small bump, or a substantial spine. Figure 1 indicates the range of spine shapes. The shape of the spine is thought to be important in the modulation of synaptic signalling; this isn't an aspect of synapses we will consider here.

The terminal bouton is filled with tiny bags or bubbles called *vesicles*, these contain special molecules called *neurotransmitters*. When a spike arrives at the terminal bouton it causes calcium gates to open in the cellular membrane, the resulting influx of calcium ions causes some of the vesicles to migrate to the membrane separating the bouton from the synaptic cleft, they burst releasing neurotransmitter into the cleft.

The membrane of the dendritic is pieced by gated ion channels; these are *ligand gated* channels. This means that they contain a receptor site which binds with a particular type of molecule, like a key designed for the receptor site's lock. When the receptor has a molecule bound to it, the gate is open and so ions can pass through the channel, like the other channels we have seen the channel is

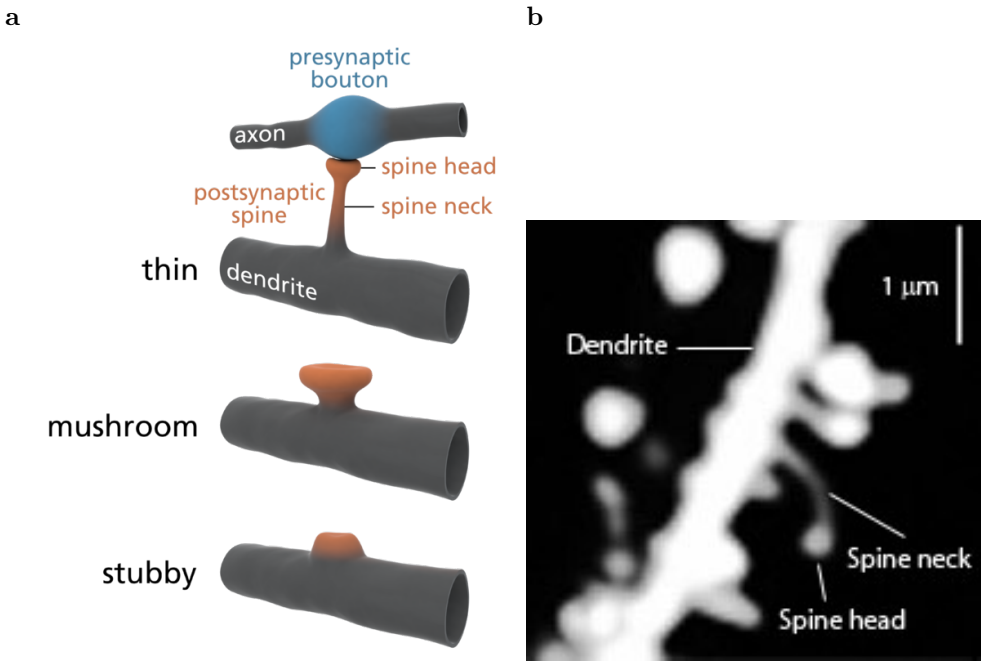

Figure 1: Types of dendritic spines: **a** shows a set of different spine types, **b** shows a photograph of a spiny dendrite of a striatal medium spiny neuron. [Both pictures from `https://en.wikipedia.org/wiki/Dendritic_spine`]

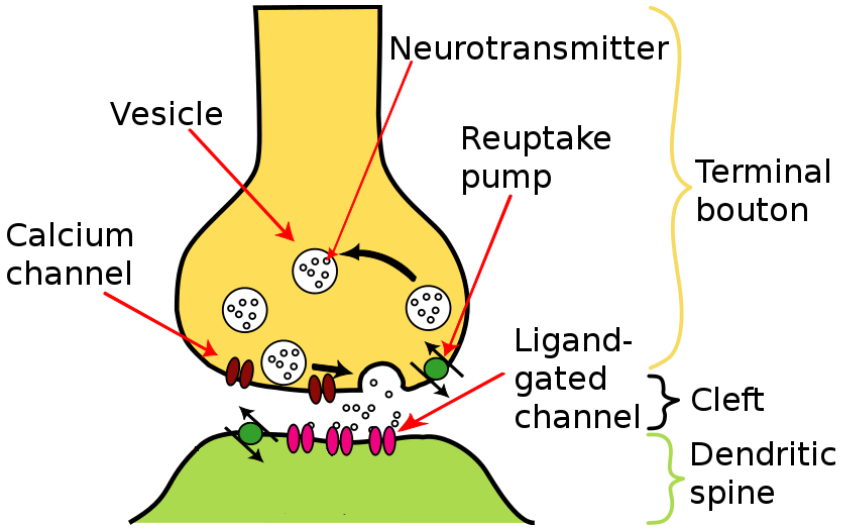

Figure 2: The major parts of the synapse; this shows a vesicle bursting, releasing neurotransmitter into the cleft, this will bind with the ligand-gated channels to allow a current across the membrane of the dendrite. Reuptake pumps are shown in the bouton and the spine, there are also pumps in the astrocyte that surrounds the cleft but isn't shown here. Some is also lost to diffusion. [Diagram modified from one in wikipedia.]

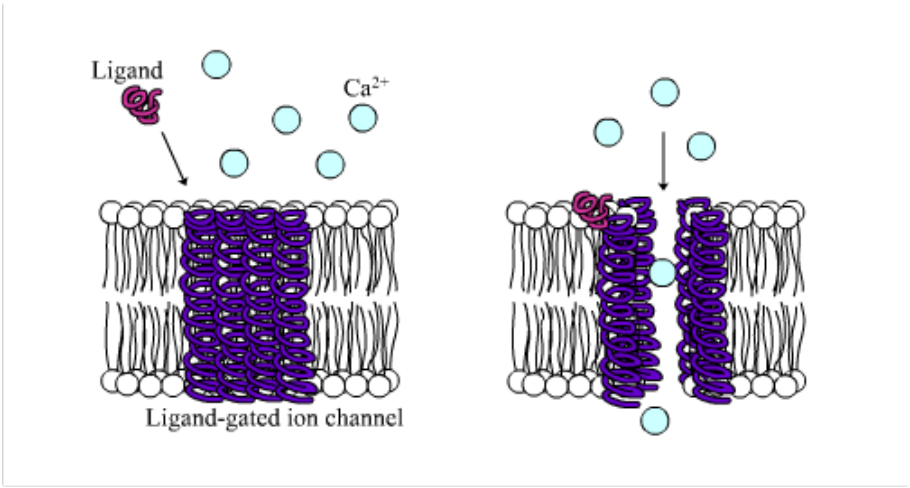

Figure 3: Sketch of a ligand-gated channel; when the neurotransmitter, the ligand, binds to the gate it opens allowing the ions to pass through. This is a Calcium channel, calcium, like sodium, is found in higher concentrations outside the cell so the chemical gradient, as well as the voltage gradient, means these ions flow into the cell from outside, increasing its potential. This is therefore part of an excitatory synapse. Inhibitory synapses have ligand-gated potassium and chlorine channels, potassium, as we have discussed, is at a higher concentration inside the cell and so will flow out, depending on the voltage gradient, lowering the potential inside the cell. Chlorine is at a higher concentration outside the cell but is a negative ion, so when it flows in it also lowers the potential. [Diagram modified from wikipedia.]

ion specific, so only one type of ion can pass through it. In the case of the ligand-gated channels in the dendritic spine, the neurotransmitter binds with the receptor, opening the gate. Hence, after a spike arrives at the synapse the cleft is filled with neurotransmitter and some of that neurotransmitter binds to the gated channels, causing them to open. This in turn allows a flow of ions in or out of the dendrite, changing the voltage there. A cartoon of a ligand-gated channel is given in Fig. 3.

Which ion and which direction, depends on the synapses, we will return to that. For now, though, let us continue describing what happen; after the neurotransmitter floods the cleft it is quickly reabsorbed through neurotransmitter reuptake pumps. Some of the neurotransmitter is absorbed into the bouton, some into the spine and some is absorbed by the astrocyte, the important thing is that the concentration of neurotransmitter in the cleft falls rapidly. Now, the fluid of the cleft has little neurotransmitter, but there is still neurotransmitter bound to the receptors of the ligand gated channels. This gradually unbinds, this is usually imagined to be a random process, because of the Brownian motion

of molecules in the fluid of the cleft and the thermal vibration of the receptor itself, the neurotransmitters unbind as the result of random collisions and thermal variations. As they do so, the channels close again and the conductivity of the dendritic spine's membrane falls back towards zero.

Post-synaptic potential

One important property of neurons is that a given neuron is either *excitatory* or *inhibitory*. If a neuron is excitatory, this means all its synapses are excitatory, that is, they make the post-synaptic neuron more likely to spike by increasing its voltage. In an excitatory neuron opening the ligand-gated channels causes a positive current into the cell, typically this means that they are sodium or calcium channels, so that when they open positive sodium or calcium ions flow into the dendrite. Conversely, if a neuron is inhibitory all its synapses are inhibitory, they make the post-synaptic cell less likely to fire by decreasing its voltage. In an inhibitory synapse opening the ligand-gated channels causes a positive flow out of the dendrite, lowering the voltage. Typically inhibitory channels are either potassium gates, allowing postive potassium to leave the dendrite, or chlorine gates, allowing negatively charged chlorine to flow in.

The post-synaptic change in potential that results from a pre-synaptic spike is called a *post-synaptic potential*; if the synapse is excitatory this is called an *excitatory post-synaptic potential* or EPSP, if it is inhibitory it is called an *inhibitory post-synaptic potential* or IPSP. The profile of PSPs reflects the neurotransmitter dynamics, it rises fast as the neurotransmitter floods the cleft and the ion-channels open, it then decays back to zero following an exponential decay, reflecting the constant rate unbinding process: since any bound molecule has a constant probability of shaking free the number of unbinding events depends on the number of bound molecules, giving an exponential decay.

Often the post-synaptic conductivity is taken to be a what is called an *alpha* function:

$$I_s(t) = g_s s(t)(E_s - V) \tag{1}$$

where $I_s(t)$ is the synpatic current, E_s is the reversal potential of the synapse and $g_s s(t)$ is the conductance, g_s is a constant describing the strength of the synapse and $s(t)$ is

$$s(t) = te^{-t/\tau_s} \tag{2}$$

where τ_s is a time scale, see Fig. 4. Basically the rising part of the α function models the period when there is neurotransmitter in the cleft, this is binding to the channels increasing the conductance; the falling part represents the period where the unbound neurotransmitter has been cleared from the cleft and the bound neurotransmitter is unbinding randomly due to the thermal motion of molecules. It is possible to understand these dynamics in terms of the bucket-like equations we have examined before, but this won't be done here. It is also common to leave out the rising part and just model the conductance as

$$\tau_s \frac{ds}{dt} = -s \tag{3}$$

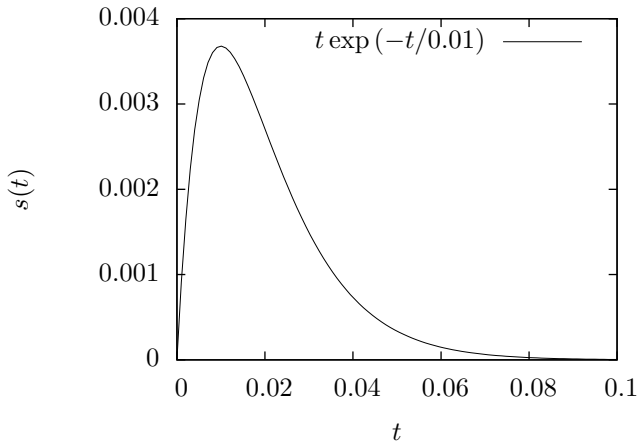

Figure 4: The α-function profile often used to model synaptic conductances, shown here with $\tau_m = 10$ ms.

with

$$s(t) \to s(t) + 1 \tag{4}$$

whenever there is a spike. This is what is done in the coursework, for example.

The complexity of synapses

The chemical synapse is complicated and there are many details of the synapse that can effect the dynamics. For example, the strength of the synapse, that is, the amplitude of the change in conductance that follows a pre-synaptic spike, depends on the number of vesicles released, on the size of the cleft, the speed of reuptake and the number of ligand-gated channels; the shape and duration of the PSP depends on the detailed dynamics of binding, reuptake and unbinding and the effect of the PSP on the post-synaptic soma depends on the shape of the dendritic tree and the details of the diffusive process which conducts the PSP to the soma, a distal synapse will have a different effect to a proximal one. The shape of the dendritic spine can also filter the PSP, modulating its shape.

Some aspects of synaptic dynamics vary from synapse to synapse; usually the length of a timescale depends on the neurotransmitter and receptor; excitatory synapses tend to have shorter time constants than inhibitory ones, but excitatory synapses have two common receptors for glutamate, the most common excitatory transmitter: NMDA-receptors which are quick and AMPA receptors, which are slow. In the case of inhibitory synapses the most common transmitter is called GABA and the common receptors are the simpler GABA-A receptor

and the more complicated GABA-B receptors. We will see that some special synapses release neuromodulators rather than neurotransmitters; these often change behaviors in subtler ways.

There are typically spike-to-spike effects usually described as *short term plasticity*, for example if two spikes arrive one soon after the other, the first might have already opened a substantial quantity of the gates, reducing the effect of the second. If there is a high rate of pre-synaptic spike arrivals the vesicles may be depleted reducing the size of PSPs, this is called *short term depression*; sometimes the opposite is true, the build up of calcium ions in response to a high rate of pre-synaptic spiking can increase the size of PSPs, this is *short term facilitation*. Short term plastic effects, with timescales of 10 ms up to seconds are thought to play an important role in neural computation [1]. This short term plasticity is usually distinguished from long term plasticity, the long term changes in the structure of the synapses that are thought to be responsible for learning and development in the brain.

Synaptic plasticity

Synaptic plasticity usually refers to the long-term changes in synapse strength, an long term increase in synaptic strength is called *long term potentiation* of LTP, a decrease is called *long term depression* or LTD. It is believed that synapses respond to their pre- and post-synaptic activity, so that the changes depend on the behavior of the pre- and post-synaptic neurons. It is not known in detail what rules govern this plasticity, it seems different neurons have different plasticity rules.

The closest thing to an overall rule was formulated by Hebb in 1949 when he said [2]:

> Let us assume that the persistence or repetition of a reverberatory activity (or 'trace') tends to induce lasting cellular changes that add to its stability. [...] When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

In other words, if one neurons tends to cause another to fire, the synapse from the first to the second will get stronger. In artificial neural networks the nodes, modelling neurons, often lack spiking dynamics and so have a continuous state or rate variable; since *Hebbian plasticity* often plays a role in artificial neural networks it is often applied to a rule that strengthens synapses between neurons that are active at the same time, that is, the explicit causal structure is ignored in favor of

> Neurons that fire together wire together.

This leads to a plasticity rule

$$\delta w_{ij} = \eta x_i x_j \tag{5}$$

where w_{ij} is the strength of the synapse from neuron i to neuron j, x_i and x_j are the states of the two neurons and η is a learning rate. Another version is

$$\delta w_{ij} = \eta(x_i - \theta)(x_j - \theta) \tag{6}$$

where θ is a threshold, this allows negative changes, when $x_i > \theta$ and $x_j < \theta$, or visa versa.

Spike-timing dependent plasticity

The late nineties saw a revival of interest in causal, spike-timing dependent plasticity (STDP). A series of papers pointed to experimental evidence for timing effects in plasticity [3, 4, 5, 6, 7] including a definitive demonstration of a STDP changes *in vitro* in [4], the observation of asymmetric STDP *in vivo* in developing Xenopus in [8] and a clear graph of the time dependence of plastic changes *in vitro* in [9].

The famous graph of STDP is shown in Fig. 5. This shows measurements of plastic changes made in an *in vitro* preparation. Electrodes are inserted into two synaptically connected cells and currents are used to cause both to spike periodically with a gap of δt between the pre- and post-synaptic spikes. This causes the synaptic strength to change, if the pre-synaptic spike precedes the post-synaptic spike the synapse gets stronger with the degree of strengthening depending on the size of $|\delta t|$, the bigger the gap the smaller the effect with a roughly exponential profile. The opposite is observed if the pre-synaptic spike arrives after the post-synaptic spike has left, in this case the synapse gets weaker, again the size of the effect falls like an exponential as $|\delta t|$ gets bigger.

There are lots of caveats to be added to this, it is quite an artificial situation, in vitro with periodic spiking; since the changes are only tracked over a show period it isn't clear whether the changes are additive

$$w \to w + \delta w \tag{7}$$

or multiplicative

$$w \to \lambda_w w \tag{8}$$

However, it does give a striking picture of how STDP might work.

In fact, an example of how STDP might support unsupervized learning was given in [10, 11]. A toy model is introduced with multiple neuron inputs feeding forward to a single integrate-and-fire neuron. The inputs are divided into two groups and given a correlation structure so that inputs in the same group are more likely to spike at roughly the same time. This is sketched in Fig. 6. The synapses are then adjusted according to a simple STDP rule. It is seen that one of the two groups 'wins out', its synapses get stronger while the synapses corresponding to the other group gets weaker. Basically if one group, by chance, is slightly more likely to cause the post-synaptic neuron to spike than the other, then the post-synaptic spikes are more likely to occur after the pre-synaptic spikes for that group, so the synapses will get stronger, increasing the effect.

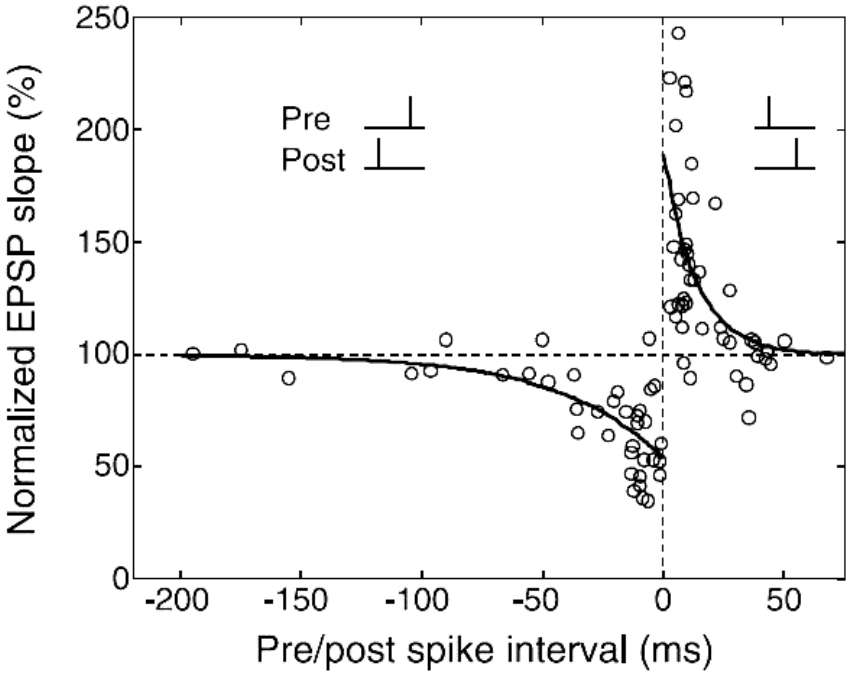

Figure 5: Spike timing dependent plasticity. This shows the change in synapse strength as a function of the timing gap between the pre- and post-synaptic spike.

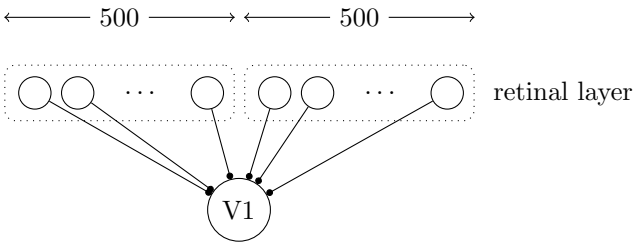

Figure 6: The STDP of Song and Abbott. 1000 input neurons, refered to as retinal neurons, feed forward to a single V1 neuron. The retinal neurons are divided into two groups: the first 500 and the second 500, the two groups provide noisy output, these give the input to the V1 neuron. The inputs from neurons in the same group are correllated, meaning they are more likely to be similar to each other in their activity than neurons from different groups.

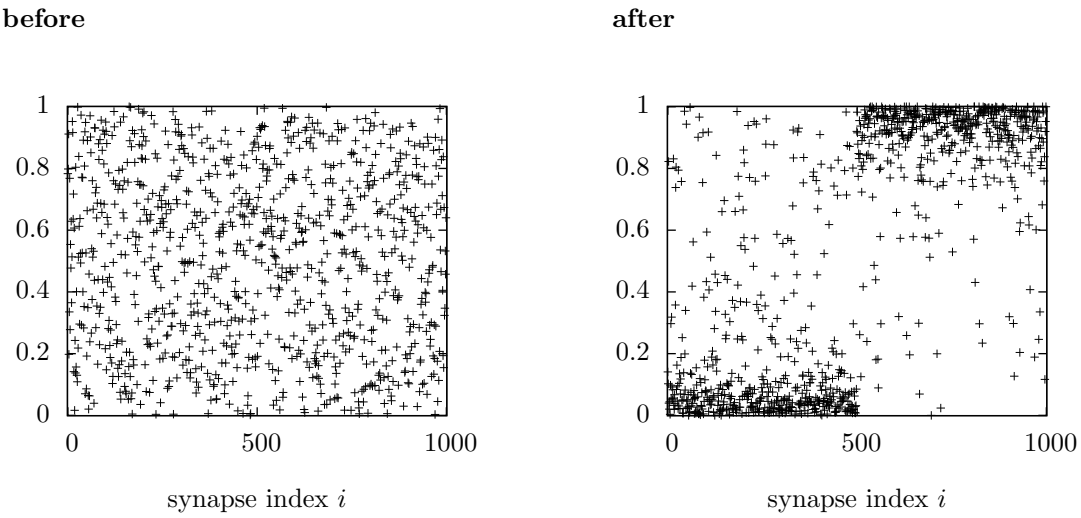

Figure 7: Synapse strengths before and after in Song and Abbotts simple model. At first they are all random, after the STDP has had an effect the synapses from one of the two groups have approached their maximum value, the others are near zero.

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