Synaptic Learning Rules with Consolidation

THÈSE N^{O} 6126 (2014)

PRÉSENTÉE LE 10 AVRIL 2014

À LA FACULTÉ INFORMATIQUE ET COMMUNICATIONS
LABORATOIRE DE CALCUL NEUROMIMÉTIQUE (IC/SV)
PROGRAMME DOCTORAL EN NEUROSCIENCES

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

POUR L'OBTENTION DU GRADE DE DOCTEUR ÈS SCIENCES

PAR

Lorric ZIEGLER

acceptée sur proposition du jury:

Prof. C. Sandi, présidente du jury
Prof. W. Gerstner, directeur de thèse
Prof. A. Ijspeert, rapporteur
Prof. W. Senn, rapporteur
Prof. M. Van Rossum, rapporteur

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Suisse
2014

En réalité nous sommes tous morts !
Mais c'est camouflé par la vie ! . . .
— Jean-Luc Coudray

ACKNOWLEDGEMENTS

I wish to thank all the lab members who shared parts of their lives and experiences with me at the LCN. A special thanks goes to Friedemann who, albeit a constant grumpiness, was always here to listen to my neverending questioning, especially on nerdy technical matters. I should also acknowledge all my colleagues for offering an escape door to pure work related environment.
All of this of course would not have been possible without the precious help of my adviser Wulfram Gerstner, who always found time and perspicacity to give insightful advices when I needed to see him.

Most importantly I thank my parents Michèle and Marco for giving me life. My two brothers Mathieu and Benoît were always a source of inspiration to me but have also become the closest to real friends one could have become to me. I would also like to thank all my friends (the list would probably be too long, but people belonging in it would know) for making my life what it is and helping me cope with some lengthy periods of my PhD experience.

Lausanne, le 20 mars 2014 L. Z.

ABSTRACT

How do we remember the past ? By what means can we make sense of our environment and store its most relevant aspects ? Learning and memory is very important for the existence of complex behaviours in living animals since it is what enables the creation of an internal model of the world in order to take the best possible decisions.

The theory of *synaptic tagging and capture* (STC) represents a possible implementation of learning and memory at the level of cellular neurobiology. This framework proposes that memory engrams be first *encoded* in the synapses of relevant brain networks, *tagged* for future maintenance, and finally *consolidated* after their pertinence has been assessed by other brain networks. These processes are highly dependent on neuromodulation of synaptic plasticity, a phenomenon that originates from higher level cognitive concepts such as attention or emotions.

But the hypothesis that STC is indeed underlying learning and memory remains to be evaluated. I use theory and simulations to do so in a behavioural experimental paradigm. I first introduce synapse models that include internal variables representing the properties of the synaptic weight, the tag and the consolidation process. Along with these models I propose learning rules exhibiting metaplasticity that can account for experimental findings. Finally I assess the consequences of such learning rules on memory traces in neural networks.

I find that increasing the number of internal variables is necessary for the implementation of several metaplasticity phenomena observed experimentally. I also show that synaptic plasticity together with tagging and capture could be an explanation to behavioural observations on live rats undergoing inhibitory avoidance training, thereby refining the link between cellular mechanisms and behaviour.

Keywords Synaptic plasticity, metaplasticity, neuromodulation, dopamine, tagging, consolidation, behavioural tagging, memory

RÉSUMÉ

Comment nous rappelons-nous notre passé ? Par quels biais sommes-nous capables de donner un sens à notre environnement et d'enregistrer ses caractéristiques pertinentes ? L'apprentissage et la mémoire sont deux aspects importants pour l'existence de comportements complexes chez les animaux vivants car ils rendent possible la création d'un modèle interne du monde afin de prendre les meilleures décisions possible.

La théorie de l'étiquetage synaptique et de la capture (*synaptic tagging and capture* ou STC en anglais) représente une possible implémentation de l'apprentissage et de la mémoire au niveau de la neurobiologie cellulaire. Ce cadre théorique suggère que les engrammes mémoriels soient tout d'abord *encodés* dans les synapses de réseaux neuronaux adéquats dans le cerveau, *étiquetés* pour un futur maintien, et finalement *consolidés* après que sa pertinence a pu être jugée par un autre réseau de neurones. Ces processus dépendent de la neuromodulation de la plasticité synaptique, un phénomène qui prend racine dans des concepts cognitifs de plus haut niveau tels que l'attention ou les émotions.

Cependant, l'hypothèse de la théorie du STC comme étant effectivement à la base de l'apprentissage et de la mémoire reste encore à être évaluée. Pour ce faire, j'utilise de la théorie et des simulations dans le cadre d'un paradigme expérimental comportemental. J'introduis tout d'abord des modèles de synapse qui incluent des variables internes représentant les propriétés que sont le poids synaptique, l'étiquette et le processus de consolidation. En addition, je propose des règles d'apprentissage qui montrent de la métaplasticité et qui sont capables d'expliquer certains résultats expérimentaux. Enfin, j'évalue les conséquences de telles règles d'apprentissage sur la mémoire dans les réseaux neuronaux.

J'arrive à la conclusion que l'augmentation du nombre de variables internes est nécessaire à l'implémentation de plusieurs phénomènes dans le domaine de la métaplasticité observés expérimentalement. Je montre également que la plasticité synaptique de concert avec l'étiquetage et la capture peut former une explication aux observations comportementales sur des rats sujets à une expérience d'évitement inhibitoire (en anglais *inhibitory avoidance task*), affinant ainsi le lien entre les mécanismes cellulaires et le comportement.

Mots clefs Plasticité synaptique, métaplasticité, neuromodulation, dopamine, tagging, consolidation, tagging comportemental, mémoire

Contents

List of Figures

List of Tables

1 INTRODUCTION

> One has to know the size of one's stomach.
>
> — FRIEDRICH NIETZSCHE

We are in the 6th century B.C. Apollo rules on Delphi and the Oracle, which radiates its teachings throughout the whole Greek empire. "Know thyself !", the principal aphorism of the Delphic maxims, resonates in all minds, revealing what should be the aim of anyone's inquiries about reality.

Since these ancient times, the understanding of our minds has always been an essential enigma to the great philosophers — from Socrates to Descartes and to Freud. This self-awareness is what defines us as human beings. But how would we exhibit metacognition without our ability to acquire knowledge about the world and to store it? Gabriel García Márquez in his novel "*One hundred years of solitude*" tells us about a mysterious plague erasing all sense of memory. His protagonist resolves to label all objects in his house, temporarily putting a halt to the effects of the disease. But he soon finds himself forgetting the meaning of these labels, rendering his life hopeless.

This metaphor exposes the extent to which our self is predicated on memory and learning. Without our ability to learn about the world and memorize this information, we would forget our home, our language, the sad or happy moments of our existence, our motor skills and even our personal identity.

Thus, understanding memory is a key to elucidating our minds. Yet, how can one define memory? What are its intrinsic mechanisms? In the 6th century B.C., under the watch of the Greek goddess of memory Mnemosyne living alongside Apollo on Olympus, the poet Simonides invented the art of mnemonics, or method of *loci*. Loci is the plural of *locus*, the Greek word for place or location. This method consists in associating facts or names with the different rooms of a building, or the different places of a map, in order to better remember them. Cicero, the philosopher of the early 1st century B.C., was renowned as a great orator

who used the method of loci for his discourses. Referring to a tragic event where a roof fell on the guests of a banquet in which Simonides took part but survived and later remembered the places where all the guests were seated – constituting the origin of the invention of the method of loci – Cicero wrote in his *De oratore*

> He [Simonides] inferred that persons desiring to train this faculty (of memory) must select places and form mental images of the things they wish to remember and store those images in the places, so that the order of the places will preserve the order of the things, and the images of the things will denote the things themselves, and we shall employ the places and images respectively as a wax writing-tablet and the letters written on it.

This excerpt entails all core constituents of a modern theory of memory. Cicero starts by saying that persons must "form mental images", which denotes what we would refer to as the *encoding* of memory. This is the process by which we receive and combine information about the external world. He then goes on with the words "store those images", which reflects the creation of a permanent record of the encoded information, called the *storage* of memory. Finally these persons "shall employ the places and images", constituting the final phase of *retrieval* where one has to recall the stored information.

In addition, there exists the notion of *associativity*, which refers to the process whereby things are to be stored in "places" and to the fact that "the images of the things will denote the things themselves". We will see that this concept plays a very important role in the study of memory and of its underlying processes. Finally, the fact the method of loci was inspired by a tragic event will also transpire to be significant in the sense that strong emotions can help memorize unrelated coinciding events.

Nowadays, much and more is known about the fundamental principles forming the basis of learning and memory. We know, for instance, that it takes place in the brain in dedicated subsystems formed by densely interconnected neurons. However, it remains unclear what are the details of the implementation of learning and memory in the brain. Neither is it known whether we humans are able to fully understand this idea and replicate it on an arbitrary substrate. [1]

The aim of this thesis is to give a tentative explanation of the foundations of memory or behaviour by means of *computational neuroscience*. I aim to construct a bridge from cellular mechanisms taking place at the level of the brain, to the behaviour of rodents involving memory. I do this using mathematical models of these phenomena while also relying on computer simulations of these models.

In this chapter I introduce the concepts, both neurobiological and theoretical, required for the comprehension of the main results of this thesis. For the reader interested in more in-depth

1. But maybe it should stay in the hands of the Greek gods like Apollo and Mnemosyne...

descriptions, a number of highly recommended textbooks are available in the domain of neuroscience (Kandel et al., 2000), and computational neuroscience (Dayan and Abbott, 2001; Gerstner and Kistler, 2002; Izhikevich, 2006). The site www.scholarpedia.org constitutes also a very comprehensive source of information.

1.1 General concepts

I start by introducing the concept of behaviour, the motivation of this work, on a broad perspective. I then turn to the two closely related notions of learning and memory since they constitute the key to behaviour instantiation. Finally I give an overview of the field of computational neuroscience, representing the tool of investigation of this thesis.

1.1.1 Behaviour

In this work, I focus on unconscious phenomena such as emotions or homeostasis, which constitute a substantial part of animal behaviour (Kandel et al., 2000). One drive of unconscious behaviour is homeostasis, i.e. the need to maintain essential physiological variables within a certain range in order to sustain life, for example body temperature or nutrient availability. The motivational states that lead to such behaviours depend both on internal input, the difference between the current physiological state of the animal and the target value it needs to achieve, and external input in the form of incentive stimuli. Going to a cafeteria to buy a coffee or a tea and getting a chocolate cake instead (supposedly because the sugar concentration level in the blood was too low) is an example of being affected by an incentive stimulus (the cake).

Unlike Pavlov's view of behaviour as a complex chain of associations between stimuli and responses (Pavlov, 1927), a current theory of goal directed behaviour states that an animal needs to create a model of the world and to maximize the outcome of external rewarding signals (or to minimize the difference between internal variables and the representation of this signal) (Dickinson and Balleine, 1994-03-01; Robbins and Everitt, 1996). This maximization process would not be possible without the capacity to learn, encode and store new associations between internal states or actions and the reward that followed.

1.1.2 Learning and memory

Kandel et al. (2000) define learning as being a "change in behaviour that results from acquiring knowledge about the world", and memory as the "process by which that knowledge is encoded, stored and later retrieved". But where do these processes take place? The first person to give the beginning of an answer to this question was Pierre Paul Broca, a french physician who realized after a postmortem autopsy in 1861 on a patient who, during his lifetime was able to comprehend language but was unable to speak, that the patient had a lesion in the frontal lobe region of the left hemisphere of the brain. Following that discovery, the theory that brain

functions are localized started to convince scientists and spread to the field of memory.

Thus, different types of memory are localized in different brain regions. Two aspects classify the different memory types, (i) the time course of storage and (ii) the nature of the stored information. Concerning the time scales we distinguish *working memory* from *short-term memory* (STM) and *long-term memory* (LTM). Working memory ranges from milliseconds to minutes and obeys somewhat different rules than the two other forms (Miller et al., 1986). STM however, can last up to days and LTM for months or even a lifetime. Since working memory is outside the scope of this thesis, I will directly proceed to the description of short and long term memories.

STM consists of transient representations serving immediate goals. In order to be remembered for an extended time, such a memory has to undergo a consolidation process. Both these processes, encoding and consolidation, were found to take place in the hippocampal region of the medial temporal lobe. This was first discovered by the psychologist Brenda Milner and the surgeon William Scoville who performed a study on epileptic and schizophrenic patients (Scoville and Milner, 1957) who suffered a segmentectomy in the medial temporal lobe. They observed that these patients could remember things like phone numbers for a certain period but were unable to recall day-to-day facts such as their way to the bathroom or the identities of the nursing staff. They concluded that the hippocampal region of the human brain must have an essential function in the transfer of STM into LTM. Further studies have confirmed this hypothesis (Marr, 1970; McClelland et al., 1995; O'Keefe and Burgess, 1996).

Note that there exists different types of memories, mainly separated into two groups, declarative and procedural memories (Dudai, 1989). Declarative memories have a very large range of association between multiple pieces of information. They encompass an important subgroup, the so-called episodic memories which represent personal experiences or facts often associated to a specific context (Tulving and Markowitsch, 1998). Procedural memories on the other hand, are related to skill learning, habit or conditioning.

Fear learning, famously discovered by Pavlov in 1927 (Pavlov, 1927) [2], was one of the first paradigms used to study the way procedural memories are learned. Following studies showed the implication of the amygdala for fear memory (Davis, 1992; Fanselow and LeDoux, 1999). This region of the brain associates information about unconscious fear responses (the emotional state) and about its cognitive processing (the feelings).

1.1.3 General anatomy

At this point we know that behaviour in mammals is related to maintaining certain physiological variables as close as possible to a objective value in order to sustain life. We also know that this cannot occur without learning and memory which take place in specific and functionally defined regions of the brain. The question remains of the actual implementation of these

2. It was actually co-discovered by Freud.

phenomena. Therefore I now introduce basic anatomy, required for the understanding of memory and behaviour.

The brain is composed, among many other constituents, of a large quantity of densely interconnected cells called *neurons* (Kandel et al., 2000). Those communicate to each other via chemical or electrical *synapses*, which are the connections between neurons. A difference between internal and external concentration of charged ions (mainly Sodium, Chloride and Calcium) is maintained in the cell. This gives rise to a *membrane potential* due to a tight balance induced by ion pumps and ion channels. This function is well described by a simple RC circuit as long as the potential remains under a spiking threshold, where highly non linear dynamics intervenes (Hodgkin, 1948).

Communication between neurons occurs via the mechanism described above; through the propagation of short pulses of membrane potential along the axon of the sender neuron connecting to the dendrites of the receiver. A pulse or *action potential*, triggers the release of neurotransmitters which bind to receptors on the receiver side of the synapse (the *postsynaptic site*), which in turn let different ions in or out of the cell, thereby altering the membrane potential. A cell has only one type of neurotransmitter that can have either a positive or a negative effect on the postsynaptic potential. The main neurotransmitters are glutamate, which upon binding to its associated receptor lets Ca^{2+} enter the cell, or gamma-aminobutyric acid (GABA) triggering an inflow of Cl^{-}.

The strength of these synapses is not constant in time. A change in presynaptic release of neurotransmitter or in the amount of postsynaptic receptors for example can enhance or diminish the efficacy of a synapse. Detailed descriptions can be found in (Lisman and Zhabotinsky, 2001; Rubin et al., 2005) This phenomenon is called *synaptic plasticity* and is thought to be crucial for learning and memory. Several experimental studies show a clear link between these two aspects, and this thesis will, I hope, play one's part in the refinement of this link.

First connections were established by pharmacologically blocking plasticity and realizing that it impaired learning in rats (Abraham and Mason, 1988; Morris et al., 1982). The same was shown for memory (Pastalkova et al., 2006; Steele and Morris, 1999). Moreover the transposed logical implication was also shown in the sense that learning was proved to actually trigger plastic changes in the brain of living animals (Rogan et al., 1997; Sigurdsson et al., 2007; Whitlock et al., 2006).

1.1.4 Computational neuroscience

Now that I have introduced the main biological concepts necessary to an understanding of this work, I turn to its core, namely computational neuroscience.

Computational neuroscience consists in creating mathematical models of the brain, its neurons, their connections and assemblies of these neurons. These models can be both analyzed analytically and simulated via computer programs. A beautiful article by Abbott (2008) exposes

the ways theoretical models can have a beneficial impact on the field of neuroscience. He argues that models are intrinsically precise and self-consistent so that all their implications can be derived. They help getting a clearer view of the biological phenomena and diffusing ideas that are clear enough to be analyzed and understood. And this process doesn't necessarily has to be pioneering research but can also come after the explained mechanism has been discovered. Abbott writes

> Many of the most celebrated moments in quantitative science – the gravitational basis of the shape of planetary orbits, the quantum basis of the spectrum of the hydrogen atom, and the relativistic origin of the precession of the orbit of Mercury – involved postdictions of known and well-characterized phenomena.

The main focus of computational neuroscience is how neurons integrate information and communicate with each other. Very good textbooks on the subject are available (Dayan and Abbott, 2001; Gerstner and Kistler, 2002; Izhikevich, 2006). The way the connections between neurons change according to neuronal activity and how this affects information transmission is also a widely analyzed topic.

Another important research subject is how connecting a large amount of modeled neurons, their connections obeying models of synaptic plasticity, affects neural network dynamics (Vogels et al., 2005). A more thorough description can be found in Section 1.3.

1.2 Neurobiological basis of synaptic plasticity

So far I explained that neurons and the change in their connections efficacy are crucial to learning and memory and hence to behaviour. Thus, in this section, I want to focus on the neurobiological basis of synaptic plasticity. I first give a short historical introduction and move to the different forms of plasticity, including some theoretical work that was biophysically inspired. I also introduce the concept of *metaplasticity* which will turn out to be essential for goal oriented learning and for memory.

1.2.1 History of synaptic plasticity

One of the founders of modern neuroscience is the Spanish histologist Santiago Ramón y Cajal, who conducted pioneering investigations on the delicate arborizations of brain cells. He inferred that, in the absence of postnatal neurogenesis, learning must happen through modifications of the connections between neurons (Ramòn y Cajal, 1909). This was the first time the idea that synaptic plasticity might underlie learning and memory was articulated. A refinement of the concept came later with the Canadian psychologist Donald O. Hebb who wrote in his book (Hebb, 1949) the now famous sentence

> When an axon of cell A [...] excites cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased.

This contains three important notions, that of *causality*, in order to induce any change firing of A must precede firing of B; the notion of *associativity*, the activity of the two cells must be co-occurring within a certain time window; and finally these changes only depend on *local* variables, such as the activity of A and B.

Hebb's postulate was later confirmed by Bliss and Lomo (1973) (see also Bliss and Gardner-Medwin (1973)). They looked at connection strengths of neurons in the hippocampal region of rabbit brains and measured changes depending on the stimulation they applied. This phenomenon was called *long-term potentiation* (LTP).[3] Along with this discovery, it was suggested that an inverse mechanism must exist to avoid a runaway in the strengths of synaptic connections (Stent, 1973). This was confirmed a few years later by Lynch et al. (1977) in a phenomenon named *long-term depression* (LTD).

The first ways to interpret the hebbian concept were using neurons as rate units, where a high presynaptic rate occurring at the same time as a high postsynaptic rate leads to an increase in the connection strength. But eminent scientists wondered about the utility of the action potentials giving rise to these rates. Are they only an epiphenomenon due to energy efficiency constraints? Or does their timing encode information? If the second idea revealed to be true this would lead to a dramatic increase in the dimensionality of information space and hence could be a key to solving the complexity of the brain.

Such a form of plasticity was first postulated (Gerstner et al., 1993, 1996) and then measured by electrophysiology (Bi and Poo, 1998; Markram et al., 1997). It was measured that a pair of pre- and postsynaptic spikes elicits a different change in synaptic efficacy depending on the time lag between the two. A 'pre-before-post' pair gives rise to potentiation if the time difference is under a certain limit and a 'post-before-pre' pair induces depression. The name *spike-timing dependent plasticity* (STDP) appeared in Song and Abbott (2001) and is since then widely accepted. For a review see Markram et al. (2011).

1.2.2 Short to intermediate time scales of plasticity

Synaptic plasticity exhibits phenomena spanning different time scales. The shortest form is *short-term plasticity* (STP), a type of plasticity whose time scale lies between that of fast neural signaling (on the order of milliseconds) and of experience-induced learning (on the order of minutes). It is presynaptically expressed by a change in neurotransmitter release (Gupta et al., 2000; Markram et al., 1998) and can be both facilitating or depressing. A model wins unanimous support (Abbott et al., 1997; Markram and Tsodyks, 1996).

Long-term potentiation and depression are extending over longer periods of time up to several hours.[4] Many different protocols are known to induce these sorts of plasticity, by varying

3. We will see that this had tragic consequences for nomenclature in the field of plasticity when phenomena lasting longer than long-term potentiation were observed...

4. I called those *intermediate* time scales, because we will see in Section 1.2.4 that even longer ones exist.

the presynaptic firing rate (Dudek and Bear, 1992; Kelso et al., 1986; O'Connor et al., 2005b); by spike timing pairings with different time lags (Magee and Johnston, 1997; Markram et al., 1997); by voltage clamp on the postsynaptic cell and stimulation of the presynaptic cell (Artola et al., 1990; Ling et al., 2002; Ngezahayo et al., 2000); by bursts, triplets or quadruplets of spikes (Froemke and Dan, 2002; Nevian and Sakmann, 2006; Wang et al., 2005); or by natural stimuli (Froemke and Dan, 2002).

On a molecular level, LTP and LTD occur mainly via chemical reaction cascades triggered by the calcium that entered the *postsynaptic density* (PSD) via N-methyl-D-aspartate (NMDA) receptors (Neveu and Zucker, 1996; Yang and Schulman, 1999). These include kinases and phosphatases (Lisman et al., 2002) and act mainly by inserting more α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the membrane of the PSD. Co-activation of AMPA and NMDA receptors is necessary (Herron et al., 1986). For a review on the matter see (Malenka and Nicoll, 1999).

There exists many biophysically inspired models of LTP and LTD which try to capture the details of biochemical signaling occurring in and around the synapses at the time of induction of plastic changes. Some model the postsynaptic voltage (Abarbanel et al., 2002); others calcium levels (Abarbanel et al., 2003; Cai et al., 2007; Karmarkar and Buonomano, 2002; Karmarkar et al., 2002; Rubin et al., 2005; Shouval et al., 2002); or finally AMPA (Saudargiene et al., 2003) or NMDA receptors (Senn et al., 2001).

Notably, a subgroup of models looking at calcium levels focus on the question of how can a synapse maintain an elevated efficacy for several hours despite the constant turnover of AMPARs being endocytosed to or exocytosed from the postsynaptic membrane. The idea that this could occur via bistability of certain molecules in the PSD was introduced by Crick (1984). This was later measured by minimal stimulation protocols, supposedly acting on single synapses (O'Connor et al. (2005a); Petersen et al. (1998); see also Bagal et al. (2005); Blitzer et al. (1998)). Synaptic bistability is shown to depend on feedback loops in the protein network (Bhalla and Iyengar, 1999; Hayer and Bhalla, 2005) or on a balance between auto- and dephosphorylation of chemical compounds (Lisman, 1985; Miller et al., 2005; Okamoto and Ichikawa, 2000; Zhabotinsky, 2000).

1.2.3 Metaplasticity

The mechanisms and models reviewed so far give a very good insight into a large panel of brain mechanisms such as early sensory streams or receptive field formation where neurons have to adapt to, process and encode the statistical properties of the external world being observed. However, when it comes to goal-oriented behaviours the restriction of the synaptic change inducing parameters to sole local variables such as presynaptic neurotransmitter release or postsynaptic ion concentration is not sufficient. The global homeostatic signal or the reward need to be available to the neurons *somehow*.

A way to incorporate these features into the framework of synaptic plasticity is via metaplasticity. This term (from the Greek preposition meta, "beyond" or "adjacent") can be rephrased as the 'plasticity of plasticity' (Abraham and Bear, 1996). For a review on metaplasticity see (Abraham, 2008). [5]

The first study on this matter consisted in letting rats self administrate stimuli targeting the hypothalamus in a so-called *intra-cranial self stimulation* paradigm (Olds and Milner, 1954). Rats were found to self stimulate up to sixty times per second, halting only out of exhaustion. This raised the question of what could be responsible for such a destructive behaviour.

It was later established that one of the key to this puzzle was dopamine (Yokel and Wise, 1975), a *neuromodulator* discovered in 1957 by a Swedish pharmacologist (Carlsson et al., 1957). Later, in the 90's, Schultz and colleagues thoroughly investigated this question and showed that dopamine encoded reward, or more precisely the deviation of the reward with respect to an internally encoded signal (Hollerman and Schultz, 1998). This resonates with the fact that behaviour is driven by a homeostatic signal, as I explained in Section 1.1.1.

Dopamine is known to interact with plasticity in at least two different ways, one consisting in a *gating* of plasticity and the other inducing a *consolidation* process. The first process is important in learning and the second one in memory, the main distinction between those two phenomena being that memory implies a following retrieval at later stages. As already stated, the focus in this thesis is on memory. However, since metaplasticity is a key feature when it comes to its modeling, I give a short overview of the gating of plasticity by dopamine.

Kerr and Wickens (2001) showed by pharmacologically blocking dopamine D1/D5 receptors in corticostriatal synapses [6] that dopamine was necessary for the induction of LTP in this brain region. More experiments were conducted and overall the results of rate-based simulations modulated by dopamine were confusing, since many factors seemed to influence the outcome of given stimuli. However Reynolds and Wickens (2002) suggested an interpretation, proposing that very low levels of dopamine do not enable any plasticity, intermediate levels causing LTD and higher levels LTP. It turned out that again spike timing was decisive in giving an explanation to the phenomena, with dopamine having modulatory effect at the level of the learning window (Pawlak and Kerr (2008); for a review see Pawlak et al. (2010)).

Note that dopamine is not the only known neuromodulator affecting learning in mammal brains. *Acetylcholine* has been shown to increase the threshold for STDP in prefrontal cortex by its action on nicotinic receptors (Couey et al., 2007). *Noradrenaline* on the other hand relaxes the time constraints of the pre-before-post pairings in the rat hippocampus (Lin et al., 2003). Another very complete study looked at spike timings and also at neuromodulators

5. Note that there is some confusion about the terminology (not surprising when one thinks about the complexity of this field and the way names and titles are to be invented in a chronological manner). Historically, metaplasticity referred to mechanisms *preceding* plasticity that would alter it. I myself use this term in a broader sense, as in the Greek definition, for *any* modification of plasticity, that is also post induction.

6. Corticostriatal synapses connect the cortex, an important source of encoded sensory information, to the striatum, a 'gateway' to the basal ganglia, involved in motor control and learning.

concentration, but the fact that two of those were present (in this case noradrenaline and acetylcholine) makes it hard to build precise links between causes and effects (Seol et al., 2007). *Serotonine* is another major neuromodulator. [7] Note that acetylcholine and noradrenaline mainly interact with plasticity by preceding the synaptic changes, hence they are mainly related to higher level processes like attention or arousal.

The mechanisms underlying metaplasticity are mainly acting indirectly on the postsynaptic potential via second messengers (Kandel et al., 2000). Two types of receptors can be distinguished in synapses, ionotropic receptors like AMPA and NMDA, and metabotropic receptors. The later, when activated by neuromodulators, induce chemical reactions eventually acting on ionotropic receptors, or control transcription factors that in turn control mRNA synthesis. Examples of molecules involved are the kinases PKA, PKC or MAPK which can phosphorylate CREB, one of those transcription factors (Malenka and Bear, 2004). These processes which involve complex transduction cascades are intrinsically slow and can last for extended periods of time. Which makes them good candidates as the mechanisms constituting a neurological basis to memory.

1.2.4 Late stages of plasticity

The duration of plasticity effects described so far ranged from milliseconds in STP to hours or days for LTP or LTD. But by what means can we humans, or other mammals, remember facts or events for months or years? How, after its encoding, is information stored and later retrieved? The answer to these questions lies in consolidation mechanisms, which I introduce here.

A major theory accounting for such phenomena is that of *synaptic tagging and capture* (STC), proposed by Frey and Morris in 1997. This theory suggests that, along with the initial expression of plasticity, a synaptic *tag* is set that serves as a marker for potential further consolidation of the changes in synaptic efficacy. There exist very good reviews on the subject, one by Reymann and Frey (2007) gives insights on the temporal phases of STC and on the mechanisms involved. Another by Lisman et al. (2011) focuses on dopamine interactions. Lisman suggested to call this framework 'neo Hebbian' due to the importance of other factors than just pre- and postsynaptic firing activities. Finally the review by Redondo and Morris (2011) analyzes the experimental findings and the molecular basis on a functional perspective. [8]

The phases of the process leading a synapse from a basal strength to a stronger one can be summarized in this way, (*i*) STP a decremental form of LTP dependent on NMDA activation and on Ca^{2+} and calmodulin, (*ii*) LTP1 dependent on *metabotropic glutamate receptors* (mGluR) and phosphorylation of PKC and CaMKII (two kinases), also decaying without additional

7. Coffee lovers will be glad to learn that a very recent study showed an enhancement effect of caffeine on human memory (Borota et al., 2014). Careful though! Past a certain threshold, too much caffeine has a detrimental effect.

8. I gave here an example of a 'metareview'.

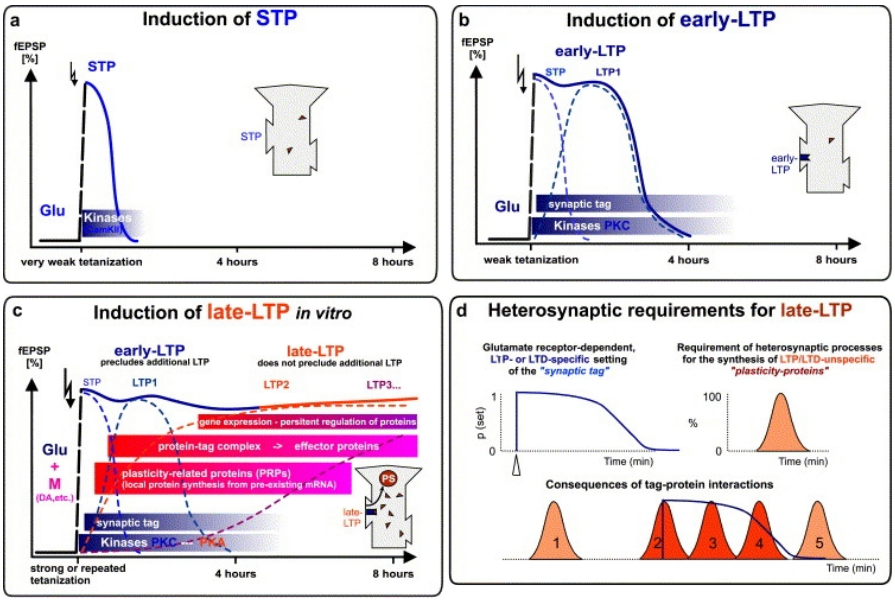


Figure 1.1 – **Schematic illustration of the phases of LTP**. (**a**) STP is a decremental form of LTP dependent on NMDA activation and on Ca^{2+} and calmodulin (**b**) LTP1 depends on mGluR and phosphorylation of PKC and CaMKII (two kinases), and also decays without additional mechanisms (**c**) LTP2 depends on the capture of proteins, this phase is stable for much longer times (past three hours) (**d**) LTP3 depends on gene transcription and mRNA synthesis (Figure taken from (Reymann and Frey, 2007)).

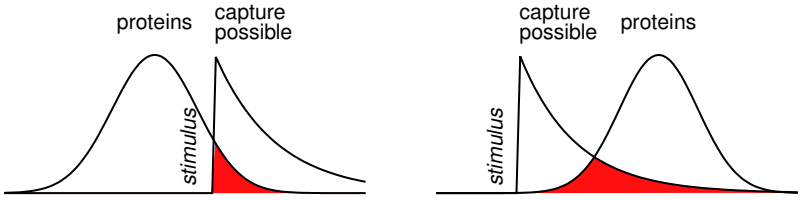
mechanisms, (*iii*) LTP2 dependent on the capture of proteins, this phase is stable for much longer times (past three hours), (*iv*) LTP3 dependent on gene transcription (Reymann and Frey, 2007). See Figure 1.1 for an illustration of the different phases and their requirements. The first two phases together constitute the phase of *early* LTP (e-LTP) and the other two *late* LTP (l-LTP). To be consistent throughout this work, I will not use the terminology LTP1/2/3 but will keep STP or LTP, and specify the phase explicitly.

Let me now give some more details about the biochemical implementation of the different phases. Induction of LTP, as already stated in Section 1.2.2 depends on NMDA activation which, if not completed by activation of other metabotropic or aminergic receptors, decays within a few hours (Collingridge, 1985). Expression of LTP is mediated via AMPARs. It has been shown that AMPAR antagonists block synaptic weight increases (Davies et al., 1989). Studies using mGluR blockers on the other hand, showed that PKC, activated by mGluRs, is necessary for the second phase of LTP (Anwyl, 1999; Bashir et al., 1993). Finally late stages are mediated by a cAMP cascade which activates PKA, a reaction which is initiated only by threefold tetanization, one of the standard stimulation protocol, in hippocampal CA1 cells (Matthies and Reymann, 1993).

Note also that the functional effects described above are not the only consequences of plasticity-inducing stimuli. They occur alongside structural modifications, via cytoskeleton remodeling of the PSD (Redondo and Morris, 2011). These two mechanisms are independent

and occur in parallel.

The key to consolidation of early synaptic efficacy modifications are the *plasticity-related proteins* (PRP)s. Experiments where protein synthesis was blocked by anisomycin (a translation inhibitor) revealed that no LTP longer than three hours was possible (Krug et al., 1984). Since availability of these proteins is crucial for the transformation of e-LTP to l-LTP, there is a temporal window around the time of induction of plastic changes within which synthesis must occur. The extent of this temporal window is given by the protein half-life, on the order of one to two hours (Korz and Frey, 2004), on one side and the extent to which these proteins can be captured, around ninety minutes, on the other side



The synthesis of PRPs is triggered by phasic dopamine concentration increase (Lisman and Grace, 2005). This dopamine signal can have many different causes such as novelty, reward prediction error, aversive events or attention (Lisman et al., 2011). For the latest phases of LTP synthesis of mRNA through transcription is necessary (Nguyen et al., 1994). Redondo and Morris hence suggested that PRP should stand for plasticity related *products*, instead of proteins. Notably, production of PRP can occur in different compartments and is not necessarily spread throughout the whole neuron (Sajikumar et al., 2007). Different pathways are triggering synthesis in different compartments, or even cell-wide in the case of stress (Reymann and Frey, 2007), leading to different functional conclusions. One interpretation of such a finding is the theory of 'clustered plasticity engrams' (Govindarajan et al., 2006) where nearby synapses collaborate to form memory traces.

The second key aspect of the STC theory is the synaptic *tag*. This is what permits protein capture and implements synapse specificity amidst the larger spatial range of PRP availability (Frey and Morris, 1997). These tags represent somehow a hidden flag identifying what synapses would be eligible to further consolidation via capture of proteins. They are also the functional units actually enabling this mechanism. Involved in this process are the actin network (Ramachandran and Frey, 2009) and autophosphorylation of CaMKII (Redondo et al., 2010). The tags have been shown to have a limited lifetime of about ninety minutes (Frey and Morris, 1997). Direct action on the tags, either pharmacologically (Gribkoff and Ashe, 1984; Huang and Kandel, 1995; Navakkode et al., 2007) or via natural place cell replay (Isaac et al., 2009), can produce a slow onset LTP, where synaptic efficacy rises gradually in the time course of two to three hours.

It is important to note that the two mechanisms leading to consolidation of synaptic changes do not have to be triggered by the same stimulus. This allows for heterosynaptic effects where

a synapse that has been potentiated and tagged by an event can capture PRPs whose synthesis has been triggered by another event. [9] An illustration of this phenomenon can be found in Figure 1.2.

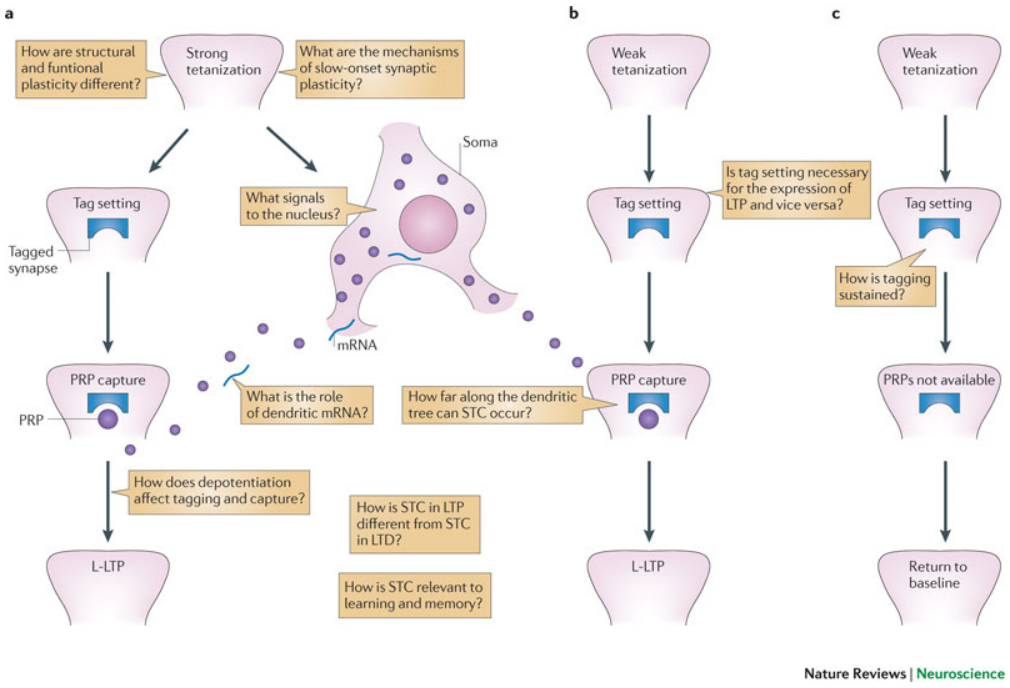


Figure 1.2 – **Illustration of the interaction between tag and PRPs.** Together with the initial expression of synaptic plasticity, a tag is set that serves as a marker for potential further consolidation of those changes. PRPs synthesis is triggered by neuromodulation and these proteins bind with the tag compound to maintain previous changes in synaptic strength. Hence synaptic specificity is only available through the tag, whereas the large spatial range of PRPs can lead to heterosynaptic effects (Figure taken from Redondo and Morris (2011)).

All phenomena I exposed so far were LTP-related phenomena. Same conclusions hold in the case of LTD, however with different signaling pathways (Kauderer and Kandel, 2000; Sajikumar and Frey, 2004b; Sajikumar et al., 2005). A very recent article by Li et al. (2014) gives more insights on the pathways involved and on priming of STP via ryanodine receptors activation.

For a summary of the main articles who were involved in the discovery or further refinement of the different functions and phenomena introduced in this section, see Table 3.3.

1.2.5 Behavioural tagging

In the preceding section I described a mechanism likely capable of implementing a memory storage function in the synaptic connections of hippocampal neurons. The question remains

9. This could be an explanation of the phenomenon of 'flashbulb memories', where very vivid memories of irrelevant contexts can be formed. A good example is the fact that many people remember where they were during the terrorist attack on New-York in 2011.

whether there exists any link between STC and memory in living animals? A potential answer to this question can be found in *Behavioural tagging*, a promising paradigm which I introduce here.

Before a link between STC and behaviour could be made, it was already shown that consolidation was necessary for memory. A study showed in 2006 that spatial memory in rats is mediated by PKMζ, an isoform of PKC involved in the consolidation process of LTP (Pastalkova et al., 2006). They injected ZIP, a PKMζ inhibitor, in the hippocampus of rats and observed retrograde amnesia, demonstrating that late forms of plasticity were necessary for LTM. The same was shown in a non aversive task by Serrano et al. (2008).

Later a group in Argentina conducted the first experiment of behavioural tagging per se (Moncada and Viola, 2007). The experimental paradigm was an *inhibitory avoidance* (IA) task taking place in a cage with an elevated platform. When the rats jumped from the platform they received an electrical foot shock eliciting a short term fear memory. The experimentalists then tested the rats for different times between training and the test session, by measuring the latencies from the moment the rats were put on the platform until they jumped down. They measured high latencies fifteen minutes after training, but these were slowly decreasing until being exactly the same as during training when measured twenty four hours later. Note that the time course of this phenomenon resembles decremental e-LTP measured in vitro (see Section 1.2.4).

Interestingly this decaying memory trace could be saved by giving a stronger foot shock at the time of encoding. Rats who received a strong electrical shock showed high latencies even one day after training. Since aversive stimuli can trigger dopamine release in the medial temporal lobe due to sustained firing of *ventral tegmental area* (VTA) neurons (Lisman et al., 2011), consolidation of previously potentiated synapses is a plausible explanation of how a stronger stimulus induces LTM whereas a weaker one only induces STM.

But there is more, letting the rats explore a novel environment, either before or after the training session, was able to rescue short into long term memory. Again compatible with the time window allowing for capture of heterosynaptically induced plasticity proteins by tagged synapses.

This is the experience I have modeled and simulated in order to show that STC can indeed be a plausible explanation of this phenomenon. Details of the implementation and results can be found in chapter 4.

Note that other paradigms have been used such as an object recognition task or a taste aversion task by the same group two years later (Ballarini et al., 2009), or in a task closer to our day-to-day experiences in a matching-to-place setup by the Morris group (Wang et al., 2010). It has since then also been shown in humans (Ballarini et al., 2013; Bunzeck et al., 2010; Fenker et al., 2008). [10]

10. Even if not totally related, I would like to point to a wonderful experiment where researchers were able

Finally a link between STC and STDP has also been established, however only in invertebrates (Cassenaer and Laurent, 2007, 2012).

1.3 Our tools: models of synaptic plasticity and memory

Having introduced the biological concepts necessary for the understanding of this thesis, and the putative neurological processes underlying them, I now go on with the tool I used to perform my investigations, i.e. mathematical models of those processes. I start with models of neurons which are the basic elements of neural dynamics, and continue with models of plasticity which constitute the core of the implementation of a learning or memory mechanism. I span the different time scales of plasticity, from STP to l-LTP. Finally I describe models looking at network dynamics and abstract models of memory.

Good textbooks for this part are (Dayan and Abbott, 2001; Gerstner and Kistler, 2002; Izhikevich, 2006).

1.3.1 Neuron models

Neurons are well described by small electrical devices following the dynamic of a standard RC circuit

$$\tau_m \frac{dV}{dt} = -V(t) + V_r + RI(t) \tag{1.1}$$

V represents the membrane potential of the cell which tends to relax to V_r its resting value, usually around -70 mV for the types of neurons found in the regions introduced in Section 1.2. The time constant τ_m of a membrane is around 20 ms. As I explained earlier, this potential arises from a difference in ion concentration inside and outside the cell.

A neuron receive inputs $I(t)$ through synapses distributed on its dendrites, whose AMPA and NMDA receptors let ions enter the cell, thereby changing the voltage. Note that we leave out the spatial distribution of those and model only *point* neurons, ignoring complex non linear behaviours occurring at the level of dendrites. Incoming action potentials induce short pulses of current called *excitatory postsynaptic potential* (EPSP) (they can also be inhibitory, in which case the polarity is reversed). I define the spike train of neuron j as a sum of delta pulses centered on its spike times

$$X_j = \sum_k \delta\left(t - t_j^k\right) \tag{1.2}$$

From this point, there is two ways of describing the action of incoming spikes on the membrane potential of a neuron The first way is by direct pulses of current modeled as Dirac deltas modulated by the synaptic weights of individual synapses and acting directly on the voltage V. In this case the input term can be written $I(t) = \sum_j w_j X_j$, where w_j is the synaptic weight

to create a false memory in rats by optogenetically stimulating neurons in the hippocampus which had been measured to take part in the encoding of a certain context (Ramirez et al., 2013). This, I believe, helps refining the link between cell assemblies and context encoding in the hippocampus of rodents.

coming from neuron j.

Another way consists in modeling the input as conductances $g(t)$ following a similar dynamic as the membrane potential with a rest value of 0 and which tend to drive the voltage towards their respective reversal potential. Equation 1.1 then becomes

$$\tau_m \frac{dV}{dt} = -V(t) + V_r + \sum_\alpha g_\alpha(t)(V_\alpha - V) \tag{1.3}$$

where $\alpha \in$ {AMPA,NMDA,GABA} represents the different sorts of receptors present in synapses. In this case, the input term is acting on the variables g_α, influencing the voltage only indirectly. This method is more realistic, however it is computationally more costly since it requires additional variables for the conductances.

This represents the behaviour of a cell in the so-called subthreshold regime. Past a certain voltage, usually around -50 mV, neurons emit a spike, which is then propagated through its axon and in turn excite or inhibit other downstream neurons. To model this behaviour we add a threshold θ and say that a neuron spikes whenever its membrane voltage reaches this threshold. The spike is then propagated to the other neurons, modeled by a Dirac delta, and the voltage is reset to its rest value.

This model is called the *leaky integrate and fire* (LIF).

Spiking activity triggers several internal processes. First, there is a short time after a neuron has emitted an action potential where it cannot fire again, called a refractory period. This is often modeled by setting the threshold θ to a high value right after a spike, and letting it relax to its rest value on a time scale of the order of the refractory period. There exists also a spike triggered adaptation mechanism that we model by an additional inhibitory current or conductance pulse following an internal spike. A theoretical study on adaptation mechanisms showed that it could help neurons encode information in an optimal way (Pozzorini et al., 2013).

This is one of the most simple ways of mathematically describing a neuron. Another standard model is the Hodgkin-Huxley[11] model which is similar to a conductance-based LIF but which adds to it other variables that represent the dynamic of opening and closing of ion channels. This model is computationally much more costly but has an intrinsic explanation of a spike and therefore doesn't require a spiking threshold. There are ways of reducing a Hodgkin-Huxley model to a LIF (Gerstner and Kistler, 2002).

There are also other kinds of model, not based on biological grounds but who nevertheless perform well. One example is the Izhikevich neuron (Izhikevich, 2003). The way to assess whether a neuron model is a good one is by verifying that it faithfully captures the responses to arbitrary stimuli (Gerstner and Naud, 2009). A model from the family of integrate and fire

11. After the famous scientists Alan Lloyd Hodgkin and Andrew Huxley who designed their model in 1952 to describe action potentials in the squid giant axon, and received a Nobel prize for it.

models that includes an exponential term in the voltage evolution equation and adaptation is shown to be nearly as good as more complicated models (Brette and Gerstner, 2005).

1.3.2 Models of early phases of plasticity

I now turn to models of synaptic plasticity. STP [12] is very well captured by a model from Tsodyks et al. (1998). It takes into account a release probability and a depletion variable, and is able to capture both facilitating and depressing synapses. Theoretical studies show that it can have frequency filtering effects on information transmission either for low or high frequencies depending on the synapse type (Abbott et al., 1997).

I now turn to models of mechanisms showing longer time scales. There are two families of models for LTP or LTD, rate and spiking models. In the simpler case, the rate versions, it is straightforward to derive a rule that satisfies Hebb's postulate (see Section 1.2.1) in an intuitive fashion. It is by considering the following fact, a *learning rule* – the way synaptic weights are changing in time – can only depend on pre- and postsynaptic activity $\dot{w} = F\left(x, y\right)$. Taking a polynomial expansion of this function yields $\dot{w} \sim a_0 + a_1 x + a_3 y + a_4 x y + \ldots$ Now setting all coefficients but a_4 to zero produces the rule $\dot{w} \propto x y$, which reproduces Hebb's statement in that two neurons active together will wire together. Keeping a negative a_0 will act as depression whenever co-activity of two neurons is less than a baseline value (Sejnowski and Tesauro, 1989).

An example of weight modulated rule is Oja's rule (Oja, 1982). It takes the form $\dot{w} = a\left(x y - y^2 w\right)$ which can be shown to perform principal component analysis of its input stream. The BCM rule (Bienenstock, Cooper, and Munro, 1982) has a dynamic threshold on the postsynaptic activity $\dot{w} = a y \left(y - \theta\right) x$. If θ is a filtered version of a (high enough) power of y, then this rule performs selectivity on the input and provides a mechanistic explanation to the formation of receptive fields in the primary visual cortex. It is a very popular rule because it has the advantage of being biologically plausible.

For obvious reasons, none of those models can reproduce the STDP learning window measured by Bi and Poo (1998). For this we have to look at the second family, composed of spiking models. The theoretical suggestion for such models was made by Gerstner et al. (1996). Many other models were later proposed trying to reproduce data or looking at functional properties like information transmission (Gütig et al., 2003; Karmarkar and Buonomano, 2002; Kempter et al., 1999a; Rubin et al., 2001; Senn et al., 2001; Song et al., 2000). Multiplicative rules, i.e. exhibiting weight dependence, were shown to be disastrous for synaptic memory by producing a unimodal distribution of synaptic weights in the long run (Billings and van Rossum, 2009; Gütig et al., 2003; van Rossum et al., 2000). In order to account for frequency effects observed in experiments (Dudek and Bear, 1992), models incorporating higher order effects beyond spike pairs were introduced (Froemke and Dan, 2002; Gutig and Sompolinsky, 2006; Pfister and Gerstner, 2006b; Senn et al., 2001).

12. Here I mean the very short type of plasticity, not the version described in Section 1.2.4

In this thesis I make use in chapter 3 and in chapter 4 of the triplet model by Pfister and Gerstner (2006b) because it corresponds to the philosophy behind my work. It is a simple model that captures the main features necessary for a good representation of experimental findings and that enables interpretation and understanding. To account for triplet effects this model makes use of filtered versions of the pre- and postsynaptic spike trains with various time constants

$$\tau_\beta \dot{x}_\beta = -x_\beta + X \tag{1.4}$$

where X is the spike train of a neuron as defined in Equation 1.2. These traces are read at spike times and enter the learning rule in a non linear fashion, allowing for spike interactions beyond nearest neighbour effects.

1.3.3 Models with more than two factors

As I showed in Section 1.2.3, Hebbian learning is not enough to explain several behavioural observations. In the theoretical community models incorporating other variables than the two factors represented by pre- and postsynaptic activity are sometimes called *third factor rules*. There exists different types of those models.

Optimal models are derived in a top-down approach. They define a value to maximize and infer from it what the learning rule should look like. The first published model maximizing reward by Xie and Seung (2004) used a policy gradient approach to derive the plasticity rule. The result was later extended to neurons with refractory periods by Pfister et al. (2006) and then re-derived by Florian (2007a). All three rules are very similar and lack somehow of biological plausibility. Some were applied to learning task but this was limited to the XOR problem in small networks. Other optimality models maximized information transmission (Bell and Sejnowski, 1995; Toyoizumi et al., 2005), sparseness (Olshausen and Field, 1996) or slowness (Sprekeler et al., 2007; Wiskott and Sejnowski, 2002).

The next family is composed of phenomenological models, called R-STDP models. They are biologically more plausible than optimal models in the sense that they are based on the simple assumption of modulating a Hebbian rule by a reward signal (Florian, 2007b; Izhikevich, 2007). [13] To bridge the gap between induction of synaptic changes and delivery of the reward signal, they make use of an *eligibility trace*, a hidden variable that keeps track of potential weight changes and that updates the weights only upon the presence of reward. Another model by Farries and Fairhall (2007) has instantaneous weight updates but reward delivery via extended kernels. It is interesting to remark that the theory of STC exposed in Section 1.2.4 combines these two mechanisms, an reward extended in time and a semblance of an eligibility trace in the form of the synaptic tag – with the notable differences of the time scales involved, much longer in the case of STC and of the eligibility trace as a hidden variable, whereas early expression of plasticity represent a *real* change in synaptic efficacy.

13. Eugene Izhikevich actually has a patent on R-STDP.

The idea of an eligibility trace is also found in the field of *reinforcement learning* (RL) (Sutton and Barto, 1998). This theory takes its roots in control theory and bases its algorithms on the interaction of an agent with a set of available states and actions. It is based on Bellman optimality principle (Bellman, 1957) stating that an agent should optimize the sum of *all future reward* outcomes starting from the actual state. It has recently been applied successfully to neural networks in various learning paradigms by Frémaux et al. (2013).

Finally the model by Urbanczik and Senn (2009) uses a binary decision task and compares the local population decision, encoded via a second neuromodulator, to the global reward, in order to make available to the neurons the information about their true contribution to the final decision. It showed that it could make learning faster in large populations but this was restricted to binary decision.

1.3.4 Consolidation, network and memory models

To this day, there exists only two models of synaptic consolidation. One of them is the one presented in chapter 2 (Clopath et al., 2008). I briefly review here the second one, published at the same time by Barrett et al. (2009).

This model is composed of six states, three states representing a high synaptic weight and the other three a low one. Among each set of three states, one represents a neutral state, one a tagged state and one a consolidated state. Transition probabilities between the different states is adjusted in an ad hoc manner depending on the nature of the stimulus (potentiating, depressing or consolidating) – in this sense, it is neither a spiking model nor a rate model, but nevertheless captures well the basic phenomena inherent to STC theory. Moreover the authors also made predictions on the statistical properties of the field EPSP.

A more detailed comparison of the two models can be found in Section 5.1.

An interesting line of research launched by Willshaw et al. in 1969 studies memory lifetimes in neural networks by looking at the signal-to-noise ratio of a previously encoded memory trace under constant stream of incoming information. These studies show that past a certain capacity, growing linearly with the amount of synapses but decreasing with the square root of the number of patterns to store, memory traces ineluctably decay. This was called the stability versus plasticity dilemma (Abraham and Robins, 2005). Different ways of enhancing memory times were proposed, unbounded synapses was one of them. But since it was necessary to avoid a runaway of the synaptic weights, it reduced the capacity (Nadal et al., 1986). Another way was via complex synapse models involving metaplastic states. These models delayed forgetting but couldn't avoid it (Fusi et al., 2005; Fusi and Senn, 2006; Rubin and Fusi, 2007). Another group found that binary synapses showed the same capacity but that they were more resistant to noise (Barrett and van Rossum, 2008).

Interestingly a recent paper by Elliott and Lagogiannis (2012) showed that a synapse model integrating the plasticity inducing events before expressing an actual change in synaptic

efficacy could help solve the oblivescence problem by inducing a period of enhanced memory signal. This period was also followed by a forgetting of the memory trace but the authors argued that a system mechanism of reconsolidation occurring at the right moment would encode a memory trace for an indefinite period of time.

Finally I briefly introduce models of the hippocampal formation as they are important for spatial information storage. The first computational model of the hippocampus was that of Marr (1971). He postulated that its function was to store memories non specifically and to retain them until their usefulness could be assessed. This is surprisingly in line with the theory of STC. Later studies by Treves and Rolls (Treves and Rolls, 1992, 1994) looked at the mechanisms responsible for CA3 and CA1 different firing patterns – CA3 involving several assemblies and CA1 a unique, sparser representation of the information – and how to efficiently convey information between these two structures. Orthogonalization of the input performing pattern separation is an important feature accomplished by the hippocampus (O'reilly and McClelland, 1994). Computational studies had suggested that this was the role of the dentate gyrus and modeled it via an Oja type learning rule (Yassa and Stark, 2011).

1.4 Objective of the thesis

The main goal of this thesis is to refine the link from the cellular mechanisms of synaptic plasticity to the behavioural effects of memory measured on living animals. This involves creating a complex model of a synapse that accounts for neuromodulatory and metaplastic effects that have been measured in the hippocampus region of the rat.

I first present a first version of such a model that I published together with Claudia Clopath in 2008 (Clopath et al.).

I then turn to a refined model that accounts for more experimental findings and that is furthermore better suited for the analysis of functional aspects.

I also show an application of this refined model on a behavioural tagging experiment with the claim that STC theory could bear explanatory power in the way memories are formed, stored and recalled in living animals

Finally I discuss consequences and open questions inherent to the framework built throughout this thesis.

2 Model of early and late Long Term Plasticity

This chapter presents the following article:

> Tag-Trigger-Consolidation: a Model of Early and Late Long-Term-Potentiation and Depression
> C. Clopath, **L. Ziegler**, E. Vasilaki, L. Büsing and W. Gerstner (2008) [1]
> *PLoS Computational Biology*, 4(12), e1000248

2.1 Introduction

Changes in the connection strength between neurons in response to appropriate stimulation are thought to be the physiological basis for learning and memory formation (Bliss and Collingridge, 1993; Malenka and Bear, 2004). A minimal requirement for proper memory function is that these changes, once they are induced, persist for a long time. For several decades, experimentalists have therefore focused on Long-Term Potentiation (LTP) and Long-Term Depression (LTD) of synapses in hippocampus (Bliss and Gardner-Medwin, 1973; Dudek and Bear, 1992) and cortical areas (Artola et al., 1990; Markram et al., 1997). LTP can be induced at groups of synapses by strong 'tetanic' high-frequency stimulation of the presynaptic pathway (Bliss and Gardner-Medwin, 1973) while stimulation at lower frequency leads to LTD (Dudek and Bear, 1992). Both LTP and LTD can also be induced at a single synapse or a small number of synaptic contacts if presynaptic activity is paired with either a depolarization of the postsynaptic membrane (Artola et al., 1990; O'Connor et al., 2005a) or tightly timed postsynaptic spikes (Bi and Poo, 2001; Markram et al., 1997).

While the induction protocol for LTP and LTD is often as short as a few seconds, the changes in synaptic efficacy persist for much longer (Abraham, 2003). In typical slice experiments on LTP [and similarly for LTD or Spike-Timing Dependent Plasticity (STDP)] the persistence of the change is monitored for 30 minutes to 1 hour. Accumulating evidence suggests, however, that after this early phase of LTP (E-LTP) different biochemical processes set in that are necessary

1. C. Clopath and I contributed equally to the work. C. Clopath performed the research on the induction of *early phase* of plasticity.

for the further maintenance of potentiated synapses during the late phase of LTP (L-LTP) (Krug et al., 1984; Sajikumar et al., 2005). For an understanding of the transition from early to late LTP, the concept of 'synaptic tagging and capture' has become influential (Frey and Morris, 1997; Reymann and Frey, 2007). During induction of the early phase of LTP, each potentiated synapse sets a tag that marks that it has received a specific afferent signal. A candidate molecule, involved in the tag signaling LTP induction in apical dendrites of hippocampal neurons, is the calcium-calmodulin dependent kinase II (CaMKII) (Reymann and Frey, 2007). Newly synthesized plasticity-related proteins are 'captured' by the tagged synapse and transform E-LTP into L-LTP that can be maintained over hours or days. A candidate protein involved in the maintenance of potentiated hippocampal synapses is the protein kinase Mζ (PKMζ) (Pastalkova et al., 2006; Sajikumar et al., 2005).

The stabilization and maintenance of potentiated synapses poses a number of theoretical challenges. First, on the level of single synapses we must require synaptic strength to remain stable, despite the fact that AMPA channels in the postsynaptic membrane are continuously exchanged and recycled (Crick, 1984; Lisman, 1985; Newpher and Ehlers, 2008). Thus the synapse is not 'frozen' but part of a dynamic loop. Second, on the level of neuronal representation in cortical areas, one finds representations of input features that are stable but at the same time sufficiently plastic to adjust to new situations (Buonomano and Merzenich, 1998). In the theoretical community, this paradox has been termed the stability-plasticity dilemma in unsupervised learning (Carpenter and Grossberg, 1987). Third, humans keep the ability to memorize events during adulthood, but can also remember earlier episodes years back. However, continued learning of new patterns in theoretical models of associative memory networks forces the erasure or 'overwriting' of old ones, the so-called palimpsest property (Amit and Fusi, 1994; Nadal et al., 1986). In the context of continued learning, theoretical arguments show that synaptic plasticity on multiple time scales cannot prevent, but at most delay the erasure of memories in the presence of ongoing synaptic activity (Fusi et al., 2005). This suggests that additional mechanisms are necessary to further protect existing memories and 'gate' the learning of new ones.

Despite these challenges for the long-term stability of synapses, most classical models of synaptic plasticity focus on the induction and early phase of LTP or LTD and completely ignore the question of maintenance. Traditional models of associative memories separate the learning phase from the retrieval phase (Hopfield, 1982) and the same holds for standard models of STDP (Gerstner et al., 1996; Kempter et al., 1999b; Song et al., 2000). Detailed biophysical models of LTP and LTD describe calcium dynamics and Calcium/Calmodulin-Dependent Protein Kinase II (CaMKII) phosphorylation during the induction and early phase of LTP (Graupner and Brunel, 2007; Lisman, 1989; Miller et al., 2005). While these models show that switches built of CaMKII proteins can be stable for years, they do not address aspects of tagging leading to heterosynaptic interaction during L-LTP and L-LTD. Moreover, while CaMKII phosphorylation is necessary for induction of LTP and mediate tags in the apical dendrites of hippocampal CA1 neurons (Sajikumar et al., 2007), it is less clear whether it is necessary for its maintenance (Otmakhov et al., 1997) . On the other hand protein kinase Mζ

is essential for maintenance of some synapse types (Pastalkova et al., 2006; Reymann and Frey, 2007; Sajikumar et al., 2005) but the same molecule is potentially relevant for *induction* in others (Sajikumar et al., 2007).

We wondered whether a simple model that connects the process of LTP induction with that of maintenance would account for experimental results on tagging and 'cross-tagging' (Frey and Morris, 1997; Reymann and Frey, 2007; Sajikumar and Frey, 2004b; Sajikumar et al., 2005) without specific assumptions about the (partially unknown) molecular pathways involved in the maintenance process. If so, the model should allow us to discuss functional consequences that are generic to the tagging hypothesis independent of the details of a biophysical implementation in the cell. Even though we believe that the model principles are more general, we focus on synapses from the Schaffer-Collaterals onto the CA1 neurons in hippocampus as an experimentally well-studied reference system for synaptic plasticity. Since typical tagging experiments involve the extracellular stimulation of one or several *groups* of synapses (rather than single synapses), our model of early and late LTP/LTD is developed in the context of a neuron model with hundreds of synapses. The application of the principles of synaptic consolidation to experiments inducing E-LTP/E-LTD at *single* synapses is considered in the discussion section.

2.2 Results

We study a model with a large number of synapses i onto a single postsynaptic neuron. To be specific, we think of a pyramidal neuron in the CA1 area of hippocampus. Our model combines features of traditional models for the *induction* of potentiation (Bienenstock et al., 1982; Fusi, 2002; Gerstner and Kistler, 2002; Gerstner et al., 1996; Kempter et al., 1999b; Pfister and Gerstner, 2006a; Song et al., 2000) with a simple description of tagging and synthesis of plasticity related proteins that finally lead to the *maintenance* of the induced changes. The section is organized as follows: We first introduce the essential components of the model step by step ('Constructing the Model'). We then test the performance of the model with a set of stimuli typically used to induce long-term changes of synapses ('Tests of the Model').

2.2.1 Constructing the Model

Our model contains three elements (Figure 2.1). The first one sets the *tag* during the induction of E-LTP or E-LTD. A tag is indicated by a value $h = 1$ for LTP or $l = 1$ for LTD. In the absence of tags we have $h = l = 0$. The second one describes the process that *triggers* the synthesis of plasticity related proteins. The final component describes the up-regulation of a maintenance-related process from a low value ($z = 0$) to a high value ($z \approx 1$). The dynamics of this component is intrinsically bistable and leads to a *consolidation* of the previously induced change at the labeled synapses upon interaction with the protein p ('protein capture'). The total change Δw of the synaptic strength reported in experiments contains contributions (Reymann and Frey, 2007) of the early components l and h as well as the late component z. Since the model

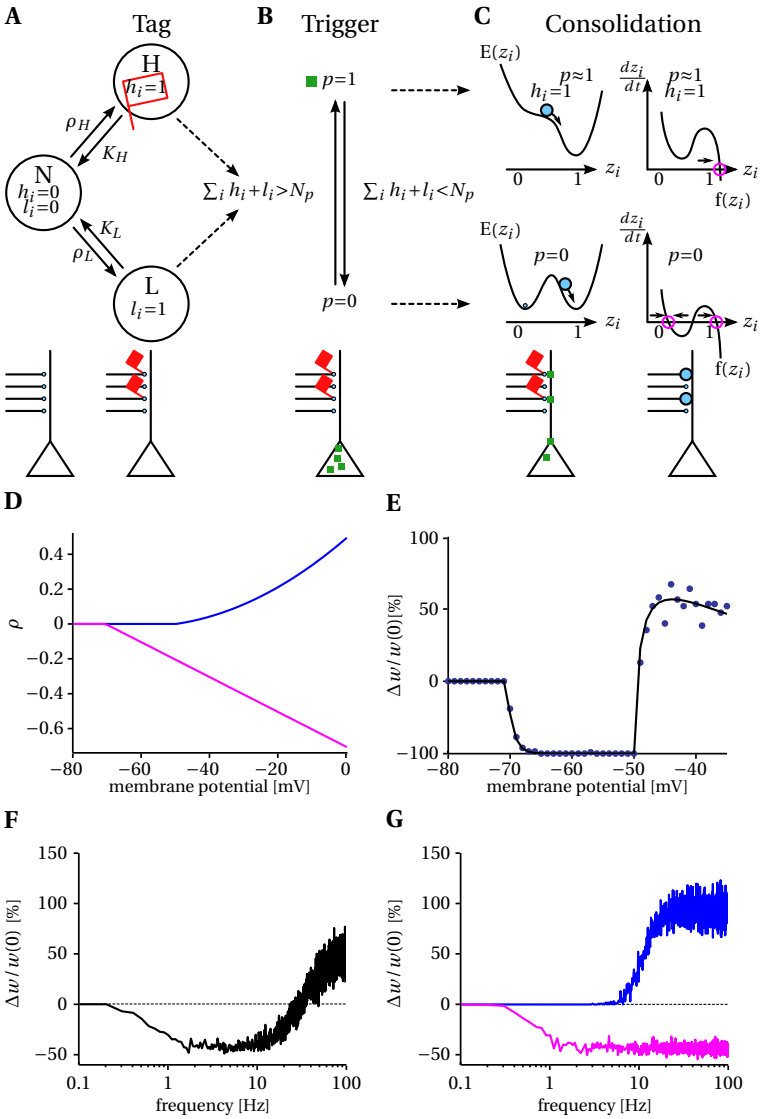


Figure 2.1 – The three components of the Tag-Trigger-Consolidation (TagTriC) model. **A** A synapse can be in the non-tagged state N, the high state H or the low state L. A synapse i in H (or L) has a tag $h_i = 1$ (or $l_i = 1$, respectively). Transitions to a tagged state occur with rates ρ_H for potentiation and ρ_L for depression. The tag $h_i = 1$ is indicated by a red flag in both the flow graph and the schematic drawing below. **B** Synthesis of plasticity related proteins p (green squares) is triggered if the total number of set tags is larger than a critical number N_p. If the trigger threshold N_p is not reached, the protein concentration decays back to zero. **C**. The consolidation dynamics can be visualized as downward motion in a potential surface $E(z)$. The function $f(z)$ (shown to the right) is the derivative of E and characterizes the dynamics $dz/dt = f(z)$. If a tag is set at the synapse ($h_i = 1$) and protein synthesis has been triggered ($p \approx 1$), the dynamics can be imagined as downward motion into the right well of the potential $E(z)$. In this case, $z \approx 1$ is the only fixed point of the dynamics (magenta circle). In the absence of tags ($h_i = l_i = 0$, below) the consolidation variable z_i of synapse i is bistable and approaches (direction of flow indicated by arrows) stable fixed points at $z_i = 0$ or $z_i = 1$ (magenta circles). The steps of synaptic tagging and capture are indicated immediately below the flow diagram (Continued on next page).

describes a sequence of three steps 'Tag-Trigger-Consolidation' we call it in the following the TagTriC-Model (Figure 2.1).

2.2.2 Tag and induction of LTP/LTD

Results from minimal stimulation protocols which putatively activate only a single synapse suggest that the induction of LTP is a switch-like process (O'Connor et al., 2005a; Petersen et al., 1998). We therefore model individual synapses as discrete quantities that can switch, during the induction of LTP, from an initial 'non-tagged state' (N) to a 'high state' (H) with a transition rate ρ_H that depends on the induction protocol. Similarly, induction of LTD moves the synapse from the initial non-tagged state (N) to a 'low state' (L) at a rate ρ_L. If synapse i is in the high state, the synaptic variable h_i is equal to one. If it is in the low state, another local variable l_i is set to one. These local variables h_i and l_i do not only control the weight of the synapse during E-LTP and E-LTD, but also serve as 'tags' for up- or down-regulation of the synapse. Tags reset to zero stochastically with a rate k_h and k_l, respectively. If both tags are zero, the synapse is in the non-tagged state N. Since the synapse is either up-regulated OR down-regulated, at most one of the tags can be non-zero (Figure 2.1A).

The stochastic transitions from the initial state N with $h_i = 0$ and $l_i = 0$ to the down-regulated state $l_i = 1$ or an upregulated state $h_i = 1$ depend in a Hebbian manner on presynaptic activity and the state of the postsynaptic neuron. In the absence of presynaptic activity, the LTD rate ρ_L vanishes. Presynaptic activity combined with a time-averaged membrane potential $\bar{u}$ above a critical value ϑ_{LTD} leads in the TagTriC model to a LTD transition rate ρ_L proportional to $[\bar{u}(t) - \vartheta_{\mathrm{LTD}}]$. For a transition from the initial state to the high state, we require in addition that the *momentary* membrane potential is above a second threshold ϑ_{LTP}. Hence the transition rate ρ_H is proportional to $[\bar{u}(t) - \vartheta_{\mathrm{LTD}}]\,[u - \vartheta_{\mathrm{LTP}}]$ whenever these threshold conditions are satisfied; see Methods for details.

Our assumptions regarding the transition rates essentially summarize the qualitative voltage dependence seen in the Artola-Bröcher-Singer experiments (Artola et al., 1990). Indeed, when

(Figure 2.1) **D** The tagging rates for depression ($-\rho_L$,(magenta)) and for potentiation ρ_H (blue) are shown as a function of the clamped voltage under the assumption that a presynaptic spike has arrived less than 1 millisecond before. Note that for depression we plot the negative rate $-\rho_L$ rather than ρ_L to emphasize the fact that depression leads to a down-scaling of the synapse. **E** Voltage dependence of early LTP and LTD. The weight change $\Delta w/w(0)$ induced by a stimulation of 100 synapses at 2Hz during 50s while the postsynaptic voltage is clamped is shown as a function of voltage. The percent change $\Delta w/\hat{w}$ in simulations (circles) of LTP/LTD induction experiments can be predicted from a theory (solid line) based on the difference in transition rates $\rho_H - \rho_L$. The simulation reflects the voltage dependence seen in experiments (Artola et al., 1990; Ngezahayo et al., 2000). **F** and **G**. Frequency dependence of early LTP and LTD. Simultaneous stimulation of 100 synapses by 3 trains (separated by 5 min) of 100 pulses at rates ranging 0.03 to 100 Hz shows LTD at low frequencies and LTP at frequencies above 30 Hz. **G** If LTP is blocked in the model, LTD (pink line) occurs up to high frequencies as in experiments (O'Connor et al., 2005a). Blue line: LTP with blocked of LTD.

100 synapses in the TagTriC model are stimulated at low frequency during 50 seconds while the membrane voltage is kept fixed at different values (Figure 2.1D), the total weight change summed across all synapses exhibits LTD at low voltage and LTP at high voltage (Artola and Singer, 1993; Ngezahayo et al., 2000). As expected, the resulting weight changes in the simulations of Figure 2.1E reflect the voltage dependence of the transition rates in Figure 2.1D.

2.2.3 Trigger for protein synthesis

Previously induced LTP or LTD needs to be consolidated in order to last for more than one hour. Consolidation requires that protein synthesis is triggered. Experimental evidence indicates that triggering of protein synthesis needs the presence of neuromodulators such as dopamine (in the apical CA1 region) or other modulators (in other regions). In typical tagging experiments, extracellular stimulation co-stimulates dopaminergic input leading to a phasic dopamine signal (Frey et al., 1990; Reymann and Frey, 2007). In our model, induction of E-LTP or E-LTD through appropriate stimulation protocols changes the synaptic efficacy and sets tags at the modified synapses, both described by the variables $h_i = 1$ or $l_i = 1$. Protein synthesis in the model is triggered (see methods for details) if the total number of tags $\sum_i (h_i + l_i)$ (which indirectly reflects the phasic dopamine signal) reaches a threshold N_p which depends on the level of background dopamine (and other neuromodulators). More specifically, N_p decreases with the concentration of background dopamine so that the presence of dopamine facilitates the trigger process (Sajikumar and Frey, 2004b).

If the trigger criterion is satisfied, the concentration p of synthesized plasticity related proteins approaches with rate k_p a value close to one. If the number of tags falls below the threshold N_p, the protein concentration p decays with a time constant τ_p back to zero. Further details on the role of the trigger threshold and its relation to neuromodulators can be found in the discussion section.

2.2.4 Consolidation and late LTP

The total weight w_i of a synapse i depends on the present value of the tags h_i or l_i as well as on its long-term value z_i. The slow variable z_i is a continuous variable with one or two stable states described by a generic model of bistable switches, that could be implemented by suitable auto-catalytic processes (Lisman, 1985). While the concentration p of plasticity related proteins is zero, the variable z_i has two stable states at $z_i = 0$ and $z_i = 1$, respectively. If the protein concentration takes a value of $p \approx 1$, one of the stable states disappears and, depending on the tag that was set, the long term-value of the synapse can be up- or down-regulated; see methods and Figure 2.1C for details.

In order to illustrate the mechanism of induction of L-LTP, let us suppose that the synapse has been initially close to the state $z_i = 0$. The dynamics of the synapse can be imagined as downward motion in a 'potential' E. The current stable state of the synapse is at the bottom

of the left well in the potential pictured in Figure 2.1C. We assume that during a subsequent LTP induction protocol the synapse has been tagged with $h_i = 1$ and that the total number of tags set during the LTP induction protocol surpasses the trigger threshold N_p. If the protein concentration p approaches one, the potential surface is tilted so that the synapse now moves towards the remaining minimum at $z \approx 1$. After decay of the tags, p returns to zero, and we are back to the original potential, but now with the synapse trapped in the state $z = 1$. It can be maintained in this state for a long time, until another strong tagging event occurs during which the synapse is tagged with $l_i = 1$ as a result of LTD induction. In this case the potential surface can be tilted towards the left so that the only equilibrium point is at $z = 0$. Since consolidation is typically studied in animals that are more than 20 days old (Reymann and Frey, 2007), we assume that before the beginning of the experiment 30 percent of the synapses are already in the upregulated state $z = 1$ and the remaining 70 percent in the state $z = 0$; see also (O'Connor et al., 2005a). Because of the bistable dynamics of consolidation, only synapses that are initially in the upregulated state $z = 1$ can undergo L-LTD and only synapses that start from $z = 0$ can undergo L-LTP; compare (O'Connor et al., 2005a). Note, however, that tags for potentiation and depression can be set independently of the value of z. We may speculate that the variable z is related to the activity of PKMζ (Pastalkova et al., 2006; Sajikumar et al., 2005), or to the self-sustained clustering of AMPA receptors (Hayer and Bhalla, 2005), but the exact biochemical signaling chain is irrelevant for the functional consequences of the model discussed in the results section. In our model, the bistable dynamics of the z-variable captures the essence of synaptic persistence despite molecular turnover (Crick, 1984; Lisman, 1985; Miller et al., 2005) and mobility of AMPA receptors (Hayer and Bhalla, 2005).

2.2.5 Tests of the model

The TagTriC model has been tested on a series of stimulation protocols that reflect induction of LTP and LTD as well as the consolidation of plasticity events.

2.2.6 Induction of synaptic changes

A typical LTP induction experiment starts with extracellular stimulation of a bundle of presynaptic fibers (i.e., the Schaffer collaterals leading from CA3 to CA1) that activate a large number (typically hundreds (Reymann and Frey, 2007)) of presynaptic terminals. With an extracellular probe electrode placed close to one of the postsynaptic neurons, a change in synaptic efficacy is measured via the amplitude (or initial slope) of the evoked postsynaptic potential, representing the total response summed across all the stimulated synapses. In our simulations, we mimic these experiments by simultaneous stimulation of 100 synapses. The state of the postsynaptic neuron is described by the adaptive exponential integrate-and-fire model (Brette and Gerstner, 2005) and can be manipulated by current injection.

In a preliminary set of simulation experiments done with presynaptic stimulation alone (no manipulation of the postsynaptic neuron), the TagTriC model exhibits LTD or LTP depending

on the frequency of the presynaptic stimulation (Figure 2.1F) in agreement with experimental results (Dudek and Bear, 1992; O'Connor et al., 2005b). Moreover, under the assumption that LTP has been blocked pharmacologically ($\rho_H = 0$ in the model), our model shows LTD even for high stimulation frequencies (Figure 2.1G). This stems from the fact that LTD and LTP are represented in the TagTriC model by two independent pathways (Figure 2.1A) which are under control condition in competition with each other, but show up individually if one of the paths is blocked (O'Connor et al., 2005b). Together with the voltage dependence of Figure 2.1E, the above simulation results indicate that our model of LTP and LTD induction can account for a range of experiments on excitatory synapses in the hippocampal CA1 region, in particular, voltage and frequency dependence.

2.2.7 Consolidation of synaptic changes

In order to study whether consolidation of synaptic changes in our model follows the time course seen in experiments, we simulate standard experimental stimulation protocols (Frey and Morris, 1997; Reymann and Frey, 2007). A weak tetanus consisting of a stimulation of 100 synapses at 100Hz for 0.2 seconds (21 pulses) leads in our model to the induction of LTP (change by +15 percent) which decays back to baseline over the time course of two hours (Figure 2.2A). Thus, after the early phase of LTP the synapses are not consolidated. A stronger stimulus consisting of stimulating the same group of hundred synapses by 100 pulses at 100Hz (repeated 3 times every 10 minutes) yields stronger LTP that consolidates and remains elevated (weight change by 22±5 percent) for as long as the simulations are continued (more than 10 hours, only the first 5 hours are shown in Figure 2.2B). Thus our model exhibits a transition from early to late LTP if E-LTP is induced by the strong tetanic stimulation protocol, but not the weak one, consistent with results in experiments (Frey and Morris, 1997; Reymann and Frey, 2007). If, however, the weak tetanus at a first group of 100 synapses is given 30 minutes before or after a strong tetanus at a second group of 100 synapses, the synapses in both the weakly and strongly stimulated groups are consolidated (Figure 2.2C and D). If the weak tetanus in group one is given 120 minutes after the strong tetanus in group two, then consolidation of the synapses in the weakly stimulated group does not occur (Figure 2.2E). Thus our model exhibits a time course of heterosynaptic interaction between the two groups of synapses as reported in classical tagging experiments (Frey and Morris, 1997; Reymann and Frey, 2007).

An advantage of a modeling approach is that we can study the dependence of the heterosynaptic interaction between the two groups of synapses upon model parameters. A critical parameter in the model is the trigger threshold N_p that needs to be reached in order to start protein synthesis (Figure 2.1B). With our standard choice of parameters, where $N_p = 40$, we can plot the consolidated weight change $\Delta w / w(0)$ in the weakly stimulated group (measured 10 hours after the induction) as a function of the time difference between the stimulation of the group receiving the strong tetanus and that receiving the weak tetanus. The curve in Figure 2.2F shows that for a time difference up to 1 hour there is significant interaction between the two groups of synapses leading to synaptic consolidation, whereas for time differences

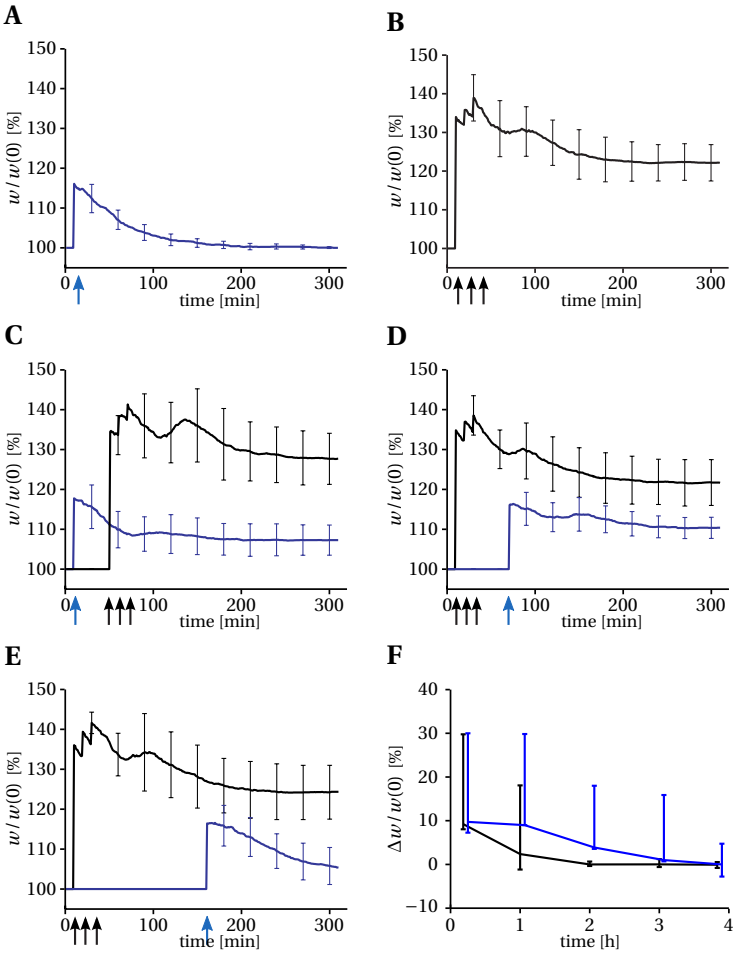


Figure 2.2 – The model accounts for tagging paradigms. **A** A weak tetanus (21 pulses at 100 Hz) applied at a group of 100 synapses at $t = 10$min (arrow) leads to an increased connection weight ($w/w(0)$, blue line) that decays back to baseline. **B** A strong tetanus (100 pulses at 100 Hz repeated three times, arrows) leads to late LTP that is sustained for 5 hours (black line). **C** If the weak tetanus (blue arrow) in a first group of synapses is followed thirty minutes later by a strong tetanus (black arrows) in a second group of synapses, the weights in the first group (blue line) and the second group (black line) are stabilized above baseline. **D** Stimulating a group of synapses by a weak tetanus (blue arrow) 30 minutes *after* the end of the strong tetanic stimulation of a second group also leads to stabilization of the weights in both groups above baseline. **E** If the weak tetanic stimulation occurs 2 hours after the strong tetanic stimulation of the other group, only synapses in the strongly stimulated group will be stabilized (black line), but not those in the weakly stimulated group (blue line). **F** Fraction of stabilized weights $\Delta w/w(0)$ in the weakly stimulated group measured 10 hours after induction of LTP as a function of the time difference between the weak stimulation and the end of the strong tetanic stimulation in the second group. Blue line: normal set of parameters ($N_p = 40$). Black line: protein trigger threshold increased to $N_p = 60$. In panels A-E, lines indicate the result averaged over 10 repetitions of the simulation experiments and bars standard deviation. In panel F, line indicates the result averaged over 100 repetitions. 90 of the 100 individual trials stayed within the bounds indicated by the error bars.

beyond 2 hours this is no longer the case. If the trigger threshold is increased to $N_p = 60$ (corresponding to less available neuromodulator), then the maximal time difference that still yields L-LTP in the weakly stimulated group of synapses is reduced to about 20 minutes (Figure 2.2F) whereas a reduction of N_p yields an increased time window of interaction (data not shown). If N_p is reduced much further, the weak tetanus alone will be sufficient to allow a transition from the early to the late phase of LTP. We speculate that N_p could depend on the age of the animal as well as on the background level of dopamine or other neuromodulators so as to enable a tuning of the degree of plasticity (see discussion for details).

2.2.8 LTD and Cross-tagging

We consider two experimental protocols known to induce LTD – a weak low-frequency protocol consisting of 900 pulses at 1 Hz and a strong low-frequency protocol consisting of 900 repetitions at 1 Hz of a short burst of three pulses at 20 Hz. This strong low-frequency protocol applied to 100 model synapses leads to a significant level of LTD (reduction of weights to 70±4 percent of initial value) which is consolidated 5 hours later at a level of 83±3 percent of initial value. If a group of 100 synapses is stimulated with the weak low-frequency protocol, an early phase of LTD is induced that is not consolidated but decays over the time course of 3 hours (Figure 2.3A and B). However, if the weak low-frequency stimulation occurs after another group of 100 synapses had been stimulated by the strong low-frequency protocol, then the group that has received the weak stimulation shows consolidated synapses (at 90±2 percent 5 hours after stimulus induction, Figure 2.3C). Moreover, consolidation of LTD (at 92±3 percent 5 hours after stimulus induction) in the group of synapses receiving the weak low-frequency protocol also occurs if it was stimulated thirty minutes after the stimulation of a second group of synapses by a strong tetanus, leading to LTP (Figure 2.3D). Thus, the TagTriC model exhibits cross-tagging consistent with experiments (Sajikumar and Frey, 2004b; Sajikumar et al., 2005). In our model, cross-tagging occurs because the tags for LTP and LTD (h_i and l_i, respectively) enter in a symmetric fashion into the trigger criterion for the synthesis of plasticity-related proteins (see Figure 2.1 and Methods).

2.2.9 Model Mechanism for tagging, cross-tagging, and consolidation

In order to elucidate how the model gives rise to the series of results discussed in the preceding paragraphs, we have analyzed the evolution of the model variables during and after induction of LTP (Figure 2.4). Critical for consolidation is the synthesis of plasticity related proteins, characterized by the variable p in the model. Synthesis is only possible while the total number of tags $\sum_i^N h_i + l_i$ is above the protein triggering threshold N_p. For the strong tetanic stimulus this criterion is met for about 90 minutes (shaded region in Figure 2.4A) leading to high levels of plasticity related proteins. After 90 minutes the concentration of proteins starts to decay back to baseline. While the level of proteins is sufficiently elevated the consolidation variable z_i of each tagged synapse moves towards $z_i \approx 1$ since this is the only stable fixed point of the dynamics (Figure 2.1C). This leads to a consolidation time of about 2 hours, enough to switch

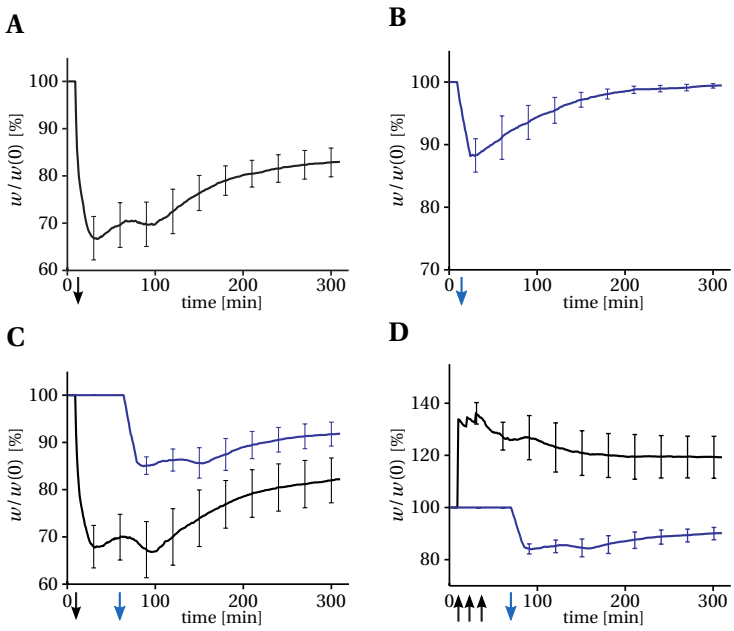


Figure 2.3 – The model accounts for cross-tagging between LTP and LTD. **A** A strong low-frequency stimulus (3 pulses at 20 Hz, repeated 900 times every second) applied to a group of $N = 100$ synapses induces LTD with mean weights ($w/w(0)$) stabilized at 83 ±3% of initial value after 5 hours (black line). **B** A weak low-frequency stimulus (1 pulse repeated 900 times at 1 Hz) induces early LTD, which is not consolidated. **C** If the weak low-frequency stimulus is applied 30 minutes after a second group of synapses has received the strong low-frequency protocol, the weights in both groups (blue, weak stimulus; black, strong stimulus) are consolidated at values below baseline. **D** Consolidation of LTD in the group receiving weak low-frequency stimulation (blue line) also happens if induction occurs 30 minutes after stimulating a second group of synapses with a strong tetanic protocol (see Figure 2.2) inducing LTP (black line). Downward arrows indicated the period of weak (blue arrow) or strong (black arrow) low-frequency protocols. The black upward arrows indicate strong tetanic stimulation. Lines show mean results, averaged over 10 repetitions of the simulation experiment. Error bars are standard deviation.

a large fraction of synapses into the up-regulated state $z \approx 1$ (green line, Figure 2.4A). Hence the average weight of the stimulated synapses stabilizes at a value above baseline, indicating L-LTP (Figure 2.4A, solid line).

If, in a different experiment, 100 synapses are stimulated by the weak tetanus, the synthesis of plasticity related proteins is only possible during a few minutes (Figure 2.4B, red line), which is not sufficient to switch tagged synapses from $z = 0$ into the upregulated state $z \approx 1$. Hence the weights (Figure 2.4B, black line) decay together with the tags (Figure 2.4B, magenta line) back to baseline and the transition from early to late LTP does not occur. The decay of the weights is controlled by the rate k_H at which tags stochastically return to zero. The evolution of the protein concentration p and the consolidation variable z after a strong tetanus that leads to 90 minutes of protein synthesis and a weaker tetanus that only leads to 40 minutes of protein synthesis has been illustrated in (Figure 2.5A).

The total amount of available protein that is synthesized depends in our model on the time that

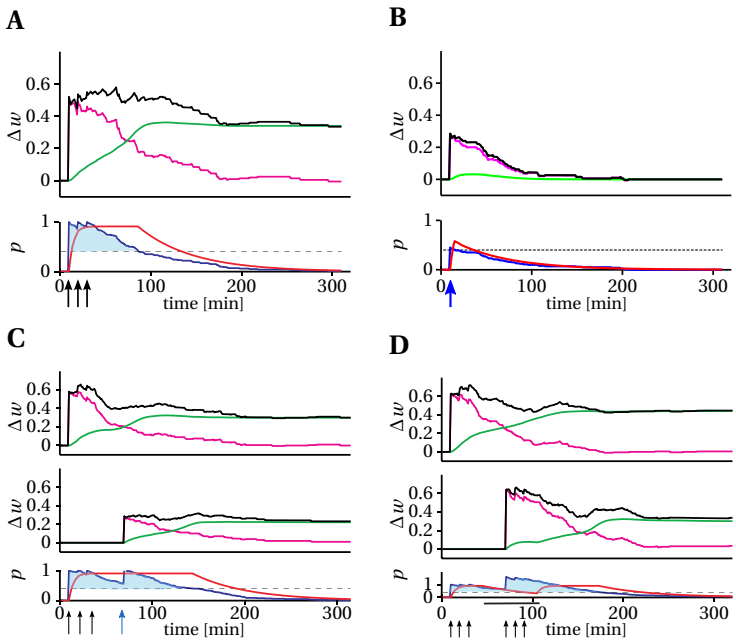


Figure 2.4 – Dynamics of the TagTriC Model during different tagging protocols and protein synthesis blocking. The change of the total synaptic weight (top panels, black line $\Delta w = \sum_{i=1}^{N} [w_i(t) - w_i(0)/N)$ has contribution from early LTP (top panels, magenta line represents $\sum_{i=1}^{N}(h_i - \alpha l_i)/N$) and from late LTP (top panels, green line represents $\sum_{i=1}^{N} \beta (z_i - z_i(0))/N$). The protein variable p (red line, bottom panels) grows as long as the average number of tags ($\sum_{i=1}^{N}(h_i + l_i)/N$, blue line) is above the protein synthesis trigger threshold (N_p/N, dashed horizontal line). For better visibility, the regions where the blue line is above the trigger threshold is shaded. **A**. A strong tetanus (N=100 synapses, stimulated by 100 pulses at 100Hz, repeated three times every ten minutes) leads to a sustained period of about 90 minutes where the number of tagged synapses is above the protein synthesis triggering threshold (lower panel, blue shaded). During this time the protein synthesis variable p is close to one (red line, lower panel), causing an increase in the fraction of consolidated weights (green line, top panel). **B** During a weak tetanus (N=100 synapses, stimulated by 21 pulses at 100Hz) the number of tags surpasses the protein triggering threshold only for a short time which does not enable switching of the z variable (top panel, green line) to the up-regulated state. **C** If the weak tetanus is given 30 minutes after the strong one, the number of tags set by the strong tetanus is still above the threshold, which allows protein synthesis stabilizing both the group of 100 synapses receiving the strong tetanus (top panel) and the group of 100 synapses receiving the weak tetanus (middle panel). **D** Protein synthesis is blocked for 1 hour (indicated by black bar at bottom of panel) starting 35 minutes after a first group of 100 synapses has been stimulated by a strong tetanus. Despite protein synthesis blocking, both the first group of synapses (top panel) and a second group of 100 synapses that received a strong tetanus during the blocking period (middle panel) develop late LTP because proteins synthesized during the induction of early LTP in the first group decay only slowly (bottom panel).

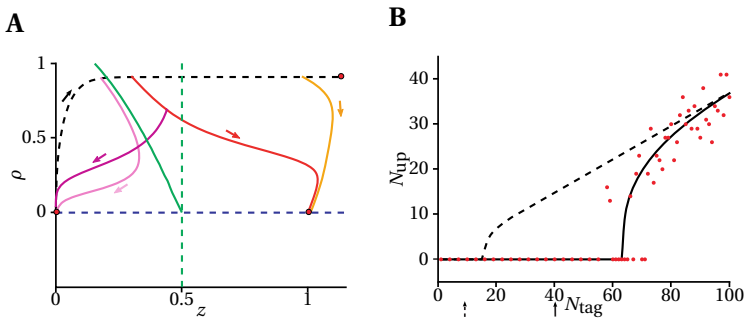


Figure 2.5 – Theory and predictions. **A** Evolution of the variables p and z during tagging. If protein synthesis is 'ON' and the synapse tagged, p and z move along the black dashed line towards the stable fixed point on the upper right $(p \approx 1, z \approx 1)$ (red filled circle). If protein synthesis stops after some time (yellow line, after 90 min; orange line, after 40 minutes) but the synapse remains tagged, the dynamics converges towards the fixed point $p = 0, z = 1$ (red filled circle) indicating that the synapse is consolidated (yellow and orange trajectories). However, if protein synthesis stops too early (after 25 min, pink line), or if the synaptic tag is lost too early (after 60 min, magenta line), the synapse is not consolidated and the trajectories converge towards the non-tagged initial state $p = 0, z = 0$ (red filled circle). The green dashed vertical line at $z = 0.5$ indicates the threshold beyond which a loss of the tag does not affect consolidation; the green solid line indicates the separatrix between the stable fixed points at $z = 0$ and $z = 1$. The minimal duration of protein synthesis to allow any consolidation is given by the intersection of the black dashed line with the separatrix. **B**. Number of consolidated synapses (N_{up}, vertical axis) as a function of the number of initially tagged synapses (N_{tag}, horizontal axis) in simulations (red filled circles) and theory (solid line). Some of the initially tagged synapses fail to be consolidated because either they loose their tag or protein synthesis stops too early (see A). With a protein synthesis threshold $N_p = 40$ (arrow) we need about 60 initially tagged synapses to achieve any consolidation (solid line). If the protein synthesis threshold is reduced to $N_p = 10$ (dashed arrow), we need at least 15 tagged synapses to see any consolidation (dashed line).

the total number of tags stays above the protein triggering threshold N_p. Even though always 100 synapses are stimulated in our model, not all receive tags in each experiment; moreover because of the competition for potentiation tags ($h_i = 1$) and depression tags ($l_i = 1$) during induction of plasticity, different synapses can receive different tags in the same experiment. With our strong tetanus protocol, on average 70 (out of 100) synapses receive a potentiation tag and 30 a depression tag while with the weak tetanus the numbers are 30 and 10, respectively. For the depression protocols, on average 10 synapses receive a potentiation tag and 90 a depression tag under strong low-frequency stimulation, and typically zero a potentiation tag and 40 a depression tag under the weak low-frequency protocol. These numbers vary from one trial to the next so that sometimes the protein trigger threshold $N_p = 40$ is reached with the weak protocols and sometimes not. The important aspect is that even if the threshold is reached for a short time, the duration of protein synthesis is not long enough to provide a sufficient protein concentration p for consolidation of the tagged synapses; see Figure 2.4B and Figure 2.5A.

Since the concentration p of plasticity related proteins is crucial for the transition from early to late LTP we wondered how a block of protein synthesis would interfere with the consolidation of weights in the TagTriC model. Application of a protein synthesis inhibitor

(modeled by setting the rate k_p of protein synthesis to zero) during 1 hour starting thirty minutes before a strong tetanus is given to a group of 100 synapses that would normally lead to L-LTP, induced E-LTP but prevented consolidation into L-LTP (data not shown). However, if the same simulation experiment was repeated after a second group of synapses had received a strong tetanic stimulation 35 minutes prior to the application of protein synthesis blocker, then both groups of synapses showed consolidation of weights (Figure 2.4D), consistent with experiments (Frey and Morris, 1997). Closer inspection of the lower panel in Figure 2.4D shows that two components contribute to consolidation: Firstly, the concentration of plasticity related proteins (red line) that has increased because of the first strong tetanic stimulus decreases only slowly back to baseline enabling the switching of the slow components (variable z, green line) even in the presence of protein synthesis blocker. Secondly, even after the end of the application of the blocker, the total number of tags that has been set by LTP induction is still above the critical value N_p (shaded region in Figure 2.4D) so that protein synthesis can be resumed after the end of the blocking period. In summary, the detailed analysis of the TagTriC model allows to account for many aspects of tagging experiment in terms of a limited number of variables.

2.3 Discussion

2.3.1 Relation of Models to Experiments

Synaptic plasticity is based on intricate signal transduction chains involving numerous processing steps and a large number of different molecules (Malenka and Bear, 2004; Newpher and Ehlers, 2008; Reymann and Frey, 2007). Despite the complexity of the molecular processes, synaptic plasticity has experimentally been characterized by a small set of distinct phenomena such as short-term plasticity (Markram et al., 1998) as well as early and late phases of LTP and LTD (Reymann and Frey, 2007).

Existing models of synaptic plasticity have focused on the description of short-term plasticity (Markram et al., 1998) and on the induction of LTP and LTD (Bienenstock et al., 1982; Fusi, 2002; Gerstner and Kistler, 2002; Gerstner et al., 1996; Kempter et al., 1999b; Pfister and Gerstner, 2006a; Song et al., 2000). The question of maintenance has received much less attention and was mainly addressed in the context of bistability of the CaMKII auto-phosphorylation process (Graupner and Brunel, 2007; Lisman, 1989; Miller et al., 2005), AMPA receptor aggregation (Hayer and Bhalla, 2005), or four identified kinase pathways (Smolen et al., 2006). While CaMKII is necessary for induction of long-term potentiation (Lisman et al., 2002), it is probably too narrow to focus modeling studies only on a single or a few kinases such as CaMKII and neglect other proteins and signaling cascades that are involved in synaptic maintenance (Reymann and Frey, 2007). For example, there is strong evidence that PKMζ is involved in synaptic maintenance and necessary for the late phase of LTP in vitro (Sajikumar et al., 2005) and in vivo (Pastalkova et al., 2006). However, the actual processes are complex and the molecules involved in setting tags may differ between different parts of the dendrite. For

example PKMζ is involved in setting tags during E-LTP in the basal dendrite, whereas CaMKII (or MAPK for E-LTD) plays a similar role in apical dendrites (Sajikumar et al., 2007).

Instead of focusing on specific signaling cascades, the TagTriC model presented in this paper aims at describing the essential ingredients of any possible functional model of L-LTP and tagging. These ingredients include (i) a bistable switch (described by the dynamics of the z_i-variable) for each synapse that guarantees long-term stability in the presence of molecular turn-over (Lisman, 1985); (ii) a global triggering signal for protein synthesis (described by the dynamics of the p variable); a formalism to (iii) induce early forms of LTP and LTD and (iv) set synaptic tags. Since we aimed for the simplest possible model, we have identified the synaptic tags h_i and l_i for potentiation and depression with the synaptic weights during the early phase of LTP and LTD, respectively, so that points (iii) and (iv) are described by the same transition of the synapse from an initial non-tagged state to the high or low state, respectively. Variants of the model where the weight during the early phase of LTP and LTD is not directly proportional to the value of the tags are conceivable.

Even though we do not want to identify the synaptic variables h_i, l_i, z_i with specific biochemical signals, a couple of candidate molecules and signaling chains should be mentioned. The setting of the tag for LTP under normal physiological conditions involves NMDA receptor activation and elevated levels of calcium which in turn trigger a signaling chain involving Calmodulin and CaMKII. We therefore think that the h_i variable (representing both the tag for LTP induction and the weight increase during the early phase of LTP) should be related to the activation of CaMKII (Lisman et al., 2002; Reymann and Frey, 2007). The molecular interpretation of the tag l_i for LTD is less clear (Reymann and Frey, 2007). In our model we have taken the tags as discrete quantities that decay stochastically, but a model with continuous tags that decrease exponentially gives qualitatively the same results (data not shown). The reason is that triggering protein synthesis in our model requires a large number of tags to be set, so that even in the stochastic model only the *mean* number of tags is relevant – and the mean (more precisely, its expectation value) is a continuous variable. Nevertheless, we prefer the model with discrete values over the continuous one in view of the switch-like transitions of synapses after induction of LTP and LTD (O'Connor et al., 2005a; Petersen et al., 1998). Maintenance of enhanced synaptic weights is probably implemented by an increased number of AMPA receptors in the postsynaptic membrane. Whether the stability arises from a self-organization process of receptors (Hayer and Bhalla, 2005) or from interaction with persistently activated CaMKII molecules (Lisman et al., 2002) or from additional kinases such as PKMζ (Pastalkova et al., 2006; Sajikumar et al., 2005) is an open problem of experimental investigation. Similarly, the exact identity of many plasticity related proteins is still unknown (Reymann and Frey, 2007). In our model we assume that recently synthesized plasticity related proteins are accessible to all synapses onto the same postsynaptic neuron. However, a distinction between proteins synthesized in, say, basal dendrites and that synthesized in apical dendrites would be possible by replacing the variable p by two or more distinct variables p_k with similar dynamics (but potentially different trigger thresholds N_p), allowing for a compartmentalization of tagging (Reymann and Frey, 2007).

Experimental cross-tagging results clearly indicate that there are two different types of synaptic tags, one for LTP and one for LTD (Reymann and Frey, 2007; Sajikumar and Frey, 2004b), which we called h_i for LTP and l_i for LTD, leading to three different states during tagging (Figure 2.1A). Since we have identified the tagging with the early phase of LTP and LTD, our model of E-LTP and E-LTD also has three different states (whereas our model of late LTP/LTD has only two states characterized by $z_i = 0$ and $z_i = 1$). The three-state model of early LTP/LTD presented in this paper would predict that all non-tagged synapses can undergo a transition to E-LTP or E-LTD depending on the induction protocol - whereas experiments suggest that about 70 percent of synapses show LTP but not LTD and the remaining 30 percent LTD but not LTP (O'Connor et al., 2005a). Moreover, only those synapses that are initially weak can be potentiated and only those that are initially strong can be depressed (O'Connor et al., 2005a). This aspect can be included in our model if we replace the induction rates ρ_H for LTP by $\rho_H\,(1-z_i)$ and ρ_L for LTD by $\rho_l\,z_i$ so LTP is only possible from a state with $z_i = 0$ and LTD only from an initial state $z_i = 1$ — in agreement with a two-state model of early LTP/LTD (O'Connor et al., 2005a). For the tagging and induction experiments presented in this paper, the results do not change significantly when we implement this extension of the induction model.

2.3.2 Functional Consequences and Predictions

One of the advantages of a simple phenomenological model is that it should be capable of illustrating the functional consequences of tagging and L-LTP or L-LTD in a transparent manner. What are these functional consequences?

A characteristic feature that is made transparent in our model (and which we expect to be present in any model of tagging) is that, under typical experimental conditions, the transition from early to late LTP is only possible if a sizable group of synapses have undergone E-LTP or E-LTD. Hence, while induction of E-LTP is a local Hebbian process that is likely to take place at the postsynaptic site of the synapse (e.g., the dendritic spine), the transition from the early to the late phase of LTP requires a minimum number of synapses to be activated by appropriate stimulation including co-activation of neuromodulatory input so as to trigger synthesis of plasticity related proteins. A direct consequence of this is that synapses cannot be considered as independent. In order to predict whether a synapse memorizes an item for a long time or forgets it and re-learns some other item, it is not sufficient to consider a 'Hebbian' induction model, where synaptic changes depend only on the activity of pre- and postsynaptic neurons. For maintenance, it is not the synapse which decides individually, but it is the neuron as a whole (or a large functional compartment sharing the same site of synthesis of plasticity-related proteins (Govindarajan et al., 2006; Reymann and Frey, 2007; Sajikumar et al., 2007)) which 'decides' whether it is going to store the present information, or not. Hence, classical (Amit and Fusi, 1994; Fusi, 2002; Nadal et al., 1986) and recent (Fusi et al., 2005) theoretical models which studied memory maintenance in the presence of ongoing neuronal activity on the level of *single* synapses need to be reconsidered, since the assumption of independent synapses does not hold (Figure 2.5A and B). In particular, our model predicts

that, after an ensemble of identical neurons have received the same stimulus, some neurons learn (adapt a *large* fraction of their synapses to the stimulus) and others don't (keep all their synapses unchanged). With our choice of parameters, this happens in the TagTriC model if the number of synapses that have been tagged during the induction protocol is between 55 and 70 (Figure 2.5B). This neuronal, rather than synaptic, decision about memorizing an input (see also (Toyoizumi et al., 2007)) is potentially attractive for prototype learning - a standard paradigm in neuronal clustering and categorization algorithms, e.g. (Carpenter and Grossberg, 1987). In contrast to traditional neuronal clustering models where learned memories need to be protected against overwriting by completely different memory items (Carpenter and Grossberg, 1987), a model based on tagging would have an intrinsic vigilance threshold via the trigger threshold N_p. Hence it is resistant to changes at a single synapse.

In our view, the protein synthesis trigger threshold N_P is an important control parameter in the model. The results of Figure 2.2F show that an increase of the trigger threshold reduces the maximal delay after which a weak tetanus leads to L-LTP after a strong tetanic stimulation in a different group of synapses. With our normal value of $N_p = 40$ we need around 60 synapses to be initially tagged in order to retain any memory. If we decrease the trigger threshold to $N_p = 10$ and keep all other parameters of the model unchanged, then we need at least a group of 15 synapses tagged during the induction protocol to get any consolidation since some of the initially tagged synapses loose their tag too early to get consolidated (Figure 2.5B). Only for a very small trigger threshold, say $N_p = 1$, (which could occur at high concentration of neuromodulators) synapses become (nearly) independent, since a tag at a single synapse would be sufficient to trigger the synthesis of proteins which would then become available at that synapse. Repeated stimulation of the synapse alone would then be sufficient to transform E-LTP into L-LTP.

In our opinion, the trigger threshold N_p is significantly lower in the presence of neuromodulators such as, for example, dopamine (for synapses from Schaffer collaterals onto CA1 pyramidal neurons) or noradrenaline (for synapses in the dentate gyrus). A simple model for the dependence of N_p on dopamine would be $N_p = n_0 / \left(\mathrm{DA}_{\mathrm{bg}} + c_0\right)$ where n_0 is some arbitrary number (say $n_0 = 1$), c_0 a small number (say 0.001) and DA denotes the stationary 'background' concentration of dopamine (that is, before the start of the experiment), normalized to $0 < \mathrm{DA}_{\mathrm{bg}} < 1$. The phasic dopamine signal caused by co-stimulation of dopaminergic input during tagging experiments is assumed to be proportional to the number of tags $\sum_i^N h_i + l_i$. The trigger condition $\sum_i^N h_i + l_i > N_p$ becomes then equivalent to the condition $\left(\sum_i^N h_i + l_i\right)\left(\mathrm{DA}_{\mathrm{bg}} + c_0\right) > n_0$ which shows a trade-off between the phasic dopamine signal and the stationary background level of dopamine. In particular in the presence of a large concentration of dopamine (DA $\approx$1), single synapses can be consolidated. With the assumption that standard tagging experiments in a large group of synapses are performed at a low dopamine concentration of DA=0.024 before stimulation, we retrieve the value of $N_p = 40$ used in the main part of the results section. The dependence of the trigger criterion on the number of tags $\sum_i^N h_i + l_i$ takes implicitly the co-activation of neuromodulatory input during the experimental stimulation protocol into account: the larger the number of stimulated neurons and the stronger the stimulus, the

higher the probability of co-activation of dopaminergic fibers. Blocking dopamine receptors amounts in the model to setting both the background and the phasic dopamine signal to zero. In this case, protein synthesis is not possible.

Our model of LTP/LTD induction does not only account for voltage and frequency dependence of LTP/LTD induction, but also for spike timing dependence. In fact, for a stimulation paradigm where postsynaptic spikes are induced by short current pulses of large amplitude either a few milliseconds before or after presynaptic spike arrival, the model of LTP/LTD induction used in the TagTriC model becomes formally equivalent to a recent model of spike-timing dependent plasticity (Pfister and Gerstner, 2006a) which can be seen as an extension of classical models of STDP (Gerstner et al., 1996; Kempter et al., 1999b; Song et al., 2000). In the case of stochastic spiking of pre- and postsynaptic neurons our model shares important features with the Bienenstock-Cooper-Munro model (Bienenstock et al., 1982), in particular the quadratic dependence upon the postsynaptic variables. In addition, our model also accounts for the voltage dependence of the Artola-Bröcher-Singer model (Artola and Singer, 1993). Thus, the model of LTP/LTD induction shares features with numerous established theoretical models and covers a large range of experimental paradigms known to induce LTP or LTD (Artola et al., 1990; Bi and Poo, 2001; Bliss and Gardner-Medwin, 1973; Dudek and Bear, 1992; Markram et al., 1997).

Since the subsequent steps of protein synthesis trigger and stabilization are independent of the way early phase of LTP is induced, our model predicts that tagging experiments repeated with different stimulation paradigms, but otherwise identical experimental preparation and age of animal, should give similar results as standard tagging protocols. In particular we propose to stimulate a group of synapses in hippocampal slices by 40-60 extracellular current pulses at 10 Hz while the postsynaptic neuron is receiving intracellular current injection that triggers action potential firing either a few milliseconds before or after presynaptic spike arrival and keeps the membrane potential at a depolarized level between postsynaptic action potential firing. Our model predicts that this will induce early LTD or LTP depending on spike timing and depolarization level that is not maintained beyond 1 or 2 hours. However, if the same stimulation occurs after a second group of synapses has received a strong tetanus, then stabilization of synapses at potentiated or depressed levels should occur, similar to standard tagging and cross-tagging experiments. In our opinion, these predictions should not depend on model details, but hold for a broad class of models that combine a mathematical description of induction of synaptic plasticity with a mechanism of consolidation.

Another finding, — which is somewhat unexpected and in contrast to other conceptual models of synaptic tagging and capture (Frey and Morris, 1997; Govindarajan et al., 2006; Reymann and Frey, 2007) — , is that during a strong tetanic stimulation a fraction of synapses receives tags for depression (while most, but not all, receive tags for potentiation). This is due to the fact that during induction of plasticity, transition to E-LTP and E-LTD act in parallel (O'Connor et al., 2005a). The prediction is that after consolidation (say 2 hours after the strong tetanic stimulation) a small fraction of synapses would show L-LTD, rather than L-LTP.

An essential ingredient of our model that allows long-term stability of consolidated synapses is the bistable dynamics of the variable z. In our opinion, such bistability (or possibly multistability (Lisman, 2003) with three or four stable states) is necessary for synaptic maintenance in the presence of molecular turn-over, as recognized in earlier theoretical work (Crick, 1984; Fusi, 2002; Lisman, 1985). Our model therefore predicts that L-LTP and L-LTD should have bistable, switch-like properties. While there is evidence for switch like transitions during the induction of E-LTP and E-LTD (O'Connor et al., 2005a; Petersen et al., 1998), the bistability of the late phase of synaptic plasticity has so far not been shown. A possible experiment would be to combine a minimal stimulation protocol (e.g. a weak tetanus) at a single synapse (O'Connor et al., 2005a; Petersen et al., 1998) with a medium to strong stimulus at a group of other synapses (e.g., tetanic stimulus varying between 30 and 100 pulses). The prediction is that the weight of the single synapse shows an all-or-none phenomenon with transition probabilities that depend on the stimulation of the group of other synapses. In particular, as the number of pulses of the tetanic stimulation is reduced (covering a continuum from strong to weak tetanic stimulation), the maintenance in the potentiated state should become less likely (averages across many experiments decrease) whereas the results of individual experiments show either full potentiation or none, which should give rise to a bimodal distribution of normalized synaptic weights.

2.3.3 Open questions and perspectives

A lot of questions remain open and need to be addressed in future studies. First, can a synapse that has been potentiated in the past and is maintained after a transition to late LTP undergo a further potentiation step (Reymann and Frey, 2007)? In our current model this is not possible since the consolidation variable z has only two stable fixed points. If we replace the function $f(z)$ depicted in Figure 2.1 by another one with more than two stable fixed points, then the answer to the above question would be positive. Indeed, there have been suggestions that self-organization of receptors into stable sub-groups could lead to multiple stable states (Lisman, 2003).

Second, induction of LTP or LTD is not only possible by strong extracellular stimulation of groups of synapses, but also at single synapses if presynaptic activity is paired with either a depolarization of the postsynaptic membrane (Artola et al., 1990; O'Connor et al., 2005a) or tightly timed postsynaptic spikes as in STDP experiments (Bi and Poo, 2001; Markram et al., 1997). How can it be that the change induced by STDP seems to be maintained over one hour without visible degradation? (Markram et al., 1997; O'Connor et al., 2005a). Are synapses in these experiments consolidated, and if so what is the concentration of neuromodulators? In the TagTriC model with the choice of parameters used in the present paper, consolidation would not be possible, since the minimum number of synapses that have undergone E-LTP or LTD is $N_p = 40$ in order to trigger protein synthesis, but, as explained above, an increased neuromodulator concentration would make consolidation possible.

Third, what is the role of NMDA receptor activation during synaptic consolidation? In our present model, protein synthesis is triggered by appropriate induction protocols, but is independent of synaptic activity during the consolidation process. However, recent experimental results suggest that protein synthesis blocker needs synaptic stimulation during the consolidation period to become effective (Fonseca et al., 2006), suggesting a subtle interplay between protein synthesis and synaptic activation that cannot be captured by our model.

Fourth, has each neuron a single protein synthesis unit or is protein synthesis a local process confined to each dendritic branch? In the first case, there is a single neuron-wide protein synthesis trigger threshold (Frey and Morris, 1997) and the neuron as a whole 'decides' whether early forms of synaptic potentiation and depression will be consolidated or not. This is the paradigm posited in the TagTriC model. In the alternative model of local protein synthesis (Govindarajan et al., 2006; Reymann and Frey, 2007), the critical unit for consolidation are local groups of synapses on the same dendritic branch. Thus, for the same number of tagged synapses, a local group of synapses on the same dendritic branch is more likely to undergo consolidation than a distributed set of tagged synapses, leading to a form of clustered plasticity (Govindarajan et al., 2006). The TagTriC model can be easily adapted to the case of clustered plasticity by (i) replacing the point-neuron model by a neuron model with spatially distributed synapses and (ii) replacing the neuron-wide trigger equation (see Equation 2.4 and Figure 2.1B) by a finite number of analogous, but dendrite-specific equations.

Fifth, how can tags be reset? Experiments show that a depotentiating stimulus given 5 minutes after a weak tetanus erases the trace of E-LTP (resets the tag) whereas depotentiation 10 or 15 minutes after the strong tetanus only transiently suppresses the E-LTP, making the consolidation of the synapse by protein capture possible (Sajikumar and Frey, 2004a). We have checked in additional simulations that our present model cannot account for these experiments. In our opinion, the above tag-reset experiments show that the synapse has additional hidden states currently not included in the TagTriC model. Additional states would allow to (i) separate the measured early LTP during the first 5 minutes from setting the tag; and (ii) distinguish between depotentiation and depression of synapses. One interpretation of the tag-reset experiments (Sajikumar and Frey, 2004a) is that during the first five minutes the tag is not yet set whereas early LTP is already visible. The tag would be set only with a delay of 5-10 minutes. Application of a depotentiating stimulus more than 10 minutes later would then leave the potentiation tag intact, but move the synapse to a transiently depotentiated state.

The final and potentially most interesting question is that of functional relevance: Can the TagTriC model be used to simulate reward-based learning in experiments in vivo (Reymann and Frey, 2007)? The formal theory of reinforcement learning makes use of an eligibility trace (Sutton and Barto, 1998) which can be interpreted as a synapse specific tag. In the future we want to check whether the TagTriC model can be linked to reinforcement learning models (Arleo and Gerstner, 2000; Izhikevich, 2007; Legenstein et al., 2008; Pfister et al., 2006) under the assumption that reward prediction errors are represented by a dopamine signal (Schultz et al., 1997) which influences the protein synthesis dynamics in our model. This open link to

reward-based learning is of fundamental functional importance.

2.4 Methods

2.4.1 Model of early LTP/LTD and tagging

In our model we assume that presynaptic spike arrival needs to be combined with a depolarization of the postsynaptic membrane (e.g. (Artola et al., 1990)) in order to induce a change of the synapse. In voltage clamp experiments (e.g., (Ngezahayo et al., 2000)) the postsynaptic voltage would be constant. However, in general the voltage is time-dependent and described by a variable $u(t)$. In the TagTriC model, we assume that the low-pass-filtered voltage

$$\bar{u}(t) = \frac{1}{\tau_{\text{lowP}}} \int_0^\infty \exp\left(-\frac{s}{\tau_{\text{lowP}}}\right) u(t-s-\epsilon)\, ds.$$

needs to be above a critical value ϑ_{LTD} to make a change of the synapse possible. τ_{lowP} is the time constant of the low-pass filter and $\epsilon = 1\text{ms}$ is a short delay twice the width of a spike (see Table 2.1). This short delay ensures that $\bar{u}$ includes effects of previous presynaptic inputs and postsynaptic spikes, but not of an ongoing postsynaptic action potential.

Combining presynaptic spike arrival at synapse i (represented by x_i) with a depolarization $\bar{u}$ of the postsynaptic neuron above a threshold ϑ_{LTD} we get a rate of LTD

$$\rho_L = A_{\text{LTD}}\, x_i(t)\, [\bar{u}(t) - \vartheta_{\text{LTD}}]^+ \tag{2.1}$$

where $A_{\text{LTD}} > 0$ is a parameter and $[.]^+$ denotes rectification, i.e., $[y]^+ = y$ if $y > 0$ and zero otherwise. Here $x_i(t) = \sum_f \delta\left(t - t_i^f\right)$ denotes the presynaptic spike train with pulses at time t_i^f and δ the Dirac-delta function. Formally, ρ_L describes the rate of stochastic transitions from the non-tagged state $h = 0, l = 0$ to the low state $l = 1$, Figure 2.1. In simulations we work with discrete time steps of $\Delta = 1\text{ms}$. Equation 2.1 indicates that the probability $P_{l=0\to l=1}$ of a transi-

Tag				**Trigger**		**Consolidation**	
N	100	k_h	1/h	k_p	1/ (6 min)	N	100
A_{LTD}	0.01	k_l	1/ (1.5 h)	τ_p	60 min	γ	0.1
A_{LTP}	0.014	Θ_{LTD}	−70.6 mV	N_p	40	τ_z	6 min
τ_x	100 ms	Θ_{LTP}	−50 mV			β	2
$\tau_{\text{lowP}}^{\text{LTP}}$	100 ms	α	0.5			initialization:	
$\tau_{\text{lowP}}^{\text{LTD}}$	1 s	initialization:				$N(z_i=1) = 30$	
ϵ	1 ms	$l_i = h_i = 0$					

Table 2.1 – Parameter values used throughout all simulations, except Figure 2.1E - G where $N_p = 10$ and initial percentage of $z_i = 1$ was 10%, because these simulations refer to experiments with younger animals.

tion to the low-state during the time step Δ vanishes in the absence of presynaptic spike arrival and takes a value of $P_{l=0\to l=1} = 1 - \exp\left(-A_{\text{LTD}}\,[\bar{u}(t) - \vartheta_{\text{LTD}}]^+\,\Delta\right) \approx A_{\text{LTD}}\,[\bar{u}(t) - \vartheta_{\text{LTD}}]^+\,\Delta$ if a presynaptic spike arrives at the synapse i during the time step Δ. Note that the transition from $l = 0$ to $l = 1$ is only possible if $h = 0$ and h remains zero during the transition.

Similarly, a switch from the non-tagged state $h = 0, l = 0$ to the high state $h = 1$ occurs at a rate ρ_H which also depends on postsynaptic voltage and presynaptic spike arrival. We assume that each presynaptic spike at synapse i leaves a trace $\bar{x}_i$ that decays exponentially with time constant τ_x. The exact biophysical nature of the trace is irrelevant, but could, for example, represent the amount of glutamate bound to the postsynaptic receptor. The value of the trace at time t caused by earlier spike arrivals at time t_i^f is then $\bar{x}_i(t) = (1/\tau_x)\sum_f \exp\left[-\left(t - t_i^f\right)/\tau_x\right]$ where the sum runs over all firing times $t_i^f < t$. With the trace $\bar{x}_i$ we write

$$\rho_H = A_{\text{LTP}}\,\bar{x}_i(t)\,[\bar{u}(t) - \vartheta_{\text{LTD}}]^+\,[u(t) - \vartheta_{\text{LTP}}]^+ \tag{2.2}$$

which indicates that, in addition to the conditions for LTD induction we also require the *momentary* membrane potential $u(t)$ to be above a second threshold ϑ_{LTP}. This threshold could change on the time scale of minutes or hours as a function of homeostatic processes. To summarize, the rate of LTP transition ρ_H is different from ρ_L in five aspects. First, the constant A_{LTP} is not the same as A_{LTD}. Second, LTP is caused by the *trace* $\bar{x}_i$ left by presynaptic spikes, rather than the spikes themselves. This trace-formulation ensures that presynaptic spikes can interact with later postsynaptic spikes as in classical models of STDP (Gerstner et al., 1996; Kempter et al., 1999b; Song et al., 2000). Third, the time constant of the low-pass filter in $\bar{u}$ is different; fourth, the momentary voltage needs to be above a threshold ϑ_{LTP}; and fifth, the total dependence upon the postsynaptic voltage is quadratic, rather than linear. The quadratic dependence ensures that for large depolarization LTP dominates over LTD (Ngezahayo et al., 2000). Tagged synapses with $h_i = 1$ decay with probability $P_{h=1\to h=0} = k_H\,\Delta$ back to the non-tagged state (and analogously, but with rate k_L for the transition $l_i = 1 \to l_i = 0$).

In the TagTriC model, the local synaptic values $h = 1$ for potentiation or $l = 1$ for depression act as tags indicating potential sites for further consolidation, but are also directly proportional to the weight of the synapse after induction of LTP or LTD. Since in minimal stimulation experiments LTD leads to a reduction of about 50 percent of the synaptic efficacy whereas LTP leads to an increase by up to 100 percent (O'Connor et al., 2005a), we model the weight change during the early phase of LTP as $\Delta w_i = (h_i - \alpha\, l_i)\;\hat{w}$ where $\hat{w}$ is the weight of the non-tagged synapse and $\alpha = 0.5$. The total weight change $\Delta w/\hat{w}$ measured shortly after induction of LTP or LTD with extracellular protocols corresponds to the fraction of synapses in the high or low states, respectively, hence, if all synapses start from the non-tagged state the measured weight change is $\Delta w/\hat{w} = \sum_{i=1}^{N}(h_i - \alpha\, l_i)/N = \langle h\rangle - \alpha\langle l\rangle$ where N is the number of synapses stimulated by the protocol. The set of parameters of LTP/LTD induction and tagging is given in Table 2.1.

2.4.2 Trigger

The triggering process is controlled by the dynamics of a variable p which describes the amount of plasticity related proteins synthesized in the postsynaptic neuron. Protein synthesis is triggered and the variable p increases while the concentration of dopamine exceeds a critical level ϑ_p (Navakkode et al., 2007). If the dopamine concentration DA falls below ϑ_p, the protein concentration decays with a time constant τ_p. Assuming standard first-order kinetics we have

$$\frac{dp}{dt} = k_p \left(1-p\right) \Theta\left[\mathrm{DA} - \vartheta_p\right] - \frac{p}{\tau_p} \tag{2.3}$$

Protein synthesis has a maximum rate dp/dt of k_p and saturates if the amount of protein approaches a value one. $\Theta\left[y\right]$ denotes the unit step function with $\Theta\left[y\right] = 1$ for $y > 0$ and zero otherwise.

Dopamine is present at a low stationary background value. In addition a phasic dopamine component is induced in standard tagging experiments in hippocampal slices, because of co-stimulation of dopaminergic inputs during extracellular stimulation of presynaptic fibers (Frey et al., 1990). To describe the time course of the phasic dopamine component in our model, we assume that the dopamine is proportional to the total number of tags $\sum_i (h_i + l_i)$ induced by the stimulation protocol. The stationary background level of dopamine $\mathrm{DA_{bg}}$ is included in the threshold $\vartheta_p = N_p\left(\mathrm{DA_{bg}}\right)$ for protein synthesis. Hence Equation 2.3 can be rewritten in the form

$$\frac{dp}{dt} = k_p \left(1-p\right) \Theta\left[\sum_i (h_i + l_i) - N_p\left(\mathrm{DA_{bg}}\right)\right] - \frac{p}{\tau_p} \tag{2.4}$$

Note that we have chosen units so that the threshold for protein synthesis N_p can be interpreted as the minimal number of tags necessary to stimulate protein synthesis. This interpretation is important for the discussion of the model results, in particular Figure 2.4 and Figure 2.5.

A suitable model for dependence of the protein synthesis threshold on the background level of dopamine is $N_p\left(\mathrm{DA_{bg}}\right) = n_0 / \left(\mathrm{DA_{bg}} + c_0\right)$ where $n_0 = 1$ is a scaling factor, $c_0 = 0.001$ a constant and $0 \leq \mathrm{DA_{bg}} \leq 1$ is the normalized dopamine concentration. We note that the trigger condition $\left[\sum_i (h_i + l_i) - N_p\left(\mathrm{DA_{bg}}\right)\right] > 0$ is then equivalent to the condition $\left(\mathrm{DA_{bg}} + 0.001\right)\left[\sum_i (h_i + l_i)\right] > 1$. This formulation shows that there is a trade-off between background levels and phasic dopamine. Unless stated otherwise we always use in the simulation a fixed dopamine level $\mathrm{DA_{bg}} = 0.024$ so that $N_p = 40$. The specific model $N_p\left(\mathrm{DA_{bg}}\right)$ of the dependence upon background dopamine levels is therefore irrelevant.

We assume that the plasticity related protein p synthesized in the postsynaptic neuron is diffused in the dendrite of the postsynaptic neuron and hence available to all the synapses under consideration. Hence, the tags h_i and l_i have indices, since they are synapse-specific, whereas p in Equation 2.4 does not.

2.4.3 Consolidation and late LTP

The consolidation variable z describes the late phase of LTP and follows the dynamics

$$\tau_z \frac{dz_i}{dt} = f(z_i) + \gamma(\mathrm{DA})\,(h_i - l_i)\,p. \tag{2.5}$$

The scaling factor γ is a function of the dopamine level DA. In the simulations we always assumed a fixed dopamine level and set $\gamma(\mathrm{DA}) = 0.1$.

In the absence of plasticity related proteins ($p = 0$), or if no tags are set ($h_i = l_i = 0$), the function $f(z) = z(1-z)(z-0.5)$ generates a bistable dynamics with stable fixed points at $z = 0$ and $z = 1$ and an unstable fixed point at $z = 0.5$ marked by the zero crossings of the function f, Figure 2.1C. In the presence of a finite amount of proteins $p > 0$ and a non-zero tag, the location of the fixed points changes and for $p > 0.47$, only one of the stable fixed points remains. The potential shown in Figure 2.1C is a function E with $dE/dz = -f(z)$ so that $dz/dt = -dE/dz$. We note that a synapse i can change its consolidated value only if both a tag ($h_i = 1$ or $l_i = 1$) and protein $p > 0.47$ is present - summarizing the essence of 'synaptic tagging and capture' (Frey and Morris, 1997; Reymann and Frey, 2007).

2.4.4 Synaptic weight

The synaptic weights have contributions from early and late LTP and LTD. The total synaptic weight of a synapse i is $w_i = \hat{w}\left(1 + h_i - \alpha\, l_i + \beta z_i\right)$ where $\hat{w}$ is the value of a non-tagged synapse, $\alpha = 0.5$ and $\beta = 2$ are parameters, h_i and l_i are binary values indicating E-LTP and E-LTD, respectively, and z_i is the value of the L-LTP trace of synapse i. Since we model slice experiments in animals older than 20 days, we assume that 30 percent of the synapses have undergone previous potentiation and have $z = 1$ while the remaining 70 percent of synapses are in the state $z = 0$ (O'Connor et al., 2005a). In all simulation experiments we stimulate one or several groups of N =100 synapses each. Assuming that no tags have been set in the recent past ($h_i = l_i = 0$), the initial value of the average weight in a group of N synapses is then $w(0) = \hat{w}\left[\sum_{i=1}^{N} 1 + \beta z_i\right]/N = 1.6\,\hat{w}$.

2.4.5 Neuron Model

For all simulations in this paper we use the adaptive exponential integrate-and-fire model (Brette and Gerstner, 2005) as a compact description of neuronal firing dynamics. Briefly, it consists of two equations. The voltage equation has an exponential and a linear term as measured in experiments (Badel et al., 2008). The second equation describes adaptation. Although firing rate adaptation is not important for the present study, it would be relevant in the context of other stimulation paradigms. Parameters for the neuron model are as in (Brette and Gerstner, 2005) and are kept fixed for all simulations presented in this paper. The voltage threshold V_s of spike initiation by a short current pulse is 25mV above the resting potential

of -70.6mV (Brette and Gerstner, 2005). Synaptic input is simulated as a short current pulse. The initial connection weight $\hat{w}$ was adjusted so that simultaneous activation of 40 or more synapses triggers spike firing in the postsynaptic neuron. Hence the amplitude of a single EPSP is about 0.6mV.

The adaptive exponential integrate-and-fire model is defined in continuous time. If a spike is triggered by a strong current pulse, the voltage rises within less than 0.5 millisecond to a value of 20mV where integration is stopped. The voltage is then reset to resting level, and integration restarted after a refractory time of 1ms. In order to enable us to perform simulations of plasticity experiments with a time step of $\Delta = 1$ms, the voltage equation during the rising slope of the action potential was integrated once at a much higher resolution (time step 0.02ms), so as to determine the exact contribution of each postsynaptic spike to the probability of LTP induction. Every postsynaptic spike was then treated as an event in the plasticity simulations that contributed a probability $P_{h=0\to h=1}$ of flipping the tag from $h = 0$ to $h = 1$ in a time step $\Delta = 1ms$ which we can write as $P_{h=0\to h=1} = a_\Delta \bar{x}(t)\,[\bar{u}(t) - \vartheta_{\rm LTD}]^+$ with a numerical conversion factor $a_\Delta = A_{\rm LTP}\,5ms\,mV$ derived by the above procedure; see Equation 2.2.

2.4.6 Number of consolidated synapses

In Figure 2.5 we plot the number of synapses that have been consolidated as a function of the number $N_{\rm tag}$ of initially tagged ($h_i = 1$) synapses. Since the number of tags decays exponentially with rate k_H, the expected duration $T_P^{\rm ON}$ of protein synthesis is $T_P^{\rm ON} = (1/k_H)\,ln\left(N_{\rm tag}/N_p\right)$ where N_p is the protein trigger threshold. While protein synthesis is 'ON' the variables p and z move along the black dashed line in Figure 2.5A which crosses after a time t_1 the separatrix (green line in Figure 2.5A) and at a time t_2 the line $z = 0.5$ (vertical dashed green line). Different cases have to be distinguished. (i) $T_P^{\rm ON} < t_1$, no consolidation takes place (see pink trajectory), hence $N_{\rm up} = 0$. (ii) $T_p^{\rm ON} > t_2$, consolidation is guaranteed for all synapses that are still tagged at time t_2, hence $N_{\rm up} = N_{\rm tag}\exp(-k\,t_2)$. (iii) In the case of $t_1 < T_p^{\rm ON} \le t_2$, the time $t_{\rm cross}$ needed to cross the vertical line $z = 0.5$ is numerically calculated by integrating the equations $dp/dt = -p/\left(\tau_p\right)$ and $dz/dt = f(z) + \gamma\,p$ starting at $t = T_p^{\rm ON}$ at the point $p\left(T_p^{\rm ON}\right), z\left(T_p^{\rm ON}\right)$ on the black-dashed line (see orange line in Figure 2.5A for a sample trajectory). The number of consolidated synapses is then $N_{\rm up} = N_{\rm tag}\exp(-k\,t_{\rm cross})$. The solid line in Figure 2.5B represents $N_{\rm up}$ as a function of $N_{\rm tag}$ calculated for the cases (i) - (iii). With our standard set of parameters, we have $t_1 \approx 28$min and $t_2 \approx 60$min.

2.5 Conclusion

In this chapter I presented a mathematical model describing the different phases of synaptic plasticity. These phases cover the early or induction phase, the setting of synaptic tags, a trigger for protein synthesis and a slow transition leading to synaptic consolidation during the late phase of synaptic plasticity. The model explains a large body of experimental data on synaptic tagging and capture, cross-tagging, and the late phases of LTP and LTD. Moreover, it

accounts for the dependence of LTP and LTD induction on voltage and presynaptic stimulation frequency. The stabilization of potentiated synapses during the transition from early to late LTP occurs by protein synthesis dynamics that is shared by groups of synapses. The functional consequence of this shared process is that previously stabilized patterns of strong or weak synapses onto the same postsynaptic neuron are well protected against later changes induced by LTP/LTD protocols at individual synapses.

However, several important phenomena were not captured by the model. The main aspect that was not accounted for is that of the separation of the early expression of synaptic changes and the tag. Even if these two mechanisms occur mainly together, they are chemically distinct, which leads to interesting behaviours in depotentiation experiments for instance. The next chapter introduces a newer model closer to experimental observations and able to reproduce more data.

3 LAYERED SYNAPSE MODEL

The main caveat of the model in the preceding chapter is that it does not account for several mechanisms that have been observed and that are important for the behavioural modeling of chapter 4.

The first phenomenon unaccounted for is that of the separation of the tag and the initial expression of synaptic plasticity. Indeed, the two processes were identified in the TagTriC model (Clopath et al., 2008).

Second, depotentiating effects and their consequences (Bashir and Collingridge, 1994; Martin, 1998; Sajikumar and Frey, 2004a; Stäubli and Chun, 1996) are not present since the transition probabilities are unidirectional, leaving the reversal of plasticity to the sole control of the decaying mechanisms, with long time scales. This had non desirable effects like freezing of all synapses in a high or low state for very long times even if their transitions had been caused by meaningless noise.

Nevertheless, the independence of the two 'layers' of the mechanism of induction and that of consolidation is to my opinion a promising aspect. This extension in dimensionality compared to other models (Barrett et al., 2009; Fusi et al., 2005) could represent the key to solving the dilemma of stability versus plasticity.

I propose here a model that keeps the advatanges of all existing ones – the independence of the different layers and the multiplication of the transition possiblities – together with a way of instantiating metaplasticity in computational models in a biologically plausible way even if the internal variables used to do so are abstract.

3.1 Synapse model

In this section I first introduce my new synapse model and describe the dynamic of its components and how they are coupled together. I then validate the model by applying it to various experimental setups in the field of *synaptic tagging and capture* (STC) spanning the main

characteristics of the theory.

Experimental studies on synaptic plasticity seem to point towards several independent and interdependent processes, both functional and structural, which imply that the action of a synapse is not determined by a simple and singular parameter, such as the synaptic weight (Redondo and Morris, 2011). These phenomena span different time scales, from short to long term effects and even beyond where different biochemical processes intervene, that can prolong the extent of synaptic changes to days or even a lifetime. Since 'long' was already part of the nomenclature, the term *early* and *late long-term potentiation* (LTP) (or depression) were introduced (Frey and Morris, 1997; Reymann and Frey, 2007). Previous models either disregard the question of the very long time scales (Gerstner et al., 1996; Song et al., 2000) or have shown that six synaptic states are not enough to explain various phenomena such as depotentiation (and possibly re-setting of the tag) or slow onset LTP (Barrett et al., 2009; Clopath et al., 2008). I thus designed a synapse model that aims at functionally describing as accurately as possible these mechanisms in a biophysically relevant manner. For these reasons I included in my synaptic model two variables in addition to the synaptic weight which is commonly looked at. This grants both a close biological interpretation and the necessary number of states to cover a large span of experimental work, while being simple enough so that is can be understood and interpreted.

A synaptic state consists of three 'layers', a *weight* w, a *tag* η and a *scaffold* z (Figure 3.1A). The weight is the only visible part in the sense that it influences the size of the postsynaptic potentials triggered in the synapses by incoming presynaptic spikes. The other two layers are hidden but are nonetheless important parts of the synaptic dynamic since they define the stability of the weight. Minimal stimulation paradigms suggest that synaptic efficacies may be bistable entities (O'Connor et al., 2005a; Petersen et al., 1998). Other studies, experimental or analytical, mainly involving autophosphorylating chemical compounds, point to multiple stable configurations of single elements (Graupner and Brunel, 2007). I thus describe my three layers as noisy variables evolving in double well potentials (Figure 3.1B), the depth of which determines the stability of the local dynamic. An isolated variable x has two fixed points, a low state $x = -1$ and a high state $x = +1$, with basins of attraction of equal sizes. In addition to this, layers are influenced by their neighbours, thereby reshaping their energy landscape. These couplings are implemented by two gating variables, g linking the weight to the tag, and p from the tag to the scaffold. Both gates are 'closed' under rest conditions $g = p = 0$ and can

(Figure 3.1) It allows either for capture of PRPs if there was any dopamine release or for decay to the synapse's low state. This stands in contrast to the case where depotentiation occurs before a tag had time to be set. In this situation, the synapse is directly set back to the LO state ($ii - i$). (**C**) Sketch of the HI state of a synapse. In contrast to (A) the weight is high, the tag is up and the scaffold is large. (**D**) Typical behaviour of a synapse during an e-LTP inducing protocol. I show the time course of the three layers of a synapse (blue, yellow and green lines) and the synaptic state it corresponds to ($i - viii$). (**E**) As in D, in the case of a stronger stimulus, inducing l-LTP. Note that consolidation occurs thanks to the presence of PRPs. (**F**) As in E, with a resetting stimulus short after potentiation.

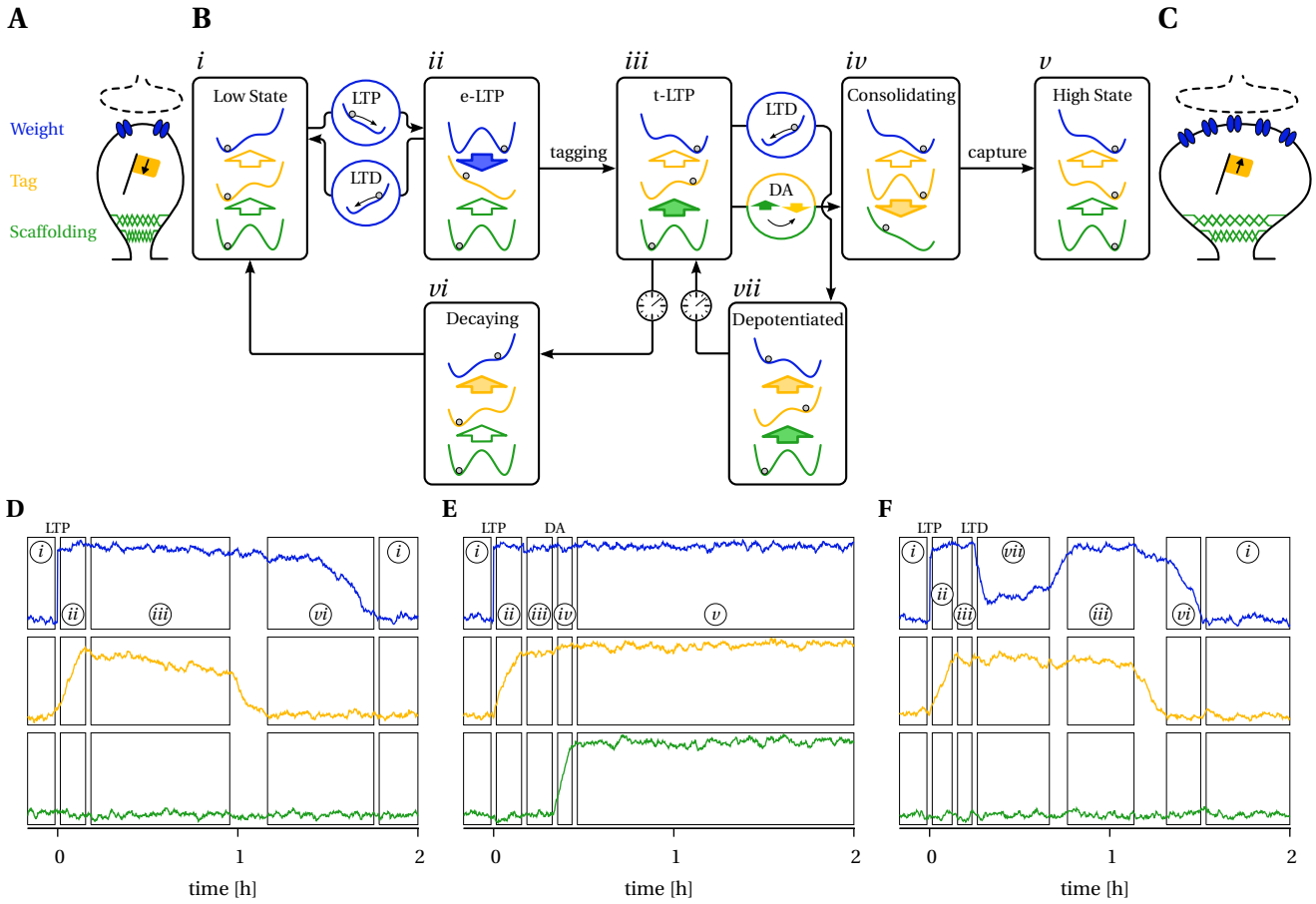


Figure 3.1 – **Synapse's states and transitions.** Potentiating protocols applied on the model have different outcomes. (**A**) Sketch of the LO state of a synapse. It consists of three elements, a low weight (blue) and two hidden variables, a down tag (yellow) and a small scaffold (green). (**B**) Diagram of different synapse states, focused on potentiation. The synapse's internal variables are represented by three double well potentials (showed by large arrows). These variables are coupled to each other, altering their stability properties. A variable in its low state is represented by a ball on the left side of a panel, and a variable in its high state by a ball on the right side. The direction of the couplings depends on the synapse state and on its recent history. ($i-ii$) In the LO state, all three variables are in the lower potential well, and the couplings are upstream, from the scaffold to the tag and from the tag to the weight. A potentiating plastic event carries the weight to its upper state ($w=+1$), without affecting the two other layers. It also reverses the coupling from the weight to the tag. The synapse exhibits then e-LTP. ($ii-iii$) Following LTP induction, within about 10 minutes, a tag is set due to the influence of the first layer on the second (filled blue arrow). The coupling between the first two layers then comes back to its resting direction, from bottom to top. ($iii-iv-v$) If dopamine is delivered to the postsynaptic neuron, production of PRP is triggered, allowing for stabilization of recent plastic changes. It reverses the direction of the coupling between the tag and the scaffold for approximately 2 hours enabling the last layer to follow its neighbour to the high state ($z=+1$). This changes the long term stability of the synapse. (vi) In the absence of external input a tagged synapse decays back to its resting state within a few hours. The timescale of the decay is determined by the time needed for diffusive noise to push the tag out of the metastable potential well it is trapped in. (vii) When a depotentiating protocol is applied to a tagged synapse the weight is reset to its low state. Both the first and the second layers are then in a metastable situation. Because the potential barrier for the weight is lower than for the tag, the weight will bounce back up setting the synapse back into the t-LTP state. (Continued on previous page)

be 'opened', i.e. g or $p \to 1$, by external factors, be it *spike-timing dependent plasticity* (STDP) or neuromodulation.

3.1.1 Synaptic weight

The first layer of my synapse model is the synaptic weight w. One possible interpretation of it is the mean amount of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) in the postsynaptic membrane (Correia et al., 2008). However other factors are known to influence synaptic strengths in general, like presynaptic vesicle release.

Under rest conditions the weight dynamic is partially determined by the position of its neighbouring tag variable with a strength proportional to the difference $\eta - w$. For a synapse in the *low* (LO) state all layers are in their respective low state ($w = -1$, $\eta = -1$ and $z = -1$). In this situation a low weight ($w = -1$) is a stable fixed point since the difference between the weight and the tag vanishes. A weight in the high state however ($w = +1$), quickly decays back to the low state pulled by the coupling $\eta - w$. For more details see the Methods section.

3.1.2 Induction

Standard electrophysiological protocols induce different functional outcomes, either LTP or *long-term depression* (LTD). Moreover, these changes can last only a few hours or persist for a longer time. For example a *tetanus* (TET), a very high firing rate stimulation protocol ranging from 0.2 to 3 seconds at 100 Hz, induces LTP on hippocampal slices *in vitro*. In my model this happens via an STDP input term I_w in the first layer dynamic which pushes the weight to its high state ($w = +1$). The synapse then finds itself in a state of *early* LTP (e-LTP) (Figure 3.1B*ii*).

3.1.3 Tagging

Without any further modifications, the weight would rapidly decay back to its low state ($w = -1$) thus not enabling long lasting changes. But this is altered by structural changes of the spine which occur alongside functional changes following LTP protocols. These changes are not necessary for induction of plasticity but are crucial for the next phases of LTP. This altered biochemical configuration is believed to act as a 'tag', i.e. as storage of the potential for a lasting change of synaptic efficacy (Redondo and Morris, 2011). I model this *tagging* process by opening the gating variable g between the weight and the tag (and thereby temporarily cutting out the reciprocal influence of the tag on the weight) the effect of which will be to drag the tag along to the high state ($\eta = +1$). This opening typically lasts for around ten minutes.

The synapse now finds itself in a *tagged* LTP (t-LTP) state where the weight is stably held up by the tag (Figure 3.1B*iii*). The latter however is in a metastable situation under the influence of the scaffold which hasn't moved from the low state ($z = -1$). Note that the coupling strength from the scaffold to the tag is slightly smaller as compared to the one from the tag to the weight,

enabling this metastable situation instead of a simple decay. The escape rate of a variable trapped in a potential well with a barrier height ΔU we know from Kramer's law is of the order $\sim \exp\left(-\Delta U/\sigma^2\right)$ if σ is the noise amplitude. Parameters of the model have been tuned to obtain a mean decay time of approximately one hour (see Methods). A typical example of a synapse undergoing e-LTP and then decaying back to its LO state can be seen in Figure 3.1D.

3.1.4 Consolidation

So far synaptic modifications were only potential changes and were noncommittal about persistence for more than a few hours. In order to last for a day or more a synapse must undergo a *consolidation* step which stabilizes previous changes against noise fluctuation or depressing events. Stabilization happens through complex intracellular signal transduction cascades relying on several factors. One of which are *plasticity-related proteins* (PRP) (proteins or 'products' if we include diffusion of mRNAs in the dendrites) who play a key role in this process (Redondo and Morris, 2011). Only through their capture by the chemical compound of the tag can a synapse maintain functional changes in efficacy. Synthesis of these PRPs takes place in the soma or in dendritic compartments, apical or basal (Sajikumar et al., 2007). Proteins then have to diffuse to tagged synapses within a specific time window following LTP induction in order to have any effect. This cell wide scope stands in contrast to local mechanisms of synaptic tagging. Interestingly, the trigger for protein production is a novelty or reward signal instantiated by a phasic change in concentration of dopamine (in the CA1 region of hippocampus) or of other neuromodulators. In the theoretical community this is referred to as a 'three factor rule' (the first two being the firing activities of pre- and postsynaptic cells).

The mechanism responsible for stabilization of previous changes in my model is similar to the tagging process. Just like opening of the g gating variable brings the synapse from e-LTP to t-LTP, the passage from t-LTP to *late* LTP (l-LTP) occurs through the variable p (as in proteins). The gating variable is opened by the presence of an ad hoc novelty, reward or surprising signal (DA). The tag loses its metastability and is able to drag along the scaffold to the high state ($z = +1$) thereby maintaining whatever changes occurred recently. Even after protein level has decayed to normal concentration the synapse remains in a *high* (HI) state, meaning that all of its components, the weight, the tag and the scaffold, are in their respective high states ($w = +1$, $\eta = +1$ and $z = +1$) (Figure 3.1C,E).

All the explanations above remain valid in the case of LTD, but in a reversed fashion (see Supplementary Figure 3.4).

3.1.5 Tag resetting and re-setting

One startling issue which has attracted a lot of attention in the field of hippocampal plasticity is the phenomenon of depotentiation. It seems to be governed by rules diverging from those of synaptic depression (Martin, 1998). A resetting protocol applied on a previously potentiated

synapse will have a different outcome depending on the time interval between the two stimuli. If a resetting protocol is given five minutes only after LTP induction, the synapse is brought back to its LO state and is henceforth not able to capture any PRPs. However if the interval exceeds ten minutes, e-LTP is only transiently turned down before being re-established. Moreover the tag has had time to be set allowing for further capture of PRPs, if available (Sajikumar and Frey, 2004a).

In my model, a weight experiencing depotentiation after having been moved upward by an external stimulus, reverts back to its low state ($w = -1$). Depending on whether the tag has had time to be set and whether the gating variable g is still open, the weight either drags along the tag, finally leaving the synapse in its LO state (Figure 3.1B *ii-i*) or leaves it alone in the high state ($\eta = +1$) (Figure 3.1B *iii-vii*). In the first case the synapse simply remains in its LO state. The other scenario is more interesting in the sense that the synapse is now in a double metastable situation where the weight is low but will eventually decay towards the high state ($w \to +1$) and inversely for the tag ($\eta \to -1$). Since the potential barrier for the weight is lower than that for the tag, the decay rate of the weight is highest (see Figure 3.1F). On a neuron with many synapses the net effect on the mean incoming synaptic weight is a rebound before the usual decay back to baseline. Note that the tag being still up, any PRP synthesis triggering event happening closely in time will be able to consolidate a reset synapse eventually leading it to the HI state.

3.1.6 Learning rule

In my model, the synaptic learning rule takes the form of an external input term I_w in the weight dynamic. I use a standard STDP learning rule, namely the triplet rule by Pfister and Gerstner (2006b), which has been shown to reproduce different aspects of plasticity, such as the STDP learning window or stimulation frequency effects (Bi and Poo, 1998; Dudek and Bear, 1992). Nevertheless this rule does not account for any metaplastic effect that could affect the synapse. I explained earlier that metaplasticity was a key process in the ability to create complex behaviours in living organisms. I show here that the intrinsic architecture of my model is well suited to modifications of existing learning rules that can broaden their range of applicability.

The main modification on the standard triplet rule comes from the observation of depotentiation effects (Sajikumar and Frey, 2004a). Since certain protocols are able to reset previously potentiated synapses without producing any depression on other ones, I had to distinguish a standard plasticity inducing event from a resetting one. In nature 'reset' is thought to be a mechanism acting on an ongoing signal transduction chain and not just on a simple synapse component (Redondo and Morris, 2011). Furthermore depotentiation and depression have been shown to be different biochemical processes (Lisman et al., 2011). Fortunately, the fact that my synaptic model contains more than one variable allowed me to make that distinction by giving my learning rule a dependence on internal parameters.

I defined standard potentiation to take place whenever the weight is pushed *away* from the scaffold, which determines the long term stable state of a synapse. This happens when the difference $w - z$ is positive (the opposite assumption holds in the case of depression). Using this difference I separated the triplet input term into $I_{\text{triplet}} = I_{\text{std}} + I_{\text{reset}}$ (see Methods for details) and multiplied the reset term by an enhancing factor.

Another modification consisted in adding soft bounds by multiplying all potentiating terms by $1 - w$, and by $1 + w$ for depression. This is to ensure that STDP doesn't push the weight beyond the fixed points of the bistable dynamic. Since the coupling from the weight to the tag depends on the difference $\eta - w$, a very high weight (respectively very low) would alter dynamical properties of my system.

3.2 Application of the model to tagging and capture experiments

The large panel of phenomena I have described so far as well as a number of additional experiments in the field of synaptic tagging and capture (see Table 3.3) need to be explained in a single model. Previous ones were able to explain basic paradigms, however they did so either by adding a very long time constant to the depression induction rule (Clopath et al., 2008), not consistent with measurements, or with an ad hoc model for the induction of long term plasticity (Barrett et al., 2009). Here I used a standard STDP learning rule from the literature without modifying the time constants to reproduce experimental results from different groups. Due to the external recording methods used in the experiments some averaging of the recorded synapses takes place automatically. I thus restricted my simulations to a few output cells receiving sparse connections from input units summing to a total of a few thousands synapses (Figure 3.2A). Since only synapses in the LO state can experience potentiation and only those in the HI state can experience depression, I initialized my network with a third of the synapses in the HI state and the other two thirds in the LO state.

It is important to stress the fact that I designed this model to account for a small subgroup of experiments, namely early and late LTP and LTD, rescue of early into late plasticity and resetting experiments. The other results produced here happened to be captured as well by the present model.

Depending on the stimulation protocol, I simulated either one or two groups (S1 and S2) of these input neurons. I focused on two types of stimuli, the TET at 100 Hz for potentiation, and the *low frequency stimulation* (LFS) at 1 Hz for LTD and for depotentiation. Pulses used in such stimulation paradigms usually last 0.2 ms. I assumed that each pulse triggered exactly one spike per presynaptic neuron and that they arrived with some jitter due to their traveling down bundles of axons, the Schaffer collateral for example. I modeled the spike arrival times to the postsynaptic neurons as Gaussian packets with a standard deviation of 3 ms. In the absence of stimulus the activity of the presynaptic units was null.

Postsynaptic neurons were modeled as adaptive integrate and fire units (AIF) (Brette and

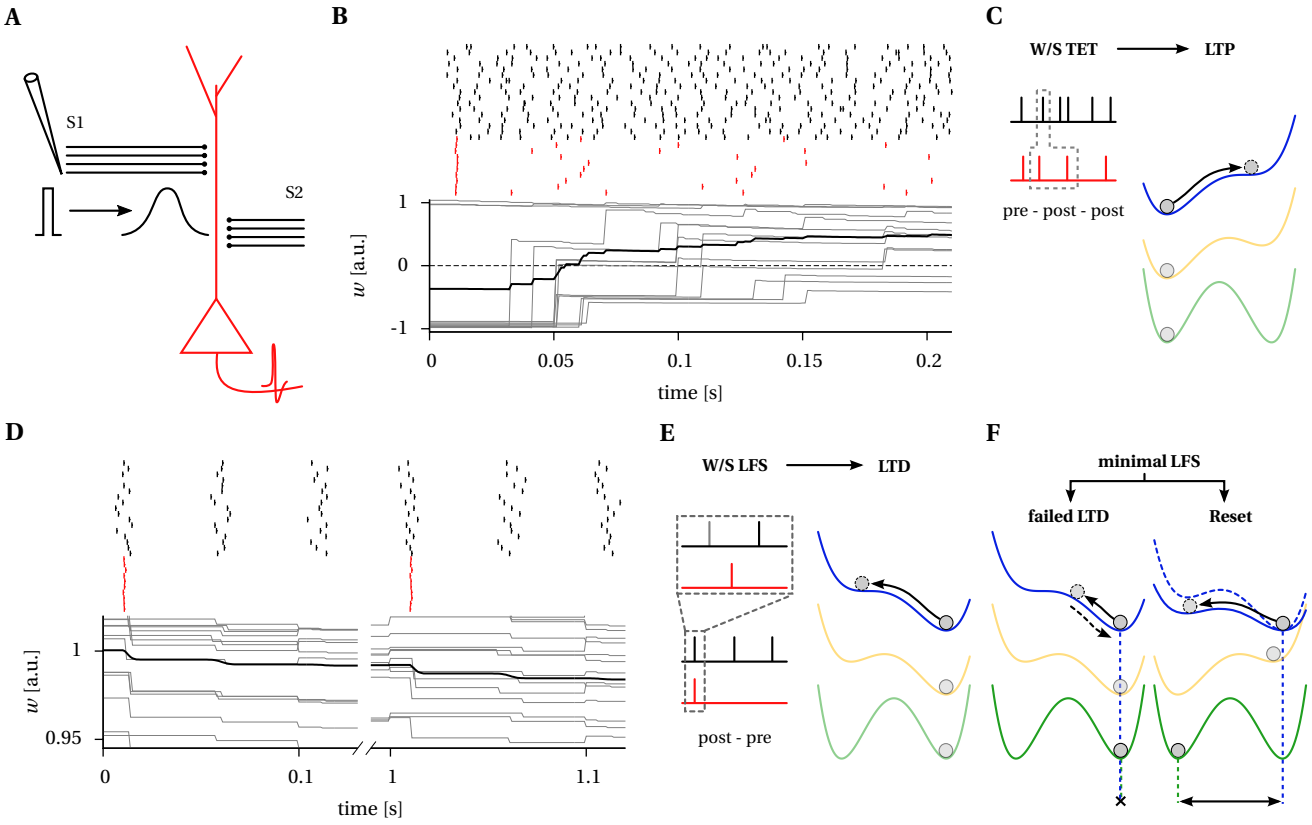


Figure 3.2 – **Stimulation protocols.** (**A**) My network consists of one or two groups (S1&S2, black) of 2000 input units projecting onto 10 AIF neurons (red) with a connection probability of 10%. I modeled the stimulus pulses by a gaussian packet of action potentials with a standard deviation of 3 ms, where each of the inputs emits exactly one spike. Adaptation was tuned so as to obtain only one postsynaptic spike for up to three consecutive packets separated by 50 ms (as in a sLFS protocol, see D). (**B**) Detailed view of a wTET protocol. A raster of a few input units is shown (black bars) as well as all 10 postsynaptic units (in red). The effect on individual weights can be seen in the lower panel (gray lines). Only those crossing the zero line will undergo a long lasting effect. The mean over all weights is shown in black. (**C**) Tetanic stimulation protocols. A wTET (21 pulses @ 100Hz) or a sTET (3x100 pulses @ 100Hz) is strong enough to overcome adaptation, so that the high postsynaptic frequency gives rise to LTP via the triplet effect of the plasticity rule. (**D**) As in (B) in the case of the two first bursts of a sLFS protocol. In the lower panel only synapses initially in the HI state are shown for the sake of visibility. (**E**) Low Frequency Stimulation protocols. During a wLFS (900 @ 1Hz, top) the postsynaptic neuron spikes approximately in the middle of the packet so that the second half of the incoming spikes contribute to a small LTD outcome. Only the accumulation of the 900 pulses makes the stimulus strong enough to have any long lasting effect. In the case of a sLFS (900x(3 @ 20Hz) @ 1Hz, bottom) the bigger amount of pre-after-post spikes gives rise to a quicker effect. (**F**) Resetting effect. A reset protocol (250 @ 1Hz) is not enough to produce any LTD on a synapse in the HI state (left panel) because the amount of pulses is not enough to push the weight variable over the potential barrier. For a synapse in the e-LTP state (right panel) the enhanced depressing STDP term can be seen as a lowered barrier for plasticity. This enables softer protocols to have a clear effect.

Gerstner, 2005), with strong adaptation. Nevertheless tetanic stimuli were strong enough to overcome this adaptation and induce a firing rate in the output neurons of about 20 Hz (Figure 3.2B). This high activity in the postsynaptic units produced potentiation via the triplet effect of the learning rule. Each 'pre-post-post' triplet close enough in time contributed to the final potentiation outcome, pushing the weight upward (Figure 3.2C).

Low frequency stimuli induced no more than one postsynaptic spike per neuron and per second (Figure 3.2D), for which no potentiation occurred. However all the presynaptic spikes arriving after the postsynaptic action potential contributed a small amount to depression via a 'post-pre' effect (Figure 3.2E). Only the accumulation of enough of those pulses allowed the weight to overcome the potential barrier separating it from the low state (Figure 3.2F).

3.2.1 Induction of early *or* late LTP and LTD

Isolated stimulation protocols produce potentiation or depression depending on their pulse pattern and both can be maintained or not depending on the stimulus strength. In the model of the previous chapter it was thought that the trigger for PRP production was specific to the neurons receiving the stimulus in the form of an internal vigilance factor (Carpenter and Grossberg, 1987; Clopath et al., 2008). It turns out that protein synthesis depends only on the presence of neuromodulators, dopamine in the CA1 region of the hippocampus. In slice experiments it occurs through the external stimulation methods which co-stimulate dopaminergic fibers and thereby transiently increase the concentration of DA if the stimulus is strong enough (Lisman et al., 2011; Reymann and Frey, 2007).

I modeled this phenomenon by switching to one my neuromodulation signal (DA) at the end of a strong stimulus in a supervised manner.

Figure 3.3A shows the outcome of six hours of simulation of four separate stimuli. As expected, weak protocols only induced early forms of long term plasticity, because dopamine was not turned on, in line with experimental findings (Frey and Morris, 1997; Sajikumar and Frey, 2004b). In these two cases the mean incoming synaptic weight decayed to baseline within approximately three hours. Strong protocols on the other hand made it possible to switch from the early to the late phase. Both the traces for the strong TET and for the strong LFS were maintained to respectively 180% and 70% of initial conditions.

3.2.2 Rescue of early forms of plasticity

Early forms of plasticity can be rescued if PRP synthesis is triggered in the cell. The event responsible for this needs not necessarily be related to the event that induced the synaptic change in the first place, but can be heterosynaptic. Synthesized proteins and other transcription factors can travel along dendritic compartments to reach any tagged synapse within a certain range. This allows for consolidation of all previous changes regardless of whether the synapse belonged or not to the engram related to the event that triggered PRP production

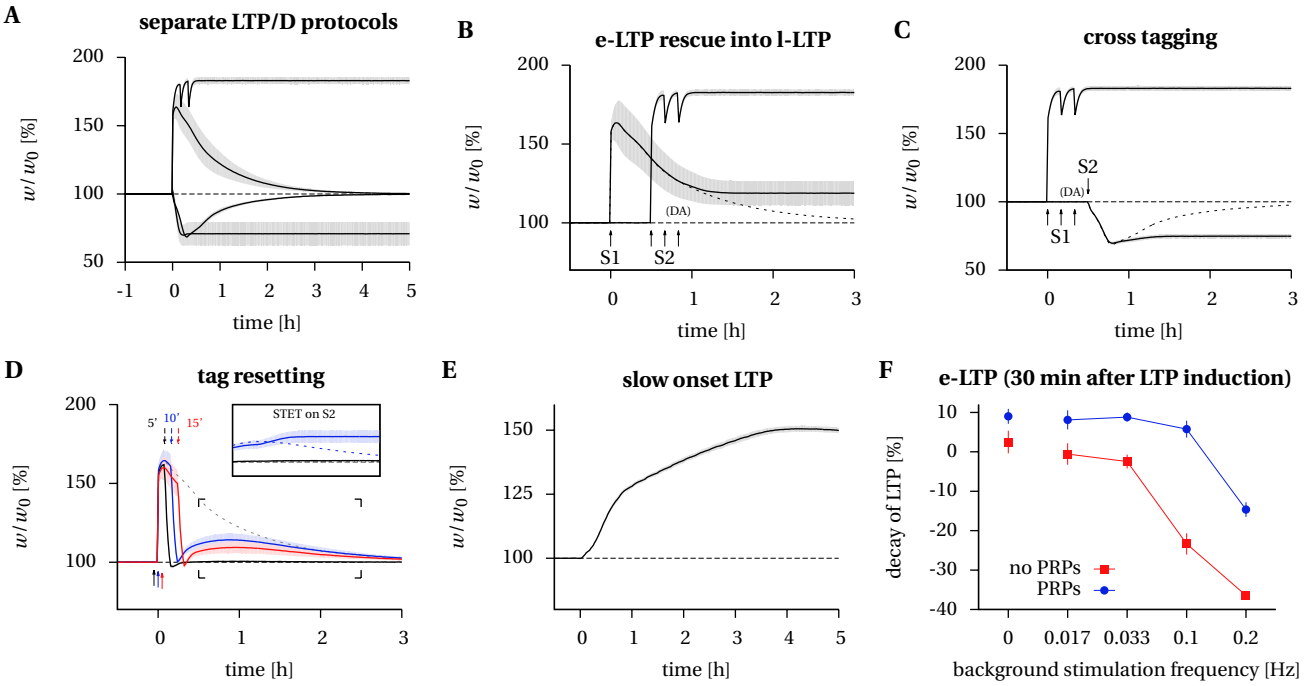


Figure 3.3 – **The model accounts for tagging experiments.** One (A, D*, E, F) or two groups (B, C, D (inset)) of 2000 Poisson neurons project onto 10 postsynaptic AIF neurons with 10% connection probability. (**A**) I simulated independently 4 standard stimuli used in hippocampal slice tagging experiments: a wTET consisting of 21 pulses at 100 Hz (upper decaying curve), a sTET, 3 blocks of 100 pulses at 100 Hz separated by 10 minutes (upper stabilized curve), a wLFS, 900 pulses at 1 Hz (lower decaying curve) and a sLFS, 900 blocks of 3 pulses at 20 Hz separated by 1 second (lower stabilized curve). The evolution of the change in synaptic weight w/w_0 is shown (black lines) and the standard deviation over 10 repetitions (grayed area). Only the two strong stimuli involve delivery of dopamine, necessary for stabilization of the changes. The weak stimuli decay to baseline within a few hours (**B**) e-LTP rescue by another independent strong stimulation. 30 minutes after a wTET has been applied on a first pathway (S1) another set of synapses onto the same neurons (S2) experience a sTET, making PRPs available to every synapse in a non stimulus specific manner. The dashed line represents an independent weakly tetanized pathway, for comparison. (**C**) Example of cross tagging between potentiation and depression. A sTET in one pathway (S1) can provide the PRPs necessary for the stabilization of a wLFS applied on another pathway (S2). The time course of a wLFS alone is shown for comparison (dashed line). (**D**) If a depressing stimulus is applied shortly after a wTET on the same pathway, the synaptic weights are reset to their low state ($w = -1$). If the reset happens 5 minutes after potentiation no tag had time to be set ($\eta = -1$)and the mean weight lies on the 100% line (black line). When the time difference is longer than 10 minutes a rebound can be observed (blue and red lines) due to the synaptic tags dragging along the corresponding weights back to the up state ($\eta = +1$, $w \to +1$). The inset shows that the synapses still can experience consolidation if PRPs are made available via a strong tetanization on a second pathway (S2). (**E**) Slow onset LTP is generally accomplished via pharmacology targeting dopamine D1/D5 receptors. Here I turn the DA signal on and randomly set tags to +1 at different recording times following drug injection and let the individual weights decay upwards ($w \to +1$) producing this slowly rising curve. (**F**) The decay of e-LTP also shows a dependence on activity. To mimic electrophysiological measurements I stimulated my neurons with different background frequencies. I show the amount of decay 30 minutes after tetanization (consisting of 100 pulses at 100 Hz) with (blue line) or without PRPs available (red line). Increasing the frequency accelerates the decay when no consolidation is present. This is due to the resetting effect as the frequency approaches 1. Up to 0.1 Hz, PRPs are able to rescue early changes. Past this limit the weights are reset before tags are set.

(Frey and Morris, 1997; Sajikumar and Frey, 2004b).

In my simulations, a weak LTP protocol on one pathway followed by a strong one after thirty minutes induced a weight change that didn't decay to baseline but was maintained at 120% of its initial value even five hours after stimulus onset (I only show the three first hours after stimulus onset since nothing changes after that limit, Figure 3.3B). Other configurations led to the same conclusions when a weak TET followed a strong TET or in the same situations but in the case of LTD induced by LFS protocols (see Supplementary Figure 3.5).

3.2.3 Cross tagging

The rescue of early forms of plasticity also happened across modalities, i.e. a strong LFS protocol can trigger the machinery for consolidation of tagged potentiated synapses, and inversely. Simulations of a strong TET followed thirty minutes later by a weak LFS showed maintenance of the depressed weights at about 75% (Figure 3.3C). All other combinations of cross tagging (weak or strong TET or LFS, preceding or following another, weak or strong TET or LFS), can be reproduced (Supplementary Figure 3.5).

3.2.4 Tag resetting

As mentioned earlier there exists a time window after induction of e-LTP in a cell in which the setting of tags can be prevented. Past the critical limit of approximately ten minutes a depressing protocol only has an effect on the synaptic weights but not on the tags which had time to be set.

For intervals of 10 or 15 minutes my simulations showed a rebound in the mean incoming weight but not for a 5 minutes interval (Figure 3.3D). This is because the coupling between the first two layers leaves the weights in a metastable situation where they have to eventually decay upward to the high state ($w \rightarrow +1$). Moreover, if a PRP synthesis inducing event was given some time after the resetting stimulus, the synapses were able to capture those and consolidate into l-LTP since the tags were still up (Sajikumar and Frey, 2004a).

3.2.5 Slow onset LTP

An important experiment in the characterization of the independence of the LTP expression versus the tagging process is the induction of slow onset LTP. Applying dopamine receptors D1/D5 agonists to a hippocampal slice makes it possible to express a much slower form of LTP than with standard protocols (Navakkode et al., 2007). This process has been shown to depend on N-methyl-D-aspartate (NMDA), known to mediate the tagging process, and to rely on the presence of PRPs. The slow rise in synaptic weight is then restricted to situations where a stimulus, even a weak one, is applied regularly. No recordings during three hours after drug application gave no potentiation whatsoever.

I modeled this phenomenon by turning on my dopamine signal for 60 seconds at time zero and by randomly setting 5% of the tags $\eta \to +1$ at each recording pulse for the first three hours following the start of the protocol (Figure 3.3E). Because of the opened p variable the manually raised tags stay in their high state ($\eta = +1$) and pull the weights upwards, eventually leading the synapse to its HI state. The simulation showed a slowly rising mean synaptic weight stabilizing at about 150% of initial conditions.

3.2.6 E-LTP dependence on recording frequency

The final test I subjected my model to was the dependence of e-LTP on stimulation frequency. It has been shown that not only l-LTP but also the early phase of plasticity is dependent on protein synthesis at high levels of synaptic activity (Fonseca et al., 2006). In experiments synaptic weights are usually recorded at most once per minute, corresponding to a frequency of 0.0167 Hz. However going to higher recording frequencies accelerates the decay of LTP when no PRPs are available.

I tried this on my network by applying pulses at different frequencies and found that indeed thirty minutes after induction LTP had decayed much more for higher frequencies. The mean synaptic weight was up to 40% lower when recorded at 0.2 Hz than when recorded at one pulse per minute or without recording at all (Figure 3.3F).

3.3 Methods

3.3.1 Neuron model

In my simulations I used leaky integrate-and-fire neurons with conductance based synapses. The evolution of the membrane potential of neuron i is given by

$$\tau_m \frac{dV_i}{dt} = \left(V^{\text{rest}} - V_i\right) + g_i^{\text{exc}}(t)\left(V^{\text{exc}} - V_i\right) + g_i^{\text{inh}}(t)\left(V^{\text{inh}} - V_i\right) \tag{3.1}$$

where g_i^{exc} is the excitatory conductance and V^{exc} the corresponding reversal potential (and similarly for inhibition). A spike is emitted when the potential reaches the threshold ϑ_i. After a spike, V_i is reset to V^{rest} and ϑ_i is set to ϑ^{spike} to implement refractoriness. The threshold then relaxes back to its rest value according to

$$\tau_{\text{thr}} \frac{d\vartheta_i}{dt} = \vartheta^{\text{rest}} - \vartheta_i \tag{3.2}$$

The spike train of neuron j is defined as $S_j(t) = \sum_k \delta\left(t - t_j^k\right)$, with t_j^k being its k^{th} spike time. We can now write the AMPA and GABA input on neuron i as

$$\frac{dg_i^\alpha}{dt} = -\frac{g_i^\alpha}{\tau_\alpha} + \sum_{j\in\alpha} \tilde{w}_{ij} S_j(t) \tag{3.3}$$

where $\alpha \in \{\text{ampa, gaba}\}$ for excitatory, respectively inhibitory neurons and $\tilde{w}_{ij}$ is the synaptic weight of the connection from neuron j to i. The inhibitory conductance is simply $g_i^{\text{inh}} = g_i^{\text{gaba}}$ and the excitatory conductance is the sum $g_i^{\text{exc}} = \beta g_i^{\text{ampa}} + (1-\beta) g_i^{\text{nmda}}$. The NMDA conductance is a filtered version of the AMPA conductance with a slower rise and a longer tail

$$\tau_{\text{nmda}} \frac{dg_i^{\text{nmda}}}{dt} = -g_i^{\text{nmda}} + g_i^{\text{ampa}} \tag{3.4}$$

I skip the voltage dependence of NMDA for computational efficiency.

Some nodes are composed by adaptive integrate-and-fire neurons. The adaptation mechanism has the form of a spike triggered current. In this case, the inhibitory conductance becomes the sum $g_i^{\text{inh}} = g_i^{\text{gaba}} + g_i^{\text{adapt}}$ where the adaptation conductance is added a value g^{spike} at each spike of neuron i, and else relaxes exponentially to zero

$$\frac{dg_i^{\text{adapt}}}{dt} = -\frac{g_i^{\text{adapt}}}{\tau_{\text{adapt}}} + g^{\text{spike}} S_i(t) \tag{3.5}$$

Membrane		**Threshold**		**Synapses**				**PRPs**	
V^{exc}	0 mV	τ_{thr}	5 ms	τ_{ampa}	5 ms	τ_{adapt}	100 ms	k_{up}	$1\ s^{-1}$
V^{rest}	-70 mV	ϑ^{rest}	-50 mV	τ_{gaba}	10 ms		250 ms†	k_{down}	$1/7200\ s^{-1}$
V^{inh}	-80 mV	ϑ^{spike}	100 mV	τ_{nmda}	100 ms	g^{spike}	1		
τ_m	20 ms			β	0.5		10 †		
	10 ms*								

*) for inhibitory neurons (Figure 4.2) †) used in the simulations of chapter 3

Table 3.1 – Neuron model parameters.

3.3.2 Synaptic state

The state of a synapse consists of a linear transform of its weight w_{ij} and of two hidden variables, the tag η_{ij} and the scaffold z_{ij}. All three variables follow the same bistable dynamics $\tau_x \dot{x} = -\frac{dU}{dx}$ with $U(x) = \frac{x^4}{4} - \frac{x^2}{2}$ corresponding to the double well potential of Figure 3.1. This dynamic has two stable fixed points $x = +1$ and $x = -1$ corresponding to the *high* and *low* states respectively. Moreover each variable is coupled to its nearest neighbour(s) via time dependent gating variables. The full system reads (I skip the indices (ij) for clarity)

$$\begin{aligned}
\dot{w} &= \frac{1}{\tau_w} f(w) &&+ \frac{a_{\eta w}}{4\tau_w} \bar{g}(t)(\eta - w) + \sigma \xi_w(t) + I_w \\
\dot{\eta} &= \frac{1}{\tau_\eta} f(\eta) + \frac{a_{w\eta}}{4\tau_\eta} g(t)(w - \eta) + \frac{a_{z\eta}}{4\tau_\eta} \bar{p}(t)(z - \eta) &&+ \sigma \xi_\eta(t) \\
\dot{z} &= \frac{1}{\tau_z} f(z) + \frac{a_{\eta z}}{4\tau_z} p(t)(\eta - z) &&+ \sigma \xi_z(t)
\end{aligned} \tag{3.6}$$

where $f(x) = -x(x-1)(x+1)$ is the derivative of U and the terms $\xi_i(t)$ are independent Gaussian white noise processes with the properties $\langle \xi(t) \rangle = 0$ and $\langle \xi(t)\xi(t') \rangle = \delta(t-t')$.

The real weight is given by the formula

$$\tilde{w} = \frac{w_{\text{low}}}{2}\left((k_w - 1)\, w + k_w + 1\right) \tag{3.7}$$

where $k_w = w_{\text{high}} / w_{\text{low}}$ is the ratio between the high and the low weight.

The different variables are coupled to each other through two functions g and p acting as gating variables, meaning that they take values $g, p \in [0,1]$ and that $\bar{g} = 1 - g$ and $\bar{p} = 1 - p$. The variable g couples the weight and the tag and hence represents the tagging mechanism. I modeled it as a threshold on a variable γ which can be opened by plastic events occurring to the synapse under the condition that it goes in the right direction (LTD for a synapse in the HI state or LTP for a synapse in the LO state, see section Learning rule)

$$g = H(\gamma - \vartheta_\gamma), \quad \text{with} \quad \tau_\gamma \dot{\gamma} = -\gamma + I_\gamma \tag{3.8}$$

where $H(x) = \begin{cases} 1 & \text{if } x > 0 \\ 0 & \text{else} \end{cases}$ is the Heaviside function.

The other coupling variable p, between the tag and the scaffold, stands for PRP and can be seen as the concentration thereof. The trigger for opening the gating is an external reward or novelty signal. Whenever active, this external signal (DA) dominates the constant decay term and pulls p towards 1

$$\dot{p} = (\text{DA}) \cdot k_{\text{up}} \cdot (1 - p) - k_{\text{down}} \cdot p \tag{3.9}$$

Synaptic state				**Learning rule**	
τ_w	200 s	$a_{w\eta/\eta z}$	3.5	A_-	2×10^{-4}
τ_η	200 s	$a_{\eta w}$	1.3	A_+	5×10^{-4}
τ_z	200 s	$a_{z\eta}$	0.95	τ_x	16.8 ms
k_w	3	τ_γ	600 s	τ_y	33.7 ms
σ	10^{-4}	ϑ_γ	0.37	τ_{triplet}	40 ms

Table 3.2 – Synapse model parameters.

3.3.3 Learning rule

In this section I describe the input terms I_w and I_γ acting on the weight and on the gating variable responsible for the tagging process. They both share a standard hebbian learning rule but differ in their modulation by internal parameters.

The standard rule is the triplet STDP rule by Pfister and Gerstner (2006b) in its minimal form with the parameter set corresponding to hippocampal cultures. In this framework, the changes

in the synaptic weights are given by

$$\left(\frac{dw_{ij}}{dt}\right)_{\text{triplet}} = A^+ x_j^+(t)\, y_i^{\text{slow}}(t-\varepsilon)\, S_i(t) - A^- y_i^-(t)\, S_j(t) \equiv I^+_{\text{triplet}} - I^-_{\text{triplet}} \tag{3.10}$$

where ε is a small positive number and $x_j^+(t)$, $y_i^{\text{slow}}(t)$ and $y_i^-(t)$ are filtered versions of the pre- and postsynaptic spike trains $\frac{d\xi_k^\alpha}{dt} = -\frac{\xi_k^\alpha}{\tau_\alpha} + S_k(t)$, $\xi^\alpha \in \{x^+, y^{\text{slow}}, y^-\}$.

This rule doesn't account for the fact that certain stimuli are able to reset formerly potentiated synapses without having any effect on other synapses. Resetting happens when the weight is pushed back in the direction given by the scaffold, that is depressing stimuli for small synapses (when $w-z>0$) and potentiating ones for big synapses (when $w-z<0$). I call small a synapse which has a low scaffold, and the opposite for a big synapse. Using the fact that $1 = H(w-z) + H(z-w)$ I write

$$\begin{aligned} I_{\text{triplet}} = &\overbrace{I^+_{\text{triplet}} H(w-z) - I^-_{\text{triplet}} H(z-w)}^{\text{standard STDP term}} + \\ &\underbrace{I^+_{\text{triplet}} H(z-w) - I^-_{\text{triplet}} H(w-z)}_{\text{reset term}} \quad \equiv I_{\text{std}} + I_{\text{reset}} \end{aligned} \tag{3.11}$$

To account for differential effects of resetting protocols I modulated both input terms $I_\alpha \sim A_\alpha^{\text{std}} \cdot I_{\text{std}} + A_\alpha^{\text{reset}} \cdot I_{\text{reset}}$ where $\alpha \in \{w, \gamma\}$, the weight and the tag gating variable. For the weight input, I only enhanced the reset term, I chose $A_w^{\text{std}} = 1$ and $A_w^{\text{reset}} = 1 + |w-z|$, i.e. the bigger the difference between the weight and the scaffold, the stronger the reset term. The final form of my plasticity rule reads

$$I_w = I^+_{\text{triplet}} \cdot (1 + [z-w]_+) \cdot (1-w) - I^-_{\text{triplet}} \cdot (1 + [w-z]_+) \cdot (1+w) \tag{3.12}$$

where $[x]_+ = xH(x)$ is the linear rectifier. Note that I multiplied the potentiation and depression terms by factors $(1 \pm w)$ to ensure that STDP doesn't push the weight beyond the boundaries of the bistable dynamics.

Since I wanted resetting protocols to reset weights but not to 'untag' synapses, I set $A_\gamma^{\text{reset}} = 0$. However when the stimulus is not a resetting protocol, both potentiation and depression should open the tag gating variable g, i.e. driving it to 1. Remember that the standard STDP input term consists of potentiation for small synapses ($w-z>0$) and depression for big synapses ($w-z<0$). In order to have a positive term always, I needed to take the opposite of I_{std} for $w-z<0$. I thus chose $A_\gamma^{\text{std}} = \text{Sign}(w-z)$ to get

$$I_\gamma = \left[I^+_{\text{triplet}} \cdot H(w-z) + I^-_{\text{triplet}} \cdot H(z-w) \right] \cdot \left(1-\gamma\right) \tag{3.13}$$

here again the term $1-\gamma$ is to ensure that the variable stays between 0 and 1.

3.3.4 Tables and supplementary figures

mechanism	protocol	paper	Z	CZ	BB
early/late LTP & e-LTP → l-LTP	TET	Frey and Morris (1997)	✓	✓	✓
early/late LTD & e-LTD → l-LTD	LFS	Sajikumar and Frey (2003)	✓	✓	✓
cross tagging	TET, LFS	Sajikumar and Frey (2004b)	✓	✓	✓
e-LTP / tag setting dissociation	pharmacology (actin) pharmacology (CaMKII)	Ramachandran and Frey (2009) Redondo et al. (2010)	✓	✗	✓
depotentiation	TET, LFS TET, LFS (2Hz) TBS, TPS TET (250Hz), LFS (5Hz)	Sajikumar and Frey (2004a) Bashir and Collingridge (1994) Stäubli and Chun (1996) Martin (1998)	✓ ✓* ✓* ✓*	✗	✗
measurement frequency influence on e-LTP	TET	Fonseca et al. (2006)	✓	✗	✗
slow onset LTP	pharmacology	Navakkode et al. (2007)	✓	✗	✗
tag lifetime	TET LFS	Frey and Morris (1997) Sajikumar and Frey (2004b)	✗	✗	✗
synaptic competition	TET	Fonseca et al. (2004)	✗	✗	✗
consolidation is activity dependent	TET	Fonseca et al. (2006) Navakkode et al. (2007)	✗	✗	✗
compartments	TET, LFS TET, LFS TBS, TET, LFS	Sajikumar et al. (2007) Parvez et al. (2010) Sajikumar and Korte (2011)	✗	✗	✗
STP	TET, LFS	Sajikumar et al. (2009)	✗	✗	✗

*) small modifications on A^+, A^-, g^{spike} and σ were sometimes necessary

Table 3.3 – **Paper reproducibility**. This table presents the main articles which studied important aspects of the STC theory. A check sign (✓) means a particular model can account for the data of the paper of the same line, whereas a (✗) means that it cannot. **Z**=Ziegler, the new model presented in this chapter, **CZ**=Clopath & Ziegler, the model from Clopath et al. (2008), **BB**=Barrett & Billings, the model from Barrett et al. (2009)

3.4 Conclusion

In this chapter I presented a novel mathematical model describing the different phases of synaptic plasticity. As in the preceding chapter, these phases cover the early or induction phase, the setting of synaptic tags, a trigger for protein synthesis and a slow transition leading to synaptic consolidation during the late phase of synaptic plasticity. Compared to the preceding one, the model explains an even larger body of experimental data on synaptic tagging and capture, cross-tagging, and the late phases of LTP and LTD. Conclusions regarding the stabilization of potentiated synapses by shared protein synthesis and its consequence on the protection of individual synapses hold. Furthermore, the introduction of two 'hidden layers' – the tag and the scaffold – allows for the description of metaplastic effects very important in depotentiation experiments.

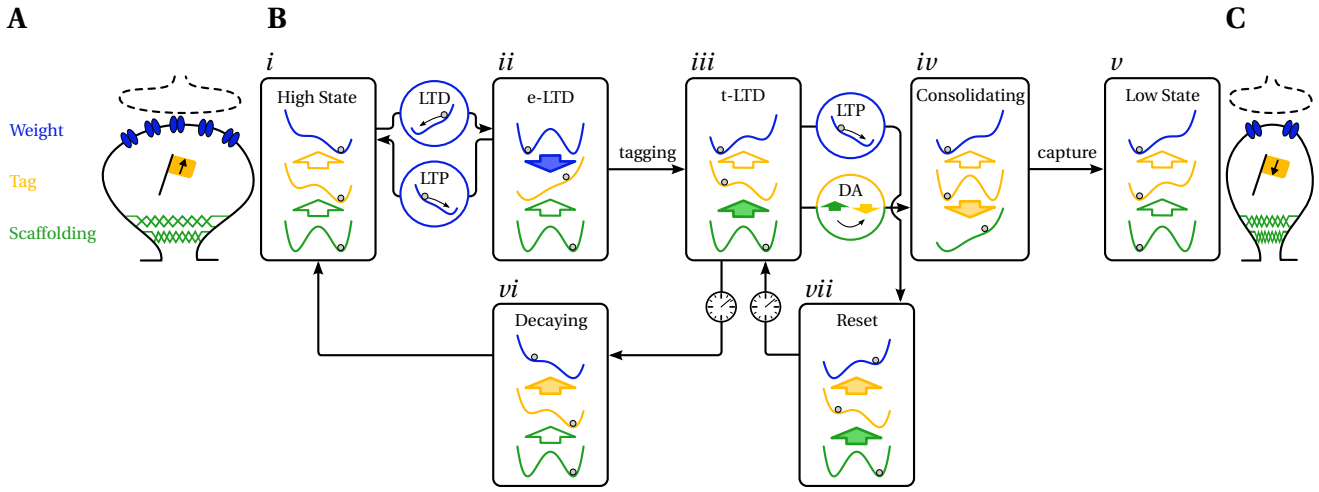


Figure 3.4 – **Synapse's states and transitions, from the high to the low state.** See caption of Figure 3.1.

The main aim of this thesis is to build a bridge from molecular mechanisms to the behaviour of live animals. This is what I do in the next chapter by means of the simulation of a neural network representing the memory system of rats. The synaptic model introduced here constitutes the key to the balance between forgetting and consolidation of different memory traces.

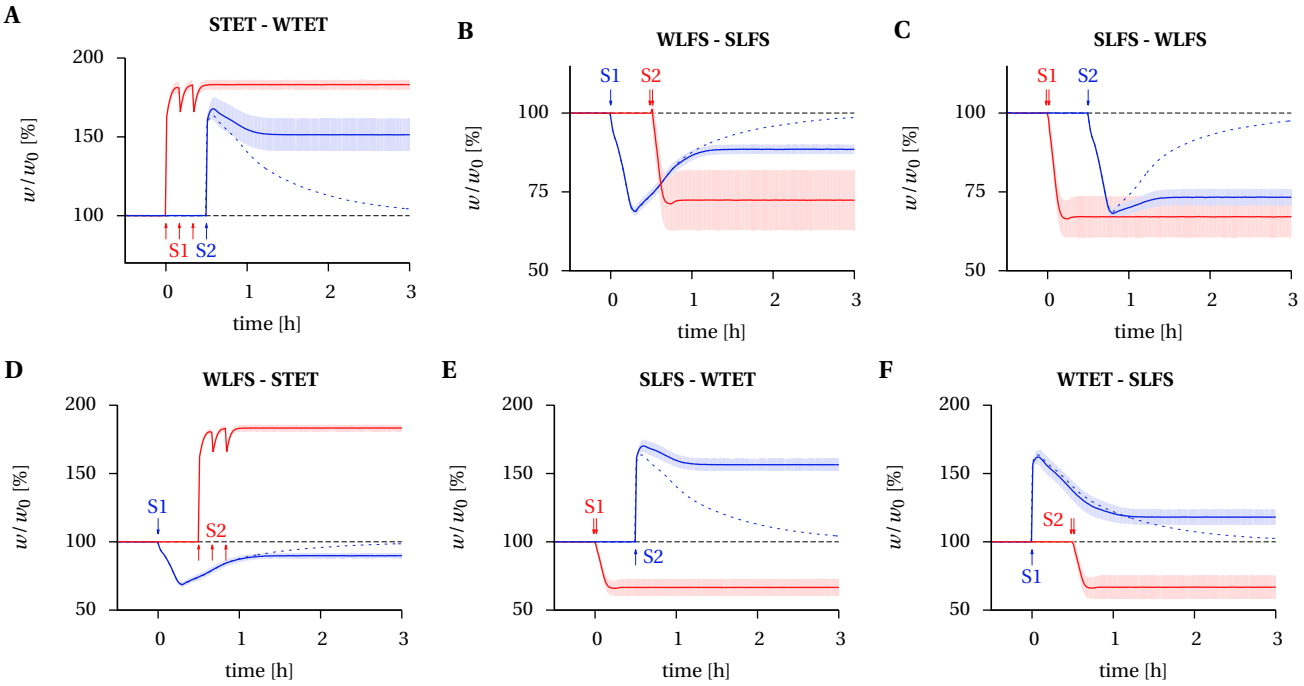


Figure 3.5 – **All configurations of early plasticity rescue and cross tagging.** Strong protocols are shown in red, weak protocols in blue. Dashed lines show what occurs in the case where no strong protocol is given through the other input pathway. See caption of Figure 3.3 for details on the stimulation protocols.

4 BEHAVIOURAL MODELING

In the previous chapter I described my new synapse model and showed the extent of experimental paradigms it accounts for. As I stated in the Introduction, the aim of this thesis is to provide a tentative link between molecular mechanisms and behaviour of live animals through models of synaptic plasticity incorporating neuromodulatory effects.

This is what I show in this chapter by the modeling of an inhibitory avoidance task showing tagging and capture effects at the level of the behaviour of rats (Ballarini et al., 2009; Moncada and Viola, 2007).

4.1 Behavioural tagging

Now that I showed the span of sliced-based experiments that my model can capture, I want to turn to one of the biggest challenges of the STC hypothesis, namely its relevance to learning and memory. Even if making the claim that the STC theory underpins memory engrams, only few studies show conclusive measurements *in vivo*. A promising direction is that of behavioural tagging where an analog of STC recordings *in vitro* has been shown to have very similar features. Experiments on this matter include inhibitory avoidance training, object recognition tasks (Ballarini et al., 2009), extinction of fear memories (de Carvalho Myskiw et al., 2013), taste aversion paradigm and an experiment closer to our day to day memories in the form of a matching-to-place task (Wang et al., 2010). One of these experiments used an *inhibitory avoidance* (IA) setup (Moncada and Viola, 2007) where rats were placed in a cage on an elevated platform and were given an electrical foot shock when jumping down. If put back in the same environment up to one hour later, a rat remembered the negative reward of the electric shock and took a longer time to jump. A day later though, the rats had forgotten about it and showed the same average latency on the experimental platform. This showed a striking similarity with the time scale and the shape of decaying e-LTP measured in rat hippocampus (Figure 4.1).

Interestingly the memory trace of the rats could be saved by giving a stronger foot shock.

Furthermore this transformation into a *long-term memory* (LTM) was shown to depend on protein synthesis. Another way of rescuing short lived memories was to expose the rats either before or after the IA protocol to a novel environment during five minutes. When the difference between the time at which the rats were allowed to freely explore this *open field* (OF) and the time of the IA training, was within a specific window, the rats still remembered the setup one day later.

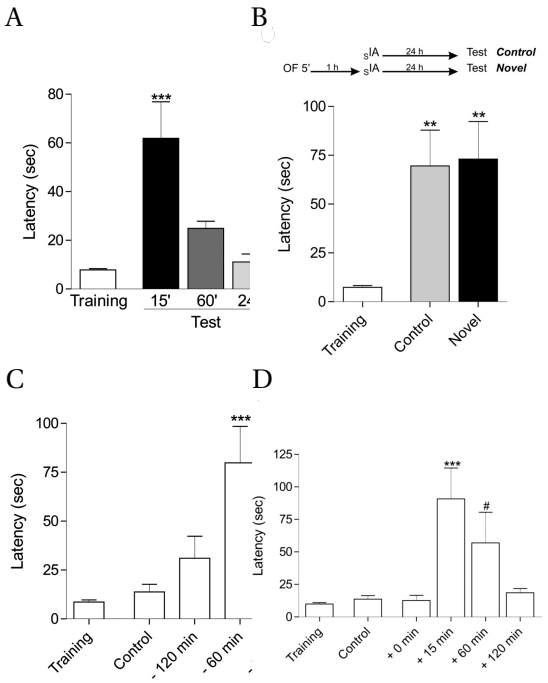


Figure 4.1 – **Behavioural tagging experimental results.** (**A**) LTM decays within a few hours. Rats who were given an IA training showed high latencies when tested 15 minutes after training but showed less fear when tested one hour later and completely lost the fear memory one day after training. (**B**) A stronger foot shock induces LTM at least one day long (whether or not coupled to an OF exploration). (**C**) OF exploration enhanced retention of the fear memory when it occurred between 2h and 3h before the training session. Note that there is no effect when the separation between the OF and the training is of 30 minutes. (**D**) An OF occurring after the IA also transforms STM into LTM, except when it directly follows the training session (Figure taken from Moncada and Viola (2007)).

Since OF exploration for at least five minutes is known to trigger dopamine release in the rat hippocampus (Li et al., 2003), this could well be related to the rescue of early into late LTP by heterosynaptic protein synthesis triggering events.

I wanted to examine the idea of the STC hypothesis as a foundation for memory engrams from a theoretical point of view. I thus implemented a neural network model of a rat, that aimed at reproducing the results of the IA experiment.

4.2 Neural network model

Contextual fear memory takes place in the limbic system and more specifically implies the hippocampus and the amygdala. Context is formed and stored in the hippocampal formation via a conjunction of spatial and non spatial stimuli (Treves and Rolls, 1992). Lesion or inactivation studies but also optogenetics in vivo has shown the necessity of the hippocampus in spatial memory encoding.

The actual fear memory is encoded in the amygdala. This region associates conditioned to unconditioned stimuli via dedicated thalamic inputs (Fanselow and LeDoux, 1999).

Without being specific about which parts I am actually modeling, I got inspired by this configuration in the design of my 'rat' *in silico*. I used mainly a feedforward architecture linking an input pattern to a spatial module to a fear area and finally to an action population (Figure 4.2A). The input englobes three patterns, each coding for a different context.

The first one codes for the *home cage*, the second one for the *training cage* containing the platform and the last one for the *novel environment*. The spatial module consists of a pool of excitatory neurons with recurrent inhibition whose aim is to re-encode contextual information available through the different input patterns. When an unknown pattern is presented the excitatory neurons of the spatial population fire irregularly at about 1 Hz and with a log-normal distribution (Figure 4.2B) as reported by experiments and showed theoretically (Amit and Brunel, 1997). After encoding, a pattern of highly active neurons is formed as in a k-winner-take-all system due to the strong recurrent inhibition (Maass, 2000). This encoding occurs through spike timing dependent plasticity in the connection between the two groups which is composed of the synapse model I discussed in the previous sections. I chose a fear encoding time of one second, corresponding more or less to the foot shock duration of the experiments. I used the same encoding time for the home cage than for the fear training and my Open Field simulations lasted for five minutes (see Methods).

The excitatory population of the spatial module projects to the fear population whose function is to capture associations of contextual and emotional information. In non fearful situations the fear neurons have a low firing rate, not enabling any change in the weights of its incoming synapses. In the case of a fearful event a strong external input increases their activity opening a window for plasticity. The network has been tuned so as to permit long lasting potentiation only in the synapses projecting from presynaptic neurons being part of the encoded spatial pattern and not in the other synapses. The later do experience some potentiation due to the high postsynaptic firing rate but only a short term version since the weight traces do not reach the basin of attraction of the high state (Figure 4.2C).

Finally since fear in rodents is mainly expressed as a freezing behaviour, I chose GABAergic synapses for the projections from the fear population to the action neurons. An active fear population signifies a lowered activity of the action units and thereby modifies behaviour. The action neurons also receive input from the pattern coding for the training cage, because of the

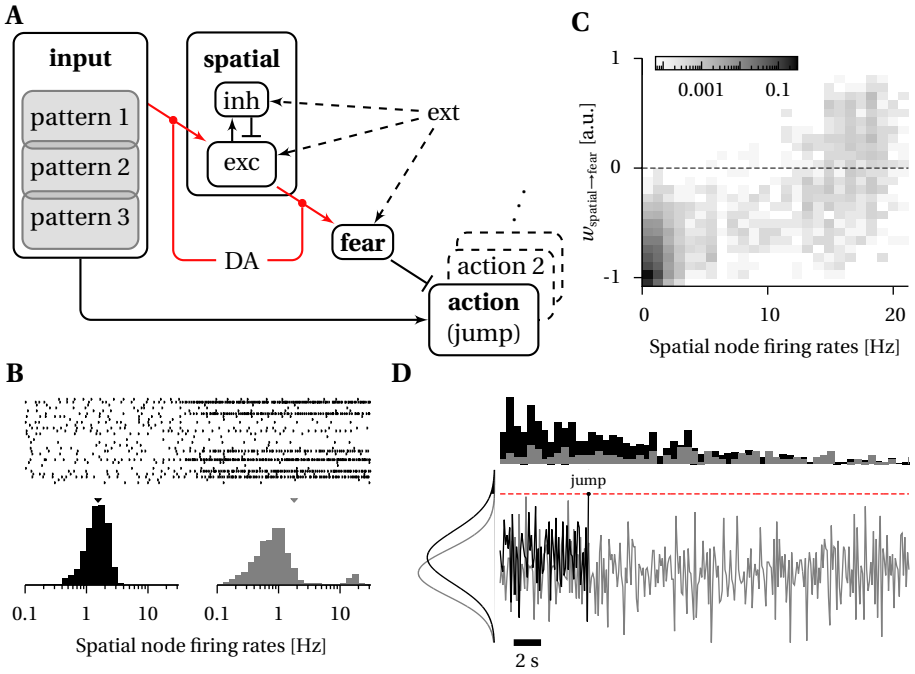


Figure 4.2 – **Behavioural simulation paradigm.** (**A**) Network architecture. The input consists of three patterns of approximately 500 Poisson neurons each, with a 10% overlap. It projects to the spatial population and to the action units. The spatial cluster is composed of 1000 excitatory AIF neurons and 250 inhibitory LIF neurons. They project to the fear population, consisting of 100 LIF neurons which inhibit the 100 AIF action neurons. Background Poisson input (ext) is given to the spatial cluster and to the fear neurons via one-to-one connections (dashed arrows). Plastic connections (or neuromodulation thereof) are shown in red. (**B**) Rate distribution in the spatial module before (black) and after (gray) encoding. An example of corresponding raster plot is shown on top. (**C**) Two dimensional histogram of the synaptic weights from spatial to fear during inhibitory avoidance encoding. Only the pattern encoded by the highly active neurons of the spatial population are linked to the fear neurons (top right corner). Other connections do not cross the zero line and hence decay back to their low state. (**D**) Jump mechanism. The simulations are stopped when the population rate of the fear population, filtered on a 100 ms time scale, hits a threshold (dashed red line), and the jump time is recorded. I show an example trace in a naive scenario (black) and in a situation where fear is present (gray). On the left firing rate distributions show the inhibitory effect of encoded fear. Histograms of jump times in the naive case (black) and in a case where fear is present (gray) are shown on top.

platform that produces on the rat an urge to jump down. In order to create a random latency out of a pool of neurons I set a threshold on the population activity of the action population, filtered with a 100 ms time scale, and recorded jump times as the first hit of neural activity on this threshold (Figure 4.2D; see Methods for details).

Only the connection from the input to the spatial module and from there to the fear population are plastic and they are both modulated by a dopamine signal, constituting the only gate to consolidation of induced synaptic changes. I turned on this signal in two situations, during a strong electric foot shock and at the end of a five minutes exploration of a novel environment (Lisman et al., 2011).

4.3 Behavioural simulations results

The first set of simulations consisted in one single trial of fear memory encoding and a test session after different waiting times (Figure 4.3A). For each experimental setup I performed ten complete simulations, corresponding to a group size of ten 'subjects'. During training my electronic rats stayed about 10 seconds on their virtual platform. Fifteen minutes after fear encoding the latency raised to about 80 seconds, a significant increase due to the inhibition of the action neurons by the fear group. After sixty minutes another set of simulations yielded latencies of about 20 seconds, still significantly higher than the training sessions. One day after the fearful event though, all memory was lost.

A stronger foot shock during the IA session can rescue LTM. In my case it is modeled by including dopamine delivery to the two plastic connections – input to spatial and spatial to fear – of the neural network. In this situation PRPs consolidate the training environment and its association to the unpleasing shock experience which are encoded in the synapses. This reduces the activity of the fear population and hence produces longer waiting times of about 100 seconds.

The second set of simulations dealt with LTM rescue by a novelty signal. The mechanism responsible for this in my network was the transformation of e-LTP to l-LTP of the neural assemblies representing the spatial and fear memories. Here open field sessions were inserted before or after the training sessions, and consisted of five minutes of constant activity of the third of my input patterns together with dopamine delivery towards the end. In trials where the OF preceded the IA, the outcome was determined by the extent of PRP concentration that remained at the time of encoding. The closer the novelty exploration to the IA, the higher the protein concentration and hence the stronger the consolidation of any encoded change in synaptic efficacy. Thus OF preceding IA by two hours gave latencies of about 30 seconds and when the interval was reduced to sixty minutes the effect was stronger with jump times of about 100 seconds (Figure 4.3B).

When OF came after the fear session some interference emerged in the spatial encoding of the different contexts. The low activity during the creation of a neural representation in the spatial

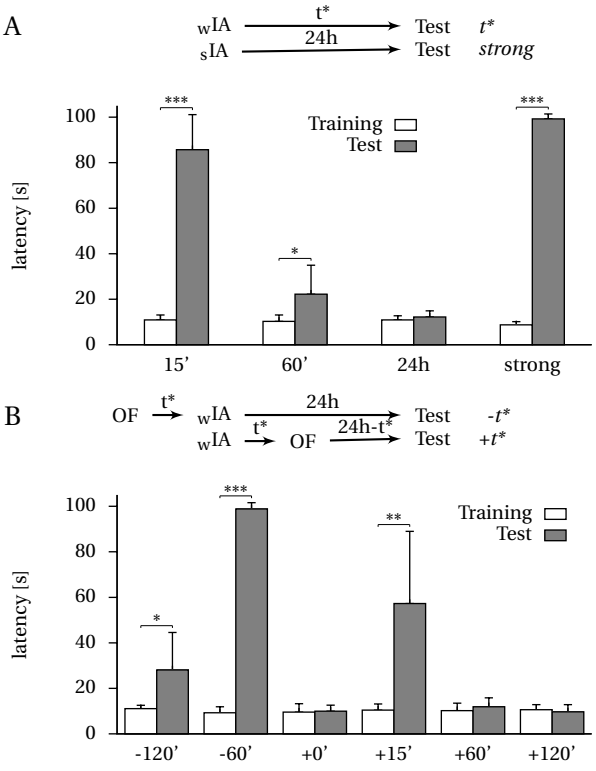


Figure 4.3 – **Behavioural simulations results.** (**A**) Latencies during inhibitory avoidance training (white boxes) and different times after training (gray boxes) in the case of a weak foot shock (paired t tests, $n = 10$; $t = 15$, $p < 0.001$; $t = 60$, $p = 0.029$). A stronger version involving dopamine delivery (strong) is able to rescue an otherwise decaying memory trace ($p < 0.001$). (**B**) LTM can also be rescued by novelty. If an OF setup was applied to the network either before ($-t$) or after ($+t$) the fear encoding in a specific time window, the dopamine delivery associated to it could trigger the necessary protein synthesis to consolidate the synaptic connections (paired t tests, $n = 10$; $t = -120$, $p = 0.013$; $t = -60$, $p < 0.001$; $t = +15$, $p = 0.002$). The hole at $t = +0$ is due to a reset of previously formed connections during the OF stimulation. Since it happens within the 10 minutes window where tags were not set yet, the memory trace is totally erased.

module produced a resetting of the previously potentiated synapses. This means that only if the novelty environment session took place longer than ten minutes after the IA were the training cage related tags already set. And only then they could take advantage of the PRPs whose synthesis was triggered by the OF exploration. This explains the difference between +0 and +15 minutes in the graph of Figure 4.3B. In the first case latencies are at the same level as for training, because all spatial information about the training environment has been lost. Fifteen minutes after encoding synapses were already tagged and hence more stable against interferences. I see values of about 60 seconds in this case.

For intervals longer than one hour no strong effect can be reported. This is because of the accumulation of OF interference and natural weight decay during that period. This stands in contrast to experimental results where those latencies somehow agree with the standard

situation without novelty exploration. Obviously natural neurobiological implementations of that system involve much more complex features such as theta cycles and memory replay during sharp-wave ripples which modify the outcome of such experiments (Lubenov and Siapas, 2008).

4.4 Methods

4.4.1 Input patterns

The three patterns of my input population were created randomly such that each group has a size of $N = 500 \pm 5$ and each pair of patterns has an overlap of $o = 0.1$. I did this by drawing randomly three groups out of an ensemble of size $\frac{1}{o}N$, each of these groups having their size drawn randomly from a Gaussian $\mathcal{N}(500, 5)$.

4.4.2 Connectivity matrices

The k-winner-take-all behaviour in my spatial population was created via feedback inhibition. One main property I wanted it to exhibit was to show a dynamic as random as possible, i.e. different initial conditions should yield different representations of the input. For this I needed to minimize the quenched connectivity noise while maximizing the degree of *different* inputs for each separate neuron. This is realized when $P \to 0$ where P is the connection probability. Since I did not want for computational reasons to have a too large number of input units I opted for another solution. I kept the in-degree constant for all connection matrices in my neural network, meaning that I drew randomly exactly $N_{\text{in}}P$ connections for each postsynaptic neuron (with N_{in} the number of presynaptic neurons and $P = 0.1$).

Group size		**Connection weight**		**Rate**	
N_{input}	$3 \times (500 \pm 5)$	$w_{\text{input}\to\text{spatial}}$	0.2*	$\nu^{\text{on}}_{\text{input}}$	10 Hz
$N^{\text{exc}}_{\text{spatial}}$	1000	$w_{\text{exc}\to\text{inh}}$	0.1		8 Hz†
$N^{\text{inh}}_{\text{spatial}}$	250	$w_{\text{inh}\to\text{exc}}$	0.4	$\nu^{\text{off}}_{\text{input}}$	0.1 Hz
N_{fear}	100	$w_{\text{spatial}\to\text{fear}}$	0.1*		1 Hz†
N_{action}	100	$w_{\text{fear}\to\text{action}}$	1	$\nu^{\text{spatial}}_{\text{ext}}$	100 Hz
		$w_{\text{input}\to\text{action}}$	0.5	$\nu^{\text{fear}}_{\text{ext}}$	20 Hz
		$w_{\text{ext}\to\text{exc/inh/fear}}$	0.5		150 Hz‡

*) plastic connections
†) rates during OF exploration
‡) rate during a foot shock

Table 4.1 – **Behavioural network parameters.**

4.4.3 Jumping times

To emulate a behaviour out of a group of spiking neurons I defined a threshold ϑ_{jump} and recorded the first time it was reached by the population rate ν of the fear population. The rate

was calculated on line via

$$\tau_\nu \dot{\nu}(t) = -\nu(t) + \frac{1}{N_{\text{fear}}} \sum_k \delta\left(t - t^k\right) \tag{4.1}$$

where N_{fear} is the population size and t^k is the time of the k^{th} spike among all neurons in the population. I chose a time scale of $\tau_\nu = 100$ ms.

It is known that such a mechanism yields exponentially distributed jumping times. I took as final jump time for each of my 'rat' in silico the mean over ten random repetitions of the above setup. The sum of independent exponential random variables follows a gamma distribution, a method often used to model real waiting times.

4.4.4 Numerical simulations

Numerical simulations were performed with a time step of 0.1 ms. For differential equations which could be solved analytically I used the exact solution. For all the others, a forward Euler method with the same time step was used. Except for the three internal synaptic variables w, η and z for which I used a time step of $\Delta t = 100$ ms. This updating time was chosen so that $\left|\frac{dx}{dt}\right| \Delta t < 10^{-3}$ for all $x \in \{w, \eta, z\}$.

The code was written in C++ using Open MPI and the Boost libraries, and compiled with the GNU C compiler. Simulations were run on a Linux workstation equipped with Intel(R) Core(TM) i7 CPUs. The bottleneck for simulation time was the total number of plastic synapses, first because their number grow as $\sim N^2$ (with N the number of neurons), and second because of their large amount of internal variables. For simulating my behavioural network the speeding factor was about 2, meaning that it took about half a day to simulate 24h of biological time.

In all behavioural paradigms where the interval between IA training and the final testing was one day, I stopped the simulations after 8h biological time. I justify this choice by the fact that no significant weight change compared to the level of noise could be measured after this time.

context	**input → spatial**				**spatial → fear**			
familiar	A^-	$1.5 \cdot 10^{-4}$	A^+	10^{-4}	A^-	10^{-6}	A^+	10^{-6}
new	A^-	$5 \cdot 10^{-3}$	A^+	10^{-4}	A^-	10^{-6}	A^+	10^{-6}
IA training	A^-	$1.5 \cdot 10^{-4}$	A^+	$3 \cdot 10^{-2}$	A^-	10^{-6}	A^+	10^{-4}

Table 4.2 – **Learning rule parameters**. Note that in this chapter $\tau_w = 20$ s and k_w=5 for the spatial → fear connection.

4.5 Conclusion

In this chapter, I applied the synapse model of chapter 3 to a neural network in order to reproduce experimental findings in a behavioural tagging paradigm. I showed that the molecular

theory of STC can suffice to explain an inhibitory avoidance task in live rats involving tagging and neuromodulatory effects.

In my model, memory traces are represented by neural assemblies linked in a feedforward architecture. Incoming synaptic weights to a certain assembly determine its activation by former network layers. Hence, a memory can be forgotten or consolidated depending on (*i*) the strength of the stimulus or (*ii*) whether it was rescued by another, novel stimulus happening closely in time. A key result is that when a novel stimulus occurs too shortly after the fear event, the fear memory is killed via a depotentiation effect in the synapses of the modeled network.

In the next chapter, I discuss functional consequences of the synapse model of chapter 3 as well as possible future directions enabled by my work.

5 FUNCTIONAL CONSEQUENCES

So far I have described a new synapse model that consists of three variable, the usual synaptic *weight*, a *tag* and a *scaffold*. All three follow a bistable dynamic and are coupled together through two gating variables representing the *tagging* and the *consolidation* processes.

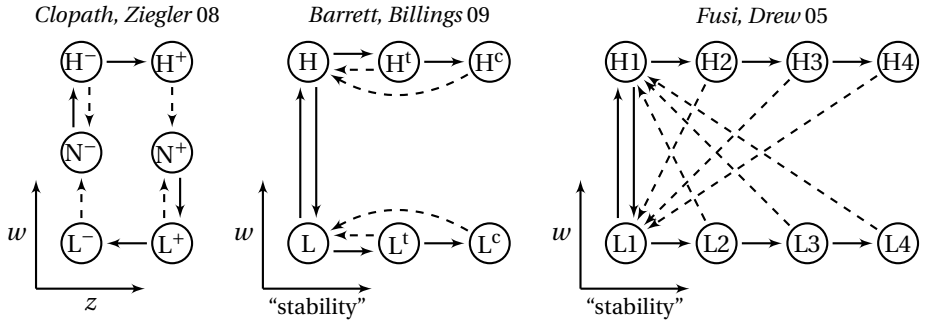
I showed that it can account for many of the experimental findings in the field of synaptic and capture theory. I also showed that it can reproduce a behavioural experimental paradigm putatively involving tagging and capture mechanisms, thereby refining the link from molecular plasticity to behaviour and memory.

In this chapter I expose some functional interpretations of these results. I also propose questions and the possible future research directions that my work enables.

5.1 Synaptic level

A crucial aspect of our synapse model in our view is the description of a synaptic state through three *independent* variables – even if they are at the same interdependent. This increase in dimensionality (compare the following illustration to Figure 5.1) in contrast to classical models grants more states and transitions, allowing for more flexibility in the implementation of plastic and metaplastic interactions. For example it has been stated that a minimal requirement stemming from experimental results was for a synapse to express tristability in its weight (Pi and Lisman, 2008). Even though our model is composed of bistable variables, effectively it holds $2^3 = 8$ states (not all being necessarily stable states). This allows for a distinction between numerous different functional or biochemical configurations. That includes the separation of depression from depotentiation which is done by comparing the weight to its long term stable state defined by the scaffold.

Furthermore the model exhibits a trade off between variability, due to the independence of the variables, and stability, due to the anchoring of the weight through its coupling with the tag, in turn coupled with the scaffold.



Although my model functions independent of the underlying biophysical implementation, capturing the core emergent properties, I can nonetheless relate features of the model to its implementation in the hippocampus. Initial weight change following LTP induction is implemented by an increase in the mean amount of AMPA receptors endo- and exocytosed to and from the membrane of the *postsynaptic density* (PSD). Following AMPAR increase, presynaptic factors have also been shown to participate in the altering of synaptic efficacy (Redondo and Morris, 2011). The tag is thought to be not a single component but a state including several molecules and signaling cascades. These include CaMKII for LTP and calcineurin for LTD. Both the tagging process and the induction of the early phase of plasticity are activated by Ca^{2+} influx in the PSD through NMDA receptors. The scaffold too cannot be reduced to a single molecule. At least two mechanisms are responsible for a sustained change in synaptic efficacy, new slots for inserting AMPARs in the membrane as well as a structural reconfiguration of the whole PSD. Plasticity proteins are still partially unknown but they include GluR1, Homer1a, PKMζ and ARC.

An important feature of modeling is that it provides an easy access to all the variables at stake. Hence without specific assumptions about the detailed biophysical implementation one can still discuss generic functional aspects of the theory.

The PRPs, or the p trace in my model, play a key role since it is where LTP/D loses synapse

Visualization of the model. A All states and the main transitions are shown. Boxes represent a synaptic state with a low weight (blue ball) on the left or a high weight on the right, and similarly for the tag (yellow ball) and the scaffold (green ball). Labeled arrows represent transitions which need external input (potentiation or depression, blue) or the opening of one of the internal gating variable (yellow and green). Single arrows denote transitions which occur naturally through internal dynamic. A clock on one arrow signifies that transition time is random. On the right are the internal axes (weight, tag and scaffold) and the effect of external input in the form of potentiation (upward big blue arrow) or depression (downward big blue arrow). **B-E** Stable states are highlighted, the shaded ones being unstable or no fixed point at all. Only the internal dynamics is shown, i.e. transitions occurring without external input. Four contexts are shown: **B** The synapse is in its resting state, with couplings going from the scaffold to the tag and from the tag to the weight. **C** Tagging is turned on, the weight determines the tag's fate. **D** PRPs are present, due to the action of external reward or novelty signal, the scaffold follows the tag. Dashed arrows represent a case where a synapse trajectory depends on initial conditions or on randomness. **E** Both the tagging and PRPs are on. For details on the fixed points see Appendix A.1.

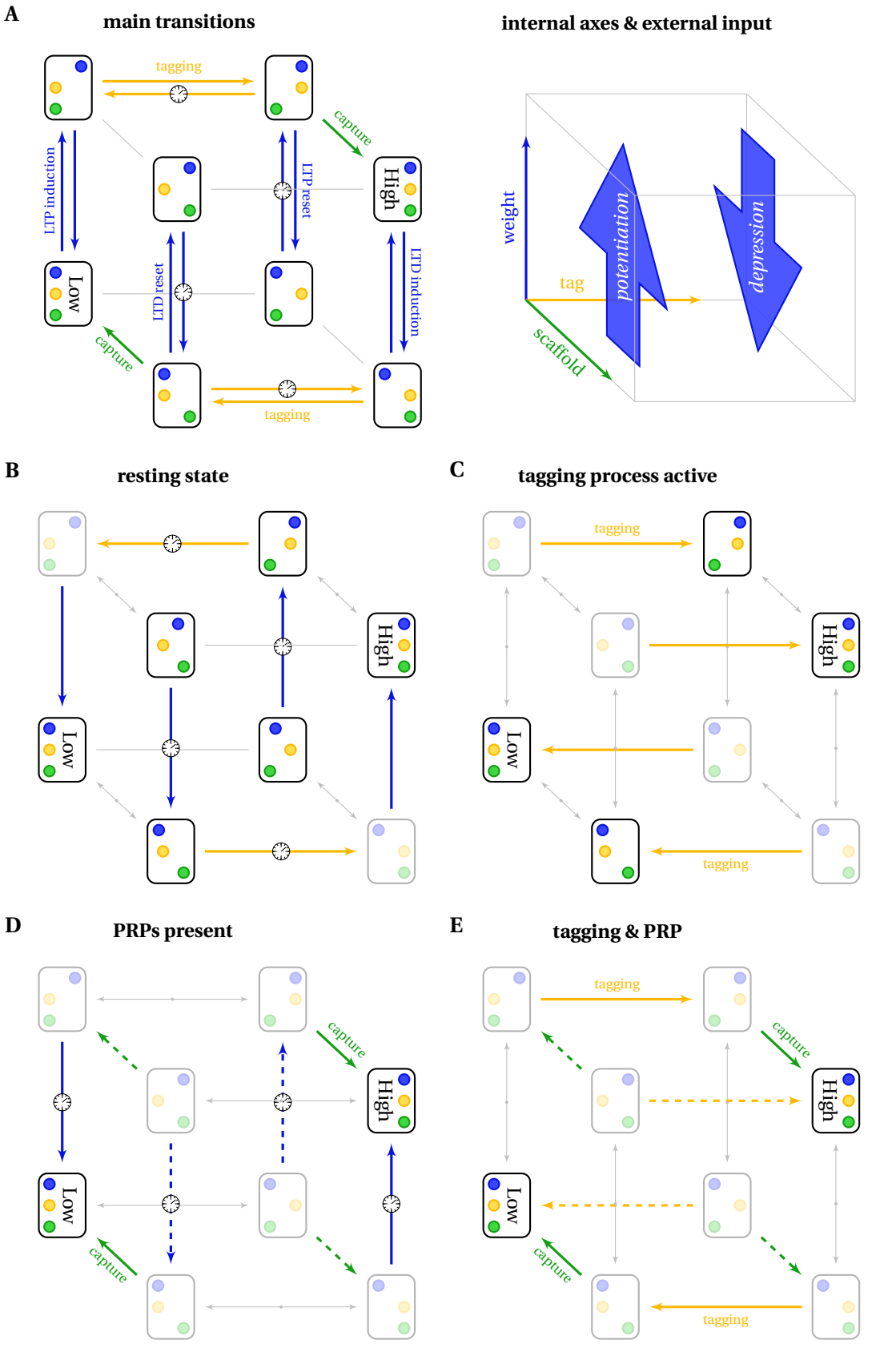


Figure 5.1 – (Caption on previous page.)

specificity. By this I mean that the 'decision' as to whether to consolidate encoded experiences or not is left to the *whole cell*. This implies that, upon dopamine delivery, any experience that took place in the preceding few hours is going to be memorized. In reality release of different neuromodulators caused by various internal pathways target different dendritic compartments of the neuron (Reymann and Frey, 2007). This opens the possibility of an alternate framework of clustered engrams where nearby synapses together with intrinsic dendrite dynamic may participate in local memory 'sub-traces' (Govindarajan et al., 2006).

The complexity in the internal synaptic state transposes into a wide range of potential modifications of the learning rule, weight dependence being only one of them. The synaptic learning rule takes the form $\frac{dw}{dt} = F\left(x, y, \theta_w\right)$ with x, y being the pre- and postsynaptic activities and θ_w an arbitrary set of internal parameters. It allowed us for example to circumscribe depotentiation from depression, but many other potential applications are at hand. For instance, since internal variables are all interdependent, modification of *any* of them will alter the learning rule even if it doesn't appear explicitly in it. Giving more realistic properties to the p dynamic, one of the two gating variables, is one example. This framework, involving the dependence on internal parameters and the non-locality of PRPs availability, has been designated as 'neo Hebbian' (Lisman et al., 2011).

5.2 System level

To validate my model I restricted my analyzes to a specific line of experiments using a limited set of stimuli. However many other protocols, some more realistic than others, have been tested including a repetition of a real recording of a place cell activity in vivo (Isaac et al., 2009). I extended the reproducibility range of my model to some of those stimuli, mainly in the field of depotentiation (see Table 3.3). This includes for potentiation, 100 Hz *high frequency stimulation* (HFS), *theta burst stimulation* (TBS) consisting of a sequence of short bursts given at 5 Hz, and 250 Hz tetanic stimulation; and for depression, 2 Hz LFS, and 5 Hz *theta pulse stimulation* (TPS) (Bashir and Collingridge, 1994; Martin, 1998; Stäubli and Chun, 1996). To accomplish this I had to modify the learning constants A^+ and A^- and sometimes noise level (data not shown).

On the level of neural assemblies, the rescue of early into late long term plasticity has important consequences. It implies that events at the time of encoding are not the unique factors determining the persistence of memories. A dopamine signal coding for novelty, aversive stimuli or reward expectation (Lisman et al., 2011; Schultz et al., 1997) determines what changes are going to be maintained or not. In this sense, it resembles the reward signal of *reinforcement learning* (RL) and R-STDP (Izhikevich, 2007; Sutton and Barto, 1998). In these theories, learning rules make use of an *eligibility trace* which represents *potential changes*, only transformed into effective synaptic alterations upon arrival of an external reward signal. This eligibility trace is analogous in my synaptic architecture to the w variable whose stabilization rests on the presence of neuromodulators. A crucial difference however, is that these transitions aren't

potential but *real* weight changes.

Another important difference is the time scales involved. In RL, effects take place at the level of one second, whereas the decay time of the tags η, which dominates the time scale of the eligibility of weight changes to be consolidated, is of the order of an hour. One way of reconciling the two phenomena stems from the intrinsic architecture of my model. It would be feasible to add a new layer on top of w, and to move the STDP input term to that level, thereby replacing my rule for the induction of plasticity by one compatible with RL. Though the question whether such a biological mechanism or signaling cascade could exist in neurons remains open.

The early phase of LTP is a revertible phenomenon. There is a critical time window of about ten minutes in which a resetting protocol on a previously potentiated synapse leads to absolutely no change because the synaptic tag either couldn't be set or is reset at the same time as the weight. The question arises of the utility of a complete reset. Does it help dissociate irrelevant from salient events? Or does it hinder the positive effect of memory retention enhancement? It is unclear whether a reset is evolutionary advantageous or whether it is merely a side effect of the biological time needed to set the tag. One possible theoretical argument is the fact that a reset allows to accumulate evidence before enduring plasticity (Elliott and Lagogiannis, 2012). Under the assumption of a discrete synapse experiencing a noisy but meaningless signal, I show that the probability of staying in the same state after a period T is in the order of $P_{\text{reset}} = \mathcal{O}\left(\frac{1}{\sqrt{\lambda T}}\right)$ with λ the probability of plasticity event-induced transition per unit time (that I take to be equal for potentiation and depression). This goes to zero much slower than the survival probability in the case where there is no possible reset $P_{\emptyset} = \exp(-\lambda T)$.

All the examples treated in chapter 3, and especially the slow onset LTP experiment point to the crucial role played by metaplasticity. It represents an important means of communication from a brain region to the next and hence at the system level it cannot be set aside. This is why I think essential to propose a synaptic model as simple as can be but still supporting this idea, that can be incorporated in common simulators like NEST or Auryn.

The experiment on dependence of the early phase of LTP to measurement frequency raises the question of the stability of an encoded engram against background activity. It is known that multiplicative rules are catastrophic for memory since they produce a unimodal distribution of synaptic weights in the long run (Billings and van Rossum, 2009). If low frequency firing can erase recently induced changes, how could any trace be stored at all in a live brain? Are synaptic weights sitting in their high potential well ($w = +1$) stable enough to endure background activity? Probably spike correlations or more complex features such as rhythms or sharp waves become here very important. Reconsolidation might also bring clues (Inda et al., 2011). Reactivation of the memory traces at the right moment (where one would have to define what right actually means) could stop forgetting in neural networks.

5.3 Relevance to behaviour

Various studies have shown the necessity of tagging and capture in the formation and maintenance of LTM (Bekinschtein et al., 2007; Wang et al., 2010). I believe that, along with this accumulating experimental evidence, my simulations play one's part in closing the gap between cellular and behavioural consolidation mechanisms. I showed that it is possible to explain behavioural findings with a simulated neural network based on simple assumptions and a synapse model consistent with experimental observations in the field of STC. Nevertheless there are a few points I would like to be transparent about.

Most models dealing with learning or memory separate the learning from the retrieval phase (Gerstner et al., 1996; Hopfield, 1982; Kempter et al., 1999b; Song et al., 2000), whereas I leave plasticity active during the full simulations. However I did distinguish different phases by modulating the strengths of potentiation and depression depending on the contexts (see Table 4.2). I justify this by the fact that plasticity in the hippocampus has been shown to be strongly affected by neuromodulation. One major source is the dopaminergic neurons of the *ventral tegmental area* (VTA) which get highly active in situations where there is reward, novelty or during aversive stimuli (Lisman et al., 2011).

Another issue is that of the 'hole' at +0 minutes in Figure 4.3B. Novelty can rescue LTM when given either before or after fear memory encoding but not if it directly follows the IA training. I explained it by the depotentiation effect which, if it occurs less than ten minutes after induction of LTP, completely aborts the memory encoding process. This has a strong implication, namely the hole has to be asymmetric in time, i.e. a stimulus that preceded an encoding event would have no mean to reset it simply because it was given before. This is not what was measured in one behavioural experiment where an OF exploration thirty minutes *before* IA training also interfered with the memory (see Figure 4.1) (Moncada and Viola, 2007). Note that this was not reported again in another later study by the same group (Ballarini et al., 2009). Thus my model has its limitations since it was not designed to capture every aspects of biological reality in all its tremendous complexity. Many more mechanisms at the system level are affecting memory formation. For example theta rhythms and replay during sharp-wave ripples play an important role in memory formation, even several hours after encoding (Rossato et al., 2009). Furthermore it has been shown that synchronous bursts occurring during slow-wave sleep can selectively erase information in the hippocampus (Lubenov and Siapas, 2008). Nonetheless, I have been able to show that the STC data is sufficient to capture the behavioural phenomenon.

5.4 Insights and open questions

There are further aspects of the theory that my model fails to capture. First it is tempting to describe some forms of *short-term plasticity* (STP), lasting for about fifteen minutes, by a drive of the variable w through the STDP input term towards the high potential well, but not enough to cross the barrier separating the two wells. In this situation it would then decay back to the

bottom of the basin of attraction corresponding to the low state on a time scale matching that of STP experiments (data not shown). However it seems that priming of a hippocampal slice by ryanodine enables an STP inducing protocol to set a tag (Sajikumar et al., 2009). This is not coherent with the mechanism I proposed since setting a tag would alter the weight dynamic and lengthen its decay to the low state, effectively transforming STP into LTP.

Two other phenomena raise the same issue, namely that the weight and the tag seem to be even more independent than the way I built my model. The fact that the traces in LTP resetting experiments bounces all the way up to the level it had before the resetting protocol means that *all* tags are still set ($\eta = +1$), so that they can pull their respective weight to the high state ($w = +1$). Besides, STC experiments have established a tag lifetime by showing that after about ninety minutes it is not possible anymore to consolidate changes in synaptic weight (Frey and Morris, 1997; Sajikumar and Frey, 2004b). This all seems to point towards a synaptic model where a synapse in the tagged LTP state can see its weight decay before the tag; a feature that is not possible in my model since it is always the tag which decays first and then pulls the weight down.

It appears from experiments on slow onset LTP that tags can be set alone without a change in the weight. However I believe that one cannot assess this directly because no drug to my knowledge can disrupt tag setting without disrupting induction of LTP at the same time since those drugs act on NMDA receptors, responsible for both mechanisms. If such a drug was available, my model would predict that, if injected before encoding (in a behavioural paradigm), it would, like protein synthesis inhibitors, leave *short-term memory* (STM) unchanged but would disrupt consolidation into LTM. In my view tag setting and induction of weight change, though being separable, do not occur separately in nature. This is the reason why I modeled the tag input term as acting on the *tag setting mechanism* $g(t)$ and not on the tag variable itself η.

PRP dynamic in my model is very simple and doesn't capture the phenomenon of synaptic competition. One way of modeling it would be to define a pool of proteins – possibly a sum of separate pools p_k corresponding to k different dendritic compartments – whose value would be decreased by nearby consolidating synapses. Furthermore the capture of PRPs is a complex process which depends on the neuronal activity (Fonseca et al., 2006). In order to be accounted for, this would also require a more complex p dynamic, with possibly an external input term similar to those for w and the gating g. This internal competition is interesting theoretically since it could restore the intrinsic vigilance factor that was lost compared to the previous model (Clopath et al., 2008) when setting the p dependence on external neuromodulation alone and not on the amount of tags set (Carpenter and Grossberg, 1987; Clopath et al., 2008).

5.5 Conclusion and future work

In this work, I have presented a new synapse model that includes several internal variables in concordance with biology. I showed the extent to which it accounts for current experimental

paradigms in the field of synaptic tagging and capture. Finally I have demonstrated that a link from cellular to behavioural aspects of consolidation can be built, at least in a theoretical perspective.

A key aspect of this new model is its ability to incorporate metaplastic effects alongside standard learning rules via dependencies on the internal variables. The separation of the triplet rule by Pfister and Gerstner (2006b) into a standard and a reset term is one example.

Functionally, the model integrates several crucial aspects for memory lifetimes found in other existing models. By this I mean

– a multiplication of *metaplastic states*, giving it a way of protecting certain traces against overwriting
– a *binary behaviour*, making it more resistant to noise
– an *integration of plastic events* before its expression, through the potential barrier stemming from the intrinsic dynamic of the internal variables

On top of this, it shows *independence* of the different variables, which could be an essential aspect for memory.

However, investigations on this matter remain to be conducted. Building an analytical framework and looking at memory lifetimes in a system that integrates my model, or a binary version of it, is one of the directions I would like to take for future work.

Another point which deserves attention is that of the implementation of a *critic*. In this work I gave a reward or surprise signal in a supervised manner. Ways of automatizing this process include building a more complex hippocampal network that would compare its representation of a stimulus to stored ones in order to infer novelty, and thus activate or not VTA neurons which would in turn induce dopamine release.

Finally, since late stages of LTP do not preclude further potentiation, it would be interesting to propose a model with a large number $n > 2$ of stable states for each internal variable, or for the weight only. This would open many questions on analytical and computational properties of such a model.

A ANALYTICAL INVESTIGATIONS

A.1 Stability analysis

In this section I discuss the stability of an N-dimensional version of the second refined version of my synaptic model. I describe the state of a synapse by a vector $x \in \mathbb{R}^N$ whose components represent all the variables of the model. In the three dimensional version used in Section 3.3, this vector would correspond to the weight, the tag and the scaffold, $x = (w, \eta, z)$. The evolution of the synaptic state can thus be written

$$\dot{x} = \mathrm{f}(x) + \Gamma x + I + \sigma\xi \tag{A.1}$$

where the non linear function $\mathrm{f} : \mathbb{R}^N \to \mathbb{R}^N$, whose components are given by $\tau_i f_i(x) = -x_i(x_i - 1)(x_i + 1)$, implements the bistable behaviour of the variables, with stable fixed points $+1$ and -1; the matrix Γ couples the variables together; finally I is an external input term and ξ is a noise vector, each of its components being independent and sharing the same properties as in Equation 3.6. The coupling matrix is tridiagonal, meaning that each variable is only influenced by its two nearest neighbours. I set its components to follow these rules

$$\begin{aligned} \Gamma_{ii} &= -\left(\Gamma_{i,i-1} + \Gamma_{i,i+1}\right) \\ \Gamma_{ij} &= 0 \quad \forall \{i, j\} \text{ s.t. } |i - j| > 1 \end{aligned} \tag{A.2}$$

so we get as coupling for the i^{th} component $(\Gamma \cdot x)_i = \Gamma_{i,i-1}(x_{i-1} - x_i) + \Gamma_{i,i+1}(x_{i+1} - x_i)$.

To get back to the three dimensional case of Chapter 3 one would have to set

$$\Gamma_{1,0}=\frac{a_{w\eta}}{4\tau_\eta}g(t) \qquad \text{and} \qquad \Gamma_{0,1}=\frac{a_{\eta w}}{4\tau_w}\big(1-g(t)\big) \tag{A.3}$$
$$\Gamma_{2,1}=\frac{a_{\eta z}}{4\tau_z}p(t) \qquad\qquad \Gamma_{1,2}=\frac{a_{z\eta}}{4\tau_\eta}\big(1-p(t)\big)$$

as well as $I_i = 0\ \forall i > 1$, so that only the weight (x_0) would get external input.

Referring again to the N-dimensional case, I show that it is possible to find a Lyapunov function for the system of equations A.1 in the case where there is no input $I = 0$ and no noise. The Lyapunov function E is defined by

$$E(x_i) = \sum_{i=0}^{N-1} C_i \left\{ \frac{U(x_i)}{\Gamma_{i,i+1}} - x_i x_{i+1} - \frac{\Gamma_{ii}}{2\Gamma_{i,i+1}} x_i^2 \right\} + C_{N-1}\left\{ \frac{U(x_N)}{\Gamma_{N,N-1}} + \frac{x_N^2}{2} \right\} \tag{A.4}$$

under the condition that $C_i = \frac{\Gamma_{i,i+1}}{\Gamma_{i,i-1}} C_{i-1}$ and for an arbitrary $C_0 > 0$. We see also that the coefficients Γ_{ij}, i.e. the couplings, should be non zero, which is reasonable if we define a 'closed' gating variable as being equal to a small $\varepsilon > 0$.

The condition for E to be a Lyapunov function is that it is locally positive definite in a neighbourhood $\mathscr{B}$ of a fixed point x_0 of the dynamical system. Then the point x_0 is stable if the 'energy' of a point in $\mathscr{B}$ under the flow given by the dynamical system always decreases

$$\frac{dE}{dt} = \nabla E \cdot \dot{x} < 0 \quad \forall x \in \mathscr{B} \setminus x_0 \tag{A.5}$$

The function E has been defined so that the condition A.5 is fulfilled. Proving that E is positive definite in a certain domain revealed harder. I did prove however (calculations not shown) that for a reasonable choice of coupling values and for the case where Γ is independent of t (in rest conditions) the two points corresponding to the LO ($x_i = -1\ \forall i$) and the HI ($x_i = +1\ \forall i$) states of Chapter 3 are stable.

To find all the stable fixed points in the three dimensional case for Figure 5.1, I used Mathematica to numerically calculate the eigenvalues of the Jacobian of the system 3.6, and to assess their sign. The HI and LO states are stable fixed points of the system in all conditions and are even the only ones when PRPs are present, the others are

rest condition: $g = 0$ and $p = 0$
- $x = (+0.94, +0.61, -1)$, the t-LTP state
- $x = (-0.94, -0.61, +1)$, the t-LTD state
- $x = (-0.57, +0.61, -1)$, the depotentiated state

– $x = (+0.57, -0.61, +1)$, the LTD-reset state

tagging condition: $g = 1$ and $p = 0$

– $x = (+1, +0.81, -1)$, the t-LTP state

– $x = (-1, -0.81, +1)$, the t-LTD state

Even though it is hard to use the Lyapunov function to assess the stability of all fixed points of the system, it can be used for visualization as an energy landscape. See Figure A.1 for an example.

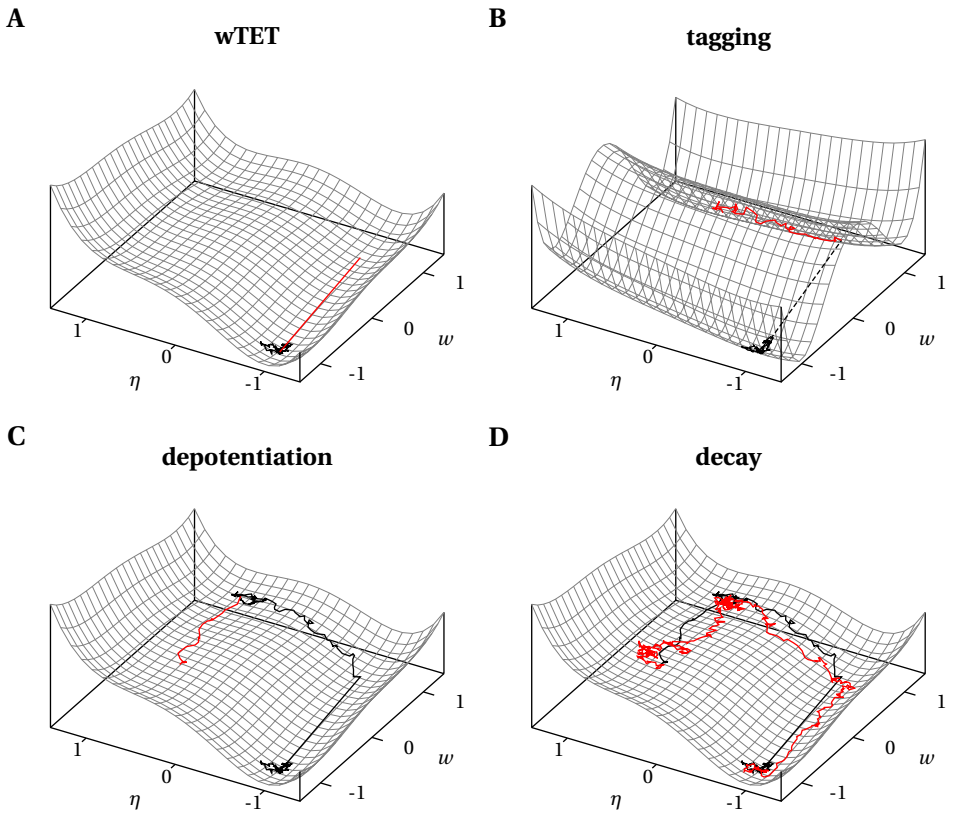


Figure A.1 – **A 3D resetting protocol**. The 'energy landscape' for the two variables x and η is shown (gray grid). The black or red line represents the trajectory of a synapse in the $w\eta$-phase plane adjusted on the z axis at the value of the Lyapunov function for the 2-dimensional system. **A** wTET protocol. The black trace represents the trajectory of the synapse before the stimulus and in red during the wTET protocol. **B** Tagging process. Following potentiation, a tag is set due to the opening of the gate variable ($g \to 1$). **C** Depotentiation protocol. 15 minutes after the wTET a resetting protocol depotentiates the weight ($w \to -1$) while leaving the tag up ($\eta = +1$). **D** Decay. Because of a smaller potential barrier for w the weight decays first towards the state dictated by tag ($w \to +1$), before the tag and then also the weight finally decay bringing the synapse to the LO state.

A.2 Effective learning rule

In this section I compute, in a rate version, the limit between effective potentiation and depression in the case where the intrinsic dynamic of w can be neglected (which is reasonable with a time constant of $\tau_w = 200$ s). This is done by equating the magnitude of plastic change to zero and then solving that equation.

I define the potentiation term as $p(x,y)$ and depression as $d(x,y)$ (in the case of the triplet rule by Pfister and Gerstner (2006b) these would correspond to $p = A^+ x y^2$ and $d = A^- x y$). Removing the dynamic of w and keeping only the input (as in other synaptic plasticity models), its evolution is given by

$$\frac{dw}{dt} = p(x,y)(1 + k[z-w]_+)\cdot(1-w) - d(x,y)(1 + k[w-z]_+)\cdot(1+w) \tag{A.6}$$

Note that I added a modulation of the resetting term by an arbitrary factor k. In the case of a synapse whose scaffold is in the low state ($z = -1$) this becomes

$$\frac{dw}{dt} = p(x,y)(1-w) - d(x,y)(1 + k(1+w))(1+w) \tag{A.7}$$

I now solve $\dot{w} = 0$ to get a relation between the potentiation and the depression terms. This yields

$$p(x,y) = d(x,y)\frac{(1+w)[1+k(1+w)]}{1-w} \equiv d(x,y)\cdot C(w) \tag{A.8}$$

We get for $z = +1$, $d(x,y) = p(x,y)\cdot C(-w)$.

The outcome of a plasticity inducing protocol depends on which side of the potential barrier w finds itself at the end of the protocol. This point will depend on the internal state of the synapse through the coupling terms. But we can get a rough estimate of the condition for potentiation or depression by setting $w = 0$ in these relations. We get, for potentiation

– small synapse ($z = -1$): $p(x,y) > d(x,y)(1+k)$
– big synapse ($z = +1$): $p(x,y) > \frac{d(x,y)}{(1+k)}$

And for depression

– small synapse ($z = -1$): $d(x,y) > \frac{p(x,y)}{(1+k)}$
– big synapse ($z = +1$): $d(x,y) > p(x,y)(1+k)$

This helps to understand the mechanism of how depressing protocols have a stronger effect on potentiated synapses ($w = +1$ and $z = -1$) than on synapses in the HI state ($w = +1$ and $z = +1$).

BIBLIOGRAPHY

H. Abarbanel, R. Huerta, and M. Rabinovich. Dynamical model of long-term synaptic plasticity. *Proc. Natl. Academy of Sci. USA*, 59(10137-10143), 2002.

H. D. Abarbanel, L. Gibb, R. Huerta, and M. I. Rabinovich. Biophysical model of synaptic plasticity dynamics. *Biological cybernetics*, 89(3):214–226, 2003.

L. F. Abbott, J. A. Varela, K. Sen, and S. B. Nelson. Synaptic depression and cortical gain control. *Science*, 275:220–224, 1997.

L. Abbott. Theoretical neuroscience rising. *Neuron*, 60(3):489–495, 2008.

W. Abraham. How long will long-term potentiation last? *Philosophical Transactions R. Soc. Lond B: Biological Sciences*, 358:735 – 744, 2003.

W. Abraham and S. Mason. Effects of the nmda receptor/channel antagonists cpp and mk801 on hippocampal field potentials and long-term potentiation in anesthetized rats. *Brain research*, 462(1):40–46, 1988.

W. C. Abraham. Metaplasticity: tuning synapses and networks for plasticity. *Nat Rev Neurosci*, 9(5):387, May 2008.

W. C. Abraham and M. F. Bear. Metaplasticity: the plasticity of synaptic plasticity. *Trends in neurosciences*, 19(4):126–130, 1996.

W. C. Abraham and A. Robins. Memory retention–the synaptic stability versus plasticity dilemma. *Trends in neurosciences*, 28(2):73–78, 2005.

D. J. Amit and N. Brunel. Dynamics of a recurrent network of spiking neurons before and following learning. *Network*, 8:373–404, 1997.

D. Amit and S. Fusi. Learning in neural networks with material synapses. *Neural Computation*, 6:957–982, 1994.

R. Anwyl. Metabotropic glutamate receptors: electrophysiological properties and role in plasticity. *Brain Research Reviews*, 29(1):83–120, 1999.

A. Arleo and W. Gerstner. Spatial cognition and neuro-mimetic navigation: a model of hippocampal place cell activity. *Biological Cybernetics*, 83(3):287–299, 2000.

A. Artola, S. Bröcher, and W. Singer. Different voltage dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. *Nature*, 347: 69–72, 1990.

A. Artola and W. Singer. Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation. *Trends Neurosci.*, 16(11):480–487, 1993.

L. Badel, S. Lefort, R. Brette, C. C. Petersen, W. Gerstner, and M. J. Richardson. Dynamic iv curves are reliable predictors of naturalistic pyramidal-neuron voltage traces. *Journal of Neurophysiology*, 99(2):656–666, 2008.

A. A. Bagal, J. P. Kao, C.-M. Tang, and S. M. Thompson. Long-term potentiation of exogenous glutamate responses at single dendritic spines. *Proceedings of the National Academy of Sciences of the United States of America*, 102(40):14434–14439, 2005.

F. Ballarini, D. Moncada, M. C. Martinez, N. Alen, and H. Viola. Behavioral tagging is a general mechanism of long-term memory formation. *Proceedings of the National Academy of Sciences of the United States of America*, 106(34):14599–604, August 2009.

F. Ballarini, M. C. Martínez, M. Díaz Perez, D. Moncada, and H. Viola. Memory in Elementary School Children Is Improved by an Unrelated Novel Experience. *PloS one*, 8(6):e66875, January 2013.

A. B. Barrett and M. C. van Rossum. Optimal learning rules for discrete synapses. *PLoS computational biology*, 4(11):e1000230, 2008.

A. B. Barrett, G. O. Billings, R. G. Morris, and M. C. Van Rossum. State based model of long-term potentiation and synaptic tagging and capture. *PLoS computational biology*, 5(1):e1000259, 2009.

Z. I. Bashir and G. L. Collingridge. An investigation of depotentiation of long-term potentiation in the ca1 region of the hippocampus. *Experimental brain research*, 100(3):437–43, January 1994.

Z. I. Bashir, Z. A. Bortolotto, C. H. Davies, N. Berretta, A. J. Irving, A. J. Seal, J. M. Henley, D. E. Jane, J. C. Watkins, and G. L. Collingridge. Induction of ltp in the hippocampus needs synaptic activation of glutamate metabotropic receptors. *Nature*, 363:347–350, 1993.

P. Bekinschtein, M. Cammarota, L. M. Igaz, L. R. M. Bevilaqua, I. Izquierdo, and J. H. Medina. Persistence of long-term memory storage requires a late protein synthesis- and BDNF-dependent phase in the hippocampus. *Neuron*, 53(2):261–77, January 2007.

A. Bell and T. Sejnowski. An information maximization approach to blind separation and blind deconvolution. *Neural Computation*, 7:1129–1159, 1995.

R. Bellman. A markov decision process. *J. Mathematical Mechanics*, 6:679–684, 1957.

U. S. Bhalla and R. Iyengar. Emergent properties of networks of biological signaling pathways. *Science*, 283(5400):381–387, 1999.

G. Bi and M. Poo. Synaptic modification of correlated activity: Hebb's postulate revisited. *Ann. Rev. Neurosci.*, 24:139–166, 2001.

G. Bi and M. Poo. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J. Neurosci.*, 18:10464–10472, 1998.

E. L. Bienenstock, L. N. Cooper, and P. W. Munro. Theory for the development of neuron selectivity: Orientation specificity and binocular interaction in visual cortex. *Journal of Neuroscience*, 2(1):32–48, 1982.

G. Billings and M. C. van Rossum. Memory retention and spike-timing-dependent plasticity. *Journal of neurophysiology*, 101(6):2775–2788, 2009.

T. V. P. Bliss and G. L. Collingridge. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, 361:31–39, 1993.

T. Bliss and A. Gardner-Medwin. Long-lasting potentation of synaptic transmission in the dendate area of unanaesthetized rabbit following stimulation of the perforant path. *J. Physiol.*, 232:357–374, 1973.

T. Bliss and T. Lomo. Long-lasting potentation of synaptic transmission in the dendate area of anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.*, 232:351–356, 1973.

R. D. Blitzer, J. H. Connor, G. P. Brown, T. Wong, S. Shenolikar, R. Iyengar, and E. M. Landau. Gating of camkii by camp-regulated protein phosphatase activity during ltp. *Science*, 280 (5371):1940–1943, 1998.

D. Borota, E. Murray, G. Keceli, A. Chang, J. M. Watabe, M. Ly, J. P. Toscano, and M. A. Yassa. Post-study caffeine administration enhances memory consolidation in humans. *Nature Neuroscience*, 2014.

R. Brette and W. Gerstner. Adaptive Exponential Integrate-and-Fire Model as an Effective Description of Neuronal Activity. *Journal of Neurophysiology*, 94(5):3637–3642, 2005.

N. Bunzeck, P. Dayan, R. J. Dolan, and E. Duzel. A common mechanism for adaptive scaling of reward and novelty. *Human brain mapping*, 31(9):1380–1394, 2010.

D. Buonomano and M. Merzenich. Cortical plasticity: From synapses to maps. *Annual Review of Neuroscience*, 21:149–186, 1998.

Y. Cai, J. P. Gavornik, L. N. Cooper, L. C. Yeung, and H. Z. Shouval. Effect of stochastic synaptic and dendritic dynamics on synaptic plasticity in visual cortex and hippocampus. *Journal of neurophysiology*, 97(1):375–386, 2007.

A. Carlsson, M. Lindqvist, and T. Magnusson. 3, 4-dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature*, 180:1200, 1957.

G. Carpenter and S. Grossberg. Art 2: Self-organization of stable category recognition codes for analog input patterns. *Applied Optics*, 26:4919–4930, 1987.

S. Cassenaer and G. Laurent. Hebbian stdp in mushroom bodies facilitates the synchronous flow of olfactory information in locusts. *Nature*, 448(7154):709–713, 2007.

S. Cassenaer and G. Laurent. Conditional modulation of spike-timing-dependent plasticity for olfactory learning. *Nature*, 482(7383):47–52, 2012.

C. Clopath, L. Ziegler, E. Vasilaki, L. Buesing, and W. Gerstner. Tag-trigger-consolidation: A model of early and late long-term-potentiation and depression. *PLoS Comput Biol*, 4(12): e1000248, Dec 2008.

G. L. Collingridge. Long term potentiation in the hippocampus: mechanisms of initiation and modulation by neurotransmitters. *Trends in Pharmacological Sciences*, 6:407–411, 1985.

S. S. Correia, S. Bassani, T. C. Brown, M.-F. Lise, D. S. Backos, A. El-Husseini, M. Passafaro, and J. A. Esteban. Motor protein-dependent transport of ampa receptors into spines during long-term potentiation. *Nature Neuroscience*, 11(4):457–466, Apr 2008.

J. J. Couey, R. M. Meredith, S. Spijker, R. B. Poorthuis, A. B. Smit, A. B. Brussaard, and H. D. Mansvelder. Distributed network actions by nicotine increase the threshold for spike-timing-dependent plasticity in prefrontal cortex. *Neuron*, 54(1):73–87, 2007.

F. Crick. Memory and molecular turnover. *Nature*, 312(5990):101, 1984.

S. N. Davies, R. A. Lester, K. G. Reymann, and G. L. Collingridge. Temporally distinct pre-and post-synaptic mechanisms maintain long-term potentiation. *Nature*, 338:500–503, 1989.

M. Davis. *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction*, chapter The role of the amygdala in conditioned fear, pages 255–306. Wiley-Liss, 1992.

P. Dayan and L. F. Abbott. *Theoretical neuroscience; Computational and Mathematical Modeling of Neural Systems*. The MIT Press; Cambridge, Massachusetts; London, England, 2001.

J. de Carvalho Myskiw, F. Benetti, and I. Izquierdo. Behavioral tagging of extinction learning. *Proceedings of the National Academy of Sciences of the United States of America*, 110(3): 1071–6, January 2013.

A. Dickinson and B. Balleine. Motivational control of goal-directed action. *Learning & Behavior*, 22(1):1–18, 1994-03-01.

Y. Dudai. *The neurobiology of memory: Concepts, findings, trends*. Oxford University Press, 1989.

S. M. Dudek and M. F. Bear. Homosynaptic long-term depression in area ca1 of hippocampus and effects of n-methyl-d-aspartate receptor blockade. *Proc. Natl. Acad. Sci. USA*, 89:4363–4367, 1992.

T. Elliott and K. Lagogiannis. The rise and fall of memory in a model of synaptic integration. *Neural computation*, 24(10):2604–54, October 2012.

M. S. Fanselow and J. E. LeDoux. Why we think plasticity underlying pavlovian fear conditioning occurs in the basolateral amygdala. *Neuron*, 23(2):229–232, 1999.

M. A. Farries and A. L. Fairhall. Reinforcement Learning With Modulated Spike Timing Dependent Synaptic Plasticity. *J Neurophysiol*, 98(6):3648–3665, 2007.

D. B. Fenker, J. U. Frey, H. Schuetze, D. Heipertz, H.-J. Heinze, and E. Duzel. Novel scenes improve recollection and recall of words. *Journal of cognitive neuroscience*, 20(7):1250–1265, 2008.

R. V. Florian. Reinforcement learning through modulation of spike-timing-dependent synaptic plasticity. *Neural Computation*, 19:1468–1502, 2007a.

R. V. Florian. Reinforcement Learning Through Modulation of Spike-Timing-Dependent Synaptic Plasticity. *Neural Computation*, 19(6):1468–1502, 2007b.

R. Fonseca, U. Nägerl, R. Morris, and T. Bonhoeffer. Competition for memory: Hippocampal ltp under the regimes of reduced protein synthesis. *Neuron*, 44:1011–1020, 2004.

R. Fonseca, U. V. Nägerl, and T. Bonhoeffer. Neuronal activity determines the protein synthesis dependence of long-term potentiation. *Nature neuroscience*, 9(4):478–80, April 2006.

N. Frémaux, H. Sprekeler, and W. Gerstner. Reinforcement learning using a continuous time actor-critic framework with spiking neurons. *PLOS Computational Biology*, 9(4):e1003024, 2013.

U. Frey and R. Morris. Synaptic tagging and long-term potentiation. *Nature*, 385:533 – 536, 1997.

U. Frey, H. Schroeder, H. Matthies, et al. Dopaminergic antagonists prevent long-term maintenance of posttetanic ltp in the ca1 region of rat hippocampal slices. *Brain research*, 522(1): 69–75, 1990.

R. Froemke and Y. Dan. Spike-timing dependent plasticity induced by natural spike trains. *Nature*, 416:433–438, 2002.

S. Fusi. Hebbian spike-driven synaptic plasticity for learning patterns of mean firing rates. *Biol. Cybern.*, 87:459–470, 2002.

S. Fusi, P. Drew, and L. Abbott. Cascade models of synaptically stored memories. *Neuron*, 45: 599–611, 2005.

S. Fusi and W. Senn. Eluding oblivion with smart stochastic selection of synaptic updates. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 16(2):026112–026112, 2006.

W. Gerstner and W. K. Kistler. *Spiking Neuron Models*. Cambridge University Press, Cambridge UK, 2002.

W. Gerstner, R. Ritz, and J. L. van Hemmen. Why spikes? Hebbian learning and retrieval of time–resolved excitation patterns. *Biol. Cybern.*, 69:503–515, 1993.

W. Gerstner, R. Kempter, J. van Hemmen, and H. Wagner. A neuronal learning rule for sub-millisecond temporal coding. *Nature*, 383(6595):76–78, 1996.

W. Gerstner and R. Naud. How good are neuron models? *Science*, 326(5951):379–380, 2009.

A. Govindarajan, R. Kelleher, and S. Tonegawa. A clustered plasticity model of long-term memory engrams. *Nature Reviews Neuroscience*, 7:575–583, 2006.

M. Graupner and N. Brunel. Stdp in a bistable synapse model based on CaMKII and associate signaling pathways. *PLOS Comput. Biol.*, 3:e 221 doi:10.1371/journal.pcbi.0030221, 2007.

V. K. Gribkoff and J. H. Ashe. Modulation by dopamine of population responses and cell membrane properties of hippocampal ca1 neurons in vitro. *Brain research*, 292(2):327–338, 1984.

A. Gupta, Y. Wang, and H. Markram. Organizing principles for a diversity of gabaergic interneurons and synapses in the neocortex. *Science*, 287:273–278, 2000.

R. Gütig, S. Aharonov, S. Rotter, and H. Sompolinsky. Learning input correlations through nonlinear temporally asymmetric Hebbian plasticity. *Journal of Neuroscience*, 23(9):3697–3714, 2003.

R. Gutig and H. Sompolinsky. The tempotron: a neuron that learns spike timing-based decisions. *Nat Neurosci*, 9(3):420–428, March 2006.

A. Hayer and U. S. Bhalla. Molecular switches at the synapse emerge from receptor and kinase traffic. *Plos Computational Biology*, 1(2):e20, 2005.

D. O. Hebb. *The Organization of Behavior*. Wiley, New York, 1949.

C. E. Herron, R. A. Lester, E. J. Coan, and G. L. Collingridge. Frequency-dependent involvement of nmda receptors in the hippocampus: a novel synaptic mechanism. *Nature*, 322:265–268, 1986.

A. L. Hodgkin. The local electric changes associated with repetitive action in a non-medullated axon. *J. Physiol. (London)*, 107:165–181, 1948.

J. Hollerman and W. Schultz. Dopamine neurons report an error in the temporal prediction of reward during learning. *Nature Neuroscience*, 1:304–309, 1998.

J. J. Hopfield. Neural networks and physical systems with emergent collective computational abilities. *Proc. Natl. Acad. Sci. USA*, 79:2554–2558, 1982.

Y.-Y. Huang and E. R. Kandel. D1/d5 receptor agonists induce a protein synthesis-dependent late potentiation in the ca1 region of the hippocampus. *Proceedings of the National Academy of Sciences*, 92(7):2446–2450, 1995.

M. C. Inda, E. V. Muravieva, and C. M. Alberini. Memory retrieval and the passage of time: from reconsolidation and strengthening to extinction. *The Journal of Neuroscience*, 31(5): 1635–1643, 2011.

J. T. Isaac, K. A. Buchanan, R. U. Muller, and J. R. Mellor. Hippocampal place cell firing patterns can induce long-term synaptic plasticity in vitro. *The Journal of Neuroscience*, 29 (21):6840–6850, 2009.

E. M. Izhikevich. Simple model of spiking neurons. *IEEE Trans Neural Netw*, 14(6):1569–1572, 2003.

E. Izhikevich. Solving the Distal Reward Problem through Linkage of STDP and Dopamine Signaling. *Cerebral Cortex*, 17(10):2443–2452, 2007.

E. M. Izhikevich. *Dynamical systems in neuroscience: the geometry of excitability and bursting (Computational Neuroscience)*. The MIT Press, 2006.

E. Kandel, J. Schwartz, and T. Jessell. *Principles of Neural Science*. McGraw-Hill Medical, 07 2000.

U. Karmarkar and D. Buonomano. A model of spike-timing dependent plasticity: one or two coincidence detectors. *J. Neurophysiology*, 88:507–513, 2002.

U. Karmarkar, M. Najarian, and D. Buonomano. Mechanisms and significance of spike-timing dependent plasticity. *Biol. Cybernetics*, 87:373–382, 2002.

B. S. Kauderer and E. R. Kandel. Capture of a protein synthesis-dependent component of long-term depression. *Proceedings of the National Academy of Sciences*, 97(24):13342–13347, 2000.

S. R. Kelso, A. H. Ganong, and T. H. Brown. Hebbian synapses in hippocampus. *Proc. Natl. Acad. Sci. USA*, 83:5326–5330, 1986.

R. Kempter, W. Gerstner, and J. L. van Hemmen. Spike-based compared to rate-based hebbian learning. In M. Kearns, S. Solla, and D. A. Cohn, editors, *Advances in Neural Information Processing Systems 11*, pages 125–131. MIT-Press, 1999a.

R. Kempter, W. Gerstner, and J. L. van Hemmen. Hebbian learning and spiking neurons. *Phys. Rev. E*, 59:4498–4514, 1999b.

J. N. Kerr and J. Wickens. Dopamine d-1/d-5 receptor activation is required for long-term potentiation in the rat neostriatum in vitro. *Journal of Neurophysiology*, 85(1):117–124, 2001.

V. Korz and J. U. Frey. Emotional and cognitive reinforcement of rat hippocampal long-term potentiation by different learning paradigms. *Neuron Glia Biology*, 1(03):253–261, 2004.

M. Krug, B. Loessner, and T. Ott. Anisomycin blocks the late phase of long-term potentiation in the dentate gyrus of freely moving rats. *Brain Res. Bull.*, 13:39–42, 1984.

R. Legenstein, D. Pecevski, and W. Maass. A learning theory for reward-modulated spike-timing-dependent plasticity with application to biofeedback. *PLOS Comput. Biol.*, 4: e1000180, 2008.

Q. Li, M. Rothkegel, Z. C. Xiao, W. C. Abraham, M. Korte, and S. Sajikumar. Making synapses strong: metaplasticity prolongs associativity of long-term memory by switching synaptic tag mechanisms. *Cerebral cortex (New York, N.Y. : 1991)*, 24(2):353–63, February 2014.

S. Li, W. K. Cullen, R. Anwyl, and M. J. Rowan. Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nature neuroscience*, 6(5): 526–31, May 2003.

Y.-W. Lin, M.-Y. Min, T.-H. Chiu, and H.-W. Yang. Enhancement of associative long-term potentiation by activation of β-adrenergic receptors at ca1 synapses in rat hippocampal slices. *The Journal of neuroscience*, 23(10):4173–4181, 2003.

D. S. F. Ling, L. S. Benardo, P. A. Serrano, N. Blace, M. T. Kelly, J. F. Crary, and T. C. Sacktor. Protein kinase mzeta is necessary and sufficient for ltp maintenance. *Nat Neurosci*, 5(4): 295–296, Apr 2002.

J. Lisman. A mechanism for memory storage insensitive to molecular turnover: a bistable autophosphorylating kinase. *Proc. Natl. Acad. Sci. USA*, 82:3055–3057, 1985.

J. Lisman. A mechanism for hebb and anti-hebb processes underlying learning and memory. *Proc. Natl. Acad. Sci. USA*, 86:9574–9578, 1989.

J. Lisman. Long-term potentiation: outstanding questions and attempted synthesis. *Phil. Trans. R. Soc. Lond B: Biological Sciences*, 358:829 – 842, 2003.

J. Lisman and A. Zhabotinsky. A model of synaptic memory: A CaMKII/PP1 switch that potentiates transmission by organizing an AMPA receptor anchoring assembly. *Neuron*, 31: 191–201, 2001.

J. Lisman, H. Schulman, and H. Cline. The molecular basis of camkii function in synaptic and behavioural memory. *Nature Reviews Neuroscience*, 3(3):175–190, 2002.

J. Lisman, A. a. Grace, and E. Duzel. A neohebbian framework for episodic memory; role of dopamine-dependent late ltp. *Trends in neurosciences*, 34(10):536–47, October 2011.

J. E. Lisman and A. A. Grace. The hippocampal-vta loop: controlling the entry of information into long-term memory. *Neuron*, 46(5):703–713, 2005.

E. V. Lubenov and A. G. Siapas. Decoupling through synchrony in neuronal circuits with propagation delays. *Neuron*, 58(1):118–31, April 2008.

G. S. Lynch, T. Dunwiddie, and V. Gribkoff. Heterosynaptic depression: a postsynaptic correlate of long-term potentiation. *Nature*, 266:737–739, 1977.

W. Maass. On the computational power of winner-take-all. *Neural Computation*, 12(11): 2519–2535, 2000.

J. C. Magee and D. Johnston. A synaptically controlled, associative signal for hebbian plasticity in hippocampal neurons. *Science*, 275:209–213, 1997.

R. Malenka and R. Nicoll. Long-Term Potentiation–A Decade of Progress? *Science*, 285(5435): 1870–1874, 1999.

R. C. Malenka and M. F. Bear. LTP and LTD: An embarassment of riches. *Neuron*, 44:5–21, 2004.

H. Markram and M. Tsodyks. Redistribution of synaptic efficacy between neocortical pyramidal neurons. *Nature*, 382:807–810, 1996.

H. Markram, J. Lübke, M. Frotscher, and B. Sakmann. Regulation of synaptic efficacy by coincidence of postysnaptic AP and EPSP. *Science*, 275:213–215, 1997.

H. Markram, Y. Wu, and M. Tosdyks. Differential signaling via the same axon of neocortical pyramidal neurons. *Proc. Natl. Acad. Sci. USA*, 95:5323–5328, 1998.

H. Markram, W. Gerstner, and P. J. Sjöström. A history of spike-timing-dependent plasticity. *Frontiers in synaptic neuroscience*, 3, 2011.

D. Marr. A theory for cerebral neocortex. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, pages 161–234, 1970.

D. Marr. Simple memory: a theory for archicortex. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, pages 23–81, 1971.

S. J. Martin. Time-dependent reversal of dentate ltp by 5 hz stimulation. *Neuroreport*, 9(17): 3775–81, December 1998.

H. Matthies and K. G. Reymann. Protein kinase a inhibitors prevent the maintenance of hippocampal long-term potentiation. *Neuroreport*, 4(6):712–714, 1993.

J. L. McClelland, B. L. O'Reilly, and R. C. McNaughton. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, 102(3):419–457, 1995.

G. A. Miller, E. Galanter, and K. H. Pribram. *Plans and the structure of behavior*. Adams Bannister Cox, 1986.

P. Miller, A. M. Zhabotinsky, J. E. Lisman, and X.-J. Wang. The stability of a stochastic camkii switch: dependence on the number of enzyme molecules and protein turnover. *PLoS biology*, 3(4):e107, 2005.

D. Moncada and H. Viola. Induction of Long-Term Memory by Exposure to Novelty Requires Protein Synthesis: Evidence for a Behavioral Tagging. *J. Neurosci.*, 27(28):7476–7481, 2007.

R. Morris, P. Garrard, J. Rawlins, and J. O'Keefe. Place navigation impaired in rats with hippocampal lesions. *Nature*, 297:681–683, 1982.

J.-P. Nadal, G. Toulouse, J.-P. Changeux, and S. Dehaene. Networks of formal neurons and memory palimpsests. *Europhysics Letters*, 1:349–381, 1986.

S. Navakkode, S. Sajikumar, and J. Frey. Synergistic requirements for the induction of dopaminergic D1/D5-receptor-mediated ltp in hippocampal slices of rat ca1 in vitro. *Neuropharmacology*, 52:1547–1554, 2007.

D. Neveu and R. S. Zucker. Postsynaptic levels of $[Ca^{2+}]_i$ needed to trigger ltd and ltp. *Neuron*, 16(3):619–629, 1996.

T. Nevian and B. Sakmann. Spine Ca^{2+} signaling in spike-timing-dependent plasticity. *J. Neurosci.*, 26(43):11001–11013, 2006.

T. M. Newpher and M. D. Ehlers. Glutamate receptor dynamics in dendritic microdomains. *Neuron*, 58(4):472–497, May 2008.

A. Ngezahayo, M. Schachner, and A. Artola. Synaptic activation modulates the induction of bidirectional synaptic changes in adult mouse hippocamus. *J. Neuroscience*, 20:2451–2458, 2000.

P. V. Nguyen, T. Abel, E. R. Kandel, et al. Requirement of a critical period of transcription for induction of a late phase of ltp. *Science*, 265(5175):1104–1107, 1994.

D. H. O'Connor, G. M. Wittenberg, and S. S.-H. Wang. Graded bidirectional synaptic plasticity is composed of switch-like unitary events. *Proceedings of the National Academy of Sciences of the United States of America*, 102(27):9679–9684, 2005a.

D. H. O'Connor, G. M. Wittenberg, and S. S.-H. Wang. Dissection of bidirectional synaptic plasticity into saturable unidirectional processes. *Journal of neurophysiology*, 94(2):1565–1573, 2005b.

E. Oja. A simplified neuron as a principal component analyzer. *Journal of Mathematical Biology*, 15:267–273, 1982.

H. Okamoto and K. Ichikawa. Switching characteristics of a model for biochemical-reaction networks describing autophosphorylation versus dephosphorylation of ca2+/calmodulin-dependent protein kinase ii. *Biological cybernetics*, 82(1):35–47, 2000.

J. O'Keefe and N. Burgess. Geometric determinants of the place fields of hippocampal neurons. *Nature*, 381:425–428, 1996.

J. Olds and P. Milner. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology*, 47(6): 419–427, 1954.

B. A. Olshausen and D. J. Field. Emergence of simple-cell receptive field properties by learning a sparse code for natural images. *Nature*, 381:607–609, 1996.

R. C. O'reilly and J. L. McClelland. Hippocampal conjunctive encoding, storage, and recall: Avoiding a trade-off. *Hippocampus*, 4(6):661–682, 1994.

N. Otmakhov, L. C. Griffith, and J. E. Lisman. Postsynaptic inhibitors of calcium/calmodulin-dependent protein kinase type ii block induction but not maintenance of pairing-induced long-term potentiation. *J Neurosci*, 17(14):5357–5365, Jul 1997.

S. Parvez, B. Ramachandran, and J. U. Frey. Functional differences between and across different regions of the apical branch of hippocampal CA1 dendrites with respect to long-term depression induction and synaptic cross-tagging. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 30(14):5118–23, April 2010.

E. Pastalkova, P. Serrano, D. Pinkhasova, E. Wallace, A. A. Fenton, and T. C. Sacktor. Storage of spatial information by the maintenance mechanism of ltp. *Science*, 313(5790):1141–1144, Aug 2006.

I. P. Pavlov. *Conditioned reflexes*. Oxford Univ. Press, 1927.

V. Pawlak, J. Wickens, A. Kirkwood, and J. Kerr. Timing is not everything: neuromodulation opens the stdp gate. *Frontiers in Synaptic Neuroscience*, 2(146):1–14, 10 2010.

V. Pawlak and J. N. D. Kerr. Dopamine receptor activation is required for corticostriatal spike-timing-dependent plasticity. *J Neurosci*, 28(10):2435–2446, Mar 2008.

C. C. H. Petersen, R. C. Malenka, R. A. Nicoll, and J. J. Hopfield. All-or-none potentiation at CA3-CA1 synapses. *Proceedings of the National Academy of Sciences*, 95:4732–4737, 1998.

J.-P. Pfister and W. Gerstner. Beyond pair-based stdp: a phenomenological rule for spike triplet and frequency effects. In Y. Weiss, B. Schölkopf, and J. Platt, editors, *Advances in Neural Information Processing Systems 18*, pages 1083–1090. MIT Press Cambridge, 2006a.

J.-P. Pfister, T. Toyoizumi, D. Barber, and W. Gerstner. Optimal Spike-Timing-Dependent Plasticity for Precise Action Potential Firing in Supervised Learning. *Neural Comp.*, 18(6): 1318–1348, 2006.

J. Pfister and W. Gerstner. Triplets of Spikes in a Model of Spike Timing-Dependent Plasticity. *Journal of Neuroscience*, 26(38):9673–9682, 2006b.

H. J. Pi and J. E. Lisman. Coupled phosphatase and kinase switches produce the tristability required for long-term potentiation and long-term depression. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 28(49):13132–8, December 2008.

C. Pozzorini, R. Naud, S. Mensi, and W. Gerstner. Temporal whitening by power-law adaptation in neocortical neurons. *Nature neuroscience*, 2013.

B. Ramachandran and J. U. Frey. Interfering with the actin network and its effect on long-term potentiation and synaptic tagging in hippocampal CA1 neurons in slices in vitro. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 29(39):12167–73, September 2009.

S. Ramirez, X. Liu, P.-a. Lin, J. Suh, M. Pignatelli, R. L. Redondo, T. J. Ryan, and S. Tonegawa. Creating a False Memory in the Hippocampus. *Science*, 341(6144):387–391, July 2013.

S. Ramòn y Cajal. *Histologie du système nerveux de l'homme et des vertébrés*. A. Maloine, Paris, 1909.

R. L. Redondo and R. G. M. Morris. Making memories last: the synaptic tagging and capture hypothesis. *Nature Reviews Neuroscience*, 12(1):17–30, January 2011.

R. L. Redondo, H. Okuno, P. A. Spooner, B. G. Frenguelli, H. Bito, and R. G. Morris. Synaptic tagging and capture: differential role of distinct calcium/calmodulin kinases in protein synthesis-dependent long-term potentiation. *The Journal of Neuroscience*, 30(14):4981–4989, 2010.

K. G. Reymann and J. U. Frey. The late maintenance of hippocampal ltp: requirements, phases, 'synaptic tagging', 'late-associativity' and implications. *Neuropharmacology*, 52(1):24–40, Jan 2007.

J. N. J. Reynolds and J. R. Wickens. Dopamine-dependent plasticity of corticostriatal synapses. *Neural Netw*, 15(4-6):507–521, 2002.

T. W. Robbins and B. J. Everitt. Neurobehavioural mechanisms of reward and motivation. *Current Opinion in Neurobiology*, 6(2):228–236, 4 1996.

M. T. Rogan, U. V. Stäubli, and J. E. LeDoux. Fear conditioning induces associative long-term potentiation in the amygdala. *Nature*, 390(6660):604–607, 1997.

J. I. Rossato, L. R. M. Bevilaqua, I. Izquierdo, J. H. Medina, and M. Cammarota. Dopamine controls persistence of long-term memory storage. *Science (New York, N.Y.)*, 325(5943):1017–20, August 2009.

D. D. B. D. Rubin and S. Fusi. Long memory lifetimes require complex synapses and limited sparseness. *Frontiers in computational neuroscience*, 1, 2007.

J. Rubin, D. D. Lee, and H. Sompolinsky. Equilibrium properties of temporally asymmetric Hebbian plasticity. *Physical Review Letters*, 86:364–367, 2001.

J. Rubin, R. Gerkin, G.-Q. Bi, and C. Chow. Calcium time course as a signal for spike-timing-dependent plasticity. *J. Neurophysiology*, 93:2600–2613, 2005.

S. Sajikumar and J. U. Frey. Resetting of 'synaptic tags' is time- and activity-dependent in rat hippocampal ca1 in vitro. *Neuroscience*, 129(2):503–507, 2004a.

S. Sajikumar and J. U. Frey. Anisomycin inhibits the late maintenance of long-term depression in rat hippocampal slices in vitro. *Neuroscience letters*, 338(2):147–50, February 2003.

S. Sajikumar and J. U. Frey. Late-associativity, synaptic tagging, and the role of dopamine during ltp and ltd. *Neurobiol Learn Mem*, 82(1):12–25, Jul 2004b.

S. Sajikumar and M. Korte. Metaplasticity governs compartmentalization of synaptic tagging and capture through brain-derived neurotrophic factor (BDNF) and protein kinase Mzeta (PKMzeta). *Proceedings of the National Academy of Sciences of the United States of America*, 108(6):2551–6, February 2011.

S. Sajikumar, S. Navakkode, T. C. Sacktor, and J. U. Frey. Synaptic tagging and cross-tagging: the role of protein kinase mζ in maintaining long-term potentiation but not long-term depression. *The Journal of neuroscience*, 25(24):5750–5756, 2005.

S. Sajikumar, S. Navakkode, and J. U. Frey. Identification of compartment- and process-specific molecules required for "synaptic tagging" during long-term potentiation and long-term depression in hippocampal ca1. *J Neurosci*, 27(19):5068–5080, May 2007.

S. Sajikumar, Q. Li, W. C. Abraham, and Z. C. Xiao. Priming of short-term potentiation and synaptic tagging/capture mechanisms by ryanodine receptor activation in rat hippocampal CA1. *Learning & memory (Cold Spring Harbor, N.Y.)*, 16(3):178–86, March 2009.

A. Saudargiene, B. Porr, and F. Wörgötter. How the shape of pre- and postsynaptic signals can influence stdp: A biophysical model. *Neural Computation*, 16:595–626, 2003.

W. Schultz, P. Dayan, and P. R. Montague. A neural substrate of prediction and reward. *Science*, 275(5306):1593–1599, Mar 1997.

W. B. Scoville and B. Milner. Loss of recent memory after bilateral hippocampal lesions. *Journal of neurology, neurosurgery, and psychiatry*, 20(1):11, 1957.

T. J. Sejnowski and G. Tesauro. The Hebb rule for synaptic plasticity: algorithms and implementations. In J. H. Byrne and W. O. Berry, editors, *Neural Models of Plasticity*, chapter 6, pages 94–103. Academic Press, 1989.

W. Senn, M. Tsodyks, and H. Markram. An algorithm for modifying neurotransmitter release probability based on pre- and postsynaptic spike timing. *Neural Computation*, 13:35–67, 2001.

G. H. Seol, J. Ziburkus, S. Huang, L. Song, I. T. Kim, K. Takamiya, R. L. Huganir, H.-K. Lee, and A. Kirkwood. Neuromodulators control the polarity of spike-timing-dependent synaptic plasticity. *Neuron*, 55(6):919–929, Sep 2007.

P. Serrano, E. L. Friedman, J. Kenney, S. M. aubenfeld, J. M. Zimmerman, J. Hanna, C. Alberini, A. E. Kelley, S. Maren, J. W. Rudy, J. C. P. Yin, T. C. Sacktor, and A. A. Fenton. Pkmz maintains spatial, instrumental, and classically conditioned long-term memories. *PLoS Biology*, 6(12): e318, 2008.

H. Shouval, M. Bear, and L. Cooper. A unified model of NMDA receptor-dependent bidirectional synaptic plasticity. *Proceedings of the National Academy of Sciences*, 99(16):10831, 2002.

T. Sigurdsson, V. Doyère, C. K. Cain, and J. E. LeDoux. Long-term potentiation in the amygdala: a cellular mechanism of fear learning and memory. *Neuropharmacology*, 52(1):215–227, 2007.

P. Smolen, D. A. Baxter, and J. H. Byrne. A model of the roles of essential kinases in the induction and expression of late long-term potentiation. *Biophysical journal*, 90(8):2760–2775, 2006.

S. Song and L. Abbott. Column and map development and cortical re-mapping through spike-timing dependent plasticity. *Neuron*, 32(339-350), 2001.

S. Song, K. Miller, and L. Abbott. Competitive Hebbian learning through spike-time-dependent synaptic plasticity. *Nature Neuroscience*, 3:919–926, 2000.

H. Sprekeler, C. Michaelis, and L. Wiskott. Slowness: An objective for spike-timing-plasticity? *PLoS Computational Biology*, 3(6):e112, 2007.

U. Stäubli and D. Chun. Factors regulating the reversibility of long-term potentiation. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 16(2):853–60, January 1996.

R. Steele and R. Morris. Delay-dependent impairment of a matching-to-place task with chronic and intrahippocampal infusion of the nmda-antagonist d-ap 5. *Hippocampus*, 9(2):118–136, 1999.

G. S. Stent. A physiological mechanism for hebb's postulate of learning. *Proceedings of the National Academy of Sciences*, 70(4):997–1001, 1973.

R. Sutton and A. Barto. *Reinforcement Learning: An Introduction*. MIT Press, 1998.

T. Toyoizumi, J.-P. Pfister, K. Aihara, and W. Gerstner. Generalized bienenstock-cooper-munro rule for spiking neurons that maximizes information transmission. *Proc. National Academy Sciences (USA)*, 102:5239–5244, 2005.

T. Toyoizumi, J.-P. Pfister, K. Aihara, and W. Gerstner. Optimality model of unsupervised spike-timing dependent plasticity: Synaptic memory and weight distribution. *Neural comutation*, 19:639–671, 2007.

A. Treves and E. T. Rolls. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. *Hippocampus*, 2(2):189–99, April 1992.

A. Treves and E. T. Rolls. A computational analysis of the role of the hippocampus in learning and memory. *Hippocampus*, 4(3):373–391, 1994.

M. Tsodyks, K. Pawelzik, and H. Markram. Neural networks with dynamic synapses. *Neural computation*, 10(4):821–835, 1998.

E. Tulving and H. J. Markowitsch. Episodic and declarative memory: role of the hippocampus. *Hippocampus*, 8(3):198–204, 1998.

R. Urbanczik and W. Senn. Reinforcement learning in populations of spiking neurons. *Nat Neurosci*, 12(3):250–252, Mar 2009.

M. C. W. van Rossum, G. Bi, and G. G. Turrigiano. Stable Hebbian learning from spike timing-dependent plasticity. *Journal of Neuroscience*, 20(23):8812–8821, 2000.

T. P. Vogels, K. Rajan, and L. F. Abbott. Neural network dynamics. *Annu Rev Neurosci*, 28: 357–376, 2005.

H.-X. Wang, R. Gerkin, D. Nauen, and G.-Q. Wang. Coactivation and timing-dependent integration of synaptic potentiation and depression. *Nature Neuroscience*, 8:187–193, 2005.

S.-H. Wang, R. L. Redondo, and R. G. M. Morris. Relevance of synaptic tagging and capture to the persistence of long-term potentiation and everyday spatial memory. *Proceedings of the National Academy of Sciences*, 107(45):1–6, October 2010.

J. R. Whitlock, A. J. Heynen, M. G. Shuler, and M. F. Bear. Learning induces long-term potentiation in the hippocampus. *science*, 313(5790):1093–1097, 2006.

D. J. Willshaw, O. P. Bunemann, and H. C. Longuet-Higgins. Non-holographic associative memory. *Nature*, 222:960–962, 1969.

L. Wiskott and T. Sejnowski. Slow feature analysis: Unsupervised learning of invariances. *Neural Computation*, 14(4):715–770, 2002.

X. Xie and H. Seung. Learning in neural networks by reinforcement of irregular spiking. *Physical Review E*, 69(4):41909, 2004.

E. Yang and H. Schulman. Structural examination of autoregulation of multifunctional calcium/calmodulin-dependent protein kinase ii. *Journal of Biological Chemistry*, 274 (37):26199–26208, 1999.

M. a. Yassa and C. E. L. Stark. Pattern separation in the hippocampus. *Trends in neurosciences*, 34(10):515–25, October 2011.

R. Yokel and R. Wise. Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. *Science*, 187(4176):547–549, 02 1975.

A. M. Zhabotinsky. Bistability in the Ca^{2+}/calmodulin-dependent protein kinase-phosphatase system. *Biophysical journal*, 79(5):2211–2221, 2000.

Lorric ZIEGLER

EPFL IC ISIM LCN1
AAB 1 39
Station 15
CH - 1015 Lausanne

Nationality: Swiss
Phone: +41 21 693 52 65
Date of birth: March 12, 1982
Email: lorric.ziegler@epfl.ch
Webpage: http://people.epfl.ch/cgi-bin/people?id=183007&lang=en

Education, Awards

Up to date — **Neuroscience Doctoral School**, Swiss Federal Institute of Technology, EPFL Lausanne, Switzerland
Thesis work on synaptic plasticity rules with consolidation

August 2007 — **Master of Science in Theoretical Physics**, University of Geneva, Switzerland
Thesis and research at Concordia University, Montreal, Canada
Thesis work on Casimir force in Randall-Sundrum models

June 2005 — **Bachelor of Science in Mathematics**, København Universitet, Copenhagen, Denmark
Socrates-Erasmus program

June 2004 — **Bachelor of Science in Physics**, University of Geneva, Switzerland

July 2001 — **Federal Maturity**, Collège de Candolle, Geneva, Switzerland
Scientific section, high honours; with awards:
- City of Geneva (best college average)
- Marc Birkigt (mathematics, applied mathematics, physics)
- Givaudan-Roure (physics, chemistry)

Publications

Journal Articles

C. Clopath, L. Ziegler, E. Vasilaki, L. Büsing, W. Gerstner, *Tag-Trigger-Consolidation: A Model of Early and Late Long-Term-Potentiation and Depression*, 2008, PLoS Comput Biol 4(12): e1000248

M. Frank, I. Turan, L. Ziegler, *Casimir force in Randall-Sundrum models*, 2007, Phys. Rev. D 76, 015008

Proceedings

C. Clopath, L. Ziegler, E. Vasilaki, L. Büsing, W. Gerstner, *Modeling plasticity across different time scales: the TagTriC model* – Poster at CNS, Berlin, Germany, 2009

L. Ziegler, W. Gerstner, *Synaptic tagging and capture: a bridge from molecular to behaviour* – Poster at Cosyne, Salt Lake City, UT, USA, 2012

Work Experience

Current **Doctoral Candidate** in *Laboratory of Computational Neuroscience*, EPFL
Development of a novel plasticity rule, mathematical description, computer simulations, and functional consequences
Reviewer for *Frontiers in Computational Neuroscience* and *Neural Computation*
Teaching assistant for *Computer Science I*, 1^{st} year Bachelor course; *Machine Learning & Pattern Recognition*, and *Neural Networks & Biological Modeling*, Master level courses

2005 – 2006 **Highschool teacher** at secondary school level in Geneva, Switzerland
Taught as a substitute during 8 months all 1^{st} & 2^{nd} grade *Physics* classes of a teacher absent for a pregnancy break
Occasional substitute for *Physics, Mathematics, Natural Sciences*

2001 – 2004 **Private lessons**
Helped secondary level students in *Physics, Mathematics, Chemistry, German*

Skills

Languages

French	Mother tongue
English	Fluent current research in english and 2 academic years in english at *København Universitet*, Denmark & *Concordia University*, Canada
German	Fluent 3 months normal cursus at *Ratsgymnasium Peine*, Germany
Danish	Proficient danish classes twice a week for 11 months in Copenhagen, Denmark
Portuguese	Bases
Italian	Bases

Computer science

OS	Linux, Windows
Programming	C/C++, Python
Development	Mathematica, Matlab, LaTeX, Office, Inkscape

Other

Research methodologies, data and information collection, writing and presenting reports

Interests

Languages, reading, sports, cooking, hiking, nature, travelling

Personality

Open-minded, novelty seeking, fast learner

Last updated: January 20, 2014