Synaptic Activity

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Learning in Neural Systems

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March 2002

Digital Signal Processing Group
Department of Informatics and Mathematical Modelling
The Technical University of Denmark

Master of Science Thesis

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Abstract

Based on the findings that certain types of Long Term Potentiation (LTP) and Long Term Depression (LTD) are found to be dependent on the inflow of Ca^{2+} following a postsynaptic depolarization, a model of synaptic plasticity is proposed. This is done by the suggestion of an 'imaginary' function, the conversion function, intended to mimic the underlying behavior of the Ca^{2+} level.

The model incorporates the dynamic effects, depression and facilitation, found to occur at specific synapses, caused by presynaptic depletion and presynaptic residual Ca^{2+} phenomena. The proposed model combines the short term dynamics with the longer lasting plastic effects.

The computational implications are investigated and it is found that like the model proposed by Song et al. (2000) this synapse produces stable competitive learning.

The model involves some level of biological realism as it demonstrated the ability to comply with the features seen in connection with long term potentiation: Cooperativity, associativity, and specificity.

Preface

This thesis constitutes part of the requirements for obtaining the Master of Science degree at the Technical University of Denmark. The work has been carried out in the period September 1st 2001 to March 1st 2002 in the Signal Processing Group, Department of Informatics and Mathematical Modelling.

»*We are interested in learning!*«

Probably any potential supervisor approached with an utterance like that by two potential project students are withholding a smile. Nevertheless, the supervisor took the bait and here we are, introducing a report on 'Synaptic Activity' and 'Learning in Neural Systems'.

The choice of institute and supervisor was, however, not obvious. People from different fields could all contribute to what we found interesting – learning. How, it comes about and how it can be modeled. Long discussions went into the choice, and there is no telling in which direction a different choice would have taken us. However, as it turned out we could not have asked for a better setting.

The last six months have been hard work and lots of fun. Unraveling the mysteries of the brain has led to many philosophical discussions, not all concerning learning – but certainly many to learn from.

Acknowledgements

Before we commence the presentation of our work we would like to thank the people who have helped us during the project.

First we would like to thank the people who inspired us to choose the topic, Rodney Cotterill, Hans Heinrich Bothe, Alexander Lerchner, Erik Mosekilde and Lars Kai Hansen furthermore for taking the bait.

All at the IMM Signal Processing Group, especially PSKH for MATLAB assistance, Mogens Dyrdal for setting up the computers and shaving in the middle of the night, Niels and Mads for setting up the CVS-server. Ole Winther for answering general questions and finally Lau Kingo Mar-kussen for saying the F. word.
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Lasse Engbo Christiansen, for lunch conversations.

Thanks also to all other people who have spent time listening to us or reading in the report. Mark Wrobel, Claus Elmholdt, Søren Agger, Morten Birk Sabroe

Madsen (ham med Snickers'en), John Hertz, Bjørn G. Nielsen (hopefully not forgetting any...)

But the ones who should be thanked the most are the ones who have helped us the most: Inger and Christine, for proofreading but especially patience.

Contents

1 Introduction

Tomorrow computers will be faster than today. If not tomorrow then at least in the near future. The computational power of an ordinary PC just keeps on increasing. Ask a person for the square root of five and compare the computation time with a computer. Probably, most people will not even come up with an answer, whereas the time used by the computer is practically zero.[1]

But, if you show a caricature of a person to a face recognizing computer, it does not – yet – laugh. And, even the face recognition task itself is not an easy task to implement in a machine. Apparently, the human 'thinks faster' in such a situation where different associations are to be put together to produce the amusement.

From a computational point of view, some of the reasons for the brain being superior is already known. Its inherent 'processors' benefit from extensive parallelism, distributed representations, generalization abilities, and robustness to degrees that are incomprehendable to most people.

One cannot be but fascinated by how it is possible for the 'three pounds of oatmeal on top' to acquire new knowledge, adapt to new situations, recall old memories, compare the present with past and from there, infer what to do next.

Consulting the literature reveals that fascination of the human brain is widespread and has finally borne fruit: Titles like 'How the Brain Works' and 'Consciousness Explained' suggest that all secrets are revealed. The work with this report has uncovered that maybe one or two stones remain unturned...

The work of the present report has been a journey back and forth between different fields. From physiological models, to computational, to purely abstract, to hybrid models, modeling a model of reality and back and forth again. Despite the iterative nature of the – learning – process, the report has been divided into chapters separating yet gathering related subjects.

At first in **chapter 2**, the physiology of the human brain will be outlined. This mainly to illuminate concepts on which the latter chapters rely.

[1] In case you wondered: $\sqrt{5} = 2.236067977\ldots$

From the basic physiology, **chapter 3** engages the question of what learning is. Starting with a general introduction, it moves into a study of the biochemical mechanisms involved in conformational changes on a microscopic level.

Having examined the physiological basis for learning, it is interesting to view how these concepts have been treated in terms of artificial models. **Chapter 4** deals briefly with the 'classical artificial neural networks' and motivates the use of temporal signals. In the last part of chapter 4, the tie between physiology and artificial learning represented by Hebbian learning rules is discussed for 'classical neural networks' and extended to 'networks of spiking neurons'.

To examine existing models and create new ones, a modeling tool is necessary. In **chapter 5** the development of a new tool is described. In **chapter 6**, the tool is used to test and examine existing models of in particular synapses.

The knowledge gathered and the tool created in the previous chapters come to full use in **chapter 7**, in which the development and testing of a new synapse model incorporating an activity-based local learning rule is described.

Finally, **chapters 8 and 9** discuss possible extensions to the model and conclude this thesis.

When reading this report, it is important to remember that the biological terms are not always used in the strictly biological sense. For example, 'synapse' is sometimes used more in the sense weight than synapse. And even more often the same word 'synapse' is used of models proposing to be representing synapses, but are not. Therefore it might be appropriate to rephrase a famous sentence to: »*Ceci n'est pas une synapse*«?[2] And by that urge the reader to have an eye on the glossary, where hopefully guidance to some of the words can be found.

Enjoy!

[2] Or as René Magritte puts it »*Ceci n'est pas une pipe*«

2 The Brain

» *To say that a man is made up of certain chemical elements is a satisfactory description only for those who intend to use him as a fertilizer.*«

Hermann Joseph Muller (1890-1967)

2.1 Where and what?

Although containing the same genetic material, it is remarkable how different the cells of a human being are. Skin, hair, feet, heart, pancreas, ear – although they all basically consist of copies of copies of copies of the very first fertilized egg-cell they, somehow, through differentiation end up being very different entities.

Throughout history, the body has gone from being seen as a collection of such entities (organs, fluids and tissue) shrouded in mystery, into something more tangible with well defined connections and understood functionalities; even to such an extent that some organs can now be successfully replaced by new ones.

Yet, at least one organ is, probably due to its complexity, still considered somewhat mysterious – the human brain.

It is not the intention to give a complete description of the human neurophysiology, but rather to outline the foundation on which the field of computational neuroscience is inspired.

2.1.1 Overview of the human brain

The central nervous system consists of the spinal cord and a specialized extension thereof, the brain. The latter is composed of the brain stem[1], taking part in controlling respiration and circulation; the cerebellum, playing an important

[1] Comprising the medulla oblongata, pons and mesencephalon.

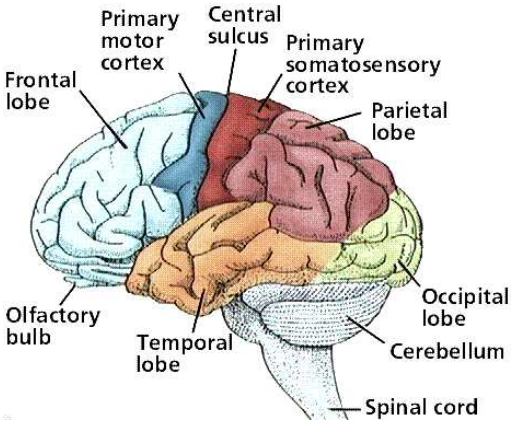


Figure 2.1 A schematic illustration[a] of the brain seen from the left, showing the four main lobes of the brain: The frontal, parietal, occipital, and temporal lobe. The occipital lobe and cerebellum are located in the back of the head. Below the frontal lobe is the olfactory bulb involved in the sense of smell. On each side of the central sulcus are the motor- and sensory cortices, concerned with muscle movement and sensory reception, respectively.

[a] From the web page: http://eduweb.brandonu.ca/~science/diagrams/cerebrum_1.gif

role in motor control, and the cerebrum: The site of origin of all conscious and various subconscious actions.

The cerebrum is the biggest part of the brain. It is divided lengthwise from nose to neck in two symmetric halves – hemispheres – communicating through the corpus callosum.[2] The cerebral surface is the latest extension of the nervous system in evolutionary terms, and is termed the cerebral cortex (the gray matter). Being about $2-3\ mm$ thick[3] and having a total area of about 2200 cm^2 makes it difficult for the cortex to fit inside the skull. This is why the surface is folded, creating 'hills and valleys' also known as gyri and sulci. As seen in most pictures, this wrapping gives the cortex its convoluted appearance.

The crumbled nature is also evident in figure 2.1, giving an overview of the brain. Using prominent gyri and sulci as guidance, the cerebrum has been divided into four main lobes. Each of these are related to different features or activity

The frontal lobe Concerned with thought, problem solving, planning, parts of speech, emotional behavior, and movement (motor cortex).

The parietal lobe Involved in perception of stimuli related to touch, pressure, temperature and pain.

The occipital lobe Participating in all aspects of vision.

[2] Large bundle of fibers, see glossary.
[3] Jain et al. (1996).

The temporal lobe Engaged in perception and recognition of auditory stimuli. Also involved in memory processes.

Often the lobes themselves are divided into smaller segments with boundaries determined in accordance with different observed functionalities. As an example, the frontal lobe can be divided into: The prefrontal cortex, the motor association cortex, and the primary motor cortex.[4] A division also separating the features mentioned above for the frontal lobe; the prefrontal cortex is involved in problem solving, complex thought, and emotion. The motor association cortex takes care of coordination of movement, whereas the primary motor cortex acts as the initiator of such (voluntary) movement.

Continuous division of the different areas into smaller parts can be carried out and involves the principle that as the region of interest gets smaller, the more its functionality is specialized.

However, instead of exploring the brain from top to bottom, it is also of interest to take the different view and investigate what the building blocks are that allow for these functionalities to come about.

2.2 The basic unit: The neuron

A neuron is a highly specialized cell capable of receiving and eliciting signals by means of electrochemical processes. Intense studies have been carried out both at the molecular level and at the functional level. This approach will focus on the general aspects and some of the prototypical properties seen in connection with neurons.

2.2.1 Dendrite, soma, and axon

Although different, depending on which specific region of the brain they belong to, neurons do have some things in common. Almost every introductory description separates the neuron in three parts, the same here: Dendrite, soma, and axon.

The dendrites are the input fibers, along which signals from other neurons enter the cell. Via the dendrites, the signal reaches the cell body also known as the soma. In the soma, as shall be described later, processes are taking place to determine whether signals are to be sent further on. If signals leave the

[4] Of which the latter is seen in figure 2.1.

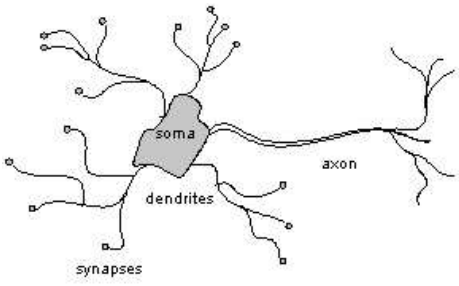


Figure 2.2 A crude caricature of a nerve cell. The dendrites function as receivers of signals, which they send on to the cell body, the soma. From the soma, signals are sent out along the axons to reach the dendrites of other neurons. The 'synapses' in the picture will be discussed in section 2.3.

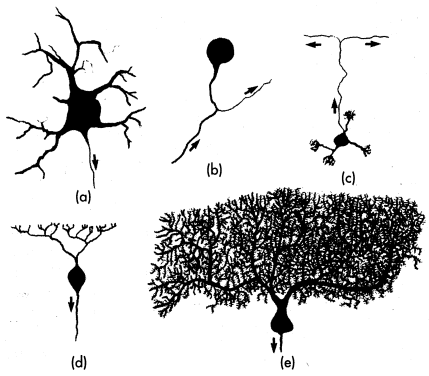


Figure 2.3 Different neuron types from the central nervous system. The small arrows indicate the axons. (a) Motor neuron. (b) Dorsal root (unipolar) neuron. (c) Granule cell, cerebellum. (d) Bipolar cell, retina. (e) Purkinje cell, cerebellum (figure from Carpenter (1996)).

neuron, they do so along the output fiber, the axon. See figure 2.2 for a fictitious representation.

To prevent misunderstandings, it must be emphasized that figure 2.2 deliberately has been chosen because of its naive qualities; hopefully it is obvious that it is not a correct representation of a real neuron. With this in mind, figure 2.3 brings examples of how unlike neurons can actually be; although these pictures are also idealizations – better than the naive illustration though. One notices that all[5] neurons in figure 2.3 share the same features as the naive neuron: They have a widely branched dendritic tree[6] and a single axon. In both the naive figure and in figure 2.3(c) the axon divides shortly after the soma, to produce axon collaterals. These also display widespread branching at their extremities.

Another shared feature is indistinguishable from the figures. In all cases the membrane forming the neurons is a phospholipid bilayer with trans-membrane proteins acting as channels.

[5]Except one, figure 2.3(b), to illustrate that in biology there is an exception to every rule.
[6]The considerable ramification is sometimes referred to as dendritic arborization.

Resting in imbalance (active pump)

The neuronal membrane acts as an impenetrable barrier between the interior and the exterior of the nerve cell. Exchange of substances across the membrane can only happen through gated channels. As shall be seen, the guards at the gates come in (at least) two varieties. Some are susceptible to influence from voltage differences and some to neurotransmitter.

In the steady state, the neural membrane is actually in imbalance. A resting potential exists across the membrane due to differences in the ionic concentrations on both sides. Although the membrane is leaky[7] and ions seep out, the instability is maintained by the Na^+-K^+ pump.[8] By use of energy in the form of ATP, this pump moves three Na^+ ions out of the cell and two K^+ ions into the cell by each turn of the crank. This mechanism defeats the leakage and the membrane resting potential is maintained. A typical value of the resting potential is $V_{rest} \approx -70\ mV$, which by definition is negative intracellularly.

The steady state potential can be segregated into several parts each stemming from a specific type of ion. If the ionic concentration of a species, e.g. sodium $[Na^+]$, is known extra- and intracellularly, its contribution to the resting potential can be equated by using Nernst's equation

$$E_{Na^+} = \frac{k_B T}{q} \ln \left(\frac{[Na^+]_{ext}}{[Na^+]_{int}} \right) \quad , \tag{2.1}$$

where k_B is the Boltzmann constant, T is the temperature, and q is the ionic charge.[9] Equation (2.1) is also known as the Nernst potential or the *reversal potential*. This latter name is used to describe the potential reached when ionic currents through channels balance or cancel out. Of course, with Na^+ being positive, it urges to get inside the negatively charged cell; also, as the sodium concentration $[Na^+]$ is higher outside (due to the aforementioned pump), a concentration gradient tries to push Na^+ ions inside the cell. If the Na^+ ions were allowed to move freely, the intracellular potential would reach about $+50\ mV$, before the direction of the net flow of ions reverses; therefore sodium has the reversal potential $E_{Na^+} \approx 50\ mV$.

So, at rest the cell is in a polarized state. Then, if the internal potential moves towards the zero-level, one speaks of a *de*polarization, whereas if it gets even more negative a *hyper*polarization has occurred.

[7] Some of the guards might be sleeping on their shift.

[8] Whose discovery lead to that the Danish professor Jens C. Skou received the 1997 Nobel Prize in chemistry.

[9] Here, with sodium being singly positively charged this amounts to e.

2.2.2 Activity - action potential

Incoming electrochemical signals from the dendrites to the soma affect its steady level. The somatic integration slowly depolarizes the cell body. This is where the ion-channel guards re-enter the business: Their opening of the gates is directly dependent on the voltage across the membrane. The channels can be considered as having voltage dependent opening probabilities.[10] Especially the Na^+ channel is very sensitive to changes in the membrane potential; at a certain level of depolarization,[11] the opening probabilities of the Na^+ channels increase abruptly, and the channels open – for a short while $\approx 1\ ms$. A bit later than the Na^+ channels, also the K^+ channels open. This is a combined action involving very fast dynamics in terms of exchange of ionic species across the membrane, leading to drastic fluctuations in the membrane potential – an *action potential.* Due to the need for the membrane potential to be increased to a certain level before the Na^+ channels open, the process has often been viewed as happening in an all-or-none manner.[12]

Figure 2.4 shows the processes involved in the creation of an action potential (AP). In the figure, conductances g_{Na} and g_{K} are used as representatives of the opening probabilities. These are interchangeable: If the probability of a channel to be open is high, it conducts well. A few comments to figure 2.4: A1) The cell is in its resting state,[13] and the little wheel in the middle symbolizes the Na^+-K^+ pump upholding the imbalance. Abbreviations are used for extracellular- and intracellular fluid (ECF and ICF). A2) The membrane potential is increased and Na^+ ions enter the cell, indicated by the large arrow. A3) Shortly after the channels close, and a repolarization is initiated.

It is important to note the shape of the action potential in figure 2.4.B as it captures the essence of all action potentials. A remarkable feature of action potentials (APs) are that they all look alike without much divergence. It is this stereotype appearance that sometimes leads to simplified representations. Namely, when viewed on a large time scale the action potential looks like a narrow pulse. The present report reflects that people name the process of an AP with great variability, and words like spike, pulse, action potential, depolarization, activation, event, firing will be used indifferently.

The ultimate integration of dendritic inputs[14] is made at the initial segment

[10] This will return in section 6.1.

[11] As also seen in section 6.1, this is often modeled with a simple threshold.

[12] Again a rule with an exception. If depolarization is done by stimulating in a sequence of small steps the neuron may not elicit an action potential at all. An effect known as accommodation (see e.g. Carpenter (1996)).

[13] With a resting potential of $-90\ mV$. These depend on the type of neuron.

[14] Formerly dendrites have been viewed as cables passively conducting signals, this is indeed not the case. However, it will not be discussed here any further, see e.g. Scott (1995).

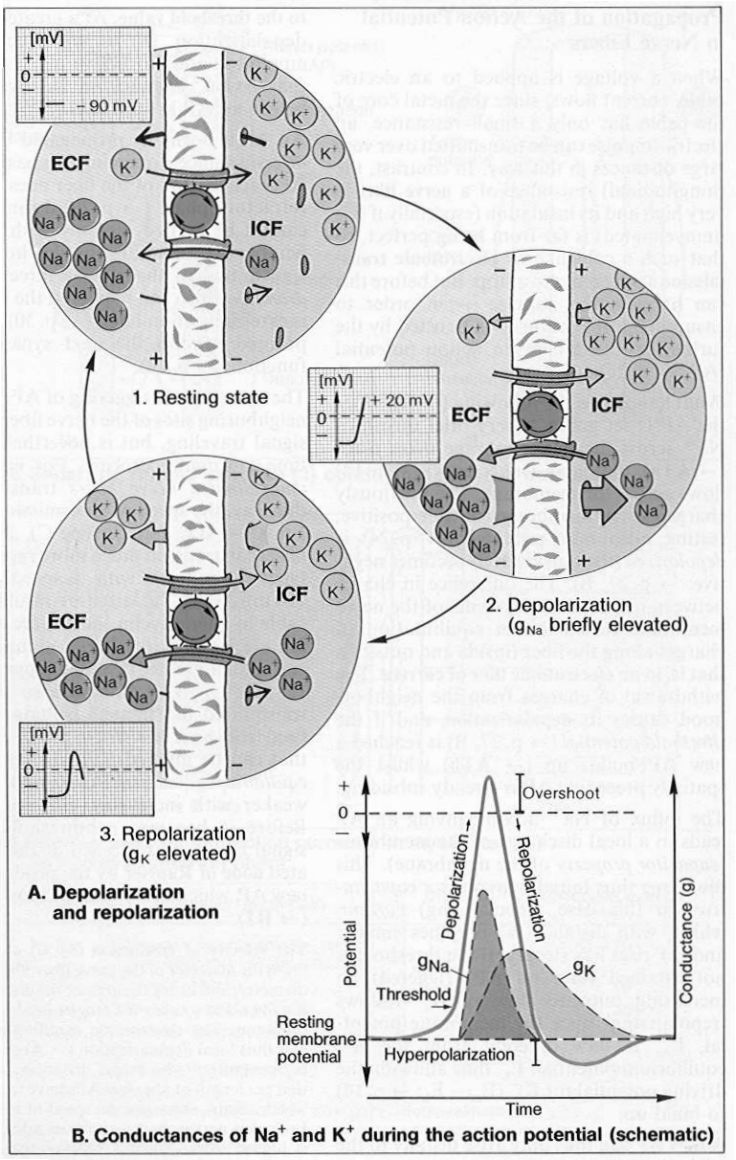


Figure 2.4 A: The ion transfer involved in an action potential. B: The shape of the action potential. See text for further explanation (figure from Despopoulos and Silbernagel (1991)).

of the axon, the axon hillock. Here, the cell contains the highest density of Na^+ channels and depolarization needs only be 10 mV to reach the threshold.[15]

When initiated at the axon hillock, the action potential moves out along the axon towards other neurons; as the AP moves on, its shape is preserved.[16] This comes about by continuous regeneration of action potentials along the line; the AP in progress depolarizes the membrane, which causes a new AP to move along, and so on and so forth. The velocity of the AP is highly dependent on myelin sheet 'wrappings' around the axon. Small gaps in the sheets, nodes of Ranvier, enables the AP to 'jump' from node to node, increasing its speed. The myelin sheets are insulators made of lipid (fatty) layers, forming what is known as the white matter of the brain.

That signals are not sent 'back-wards' in the axons is due to conformational changes of the membrane, hindering the initiation of a another action potential in some time after the first one. This time is known as the *absolute refractory period* and lasts for about 2 ms. Also a *relative refractory period* exists, in which the neuron can be brought above its firing threshold but only by a larger amount of depolarization.

Considering the neuron as a signal generator, the all-or-none action potential moving without attenuation makes sense as it prevents the 'spreads with decay' or dispersion often seen in signals sent over some distance. The missing attenuation is also part of the explanation for the above mentioned synonyms: It *is* only a matter of whether a 'spike' is there or not – if there, the shape is known.

2.2.3 Neurons and numbers

There are about 100·000·000·000 neurons in the cerebral cortex, that is 10^{11} or one hundred billion. To cope with such a large number, analogies are often made.[17] It is almost the same as the number of stars in the Milky Way; or, as Brunak and Lautrup mention »*... comparable to the number of grains of sand in 1* m^3 *of fine beach sand.*«[18] A microliter of cortex (1 mm^3) contains about 4 km of axons.[19]

[15] Compared to about 30 mV at the soma (Kandel et al., 1991).

[16] The AP could be regarded as a traveling wave or a soliton since it does not lose power when moving along (see e.g. Scott (1999)).

[17] Obviously, a billion in itself is a large number. As of February 27th, the popular Internet search engine Google™ had 2,073,418,204 webpages in its database. That is roughly two billion. If Google™ visits a web-page every second, it will take more than 63 years to visit them all! (thereby suggesting that the visiting period were wrongly estimated).

[18] Although they mention the number as being 1000 billion, probably because they count supportive glial cells as well (Brunak and Lautrup, 1988, p. 30).

[19] Chklovskii and Stevens (2000).

As seen in figure 2.3, the neurons look differently depending on their location. Functionally, they can be divided in at least three distinct classes with regards to their interaction range. Principal neurons or projecting neurons; intrinsic, local or interneurons;[20] or, input fibers. Long range, projecting neurons are for example the pyramidal neurons acting as the main excitatory neuron in the brain.

A central neuron is typically receiving about 10000 afferent (incoming) fibers from other neurons. This is known as convergence and in e.g. the rabbit, around 50 million receptors converge onto 175000 primary cells in its olfactory center.[21] The opposite effect, divergence, is also seen in connection with branching of the axon collaterals.

The cortex is divided vertically into six layers counted from the outer to the inner. The division is made on the basis of neuronal types, density, and distribution. Signals are sent back and forth between the layers and also transversally inside the layers. Projecting nerve fibers can therefore come from several places and arrive in the cortex where they diverge out like branches on a tree and establish contact with several other cells. How the signals are conveyed from one neuron to the next is the topic of the next section.

2.3 Synapses

»*... the purpose of a neurone is not to generate action potentials – or any other kind of potential – but to* release transmitter *...*«[22]

Signalling from one neuron to another happens across a small gap separating the sending neuron from the receiving neuron. Altogether, the conglomerate consisting of the terminal membrane regions on both sides of the gap, and the gap itself, is called a synapse; the gap is termed the synaptic cleft.

Formerly, synapses have been viewed as rather simple contact sites capable of imposing either excitation or inhibition on the contacted neuron. Substantial experimental evidence has changed this view into an appreciation of the intricate functional complexity these synaptic connections between neurons can present.

Boutons,[23] specialized membrane enlargements or swellings, are typically the sites where synaptic contact occurs. The boutons form as terminal bulbs at the end of an axon, and/or along the length of individual axons as boutons *en*

[20] About 20% of the neurons in the brain are inhibitory interneurons (O'Reilly, 1998).
[21] Gluck and Granger (1993).
[22] Carpenter (1996, p. 45).
[23] Also known as synaptic knobs.

passant.

The synaptic cleft acts as the borderline determining which prefix to use when describing activity or region of interest: *Pre-* or *post*-synaptic. As this indicates, synapses have an orientation in the sense that they convey signals from the presynaptic to the postsynaptic neuron. In general, an electrical signal is converted into a chemical signal by the presynaptic membrane, and back into an electrical signal at the postsynaptic membrane from where it moves on.[24]

2.3.1 Presynaptic activity

The key feature of the presynaptic bouton is its activity dependent release of neurotransmitter into the synaptic cleft. When a synapse is active, a variety of mechanisms come into play; in fact, there is an ongoing debate concerning the exact processes involved in transmitter release. The following, highly general description, touches on some main features on which a common agreement has evolved – features that are remarkably similar in all neurons.

Initiator of activity is an incoming action potential depolarizing the presynaptic membrane and thereby causing voltage-gated Ca^{2+} channels to open (see figure 2.5). Influx of Ca^{2+} activates a calcium-binding protein which itself binds to transmitter-containing vesicles – a process termed *priming*. The primed vesicles join the *readily releasable pool* (RRP) by docking at membrane release sites from where the vesicle fuses with the membrane (exocytosis) and liberates a quantum of neurotransmitter into the synaptic cleft. In the cleft, transmitter diffuses towards the postsynaptic membrane (see below) and is also re-absorbed into the presynaptic terminal by endocytosis. The latter process recycles membrane when putting neurotransmitter filled vesicles back into the 'storage'.

It is worth noticing that 'release' above is to be considered a 'probability of release'. On average, less than one vesicle is released in response to a stimulus;[25] although not all synapses are equally unreliable. The reason for the probabilistic nature is due to blocking mechanisms; once a vesicle has begun to fuse with the membrane, all other vesicles in the RRP are inhibited from undergoing exocytosis. This is also known as the univesicular hypothesis.[26]

When looking isolated at the presynaptic *mechanisms* described above, which lead to liberation of transmitter, they are rather general for the various types of neurons found in the brain. The particular type of transmitter released and its effect on the synapse is, in contrast, not general at all.

[24] As noted in Shepherd (1998), this is a process known as a nonreciprocal two-port.
[25] As noted by Terrence J. Sejnowski in Maass and Bishop (1999).
[26] Senn et al. (2001).

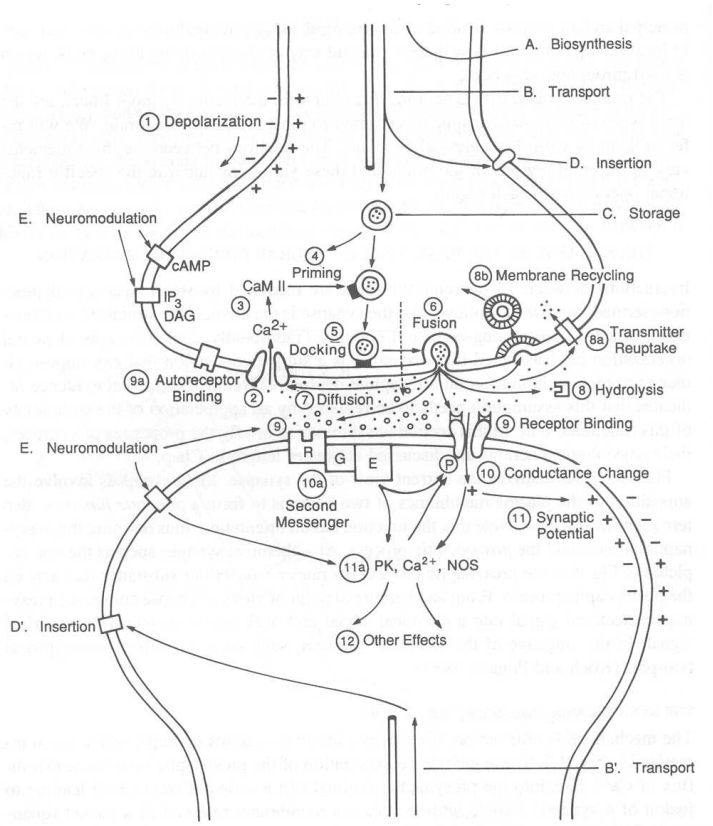


Figure 2.5 An overview of some of the main mechanisms happening in synapses (upper part is presynaptic). ① Arrival of an action potential opens Ca^{2+} channels ②. Influx of Ca^{2+} leads to priming of vesicles ③+④ allowing these to dock in the readily releasable pool ⑤ from where they undergo exocytosis ⑥ releasing neurotransmitter into the cleft. From here the transmitter can be reabsorbed ⑧a, metabolized ⑧, or diffuse towards the postsynaptic side ⑦. At the postsynaptic side, transmitter binds to receptors ⑨ and changes their ion-channel conductances ⑩, i.e. they open, and ions can flow in, thereby affecting the synaptic potential or initiating internal cascade processes ⑪+⑫. Another internal process could be activation of second messengers. Some abbreviations: PK, protein kinase; R, receptor; NOS, nitric oxide synthase (figure from Shepherd (1998)).

2.3.2 Postsynaptic activity

It is chemical neurotransmitters that by means of diffusion bridge the gap between the presynaptic and the postsynaptic side in synapsing neurons. A common type of receptor acts as a transmitter-gated ion-channel. In the open state, influx and efflux of ions lead to a modification of the postsynaptic membrane potential[27]. Depending on the transmitter and, even more important, the effect it has at postsynaptically resident receptors ready to receive transmitter, synapses are often divided into either of two groups: Excitatory or inhibitory.

The division reflects the influence that interaction between transmitter and receptor has on the postsynaptic potential (PSP). When causing a depolarization, it is termed an *excitatory* postsynaptic potential (EPSP); when leading to hyperpolarization, it is called an *inhibitory* postsynaptic potential (IPSP).

As stated, alteration of the postsynaptic potential occurs through a direct link between receptor and membrane conductance, i.e. by opening of ion-channels. Notice the large difference between voltage-gated and transmitter-gated ion channels: Voltage-gated channels react in an all or none manner while transmitter-gated channels just add to the current current,[28] meaning that the number of channels opening in the presence of transmitter depends largely on the concentration of transmitter.

Although excitation and inhibition are not determined by the type of presynaptic transmitter (but on the postsynaptic response thereto), a rule of thumb is that the major excitatory transmitter is glutamate (an amino acid), and that the major inhibitory transmitters are γ-aminobutyric acid (GABA) and glycine.[29] This is indeed a simplification since various types of chemicals act as neurotransmitter substances: Acetylcholine (ACh), dopamine (DA), serotonine, histamine, aspartate, noradrenaline, glucagon, β-Endorphin, enkephalin, norepinephrine, and epinephrine (just to name a few). To this comes the large range of different classes of receptors. Each class exhibits a substantial range of physiological subtypes depending on the molecular composition of the receptor. In section 6.2, different synaptic models are presented including varying degrees of physiological complexity; here, for clarity, an outline has been preferred.

Receptors can be divided into two different classes: Ionotropic and metabotropic. In ionotropic receptors, the transmitter reception site and the ion-channel are part of the same protein complex. Metabotropic receptors are independent of the channel, and gating is mediated by intracellularly produced second messengers; an indirect activation providing the possibility for amplification of a signal

[27] The resistive membrane and Ohm's law converts ion current to potential.
[28] No pun intended.
[29] Kandel et al. (1991).

e.g. via cascade effects (10a in figure 2.5).[30]

If present, diffusible second messengers produced in the postsynaptic process can modulate transmitter release presynaptically in an activity-dependent manner (so-called retrograde messengers). However, whereas presynaptic to postsynaptic activity works on time scales down to fractions of a millisecond, retrograde messengers are likely to act more slowly (Shepherd, 1998).

The major types of synapses in the central nervous system are the AMPA, GABA, and NMDA receptor type synapses, whose abbreviations will be explained in the following. Also, even though it will not be described any further, a very common type of receptor is the nicotinic acetylcholine (ACh) receptor found in the periphery at the neuromuscular junctions where neurons synapse onto the muscles.

The α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA)[31] receptor responds to glutamate and is mentioned as being prototypical[32] in mediating fast excitatory synaptic currents in the brain (Destexhe et al., 1998).

As mentioned, the majority of IPSPs in the brain is invoked by γ-aminobutyric acid (GABA) receptors coming in two varieties, a fast and a slow. Fast inhibition is related to $GABA_A$ receptors, a ionotropic receptor having a high affinity for GABA and requiring minimal stimulation to elicit response when compared to its 'cousin' the $GABA_B$ receptor. The latter is metabotropic and needs a high level of presynaptic stimulation in order to be activated.

A particular interesting type of receptor that has drawn a lot of attention recently is the NMDA receptor. It is a glutamate receptor, but has obtained its name because of a high affinity for the artificial substance *N*-methyl-D-aspartate. The reason why this receptor is especially interesting is its correlation capturing abilities. When glutamate is bound at the receptor, Mg^{2+} ions still block the Ca^{2+} ion-channels and can only be removed if the postsynaptic membrane is depolarized *at the same time*. The fact that this leads to conformational changes with implications of learning will be treated further in section 3.3.3.

By having various channels, the same ion can be used for different purposes.

A probably well-known example of receptor flexibility is that chilis (Capsicum) are sensed as being hot when eaten. This is due to the fact that capsaicin[33] from the chili is able to dock on vanillin nociceptors (pain receptors). When capsaicin

[30] Dayan and Abbott (2000).

[31] Resembles another receptor, the kainate receptor, and often a combination is seen, the AMPA/kainate receptor. Here the term AMPA will be used as a common name for the three.

[32] A simplification ignoring the fact that AMPA receptors with significantly different properties can be found in particular types of neurons (Destexhe et al., 1998).

[33] The active substance phenolic amide $C_{18}H_{27}NO_3$.

comes into contact with these receptors, a cascade of intra-cellular reactions are triggered similar to those produced by damaging heat.

2.3.3 Organization

A common synaptic specialization of dendrites is what the Spanish anatomist Ramon y Cajal called "espinas" (spines) due to a resemblance with thorns on a flower stem. Spines are small[34] membrane protrusions frequently found on the dendrites of principal cells in most brain regions, especially on the pyramidal cells of cerebral cortex and the Purkinje cells of the cerebellar cortex. Among these two cell types, above 90% of excitatory synapses occur on dendritic spines (Synapse Web, 2001).

Spines are not the only contact sites though, in fact, the connectivity between neurons introduces another level of variability as different types of synaptic connections are seen: Axo-somatic, axo-dendritic (shaft or spine) and axo-axonic. Dendro-dendritic and soma-somatic synapses are also found but rare. Evidently, this variety of possible connections between neurons allows for – and indeed imposes – different functionalities. For example, the axo-axonic synapses can have selective purposes in the sense that they can control behavior at individual branches of a neuron. Although large variability exists, some general observations are that: Synapses on the soma are often inhibitory, synapses on dendritic spines are often excitatory, and synapses on axon terminals are often modulatory.

Two principles come into play when looking at neurons and their connectivity. Synaptic convergence: Several neurons make synaptic contact with a single neuron. Synaptic divergence: A single presynaptic terminal can transmit signals to many postsynaptic terminals. The convergence property allows for spatial and temporal summation: A single EPSP is insufficient to trigger an action potential, but adding contributions from a large area (spatial) possibly arriving at the same time (temporal) may bring the somatic potential above its threshold.

2.3.4 Characteristic behavior

The above description of the underlying processes involved in inter-neuron communication provides a physiological foundation for understanding the origin of various activity dependent behavior seen in connection with synapses and neurons.

Three such activity related mechanisms are synaptic *facilitation*, synaptic *augmentation* and synaptic *potentiation*. All of these processes are similiar in the

[34] Often less than 1 μm in diameter (Synapse Web, 2001).

sense that they lead to a more potent synapse – an enhancement. The fact that the processes can be distinguished from one another based on magnitude, time course, and in some cases pharmacology, indicates that the underlying mechanisms are different. Facilitation, the briefest of them, are sometimes divided into two separate components with different time scales.[35] Table 2.1 gives an overview of different mechanisms, their related time scales and synaptic location.

Mechanism	Duration	Synaptic Location
Short-term Enhancement		
Paired-pulse facilitation (PPF)	100 ms	Pre
Augmentation	10 s	Pre
Post-tetanic Potentiation	1 min	Pre
Long-term Enhancement		
Short-term Potentiation (STP)	15 min	Post
Long-term Potentiation (LTP)	$>$ 30 min	Pre and Post
Depression		
Paired-pulse depression (PPD)	100 ms	Pre
Depletion	10 s	Pre
Long-term depression (LTD)	$>$ 30 min	Pre and Post

Table 2.1 Activity dependent synaptic mechanisms and a rough estimate of their decay constants. An indication of whether they depend on presynaptic or postsynaptic activity or both is also given (adapted from Maass and Bishop (1999)).

A possible explanation for e.g. the facilitative mechanism is indicated by what is known as 'the residual calcium hypothesis'[36]. The idea behind this hypothesis is that, after the first nerve impulse is over, a little portion of the calcium that entered the nerve terminal is not re-absorbed but stays behind. This residual is not enough to enhance or trigger release on its own but adds to the calcium entering during the next nerve impulse. Similar models based on this idea of residual calcium have been developed to explain augmentation and potentiation[37].

Another activity dependent mechanism, adaptation, was discovered by E. D. Adrian[38] as early as 1928. Adaptation means that the response to a constant stimulus fades, and both the extent to which it falls to zero and the time con-

[35] See e.g. Carpenter (1996) or Kandel et al. (1991).
[36] A concept introduced by Katz and Miledi (1968).
[37] In table 2.1, 'post-tetanic' refers to a preceding high rate of stimulation.
[38] Later he, together with Sir Charles S. Sherrington, received the 1932 Nobel Prize in 'Physiology or Medicine' for work on the function of the neuron.

stant involved are crucial parameters. Adaptation acts as a form of redundancy reduction and improves the signal to noise ratio by providing a sliding scale.

Habituation is a phenomenon related to adaptation since it also involves a decline in response to a constant input. The subtle difference is that habituation is caused by stimuli that are periodically applied rather than continuous. Also, habituation is a high-level phenomenon not seen in sensory receptors but rather in later areas of the brain as a learned suppression of the response.[39]

Along the lines of activity moderation one finds the mechanisms leading to a depression of signal transduction. As seen in the bottom of table 2.1, three different time scales are involved. During a long train of stimuli the postsynaptic potential could first become larger and then become progressively smaller in amplitude both during and after the train. The location of moderation has e.g. been demonstrated by measurements showing a reduction of the amount of transmitter released presynaptically with each stimulus, rather than a loss of sensitivity in the postsynaptic receptors. The favored candidate when it comes to the cause of the homosynaptic use-dependent depression is a depletion of the readily releasable store of synaptic vesicles.

It is worth noticing that these dynamic effects are responsible for »*... complex postsynaptic responses that cannot be reduced to a linear sum of responses to single presynaptic action potentials...*«[40]. This imposes a simple form of activity dependent cellular memory – short-term though – later on, longer lasting effects like long-term potentiation will be described.

Summary

Having dealt with neurons and in particular synapses at some level of detail, it is time to recapitulate. The lesson to be learned from the brief introduction to the neuronal physiology is that emission of signals happens in an all-or-none manner by means of stereotype action potentials, not changing their shape as they move out along the axon. Having a temporal width of only about a millisecond has led to the notion of considering the action potential as an electrical *spike*.

The probabilistic synaptic conversion of incoming electrical activity into a transmitter based internal signal opens for a multifaceted functional complexity. Here, attention is drawn to the possible activity dependent dynamics associated with the residual calcium hypothesis and depletion of vesicles, leading to short term enhancement and, respectively, depression of the synaptic transmission efficiency.

[39] Investigated by Ivan Pavlov and Charles S. Sherrington among others, in connection with certain reflex forms of behavior, such as limb withdrawal to a tactile stimulus (Kandel et al., 1991, p. 1010).

[40] Tsodyks and Markram (1997, p. 719).

Obviously, this enables the synapse to perform filter-like processing of the incoming signals.

Whereas the presynaptic transmitter release mechanisms are rather general, the postsynaptically induced response to transmitter is not. Yet, the overall feature of the postsynaptic receptors is their 'conversion' of docking transmitter into a postsynaptic potential. To this comes the NMDA receptor of the glutamate type the activity of which is dependent on the cooperativity of presynaptically released transmitter and postsynaptic feedback signals, allowing the synapse to capture correlations between signals.

Finally, it should be mentioned that although the large selection of possible types of synaptic connections complicates things, the operational gain it involves is not to be underestimated. That, for example, synaptic contact at the initial part of an axon can 'veto' an action potential or that a synapse onto an axon terminal can have modulatory effects provides convenient building blocks for everyone who might consider constructing a brain (or models of parts thereof).

3 Learning

» *Learning is the process by which we acquire knowledge and memory is the process by which we retain that knowledge over time.*«

(Kandel and Hawkins 1992)

Is it possible for a human to learn all kinds of things or are there things which are beyond our capabilities? Is it possible for machines? How do humans learn? And how can learning be defined?
Is it a child memorizing a book or mastering how to ride a bicycle; is it society improving from generation to generation; is it a synapse being trained to convey the correct information?

Many different notions exist of learning as a concept, making it difficult to capture the essence in a few words. This chapter is intended to sum up some of the main ideas and relate them to the topics dealt with in the present report.

3.1 Concepts

Using terminology from machine learning, three main learning concepts are defined. Each of these has its counterpart in the theories of human learning.

Supervised learning: A teacher (supervisor) provides a measure of correctness (an error signal) to the student, and the student reacts by changing his behavior to minimize the error. In other words, adapting to the knowledge of the teacher. An example of this is when a mathematic assignment or an essay is handed in to the teacher; when returned the errors are marked with red lines and the right answer is written in the margin. Hopefully, the same error will not be made in the next set of assignments.

Reinforcement learning also involves a teacher but this time no correct answer is provided, only a pad on the head when a good deed is performed or an angry yell in case of an unwanted action. To illustrate, consider a game of MasterMind^{TM},

where the objective is to learn the correct location of small colored pins.[1] Information is only available on whether the present guess is correct – but not what the error is.[2]

The third type of learning is unsupervised learning: Without feedback from the world, it is still possible to learn. Examine figure 3.1 for a moment; when presented with such a picture, it is at first impossible to see the hidden object. However, once the object is found, it poses no problem to find it again.[3]

Figure 3.1 At first glance it is not possible to find the object in the picture. However, by closer inspection the optical illusion gets exposed. Next time the picture is presented the object is found without problems (the picture can be found in e.g. Cotterill (1998)).

The task uses the ability to associate new impressions with old ones. Once the association is formed, it becomes part of the memory and can be retrieved without problems. The creation of this association, the learning process, can (usually) be performed without any error signals. This is a general feature of associative memories: They can be formed unsupervised.

A property of associative memories is also that they are robust in the retrieval phase. This will be returned to with an example in section 4.1.

3.1.1 Synaptic modifications

Observing how humans can learn in both a supervised and unsupervised manner, has naturally led to the question of how this learning may come about: "How may this learning come about?". Looking for an answer has, on the microscopic level, led to the study of neurons and synapses. A main paradigm in artificial learning is the hypothesis Donald O. Hebb proposed in 1949:

[1] Although, hopefully not too much yelling will take place during such a game ...

[2] In the mathematic assignment, a red line still marks the error but this time the correct answer is not given.

[3] If it is not possible to see an object, here is a little supervision: Look for a dog.

> »*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. The most obvious and I believe much the most probable suggestion concerning the way in which one cell could become more capable of firing another is that synaptic knobs develop and increase the area of contact between the afferent axon and efferent soma.*«[4]

Actually Hebb did not think of this postulate as being original.[5] Perhaps he were aware of the antecedent ideas of W. James, who in 1890 maintained that:

> »*...[T]here is no other elementary causal law of association than the law of natural habit: When two elementary brain processes have been active together or in immediate succession, one of them, on reoccurring, tends to propagate its excitement into the other...*«[6]

A quote revealing that notion of learning as being dependent on the co-occurence of activities, is more than a hundred years old.[7]

Even though Hebb was not the inventor of the idea that synapses are strengthened on use, he incorporates this idea into a theory concerning assemblies of neurons:

> » *Any frequently repeated, particular stimulation will lead to the slow development of a 'cell-assembly', a diffuse structure comprising cells ... capable of acting briefly as a closed system, delivering facilitation to other such systems and usually having a specific motor facilitation. A series of such events constitutes a 'phase sequence' – the thought process. Each assembly may be aroused by a preceding assembly, by a sensory event, or – normally – by both. The central facilitation from one of these activities on the next is the prototype of 'attention'.*«[8]

[4] Reprinted in Cotterill (1998).

[5] See e.g. Scott (1995).

[6] Reprinted in Brown et al. (1990).

[7] Brown et al. (1990) reports that contemporary to W. James, E. Tanzi in 1893 identified the synapse as being the locus of the modifications. And Nielsen (2001) reports that Bain in 1873 in his book "Mind and matter" proposes that: »*...[W]hen two impressions concur, or closely succeed one another, the nerve currents find some bridge or place of continuity, better or worse according to the abundance of nerve matter available for the transition. In the cells or corpuscles where the currents meet and join, there is, in consequence of the meeting, a strengthened conexion or diminished obstruction...*«.

[8] As reproduced in Scott (1995).

The real contribution from Donald Hebb is thus, not the concept of synaptic modifications but rather the concept of cell assemblies. However, no matter who got the idea or when it was first conceived, it was Hebb who – as the name implies – made Hebbian learning famous.

To conclude this short introduction to synaptic modifications, a few words to summarize what the Hebbian hypothesis implies: Synapses are locally enabling an unsupervised form of learning qua their ability to change when action before the synapse precedes action after the synapse. This does not exclude reinforcement-like signals to perform a neuromodulatory control over the modifications. A large population of Hebbian synapses – or cell assemblies – can in this way be influenced in a 'global' manner. Hebbian synapses are also not excluded from feedback receiving signals directly from other parts of the brain.

3.2 Synaptic plasticity

As Hebb proposed, learning in terms of synapses amounts to changes in their transmission strengths. Different mechanisms and time scales are involved in these changes. As described in section 2.3, a synapse is a dynamic unit and will react differently to temporally different spike trains – even though the rate is the same. This dynamic, activity dependent behavior can be thought of as learning with a brief time constant.

Longer lasting synaptic changes often involve plastic changes, affecting the basic properties of the synapse. Plasticity can be thought of as changing the working point; the synapse will still be dynamic on a short time scale – not necessarily with the same dynamics – but the general transmission behavior is different.

An example is redistribution of synaptic efficacy (see figure 3.2). This phenomenon, obtained by pairing the occurrences of presynaptic and postsynaptic spikes, is reported in Markram and Tsodyks (1996) and involves an increase in the synaptic response following low frequency input. Redistribution represents a mechanism altering the existing content instead of the actual gain of the signal – a plastic change of the dynamics. Markram and Tsodyks ascribe the effect to either an increase in the probability of transmitter release or an affinity increase for the postsynaptic glutamate receptors.

Several mechanisms are labelled as being of short term duration.[9] On the shortest time scale (ms – min), paired pulse facilitation and post-tetanic potentiation accounts for some of the facilitating effects, whereas depletion is an example of a depressive mechanism. However, these are not lasting effects and have to

[9] See eg. table 2.1.

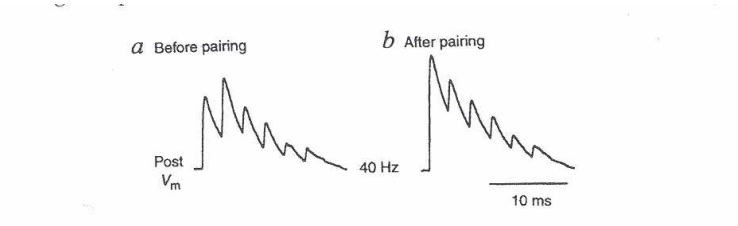


Figure 3.2 Redistribution of synaptic efficacy. The postsynaptic potential before and after pairing of presynaptic and postsynaptic activity (spikes). The average output is the same and only the temporal structure of the signal is changed (figure from Markram and Tsodyks (1996)).

do more with the particular decoding of information than with learning. These short term effects are known to involve changes of the postsynaptic potential with up to several hundred percent.

Generally, only synaptic changes happening on a longer time scale (*hours – days*) are regarded as being learning. But, it is worth remembering that the short term and longer term effects are additive. Even after learning has occurred, paired pulse facilitation, post-tetanic potentiation, or depletion can be observed.

Temporal pairing

The redistribution of efficacy mentioned above is an example of Hebbian learning in the sense that pairing of presynaptic *and* postsynaptic activity is necessary to induce the effect.[10]

Other activity driven plasticity types also require this kind of co-existent firing on both sides of the synaptic cleft. To this comes that the temporal order of the presynaptic and postsynaptic spikes can be of importance; this is known as spike–timing dependent (synaptic) plasticity (STDP). Examples of such timing dependent mechanisms are shown in figure 3.3, where the baseline in each subplot indicates a steady level. Moving above the baseline implies a potentiation while going below expresses a depression.

In figure 3.3, abbreviations for Long Term Potentiation (LTP) and Long Term Depression (LTD) are used to characterize the changes as being either a prolonged increase or a prolonged decrease of the synaptic response.

Investigation of these long term effects is an area of research that has been object

[10]Burst firing only presynaptically or postsynaptically did not produce the effect.

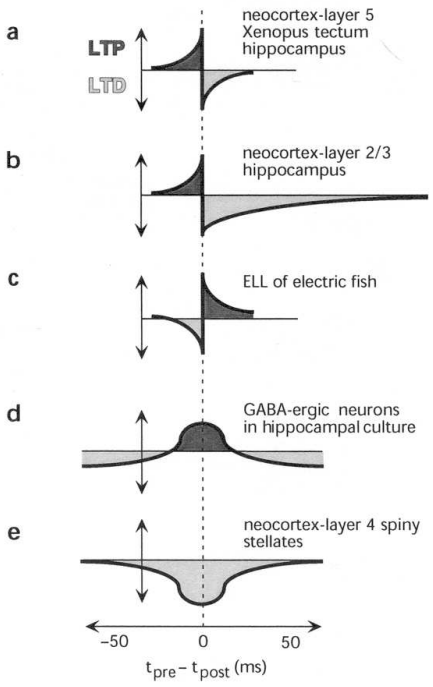


Figure 3.3 Spike–timing dependent synaptic plasticity (STDP) as found in different preparations of neural tissue. Long term effects are evoked by repeated pairing of pre- and postsynaptic activity. Dark colors represent potentiation and light colors depression. In the upper three figures (a, b, and c), it is of importance whether presynaptic activity precedes postsynaptic activity or if it is the other way around. In the lower figures (d and e), only the relative timing matters. Figure from Abbott and Nelson (2000).

to a remarkable intense activity for at least the last twenty years. This is partly why they will be dealt with at some length in the following section, but the main reason is their close relations to mechanisms involved with forming and storing memory – learning.

3.3 Long Term Potentiation

Long term potentiation is a use-dependent, long-lasting enhancement of the synaptic strength. The first discoveries of LTP were made in 1966 by Terge Lømo and were presented in an article[11] seven years later. The effect was found in the rabbit hippocampal formation.[12] Since then it has been demonstrated to occur in various excitatory synapses of the central and peripheral nervous system.[13]

The discovery of the long term potentiation effect in the hippocampus made it widely believed to be associated with learning. Indications that this is indeed the case, include the finding that LTP is present in the hippocampus during learning.[14] This latter knowledge has also meant that most of the experiments on LTP have been performed on excitatory synapses in or from the hippocampus.

Citation counts prove that the LTP field has been given a lot of attention.[15] As Malenka and Nicoll put it, long term potentiation is »*... the leading experimental model for the synaptic changes that may underlie learning and memory.*«.[16] Evidently, long term potentiation is a popular model – perhaps too popular. And, possibly, one of the reasons for its popularity might be that the three letter abbreviation, LTP, has been used indiscriminately to label various incidents where a protracted enhancement of synaptical transmission efficiency has been observed – but where the underlying mechanisms might be different.

This is exemplified by e.g. Bliss and Collingridge, who, in the studies of LTP, have identified at least three different time scales,[17] each covering mechanistically

[11] Bliss and Lømo (1973), as reported in Shors and Matzel (1997).

[12] Induced in the dentate gyrus granule cells when the perforant path was stimulated.

[13] See e.g. Shors and Matzel (1997) or Brown et al. (1990).

[14] LTP can e.g. be induced by synchronized patterns of theta bursts (e.g. bursts of 4 shocks at 100 Hz delivered at an inter-burst interval of 200 ms) which are similar to patterns found in the hippocampus during learning (Bliss and Collingridge, 1993).

[15] A quick incomplete search tells that the original article is cited at least 2500 times. Also, in Malenka and Nicoll (1999), it is mentioned that a simple MEDLINE search with 'long-term potentiation' as keywords, brings forth more than 3000 papers – alone from within the last decade.

[16] Malenka and Nicoll (1999, p. 1870).

[17] Bliss and Collingridge (1993). Also in Brown et al. (1990) three models for LTP are mentioned.

distinct components:

LTP1 Duration 3-6 hours, blocked by kinase inhibitors but not by protein inhibitors.

LTP2 Blocked by translation inhibitors independent of gene expression.

LTP3 Duration days, may require gene expression.

Obviously, this blurs the picture a bit and has caused some scepticism; an issue that will re-occur once the prevailing notions of LTP are laid forward.

3.3.1 Features

Before going into the origins of this longer lasting effect, it might be appropriate to mention some of the features often associated with it.[18] Figure 3.4 illustrates the concepts

Cooperation: Several spikes are required within a short time. One spike (or a few) does not depolarize the postsynaptic neuron in a manner producing LTP.

Associativity: Input pathways that are weak and insufficient can, nevertheless, be potentiated if active at the same time as strong input pathways. An interaction often mentioned as a characteristic necessity for explaining associative learning such as classical conditioning.

Input-specificity: Only input pathways that are active in close proximity to postsynaptic depolarization are potentiated.

An associativity example is given by Brown et al. (1990). They mention that the synapses at the Schaffer collateral/commisural inputs in the hippocampus have been shown to display an associative form of LTP. From figure 3.4, it is clear that the interplay between pre- and postsynaptic activity is important.

3.3.2 Induction of LTP, pre- or postsynaptic ?

What causes LTP is not fully understood. There is an ongoing debate whether the mechanism takes place presynaptically, postsynaptically, or both.

[18] See e.g. Kandel et al. (1991); Bliss and Collingridge (1993); Malenka and Nicoll (1999).

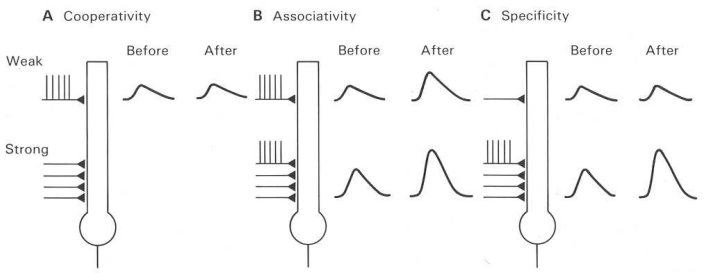


Figure 3.4 Features connected to long term potentiation. A single schematic pyramidal cell receives weak and strong input, respectively, along two different pathways and the resulting EPSP is monitored. A: Weak stimulation alone does not induce LTP (the EPSP does not change), stronger stimulation – higher cooperativity – is needed. C: Stimulation of the strong input alone is enough to cause LTP – for this specific pathway, the 'weak' pathway is not potentiated. B: When acting together, the strong stimulation 'drags along' the weak, yet active, pathway; potentiation happens in both pathways (figure from Kandel et al. (1991)).

Originally, LTP was produced by high-frequency presynaptic stimulation, but it can also be induced by pairing single presynaptic stimuli with postsynaptic depolarizations (properly timed as indicated in figure 3.3); these pairings do often not have to occur at high repetition rates.[19]

A mechanism involving an increase in presynaptic transmitter release probability is a possible candidate as the underlying process for inducing LTP. Different suggestions, for how this alteration of the release probability can come about, have been made. One particular is by addition of new docking sites to the readily releasable pool. To see why this can account for an increase in the synaptic response, one can assume that the probability of release is somewhat similar at every release site. Although only one release site at the time can release a vesicle (see section 2.3), the overall release probability for this one will be increased as a consequence of the enlarged readily releasable pool. In an assembly of synapses, this would also lead to less variation in the total transmitted signal.

Such a presynaptic change in release probability can account for synaptic redistribution (figure 3.2), using the argument that the release happens faster.

If the observed pairing effects are to be incorporated in LTP models favoring

[19] See e.g. Brown et al. (1990).

changes on the presynaptic side, a requirement is that a signal travels back across the synaptic cleft from the postsynaptic side. This transfer of information could be performed by retrograde messengers such as arachidonic acid or nitric oxide where at least the latter has been proven to be involved in long term changes.[20]

Other proposed candidates for LTP induction include reduced extra-synaptic glutamate uptake (which would in effect be similar to increased transmitter release) and, especially, NMDA receptor mediated changes on the postsynaptic side.

3.3.3 The role of NMDA receptors

Throughout the material documenting various findings of long term potentiation, one inevitably comes across descriptions of the NMDA receptor, and how it might be involved in the induction of LTP.

A key observation is that antagonists of the NMDA receptors block induction but not expression, thereby suggesting that once the synapse has learned, NMDA receptors are no longer important – but, also suggesting that during learning, or at least during a specific kind of learning, the presence of NMDA receptors is of vital importance.[21]

As described in section 2.3, glutamate is the main transmitter in excitatory synapses, and two major receptors for glutamate are the AMPA receptor and the NMDA receptor. When glutamate is released into the synaptic cleft, it binds to these receptors on the postsynaptic side. There, the AMPA receptor provides the majority of the flux of Na^+ and K^+ ions and hence is primarily responsible for generating the postsynaptic potential.

Activation of the NMDA receptor, on the other hand, requires that glutamate is bound *and* that the postsynaptic cell is depolarized. This is due to 'doubly gated' ion channels: When glutamate binds to the receptor, the channel opens on the outside, but, Mg^{2+} is still blocking the ion channel on the inside. Removal of the Mg^{2+} block is voltage dependent and therefore happens when the postsynaptic neuron fires an action potential.

When open, the NMDA receptor primarily conducts Ca^{2+} ions into the post-synaptic cell. It is well known that an increase in Ca^{2+}, within the dendritic terminal, initiates a chain of biochemical reactions ultimately affecting AMPA receptors. Figure 3.5 shows a simplified model of the processes involved. Rather than going into the specific reactions following Ca^{2+} increase, this sentence shall be used to emphasize the possible end-product: The conduction of the AMPA

[20] Arancio et al. (1996).
[21] See e.g. Brown et al. (1990).

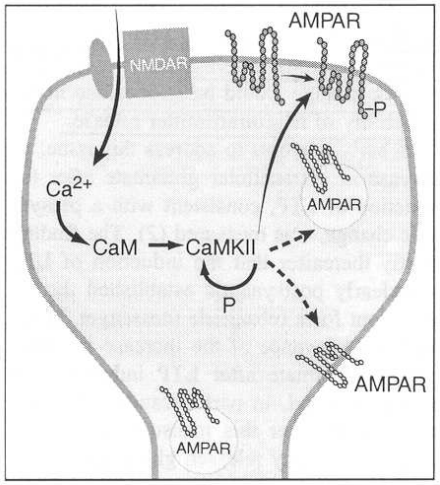


Figure 3.5 Activation of NMDA receptors (NMDAR) requires presence of glutamate and a depolarization of the postsynaptic cell. When active, the NMDA receptor mediates an influx of Ca^{2+} ions. Once inside the cell, Ca^{2+} binds to calmodulin (CaM) to activate CaMKII, which in itself can phosphorylate AMPA receptors (AMPAR) effectively increasing their conduction. It is even possible that CaMKII can promote the activation of 'sleeping' AMPA receptors,[a] or the creation of new ones (figure from Malenka and Nicoll (1999)).

[a] Shi et al. (1999).

receptors is increased, and/or the number of receptors goes up.

An increase in the number of receptors in the membrane could happen as a result of gene expression. Another possibility is reported by Shi et al. (1999) who, by labelling AMPA receptors with a fluorescent marker, could locate them as being inactive in the interior of the cell. However, when LTP was induced, the marked AMPA receptors rapidly moved to the membrane surface and became activated.

The theory that the postsynaptic Ca^{2+} concentration, building in the terminal after a depolarization, is an important factor in LTP induction, has been supported by a study carried out by Artola, Bröcher and Singer (1990).[22] They found that at low Ca^{2+} concentrations nothing happens. At an intermediate Ca^{2+} level, LTD effects set in. And, high Ca^{2+} levels resulted in LTP. By defining thresholds for on- and offset of LTD and LTP, these findings have been termed the ABS rule.

It is worth noticing how the coincidence detection properties of the NMDA receptor – contributed by its requirement of simultaneous pre- and postsynaptic activity – implies spatio-temporal specificity: Only the active pathway, and not other pathways[23] converging on the same cell, is potentiated (spatial) and, only when receiving the pre- and postsynaptic signal in close (temporal) proximity alterations occur. As Markram et al. put it »*... the back-propagating AP [action potential] could be regarded as a "binding signal" for active synaptic contacts.*«.

[22] As reported in Nielsen (2001) and Gerstner and Kistler (2000).
[23] Unless they are also active, of course.

Actually, where the maximal amount of glutamate binding occurs with only a short delay after the presynaptic spike, the process of unbinding (dissociation) takes longer.[24] Therefore the combined action of the pre- and postsynaptic side does not have to come at exactly the same time. In fact, as figure 3.3 indicates, the important measure is the temporal *difference* between the presynaptic and the postsynaptic spike. When the presynaptic spike arrives to the synapse slightly before the postsynaptic depolarization, it is likely that the presynaptic spike has contributed to the firing of the postsynaptic neuron, thus the connection should be strengthened. And, vice versa, if postsynaptic depolarization occurs before the presynaptic spike there is no causal connection, and the synapse should be weakened.

3.3.4 Long Term Depression

The potentiation effects mentioned above are adding to the synaptic strength. However, as already revealed in figure 3.3, the opposite effect is also present in various forms in synapses. Long term depression (LTD) is a use-dependent prolonged depression of the synaptic transmission efficiency. The existence of such an 'unlearning' mechanism seems reasonable from a physiological, and certainly from a computational point of view, since it makes sense that synapses in this way can compete for influence and, additionally, avoid saturation.

Long term depression was discovered in the 1980's by Masao Ito. The early studies described the LTD phenomenon as a unique, characteristic form of synaptic plasticity taking place in the cerebellum and regarded the mechanism as being a cellular substrate of motor learning; a hypothesis that is still maintained.[25]

Many of the properties that are true of long term potentiation can be applied to long term depression as well. In fact – although still debated – it seems as if a general agreement is emerging on the validity of the suggestion that LTD is more or less a reversal of the mechanisms underlying LTP. This means if LTP is a postsynaptic process, as suggested by e.g. Malenka and Nicoll (1999), LTD could be due to a dephosphorylation or even removal of the AMPA receptors. This is supported by e.g. Carroll et al. (1999), who discovered that induction of LTD caused a decrease in the number of AMPA receptors on the surface of the membrane.

[24] See e.g. Brown et al. (1990) or Destexhe et al. (1998).
[25] Ito (2000), with references to Ekerot and Kano (1985); Ito (1989); Ito et al. (1982).

3.3.5 Scepticism

The hypotheses and theories regarding LTP and LTD presented above merely scratches the surface of a topic where lots of scientists, and people claiming to be, have quite diverging interpretations of what is going on. It is beyond the scope of this report to judge between right and wrong (if this is possible), but a few remarks might be appropriate.

Browsing through only a minute fraction of the published literature, it seems as if the 'LTP' name has been used rather uncritical to describe long-lasting increases of synaptic strength. This is supported by e.g. Shors and Matzel, who note that »*...phenomena fitting the general description of LTP occur ubiquitously throughout the nervous system.*«[26]

Given the great variability in time scales, loci of discovery, stimulation patterns, mechanistic components etc., it is highly unlikely that all cases refer to the same thing. But then again, who says they have to? If not being too focused on the importance of whether the findings exactly match the original definition of the words, one might be tempted to state that it is only a matter of calling a thing by its right name; when it is reported that a *long term potentiation* has taken place, it is just a word-for-word description of the actual findings.

With these considerations in mind, findings of e.g. non-associative forms of LTP or NMDA receptor independent LTP,[27] do not rule each other out or disqualify the hypotheses advocating for either, they simply supplement each other in the quest for a deeper understanding of the underlying processes of synaptic plasticity.

3.4 Chemicals and climbing fibers

In matters of neuronal circuitry, learning is centered around the cellular changes occurring within individual neurons and synapses. These changes happen locally, but might affect or be affected by non-local activity; it could e.g. be another circuitry influencing the dendritic tree from quite a long way away.[28] The LTP mechanisms described in section 3.3 demonstrated the ability to capture associations between pathways. A requirement for the effects to appear is that the pathways converge somewhere along the line; it is also a matter of getting signals there in the first place.

[26] Shors and Matzel (1997, p. 599).
[27] Bliss and Collingridge (1993) and Shors and Matzel (1997) respectively.
[28] »*Number one – the larch.*«

3.4.1 Specialized circuitry

An example of the interplay between local and more global actions is found in the cerebellum, where each Purkinje cell makes synaptic connections with around 200·000 parallel fibers and receives synapses from only a single climbing fiber. The work of Ito[29] proved the conjectures put forward by Marr and Albus.[30] These regarded the possibility that mossy fibers deliver sensory input to the Purkinje cells, by means of parallel fiber inputs; whose synaptic efficacy are modified by the presence (or absence) of coincident climbing fiber input. In this respect, the climbing fiber signal can be thought of as a 'teacher signal', reorganizing associations (e.g. sensory-motor) conveyed along mossy and parallel fibers.[31] It is not clear whether other architectures support the existence of error signals at target neurons in the same manner.

Recently, the hypothesis that reorganization of the neuronal circuit by error-driven induction of LTD is to be considered the primary memory and learning mechanism of the cerebellum has been maintained.[32]

Another situation where one can think of 'teacher-like' interference is in acquisition of a new skill in terms of voluntary movements. Here, sensory feedback projections are necessary, at least in the beginning, to help correct wrong moves. Inhibitory interneurons can help correction as they can modify spontaneously active nerve cells in a controlling manner. Unfortunately, finding the exact wiring patterns and the functionalities thereby implied is not a trivial matter, as Chklovskii puts it »*... experimental studies of inter-neuronal connectivity are difficult and the connectivity data is scarce*«.[33]

Yet, the hippocampal formation has been mapped in quite some detail despite its intricate architecture. And, much of its functionality is known, although not in every detail.[34] A highly schematic version of the hippocampus is seen in figure 3.6, where its strongly hierarchical arrangement is evident.[35]

Signals traverse the structure in an almost sequential manner – in the figure from top to bottom – allowing for different 'processing steps' as they move along. The

[29] Mentioned in section 3.3.4 on page 32.

[30] Proposed in the 1970's. See e.g. Gluck and Granger (1993).

[31] See also Gluck and Granger (1993), mentioning how the Purkinje neuron exemplify computational capabilities of dendritic trees; for example 'AND' functions for multiple parallel fibers.

[32] Ito (2000).

[33] Chklovskii (2000, p. 108).

[34] »*While the anatomy of the hippocampus is fairly well known, the functional interactions among pyramidal cells and interneurons has not been fully determined*« Booth and Bose (2001).

[35] That most areas have onward projections to more than one of the following areas, is not shown. See e.g. Arbib et al. (1997) or Cotterill (1998).

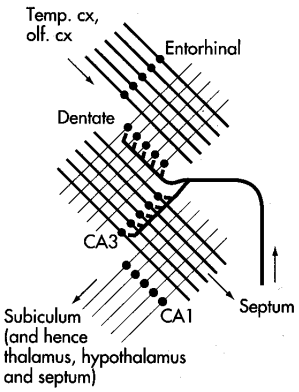


Figure 3.6 A highly stylized representation of the neural architecture of the hippocampus. Incoming signals from the cortex[a] run through the structure in a sequential manner. The hierarchical arrangement allows for the hippocampus to act as an associative network and to capture correlations between the signals. Neurons projecting outwards from the CA3 area folds back onto themselves; a property resembling that of Hopfield networks (figure from Carpenter (1996)).

[a]Temp.cx: Temporal cortex.
olf.cx: Olfactory cortex.

grid-like structure resembles the one used for associative networks;[36] and, indeed, the hippocampus is known to be well adapted to integrate together information from various cortical areas. That fibers projecting out from the CA3 area 'folds back' onto themselves (recurrent collaterals), provides feedback information to the system, a setup resembling the one used when depicting artificial Hopfield networks.[37]

3.4.2 Global changes

Although the Hebbian learning mechanisms discussed previously use local information, the modification processes may also be subject to global control signals. It is demonstrated that diffusive substances such as e.g. catecholamines, acetylcholine, and norepinephrine act neuromodulatory.[38] Rather than being an external teacher instructing changes in specific synapses, these substances exert what could be considered as non-specific reinforcement signals; especially dopamine release has been found to act as a reward signal in the mammalian brain.[39]

Hebbian plasticity involves positive feedback, since active synapses gets even more active and inactive synapses might be likewise weakened. To prevent instabilities from arising, early models of learning and memory often incorporated global signals or mechanisms. Since experimental findings supporting these global modifications were vague, the adjustments were put into the models *ad hoc*.[40]

[36]If not the other way around.
[37]Capable of acting as an associative, distributed memory storage. See also section 4.1.
[38]Brown et al. (1990).
[39]See Schultz et al. (1997), explaining how dopaminergic activity might be encoding reward information.
[40]Hebbian learning rules are discussed in section 4.3.

It is noted in Bliss and Collingridge (1993) that mechanisms are observed by which postsynaptic activity enhances all synapses, including those not active. Also other non-specific changes like this have been seen but only sporadically explained.

However, as mentioned in Abbott and Nelson (2000), recent findings of biological mechanisms altering the synaptic strengths globally – called synaptic scaling – allows for future models to incorporate 'true' global modification of synaptic efficacies. Although only some of the biophysical mechanisms underlying synaptic scaling are fully understood, it seems as if the modelers by use of global modulatory intervention have been ahead of their time.

Summary

In the context of the present report, the notion of learning amounts to synaptic plasticity. Based on experimental findings, it has been substantiated that Hebb-like pairing of pre- and postsynaptic activity is of great significance for establishing long-term effects. In addition, the temporal difference between presynaptic and postsynaptic spikes is found to be of vital importance for whether this pairing results in a strengthening or a weakening of the synaptic efficacy.

By regarding the NMDA receptor as being responsible for capturing correlations, the origin of induction is assigned to be the postsynaptic membrane. The experimental findings suggest a clear connection between the postsynaptic Ca^{2+} level following depolarization and the number of active AMPA at the surface of the membrane. The ABS rule supports these discoveries by suggesting that regulation of LTP and LTD is done in accordance with the Ca^{2+} level.

4 Artificial

»Look to the past for guidance into the future.«

Robert Jacob Goodkin

In the hope that some of the brains extraordinary signal processing abilities could be mimicked, the attempts to reproduce artificial copies of the neural organization of the brain has gone a long way.

4.1 Classic artificial neural networks

An Artificial Neural Network (ANN) is a signal processing paradigm highly inspired by the manner in which biological neural networks, for example the brain, process signals or information. In general, an ANN is composed of a number of interconnected elements (neurons) working together to solve the given problem. Depending on the specific application, both the structure of the ANN and the type of its constituents are tailored to generate the optimal result.

Traditionally, artificial neural network techniques have found use in e.g. regression, pattern recognition and data classification. When analytical models are either unknown or perhaps very complex, ANN's are often used, as they provide general mechanisms for building models from data.

Like children, the ANNs learn by example; they are 'trained'. As described in section 3.2, learning in neural systems involves adjustments of the synaptic connections linking neurons together. Likewise for artificial networks – the synapses of which are called weights – learning amounts to adjusting the weights. Figure 4.1 shows a schematic representation of a neuron in an ANN.[1] Weights, w, represent the synaptic strengths assigned to each connection made by input neurons, x. The larger circle symbolizes the soma, where a summation is performed, yielding the activation $a = \sum_i w_i x_i$.

[1] To separate the true from the artificial, other words than neuron are often used, e.g. node or unit.

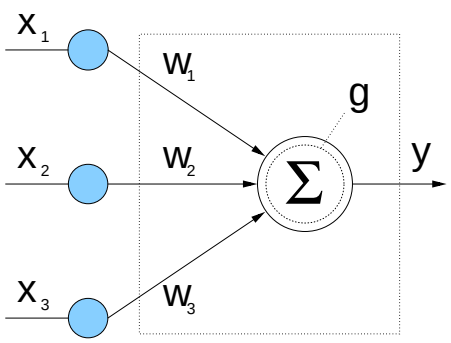


Figure 4.1 A schematic representation of a typical 'neuron' in an artificial neural network. Inputs, x, arriving to the left, get multiplied with the weights, w, and are summed to yield the output, y. Also, a possible functional transformation is implied, g. Narrowing the view to the dotted box, its left side holds the 'dendrites' impinging on the circular 'soma', from which a single 'axon' departs.

Output, y, is produced by applying an activation function, $g(\cdot)$, to the summed and weighted input

$$y = g(a) = g\left(\sum_i w_i x_i\right) \tag{4.1}$$

Which particular type of activation function to choose depends on the application but often a non-linear function is used.[2] An artificial neural *network* is then designed by putting a lot of these units together in various ways. Extensive amounts of effort have been, and are being, put into the entire field of artificial neural network theory. Appendix B contains brief reviews of some of the early findings.[3]

Typically a feed-forward structure is used, meaning that the network is directed and without reverberating signals. Recurrent networks containing feedback from later to earlier neurons are also seen, but these can be unstable, and have very complex dynamics. The perceptron is an example of a feed-forward network consisting of a single layer[4] and having threshold activation functions.[5] It is able to perform classification of data using linear decision boundaries.[6] An interesting feature is that for linearly separable datasets this is bound to happen in a finite number of training steps. This is known as the perceptron convergence theorem.

In a very popular type of networks – multi-layer perceptrons – a 'hidden' layer is introduced. The hidden and output layer neurons are each connected to all

[2] And often a non-linear 'squashing function' is chosen; accepting input in any range and giving output in a limited range (e.g. the logistic function).

[3] For further reading refer to e.g. Hertz et al. (1991), Bishop (1995), Cybenko (1996) or Jain et al. (1996).

[4] Depending on the definition of layers; most often the input side is not counted as a layer in itself.

[5] As $y = \mathcal{H}\left(\sum_i w_i x_i - \theta\right)$, with $\mathcal{H}$ being the Heaviside step function and θ the threshold.

[6] Hyperplanes when going into higher dimensions.

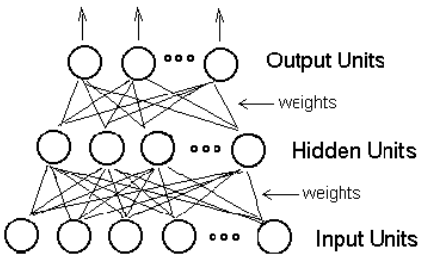


Figure 4.2 Diagram of a fully-interconnected feed-forward multi-layer perceptron; so called even though sigmoidal activation functions are used. It consists of a single hidden layer and two layers of adjustable weights. In general, networks with two layers of weights are able to approximate any continuous functional mapping.

of the units in the preceding layer.[7] In figure 4.2, such a multi-layered structure is shown. Both the transformation from inputs to hidden-layer and from hidden to output-layer takes place by means of activation functions, as given in equation (4.1); not necessarily the same activation function though.

Training and use of the networks happen by presenting data on the input side and watching the output. Depending on what information is available to the network, the three main learning paradigms from section 3.1 can be applied to these networks as well.[8] Here, supervised learning will be considered.

In supervised learning, the network user gathers a set of training data containing examples of inputs matched with corresponding outputs. The data set is used to adjust the network weights so that a minimization of the error in its predictions on the training set is obtained. Trained properly, the network has learned to model the (unknown) functional relation between input and output variables; meaning that, subsequently, the network can be fed input, and from that, be used to predict output that is not known. It is this ability to learn from examples, rather than following pre-specified rules that has made the ANN's very attractive.

The idea of minimizing error-functions or cost-functions (or surfaces) is a common tool used when training artificial neural networks. Typically, these surfaces have analytically indeterminable global minima, which is why network training can be thought of as corresponding to an 'exploration' of the error surfaces.[9] If the networks have differentiable activation functions, powerful methods for evaluating the gradient vector of the error function exist.[10] Since the gradient vector points along the line of steepest descent from the current point, one knows that following this direction will decrease the error.

[7]Partially-connected networks do exist but for most applications fully-connected networks are better. Pruning algorithms (removing unimportant weights) is a way to combine the two.

[8]The three types being: Supervised, unsupervised, and reinforcement learning.

[9]Often by setting out from a random initial configuration of the network and then incrementally search for a minimum – local sometimes, unfortunately.

[10]One such method that is very efficient and widely used is the back-propagation algorithm.

Allowing the artificial networks and their components to gradually diverge from being directly comparable to the 'real' networks, other classes of computationally very efficient models arise.

An example is radial basis function networks (RBF), whose architecture resembles that of a multi-layer perceptron (MLP), the difference being the choice of activation function. In general, the MLP's use of a sigmoidal activation function leads to a division of the pattern space into hyperplanes.[11] Instead, RBF networks make use of bell-shaped activation functions, e.g. gaussians, and the inputs to these, the activations, are determined on grounds of the distance between an input vector and some prototype vector; this ultimately leads to a division of pattern space into hyper*spheres*.

The use of ANN in estimation of probability density functions (PDF's) from data has also been widespread. It is an area strongly connected to Bayesian statistics. The RBF can be considered an alternative approach to PDF estimation belonging in the class of kernel-based approximation schemes where somewhat simple functions are located at each available training case, and their combination yields an estimate of the overall probability density function.

Another big area of ANN research is graphical models. Depending on their connectivity, these can lead to e.g. Markov Random Fields (undirected) or Bayesian Networks (directed) also known as Belief Networks. In brief, the graphical model theory provides a general formalism in which many of the classic probabilistic systems can be considered special cases.

Here, a break back to the 1980's is appropriate to catch up with a fully-connected feedback network, learning in an unsupervised manner – the Hopfield network. An interesting feature of the Hopfield networks is that they can associate memories (or patterns). An example: Imagine a network containing an area representing e.g. 'a house' and another area holds the notion of 'a tree'; then, if the two areas are stimulated simultaneously ('shown' a picture of a house with a tree in front), associations between the areas will build. This means that later presentations of e.g. the house alone will also bring forth the tree; a feature called content addressability or pattern completion. That memories can be stored in a content addressable fashion can be a powerful ability as it makes the network robust against loss of data. Also, it enables the network to come up with the right pattern even though erroneous input is given. This is demonstrated by another (old)[12] example: Try to recall 'a 20th century American actor who was a politician and very intelligent'. See the following footnote for an answer.[13]

[11] Like a cliff by the sea – sigmoidally shaped that is.

[12] According to an on-line draft by David J. C. MacKay, available at http://www.inference.phy.cam.ac.uk/mackay/

[13] Most people come to think of ex-president Ronald Reagan – even though one of the cues contains an error.

No 'teacher' is needed in the learning process of Hopfield networks, it all amounts to, unsupervised, local learning rules.

4.2 Networks of spiking neurons

The shapes of the action potentials sent out by a neuron are practically all alike. This means that the information they are carrying must lie in the number of pulses transmitted and the interval between them.

A widely used tool for describing the properties of a neuron has been to average the number of spikes occurring in a given time T and get a average firing rate – the activity a.[14]

$$a = \frac{number\ of\ spikes\ in\ time\ T}{T} \tag{4.2}$$

The algorithms based on this assumption[15] have proven quite powerful. However, by neglecting the exact timing of emitted spikes, temporal information is lost. When considering algorithms working on signals with temporal or spatio-temporal coding this is clearly unfortunate.

In a *network of spiking neurons* this information is utilized, the timing of spikes is taken into account.

To get a feeling of the computational power of spiking networks consider the following line of thought: If a neuron can fire at 100 Hz during 100 ms, a temporal pattern consisting of ten binary values (firing or non-firing) can be created. It is then possible for a single neuron to encode a total of 2^{10} patterns during the 100 ms.[16] Of course, in real life the information content of spike trains is not this high. Dayan and Abbott mention that measurements on a fly has revealed that the signal stemming from a single neuron contains $\approx 200\ bits/s$.[17]

From a biophysical point of view, taking the temporal information into account seems necessary. An example is that a fly can react on visual input within $30 - 40\ ms$ thereby allowing it to land on the edge of a cup.[18]

[14] Note that the activity, is *not the* the same as the activation in section 4.1.

[15] By which some of the most important has been mentioned in the previous section.

[16] Liaw and Berger (1997).

[17] The information content is found by considering the entropy of the signal from a visual neuron (H1) in a fly responding to randomly moving images.

[18] Rieke et al. (1997).

4.2.1 Neural coding

How then, is information encoded in nature? This is still an unsolved question.[19] The above examples indicate that at least sometimes information is encoded in the temporal sequence. If spikes are considered binary i.e. no information is encoded in the shape of the spike, only the timing and quantity of spikes matter. A short list of different coding schemes which can be of interest.

Time-to-First-Spike The timing of the first spike after an event holds all the information. A short time could for example signal a strong stimulation.

Phase The information lies in a comparison between the firing time and the phase of some intrinsic or background oscillation serving as a reference signal.

Correlations and Synchrony Spikes from other neurons can be used as the reference signal.

Sequence Information is coded in the sequence of the spikes, i.e. the interval between spikes.

Bursts Spikes appear three or more at a time. Information is then encoded in the patterns of bursts.

As shall be shown later, burst coding is in good agreement with the facilitating and depressing behavior seen in synapses.

Facilitation can be thought of as noise reduction. The second spike is transmitted more effectively than the first spike – making lonely spikes less important.

Attempts have been made to read the neural code.[20] A useful tool for this is reverse correlation. The typical time course leading to a postsynaptic spike is recorded. It is then possible to measure to what stimuli the particular neuron reacts.[21]

An example illustrates the capabilities of sequence encoding. When information is stored in the relative timing of the spikes, a common additive constant will not influence the decoding. Let the sequence $x = \{1.5,\ 2,\ 5,\ 5.5\}$ denotes an external stimuli, e.g. a visual pattern and $y = \lambda x$ denote the same stimuli but with another intensity. Applying the logarithm makes it possible to recognize

[19] Rieke et al. (1997).

[20] Rieke et al. (1997).

[21] For certain synaptic models Natschläger and Maass (2001b) has calculated the spike train given optimal transmission strength. The results were similar to experimentally found spike trains from recordings on neurons.

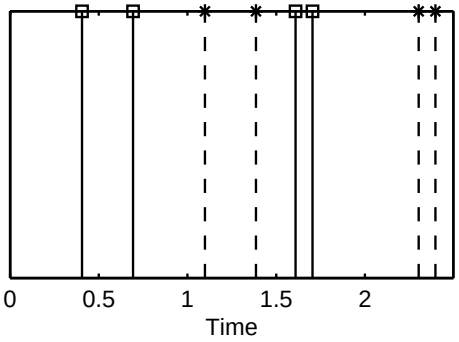


Figure 4.3 Encoding information in sequences makes the response of a neuron independent of the onset of a stimulus. This can e.g. be used to construct an intensity-independent detection mechanism. If the logarithm of the signal is considered, multiplicative constants can be eliminated ($\log x$ solid, $\log y$ dashed, $\lambda = 2$).

the stimuli as being identical. The only difference is an additive constant $\tilde{y} = \log y = \log \lambda x = \log \lambda + \log x$ (see figure 4.3). As seen the relative timing is independent of intensity.

Because networks of spiking neurons employing sequential coding can detect temporal patterns disregarding the onset time, this then provides a method for eliminating intensity when comparing signals. In real life this could be how it is possible to distinguish objects in different lighting conditions.

4.2.2 Performance

Theoretical studies of networks of spiking neurons have shown that they are computationally more efficient than classic artificial neural networks. In the following theoretical results will render this probable, for a thorough investigation see Maass (1997b).

A necessary condition for the introduction of spiking neural networks is that they can do every thing that classic neural networks can.

It is well known from artificial network theory (see section 4.1) that feed-forward nets – e.g. multilayer perceptrons – can approximate any continuous function arbitrarily well. A requirement is that it consist of neurons employing a suitable activation function e.g. the *sat* function (see figure 4.4). Spiking networks inherits this property since it is possible to approximate any classical networks with spiking networks:

> Any feed-forward or recurrent analog neural net (for example any multilayer perceptron), consisting of s sigmoidal neurons (where c is a small constant) that employs the gain function *sat*, can be simulated arbitrarily closely by a network of c spiking neurons with analog inputs and outputs encoded by temporal delays of spikes. This holds

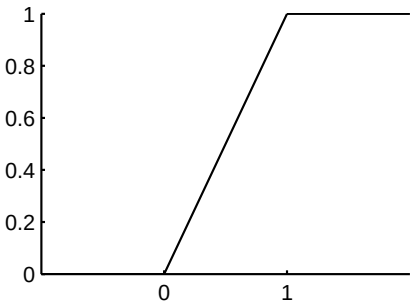


Figure 4.4 The activation function sat. With this activation function a multilayer perceptron can approximate any continuous function arbitrarily close. Spiking networks can approximate any classical feed-forward network and thus inherits this approximation competence.

> even if the spiking neurons are subject to noise. (Maass and Bishop, 1999, Theorem 2.3)

In some cases spiking networks are even more efficient than classical networks. One example is the ability to detect whether two events happen at the same time – coincidence detection. The coincidence function $CD_n : \{0,1\}^{2n} \rightarrow \{0,1\}$ is given by

$$CD_n(x_1, \ldots, x_n, y_1 \ldots, y_n) = \begin{cases} 1, & x_i = y_i = 1, i \in 1, \ldots, n \\ 0, & otherwise \end{cases} \tag{4.3}$$

The function returns true (one) if one pair of x_i and y_i are identical. This can for example be used in delay lines to determine the delay in arrival times. An example of this is sound source localization. The distance between the ears result in a delay in perception of a sound between the ears. This delay can be used to determine the direction to the sound.[22] Let a signal arrive at

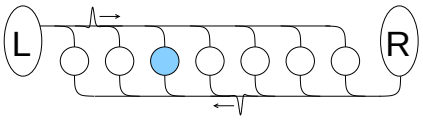


Figure 4.5 Coincidence detectors (circles) calculate the difference in arrival times of a signal at the right and left ear. In this example the signal arrived at the right ear before the left resulting in activation of the colored coincidence detector.

slightly different times to the left and right ear respectively. The signal travels down two different lines and at some point it arrives simultaneously, the location of this point contains information about the delay. Via coincidence detection information about the delay can be extracted, see figure 4.5.

[22] Using more sophisticated methods – such as regarding resonance in the skull – it is also possible to get the precise location.

Coincidence detection can be performed by a single spiking neuron simply by receiving input from several sources and cross the firing threshold only when the input signals x_i and y_i are sufficiently close.[23] This is, by far less complicated than in classical neural networks.

> - Any threshold circuit that computes CD_n has at least $\frac{n}{\log(n+1)}$ gates.
> - Any sigmoidal neural net with piecewise polynomial activation functions that computes CD_n has $\Omega(n^{\frac{1}{2}})$ gates. For the case of piecewise exponential activation functions the lower bound is $\Omega(n^{\frac{1}{4}})$.
> - A single spiking neuron with variable delays can compute CD_n.
>
> Maass (1997b, pp. 9–10)

In this context *gates* is the same as non-spiking neurons. $\Omega()$ means 'in the order of'.

Finally it should be mentioned that Maass and Sontag (2000) has proved that neural networks with dynamic synapses[24] can approximate any nonlinear filter that can be characterized by Volterra series.

4.3 Learning and Hebb rules

From the above sections it is evident that with the right setting of parameters, artificial neural networks can perform well. However, the question of how to find the right parameters has not yet been answered.

A way to modify the parameters – weights – is to use error minimization. If a suitable error-function can be constructed, it is possible to apply an optimization algorithm and search parameter space for a minimum. For multilayer perceptrons the error-function can be used in back-propagation. For networks of spiking neurons a similar approach called 'spikeprob' can be applied.[25]

However, when considering learning without error-functions, unsupervised learning, other methods are needed. It is necessary that the learning rule incorporates some kind of competition among the weights, making some of them gain strength and others lose strength, until the correct balance has been found. What is

[23] The delays should be tuned so that x_i, y_i does not influence x_{i+1}, y_{i+1}.
[24] The notion of dynamic synapse will be returned to in section 6.2.
[25] Bohte et al. (2000a).

needed is a way to adjust the weights by looking at how much they are used – how successful they are.

A particular approach to obtain this kind of competition is to use weight updates in accordance with the Hebbian learning rule. As for the networks, the Hebbian approach comes in two varieties: A rate-based and a spike-based.

4.3.1 Rate based rules

It has been estimated that around 50-100 algebraic equations have been proposed to describe theoretical activity based synaptic modification, in other words learning rules.[26] Many of these are not intended as being detailed biophysical models of synaptic function but rather developed with computational properties in mind.[27]

A general mathematical formulation[28] can be used to describe most of the variants of Hebbian learning rules

$$\Delta w_{ij} = F(w_{ij}; a_i, a_j) \quad , \tag{4.4}$$

where F is some function, dependent on the current weight w_{ij} and measures of presynaptic activity, a_i, and postsynaptic activity, a_j. The variables are constrained to be real ($w_{ij}, a_i, a_j \in \mathbb{R}^+$).

Expanding F in the activities around $a_i = a_j = 0$ to second order, yields an expression containing correlational and non-correlational terms

$$\begin{aligned} \Delta w_{ij} \quad \approx \quad & c_0(w_{ij}) + c_1^{pre}(w_{ij})a_i + c_1^{post}(w_{ij})a_j + \\ & c_2^{pre}(w_{ij})a_i^2 + c_2^{post}(w_{ij})a_j^2 + c_2^{corr}(w_{ij})a_i a_j + \mathcal{O}(a^3) \end{aligned} \tag{4.5}$$

The simplest way to implement Hebb's rule, is to look at the activities on both sides of the synapse and adjust the strength according to the firing rates, i.e. neglecting all terms but the correlational term

$$\Delta w_{ij} = c_2^{corr}(w_{ij})a_i a_j \tag{4.6}$$

This approach, however, suffers from the major disadvantage that the synapse can only be strengthened, implying that weights must grow perpetually.

Perpetual growth in itself does not pose a problem, since a constraint, soft or hard, can be imposed on the weights ensuring that they are positive and

[26] According to Brown et al. (1990). It is an estimate from 1987, why the number probably have increased since.

[27] See e.g. Arbib et al. (1997).

[28] Adopted from Gerstner and Kistler (2000).

bounded. A hard constraint simply 'clips' the weights if they go beyond a specified boundary.[29] A soft constraint acts a little more elegantly by multiplying the weight change Δw_{ij} with a bounding function, leading to a 'bounded' weight change Δw^*_{ij}

$$\Delta w^*_{ij} = \eta \cdot w_{ij}(1 - w_{ij}) \cdot \Delta w_{ij} \tag{4.7}$$

where η is a constant parameter. This confines the weights to $w_{ij} \in [0; 1]$, as the weight change becomes smaller if approaching one of the limits.

However, perpetual growth is not the only problem with the basic Hebb rule (equation (4.6)). If weights are always increased towards an upper limit, it is, eventually, not possible to store any information since all weights will end up at the maximum value. To deal with this problem, it is necessary not only to have increasing weights, some of the weights must also be decreased. This can be thought of as an necessity of competition between the weights.

A simple way to do this, is to require that the sum of the weights are constant $\sum w_{ij} = c$. This can be done e.g. by normalization of the weight vector after each change. If one weight is increased, all others must suffer. This solution is non-local since it requires information about the other weights.

Another simple way to deal with the problem, is to also consider the zeroth order term of equation (4.5). Keeping this term negative, $c_0 < 0$, the weights decay back towards zero when not stimulated

$$\Delta w_{ij} = c_0(w_{ij}) + c_2^{corr}(w_{ij})a_i a_j \quad , \quad c_0 < 0 \tag{4.8}$$

More complex learning rules can be found by looking at the uncorrelated activities. Introduction of linear terms from equation (4.5), implies that the activities on either side of the weight are compared to a threshold, to see if the weight should be strengthened. These variations of Hebb's rule are sometimes called hetero- and homo-synaptic depression. Hetero-synaptic depression decreases synaptic strength if there is postsynaptic activity but little presynaptic activity. Homo-synaptic depression occurs if there is activity only on the presynaptic side. Considering hetero-synaptic depression

$$\Delta w_{ij} = c_1^{post}(w_{ij})a_j + c_2^{corr}(w_{ij})a_i a_j \tag{4.9a}$$

$$= k(w_{ij})a_j\big(a_i - \theta(w_{ij})\big) \quad , \tag{4.9b}$$

it is easily seen that a certain level of presynaptic activity is necessary to strengthen the weight. If the presynaptic activity is below threshold θ, the weight is decreased.

[29] Simply an IF–statement in algorithms.

Hetero-synaptic modifications have the property that a fixed point occurs when presynaptic activity equals the threshold. If this fixed point is stable, the weight will converge towards a steady level. Consider e.g. equation (4.9b) with $\theta(w_{ij}) = w_{ij}$. In this case, the average presynaptic activity becomes the fixed point and the weights will store an average of the presynaptic stimulus pattern.[30]

Homo-synaptic modifications can in a similar manner be used to introduce depression of the synapses

$$\begin{aligned} \Delta w_{ij} &= c_1^{pre}(w_{ij})a_i + c_2^{corr}(w_{ij})a_i a_j && (4.10a) \\ &= k(w_{ij})a_i\big(a_j - \theta(w_{ij})\big) && (4.10b) \end{aligned}$$

As for hetero-synaptic modifications, it is worth considering a simple example of a homo-synaptic modification property. With $k < 0$ and $\theta(w_{ij}) = \theta$, the output activity (a_j) in equation (4.10b) will tend towards the threshold θ yielding a normalization of the output.[31]

Inserting the average activities $\langle\cdot\rangle$, as thresholds on both the presynaptic and the postsynaptic side, a rule based on covariance emerges. This rule was developed by T.J. Sejnowski in the 70's.[32] When pre- and postsynaptic activity are out of phase, the synapse is depressed

$$\Delta w_{ij} = k\Big(a_i - \langle a_i\rangle\Big)\Big(a_j - \langle a_j\rangle\Big) \tag{4.11}$$

An unfortunate property of this rule is that when activities are low on both sides, the synapse is strengthened.[33]

Including higher order terms from equation (4.5), more complex learning rules with highly desirable qualities can be obtained. Oja's rule is an example of hetero-synaptic depression which employs second-order postsynaptic activity

$$\Delta w_{ij} = k a_j(a_i - a_j w_{ij}) \tag{4.12}$$

Oja's rule ensures that the weights are normalized and that the weight vector converges towards the largest eigenvalue in the input.[34]

Another example of hetero-synaptic depression with higher order terms, is the Bienenstock, Cooper, Munro model

$$\begin{aligned} \Delta w_{ij} &= c_1^{pre}(w_{ij})a_i\theta(a_j) + c_2^{corr}(w_{ij})a_i a_j && (4.13) \\ &= k(w_{ij})a_i\big(a_j - \theta(a_j)\big) && (4.14) \end{aligned}$$

[30] See Gerstner and Kistler (2000).
[31] Also mentioned in Gerstner and Kistler (2000).
[32] See Churchland and Sejnowski (1992).
[33] At least from a physiological point of view. In some applications this property might actually be an advantage.
[34] See e.g. Hertz et al. (1991).

The model incorporates a 'sliding threshold' dependent of the postsynaptic activity, i.e. the higher average activity, the higher the threshold. Competition between weights occur because strengthening of weights increases postsynaptic activity, thereby increasing the threshold. This makes it harder for other weights to be strengthened. A specific example of a sliding threshold function is[35]

$$\tau_\theta \frac{\mathrm{d}\theta}{\mathrm{d}t} = a_j^2 - \theta \tag{4.15}$$

These general Hebbian learning rules are all developed for average activity measures. In the following, the rules are viewed in a spike-based formalism.

4.3.2 Spike based learning

As mentioned in section 4.2.1, the precise coding of information has not yet been understood. There is, however, indications that at least in some parts of the brain, a temporal coding scheme is used. In this section, learning rules reacting to single spikes are described. Many of the principles from the learning rules above, acting on average activities, can be reused. Certainly, the important properties are the same: An effective learning rule should be competitive, stable, and local.

In the section above, a function – equation (4.4) – capturing the dynamics of most rate based learning rules was introduced. A generalization of this function to a functional, allows it to cover spike based learning rules as well

$$\frac{\mathrm{d}w_{ij}}{\mathrm{d}t} = \mathcal{F}(w_{ij}(t); S_i(t), S_j(t)) \tag{4.16}$$

In this case $\mathcal{F}$ is a functional of $S_i(t)$, $S_j(t)$, and $w_{ij}(t)$. The $S_{i,j}(t)$ represent functions of the pre- and postsynaptic spiketrains, respectively. And, the time dependency introduced to $w_{ij}(t)$, indicates that it is a function of the weight itself. As with equation (4.4) this equation can be expanded around activities. However since equation (4.16) is a functional, the expansion is extensive and will not be shown here.[36] Instead, an extract of the expansion will be shown, to introduce the concept of a learning window.

If the activity functions S_i and S_j are chosen properly, the functional (4.16) reduces to (4.4).

Considering the special case, in which weight changes are taken to be instantaneous when a spike occurs, the expansion to second-order has the following

[35] See Dayan and Abbott (2000).
[36] See Gerstner and Kistler (2000) for a detailed description.

form

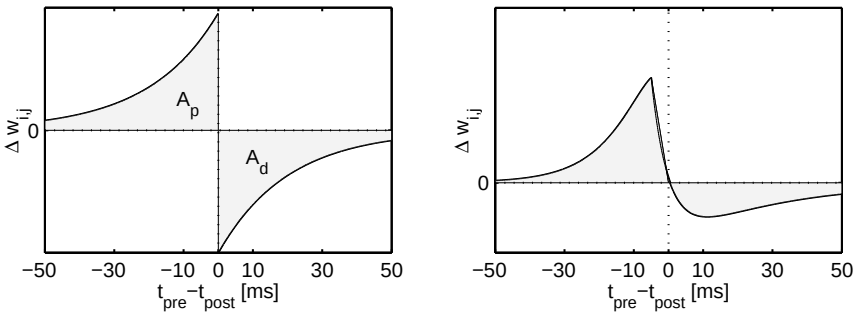
$$\Delta w_{ij} = \delta(t-t_i)\sum_{t_j<t_i} W(w_{ij}, t_i - t_j) + \tag{4.17}$$

$$\delta(t-t_j)\sum_{t_j>t_i} W(w_{ij}, t_i - t_j) + \tag{4.18}$$

$$\delta(t-t_j)a_1^{post}(w_{ij}) + \delta(t-t_i)a_1^{pre}(w_{ij}) + a_0(w_{ij})$$

The function W is dependent on the spike arrival times t_i (presynaptic) and t_j (postsynaptic). The two terms in 4.17 and 4.18 has to do with correlations between spikes. Together, the two W terms have been called the *learning window*.

What distinguishes spike based learning from rate based learning, is the relative timing of the spikes. For neuron a to participate in the firing of neuron b, it must not only be active, it must be active at the right time. Therefore the shape of the learning window is quite important in spike based learning.



(a) The area A_d in the right half plane is slightly larger than in the left A_p, which makes the synapse depress input that are not correlated with output. This window is used in section 6.3.1.

(b) The curve is continuous and the maximum is shifted to the left. This is done to capture the fact that in real synapses, the signal from the pre- to the postsynaptic side is delayed.

Figure 4.6 Two examples of learning windows, where $t_{pre} = t_i$ and $t_{post} = t_j$. The one in figure 4.6(a) is proposed by Song et al. (2000). Figure 4.6(b) shows a learning window proposed by Gerstner and Kistler (2000).

It is the relative timing of pre- and postsynaptic spikes that are decisive for changes in the weights. The learning window can e.g. be chosen so that postsynaptic spikes preceding presynaptic spikes are depressed; the *shape* of the learning window then determines *how* the weights are modified. In figure 4.6 examples of learning windows are shown.

The construction of learning windows are often biologically inspired; as described in section 3.2 (see e.g. figure 3.3), the learning windows found experimentally have widths of approximately 50 ms and are roughly exponentially decaying. This has inspired e.g. Song et al. (2000) to the learning window (figure 4.6(a)) used in their model.[37]

The actual structure of the learning window can be chosen in different ways. It is important though, that it promotes competition between synapses. A way to do this, is by having an asymmetric learning window. If the area of the depressing part of the learning window ($t_{pre} - t_{post} > 0$) is slightly larger than under the potentiating part, random behavior will be depressed. Consider a case where there are no correlations between pre- and postsynaptic activity. Postsynaptic spikes are then just as likely to appear shortly before as shortly after the presynaptic spike. With a larger area in the depressing part of the learning window, these uncorrelated inputs will then be depressed (see figure 4.6(a)). On the other hand, if input and output are correlated, in the sense that postsynaptic spikes almost always occur shortly *after* the presynaptic spike, the synapse will be potentiated.

Unlike the rate based rules, it is not necessary to include weight decay, homo- or hetero-synaptic modifications or higher order terms to induce depression. A spike based learning rule, depending only on the correlational or the 'pure Hebbian term', is able to depress some synapses and enhance others, by introducing competitive learning.

As for the rate models above, the stability of a 'correlation only' rule must be imposed either by hard or soft boundaries, ensuring that weights are always positive and bounded. It is likely that the introduction of non-correlational terms[38] could ensure stability and cause the weights to converge, e.g. to the maximal eigenvector as in Oja's rule. However, it has not been possible to find examples of – or theories describing – the use of such mechanisms in the available literature.

Summary

Spiking neural networks differ from classical neural networks by utilizing the temporal structure of signals. Besides performing the same tasks as e.g. multi-layer perceptrons, a spiking neural network can – with correctly adjusted weights – perform signal processing tasks on temporal signals in a very simple manner.

[37] Their model of 'Competitive Hebbian learning through spike-timing dependent synaptic plasticity' will be described in section 6.3.1.

[38] Equal to using zero'th or first order terms from equation (4.17) or using higher order terms similar to e.g. Oja's rule.

The much studied Hebbian rules for rate-based activity provide a basis for unsupervised learning in spiking networks as well. The basic concepts are the same, a learning rule must obey the principles of stability and competition.

Hebbian rules for update of weights in a spiking network are constructed in a way similar to the rate-based case. However, a major difference is that in the case of spike based learning it is not necessary to incorporate other terms in the learning rule than the purely correlational to induce competition. The main requirement for this competitive nature is the learning window. Different shapes can be used, but of particular interest is the result that a synapse should be decreased on average when the firing of the pre- and postsynaptic neuron is uncorrelated.

5 Tools

»Is simplicity best. Or simply the easiest?«

Depeche Mode

Although tools are available to simulate biological models e.g. Neuron and Genesis, a new tool was developed during this project. This, for two main reasons: The first is that when a tool is developed from the bottom, total control of the functionality is ensured. 'Bug hunting' is also considerably easier when using self-written code rather than preprogrammed packages. The second but not less important reason was the desire to gain insight of how larger functional object oriented programs are designed. This would not have been possible without the help from Carsten Knudsen and especially Martin Egholm Nielsen who has assisted many times during the project.

5.1 Janet – JAva Nonlinear Explorations Tools

JAva Nonlinear Exploration Tools has been developed at the Department of Physics at DTU[1] and is designed to investigate nonlinear systems of either differential equations or time discrete maps. The package provides different tools in the form of Java classes and can be used either as a stand alone application or incorporated in new software. The motivation for using Janet in this project was the possibility to use symbolic calculations via the Janet.symbolic package and the advantage of the many numerical integrators readily available.

In Janet it is possible to build symbolic expressions of e.g. the right hand side of a differential equation. This gives the opportunity to evaluate and manipulate expressions, and to return them as Java, C++ or XML code, directly usable in auto-generation of code.

[1] See http://www.fysik.dtu.dk/~janet

When implementing the Map interface from Janet and defining whether the system is *TimeContinuous* or *TimeDiscrete* and *Autonomous* or *NonAutonomous*, different analyses can be performed.

5.2 Creation of the modeling tool

Classically most neuronal models are described by differential equations and so are the models of synapses. However, the link between the two often uses the fact that an action potential fired by a neuron is well approximated only by the time of threshold crossing i.e. by firing of a discrete event. It is essential that the simulation tool can handle both integration of differential equations and the firing of events.

When experimenting with different implementations of neurons and synapses, flexibility is a key issue. Easy replacement of one part of the network with another is of great importance. In this way changes to the network can be made swift and with little extra programming effort. Furthermore, object oriented programming provides a higher level of abstraction when connecting models. Instead of considering which differential equations to couple, it is possible to concentrate on coupling building blocks.[2]

Much consideration has gone into the design of the program and discussions with Martin Egholm Nielsen and Carsten Knudsen at the Department of Physics has been essential for the development. With the construction of Janet in mind object oriented Java code seemed the way to go.

5.2.1 Netparts

The most important components in this network are somas and synapses. The basic concept is that a soma receives a continuous signal, which is either an external stimuli or input from synapses. All components are in this framework denoted *Netparts*. The soma changes its membrane potential according to the input and at some point it depolarizes and sends out a spike. An example of a soma is the integrate-and-fire neuron, it integrates the input and produces a spike when a threshold level is reached. In section 6.1 various somas are described. Since somas share many common features the abstract *Soma* class was implemented.

A synapse releases transmitter into the synaptic cleft when it receives a firing

[2]The differential equation must of course be coupled correctly, but it is only necessary to write the equations once.

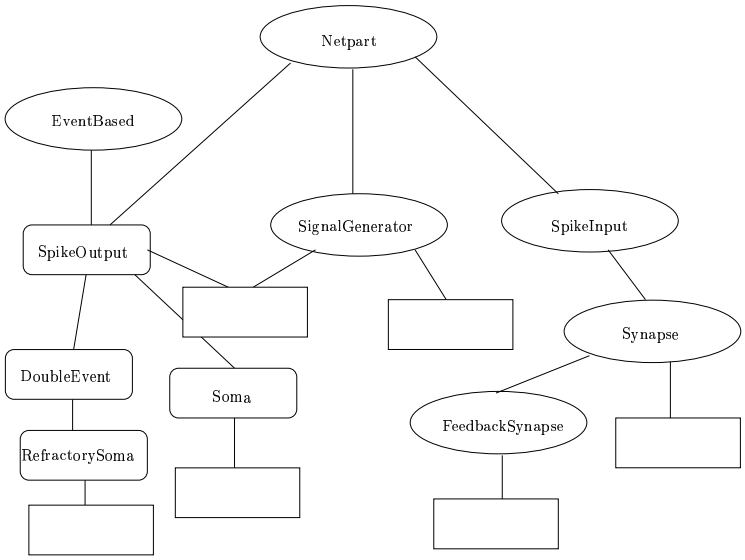


Figure 5.1 Class hierarchy for the netparts. Ovals denote interfaces, squares with round corners are abstract classes. The squares denote classes that have some kind of functionality. In table 5.1 an overview of these classes are shown.

event (spike) either from an external source or from a soma. This transmitter is turned into a continuous output, in the form of either a current, a voltage or a conductance which can be fed into a soma. In section 6.2 different types of synapses are described. The *Synapse* interface captures the two essential things about a synapse, it should receive spikes and deliver a continuous signal.

In order for synapses to learn, it is important that they have information about the postsynaptic activity, in order to change their conductance characteristics. Because synapses that learn need information about postsynaptic firing, the *FeedBackSynapse* interface was implemented.

A third component – wires – can be introduced if delays or dissipation is necessary. Wires should be able to receive either a spike or a continuous signal and deliver the same signal, possibly with modifications after a delay, this netpart has not yet been implemented. In figure 5.1 a schematic representation of the hierarchy can be seen.

Soma	Song integrate-and-fire
Refractory soma	Song refractory IAF SLS refractory IAF
Spike signal generator	Poisson spike generator Periodic spike generator Spike from file
Continuous signal generator	Constant signal Sine signal
Synapse	Liaw-Berger Destexhe-Mainen-Sejnowski Markram-Tsodyks
Feedback synapse	Song Excitatory synapse SLS synapse

Table 5.1 Overview of implemented classes corresponding to the empty squares in figure 5.1. The text to the left corresponds to the abstract class or interface just above in the hierarchy. The names denotes authors, e.g. Song denote that the models are proposed by Song et al.

To connect the netparts to each other a mediator is necessary, something to keep track of the different parts. Netparts can be connected to each other, if they are of compatible types, e.g. an instance of *SpikeOutput* can be connected to an instance of *SpikeInput*.

To keep track of all the different parts of a network, the *Model* object was introduced; all netparts must be added to a model. So that when the network is build and it is time to create a runnable code or a Map (see below), it is only

Factbox 5.1 *Creation of a model containing a synapse of the Song type and a neuron of the Song type, the synapse receives inputs from a Poisson generator with ≈ 5 spikes per second and a periodic spike generator creating one spike every second.*

```
Model model = new Model( "TestModel 2002" );
SongExKernelSynapse synapse =
  new SongExKernelSynapse( "synapse1" );
double lambda = 5;
long seed = 5;
PoissonSpikeEvent poisson =
  new PoissonSpikeEvent("poisson1",
                        1.0/lambda, seed );
double period = 1;
double phase = 0.2;
PeriodicSpikeEvent periodic =
  new PeriodicSpikeEvent("periodic1",period, phase);
SongIAFsoma soma = new SongIAFsoma("soma1");

soma.addInput( synapse );
synapse.addInput( periodic );
synapse.addInput( poisson );
synapse.addFeedbackInput( soma );

model.addNetPart( periodic );
model.addNetPart( poisson );
model.addNetPart( synapse );
model.addNetPart( soma );
```

necessary to have a handle in the model, this is schematised in figure 5.2. An example of the creation of a simple model can be seen in factbox 5.1

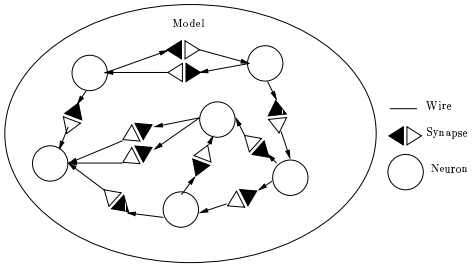


Figure 5.2 Structure of a network. Netparts (synapses and neurons) are connected, then added to the model. The model keeps track of the differential equations and events from each netpart.

5.2.2 First program

The construction of a tool which can both integrate differential equations and handle events in a satisfying fashion began with the creation of an object to gather the differential equations and events from the model, and from this information automatically generate a compilable program. Even though each of the netparts are written in Java, the auto-generation of the code could almost as easily deliver C++ compilation ready sources or XML coded programs.

The output from the tool, whether it is code in Java or XML, is divided into two parts. One containing the system of coupled differential equations and one wrapping the differential equations. The latter should provide a way to integrate the differential equations and a way to take action when an event occurs.

In the first implementation, a class called GenerateCode collects the equations from the model and delivers compilable Java code. In this way it was possible to take advantage of the numerical integrators already existing in Janet.

The tool proved to be very easy to use, as a desired change to the structure of a network architecture was easy. Speed and accuracy of the numerics was high.

However, when the number of differential equations became too large ($\gtrapprox 100$) and the number of events to take care of was of the same magnitude, a problem occurred concerning the Java compiler. When the size (in bytes) of a single method exceeds 64 kb the compiler cannot handle it and gives up. This limit is in general never a problem for user written code.

To deal with this problem a slightly different approach was chosen.

5.2.3 Next generation

The next generation of the program is true object oriented, meaning that no runnable code is auto-generated. The netparts has a symbolic representation of their equations and events, and can, when asked, return lists with their state equations along with lists of parameters and events.

The model wrapping the netparts, collects symbolic equations from them, still acting as a mediator. In this way the model has access to all states, parameters and events – so far nothing is different from the first generation.

The main difference between the two generations of the program is that in the first generation, the differential equations was collected by GenerateCode and written in a file which was then a stand alone Java program. In the new version no source is generated, instead a *Janet Map* is created from the model. This map does not need to be written in a file, but exist only in the Java virtual machine. In this way, instead of being limited to 64 kb, the limiting factor is the working memory of the computer. On a fairly large machine (1 Gb ram) 2000 coupled differential equations could be simulated without problems.

Factbox 5.2 *Creation of a* TimeContinuous Janet Map *from a model, once the map is created it can be integrated using the integrators from Janet.*

```
TimeContinuous tMap =
   MapGenerator.
     generateTimeContinuous( model );
ExtendedButcherTable table =
   ExtendedButcherTable.
      getExtendedButcherTable( "RKV(5,6)" );
double tStart = 0;
double initTimeStep = 0.0021;
Integrator integrator  =
   new RungeKuttaPairIntegrator( table, tMap,
                        tStart, initTimeStep );
SCSIntegrator scsIntegrator =
   new SCSIntegrator( integrator );
EventIntegrator eventIntegrator =
  new EventIntegrator( scsIntegrator );
```

5.2.4 Data collection

To gather output from the model the *DataCollector* class was created. A *DataFileGenerator* object can be instantiated and then various different *DataCollector* classes can be added to it. The *DataFileGenerator* handles generation of files and collects the relevant information from the *DataCollectors*.

The output can be stored in two different ways, either as a conventional datafile with information about the temporal evolution of the states, or in 'feature' files. Feature files are MATLAB scripts which produce structs with relevant informations about the simulation, initial conditions, what integrator was used etc.

It is possible to split a simulation up in different succeeding data files. In this way it is not necessary to wait until the end of long simulations to view data. It is also possible to test the effect of changing a parameter by resetting the model to the initial conditions and change the parameter, during the same simulation.

Some of the different *DataCollectors* that can be added to the *DataFileGenerator* are:

DataToFile Generates header information in data files and writes to the data file with the specified precision. Typically the states in the datafile, but also parameters or auxiliaries can be written.

EventsToFile Similar to DataToFile but instead of states it puts the boolean value of spike occurrence in the interval. Spikes are written in the data file at the end of the interval and not at the exact time of their occurrence.

BasicFeatureExtractor Extracts the basic informations about the simulation, when was the simulation performed, what are the initial conditions, how often is data written to the datafile etc.

EventsToFeature Adds a list to the feature file containing the exact timings of the desired events.

AreaExtractor Integrates the area under a state using the information available on integrator.

ResetModelRunLevel Resets the model between each run. This is useful when the same model is tested for changes in a single parameter.

If other characteristics of a simulation are of interest, new DataCollectors can easily be implemented and added to the *DataFileGenerator*.

5.2.5 Other tools

Since modeling synapses is not confined to this project a wide variety of tools have been developed around the world. Browsing the web for inspiration on how to create the model it seems that everyone is writing their own software probably thinking, 'then I will have complete control and at the same time learn how to program' and that every one are trying to create general tools which can be used by many others. Unfortunately these two things do not coincide very well since everyone writes their own general code hoping that someone else will use it.

It seems, however, that people are beginning to realize that no one will use their software if it is not easily modifiable, and standards have begun to emerge.

In the field of neuroscience the packages which have had success in setting a standard for how modeling should be done includes Neuron and Genesis. Both specialized in making accurate physiological models of neurons and keeping large databases with information of experimentally found topologies.

More promising for this kind of work are the XML based standard *Neuro-ML* (Goddard, Hucka, Howell, Cornelis, Shankar and Beeman, 2001). It provides a basis for modeling networks of spiking neurons and a collection of classical neuron and synapse models (www.neuroml.org).

6 Modeling

»Shall I refuse my dinner because I do not fully understand the process of digestion?«

Oliver Heaviside (1850-1925)

6.1 Neuron models

Even though the biophysics of a neuron has been studied intensively, and is by now well understood, no such thing as a prototype neuron can be defined. As is seen in section 2.2 a wide variety of neurons can be found in the human brain. Neurons are characterized by emitting action potentials due to rapid changes in their membrane potential (depolarization). Ionic currents plays an important role in this change. It is now possible to model these different kinds of neurons in substantial detail. The ionic currents in and out of the cells but also molecules diffusing such as ATP, ADP or CaMKII, can be modeled by dividing the nerve cells into compartments. In this way almost any level of detail can be captured.

When modeling the functional effects of neurons transmitting signals, it is often not necessary to use as high a level of detail, and certain generalizations can be applied. Often it suffices to know whether the neuron has fired or not.

As also mentioned in section 2.2, a neuron is composed of several parts. A gross division separates it to the axons, the dendrites, and the soma. The neuronal models in this sections are mainly models of somas. How the currents propagate to and from the somas are not accounted for, an exception is the Spike Response Model.

6.1.1 Hodgkin-Huxley

The first single compartment model based on ionic currents was proposed by Hodgkin and Huxley (1952). This model is still one of the most widely used

descriptions of neuronal dynamics and it is the mother of all neuronal models based on ionic currents. A wide range of physiological models either extend or simplify the Hodgkin-Huxley model. Extensions include the Kopell-Ermentrout-Whittington-Truab- and the Huber-Braun- model; simplifications the FitzHugh-Nagumo-, the Morris-Lecar- and the Integrate-And-Fire model (IAF model). The latter will be presented later in this section.

After studies of the giant axon in squids, Hodgkin and Huxley came to the conclusion that especially the currents given by the fluxes of Na^+ and K^+ ions where of importance, other ions e.g. Cl^- where also found to have an effect.

The object of their model was the membrane potential V. The potential in the soma is changed by the flux of ions through the membrane, where each ion has its own reversal potential and conductance. This led to the following equation for the membrane potential

$$\begin{aligned} c\frac{\mathrm{d}V}{\mathrm{d}t} &= g_l(V-E_l) - g_{Na}m^3h(V-E_{Na}) \\ &\quad -g_K n^4(V-E_K) + I_{ext} \quad , \end{aligned} \tag{6.1}$$

where c is the membrane capacitance, g's represent conductances[1] for Na^+–, K^+–, and leakage-ions, l, respectively. The E's are the reversal potentials. The variables m, n, and h are gating variables comparable to opening probabilities.[2] The gating of the current depends on the membrane potential and as it is expected the dynamics are very fast. As described in section 2.2 a depolarization last in the order of one millisecond, this is also the time scale for changes in the gating variables

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(V)(1-m) - \beta_m(V)m \tag{6.2a}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V)(1-n) - \beta_n(V)n \tag{6.2b}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(V)(1-h) - \beta_h(V)h \quad , \tag{6.2c}$$

where V is the membrane potential from before, and the α's and the β's are rate constants. The gating variables also ensure that the neuron after it fires is less likely to fire again (relative refractory period). In fact, just after firing it requires a very high[3] input to make the neuron fire, the period of absolute refractoriness.

[1] Values of the conductances and reversal potentials can be found in e.g. Gerstner and Kistler (2000) or Scott (1995).

[2] The 'guards' from section 2.2.

[3] Certainly, unphysiologically high.

The Hodgkin-Huxley neuron has been widely used to simulate neuronal activity and it has proved its worth in thousands of experiments throughout the past 50 years.[4] Because of its impact in reproducing experimental results it has also been the focus of extensive theoretical studies. The dynamic properties have been shown to be very complex, and reports have been written studying only a few coupled neurons of this type.[5]

6.1.2 Integrate-and-fire

The fast dynamics of the neuron are dependent on the opening and closing of ion channels as described above. However the triggering of the fast dynamics are well described by the voltage-gating of the channels. The fast ion channel dynamics are triggered when the potential crosses a threshold. This gives rise to the simplified model of neuronal dynamics known as the integrate-and-fire model. Instead of focusing on the exact shape of the fast changes, only the slow dynamics leading to a threshold crossing is modeled.

In this model the currents flowing into the neuron from different sources are multiplied by the membrane resistance

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = V_{rest} - V + R \sum_i I_i^{input} \quad , \tag{6.3}$$

with R being the membrane resistance, τ_m the membrane time constant, and I_i^{input} represents input currents from 'source' i. If the neuron does not receive inputs, the potential will decay towards the resting potential V_{rest}. If the neuron do receive input, the input is integrated in a leaky fashion, and when the neuronal potential reaches a threshold the neuron fires. The integrate-and-fire neuron makes use of the fact that the action potentials produced by neurons are always similar in shape. Instead of producing a physiological plausible temporal behavior it simply gives out a spike (or fires); at the same time the potential is reset.

Substituting the input current in equation (6.3) with a sum of currents each stemming from its own conductance gated ionic flux, the integrate-and-fire neuron can be used in settings where inputs are described in terms of conductances,

[4] That Hodgkin and Huxley in 1952 simulated the behavior of their model only using a mechanical calculator, just adds to their esteem.

[5] Small masterpieces, really. See e.g. 'Analysis of a Minimal Network of Cortical Neurons' by Anders Fausbøll.

g, and reversal potentials, E

$$I_i^{input} = \sum_j g_i^j (E^j - V) \tag{6.4}$$

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = V_{rest} - V + R \sum_i \sum_j g_i^j (E^j - V) \tag{6.5}$$

This transformation will prove to be useful when modeling receptor dynamics (see section 6.2.1).

Integrate-and-fire neurons do not *per se* incorporate any refractory period. However, in the implementation it is easy to create an absolute refractory period by keeping the action potential on the reset value until the refractory period is over. A relative refractory period can be implemented by raising the threshold when the neuron fires and then let it relax back towards the steady value.

6.1.3 The spike-response-model

When studying networks of spiking neurons, it is not enough to consider only the neuron, also weights or synapses must be studied. Most models keep these things as separate units, but some models incorporate the soma and the synapse into a single model. An example of the latter is the spike-response-model.

As with the integrate-and-fire model, the spike response model uses the fact that the temporal behavior of a neuron is quite standardized. However, unlike the integrate-and-fire model, the spike-response-models starts a kernel function in response to threshold crossing.

The input to this neuron is spikes from previous neurons; similar to the depolarization, the arrival of spikes can be described by a kernel function. The excitatory - or inhibitory postsynaptic potential created by the synapses on arrival of an incoming spike are modeled by kernels. Typical shapes of the kernels are α-functions in accordance with experimental findings. It is the use of kernels to describe the voltage response to spike emission and spike reception that has given the model its name.

The spike-response-model produces temporal output quite similar to the Hodgkin-Huxley neuron, but is computationally only slightly more complicated than an integrate-and-fire neuron. However, the fact that it incorporates the synapse, makes it unsuited for investigations of synaptic models.

6.2 Synapse modeling

Modeling of synapses can be approached bottom up or top down, either one can focus on the exact mechanism causing the effects or the focus can be the effects, neglecting (or at least down-toning) exactly how the effects arise. Both approaches can produce interesting results and complement each other.

Sometimes bottom up modeling cannot produce the desired effects because the model is too simple, and sometimes this can provide new insight.[6] Of course, the top down models cannot directly provide information of how the underlying mechanisms work, but they can shed light on which experiments are interesting to perform.

In the following, models of both types will be described with the intention to gain insight of which processes are essential and which can be simplified away. Somehow, the models are all based on the physiology described in section 2.3. The reason for investigating non static synapses is that they can be used for temporal coding of information as described in section 4.2.1.

In 1996, Liaw and Berger proposed a concept for modeling short term dynamics in synapses, *dynamic synapses*. The synapse performs a temporal pattern transformation from a sequence of incoming action potentials to a sequence of postsynaptic potentials. The strength of a dynamic synapse is determined by the temporal structure of the incoming spike train.

This was in accordance with experiments, but no bottom up model had captured the effects. In this section, different models of synaptic behavior are presented. Although they are all of interest, reading through too many models can become tiresome. Thus, the description of the models which will not be used later in this report is degraded to appendix A.

Liaw & Berger

Dynamic synapses as proposed by Liaw and Berger do not model a particular part of the brain. Inspired by experimental work by Berger et al. (1994) on populations of synapses, Liaw and Berger try to capture some of the essential features by using sums of exponential kernels with different time constants. The assumption is that a sum of exponentially decaying functions can describe the probability of transmitter release, and that another sum of decaying exponentials can account for the receptor dynamics. Parameters in the kernels cannot be estimated directly from experiments, but they can be fitted to reproduce experimental results. The model provides a general formulation of a phenomenological

[6] Perhaps the effect does not exist and was only a measurement artifact.

model, and a way to modify the potency of different presynaptic mechanisms.

Liaw and Berger have also proposed a way to modify the synapses – a learning rule – based on correlations between presynaptic and postsynaptic activation. The coefficients on the presynaptic side of the synapse are modified when a postsynaptic action potential occurs. Results from using such learning, dynamic synapses in »*learning in robust speech recognition*« are reported in Liaw and Berger (1997, 1999).

The model has been implemented and preliminary simulations conducted. These show that in effect the model is similar to that of Markram and Tsodyks presented in section 6.2.2. The Liaw-Berger model is described in appendix A.1.

Maass & Zador

As Liaw and Berger, Maass and Zador (1999) present a phenomenological model using exponentially decaying function to capture release dynamics. On the basis of experiments revealing the dynamics of single release sites, a discrete stochastic model is presented and analyzed. As described in section 4.2.2 Maass (1996, 1997b); Maass and Sontag (2000) have provided theoretical results regarding the computational power of dynamic synapses.

By varying the parameters in the model it is possible to obtain any desired release probability for two consecutive spikes. This yields great possibilities for using this kind of synapse as a filter. The model is presented in appendix A.2.

6.2.1 Destexhe, Mainen and Sejnowski

The above mentioned models are phenomenological accounting for the effects of a synapse (or at least the presynaptic side), but they do not account for the mechanisms causing the effects. In contrast, a different category of models which are far more extensively studied celebrates physiological accuracy. Important work in this field has been performed by Katz and Miledi (1968); Magleby (1987); Zucker (1989) and many others[7]. A fairly simple model which captures much of the physiology is proposed by Destexhe, Mainen and Sejnowski (1998). In this model the Ca^{2+} flow is of great significance for the synaptic dynamics, both triggering transmitter release and catalyzing receptor response.

As in most synapse models this model is split into two parts the pre- and the

[7] As mentioned in Markram, Gupta, Uziel, Wang and Tsodyks (1998).

postsynaptic. The processes essential for transmitter release are described by

$$4\mathrm{Ca}^{2+} + X \underset{k_u}{\overset{k_b}{\rightleftarrows}} X^* \tag{6.6a}$$

$$X^* + V_e \underset{k_2}{\overset{k_1}{\rightleftarrows}} V_e^* \tag{6.6b}$$

$$V_e^* \overset{k_3}{\rightarrow} nT \tag{6.6c}$$

$$T \overset{k_3}{\rightarrow} \ldots \tag{6.6d}$$

Calcium binds to the calcium-binding protein X, leading to an activated calcium-binding protein X^*, X^* then binds to the vesicles V_e activating them. The vesicles release transmitter into the synaptic cleft, from which it is cleared with a very fast time constant.[8]

It is seen from equations (6.6) that in this model transmitter release is a direct function of the Ca^{2+} level, unfortunately no way of calculating the Ca^{2+} level as a function of presynaptic potential is provided, making the presynaptic side of the model difficult to implement directly. Consequently, it has not been tested whether this model provides the desired facilitating and depressing effects.

A simplified version of transmitter release is also proposed, given as the concentration of transmitter $[T]$, dependent on presynaptic potential V_{pre}

$$[T](V_{pre}) = \frac{T_{max}}{1 + e^{(\frac{V_p - V_{pre}}{K_p})}} \quad , \tag{6.7}$$

where T_{max}, V_p and K_p are constants. It is, however, evident that this equation cannot provide the desired facilitating and depressing effects. Therefore, the presynaptic side of the model is not considered further.

Instead the dynamics on the postsynaptic side are studied and kinetic models for AMPA, GABA and NMDA receptors are proposed. The AMPA receptor can be described by three closed states C_0, C_1, C_2 two de-sensitized states D_1, D_2 and one open state O. The transition rates from C_0 to C_1 and from C_1 to C_2 depend on the level of transmitter

$$\begin{array}{ccccccc} C_0 & \overset{R_b T}{\underset{R_{u1}}{\rightleftarrows}} & C_1 & \overset{R_b T}{\underset{R_{u2}}{\rightleftarrows}} & C_2 & \overset{R_o}{\underset{R_c}{\rightleftarrows}} & O \\ & & R_d \downarrow\uparrow R_r & & R_d \downarrow\uparrow R_r & & \\ & & D_1 & & D_2 & & \end{array} \tag{6.8}$$

From the amount of open receptors the current due to AMPA receptors can be calculated using the maximal conductance $\tilde{g}_{AMPA}$ the reversal potential E_{AMPA}

[8] Parameters can be seen in appendix A.3, table A.2.

and the postsynaptic voltage V

$$I_{AMPA} = \tilde{g}_{AMPA}[O](V - E_{AMPA}) \tag{6.9}$$

With parameter values shown in table A.3, the model closely fits experimental result. However, even with extensive simplifications it is possible to get behavior very similar to experimental data. The simplest possible model involves only a closed and an open state and the transition between them mediated by transmitter

$$C + T \underset{\alpha}{\overset{\beta}{\rightleftarrows}} O \tag{6.10}$$

This can be written as a single first order differential equation describing the fraction of open receptors r

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \alpha[T](1 - r) - \beta r \tag{6.11}$$

Substituting $[O]$ with r in equation (6.9) the postsynaptic current as a function of transmitter is described by a single differential equation and Ohm's law with variable conductance.[9] As it shall be seen later, these simple equations can, combined with a mechanism for transmitter release, serve as a good approximation to physiology.

A similar model is provided for the NMDA receptor. The fraction of open receptors are calculated in the same way as for the AMPA receptor, equation (6.11), however, the parameters are different (see table A.5) keeping the receptors open for a longer period. The current through the receptor is a little different. Since NMDA receptors are 'doubly gated' the membrane potential of the neuron are also considered. $B(V)$ describes the voltage dependence of the Mg^{2+} block[10]

$$I_{NMDA} = \tilde{g}_{NMDA}B(V)[O](V - E_{NMDA}) \tag{6.12}$$

Destexhe et al. (1998) provides a physiologically founded model of the synapse. The transmitter release dynamics in the model are constructed for handling single occurring presynaptic action potentials, and thus do not provide facilitating and depressing mechanisms. The receptor dynamics are only depending on the amount of transmitter in the synaptic cleft and are therefore not subject to restraints about the presynaptic action potentials. Physiologically plausible and simple to implement, the receptor dynamics of this model are worth keeping in mind. In this section only the model of AMPA and NMDA receptors are described, but similar models are made for other receptors including GABA.

[9] Parameters in table A.4.
[10] Also shown in appendix A.3.

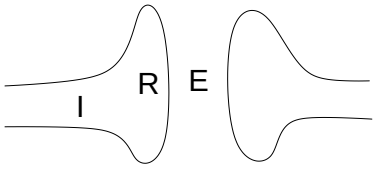


Figure 6.1 In the Markram-Tsodyks synapse model, the assumed finite pool of neurotransmitter is subdivided into three different pools. The fraction of active transmitter in the cleft is called the *effective transmitter*, E. Deactivated transmitter (metabolized, reabsorbed etc.) is represented by the *inactive transmitter* pool, I. Finally, the transmitter ready for release is contained in the *recovered* pool, R.

6.2.2 Markram & Tsodyks

Markram and Tsodyks has defined a phenomenological synaptic model based on synapses in neocortex (Tsodyks and Markram (1997)). Given a spike train, a single synapse in this model reproduces the response generated by an assembly of synapses in the neocortex; the stochastic element of each synapse is thus removed by modeling synapses in parallel.

Despite the phenomenological approach, the different states in the model have a physiological counterpart, along the lines of the introduction to synaptic construction given in section 2.3 and depicted in figure 2.5. An underlying assumption in their model is that the total amount of neurotransmitter in the synaptic region is limited, constant, and divided into either of three different pools as illustrated in figure 6.1.

The model emphasizes the presynaptic side. When a spike (an action potential) arrives at the synapse at time t_{sp}, a certain fraction, U_{SE}, of the transmitter in the recovered[11] state, R, is instantaneously released into the synaptic cleft where it joins the pool of effective transmitter, E. From the cleft, the transmitter is inactivated with a relatively fast time-constant, τ_{inact}, into the inactive state, I, from where it slowly recovers into R with the time-constant, τ_{rec}. This three state process is governed by the equations

$$\text{Effective transmitter}: \quad \frac{\mathrm{d}E}{\mathrm{d}t} = -\frac{E}{\tau_{inact}} + U_{SE} \cdot R \cdot \delta(t - t_{sp}) \tag{6.13a}$$

$$\text{Recovered transmitter}: \quad \frac{\mathrm{d}R}{\mathrm{d}t} = \frac{I}{\tau_{rec}} - U_{SE} \cdot R \cdot \delta(t - t_{sp}) \tag{6.13b}$$

$$\text{Inactive transmitter}: \quad I = 1 - R - E \tag{6.13c}$$

where the $\delta(t - t_{sp})$ function represents the instantaneous transfer of transmitter from the recovered to the effective state; only a fraction though, controlled by the utilization of synaptic efficacy parameter U_{SE}.

[11] Can be thought of as representing the readily releasable pool.

Conversion of synaptic activity to a postsynaptic current, I_{post}, happens continuously by multiplying the present fraction of effective transmitter, E, with an absolute synaptic efficacy, A_{SE}. Then, using a passive leaky membrane mechanism to model a simple form of dendritic conduction, they arrive at a postsynaptic membrane potential, V, as

$$I_{post} = A_{SE} E \tag{6.14a}$$

$$\tau_{mem} \frac{\mathrm{d}V}{\mathrm{d}t} = -V + R_{in} I_{post} \tag{6.14b}$$

Most of the parameters have been measured experimentally and together, the expressions in equations (6.13) and (6.14), define a system accounting for synaptic depression; given a steady input, depletion like effects might – if spikes arrive faster than R is replenished – gradually diminish the postsynaptic membrane potential. This fits well with the behavior of neocortical layer V pyramidal neurons between which facilitation is not evident – the synapses in this area are mainly depressing.

However, in synapses between pyramidal neurons and inhibitory interneurons facilitation is commonly observed. A facilitative mechanism is incorporated in later versions of the synapse model.[12] This is done to capture the presynaptic aggregation effects involved with the residual calcium hypothesis. The idea is to let the utilization parameter U_{SE} be time varying as well

$$\frac{\mathrm{d}U_{SE}}{\mathrm{d}t} = -\frac{U_{SE}}{\tau_{facil}} + \widetilde{U}_{SE}(1 - U_{SE}) \cdot \delta(t - t_{sp}) \quad , \tag{6.15}$$

where the arrival of the first spike initializes the utilization to the value used in the purely depressing case, $\widetilde{U}_{SE}$.

Behavior

The default parameter values used in the depressing and facilitative models are given in table 6.1. An example of how the different states for a facilitative synapse evolve in response to a regular spiketrain is shown in figure 6.2. All initial state values have been set to zero[13] resulting in that the only effect of the first spike, at t = 0, is to initialize $U_{SE}(0) = \widetilde{U}_{SE}$.

[12] Various representations in Markram, Gupta, Uziel, Wang and Tsodyks (1998); Markram, Pikus, Gupta and Tsodyks (1998); Markram, Wang and Tsodyks (1998); Tsodyks et al. (1998, 2000).

[13] Obviously apart from $I(0) = 1$ due to its definition.

Parameter	Depressing	Facilitating	Unit
R_{in}	0.1	1	$G\Omega$
τ_{mem}	40	60	ms
τ_{inact}	3	1.5	ms
τ_{rec}	800	130	ms
τ_{facil}	–	530	ms
$\widetilde{U}_{SE}$	0.5	0.03	–
A_{SE}	250	1540	pA

Table 6.1 Default parameter values used in the Markram-Tsodyks synapses

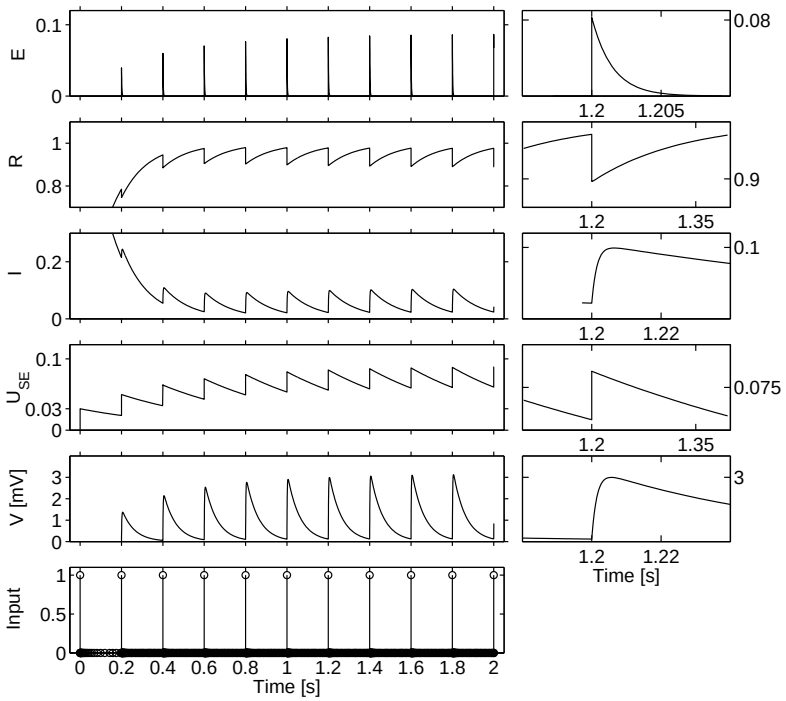


Figure 6.2 Internal states in a facilitating synapse, when fed with a regular 5 Hz input spiketrain. The rows show how the states evolve; besides each state, to the right, is an enlargement of the response to the spike arriving at t = 1.2 s. The spike at t = 0 s, initializes the U_{SE} value to $\widetilde{U}_{SE} = 0.03$. Notice that the U_{SE}, R, and E states are changed immediately by the influence of the δ-function, whereas the I and V states exhibit a more integrative behavior.

To the right in figure 6.2 the response of the different states to a single spike is plotted, thereby giving a better idea of the time-constants involved and, also, the shape of the curve around the arrival time of a spike.

If using spike bursts as input, the facilitating effect is noticeable. The difference between feeding the synapse with, e.g. four spikes in succession versus two times two spikes temporally separated, is indicated by figure 6.3. By comparing the measure of the area under the curves[14] one notices that the area 'created' by four spikes is more than two times the area stemming from two spikes; this is due to the facilitative mechanism.

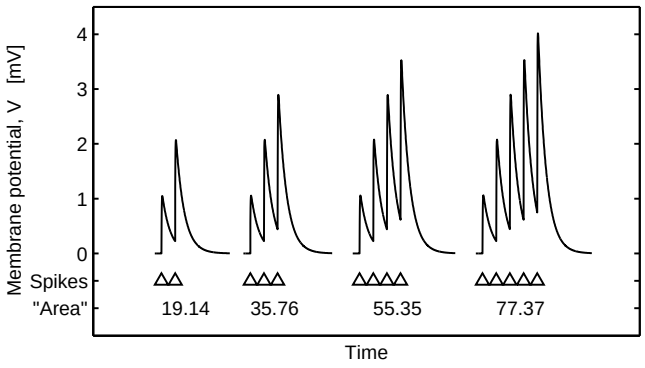


Figure 6.3 Feeding the synapse with 10 Hz spike bursts of varying lengths reveals the facilitating effect. Beneath each burst is a measure of the area under the curves. Dividing the areas for four and two spikes respectively gives $A_4/A_2 \approx 2.9$

Returning to figure 6.2 one might notice how steady input relatively quickly brings the synapse into an equilibrium where the decay (rise) of a state, matches the δ-term increment (decrement) caused by an incoming spike. For e.g. equation (6.15), this equilibrium can be calculated as a function of the input frequency ν by requiring that U_{SE} must be incremented exactly as much as it decays during the time $\Delta t = 1/\nu$ between spikes. This results in the steady level U^*_{SE}

$$U^*_{SE} = U^*_{SE} \exp\left(-\frac{\Delta t}{\tau_{facil}}\right) + \widetilde{U}_{SE}\left(1 - U^*_{SE} \exp\left(-\frac{\Delta t}{\tau_{facil}}\right)\right) \quad (6.16a)$$

$$U^*_{SE} = U^*_{SE}(1 - \widetilde{U}_{SE}) \exp\left(-\frac{1}{\nu\tau_{facil}}\right) + \widetilde{U}_{SE} \quad (6.16b)$$

$$U^*_{SE} = \frac{\widetilde{U}_{SE}}{1 - (1 - \widetilde{U}_{SE}) \exp\left(-\frac{1}{\nu\tau_{facil}}\right)} \quad (6.16c)$$

It is not given whether this steady value should be calculated before or after it itself has been incremented. Observing that $\widetilde{U}_{SE} \ll U^*_{SE}$ it is evident that the

[14] Equally scaled by the same factor.

incrementation time is not of great importance (see equation (6.15)). Simulations confirm this.

Under the assumption that the simplification $I \approx 1 - R$ is justified, due to the brief time constant involved with the E decay, an equilibrium level can likewise be calculated for R

$$R^* = \frac{1 - \exp\left(-\frac{1}{\nu\tau_{rec}}\right)}{1 - (1 - U^*_{SE}) \exp\left(-\frac{1}{\nu\tau_{rec}}\right)} \tag{6.17}$$

In order to investigate the frequency dependence of the membrane potential, V, a series of simulations similar to the one behind figure 6.2 was performed – leading to figure 6.4, where the frequency of the regular input spike train is gradually increased. When increasing the frequency the oscillation amplitude goes down and the membrane potential steady level goes up; rightmost in figure 6.4 an average of the endlevel is plotted, showing the frequency dependent increase.

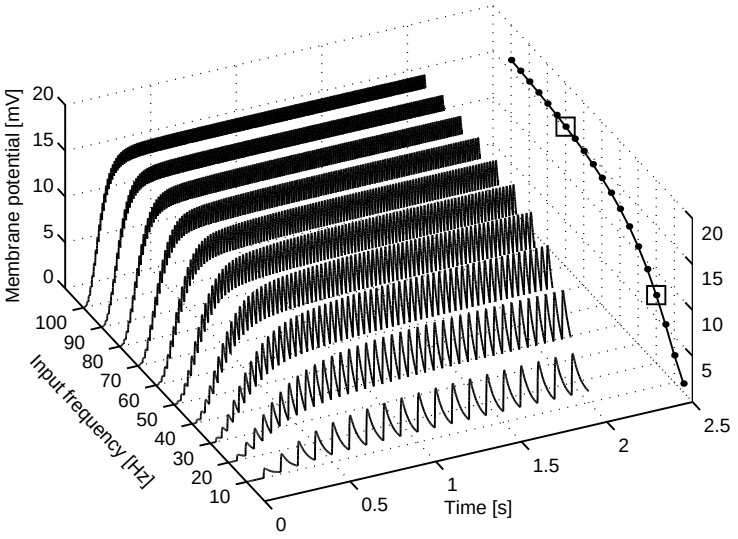


Figure 6.4 Membrane potential V for the Markram-Tsodyks synapse at different frequencies for a regular spike train input. To the right, an average of the steady level, where the values at 20 Hz and 70 Hz have been marked by boxes to ease comparison with the original data from Tsodyks et al. (1998) and reprinted in figure 6.5.

A comment

In Tsodyks et al. (1998) simulations are carried out like the ones performed in connection with figure 6.4. A reprint of the results are shown in figure 6.5, where the subplots B, C, and D are of special interest, as these concern the facilitating version of the synapse. Horizontal lines have been added to the figure to emphazise the steady levels for the simulated membrane potential; comparing the curves and steady levels with the ones obtained in figure 6.4 (marked with boxes) indicates fine agreement between the two implementations[15].

However, which interpretation the latter subplot, D, in figure 6.5 is to be given, involves some level of ambiguity. The figure caption (repeated in this figure) is not quite in agreement with the accompanying explanation in the main text part of the article: »*Figure 1C illustrates the buildup of depression in facilitating synapses when they are stimulated at high frequencies. As a result, the stationary level of response exhibits a tuning curve dependence on the frequency, in agreement with experimental results (see Figure 1D).*«[16] thereby indicating that the ways of measuring steady levels in C and D are alike.

The inserted lines point out that the potentials reached in B and C are not the same as depicted in D; in fact, figure 6.4 of the present report shows that it is not just a matter of wrongful scaling: The membrane potential tuning curve is not bell shaped at all.

Having spent quite some time figuring out how this discrepancy comes about,[17] figure 4 in Markram, Wang and Tsodyks (1998, p. 5326) gave a hint to how the experimental match was obtained. If still feeding the facilitating synapse with regular spiketrains, and then plotting the peak amplitude of the effective transmitter E (after a steady level has been reached) as a function of input frequency, one gets the curve shown in figure 6.6; now the peak values of E follow a frequency dependent bell shaped curve.

In figure 6.6 there is no units on the left axis, as the E state represents a fraction of efficacy. Since the experimental results are reported in units of mV, the fraction E must be multiplied with the absolute synaptic efficacy A_{SE} and, in turn, with the membrane input resistance R_{in}, in order to obtain an EPSP value. Using the reported parameter values for facilitating synapses (see table 6.1) this total multiplicative factor is around forty times too big when compared[18] with the one needed to create the 'best fit' seen in figure 6.6 – the reason for this discrepancy is unknown.

[15] Although the Tsodyks et al. (1998) model uses three differential equations to describe the transmitter states (labelled x, y, and z) transformation of variables proves that the models are exactly equal.

[16] Tsodyks et al. (1998, p. 824).

[17] And actually having discarded the Markram-Tsodyks model for a while.

[18] Table values: $A_{SE} \cdot R_{in} = 1540\,\mathrm{pA} \cdot 1\,\mathrm{G\Omega} = 1.54\,\mathrm{V}$. The one used is $\approx 0.038\ V$.

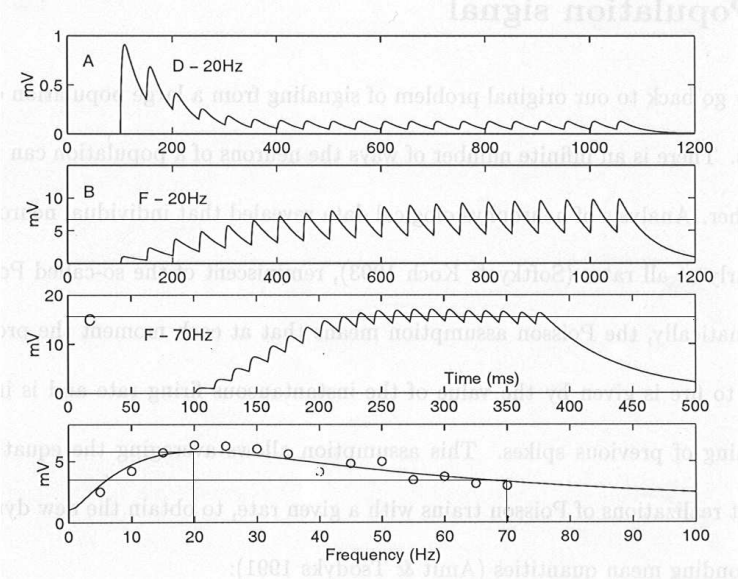


Figure 6.5 Reprint of figure 1 from Tsodyks et al. (1998). (A) Simulated postsynaptic potential for a regular spike train of 20 Hz through a depressing synapse. (B) Same as A for a facilitating synapse (line inserted to indicate steady level). (C) Same as B with an input frequency of 70 Hz (line inserted). (D) Original caption: »*Stationary level of excitatory presynaptic* [sic!] *potentials versus presynaptic frequency for facilitating synapses. Open circles: Experimental results for one of the recorded synaptic connections between pyramidal neuron and inhibitory interneuron. . . Solid line: Model results.*« As indicated by the lines figure D can not be generated from the levels in figures B and C.

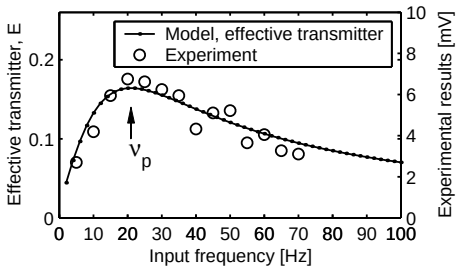


Figure 6.6 Steady level peak amplitude of effective transmitter E in a facilitating synapse, to a regular spiketrain input. Circles represent experimental data from figure 6.5(D). The dissimilarity between the units (or partial lack thereof) on the axes is explained in the text. The peak frequency, ν_p can be determined analytically.

A sceptical person might wonder how the experimental measurements of only the EPSP's were made, since the 'methods' parts in the articles speak of *somatic whole-cell recordings*, thereby suggesting that the monitored entity is rather the somatic membrane potential.

Not being experimentalists – and judging from the widespread popularity of the Markram-Tsodyks synaptic model – these questions are probable to be due to misinterpretations. And, anyhow, since the model are able to express the wanted facilitative and depressing behavior, the above mentioned issues are given the benefit of the doubt, and the model will be used onward.

Parameters

In the bell shaped curve in figure 6.6, the peak frequency ν_p can be derived from the model equations analytically.[19] It is done by finding the input frequency where the δ-increment to E is maximal, i.e. when the product of the steady values U^*_{SE} and R^* is maximal. The peak frequency is

$$\nu_p = \frac{1}{\sqrt{\widetilde{U}_{SE} \cdot \tau_{facil} \cdot \tau_{rec}}} \quad , \tag{6.18}$$

determined by the actual parameter values.[20] In general, as discussed in e.g. Markram, Pikus, Gupta and Tsodyks (1998), the parameters of the model have references to different biophysical properties of the synapse and individual influence on the behavior:

A_{SE} A measure of the absolute synaptic strength. Comprises the number of release sites, quantal size, number and efficacy of postsynaptic receptors, and electrotonic attenuation, i.e. all processes involved with going from E to excitatory postsynaptic potential.

$\widetilde{U}_{SE}$ Related to probability of release and to the properties of frequency dependence. The higher $\widetilde{U}_{SE}$ the faster depression. Range for $\widetilde{U}_{SE}$ in facilitating[21] synapses is $[0.01 - 0.05]$.

τ_{inact} Inactivation of transmitter in the synaptic cleft; represents effects like reabsorbation, and enzymatic metabolization.

[19] As mentioned in Markram, Wang and Tsodyks (1998).

[20] Using the default parameter values from table 6.1 gives $\nu_p = 22$ Hz.

[21] From Tsodyks et al. (1998). For depressing synapses, $\widetilde{U}_{SE} \in [0.1 - 0.95]$ (Tsodyks and Markram, 1997).

τ_{rec} Involved with recovery from the inactive pool, thereby linked to e.g. vesicle depletion.

τ_{facil} Governing the extent of the residual calcium mechanism. Could represents an average over the first two (fast) types of facilitation and part of augmentation. For $\tau_{facil} \to 0$ facilitation is not exhibited and the synapse resembles the depressing version.

As seen from equation (6.14a), the absolute synaptic efficacy, A_{SE}, is a multiplicative factor only affecting the postsynaptic current. Changing it causes overall effects, independent of input frequency. This is not the case for the other parameters in the model. In figure 6.7 examples are given of how the influence of parameter changes are dependent on the frequency of the input.

An increase in either $\widetilde{U}_{SE}$ or τ_{facil} mainly affects low frequencies, thereby shifting the turn-over frequency between facilitation and depression to the left – in agreement with equation (6.18). The lowering of the peak frequency ν_p, is also an evident consequence of an increase in τ_{rec}, the recovery time constant, whose change otherwise is generally influential on the higher frequency part of the tuning curve.

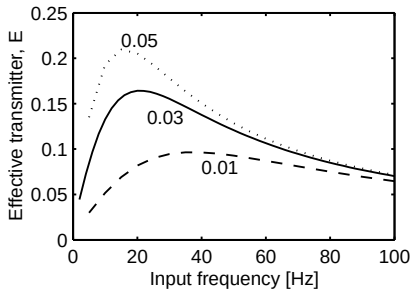
The parameter variation also revealed that the facilitation parameter τ_{facil} is, in general, involved with the intermediate frequency part of the tuning curve – a trend that is somewhat indicated by figure 6.7(c).

6.3 Synapses that learn

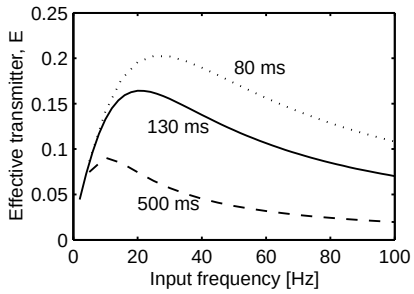
Incorporation of activity based learning in synaptic models have, as seen in section 4.3, been done in various ways. Before looking at a particular model, it should be mentioned that also Markram and Tsodyks from above, have made contributions in this direction.

Presented in Senn, Markram and Tsodyks (2001) is a plastic synaptic model, whose modification depends on the precise timing between pre- and postsynaptic action potentials. The way it is done, is by adjusting the probability of vesicle discharge from the presynaptic membrane. If a presynaptic spike comes before a postsynaptic spike, the probability is upregulated and vice versa.[22] The regulation is limited to happen within a temporal window of 50 ms in agreement with the findings presented along with figure 3.3 in section 3.2. Specifically, the events associated with presynaptic regulation is determined by a postsynaptic

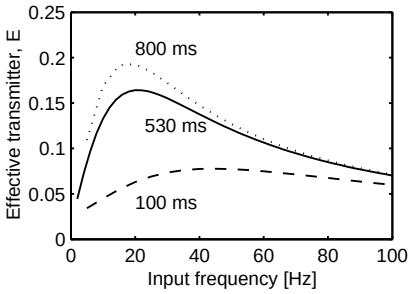
[22] A presynaptic spike *after* a postsynaptic spike leads to a downregulation of the probability.



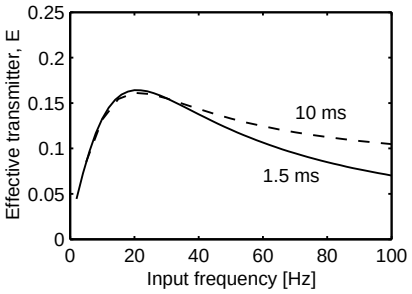
(a) Changing $\widetilde{U}_{SE}$. Increasing the utilization parameter advances the onset of depression.



(b) Changing τ_{rec}. Fast recovery 'delays' depression.



(c) Changing τ_{facil}. As for the utilization parameter, mainly low frequencies are affected.



(d) Changing τ_{inact}. Increasing the inactivation time constant is only concerning the higher frequencies.

Figure 6.7 Parameter variation and the effects involved. In all figures the solid line represents the default values also used in figure 6.6. Apart from the parameter in question, the rest are kept at their default value.

activity measure, mediated by an NMDA receptor model.[23]

6.3.1 Song, Miller & Abbott

Another model of activity induced Hebbian learning has recently been formulated by Song, Miller and Abbott (2000). The model involves excitatory and inhibitory synaptic input coupled to a leaky integrate-and-fire neuron determined by

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = V_{rest} - V + g_{ex}(t)(E_{ex} - V) + g_{in}(t)(E_{in} - V) \tag{6.19}$$

Whenever the membrane potential V reaches a threshold of $V_\theta = -54\ mV$, it is reset to $V_{init} = -60\ mV$. To avoid unphysiological inter-spike intervals and to ensure an upper limited firing rate, the Song, Miller and Abbott model (Song–Synapse from now on) has in the present implementation been extended to include an absolute refractory period θ_R. The synaptic conductances g_{ex} and g_{in} are dimensionless and both decay exponentially like

$$\tau_{ex} \frac{\mathrm{d}g_{ex}}{\mathrm{d}t} = -g_{ex} \quad \text{and} \quad \tau_{in} \frac{\mathrm{d}g_{in}}{\mathrm{d}t} = -g_{in} \tag{6.20}$$

On the arrival of a presynaptic spike, the conductances are incremented by amounts $\bar{g}_a$ and $\bar{g}_{in}$ respectively

$$g_{ex}(t) \rightarrow g_{ex}(t) + \bar{g}_a \quad \text{and} \quad g_{in}(t) \rightarrow g_{in}(t) + \bar{g}_{in} \quad , \tag{6.21}$$

where the $\bar{g}$'s are both acting as *peak* values, i.e. immediately after an isolated presynaptic spike. The subscript in $\bar{g}_a$ refers to excitatory synapse a.

Synaptic modification is incorporated by two other exponentially decaying functions M and P_a. The M-function is used to decrease synaptic strength and is negative, meaning that it 'decays towards zero'; the other, P_a, is used to increase synaptic strength for synapse a

$$\tau_- \frac{\mathrm{d}M}{\mathrm{d}t} = -M \quad \text{and} \quad \tau_+ \frac{\mathrm{d}P_a}{\mathrm{d}t} = -P_a \quad , \tag{6.22}$$

These functions are governing the correlation capturing part of the synapse. A postsynaptic spike decrements M by an amount A_-, whereas a presynaptic spike in synapse a increments P_a by an amount A_+. Together, the M and P_a functions constitute the exponential pieces in a 'learning window' limited in time through their time constants (see figure 4.6(a)). In order for stable

[23] See also Gerstner and Kistler (2000) for a close examination of the model.

Parameter	Value	Unit
τ_m	20	ms
τ_{ex}	5	ms
τ_{in}	5	ms
τ_-	20	ms
τ_+	20	ms
θ_R	2	ms
V_{rest}	-70	mV
V_θ	-54	mV
V_{init}	-60	mV
E_{ex}	0	mV
E_{in}	-70	mV
$\bar{g}_{in}$	0.05	
$\bar{g}_{max}$	0.015 - 0.035	
A_+	0.005 - 0.02	
A_-	$1.05 \cdot A_+$	

Table 6.2 Parameters used in the Song, Miller and Abbott model. The present implementation introduces an absolute refractory period θ_R and synaptic gains to the model.

competitive synaptic modification to occur, the integral of the learning window function must be negative, thereby ensuring that uncorrelated presynaptic and postsynaptic activity results in an overall weakening of the synapse. This is why the ratio $A_-/A_+ > 1$, as can be seen in table 6.2.

The peak conductance $\bar{g}_a$ is modified in step with incoming action potentials:

- A presynaptic spike results in $\bar{g}_a \rightarrow \bar{g}_a + M(t)\bar{g}_{max}$ and, if negative, $\bar{g}_a = 0$.
- A postsynaptic spike leads to $\bar{g}_a \rightarrow \bar{g}_a + P_a(t)\bar{g}_{max}$ and, if $\bar{g}_a > \bar{g}_{max}$, $\bar{g}_a = \bar{g}_{max}$.

In the model, g_{ex} is modified before[24] $\bar{g}_a$. The other peak conductance $\bar{g}_{in}$ is held fixed.

Song et al. concentrates on the statistical properties of large populations of synapses and examines how input from $a = 1, 2, \ldots, 1000$ excitatory and 200 inhibitory synapses affects a single integrate-and-fire neuron.

To fit into the object oriented model architecture, the synapses have been parted from the neuron. Also, aiming at building networks with several neurons, gain

[24] Changing the order does, however, not change the results.

constants, k_{ex} and k_{in}, have been introduced to make a single synapse have a larger impact at the neuron and thereby, in practice, to represent a number of equally acting synapses in parallel. This modifies equation (6.19) to

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = V_{rest} - V + V_{ext} + \sum_{n=1}^{N_{ex}} k_{ex,n} g_{ex,n}(t)(E_{ex} - V) + \sum_{n=1}^{N_{in}} k_{in,n} g_{in,n}(t)(E_{in} - V) \quad , \tag{6.23}$$

where n represents the possibility of having N different groups of equally acting synapses. Additionally, for testing purposes, an injection of an artificial, external current has been made optional (leading to V_{ext}).

A snapshot of a run with the Song-Synapse is shown in figure 6.8, illustrating the dependencies between the internal states in the excitatory part. Whenever a presynaptic spike arrives, the P_a modification function is incremented and likewise the conductance g_{ex} (equation (6.21)). Postsynaptic spikes offsets the M function. In either case, the peak conductance, $\bar{g}_a$, is altered in accordance with the values of the modification functions.

Figure 6.9 illustrates how up- and downregulation of g_a depends on the actual timing between the incoming spikes. Two groups, of three presynaptic spikes each, are shown. In the first group (left), the postsynaptic feedback input are given 20 ms after the firing of the presynaptic stimuli – an increment of g_a is seen due to the temporally 'correct' pairing. To the right in figure 6.9, the firing pattern is reversed; now the postsynaptic stimuli comes 20 ms before the presynaptic – leading to a decrease. Looking closely, one will notice that the endlevel for g_a is slightly below its initial value, even though the activity patterns are 'mirrored' and should cancel each other out. That they do not, is due to the skewness of the learning window; as mentioned, a feature deliberately chosen so, to ensure a general weakening of the synapse when presented with uncorrelated input.

In figure 6.10, an enlargement is shown of the light-gray area in the upper left corner of figure 6.8. It only holds the conductance curve g_{ex} and the presynaptic spike times. When comparing the figures, one can see that the M modification function is zero when the spikes arrive. This means that the value of g_a remains the same during all three spikes – the g_a parameter is flat in the beginning of figure 6.8. Now, as seen from figure 6.10, in g_{ex} this results in an equally valued increase for each of the three incoming spikes.

In the article in which the model is presented, Song et al. (2000), a description of the properties of this model are presented. Among those are the fact that synapses started at random values and given different uncorrelated inputs, competition will cause some synapses to be weakened and other to be strengthened.

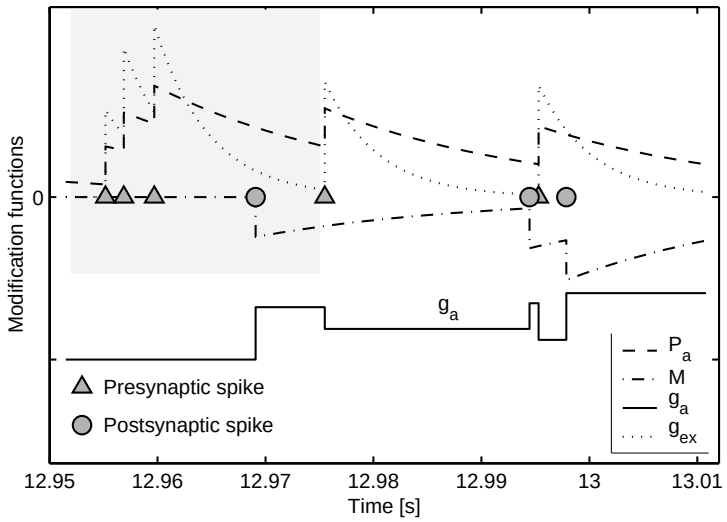


Figure 6.8 An excerpt of a run using the Song-Synapse, showing some of the internal states. The scale on the ordinate is arbitrary, except for the zerolevel, and g_a is translated downwards to make it easier to see. Presynaptic spikes affect P_a and g_{ex} but not M, which is only altered when postsynaptic spikes are present (then having no effect on P_a or g_{ex}). The peak conductance $\bar{g}_a$ is modified by both pre- and postsynaptic spikes – except for the first three, as M is zero here. The accentuated area in the upper left corner will reappear in figure 6.10.

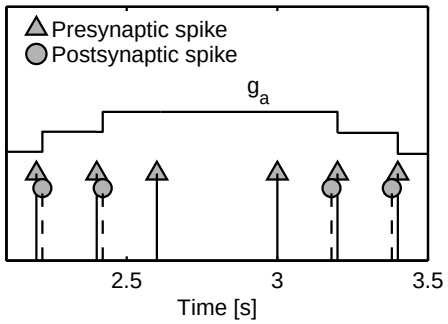


Figure 6.9 The dependence of timing between pre- and postsynaptic spikes in regulation of g_a. When the postsynaptic neuron fires after (20 ms) the presynaptic, the peak conductance is increased (left); if the firing pattern is reversed in time, the peak conductance is lowered (right).

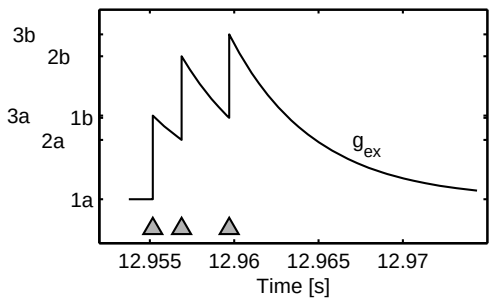


Figure 6.10 An extract of g_{ex} from the upper left corner of figure 6.8, with which it can be compared. The rise of g_{ex} due to the three incoming spikes looks almost facilitating. Closer inspection, however, reveals that the height of the increase, with each spike, is the same: $\Delta ab_1 = \Delta ab_2 = \Delta ab_3$.

Thus some synapses gain control of the neuronal firing times.

Another key factor

> »*... is that the mean input to the neuron should only be sufficient to raise the membrane potential to a point below, or slightly above, the threshold for action potentials generation, so that spike times are determined primarily by positive fluctuations in the total level of input.*«

As argued in the next section, this is a desirable property.

Summary

The synaptic models presented in this chapter concentrate on different aspects of the synapse.

The dynamic behavior which includes short term changes in synaptic efficacy are treated in the model by Markram et al., the physiology of receptors are modeled by Destexhe et al. and the plastic behavior – the long term effects of stimulation – are considered by Song et al..

The model of the fast dynamics – facilitation and depression – is mainly concerned with transmitter release. All effects are captured by the presynaptic side of the model and the postsynaptic side comprises a multiplicative constant. This model has been studied in some detail and the change in dynamic properties by varying the parameters have been examined.

The model of receptor dynamics provides a more physiological approach to receptor modeling. Although a physiological presynaptic model is also provided, synaptic dynamics in the form of facilitative and depressing mechanisms is not captured.

The third model does not engage in physiological explanations of the variables. Instead it concentrates on capturing the long term effects of stimulation. By introduction of a learning window it becomes possible to change synaptic efficacy according to correlations between spikes on the pre- and postsynaptic side.

7 The model

»Never make a calculation until you know the answer: Make an estimate before every calculation, try a simple physical argument (symmetry! invariance! conservation!) before every derivation, guess the answer to every paradox and puzzle. Courage: No one else needs to know what the guess is. Therefore make it quickly, by instinct. A right guess reinforces this instinct. A wrong guess brings the refreshment of surprise.«[1]

Edwin F. Taylor and John A. Wheeler.

Based on the knowledge acquired by working through the material presented in the previous chapters, it was decided to propose a synapse model containing a number of appropriate mechanisms enabling it to exhibit the desired behavior. This naturally led to the questions: "What are the appropriate mechanisms?", and "What is the desired behavior?". Obviously, various answers fit these questions depending on whose answering. What the main objectives behind the answers suitable for the present report were, is discussed in the following.

The synapse should incorporate the use dependent properties seen in dynamic synapses: Facilitation and depression. And these should be connected to the presynaptic side.

The synapse should have the ability to learn in terms of being capable of expressing spike-timing dependent plasticity; effects connected to the postsynaptic side and under influence of the Ca^{2+} level. Also, its learning ability should not be at the expense of the short term dynamic properties.

The synapse should be designed so that uncorrelated activity leads to an overall weakening of its efficacy.

The considerations made to incorporate the desired properties are presented in the following.

[1] Taylor, Edwin F. and Wheeler, John Archibald. Spacetime Physics: Introduction to Special Relativity. New York: W.H. Freeman, 1966.

7.1 Building the model

7.1.1 The presynaptic side

The model developed by Markram and Tsodyks fits the above requirements to the dynamic behavior of a synapse. The dynamic qualities of this model are described in section 6.2.2, where it is seen that facilitating and depressing effects are expressed in terms of changes to the postsynaptic current.

The postsynaptic part of the model consists of a multiplicative constant, the dynamic effects is situated in the presynaptic side of the synapse. This part of the model is concerned with the release of neurotransmitter. In other words, the model by Markram and Tsodyks translates incoming spikes into a concentration of neurotransmitter, the interesting part – the facilitating and depressing effects – are fully described by presynaptic action.

Since the model captures the desired effects and are easily extendable, it was chosen as a building block. The equations and a description thereof are given in section 6.2.2. The most important variable, the relative amount of neurotransmitter in the synaptic cleft, is denoted E.

7.1.2 Postsynaptic AMPA receptors

The postsynaptic mechanism used in the model by Markram and Tsodyks consist of multiplying the transmitter with a constant value, to get the excitatory postsynaptic current.

By extending the synapse to include a model of the postsynaptically resident AMPA receptors[2] instead, a more physiologically plausible shape of the postsynaptic activity curve is obtained; this not just for cosmetic reasons, the rise time incorporated in the latter introduces a natural delay between pre- and postsynaptic activity. In figure 7.1, the course of E from Markram and Tsodyks is compared to the fraction of open AMPA receptors, $r(t)$, after transmitter release due to a single incoming presynaptic spike. Later it comes in handy to know that the area under $r(t)$ following this single spike is $\overline{r} \approx 0.6\,ms$.

The receptor conductance g_{AMPA} is directly proportional to the fraction of open receptors, with the proportionality constant being the maximal conductance $\tilde{g}_{AMPA}$.

[2]Described in section 6.2.1 by equation (6.11), similar to equation (7.1a) of this section.

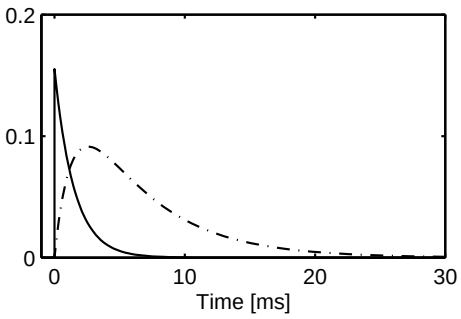


Figure 7.1 The variable E (solid line) from the model of Markram and Tsodyks. Multiplication of A_{SE} and E constitutes the postsynaptic current. In the model of Destexhe et al., the fraction of open postsynaptic AMPA receptors following transmitter release, is indicated by the dot-dashed line. The latter exhibits a rise time in contrast to the abrupt change seen in E.

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \alpha_r[T]\big(1 - r(t)\big) - \beta_r r(t) \tag{7.1a}$$

$$g_{AMPA} = \tilde{g}_{AMPA} r(t) \tag{7.1b}$$

In equation (7.1a), the $[T]$ represents concentration of transmitter in the synaptic cleft and it is found by multiplying the relative amount of transmitter E by a maximum value $[T_{max}]$. Since E is confined[3] to $[0; 0.2]$, the value of $[T_{max}]$ should be around five times the maximal physiological value. Clements (1996) reports that under normal conditions, the maximal transmitter concentration is around $1 - 5\,mM$; therefore $[T_{max}] = 25\,mM$ is chosen

$$[T] = E[T_{max}] \tag{7.2}$$

The above equations combined yield the following expression for the current through AMPA receptors

$$I_{AMPA} = \tilde{g}_{AMPA} r(t)(V - E_{AMPA}) \tag{7.3}$$

7.1.3 The conversion function

Along the lines of chapter 3, the learning processes involving synaptic plasticity are here expressed through postsynaptic effects; in particular by using NMDA receptor like mechanisms.

The NMDA receptor model provided by Destexhe involves a slowly varying α function[4] multiplied with a voltage dependent function, $B(V)$, representing the fast dynamics involved with the Mg^{2+} ion block removal following a postsynaptic

[3] As seen from simulations in section 6.2.2, using default values.
[4] Modeled like the AMPA receptor but with other time constants.

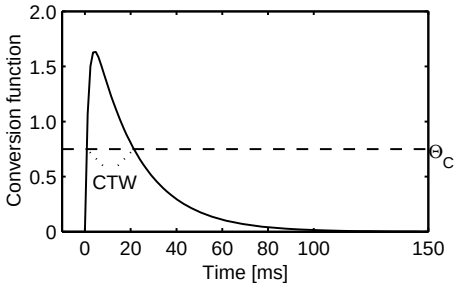


Figure 7.2 The shape of the conversion function when the synapse, from its resting level, receives a single input spike. The dashed line defines the threshold, Θ_C, at an arbitrary value. The time spent above the threshold is labelled the *coherent temporal window* (CTW).

spike. This product yields an NMDA current mainly caused by influx of Ca^{2+} ions, leading to a spike-timing dependent Ca^{2+} concentration.

Induction of LTP/LTD is strongly correlated with the Ca^{2+} concentration as shown in section 3.3.3. Therefore the model incorporates an AMPA conductance g_{AMPA}, the alteration of which is performed continuously depending on measures mimicking the actual Ca^{2+} concentration in the postsynaptic terminal.

Quite similar to the function used for modeling the NMDA receptor by Destexhe et al., is the function used here to represent the Ca^{2+} level; it is a transmitter dependent, slowly decaying function: The conversion function, C

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \alpha_C[T](1-C) - \beta_C C \quad , \tag{7.4}$$

with $[T]$ given as in equation (7.2). This conversion function is a purely phenomenological description of the integrated Ca^{2+} flux through NMDA receptors, combined with a slow use or leakage of Ca^{2+} ions. Furthermore, C is 'imaginary' in the sense that its value, at a given time, represents the integrated Ca^{2+} level *as it would have been* if a postsynaptic spike arrived. Thus, the conversion function is a fabricated composite measure, and, as a consequence hereof, its parameters α_C and β_C cannot be found directly in the literature but have to be chosen more or less arbitrarily.

First, the rise constant, α_C, is chosen to be $7.2 \cdot 10^4\, M^{-1}s^{-1}$, the same as α_n for the NMDA receptor. The rationale for this choice is that Ca^{2+} cannot flow in faster than the receptors can open. Second, β_C is chosen to be $\frac{1}{50\ ms}$ since this decay leads to a shape approximating the experimentally found maximal learning window for changing the synaptic efficacy[5]. Also, the value of this latter time constant makes sense, if one has an eye to the membrane time constant of the postsynaptic neuron – they are alike. Figuratively speaking, this means that as

[5]As described in e.g. Song et al. (2000). See also chapter 3.

long as the neuron 'remembers' having received a signal, the synapse remember having sent it.

As described in section 3.3.3, the physiology behind spike-timing dependent alterations of synaptic efficacy involves a cascade of processes ultimately leading to a change in either the number or efficiency of active AMPA receptors – whether this change is an up- or down-regulation is heavily influenced by the Ca^{2+}–level at the time of postsynaptic firing.

Here, this amounts to evaluating the conversion function when a postsynaptic (back-propagated) spike arrives and comparing the value to a threshold Θ_C. Figure 7.2 shows the conversion function after a single presynaptic spike and how the threshold Θ_C confines a *coherent temporal window* (CTW) in which the conversion function is above threshold.

Of course, presynaptic activity will not always consist of single, well separated spikes – especially not if one wants to bring the dynamic mechanisms residing presynaptically into business – which is why input spikes as bursts are treated in the following.

The behavior of the conversion function, when fed with input bursts of three spikes, is shown in figure 7.3, where two different sets of bursts have been used, the difference between them being their inter-spike intervals.

To the left in figure 7.3, the spikes in the burst are separated by $200\,ms$, allowing for the conversion function to return to zero between the inputs; that the peak values are increasing in step with spike number two and three are due to the facilitating effects of the synapse, reckoned by observing that the facilitation variable U_{SE} does not reach its resting level.

In the right side of figure 7.3, the spikes are separated by $25\,ms$, not leaving time for the conversion function to return to zero before the next spike arrives, resulting in a 'facilitative' appearance. Arbitrary conversion thresholds have been inserted to point to the fact that shortening the inter-spike interval (increasing the burst frequency) widens the CTW at a given threshold Θ_C. Looking at e.g. the dashed line, the 40 Hz burst train results in a continuous learning window, whereas for 5 Hz it is broken in three.

By slowly increasing the inter-spike burst frequency, one can imagine how the initially parted peaks of the conversion function gradually approach each other and finally merges, thereby 'lifting' the curve off from the zero level. The conversion function surface evolving, when performing this gradual increase of the inter-spike frequency of bursts of three spikes, is shown in figure 7.4.

One of the reasons for producing the surface in figure 7.4 was to be able to, easily, get a feeling of how wide the coherent temporal window (CTW) was at a

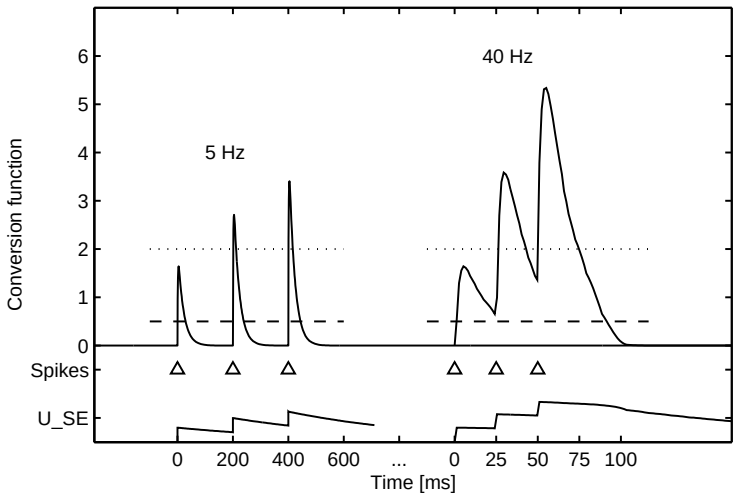


Figure 7.3 The conversion level after two different bursts of three spikes, showing that a decreased inter-spike interval (raise in frequency) leads to accumulation. Two arbitrary conversion thresholds Θ_C are indicated by a dashed and a dotted line respectively. Despite the unequal scaling of the time axis, one notices that the times spent above the thresholds are larger for the fast spike train: The coherent temporal window is wider.

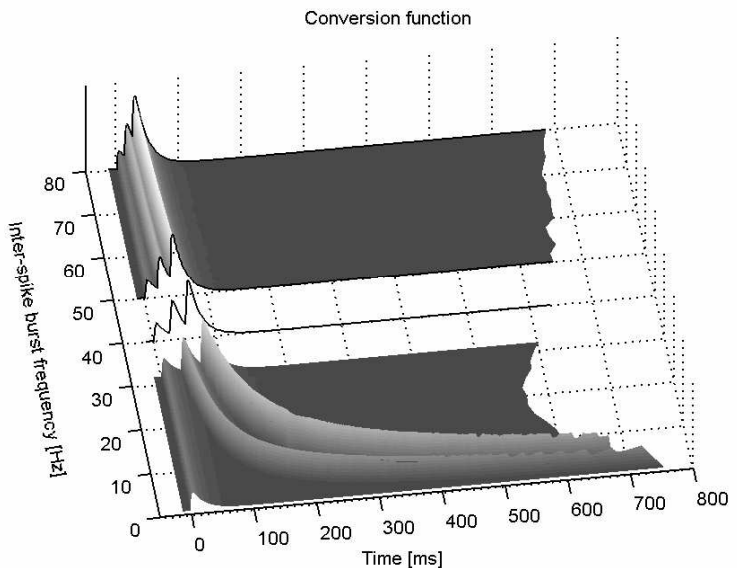
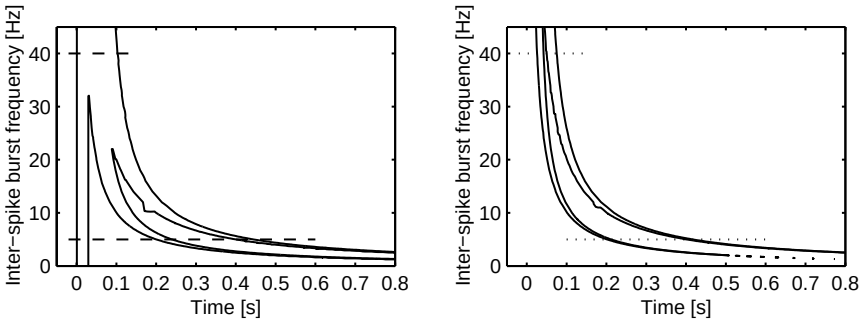


Figure 7.4 When slowly increasing the inter-spike frequency for three-spike bursts, the conversion function can be viewed as a surface. The curve related to a 40 Hz burst train has been isolated and can be compared to the right hand side of figure 7.3.

given spike separation and at a given conversion threshold, Θ_C. The latter was specified by 'cutting' the surface at the desired height, producing contour curves as the ones shown in figure 7.5.



(a) A slight magnification of the contours arising, when cutting the conversion surface in figure 7.4 at $\Theta_C = 0.5$. The dashed lines are inserted to aid comparison with the lower cut in figure 7.3.

(b) As for (a) but know with $\Theta_C = 2$. Again, guide lines (dotted) have been added to help rediscovering the level depicted in figure 7.3.

Figure 7.5 Cutting the conversion function surface in order to obtain contour curves helping to determine the width of the coherent temporal window (CTW) at given values of the conversion threshold.

The first spike in the train always affects the conversion function in the same way, regardless of how many spikes is succeeding it – this effect is indicated by the two vertical lines to the left in figure 7.5(a). These lines are missing in figure 7.5(b) since the threshold $\Theta_C = 2$ is above the maximal possible conversion value after a single spike (see figure 7.2).

In fact, the effects arising from putting more spikes into the input burst train, are just added 'to the back of the contour curves', i.e. the rightmost side. This is seen from figure 7.6, where the burst train consists of seven spikes. The conversion threshold $\Theta_C = 0.5$ produces a contour plot whose first part (left) exactly matches the same cut for three spikes (figure 7.5(a)), the extra spikes are only evident in the later part.

After having gotten acquainted with the conversion function, it is time to look at what its activity measure is 'converted' into.

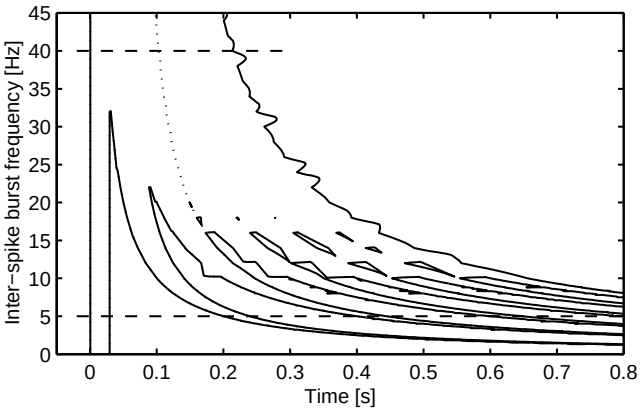


Figure 7.6 Contour lines of the conversion function for seven spikes in an input burst train ($\Theta_C = 0.5$). The wiggles are unfortunately artifacts from the automated contour determination performed by Matlab. The dotted line indicates the conserved structure of the three-spike contour from figure 7.5(a).

7.1.4 Capturing correlations – the learning function

As mentioned above the dependence of Ca^{2+} in learning is found to be of great importance. Findings by e.g. Artola, Bröcher and Singer shows that change of synaptic strength is highly correlated with the amount of Ca^{2+} flowing into the postsynaptic terminal when the postsynaptic neuron is depolarized. Afterwards, if the Ca^{2+} level in the terminal is very low, the strength of the synapse will not change at all. However, as the amount is increased depression will set in, and for high levels of Ca^{2+} the synapse is strengthened. In section 3.3.3 the processes behind these effects are explained.

On basis of the physiological findings,[6] a learning rule based on the Ca^{2+} level is introduced. Each time the postsynaptic neuron depolarizes, the strength of the synapse is adjusted. This adjustment is done according to the Ca^{2+} level, here represented by the conversion function introduced in equation (7.4).

The strength of the synapse is modeled by the multiplicative constant L. L is confined to the interval $[0; 1]$ by imposing a hard bound as described in section 4.3. By introducing L, the current stemming from ions flowing through AMPA receptors (equation (7.3)) is modified to

$$I_{AMPA} = \tilde{g}_{AMPA} r(t)(V - E_{AMPA})L \tag{7.5}$$

From equation (7.5) it is clear that the newly introduced parameter L controls

[6] See section 3.3.3.

the efficacy of the synapse. If one were to assign a physiological meaning to L it could represent the number – or effect – of AMPA receptors located on the postsynaptic bouton.

A simple affine transformation is chosen to represent the connection between the conversion function C (representing the Ca^{2+} level) and the changes to the synaptic strength:

$$\Delta L = aC + b \tag{7.6}$$

This learning rule implies that when the conversion function is above a threshold $\theta_c = \frac{-b}{a}$ the synapse is strengthened and when below threshold, the synapse is weakened.

Looking back at the figures in the previous section describing the behavior of the conversion function (figures 7.2 – 7.6), it is worth noting that the coherent temporal window (CTW) is in fact exactly the time interval in which a postsynaptic spike must occur to induce potentiation. If the threshold is subtracted the figures can be thought of as representing the learning window for the model (see section 4.3).

Equation (7.6) is not completely in accordance with the ABS rule. At very low Ca^{2+} concentrations the synapse strength is weakened when using equation (7.6) where it, according to the ABS rule, should remain constant.

7.1.5 Comparison with other spike–based rules

Summing up all the above steps in the creation of the learning rule, it is possible to describe it using the terminology from equation (4.16).[7]

To see this, it is useful to unravel the learning rule, starting from the back with equation (7.6). Substituting the more commonly used w for the learning parameter (or weight) L, and denoting the history of all spikes S

$$\begin{aligned}
\Delta L &= f_1(L, C, S_{post}) && \text{(7.7a)}\\
\Delta w &= f_1(w, C, S_{post}) && \text{(7.7b)}\\
C &= f_2([T]) = \widetilde{f}_2(E, [T_{max}]) && \text{(7.7c)}\\
E &= f_3(S_{pre}) && \text{(7.7d)}\\
&\Downarrow &&\\
\Delta w &= \mathcal{F}(w, S_{pre}, S_{post}) && \text{(7.7e)}
\end{aligned}$$

The learning rule thereby fits into the general description of learning rules accounted for in section 4.3. However, as shall be seen below, it differs from both

[7] Gerstner and Kistler (2000).

the model proposed by Song et al. and Gerstner and Kistler.

Comparing the present learning rule to the ones proposed by Song et al. and Gerstner and Kistler,[8] two major differences are found. The first has to do with when the synapse is modified. In the model of Song et al., the strength is modified on arrival of both pre- and postsynaptic spikes. The rule proposed by Gerstner and Kistler modifies the synapse by – from the outside – looking at the time difference between the spikes, summing the contributions, and modify the synapse at the end of a run. The present model only modifies the synapse when the postsynaptic neuron fires. As a result, the learning window has no direct contribution when postsynaptic firing occurs before presynaptic firing. If this happens, the C contribution from the last presynaptic spike is considered and L is down regulated if below threshold.[9]

The other main difference is that in the models by Song et al. and Gerstner and Kistler, the learning window is a static property. Each time spikes occur, the same learning window is consulted. As accounted for in section 7.1.3 the learning rule proposed here employs a window that is varying from spike to spike, accounting for presynaptic facilitating and depressing effects. A result of this modification is e.g. that the synapse is more likely to be potentiated when presented with bursts rather than with single spikes.

7.1.6 Soma

To test the synapse a postsynaptic neuron was required. In section 6.1 the most commonly used neuronal models are described. Since the primary goal was to test the synapse, a simple yet well performing neuronal model was chosen, the integrate-and-fire neuron.

Introducing the postsynaptic current from equation (7.5) into the soma modified from equation (6.23), the following equation for postsynaptic potential comes out

$$\tau_m \frac{\mathrm{d}V}{\mathrm{d}t} = V_{rest} - V - VR \sum_{n=1}^{N} k_n g_n L_n r_n(t) \tag{7.8}$$

The gain constant k introduced in section 6.3.1 is also used here to allow for single synapses to act as a representation of many.

The desired operational level for the neuron is to be, on average, slightly below threshold. Denoting this level V_{eq} it is possible to calculate the condition for this to happen.

[8] See figure 4.6.
[9] Compare e.g. figure 4.6 with figure 7.2.

Parameter	Value	Unit
$[T_{max}]$	25	mM
α_C	$7.2E4$	$s^{-1}M^{-1}$
β_C	20	s^{-1}
R	1	$G\Omega$
k	$\frac{1200}{N}$	see text
g	150	pS
Θ_C	4	
α_r	$1.1E6$	$s^{-1}M^{-1}$
β_r	190	s^{-1}
E_{AMPA}	0	mV
V_{rest}	-70	mV
V_θ	-54	mV
τ_{inact}	1.5	ms
τ_{rec}	130	ms
τ_{facil}	530	ms
$\widetilde{U}_{SE}$	0.03	–

Table 7.1 Parameter values used for simulations.

The 'equilibrium' state is reached when $\frac{\mathrm{d}V}{\mathrm{d}t} = 0$. However since inputs are fluctuating this is not a steady level, but rather an average level around which fluctuations occur.

Assume that a large number of synapses[10] participate in firing of the postsynaptic neuron (N large). The contribution from each synapse must then be small if the neuron is not to be overstimulated. Furthermore, assume that each synapse receives spikes at random times drawn from a Poisson distribution with low parameter λ. The low value of λ ensures that on average the spikes are well separated. This does that the output from each synapse has the shape of a 'single' conversion function as shown in figure 7.2.

If the parameters k, g and L are similar for all synapses the sum in equation (7.8) is only over $r_n(t)$ and its equilibrium can be written as

$$0 = \frac{V_{rest}}{V_{eq}} - 1 - RkgL\sum_{n=1}^{N} r_n(t) \tag{7.9}$$

A further simplification uses that for small λ two successive spikes does not

[10] Or groups of synapses.

influence each other

$$\lim_{N\to\infty} \sum_{n=1}^{N} r_n(t) = N\lambda\overline{r}$$

Where $\overline{r}$ denotes the area under $r(t)$ after a single spike. The product of the parameters kgL needed to keep the neuron slightly below threshold, can now be estimated

$$kL = \left(\frac{V_{rest}}{V_{eq}} - 1\right) \frac{1}{RgN\lambda\overline{r}} \tag{7.10}$$

The value k was originally introduced to allow bundling of synapses. Therefore, to obtain a reasonable equlibrium for the membrane potential (V_{eq}) the k to be chosen depend on the number of synapses.

For values $\overline{r} = 0.6\ ms$, $g = 150\ pS$, $L = 0.5$, $p = 5\ s^{-1}$, $V_{eq} = -55\ mV$ and the values from table 7.1, the gain is estimated to

$$\begin{aligned} k &= \left(\frac{V_{rest}}{V_{eq}} - 1\right) \frac{1}{RgN\lambda\overline{r}L} \\ &= \left(\frac{-70}{-55} - 1\right) \frac{1}{N \cdot 1G\Omega \cdot 150pS \cdot 0.5 \cdot 5s^{-1} \cdot 0.6ms} \\ &\approx \frac{1200}{N} \end{aligned} \tag{7.11}$$

As the approximations involved in this calculation are somewhat crude, simulations was performed to decide a reasonable value for the gain, and to see how many synapses were necessary to get a reasonable steady level. In equation (7.11), $\lambda = 5\ s^{-1}$ was realized by using Poisson spike trains with, in average, five spikes per second as input. The threshold for the postsynaptic neuron to fire is $V_\theta = -54\ mV$. In figure 7.7 the mean value of the neuronal potential is subtracted from the threshold, indicating how far the neuron on average is from firing. The gray scale represents the standard deviation. A low standard deviation along with a low distance from threshold is optimal. With this setting, the neuron will seldomly fire, but are ready to act on external stimuli. From figure 7.7 it is seen that the higher the 'gain' kN, the lower the distance to firing. And, the more synapses that are used, the lower the standard deviation. With a high number of synapses it is possible to keep the neuron at a steady level just below threshold. However, as each synapse is composed of 5 differential equations, the computations are non-trival. If e.g. 400 synapses are used 2000 differential equations are integrated.[11]

[11] A simulation of 25 s were performed on a 800 MHz machine in 5-6 hours.

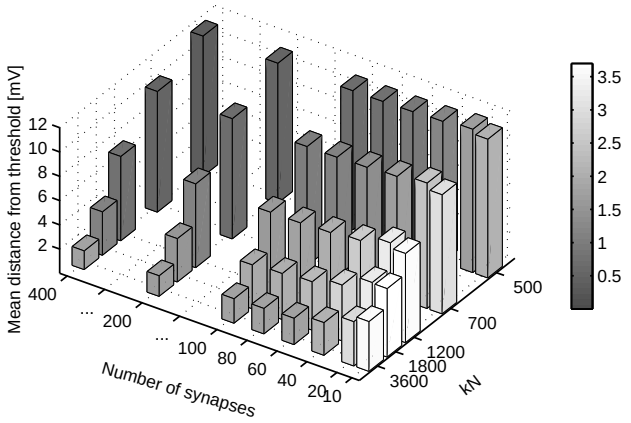


Figure 7.7 The margin between the average neuron potential and its threshold is depicted on the z-axis. Standard deviation is represented by the grayscale. A large number of synapses keeps the fluctuations around the mean value small.

When demanding a low postsynaptic firing rate in responce to random input, the gain must be chosen so that the margin between the meanvalue and the threshold is larger than the standard deviation.

7.2 Testing the model

To test the computational capabilities of the synapse, settings were chosen in accordance with the preliminary investigations. The gain was set to $k = 1200/N$ and the number of synapses was chosen to be $N = 40$, to balance simulation time with low variance of the postsynaptic potential. As above, the synapses were coupled to a single postsynaptic neuron.

7.2.1 Uncorrelated input

A desired property for synapses is to be able to suppress uncorrelated inputs, in this context regarded as noise. Therefore, each synapse was given a low level noise input. The noise input was imitated by uncorrelated Poisson processes with $\lambda = 5$, i.e. approximately five spikes per second.

The learning parameter L was initialized at random in the interval $[0.1; 1]$.

Using the above configuration, the model was tested with no external inputs, i.e. the only stimulations were the Poisson trains.

In figure 7.8 the temporal development of the learning parameters L are shown. As desired, uncorrelated input weakens all synapses. With weaker synapses the average postsynaptic potential is also weakened and the neuron fires less frequently. As the learning parameter is changed only at postsynaptic firing, its adjustment becomes less frequent, leading to a stabilization of the neuron. In the stable state the neuron's membrane potential remains slightly below threshold, making it ready to react if correlations should occur in the input.

In figure 7.9 the firing pattern of the neuron is shown for the beginning and the end of the simulation. Towards the end, the neuron is almost inactive.

From this behavior it is seen that without cooperation, synapses are weakened and the neuron will cease to fire. The configuration blocks the incoming noisy signal.

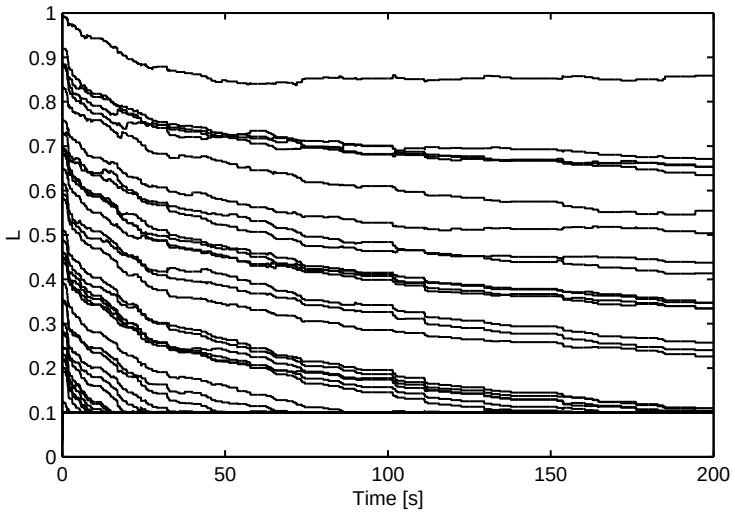


Figure 7.8 40 synapses are connected to a single postsynaptic neuron. Each synapse receives Poisson spike trains with $\lambda = 5$. Since the input is not correlated, the learning parameters L decrease. After a while, the learning parameters are to low to influence the postsynaptic neuron and firing almost stops. This can be seen by noticing that only small changes in L occur towards the end of the simulation. In other words, the postsynaptic neuron is kept slightly below threshold allowing only for occasional spikes (see figure 7.9).

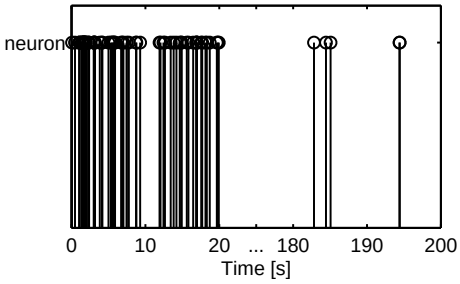


Figure 7.9 The postsynaptic neuron firing pattern before and after learning. The random stimuli decreases the weights until they can only elicit sparse firing.

7.2.2 Dynamic effects

The presynaptic side of the synapse was included to capture the dynamics of the temporal structure of an incoming signal. The effects of this were tested in two analogous simulations.

Once every two seconds an extra input signal consisting of 20 spikes was added. The extra spikes were applied in two different ways, figure 7.10 explains the difference. In the first simulation, five synapses received an extra spike at the time indicated by 'spike1' in the figure, ten milliseconds later five *other* synapses received a 'spike2' signal, etc. So, in groups of five, twenty synapses in total received twenty extra spikes. In the second simulation, burst input was used. Here five synapses received an extra spike at time = 10 ms, ten milliseconds later *the same* five synapses received another spike, etc. In figure 7.10 this is indicated by 'burst'.[12] So, in one group, the five synapses in total received twenty extra spikes.

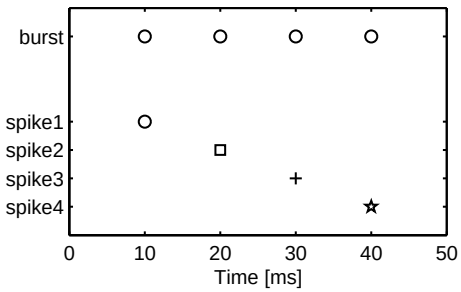


Figure 7.10 Illustration of input patterns applied to test facilitating effects of the synapse. In two separate simulations the synapses were exposed to extra input spikes. In the first simulation, the extra input was distributed over different synapses. In the second simulation, a single synapse received bursts.

The number and the timings of the extra spikes are identical. The only difference is that in one case a burst is applied to a single synapse, whereas in the other case only single spikes are applied at each synapse. With no dynamic effects the two simulations would be identical.

Distributed signal

First, consider the case where the extra inputs are distributed. Like the situation where the synapses received only noise input, postsynaptic firing in response to the noise is suppressed. This does, however, not imply that firing stops. On the contrary, after learning the postsynaptic firing is aligned exactly with the incoming signal (see figure 7.11). This is important, since it shows that the

[12] This stimulus pattern is also known as a theta burst. As described in section 3.3 this is similar to the signal used in *in vitro* induction of LTP.

noise reduction encountered above *is not* just a reduction of all inputs, but in fact allows signals to pass.

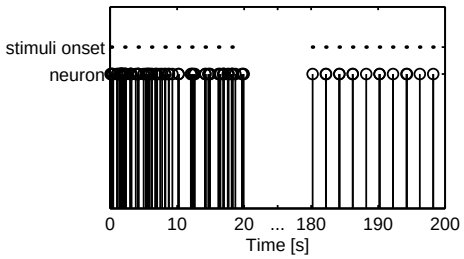


Figure 7.11 The firing pattern of the postsynaptic neuron before and after learning. The dots indicate the onset of the stimuli. In this case the stimuli was distributed over 20 synapses (compare to figure 7.10 and figure 7.12).

It is worth noticing that the addition of five groups of four spikes every two seconds is less than the noise spikes in the same interval. Since 40 synapses in total receive ≈ 5 noise spikes per second

$$\frac{\text{Extra input signal in two seconds}}{\text{Poisson noise spikes in two seconds}} = \frac{5 \cdot 4}{40 \cdot 5 \cdot 2} = \frac{1}{20} \tag{7.12}$$

it means that on average there is twenty times more noise spikes than signal spikes.

As shown in figure 7.12 the learning parameter L decays in the beginning as in the case with only random input. After the average firing level of the postsynaptic neuron is brought down, it is only possible for correlated input to induce firing of the neuron. It is noted that cooperativity is needed for the neuron to fire, and thus uncorrelated inputs are depressed. As the figure also shows, only synapses receiving extra input are not depressed, competition among the synapses has been achieved.[13]

Burst signal

Instead of distributing the extra input to 20 synapses, a burst of four spikes were now given to five synapses. The number and timing of the extra spikes are not changed (see figure 7.10). However, due to facilitating effects described in connection with the conversion function, the effective strength of the signal is increased. As can be seen in figure 7.13, the effect this has on the learning parameters is tremendous. Within a short time[14] all synapses are depressed except the ones that receive extra input. The synapses compete for control of

[13] In appendix C the simulation has been continued for 1000 seconds (figure C.1), which makes the competitive effects even more clear.

[14] Note that the figure only shows 80 seconds compared to 160 seconds in figure 7.12.

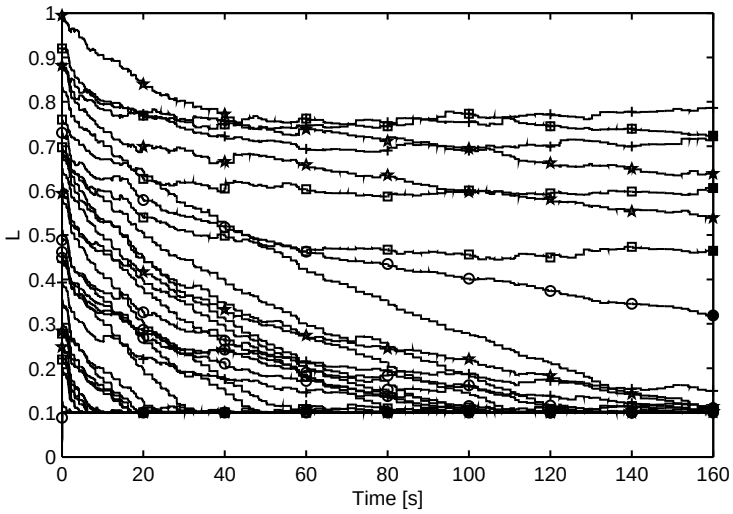


Figure 7.12 All forty synapses receive the same noise signal as in figure 7.8. Furthermore 20 synapses receive extra input as illustrated in figure 7.10. Every other second, four groups of five synapses are stimulated with a single spike. The extra incoming spikes are distributed over 20 synapses. Synapses receiving extra input are tagged with a marker, the shape of the marker indicates the temporal order of the input, see figure 7.10 (see also appendix C figure C.1 where the simulation has been continued for 1000 seconds).

the neuronal firing and the ones receiving extra input wins. After learning, the neuron is highly sensitive to inputs from the winning synapses but not to inputs from the losing synapses.

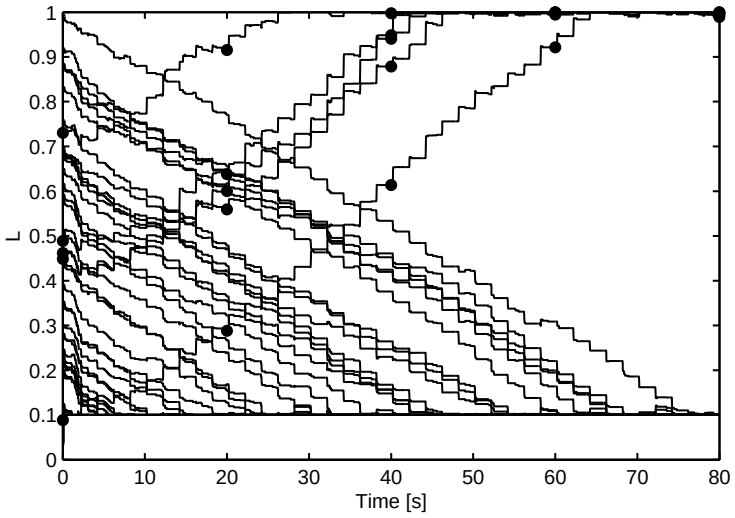


Figure 7.13 The number and timing of the incoming spikes are equal to what is used in figure 7.12, the difference being that the signal here is coded in bursts. The circles represent synapses receiving extra input.

The winning synapses are in fact so successful that after learning their need to cooperate is reduced. This is seen from figure 7.14. After learning, the postsynaptic neuron is active each time a stimulus is applied. However, the individual winning synapses are strong enough to sometimes make the neuron fire without highly correlated input. This indicates that after learning it is only necessary to stimulate some of the synapses to activate the neuron.

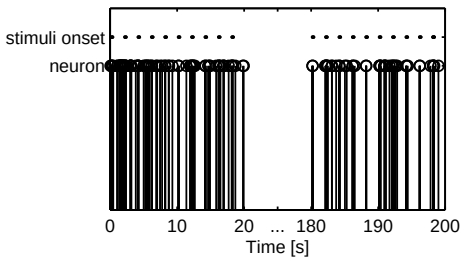


Figure 7.14 The firing pattern of the postsynaptic neuron before and after learning. the dots indicate the onset of the burst stimuli.

Two important things can be deducted from this simulation. First, regard the input as being divided into two groups: One containing four synapses, a strong group, and one containing a single synapse, a weak group. When the strong and the weak groups are stimulated together, both groups are strengthened. If the weak group was stimulated by itself, no effect would have been seen. In other words, the model has the ability to associate weak inputs with strong.

Second, once the synapses have adapted to a pattern, it is possible to achieve activation of the neuron by only stimulating part of the pattern. This is a consequence of the reduced need to cooperate mentioned above.

It is worth mentioning that when presented with both kinds of input – burst stimulation on 5 synapses and distributed stimulation on 20 synapses – the bursting behavior wins (see figure C.2 in appendix C). Like the 'Poisson only' synapses, the synapses with distributed stimulation were depressed.

Summary

The presynaptic dynamics inherited by using the Markram and Tsodyks model for transmitter release have been coupled to a simplified model of an AMPA receptor. Also, the effective transmitter variable E, has been used as input for the 'imaginary' conversion function C, invented to imitate the postsynaptic Ca^{2+} level. Due to the facilitative and depressive effects, the shape of the coherent temporal window (CTW) is strongly influenced by the input activity pattern fed to the synapse. By chosing a threshold, θ_C, the coherent temporal window is comparable to the notion of learning windows presented in section 4.3. The main difference between those reviewed there and the present is, that the CTW is dynamic rather than static.

To get aquainted with the dynamic properties of the learning window, the activity dependence of the conversion function was investigated at some length. The synaptic gain constants needed to set up models of computionally reasonable sizes were likewise examined.

By setting up a model of 40 synapses coupled to a single postsynaptic neuron and testing its reaction to different stimulus patterns, the synapse model here proposed revealed that it is able to express the properties for which is was designed.

When comparing the results of the previous section with figure 3.4, it is seen that the synapse model can reproduce the effects characteristic for long term potentiation.

Cooperativity It is not possible for single inputs as in figure 7.8, to elicit firing of the neuron. An assembly of cooperating synapses is needed, like depicted in figure 7.12 or figure C.1.

Association When presented with a strong stimulus on some synapses and a correlated weak stimulus on others, the weak stimulus will be potentiated as well. This is illustrated by figure 7.13 if one considers the input as coming along two different pathways.

Specificity That only the synapses participating in firing of the neuron are enhanced, can be deducted from all figures.

Furthermore, the model incorporates facilitating and depressing effects as reported and modeled by Markram and Tsodyks (1996). This is seen by the clear difference between the behavior when fed with bursting input rather than distributed input; although the number of spikes was the same, the effects were different. This points out the non-linear fashion of the synapse: The sum is more than the sum of its parts.

Along the lines of the Hebbian learning rules presented in section 4.3, the performance of the synapse model demonstrates some beneficial properties

Stability The synapse is stable per design, since it employs clipping of the weights.

Competition Synapses compete for control over the firing times of the postsynaptic neuron. When some synapses receive correlated input, these synapses will be strengthened at the expense of synapses not receiving input. In particular illustrated by the longer simulation in figure C.1.

Locality The learning rule is local, using only the pre- and postsynaptic firing times to update the efficacy.

Finally, as seen in figure 7.11, the coorporative nature of the synapse enables it to suppress low intensity uncorrelated inputs – noise.[15]

[15] Although, one mans noise might be another mans signal.

8 Discussion

»The moment one gives close attention to anything, even a blade of grass, it becomes a mysterious, awesome, indescribably magnificent world in itself.«

Henry Miller (1891-1980)

With March 1st approaching, the six months spent working on this report is about to come to an end. Before finishing of, a few things that have come up along the way, deserves a comment.

8.1 Discussion

Although the learning function L introduced is constructed to indirectly model the Ca^{2+}–level, as proposed by Artola, Bröcher and Singer, *it does not* correspond to the ABS rule. The reason being that the learning function L is not incorporating an LTD threshold. A possible extension to the model is to implement a changed weight update. Instead of using a linear connection between Ca^{2+} and learning, a more physiological link could be chosen. This would bring the model more along the lines of the ABS rule, creating a lower bound on the Ca^{2+} concentration below which no modifications occur. The inclusion of this threshold might improve the computational properties as well, by changing the competition from a win/lose situation to instead converging properties similar to Oja's rule.

Noting that the presynaptic side of the proposed model is exactly the model of Markram and Tsodyks, one could ask if it not as well could have been another presynaptic model. The model of Markram and Tsodyks was chosen because of its physiological properties. The presynaptic dynamics act as a filter on the input, and it could be interesting to see the effect of changing this filter. The parameter investigation performed in section 6.2.2 has, so to speak, facilitated this investigation.

For further improvement of the filtering properties, an idea is to make an adaptive filter. To do this, it is necessary to change the presynaptic side. Physiologically this could be possible by including second messengers. Markram and Tsodyks has proposed a model of second messengers effecting the presynaptic side of the synapse. This model modifies the release probability of vesicles, and thus leads to synaptic redistribution but not to changes in the conductance properties postsynaptically.

A step in another direction would be to try an simplify the model, by cutting away all the physiologically inspired states and aim at pure computational properties along the lines of Maass and Zador. In this way a computationally more efficient unit might be produced – unless none of the equations are expendable.

The analysis performed on the gain constants provides insight into how to adjust the internal parameters of the synapse in accordance with the size of the model they are situated in. With this information available, an interesting step would be to incorporate the synapses in larger networks, to investigate the overall behavior.

In this respect, the type of coupling chosen – the network architecture – is of significant importance for the possible outcome.

The associative element inherent in the synapse points to that a natural setting would be in associative networks. Within this class, the 'original' fully-connected version referred to in section 4.1 is a reasonable starting point. Another choice could be copies of real network structures or abstractions thereof.[1] One could also change the connectivity to be purely random. However, still another presumably very promising candidate is the 'small-world' architecture proposed recently.[2] Instead of having completely regular or completely random connections, the 'small-world' networks can be adjusted to lie somewhere in between.

In the construction of networks of spiking neurons both excitatory synapses – like the one presented in the present report – and inhibitory synapses could be necessary. By inclusion of other types of neurotransmitter and receptors it might be possible to catch the inhibitory effects by the present model.

The use of associative networks in cooperation with temporal encoding of information could be a way to 'get in clinch' with the binding problem. If the encoding of e.g. visual and auditory stimuli is similar, correlated activity of two stimuli could possible lead to a coupling of the two.

When continuing the development of the object oriented modeling tool, it might be well worth the investment to spend some time getting insight into the specific

[1] Like Scarpetta et al. (2001) uses a structure inspired by the hippocampus and olfactory cortex.

[2] See e.g. Watts and Strogatz (1998) or Bohland and Minai (2001).

standards defined by the NeuroML language (Goddard et al., 2001). Although still at the prototype stage, the intentions of the NeuroML project are commendable. Functioning as an interchange format allowing various programs to cooperate, it gives modelers the opportunity to easily simulate, test, and compare their models with others. Fully developed, the outlined databases will function as a publishing forum, saving future researchers some of the steps in re-invention of the wheel.

Another natural extension of the here presented modeling tool is to add a graphical interface on top of the object oriented environment. Although already fully functional, this would ease manipulation of the different objects. Of course, one would have to assess whether the operational gain bear comparison with the perhaps tiresome programming.

As the scepticism in connection with the discussion of LTP revealed, scientist do still not agree on the origins or importance. Perhaps a lesson can be learned from the hippocampus. Memory is consolidated from short term to long term by the hippocampus. Memories are, however not not stored there. And since LTP has been found in the hippocampus, it might be involved, if not as *the* memory mechanism, perhaps rather then as an attention directing mechanism.

9 Conclusion

9.1 Conclusion

The work in the present report concentrates on activity dependent learning in biological synapses and models thereof.

A brief review of the multifaceted neuronal and synaptic physiology realized the need to direct the attention to some prototypical properties. For neurons, emphasis was placed on their stereotype behavior when emitting signals. Synaptic activity showed to possess filter-like properties involving use dependent dynamics mediated by neurotransmitter redistribution.

Narrowing the view to the physiological origins of long term synaptic plasticity denoted the importance of temporal pairing of activity in a Hebbian fashion. An influential factor hereto was the correlation capturing nature of the NMDA receptor, governing the postsynaptic influx of Ca^{2+} ions. Neuroscientists have established that these ions are directly involved in up- and down-regulation of AMPA receptors in a manner allowing for LTP and LTD to be reverse processes. LTP displaying characteristic features like cooperativity, associativity and specificity.

An outline of artificial network models soon led to a focus on local Hebbian learning rules in both a rate- and spike-based setting. The spike-timing dependencies encountered by experiments found their equivalent in the notion of the learning window, the shape of which controls the synaptic modifications. In particular, an asymmetric learning window produces competition among synapses.

To aid the implementation of models, an object oriented simulation tool was constructed. The object oriented structure provided a convenient platform, helping to easily modify a given model setup and facilitated the addition of new, never dreamt of components.

With this tool, various existing models of synapses exhibiting use dependent dynamics were implemented. Especially the model by Markram and Tsodyks

was investigated in some detail, as it, based on biologically founded variables, demonstrated to have both depressive and facilitative properties.

The simplified version of an AMPA receptor suggested by Destexhe et al. was laid forward. Also, the spike timing-dependent plasticity model by Song et al. was looked into. The latter leads to competition among synapses but does not include short term, e.g. facilitative dynamics.

Taught by experience, it was decided to let some of the gained knowledge manifest itself in a self-developed plastic, synaptic model. The requirements were that it should incorporate spike-timing dependent plasticity alongside short term dynamics as depression and facilitation. It was desired that the plastic effects were to be expressed under influence of the postsynaptic Ca^{2+} level.

Inspired by the role of the NMDA receptor, an 'imaginary' function – the conversion function – was fabricated to mimic the Ca^{2+} level. Directly affected by presynaptic short term dynamics, the shape of the conversion function is also a dynamic entity, providing the synapse with a dynamic learning window. An examination of this learning window together with computations and simulations of the effect of synaptic gain constants laid the foundation for building models of several synapses.

A model setup comprising forty synapses confirmed that the requirements of the here proposed synapse are met. The short term dynamics were affirmed by a clear difference between the outcome of two stimulation protocols – favoring the one assisting facilitative effects. Indeed these simulations illustrated the non-linear fashion of the synapse by implying that the sum is more than the sum of its parts.

By stimulating half of the model setup with correlated input, competition among synapses evolved. Synapses receiving correlated inputs were strengthened at the expense of the remaining part.

The model involves some level of biological realism as it demonstrated the ability to comply with the features seen in connection with long term potentiation: Cooperativity, associativity, and specificity.

Cooperativity was verified by the fact that single or weak inputs are insufficient in getting the model neuron to fire whereas coordinated input signals succeed. Indeed, the cooperative nature of the synapse enables it to actually suppress low intensity uncorrelated inputs.

Considering the stimulated pattern as being presented along a strong and a weak pathway respectively, suggested an associative potentiation of the weak stimulus with the strong stimulus. Specificity was a prevalent feature in the performed simulations as only synapses participating actively in engagement of the model neuron were enhanced.

Glossary

»Science is facts; just as houses are made of stone, so is science made of facts; but a pile of stones is not a house, and a collection of facts is not necessarily science.«

Jules Henri Poincaré (1854-1912).

Absolute refractory period A short time interval (2 ms) after the neuron depolarizes in which it cannot be depolarized again.

Accommodation Slow depolarization increases the threshold and, if sufficiently slow, might result in no action potential at all.

Acetylcholine A neurotransmitter. The general one involved in excitation of muscles.

Adaptation A decline (fast or slow) in receptor sensitivity to a maintained, continuous stimulus. A mechanism reacting to changes in the degree of stimulation rather than to a steady level.

Afferent Inward conduction, e.g. nerve fibers carrying signals toward the brain or dendrites conducting signals toward the soma.

Agonist Chemically used of a substance that, when binding to a receptor, leads to a reaction or activity. In muscles the word is used of the active muscle (paired with a limiting antagonist).

α-function A function comprised by two exponential functions, one rising and one decaying.

AMPA receptor The major glutamate receptor in the brain, also affected by the agonist, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate .

Antagonist One acting against action, e.g. when blocking a receptor. Also used about muscles limiting the action of the agonist.

ATP Adenosine triphosphate. A molecule acting as a storage of and a transportation mechanism for energy.

Augmentation Involves an increase in transmitter release. Believably due to calcium residuals at the presynaptic terminal after a recent stimulation, as with facilitation but on a longer timescale.

Axon Nervefiber projecting *outwards* from the soma. The word axon has roots in the Greek word for axle.

Axon hillock Region of axonal departure from the soma. Origin of action potentials due to high density of

Na^+ channels resulting in a low depolarization threshold.

Bouton Swelling at the terminal end of a neurite. Most often involved in synaptic contact.

Brainstem The upper part of the spinal cord; also known as hindbrain. Comprising the medulla, midbrain, and pons.

Cerebellum Lies above and behind the pons. Integrates sensory, motor, and position information in order to influence outgoing motor pathways in coordination of movement. May be involved in language and similar cognitive functions.

Cerebrum The largest part of the brain containing the white and grey matter. Consists of two almost symmetrical hemispheres, whose outer layer is the cerebral cortex.

Classical conditioning Introduced by Ivan Pavlov to describe the underlying process, enabling an individual to respond (conditioned response) to a stimulus that initially was insufficient (conditioned stimulus), when this ineffective stimulus is paired with a stimulus (unconditioned stimulus) that in itself is able to provoke a response (unconditioned response).

Climbing fiber Afferent to the cerebellum (there are two such types, the others being mossy fibers). A Purkinje cell makes synaptic contact with a single climbing fiber.

Corpus callosum A large bundle of nerve fibers connecting the two hemispheres of the cerebral cortex. Consists of about 200 million fibers.

Dendrite Nervefiber projecting *towards* the soma. The name comes form the Latin word for tree.

Depression Continued stimulation, at a relatively high rate, leads to a reduction in synaptic efficiency because of a depletion of presynaptic transmitter available for release.

Efferent Outward conduction, e.g. nerve fibers carrying signals away from the brain or axons conducting signals away from the soma.

Endocytosis Invagination of the cell membrane around substances exterior to the cell thereby enclosing the substances in intracellular vesicles.

Enhancement Another word for facilitation.

EPSP Excitatory postsynaptic potential.

Exocytosis Release of cellular substances (as secretory products) contained in cell vesicles by fusion of the vesicular membrane with the plasma membrane and subsequent release of the contents to the exterior of the cell (Merriam-Webster, 2001).

Facilitation An increase in transmitter release. Believably due to calcium residuals at the presynaptic terminal after a recent stimulation, as with augmentation but on a shorter time-scale.

GABA The amino acid γ-aminobutyric acid considered acting as the major inhibitory neurotransmitter in the brain. Operates at e.g. the fast ionotropic $GABA_A$ receptor and the slower metabotropic $GABA_B$ receptor.

Glutamate The main excitatory neurotransmitter in the cortex.

Granule cell The most common neuron type in the brain. Also, the only excitatory cell type of the cerebellum (see parallel fibers).

Gyrus Plural: Gyri. The 'bumps' on the cortex bulging outwards.

Habituation Reduction of the magnitude of a response to a constant, repeated stimulus. A high-level phenomenon not seen in sensory receptors but rather in behavioral responses to stimuli. A form of non-associative learning. Appears in a short-term (minutes) and a long-term (hours) version.

Hippocampus Brain structure below the cortex involved in forming memories; particularly in consolidating short-term memories into long-term. Believed to take part in capturing correlations between activity in different brain areas, e.g. motor planning in the frontal lobe and sensory cortex activity.

Hypothalamus Hypo-, under, the thalamus. Contains nuclei controlling hormonal secretion from the pituitary gland. Also involved in behavior with connection to the daily light/dark cycle (circadian rhythm).

In situ In the natural place or original position.

In vitro Latin for 'in a glass'. Used to describe things as happening outside the living body, i.e. in an artificial environment.

In vivo Latin for 'in the living'.

Ionotropic receptor Class name used when the neurotransmitter receptor and the controlled ion-channel are part of the same protein complex (as opposed to metabotropic receptors), e.g. AMPA, NMDA, and $GABA_A$.

IPSP Inhibitory postsynaptic potential.

Kinase An enzyme involved in phosphorylation, the transferring of phosphate groups to a substrate.

Lalapalooza Something superior, unusual or outstanding (perhaps the word itself is lalapalooza).

Medulla oblongata Part of the brainstem prolonging the spinal cord. Contains nuclei for regulatory purposes such as blood pressure and breathing.

Metabotropic receptor Class name used when the ion-channel is independent of the neurotransmitter receptor and the gating occurs by means of intracellular second messengers (as opposed to ionotropic receptors), e.g. $GABA_B$.

Midbrain Containing nuclei linking various parts of the brain involved in motor functions. Holds the substantia nigra possibly involved in voluntary movement.

Mossy fiber Two different meanings. a) Axon running internally in the hippocampus (from dentate gyrus to CA3). b) Afferent to the cerebellum (there are two such types, the others being climbing fibers).

Neurite Axon or dendrite.

NMDA receptor A glutamate receptor especially sensitive to the artificial substance *N*-methyl-D-aspartate . The requirements for the ion channels of this receptor to open are that glutamate are docked *and* that the membrane is depolarized. This correlation

capturing functionality is believed to be of importance in learning.

Parallel fibers Highly regular axons of granule cells in the cerebellum. Distributes excitation to all other cerebellar neurons.

Pons Connecting the medulla oblongata and the midbrain in the brainstem. Relay information about movement and position from the cerebellum to the cortex.

Potentiation Getting stronger. Often associated with transmitter release as in e.g. *post tetanic potentiation* where the presence of an action potential is believed to promote mobilization of presynaptically stored transmitter, making it more readily available.

Priming Establishing short-term memory at the sub-conscious level e.g. by quickly flashing a picture. Also used of vesicles to which calcium-binding proteins catalyzing release are bound.

Purkinje cell The predominant neuron type (inhibitory) in the cerebellum, whose output only goes through this type of cells.

Pyramidal cell In cerebral cortex the main excitatory cell, whose axons form the white matter.

Readily Releasable Pool (RRP) Specific membrane sites at the presynaptic terminal from where docked vesicles can undergo exocytosis.

Regression Statistical analysis with the objective to predict the value of a (usually) continuous variable.

Reinforcement learning A variant of supervised learning in which the critique given, only regards the correctness of an answer, not what the correct answer is.

Retrograde messenger Postsynaptically produced diffusible second messengers acting presynaptically.

Reversal potential The potential reached, when the ionic currents through membrane channels for a given ion type balance or cancel out. Can be calculated by Nernst's equation, given in equation (2.1) at page 7.

Second messenger Intracellular molecule, whose concentration or activity is affected by binding of transmitter.

Sensitization A high-level phenomenon enhancing the efficiency of synapses. Like habituation, a form of non-associative learning operating on shorter or longer time-scales from minutes to hours.

Soma The cell body of a nerve cell.

Spine Small membrane protrusion on especially dendrites. Common sites for synaptic contact.

STDP Spike timing dependent plasticity. Long-term synaptic (plastic) changes depending on the relative timing between paired presynaptic and postsynaptic action potentials.

Substantia Nigra Malfunction often leads to tremor as in Parkinson's disease.

Sulcus Plural: Sulci. The furrows or 'valleys' in the cortex.

Supervised learning Often referred to as 'learning with a teacher', telling the correct answer if being wrong.

Synapse The contact site between neurons. It comes from Greek, with 'syn' meaning 'together' and 'haptein' meaning 'to clasp'. Probably the word was first used by Charles S. Sherrington around 1897.

Synaptic redistribution A modification of the short-term dynamics of synapses. Primarily enhances the amplitude of synaptic transmission for the initial spikes in a train, while having little or no effect on the ultimate, steady-state behavior.

Synaptic scaling A global modification of synaptic strength possibly due to a postsynaptic change in the number of functional glutamate receptors (Abbott and Nelson, 2000).

Tabula rasa The notion of the mind in its hypothetical blank or empty state before receiving outside impressions. Often used to describe something as existing in its original (or even pristine) state.

Tetanic stimulation High-frequency stimulation of the presynaptic neuron (in some cases 500-1000Hz).

Thalamus Relays incoming sensory pathways to the cortex and also the feedback fibers. An internal structure (the intralaminar nuclei) is believed to be implicated in consciousness.

Vesicle In synapses, a lipid bilayer membrane sack containing neurotransmitter.

Universal computation The ability to carry out any computation that an ordinary digital computer can.

Unsupervised learning 'Learning without a teacher'. Does not require to be guided by correct answers but learns the underlying structure or pattern from the input data themselves.

A Synapse modeling

In this appendix some of the models which have been investigated in some detail during the project are presented. Even though they are not used directly in the creation of the final synapse, they have contributed to the development and provide background knowledge on how synapses are modeled.

A.1 Liaw and Berger

At the presynaptic side a number of different terminals (i) are involved in the release of transmitter. At each of these release sites, different mechanisms (m) are involved in the release. At a particular terminal only one type of transmitter can be released. The probability of release, Pr_i, is simply the sum of the mechanisms $F_{i,m}$; the size and sign of the 'weight' $K_{i,m}$, determines whether the mechanism is depressing or facilitating and to which degree

$$\tau_{i,m}\frac{\mathrm{d}F_{i,m}}{\mathrm{d}t} = -F_{i,m} + \delta(t - t_{sp}) \tag{A.1a}$$

$$Pr_i(t) = \sum_m K_{i,m}(t)F_{i,m}(t) \tag{A.1b}$$

As described in section 2.3, transmitter release is a stochastic mechanism, which can only occur if the readily releasable pool of this particular transmitter is not empty ($N_i^{total} > 0$). When an action potential arrives at the synapse, a vesicle is released with probability Pr_i. However, in this model Pr_i is compared to a threshold Θ_i and release occurs deterministically when $Pr_i > \Theta_i$ at the time of arrival of a presynaptic action potential.

Release of a vesicle adds a quantum neurotransmitter of Q_i to the pool of transmitter of type i in the synaptic cleft, N_i. This pool decays exponentially

$$\frac{\mathrm{d}N_i}{\mathrm{d}t} = \frac{-N_i}{\tau_i^{Nt}} + Q_i \cdot \delta(t - t_{sp})\mathcal{H}(Pr_i - \Theta_i) \tag{A.2a}$$

$$\frac{\mathrm{d}N_i^{total}}{\mathrm{d}t} = \frac{N_i^{max} - N_i^{total}}{\tau_i^{rp}} - Q_i \cdot \delta(t - t_{sp})\mathcal{H}(Pr_i - \Theta_i) \quad , \tag{A.2b}$$

where τ_i^{Nt} is the time constant for clearing neurotransmitter from the cleft, τ_i^{rp} the time constant for replenishing neurotransmitter, N_i^{max} the maximal amount of available neurotransmitter, and $\mathcal{H}()$ denotes the Heaviside function. At the postsynaptic side, the potential is a function, $G_{j,n}$, of transmitter in the synaptic cleft.[1] As on the presynaptic side different mechanisms, n, at different sites, j, are involved in creation of the signal

$$PSP_j(t) = \sum_n W_{j,n}(t) G_{j,n}(N_i)(t) \tag{A.3}$$

where $W_{j,n}(t)$ denotes the efficacy of the postsynaptic mechanism n, at site j. This is the general formulation of the dynamic synapse found in Liaw and Berger (1999); the time constants $\tau_?$, the weights for the presynaptic activities $K_{i,m}$, the weights for the postsynaptic activities $W_{j,n}$, and the function $G_{j,n}$ are not defined in this article.

In earlier articles by Liaw and Berger (1997, 1998), the constants and functions are defined for a less general model.[2] The simple model by Liaw and Berger (1997) has only one presynaptic terminal with four different mechanisms. One very fast representing the action potential R, two facilitating F_1, F_2 and one feedback mechanism Mod. Mod represents a negative feedback from the postsynaptic neuron.

The presynaptic side of this synapse is

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{-R + \delta(t - t_{sp})}{\tau_R} \tag{A.4a}$$

$$\frac{\mathrm{d}F_1}{\mathrm{d}t} = \frac{-F_1 + \delta(t - t_{sp})}{\tau_{F1}} \tag{A.4b}$$

$$\frac{\mathrm{d}F_2}{\mathrm{d}t} = \frac{-F_2 + \delta(t - t_{sp})}{\tau_{F2}} \tag{A.4c}$$

$$\frac{\mathrm{d}Mod}{\mathrm{d}t} = \frac{-Mod + \delta(t - t_{sp,post})}{\tau_{Mod}} \tag{A.4d}$$

$$\frac{\mathrm{d}N^{total}}{\mathrm{d}t} = \frac{N^{max} - N^{total}}{\tau_{rp}} - Q_i \cdot \mathcal{H}(Pr - \Theta)\delta(t - t_{sp}) \tag{A.4e}$$

$$Pr(t) = K_R R + K_{F1} F1 + K_{F2} F2 + K_{Mod} Mod \tag{A.4f}$$

[1] In Liaw and Berger (1999) it is mentioned that $G_{j,n}$ typically has the form of equation (A.1a).

[2] In these articles, however, an inconsistency appears, one of the equations is formulated as a difference equation rather than a differential equation, leading to some trouble with the integration.

The activity in the cleft and on the postsynaptic side is

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \frac{-N}{\tau_{Nt}} + Q_i \cdot \mathcal{H}(Pr - \Theta)\delta(t - t_{sp}) \quad \text{(A.5a)}$$

$$\frac{\mathrm{d}EPSP}{\mathrm{d}t} = \frac{-EPSP + K_{epsp}N}{\tau_v} \quad , \quad \text{(A.5b)}$$

where τ_v is the membrane time constant. Parameter values can be seen in table A.1.

Liaw and Berger have also proposed a way to modify the synapses, a learning rule based on correlations between presynaptic and postsynaptic activation. The coefficients on the presynaptic side of the synapse $K_{i,m}$ (equation (A.1b)) are modified when a postsynaptic action potential (Ap) occurs

$$\Delta K_{i,m} = \alpha_m L_{m,i} Ap \quad , \quad \text{(A.6)}$$

where α_m is the learning rate for the particular mechanism and $L_{m,i}$ is the activation level for mechanism m in synapse i. It is a little vague what exactly is meant by »*the activation level of m in synapse i*« since no further description is given and, to our knowledge, no more recent articles comment on the matter. A guess is that it is $F_{m,i}$ in equation (A.1a) since this represents how much the m^{th} mechanism is active at the time of the postsynaptic action potential.

Results from using learning dynamic synapses in »*learning in robust speech recognition*« are reported in Liaw and Berger (1997, 1999).

To sum up, the model of Liaw and Berger uses sums of exponential functions to model both the pre- and postsynaptic side of the synapse. By introducing the Dynamic Synapse, a very general model is presented which seems capable of approximating any physiological effect. With little biological argumentation a learning rule modifying the presynaptic coefficients is introduced. Judging from the sparse data published, the learning rule is efficient. The model is used in a commercial application for speech recognition, perhaps explaining the scarcity of published results.

A.2 Maass & Zador

As Liaw and Berger, Maass and Zador (1999) present a phenomenological model using exponentially decaying function to capture release dynamics. On the basis of experiments revealing the dynamics of single release sites, a discrete stochastic model is presented and analyzed. As described in section 4.2.2, Maass (1996, 1997b); Maass and Sontag (2000) have provided theoretical results regarding the computational power of dynamic synapses.

Parameter	Value	Unit
τ_R	0.5	ms
τ_{F1}	66.7	ms
τ_{F2}	300	ms
τ_{Mod}	10	ms
τ_{Nt}	1.0	ms
τ_{rp}	3.33	ms
τ_{epsp}	5.0	ms
K_R	10	–
K_{F1}	0.16	–
K_{F2}	80	–
K_{Mod}	-20	–
K_{epsp}	0.5	–
N^{max}	3.2	–
Θ	1.0	–
Q	1.0	–

Table A.1 Parameters used in the Liaw and Berger Synapse.

The model concentrates on capturing the release dynamics, and thus has no postsynaptic side. In fact, it provides a mapping $S(\mathbf{t})$ from a time series of presynaptic spikes $(\mathbf{t}|t_i \in \mathbb{R}, t_1 < t_2 < \ldots)$ to a pattern of release events $(\mathbf{q}|q_i \in \{R, F\})$. Meaning that the synapse maps every input spike into a release event which is characterized by either Release (R) or Failure of release (F). *One* release event, q_i, is associated with every input spike, t_i. The probability of release at time t is

$$p(t) = 1 - \exp^{-C(t)V(t)} \tag{A.7a}$$

$$C(t) = C_0 + \sum_{t_i<t} c(t - t_i) \tag{A.7b}$$

$$V(t) = \max(0, V_0 - \sum_{t_i|t_i<t \ \wedge \ q_i=R} v(t - t_i)) \tag{A.7c}$$

$C(t)$ is the facilitating term, whenever a spike arrives the probability of release is increased. The $V(t)$ is a depressing term, whenever a vesicle is released the probability of release is decreased. The functions $c(t)$ and $v(t)$ are exponentially decaying with different scaling and time constants. In figure A.1, the effects of the facilitating and depressing synapses can be seen. The reaction of this model is similar to the presynaptic part of the model by Liaw and Berger.[3]

[3]Although Maass and Zador present a less general model, they account more thoroughly for the parameters and extensive theoretical results that are provided.

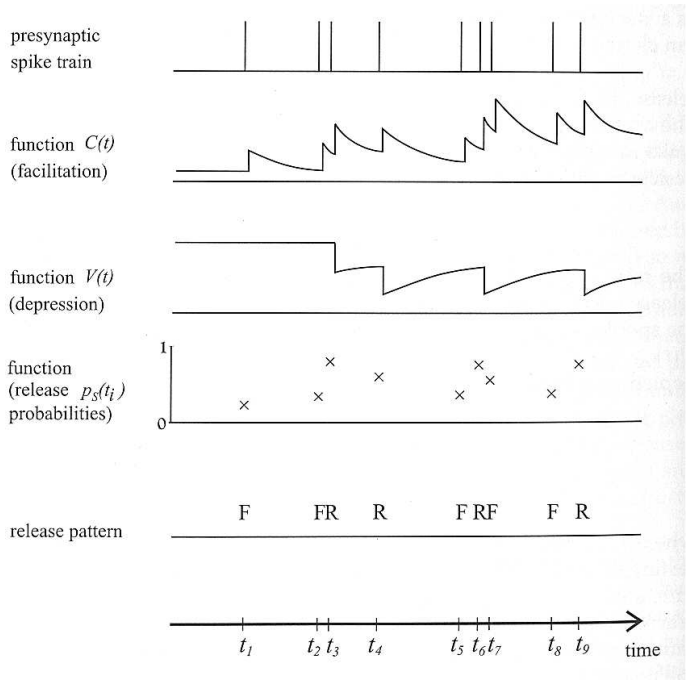


Figure A.1 figure from (Maass and Zador, 1999, p.906)

Parameter	Value	Unit
k_b	10^5	$s^{-1}mM^{-4}$
k_u	100	s^{-1}
k_1	10^6	$s^{-1}mM^{-1}$
k_2	100	s^{-1}
k_3	4000	s^{-1}
k_c	10^4	s^{-1}
X^{max}	0.001	mM
n	100000	–

Table A.2 Parameters used in the presynaptic part of the Destexhe, Mainen and Sejnowski Synapse.

Parameter	Value	Unit
R_b	$13E6$	M^-1s^{-1}
R_{u1}	5.9	s^{-1}
R_{u2}	$8.6E4$	s^{-1}
R_d	900	s^{-1}
R_r	64	s^{-1}
R_o	$2.7E3$	s^{-1}
R_c	200	s^{-1}
g_{AMPA}	0.35 - 1	nS
E_{AMPA}	0	mV

Table A.3 Parameters used in the full model of AMPA receptors.

By varying the parameters C_0 and V_0, it is possible to obtain any desired release probability for two consecutive spikes, yielding great possibilities for using this kind of synapse as a filter.[4]

A.3 Destexhe, Mainen and Sejnowski

The parameter values of the different parts of the Destexhe et al. (1998) model, treated in section 6.2.1 on page 68.

$$B(V) = \frac{1}{1 + \exp(-0.062V)[\mathrm{Mg}^{2+}]/3.57} \tag{A.8}$$

[4]Which is exactly what Maass and Zador wish, see section 4.2.2.

Parameter	Value	Unit
α	$1.1E6$	$s^{-1}M^{-1}$
β	190	s^{-1}
g_{AMPA}	0.35 - 1	nS
E_{AMPA}	0	mV

Table A.4 Parameters used in the reduced model of AMPA receptors.

Parameter	Value	Unit
α	$7.2E4$	$s^{-1}M^{-1}$
β	6.6	s^{-1}
$\left[\mathrm{Mg}^{2+}\right]$	1-2	mM
E_{NMDA}	0	mV

Table A.5 Parameters used in the model of NMDA receptors.

B ANN Timeline

A brief run-through of some of the early findings in the field of Artificial Neural Network theory. For further reading refer to e.g. Hertz et al. (1991), Bishop (1995), Cybenko (1996) or Jain et al. (1996).

1943 McCulloch and Pitts. Binary output from a threshold model of a single neuron, linearly combining real scalar inputs. The Heaviside step function $\mathcal{H}$ were used as the particular choice of activation function together with a threshold: $\mathcal{H}\left(\sum_i w_i x_i - \theta\right)$. They proved that an assembly of these units are able to perform universal computation.

1960's Rosenblatt. Introduced the perceptron, a network of threshold units. As long as a monotonic activation function is used, separation can only happen for linearly separable patterns. However, such patterns justify the perceptron convergence theorem: A perceptron learning procedure converges after a finite number of iterations.

1960's Widrow and Hoff. Developed the ADAptive LInear Element (ADALINE) an analogue electronic device. Resembling the perceptron although the learning method was different.

1960's Minsky and Papert. Establishment of the limitations of a simple perceptron; dampened the enthusiasm for almost 20 years.

1965 Zadeh. Fuzzy sets. Modeling systems where descriptions of the involved processes are vague and encumbered with uncertainty. By the means of proper sets of rules and membership functions, fuzzy inference deals with obtaining knowledge or data based on these vague descriptions. It is only the human interpretation of the problem that is fuzzy; the mathematics used to solve the fuzzy problem are precise and 'non-fuzzy'.

1968 Kohonen. Self-organizing feature map (SOM). A grid imposes an initial topological structure defining neighborhoods. Cycling through the data, the grid value 'closest' to the data point is perturbed in direction of the data. Finally the neighborhood structure of the grid imposes a clustered

structure with particular grid points emerging as representatives for the various clusters.

1974 Werbos. Developed the back-propagation learning method, but it was not widely used until several years later (see 1986).

1980's Grossberg and Carpenter. Adaptive resonance theory (ART). Another approach to self-organization and clustering. Data are cycled through repeatedly and assigned to the closest representative. Too large a distance leads to the creation of a new representative. Balancing the tradeoff between assigning to existing representatives or generation of new ones can be controlled be a so-called vigilance parameter (effectively a threshold).

1982 Hopfield. Introduced an associative network able to store memories or patterns in a manner allowing for the full pattern to be recovered, even though only partial information is given as input.

1986 Rummelhart, Hinton, and Williams. Popularization of the back-propagation learning algorithm first proposed by Werbos. Back-propagation networks are so called because they distribute pattern recognition errors 'back' through the network. A very widely used type of networks.

C Extra figures

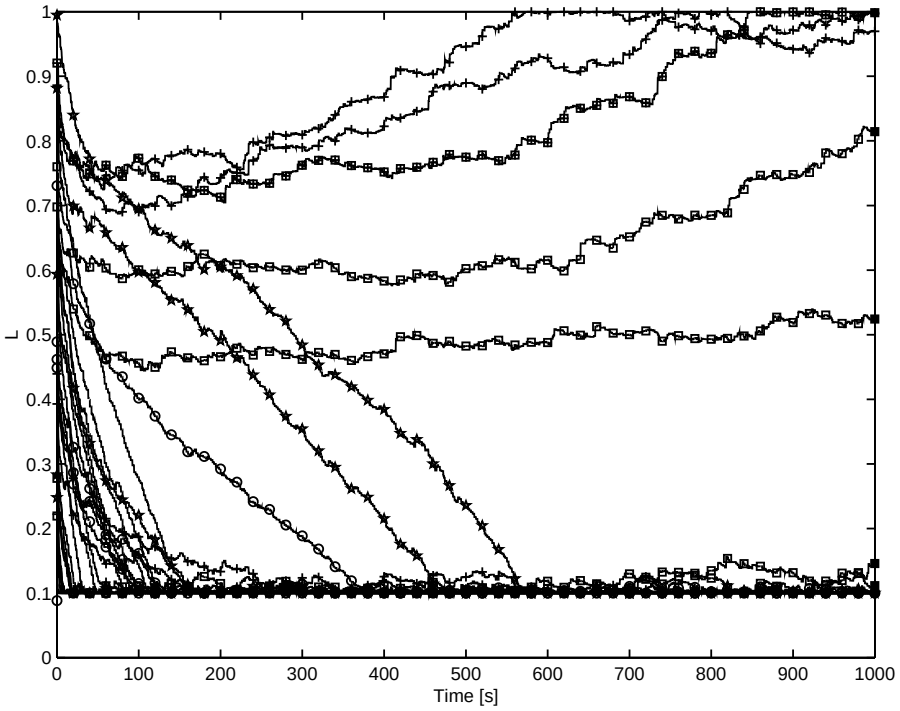


Figure C.1 Supporting the presentation given in section 7.2.2, comparable with figure 7.12. All forty synapses receive the same noise signal as in figure 7.8. Furthermore 20 synapses receive extra input as illustrated in figure 7.10. Every other second, four groups of five synapses are stimulated with a single spike. The extra incoming spikes are distributed over 20 synapses. Synapses receiving extra input are tagged with a marker, the shape of the marker indicates the temporal order of the input.

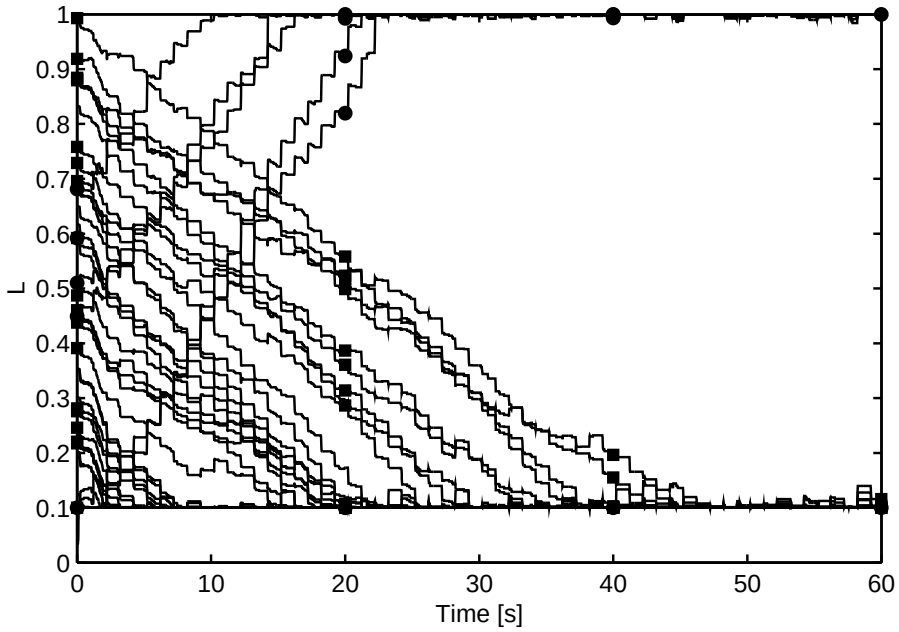


Figure C.2 Supporting the presentation given in section 7.2.2. Comparable with figure 7.12 and figure 7.13, as the stimulation pattern used in this figure was a combination of the ones used in those figures. Here, the synapse model received both distributed and burst signals. The two types of stimulation were separated by one second. All five 'burst-receiving' synapses win.

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