Master thesis : Neuromodulation of phenomenological plasticity rules

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Neuromodulation of phenomenological plasticity rules

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Abstract

Despite utterly different life courses during the day, once night appears and the calm falls over the cities and the campaigns, switch from wake to sleep is one of those things that draws individuals back together. Beyond being a time dedicated to dreams (both the good and the ugly), to unwinding and to ensuring the proper functioning of the human body, the role that sleep has on our ability to remember is now deemed to be proven. However, in practice, a complete understanding of cellular mechanisms of memory consolidation during sleep is still lacking for scientists in the field.

During the day, some learning takes place. At the cellular level, this takes the form of a change in the strength of the connection that binds neurons together, resulting in networks that are subject to a phenomenon known as *synaptic plasticity*. The belief that learning is enhanced, and therefore synaptic strength modulated, when neurons switch from an awake to a sleeping state is supported by the differences in rhythms between these two states, both at the organ level (cerebral waves) and at the cellular level (tonic vs. burst). Moreover, various neuromodulators such as acetylcholine, dopamine, noradrenaline and serotonin are known to be at the origin of this switch between wakefulness and sleep.

Computationally, synaptic plasticity can be modelled by biologically related rules called *calcium models* or more abstract rules called *phenomenological models*. This thesis will focus on the latter. Phenomenological models applied during arousal have proven to be good candidates to study synaptic plasticity. However, when they are applied in sleep without any modifications, they do not prove the link between memory consolidation and sleep. Indeed, [Jacquerie et al., 2022] have shown that regardless which neurons had learned more or less during the day, they all followed the same course during the night. From this observation, this phenomenon was referred to as the *homeostatic reset*.

Thus, in this thesis, we integrate the effect of neuromodulators in the phenomenological rules during sleep in order to overcome this homeostatic reset. As neuromodulators are involved in the switch from wakefulness to sleep, we hope that incorporating them into the shift of phenomenological rules from one state to the other could lead to a behaviour compatible with memory consolidation. In order to achieve this goal, a review of the effects of neuromodulators on phenomenological rules during arousal and a review of papers that have implemented neuromodulated computational rules were conducted. Based on this information, computational tests have been performed in which parameters of *the pair-based model* have been modulated in order to reproduce the effect of certain neuromodulators. Some tests were unsuccessful while others were more compatible with our target scenario. However, in both cases, the gap between the computational implementation and the physiological reality and the fragility of the models have been revealed. As a perspective, we propose another way to integrate neuromodulation with the phenomenological rules of plasticity. Instead of touching the parameters of the latter, neuromodulators will tag certain synapses during the day which will allow them to be eligible for synaptic change at night. This approach would be compatible with the *synaptic tag and capture hypothesis*.

Acknowledgements

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In addition, I would also like to emphasise the opportunity that I had to work in parallel with a person who is precious to me. Indeed, without my numerous co-working sessions with Juliette Ponnet, this semester would not have had the same flavour. I have also enjoyed working with Nora Sautois and Pauline Garcia Garcia and being able to appreciate the progress of each of them in our weekly progress meetings.

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Nora Benghalem

Contents

Chapter 1

Introduction

1.1 Motivation: understanding the effect of neuromodulation on memory consolidation during sleep

Nowadays, many researchers are struggling to prove the link between memory consolidation and sleep. The popular belief that sleep is one of the keys to our learning is well supported by scientific evidence. However, the cellular mechanisms that would actually prove the effect of sleep on memory are still a work in progress. In order to explore and unravel the mystery that still hangs over this subject, a clever combination of experimental and computational methods is used. In both cases, the effect of neuromodulators has been highlighted in recent research on synaptic plasticity and on our capacity to learn [Frémaux and Gerstner, 2015, Pedrosa and Clopath, 2017, Zannone et al., 2018, Brzosko et al., 2019]. It has been shown that they (mainly acetylcholine and dopamine) have an impact on the latter. Most of these studies are limited to models applied to wake. However, biologically speaking, we also know that the levels of certain neuromodulators vary from wakefulness to sleep and during the different phases of sleep. Therefore, supposing that these could be involved in memory consolidation seems an interesting hypothesis and a strong motivation to constitute a research topic for a master thesis.

The latter is limited to computational (not experimental) tests. In this field, we will focus on one type of plasticity rule: phenomenological plasticity rules while we will be working in parallel with Juliette Ponnet who will computationally modulate another type of rule: biological plasticity rules. The final goal of this project will therefore to address the following question: *What are the effects of neuromodulators on phenomenological plasticity rules and how they might shape memory?*

1.2 Structure

In order to test the above hypothesis, this thesis is divided into 4 main parts:

Part I is dedicated to the reminder of essential notions in order to properly immerse oneself in the subject of this thesis. Thus, notions such as the physiology of a neuron as well as the way to model it will first be evoked in Chapter 2. Then, synaptic transmission and synaptic plasticity will be discussed from a biological point of view in this same chapter. Since our topic is the effect of neuromodulators on the rules of synaptic plasticity during sleep, the latter will be reviewed before coming to basic knowledge about sleep and memory. Finally, Chapter 3 of this first part is dedicated to the presentation of the synaptic plasticity model on which we will focus during this thesis. Indeed, many models can be used to model synaptic plasticity and these are often grouped into two categories:

biological models and phenomenological models. It is on the latter that we will evaluate the effect of neuromodulators and more particularly on spike-timing dependent plasticity (STDP).

Part II draws a review of the effect of neuromodulators on sleep as well as on STDP. Indeed, over the years, neuromodulators have been shown to change different properties of the STDP rule such as its polarity, magnitude or temporal requirements. All these changes will therefore be scrutinised in CHAPTER 4. After that, CHAPTER 5 will briefly list some computational studies that have highlighted the role of certain neuromodulators on synaptic plasticity during wakefulness. This study is also intended to confirm that applying these theories to sleep is not only innovative but also makes sense.

Part III first focuses, in CHAPTER 6 on the description of the circuit that we use to carry out our computational study. This allows us to mention the limitations of this circuit and in particular the observation of the *homeostatic reset* phenomenon [Jacquerie et al., 2022]. Then the rest of this chapter will be dedicated to the the mathematical demonstration of the latter. Finally, in CHAPTER 7, different experimental protocols will be implemented in order to test the effect of neuromodulation on synaptic plasticity during sleep and in particular the capacity of neuromodulation to counteract the reset phenomenon.

Part IV draws the conclusion regarding the effect of neuromodulators on phenomenological plasticity rules during sleep and their inability to counteract the homeostatic reset. As inherent limitations of the plasticity model we use, i.e. pair-based STDP will prevent us to conclude to consolidation of memory during sleep, another way to study the effect of neuromodulators on synaptic plasticity during sleep using the concept of *eligibility trace* will be touched upon.

Part I

Background

Chapter 2

Elements of neurophysiology and neuronal modeling

2.1 Neurons

2.1.1 Morphology

The organisation of a neuron is not very different from that of another cell. Indeed, it is composed of a nucleus, a plasma membrane and organelles endowed with specific functions. However, the latter nevertheless has visible morphological and organizational characteristics that allow it to be specialised for intercellular communication and transmission. Like a century-old oak tree, the neuron has branch-like extensions that start from its cell body and extend to transmit synaptic impulses (see Figure 2.1). These extensions are called *dendrites*. The complexity of the dendritic tree determines the number of inputs a particular neuron is able to receive: nerve cells that lack dendrites are innervated by just one or a few other nerve cells, whereas those with increasingly elaborate dendrites are innervated by a commensurately larger number of other neurons [Purves, 2004].

Dendrites are, for the most part, known to make contact between one another at a place that is called *synapse*. Synapses are divided into a presynaptic and a postsynaptic terminals which are not in close contact. Indeed, pre- and postsynaptic components communicate via this *synaptic cleft* by releasing molecules from the presynaptic terminal to the postsynaptic terminal to which they bind.

Another important part in the communication function of the neuron is the *axon*. The latter, equipped with a distinct cytoskeleton, is the portion of the nerve cell which is specialized for signal conduction. Depending on the type of neuron, the axonal compartment varies in size from one meter, to a few millimeters long, to being almost non-existent. The electrical event that is carried out from one neuron to another via the axon is called the *action potential* which is defined as a "self-regenerating wave of electrical activity that propagates from its point of initiation at the cell body (called the axon hillock) to the terminus of the axon where synaptic contacts are made" [Purves, 2004]. The chemical and electrical process by which the information conveyed by action potential is transmitted from one cell to another is called *synaptic transmission* and will be reviewed in details in a following section.

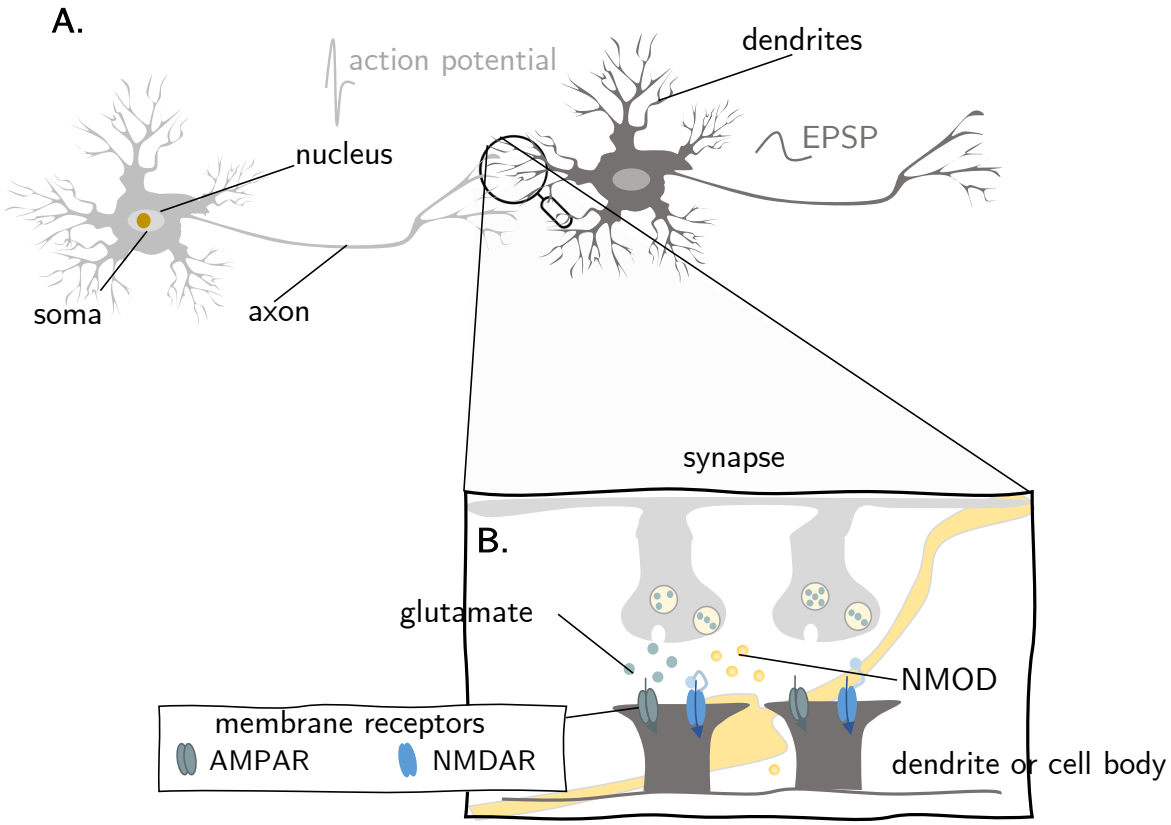


Figure 2.1: *Schematic representation of neurons and communication at an excitatory synapse* **A.** A presynaptic neuron (light grey) and a postsynaptic neuron (dark grey) communicate and transmits neuronal information from one to the other thanks to their particular morphology. At the level of the synaptic terminal, the presynaptic neuron sends information through its axon to the dendrites of the postynaptic neuron. **B.** A zoom at the level of the synapse allows to see synaptic transmission at a smaller scale. An action potential is generated at the level of the presynaptic neuron and induces a depolarization at the presynaptic level as well as a small input current at the postsynaptic level. This action potential then triggers the activation of voltage-gated calcium channels (in blue) allowing the influx of calcium ions. The latter activates intercellular cascades which trigger the fusion of vesicles filled with neurotransmitters. Neurotransmitters (in yellow) diffuse into the synaptic space and bind to their specific receptors in function of whom different responses will be elicited [Chua et al., 2010]. Inspired by [Graupner, 2017]

2.1.2 Neural signaling

Like every cell, the neuron has a cell membrane that acts as a separation between the interior of the cell and the extracellular environment. Its main constituents are lipids, proteins and sugars. The cell membrane has a particular arrangement of these components. More particularly, the lipids are organised in an impermeable bilayer interspersed with proteins permeable to specific ions depending on the structure of the protein. These are therefore crucial for cell behaviour. Indeed, the electrical behaviour of neurons is established by the transfer and storage of charges on both sides of the cell membrane. These charges are often transported by sodium (Na^+) or potassium ions (K^+). The distribution of ions on either side of the cell membrane will therefore give the latter a membrane potential. Signalling in neurons is then established by abrupt changes in this membrane potential. Due to their distribution in the membrane, their charge and their nature, the electrical and osmotic forces oppose each other and thus create a membrane potential at which these forces cancel each other

out. This equilibrium potential is defined using Nernst's law as follows:

$$V_{Nernst} = \frac{RT}{zF} ln \frac{[ion]_{out}}{[ion]_{in}} = \frac{kT}{zq} ln \frac{[ion]_{out}}{[ion]_{in}}. \tag{2.1}$$

where R,F and k are the perfect gas constant, Faraday's constant and Boltzmann's constant respectively, T is the temperature in Kelvin, z is the valence of the ion considered and q is the charge of the electron.

Considering all the ions present in the vicinity of the cell membrane, the following resting membrane potential can be defined:

$$V_m = -\frac{RT}{zF} ln(\frac{\sum_{ion^+} P_{ion^+}[ion^+]_{out} + \sum_{ion^-} P_{ion^-}[ion^-]_{in}}{\sum_{ion^+} P_{ion^+}[ion^+]_{in} + \sum_{ion^-} P_{ion^-}[ion^-]_{out}}) \tag{2.2}$$

where ion^+ represents positively charged ions, ion^- represents negatively charged ions and P_{ion} represents the relative membrane permeability of each ion.

2.1.3 Neuronal modeling

From a modeling point of view, the neuron can be described by two main types of models: conductance-based models and integrate and fire models. The former tries to describe the neuron in a way that is very close to biological reality, while the latter tries to model specific properties of the neuron such as its excitability(for more details about *Conductance-based model* and *Integrate and Fire model*, see B.2 and B.3).

2.2 Synaptic transmission

In order for information to go from one neuron to another and then propagate to the whole brain, neurons need fast and efficient communication channels. These channels are actually synapses combining both chemical and electrical signaling in order to from neuronal networks. Communication between neurons is therefore made via this synaptic transmission mode.

As mentioned just above, there are two main types of synapses: chemical synapse and electrical synapse. Communication via chemical synapse is said to be *bidirectional*. It occurs when, after an action potential has been generated by a presynaptic neuron, the latter generates a small input current at the postsynaptic neuron level. These action potentials are generated in the axon hillock, propagate along the axon before reaching its target: the presynaptic terminal. In this place, it induces a depolarization which allows to activate voltage-gated calcium channels. This activation will allow the influx of calcium ions. The latter leads to intercellular signaling which triggers the fusion of synaptic membrane vesicles filled with neurotransmitter to the presynaptic cell membrane. These neurotransmitters will then disperse and diffuse into the synaptic cleft, the space between the pre- and postsynaptic compartments, where they will then bind to their assigned receptors and modulate the electrical activity therein [Chua et al., 2010].

As can be seen on Figure 2.1, when they reach the postsynaptic compartment, neurotransmitter molecules can bind to two main types of synaptic receptors: ionotropic receptors and metabotropic receptors [Frohlich, 2016]. The first ones have both the function to bind neurotransmitter and, acting as ion channels, to change the electrical state of the postsynaptic neuron allowing ion flow across

the cell membrane making them the ideal receptors for fast synaptic communication. Metabotropic receptors also have the obvious role to bind neurotransmitter molecules but rather than acting as ion channels, they use intracellular biochemical signaling cascades to modulate ion channels. Knowing that, it is clear that metabotropic receptors are related to slower communication, compared to their counterpart (see Table 2.1).

Name	Ionotropic receptors	Metabotropic receptors
Type	Ligand-gated ion channels	G protein-coupled receptors
Response	Ion flux is responsible for changing the cellular voltage	Secondary messengers trigger cascades of cellular effects.
Speed of response	Rapid	Slow
Length of response	Short-acting	Prolonged response

Table 2.1: *The two main types of postsynaptic receptors.*

Electrical synapses for their part, instead of using long-range communication links enabled by axons and the chemical synapses at their terminals, prefer to rely on short-distance communication with their direct neighbors via gap junctions. The latter are not the focus of this thesis and will therefore not be discussed further.

2.3 Neuronal receptors

It was mentioned in the previous section that one of the steps in synaptic transmission is the binding of neurotransmitters to specific receptors. There are many such receptors, each of which induces a different response, according to the subtype of neurotransmitter receptors as well as their abundance at synapses [Sheng and Kim, 2011], even when activated by the same neuromodulator. Among these receptors, this section is dedicated to the description of two major types of neuronal receptors whose role is fundamental to understand: glutamate receptors and γ-aminobutyric acid (GABA) receptors. Indeed, the former handle almost all excitatory signals that a neuron receives whereas the latter are devoted to inhibitory signals [Cherubini et al., 1991, Hollmann and Heinemann, 1994].

Glutamate receptors As mentioned previously, glutamate receptors are the major excitatory neurotransmitter receptors in the brain which gives them a major role in neural plasticity as well as in development. In the field of neuroscience, well known metabotropic glutamate-gated ion channels comprise N-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors (AMPARs) and kainate receptors while metabotropic glutamate receptors (mGluRs) are G-protein-coupled receptors (GPCRs). The latter involve a downstream cascade of signalisation that brings heterotrimeric G-proteins into play. Among glutamate receptors, it also exists different subclasses in which receptors subtypes comprise multiple subunits such as NMDA receptors (GluN1 to GluN3), AMPA receptors (GluA1 to GluA4), kainate receptors (GluK1 to GluK5) and mGlu receptors (mGluR1 to mGluR8) [Kantamneni, 2015].

GABA receptors Conversely, GABA receptors are known to be responsible for most of the inhibitory responses in the brain. Metabotropic GABA receptors (GABABRs) are G-protein coupled receptors that can mediate slow inhibitory neurotransmission in the central nervous system (CNS). They are located at presynaptic compartments as well as at postsynaptic compartments. And as was the case with glutamate receptors and excitation level, changes in the number, localization and activity

of GABABRs affect the level of synaptic inhibition. This inhibition is achieved through the inhibition of Ca^{2+} channels which in turn inhibits the release of neurotransmitter. On the postsynaptic side, slow inhibitory postsynaptic potentials are generated by the activation of K^{+} channels [Kantamneni, 2015].

In the manner of glutamate receptors, GABABR is divided into 2 subunits: GABAB1 and GABAB2 which lead to longer lasting synaptic inhibition compared to GABAA ion channels [Marshall et al., 1999, Watanabe et al., 2002].

2.4 Synaptic plasticity

In 1949, Hebb developed his famous theory stipulating that "memories are stored in the mammalian brain as stronger synaptic connections between neurons active during learning" [Hebb, 1949b]. According to this theory, the association of pre- and postsynaptic activity in between two neurons is the main driver of change in both neurons, change which will then lead to a strengthening or a weakening of synaptic connections. On this basis, synaptic plasticity is therefore defined as "the experience-dependent change in connectivity between neurons that is believed to underlie learning and memory" [Maren and Baudry, 1995]. In this section, synaptic plasticity is reviewed from a biological point of view.

2.4.1 Short-term synaptic plasticity

As its name implies, short-term synaptic plasticity is defined by a bidirectional form of plasticity that lasts from seconds to minutes. This change in synaptic plasticity allows for the dynamic regulation of neural information processing and short-term memory [Heidelberger et al., 2014]. When short-term synaptic plasticity is induced, it can either lead to a temporary increase or decrease in synaptic transmission and connection. The former is known as *facilitation* while the latter is gathered under the term *depression*.

- **Facilitation**:
  - *Biological mechanisms*: Short-term synaptic facilitation (STF) is caused by influx of calcium into the axon terminal after spike generation, which increases the release probability of neurotransmitters [Tsodyks and Wu, 2013].
  - *Induction protocol*: At the synapse between two neurons, "paired-pulse facilitation" is induced when a single action potential occurs in the first neuron which gives rise to an excitatory postsynaptic potential (EPSP) in the other neuron with a particular amplitude. If a second action potential is elicited shortly after the first one, the second EPSP may be larger than the first one giving rise to what we call STF [Heidelberger et al., 2014].
- **Depression**:
  - Biological mechanisms: Short-term synaptic depression (STD) is caused by depletion of neurotransmitters consumed during the synaptic signaling process at the axon terminal of a presynaptic neuron [Tsodyks and Wu, 2013].
  - *Induction protocol*: In the same way that for the facilitation process, "paired-pulse depression" is induced when a second EPSP is induced shortly after the first one in a neuron and that this second EPSP is of smaller amplitude.

2.4.2 Long-term synaptic plasticity

In the same way as for short-term plasticity, long-term plasticity is mainly defined on the basis of its timing. Thus, long-term plasticity is referring to the bidirectional changes in synaptic plasticity that last between hours, days and sometimes lifetime. A long-lasting increase in synaptic efficacy is termed "LTP" for Long-Term-Potentiation while a long-lasting decrease in synaptic efficacy is known as "LTD" for Long-Term Depression [Heidelberger et al., 2014].

Induction protocol of long-term synaptic plasticity The first actor that is involved in the induction of long-term plasticity is the NMDA receptor. As a reminder, this type of receptor is a voltage-dependent subtype of glutamate receptor that allows permeation of calcium and other cations only when two conditions are fulfilled:

1. glutamate is released from the presynaptic terminal allowing binding of neurotransmitters.

2. sufficient depolarization of the postsynaptic membrane is achieved which allows the ejection of Mg^{2+} ions. In normal conditions, the latter block the ion pore of NMDARs and similarly the calcium flow [Maren and Baudry, 1995].

It also exists other forms of LTP and LTD that do not rely upon the NMDAR for example LTD that is induced through activation of the mGluR.

Quite logically, LTP and LTD are induced by specific pattern of activity[Bear and Malenka, 1994]. LTP is induced when both pre- and postsynaptic neurons are active at the same time. Indeed, as depicted in Figure 2.2, the postsynaptic neuron must be depolarized when glutamate is released from the presynaptic button to fully relieve the Mg^{2+} blockade of NMDARs. The association of depolarization and glutamate binding leads to a maximal calcium influx through NMDARs. Then, calcium activates intracellular signaling cascades that are responsible for the final long-lasting change in synaptic efficacy. In the same way, repeated activation of the presynaptic neuron at low frequencies without postsynaptic activity leads to LTD. NMDAR-dependent calcium influx induces both LTP and LTD. Therefore, in order to decide whether a synaptic connection needs to be potentiated or depressed, NMDARs activation have to be varied. Thus, modest increases in postsynaptic calcium are optimal for triggering LTD, whereas much stronger activation of NMDARs leading to much larger increases in postsynaptic calcium are required to trigger LTP [Bear and Malenka, 1994, Lüscher and Malenka, 2012].

LTP and LTD can also be produced by spike timing-dependent plasticity in which the relative timing of pre- and postsynaptic spikes leads to changes in synaptic strength [Ho et al., 2011].

For more details about expression of long-term synaptic plasticity see AnnexA.

Maintenance of long-term synaptic plasticity After induction and expression of LTP, in order for it to last, involvement of new actors is necessary. One of these actors are specific kinases such as:

- CAMKII: which is involved in long-term maintenance mechanism for LTP because it can phosphorylate itself.

- PKMZ: which remains active after LTP induction and whose role is to increase the number of AMPARs in the synapse leading to the maintenance of synaptic transmission potentiation.

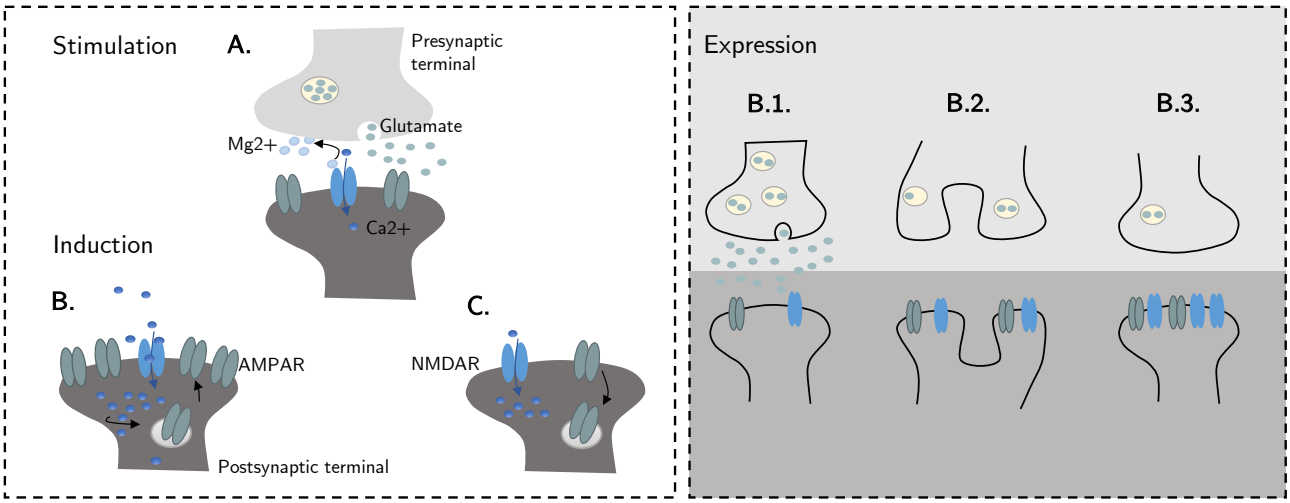


Figure 2.2: *Induction mechanisms of LTP and LTD at excitatory synapses* **A.** The induction of LTP and LTD involves two main actors: NMDA receptors (in blue) and AMPA receptor (in grey). The former is a voltage-dependent subtype of glutamate receptor permeable to Ca^{2+}, K^{+} and Na^{+} ions when two conditions are fulfilled: (1) glutamate is released from the presynaptic terminal to allow the binding of neurotransmitters and (2) sufficient depolarization of the postsynaptic membrane is achieved in order to relieve the blockage of NMDARs' ion pores by Mg^{2+}. AMPARs are also sensitive to glutamate released by the presynaptic cell and are permeable to sodium ions [Maren and Baudry, 1995]. **B.** Induction of LTP occurs when both pre- and postsynaptic neurons are active. The association of depolarization and glutamate binding leads to a maximal calcium influx through NMDARs. Calcium ions then activate intracellular signaling cascades responsible for the final long-lasting change in synaptic efficacy. These effects are notably an increase of neurotransmitters release from the presynaptic neuron **B.1.**, an increase of the synaptic surface between the neurons **B.2.** and an increase in the number of postsynaptic receptors **B.3.**. **C.** Induction of LTD occurs when the presynaptic neuron is activated repeatedly at low frequencies without postsynaptic activation. This time, the flux of calcium ions is not sufficient to induce activate the cascade necessary to induce LTP.

Apart from these molecular actors, presynaptic changes in the probability of neurotransmitter release are needed to maintain LTP as well as structural changes in the size and shape of pre-and postsynaptic specialization. Moreover, these actors alone are not sufficient to maintain LTP over the long term. Indeed, although the early phase of LTP depends on the actors and pre- and postsynaptic mechanisms cited just above, later phases of LTP require new gene transcription and protein synthesis [Abraham and Williams, 2003].

In order to make possible the transition from the early phase of LTP to its later phases, newly synthesized proteins are selectively targeted to, or captured by, potentiated synapses [Abraham and Williams, 2003]. This is thought to be achieved via two ways:

1. Via regulated translation at or near synaptic junctions. Indeed, mRNA, ribosomes and all the translation machinery is localized in dendritic and synaptic regions. Therefore, during LTP expression, translation is stimulated in these areas leading to a rapid modification of the synaptic proteome.

2. Via a synaptic "tag" at potentiated synapses. The latter is thought to enable synapses to capture the new proteins that are carried out in the dendritic tree. Synthesis of these new proteins can therefore be conducted at the location of the tetanized synapses [Frey and Morris, 1997].

Finally, LTP and LTD possess specific properties that notably help to understand the link between them and learning and memory. For more details about those, see AppendixA.

2.5 Neuromodulators

Neuromodulators assume different roles, mainly to signal events such as risks, rewards, novelty, effort or social cooperation while taking part in higher cognitive functions as in attention, decision-making, emotion or goal-directed behavior [Avery and Krichmar, 2017]. Over the years, they have therefore emerged as playing a key role in the study of memory consolidation during sleep. The main neuromodulators that we will take into account in this work are summarised in Table 2.2

Box1| Neurotransmitter vs neuromodulator

A neurotransmitter is a "chemical substance released at the end of a nerve fiber by the arrival of a nerve impulse and, by diffusing across the synapse or junction, affects the transfer of the impulse to another nerve fiber, a muscle fiber or some other structure."

A neuromodulator is a "substance other than a neurotransmitter, released by a neuron and transmitting information to other neurons, altering their activities" [Lakna, 2019].

2.5.1 Acetylcholine

Cholinergic neurons are mostly located in subcortical regions, mainly the basal forebrain and the mesopontine tegmentum area [Sam and Bordoni, 2022], and are often associated with the dopaminergic system such as in the striatum (for more details about brain anatomy, see Appendix A. Logically enough, depending on their location, their role and activity will vary slightly. But, most of the time, cholinergic system is activated during arousal and attention or when the brain needs to respond to unfamiliar stimuli,for neurons located in the cortex. They will therefore enhanced the response to sensory stimuli but also when unpredicted and predicted rewards are presented to our brain [Pawlak, 2010]. Interestingly enough, a couple of sleep-wake cycles studies have highlighted acetylcholine as a major player in memory consolidation. Indeed, when the level of acetylcholine is low, recurrent connections are stronger and memories are retrieved while high acetylcholine levels lead to sensory inputs enhancement, recurrent inputs reduction and memory encoding [Avery and Krichmar, 2017].In addition, acetylcholine is also implicated in sensory processing, mood, attention, aggressive and ingestive behaviors(Ingestive behaviors encompass all eating and drinking behaviors), thermoregulation and sexual behavior [Gu, 2002].

Acetylcholine targets two major classes of receptors:

- *muscarinic receptors*: are G-coupled protein receptors involved, for most of them, in the parasympathetic nervous system. They are named as such due to their increased sensitivity to muscarine, a component found in certain species of mushrooms [Kudlak and Tadi, 2021]. Muscarinic responses can be either excitatory or inhibitory and have a longer onset latency [Gu, 2002].
- *nicotinic receptors*: ionotropic ligand-gated receptors that are also able to bind acetylcholine (ACh) but these are mostly located in the central nervous system [Kudlak and Tadi, 2021]. Here, the responses are always excitatory and very rapid [Gu, 2002]. Nicotinic acetylcholine receptors (nAChRs) are composed of ligand binding subunits ($\alpha 2 - \alpha 8$) and structural subunits ($\beta 2 - \beta 4$) [Gu, 2002].

2.5.2 Noradrenaline

Noradrenaline, for its part, is mostly located in the locus coeruleus from which it projects to nearly every cortical and subcortical regions. These regions contain specific receptors which have different affinity for noradrenaline and are divided into two broad families:

- α receptors: which are relatively insensitive to the classic adrenergic agonist isoproterenol. They are further divided into 2 subcategories according to their pharmacological profile:
  - $\alpha 1$ receptors which stimulate phospholipase C activity leading to the production of the second messengers inositol (IP_3) and diacylglycerol (DG)
  - $\alpha 2$ receptors which inhibits adenylyl cyclase through the action of an inhibitory G-protein (Gi) and reduces the formation of cAMP.
- β receptors: which are stimulated by isoproterenol. They are divided into 3 subtypes: $\beta 1$, $\beta 2$ and $\beta 3$ and are known to enhances the synthesis of cAMP via their coupling with adenylate cyclase and Gs [Gu, 2002].

Traditionally, the noradrenergic system plays a role in vigilance, mediating arousal levels through slow changes in tonic levels of activation. Indeed, noradrenergic neurons fire at lower rate during Slow Wave Sleep (SWS), the deepest phase of non-rapid eye movement (NREM) sleep, at a regular rate during quiet wakefulness and in burst mode when there is some stimuli such as primary rewarding stimuli or aversive stimuli, unpleasant stimuli that induce changes in behavior via negative reinforcement or positive punishment [Pawlak, 2010]. Finally, noradrenaline signal is also thought to be involved in more memory-related functions such as working memory and memory formation.

2.5.3 Dopamine

Dopaminergic neurons originate in either the ventral tegmental area (VTA) or substantia nigra pars compacta (SNc) and send projections to the striatum, thalamus, amygdala, hippocampus and prefrontal cortex including a feedback loop in their circuitry. They take part in nearly every brain functions going from cognitive to behavioral ones. In fact, dopamine receptors are divided into five subtypes of dopaminergic receptor ($D_1 - D_5$) which can be grouped into two main categories with each of them being more linked to a specific type of functions. D_2-like(D_2, D_3, D_4) receptors, which result a decrease of cAMP levels, in play a preferential role in behavior and reward processing whereas D1-expressing neurons (D_1, D_5receptors), which result in an increase of cAMP levels [Palacios-Filardo and Mellor, 2019], are involved in working memory and attentional modulation of visual cortices [Avery and Krichmar, 2017].

Regarding stimuli, dopaminergic neurons are known to be activated by unexpected or "better than predicted" reward leading to the fact that when the reward is omitted, one can observe a decrease in the firing rate of these neurons. But, they are also reactive to any salient or novel input in the environment regardless of its reward value.

2.5.4 Serotonin

Serotonergic neurons find their origin in the raphe nuclei of the brainstem and send projections to almost all forebrain areas as well as in the cortex, the ventral striatum, the hippocampus and the amydgala. Serotonin (5-HT) receptors are composed of seven families (5-HT1 to 5-HT7) which are coupled to G-protein-coupled receptors (GPCRs) except for the ionotropic 5-HT3 receptors and all 5-HT receptors are expressed in the hippocampus [Palacios-Filardo and Mellor, 2019].More precisely:

- $5-HT_1$ receptors are negatively coupled to adenylyl cyclase and inhibit the formation of cAMP.
- $5-HT_2$ receptors stimulate the hydrolysis of phosphatidylinositol.
- $5-HT_3$ receptors are ligand-gated cation channels.
- $5-HT_4, 5-HT_6$ and $5-HT_7$ receptors enhance adenylyl cyclase activity, and promote intracellular accumulation of cAMP.

Their main functions are decision-based functions such as reward assessment, cost assessment, impulsivity, harm aversion and anxious states [Avery and Krichmar, 2017].

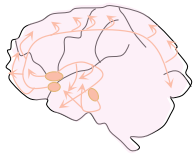
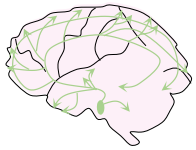
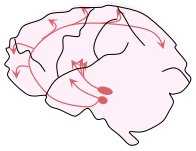
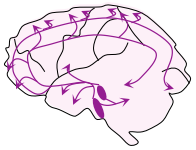
Neuromodulator	Acetylcholine (ACh)	Noradrenaline (NA)	Dopamine (DA)	Serotonin (5-HT)
Area of the brain				
Receptors	- Muscarinic receptors - Nicotinic receptors	- α-receptors - β-receptors	- 5 subtypes of receptors grouped into: D1-liked and D2-liked receptors	- 7 families of receptors: 5-HT1 to 5-HT7
Main action(s)	- Memory consolidation - Sensory processing - Mood - Attention	- Vigilance - Arousal - Memory related functions	- Behavior - Reward processing - Working memory	- Reward and cost assessment - Impulsivity - Anxiety

Table 2.2: *Summary of the main neuromodulators, their circuits in the brain, their receptors and their main action(s).*

2.5.5 Other components

BDNF

The brain derived neurotrophic factor (BDNF) is part of the neurotrophins family which, as their name implies, have a crucial role in survival and differentiaion of neuronal populations during development [Huang and Reichardt, 2001]. In the mature brain, BDNF still has important functions such as to maintain high expression levels and regulate both excitatory and inhibitory synaptic transmission and activity-dependent plasticity [Tyler et al., 2002, Wardle and Poo, 2003].

BDNF is mainly expressed in the hippocampus where the highest levels are found, amygdala, cerebellum and cerebral cortex. Apart from neurogenesis, BDNF has critical role in the regulation of plasticity in the brain such as in the regulation of the trafficking, the phosphorylation and the expression levels of NMDARs which are associated with augmented synaptic strength. Interestingly, BDNF is known to be linked with learning and memory as it favors changes in spine morphology leading to the stabilization of LTP or as it increases the number, size and complexity of dendritic spines [Miranda et al., 2019].

Glutamate

Glutamate is an excitatory neurotransmitter that can be found associated with several types of receptors in many structures of the central nervous system [Pal, 2021]. Glutamate interacts with both ionotropic and metabotropic receptors. The former involve NMDARs, AMPARs and kainate receptors whereas the latter are subdivide into three main types of metabotropic glutamate receptor (mGluRs) [Purves, 2004]. Glutamate assumes different functions such as memory, mood, cognition and regulation [Pal, 2021].

GABA

While glutamate was excitatory, GABA is more of an inhibitory amino acid. Indeed, its primary function is inhibition in the central nervous system leading to the reduction of neuronal excitability. GABAergic neurons are located in the hippocampus, thalamus, basal ganglia, hypothalamus and brainstem. In the central nervous system, balance between excitation represented by the glutamate and inhibition via GABA is essential for the proper functioning of neurologic function [Allen et al., 2018].

2.6 Memory

Memory is defined as the process by which learned information are stored in the brain which is crucial for adaptive behavior in animals [Tonegawa et al., 2015]. Over time, several theories have emerged linking synaptic transmission and synaptic plasticity to memory. Kandel suggested that "synaptic connections between neurons are not immutable and can be modified by learning, and that those anatomical modifications serve as elementary components of memory storage" [Mayford et al., 2012]. While Richard Semon developed a similar theory, under the name of *memory engram* [Semon, 1904], which stipulates that "learning induces persistent changes in specific brain cells that retain information and are then reactivated upon appropriate retrieval conditions" [Tonegawa et al., 2015]].

Over time, rodents behavioral studies have helped scientists to identify the hippocampus as a central brain region for contextual memory storage and retrieval [Tonegawa et al., 2015]. This area of the brain is actually more associated with a specific type of memory. Indeed, there are two major systems in the brain. *Declarative* (explicit) system is the one involving the medial temporal lobe and in particular the hippocampus in order for the brain to remember information such as facts and events. The second system is called *procedural* (implicit) system as it relates to memory for perceptual and motor skills. It involves a number of brain systems depending on the specific type of learning [Kandel et al., 2015].

2.7 Sleep

Wakefulness is known to be a period of active acquisition of memories, feelings and sensations. However, sleep is the state during which memory is thought to be consolidated through strengthening of the neural connections that are at the basis of our memories.

2.7.1 Sleep vs wake

In the same way as breathing, when an individual goes to bed at night and falls into the arms of Morpheus, he or she is not aware of the multitude of phenomena that come into play to allow this change of state, from wakefulness to sleep. Sleep is defined as a" naturally reoccurring and reversible brain state in which movements of the body and consciousness of mind are suspended" [Sun et al., 2005]. It occurs in all known vertebrates, and sleep-like states are widely present in invertebrates (flies, bees). On an EEG trace, this switch between wakefulness and sleep is marked by a change in the amplitude and frequency of waves characteristic of brain activity. More precisely, the awake status is characterised by high-frequency and low voltages waves while slow wave sleep shows higher voltage and slower waves. In humans, this brain state change takes place within a time window of a few seconds to a few minutes [Saper et al., 2010]. The speed of this transition is actually due to multiple and complex interactions between specific neural circuits that will be reviewed later in this section.

2.7.2 Sleep stages

From the moment an individual goes to bed until the morning alarm clock, an individual's night is interspersed with different phases. Indeed, sleep is divided into different successive stages as can be seen on Figure 2.3. During the latter, the human body goes through both rapid-eye-movement (REM) sleep and non-rapid-eye-movement (NREM) sleep. The latter being the most represented during a night of sleep: 80% of NREM sleep against 20% REM sleep which is known to be the cradle of dreams that animate our nights [Lüthi, 2014]. On one hand, NREM is further divided into the four stages [Bear et al., 2016, Reyes-Resina et al., 2021]:

- Stage I sleep which is characterised by lower frequency values of the EEG compared to wakefulness as well as a reduced amplitude of cortical waves.

- Stage II sleep is characterised by a decrease in the frequency of EEG waves and an increase in their amplitude. These high amplitude waves are interrupted by high-frequency spike clusters called *sleep spindles.* The latter are defined as periodic burst of activity resulting from the interactions between thalamic and cortical neurons.

- Stage III sleep represents a stage of deep sleep in which frequency of EEG waves continues to decrease while their amplitude is still increasing.

- Stage IV is also termed SWS and consists in very low frequency, high amplitude fluctuations called *delta waves.*

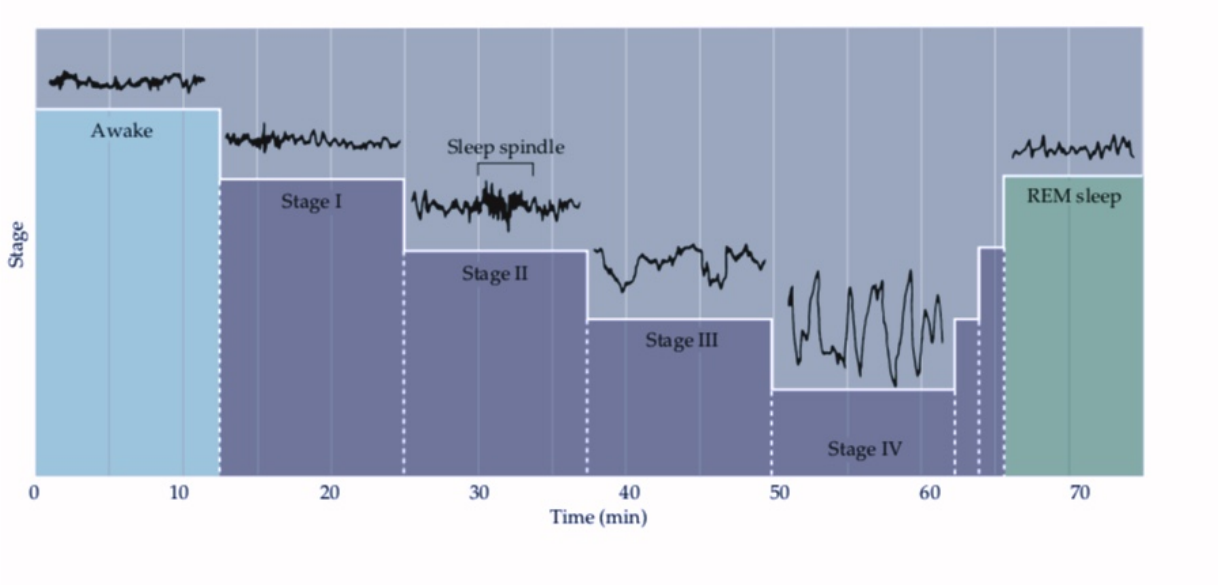


Figure 2.3: *Sleep stages.* Sleep stages are defined by criteria visible on an EEG such as amplitude and frequency of waves during sleep [Bear et al., 2016]

2.7.3 Brain and neurons electrical activity

As mentioned just above, at the network level, sleep status is noticeable on an EEG of cortical activity by the presence of low frequency synchronous slow waves while thalamic activity is marked by low frequency delta waves. These delta and slow waves are gathered under the term *slow oscillations* (SOs) which are known to be a succession of alternating depolarizing "up" and hyperpolarizing down states as can be seen on Figure 2.4.

These synchronized slow waves are the result of the synchronization and desynchronization of cells (thalamic, cortical and hippocampal neurons) firing in two distinct modes:

- Tonic firing is characterized by trains of action potentials at a frequency proportional to the amplitude of depolarizing stimuli.

- Bursting is, for its part, characterized by bursts of action potentials which are drawn by slow-calcium mediated spike associated with high-frequency action potentials [Destexhe and Sejnowski, 2002].

Which of these two states the neuron will adopt is determined by the inactivation state of low-threshold, voltage-gated, transient (or T-type) Ca2+ channels [Zagha and McCormick, 2014]. When T channels are inactivated via a depolarization of the membrane, the neuron chooses the tonic firing mode whereas activation of T channels by a hyperpolarization of the membrane leads to burst firings. Quite logically, these two response modes have very different effects on the relay of information to the cortex [Steriade and Timofeev, 2003]. Actually, the two modes of firing we have just mentioned: tonic and bursting can further be categorised by their pattern of activity: either exogenous our endogenous but also by the brain structures in which the neurons are localized. Firstly, the neurons can have two different activities to produce synchronous oscillations:

- Endogenous activity: When an additional ionic current is present in the neuronal membrane, thalamic neurons are able to switch from a tonic to a burst mode. This additional calcium current

that appears when the cell is hyperpolarised is called *T-Type Calcium current* [Steriade et al., 1993, Jacquerie, 2017].

- Exogenous activity: in the pyramidal cells of the cortex however, presence of T-Type ionic currents is not so obvious. Some cortical cells have been identified as being able to switch to burst mode through other ionic currents [Franceschetti et al., 1995] whereas other need the thalamic endogenous bursts to be passed to the cortex in order to fire accordingly [Purves, 2004].

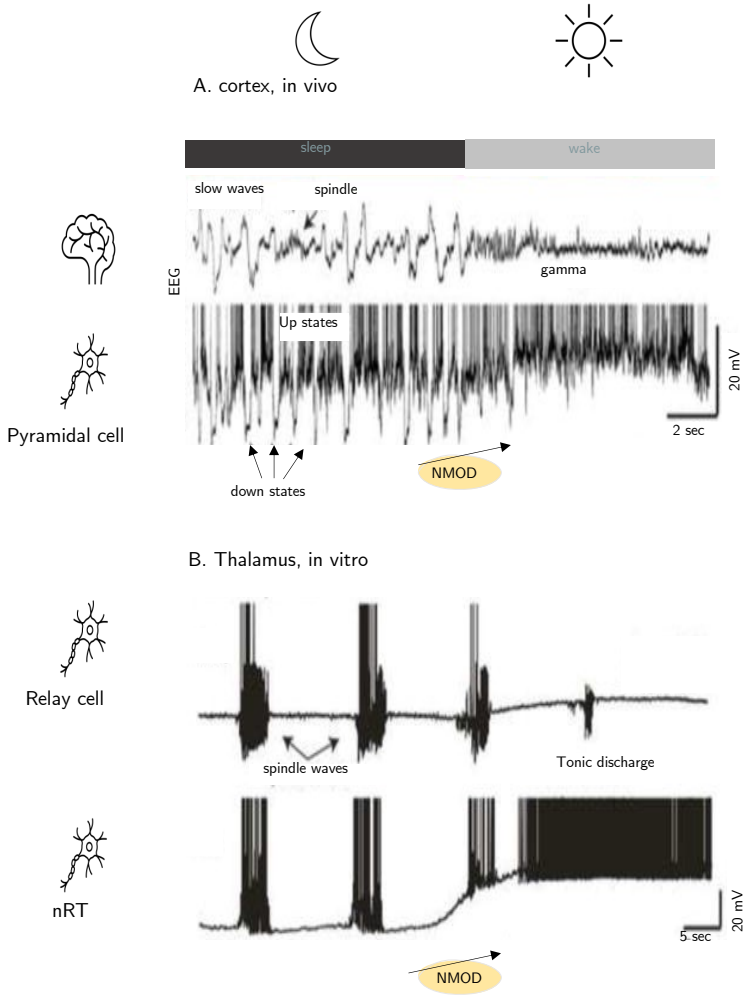


Figure 2.4: *State-dependent changes at the network and cellular level in the neocortex and thalamus.* **A.** On an EEG i.e. at the network level, the cortical activity is characterised by slow waves of high amplitudes as well as spindles during SWS. During wake, this network activity is represented by gamma waves. Logically, this global activity is the reflection of cortical cellular activity and more precisely of UP and DOWN states. This switch from sleep to wakefulness (and vice versa) is due to a change in neuromodulators (yellow circle) (such as ACh, NE, 5-HT, Glu) levels. **B.** Cells of the thalamus , more precisely nRT and relay cells, exhibit two mode of discharge in function of the state the brain is in: either sleep or wake. During sleep, these cells exhibit burst firing patters whereas they exhibit tonic discharge during wake. Once again, neuromodulators enable the switch from wakefulness to sleep by depolarizing thalamic circuits [Zagha and McCormick, 2014]. Adapted from [Zagha and McCormick, 2014].

2.7.4 Sleep and wake-promoting networks

In order for the brain to switch from wake to sleep and vice-versa in a rapid manner, an important circuitry composed of several networks comes into play. These networks can be divided into three main groups according to the state they are promoting i.e. wake-promoting networks, NREM sleep-promoting networks and REM sleep-promoting networks.

Neurotransmitters/neuromodulators	Localization of the neuron	Activity profile
WAKEFULNESS-PROMOTING		
Acetylcholine	LDT-PPT and BF	W-on
Serotonin	Dorsal raphe nucleus	W-on
Noradrenaline	Locus coeruleus	W-on
Dopamine	VTA and SN	Burst discharge during W and REM
GABA	Nucleus pontis oralis	W-on
Glutamate	Nucleus pontis oralis	W-on
NREM-SLEEP PROMOTING		
GABA	Nucleus pontis oralis	NREM-on
REMP-SLEEP PROMOTING		
Acetylcholine	LDT-PPT and BF	W/REM-on and REM-on
Glutamate	Nucleus pontis oralis	W/REM-on

Table 2.3: inspired by [Torterolo et al., 2019]

For more details see Appendix A.

2.7.5 Common hypotheses about sleep function(s)

Given the vulnerable state in which sleep places us, it seems apparent that the functions of sleep must provide a significant evolutionary advantage. These include immune and metabolic functions such as reducing caloric use and restoring brain energy stores as well as glymphatic and connectivity functions [Krueger et al., 2016]. However, in the scope of this thesis, the focus will be on functions that involve plasticity and memory. Indeed, it is well known that sleep is also said to serve homeostatic function as well as being a key actor in synaptic plasticity and consolidation of long-term memories. In the field, there are two main hypotheses for the mechanisms underlying the consolidation of memory during sleep:

- **The synaptic homeostasis hypothesis (SHY) of sleep**: this hypothesis claims that one of the important functions of sleep is to maintain synaptic balance. According to this hypothesis, the awake state allows synaptic potentiation and increase in synaptic strength, increase that would be unsustainable in the long term because of increased demand for energy, space and risk of synaptic saturation. Sleep would therefore allow a return to normalcy which will be beneficial if not essential for memory and performance [C. Hanlon et al., 2011]. This return to normalcy is called "downscaling" and is known to be associated with slow oscillations. Indeed, at the beginning of sleep, when synaptic strength is high, due to learning during the day, slow oscillations are of maximum amplitude and decrease little by little during slow wave sleep cycles in conjunction with synaptic depotentiation. Depotentiation is therefore the principal effect of sleep but potentiation is also observed in specific regions of the brain especially if sleep was preceded by learning experience [Diekelmann and Born, 2010].

- **The active systems consolidation**: in this second hypothesis, the main function attributed to sleep is no longer the homeostasis of the brain but rather memory consolidation by reactivation of the synaptic connections. Indeed, to achieve this goal, it uses a circuit in which neocortical networks and the hippocampus work and dialogue in parallel. In this arrangement, the hippocampus is seen as a "hub" that binds together cortical information. During NREM sleep and specifically SWS, newly acquired memory traces are re-actived leading to a strengthening of the connections within the neocortex. This strengthening allows the formation of more persistent memory representations [Feld and Born, 2020, Diekelmann and Born, 2010]. This reactivation of hippocampal networks during SWS appears to be link with the fluctuation of ACh levels. Indeed, during active wakefulness, ACh levels are high enabling the encoding of memory traces into the hippocampus while information is moved from the hippocampus to the neocortex during SWS, when ACh levels are low [C. Hanlon et al., 2011, Feld and Born, 2020].

Box2|Glossary

Reactivation is the term used to depict the re-emergence of activity in neuronal ensembles (a group of neurons) that were active during an experience. This reactivation allows encoding of the information. During sleep, such phenomenon is, for example, detected by changes in firing rates of individual cells [Klinzing et al., 2019a].

Replay is the term used to point out the re-occurrence of cell activities that have occurred during the day but with a much faster time scale [Klinzing et al., 2019b].

Engram refers to the encoding of information in the brain from a biological perspective. This encoding is due to structural and chemical changes that alter the strength of synaptic connections [Klinzing et al., 2019b]

Chapter 3

Review of spike-timing dependent plasticity

3.1 Global modeling approach

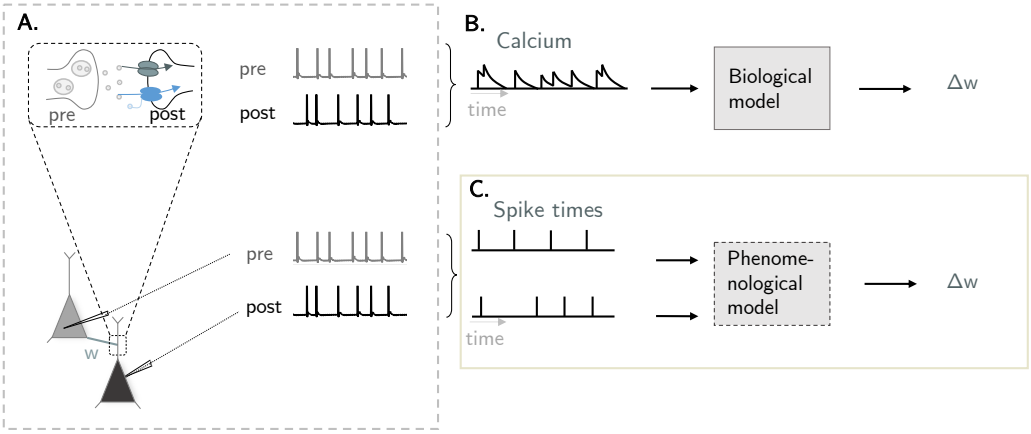


Figure 3.1: *Illustration of the two main approaches that can be used to model synaptic plasticity* **A.** When we move from biology and physiology to computational models, the synaptic strength between two neurons is now represented by a variable w called the synaptic weight. In the same way, synaptic plasticity is now translated into a synaptic rule dedicated to the description of the evolution of the weight through time dw/dt (grey boxes). In order to describe this synaptic weight change, two main types of modeling approach can be used: **B.** models that take into account the calcium dynamics aka biological models and **C.** models that are based on the spike times of two correlated neurons aka phenomenological models. The latter are really the focus of our study. [Jacquerie et al., 2022]

In Chapter 2, we have discussed synaptic plasticity from a biological point of view. As a reminder, the latter refers to "the activity-dependent modification of the strength or efficacy of synaptic transmission at preexisting synapses" [Citri and Malenka, 2008]. Now, to describe synaptic plasticity from a computational point of view, as can be seen on Figure 3.1.A., two broad categories of synaptic plasticity models can be used:

- Phenomenological models: as depicted in Figure 3.1.C., these simple models are based on an input-output relationship between neuronal activity and synaptic plasticity. They are used in simulations and computational study to account for phenomena such as the formation of memory or the development of neuronal selectivity. In phenomenological rules, synaptic strength is modelled by a *synaptic weight* w which is affected by the synaptic rule. This can be written $\frac{dw}{dt} = F$

[Jacquerie et al., 2022] where F is an arbitrary function of the presynaptic and postsynaptic neuron. These models are really the focus of this thesis.

- Biological/biophysical models: as illustrated in Figure 3.1.B., these more detailed models describe cellular and synaptic processes more accurately [Shouval, 2007].These models are also known to use calcium as a key signal to modify synaptic strength.

3.2 Experimental evidence

Before becoming one of the most widely used phenomenological models to describe synaptic plasticity, Spike Timing-Dependent Plasticity (STDP) is primarily an experimental protocol. Indeed, this form of plasticity has been shown to appear as a result of tight temporal correlations between the spikes of pre- and postsynaptic neurons in the cortex [Markram et al., 1997] and in the hippocampus [Bi and Poo, 1998].
As for the other models of synaptic plasticity, it is assumed that the latter is linked to learning and memory in the brain [Bi and Poo, 2001]. STDP is induced by trains of spikes belonging to neurons that fire together. As such, "repeated presynaptic spike arrival a few milliseconds before postsynaptic action potentials leads in many synapse types to Long-Term Potentiation (LTP) of the synapses, whereas repeated spike arrival after postsynaptic spikes leads to Long-Term Depression (LTD) of the same synapse" [Sjöström and Gerstner, 2010]. In addition to this causality between spikes, synaptic plasticity is also known to be affected by other parameters such as:

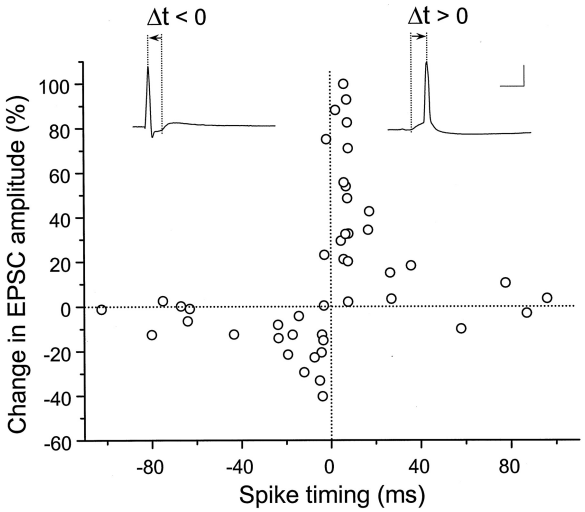


Figure 3.2: *STDP in hippocampal cell culture.* The % change in excitatory postsynaptic current (EPSC), which can be seen as a marker of synaptic strength, is plotted in function of spike timing (60 pulses at 1Hz). Spike timing is defined by the time interval (Δt) between the onset of the excitatory postsynaptic potential (EPSP) and the peakl of the postsynaptic action potential (traces on top). Synaptic potentiation arises when $\Delta t > 0$ whereas $\Delta t < 0$ corresponds to the critical window for the induction of synaptic depression [Bi and Poo, 1998].

- The frequency of the pairing: this parameter is taken into account when bursts of action potentials (APs) are considered. Higher frequencies tend to increase the strength of LTP at positive timings[Sjöström et al., 2001) and sometimes even convert LTD at negative timings into LTP, not taking into consideration the pre-post timing requirement [Sjöström et al., 2001a].

- The location of synapses along the dendritic tree: LTP has been shown to become more important in distal synapses because of the attenuation of the voltage of action potentials in dendrites [Sjöström and Häusser, 2006].

- The regulation by neuromodulator [Pawlak and Kerr, 2008, Seol et al., 2007, Abbott and Nelson, 2000].

3.3 Modeling STDP: pair-based model

The standard rule for STDP, which specifies the change $W(\Delta t)$ of the synaptic weight of an excitatory synapse in dependence on the time difference $\Delta t = t_{post} - t_{pre}$ between the firing times t_{pre} and t_{post} of the pre- and postsynaptic neuron, is based on numerous experimental data [Legenstein et al., 2008].

$$\Delta w(\Delta t) = \begin{cases} A_+ \exp\left(-\Delta t/\tau_+\right) & \Delta t > 0 \\ -A_- \exp(\Delta t/\tau_-) & \Delta t < 0 \end{cases} \tag{3.1}$$

where A_+ and A are both positive constants which scale the strength of potentiation and depression respectively, and τ_+ and τ are also positive time constants defining the width of the positive and negative learning window.

A STDP protocol is characterized by the induction of several repeated pre- and postsynaptic spike during a certain time window. Based on that sequence of spikes, either positive (succession of pre-post) inter-spike intervals or negative (succession of post-pre) inter-spike intervals can be described. By analyzing the direction and magnitude of plasticity over a range of these inter-spike intervals, the STDP function can be plotted. The latter represents the plasticity at a given synapse and the time windows for the induction of LTP and LTD. Moreover, this function allows to analyze the ratio of LTP versus LTD. Quite logically, if LTP and LTD windows are equal in area, the synaptic strength will not change whereas if the LTD area is larger, a decrease in synaptic strength will be observed [Liu and Buonomano, 2009].

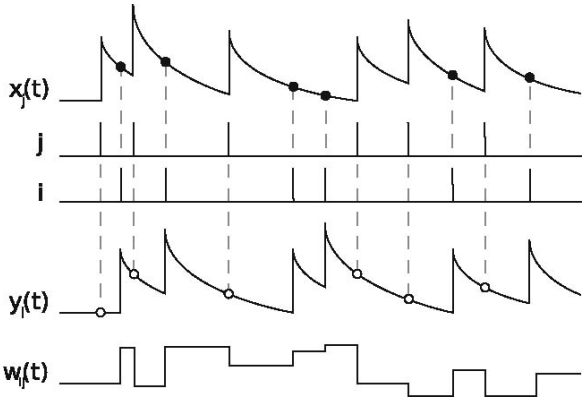


Figure 3.3: *Implementation of pair-based plasticity using the traces of the pre- and postsynaptic neuron* When they are spiking, both pre- and postsynaptic neurons leave a trace $x_j(t)$ and $y_i(t)$ respectively. The synaptic weight w_{ij} is updated accordingly. When a pre-post (resp. a post-pre) pair of spikes is recognised by the model, the weight w is increased (resp. decreased) by an amount of potentation (resp. depression) proportional to the value of the trace $x_j(t)$ (resp. $y_i(t)$ at the moment of the post (resp. pre) spike [Morrison et al., 2008]

Usually pair-based update rule is implemented using two local variables: one for the presynaptic spike train i and one for the postsynaptic spike train j. As can be seen on Figure 3.3, each of these spike leaves a trace decaying exponentially and each time the neuron spikes, respectively, this trace is incremented by an amount A_+ or A_-. The biophysical explanation - which is, by the way, not necessary for phenomenological models but still interesting to mention - of such a presynaptic and postsynaptic traces could for example represent respectively the decaying amount of neurotransmitters in the synaptic cleft and the calcium influx into the postsynaptic cell. If we denote $x_j(t)$ (resp. $y_i(t)$) the trace left by the presynaptic (resp. postsynaptic), the local variables can be described by the

following equations:

$$\frac{dx}{dt} = \frac{-x}{\tau_x} + \delta(t - t_{pre})$$
$$\frac{dy}{dt} = \frac{-y}{\tau_y} + \delta(t - t_{post}).$$
$$w_{new}(t) = w(t) + A_+ x(t) \text{ if } t = t^{post}$$
$$w_{new}(t) = w(t) - A_- y(t) \text{ if } t = t^{pre}.$$

To model a continuous change in the synaptic weight and avoid an abrupt change in the synaptic value, the following differential equation is implemented [Jacquerie et al., 2022]:

$$\tau_w \frac{dw}{dt} = (w_{new} - w). \tag{3.2}$$

3.4 Variants of STDP models

3.4.1 Different forms of STDP

Among the variety of STDP forms, three major classes of STDP can be distinguished:

- Canonical Hebbian STDP: in this form of STDP pre- before postsynaptic spike leads to LTP while post- before pre leads to LTD. We mostly find this form of STDP at excitatory synapses onto cortical pyramidal neurons [Bi and Poo, 1998, Sjöström et al., 2001a], nonpyramidal excitatory neurons in the auditory brainstem and excitatory synapses onto some neurons of the striatum.

- Anti-Hebbian STDP: is the exact opposite of the previous case i.e. a pre- before postsynaptic spike leads to LTD while a post- before presynaptic spike leads to LTP. This form of STDP has been observed in the human brain at excitatory synapses onto medium-sized spiny neurons of the striatum, which are GABAergic output neurons, as well as excitatory inputs onto cholinergic striatal interneurons

- All-LTD STDP: here, LTD of synaptic transmission occurs irrespective of pre–post temporal order but only for pre–post intervals within a defined time window, precisely of 0 to 20-50 ms. This form of STDP occurs at excitatory inputs onto different excitatory and inhibitory neurons [Shulz and Feldman, 2013, Abbott and Nelson, 2000].

As shown in Figure **??**, distinct forms of STDP can occur at different structures of the brain but also in the same brain structure and even at synapses made by single axons on two distinct target cell types [Shulz and Feldman, 2013]. For example, in the dorsal cochlear nucleus, fusiform principal neurons show classical Hebbian STDP while glycinergic cartwheel neurons show an all-LTD form of STDP [Shulz and Feldman, 2013]. One explanation for this difference is the interaction of different transmitter systems. Another example, still in the striatum, is cholinergic interneurons which show either anti-Hebbian STDP or LTD-only STDP depending on the excitability state of the postsynaptic neuron. This shows that multiple form of STDP can coexist in the striatum.

Everything we have just developed applies to excitatory synapses. Less is known about inhibitory synapses, but we know that the mechanisms are different. For example, in the hippocampus, inhibitory inputs to CA1 pyramids exhibit a symmetrical curve, with potentiation induced by both pre–post and post–pre pairings within 20 ms and depression induced by longer negative or positive

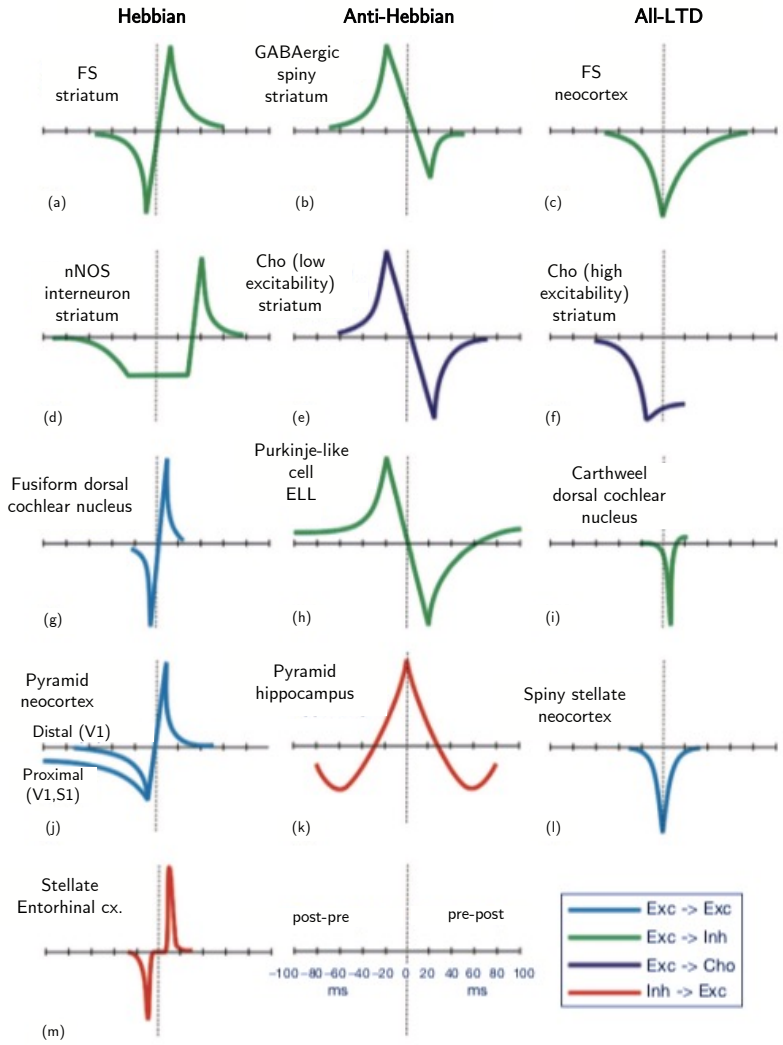


Figure 3.4: *Spike Timing-Dependent Plasticity (STDP) evoked by repeated pre- and postsynaptic firing in different preparations* [Shulz and Feldman, 2013, Abbott and Nelson, 2000]

intervals [Shulz and Feldman, 2013, Woodin, 2013].

In conclusion, STDP has diverse forms, though three main classes can be distinguished. However, among these three classes, canonical Hebbian STDP (the classical one) remains the most studies and the most used in current research. Additional regional variation in STDP may result from neuromodulatory gradients [Reynolds and Wickens, 2002].

3.4.2 Different types of bounds

If we recall the classical Hebbian learning theory developed by Hebb in 1949 and often illustrated by this famous postulate: “Cells that fire together, wire together” [Hebb, 1949a], we realise that the latter is not optimal in the sense that synaptic weights will tend to increase in an uncontrolled way as there is no "bounding" in the equation. Indeed, neural activities are rates of spiking and therefore positive quantities. Not only for computational reasons, but also for biological ones, it is important to keep the synaptic weights in a defined range such that $w_{min} < w_j < w_{max}$. One way to achieve this goal is to define bounds, appropriately choosing the functions $A_+(w_j)$ and $A_-(w_j)$.

Here, we introduce a family of nonlinear updating functions in which the weight dependence has the

form of a power law with a non-negative exponent μ aka "polynomial plasticity rule"[van Rossum et al., 2012] :

$$\Delta w_+ = A_+(1-w)^\mu$$
$$\Delta w_- = A_- w^\mu$$

where A_+, A_- allow to shape the STDP rule with different amounts of potentation and depression. As depicted on Figure 3.5, the case $\mu = 0$ corresponds to the implementation of "hard-bounds" also known as "additive model" [Gütig et al., 2003] whereas $\mu = 1$ corresponds to a plasticity model using "soft-bounds" aka "multiplicative model". Intermediate values of the updating parameter μ determine the range of the boundary effects that will be used to update the value of the synaptic weight w [Gütig et al., 2003]

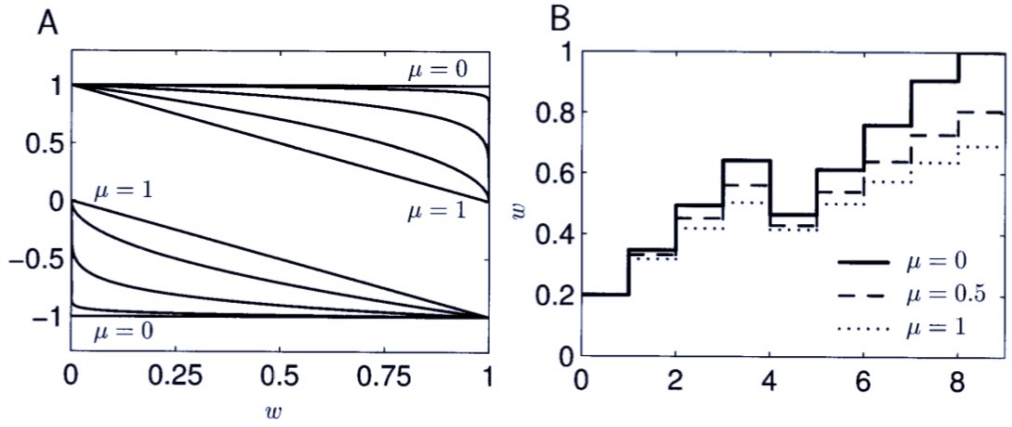


Figure 3.5: *Illustration of the interpolation between soft-bounds and hard-bounds.* **A.** Effect of the parameter μ on the updating function of the weight. When μ increases, the curves varies from the hard bounds curves (horizontal lines in -1 and 1) to the linear-soft bound lines with a slope equal to -1. **B.** Illustration of the effect of μ on synaptic changes. One can observe that, for hard-bounds ($\mu = 0$), potentiation changes have the same magnitude because it is assumed that Δt is constant and as we are in the hard bound case, the update of the weight is independent of the synaptic efficacy. On the contrary, when $\mu > 0$, the actual change is synaptic efficacy is not constant anymore. As we have $(1-w)^\mu$, the stronger the synapse, the smaller the change. [Gütig et al., 2003].

Hard bounds: $\mu = 0$

The first type of bounds that can be used in order to constrain synaptic weight in physiological limits, are called "hard bounds". For plasticity rules using that type of bounds, potentiation is said to occur when the input x is high and depression when this same input is low [van Rossum et al., 2012]. In other words, from the classical expression of the STDP, we can say that $A_+ = 0$ if $w > w_{max}$ whereas $A_- = 0$ if $w < w_{min}$ where w_{max} is usually set to 1 and w_{min} to 0 [Sjöström and Gerstner, 2010].

Soft bounds: $\mu = 1$

When $\mu = 1$, unconsidered growth of synaptic weight is avoided by using soft bounds meaning a model in which the updating functions linearly attenuate positive and negative synaptic changes as a synapse approaches the upper or lower boundary of the allowed range [Gütig et al., 2003]. In other

words, it means that, for large weights, synaptic depression dominates over potentiation. Following this reasoning, weaker synapses are more easily strengthened than already strong ones [Gütig et al., 2003]. Visually, this can be understood when looking at the kernel in Figure 3.6. A.. From then on, we can see that the difference with the previous bounds is the introduction of a weight dependency in the learning rules.

Mathematically, this can be written:

$$A_+(w_j) = (w_{max} - w_j)A_+.$$
$$A_-(w_j) = w_j A_-.$$

where A_+ and A_- are positive constants [Sjöström and Gerstner, 2010].

Studies have attempted to evaluate the performance of soft bounds compared to hard bounds. In 2012, Van Rossum et al., conducted a study which revealed that "soft-bound plasticity increased a variety of performance criteria by about 18% over hard-bound plasticity, and maximizes the storage capacity of synapses in the same way" [van Rossum et al., 2012]. Moreover, soft bounds are known to lead to a more stable model of plasticity but with lower Hebbian competition while hard bounds lead to less stable models but allow Hebbian competition [Babadi and Abbott, 2016]. In fine, it was not obvious whether soft-bound plasticity is better or worse for information storage compared to hard-bound plasticity [van Rossum et al., 2012].

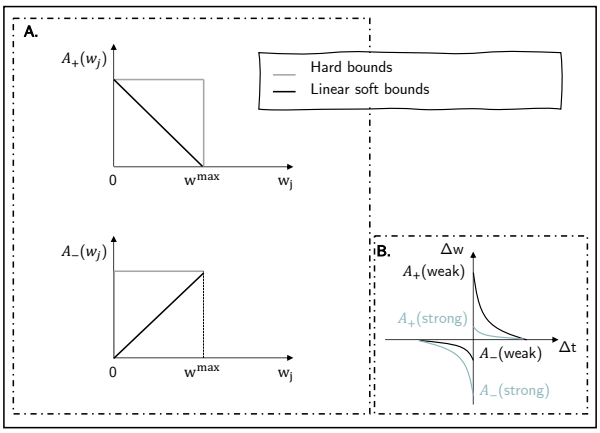


Figure 3.6: *Hard bounds and soft bounds* **A.** Illustration of hard bounds (grey) and linear soft bounds (pink). In case of hard bounds, the update rule with parameters, A_+ and A_-, of w_{ij} is used until the bounds w^{max} and w^{min} are reached. Then, the update stops at this value. In case of soft bounds, the parameters of the model, $A_+(w_j)$ and $A_-(wj)$, are weight-dependent in order to keep w_{ij} bounded. **B.** Illustration of the modulation of the STDP Kernel by soft bounds rule. For large weights (strong in orange), synaptic depression dominates over potentiation whereas for small weights (weak in pink) synaptic potentiation dominates over synaptic depression. *adapted from* [Sjöström and Gerstner, 2010])

Symmetric bounds

Another type of bounds that can be used in STDP model is named "symmetric bounds". In this model, Δw is maximum around the mid-range of w (=0.5) for both LTP and LTD and decreases as w increases to $'1'$ or decreases to $'0'$. Therefore, with this model, we can observe that once a synapse becomes very weak or very strong after a day of learning, it tends to retain its synaptic weights [Park et al., 2017].

Mathematically, the SR model is defined by:

$$A_+(w_{ij} = A_-(w_{ij}) = 2\min(w_{max} - w_{ij}, w_{ij} - w_{min}) \tag{3.3}$$

Hybrid model (mix between asymmetric and symmetric bounds)

Another model, someone could think off can be built by mixing asymmetric and symmetric bounds. Where the latter has been described previously and the former corresponds to hard bounds. Knowing that, mathematically, this can be written:

$$A_{HY}(w_{ij}) = \alpha A_{SR}(w_{ij}) + (1 - \alpha)A_{AR}(w_{ij}) \tag{3.4}$$

where $0 < \alpha < 1$

3.5 Unimodal versus bimodal distributions

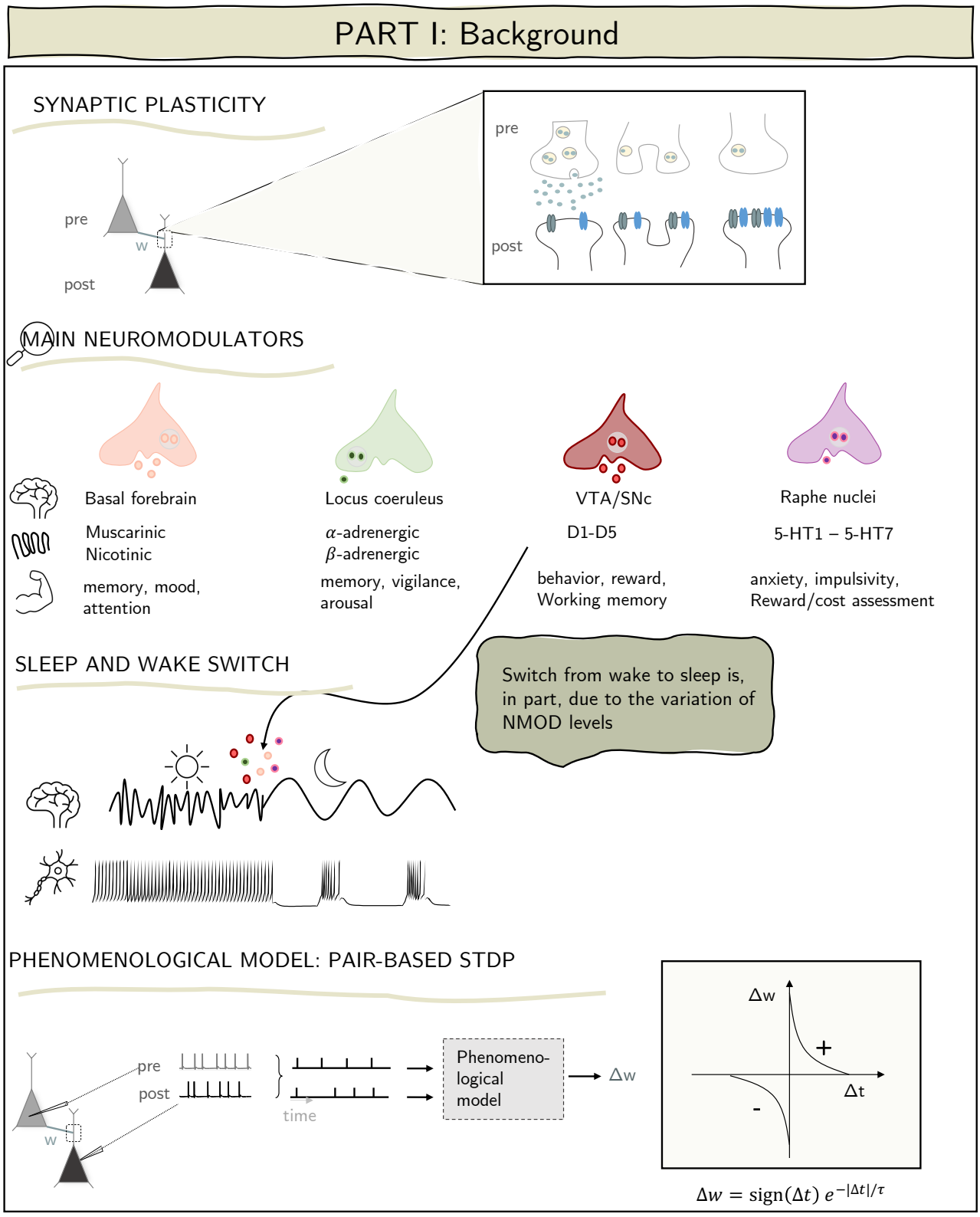
Over time, it became apparent that the learning rule used in STDP model can have a large influence on the equilibrium weight distribution of the inputs [Morrison et al., 2008]. Indeed, it has been demonstrated that an additive STDP rule, which corresponds to a hard-bound rule, was leading to a bimodal distribution of the weights whereas a multiplicative rule, which corresponds to a soft-bound rule, was leading to a unimodal equilibrium distribution [Rubin et al., 2001]. These two different behaviours, can be explained the following way:

- Bimodal distribution depicts hard bound rules which constrains synaptic weights in order to avoid synaptic saturation. Therefore, for uncorrelated synaptic activity, the overall effect of the plasticity rule has to lead to a weakening of the synaptic weights. This explains the part of the distribution that peaks close to zero weight. However, stronger synapses correspond to a pairing activity of neuronal spikes that is more correlated creating a positive feedback which eventually leads to the other part of the distribution close to one i.e. the maximum synaptic strength that we allow [Barbour et al., 2007].

- Unimodal distribution depicts soft bound rules meaning that for these rules, a synaptic change depends on the strength of the synapse. Therefore, we understand that, for example unimodal distribution can be encountered when depression increases with synaptic strength [Barbour et al., 2007].

In the context of our thesis, the interest of these two types of distribution lies in their link with memory. Indeed, as bimodal distribution allows to separate the evolution and behaviour of strong and weak synapses, it is thought to be associated with long-term memory. On the contrary, unimodal distribution of synaptic weights has the problem that it does not lead to long-term stability of the weights in particular if, after a period of learning, all synapses weights converge to a weak synaptic weight value. "This would mean that the neuron forgets its synapse pattern as rapidly as it was learned" [Gerstner and Toyoizumi,].

3.6 Summary


PART I: Background
SYNAPTIC PLASTICITY
pre
w
post
pre
post
MAIN NEUROMODULATORS
Basal forebrain
Muscarinic
Nicotinic
memory, mood, attention
Locus coeruleus
α-adrenergic
β-adrenergic
memory, vigilance, arousal
VTA/SNc
D1-D5
behavior, reward, Working memory
Raphe nuclei
5-HT1 – 5-HT7
anxiety, impulsivity, Reward/cost assessment
SLEEP AND WAKE SWITCH
Switch from wake to sleep is, in part, due to the variation of NMOD levels
PHENOMENOLOGICAL MODEL: PAIR-BASED STDP
pre
post
w
time
Phenomeno-logical model
Δw
Δw
Δt
+
-
$\Delta w = \text{sign}(\Delta t)\, e^{-|\Delta t|/\tau}$

Part II

Neuromodulation of phenomenological plasticity rules

Chapter 4

Review of the effects of neuromodulators on phenomenological plasticity rules and on sleep

This section is dedicated to reviewing the effects of neuromodulators on sleep and the **phenomenological rules** of plasticity. At this point, it is important to stress again that our study will really focus on the effect of neuromodulators on these phenomenological rules and more precisely on the pair-based STDP. Indeed, their effect on the calcium cascade is reviewed by Juliette Ponnet in her master thesis. This work is therefore carried out in parallel on two different models, which explains the homogeneity of the colour codes and annotations.

In CHAPTER 2 we reviewed the different neuromodulators, focusing on their location in the brain and their effects. Here, we will focus on how they manage to tune the STDP and sleep. The role More specifically, the effect of noradrenaline, acetylcholine, dopamine, serotonin and some other components such as BDNF or GABA will be addressed in this section. These neuromodulators can change different properties of the STDP rule which will be divided into three main categories:

- Change in STDP **polarity** meaning that the neuromodulatory state can determine whether the same timing between the activity of the pre- and postsynaptic neurons strengthens or weakens the synaptic weights e.g. conversion of bi- to unidirectional STDP and vice versa (Figure 4.1.B.).
- Change in STDP **magnitude** e.g. increase or decrease of the magnitude of STDP (Figure 4.1.D.).
- Effects in the expression/induction of STDP e.g. enlargement of the **time window**, increase or decrease of the threshold for plasticity induction (Figure 4.1.C.).

It should be mentioned that, when reviewing the ability of neuromodulators to modify the STDP kernel, we will not focus on the different spike pairing protocols that may have been used in order to arrive at the conclusions that we will present. Instead, we will focus on the brain structure involved and the activation or inhibition of the receptors that enable this modulation of synaptic plasticity.

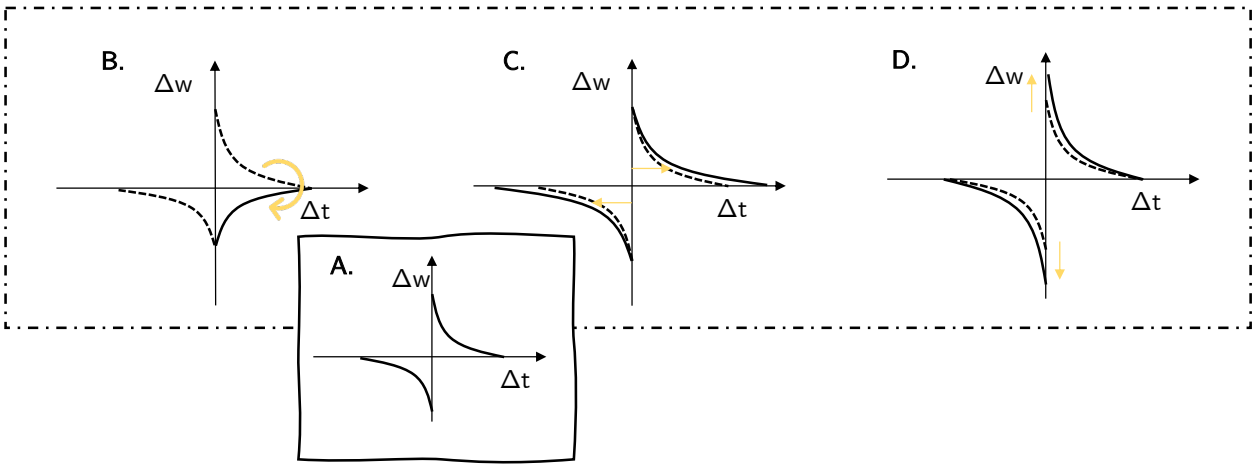


Figure 4.1: *Modulation of Spike Timing-Dependent Plasticity (STDP)* **A.** The classic Hebbian STDP window: synaptic potentiation is induced by repeated pre-before-post spike-timing intervals whereas synaptic depression is induced by repeated post-before-pre spike-timing intervals. However, spike timing is not the only factor able to modify STDP shape. The latter is malleable in different ways. Here, an illustration of the three main changes that an external factor: here, neuromodulation can make to the classical STDP. **B.** Polarity can be reversed. **C.** Temporal requirements for STDP can be modulated. **D.** Finally, magnitude can also be varied. *Adapted from* [Brzosko et al., 2019]

4.1 Acetylcholine

4.1.1 Effect on sleep

During sleep, levels of acetylcholine have appeared to vary according to the sleep stage the asleep individual is in: ACh is high during REM sleep and active wakefulness and low during quiet wakefulness and SWS [Herz and Atherton, 1992]. This increase in ACh levels during REM sleep is therefore a potential mechanism by which sleep will modulate specific cellular signaling pathways that also happen to be involved in hippocampal function such as memory storage. Moreover, it has been shown that application of ACh to hippocampal slices produces a theta rhythm of neuronal activity [Graves, 2001] which could create a good environment for LTP induction and reinforce the link between ACh, sleep and memory consolidation.

In the same way as in the hippocampus, there is evidence for the effect of acetylcholine on synaptic plasticity during sleep in the cortex. Indeed, one study [Fink et al., 2013] tested ACh potential role in an important function of sleep discussed in Chapter 2, the *synaptic renormalization hypothesis*. Indeed, we recall that, according to this hypothesis, in order to avoid synaptic saturation and thus allow our synapses to remain plastic and to be able to induce LTP and LTD phenomena, a large-scale synaptic downscaling is said to be of importance and occurs during sleep. How this synaptic renormalisation is produced remains a subject of current research. However, among the hypotheses mentioned, one that interests us is the difference in the levels of neuromodulators present during wakefulness and the different NREM sleep states. This difference in concentration could indeed explain the different effects in terms of neuronal potentiation levels between wakefulness and sleep [Fink et al., 2013]. More practically, the above-mentioned study showed that variation in ACh levels between wake and NREM could provide a mechanism for both upscaling and downscaling in cortical synapses. Indeed, experimental studies showed that ACh was able to modulate the phase-dependence of neural responses in cortex [Stiefel et al., 2008, Stiefel et al., 2009]. In [Fink et al., 2013], computational evidences have showed, using STDP rule, that high levels of ACh in cortical circuits during waking could favour global

synaptic potentiation whereas the absence of ACh (or at least lower levels of ACh) during NREM sleep may lead to global depotentiation.

4.1.2 Effect on STDP rule

Activation/inhibition of muscarinic receptors (mAChRs)

In Figure 4.2.C., it can be seen that hippocampal CA1 pyramidal cells, acetylcholine first allows to reverse the polarity of STDP by converting bidirectional Hebbian STDP into unidirectional tLTP [Brzosko et al., 2017]. On the contrary, inhibition of mAChRs prevents post-pre tLTD and converts pre-post tLTP into tLTD [Sugisaki et al., 2011, Sugisaki et al., 2016]. Conversely, activation of mAChRs can also change t-LTD into t-LTP at the Schaffer collateral–CA1 synapses in rat hippocampus [Sugisaki et al., 2016], as in L2/3 of the rat prefrontal cortex [Zaitsev and Anwyl, 2012]. It has also been noticed that mAChRs expressed in GABAergic interneurons and pyramidal cells are the main drivers of the excitation/inhibition balance that exists in CA1 pyramidal neurons and that leads to Hebbian STDP in this area. Indeed, as an example, we can mention that, still at synapses of CA1 pyramidal neurons, pre-post pairings induce tLTP of excitatory pathway while it triggers tLTD at inhibitory pathways via the co-activation of mAChRs and CB1R [Ahumada et al., 2013]. Therefore, it appears that the main effect of acetylcholine, when acting alone in the hippocampus CA1 pyramidal cells, is to promote unidirectional plasticity (tLTP- or tLTD-only) over bidirectional one. However, when its action is coupled i.e. when we are in the case of a co-activation of mAChRs and Gs coupled pathways, acetylcholine is also capable of promoting bidirectional plasticity by restoring Hebbian tLTP in the cortex for ΔtSTDP$>$0 [Seol et al., 2007].

Then, acetylcholine also has an effect on STDP induction. In a general way, induction of STDP is facilitated and coincidence window for synaptic modification is broaden thanks to the enhancement of presynaptic depolarization by acetylcholine. Moreover, induction of t-LTP can also be facilitated thanks to the activation of mAChRs that decrease membrane conductance which increases the amplitude and decay of EPSPs [Fuenzalida et al., 2021]. Finally, mAChR activation promotes action potential backpropagation in CA1 pyramidal dendrites [Tsubokawa and Ross, 1997] which lowers the threshold of t-LTP induction and ultimately facilitates LTP.

Conversely, the temporal window for t-LTP can also be narrowed by a reduction of the amplitude and decay time constant of the glutamate-evoked excitatory postsynaptic potential (EPSP) [Fuenzalida et al., 2021].

Another important factor to consider is the link between the response induced by the application of acetylcholine and the particular muscarinic receptor it targets. Thus, M2Rs are known to promote excitatory LTP at the associational/commissural fiber-CA3 synapses, in the hippocampus, while reduce the amplitude of LTP at mossy fiber -CA3 synapses [Zheng et al., 2012]. This result highlights the fact that, within the CA3 area, some rules can be specific to certain synapses via the modulation of mAChR. Moreover, at Schaffer collateral-CA1 synapses, activation of M2Rs help to enhance LTP [Shimoshige et al., 1997].

In the dorsal cochlear nucleus (see Figure 4.2.E.), acetylcholine is able to convert t-LTP into t-LTD. Indeed, pharmacological activation of postsynaptic M1/M3 mAChRs changes postsynaptic Hebbian t-LTP to presynaptic anti-Hebbian t-LTD [Zhao and Tzounopoulos, 2011, Brzosko et al., 2019].

Activation/inhibition of nicotinic receptors (nAChRs)

As one can observed in Figure 4.2.D., activation of nAChRs have several reported effects on synaptic plasticity mainly, depolarization and possible increase in calcium influx but also, regulation of the magnitude of STDP rather than its polarity or expression [Sugisaki et al., 2016]. In the cortex, nicotine has various effects on STDP. First, it increases the threshold for induction of Hebbian tLTP at excitatory synapses in this area of the brain. Then, when applied at a high concentration (-10μM), it is even able to convert tLTP into tLTD [Couey et al., 2007]. Interestingly enough, it has been demonstrated that, in the cortex, the effects of nicotine on STDP were different according to the developmental stage. Thus, nicotine reduces the magnitude of tLTP in juvenile rats while it increases it in adult rats [Goriounova and Mansvelder, 2012].

In the same way as for mAChRs, activation of nAChR can also change t-LTD into t-LTP at the Schaffer collateral–CA1 synapses in rat hippocampus [Sugisaki et al., 2016], as in L2/3 of the rat prefrontal cortex [Zaitsev and Anwyl, 2012].

In the hippocampus, the polarity of acetylcholine-modulated plasticity can also depend on the concentration and specific cholinergic receptor subtype activated. In the same way, different subtypes of nAChR are given different roles in memory tasks. Indeed, activation of α7 nAChRs gates t-LTP and is needed for encoding of associative recognition memory, while activation of α4b2 nAChRs, which gate t-LTD, is critical for memory retrieval [Sabec et al., 2018, Brzosko et al., 2019].

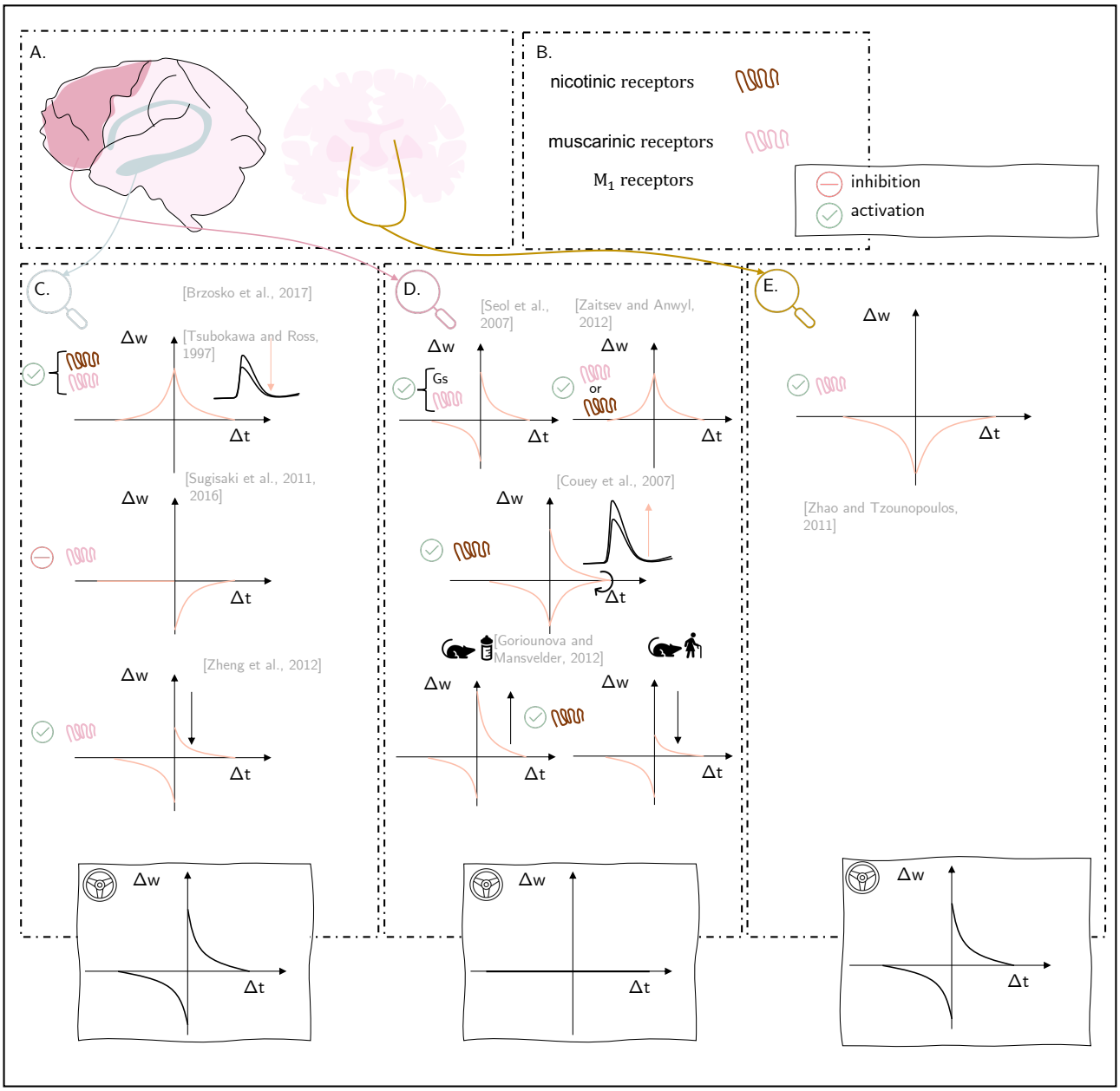

A.
B.
nicotinic receptors
muscarinic receptors
M_1 receptors
inhibition
activation
C.
D.
E.
[Brzosko et al., 2017]
[Tsubokawa and Ross, 1997]
[Sugisaki et al., 2011, 2016]
[Zheng et al., 2012]
[Seol et al., 2007]
[Zaitsev and Anwyl, 2012]
[Couey et al., 2007]
[Goriounova and Mansvelder, 2012]
[Zhao and Tzounopoulos, 2011]
Gs
or
Δw
Δt

Figure 4.2 *(previous page)*: *Acetylcholine shapes STDP in hippocampus, cortex and dorsal cochlear nucleus.* **A.** Location of brain sites where acetylcholine influences synaptic plasticity. **B.** Acetylcholine mainly exerts its action via nicotinic (brown) and muscarinic (pink) receptors. **C.** In the hippocampus, high levels of ACh allow to convert the classical Hebbian STDP that can be found in this area of the brain into unidirectional tLTP. Moreover, it facilitates LTP by lowering the threshold for its induction [Brzosko et al., 2017, Tsubokawa and Ross, 1997]. On the contrary, inhibition of muscarinic receptors prevents post-pre tLTD and converts pre-post tLTD into tLTP [Sugisaki et al., 2011, Sugisaki et al., 2016]. Finally, activation of muscarinic receptors also allows to decrease the magnitude of tLTP [Zheng et al., 2012]. **D.** In the cortex, activation of M_1R agonists and Gs protein allow to switch from an absence of plasticity to the classical Hebbian STDP Kernel[Seol et al., 2007] whereas the activation either of muscarinic or nicotinc receptors lead to unidirectional LTP [Zaitsev and Anwyl, 2012]. ACh in the cortex also induces tLTD and increases the threshold for tLTD by activation of nicotinic receptors [Couey et al., 2007]. Finally, In the rat prefrontal cortex, activation of nicotinic receptors allow to induce Hebbian STDP. Depending on its age, magnitude of LTP can be increased (juvenile rats) or decreased (adult rats) [Goriounova and Mansvelder, 2012]. **E.** In the dorsal cochlear nucleus, activation of muscarinic receptors permits to convert t-LTP into t-LTD [Zhao and Tzounopoulos, 2011] N.B.: for each area of the brain, the usual control curve that is found with specific pairing protocols is encased in a small box at the bottom of the figure.

4.2 Noradrenaline

4.2.1 Effect on sleep

It is tempting to speculate that the 'tones' of noradrenaline during wakefulness and sleep participate in reorganizing cortical synaptic weights in a spike-timing dependent manner. The higher NE levels present during wakefulness and non-REM stages could promote bidirectional plasticity of active sensory inputs, while the lower NE levels found during REM sleep may favor the generalized build-up of synaptic depression of active synapses. [Salgado et al., 2012].

4.2.2 Effect on STDP rule

In several brain regions, noradrenaline can modify the shape of the STDP curve. As for each neuromodulator that will be reviewed in this section, noradrenaline effects will vary according to the receptors that are targeted.

Activation/inhibition of β-adrenergic receptors

In the hippocampus, noradrenaline can first act on the induction of STDP, tending to promote t-LTP [Brzosko et al., 2019]. Indeed, as can be seen on Figure 4.3.C., activation of β-adrenergic receptors enlarges the range of ΔtSTDP for Hebbian tLTP expression by increasing the excitability of CA1 pyramidal cells [Lin et al., 2003].

Moreover, in L2/3 of visual cortex, activation of $\beta-$adrenergic receptors promotes induction of t-LTP and suppresses t-LTD [Seol et al., 2007].

Activation/inhibition of α1-adrenergic receptors

α1-adrenergic receptors have a higher affinity for noradrenaline than their β fellows. Thus, in low noradrenaline concentration, unidirectional anti-hebbian STDP is observed while higher concentration

will allow bidirectional Hebbian STDP [Salgado et al., 2012].

Moreover, in L2/3 of visual cortex, activation of $\alpha-$adrenergic receptors holds the opposite role of $\beta-$adrenergic receptors by promoting the induction of t-LTD and suppressing t-LTP. [Seol et al., 2007] (see Figure 4.3 **B.**).

Activation/inhibition of both β- and α1-adrenergic receptors

In the visual cortex, under classical conditions of stimulation of the postsynaptic region, activation of adrenergic receptors is necessary to induce bidirectional Hebbian STDP in pyramidal cells of layer 2/3 in rodents, primates as well as in fast-spiking and non-fast-spiking interneurons [Wang et al., 2012, Huang et al., 2014].

To conclude, a pattern emerges from the effects of noradrenaline: the activation of Gs-coupled -adrenergic receptors tends to promote tLTP, whereas the activation of Gq-coupled 1-adrenergic receptors tends to favor tLTD [Brzosko et al., 2019].

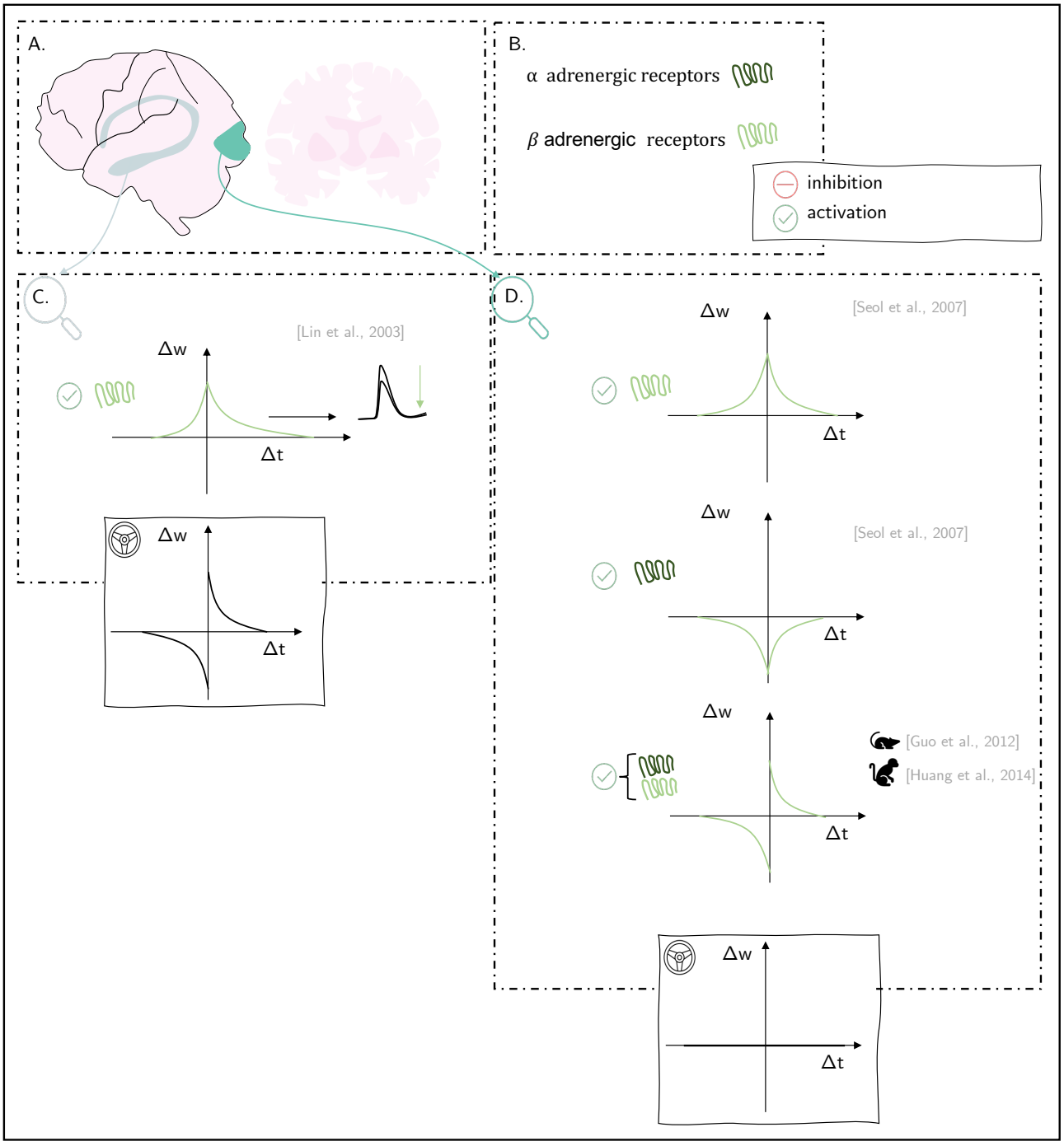


Figure 4.3: *Noradrenaline shapes STDP in the hippocampus and visual cortex* **C.** In CA1 pyramidal cells of the hippocampus, activation of β-adrenergic receptors lead to the enlargement of STDP time window Δt_{STDP} (green curve). **D.** In layer 2/3 of the visual cortex, STDP protocols do not produce STDP in control conditions. When both α_1- and β-adrenergic receptors are activated, bidirectional Hebbian STDP can be observed [Wang et al., 2012, Huang et al., 2014]. This case corresponds to the one in which NA concentration would be high. The sole activation of *beta*-adrenergic receptors leads to unidirectionnal Hebbian tLTP whereas the activation of α_1-adrenergic receptors induces unidirectionnal anti-Hebbian tLTD [Seol et al., 2007]. This last case is induced when the concentration of noradrenaline in the medium is low as the affinity for NA of those receptors exceeds that of β-adrenergic receptors.

4.3 Dopamine

As for noradrenaline, dopamine is able to modify the STDP learning rule in various ways depending on the receptors to which it binds. Indeed, dopaminergic receptors belong to two groups based on their G-protein coupling:

- D_1-class receptors, which gathers D_1 and D_5 receptors, are coupled to G_s- or G_{olf}-proteins.
- D_2-class receptors i.e. D_2R, D_3R and D_4R are coupled to $G_{i/o}$-proteins.

These two classes of receptors are know for their opposite action on the cAMP second messenger pathway and the protein kinase (PKA) which are involved in long-term memory processing [Foncelle et al., 2018].

Box 3| G-protein signaling

G-protein coupled receptors are receptors located at the surface of the cell. Once activated, they trigger the activation of cellular cascades. They can be classified into three categories:

- G_q which is a stimulatory receptor known to activate the phospholipase C (PLC) pathway.
- G_s which is also stimulatory and whose role is to activate the protein kinase C (PKC) pathway via the cyclic adenosine monophosphate (cAMP).
- G_i on the contrary is inhibitory and therefore, inhibits signaling cascades in the cell [Kim et al., 2020].

4.3.1 Effect on sleep

Dopamine has various effects on sleep. Firstly, when D_1 receptor agonist is administrated, an increase in wake and a reduction of SWS and REMS can be observed. In the same manner, injection of a dopamine D_2 receptor agonist induces effects on sleep but here the latter are biphasic: a low dose of the agonist reduces wake and increase SWS and REMS whereas large dose induce the opposite effect. Therefore, compounds that are able to block DA D_1 or D_2receptors augment non-REMS and reduce wake [Monti and Monti, 2007].

Box 4|Agonist vs antagonist

Agonist is a term used in order to designate a molecule that binds to a receptor causing activation and resultant cellular changes.

Antagonist is referring to a molecule that attenuates the action of an agonist [Pleuvry, 2004].

4.3.2 Effect on STDP rule

In the hippocampus first, dopamine is know for its capacity to promote tLTP. Indeed, as can be seen in Figure 4.4.C., when dopamine is added during STDP pairings or immediately after STDP pairings, the usual tLTD which is observed in control conditions for negative $_{STDP}$ (i.e. post-pre pairings) is converted to tLTP [Zhang et al., 2009, Brzosko et al., 2015]. One can notice that the timing of dopamine addition in STDP protocol is of tremendous importance e.g. dopamine addition during STDP induction lead to the enlargement of the temporal window of tLTP expression while dopamine effects disappear when dopamine is added long after STDP pairings. Indeed, dopamine addition 10 minutes after pairings leads to the absence of plasticity while dopamine addition after 30 minutes, leads to the recovery of tLTD normally observed in control conditions [Brzosko et al., 2015].

Still in the hippocampus, the activation of D_1 receptors allows to affect STDP polarity by converting bidirectional STDP to unidirectional tLTP while this effect is not encountered with D_2R [Zhang et al., 2009, Brzosko et al., 2015].

In a previous section, acetylcholine effects on STDP rule have been reviewed in details. One of these effects is, in among other things, to transforms bidirectional Hebbian hippocampal STDP into unidirectional tLTD [Brzosko et al., 2017] (see Figure 4.4.G.). In fact, one of the effect of dopamine is actually to be able to reverse the effect of acetylcholine, and recover tLTP, when added 1s after STDP pairings [Brzosko et al., 2017]. This result opens the way to theories on the retroactive effect that dopamine may have on Hebbian plasticity rules [Gerstner et al., 2018].

There are other examples for the presumed role of dopamine for promoting hippocampal tLTP. Indeed, in STDP protocol during which the dopamine level is reduced below its physiological level, induction of tLTP is prevented whereas it is rescued after addition of dopamine and activation of D_1 receptors [Edelmann and Lessmann, 2011].

In the hippocampus, dopamine application is also capable of changing the shape of the STDP window, enabling longer pre-post timing delays which permits to increase synaptic efficiency. D_1 and D_5 receptors are know to be the mediators of this widening effect, expanding the t-LTP window by at least 25 ms [Foncelle et al., 2018]. Not only is dopamine able to modify the STDP window, but it can also modify the number of pre–post pairing episodes required to induce plasticity in hippocampal neurons [Zhang et al., 2009]. Indeed, activation of D_1 and D_5 receptors allows tLTP to be induced by less (i.e. 10 pairings) than the reglementary 60 pairings of the classical STDP protocol. Therefore, dopamine as noradrenaline permits to favour tLTP induction by lowering its threshold [Foncelle et al., 2018].

As in the hippocampus, dopamine modulation of STDP is also important in another brain areas such as in the basal ganglia where it helps to regulate motricity, action selection and reinforcement learning [Schultz, 2007]. In the striatum, STDP is required both ex vivo and in vivo and is affected by dopamine. Experiments made in vivo in anesthetized rodents, have shed light on the ability of dopamine to elicit bidirectional STDP while negative and positive pairing STDP protocol, without the addition of dopamine, lead to tLTD only [Schulz et al., 2010, Bissière et al., 2003]. This is coherent with ex vivo studies, in which the application of dopamine is shown to allow dendritic spine enlargement and calcium increase which are characteristics of LTP [Yagishita et al., 2014]. We have already mentioned that the action induced by dopamine in an area of the brain depends on the type of receptor it binds to. In this respect, and in general, about STDP modulation by dopamine, there are actually some conflicts between researchers. Indeed, according to Pawlak and Kerr (2008), tLTD and tLTP are D_1R-mediated but not D_2R-mediated whereas Shen et al. (2008), claims that according to the pathway direct or indirect tLTP and tLTD expression in striatal neurons requires respectively D_1R activation and D_2R activation [Foncelle et al., 2018]. Methodological differences between the two studies could explain this discrepancy in results. The subject will not be developed further here. However, one can note that detailed computational models of the signaling pathways could be helpful in order to have a better understanding of the effect of dopaminergic receptors in the different forms of STDP.

In L5 of prefrontal cortex, a classic STDP protocol (60 pairings, ΔtSTDP = +10 ms, frequency = 0.1 Hz) fails to produce plasticity while Hebbian tLTP and anti-Hebbian tLTP can both be induced after dopamine addition during the STDP pairings [Xu and Yao, 2010, Ruan et al., 2014].

Then, in the lateral nucleus of the amygdala, this time, D_2R are the one necessary to induce tLTP [Edelmann and Lessmann, 2013, Foncelle et al., 2018].

In summary, these results show that dopamine is a key neuromodulator of STDP and constitutes the third factor required for the temporal credit-assignment. Overall, the effects of dopamine seem to conform to a simple general scheme: the activation of Gs/Golf-coupled D1R tends to promote tLTP whereas the activation of Gi-coupled D2R favors tLTD. However, the effects exerted by dopamine strongly depend on the brain area: dopamine either can be mandatory for STDP induction and/or maintenance or modulate STDP properties (width of the window, polarity of the STDP or magnitude of the plasticity). Moreover, network effects can add complexity to the picture, since the expression of dopamine receptors is not restricted to the examined neuron but can affect the response to e.g., local interneurons.

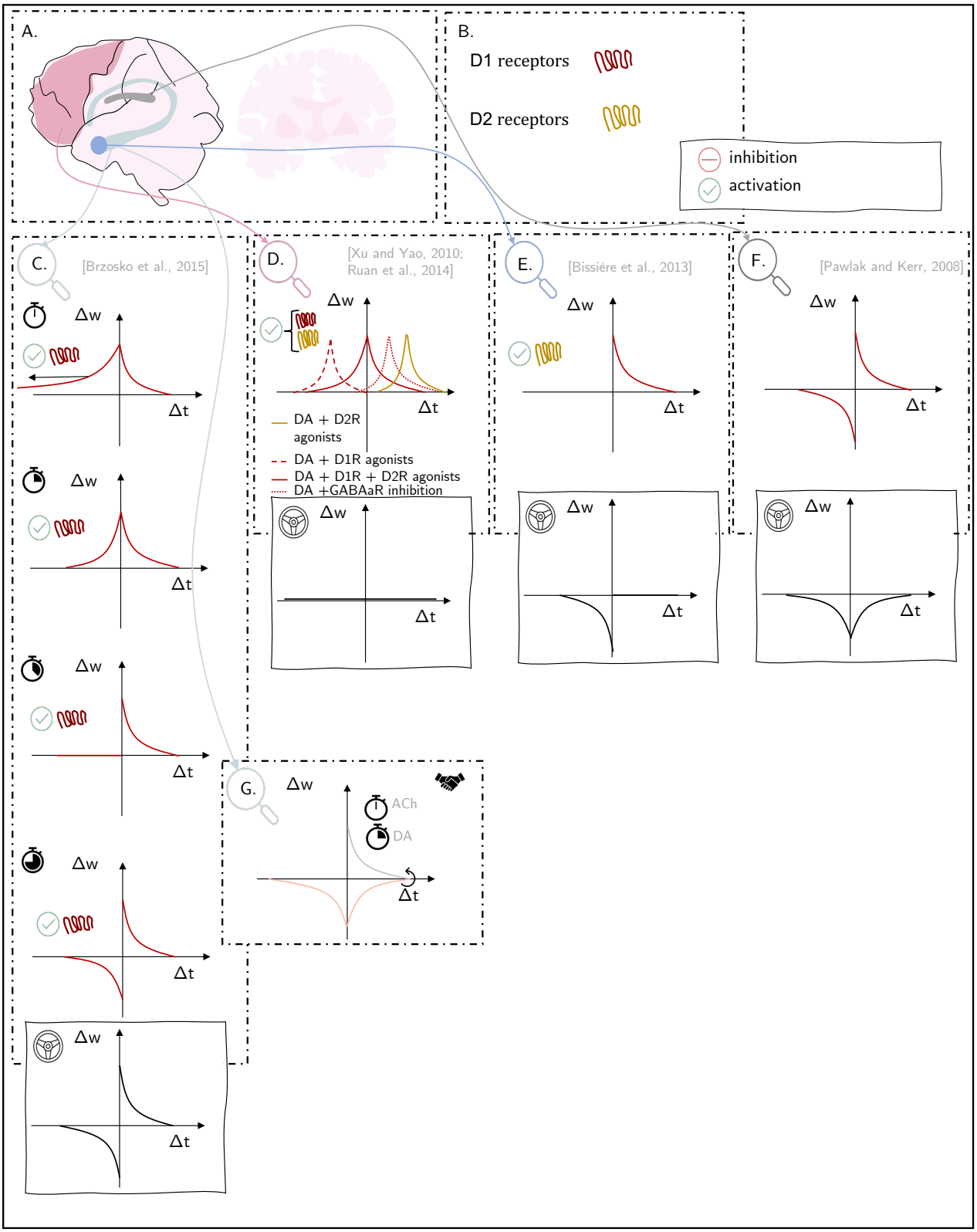

A.
B.
D1 receptors
D2 receptors
inhibition
activation
C.
[Brzosko et al., 2015]
D.
[Xu and Yao, 2010; Ruan et al., 2014]
E.
[Bissière et al., 2013]
F.
[Pawlak and Kerr, 2008]
Δw
Δt
DA + D2R agonists
DA + D1R agonists
DA + D1R + D2R agonists
DA +GABAaR inhibition
G.
ACh
DA

Figure 4.4 *(previous page)*: *Dopamine shapes STDP in hippocampus, prefrontal cortex, lateral amygdala and striatum.* **C.** In the hippocampus, the control curve corresponds to the classic bidirectional Hebbian STDP. When DA is applied during the pairing protocols or directly after it, the polarity of the STDP curve is reversed and only LTP is observed. When DA is applied 10 min after the pairings protocols, it results in an absence of plasticity whereas when it is applied 30 min after the protocol, LTD is observed [Brzosko et al., 2015, Zhang et al., 2009]. **D.** In the prefrontal cortex, following a pairing protocol that does not render any STDP, the activation of D_1- and D_2-liked receptors leads to unidirectional tLTP. Depending on the component that activate or inhibit D_1- or D_2-class receptor, tLTP is induced either for pre-post pairings or post-pre pairings [Xu and Yao, 2010, Ruan et al., 2014]. **E.** In the lateral nucleus of the amygdala, activation of D_2-class receptors is required to induce tLTP [Bissière et al., 2003]. **F.** In the striatum, addition of DA converts tLTD into tLTP for pre-post pairings [Pawlak, 2010]. **G.** Dopamine is able to reverse the effect of acetylcholine and recover tLTP in the hippcampus [Gerstner et al., 2018].

4.4 Serotonin

4.4.1 Effect on sleep

The role of serotonin in sleep/wake cycle is known to be complex and confusing. Indeed, some studies place this neuromodulator as a promoter of the sleep phase while others tend to consider it as a promoter of wakefulness. In fact, serotonin appears to alter sleep- or wakefulness-related processes in function of the receptor it binds to and the state of the individual [Vaseghi et al., 2021]. In a general way, serotonin levels, in the same way that for the other neuromodulators, vary depending on the sleep phase an individual is in. They are highest in waking, low in SWS and lowest in REM phase [Portas et al., 1998]. During waking, high levels of serotonin imposes sleep pressure and promotes the homeostatic regulation of sleep. Indeed, activation of the dorsal raphe nucleus, which is a pool of serotonergic neurons, promotes wakefulness while the principal brain area that promotes SWS is the VLPO [Vaseghi et al., 2021].

AS mentioned, during NREM and REM sleep, levels of 5-HT are decreased in the hippocampus. This reduction might be one way through which serotonin could contribute to the consolidation of memory even though further investigations are needed. In fact subtypes of 5-HT receptors are negatively or positively coupled to different actors of the cellular cascade of plasticity induction such as adenylyl cyclase, phospholiphase C or ligand-gated ion channels. Depending on the receptors towards which it binds and on the cellular actor that is linked to this receptor, different effect on memory will be observed. As such, administration of an agonist of the 5- HT1A receptor, which is negatively coupled to adenylyl cyclase, results in retrograde amnesia, whereas a 5-HT1A antagonist facilitates memory [Graves, 2001]. This observation highlights the potential role of serotonin in memory consolidation during sleep and the interest of further research in this area.

4.4.2 Effect on STDP rule

In the visual cortex and in the medial prefrontal cortex, serotonin is known to play a role pretty similar to the one that noradrenaline plays with tLTP but here, for tLTD. Indeed, if serotonin is added/released during a STDP protocol, just after the whole set of pairings or after every pairing, it enables the post-before-pre-conditioned pathway to express t-LTD with otherwise ineffective pairing protocols [Song et al., 2015]. Actually, in this region of the brain, the STDP pairings per se are not able to induce any form of plasticity. He et al. observed in 2015 that the eligibility traces are short-lived since the monoamines need to be release 5–10 s after learning to promote plasticity [Song et al., 2015]. This observation is totally in cohesion with our hypothesis that a third factor, here: neuromodulators active during sleep, are sometimes needed to induce plasticity (either tLTP or tLTD) and could allow an efficient stabilization of learning and avoid synaptic saturation.

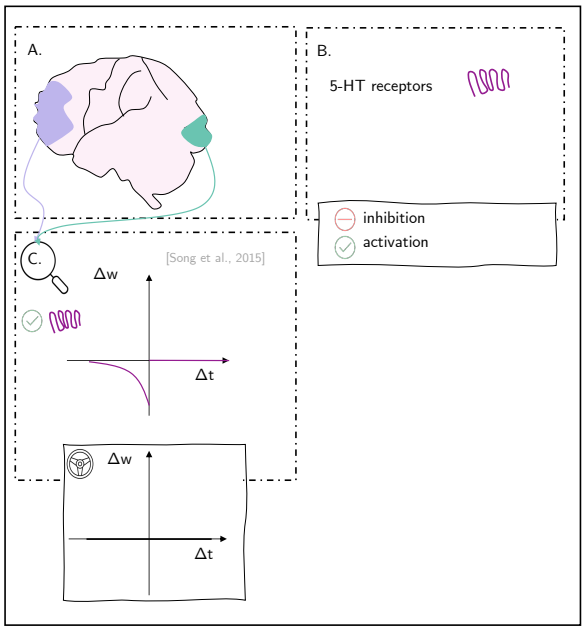


Figure 4.5: *Serotonin shapes STDP in the visual and prefrontal cortex* **C.** When serotonin is added during a STDP protocol, it allows to transform an ineffective post-pre protocol into tLTD [Song et al., 2015]

4.5 Other components

In addition to neuromodulators, other compounds present in different areas and states of the brain are also capable of modifying the rules of synaptic plasticity, in particular STDP, in which we are particularly interested.

BDNF

Effect on sleep BDNF is known for working in pair with serotonin, which plays an important role both in regulation of sleep-wake circadian cycles and in the modulation of mood states in humans. Indeed, BDNF production is stimulated by serotonin and BDNF increases serotonergic signalling. Alone, BDNF is able to induce sleep deprivation and spontaneous wakefulness in animals [Strube et al., 2015]. Moreover, in a small cortical region, local infusion of BDNF appears to induce local slow wave activity (SWA) in the region in question. The exact mechanisms by which BDNF induces this increase in SWA has not been identified yet but it has been proposed that "the coupling between waking-associated synaptic potentiation among connected cells may directly contribute to this increase in SWA" [Schmitt et al., 2016]. On the contrary, blocking BDNF expression during wakefulness induces a local SWA decrease in subsequent sleep. One can note that the increase in SWA was only observed during NREM sleep, not during REM sleep or waking [C. Hanlon et al., 2011].

Effect on STDP In the hippocampus, several studies have showed that the presence of extracellular BDNF is required to induced tLTP at CA1 synapses. The study from Lu et al. in 2014 has shown the same results as these previous studies. Indeed, experiments have been made in which a slice is

perfused with solution containing a soluble ligand that chelates extracellular BDNF, for 10 min prior to the application of pre- and postsynaptic pairing of spikes. This experiment results in no change in the EPSP amplitude meaning that the extracellular presence of BDNF during the pairing protocol is necessary for induction of LTP [Lu et al., 2014]. Shortly after this study, it has been discovered that the BDNF dependence that has been noticed in plasticity changes in function of the activity pattern during STDP pairings. Indeed, hippocampal tLTP induced with presynaptic activation paired with postsynaptic bursts of four back-propagating action potentials (1:4 pairings repeated 30 times at 0.5 Hz) is BDNF and tyrosine receptor kinase B-mediated, whereas canonical STDP pairings (1:1 pairings repeated 100 times at 0.5 Hz) induced a tyrosine receptor kinase B-independent tLTP at the same synapses [Craig et al., 2015].

In the prefrontal cortex now (Figure 4.6.C.), STDP is altered by genetic impairment of BDNF synthesis. Indeed, if one of the promoters involved in BDNF transcription is impaired, tLTP is induced in an aberrant way whereas this tLTP is not observed in wild-type mice for 50 pairings[Sakata et al.,2009]. Still in the prefrontal cortex, more precisely in the infralimbic medial region, STDP is absent in a rodent model of a human BDNF polymoprhism in which the BDNF release is impacted. In the same diseased rodent model, BDNF application helped to recover STDP [Pattwell et al., 2012] highlighting once again its importance in STDP induction.

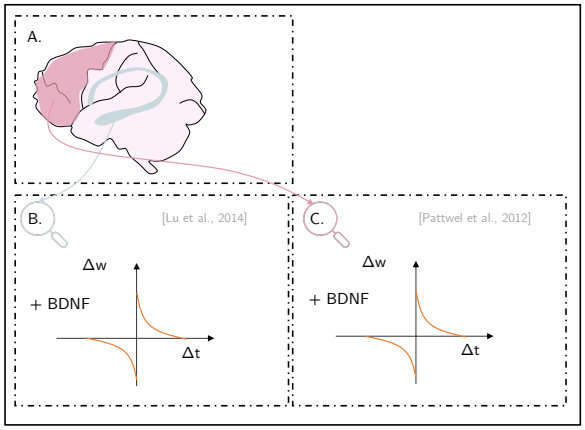


Figure 4.6: *BDNF shapes STDP in the hippocampus and prefrontal cortex* **B.** Addition of BDNF allows to draw the classical STDP Kernel in the hippocampus [Lu et al., 2014].**C.** In the same way, in the prefrontal cortex, BDNF application helps to recevor STDP [Pattwell et al., 2012].

Glutamate and astrocytes

Effect on sleep Glutamate is heavily involved in the regulation of sleep and wakefulness. Indeed, in different brain regions, higher levels of glutamate are seen during wakefulness and REM sleep except for the thalamus whose levels of glutamate are higher during NREM sleep [Watson et al., 2011]. In the same way as for neuromodulators, the effects of glutamate receptor agonists on properties of sleep and wakefulness are dependent on glutamate receptor subtype but also on agonist concentration and brain region.

Effect on STDP Glutamate dynamics tightly controls STDP as many forms of excitatory STDP rely on glutamate receptors. In fact, extent and location of glutamate receptors that are involved in the induction of tLTP or tLTD depend on the spatiotemporal profile of glutamate [Foncelle et al., 2018]. In order for STDP to be induced and bridge the gap between synaptic activity shorter timescale and the longer timescale of the iteration of pre- and postsynaptic pairings, several conditions need to be fulfilled:

- Glutamate should be released in a delayed manner to allow integration of pre- and postsynaptic activity over the time course of minutes;

- Glutamate released by the synapses during neuronal activity needs to be cleared from the extracellular space in order not to disturb the sampling of coincident pre- and postsynaptic activity during STDP pairings [Foncelle et al., 2018].

It appears that astrocytes help to control glutamate dynamics in order to fulfill these two conditions. By doing so, a concept of a tripartite synapses involving the pre- and postsynaptic neuronal elements and the astrocytes emerged, the latter being in contact with central synapses as well as being able to release and clear glutamate to and from the extracellular space [Verkhratsky et al., 2016]. Therefore, via the release and reuptake of glutamate, astrocytes are capable both to detect and control neuronal activity [Min and Nevian, 2012].

As can be seen in Figure 4.7.B., in the cortex, astrocytes need to release glutamate in order to activate presynaptic NMDARs which are required for tLTD induction [Rodriguez-Moreno and Paulsen, 2008].

In the striatum, astrocytes are also necessary to induce both tLTP and tLTD via the uptake of glutamate [Valtcheva and Venance, 2016]. In normal conditions, the excitatory amino acid transporter-2 (EAAT2), which is an astrocytic glutamate transporter, induces bidirectional anti-Hebbian STDP in a narrow temporal window. On the contrary, non-Hebbian LTP is induced when EAAT2 is blocked. Finally, the overexpression of EAAT2 prevents the expression of striatal STDP [Valtcheva and Venance, 2016] possibly by restricting glutamate availability for both the NMDARs and mGluRs required for striatal STDP [Shen et al., 2008, Fino et al., 2010].

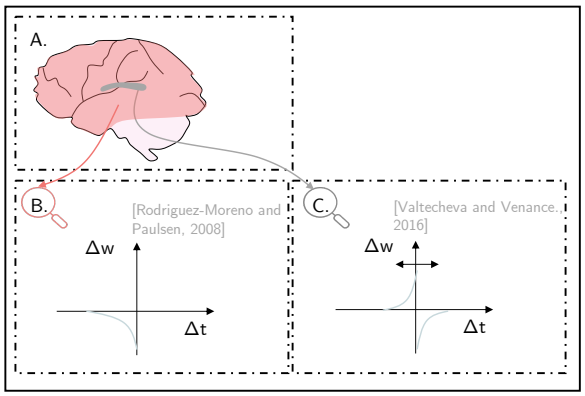


Figure 4.7: *Glutamate shapes STDP in the cortex and striatum* **B.** In the cortex, glutamate allows to activate NMDARs which are required for tLTD induction [Rodriguez-Moreno and Paulsen, 2008] **C.** In the striatum, EAAT2, an astrocytic glutamate transporter induces bidirectional anti-Hebbain STDP in a narrow temporal window [Valtcheva and Venance, 2016].

Nitric oxide

Nitric oxide (NO) is an intercellular messenger activates soluble guanylyl cyclase leading to cyclic guanosine monophosphate (cGMP) formation [Foncelle et al., 2018]. cGMP will then activate some protein kinases which trigger a cascade of reactions and regulate multiple substrates. Among the latter, cGMP inhibits phosphatases that play a role in synaptic plasticity expression.

Effect on sleep Over the years, several effects of nitric oxide on sleep have been reported. Firstly, injection of a nitric oxide synthase inhibitor at dark-onset has been reported to increase REM sleep. This highlights the potential role of nitric oxide in the promotion of arousal [Ribeiro et al., 1992]. Moreover, as said previously, acetylcholine is known to have important arousal functions. It turns out that the neurons responsible for these functions also release the nitric oxide (NO) neuromodulator.

Therefore, by regulating the release of acetylcholine, NO is also thought to regulate the occurrence of REM sleep [Gautier-Sauvigné et al., 2005]

Effect on STDP In the cortex, Hebbian tLTP is dependent on some NO-dependent presynaptic component as well as in α-amino-3-hydroxy-5methyl-4-isoxazolepropionic acid receptor (AMPAR)-subunit1. In the same way, cGMP-activated protein kinase signaling cascade, which relies on NO, enables the induction of tLTP.

GABA

Effect on sleep Like its fellow glutamate, GABAergic signaling also regulates sleep and wakefulness. In function of the region in which it intervenes, levels of endogenous GABA are at their highest during REM sleep, NREM sleep or wakefulness. GABAergic signaling can also cause an increase in wakefulness or REM sleep that varies according to the brain region. Thus, in the PnO, GABA promotes wakefulness and inhibits REM sleep [Watson et al., 2011].

Effect on STDP Unlike the neuromodulators mentioned above, GABA is not involved in the induction of STDP per se, nor its magnitude, but is able to control STDP polarity. As a reminder, STDP polarity is the association between the sign of the pairing (prepost or post-pre) and the plasticity outcome (tLTP or tLTD)[Foncelle et al., 2018].

In the dorsal striatum, as depicted in Figure 4.8.C., when GABAAR receptors are blocked, a reversal of polarity can be observed: a switch from anti-Hebbian STDP to Hebbian STDP occurs [Valtcheva et al., 2017]. A potential explanation for this change in polarity implies the depolarizing effects of GABA that would reverse calcium influx by modifying the balance between calcium influxes from NMDAR vs. voltage-sensitive calcium channels [Paille et al., 2013]. In normal conditions, GABA increases calcium influx in both NMDAR and voltage-sensitive calcium channels in a pretty similar manner but here, its depolarizing effect would allow to differentiate the impact on NMDAR and voltage-sensitive calcium channels depending on the order of pairings (post-pre vs. pre-post). Calcium influx via voltage-sensitive calcium channels would be favored by GABA for post-pre pairings and therefore would promote tLTP whereas calcium influx via NMDARs would be favored for pre-post pairings, promoting tLTD [Paille et al., 2013]. This pattern of plasticity corresponds to a form of anti-Hebbian STDP. Therefore, when GABA is blocked, this repartition of calcium influx in both type of channels is blocked and the classic Hebbian STDP window is recovered.

Still in the striatum, variation between unidirectional and bidirectional STDP as well as between Hebbian and anti-Hebbian STDP appears to be evolutionary dependent and thus, linked to change in GABAergic signaling during striatal development [Valtcheva et al., 2017]. In the hippocampus, GABA is also known to induce STDP polarity changes. Indeed, in hippocampal CA1 pyramidal cells, blockade of GABAARs converts unidirectional tLTD to bidirectional Hebbian STDP [Sugisaki et al., 2016] (see Figure 4.8.B.).

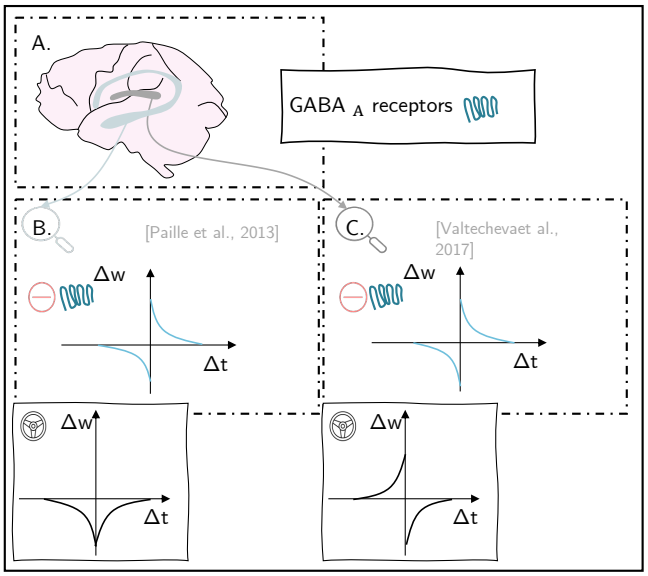


Figure 4.8: *GABA shapes STDP in the hippocampus and in the striatum* **B.** In the hippocampus, blockade of $GABA_A$ receptors converts unidirectional tLTD to bidirectional Hebbian STDP [Paille et al., 2013]. **C.** In the dorsal striatum, blockade of $GABA_A$ receptors STDP switch from anti-Hebbian to Hebbian [Valtcheva et al., 2017]

4.6 Conclusion

Taken together, we can observe that the above results i.e. the effects of neuromodulators and other components on STDP rule is mainly shaped by the type of receptors the neuromodulator targets via the activation of a specific type of G-protein. As such, D_2-class, α_1-adrenergic and M_1-class receptors all tend to facilitate tLTD one activated whereas activation of D_1-class and β-adrenergic receptors lead to tLTP expression [Foncelle et al., 2018].

Moreover, the above results indicate that the spectrum of the third factor of STDP is very large since in addition to neuromodulators it can be extended to BDNF, NO and neurotransmitters acting as neuromodulators such as GABA. STDP synaptic plasticity is thus modulated, whether in its induction, its direction or its temporal window. Though neuromodulation of STDP has been investigated for the early phase of plasticity (within the first hour, i.e., the induction phase), the effects of neuromodulators remain to be investigated for the late phases of plasticity in which the third factor is expected to have a crucial role for the maintenance of memory [Lisman et al., 2011].

4.7 Summary

	↗	↘
Switch of polarity	Induction of tLTP or tLTD	Deletion of tLTP or tLTD
Amplitude modulation	Increase in amplitude of tLTP or tLTD	Decrease in amplitude
Time window modulation	Increase in temporal window of tLTP or tLTD	Decrease in temporal window of tLTP or tLTD

Table 4.1: *Key to read Table 4.2.*

PART II: neuromodulation of phenomenological plasticity rules

Neuromodulator/ neurotransmitter	Area of the brain	Type of receptor	Activation	Inhibition	Effect on STDP					Paper
					Polarity		Time window	Magnitude		
					tLTP	tLTD	tLTP	tLTP	tLTD	
Noradrenaline	Hippocampus	β-adrenergic	×						↗	[Lin et al., 2003]
		β-adrenergic	×			↗				[Seol et al., 2007]
	Cortex	α-adrenergic	×				↗			[Seol et al., 2007]
		α-adrenergic + β-adrenergic	×		↗	↗				[Guo et al, 2012; Huang et al., 2014]
Dopamine	Hippocampus	D_1-like	×					↗		[Brzosko et al., 2015]
		D_1-like	×		↗					[Brzosko et al., 2015]
	Cortex	D_1-like + D_2-like	×		↗					[Xu and Yao, 2010; Ruan et al., 2014]
	Striatum	?			↗					[Pawlak and Kerr, 2008]
	Amygdala	D_2-like	×		↗					[Bissière et al., 2013]
Acetylcholine	Hippocampus	Muscarinic	×						↘	[Zheng et al., 2012]
		Muscarinic		×	↘	↗				[Sugisaki et al., 2011, 2016]
		Muscarinic + Nicotinic	×		↗					[Tsubokawa and Ross, 1997]
	Dorsal cochlear nucleus	Muscarinic	×			↗				[Zhao and Tzounopoulos, 2011]
	Cortex	Muscarinic + Gs	×		↗	↗				[Seol et al., 2007]
		Muscarinic or Nicotinic	×		↗					[Zaitsev and Anwyl, 2012]
		Nicotinic	×			↗				[Couey et al., 2007]
		Nicotinic	×						↗ ↘	[Goriounova and Mansvelder, 2012]
Serotonin	Cortex	5-HT	×			↗				[Song et al., 2015]
BDNF	Hippocampus	/			↗	↗				[Lu et al., 2014]
	Cortex	/			↗	↗				[Pattwel et al., 2012]
Glutamate	Cortex	/				↗				[Rodriguez-Moreno and Paulsen, 2008]
	Striatum	/			↗	↗				[Valtecheva and Venance, 2016]
GABA	Hippocampus	$GABA_A$		×	↗					[Paille et al.,2013]
	Striatum	$GABA_A$		×	↗	↗				[Valtecheva et al., 2017]

Table 4.2: *Summary table of the effects of neuromodulators on synaptic plasticity from a phenomenological point of view.* These effects fall into three categories: polarity switching, amplitude modulation and modulation of the induction time window. These effects vary from one area of the brain to another as well as in function of the receptors(activation or inhibition).

Chapter 5

Review of neuromodulated-phenomenological plasticity rules

This section is dedicated to the highlighting of recent computational studies on the effect of neuromodulators on the phenomenological rules of synaptic plasticity. These studies do not take place in the context of sleep and therefore of neurons in burst mode, but they nevertheless open up the field of possibilities in this area and provide a more precise view of what has already been demonstrated in wakefulness.

5.1 The role of neuromodulators in cortical plasticity [Pedrosa and Clopath, 2017]

5.1.1 Motivation of the study

Experiments have showed that, in juvenile mice, receptive fields in cortical neurons can develop or refine themselves only through important sensory stimuli. Therefore, this cortical plasticity does not require any form of neuromodulation. On the contrary, in adult mice, such sensory stimulation is not sufficient to induce a change in receptive fields. Indeed, in this case, the activation of neuromodulatory systems is necessary to elicit such a change in plasticity. Such systems are therefore thought to be responsible for communicating the behavioral context of sensory stimuli to other brain regions [Gu, 2002]. As reviewed in the previous chapter, neuromodulators are able to gate plasticity by modifying the spike-timing-dependent plasticity (STDP) rule in different ways.

Thus, the motivations of this study are the following:

- To review the possible effects of neuromodulators using a simple computational model of a plastic feedforward network. In order to do so:
  - four different learning windows that would result from the action of different neuromodulators are hypothesized.
  - consequences of such rules on receptive field plasticity are then highlighted.
- To compare the effect of upregulating the learning rate to the effect of upregulating activity.

5.1.2 Methods

This study uses two models of synaptic plasticity:

- **pair-based model**: As already explained in CHAPTER 3, this rule only take into account pairs of pre-post or post-pre activity and can therefore be summarized by the effect of only one pair (learning window):

$$\Delta w(_{ij}t) = \begin{cases} A_+ exp(-t/\tau_+) \text{ if } t < 0. \\ -A_- exp(-t/\tau_-) \text{ if } t > 0. \end{cases}$$

  where $t = t_j^{(f)} - t_i^{(f)}$ is the difference between the postsynaptic and presynaptic firing times. A_+ and A are both positive constants which scale the strength of potentiation and depression respectively, and τ_+ and τ are also positive time constants defining the width of the positive and negative learning window [Pedrosa and Clopath, 2017] (for more details about pair-based model, see CHAPTER 3).

- **triplet model**: see APPENDIX C

5.1.3 Results

The first result, Pedrosa et al. managed to obtain is the observation of symmetry breaking of synaptic weights i.e. some weights become strong and some weights become weak. Here, this phenomenon is observed when neuromodulators allow to obtain a rule in which the depression component of the STDP learning window is higher than the potentiation component [Song et al., 2000]. When implementing this rule, they observed that the weights were going to their upper and lower bound. For input with strong connections, this means that the spiking activities of strongly connected inputs are more correlated with the activity of the postsynaptic neuron, resulting in a further strengthening of weights. Whereas, for inputs with weak connections, there is almost no correlation between their activity and that of the postsynaptic neuron [Pedrosa and Clopath, 2017]. The final conclusion of this model is therefore that the only rule that allows for the emergence of receptive field in visual cortex via the combined action of specific neuromodulators (here: acetylcholine and noradrenaline) is the DP rule.

After that, they compared the effects of neuromodulators on learning versus on neuronal activity. They found that modulating neuronal activity can lead to a broadening or a sharpening of receptive field tuning while modulating the learning rate is only said to intensify the sharpening of receptive field tuning [Pedrosa and Clopath, 2017].

5.2 Acetylcholine-modulated plasticity in reward-driven navigation: a computational study [Zannone et al., 2018]

5.2.1 Motivation of the study

This paper aims at studying the effects of neuromodulation on STDP. Indeed, neuromodulators such as dopamine or acetylcholine have been shown to modify STDP in various ways (see CHAPTER 4). Therefore, in this study, Zannone and her team tend to demonstrate that sequential cholinergic and dopaminergic modulation of plasticity allows flexible learning which is particularly useful in experimental settings where the environments is dynamic and with changing reward locations [Zannone et al., 2018].

5.2.2 Methods

Box5| Glossary

Eligibility trace is defined as "a flag at the synapse induced by co-activation of pre- and postsynaptic neurons and leading to a weight change only if an additional factor is present while the flag is set. This third factor, signaling reward, punishment, surprise, or novelty, could be implemented by the phasic activity of neuromodulators or specific neuronal inputs signaling special events." [Gerstner et al., 2018]

This study uses a model of sequentially neuromodulated plasticity (sn-Plast) which combines a modified STDP rule and an eligibility trace that accounts for timing issues that arise when combining synaptic plasticity and neuromodulation.

The total weight update is therefore given by:

$$\Delta w_{ji}(t) = \eta A((\sum_{\bar{t}_i \in F_i^{pc}} \sum_{\bar{t}_j \in F_j^a} W(\bar{t}_j - \bar{t}_i) \circ \psi)(t), \tag{5.1}$$

where η is the learning rate, A represents the effect of different neuromodulators, W is the STDP window and ψ is the eligibility trace. F_i^{pc} and F_j^a are sets which contains $\bar{t}_i$ and $\bar{t}_j$ i.e. the arrival time of all spiked fired by place cell i and action neuron j.

The basic STDP window is

$$W(x) = e^{-\frac{x}{\tau}}, \tag{5.2}$$

with $\tau = 10ms$ and where x is the place cell centre. The expression above is always symmetric and positive but the sign of the final weight change is actually determined by the term A which represents the neuromodulators at the synapse:

$$A = \begin{cases} -1 & \text{-DA,+ACh} \\ 0 & \text{-DA, -ACh} \\ 1 & \text{+DA, } \pm\text{ACh.} \end{cases} \tag{5.3}$$

Therefore, in this model, weight changes are gated by neuromodulation. When $A = 0$ (all neuromodulators are absent), the weight stays the same. The learning rate η is also affected by neuromodulation:

$$\eta = \begin{cases} \eta_{ACh} & \text{-DA,+ACh} \\ 0 & \text{-DA,-ACh} \\ \eta_{DA} & \text{-DA,}\pm\text{ACh} \end{cases} \tag{5.4}$$

In equation 5.1, the weight change is convoluted with an eligibility trace ψ modelled as an exponential decay

$$\psi(t) = e^{-\alpha \frac{t}{\tau_e}} \Theta(t), \tag{5.5}$$

with $\tau_e = 2s$ and $\alpha = \begin{cases} 1 & \text{+DA} \\ 0 & \text{-DA} \end{cases}$

The interesting point in this paper is the use of the eligibility trace. Indeed, the latter keeps track of the active synapses and allows for a delayed update of the synaptic strength [Zannone et al., 2018]. In expression 5.5, τ_e is used to determine the length of the rewarding path learned while α acts as a flag and allows to activate the eligibility trace only when dopamine is present ($\alpha = 1$).

5.2.3 Results

The first observation that is made is that acetylcholine is able to shape the STDP learning window making it symmetric and negative under its influence. By allowing this learning from negative outcomes, acetylcholine has been observed to enhance exploration over the action space independently on the structure of the model, the environment or the task. Dopamine, for its part, is consistent with its already recognized properties and thus allows to learn the path to the reward [Zannone et al., 2018].

5.3 The functional role of sequentially neuromodulated synaptic plasticity in behavioural learning [Ang et al., 2021]

5.3.1 Motivation of the study

This study follows the previous work made by S.Zannone and her team in 2018 and described in the previous section [Zannone et al., 2018]. In the latter, one can find the description of a new form of hippocampal STDP that is sequentially modulated by acetylcholine and dopamine (Sn-Plast). This observation has been implemented as a learning rule in a computational model which is now tested. Indeed, in the present study, Ang et al. tested the model's prediction by optogenetically inactivating cholinergic neurons in mice during a hippocampus-dependent spatial learning task with changing rewards.

5.3.2 Methods

Following the same method as in [Zannone et al., 2018], as in every form of STDP rule, synaptic weight w varies as a function of the time difference between pre- and postsynaptic spikes (Δt). Here, the STDP windows (potentiation and depression) are symmetric and neuromodulators determine the sign of the weight change. As such, acetylcholine, during the exploration phase, reverse the STDP polarity and biased it towards depression. Dopamine, for its part, modifies the STDP rule via an eligibility trace. Indeed, DA is only released when a reward is encountered. The weight between place cells and action cells are modified according to the sn-Plast learning rule.

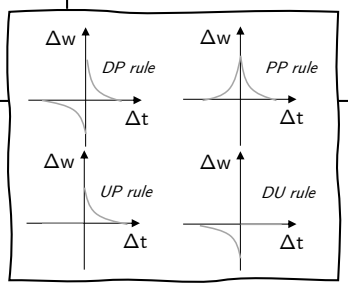
5.3.3 Results

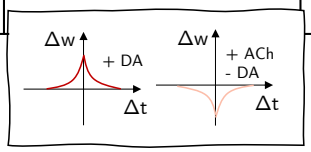
The results of this behavioural study verify the predictions of the computational model. Indeed, inactivation of cholinergic neurons does not affect learning initially but only when the reward is shifted to a new location. Therefore, acetylcholine is said to modulate plasticity notably by promoting the unlearning of old reward locations. It thus makes it possible to ignore actions that are no longer associated with a reward [Ang et al., 2021].

5.4 Summary

PART II: Neuromodulation of phenomenological plasticity rules

Authors Year	Pedrosa et al. 2017	Zannone et al. 2018	Ang et al. 2021
Motivation	Review the possible effects of neuromodulators on cortical plasticity using a simple computational model.	Demonstrate that neuromodulation of plasticity allows flexible learning.	Test the predictions of the model developed by Zannone et al. in 2018.
Area of the brain Neuromodulator	Visual cortex Mainly acetylcholine (ACh) and noradrenaline (NA)	Acetylcholine (ACh) and dopamine (DA) mainly	Hippocampus Acetylcholine (ACh)
Methods	STDP: pair-based model	Sequentially neuromodulated plasticity (Sn-plast) i.e. a combination of a modified STDP rule and an eligibility trace	Sn-Plast (see [Zannone et al., 20218])





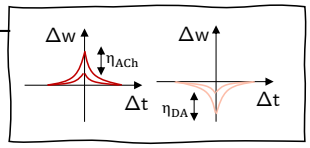


Table 5.1: *Computational studies that implement neuromodulation of STDP rule.*

Part III

Computational study

Chapter 6

Analysis and mathematical demonstration of the mechanisms underlying the *homeostatic reset*

The circuit we are going to use in order to perform our computational study has been designed by Jacquerie et al., (2022). It is composed of three neurons: two excitatory neurons (E) and (C) and one inhibitory neuron (I). The latter is connected to the two other neurons through $GABA_A$ and $GABA_B$ connections while the presynaptic neuron (E) is connected to the postsynaptic neuron (C) through $AMPA$ connections. The membrane voltage of the different neurons are described in details in Appendix 6.1. In this model of the membrane voltage, $AMPA$ synapses provide an excitatory current while $GABA$ synapses provide an inhibitory one. As depicted in Figure 6.1, an external current I_{app} is applied to the circuit in order for the cells to switch their neuronal activity from tonic mode (during wake) to burst mode (during sleep). Indeed, this rhythmic transition is allowed by the hyperpolarization of the inhibitory cell by the applied current. More practically, when cell I is in tonic mode, E and C are silenced (not represented in Figure 6.1. Then, as can be seen on Figure 6.1.B., when cells E and C are depolarized, they generate a tonic activity. Finally, a burst in the inhibitory neuron drives the whole circuit in bursting mode. For the rest of our work, we will use this circuit in order to analyse the evolution of the synaptic strength (represented by the synaptic weight w in computational models), between the pre- and the postsynaptic cells (respectively E and C) using phenomenological models and particularly the pair-based model described in Chapter 3 as illustrated in Figure 6.1.C.

The circuit we have just described is then used to investigate neuromodulation of plasticity rules during sleep in bursting mode. To do so, different sleep rhythms are represented by the application of different hyperpolarization step-currents to the inhibitory cell $I_{app,I} \in [-4 : 0.1 : -4.7][nA]$. Therefore, these different step currents induce different bursting patterns in E and C cells. In order to place ourselves in a situation in which certain neuronal connections have been strengthened during the day and new information has been learned, at the beginning of the sleep period, the synaptic connections have initial weights varying between 0 and 1 ($w_0 \in [0. : 1.]$). These therefore represent the different levels of memory after the waking period. The different hyperpolarizing currents are applied to the circuit. During the simulation performed in bursting mode (sleep), the evolution of w is examined and at the end of the night the final synaptic weight w_f is evaluated as well. The final objective is to verify if our plasticity rules have allowed the consolidation of memory during sleep.

During their individual and common work, Caroline Minne [Minne et al., 2021] and Kathleen

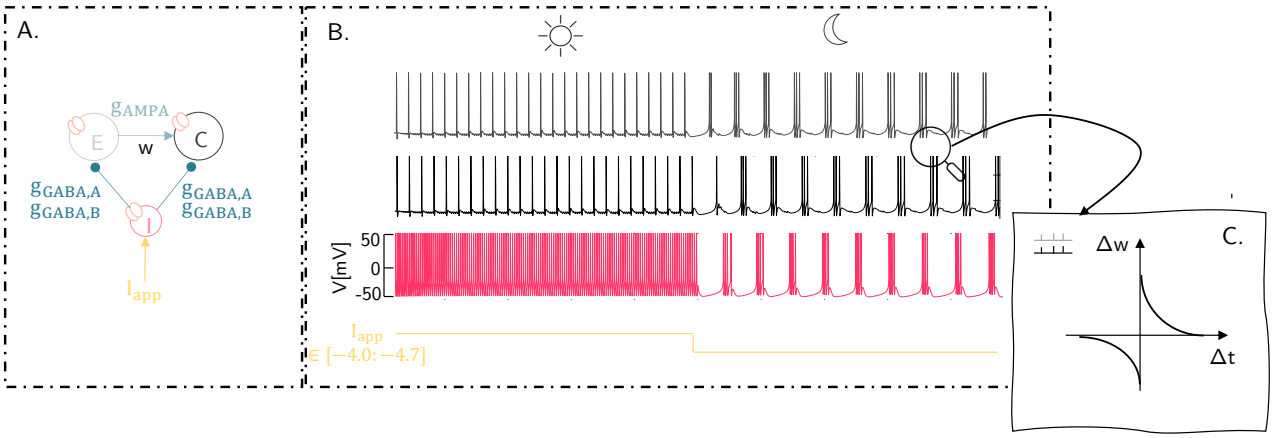


Figure 6.1: *ECI circuit and firing patterns* **A.**Schematic representation of the ECI circuit showing the different connections between the three neurons: connection between E and C cells is excitatory whereas connections from cell I to cells E and C are inhibitory. **B.** Time course of the membrane voltage [mV] of the ECI circuit and the applied currents [nA] showing two firing patterns for E and C cells: tonic mode at a given frequency (during the day) and bursting mode driven by hyperpolarisation of cell I (during the night).

Jacquerie [Jacquerie et al., 2022] have highlighted limitations and challenge in this model. Indeed, to understand the link between memory consolidation and sleep, synaptic weight change during the bursting activity characteristic of the sleeping mode have been tracked and analyzed. By comparing strong and weak initial weights acquired during wakefulness prior to network switching in bursting mode, a reset of these weights has been observed [Minne et al., 2021, Jacquerie et al., 2022]. Indeed, as can be seen on Figure 6.2.A., no matter how much certain connections between neurons may have been strengthened during the day, both large and small synaptic weights are all reset to a steady-state after a night of sleep. This homeostatic reset is observed in soft-bound rule (i.e. using $\mu = 1$). However, implementation of pair-based STDP with hard-bound also fails to show expected behaviour for the consolidation of the day's learning. Indeed, when $\mu = 0$, synaptic saturation (or depression for a specific burst pattern that will be treated in more details in Chapter 7) is observed independently of the initial synaptic weight.

This *homeostatic reset*, as well as its saturation counterpart in hard-bound rule, are therefore not compatible with memory consolidation theories. This leads to the following conclusion: maintaining the same learning rule both when awake and when asleep does not lead to sleep-dependent memory consolidation mechanisms. The focus of this thesis is therefore to explore the ability of neuromodulators to overcome this reset. But before considering the tests we could carry out to overcome this reset, this chapter will be first dedicated to the analytical demonstration of the mechanisms underlying this homeostatic reset.

Moreover, it is important to realise that the observation of this reset is linked to the model we choose to use. Here, we see that the use of the pair-based model as such as a model of synaptic plasticity during sleep is not compatible with the hypothesis of memory consolidation. However, it turns out that the observation of this reset phenomenon is also found when the model chosen is another phenomenological model such as the triplet model or even with a biological model such as a calcium model [Jacquerie et al., 2022]. Despite this, we feel it is important to really highlight the shortcomings of our model as they will obviously influence the results of our study. Therefore, an obvious limitation of the pair-based STDP is the fact that it is only based on spike timing modifications [Morrison et al., 2008].

However, other intrinsic flaws and evidence against using STDP as a first law of plasticity have been repeatedly highlighted in different studies [Morrison et al., 2008, Shouval et al., 2010, Feldman, 2012].

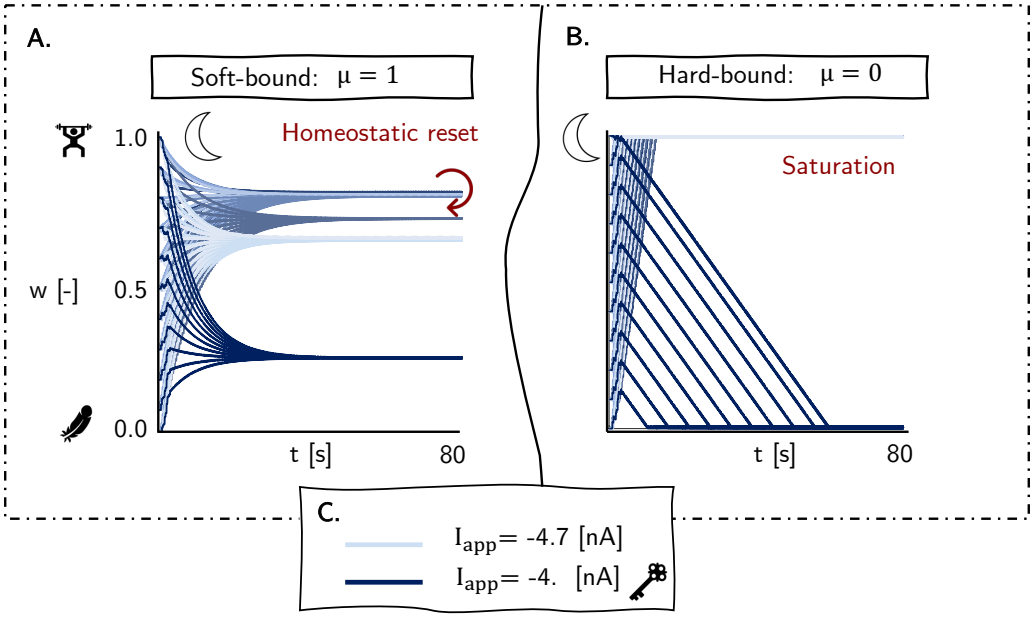


Figure 6.2: *Observation of homeostatic reset phenomenon in phenomenological models* **A.** Evolution of synaptic weight w in function of time $t[ms]$ for several currents. Observation of the homeostatic reset. **B.** Homeostatic reset is observed for STDP rule using soft bounds: all weights tend to a steady-state value but also for STDP rule using hard bounds. With hard bounds, synaptic saturation is observed after sleeping period independently of the synaptic weight at the beginning of the night. **C.** Using the circuit in Figure 6.1.A., we have that different shades of blue represent different currents I_{app} i.e. different burst patterns. Adapted from [Jacquerie et al., 2022].

6.1 Outline of the demonstration

In the continuity of the observations made by Caroline Minne in her Master thesis[Minne et al., 2021], we will here give:

- **An intuitive demonstration of the *homeostatic reset***: In order to serenely approach the notions used in the Legenstein and Maass convergence criterion such as correlations, we will first try to demonstrate the value of the reset using a simplified case.

- **An analytical explanation of the *homeostatic reset***: Then, using the *analytic criterion for the convergence of STDP* [Legenstein and Maass, 2005], we will demonstrate the value of the homeostatic reset. Firstly, using a simplified case. Indeed, for the latter we will use "fake" spike trains in order to obtain an expected result and check if the criterion works in this perfect case before applying it to our real case of neurons in burst mode during sleep. In the second case, "real" bursting pattern will be fed into the equations of Legenstein and Maass. According to the value of the parameter μ already introduced in Chapter 3, we will be able to differentiate the convergence value for STDP rule in a first case i.e.using soft-bounds ($\mu = 1$) and in a second case using hard-bounds ($\mu = 0$).

6.2 Intuitive demonstration of the *homeostatic reset* (perfect case)

This intuitive demonstration is also called the perfect case because it takes into account two perfectly aligned spike trains and a synaptic plasticity rule with equal amounts of potentiation and depression. Therefore, if we take our classical pair-based STDP formula (see CHAPTER 3 for more details), the following conditions are respected:

$$\Delta t = 0$$
$$A_+ = A_-$$

In such perfect conditions, the steady-state value of phenomenological models of plasticity such as pair-based STDP can be demonstrated quite directly and simply in a mathematical way [Jacquerie et al., 2022]:

$$\begin{aligned} & A_+(1-w) = A_- w \\ \leftrightarrow & A_+ - A_- w = A_- w \\ \leftrightarrow & w(A_- + A_+) = A_+ \\ \leftrightarrow & w = \frac{A_+}{A_- + A_+} \end{aligned}$$

Here, since we have $A_+ = A_-$, $w = 0.5$. We will therefore test Legenstein's formula in this simpler case in order to verify that the value given by it corresponds to 0.5.

6.3 Analytic demonstration of the *homeostatic reset*

Convergence of the synaptic weight towards a steady-state value when using the (STDP) pair-based model has not only been observed after a night's sleep but has also been described numerous times in the literature for models in wakefulness [Legenstein and Maass, 2005, Graupner et al., 2016, Rubin et al., 2001]. In order to demonstrate the homeostatic reset observed [Jacquerie et al., 2022] with the pair-based model applied to neuron in burst mode, we will focus on Legenstein's approach and on the equations he developed [Legenstein and Maass, 2005].

We will, however, differ to some extent from the method used in this paper. Indeed, in the paper referred to above, they use Poisson spike inputs for which they develop a criterion. The latter is constructed to take the correlation of these spike inputs and on the basis of this, using a criterion they have developed, they are able to say whether the synaptic weight converge on average for a simple model of a spiking neuron.

On our side, we will prove, thanks to its equation, the value of the homeostatic reset that we observe with our plasticity models using bursts constrained in physiological manners. We will correlate these bursts using Legenstein's way to achieve our goal. The approximate steady-state value at the end of the night will first be demonstrated when the plasticity rules use **soft bounds** and then when they depend on **hard bounds**.

As already mentioned in a previous chapter, using pair-based STDP in order to model synaptic plasticity, the weight update rule can be written as:

$$\Delta w = A_+.(1-w)^{\mu}.e^{-\Delta t/\tau_+} \text{ if } \Delta t > 0,$$
$$\Delta w = -A_-.w^{\mu}.e^{\Delta t/\tau_-} \text{ if } \Delta t \leq 0$$

where we assume that $w_{max} = 1$ and $w_{min} = 0$. Here, the model we use defines the time delay between spikes as follows $t_{post} = t_{pre} + \Delta t$ which means that $\Delta t = t_{post} - t_{pre}$.

According to [Legenstein and Maass, 2005], the change Δw can be seen as a variable with a mean drift and fluctuations around this drift. In probability theory, stochastic drift is the change of the average value of a stochastic (random) process. Related to this, the drift rate is the rate at which the average changes. Applying this concept to our case, we will be interested in the average change in synaptic weight w and particularly to its final value at the end of the night (the convergence value). If we define S_{pre} as being the spike train of presynaptic inputs and S_{post} as the output spike train of the neuron, the mean drift of the synapse at time t can be written as:

$$\dot{w}_{drift}(t) = A_+(1-w_{drift})^{\mu}\int_0^{\infty} ds e^{-s/\tau_+}C(s;t) - A_- w_{drift}^{\mu}\int_{-\infty}^{0} ds e^{s/\tau_-}C(s;t), \tag{6.1}$$

where, as already explained in CHAPTER 3, in function of the type of bounds used in the plasticity rule either soft bounds or hard bounds, μ is respectively equal to 1 and 0. For its part, $C(s;t)$ is the ensemble averaged correlation function between the presynaptic input and the output spike train of the neuron i.e. $C(s;t) = \langle S_{pre}(t)S_{post}(t+s)\rangle$. At this stage, we notice that $C(s,t)$ is independent of time at steady-state i.e. the moment of the convergence/*homeostatic reset*, therefore, we will only consider $C(s)$ for the rest of the demonstration. Coming back to Equation 6.1, this means that the integrals will be calculated as constants as we will see later in the numerical part.

This is where we will divide our demonstration into a perfect case followed by the real case. Each time we will start from the above equation and describe the implementation of each term according to the case studied.

6.4 Numerical calculations

6.4.1 First case using perfectly coordinated spiking of the pre- and postsynaptic neurons.

With the help of the given material (similar to a list of ingredients), we will therefore apply the following methodology in the same way as for a cooking recipe:

1. $C(s;t)$

   In equation 6.1 represents the cross correlation between two neuronal spike trains S i.e. $C(s;t) = \langle S(t)S(t+s)\rangle$.

   - The first step of our perfect case is therefore to create two vectors in order to model these two spike trains. So that's what we do. As we are in a "perfect" case we only define one vector, the other being a carbon copy of the first. This vector is filled with 0 except when the membrane potential crosses zero i.e. when the neuron spikes, the 0 is replaced by a 1. This discretisation is done with a time step $\zeta = 0.01$.

In order to match as closely as possible the real activity of our neurons during sleep, we gave these fake spike trains a bursting type of activity. We thus have bursts of 3 action potentials followed by silence periods.

- The second step is to calculate this correlation properly speaking. This will be done using the function "xcorr" in Matlab. The latter returns the cross-correlation of two discrete-time sequences where the cross-correlation is a measure of the similarity between a vector and shifted(lagged) copies of another vector as a function of the lag.

2. $\int_0^\infty dse^{-s/\tau_+}C(s;t)$ and $\int_{-\infty}^0 dse^{s/\tau_-}C(s;t)$

As can be seen from the two terms above, the equation requires us to choose a time window in which to calculate these integrals. However, here, as we are not using Poisson spike trains but the activity of our sleeping neurons i.e. an endogenous burst, the correlation of the latter, as we have mentioned above, will be independent of time! And this is where one realises that we are doing much more than simply following a cooking recipe to the letter... Moreover, Instead of calculating an integral, we will consider a sum of exponentials of the following shape:

- $c_+ = \sum exp(-(\xi(1,s) * \zeta))/\tau_+) * \xi(2,s)$
- $c_- = \sum exp((\xi(1,s) * \zeta))/\tau_-) * \xi(2,s)$

where s varies from the first half of the correlation vector when computing c_- to the second half of this same vector when computing c_+, $\xi(1,s)$ represents the value of the lag at index s, $\xi(2,s)$ the value of the correlation at index s, $\tau_+ = 16.8ms$ and $\tau_- = 33.7ms$. One can note that in the exponential, the value of the lag is multiplied by 0.01 which corresponds to the frequency of our discretisation.

Our recipe is coming to an end and we now have all the elements to calculate our reset value. Think of it as putting the cake batter into the pan. Well, almost. In his paper, Legenstein defines yet another equation useful for calculating our convergence value. When the equation 6.1 is set to 0 i.e. $\dot{w}_{drift} = 0$, in our case ($\mu = 1$), we obtain that our homeostatic reset value w_{HR} is equal to:

$$w_{HR} = \frac{A_+ * c_+}{A_+ * c_+ + A_- * c_-}$$

where $A_+ = 0.0096$ and $A_- = 0.0053$ [Bi and Poo, 1998].

Computing all that, we happily see that we get the expected convergence value, i.e. 0.5. We have thus reached our first objective which was to verify the validity of Legenstein's method on neurons during sleep in a perfect case where the activity of the neurons was implemented by hand.

6.4.2 Second case using real spiking of the pre- and postsynaptic neurons

Unsurprisingly, the real case will follow the same recipe except for the first step where we had, in the first case, manually built our vector to be correlated.

In this case, the two spike trains are extracted from our Julia codes. We get two vectors v_{pre} and v_{post}, respectively, the train of action potentials of the presynaptic cell and the postsynaptic cell. As

in the perfect situation, the vectors v_1 and v_3 extracted from Julia codes which implement synaptic plasticity using STDP as a phenomenological model have to be discretised. To do this, we will simply scan these two vectors in their length using an index and create two discrete vectors, $vspk_{pre}$ and $vspk_{post}$, filled with 0 and 1:

- 1 translates the fact that the value of v_{pre} at this index is > 0 and the value of v_{pre} at the previous index was less than 0 and vice versa for $vspk_{post}$.

- 0 translates all the other situations.

N.B.: One last thing that is important to note when using the xcorr function in Matlab in order to respect the Legenstein formalism is the order of the vectors to be correlated. Indeed, here, we will calculate the similarity between the vector $vspk_{post}$ and the shifted copy of $vspk_{pre}$ as $vspk_{post}$ represents our postsynaptic cell and $vspk_{pre}$ our presynaptic cell and $\Delta t = t_{post} - t_{pre}$.

We can now discriminate into the demonstration of the convergence value when the plasticity rule uses soft bounds ($\mu = 1$) and hard bounds ($\mu = 0$).

Case 1: $\mu = 1$ (Soft-bounds) Applying the whole recipe to the case where $\mu = 1$, we obtain the following table (Table 6.1).

Comparing the values obtained analytically from our demonstration with our simulation values, it can be seen that the latter are quite close and that our demonstration can be considered a validated method. However, it can be observed that some currents give better predictions than others. Indeed, if we remember that different currents represent different burst patterns, taking the same time window (here t=300ms), for all currents, the puff of action potentials corresponding to a burst will not be the same for all currents. This could therefore explain the differences in the accuracy of the predictions. In Appendix E, one can find a table with the prediction values when the whole simulation time is taken into account.

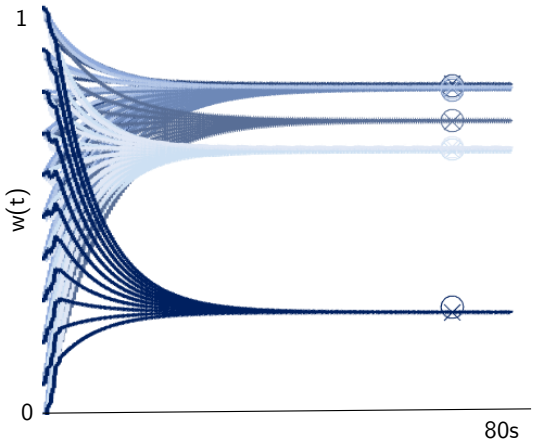


Figure 6.3: *Illustration of the prediction of the demonstration when using soft-bounds.* This demonstration predicts the value towards which all the weight converge. The value computed by the numerical simulation is represented by a cross while the value predicted is represented by a circle.

Iapp	I = - 4.7	I = - 4.6	I = - 4.5	I = - 4.4	I = - 4.3	I = - 4.2	I = - 4.1	I = - 4
analytical w (for t=300ms)	0.8182	0.7311	0.8055	0.8099	0.8112	0.6610	0.5923	0.2725
simulated w	0.8186	0.7297	0.8060	0.8120	0.8118	0.6578	0.6702	0.2713

Table 6.1: *Table summarising the convergence w values obtained from the demonstration as well as from our simulations for our different currents.*

Case 2: $\mu = 0$ **(Hard-bounds)** Starting from the equation 6.1, this demonstration is quite straightforward. Indeed, using the hard bounds, we know that we are working with a value of $\mu = 0$. So we have the following equation:

$$\dot{w}(t) = A_+ \int_0^\infty ds e^{-s/\tau_+} C(s;t) - A_- \int_{-\infty}^0 ds e^{s/\tau_-} C(s;t), \tag{6.2}$$

which is equivalent to

$$\dot{w}(t) = A_+ c_+ - A_- c_- \tag{6.3}$$

At this point, it becomes clear that this equation resembles that of a slope. It is well known that the general definition of a slope/gradient of a line is a number that describes both the direction and the steepness of the line. However, it turns out that a derivative, such as the one we try to calculate $\dot{w}_{drift}(t)$, is used to define the rate of change of a function. Therefore, here, our $\dot{w}_{drift}(t)$ represents the variation of w i.e. Δw when dividing this variation by the corresponding timing difference Δt, we obtain the expression of a slope. Therefore, we have:

$$\frac{\Delta w}{\Delta t} = A_+ c_+ - A_- c_- \tag{6.4}$$

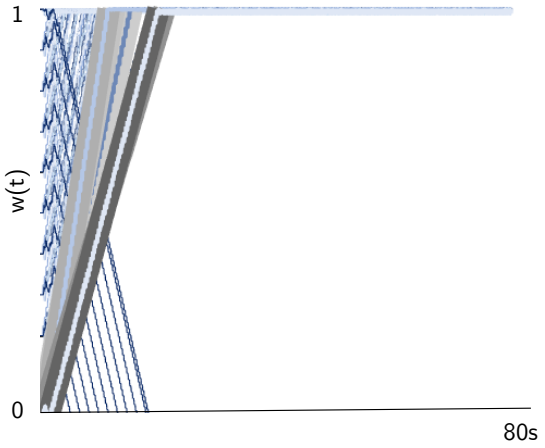


Figure 6.4: *Illustration of the prediction of the demonstration when using hard-bounds.* Predictions (grey lines) match simulation (blue lines).

The values of the slope obtained by analytical calculation as well as by simulation are listed in Table 6.2.

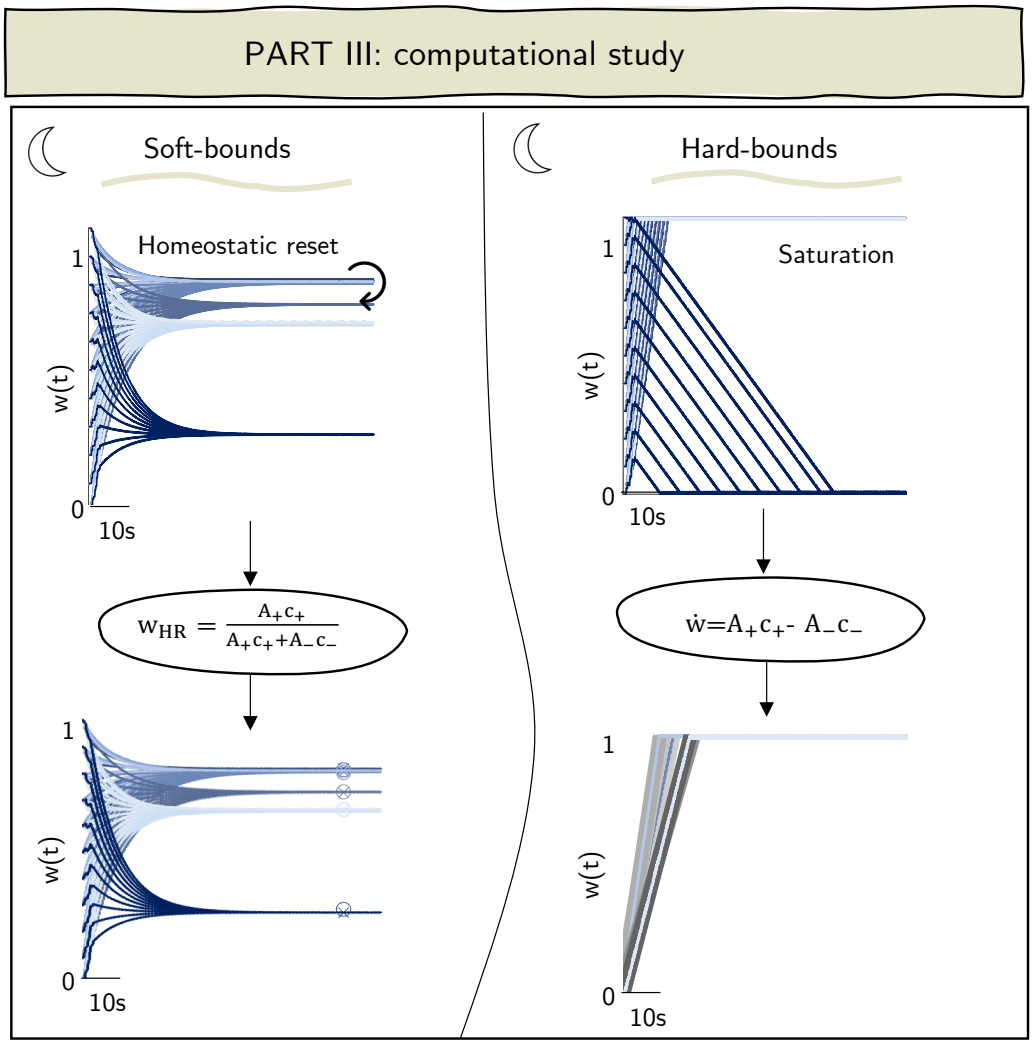
Iapp	I = -4.7	I = -4.6	I = -4.5	I = -4.4	I = -4.3	I = -4.2	I = -4.1	I = -4.0
Analytical	8.83e-5	5.03e-5	6.73e-5	8.15e-5	9.23e-5	4.82e-5	5.36e-5	-5.91e-5
Simulation	8.72e-5	5.21e-5	6.03e-5	9.02e-5	8.03e-5	4.77e-5	4.33e-5	/

Table 6.2: *Table summarising the slope values obtained from the demonstration as well as from our simulations for our different currents.*

6.5 Summary and highlight the *value* of this demonstration

In this chapter, we set out to demonstrate the phenomenon of homeostatic reset (in SB) or synaptic weight saturation (in HB) after a night's sleep observed by [Jacquerie et al., 2022]. To do so, we based ourselves on a paper by Legenstein and Maass [Legenstein and Maass, 2005]. We distinguished ourselves from their method in several ways, notably by using endogenous bursts and not Poisson spike trains. We first applied this demonstration to SBs. We find that our method allows us to efficiently calculate the value of the weight towards which the synaptic weights will converge. Then, we applied this method to HB. In the same way, it allows us to predict the slope of the line that connects the initial synaptic weight to the saturation value that it reaches during the night.

Beyond that, we would really like to highlight the fact that this demonstration is an extremely valuable tool for the topic at hand. Indeed, by giving our model the parameters that we want to test for example during the neuromodulation of the pair-based STDP, the latter will return the value towards which our synapses will tend. We can therefore efficiently and quickly predict the behaviour of our model at the end of the night thanks to the latter.



Chapter 7

Neuromodulation of *phenomenological* plasticity rules in bursting mode with the idea of overcoming the *homeostatic reset*

During wakefulness, the study of the effect of neuromodulators on the phenomenological rules of plasticity and more specifically the study of their capacity to modify synaptic plasticity at different levels has already been conducted by various groups of researchers. In this section, we aim to reproduce some of these computational experiments when neurons are in burst mode in order to corroborate our hypothesis that the effect of neuromodulators on synaptic plasticity rules allows us to prove the hypothesis of memory consolidation during sleep. Practically speaking, the goal is to play with the parameters of the classic STDP to mimic neuromodulators and apply these effects in sleep to see if it can counteract the homeostatic reset to prove memory consolidation. As mentioned in CHAPTER 4, neuromodulators have three main effects on STDP rule which we will manipulate during this computational study i.e.

- Polarity modulation (see **A.** in Figure 7.1). In practical terms, this means that we will play with the parameters A_+ and A_- representing the amplitude of potentiation and depression respectively. We will thus make $A_+ < 0$ and $A_- > 0$ and vice versa in order to implement these polarity switches.

- Magnitude modulation (see **C.** in Figure 7.1). In these experiments, we will simply play with the value of the potentiation amplitude A_+ and depression A_-.

- Time window modulation (see **B.** in Figure 7.1). Regarding the time window of the STDP, we will play with the parameters τ_+ and τ_- in order to vary the window of potentiation and depression respectively.

After that, we will also play with the type of bounds used in our STDP rule.

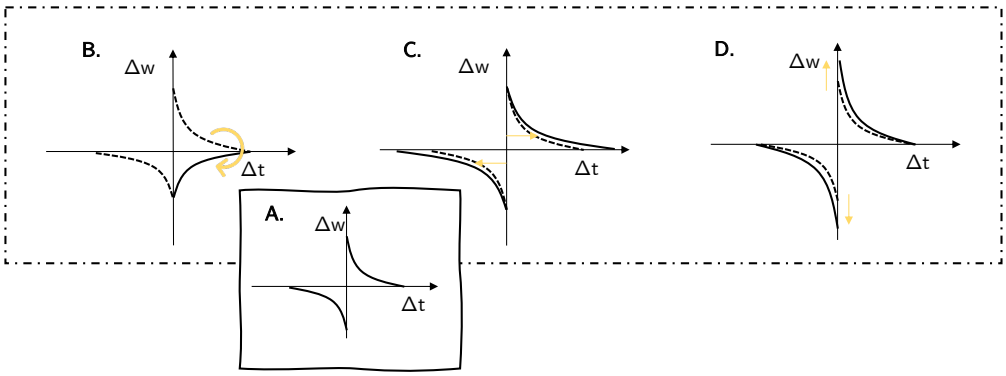


Figure 7.1: *Reminder of the parameters that can be neuromodulated* **A.** Polarity can be reversed i.e. LTP can be induced instead of LTD and vice-versa. **B.** Temporal requirements can be modified i.e. the temporal window for induction of LTP and LTD can be enlarged or restrained. **C.** Magnitude of STDP Kernel can be increased or decreased

Before starting this section of experimental tests. It seems important to recall once again the result that we are trying to infer by this means. As mentioned in CHAPTER 2, the hypothesized sleep functions that are compatible with memory consolidation during sleep include the SHY and the active system consolidation hypothesis. Other hypotheses continue to emerge, but in order to restrict our analysis, we will focus on the latter two in our work. As shown in Figure 7.2, we expect to obtain the following two behaviours at the end of the night thanks to the effect of some neuromodulators on the pair-based STDP rule: low-weight synapses are depressed while high-weight synapses are either weight preserved (SHY) or slightly potentiated (active system consolidation). It is really this reverse engineering approach that we will apply during this CHAPTER 7.

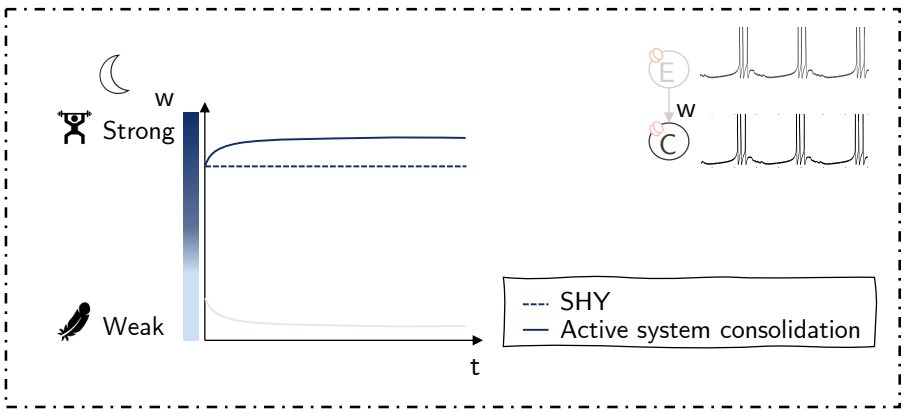


Figure 7.2: *Simplified illustration of the result we will try to infer by doing our hand-tuned parameters study which aims at mimicking neuromodulation.* The circuit that is used for these experiments has already been presented. When neurons in this circuit are in burst mode, e hope to see, at the end of the night, an evolution of synaptic weights compatible with the hypothesis of memory consolidation during sleep. We therefore hope that these weights take one of the following forms: synapses with low weights are depressed (light pink) while synapses with high weights can adopt two different behaviours depending on the hypothesis chosen: according to SHY, synapses with high weights remain unchanged or are barely depressed (dashed blue line) while according to the active consolidation hypothesis, synapses with high weights are potentiated (plain blue line).

7.1 Polarity modulation

In their study about the neuromodulation of cortical plasticity [Pedrosa and Clopath, 2017], Pedrosa and his team use four possible STDP learning rules for excitatory synapses. They consider that each STDP rule represents the action of a specific neuromodulatory state:

- The first rule is the classic antisymmetric STDP rule, in which the association of a presynaptic spike followed by a postsynaptic spike leads to potentation of synaptic connections whereas a postsynaptic spike followed by a presynaptic action potential leads to depression. Quite logically this rule is termed the Depression-Potentiation (DP rule).

- The second rule is a symmetrical STDP rule in which we only observe potentiation regardless of the order of the pre- and postsynaptic spikes. Therefore, this rule will be refered to as the Potentiation-Potentiation (PP) rule.

- The third rule is called the Unchanged-Potentiation (UP) rule as only the succession of presynaptic spiked followed by postsynaptic spikes leads to a changed in synaptic weights.

- Finally, the fourth rule is the Depression-Unchanged (DU) rule as only postsynaptic spikes followed by presynaptic action potentials lead to a weakening of synaptic weights [Pedrosa and Clopath, 2017].

Now that the context of our experiment is set, let's proceed to the actual manipulations. We now have evidence that the Kernel drawn by the STDP rules can be modified in different ways (magnitude, polarity, temporal requirements) thanks to the action of neuromodulators (see CHAPTER 4). Indeed, as far as polarity changes are concerned, we can mention in particular: "At hippocampal CA1 pyramidal cells, acetylcholine first allows to reverse the polarity of STDP by converting bidirectional Hebbian STDP into unidirectional tLTP [Brzosko et al., 2017]. On the contrary, inhibition of mAChRs prevents post-pre tLTD and converts pre-post tLTP into tLTD [Foncelle et al., 2018]".

Therefore, here we will apply these polarity switches to our model in the manner of Pedrosa, using parameters they had used and which are listed in Table 7.1. The way we differentiate and bring something new to this model is that we are going to apply it to neurons in burst mode.Thus, in this part of our work, using the evidence for the effect of neuromodulators on STDP rules, we will try to infer the result. Indeed, we know what we want to obtain as an evolution of the weight (division of the weight at the end of the night, between weak and strong synapses) and for that we will change the Kernel of STDP. In order to respect the conditions of the protocol that allows us to draw the STDP kernel experimentally, we will implement an STDP rule that respects the [Bi and Poo, 1998] conditions i.e. frequency = 1 Hz and 60 paired-pulses.

Parameters	Rules			
	DP	PP	UP	DU
A_+	0.0003	0.0003	0.0003	0
A_-	0.0003	-0.0003	0	0.0003
τ_+	8	8	8	8
τ_-	8	8	8	8

Table 7.1: *Values of STDP paramters for each plasticity rule that is tested in this polarity switch experiment.* [Pedrosa and Clopath, 2017]

7.1.1 Experiment 1: DP rule

In the visual cortex, we have mentioned in CHAPTER 4 that the control conditions does not allow any form of Hebbian plasticity. However, activation of both β- and α_1-adrenergic receptors can reshape plasticity in this brain structure revealing the bidirectional Hebbian STDP curve or depression-potentiation rule. Moreover, the activation of these receptors is seen in high acetylcholine levels. Now, we also know that during NREM sleep, noradrenaline levels are increased. We will therefore apply this rule to our sleep circuit to see if the reset of our synaptic weights is still present or if we obtain an evolution of synaptic weights more in line with memory consolidation.

As can be seen on Figure 7.3.A., unfortunately, the expected result is obtained when applying a depression-potentiation protocol. It is observed that regardless of whether the synapses are strong or weak, the synaptic weights tend to converge. This experiment is therefore inconclusive and does not allow us to overcome the homeostatic reset.

7.1.2 Experiment 2: PP rule

Since, not surprisingly, it was found that the classical depression-potentiation rule did not lead to a consolidation of daytime learning after a night's sleep, we will test a new plasticity induction protocol: the potentiation-potentiation rule. The PP Kernel, represented in Figure 7.3, is induced by different neuromodulators whose effects vary during sleep in specific area of the brain such as noradrenaline in the visual cortex, dopamine in the hippocampus and in the prefrontal cortex and acetylcholine in the hippocampus (for more details, see CHAPTER 4).

Applying this to our 3-neuron circuit in bursting mode, we see, on Figure 7.3.C. that we get a potentiation of small weights and a small potentiation or status quo of large weights. This modification is therefore not compatible with the consolidation of knowledge acquired during the day, since the neurons that are not very active would also be potentiated during the night.

7.1.3 Experiment 3: UP rule

Since our first two protocols were unsuccessful, we will test a third plasticity induction protocol: the unchanged-potentiation rule. This form of plasticity can be associated with dopaminergic action via D2 receptors in lateral amygdala [Bissière et al., 2003].

Once again, one can observe in Figure 7.3.D. that this protocol does not lead to a division of the behaviour of the weak versus strong synapses. Both types see their weight either increasing slightly or

staying the same at the end of the night. Once again each current follows the same pattern and the type of bursting activity does not allow for different behaviour either.

7.1.4 Experiment 4: DU rule

After our first three tests of Kernel's polarity change proved inconclusive, it does not seem surprising that the latter follows the same trend. Indeed, we observe that the DU rule, which is found especially in the visual and prefrontal cortex when serotonin is present during the induction protocol, leads to unchanged or slightly decreased synapse weights after sleep as can be seen on Figure 7.3.E..

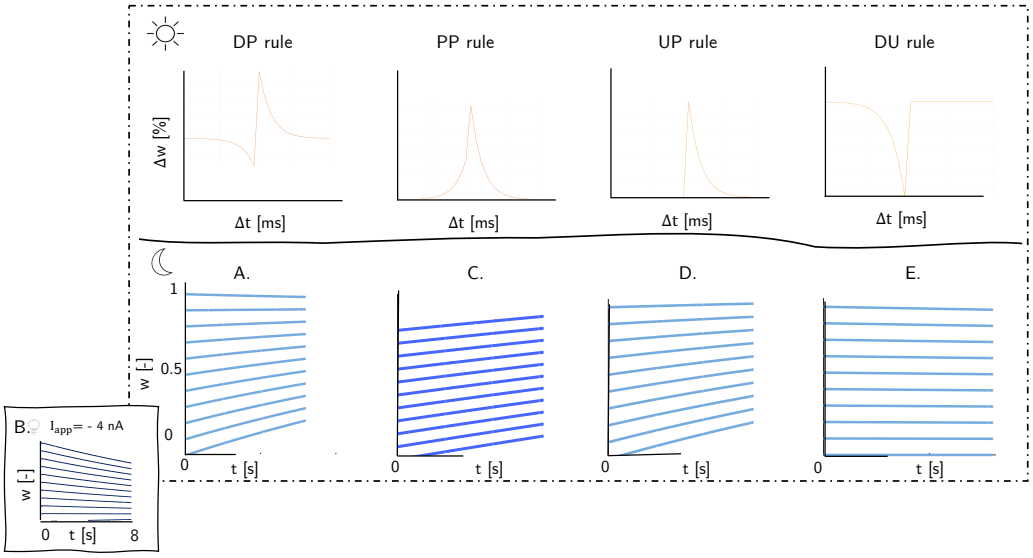


Figure 7.3: *Computational experiment: polarity switch* **A.** Temporal evolution of the weight values (w) for $I_{app} = -4.3$, potentiation is observed for the weak weights whereas strong weights remain nearly unchanged. This behaviour is not compatible with one of the hypothesis that could confirm memory consolidation during sleep. **B.** Temporal evolution of the weight values (w) for $I_{app} = -4$, weak weights remain unchanged whereas strong weights are depressed. At this moment, one can notice that, even if the same plasticity rule is applied in both cases, the behaviour of the synaptic weights over time varies according to the current applied. This intrinsic characteristic of the STDP is explained in more detail later in this work. Conclusion of this experiment is that this plasticity rule does not prove consolidation of memory during sleep as all weights follow the same tendency regardless of their initial value w_0 (at the beginning of the sleep stage).**C.** Temporal evolution of the weight values (w) for $_{app=-4.2}$ values. Weak weights as well as strong weights are potentiated. This behaviour is again not compatible with one of the scenarios that would lead to the verification of memory consolidation during sleep. **D.** Temporal evolution of the weight values (w) for $_{app=-4.3}$ values. Weak weights as well as strong weights are slightly potentiated. Once again, this behaviour is not compatible with one of the scenarios that would lead to the verification of memory consolidation during sleep.**E.** Same conclusion for the last rule.

7.1.5 Discussion and Conclusion

The results here are obvious. In the manner of Pedrosa, the Kernel of STDP during sleep can also be modulated as a result of the effect of neuromodulators. However, as far as the evolution of synaptic weights during sleep is concerned, we find that no rule allows us to obtain a consolidation of the memory. Therefore, the polarity switch effect of certain neuromodulators applied as is to our sleeping neuron circuitry is not an avenue to explore in order to prove memory consolidation during sleep.

Indeed, applying the same rule to both high and low weight synapses does not allow us to discriminate between these two states. Following the method we will use in the next two sections, we could consider applying a different rule to each synapse depending on its state at the end of the day. Thus, small synapses would be forced to follow a DU rule for example, while large synapses would be subject to an UP rule.

However, biologically and physiologically, it is difficult to imagine that it is possible for some neuromodulators to apply only to high-weight synapses and others to low-weight synapses. This is because neuromodulators act globally, whereas synaptic plasticity is a local effect. This scenario therefore seems difficult to implement while respecting this difference in spatial scale.

7.2 Magnitude modulation

Coming back to our STDP rule, two other parameters on which we can act are A_+ and A_- which represent the strength/amplitude of potentiation and depression respectively. As for polarity switch, experimental studies have shown that neuromodulators are able to modify this parameter, changing the shape of the classic STDP Kernel. We can for example remind the ability of acetylcholine to decrease tLTP magnitude in the medial prefrontal cortex of juvenile rats whereas it increases tLTP mangitude in the one of adult rats [Goriounova and Mansvelder, 2012] (for more details, see Chapitre 4).

Implementation

As mentioned in Chapter 4, activation of M2-receptors allows acetylcholine to reduce LTP amplitude in the hippocampus. Knowing also that acetylcholine levels vary from wakefulness to sleep, in this section, we will explore this modulation of the parameters A_+ and A_- in order to see if this neuromodulator is the way to go in order to corroborate our scenario.

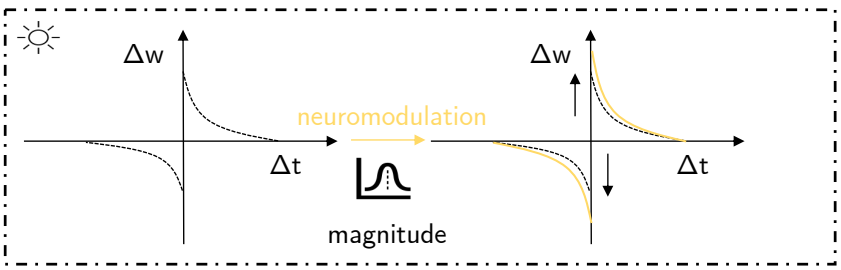


Figure 7.4: *Third experiment on STDP.* Modulation of the magnitude of Spike Timing-Dependent Plasticity (STDP). The paramaters value that are used in order to implement this rule are the following: $A_{+,STRONG} = 0.0096$, $A_{-,STRONG} = 0.1{*}0.0053$, $A_{+,WEAK} = 0$, $A_{-,WEAK} = 3{*}0.0053$ and $\tau_+ = 16.8$ $\tau_- = 33.7$ (they are left unchanged).

In this hand-tuned study, We define 4 new parameters $A_{+STRONG}$, A_{+WEAK}, $A_{-STRONG}$, A_{-WEAK}. The behaviour of the synapses will vary according to their weight: discrimination between synapses of high and low weight. Indeed, in order to "counteract" the homeostatic reset, we would like to have the following behaviour for :

- synapses of low weight: we would like them to depress in a rather important way. Indeed, if the connections between the corresponding neurons have not been strongly activated during the day, we do not want them to be kept. We will therefore define a critical value of the synaptic weight

according to which a synapse is considered to be of high or low weight. This value is $w = 0.7$. Therefore, if the synaptic weight is less than 0.7, we want the time constant _ to be replaced by $A_{-,WEAK}$.

- On the contrary, we want the strongest synapses to have little depression so as to preserve the information stored during the day. Therefore, synapses with a weight greater than 0.7 will be assigned an amplitude of potentiation equals to a normal value as well as a small depression amplitude.

The same logic is then applied to the A_+ parameter. Two new parameters are introduced: $A_{+,STRONG}$ and $A_{+,WEAK}$ and we discriminate between the behaviours of high and low weight synapses:

- For low-weight synapses, we would like them to be low-potentiated. In order not to tend towards the reset value but to undergo more depression than potentiation. It is thus assigned a value of potentiation $A_{+,WEAK}$.

- For the strong weight synapses, we hope that they are more potentiated than depressed so that they do not tend towards the reset value, so we assign them a potentiation value equivalent to $A_{+STRONG}$.

Parameters		Magnitude modulation	Time window modulation
if w<wcrit (WEAK synapses)	A_+	0	0.0096
	A_-	3*0.0053	0.0053
	τ_+	16.8	0.1*16.8
	τ_-	33.7	10*33.7
if w>wcrit (STRONG synapses)	A_+	0.0096	0.0096
	A_-	0.1*0.0053	0.0053
	τ_+	16.8	16.8
	τ_-	33.7	0.1*33.7

Table 7.2: *hand-tuned parameter values for the modulation of the amplitude and time constant of the STDP.* The parameters values are divided into strong synapses i.e. whose weight at the beginning of the night is higher than $w_{crit} = 0.7$ and weak synapses whose weight is lower.

Results

In contrast to the switch of polarity, here we see that the behaviour is more in line with a hypothesis of consolidation of memory during sleep. Indeed, the small synapses are totally depressed and are therefore at the end of the night with a synaptic weight of 0 while the large synapses remain strong. However, in this case, we always find that we obtain a convergence value of the synaptic case according to each current. However, as we had to discriminate between strong and weak synapses by arbitrarily setting a critical weight value, this implementation suffers from limitations that will all be reviewed in section 7.4.

In Figure 7.5, as well as previously mentioned when investigating the effect of a switch of polarity, we see that a value of $I_{app,i}$ (more precisely $I_{app,i} = -4nA$) causes all synaptic weights to decrease to

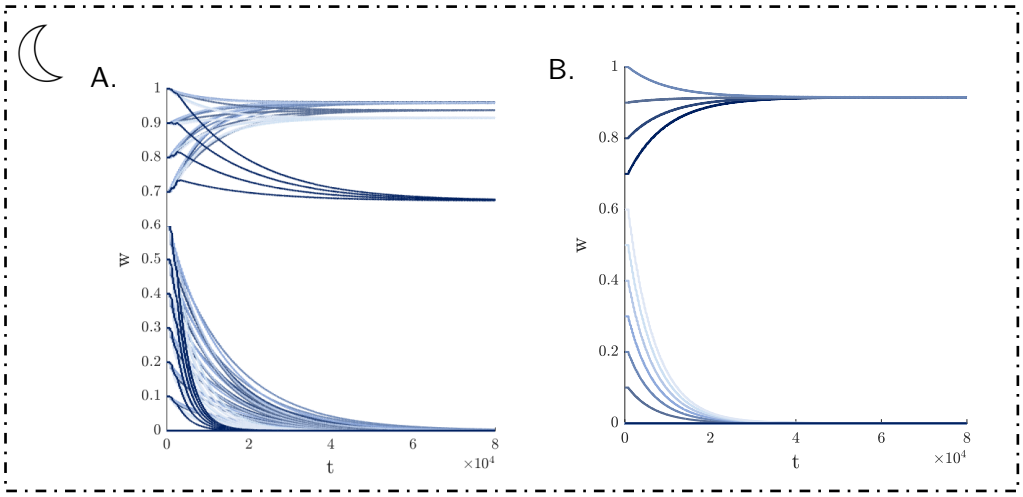


Figure 7.5: *Modulation of the magnitude of STDP.* **A.** Temporal evolution of the weight values (w) for the pair-based model implemented with soft bounds and with neuromodulation of A_+ and A_- parameters. Weak synapses ($w < w_{crit}$) decrease in weight over the course of the night, while strong synapses ($w > w_{crit}$) decrease or increase slightly in weight so as to tend towards a high convergence value at the end of the night. The different shades of blue represent the different temporal evolution of the synaptic weights as a function of the current I_{app}. **B.** Here we can see more clearly the time evolution of w for an $I_{app,i} = -4.2nA$. Again, the different shades of blue represent the evolution of the weights as a function of the initial weight at the beginning of the night.

a convergence value smaller than the initial weight or to 0 while for the same values of w_0 the other currents tend to lead to an increase of the weight to a higher convergence value or to the maximum value i.e. 1. The explanation of this behaviour is intrinsic to the model we use i.e. *pair-based models*. Indeed, as it has already been highlighted by Caroline Minne in her master thesis regarding the triplet model [Minne et al., 2021], pair-based models are highly sensitive to very small variability in the timing of the spikes of the pre- and postsynaptic neurons. Indeed, if the presynaptic spikes for example are slightly delayed or advanced, the evolution of the weight will change. In Figure 7.6, the presynaptic (grey) and postsynaptic (black) bursts for two different currents are clearly observed. The first current will lead to potentiation as the postsynaptic burst is delayed whereas the second current will lead to depression as the postsynaptic burst is advanced. As already mentioned in Chapter 6, this brings us back to the limitations of the pair-based STDP model. Indeed, these plasticity models are too rigid as they only use the exact timing of the spike to update the synaptic weight changes.

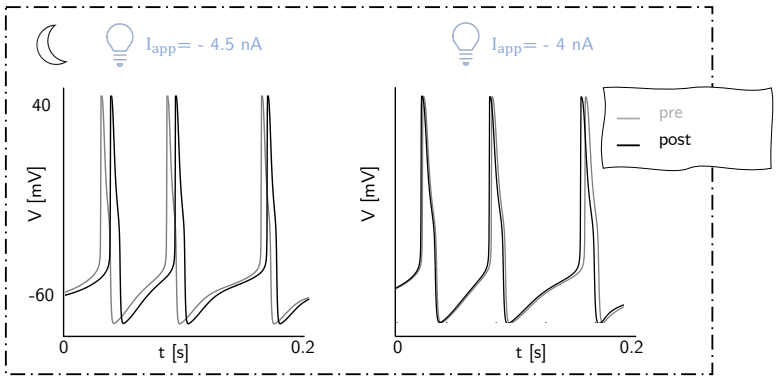


Figure 7.6: *Robustness deficiency of pair-based model* Presynaptic (grey) and postsynaptic (black) burst for two $I_{app,i}$. LEFT: $I_{app,i} = -4.5[nA]$, resulting in potentiation because the postsynaptic burst is slightly delayed whereas for RIGHT: $I_{app,i} = -4[nA]$, depression is observed as the postsynaptic burst is in advance over the presynaptic one.

7.3 Time window modulation

Fortunately, polarity switching is not the only effect that neuromodulators can have on pair-based STDP. Indeed, in certain areas of the brain, some neuromodulators are able to vary the time window of LTP or LTD induction e.g. noradrenaline in the hippocampus (for more details see CHAPTER 4). By varying our rule in this way, we will therefore try to see if neuromodulation can allow us to obtain the desired scenario. The parameters on which we will perform an analysis are therefore τ_+ and τ_- which respectively represents the width of positive and negative learning windows. For a symmetric STDP rule, these two parameters will be equivalent to, for example, 10 ms. However, in the case of the STDP developed by Bi and Poo, we see in Table 7.2 that they are equal to 16.8 ms for τ_+ and 33.7 for τ_-[Bi and Poo, 2001].

Implementation

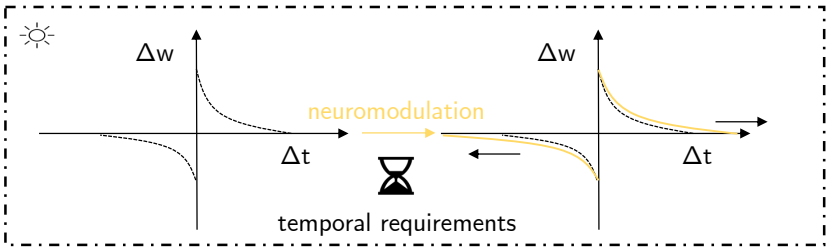


Figure 7.7: *Third experiment on STDP.* Modulation of the temporal window of Spike Timing-Dependent Plasticity (STDP).The paramaters value that are used in order to implement this rule are the following: $\tau_{+,STRONG} = 0.0096$, $\tau_{-,STRONG} = 0.1{*}33.7$, $\tau_{+,WEAK} = 0.1{*}16.8$, $\tau_{-,WEAK} = 10{*}33.7$ and $A_+ = 0.0096$ $A_- = 0.0053$ (they are left unchanged).

The implementation of this parameter study really follows the same modus operandi as the previous study on the *amplitude* parameters. We discriminate the behaviour of synapses with a small weight and those with a large weight. Thus, two new parameters will be defined: $\tau_{-,STRONG}$ and $\tau_{-,WEAK}$. The same logic is then applied to the τ_+ parameter. Two new parameters are introduced: $\tau_{+STRONG}$ and τ_{+WEAK} We discriminate between the behaviours of high and low weight synapses.

7.3.1 Results

By modifying τ_d, we see on Figure 7.8 that we can have different behaviours for small weight and large weight synapses. Indeed, if the synapse has a weight at the beginning of the night higher than the established w_{crit}, we see that the final weight at the end of the night tends towards a high w value. Thus, the heavy weight synapses retain the connections activated during the day. The same thing is observed for the low weight synapses, i.e. those with a weight lower than the w_{crit} at the beginning of the night, they will tend towards a value of w that is quite small and corresponds to the information they have stored during the day.

Unfortunately, even if the evolution of the weight is now divided between synapses with high and low weights, we still cannot overcome the homeostatic reset. And instead of having one convergence value regardless of the strength of the synapse at the beginning of the night, we get two thanks to this discrimination between the two cases.

N.B.: The fact that the eighth current strongly depresses synapses that were considered strong has not been explained and is probably still due to intrinsic flaws in the pair-based STDP. These results are consistent with those obtained by means of the numerical demonstration of the homeostatic reset (see CHAPTER 6). Indeed, as mentioned previously, thanks to the formula we have established, based on the evolution of the spike train, we can fully predict the reset value.

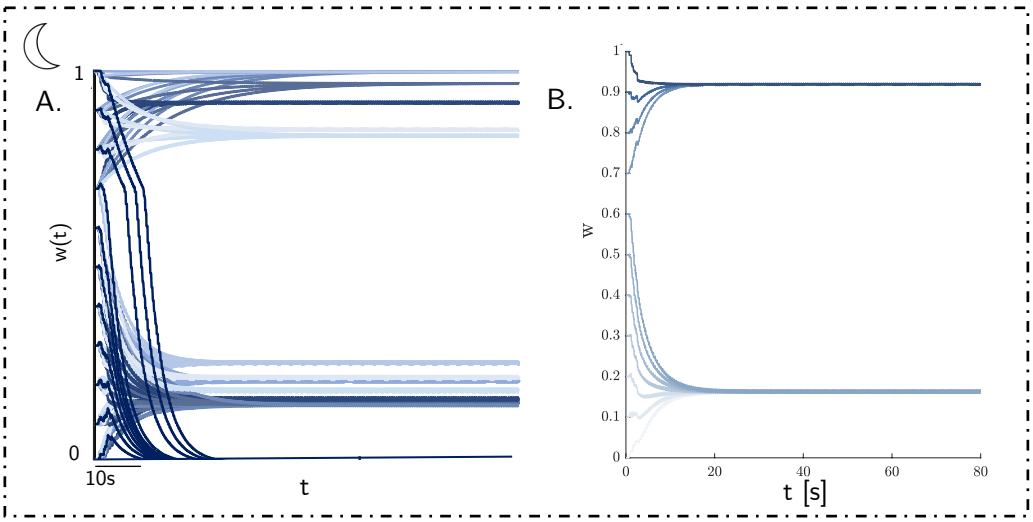


Figure 7.8: *Evolution of synaptic weight in function of time when the STDP time window is neuromodulated* **A.** Temporal evolution of the weight values (w) for the pair-based model implemented with soft bounds and with neuromodulation of τ_+, τ_- parameters. Weak synapses ($w < w_{crit}$) decrease or increase in weight over the course of the night, while strong synapses ($w > w_{crit}$) decrease or increase slightly in weight so as to tend towards a high convergence value at the end of the night. The different shades of blue represent the different temporal evolution of the synaptic weights as a function of the the current I_{app}. **B.** Here we can see more clearly the time evolution of w for an $I_{app,i} = -4.2nA$. Again, the different shades of blue represent the evolution of the weights as a function of the initial weight at the beginning of the night.

7.4 Limitations highlighted by the *hand-tuned* parameters study

Based on our review of neuromodulatory effects on the pair-based STDP in CHAPTER 4, we have here played with the parameters of this model in an attempt to combat the homeostatic reset of synaptic weights. However, it turns out that the hand-tuned parameter study we have just made is open to criticism. Indeed, the latter has several deficiencies that we will outline here

- **Discrimination between strong and weak synapses on the basis of a w_{crit}**: First of all, the way we implemented the discrimination between "small" and "large" synapses is artificial. Indeed, we have, without any biological basis, decided on a random value, here 0.7, according to which a synapse will be a high weight synapse corresponding to strongly activated connections during the day or a low weight synapse translating a weak connectivity between two neurons. Indeed, biologically, our body, and more particularly, our brain is not able to distinguish a small synaptic from a large one by using a synaptic weight. Indeed, this variable is a representation, used by phenomenological models, in order to translate the synaptic strength. The latter being, for example, represented functionally by the average amount of current or voltage excursion produced in the postsynaptic neuron by an action potential in the presynaptic neuron [Murthy, 1998]. In our case, w represents a weighting of the AMPA excitatory current so it represents the AMPA conductance strength. Synaptic downscaling is said to affect all synapses during the night and only the strongest ones will retain more or less high synaptic strength at the end of the night despite this synaptic renormalization. However, there is still a possible justification for the use of this procedure which is the synaptic tagging and capture hypothesis. This will be discussed in section 8.2.

- **Ability of the modulation to counteract the reset**: A limitation of our study is also its variability according to the modulated parameters. Indeed, the polarity switch allows us to obtain different temporal evolutions of synaptic weights depending on the rule used. However, as we followed Pedrosa's way and just implemented these rules without discrimination of synapses, we do not obtain satisfactory results. The same is observed for the modulation of τ. The latter does not succeed in fighting the tendency of the pair-based STDP which uses soft bounds to tend towards a steady-state value. Therefore, amplitude modulation is the only effect that allows us to obtain a behaviour compatible with memory consolidation.

- **Intrinsic defects of the pair-based model**: There are indeed disadvantages to using such a model. The latter takes into account the exact timing of the pre- and postsynaptic spikes in order to update the synaptic weight. Therefore, a burst pattern that would induce a small modification in the order of these spikes would lead to a totally different update of the weight and would not be compatible with the rule in place.

7.5 Bound modulation

7.5.1 Symmetric bounds [Park et al., 2017]

Having explored the parameters that we could vary using STDP, we decided to look at the effect of neuromodulation on the learning rule used and in particular on the types of bounds. Thus, in this section, we will use the symmetric learning rule developed by Park in 2017 as it is assumed to lead to a "stable" type of memory [Park et al., 2017]. Indeed, in his study, Park tested the amount of memory decaying over time in order to determine if a memory could be considered as being stable or not. With his team, he made some computational tests in which he measured the temporal degradation of memory. As a result, after the decaying session, the asymmetric model (AR) model had disturbed responses and some of the information that was encoded is erased whereas the symmetric (SR) model remained intact.

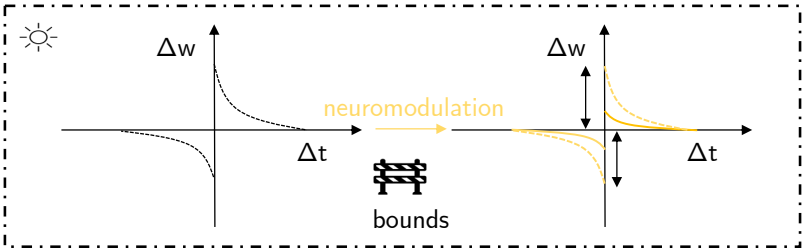


Figure 7.9: *Fourth experiment on STDP.* Modulation of the bounds of Spike Timing-Dependent Plasticity (STDP)

Implementation In this experiment, we will change the type of bounds used in our pair-based model. Indeed, instead of using hard or soft bounds, we will use symmetric bounds[Park et al., 2017]:

$$A_+(w_{ij} = A_-(w_{ij}) = 2 * min(w_{max} - w_{ij}, w_{ij} - w_{min}) \; 0 < \alpha < 1 \tag{7.1}$$

.

Results Based on the experimental results of Park and his team, it is expected that the homeostatic reset can be overcome by using symmetric bounds rather than the asymmetric bounds we are used to. As such,

- each synapse in the symmetric model converges either to 0 or to 1 i.e. synapses are stable at 0 or 1,
- each synapse of the asymmetric model converges to 0.5 i.e. synapses are stable at 0.5.

This difference in the stability profile of the synapses leads to two different behaviour in terms of memory consolidation. On one hand, the symmetric model tries to retain the synaptic weights that are located at 0 or 1 (stable synapses lead to memory consolidation). On the other hand, synapses in the asymmetric model tries to converge to the steady-state value 0.5 which leads to memory erasure phenomenon (instable synapses lead to memory erasure).

Therefore, we can make a a parallelism between the second case and our homeostatic reset situation. Indeed, in our models, no matter if some connections have been strengthened during the day leading to an increase of the corresponding synaptic weight or if the weight of some synapses has remained

low, at the end of the sleep phase, both situations tend towards a single value comparable to the 0.5 of the asymmetric case. Therefore, by using the symmetrical implementation of the learning rule developed by Park, we hope to overcome this convergence value and, like him, obtain a stability of the large and small synaptic weights and a discrimination between the two situations at the end of the night.

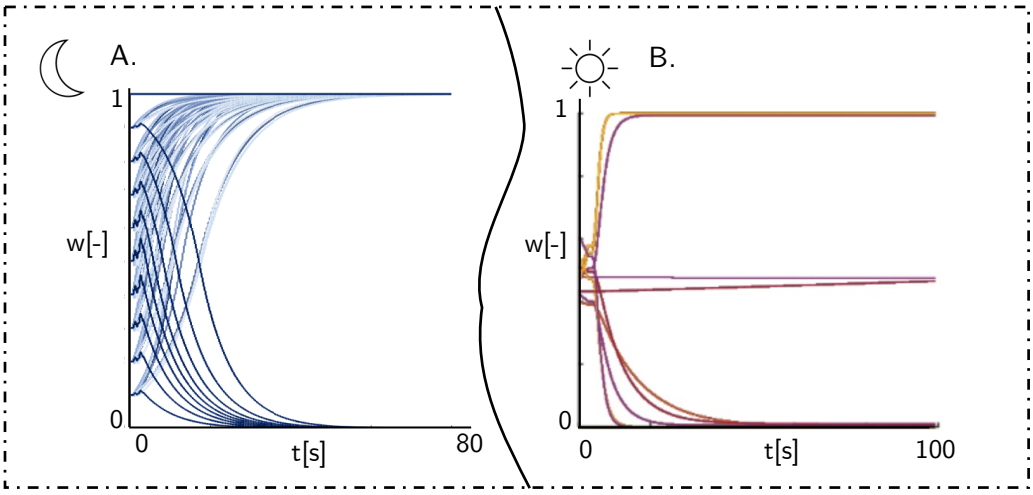


Figure 7.10: *Modulation of the bounds of STDP.* **A.** Here, regardless of their synaptic weight at the beginning of the night, the connections are strengthened during the night and all weights w are increased to the maximum value of 1 with the exception of the current, which we have already mentioned, and which generates depression irrespective of the state of the synapse at the beginning of the night. **B.** When the plasticity rule using symmetric bounds is implemented on neurons in the *tonic* mode (i.e. during wakefulness), it leads to a behaviour compatible with our desired [Park et al., 2017] scenario.

Unfortunately, in Figure 7.10 it can be seen that the desired objective is far from being achieved. Indeed, both small and large synapses tend towards 1 when using Park's model with bursting neurons. However, it can be seen that the speed of convergence varies with weight. Low weight synapses will tend to converge more slowly to this final value while high weight synapses will converge much faster. We also see that we get some depression but this is not explained by the use of the synaptic plasticity model but by the use of a known depolarising current value to depress the synaptic weights.

Such observation is not so much surprising when we keep in mind that a limitation of phenomenological plasticity rules is to be too much dependent on spike time as mentioned just above and illustrated in Figure 7.6. Indeed, models based on precise timing of spikes have the ability to reproduce spike timing protocols but fails at representing the frequency dependence of spike timing protocols [Sjöström et al., 2001b] or triplets experiments such as "post-pre-post" or "pre-post-pre" protocols [Pfister and Gerstner, 2006].

7.5.2 Polynomial plasticity rule (trade-off between hard- and soft-bounds)

The idea here is again to modulate the types of bounds used in STDP using the same type of modulation as for the study of the symmetric bound used in Park, 2017. This test will therefore aim to evaluate the role of this μ parameter and the trade-off between hard bound and soft bound in order to overcome (or at least try to overcome) the homeostatic reset. As a reminder, the plasticity rule using this parameter μ also known as "polynomial plasticity rule" can be written as:

$$\Delta w_+ = A_+(1-w)^\mu$$
$$\Delta w_- = A_- w^\mu$$

where the exponent μ allows to interpolate between both types of bounds. Indeed, when $\mu = 1$, we retrieve a soft-bound rule while the case $\mu = 0$ leads to the implementation of hard-bound[Van Rossum, 2012] (for more details, see CHAPTER2).

Implementation In order to implement this test, we will use our classic STDP codes in which we will add the μ parameter as a superscript to our learning rules. At first, different values of μ, varying between 0 and 1, will be tested. Then, values of μ that fall outside this range in a slightly more extreme way such as 10 or -10 will be tested.

After that, the final weight according to each μ is plotted in order to highlight the impact of the μ value, and thus of a learning rule closer to hard-bounds or soft-bounds on the final synaptic weight.

Before performing our neuromodulation of the mu parameter as such and analysing the temporal behaviour of the synaptic weights and their value at the end of the night, we first tried to gain some intuition about the effect this parameter would have on w.

Results As one can see on Figure 7.11, the neuromodulation of the bounds on the basis of the μ parameter present in the polynomial plasticity rule, does not allow us to verify our hypothesis according to which the neuromodulators and in particular their variation between wakefulness and sleep would have an effect on the consolidation of the memory during sleep. Indeed, in this experiment, it was assumed that neuromodulators, whose levels vary between these two stages, such as acetylcholine, were modelled by a variation of the μ parameter present in the polynomial plasticity rule presented in the equation above. However, we observe that for the tested μ values, of which a part is illustrated in Figure 7.11, none of these values leads to an evolution of the synaptic weights at the end of the night that would be in adequacy with the *SHY hypothesis* or the *active system consolidation hypothesis*.

Indeed, for μ values varying between 0 and 1 what could be assimilated to neuromodulators which would not see their concentration strongly varying from wakefulness to sleep. Indeed, this weak modulation action only allows to switch between the two known and observed behaviours in [Jacquerie et al., 2022] i.e. between *saturation* and between the *homeostatic reset*. Then, when we test the effect of neuromodulators that would have a more drastic modulation activity on the μ parameter (i.e. μ values between 1 and 20), we find that the temporal evolution of synaptic weights is again not compatible with our dream scenario. Indeed, it seems again that we get a reset phenomenon but on a longer time scale. Once again, it is clear that this phenomenon of reset and therefore convergence of the pair-based STDP to a steady-state value is very robust and that a parameter modulation study such as the one we are carrying out is not sufficient to curb this phenomenon.

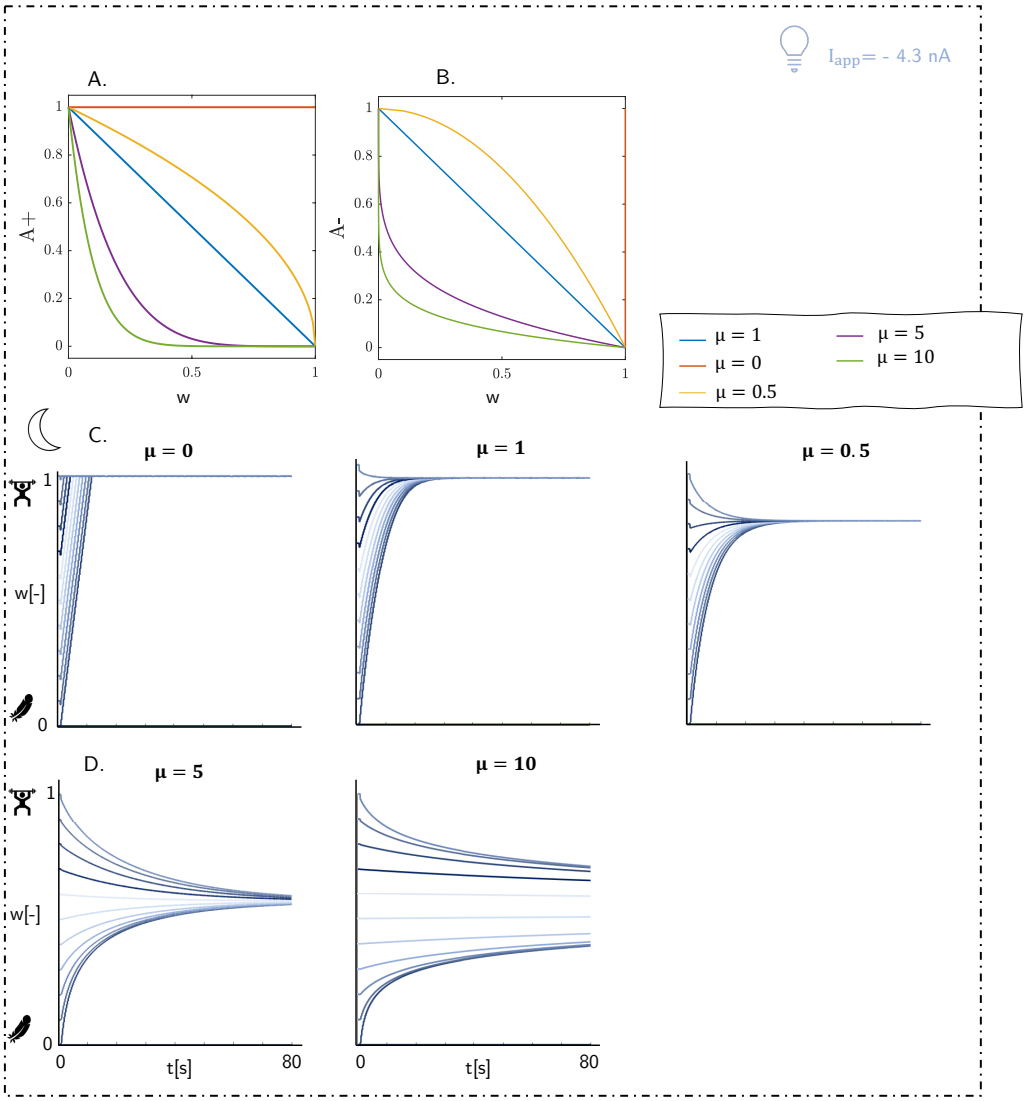


Figure 7.11: *Modulation of the bounds of STDP.* **A.**Evolution of the parameter A_+ as a function of w_0 and for different μ. **B.** Evolution of the parameter A_- as a function of w_0 and for different μ. **C.** Temporal evolution of the weight values (w) for different μ values. The values of μ between 0 which corresponds to our hard-bound rule and thus to a saturation of the synaptic weights and 1 i.e. soft bound which corresponds to a situation where the weights tend towards a stable value of convergence between the two extreme values of synaptic weights (0 and 1) do not make it possible to overcome the homeostatic reset situation. Indeed, we see with $\mu = 0.5$ that we are just at a hybrid behaviour. For values of μ higher than 1, we obtain ... Here, the different shades of blue correspond to the temporal evolution of the synaptic weights which are different according to the different w_0 values at the beginning of the night.

7.6 Discussion

In this part of our work, we applied some of the effects of the neuromodulators that we reviewed in CHAPTER 4 in order to computationally test the following hypothesis: *Does the effect of the neuromodulators allow us to validate the hypothesis of memory consolidation during sleep, i.e. when the neurons of our computational circuit are in bursting mode?* In order to test the validity of this hypothesis, we divided our study into several cases, each case corresponding to one or more parameters of the STDP that neuromodulators can vary. In order to mimic the action of the latter, we modified these

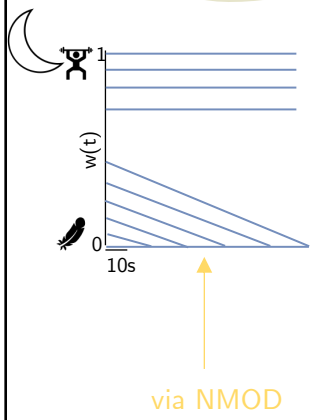
parameters by hand.

Some experiments lead to results that are quite compatible with our desired scenario, especially amplitude modulation. In the literature, the modification of this parameter is linked to the effect of acetylcholine, which is not surprising because this neuromodulator is one of the first to be evoked when analysing the switch between wakefulness and sleep. Indeed, acetylcholine is known to have a high concentration in certain brain networks during REM sleep and wakefulness while its levels are low during SWS. This increase in ACh during REM sleep could therefore be linked to certain hippocampal functions such as memory storage. It would therefore be interesting to test the effect of this neuromodulator experimentally during sleep as it has already been done in wakefulness [Zannone et al., 2018, Ang et al., 2021, Sugisaki et al., 2011, Sugisaki et al., 2016, Brzosko et al., 2017]. However, even the parameter modulation that has almost verified our hypothesis possesses some issues. Indeed, in order to obtain different behaviour for strong and weak synapses, we had to impose a critical value of w based on which the temporal evolution of both types of synaptic weights will diverge. From a biological and physiological point of view first, this discrimination based on a randomly chosen value w_{crit} is open to criticism. Moreover, from a computational point of view, this method is very fragile.

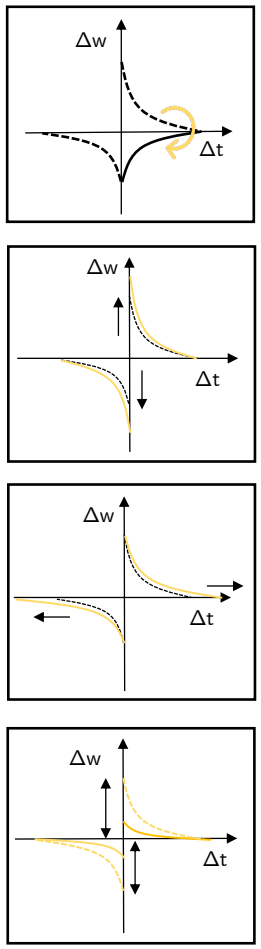
As a general observation, one can notice that it is barely impossible to overcome the homeostatic reset that is observed with phenomenological plasticity rules such as pair-based STDP "only" by varying paramaters of the latter. Indeed, the reset phenomenon we observe with this model is similar to an artefact of the equations when using a soft bounds rule (hard bounds leads to a saturation phenomenon). Therefore, one cannot escape it if this implementation with soft bounds is maintained. That's why, during our computational study, we tried to discriminate between strong synapses (large weights) and weak synapses (small weights). However, this seems hardly justifiable from a neuromodulatory point of view since the latter have a global effect on the synapses and not a local one (such as the variation of the synaptic strength). Therefore, it appears difficult to reconcile these two different spatial scales in order to obtain a physiologically justifiable phenomenon that would allow us to work with this discrimination of synaptic weights. We have therefore tried to modify these rules by playing with the use of different bounds. But we see that this does not have much impact when we work with neurons in *bursting* mode, contrary to what has been demonstrated in sleep [Park et al., 2017].

PART III: computational study

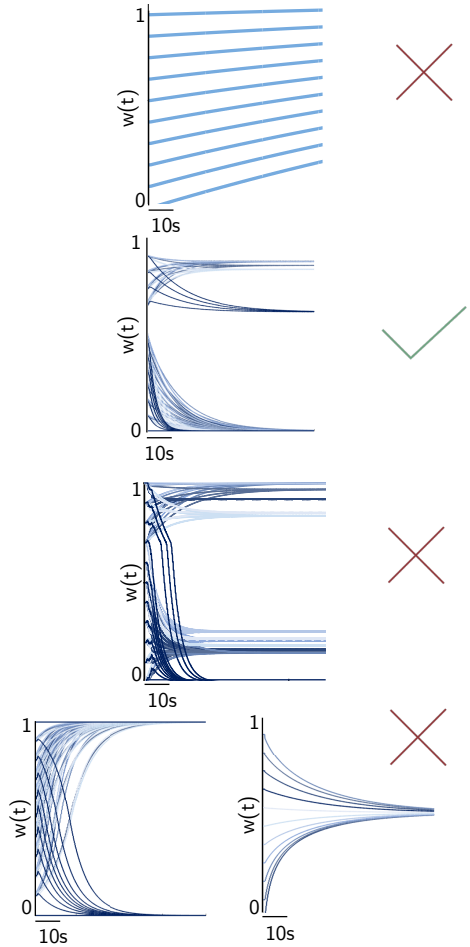
GOAL



METHODS



RESULTS



CONCLUSION

The neurmodulation of the amplitude of the potentiation and depression window used in the pair-based model is the only parameter modulation that allows to conclude to memory consolidation during sleep

The neuromodulation of the pair-based STDP model as conducted in this work does not lead to the confirmation of memory consolidation during sleep.

Part IV

Conclusions and perspectives

Chapter 8

Conclusion and perspectives

8.1 Thesis summary

The aim of this thesis was to investigate the effects of neuromodulators on pair-based STDP (a phenomenological plasticity rule) when neurons are in *bursting mode* in order to prove memory consolidation during sleep. We began our work by recalling some important notions of biology and neurophysiology: *synaptic transmission* and *synaptic plasticity*, *switch from wake to sleep* at different levels and the location, receptors and actions of the main *neuromodulators* as well as notions essential to understand the pair-based STDP which will be the neuromodulated phenomenological model in the scope of this thesis.

We then went on with a review of the effects of neuromodulators on STDP as well as on sleep in order to give an insight on what had already been done in the field both experimentally (mostly during wakefulness) and computationally. This review will also be valuable for our computational part in order to support the latter with scientific evidence. Thus, this review has enabled us to highlight three main effects of neuromodulators on the STDP kernel:

- *Modification of polarity*: Depending on the area of the brain and on the receptor that is targeted, various neuromodulateurs are able to determine whether the same timing between the activity of the pre- and postsynaptic neurons strengthens or weakens the synaptic weights. For example, these include the ability of dopamine to convert tLTD into tLTP for pre-post pairings [Pawlak, 2010].

- *Modification of magnitude*: Then, neuromodulators such as acetylcholine in the prefrontal cortex [Goriounova and Mansvelder, 2012] are also able to increase or decrease the amplitude of tLTP and tLTD.

- *Modification of time window*: Finally, like noradrenaline in the hippocampus [Lin et al., 2003], neuromodulators are able to enlarge or diminish the time window for the expression of tLTP and tLTD.

In Chapter 6, we took a closer look at the *homeostatic reset* phenomenon observed by [Jacquerie et al., 2022]. It turns out that when a synaptic plasticity rule (in our case pair-based STDP) valid during wakefulness is used on neurons that have a rhythmic activity specific to sleep i.e. *bursting activity*, at the end of the night, all synaptic weights converge to the same value regardless of their initial state. Physiologically, this would mean that regardless of the learning that occurred during the day, highly correlated and activated synapses during the day would be depressed, while poorly

activated synapses would be increased during the night to tend towards a common value. This translates into the fact that these two patterns of activity during the day would be encoded by our brain in the same way. However, it has been proven that this is not the case and that this behavior was not compatible with memory consolidation during sleep. Based on this observation, we developed an analytical model to predict the convergence value.

Once the observed reset has been demonstrated analytically and the analytical results compared to our simulations, we moved on to the heart of the matter. Indeed, the next step of our work aims to study computationally the effect of the neuromodulators mentioned in the review section and to evaluate their capacity or not to overcome the *homeostatic reset*. In order to achieve this goal, we performed several experiments based on a hand-tuned modification of parameters:

- *Switch of polarity*: In the manner of Pedrosa, we have modified the Kernel of STDP in order to obtain four different rules [Pedrosa and Clopath, 2017]. In his 2017 paper, Pedrosa and his team had equated each of these Kernels with one or more neuromodulator(s) in certain brain areas. Unfortunately, when applied to neuron in bursting mode, none of the four rules leads to an evolution of synaptic weights over time that would lead to evidence of memory consolidation during sleep.

- *Magnitude modulation*: This effect of neuromodulators is one that was highlighted in the review mentioned above. The modification of this parameter allows us here to observe a scenario at the end of the night similar to that of SHY. However, this experiment has some shortcomings such as the fragility of the pair-based model and the arbitrary definition of a critical weight in order to adapt the modification of the parameter according to the high or low weight synapses.

- *Time window modulation*: Here we see that we manage to obtain two convergence values: one for strong synapses and one for weak synapses. The behaviour is therefore a little more similar to our desired scenario, since we obtain a divergence of the behaviour of the synapses according to their weight. However, we cannot overcome the intrinsic characteristics of the STDP during sleep, i.e. tend towards a steady-state value when using soft bounds.

- *Bound modulation*: This parameter study is divided into two parts:

  - *Symmetric bounds*: The use of a symmetric plasticity rule (same amount of depression and potentiation) in sleep does not give the results found in Park's study in wakefulness [Park et al., 2017]. And therefore, does not lead to memory consolidation through the effects of neuromodulators during sleep.

  - *Polynomial plasticity rule*: Once again, the modulation of this parameter alone is not sufficient to overcome the intrinsic properties of STDP leading to the homeostatic reset.

When we take the results of all these tests, we see that the neuromodulation of the parameters of the pair-based model as it was carried out in this work does not allow us to conclude to the observation of a behaviour compatible with memory consolidation during sleep.

8.2 Perspectives

8.2.1 Eligibility trace

Throughout this work, we have been interested in the neuromodulation of a phenomenological plasticity rule, namely STDP. In this field, we know that neuromodulation can modify this rule in three different ways:

- By modifying the neuronal excitability and the spiking dynamics;
- By gating synaptic function such as the change in presynaptic glutamate release or in postsynaptic membrane potential;
- By altering the intracellular signaling cascades that shape synaptic plasticity [Brzosko et al., 2019].

During this thesis, we have translated these mechanisms by directly modifying the STDP kernel in the vein of [Pedrosa and Clopath, 2017] or [González-Rueda et al., 2018]. However, as is often the case in life, this approach may not be the only way to proceed. Indeed, another common method is to utilize an eligibility trace. The latter acts as a tag on synapses that are then eligible for change later on. This way of action aligns with the *Synaptic Tagging and Capture hypothesis (STC)* which states that "the induction of synaptic potentiation creates only the potential for a a lasting change in synaptic efficacy, but not the commitment to such a change" meaning that some other factor is necessary to determine whether a persistent change occurs [Frey and Morris, 1997, Reymann and Frey, 2007, Redondo and Morris, 2011].

Synaptic Tagging and Capture Hypothesis (STC)

This hypothesis was born in [Frey and Morris, 1997] to answer the following question: *"how can the synapse specificity of late LTP be achieved without elaborate intracellular protein trafficking?"* Indeed, LTP is known to be differentiated in an early phase and in a late phase. The latter using inhibitors of transcription and translation. However, protein synthesis occurs mainly in the cell body whereas LTP is input-specific which leads to the above-mentioned question. According to STC, the answer to that question would involve the creation of a synaptic tag independent of protein synthesis. This tag would appear at the site of potentiated synapses, which would allow the subsequent recruitment of the appropriate proteins to induce late LTP [Frey and Morris, 1997].

Therefore, in this promising section dedicated to the potential perspectives of this work, we will first play with this concept of eligibility trace when neurons are in burst mode in order to consider the effect of neuromodulators on STDP during sleep from another standpoint.

Concept

In order to address the eligibility trace subject, we will mainly rely on the 2007 paper of Izhikevich [Izhikevich, 2007] in which he add dopamine to neuromodulate the STDP curve with the aim to solve the 'distal reward problem' [Schultz, 2007]. In this paper, the synaptic strength change is computed by the product of the eligibility trace and the dopamine signal. This rule is then used in [Legenstein et al., 2008] in order to study biofeedback.

Distal reward problem

First mentioned in Pavlovian and instrumental conditioning, this conundrum involves a time gap between the action that may lead to a reward and the actual reward. This time gap raises the following question: *"How does the brain know what firing patterns of what neurons are responsible for the reward if the patterns are no longer there when the reward arrives and if all neurons and synapses are active during the waiting period of the reward ?"* [Izhikevich, 2007]
N.B.: This conundrum is known in the behavioral literature as the "distal reward problem" [Hull, 1943] and in the reinforcement learning literature as the "credit assignment problem [Minsky, 1961, Sutton, 1998]

Implementation

Mathematically Following [Izhikevich, 2007], we describe the state of each synapse using two phenomenological variables: the classical synaptic weight w which represents the biological synaptic strength-that we have used all along this work- and the activation of an enzyme important for plasticity e. This e variable aims at modeling any slow biological process acting as a synaptic tag such as the oxidation of PKC or PKA for example. This leads to the following equations:

$$\begin{aligned} \dot{e} &= -e/\tau_e + STDP(\tau)\delta(t - tpre/post), \\ \dot{w} &= ed. \end{aligned} \tag{8.1}$$

where d is the extracellular concentration of DA in [Izhikevich, 2007]. But, in our work, d will instead represent a neuromodulator whose levels vary greatly from wakefulness to sleep, such as acetylcholine for example. Indeed, here we recall that we are trying to apply this concept of eligibility trace to a scenario that involves sleep. This scenario will be described more precisely just hereafter. Then, $\delta(t)$ is the Dirac delta function that increases the variable e in a step-wise manner.
The variable d, in our model, describes the concentration (μM) of extracellular ACh, and is the same for all synapses in the model. Therefore, the time evolution of d is described by:

$$\dot{d} = -d/\tau_d + ACh(t), \tag{8.2}$$

where τ_d is the time constant of ACh uptake and ACh(t) models the source of ACh.

Scenario In order to apply the concept of trace eligibility to our hypothesis of memory consolidation during sleep, we imagine the following scenario:

- **During the day**: we implement a small neural network which will evolve during the day. Some neurons have highly correlated spiking activity while others are not correlated at all with the rest of the neural network and spike in a completely random way. When the model detects the presence of a pair of pre- and post-spikes between two neurons, the eligibility trace is incremented.

It increments each time a similar pair is noticed by the model and slowly decreases exponentially the rest of the time. A similar pattern emerges when, by chance, the joint spiking-activity of two poorly correlated neurons results in a pre-post pair.

- **During the night**: levels of certain neuromodulators vary and this variation, according to the eligibility trace theory, allows some change in synaptic strength w. Indeed, w is only modified when extracellular neuromodulator (ACh for example) is present ($d > 0$) during the critical window of a few seconds while the eligibility trace e decays to 0.

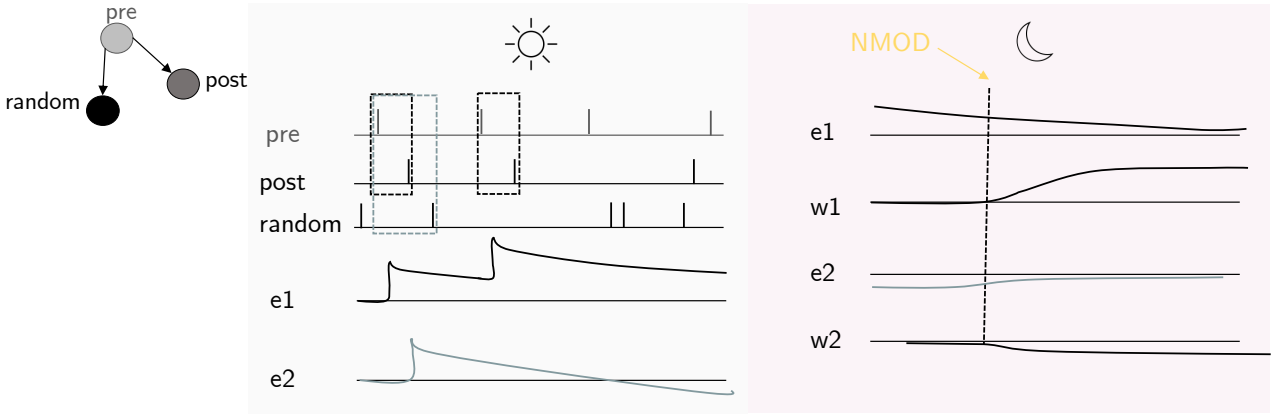


Figure 8.1:

8.2.2 Learning rule modulation

Another test we had performed in order to try to overcome the homeostatic reset and that has not led to satisfactory results is to use the synaptic plasticity rule developed by Standage in 2007 and reused by Olcese in 2010. The latter study is particularly interesting as it studies synaptic plasticity not only during wakefulness-like most of the papers we have read throughout this work- but also during sleep. Indeed, we know that there are experimental evidences that show that wake is associated with a net increase in synaptic strength which is then renormalized during sleep [Liu et al., 2010], which seems pretty close to the definition of the homeostatic reset observed in [Jacquerie et al., 2022] and which has been demonstrated in Chapter 6 of this thesis.

Implementation In this model, the change of synaptic weight can be written as:

$$\Delta w_{p,d} = k_{p,d}(w)e^{-c_{p,d}\Delta t} \tag{8.3}$$

Where Δw is the change of synaptic weight, the subscripts p and d stand for potentiation and depression, respectively, k is the learning rate, Δt is the difference between the times of post- and pre-synaptic spikes, and m is a weight-dependent factor with the following equation [Olcese et al., 2010].

$$m_{p,d} = a_{p,d}w^{b_{p,d}} \tag{8.4}$$

In practice, when we implemented this learning rule, we found that the rule itself led to a potentiation of the weights for both weak and strong synapses, and this was not limited by well-defined bounds. However, this approach seems interesting to investigate further and differs from those already used in our work.

Parameters	Values
a_p	431
a_d	-59
b_p	0.4
b_d	0.1
k_p	0.00006
k_d	-0.00006

Table 8.1: *Parameter values of the learning rule used in [Olcese et al., 2010].*

Part V

Appendix

Appendix A

Neuroanatomy basis

A.1 Brain anatomy

During this work, many structures of the brain will be mentioned, either as a pool of neurotransmitters or neuromodulators or as an area associated with such or such function. It therefore seems judicious to recall these various structures and their role.

Cortex The cerebral cortex is known to be associated with higher level functions such as consciousness, thought, emotion, reasoning, language, and memory More specifically, it is divided into four lobes, as can be seen on Figure A.1, each associated with specific functions. Thus,

- *The frontal lobe*, the largest lobe, located in front of the cerebral hemispheres, is in charge of the prospective memory, speech (Broca's area) and language, personality and movement control (the motor cortex).

- *The temporal lobe* occupies the middle cranial fossa and lies posterior to the frontal lobe and inferior to the parietal lobe. It is divided into two surfaces: the lateral and the medial surface. Therefore, depending on the surface of interest, functions vary accordingly. We can cite semantic memory, speech, recollection, episodic memory, etc.

- *The parietal lobe*located posterior to the frontal lobe and superior to the temporal lobe, is divided into two functional regions:

  - The anterior parietal lobe contains the primary sensory cortex (SI) which receives the majority of the sensory inputs coming from the thalamus, and it's responsible for interpreting the simple somatosensory signals like (touch, position, vibration, pressure, pain, temperature).

  - The posterior parietal lobe is further divided into two regions: the superior and the inferior parietal lobe which are respectively in charge of higher-order functions like motor-planning actions and higher-order complex functions like learning, language, spatial recognition, etc.

- *The occipital lobe* is the smallest lobe in the cerebrum cortex. It is located in the most posterior region of the brain, posterior to the parietal lobe and temporal lobe. Its roles are to visual processing and interpretation [Jawabri and Sharma, 2021]

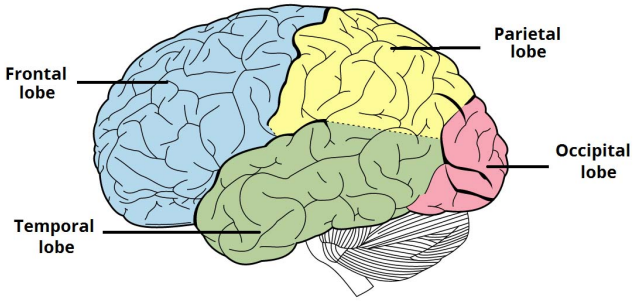


Figure A.1: Cortex anatomy [tea,]

Hippocampus Hippocampus is an extension of the temporal part of the cerebral cortex and is therefore embedded deep in the temporal lobe. From an external point of view, it is easily recognisable due to its S-shaped structure located on the edge of temporal lobe. This location makes the latter being part of the limbic lobe (as limbic means border). Hippocampus is known to be the place of learning and memory but it is also important in spatial navigation, emotional behaviour and regulation of hypothalamic functions [Anand and Dhikav, 2012]

Striatum "The "basal ganglia" refers to a group of subcortical nuclei responsible primarily for motor control, as well as other roles such as motor learning, executive functions and behaviors, and emotions." Among these subcortical nuclei, the striatum is a heterogeneous structure that receives inputs from many cortical and subcortical structures and sends back outputs to various basal ganglia nuclei [Lanciego et al., 2012]

The striatum is in charge of different roles according to regional considerations. Indeed, the tail of the striatum is known to be a key sensory-related striatal area while the dorsal striatum is critical in controlling motor, procedural, and reinforcement-based behaviors [Valjent and Gangarossa, 2021].

Locus coreuleus The locus coeruleus (LC) is referred to extensively in this work as it is known to be the main source of noradrenaline in the brain. It is a small brainstem nucleus that receives inputs from various brain regions and projects throughout the forebrain, brainstem, cerebellum, and spinal cord [Breton-Provencher et al., 2021].

In terms of its functions, the LC is closely related to the various roles of noradrenaline, mainly to mobilize the brain and body for action by increasing arousal and alertness, promoting vigilance, enhancing formation and retrieval of memory, focusing and attention but also by increasing restlessness and anxiety.

Ventral tegmental area and substantia nigra pars compacta The ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) are also two structures that are heavily mentioned in this thesis as they both play a key role in dopamine-related functions such as reward-related behaviour, motivation, addiction and motor functioning [Trutti et al., 2019].

Dorsal Raphe Nuclei The DRN is a bilateral, heterogeneous brainstem nucleus situated in the midbrain and the pons.As some of the other structures bellow, the dorsal raphe nucleus (DRN) is a major source of neuromodulators. It is notably the major source of serotonergic neurons as it contains approximatively a third of the latter [Huang et al., 2019]. The DRN is involved in the control of various physiological functions and has been implicated in brain dysfunction, especially mood disorders such as depression [Michelsen et al., 2008].

Thalamus The thalamus is a mostly made from gray matter and is located in the diencephalon. The thalamus is composed of many nuclei which are each responsible for the rely of the different sensory signals and therefore are intended to perform a particular function such as relaying sensory and motor signals or regulate consciousness and alertness [Torrico and Munakomi, 2019]. Moreover, notable roles of the thalamus include learning and episodic memory but also regulation of sleep and wakefulness.

Amygdala The amygdala is defined as an almond-shaped structure, located in the in the temporal lobe. As other structures of the brain, it is composed of different nuclei. The latter, according to their functions, are then grouped into five major categories: basolateral nuclei, cortical-like nuclei, central nuclei, other amygdaloid nuclei, and extended amygdala [AbuHasan et al., 2021].

Amygdala serves many roles. First, being one of the components of the limbic system, it is responsible for memory formation but also for the control of emotions and behavior. Indeed, the activation of the amygdala has a modulatory effect on the acquisition and consolidation of memories that are linked with an emotional response. Then, through its neural circuits, it also manages the processing of information between prefrontal-temporal association cortices and the hypothalamus. Finally, the amygdala also manages to regulate anxiety, aggression, fear conditioning, emotional memory, and social recognition [AbuHasan et al., 2021].

A.2 Anatomy of sleep

As illustrated in Figure A.2, a couple of brain structures are involved in sleep. The first one, and not the least, is the hypothalamus which is a structure containing neurons that play a role in sleep and arousal. Moreover, the hypothalamus contain another important structure in sleep function: the suprachiasmatic nucleus (SCN) which contains cells that receive information about light exposure and because of that controls the circadian rhythms.

Then, in communication with the hypothalamus in order to control wake/sleep transitions, we found the brain stem which includes three substructures: the pons, the medulla and the midbrain. Inside these two big communicating structures, sleep-promoting cells produce GABA, a brain chemical whose action is to reduce the activity of arousal centers of the above-mentioned regions. Moreover, the pons and the medulla more specifically take part into REM sleep by sending signals to relax muscles in order to ensure that the brain is the only part of the body that is highly activated during this period of vivid dreams.

Then comes the thalamus which sends sensory information to the cerebral cortex. The latter being the area of the brain that interprets and processes information from short- to long-term memory. Depending on the stages of sleep a person is into, the thalamus has a dual role. Indeed, it is rather quiet during most stages of sleep but switches to an active mode during REM sleep sending information to

the cortex, information that will fill our dreams.

Another structure promoting sleep is the basal forebrain unlike the midbrain which takes part in arousal functions. Cells of the basal forebrain release adenosine which supports sleep drive. Indeed, those who can't start the day without a large cup of black coffee, may know that caffeine counteracts sleepiness by blocking the actions of adenosine [Izac, 2006].

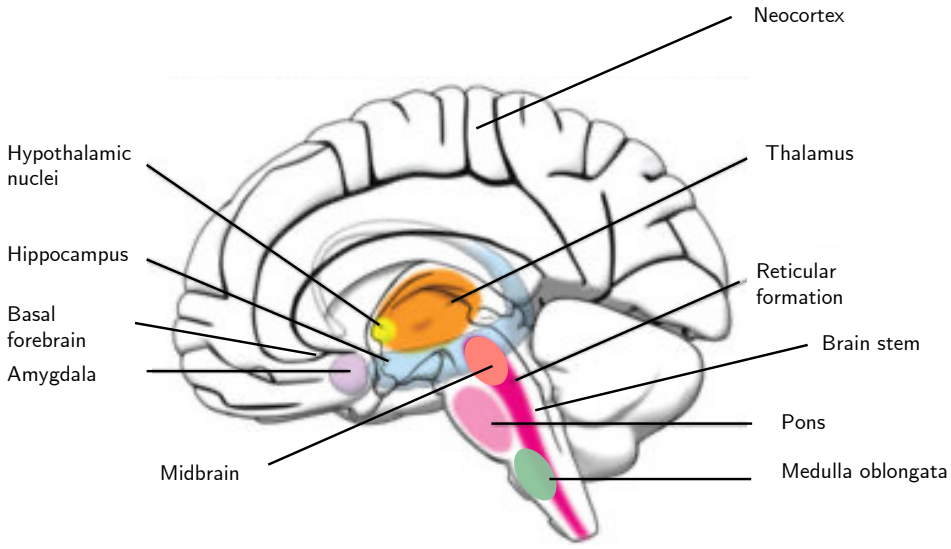


Figure A.2: *The anatomy of sleep.* Main structure that play a role in the transition from wakefulness to sleep. Adapted from [Krause et al., 2017]

A.3 Sleep and wake-promoting networks

- Wake-promoting circuits:
  - Cholinergic neurons: these are found in the pedunculopontine nucleus (PPN), a region of the pons, and the laterodorsal tegmental nucleus which is located in the brainstem. They project to the forebrain and innervate lots of important brain structures such as the prefrontral cortex (PFC) in addition to providing the main innervation from the mesopontine junction to the thalamic relay nuclei. In terms of electrical activity, cholinergic neurons see their firing rate increasing during wakefulness and REM sleep which has led to the hypothesis that those neurons would help driving cortical activation.
  - Monoaminergic neurons: these neurons include the noradrenergic neurons located in the locus coreuleus, the serotoninergic neurons of the dorsal and median raphe nuclei and the dopaminergic neurons close to the dorsal raphe nucleus. They are known to have axonal projections that target structures such as the lateral hypothalamus, the basal forebrain, the thalamus and the cerebral cortex where they terminate.
  - Glutaminergic neurons: they are also involved in the circuit associated to the awake state in which they send projections to the lateral hypothalamus, basal forebrain, and cerebral cortex.
  - Neurons producing orexin neuropeptides: they send abundant excitatory projections to the dorsal raphe nucleus, the locus coeruleus, and the tuberomammillary nucleus [Berry, 2012].

They are active during wakefulness (increased firing rate) and particularly during active exploration of the environment or during motivated behaviors. With this in mind, the roles that have been assigned to them are driving arousal from sleep, sustain wakefulness and suppress REM sleep.

  - GABAergic neurons: these neurons of the basal forebrain are also wake-active neurons which innervate and inhibit cortical GABAergic interneurons and deep layer pyramidal cells. They fire in bursts following specific EEG rhythms. When inactivated, deep NREM sleep is set on. Finally, GABAergic neurons of the reticular nucleus are known to inhibit thalamic relay neurons.

- NREM sleep-promoting network:
  - Neurons in the ventrolateral preoptic nucleus (VLPO): they innervate the histaminergic TMN. Their main role is to constitute a sleep-promoting pathway from the preoptic area that inhibits many arousal systems during sleep.
  - Neurons in the MnPO: neurons in the MnPO fire faster during sleep. More specifically, studies have shown that these neurons often fire in advance of sleep which has led some to speculate that these neurons may have a role in accumulating sleep pressure.

- REM sleep-promoting networks: they contain MCH neurons which are the exact opposite of the orexin ones, inhibiting the same targets during sleep that orexin neurons activate during wakefulness [Saper et al., 2010]

Appendix B

Neurophysiology basis

B.1 Synaptic plasticity: supplementary

Expression of long-term synaptic plasticity Both LTP and LTD expression involve transmitter release. The increase in synaptic strength, in LTP, is either due to more transmitter released from the presynaptic axons activated or the same amount of transmitter but having a greater effect on a more sensitive postsynaptic cell. One can note that the enhanced (or decreased) transmitter release that allows LTP (or LTD) is caused by synaptic transmission (see section ?) i.e. communication between the postsynaptic cell and the presynaptic terminals. This communication allows a rearrangement of the synaptic terminals and via the latter a modification of their function [Lüscher and Malenka, 2012].

Cascade of LTP induction involves two main actors:

- NMDARs: which need to open themselves in order to increase calcium concentration in the dendritic spine.

- calcium/calmodulin-dependent kinase II (CaMKII): which is activated by sufficiently high calcium concentration. CAMKII is found at very high concentration in dendritic spines and is a major contributor for LTP induction [Conti and Lisman, 2002].

Then, a certain number of proteins are phosphorylated including AMPARs. This phosphorylation of AMPAR subunits also take part in the LTP induction, at least in the early phase [Lüscher and Malenka, 2012] .

Properties of LTP and LTD Long-term plasticity is said to be:

- Associative: Associativity is a property shared by both LTP and memory. If a synapse is incapable of inducing LTP by its own (weak synapse), it can still succeed by associating with a strong synapse. Indeed, failure in the weak pathway is due to insufficient depolarization and so in failure to activate NMDARs. However, when there is this paring of the two synapses, NMDARs in the weak synapse are activated and LTP is induced. This associative property is maybe one of the most important because it serves as explanation for many forms of learning [Maren and Baudry, 1995].

- Cooperative: LTP can be induced by a sufficient tetanic stimulation of one pathway to a synapse or, if the stimulation is too weak, cooperatively, by the association of many synapses. Indeed,

when the stimulation is too weak, the postsynaptic depolarization that results from this stimulation is unable to induce LTP by itslef. However, when weak stimuli are applied to many pathways that lead to a single patch of postsynaptic membrane, the collection of all those individual postsynaptic depolarizations is able to induce LTP cooperatively.

- Specific: LTP is said to be input specific because once it is induced in one active synapse, it does not spread to other, inactive synapses that are in contact with the same neuron. It is therefore input specific in the sense that it is limited to activated synapses and not to the whole cell. Moreover, this property is coherent with the involvement of LTP in memory formation. Indeed, if even inactive synapses could be potentiated and lead to LTP, it would be difficult to selectively enhance particular sets of inputs which is required for learning and memory [Purves et al., 2001].

Other properties of long-term plasticity are: rapid induction, resistance to disruption once stabilized, ...[Maren and Baudry, 1995].

B.2 Conductance-based models

B.2.1 Theory

If we try to model the neuron, we quickly realise that it has characteristics quite similar to those of an RC type electrical circuit as can be seen on Figure B.1. Indeed, the impermeable bilayer of phospholipids that make up the cell membrane can be assimilated to a constant capacitance C_m, while the selectivity of each protein channel can be represented by a variable conductance g_i for each ion. Therefore, the fraction of open channels being assimilated to a variable conductance, Ohm's law allows us to write:

$$I_{ion} = g_{ion}(V_m - V_{ion}) \tag{B.1}$$

As mentioned, the cell membrane can be represented by a capacitance as it accumulates ions to its intracellular and extracellular sides. A capacitic current arises from changes in the distribution of charges which is defined as:

$$I_C = C\frac{dV_m}{dt} \tag{B.2}$$

where $\frac{dV_m}{dt}$ is the variation of the membrane potential per unit time.

Using Khirchhoff law and generalizing to a set of ionic currents, we obtain:

$$C\frac{dV_m}{dt} = -\sum_n g_{ion}(V_m - V_{ion}) + I_{app} \tag{B.3}$$

If we come back to the experiments of Hodgkin and Huxley on a giant squid axon, we obtain the following expression:

$$I_{ion} = I_K + I_{Na} + I_{leak} \tag{B.4}$$

in which they have identified that the ions necessary for the creation of action potentials in this axon are sodium Na^+ and potassium K^+ ions. Moreover, they have also added a term that takes into account non-specific leakage currents (through the recording electrodes in particular).

In order to establish equations for the conductances representing the transmembrane proteins, Hodgkin and Huxley performed a curve fitting. In other words, they established a certain form for their equations before choosing the parameters that best fit their experimental data. To do this, they assumed that for each ion, a maximum conductance can be reached when all channels are open. This conductance, denoted $\overline{g}_{ion}$, depends only on the density of channels at the membrane, and is therefore considered constant for a defined neuron. Considering then that these gates can have two states: open or closed and that the change from one state to the other is governed by well-defined time constants, the variations of the fraction of open channels can be described by the mass action law. This gives the following activation m and inactivation h variables and their time constant $\tau_{h,ion}$ and $\tau_{m,ion}$. Finally, the complete Hodgkin and Huxley model can be written as follows:

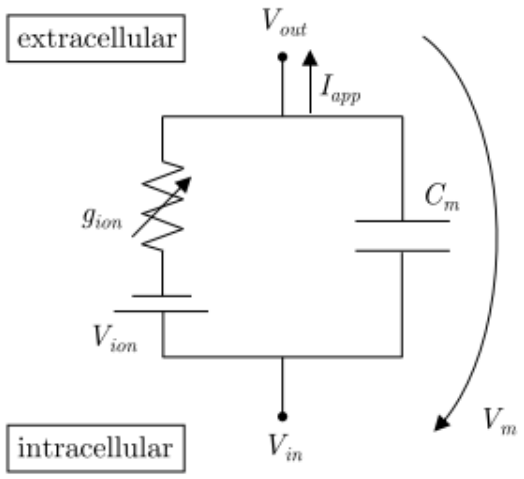


Figure B.1: *Neuronal membrane modeled as an RC circuit.* A capacitance C is representing the membrane, ion channels are modeled by a dynamic conductance g_{ion} and a Nernst potential V_{ion}. I_{app} is the applied current and the whole circuit has a potential equals to $V_m = V_{in} - V_{out}$ which represents the membrane potential [Jacquerie, 2017]

$$\begin{aligned} C\dot{V_m} &= \overline{g}_{Na} m_{Na}^3 h_{Na}(V_m - V_{Na}) - \overline{g}_K m_K^4 (V_m - V_K) - g_L(V_m - V_L) + I_{app} \\ \dot{m}_{Na} &= \frac{m_{Na,\infty}(V_m) - m_{Na}}{\tau_m N_m(V_m)} \\ \dot{h}_{Na} &= \frac{h_{Na,\infty}(V_m) - h_{Na}}{\tau_h N_m(V_m)} \\ \dot{m}_K &= \frac{m_{K,\infty}(V_m) - m_K}{\tau_{mK}(V_m)} \end{aligned} \tag{B.5}$$

B.2.2 Modeling in Julia

This section is taken from Caroline Minne's master thesis [Minne et al., 2021].

In order to use conductance models in our codes, we used Drion's model [Drion et al., 2018] using the Julia programming language:

$$C_m \dot{V}_m = -I_{Na} - I_K - I_{CaT} - I_{K,Ca} - I_H - I_{\text{leak}} + I_{app} \tag{B.6}$$

- $I_{\text{leak}} = \bar{g}_{\text{leak}} \, (V - V_{\text{leak}})$ is a leaky current,
- $I_{Na} = \bar{g}_{Na} m_{Na}^3 h_{Na} \, (V - V_{Na})$ is a transient sodium current,
- $I_{Ca,T} = \bar{g}_{Ca,T} m_{Ca,T}^3 h_{Ca,T} \, (V - V_{Ca})$ is a T-type calcium current,
- $I_{K,D} = \bar{g}_{K,D} m_{K,D}^4 \, (V - V_K)$ is a delayed-recctifier potassium current,
- $I_{K,Ca} = \bar{g}_{K,Ca} m_{K,Ca}([Ca]) \, (V - V_{Ca})$ is a calcium-activated potassium current,
- $I_H = \bar{g}_H m_H \, (V - V_H)$ is an hyperpolarisation-activated cation current,
- I_{app} an externally applied current.

where m represents activation variable and h inactivation variable. Based on that, we obtain the following equation:

$$\begin{aligned} C_m\dot{V}_m = &- \bar{g}_{Na}m_{Na}^3h_{Na}\,(V_m - V_{Na}) - \bar{g}_{K,D}m_{K,D}^4\,(V_m - V_K) - \bar{g}_{Ca,T}m_{Ca,T}^3h_{Ca,T}\,(V_m - V_{Ca}) \\ &- \bar{g}_{K,Ca}m_{K,Ca\infty}(Ca)\,(V_m - V_K) - \bar{g}_H m_H\,(V_m - V_H) - \bar{g}_{\text{leak}}\;(V_m - V_{\text{leak}}\,) + I_{\text{app}} \end{aligned} \tag{B.7}$$

For parameters values, see TABLE B.1

Model parameters			
C_m	1	g_L	0.055
V_{Na}	50	g_{Na}	170
V_K	-85	g_{Kd}	40
V_{Ca}	120	g_H	0.01
V_L	-55	$g_{K,Ca}$	4
V_H	20	$g_{Ca,T}$	0.55
K_d	170	$k1$	1e-1
		$k2$	0.1e-1

Table B.1: Conductance-based model parameters. LEFT. global parameters. RIGHT. cell parameters, identical for each cell of the ECI circuit. Potentials are in [mV], conductances in $[mS/cm^2]$ and capacitance in $[/cm^2]$

The activation (m) and inactivation (h) variables dynamics of the voltage-gated channels followed the dynamics describe in the equation just below:

$$m_{X,\infty} = \frac{1}{1+\exp((V+A)/B)} \quad \tau_X = A - \frac{B}{1+\exp((V+D)/E)} \tag{B.8}$$

Again, parameters value (here for the different channels) are summarised in a table:

Param.	A	B	Param.	A	B	D	E
$m_{Na,\infty}$	35.5	- 5.29	$\tau_{m_{Na}}$	1.32	1.26	120	-25
$h_{Na,\infty}$	48.9	5.18	$\tau_{h_{Na}}$	$(0.67/(1+exp((V+62.9)/-10.0)))*(1.5+1/(1+exp((V+34.9)/3.6)))$			
$m_{Kd,\infty}$	12.3	-11.8	$\tau_{m_{Kd}}$	.2	6.4	28.3	-19.2
$m_{CaT,\infty}$	67.1	-7.2	$\tau_{m_{CaT}}$	21.7	21.3	68.1	-20.5
$h_{CaT,\infty}$	80.1	5.5	$\tau_{h_{CaT}}$	410	179.6	55.	-16.9
$m_{H,\infty}$	80.	6.	τ_{m_H}	272.	-1149.	42.2	-8.73

Connection between cells of the 3 neurons circuit

Excitatory connection

$$I_{AMPA} = g_{AMPA} * s_{AMPA} * (V - 0) \tag{B.9}$$

where s_{AMPA} is a $AMPA$ gate whose dynamics depends on the presynaptic potential V_{Pre}:

$$\dot{s_{AMPA}} = 1.1\tau_m(V_{Pre}) * (1 - s_{AMPA}) - 0.19 * s_{AMPA}$$

Inhibitory connection connection

$$I_{GABA_A} = g_{GABA_A} * s_{GABA_A} * (V - V_{Cl}) \tag{B.10}$$

$$I_{GABA_B} = g_{GABA_B} * s_{GABA_B} * (V - V_K) \tag{B.11}$$

where s_{GABA_A} s_{GABA_B} are $GABA_{A,B}$ gates whose dynamics depend on the presynaptic potential V_{Pre}:

$$\dot{s_{GABA_A}} = 0.53\tau_m(V_{Pre}) * (1 - s_{GABA_A}) - 0.19 * s_{GABA_A}$$

$$\dot{s_{GABA_B}} = 0.016\tau_m(V_{Pre}) * (1 - s_{GABA_B}) - 0.0047 * s_{AMPA}$$

and

$$\tau_m(V_{Pre}) = \frac{1}{(1 + exp(-(V_{Pre} - 2)/5))}$$

Plasticity implementation In the ECI circuit, plasticity occurs between cell E and cell C and changes the AMPA conductance.

$$g_{EC} = g_{\bar{EC}} * w \tag{B.12}$$

where g_{EC} is g_{AMPA} between cell E and cell C and $g_{\bar{EC}}$ is a constant multiplied by the synaptic weight w [Minne et al., 2021].

B.3 Integrate and fire models

In addition to the conductance-based model, the integrate-and-fire neuron model is one of the most widely used to analyze the behavior of neural systems. This model is known to be simpler than its counterpart as it does not include changes associated with the membrane voltage and conductances driving the action potential. Rather, it uses synaptic inputs and the injected current a neuron receives to describe the membrane potential of the latter. In this model, an action potential or spike is "simply" modeled as the membrane reaching a threshold at a certain time defining action potential firing [Burkitt, 2006]. Indeed, this model uses the assumption that neuronal action potentials of a given neuron tend to have a fairly similar shape. Therefore, if the shape on an action potential is always the same, the form of the action potential cannot be the element that allows information to be transmitted. Instead, information is contained in the presence or absence of a spike and action potentials are seen as "events" that happen at a precise moment in time [Gerstner et al., 2014] .

The first time this model was mentioned was in 1907 when Lapicque decided to use its similarities with an electrical circuits to model the neuron membrane potential in terms of resistor in parallel with a capacitor by way of the leakage and capacitance of the membrane [Lapicque, 1907]. In this simple model, the membrane capacitor is charged. When it reaches a certain threshold, the capacitor discharges and in the mean time produces an action potential after which the membrane potential is reset. This section will be dedicated to the simplest integrate-and-fire model: the "leaky integrate-and-fire" model. This model possesses two fundamental characteristics: a linear differential equation to describe the evolution of the membrane potential and a threshold for spike firing [Gerstner et al., 2014].

The leaky integrate-and-fire model

As mentioned and as depicted in Figure B.2, the circuit of this model consists of a capacitor C in parallel with a resistor R driven by a current $I(t)$. If this current is set to zero, the voltage across the capacitor is given by the battery voltage u_{rest}. To analyze this circuit, we can use Kirchhoff law in order to obtain the following expression:

$$I(t) = I_R + I_C \tag{B.13}$$

I_R is the resistive current which passes through the linear resistor R and is given, using Ohm's law, by $I_R = \frac{u-u_{rest}}{R}$ while I_C is used to charge the capacitor C and is given by $I_C = C\frac{du}{dt}$. Thus, we can write:

$$I(t) = \frac{u(t) - u_{rest}}{R} + C\frac{du}{dt} \tag{B.14}$$

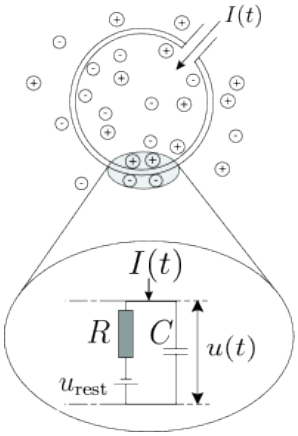


Figure B.2: *Neuron modeled by a leaky integrate-and-fire* The capacitance C represents the accumulation of charges across the membrane whereas R is a resistance that models the leakage of ions through the membrane. The membrane potential at rest is u_{rest} and the injected current is $I(t)$. [Kistler and RN, 2014]

Multiplying this equation by R and introducing the time constant of the "leaky-integrator" $\tau_m = RC$, we obtain:

$$\tau_m \frac{du}{dt} = -[u(t) - u_{rest}] + RI(t) \tag{B.15}$$

where u is the membrane potential and τ_m is the membrane time constant of the neuron.

Supposing that at time $t = 0$, the membrane potential takes the value $u_{rest} + \Delta u$. For $t > 0$, the input takes the value $I(t) = 0$. Intuitively, we expect that, if we wait long enough, the membrane potential relaxes to its resting value u_{rest}. Indeed, the solution of the differential equation with initial condition $u(t_0) = u_{rest} + u$ is [Gerstner et al., 2014]

$$u(t) - u_{rest} = \Delta u exp(-\frac{t - t_0}{\tau_m} \text{ for} t > t_0. \tag{B.16}$$

Appendix C

Modeling neurophysiology and synaptic plasticity

C.1 Phenomenological models

C.1.1 Rate-based model

The BCM model

The BCM model is another example of a rate-based model in which both LTP and LTD regions can be found. These regions are separated by a threshold which can move back an forth to overcome problems of positive feedback (Bienenstock et al., 1982). In more details, in 1982, Elie Bienenstock, Leon Cooper, and Paul Munro have proposed a theory of synaptic modification with the aim of taking into account "experiments measuring the selectivity of neurons in primary sensory cortex and its dependency on neuronal input" [Blais and Cooper, 2008]. To achieve this goal, this theory defines a synaptic change in the Hebbian manner as the product of a the presynaptic activity and a nonlinear function of postsynaptic activity to avoid stability issues:

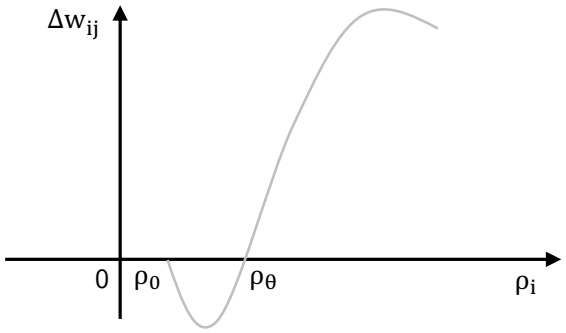


Figure C.1: *Illustration of the BCM synaptic modification rule.* Adapted from[Blais and Cooper, 2008]

$$\frac{d}{dt}w_{ij} = \phi(\rho_i - \rho_\theta)\rho_j$$

where ρ_θ is the above mentioned threshold.

For low (resp. high) values of the postsynaptic activity i.e. $\rho_i < \rho_\theta$ (resp, $\rho_i > \rho_\theta$) the efficiency of synapses actived by the presynaptic neuron is decreased (resp. increased) i.e. $\phi < 0$ (resp. $\phi > 0$).

The BCM Synaptic Modification Rule. y denotes the output activity of the neuron, M is the modification threshold.

C.1.2 Frequency-based model

Triplet model

Another model that can be used to depict synaptic plasticity is a model based on sets of three spikes (one pre and two post) hence the name "Triplet model". This model aims at correcting errors that could be encountered with the pair-based rule. The first error that could be corrected for using triplet model is the dependence on the repetition frequency of the pairs of spike. Indeed, pair-wise interaction between spikes would predict that 60 repetitions of pre-post pairings (e.g. presynaptic spikes 10 ms before postsynaptic ones) give the same result independent of whether the pairing is repeated at 1 Hz or 5Hz. At frequencies above 25 Hz, a pair-wise interaction model would predict a reduced potentiation, since in addition to the pre-post pair at 10 ms virtual post-pre pairs at 30 ms are created - that should lead to depression. However, in experiments the opposite is observed [Sjöström et al., 2001b]. This triplet model could therefore also be used to represent triplet and quadruplet experiments as well as fitting experimental data from visual cortical slices and hippocampal cultures. Finally, if a stochastic train of spikes is assumed, the triplet rule can be mapped to a BCM rule [Pfister and Gerstner, 2006].

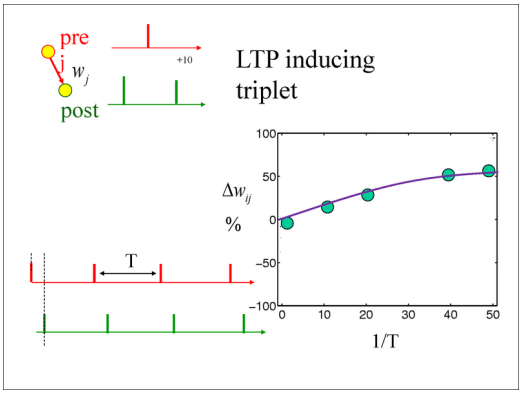


Figure C.2: *Illustration of triplet model* Unlike the pair-based model, the building block of LTP is not a pair but as the name "triplet" implies a combination of one pre and two postsynaptic spikes. A number of those triplets is repeated during at different time intervals T in order to draw the amount of LTP as a function of the repetition frequency $1/T$ [Sjöström and Gerstner, 2010].

One of the difference between the triplet and the pair-based model is in the building block of potentiation: in pair-based models the building block is made of one presynaptic spike and one postsynaptic spike whereas in the triplet model the block is constituted by one presynaptic spike and two postsynaptic spikes [Sjöström and Gerstner, 2010].

Formally, we try to depict the fact that when a presynaptic spike arrives at an excitatory synapse, glutamate is released into the synaptic cleft and bind to glutamate receptors. Therefore, r_1, which is an abstract variable that increases by one unit after spike arrival, will denote the amount of glutamate bound to a postsynaptic receptor. The latter increases when there is a presynaptic spike and decreases back to zero otherwise with a time constant of τ_+ whose situation corresponds to the first of the following equation. One can note that the r_1 variable could describe other quantity than glutamate that increase increases after presynaptic spike arrival giving this variable the name "detector of presynaptic events".

$$\frac{dr_1(t)}{dt} = -\frac{r1(t)}{\tau_+} \text{ if} t = t^{pre}\ r_1 \rightarrow r_1 + 1.$$
$$\frac{dr_2(t)}{dt} = -\frac{r2(t)}{\tau_x} \text{ if} t = t^{pre}\ r_2 \rightarrow r_2 + 1.$$
$$\frac{do_1(t)}{dt} = -\frac{o1(t)}{\tau_-} \text{ if} t = t^{post}\ o_1 \rightarrow o_1 + 1.$$
$$\frac{do_2(t)}{dt} = -\frac{o2(t)}{\tau_y} \text{ if} t = t^{post}\ o_2 \rightarrow o_2 + 1.$$

As one can note, instead of only using one equation to describe one presynaptic event, it is possible to consider several different quantities, which increase in the presence of a presynaptic spike. In this model, two different detectors of presynaptic events are considered: r_1 and r_2 where the time constant of the latter is larger than the one of the former i.e. $\tau_x > \tau_+$. Another assumption that is made is that each postsynaptic spike t_{post} induces an increase of two different quantities o_1 and o_2. In the absence of postsynaptic spiking, these postsynaptic detectors decrease their value with a time constant τ_- and τ_y, respectively.

After presynaptic spike arrival, the weight decreases by an amount proportional to the value of o_1 which is the postsynaptic variable but it is also dependent of the second presynaptic detector r_2. Knowing that, the change triggered by the presynaptic spike arrival at time t_{pre} is modeled by the following equations:

$$w(t) \rightarrow w(t) - o_1(t)[A_2^- + A_3^- r_2(t - \epsilon)] \text{ if} t = t^{pre}.$$
$$w(t) \rightarrow w(t) + r_1(t)[A_2^+ + A_3^+ o_2(t - \epsilon)] \text{ if} t = t^{post}.$$

where A_2^+ and A_2^- represent the amplitude of the weight change each time there is a pre-post pair or a post-pre pair. In the same way, A_3^+ and A_3^- denote the amplitude of the triplet term for potentiation and for depression. All amplitude parameters are greater or equal to zero. Finally, ϵ allows to ensure that r_2 is zero except if a presynaptic spike has led to an increase of r_2 [Sjöström and Gerstner, 2010].

C.1.3 Three-factor rule

Recently, in the field of synaptic plasticity modeling, mechanisms that could explain how the different timescales of spikes and neuromodulation fit together have gathered lots of interest. Indeed, different scenarios have begun to emerge in which neuromodulator release occurs after the pre-post activity which is called "unexpected reward case". The learning of attention-based scenario takes into account that the neuromodulatory receptors are activated before the coordinated pre-post activity occurs. Finally, the last scenario considers that the pre-post activity patterns "reverbate" in the local circuit for a certain amount of time during which a memory trace can be induced and transduced into a modification which aims to last if a third factor (such as neuromodulators) is present during this reverbation [Pawlak, 2010].

Then, in 2016, Nicolas Fremaux and Wulfram Gerstner further developed this idea of including a third factor into the "classical" Hebbian plasticity rule. Thus, a synaptic plasticity rule which is influenced by one or several neuromodulators will be called a "three-factor rule". In a rather abstract and general way, such a rule can be written as follows:

$$\dot{w} = F(M, \text{pre}, \text{post}) \tag{C.1}$$

in which $\dot{w}$ translates the rate at which the synaptic weight changes from a pre- to a postsynaptic neuron while M is the third factor.

Most of the time, the variable M is defined as being a global factor of the synaptic update rule compared to the variables that we call "pre" and "postsynaptic" factor which represent the spike train of the pre- and the state of the postsynaptic neuron and are considered as being local factors as the information which passes from a presynaptic to a postsynaptic terminal are available at the synapse connecting the two neurons (but not at other synapses). Indeed, if M tries for example to represent an addition of neuromodulation to this synaptic rule, we know that the information it will convey will be available to many neurons and synapses in parallel [**?**]. F for its part, is a function that specifies the exact type of learning rule used in the model. It is still difficult to find an appropriate function F to match with the experimental data[Fremaux, 2016]. However, candidate functions have been proposed to play the role of F as the following expression:

$$\dot{w} = F(M, \text{pre}, \text{post}) = g_1(M) * F_1(\text{pre}, \text{post}) \tag{C.2}$$

where $g_1(M)$ is a modulator function that multiplies the "Hebb-like" term $F_1(\text{pre}, \text{post}.$

Or we can also use a rule in which the neuromodulator is directly able to change the postsynaptic activity:

$$\dot{w} = F(M, \text{pre}, \text{post}) = F_2(\text{pre}, \text{post(M)}). \tag{C.3}$$

Many other options can still be imagined and will undoubtedly be over the years.

Then, in 2018, Foncelle et al. also decided to studied the impact of a third factor in synaptic plasticity rules and particularly in computational models of synaptic activity. Like others before them, they refer to the rule with the inclusion of a third factor (for example neuromodulators but they have also studied the effect of astrocytes) as "neo-Hebbian" plasticity [Foncelle et al., 2018].

Appendix D

Circuit

"The membrane voltage of the different neurons is defined the following way:

- The inhibitory neuron (I): $C_m \frac{dV_I}{dt} = -\sum_i I_i + I_{app,I}$
- The presynaptic neuron (E): $C_m \frac{dV_E}{dt} = -\sum_i I_i + I_{app,E} + I_{GABA_A}(V_I) + I_{GABA_B}(V_c, V_I)$
- The postsynaptic neuron (C): $C_m \frac{dV_c}{dt} = -\sum_i I_i + I_{app,C} + I_{GABA_A}(V_m, V_I) + I_{GABA_B}(V_m, V_I) + I_{AMPA}(V_m, V_E)$

where $AMPA$ synapse provides an excitatory current and $GABA$ an inhibitory one. They are modeled the following way:

$$\begin{aligned} I_{AMPA} &= \bar{g}_{AMPA} s_{AMPA}(V_{pre})(V_m - 0) \\ I_{GABA_A} &= \bar{g}_{GABA_A} s_{GABA_A}(V_{pre})(V_m - ECl) \\ I_{GABA_B}(V_I) &= \bar{g}_{GABA_B} s_{GABA_B}(V_{pre})(V_m - E_K) \end{aligned} \tag{D.1}$$

where $\bar{g}_{AMPA}$, $\bar{g}_{GABA_A}$ and $\bar{g}_{GABA_B}$ are the synaptic conductances. $AMPA$ receptor reversal potential is set to 0mV, $GABA_A$ receptor reversal potential is set to chloride reversal potential ($E_{Cl} = -70mV$) and $GABA_B$receptor reversal potential is set to potassium reversal potential ($E_K = -85mV$). Finally, gating variables of the synapses s_{AMPA}, s_{GABA_A}ands_{GABA_B} have a dynamic that depends on the presynaptic membrane potential V that we consider for each variable meaning:

- $\dot{s}_{AMPA}(V) = 1.1 T_m(V)(1 - s_{AMPA}) - 0.19 s_{AMPA}$
- $\dot{s}_G ABA_A(V) = 0.53 T_m(V)(1 - s_{GABA_A}) - 0.18 s_{GABA_A}$
- $\dot{s}_G ABA_B(V) = 0.016 T_m(V)(1 - \dot{s}_{GABA_A}) - 0.0047 s_{GABA_A}$

where $T_m(V) = \frac{1}{1+exp[-(V-2)/5]}$ [Destexhe et al., 1994]. Numerical values (1.1, 0.19, 0.53, 0.18, 0.016 and 0.0047) also originate from [Destexhe et al., 1994] and are set to these specific values to mimic the kinetics of the synaptic receptors in order that the smallest they are, the slowest the kinetics. Synaptic conductances, for their part, are chosen in order that the 3-cell circuit is allowed to perform a rhytmic transition when the inhibitory cell is hyperpolarized. Indeed, the latter is the conductor: when a tonic rhythm puts is applied to cell I, cell E and cell C are put in a resting state. If the latter are depolarized, they generate a tonic activity while a burst in the inhibitory neuron drives the whole circuit in bursting mode. Therefore, this switch between tonic and burst activity is obtained by hyperpolarizing cell I."[Jacquerie et al., 2022]

Appendix E

Supplementary results

E.1 Demonstration of homeostatic reset

E.1.1 Soft bounds

Iapp	I = - 4.7	I = - 4.6	I = - 4.5	I = - 4.4	I = - 4.3	I = - 4.2	I = - 4.1	I = - 4
w(demo)	0.8182	0.7311	0.8055	0.8099	0.8112	0.6610	0.5923	0.2725
w(demo)	0.8142	0.7304	0.8038	0.8100	0.8097	0.6614	0.6658	0.2831
w(simulation)	0.8186	0.7297	0.8060	0.8120	0.8118	0.6578	0.6702	0.2713

Table E.1

E.2 Modulation of magnitude window

E.2.1 Parameters value

Parameters	Magnitude modulation
A_+	0.0096
A_-	0.0053
$A_{+STRONG}$	3*A_+
A_{+WEAK}	0.1*A_+
$A_{-STRONG}$	6*A_+
A_{-WEAK}	0.1*A_-
τ_+	16.8
τ_-	33.7

Parameters	Magnitude modulation
A_+	0.0096
A_-	0.0053
$A_{+STRONG}$	3*A_+
A_{+WEAK}	0*A_+
$A_{-STRONG}$	6*A_+
A_{-WEAK}	0*A_-
τ_+	16.8
τ_-	33.7

Bibliography

[tea,] The cerebrum.

[Abbott and Nelson, 2000] Abbott, L. F. and Nelson, S. B. (2000). Synaptic plasticity: taming the beast. *Nature Neuroscience*, 3(S11):1178–1183.

[Abraham and Williams, 2003] Abraham, W. C. and Williams, J. M. (2003). Properties and mechanisms of ltp maintenance. *The Neuroscientist*, 9(6):463–474.

[AbuHasan et al., 2021] AbuHasan, Q., Reddy, V., and Siddiqui, W. (2021). Neuroanatomy, amygdala. In *StatPearls [Internet]*. StatPearls Publishing.

[Ahumada et al., 2013] Ahumada, J., de Sevilla, D. F., Couve, A., Buño, W., and Fuenzalida, M. (2013). Long-term depression of inhibitory synaptic transmission induced by spike-timing dependent plasticity requires coactivation of endocannabinoid and muscarinic receptors. *Hippocampus*, 23(12):1439–1452.

[Allen et al., 2018] Allen, M. J., Sabir, S., and Sharma, S. (2018). Gaba receptor.

[Anand and Dhikav, 2012] Anand, K. S. and Dhikav, V. (2012). Hippocampus in health and disease: An overview. *Annals of Indian Academy of Neurology*, 15(4):239.

[Ang et al., 2021] Ang, G. W. Y., Tang, C. S., Hay, Y. A., Zannone, S., Paulsen, O., and Clopath, C. (2021). The functional role of sequentially neuromodulated synaptic plasticity in behavioural learning. *PLoS Computational Biology*, 17(6):e1009017.

[Avery and Krichmar, 2017] Avery, M. C. and Krichmar, J. L. (2017). Neuromodulatory Systems and Their Interactions: A Review of Models, Theories, and Experiments. *Frontiers in Neural Circuits*, 11.

[Babadi and Abbott, 2016] Babadi, B. and Abbott, L. F. (2016). Stability and Competition in Multi-spike Models of Spike-Timing Dependent Plasticity. *PLoS Computational Biology*, 12(3).

[Barbour et al., 2007] Barbour, B., Brunel, N., Hakim, V., and Nadal, J.-P. (2007). What can we learn from synaptic weight distributions? *TRENDS in Neurosciences*, 30(12):622–629.

[Bear et al., 2016] Bear, M. F., Connors, B. W., and Paradiso, M. A. (2016). *Neuroscience: exploring the brain*. Philadelphia. Issue: International Edition.

[Bear and Malenka, 1994] Bear, M. F. and Malenka, R. C. (1994). Synaptic plasticity: Ltp and ltd. *Current opinion in neurobiology*, 4(3):389–399.

[Berry, 2012] Berry, R. B. (2012). Neurobiology of Sleep. *Fundamentals of Sleep Medicine*, pages 91–100.

[Bi and Poo, 1998] Bi, G.-q. and Poo, M.-m. (1998). Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *Journal of neuroscience*, 18(24):10464–10472.

[Bi and Poo, 2001] Bi, G.-q. and Poo, M.-m. (2001). Synaptic Modification by Correlated Activity: Hebb's Postulate Revisited. *Annual Review of Neuroscience*, 24(1):139–166.

[Bissière et al., 2003] Bissière, S., Humeau, Y., and Lüthi, A. (2003). Dopamine gates ltp induction in lateral amygdala by suppressing feedforward inhibition. *Nature neuroscience*, 6(6):587–592.

[Blais and Cooper, 2008] Blais, B. S. and Cooper, L. (2008). Bcm theory. *Scholarpedia*, 3(3):1570.

[Breton-Provencher et al., 2021] Breton-Provencher, V., Drummond, G. T., and Sur, M. (2021). Locus coeruleus norepinephrine in learned behavior: anatomical modularity and spatiotemporal integration in targets. *Frontiers in Neural Circuits*, 15.

[Brzosko et al., 2019] Brzosko, Z., Mierau, S. B., and Paulsen, O. (2019). Neuromodulation of Spike-Timing-Dependent Plasticity: Past, Present, and Future. *Neuron*, 103(4):563–581.

[Brzosko et al., 2015] Brzosko, Z., Schultz, W., and Paulsen, O. (2015). Retroactive modulation of spike timing-dependent plasticity by dopamine. *eLife*, 4:e09685.

[Brzosko et al., 2017] Brzosko, Z., Zannone, S., Schultz, W., Clopath, C., and Paulsen, O. (2017). Sequential neuromodulation of Hebbian plasticity offers mechanism for effective reward-based navigation. *eLife*, 6:e27756.

[Burkitt, 2006] Burkitt, A. N. (2006). A review of the integrate-and-fire neuron model: I. homogeneous synaptic input. *Biological cybernetics*, 95(1):1–19.

[C. Hanlon et al., 2011] C. Hanlon, E., V. Vyazovskiy, V., Faraguna, U., Tononi, G., and Cirelli, C. (2011). Synaptic Potentiation and Sleep Need: Clues from Molecular and Electrophysiological Studies. *Current Topics in Medicinal Chemistry*, 11(19):2472–2482.

[Cherubini et al., 1991] Cherubini, E., Gaiarsa, J. L., and Ben-Ari, Y. (1991). GABA: an excitatory transmitter in early postnatal life. *Trends in Neurosciences*, 14(12):515–519.

[Chua et al., 2010] Chua, J. J. E., Kindler, S., Boyken, J., and Jahn, R. (2010). The architecture of an excitatory synapse. *Journal of Cell Science*, 123(6):819–823.

[Citri and Malenka, 2008] Citri, A. and Malenka, R. C. (2008). Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharmacology*, 33(1):18–41.

[Conti and Lisman, 2002] Conti, R. and Lisman, J. (2002). A large sustained ca2+ elevation occurs in unstimulated spines during the ltp pairing protocol but does not change synaptic strength. *Hippocampus*, 12(5):667–679.

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

[Craig et al., 2015] Craig, T. J., Edelman, J. M., Feuersenger, H., Frank, M. M., Rojavin, M., Shapiro, R., Vegh, A. B., and Wuillemin, W. A. (2015). Efficacy and safety of a c1 esterase inhibitor concentrate for long-term prophylaxis in hereditary angioedema: Findings from a large international registry. *Journal of Allergy and Clinical Immunology*, 135(2):AB193.

[Destexhe et al., 1994] Destexhe, A., Mainen, Z. F., and Sejnowski, T. J. (1994). Synthesis of models for excitable membranes, synaptic transmission and neuromodulation using a common kinetic formalism. *Journal of computational neuroscience*, 1(3):195–230.

[Destexhe and Sejnowski, 2002] Destexhe, A. and Sejnowski, T. J. (2002). The initiation of bursts in thalamic neurons and the cortical control of thalamic sensitivity. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 357(1428):1649–1657.

[Diekelmann and Born, 2010] Diekelmann, S. and Born, J. (2010). The memory function of sleep. *Nature Reviews Neuroscience*, 11(2):114–126.

[Drion et al., 2018] Drion, G., Dethier, J., Franci, A., and Sepulchre, R. (2018). Switchable slow cellular conductances determine robustness and tunability of network states. *PLoS Computational Biology*, 14(4):1–20.

[Edelmann and Lessmann, 2011] Edelmann, E. and Lessmann, V. (2011). Dopamine modulates spike timing-dependent plasticity and action potential properties in ca1 pyramidal neurons of acute rat hippocampal slices. *Frontiers in synaptic neuroscience*, 3:6.

[Edelmann and Lessmann, 2013] Edelmann, E. and Lessmann, V. (2013). Dopamine regulates intrinsic excitability thereby gating successful induction of spike timing-dependent plasticity in ca1 of the hippocampus. *Frontiers in neuroscience*, 7:25.

[Feld and Born, 2020] Feld, G. B. and Born, J. (2020). Neurochemical mechanisms for memory processing during sleep: basic findings in humans and neuropsychiatric implications. *Neuropsychopharmacology*, 45(1):31–44.

[Feldman, 2012] Feldman, D. E. (2012). The spike-timing dependence of plasticity. *Neuron*, 75(4):556–571.

[Fink et al., 2013] Fink, C. G., Murphy, G. G., Zochowski, M., and Booth, V. (2013). A dynamical role for acetylcholine in synaptic renormalization. *PLoS computational biology*, 9(3):e1002939.

[Fino et al., 2010] Fino, E., Paille, V., Cui, Y., Morera-Herreras, T., Deniau, J.-M., and Venance, L. (2010). Distinct coincidence detectors govern the corticostriatal spike timing-dependent plasticity. *The Journal of physiology*, 588(16):3045–3062.

[Foncelle et al., 2018] Foncelle, A., Mendes, A., Jędrzejewska-Szmek, J., Valtcheva, S., Berry, H., Blackwell, K. T., and Venance, L. (2018). Modulation of spike-timing dependent plasticity: Towards the inclusion of a third factor in computational models. *Frontiers in Computational Neuroscience*, 12(July):1–21.

[Franceschetti et al., 1995] Franceschetti, S., Guatteo, E., Panzica, F., Sancini, G., Wanke, E., and Avanzini, G. (1995). Ionic mechanisms underlying burst firing in pyramidal neurons: intracellular study in rat sensorimotor cortex. *Brain research*, 696(1-2):127–139.

[Frey and Morris, 1997] Frey, U. and Morris, R. G. (1997). Synaptic tagging and long-term potentiation. *Nature*, 385(6616):533–536.

[Frohlich, 2016] Frohlich, F. (2016). *Network neuroscience*. Academic Press.

[Frémaux and Gerstner, 2015] Frémaux, N. and Gerstner, W. (2015). Neuromodulated spike-timing-dependent plasticity, and theory of three-factor learning rules. *Frontiers in Neural Circuits*, 9(JAN2016).

[Fuenzalida et al., 2021] Fuenzalida, M., Chiu, C. Q., and Chávez, A. E. (2021). Muscarinic Regulation of Spike Timing Dependent Synaptic Plasticity in the Hippocampus. *Neuroscience*, 456:50–59.

[Gautier-Sauvigné et al., 2005] Gautier-Sauvigné, S., Colas, D., Parmantier, P., Clement, P., Gharib, A., Sarda, N., and Cespuglio, R. (2005). Nitric oxide and sleep. *Sleep medicine reviews*, 9(2):101–113.

[Gerstner et al., 2014] Gerstner, W., Kistler, W. M., Naud, R., and Paninski, L. (2014). *Neuronal dynamics: From single neurons to networks and models of cognition*. Cambridge University Press.

[Gerstner et al., 2018] Gerstner, W., Lehmann, M., Liakoni, V., Corneil, D., and Brea, J. (2018). Eligibility Traces and Plasticity on Behavioral Time Scales: Experimental Support of NeoHebbian Three-Factor Learning Rules. *Frontiers in Neural Circuits*, 12(July):1–16.

[Gerstner and Toyoizumi,] Gerstner, W. and Toyoizumi, T. Unimodal or bimodal distribution of synaptic weights?

[González-Rueda et al., 2018] González-Rueda, A., Pedrosa, V., Feord, R. C., Clopath, C., and Paulsen, O. (2018). Activity-Dependent Downscaling of Subthreshold Synaptic Inputs during Slow-Wave-Sleep-like Activity In Vivo. *Neuron*, 97(6):1244–1252.e5.

[Goriounova and Mansvelder, 2012] Goriounova, N. A. and Mansvelder, H. D. (2012). Short-and long-term consequences of nicotine exposure during adolescence for prefrontal cortex neuronal network function. *Cold Spring Harbor perspectives in medicine*, 2(12):a012120.

[Graupner, 2017] Graupner, M. (2017). Synaptic Plasticity : Spike-timing dependent plasticity (STDP) Synaptic Plasticity : Spike-timing dependent plasticity (STDP).

[Graupner et al., 2016] Graupner, M., Wallisch, P., and Ostojic, S. (2016). Natural Firing Patterns Imply Low Sensitivity of Synaptic Plasticity to Spike Timing Compared with Firing Rate. *The Journal of Neuroscience*, 36(44):11238–11258.

[Graves, 2001] Graves, L. (2001). Sleep and memory: a molecular perspective. *Trends in Neurosciences*, 24(4):237–243.

[Gu, 2002] Gu, Q. (2002). Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. *Neuroscience*, 111(4):815–835.

[Gütig et al., 2003] Gütig, R., Aharonov, R., Rotter, S., and Sompolinsky, H. (2003). Learning Input Correlations through Nonlinear Temporally Asymmetric Hebbian Plasticity. *The Journal of Neuroscience*, 23(9):3697–3714.

[Hebb, 1949a] Hebb, D. O. (1949a). *The organization of behavior : a neuropsychological theory*. A Wiley book in clinical psychology. John Wiley, New York, NY.

[Hebb, 1949b] Hebb, D. O. (1949b). The organization of behavior; a neuropsycholocigal theory. *A Wiley Book in Clinical Psychology*, 62:78.

[Heidelberger et al., 2014] Heidelberger, R., Shouval, H., Zucker, R. S., and Byrne, J. H. (2014). Synaptic Plasticity. In *From Molecules to Networks: An Introduction to Cellular and Molecular Neuroscience: Third Edition*, pages 533–561. Elsevier Inc.

[Herz and Atherton, 1992] Herz, J. M. and Atherton, S. J. (1992). Steric factors limit access to the noncompetitive inhibitor site of the nicotinic acetylcholine receptor. fluorescence studies. *Biophysical Journal*, 62(1):74.

[Ho et al., 2011] Ho, V. M., Lee, J.-A., and Martin, K. C. (2011). The cell biology of synaptic plasticity. *Science*, 334(6056):623–628.

[Hollmann and Heinemann, 1994] Hollmann, M. and Heinemann, S. (1994). Cloned glutamate receptors. *Annual Review of Neuroscience*, 17(1):31–108. PMID: 8210177.

[Huang and Reichardt, 2001] Huang, E. J. and Reichardt, L. F. (2001). Neurotrophins: roles in neuronal development and function. *Annual review of neuroscience*, 24:677.

[Huang et al., 2019] Huang, K. W., Ochandarena, N. E., Philson, A. C., Hyun, M., Birnbaum, J. E., Cicconet, M., and Sabatini, B. L. (2019). Molecular and anatomical organization of the dorsal raphe nucleus. *Elife*, 8:e46464.

[Huang et al., 2014] Huang, S., Rozas, C., Trevino, M., Contreras, J., Yang, S., Song, L., Yoshioka, T., Lee, H.-K., and Kirkwood, A. (2014). Associative hebbian synaptic plasticity in primate visual cortex. *Journal of Neuroscience*, 34(22):7575–7579.

[Hull, 1943] Hull, C. L. (1943). Principles of behavior: An introduction to behavior theory.

[Izac, 2006] Izac, M. S. M. (2006). Basic anatomy and physiology of sleep. *American journal of electroneurodiagnostic technology*, 46(1):18–38.

[Izhikevich, 2007] Izhikevich, E. M. (2007). Solving the distal reward problem through linkage of stdp and dopamine signaling. *Cerebral cortex*, 17(10):2443–2452.

[Jacquerie, 2017] Jacquerie, K. (2017). Sensitivity and robustness analysis of thalamic neuron models at the cellular and network levels.

[Jacquerie et al., 2022] Jacquerie, K., Minne, C., and Drion, G. (2022). Synaptic plasticity, neuronal excitability and neuromodulation: are they compatible from a computational approach? page Unpublished Manuscript.

[Jawabri and Sharma, 2021] Jawabri, K. H. and Sharma, S. (2021). Physiology, cerebral cortex functions. In *StatPearls [internet]*. StatPearls Publishing.

[Kandel et al., 2015] Kandel, E. R., Dudai, Y., and Mayford, M. R. (2015). *Learning and memory*. The Weizmann Institute of Science.

[Kantamneni, 2015] Kantamneni, S. (2015). Cross-talk and regulation between glutamate and gabab receptors. *Frontiers in Cellular Neuroscience*, 9.

[Kim et al., 2020] Kim, H. R., Xu, J., Maeda, S., Duc, N. M., Ahn, D., Du, Y., and Chung, K. Y. (2020). Structural mechanism underlying primary and secondary coupling between gpcrs and the gi/o family. *Nature communications*, 11(1):1–12.

[Kistler and RN, 2014] Kistler, W. G. W. M. and RN, P. (2014). L.: Neuronal dynamics.

[Klinzing et al., 2019a] Klinzing, J. G., Niethard, N., and Born, J. (2019a). Mechanisms of systems memory consolidation during sleep. *Nature neuroscience*, 22(10):1598–1610.

[Klinzing et al., 2019b] Klinzing, J. G., Niethard, N., and Born, J. (2019b). Mechanisms of systems memory consolidation during sleep. *Nature Neuroscience*, 22(October). Publisher: Springer US.

[Krause et al., 2017] Krause, A. J., Simon, E. B., Mander, B. A., Greer, S. M., Saletin, J. M., Goldstein-Piekarski, A. N., and Walker, M. P. (2017). The sleep-deprived human brain. *Nature Reviews Neuroscience*, 18(7):404–418.

[Krueger et al., 2016] Krueger, J. M., Frank, M. G., Wisor, J. P., and Roy, S. (2016). Sleep function: Toward elucidating an enigma. *Sleep Medicine Reviews*, 28:46–54. Publisher: Elsevier Ltd.

[Kudlak and Tadi, 2021] Kudlak, M. and Tadi, P. (2021). Physiology, muscarinic receptor. In *StatPearls [Internet]*. StatPearls Publishing.

[Lakna, 2019] Lakna (2019). What is the difference between neurotransmitter and neuromodulator.

[Lanciego et al., 2012] Lanciego, J. L., Luquin, N., and Obeso, J. A. (2012). Functional neuroanatomy of the basal ganglia. *Cold Spring Harbor perspectives in medicine*, 2(12):a009621.

[Lapicque, 1907] Lapicque, L. (1907). Louis lapicque. *J. physiol*, 9:620–635.

[Legenstein and Maass, 2005] Legenstein, R. and Maass, W. (2005). A criterion for the convergence of learning with spike timing dependent plasticity. *Advances in Neural Information Processing Systems*, 18.

[Legenstein et al., 2008] Legenstein, R., Pecevski, D., and Maass, W. (2008). A learning theory for reward-modulated spike-timing-dependent plasticity with application to biofeedback. *PLoS computational biology*, 4(10):e1000180.

[Lin et al., 2003] Lin, Y.-W., Min, M.-Y., Chiu, T.-H., and Yang, H.-W. (2003). Enhancement of Associative Long-Term Potentiation by Activation of -Adrenergic Receptors at CA1 Synapses in Rat Hippocampal Slices. *Journal of Neuroscience*, 23(10):4173–4181. Publisher: Society for Neuroscience _eprint: https://www.jneurosci.org/content/23/10/4173.full.pdf.

[Lisman et al., 2011] Lisman, J., Grace, A. A., and Duzel, E. (2011). A neohebbian framework for episodic memory; role of dopamine-dependent late ltp. *Trends in neurosciences*, 34(10):536–547.

[Liu and Buonomano, 2009] Liu, J. K. and Buonomano, D. V. (2009). Embedding multiple trajectories in simulated recurrent neural networks in a self-organizing manner. *Journal of Neuroscience*, 29(42):13172–13181.

[Liu et al., 2010] Liu, Q., Trotter, J., Zhang, J., Peters, M. M., Cheng, H., Bao, J., Han, X., Weeber, E. J., and Bu, G. (2010). Neuronal lrp1 knockout in adult mice leads to impaired brain lipid metabolism and progressive, age-dependent synapse loss and neurodegeneration. *Journal of Neuroscience*, 30(50):17068–17078.

[Lu et al., 2014] Lu, B., Nagappan, G., and Lu, Y. (2014). Bdnf and synaptic plasticity, cognitive function, and dysfunction. *Neurotrophic factors*, pages 223–250.

[Lüscher and Malenka, 2012] Lüscher, C. and Malenka, R. C. (2012). Nmda receptor-dependent long-term potentiation and long-term depression (ltp/ltd). *Cold Spring Harbor perspectives in biology*, 4(6):a005710.

[Lüthi, 2014] Lüthi, A. (2014). Sleep spindles: where they come from, what they do. *The Neuroscientist*, 20(3):243–256.

[Maren and Baudry, 1995] Maren, S. and Baudry, M. (1995). Properties and Mechanisms of Long-Term Synaptic Plasticity in the Mammalian Brain: Relationships to Learning and Memory. *Neurobiology of Learning and Memory*, 63(1):1–18.

[Markram et al., 1997] Markram, H., Lübke, J., Frotscher, M., and Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic aps and epsps. *Science*, 275(5297):213–215.

[Marshall et al., 1999] Marshall, F. H., Jones, K. A., Kaupmann, K., and Bettler, B. (1999). GABAB receptors – the first 7TM heterodimers. *Trends in Pharmacological Sciences*, 20(10):396–399.

[Mayford et al., 2012] Mayford, M., Siegelbaum, S. A., and Kandel, E. R. (2012). Synapses and memory storage. *Cold Spring Harbor Perspectives in Biology*, 4(6):1–18.

[Michelsen et al., 2008] Michelsen, K. A., Prickaerts, J., and Steinbusch, H. W. (2008). The dorsal raphe nucleus and serotonin: implications for neuroplasticity linked to major depression and alzheimer's disease. *Progress in brain research*, 172:233–264.

[Min and Nevian, 2012] Min, R. and Nevian, T. (2012). Astrocyte signaling controls spike timing–dependent depression at neocortical synapses. *Nature neuroscience*, 15(5):746–753.

[Minne et al., 2021] Minne, C. et al. (2021). Interactions between synaptic plasticity and switches in brain states for memory consolidation: a modeling study.

[Minsky, 1961] Minsky, M. (1961). Steps toward artificial intelligence. *Proceedings of the IRE*, 49(1):8–30.

[Miranda et al., 2019] Miranda, M., Morici, J. F., Zanoni, M. B., and Bekinschtein, P. (2019). Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. *Frontiers in cellular neuroscience*, page 363.

[Monti and Monti, 2007] Monti, J. M. and Monti, D. (2007). The involvement of dopamine in the modulation of sleep and waking. *Sleep medicine reviews*, 11(2):113–133.

[Morrison et al., 2008] Morrison, A., Diesmann, M., and Gerstner, W. (2008). Phenomenological models of synaptic plasticity based on spike timing. *Biological cybernetics*, 98(6):459–478.

[Murthy, 1998] Murthy, V. N. (1998). Synaptic plasticity: step-wise strengthening. *Current biology*, 8(18):R650–R653.

[Olcese et al., 2010] Olcese, U., Esser, S. K., and Tononi, G. (2010). Sleep and synaptic renormalization: a computational study. *Journal of neurophysiology*, 104(6):3476–3493.

[Paille et al., 2013] Paille, V., Fino, E., Du, K., Morera-Herreras, T., Perez, S., Kotaleski, J. H., and Venance, L. (2013). Gabaergic circuits control spike-timing-dependent plasticity. *Journal of Neuroscience*, 33(22):9353–9363.

[Pal, 2021] Pal, M. M. (2021). Glutamate: The master neurotransmitter and its implications in chronic stress and mood disorders. *Frontiers in Human Neuroscience*, 15.

[Palacios-Filardo and Mellor, 2019] Palacios-Filardo, J. and Mellor, J. R. (2019). Neuromodulation of hippocampal long-term synaptic plasticity. *Current Opinion in Neurobiology*, 54:37–43.

[Park et al., 2017] Park, Y., Choi, W., and Paik, S.-B. (2017). Symmetry of learning rate in synaptic plasticity modulates formation of flexible and stable memories. *Scientific reports*, 7(1):1–12.

[Pattwell et al., 2012] Pattwell, S. S., Bath, K. G., Perez-Castro, R., Lee, F. S., Chao, M. V., and Ninan, I. (2012). The bdnf val66met polymorphism impairs synaptic transmission and plasticity in the infralimbic medial prefrontal cortex. *Journal of Neuroscience*, 32(7):2410–2421.

[Pawlak, 2010] Pawlak, V. (2010). Timing is not everything: neuromodulation opens the STDP gate. *Frontiers in Synaptic Neuroscience*, 2.

[Pawlak and Kerr, 2008] Pawlak, V. and Kerr, J. N. (2008). Dopamine receptor activation is required for corticostriatal spike-timing-dependent plasticity. *Journal of Neuroscience*, 28(10):2435–2446.

[Pedrosa and Clopath, 2017] Pedrosa, V. and Clopath, C. (2017). The role of neuromodulators in cortical plasticity. A computational perspective. *Frontiers in Synaptic Neuroscience*, 8(JAN):38–38.

[Pfister and Gerstner, 2006] Pfister, J. P. and Gerstner, W. (2006). Triplets of spikes in a model of spike timing-dependent plasticity. *Journal of Neuroscience*, 26(38):9673–9682.

[Pleuvry, 2004] Pleuvry, B. J. (2004). Receptors, agonists and antagonists. *Anaesthesia & Intensive Care Medicine*, 5(10):350–352.

[Portas et al., 1998] Portas, C. M., Rees, G., Howseman, A., Josephs, O., Turner, R., and Frith, C. D. (1998). A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *Journal of Neuroscience*, 18(21):8979–8989.

[Purves, 2004] Purves, D. (2004). *Neurosciences, 3rd edition.*

[Purves et al., 2001] Purves, D., Beau Lotto, R., Mark Williams, S., Nundy, S., and Yang, Z. (2001). Why we see things the way we do: evidence for a wholly empirical strategy of vision. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 356(1407):285–297.

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

[Reyes-Resina et al., 2021] Reyes-Resina, I., Samer, S., Kreutz, M. R., and Oelschlegel, A. M. (2021). Molecular Mechanisms of Memory Consolidation That Operate During Sleep. *Frontiers in Molecular Neuroscience*, 14:767384.

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

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

[Ribeiro et al., 1992] Ribeiro, M. O., Antunes, E., de Nucci, G., Lovisolo, S. M., and Zatz, R. (1992). Chronic inhibition of nitric oxide synthesis. a new model of arterial hypertension. *Hypertension*, 20(3):298–303.

[Rodriguez-Moreno and Paulsen, 2008] Rodriguez-Moreno, A. and Paulsen, O. (2008). Spike timing–dependent long-term depression requires presynaptic nmda receptors. *Nature neuroscience*, 11(7):744–745.

[Ruan et al., 2014] Ruan, H., Saur, T., and Yao, W.-D. (2014). Dopamine-enabled anti-hebbian timing-dependent plasticity in prefrontal circuitry. *Frontiers in neural circuits*, 8:38.

[Rubin et al., 2001] Rubin, J., Lee, D. D., and Sompolinsky, H. (2001). Equilibrium Properties of Temporally Asymmetric Hebbian Plasticity. *Physical Review Letters*, 86(2):364–367.

[Sabec et al., 2018] Sabec, M. H., Wonnacott, S., Warburton, E. C., and Bashir, Z. I. (2018). Nicotinic acetylcholine receptors control encoding and retrieval of associative recognition memory through plasticity in the medial prefrontal cortex. *Cell reports*, 22(13):3409–3415.

[Salgado et al., 2012] Salgado, H., Köhr, G., and Treviño, M. (2012). Noradrenergic 'Tone' Determines Dichotomous Control of Cortical Spike-Timing-Dependent Plasticity. *Scientific Reports*, 2(1):417.

[Sam and Bordoni, 2022] Sam, C. and Bordoni, B. (2022). Physiology, acetylcholine. In *StatPearls [Internet]*. StatPearls Publishing.

[Saper et al., 2010] Saper, C. B., Fuller, P. M., Pedersen, N. P., Lu, J., and Scammell, T. E. (2010). Sleep State Switching. *Neuron*, 68(6):1023–1042.

[Schmitt et al., 2016] Schmitt, K., Holsboer-Trachsler, E., and Eckert, A. (2016). Bdnf in sleep, insomnia, and sleep deprivation. *Annals of medicine*, 48(1-2):42–51.

[Schultz, 2007] Schultz, W. (2007). Reward signals. *Scholarpedia*, 2(6):2184.

[Schulz et al., 2010] Schulz, J. M., Redgrave, P., and Reynolds, J. N. (2010). Cortico-striatal spike-timing dependent plasticity after activation of subcortical pathways. *Frontiers in synaptic neuroscience*, 2:23.

[Semon, 1904] Semon, F. (1904). An address on the relations of laryngology, rhinology, and otology with other arts and sciences: Prepared for and read at the international congress of arts and sciences, st. louis, on september 21st, 1904. *British Medical Journal*, 2(2282):713.

[Seol et al., 2007] Seol, G. H., Ziburkus, J., Huang, S., Song, L., Kim, I. T., Takamiya, K., Huganir, R. L., Lee, H.-K., and Kirkwood, A. (2007). Neuromodulators Control the Polarity of Spike-Timing-Dependent Synaptic Plasticity. *Neuron*, 55(6):919–929.

[Shen et al., 2008] Shen, W., Flajolet, M., Greengard, P., and Surmeier, D. J. (2008). Dichotomous dopaminergic control of striatal synaptic plasticity. *Science*, 321(5890):848–851.

[Sheng and Kim, 2011] Sheng, M. and Kim, E. (2011). The postsynaptic organization of synapses. *Cold Spring Harbor perspectives in biology*, 3(12):a005678.

[Shimoshige et al., 1997] Shimoshige, Y., Maeda, T., Kaneko, S., Akaike, A., and Satoh, M. (1997). Involvement of m2 receptor in an enhancement of long-term potentiation by carbachol in schaffer collateral-ca1 synapses of hippocampal slices. *Neuroscience research*, 27(2):175–180.

[Shouval, 2007] Shouval, H. Z. (2007). Models of synaptic plasticity. *Scholarpedia*, 2(7):1605.

[Shouval et al., 2010] Shouval, H. Z., Wang, S. S.-H., and Wittenberg, G. M. (2010). Spike timing dependent plasticity: a consequence of more fundamental learning rules. *Frontiers in computational neuroscience*, 4:19.

[Shulz and Feldman, 2013] Shulz, D. and Feldman, D. (2013). Spike timing-dependent plasticity. *Rubenstein JLR, Rakic P. Comprehensive developmental neuroscience: neural circuit development and function in the healthy and diseased brain. San Diego, CA: Elsevier*, pages 155–81.

[Sjöström and Häusser, 2006] Sjöström, P. J. and Häusser, M. (2006). A cooperative switch determines the sign of synaptic plasticity in distal dendrites of neocortical pyramidal neurons. *Neuron*, 51(2):227–238.

[Sjöström et al., 2001a] Sjöström, P. J., Turrigiano, G. G., and Nelson, S. B. (2001a). Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. *Neuron*, 32(6):1149–1164.

[Sjöström et al., 2001b] Sjöström, P. J., Turrigiano, G. G., and Nelson, S. B. (2001b). Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. *Neuron*, 32(6):1149–1164.

[Sjöström and Gerstner, 2010] Sjöström, J. and Gerstner, W. (2010). Spike-timing dependent plasticity. *Scholarpedia*, 5(2):1362–1362.

[Song et al., 2015] Song, M.-F., Dong, J.-Z., Wang, Y.-W., He, J., Ju, X., Zhang, L., Zhang, Y.-H., Shi, J.-F., and Lv, Y.-Y. (2015). Csf mir-16 is decreased in major depression patients and its neutralization in rats induces depression-like behaviors via a serotonin transmitter system. *Journal of affective disorders*, 178:25–31.

[Song et al., 2000] Song, S., Miller, K. D., and Abbott, L. F. (2000). Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. *Nature Neuroscience*, 3(9):919–926.

[Steriade et al., 1993] Steriade, M., McCormick, D. A., and Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science*, 262(5134):679–685.

[Steriade and Timofeev, 2003] Steriade, M. and Timofeev, I. (2003). Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. *Neuron*, 37(4):563–576.

[Stiefel et al., 2008] Stiefel, K. M., Gutkin, B. S., and Sejnowski, T. J. (2008). Cholinergic neuromodulation changes phase response curve shape and type in cortical pyramidal neurons. *PloS one*, 3(12):e3947.

[Stiefel et al., 2009] Stiefel, K. M., Gutkin, B. S., and Sejnowski, T. J. (2009). The effects of cholinergic neuromodulation on neuronal phase-response curves of modeled cortical neurons. *Journal of computational neuroscience*, 26(2):289–301.

[Strube et al., 2015] Strube, W., Nitsche, M. A., Wobrock, T., Bunse, T., Rein, B., Herrmann, M., Schmitt, A., Nieratschker, V., Witt, S. H., Rietschel, M., et al. (2015). Bdnf-val66met-polymorphism impact on cortical plasticity in schizophrenia patients: a proof-of-concept study. *International Journal of Neuropsychopharmacology*, 18(4):pyu040.

[Sugisaki et al., 2016] Sugisaki, E., Fukushima, Y., Fujii, S., Yamazaki, Y., and Aihara, T. (2016). The effect of coactivation of muscarinic and nicotinic acetylcholine receptors on ltd in the hippocampal ca1 network. *Brain Research*, 1649:44–52.

[Sugisaki et al., 2011] Sugisaki, E., Fukushima, Y., Tsukada, M., and Aihara, T. (2011). Cholinergic modulation on spike timing-dependent plasticity in hippocampal CA1 network. *Neuroscience*, 192:91–101.

[Sun et al., 2005] Sun, X., Zhao, Y., and Wolf, M. E. (2005). Dopamine receptor stimulation modulates AMPA receptor synaptic insertion in prefrontal cortex neurons. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 25(32):7342–7351.

[Sutton, 1998] Sutton, R. S. (1998). Reinforcement learning: Past, present and future. In *Asia-Pacific Conference on Simulated Evolution and Learning*, pages 195–197. Springer.

[Tonegawa et al., 2015] Tonegawa, S., Pignatelli, M., Roy, D. S., and Ryan, T. J. (2015). Memory engram storage and retrieval. *Current Opinion in Neurobiology*, 35:101–109.

[Torrico and Munakomi, 2019] Torrico, T. J. and Munakomi, S. (2019). Neuroanatomy, thalamus.

[Torterolo et al., 2019] Torterolo, P., Monti, J. M., and Vanini, G. (2019). Neurochemistry and pharmacology of sleep. In *The behavioral, molecular, pharmacological, and clinical basis of the sleep-wake cycle*, pages 45–83. Elsevier.

[Trutti et al., 2019] Trutti, A. C., Mulder, M. J., Hommel, B., and Forstmann, B. U. (2019). Functional neuroanatomical review of the ventral tegmental area. *Neuroimage*, 191:258–268.

[Tsodyks and Wu, 2013] Tsodyks, M. and Wu, S. (2013). Short-term synaptic plasticity. *Scholarpedia*, 8(10):3153. revision #182521.

[Tsubokawa and Ross, 1997] Tsubokawa, H. and Ross, W. N. (1997). Muscarinic modulation of spike backpropagation in the apical dendrites of hippocampal ca1 pyramidal neurons. *Journal of Neuroscience*, 17(15):5782–5791.

[Tyler et al., 2002] Tyler, W. J., Alonso, M., Bramham, C. R., and Pozzo-Miller, L. D. (2002). From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. *Learning & memory*, 9(5):224–237.

[Valjent and Gangarossa, 2021] Valjent, E. and Gangarossa, G. (2021). The tail of the striatum: from anatomy to connectivity and function. *Trends in neurosciences*, 44(3):203–214.

[Valtcheva et al., 2017] Valtcheva, S., Paillé, V., Dembitskaya, Y., Perez, S., Gangarossa, G., Fino, E., and Venance, L. (2017). Developmental control of spike-timing-dependent plasticity by tonic gabaergic signaling in striatum. *Neuropharmacology*, 121:261–277.

[Valtcheva and Venance, 2016] Valtcheva, S. and Venance, L. (2016). Astrocytes gate hebbian synaptic plasticity in the striatum. *Nature communications*, 7(1):1–17.

[van Rossum et al., 2012] van Rossum, M. C. W., Shippi, M., and Barrett, A. B. (2012). Soft-bound Synaptic Plasticity Increases Storage Capacity. *PLoS Computational Biology*, 8(12):e1002836.

[Vaseghi et al., 2021] Vaseghi, S., Arjmandi-Rad, S., Eskandari, M., Ebrahimnejad, M., Kholghi, G., and Zarrindast, M.-R. (2021). Modulating role of serotonergic signaling in sleep and memory. *Pharmacological Reports*, 74.

[Verkhratsky et al., 2016] Verkhratsky, A., Matteoli, M., Parpura, V., Mothet, J.-P., and Zorec, R. (2016). Astrocytes as secretory cells of the central nervous system: idiosyncrasies of vesicular secretion. *The EMBO journal*, 35(3):239–257.

[Wang et al., 2012] Wang, H., Huang, Z., Shen, T., and Guo, L. (2012). Theoretical study on the hydrogen bonding interactions in 1: 1 supermolecular complexes of noradrenaline with water. *Structural Chemistry*, 23(4):1163–1172.

[Wardle and Poo, 2003] Wardle, R. A. and Poo, M.-m. (2003). Brain-derived neurotrophic factor modulation of gabaergic synapses by postsynaptic regulation of chloride transport. *Journal of Neuroscience*, 23(25):8722–8732.

[Watanabe et al., 2002] Watanabe, M., Maemura, K., Kanbara, K., Tamayama, T., and Hayasaki, H. (2002). Gaba and gaba receptors in the central nervous system and other organs. *International review of cytology*, 213:1–47.

[Watson et al., 2011] Watson, C. J., Lydic, R., and Baghdoyan, H. A. (2011). Sleep duration varies as a function of glutamate and gaba in rat pontine reticular formation. *Journal of neurochemistry*, 118(4):571–580.

[Woodin, 2013] Woodin, M. A. (2013). Electrophysiological methods for investigating inhibitory synaptic plasticity. In *Multidisciplinary Tools for Investigating Synaptic Plasticity*, pages 209–221. Springer.

[Xu and Yao, 2010] Xu, T.-X. and Yao, W.-D. (2010). D1 and d2 dopamine receptors in separate circuits cooperate to drive associative long-term potentiation in the prefrontal cortex. *Proceedings of the National Academy of Sciences*, 107(37):16366–16371.

[Yagishita et al., 2014] Yagishita, S., Hayashi-Takagi, A., Ellis-Davies, G. C., Urakubo, H., Ishii, S., and Kasai, H. (2014). A critical time window for dopamine actions on the structural plasticity of dendritic spines. *Science*, 345(6204):1616–1620.

[Zagha and McCormick, 2014] Zagha, E. and McCormick, D. A. (2014). Neural control of brain state. *Current Opinion in Neurobiology*, 29(1):178–186.

[Zaitsev and Anwyl, 2012] Zaitsev, A. V. and Anwyl, R. (2012). Inhibition of the slow afterhyperpolarization restores the classical spike timing-dependent plasticity rule obeyed in layer 2/3 pyramidal cells of the prefrontal cortex. *Journal of neurophysiology*, 107(1):205–215.

[Zannone et al., 2018] Zannone, S., Brzosko, Z., Paulsen, O., and Clopath, C. (2018). Acetylcholine-modulated plasticity in reward-driven navigation: a computational study. *Scientific Reports*, 8(1):1–20.

[Zhang et al., 2009] Zhang, J.-C., Lau, P.-M., and Bi, G.-Q. (2009). Gain in sensitivity and loss in temporal contrast of STDP by dopaminergic modulation at hippocampal synapses. *Proceedings of the National Academy of Sciences*, 106(31):13028–13033.

[Zhao and Tzounopoulos, 2011] Zhao, Y. and Tzounopoulos, T. (2011). Physiological activation of cholinergic inputs controls associative synaptic plasticity via modulation of endocannabinoid signaling. *Journal of Neuroscience*, 31(9):3158–3168.

[Zheng et al., 2012] Zheng, F., Wess, J., and Alzheimer, C. (2012). M2 muscarinic acetylcholine receptors regulate long-term potentiation at hippocampal ca3 pyramidal cell synapses in an input-specific fashion. *Journal of neurophysiology*, 108(1):91–100.