Modelling short and long-term synaptic plasticity in neocortical microcircuits

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Abstract

Learning and memory storage is believed to occur at the synaptic connections between neurons. During the last decades it has become clear that synapses are plastic at short and long time scales. Furthermore, experiments have shown that short and long-term synaptic plasticity interact. It remains unclear, however, how is this interaction implemented and how does it impact information processing and learning in cortical networks. In this thesis I present results on the mechanisms and function of this interaction.

On the mechanistic level this form of plasticity is known to rely on a presynaptic coincidence mechanism, which requires the activation of presynaptic NMDA receptors (preNMDARs). In a collaborative effort I used mathematical modeling combined with experiments to show that preNMDARs reroute information flow in local circuits during high-frequency firing, by specifically impacting frequency-dependent disynaptic inhibition mediated by Martinotti cells.

In order to accurately characterize how do preNMDARs regulate the release machinery, I developed a probabilistic inference framework that provides a distribution over the relevant parameter space, rather than simple point estimates. This approach allowed me to propose better experimental protocols for short-term plasticity inference and to reveal connection-specific synaptic dynamics in the layer-5 canonical microcircuit.

This framework was then extended to infer short-term plasticity from preNMDAR pharmacological blockade data. The results show that preNMDARs up-regulate the baseline release probability and the depression time-constant, which is consistent with experimental analysis and that their impact appears to be connection-specific. I also show that a preNMDAR phenomenological model captures the frequency-dependence activation of preNMDARs. Furthermore, preNMDARs increase the signal-to-noise ratio of synaptic responses. These results show that preNMDARs specifically up-regulate high frequency synaptic information transmission.

Finally, I introduce a pre- and postsynaptic unified mathematical model of spike-timing-dependent synaptic plasticity. I show that this unified model captures a wide range of short-term and long-term synaptic plasticity data. Functionally, I demonstrate that this segregation into pre- and postsynaptic factors explains some observations on receptive field development and enable rapid relearning of previously stored information, in keeping with Ebbinghaus’s memory savings theory.
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Now in Portuguese. Obrigado a minha família por me ter apoiado apesar de não saberem ao certo que fazia eu por terras Escocesas (avós, pais e manas). Obrigado Alex pela pausa africana, Garcia por manteres o meu sentido “crítico” apurado e à malta da garagem.

¹Special thanks to the Reading Canoe Club for the wash hanging provided during the last lap of my PhD.
Declaration

I declare that this thesis was composed by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification except as specified.

(Rui Ponte Costa)
— Capitão!
— Soldado, ladrão!

Ao meu querido avô Valdemar, mentor e amigo.
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Chapter 1

Introduction

"As long as our brain is a mystery, the universe, the reflection of the structure of the brain will also be a mystery."

— Santiago Ramón y Cajal

During development and learning our ability to extract information from an ever-changing environment is astonishing. However, many maladaptive changes can occur, severely affecting quality of life. How does the brain learn? Why can learning and memory go wrong? In order to answer these questions we need a fundamental understanding of the principles driving brain plasticity.

The human brain has billions of neural connections – synapses – that change over time, a phenomena called synaptic plasticity. Synaptic plasticity is believed to be the neural basis of learning and memory (Martin et al., 2000; Redondo and Morris, 2010; Pawlak et al., 2013; Nabavi et al., 2014). Although, thousands of experimental studies have been conducted over the last decades, we are still far off from understanding its underlying principles. Moreover, synapses are plastic across different time-scales, from a few milliseconds (Zucker and Regehr, 2002) to hours (Bliss and Lomo, 1973; Bliss and Collingridge, 1993), days (Reymann and Frey, 2007; Redondo and Morris, 2010) and supposedly even years (see Fig. 1.1). Namely, short and long-term synaptic plasticity, which have been implicated in temporal processing (Abbott et al., 1997) and memory storage in neuronal circuits respectively (Nabavi et al., 2014). Several experimental studies have shown that these two synaptic plasticity timescales interact (Bolshakov and Siegelbaum, 1995; Markram and Tsodyks, 1996; Sjöström et al., 2003, 2007; Tokuoka and Goda, 2008; Jin et al., 2012; Kintscher et al., 2013). However, it is not clear: (i) what are the mechanisms driving this interaction, (ii) whether a single model can account for both forms and (iii) what is the functional role of such
interaction.

![Synaptic plasticity time-scales](image)

**Figure 1.1**: Multiple time-scales of synaptic plasticity. Short-term synaptic plasticity operates from the millisecond up to the minute scale (Zucker and Regehr, 2002), while early and spike-timing-dependent plasticity occur at the time-scale of hours (Bliss and Collingridge, 1993; Markram et al., 2011) and finally the late-phase of synaptic plasticity has been shown to last for more than 10 hours (Redondo and Morris, 2010).

In this chapter I present an overview of theoretical models and experimental observations across different timescales, which provides the necessary background for the following chapters.  

### 1.1 Short-term synaptic plasticity

Short-term plasticity (STP) refers to transient changes in synaptic efficacy, in the range of tens of milliseconds to several seconds or even minutes (Zucker and Regehr, 2002). It is highly heterogeneous (Dobrunz and Stevens, 1997) and is correlated with developmental stage (Reyes and Sakmann, 1999), cortical layer (Reyes and Sakmann, 1999), brain area (Wang et al., 2006; Cheetham and Fox, 2010) and postsynaptic cell-type (Reyes et al., 1998; Scanziani et al., 1998; Markram et al., 1998; Tóth and McBain, 2000; Rozov et al., 2001; Sun and Dobrunz, 2006; Blackman et al., 2013). For instance, short-term depression – where postsynaptic responses rapidly decrease their amplitude in response to a presynaptic spike train (Fig. 1.2a,b) – predominates in the juvenile brain, whereas more mature circuits have a preponderance for short-term facilitation – where postsynaptic responses are more likely to rapidly increase their amplitude in response to a presynaptic spike train (see an example of a strongly facilitating connection in Fig. 1.2c) (Reyes and Sakmann, 1999; Pouzat and Hestrin, 1997). Similarly, synapses from neocortical pyramidal cells (PCs) impinging on other PCs are depressing (Fig. 1.2a,b), whereas those onto specific interneurons can be strongly facilitating.

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1 Some parts of this introduction are published in Costa and Sjostrom (2011); Costa et al. (2013b); Blackman et al. (2013).
1.1. Short-term synaptic plasticity

(Fig. 1.2c) (Reyes et al., 1998; Markram et al., 1998).

Figure 1.2: Examples of short-term synaptic plasticity. (a-c) Samples of experimentally obtained STP traces. (a) Pyramidal Cell-Pyramidal Cell connection exhibiting short-term depression. (b) Pyramidal Cell-Basket Cell (interneuron type) connection exhibiting short-term depression. (c) Pyramidal Cell-Martinotti Cell (interneuron type) connection exhibiting short-term facilitation.

Although here I focus on short-term plasticity on the time-scales of up to a few seconds; there are other forms of short-lasting plasticity. Augmentation and post-tetanic potentiation are two examples (Zucker and Regehr, 2002). These short-lasting forms of plasticity are usually induced by longer and stronger synaptic stimulation and last from seconds (augmentation) to a few minutes (post-tetanic potentiation).

1.1.1 Phenomenological models

To model short-term depression, Tsodyks and Markram (1997) introduced a phenomenological model based on vesicle depletion, here referred to as the Tsodyks-Markram (TM) model. This model is an abstraction of the depletion of neurotransmitter from vesicles with a given probability of release that occurs in response to a presynaptic action potential in the presynaptic terminal (Fig. 1.3). If the presynaptic neuron fires a second action potential before replenishment of the vesicles has occurred there will be less neurotransmitter release available when compared to the first release, which is observed as a short-term depression of the postsynaptic amplitudes (Kandel et al., 2000). This model was later extended to include short-term facilitation (Markram et al., 1998; Tsodyks et al., 1998). Short-term facilitation is a consequence of strong $Ca^{2+}$ build up in the presynaptic terminal after each presynaptic action potential – potentially through Voltage-dependent $Ca^{2+}$ Channels (VDCC), so that there is more neurotransmitter released in the following events (Kandel et al., 2000) (Fig. 1.3). Although several other STP models have been developed (Varela et al., 1997; Abbott et al., 1997; Dittman et al., 2000; Pan and Zucker, 2009; Loebel et al., 2009), the TM model has become particularly popular, probably because of its combination
Chapter 1. Introduction

of appealing simplicity and biophysically relevant parameters (Markram et al., 1998; Richardson et al., 2005; Wang et al., 2006; Le Bé and Markram, 2006; Rinaldi et al., 2008; Ramaswamy et al., 2012; Testa-Silva et al., 2012; Romani et al., 2013; Hennig, 2013).

Figure 1.3: Schematic of neurotransmitter release. In this example Glutamate (black dots inside circles) is released with a given probability of release (Prelease) from synaptic vesicles at the readily-releasable pool (delimited by dashed green line) on the presynaptic terminal. The released neurotransmitters cross the synaptic cleft and bind to the postsynaptic AMPA and NMDA receptors (red structures). This figure is based on a schematic provided by Therese Abrahamsson (McGill University).

Next I describe the extended TM model (eTM), which is a model that captures a wide range of short-term depression and facilitation and is defined by the following ODEs (Markram et al., 1998; Tsodyks et al., 1998)

\[
\frac{dR(t)}{dt} = \frac{1 - R(t)}{D} - u(t)R(t)\delta(t - t_{AP}) 
\]

\[
\frac{du(t)}{dt} = \frac{U - u(t)}{F} + f[1 - u(t)]\delta(t - t_{AP}) 
\]

The first equation models the vesicle depletion process, where the number of vesicles \( R(t) \) is decreased with \( u(t)R(t) \) after release due to a presynaptic spike (action potential) at time \( t_{AP} \), modeled by a Dirac delta distribution \( \delta(t) \). Between spikes \( R(t) \) recovers to 1 with a depression timeconstant \( D \). The second equation models the dynamics of the release probability \( u(t) \) which increases with \( f(1 - u(t)) \) after every presynaptic spike (where \( f \) is the facilitation rate), decaying back to baseline release probability \( U \) with a facilitation timeconstant \( F \).

By varying the four parameters \( D, F, U \) and \( f \) one can obtain depressing, combined facilitating-depressing and facilitating synaptic dynamics. Note that for some data a
three parameter model (setting \( f = U \), denoted the TM with facilitation model) or even a two parameter depression model with only Equation 1.1 (setting \( u(t) = U \), denoted the TM model) is sufficient. This, however, is not generally the case, as shown in Chapter 2.

### 1.1.2 Stochastic models

The release of vesicles from the presynaptic terminal is a stochastic process (Fig. 1.3) (Del Castillo and Katz, 1954). This process can be described as the following Binomial random process (Del Castillo and Katz, 1954; Martin, 1966; McLachlan, 1978)

\[
P(X = k) = \binom{N}{k} U^k (1 - U)^{N-k}
\]

which defines the probability of having \( k \) successful events (neurotransmitter vesicle release) given \( N \) trials (release sites) with equal release probability \( U \).

The statistics of the postsynaptic response can be used to infer its parameters, which is referred to as quantal analysis (Martin, 1966). The Binomial model has also been applied to support the now wide-spread CV analysis of synaptic plasticity locus of expression (pre vs postsynaptic) (Faber and Korn, 1991).

Finally, stochastic models of vesicle release can be integrated with STP models previously described, providing a framework to study the role of fluctuations in STP function (de la Rocha and Parga, 2005; Hennig, 2013).

### 1.1.3 Computational roles

The above-mentioned models have been used to suggest that STP shapes information processing in neural networks in multiple ways (Abbott and Regehr, 2004; Fung et al., 2012): to enable cortical gain control (Abbott et al., 1997), pattern discrimination (Carvalho and Buonomano, 2011), input filtering (Markram et al., 1998), adaptation (van Rossum et al., 2008), spike burst detection (Maass and Zador, 1999), synchronization (Tsodyks et al., 2000), and to maintain the balance of excitation and inhibition in local circuits (Galarreta and Hestrin, 1998).

Another complementary approach is the so called normative approach that attempts to explain observed synaptic plasticity phenomena from a top-down perspective (Lochmann and Deneve, 2011). By identifying functional objectives, this type of framework can in principle complement bottom-up model development and identify functions in which short-term synaptic plasticity can be near-optimal.
Based on a normative theoretical approach, Pfister et al. (2010) proposed that STP make postsynaptic neurons optimal estimators of presynaptic membrane potential. Although the existence of target-specific STP might at first appear to be in contradiction to this theory, another interpretation is that different neuronal types may compute different presynaptic statistical properties.

In an alternative perspective Stevenson et al. (2010) suggested that STP is a near-optimal solution of postsynaptic neurons adapting to minimize the influence of presynaptic neurons, while also describing sensory tuning curve adaptation in the visual cortex. This is important because fluctuations in neuronal excitability produce noise that can potentially induce perceptual errors.

Interestingly, the inherent probabilistic nature of neurotransmitter release could help neural systems achieve a better solution over learning. Indeed many neural network studies have used synaptic noise to obtain better global solutions (Jim et al., 1996; Graves, 2011; Hinton, 2012; Graves et al., 2013).

Finally, STP models are only valid if they can capture experimental data. Probabilistic inference provides a powerful framework to deal with the inherent experimental uncertainty and can be used for experimental protocol design (see Chapter 2).

1.2 Long-term Synaptic Plasticity

In 1894 the neuroanatomist Santiago Ramon y Cajal proposed that memories might be formed by strengthening and weakening of existing connections, rather than by forming new neurons.

More than 50 years later, Donald Hebb published his famous postulate stating that to store a memory trace, the connection from a neuron that persistently helps activate another one should be strengthened (Hebb, 1949). The first experimental support for Hebb’s postulate was found in the rabbit hippocampus by Bliss and Lomo (1973). This powerful postulate together with the first experimental evidences led to the emergence of the field of long-term synaptic plasticity, which studies the neural basis of memory and learning.

Long-term synaptic plasticity is therefore believed to be important for the development of neural connectivity (Holtmaat and Svoboda, 2009) as the patterning of synaptic connections between neurons appears to determine at least some brain functions (Nabavi et al., 2014). Changes in synaptic connections are governed by cellular learning rules. The synaptic plasticity that enables these changes to take place is at a maxi-
mum in the developing brain, which uses sensory input to refine patterns of connectivity as the animal learns about the outside world. Indeed, during a limited time-window known as the critical period, sensory input is essential for establishing proper connectivity. When the critical period is over, this potential for plasticity – and for learning – is diminished (Kuhlman et al., 2013).

In the next sections I discuss the multiple time-scales at which long-term synaptic plasticity occurs.

### 1.2.1 Early phase

The early phase of long-term synaptic plasticity refers to changes in the synaptic weights that last up to a few hours. In the classical view of long-term synaptic plasticity postsynaptic NMDA receptors act as coincidence detectors of pre and postsynaptic activity (through presynaptic neurotransmitter release and postsynaptic unblocking of the $Mg^{2+}$ block). Calcium influx through postNMDARs triggers plasticity on the postsynaptic spine. Long-term potentiation is often achieved by applying a prolonged presynaptic high-frequency protocol (e.g: theta-burst) (Bliss and Lomo, 1973; Dudek and Bear, 1992). However, synaptic strengthening can also be induced by manipulating (together with presynaptic stimulation) the postsynaptic membrane potential (Kelso et al., 1986; Artola et al., 1990; Sjöström et al., 2001), calcium entry (Lisman, 1989; Malenka et al., 1988), or spike timing (Markram et al., 1997b; Bi and Poo, 1998; Sjöström et al., 2001). Although many variables can affect synaptic plasticity here I focus on spike-timing-dependent models, which capture changes in firing rates, spike-pattern and postsynaptic potential, and in phenomenological models in particular.

### 1.2.2 Spike-timing-dependent plasticity

In more recent years, synaptic plasticity theory has been extended to include the precise timing of spikes in pre and postsynaptic neurons, based on theoretical as well as experimental studies (Gerstner et al., 1996; Markram et al., 1997b). This has led to the development of the spike-timing-dependent plasticity (STDP) paradigm, which has caused great interest as a biologically plausible neuronal basis for information storage in the brain, in particular for the learning of causal relationships, as it is temporally sensitive (Markram et al., 2011).

STDP is a learning rule, whereby changes in the strength of neuronal connections depend acutely on the precise timing of spikes, or action potentials, in connected cells.
Imagine two neurons, where neuron A is connected to neuron B (Figure 1.4). If cell A spikes a few milliseconds before cell B, the connection between the two will be strengthened, whereas if cell B spikes before cell A, the connection will be weakened. Although STDP is attractive as a cellular learning rule (Markram et al., 2012), its biological relevance has been called into question because most STDP experiments have been carried out in dissected brain tissue (Frégnaq et al., 2010; Lisman and Spruston, 2010).

Figure 1.4: In STDP, neuronal connections change strength depending on the relative timing of spikes. The lower figure shows how the strength of a connection between cell A and cell B changes as a function of the time difference between the spikes. Cell A consistently spiking before cell B (green region) strengthens the A→B connection, whereas cell B spiking before cell A (red region) weakens the connection. In dissected brain tissue, these changes occur when pairing pre and postsynaptic spikes in the range of tens of milliseconds (Markram et al., 2012). However, recently Pawlak et al. (2013) found that they occur over a time scale of approximately 250 milliseconds in the intact brain.

Neuroscientists have characterized STDP mostly *in vitro*, but it is unclear which, if any, of these have functional relevance *in vivo*. So does the brain use STDP? Pawlak et al. (2013) reported on experiments in rats that take a key step towards answering this question. They performed technically challenging *in vivo* whole-cell recordings...
of putative pyramidal neurons in layer 2/3 of the visual cortex, during the critical period when the circuitry is most plastic. Neurons in primary visual cortex are tuned to specific stimuli: a neuron may, for example, spike preferentially in response to a specific visual stimulus in a certain part of the visual field. This neuron will, in addition, produce non-spiking responses to stimuli presented in other regions of visual space, referred to here as its sub-threshold receptive field.

To assess the importance of STDP in the visual cortex, Pawlak et al. (2013) used a visual stimulus (a bar presented for half a second) to evoke a response in a neuron, and paired this repeatedly with a brief injection of current to elicit a spike (Fig. 1.5A). By varying the relative timing of these two inputs, they were able to conduct three key experiments that demonstrate cellular learning, re-learning, and unlearning.

First, they showed that a naive untuned neuron – that is, one that responds almost non-selectively to stimuli anywhere in its receptive field – could be trained to spike whenever the visual stimulus occupied a specific position chosen by the experimenter (Figure 1.5B). To do this, they presented the stimulus in the desired position, and then a few milliseconds later, injected current through the recording electrode to elicit a spike. Repeatedly pairing the visual evoked response with the spike, in that order, strengthened the association between the two in accordance with STDP. Second, they showed that a neuron tuned to a particular location could be re-trained to spike when the visual stimulus was in a different position (Figure 1.5C) by repeating what they did in the first set of experiments (that is, by injecting current a few milliseconds after the visual stimulus was presented). Again this was in agreement with STDP. Last, they demonstrated that reversing the order of repeated spike-response pairings (that is, by triggering a spike and then presenting the visual stimulus) erased the tuning (Figure 1.5D), also in agreement with STDP.

When they examined the impact of these pairing events on the sub-threshold visual responses of the neurons, Pawlak and colleagues found that responses preceding the spike were strengthened while those following it were weakened. This biphasic change is consistent with STDP (Figure 1.4), and explains why the temporal order of response-spike pairings brings about either learning or unlearning (Figure 1.5). Surprisingly, however, the biphasic changes occurred over a time scale five-fold longer than that anticipated from typical STDP studies in vitro (Markram et al., 2012). Using a computer model, Pawlak and co-workers showed that this temporal rescaling could result from noise in the spike timing of inputs. Such noise is to be expected in the intact brain, where there is always ongoing activity, but not in dissected brain tissue,
Figure 1.5: Using STDP to train visual cortex neurons in rats. (A) In the setup used by Pawlak et al. (2013), a bar was presented in one of four positions in the neuronal receptive field, position 2 in this case. An intracellular electrode recorded the activity of an individual neuron, and was also used to elicit single spikes by a brief injection of current. (B) By repeatedly eliciting a spike milliseconds after presentation of a visual stimulus in position 4, the neuron was trained to respond to that stimulus: the dark green line is the newly formed tuning curve; the pale green line is before training. (C) It was also possible to reshape an existing tuning curve by pairing the spike with the visual stimulus in a non-preferred position (in this case position 2). (D) By eliciting the spike milliseconds before a preferred visual stimulus, tuning was erased. Asterisks denote the trained position, while colors correspond to timings as in Fig. 1.4.

which is relatively inactive.

Although a previous study has already shown that sub-threshold, non-spiking responses retune in visual cortical neurons following a STDP-like setup (Meliza, 2006), Pawlak and colleagues go further by showing that STDP can control neuronal spiking output. This is important, because spikes are needed to convey stimulus feature infor-
mation to other neurons. Their work is also reminiscent of a classical study of cellular learning in cat visual cortex, where responses were altered by pairing visual input with direct visual cortex stimulation or inhibition (Frégna et al., 1988). However, Pawlak and colleagues work reveals the millisecond timing requirements for cellular learning, suggesting a physiological relevance for STDP.

It is important to note that these findings were obtained in anaesthetized animals, and remain to be confirmed in the awake state. Indeed, factors such as attention are likely to influence cellular learning processes (Markram et al., 2012). Although the current results show that STDP can support cellular learning, they do not reveal which synapses were altered. Finally, the evoked training spikes could be regarded as relatively artificial stimuli, which has been a criticism of STDP protocols in the past (Lisman and Spruston, 2010). It will also be interesting to see whether similar results can be obtained using more natural spiking patterns. Despite these limitations, the work of Pawlak et al. (2013) provides some of the strongest evidence to date that STDP may underlie cellular learning in the intact brain and receptive field development in particular.

Finally, it has been shown in vitro that STDP is not a simple function of timing between pre and postsynaptic spikes, but also frequency and postsynaptic voltage (Markram et al., 1997b; Sjöström et al., 2001). In the next sections we discuss models of increasing complexity that can capture these results.

1.2.2.1 Pair-based

Pair-based STDP is a first approximation model that captures the spike-timing dependence based on interaction of pairs of spikes alone (Song et al., 2000; van Rossum et al., 2000; Song and Abbott, 2001). Before introducing the actual model I introduce a framework that can capture any order of dependence on the pre and postsynaptic spike trains. This framework is based on a Volterra expansion (Kistler and van Hemmen, 2000; Pfister and Gerstner, 2005). In this framework we start from two arbitrary functionals $F[X,Y]$ and $G[X,Y]$, which capture any order of interaction between the spike trains $X$ and $Y$. The weight dynamics are given by

$$\frac{dw(t)}{dt} = X(t)F[X,Y] + Y(t)G[X,Y] \tag{1.4}$$

where $X(t) = \sum_k \delta(t - t_{xk})$ and $Y(t) = \sum_k \delta(t - t_{yk})$ are the presynaptic and postsynaptic spike trains, with $t_{xk}$ and $t_{yk}$ the spike times, respectively. $\delta$ is the Dirac delta function.
Next, starting from a naive point of view we can simply perform a Volterra expansion on \( F[X,Y] \) and \( G[X,Y] \), which yields

\[
G([X,Y]) = G_1^Y + \int_0^\infty G_2^{XY}(s)X(t-s)ds + \int_0^\infty G_2^{YX}(s)Y(t-s)ds \\
+ \int_0^\infty \int_0^\infty G_3^{XY}(s,s')X(t-s)X(t-s')ds'ds \\
+ \int_0^\infty \int_0^\infty G_3^{YX}(s,s')X(t-s)Y(t-s')ds'ds \\
+ \int_0^\infty \int_0^\infty G_3^{YY}(s,s')Y(t-s)Y(t-s')ds'ds + ... \quad (1.5)
\]

where \( s \) is the delay between pre and postsynaptic spikes (\( s = t^x - t^y \)). This framework captures all possible interactions, for example: \( G_1^Y \) represents a kernel that triggers changes in \( w \) based on \( Y \) alone, whereas \( G_2^{XY}(s) \) is a pair kernel that depends on \( X \) and \( Y \), while \( G_3^{XY}(s,s') \) is a triplet interaction of two \( X \) and a single \( Y \). Similarly, we can expand \( F[X,Y] \). Note that all the kernels can in principle depend on the weight itself, which has important implications for weight distribution and memory storage (van Rossum et al., 2000, 2012).

If we now define only two of the pair kernels \( G_2^{XY} \) and \( F_2^{XY} \) as

\[
G_2^{XY}(s) = A_+ \exp^{-s/\tau_+} \quad \text{for } s < 0 \quad (1.6)
\]

\[
F_2^{XY}(s) = -A_- \exp^{-s/\tau_-} \quad \text{for } s > 0 \quad (1.7)
\]

we obtain the standard pair-based STDP learning rule, which gives the characteristic STDP window (Fig. 1.4). It can also be implemented as an on-line update rule where every spike leaves a trace

\[
\frac{dx_+(t)}{dt} = -\frac{x_+(t)}{\tau_+} \quad \text{if } t = t_x \text{ then } x_+(t) \to x_+(t) + 1 \quad (1.8)
\]

\[
\frac{dy_-(t)}{dt} = -\frac{y_-(t)}{\tau_-} \quad \text{if } t = t_y \text{ then } y_-(t) \to y_-(t) + 1 \quad (1.9)
\]

the weight dynamics become

\[
\frac{dw(t)}{dt} = -A_-X(t)y_-(t) + A_+Y(t)x_+(t) \quad (1.10)
\]

Although here we have focused on a spike-interaction rule that considers all pairs of any pre with any postsynaptic spike (“all-to-all”), pair-based STDP has also been studied in the context of nearest-neighbor spike-interaction where only the temporally closest spikes are taken into account (Pfister and Gerstner, 2006). This can also be captured in this framework (Pfister and Gerstner, 2005).
1.2.2.2 Triplet-based

There have been multiple models that consider triplet-interactions of pre and postsynaptic spike trains (Senn et al., 2001; Froemke and Dan, 2002; Froemke et al., 2006; Pfister and Gerstner, 2006; Froemke et al., 2010; Clopath et al., 2010; Albers et al., 2013), also see Chapter 4 for a new model that makes explicit the weight change as a segregation between pre and postsynaptic components.

Here I describe the Pfister and Gerstner (2006) triplet model, which is a relatively simple model that can capture not only the timing, but also the frequency dependence of STDP protocols (Sjöström et al., 2001). Following the framework introduced in the previous section the Pfister and Gerstner (2006) model considers two triplets (yxx – post-pre-pre – and xyy – pre-post-post) and two pairs (yx and xy), and its weight dynamics are defined as

\[
\frac{dw(t)}{dt} = -X(t)y_-(t)[A_2^2 + A_3^3 x_-(t)] + Y(t)x_+(t)[A_2^2 + A_3^3 y_+(t)]
\] (1.11)

where \(A_k^k\) (k indicates the number of interactions) are the different amplitude parameters and the respective synaptic traces are defined as

\[
\frac{dx_+(t)}{dt} = -\frac{x_+(t)}{\tau_{x_+}} \quad \text{if } t = t_x \text{ then } x_+(t) \rightarrow x_+(t) + 1
\] (1.12)

\[
\frac{dx_-(t)}{dt} = -\frac{x_-(t)}{\tau_{x_-}} \quad \text{if } t = t_x \text{ then } x_-(t) \rightarrow x_-(t) + 1
\] (1.13)

\[
\frac{dy_-(t)}{dt} = -\frac{y_-(t)}{\tau_{y_-}} \quad \text{if } t = t_y \text{ then } y_-(t) \rightarrow y_-(t) + 1
\] (1.14)

\[
\frac{dy_+(t)}{dt} = -\frac{y_+(t)}{\tau_{y_+}} \quad \text{if } t = t_y \text{ then } y_+(t) \rightarrow y_+(t) + 1
\] (1.15)

By optimizing the model parameters with respect to experimental data Pfister and Gerstner (2006) showed that such a model can also capture the frequency-dependence results of STDP.

More recently Clopath et al. (2010) introduced a triplet model, which depends on the postsynaptic voltage as observed experimentally (Sjöström et al., 2001), while Graupner and Brunel (2012) introduced a \(Ca^{2+}\)-based bistable model that captures a wide range of experimental results on spike pattern and rate, but they did not attempt to fit voltage-dependent results.

1.2.2.3 Dendritic-dependence

The vast majority of theoretical synaptic plasticity studies treat neurons as points in space, entirely devoid of dendritic arboreations. There has been an ongoing debate in
the field regarding the extent to which dendrites are important for computations in the brain; perhaps they are merely an epiphenomenal bug rather than a feature (Häusser and Mel, 2003)? Hebb (1972) took an interestingly extreme view and surmised that dendrites are merely there to connect and therefore serve no purpose in plasticity. But dendrites are key to distinguishing neuronal types – the fan-shaped dendritic tree typifies the Purkinje cells, while the ascending thick-tufted dendritic arbor defines the neocortical layer-5 pyramidal cell – so it would seem strange if dendrites did nothing more than to hook cells up to each other (Sjöström et al., 2008). Indeed, recent studies have shown that synaptic plasticity depends on the location of a synapse in the dendritic tree (Froemke et al., 2005; Sjöström and Häusser, 2006) and that dendritic branches themselves are plastic (Losonczy et al., 2008). By measuring the coupling between local dendritic spikes and the soma before and after a synaptic plasticity induction protocol in the hippocampus, Losonczy et al. (2008) discovered that dendrites too are plastic. Based on their findings, they proposed the existence of a branch-strength potentiation (BSP) cellular learning rule, which is input-specific to a degree, suggesting that individual dendritic compartments could be involved in storing spatio-temporal features. But why is BSP needed? After all, it would seem that Hebbian learning in general and STDP in particular provide sufficient means for information storage in the brain.

Legenstein and Maass (2011) attacked this key issue using an entirely theoretical approach. They introduced a new experimentally based phenomenological model that brought together the STDP and BSP learning rules. They applied their model to a simple feature-binding problem, in which cell assemblies coding for different features (e.g., yellow, star, black, and disk) were randomly connected to the branches of the postsynaptic cell. The neuron was then trained on pairs of features, such as yellow + star and black + disk, after which the neuron responded correctly to pairs of trained features, but not to other combinations such as yellow + disk. This feature was due to the emergence of synaptic clustering and competition between dendritic branches that resulted from the interplay between STDP and BSP, allowing a single neuron to bind input features in a self-organized manner.

Despite the interesting features emerging from this model, and as happened with the perceptron, the Legenstein-Maass model was not able to solve the XOR problem (i.e., responding to either pair of features, but not to both pairs together). Indeed, the XOR problem might only be solvable at the network level, requiring inhibitory interneurons to do so. Nevertheless, whether a single neuron of the brain can or cannot perform non-linear pattern separation remains an open question (Sjöström et al., 2008).
1.2. Long-term Synaptic Plasticity

(but see Zador et al. (1992)). It would also be interesting to know the information storage capacity of such Legenstein-Maass neurons. Finally, although STDP is necessary in their model, Hebbian learning together with synaptic scaling (Turrigiano et al., 1998) are likely to yield similar results.

The take-home message of the study of Legenstein and Maass (2011) is that individual neurons can potentially operate as small networks in their own right, binding features at the single-cell level. This suggests a form of dendritic homunculus, which can dendritically bind specific feature combinations via a combination of STDP and BSP, thus acting as a substrate for the correlation theory of brain function (Von der Malsburg, 1981) as well as for the binding problem (Treisman, 1996).

However the Legenstein and Maass (2011) study does not provide a mechanistic understanding of the dendritic-dependence of STDP. Recently, based on a simplified model of calcium dynamics alone Graupner and Brunel (2012) was able to capture the dendritic dependence of STDP. Therefore providing a first step towards a better understanding of the mechanisms behind compartment-dependence of synaptic plasticity.

1.2.2.4 Probabilistic and normative approaches

STDP has attracted extensive interest from the theoretical community, and from normative approaches in particular (Toyoizumi et al., 2005; Lengyel et al., 2005; Hennequin et al., 2010; Pool and Mato, 2011; Balduzzi and Besserve, 2012; Yger and Harris, 2013; Brea et al., 2013; Nessler et al., 2013; Miyata et al., 2013).

For example, Nessler et al. (2013) showed that winner-take-all (WTA) cortical circuits embedded with STDP and homeostatic plasticity approximates a powerful machine learning technique – expectation-maximization, effectively implementing a generative model of input patterns. Although it was already known that STDP in a WTA can perform unsupervised learning of input patterns (Masquelier and Thorpe, 2007; Masquelier, 2011), this study showed that it approximates a known machine learning method.

In another study Brea et al. (2013) derived a learning rule by minimizing an upper bound on the Kullback-Leibler divergence between a target distribution and the model distribution. Interestingly, this derived learning-rule resembles data-driven triplet STDP learning rules.

On the other hand, there is a growing interest on inferring neural connectivity from neural circuits (Shababo et al., 2013). This inference process needs to consider the plasticity that might be shaping connectivity. Koerding and Stevenson (2011) proposed
a probabilistic framework which uses a model-based estimation of STDP from pairs of
spike trains to infer plasticity-driven modifications in a given network.

1.2.3 Late phase and consolidation

The late phase of long-term synaptic plasticity relates to the maintenance of the synap-
tic changes observed during the early phase, lasting more than 10 hours. For these
changes to persist for a long-time a consolidation mechanism is needed. In order to
account for this problem Frey and Morris putted forward the synaptic tagging and cap-
ture (STC) hypothesis (Frey and Morris, 1997; Redondo and Morris, 2010). The STC
hypothesis states that for consolidation to occur a given synapse needs to be tagged
through an induction protocol and new plasticity-related proteins (PRP) need to be
sensitized. These PRP consolidate the synaptic weight changes that occurred at the
tagged synapses and have been interpreted as the synaptic basis of long-term memoe-
ries. Recently, STC computational models have been introduced (Clopath et al., 2008;
Barrett et al., 2009; Clopath, 2012). Clopath et al. (2008) introduced a bistable consoli-
dation model (low and high weight), which directly models induction and goes through
three phases: tag, trigger and consolidation. Barrett et al. (2009) proposed a similar
model with also two states (low and high weight) and three meta-states (non-tagged
early-state, tagged early-state or consolidated state), where consolidation is directly
modelled as a function of the stimulation protocol. Both models can capture some of
the experimental results of late-phase synaptic plasticity.

1.3 Multi-scale unification

Synaptic plasticity occurs at different timescales. Moreover there is evidence for in-
teraction of different timescales (e.g: Markram and Tsodyks (1996); Sjöström et al.
(2003)). This suggests that it might be possible to develop unified theories, at least at
a given connection type (e.g. between layer-5 PCs).

Recently, there has been some effort in the field towards unification. The above-
mentioned STC computational models (Clopath et al., 2008; Barrett et al., 2009) are
among the first to capture some of the early and late phase long-term synaptic plas-
ticity results. However, these discard STDP results. On the other hand recent studies
in STDP have been quite successful in the unification of different datasets, such as
spike-timing and frequency dependence (Pfister and Gerstner, 2006; Clopath et al.,
Moreover, all these models have assumed implicitly that all the changes occur at the post-synapse, which can be inaccurate as the synaptic weight is always a combination of presynaptic (i.e. release of neurotransmitters) and postsynaptic components (i.e. receptor activation). By taking into account the regulation of the presynaptic terminal it is, in principle, possible to link short and long-time scales. The work by Senn et al. (2001) was the first attempt to develop a unified model of short and long-term synaptic plasticity. The Senn et al. (2001) model captures some of the spike-timing and frequency dependence results of STDP by modelling NMDA dependent retrograde signalling, which dynamically up or down-regulates the steady-state release probability on the presynaptic terminal. However, this model does not capture more recent results on the pre-post signalling (Sjöström et al., 2003, 2007), discards a postsynaptic expression for synaptic plasticity and does not model the short-term dynamics. In Chapter 4 we address these problems by formulating a relatively simple phenomenological model, which captures both pre and postsynaptic components, as well as a wide range of experimental results. Interestingly, this new model also captures changes in synaptic variability and dynamics that have been observed experimentally in vitro as well as in the intact brain.

At the same time there has been a growing experimental effort to dissect the mechanisms driving this interaction of time-scales (e.g.: (Sjöström et al., 2003; Bender and Feldman, 2006; Sjöström et al., 2007)).

1.4 Experience-dependent synaptic changes

Hebb’s postulate has remained a hypothesis up to today (Martin et al., 2000) (but see Nabavi et al. (2014)). However, recent ground-breaking research has provided some of the first in vivo experimental support for this hypothesis. By combining in vivo calcium imaging with slice recordings Ko et al. (2011) were the first to show that cells in the mouse visual cortex with similar orientation selectivity are more likely to be connected. Together with other studies (e.g: Whitlock et al. (2006); Nabavi et al. (2014)) these results support Hebb’s postulate – “cells that fire together, wire together”. More recently Ko et al. (2013) showed that this effect develops after eye-opening and the authors were able to model this effect using voltage-dependent STDP (Clopath et al., 2010; Graupner and Brunel, 2012), voltage (Clopath et al., 2010), calcium (Graupner and Brunel, 2012) and dendritic location (Clopath and Gerstner, 2010; Graupner and Brunel, 2012).

2010; Graupner and Brunel, 2012), voltage (Clopath et al., 2010), calcium (Graupner and Brunel, 2012) and dendritic location (Clopath and Gerstner, 2010; Graupner and Brunel, 2012).
Chapter 1. Introduction

2010) at intra-cortical connections. Although these studies have been instrumental in identifying plasticity correlates of visual function, they do not address whether experience causes any direct structural changes at the synaptic level. Hofer et al. (2008) imaged spine dynamics of adult mouse visual cortex during plasticity of eye-specific responses, and found an increased spine density, which can be interpreted as a synaptic basis of memory storage (Hübener and Bonhoeffer, 2010). While during development and adulthood synaptic growth is believed to be the basis of memory formation, the opposite has been suggested to occur in the ageing brain – i.e. synaptic loss and memory decay. This is supported by evidence from ex vivo studies where a reduced number of synaptic contacts have been observed. For example, using axonal bouton imaging Grillo et al. (2013) asked whether this is the case in an in vivo setup. Surprisingly rather than a change in the density and size of axonal boutons, as predicted by previous studies, they observed increased bouton turnover and destabilization rates with age. Together with decreased long-term memory recognition, these results suggest that decreased “synaptic tenacity” may underlie age-related cognitive decline. In the present thesis we propose a link between pre and postsynaptic activity and structural plasticity in the context of a novel activity-dependent learning rule (see Chapter 4).

1.5 Neocortical microcircuit

Synaptic plasticity is key for understanding the function of the nervous system, but it needs to be studied in the context of the local circuit in which it operates with different excitatory and inhibitory cell types. The neocortex has been described by a canonical microcircuit, which is fairly stereotypical across different brain areas (Douglas et al., 1989; Douglas and Martin, 2004). In this canonical view layer-4 granule cells receive inputs from the thalamus. This information is then fed onto layer-2/3 pyramidal cells and finally layer-5 pyramidal cells, which may send the filtered sensorial input to other brain areas (Fig. 1.6). This flow of information across the different layers is tightly controlled by specific types of GABAergic cells (interneurons).

In this thesis I focus on the analysis of synaptic plasticity in the context of the layer-5 canonical microcircuit (Fig. 1.7). There is a wide variety of interneuron cell-types in layer-5 (Markram et al., 2004). However, here I describe a microcircuit with the three most common layer-5 cell types: pyramidal cells (PC), basket cells (BC) and Martinotti cells (MC) (Fig. 1.7). PCs are the most abundant and the main excitatory cell type in layer-5, while BC are fast spiking inhibitory cells that are believed to be important to
Figure 1.6: Canonical microcircuit view of the neocortex (reproduced from Douglas et al. (1989)). In this simplified description of the cortical microcircuit the thalamus sends input to layer-4 (note that in some brain areas this layer does not exist as layer-2/3 receives direct input from other brain areas), which in turn feeds into layer-2/3 and finally layer-5. This communication process is tightly controlled by GABAergic cells.

maintain the network in a healthy state (Vogels and Abbott, 2009; Vogels et al., 2011). On the other hand MC are accommodating inhibitory cells with peculiar facilitatory excitatory connections from neighbouring PCs (Kozloski et al., 2001; Markram et al., 1998; Silberberg and Markram, 2007) (see example in Fig. 1.2c). Moreover, while BCs impinge onto basal dendrites of PCs, MCs have a characteristic axonal arbor that targets the distal dendrites of neighbouring PCs (see Chapter 3 for a network model and results on the function of presynaptic NMDA receptors in this local layer-5 circuit).
Figure 1.7: Canonical layer-5 microcircuit (schematic provided by Jesper Sjöström). This schematic represents the typical connectivity and morphology of the three most common layer-5 cell-types: pyramidal cells (PC), basket cells (BC) and Martinotti cells (MC) (see main text for more details). Connections with triangles represent excitatory synapses, while open circles represent inhibitory synapses. Dashed lines represent the axons, while solid lines represent the dendrites.
Chapter 2

Probabilistic inference of short-term synaptic plasticity in neocortical microcircuits

“The researcher hoping to break new ground in the theory of experimental design should involve himself in the design of actual experiments.”

— George E. P. Box, Science and Statistics.

Short and long-term synaptic plasticity interact (Sjöström et al., 2003; Markram and Tsodyks, 1996). However, exactly how the later scales of synaptic plasticity regulate synaptic dynamics is not clear. Moreover short-term synaptic plasticity is highly diverse across brain area, cortical layer, cell type, and developmental stage. Since short-term plasticity strongly shapes neural dynamics, this diversity and long-term regulation suggests a specific and essential role in neural information processing. Therefore, a correct characterization of short-term synaptic plasticity is an important step towards understanding and modeling neural systems. Phenomenological models have been developed, but they are usually fitted to experimental data using least-mean-square methods. In this chapter, together with collaborators I demonstrate that for typical synaptic dynamics such fitting may give unreliable results. As a solution, we introduce a Bayesian formulation, which yields the posterior distribution over the model parameters given the data. First, we show that common short-term plasticity protocols yield broad distributions over some model parameters. Using our result we propose a experimental protocol to more accurately determine synaptic dynamics parameters. Next, we infer the model parameters using experimental data from three
different neocortical excitatory connection types. This reveals connection-specific distributions, which we use to classify synaptic dynamics.

This approach to demarcate connection and state-specific synaptic dynamics is an important improvement on the state of the art and reveals novel features from existing data.¹ ²

2.1 Introduction

Typically, STP models are numerically fitted to electrophysiological data by least-mean-square algorithms, which yield the parameter values that minimize the error between data and model. However, such fitting algorithms can get stuck in local optima and may provide little information about the certainty of the parameter values. As shown below, such fits may produce inaccurate results and may lead to unreliable clustering. Bayesian inference is a natural alternative, because it yields a distribution of parameter values rather than a single outcome. Bayesian inference has recently been applied to neurophysiological data analysis. McGuinness et al. (2010) used this to estimate large and small action potential-evoked Ca²⁺ events, while Bhumbra and Beato (2013) used a Bayesian framework of quantal analysis to estimate synaptic parameters, which required far fewer trials compared to traditional methods. Here, we introduce a Bayesian approach to obtain the posterior distribution of TM model parameters. This enabled us to take into account the uncertainty inherent to experimental data, which provided a more complete description of STP data.

Our approach has several advantages. First, it allowed us to infer the distribution of synaptic parameters for individual connections and propose a better protocol to extract these parameters. Second, we found that parameter distributions extracted from cortical data are specific to different connection types. Third, we showed that we can automatically cluster the parameters of synaptic dynamics to at least partially classify postsynaptic cell types. We also performed model selection to determine which variant of the TM model best captures the synaptic dynamics of the connection type at hand.

¹The work presented in this chapter is published in Costa et al. (2013a).
²The experimental data used in this chapter was obtained by Kate Buchanan and Dale Elgar (University College of London) and is published in Buchanan et al. (2012).
2.2 Material and Methods

2.2.1 Short-term plasticity phenomenological model

The extended TM model (eTM), is a phenomenological model of short-term plasticity defined by the following ODEs (Markram et al., 1998; Tsodyks et al., 1998)

\[
\frac{dR(t)}{dt} = \frac{1 - R(t)}{D} - u(t^-)R(t^-)\delta(t - t_{AP}) \tag{2.1}
\]

\[
\frac{du(t)}{dt} = \frac{U - u(t)}{F} + f[1 - u(t^-)]\delta(t - t_{AP}) \tag{2.2}
\]

The first equation models the vesicle depletion process, where the number of vesicles \( R(t) \) is decreased with \( u(t^-)R(t^-) \) after release due to a presynaptic spike at time \( t_{AP} \), modeled by a Dirac delta distribution \( \delta(t) \). Between spikes \( R(t) \) recovers to 1 with a depression timeconstant \( D \). The second equation models the dynamics of the release probability \( u(t) \) which increases with \( f(1 - u(t^-)) \) after every presynaptic spike, decaying back to baseline release probability \( U \) with a facilitation timeconstant \( F \). The notation \( t^- \) indicates that these functions should be evaluated in the limit approaching the time of the action potential from below (as would be natural in forward Euler integration).

By varying the four parameters \( \tilde{\theta} = \{D, F, U, f\} \) one can obtain depressing, combined facilitating-depressing and facilitating synaptic dynamics. We note that for some data a three parameter model (setting \( f = U \), denoted the TM with facilitation model) or even a two parameter depression model with only Equation 3.11 (setting \( u(t) = U \), denoted the TM model) is sufficient. This, however, is not generally the case, as shown below.

To speed up the numerical implementation we integrated the above equations between spikes \( n \) and \( n + 1 \), a time \( \Delta t_n \) apart, yielding

\[
R_{n+1} = 1 - [1 - R_n(1 - u_n)]\exp\left(-\frac{\Delta t_n}{D}\right) \tag{2.3}
\]

\[
u_{n+1} = U + [u_n + f(1 - u_n) - U]\exp\left(-\frac{\Delta t_n}{F}\right) \tag{2.4}
\]

As we assumed that at time zero the synapse has not been recently activated, we set \( R_0 = 1 \) and \( u_0 = U \).

The postsynaptic potential \( PSP_n \) is given by

\[
PSP_n = AR_nu_n \tag{2.5}
\]
Table 2.1: The five parameter sets used for simulated data. EPR was calculated by simulating the eTM model with 5 pulses at 30Hz as shown in Figure 2.2.

where \( A \) is an amplitude factor that includes the number of release sites, the properties and number of postsynaptic receptors, and cable filtering.

The steady-state values \( R_\infty \) and \( u_\infty \) in response to prolonged periodic stimulation with rate \( \rho \) are

\[
R_\infty(\rho) = \frac{1 - \exp\left(-\frac{1}{\rho D}\right)}{1 - \left[1 - u_\infty(\rho)\right] \exp\left(-\frac{1}{\rho D}\right)} \tag{2.6}
\]

\[
u_\infty(\rho) = \frac{U + (f - U) \exp\left(-\frac{1}{\rho F}\right)}{1 - (1 - f) \exp\left(-\frac{1}{\rho F}\right)} \tag{2.7}
\]

2.2.2 Simulated data

For the simulated data we used 5 sets of STP parameters, ranging from depression to facilitation, see Table 2.1.

As the commonly used paired-pulse ratio, \( \text{PPR} = \frac{\text{PSP}_2}{\text{PSP}_1} \), only takes the first two pulses into account, we introduce the Every Pulse Ratio (EPR) as a more comprehensive measure of STP dynamics. It is defined as

\[
\text{EPR} = \frac{1}{(n-1)} \sum_{i=1}^{n-1} \frac{\text{PSP}_{i+1}}{\text{PSP}_i} \tag{2.8}
\]

This index measures the average amplitude change from the \( i \) to the \( i + 1 \) response normalized to the \( i \) response in the train. EPR is used in Table 2.1 and elsewhere to quantify the average degree of depression (EPR < 1) or facilitation (EPR > 1). Using these parameters we calculated the synaptic responses with Equation 4.17 and Equation 4.18 to a spike train of five pulses at 30Hz (Figure 2.2 and 2.4).
2.2. Bayesian formulation

The posterior distribution of the synaptic parameters follows from Bayes’ theorem as $P(\tilde{\theta}|\tilde{d}) \propto P(\tilde{\theta})P(\tilde{d}|\tilde{\theta})$, where $\tilde{d}$ is a vector of mean postsynaptic potential peaks extracted from simulated or experimental data and $\tilde{\theta}$ is a vector encompassing the model parameters. Many factors contribute to variability in the measured EPSPs, including stochastic vesicle release and experimental noise. A typical noise model of synaptic transmission is a binomial distribution (Zucker and Regehr, 2002). However, we found that our data is well described by a Gaussian noise model (see below). Therefore, we write the likelihood of the data as

$$P(\tilde{d} | \tilde{\theta}) = \prod_{i=1}^{N} \frac{1}{\sqrt{2\pi\sigma_i^2}} \exp \left[ -\frac{(d_i - \text{STP}(\text{PSP}_i | \tilde{\theta}))^2}{2\sigma_i^2} \right]$$

(2.9)

where $\text{STP}(\text{PSP}_i | \tilde{\theta})$ is the voltage response from the eTM model for $i = 1 \ldots N$ runs over the data points in the pulse train. We set the noise $\sigma_i$ independently for each pulse. For the data we extracted the CV for each pulse, while for the simulated data a fixed coefficient of variation (CV=0.5) was assumed, based on Figure 2.1B. Note that we did not include a model of stochastic vesicle release. This would be a possible extension of our model. A stochastic release model also leads to correlations between subsequent events, and Equations 4.18 and 4.17 would thus have to be extended to their history-dependent variances, which would complicate our model. We did confirm that parameters from a simulated stochastic release model, were inferred correctly using the above noise model, although the posterior distributions were somewhat widened.

The priors were modelled as independent non-informative flat distributions over the model parameters

$$P(\tilde{\theta}) = \begin{cases} P(D) = P(F) = \text{Uniform}[0, 2] \\ P(U) = P(f) = \text{Uniform}[0, 1] \end{cases}$$

(2.10)

which limits the posterior distribution within reasonable values.

Bhumbra and Beato (2013) sampled their bidimensional posterior probability using a brute-force grid search. For higher dimensions, this is computationally expensive. We therefore inferred the posterior distribution by sampling using the Slice Sampling Markov Chain Monte Carlo (MCMC) method (Neal, 2003). The width parameter $w$ was set equal to the upper limit of the flat prior distributions (i.e. $\vec{w} = \{2, 2, 1, 1\}$) and each parameter is sampled sequentially in the four orthogonal directions. We discarded
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the first 2500 samples as burn-in and use the last 7500. For the numerical implementation we use the log-likelihood \( \log P(\vec{d}|\vec{\theta}) \). The convergence of the Markov chain to the equilibrium distribution was assessed through the Gelman-Rubin statistical method (Brooks and Gelman, 1998). However, this diagnostic of convergence can only indicate a lack of convergence, but does not confirm it. Therefore, in order to ensure convergence, we used multiple chains \((n = 3)\) starting at different initial conditions (Gelman and Shirley, 2010) to ensure that the outcome was independent on the initial condition. The maximum a posteriori (MAP) estimator of the synaptic parameters is given by

\[
\hat{\theta}_{\text{MAP}} = \operatorname{argmax}_{\vec{\theta}} P(\vec{\theta}) P(\vec{d}|\vec{\theta}) \tag{2.11}
\]

The MAP estimate was obtained by keeping the most likely sample from multiple MCMC chains. In addition we also ran an optimizer to find the most precise MAP using the distribution peak as a starting point. As both approaches gave equally good fits for the sake of simplicity we decided to use the former.

We compared our estimation method with a standard stochastic optimization method, simulation annealing (SA). The SA method minimizes the RMSE

\[
\hat{\theta}_{\text{SA}} = \operatorname{argmin}_{\vec{\theta}} \sqrt{\frac{1}{N} \sum_{i=1}^{N} \left[ d_i - \text{STP}(PSP_i|\vec{\theta}) \right]^2} \tag{2.12}
\]

while trying to avoid getting stuck in local minima. We ran the SA algorithm 200 times and select the estimate with lowest RMSE. Using an objective function scaled by the variance gave similar results when compared to the non-scaled version; thus for the sake of comparison with previous literature, we used the non-scaled version. To compare the goodness of fit of both MAP and SA solutions with the data, we used the coefficient of determination \( R^2 \).

As the amplitude \( A \) is not relevant for the synaptic dynamics, we set \( A = A^{\text{MAP}} \).

\[
A^{\text{MAP}} = \frac{\sum_{i=1}^{N} d_i m_i / \sigma_i^2}{\sum_{i=1}^{N} m_i^2 / \sigma_i^2} \tag{2.13}
\]

where \( m_i = \text{STP}(PSP_i|\vec{\theta}) \). We used this value to normalize the data. Its value does not affect the dynamics estimation, because \( A \) only scales the responses.

To estimate the posterior probability distributions, we used a kernel density estimation method (Ihler and Mandel, 2007). Unless otherwise stated, the code was implemented in Matlab (inference code is available online \(^3\)).

\(^3\)https://senselab.med.yale.edu/modeldb/ShowModel.asp?model=149914
2.2. Material and Methods

2.2.3.1 Quantifying inference performance

To quantify which protocol allows for the most precise recovery of the true parameters of simulated STP data (Figure 2.3A), we computed the sample estimation error over $N = 22500$ MCMC samples $\tilde{\theta}$ to the true parameters $\theta^*$, as $E = \langle \sum_{i=1}^{4} \left[ (\theta_i - \theta^*_i) / \theta^*_i \right]^2 \rangle$, where the average is over all the runs and all 5 parameter sets (Table 2.1). To achieve similar weighting, the parameters were normalized to the true parameters. Alternatively, we normalized the estimated parameters on the upper limit of their priors, or we omitted normalization altogether. This yielded similar results. Note that in probabilistic spirit, this error also quantifies the spread in the distribution. A smaller $E$ gives more peaked distributions, which correspond to tighter parameter estimates. Note that, although similar, this error measure does not follow the standard bootstrap approach.

2.2.3.2 Model selection

For model selection, we used the Akaike Information Criterion (AIC), which is a information-theoretic measure of the goodness of fit of a given statistical model. It is defined as $\text{AIC} = 2k - 2\log P(\tilde{\theta}_{\text{MAP}}|\tilde{d})$, where $k$ is the number of estimable parameters in the model and $\log P(\tilde{\theta}_{\text{MAP}}|\tilde{d})$ the log-posterior of the MAP estimate on the normalized data. The AIC evaluates models according to their parsimonious description of the data, and is particularly suitable for probabilistic inference. We used the evidence ratio, which is a relative ranking of the Akaike weights, to find the least complex model that best describes the data (Turkheimer et al., 2003; Nakagawa and Hauber, 2011).

2.2.4 Electrophysiology

Quadruple whole-cell recordings and extracellular stimulation were performed in acute visual cortex slices of young mice (P12-P20) as previously described (Buchanan et al., 2012). The stimulating electrode was positioned in layer 5 (L5). L5 Pyramidal cells (PCs) were targeted based on their characteristic pyramidal soma and thick apical dendrite. Basket cells (BCs) were targeted in transgenic mice genetically tagged for parvalbumin, while Martinotti cells (MCs) were targeted in mice genetically labelled for somatostatin (Buchanan et al., 2012; Markram et al., 2004). Cell identities were verified by cell morphology and rheobase firing pattern. Five spikes were elicited at 30Hz using 5 ms long current injections (0.7 - 1.4nA) every 18 seconds in all neurons throughout the experiment. Excitatory postsynaptic potentials (EPSPs) were averaged from 20-40 sweeps.
For each connection, a histogram was built from the EPSP amplitudes extracted with 1-2-ms window fixed approximately on the peak depolarization. EPSP distributions were fit with a Gaussian (Equation 2.9). Recordings with mean EPSPs smaller than 0.015 mV were discarded. Electrophysiological data analysis was carried out in Igor Pro (WaveMetrics Inc., Lake Oswego, OR).

Figure 2.1: The experimental STP data was well described by a Gaussian noise model. (A) Sample EPSP distributions for the three connection types: PC-PC (top, red), PC-BC (middle, green) and PC-MC (bottom, blue) with respective Gaussian fits (solid black line) — 94% of the EPSP distributions were not statistically significant different from a Gaussian distribution using a significance level of 0.05 (see main text for more details). (B) Coefficient of variation analysis. While for facilitating synapses (PC-MC) it was more or less constant, for depressing synapses (PC-PC and PC-BC) we observed an approximately linear increase with EPSP amplitude. Error bars represent standard error of the mean.

Figure 2.1A shows typical EPSP distributions for each of the three neocortical excitatory connection types that we studied, PC-PC, PC-BC, and PC-MC. We tested whether the Gaussian noise model was a valid description of the data using the Kolmogorov-Smirnov (KS) normality test, and we found that the null hypothesis that samples were drawn from a normal distribution could not be rejected for 160 out of 170 EPSP distributions, with no connection-specific bias. Moreover, in our data analysed there was
2.2 Material and Methods

not any apparent correlation between significance and EPSP index, and we did not find a clear trend in EPSP distributions that did not follow a Guassian. This suggests that EPSPs were typically normally distributed, consistent with previously published results (e.g. Fig 5B in Markram et al. (1997a)). Due to noise, apparently negative EPSPs (Figure 2.1A) were occasionally recorded. These are consistent with our Gaussian noise model and require no special treatment. However, as discussed above a binomial noise model coupled with a model of short-term plasticity dynamics should in principle yield a better description of the statistics of synaptic.

2.2.5 Clustering and classification

Distributional clustering was introduced by Pereira et al. (1993). Here we applied a similar information-theoretic approach to cluster \( P(\vec{\theta}|\vec{d}) \). Instead of a 'soft' clustering approach we used 'hard' clustering, due to its simplicity, computation speed and comparison with standard clustering techniques. We used an agglomerative method (unweighted average distance method, Sokal (1958)) and an \( f \)-divergence metric. \( f \)-divergence metrics constitute a family of functions that measure the difference between two probability distributions. Consider two discrete probability distributions \( P \) and \( Q \) both discretized into \( N \) bins. To compare any given pair of distributions we used two \( f \)-divergence metrics: (i) the symmetrized Kullback-Leibler divergence

\[
KL_s(P, Q) = \frac{KL(P, Q) + KL(Q, P)}{2} \tag{2.14}
\]

with

\[
KL(P, Q) = \sum_{i=1}^{N} P_i(\vec{\theta}|\vec{d}) \log \frac{P_i(\vec{\theta}|\vec{d})}{Q_i(\vec{\theta}|\vec{d})} \tag{2.15}
\]

and the (ii) Hellinger distance

\[
HL(P, Q) = \frac{1}{\sqrt{2}} \sqrt{\sum_{i=1}^{N} \left( \sqrt{P_i(\vec{\theta}|\vec{d})} - \sqrt{Q_i(\vec{\theta}|\vec{d})} \right)^2} \tag{2.16}
\]

Due to the high dimensionality of our problem, we approximated these two measures first marginalizing \( P(\vec{\theta}|\vec{d}) \) over the \( d = 4 \) dimensions and then computing the sKL and HL over the \( d \) marginal probabilities. We compared our posterior-based clustering with clustering based on the SA estimates. Here, we used the Euclidian distance on the z-scored parameters found with SA.

To estimate the number of clusters we used the Pseudo-F statistic (Caliński and Harabasz, 1974). The Pseudo-F statistic captures the tightness of clusters as the ratio
of the mean sum of squares between clusters to the mean sum of squares within cluster

\[ P_{\text{pseudo-F}} = \frac{(T - P_G)/(G - 1)}{P_G/(n - G)} \]  

(2.17)

where \( T = \sum_{i=1}^{n}(P_i - \bar{P})^2 \) is the total sum of squares, \( P_G = \sum_{i=1}^{G} \sum_{j=1}^{n_i}(P_{ij} - \bar{P_i})^2 \) is the within-cluster sum of squares, \( G \) is the number of clusters, and \( n \) the total number of items. A larger Pseudo-F usually indicates a better clustering solution. The Pseudo-F statistic has been found to give best performance in simulation studies when compared with 30 other methods (Milligan and Cooper, 1985).

To evaluate the clustering quality, we computed the dendrogram purity as described by Heller and Ghahramani (2005), where we considered two classes according to EPR: class 1 for \( EPR \leq 1 \) and class 2 for \( EPR > 1 \). This threshold allows us to separate mostly depressing from mostly facilitating synaptic dynamics.

Finally, we also performed classification using the Naive Bayes Classifier: \( P(C|\tilde{\theta}) \propto P(C)P(\tilde{\theta}|C) \), where \( P(C) \) is the prior over the different synapse types \( C \) and \( P(\tilde{\theta}|C) \) the likelihood for a given class. Although information about connectivity rates could in principle be incorporated in the prior, we used a uniform prior over the classes. Our likelihood is given by the MCMC inference over the model parameters for a given training dataset \( d_C \) and synapse type \( C \), i.e. \( P(\tilde{\theta}|C) = P(\tilde{\theta}|d_C) \). As the Naive Bayes Classifier assumes independence between the different classes, we have one independent model per class with the maximum a posterior decision rule \( \arg\max_{c \in C} P(C = c)P(\tilde{\theta}_{\text{MAP}}|C = c) \). We estimated the performance of our classifier with K-cross validation \( (K=7, \text{i.e.} \sim 80\% \text{ for PC-PC and PC-MC, and} \sim 60\% \text{ for PC-BC}) \), where we sampled over \( K \) data points (i.e. recordings) for each synapse-type to obtain our likelihood model and then test the classifier with the remaining data points. This process was repeated until all possible different \( K \) partitions of the data have been used. Accuracy is defined as the percentage of correct classifications for a given connection type.

### 2.3 Results

#### 2.3.1 Parameter inference certainty is synaptic dynamics dependent

We first checked our method in extracting short term plasticity parameters from simulated data with a standard stimulus train of 5 spikes at 30Hz (see Methods). We sim-
Figure 2.2: Bayesian inference of short-term plasticity parameters using simulated data. (A) Simulated PSPs (filled circles in response to five pulses at 30Hz) for five different synaptic parameter settings ranging from strong depression (yellow) to strong facilitation (dark red). The MAP solution of the inferred distribution is shown with diamonds. (B) Posterior marginalized distributions of the model parameters for the data in A. The true parameters (see Table 2.1) are shown as filled circles and the MAP solutions as diamonds.

Simulated data with predefined parameter sets ranging from strong depression to strong facilitation. This was achieved by decreasing the baseline release probability \(U\) and the depression timeconstant \(D\), while increasing the facilitation rate \(f\) and the facilitation timeconstant (see Methods, Table 2.1). The resulting dynamics are shown in Figure 2.2A.

Figure 2.2B shows the inferred parameter distributions for the various parameter settings. As the full distribution \(P(\theta)\) is four dimensional, we plotted the marginals only. The inferred parameter distributions showed varying behavior: The distributions for \(U\) were well-tuned to values close to the true parameter values. For the \(D\) parameter the shifts in the distributions followed the changes in the true parameter, becoming broader for depressing dynamics. Both \(F\) and \(f\) were not narrowly tuned to the true parameter. Although \(f\) was tuned to small values for facilitating synapses, its distribution became broader for depressing synapses. The \(F\) parameter was not particularly tuned to any value, being close to an uniform distribution for both depressing and facilitating synapses. We explored the possibility that the broadness of \(F\) depended on the prior boundaries by extending them to 5 s and to 10 s. However, the distribution remained uniform and merely grew wider, suggesting that the broad distribution was not caused...
by an improper choice of prior. In summary, the inference procedure shows that — depending on the dynamics — the inferred parameter distributions can be narrow or broad and that some parameters are much more tightly constrained than others.

### 2.3.2 Improving experimental protocol for parameter inference

The fact that some of the inferred parameter distributions were broad suggested that the 5 pulse protocol did not yield enough information to reliably infer the true parameters. Therefore, we used our probabilistic formulation to find an experimental protocol that improves the inference quality (Figure 2.3). To this end, we compared the sample estimation error on the estimates (see Methods) for different spike trains: (i) a periodic train at 30Hz, (ii) a periodic train with recovery pulses and (iii) a Poisson train of 30Hz (Figure 2.3A). We also varied the number of spikes in the train.

The widely used protocol to probe synaptic dynamics, a paired-pulse, gave poor estimates even when coupled with 9 recovery pulses spaced exponentially across 4 seconds. Using 5 pulses in the spike train improved the performance only moderately. Some studies have inferred the TM model parameters with 8 spikes and a single recovery pulse after 500 ms (e.g. Wang et al. (2006)). This does not improved the recovery error when compared to a periodic spike train alone. A Poisson spike train, however, surpasses other protocols using only 20 spikes. Therefore, we propose a Poisson spike train with 20...100 spikes as a better protocol to obtain accurate estimates of the model parameters. However, also a spike train with 8 periodic pulses and 9 recovery pulses offers a good compromise, yielding a low recovery error in a reasonably short duration (≈ 4.23s). The distributions for these two protocols were more narrowly tuned to the true parameters (Figure 2.3B,C) compared to a periodic spike train without a full recovery phase (Figure 2.2B). Contrary to our intuition, the distributions for $D$ were more narrowly tuned for facilitation (darker colors) than for depression (lighter colors).

Although for the sake of simplicity, we do not show the results for a short periodic train followed by a Poisson train, such an approach would combine the ability to compute standard STP measures and recover information across frequencies. The reason for the poor performance of periodic trains even with many pulses is that the synapse quickly reaches steady-state, given by Equations 2.6 and 2.7. Hence additional pulses do not increase information and the estimation error quickly reaches a plateau. In contrast, a random Poisson train allows the inference process to converge to the true parameter distributions in the limit of large spike trains.
2.3. Results

Note, that both in Figure 2.2B and Figure 2.3B,C, the MAP solution is not always at the peak of the marginal distributions. The reason is that when there are dependencies in the parameters, the peak in the full distribution $P(\tilde{\theta})$ does not need to coincide with the peaks of the marginals. Indeed, when we compared the log-posterior of the MAP estimate to the log-posterior of the estimate given by the maximum of each marginal probability alone, the MAP approach yielded a much better estimate: \( \log P(\tilde{\theta}_{\text{MAP}}|\vec{d}) = -0.0038 \), compared to the maximum of the marginal probabilities, \( \log P(\tilde{\theta}_{\text{marginals}}|\vec{d}) = -0.6588 \).

2.3.3 Probabilistic inference of neocortical data reveals connection-specific distributions

Next, we performed Bayesian inference of the eTM parameters on experimental data from visual cortex L5. We recorded these data earlier using a standard five-pulse protocol, instead of the improved protocols suggested above. This means that the parameters may not be optimally constrained, but the overall findings should still hold. We inferred the posterior distributions of the parameters $U$, $D$, $F$, and $f$ from PC-PC, PC-MC, and PC-BC connections (Fig. 2.4A).

When comparing the Bayesian model inference of these three different synapse types (Figure 2.4B), the most salient difference was observed in the $U$ parameter, i.e., the baseline probability of release. PC-MC connections had a small $U$, $D$ and $f$. PC-PC connections had a medium $U$, medium to high $D$, a close to uniform $F$ and a broad $f$ with a preference for smaller values. PC-BC connections were similar to PC-PC connections, apart from a larger $U$ (PC-BC: $0.72 \pm 0.04$, $n = 12$; PC-PC: $0.53 \pm 0.05$, $n = 9$; $p < 0.01$, Mann-Whitney test based on the MAP estimates). This higher value of $U$ indicates that PC-BC synapses are generally more strongly depressing than PC-PC synapses. However, the EPRs for these two connection types were indistinguishable PC-BC: $0.63 \pm 0.04$, $n = 12$; PC-PC: $0.69 \pm 0.03$, $n = 9$; $p = 0.21$, Mann-Whitney test), suggesting that the model inference is more sensitive than the EPR measure, and is therefore better suited for picking up connection-specific differences in short-term plasticity.

We next used our Bayesian approach for synapse classification. We first clustered the data of the various connections based on the model parameters found by SA, Figure 2.5A. We next clustered based on the marginalized posterior distributions, Figure 2.5B using the Hellinger distance (see Methods). Clustering analysis showed that the
Figure 2.3: The performance of various stimulation protocols to infer short-term plasticity parameters. (A) Comparison of mean sample estimation error using different stimulation trains. Black arrow corresponds to the protocol used in Figure 2.2. A periodic spike train at 30Hz with 8 pulses and 9 recovery pulses (green arrow, (B)) already provided a better estimate of the STP parameters. However, a Poisson train provided a much smaller error when using more than 20 spikes with a close to zero error for 1000 spikes (blue arrow). (B) Posterior distribution for a periodic train with 9 recovery pulses (cf. Fig 2.2B). (C) Posterior distribution for a Poisson train with 1000 pulses. The true parameters (see Table 2.1) are shown as filled circles and the MAP solutions as diamonds. For visualization the marginal probabilities were scaled by their standard deviation.
Figure 2.4: Inference of short term plasticity parameters from experimental data from visual cortex. (A) Sample experimental STP traces are shown for PC-PC (red), PC-BC (green), and for PC-MC (blue) connections. (B) Marginalized posterior distributions obtained using slice sampling from these three different excitatory connections suggest that PC-MC (n=9) connections are quite different from PC-PC (n=9) and PC-BC (n=12) connections. Light colored lines show individual distributions, while dark colored lines correspond to their average.
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Figure 2.5: Agglomerative clustering using posterior distributions obtained from experimental data improves synaptic dynamics clustering. (A) Clustering based on the synaptic parameters found by SA did not produce good clusters. (B) Clustering of posterior distributions using the probabilistic approach with the Hellinger distance gave rise to two clusters: one for short-term depression and the other for short-term facilitation (cf. EPR, inset bottom), with the first corresponding to both PC-PC and PC-BC connections, while the other roughly mapped onto PC-MC synapses. (C) EPR-based dendrogram purity with probability distribution-based clustering is higher than the purity from SA-based clustering. (D) Maximal pseudo-F statistic suggests that the data contains 2 or 6 clusters when clustering the posterior distributions or SA-based clustering, respectively (orange filled circles). (E) A simple probabilistic classifier (Naive Bayes) achieved good performance for all the connection types, in particular for PC-MC connections (black dashed line represents chance level). Error bars represent standard error of the mean.
Bayesian approach improved the dendrogram purity (Figure 2.5C), as it split the data into two distinct clusters as assessed by the Pseudo-F statistic (Figure 2.5B, D).

With SA-based clustering, the Pseudo-F statistic suggested 6 clusters (Figure 2.5A,C) with a lower dendrogram purity (Figure 2.5C, 0.89 purity level), which indicates that these six clusters are spurious. Furthermore, with the Bayesian approach, the clusters map better to the EPR measure (Figure 2.5B, inset bottom), indicating that our approach captures the synaptic properties better than the SA approach. The two clusters found by our approach correspond to synapses that are either chiefly depressing or facilitating. Still, the clusters did not correspond well to synapse type. In particular, PC-PC and PC-BC synapses were classified as the same type.

In an alternative approach, we also clustered the Bayesian posteriors using the symmetric KL-divergence (sKL). The sKL achieved 0.78 dendrogram purity and 3 clusters according to the Pseudo-F statistic; thus performing worse.

To determine how well the posterior distributions could be classified in keeping with the three connection types, we performed Naive Bayes classification with a 7-fold cross-validation (Figure 2.5E). We obtained 100% accuracy in PC-MC connection classification. Surprisingly, however, we also obtained a 72% and 75% classification accuracy for PC-PC and PC-BC connections, respectively. These results suggest that each synapse type can be to some extent separated from the other two types in this local circuit. The ability to separate the different connection types is likely to be mostly due to differences in the baseline release probability (cf. Figure 2.4B, parameter U).

### 2.3.4 Comparison to traditional fitting methods

Above we found that for both the simulated and the experimental data, the marginalized posterior of the $F$ parameter resembles an uniform distribution (Figure 2.2B and 2.4B). This suggests that standard fitting method techniques might not perform well and may become trapped in local minima, thus explaining why the SA-based clustering is not able to separate the different synaptic dynamics as well. To test this idea, we used SA on a depressing PC-PC connection and we found that this was indeed the case (Figure 2.6A,B). Although the method found every time good fits to the data (Figure 2.6A), the fit parameters were highly variable from one run to the next (Figure 2.6B). Although this variability could be used a proxy for the parameter variance, there is no principled way in SA to estimate parameter variance. In contrast, with our Bayesian approach, the variability and exact distribution is captured in the posterior distribution.
Figure 2.6: Comparison of Bayesian approach and traditional fitting methods using experimental data. (A) STP models using either MAP or SA solutions (green and red crosses, respectively) provide good fits to the experimental data (black filled circles). (B) Marginalized posterior distributions for the depression and facilitation timeconstants (grey and black line, respectively). When fitting the data in (A) 10 times, SA yields widely different parameter values (red diamonds, all solutions provided good fits to the data $R^2 >0.99$). The MAP solution is shown with a green diamond. The red arrow indicates the SA fit used in A.

Similar observations were made by Varela et al. (1997), who occasionally found an elongated error valley when fitting their particular STP model.

### 2.3.5 Finding the best model using probabilistic inference

The Bayesian approach offers a natural way to examine which model describes the data most parsimoniously. We performed model selection to identify which formulation of the TM model better described the data (see Methods). We compared three formulations of the TM model: (i) with depression only — only Equation 3.11 with $D$ and $U$ (2 parameters) —, (ii) depression and facilitation — Equation 3.11 and 3.2 with $D$, $F$ and $U$ (3 parameters) — and (iii) the full extended model used above. Figure 2.7 shows that only the extended model is able to account for all the data from the three connection types. In contrast to Markram et al. (1998) and Richardson et al. (2005), we found that the TM-with-facilitation model does not fit the PC-MC connections well. Although for some recordings the three-parameter model was sufficient, it failed to fit other recordings (Figure 2.7B). This discrepancy might be due to experimental differences; our dataset was recorded in mice visual cortex L5 and included extracellular
stimulation experiments, while Markram et al. (1998) and Richardson et al. (2005) recorded in the somatosensory cortex of the rat using paired recordings only.

Figure 2.7: Extended TM model improves the fitting of PC-MC synapses. (A) The evidence ratio based on the Akaike Information Criterion is plotted on a logarithmic scale for the three excitatory synaptic types. Three formulations of the Tsodyks-Markram model were compared — with only depression (TM, 2 parameters), with a degree of facilitation (TM with facilitation, 3 parameters) and the extended version with full facilitation (eTM, 4 parameters). Error bars represent standard error of the mean. (B) Examples of normalized postsynaptic peak responses that can only be accurately fitted by the eTM model. Top: PC-PC recording with combined depression and facilitation. Bottom: PC-MC recording with attenuating facilitation. The postsynaptic peak responses (black filled circles) are given together with the MAP solutions from the 2, 3 and 4 parameters model, from dark to light green, respectively.

2.4 Discussion

Past studies characterizing short-term synaptic dynamics have typically used traditional fitting methods. A Bayesian approach, however, turns out to be particularly advantageous for this problem, because accurate estimation of synaptic parameters is complicated. Here, we have shown that — depending on the synaptic dynamics and experimental protocol — some parameters are not narrowly tuned but broadly distributed. This insensitivity may cause traditional least-mean-square methods to get
stuck in local minima.

When applied to experimental data, our method showed that different connections have different distributions. Such synapse-type specific plasticity supports the idea that different synapses perform different computations and subserve different functional roles in the local circuit. Our approach more robustly classifies synapses according to their synaptic dynamics than does clustering using simple point estimates of parameters obtained from standard optimization techniques. Our method might thus enable automatic and independent classification of synapses and cells taking into account the natural variability in the data. Future studies using larger datasets may better identify the synaptic properties that are specific to individual clusters. Furthermore, a model with a more detailed noise description could allow us to also infer the quantal parameters, which could in principle be combined with the Bayesian quantal analysis framework (Bhumbra and Beato, 2013).

We found that inference of the model parameters can be improved by having more pulses as well as by including a recovery phase. The data used here, however, was collected using a standard STP electrophysiology protocol with 5 pulses at 30Hz, which still enabled connection-specific clustering. To improve parameter inference further, we propose a combination of a periodic spike train and a Poisson spike train. More pulses add more information, which has an unsurprising positive impact on inference. Poisson trains cover the frequency space better without requiring excessively long experimental recordings. Indeed, Poisson trains add a considerable improvement as compared to the more standard protocol of using fixed-frequency trains (Markram and Tsodyks, 1996; Sjöström et al., 2003).

Experimentally STP has been observed to change with development (Reyes and Sakmann, 1999), drug wash-in (Buchanan et al., 2012), temperature changes (Klyachko and Stevens, 2006), and plasticity (Markram and Tsodyks, 1996; Sjöström et al., 2003). In such situations, it often becomes important to ascertain the particular parameter changes that occur. The Bayesian framework introduced here can be extended to elucidate which components of STP are affected by integrating prior knowledge, through an informative prior. For instance, inferred distributions can be tracked across development.

Our work can also be applied in constructing computer network models with short-term plasticity using posterior distributions inferred from actual biological data as a generative model. This would yield models with richer dynamics without resorting to simplistic and unrealistic ad-hoc approaches to generate synaptic variability that are
poorly grounded in biological data.

Our Bayesian approach promises improved computer models as well as a better and more nuanced understanding of biological data. Yet, this approach is not computationally intense, nor is it difficult to implement. We therefore fully expect probabilistic inference of STP parameters to become a widespread practice in the immediate future.

In the next chapter I extend this framework to study the impact of presynaptic NMDARs on short-term synaptic plasticity.
Chapter 3

Regulation of synaptic dynamics in 
the layer-5 microcircuit

“There is growing experimental evidence for the interaction of multiple timescales of synaptic plasticity (Bolshakov and Siegelbaum, 1995; Markram and Tsodyks, 1996; Sjöström et al., 2003, 2007; Tokuoka and Goda, 2008; Jin et al., 2012; Kintscher et al., 2013). For instance it is known that spike-timing-dependent plasticity leads to changes in synaptic dynamics (Markram and Tsodyks, 1996; Sjöström et al., 2003, 2007). In particular, experimental results show that time-dependent LTP (tLTP) yields synapses with stronger short-term depression (Markram and Tsodyks, 1996; Sjöström et al., 2007), while time-dependent LTD (tLTD) leads to weaker short-term depression at neocortical pyramidal cell-onto-pyramidal cell connections (Sjöström et al., 2003), which suggests that both tLTP and tLTD have a presynaptic component. However, how exactly is this interaction between synaptic plasticity scales implemented at the synaptic level is not clear. Presynaptic NMDA receptors (preNMDARs) have been implicated in this cross-scale interaction of synaptic plasticity (Sjöström et al., 2003; Duguid and Sjöström, 2006; Bender and Feldman, 2006). Traditionally NMDA receptors are thought of as solely being located postsynaptically underlying postsynaptic LTP (Bliss and Collingridge, 1993; Park et al., 2014). However, during the last 10 years preNMDARs have emerged as modulators of neocortical synaptic transmission and plasticity (Corlew et al., 2008; Duguid, 2012). Therefore the expression of preNM-
DARs can be used as a marker for the existence of specific forms of synaptic plasticity and for the study of its mechanisms.

Several studies have found that putative preNMDARs modulate short-term plasticity across different brain regions, such as: the entorhinal cortex (Berretta and Jones, 1996; MacDermott et al., 1999; Woodhall et al., 2001), cerebellum (Glitsch and Marty, 1999; MacDermott et al., 1999), spinal cord (Liu et al., 1997; MacDermott et al., 1999) and in cortical pyramidal layer-5 neurons of the rat visual cortex (Sjöström et al., 2003). Moreover, recent work by my collaborators showed that the expression of preNMDARs is target-specific in the layer-5 microcircuit (Buchanan et al., 2012). In this chapter in close collaboration with experimentalists I first present a study on the consequences for network information flow of the expression pattern of preNMDARs in the layer-5 microcircuit. Next we combined experimental analysis of the readily-releasable pool and an extension of the Bayesian inference framework introduced in the previous chapter to investigated how preNMDARs regulate the presynaptic terminal. Finally, we inferred the effect of preNMDARs on the synaptic dynamics at multiple excitatory connections types. These results shed light on how preNMDARs regulate the release machinery, which is important for our understanding of how preNMDAR-dependent spike-timing-dependent plasticity shapes synaptic dynamics.  

3.1 Presynaptic NMDARs reroute high-frequency information flow in local circuits

Recently, my experimental collaborators showed that NMDARs are indeed presynaptically expressed in the mice visual cortex and that their expression is determined by the postsynaptic cell type. The experiments demonstrating this are reported in Buchanan et al. (2012). Here I report on the model that I developed to study the functional consequences of these findings in the layer-5 microcircuit. This model consists of a simple local cortical network model with short-term plasticity tuned using pharmacological blockade data. The model was then used to predict the impact of these receptors on the flow of information in the local circuit.

Experimental results indicated that Pyramidal Cell-Pyramidal Cell (PC-PC) and Pyramidal Cell-Martinotti Cell (PC-MC), but not typical Pyramidal Cell-Basket Cell (PC-BC) connections possess preNMDARs (Buchanan et al., 2012). Based on these

1The work presented in this chapter is partially published, see individual sections for details.
3.1 Presynaptic NMDARs reroute high-frequency information flow in local circuits

findings — which are summarized schematically in Figure 3.1A — I tuned a phenomenological computer model of the local circuit that incorporated measured synaptic dynamics in control and preNMDAR blockade conditions. This model enabled us to predict the impact of preNMDAR differential expression on delayed inhibition mediated by PC-MC facilitatory connections and on fast inhibition provided by basket-cells onto a second postsynaptic pyramidal-cell in the local neocortical circuit (Silberberg and Markram, 2007).

3.1.1 Neocortical Local Network model

The computational neocortical model (Fig. 3.1A,B) was implemented in Matlab using adaptive exponential integrate-and-fire neuron models (Clopath et al., 2010; Brette and Gerstner, 2005). The parameters of the neuron model for PCs were obtained from Clopath et al. (2010), while for BCs and MCs the parameters were manually adjusted from the ones provided by Clopath et al. (2010) to yield fast (for BCs) and adapting (for MCs) firing patterns qualitatively similar to the experimental data published in Buchanan et al. (2012) (see Fig. 3.1 and Table 3.1). Moreover, for MCs the neuron models were tuned to individual recordings (see below and Table 3.2). Synapses were modelled using the Markram & Tsodyks short-term plasticity model (Tsodyks and Markram, 1997) extended with facilitation time constant and rate (Markram et al., 1998). In our implementation, we consider the amount of facilitation as being an extra parameter, \( f \), while Markram et al. (1998) assumed this to be equal to the baseline release probability. With this modification, the model provides a better fit to facilitating synapses (see Chapter 2). We refer to this model as the extended TM model (eTM), which is a phenomenological model of short-term plasticity defined by the following ODEs (Markram et al., 1998; Tsodyks et al., 1998)

\[
\frac{dR(t)}{dt} = \frac{1 - R(t)}{D} - u(t^-)R(t^-)\delta(t - t_{AP}) \\
\frac{du(t)}{dt} = \frac{U - u(t)}{F} + f[1 - u(t^-)]\delta(t - t_{AP})
\]

The first equation models the vesicle depletion process, where the number of vesicles \( R(t) \) is decreased with \( u(t^-)R(t^-) \) after release due to a presynaptic spike at time \( t_{AP} \), modeled by a Dirac delta distribution \( \delta(t) \). Between spikes \( R(t) \) recovers to 1 with

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2 The work presented in this section is published in Buchanan et al. (2012).
3 The experimental results used to tune and verify the model were obtained by Kate Buchanan and Dale Elgar from Jesper Sjostrom’s lab (University College of London).
a depression timeconstant $D$. The second equation models the dynamics of the release probability $u(t)$ which increases with $f(1-u(t))$ after every presynaptic spike, decaying back to baseline release probability $U$ with a facilitation timeconstant $F$.

EPSP amplitudes were extracted from experiments by subtracting fitted exponentials to account for temporal summation (see Sjöström et al. (2007)). The short-term plasticity parameters $U$, $f$, $D$, and $F$ were numerically fitted to a subset of recordings through minimization of the mean-squared error between the normalized EPSPs amplitudes obtained from the averaged traces and those obtained from the model output (as described in Chapter 2), by combining a genetic algorithm with constrained gradient descent to find the global MSE minimum. Note that this work was performed and published before the development of the Bayesian framework presented in Chapter 2. In Chapter 2 I showed that the protocols used here (5 pulses at 30Hz) are not informative enough to yield accurate estimations. This can in part explain the qualitative difference between the modelling and experimental results (see more details below). Although Bayesian inference allowed me to study this problem in a more principled framework, this limitation comes from the data itself rather than the optimization method used. Optimization with different initial conditions was repeated 10 times to ensure convergence. For PC-MC connections, preNMDAR blockade was simulated using the model fitted to the data recorded after the drug wash-in. Note that statistical tests and the standard error of the mean was calculated on the outcome from the different fitted models ($n = 9$), where the only variation is the MC neuron model and the PC-MC STP parameters. In the network model, all other connections — PC-BC, BC-PC, and MC-PC — were unaffected in simulated preNMDAR block. BC-PC and MC-PC connections were tuned to a single representative synapse of said type, and thus had short-term depression. Synaptic strengths at connections originating from model PCs were tuned to trigger one or a few action potentials in postsynaptic cells due to a 15-spike 70-Hz train of presynaptic spikes (see Fig. 2 in Silberberg and Markram (2007)). This usage of relatively large connective strengths thus approximates a scenario where small groups of cells are involved (Kapfer et al., 2007), with each group being represented by a single cell in our model. To obtain a degree of realistic variability in simulations, Gaussian noise with $\sigma = 50\mu A$ was added to postsynaptic responses and results were averaged over 50 trials.
3.1. Presynaptic NMDARs reroute high-frequency information flow in local circuits

Figure 3.1: PreNMDARs Reroute Information Flow in Local Circuits during High-Frequency Firing. (Continued on the following page.)
Figure 3.1: PreNMDARs Reroute Information Flow in Local Circuits during High-Frequency Firing — (A) Schematic summary of the findings, showing preNMDARs at PC-PC and PC-MC connections (closed triangles), but not at PC-BC (open triangles) and BC-PC or MC-PC connections (open circles). Frequency-independent and frequency-dependent disynaptic forms of inhibition between pairs of PCs are denoted FIDI and FDDI, respectively (in keeping with Silberberg and Markram (2007)). PC-PC are not modelled as the focus was on the delayed (PC-MC) versus fast inhibition (PC-BC). (B) A small phenomenological network model, with tuned synaptic dynamics (Markram et al., 1998), predicted that preNMDARs impact FDDI, but not FIDI, in local circuits. As a probe for FDDI, 70 Hz presynaptic PC firing was investigated (black vertical strokes), which evoked early spiking in BCs but late spikes in MCs, resulting in a characteristic biphasic inhibitory response in postsynaptic PCs (see Silberberg and Markram (2007)). Traces show the predicted outcome before (blue) and after (red) AP5. See Fig. 3.1 and 3.2 for model parameters. (C) Seventy Hertz firing in PC “1” evoked both FIDI and FDDI in PC “3” when the intermediate BC “2” was subthreshold depolarized. The intermediate MC “X” was not recorded. (D) As predicted by the model (B), FDDI (right), but not FIDI (left), in PC “3” (cf. C) was affected by AP5 washin (FDDI amplitude 0.95mV ± 0.05mV versus 0.54mV ± 0.04mV, p < 0.001; FIDI amplitude 0.72mV ± 0.05mV versus 0.84mV ± 0.04mV, p = 0.12). (E) In paired PC recordings, FDDI amplitude was consistently reversibly suppressed by AP5 compared to control experiments (25% ± 9% versus 105% ± 2%, p < 0.001). (F) The computer model predicted that preNMDARs impact both FDDI amplitude (left) and latency (right) to different degrees, depending on the specifics of PC-MC short-term plasticity. Each data point corresponds to a prediction based on an individual MC recording (see Fig. 5A-D and Experimental Procedures in Buchanan et al. (2012)). (G) FDDI experiments verified computer model predictions (F), showing a consistent increase in latency and suppression of amplitude due to AP5. Error bars represent mean ± SEM.
3.1. Presynaptic NMDARs reroute high-frequency information flow in local circuits

Table 3.1: Model parameters related to Fig. 3.1. For the neuron model we use an extension of the Adaptive-Exponential I&F model (Clopath et al., 2010; Brette and Gerstner, 2005), which captures layer-5 pyramidal cells firing profile, while the STP model is the extended Tsodyks-Markram model (see Chapter 2).

<table>
<thead>
<tr>
<th>Neuron Parameters</th>
<th>PC</th>
<th>BC</th>
<th>MC</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, membrane capacitance</td>
<td>132 pF</td>
<td>97 pF</td>
<td>Fig. 3.3</td>
</tr>
<tr>
<td>g_L, leak conductance</td>
<td>4.5 nS</td>
<td>6.9 nS</td>
<td>Fig. 3.3</td>
</tr>
<tr>
<td>E_r, resting potential</td>
<td>-70 mV</td>
<td>-70 mV</td>
<td>-61 mV</td>
</tr>
<tr>
<td>D_s, slope factor</td>
<td>2 mV</td>
<td>2 mV</td>
<td>2 mV</td>
</tr>
<tr>
<td>V_rest, resting threshold</td>
<td>-45 mV</td>
<td>-37 mV</td>
<td>Fig. 3.3</td>
</tr>
<tr>
<td>V_reset, after-spike potential</td>
<td>-65 mV</td>
<td>-80 mV</td>
<td>-56 mV</td>
</tr>
<tr>
<td>( \tau_{wa} ), adaptation timeconstant</td>
<td>144 ms</td>
<td>120 ms</td>
<td>144 ms</td>
</tr>
<tr>
<td>a, subthreshold adaptation</td>
<td>4 nS</td>
<td>4 nS</td>
<td>4 nS</td>
</tr>
<tr>
<td>b, spike-triggered adaptation</td>
<td>80.5 pA</td>
<td>8 pA</td>
<td>Fig. 3.3</td>
</tr>
<tr>
<td>( \tau_{yp} ), threshold timeconstant</td>
<td>50 ms</td>
<td>5 ms</td>
<td>50 ms</td>
</tr>
<tr>
<td>V_{max}, after-spike threshold</td>
<td>18 mV</td>
<td>7.8 mV</td>
<td>-7.4 mV</td>
</tr>
</tbody>
</table>

Table S2: Model parameters related to Fig. 3.1. STP parameters: baseline release probability \( U \), facilitation rate \( f \), facilitation timeconstant \( F \), depression timeconstant \( D \), synaptic efficacy amplitude \( A_{SE} \); Neuron parameters: membrane capacitance \( C \), leak conductance \( g_L \), resting threshold \( V_{rest} \), spike-triggered adaptation \( b \).
3.1.2 Results

This simple network model suggested that preNMDAR blockade specifically regulate frequency-dependent disynaptic inhibition mediated by MCs (FDDI; Silberberg and Markram (2007)), while leaving BC-mediated frequency-independent disynaptic inhibition (FIDI; Silberberg and Markram (2007)) unaffected (Fig. 3.1B). In the model preNMDAR blockade decreases short-term facilitation at the PC-MC synapses, while the remaining connections (including PC-BC) remain unaffected, which predicts changes in FDDI. To test the model predictions, we repeatedly sampled the local cortical circuitry using quadruple recordings, while spiking patched PCs at 70 Hz (Silberberg and Markram, 2007) and washing in AP5 to block preNMDARs. Figs. 3.1C and 3.1D illustrate one such experiment for which FDDI was both reduced and delayed by AP5, while FIDI was left unaltered. Indeed, AP5 consistently and reversibly reduced FDDI amplitude and increased latency compared to control experiments (Fig. 3.1E).

Based on the variability of synaptic dynamics measured at excitatory inputs to MCs before and after AP5 application (see Figs. 5A–5D in Buchanan et al. (2012)), the computer model predicted that the impact of preNMDARs on FDDI would also be variable, sometimes affecting latency and/or amplitude more or less (Fig. 3.1F). Interestingly, the impact of AP5 washing on FDDI observed in experiments (Fig. 3.1G) was indistinguishable from that predicted by the model (Fig. 3.1F; p = 0.43 and 0.89 for amplitude and latency, respectively). Although postsynaptic NMDARs desensitisation is known to contribute to short-term depression (Zucker and Regehr, 2002) this result suggests that the contributions to FDDI from postsynaptic NMDARs at PC-MC connections is small, as the model had no postsynaptic NMDARs. The computer model, however, predicted that FDDI should occur earlier than what experiments revealed (onset 60 ± 16 ms, n = 9 versus 110 ± 20 ms, n = 10, p < 0.05; Figs. 3.1F and 3.1G). This difference — which is due to simplifications in the model — is of little or no consequence for the main findings. Furthermore, the spike count before and after preNMDAR blockade in the network model suggest that there is a reduction in the number of spikes, which is consistent with the experimental data (not shown).

To summarize, this model predicted a synapse-specific functional impact of preNMDARs on information flow in local neocortical circuits during high-frequency firing. Together with collaborators we tested and validated this prediction experimentally. We conclude that preNMDARs are not implicated in BC-mediated FIDI but are in MC-
mediated FDDI (Silberberg and Markram, 2007). These results provide some insight into the functional consequences of preNMDARs at the network level, but is not yet clear how do they regulate the presynaptic release dynamics. In the next section we study what components of the pre-synapse are being regulated by preNMDARs.

### 3.2 Presynaptic NMDAR’s control of the release machinery

In this section through combined modeling and experimental work in collaboration with experimentalists I show how preNMDARs regulate the presynaptic release machinery. Short-term plasticity model parameters are inferred from electrophysiological data from excitatory synapses between pyramidal cells in the visual cortex layer-5 before and after preNMDAR blockade using a principled framework (an extension of the method presented in Chapter 2). Together with analyses of the vesicle pools — using a long train of evoked EPSCs to assess readily-releasable pool (RRP) — our results suggest that these receptors regulate the RRP refilling rates, which in turn changes the pool size, thus controlling the release probability. Moreover, experiments examining frequency-dependence allowed us to identify the precise frequency-dependence and the time constant of this effect. We also predict that preNMDARs do not reduce synaptic variability, but do increase the signal-to-noise ratio of synaptic transmission.

Synaptic transmission is a dynamic process, being the final output of a complex molecular and cellular release machinery. This machinery causes the membrane fusion of neurotransmitter-containing vesicles; the neurotransmitter then diffuses across the synaptic cleft to the postsynaptic terminal, where it binds to postsynaptic receptors, causing changes in the postsynaptic terminal. At short time scales, in the order of milliseconds to tens of seconds, synapses exhibit activity-dependent short-term plasticity (STP). This synaptic plasticity mechanism can be manifested as depression or facilitation, depending on the exact state of the synaptic neurotransmitter release machinery.

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5 The work presented in this section is the result of a collaborative project where different people contributed to the experimental work and respective analysis: (i) the mini EPSCs and calcium imaging data were obtained by Kate Buchanan (University College of London), (ii) the 14 evoked EPSC experiments to assess RRP were done by Therese Abrahamsson (McGill University), (iii) data for the frequency-dependence of preNMDAR activation was obtained by Kate Buchanan, Dale Elgar, Arne Blackman, Julia Oyrer (University College of London) and me, and (iv) I performed the model development and inference, theoretical analysis and designed some of the experimental research.
Chapter 3. Regulation of synaptic dynamics in the layer-5 microcircuit

This type of synaptic plasticity has an active role in neural information processing in several ways, such as filtering and adaptation (reviewed by Abbott and Regehr (2004)). For example, Abbott et al. (1997) showed that short-term depression provides synapses with a dynamic gain control mechanism and Mongillo et al. (2008) suggested that short-term facilitation contribute to working memory by conserving information from population spikes evoked by previous input patterns.

Short-term depression is thought to be due to depletion of available vesicles while facilitation is due to a temporary change in release probability. Since the first synaptic studies there has been evidence for a dynamic regulation of synaptic transmission at short time scales (Alger and Teyler, 1976; Zucker and Regehr, 2002). The central component being regulated is the neurotransmitter release, which depends mainly on the number of release-ready vesicles, the presynaptic concentration of $Ca^{2+}$ and the coupling between $Ca^{2+}$ and vesicle fusion. Therefore, there are several factors that may influence release probability, such as: different architectures and regulations of the $Ca^{2+}$ channels and the modulation of proteins involved in the release machinery (Zucker and Regehr, 2002; Branco and Staras, 2009).

Despite all efforts on studying the role and expression of preNMDARs, how they regulate synaptic transmission is still unclear. Here, we introduce a phenomenological model of preNMDAR-mediated regulation of STP. We applied a novel Bayesian inference framework for inferring the full distributions of the model parameters given the data before and after preNMDAR blockade (an extension of the method presented in Chapter 2). A decrease in the mEPSC frequency and basal $Ca^{2+}$ levels in the presynaptic boutons suggested a reduction in release probability. The STP inference revealed that the release probability and the depression time-constant are being regulated by preNMDARs. These results were supported by a steady-state analysis of the readily-releasable pool size and replenishment rate, which are regulated by preNMDARs. Furthermore, our phenomenological model captured the exact frequency-dependence activation of preNMDARs observed experimentally. Finally, theoretical analysis suggests that preNMDARs decrease the variability of the synaptic responses, while increasing their signal-to-noise ratio.

3.2.1 Materials and methods

Below I provide a description of the methods and models used.
3.2.1.1 Bayesian inference framework

We extended the Bayesian framework introduced in Chapter 2 for STP model inference to integrate in a single inference process the datasets before and after preNMDAR blockade. Note that in Chapter 2 we showed that such an approach is more reliable than standard best-fit methods.

In our extended Bayesian inference framework the key difference is that we use data from the same system under different conditions: before and after blockade of preNMDARs. These gives origin to two datasets \( \vec{d}_b \) (peak postsynaptic amplitudes before blockade) and \( \vec{d}_a \) (peak postsynaptic amplitudes after blockade) where each dataset is characterized by a latent STP parameter vector, \( \vec{\theta}_b \) and \( \vec{\theta}_a \). Therefore we extended our previously introduced Bayesian inference framework to take this into account as described by the graphical model given in Fig. 3.2.

![Graphical representation of Bayesian framework for preNMDAR blockade data.](image)

In this formulation both datasets are related through their parameters, so that we can use inference of \( \vec{\theta}_b \) when \( \vec{d}_b \) was recorded for the inference of \( \vec{\theta}_a \) given \( \vec{d}_a \). The distribution of interest is the posterior distribution \( P(\vec{\theta}_b, \vec{\theta}_a | \vec{d}_a, \vec{d}_b) \), which can be expanded as

\[
P(\vec{\theta}_b, \vec{\theta}_a | \vec{d}_b, \vec{d}_a) \propto P(\vec{d}_b, \vec{d}_a | \vec{\theta}_b, \vec{\theta}_a) P(\vec{\theta}_b, \vec{\theta}_a)
\]

\[
\propto P(\vec{d}_b | \vec{\theta}_b) P(\vec{d}_a | \vec{\theta}_a) P(\vec{\theta}_a | \vec{\theta}_b) P(\vec{\theta}_b)
\]

where \( P(\vec{\theta}_b) \) is the flat prior over the first parameter set (as the two parameter TM model is enough to capture PC-PC STP, see Chapter 2, we use \( \vec{\theta}_b = \{D_b, U_b\} \))

\[
P(\vec{\theta}_b) = P(D_b, U_b) = P(D_b)P(U_b) = \begin{cases} \[P(D_b) = U[0, 2] \\
P(U_b) = U[0, 1]\end{cases}
\]

(3.3)
Chapter 3. Regulation of synaptic dynamics in the layer-5 microcircuit

and $P(\tilde{\theta}_a|\tilde{\theta}_b)$ is the conditional prior probability that links the two datasets. As a Normal distribution allows us to easily specify the strength of this conditional prior probability through their standard deviation $\sigma$ we defined it as

$$P(\tilde{\theta}_a|\tilde{\theta}_b) = P(D_a|D_b)P(U_a|U_b)$$  \hspace{1cm} (3.6)

$$P(D_a|D_b) = N(D_a|D_b, \lambda \sigma_D^2)$$  \hspace{1cm} (3.7)

$$P(U_a|U_b) = N(U_a|U_b, \lambda \sigma_U^2)$$  \hspace{1cm} (3.8)

where $\sigma_1$ and $\sigma_2$ are the individual hyperparameters and are set according to the respective scale so that $N(D_a = 2|D_b = 0, \lambda \sigma_D^2) = N(U_a = 1|U_b = 0, \lambda \sigma_U^2) = 0.1$. To get $\sigma_D$ we solve $N(D_a|D_b, \sigma_D^2)$ with respect to $\sigma_D$ which yields

$$\sigma_D = \frac{i(D_a - D_b)}{\sqrt{W(2\pi N(D_a|D_b, \sigma_D^2)^2(D_a - D_b)^2)}}$$  \hspace{1cm} (3.9)

we get $\sigma_D \sim 3.3316$ and $\sigma_U \sim 3.8576$ following the same method for $U$. $W$ is the product log function$^6$ and $i$ is the imaginary unit $(\sqrt{-1})$. Note that the scales are defined according to the parameter upper limits as given by $P(\tilde{\theta}_b)$. This allows the prior $P(\tilde{\theta}_a|\tilde{\theta}_b)$ to relate the two parameter sets (before and after) in a scaled manner. $\lambda$ is then a global scale hyperparameter that controls the inverse strength of the prior. That is, as $\lambda \to \infty$ the prior becomes weaker and the two parameter sets independent, while for $\lambda \to 0$, $\theta_a \to \theta_b$. Therefore this formulation using a conditional prior allows us to relate the two conditions (before and after). In the results given below we used $\lambda = 1$, which provides a relatively weak prior.

As in Chapter 2 both likelihoods $P(\tilde{d}_b|\tilde{\theta}_b)$ and $P(\tilde{d}_a|\tilde{\theta}_a)$ are defined as

$$P(\tilde{d}|\tilde{\theta}) = \prod_{i=1}^{N} \frac{1}{\sqrt{2\pi \sigma_i^2}} \exp \left[ - \left( d_i - \text{STP}(\text{PSP}_i|\tilde{\theta}) \right)^2 / 2\sigma_i^2 \right]$$  \hspace{1cm} (3.10)

where $\text{STP}(\text{PSP}_i|\tilde{\theta})$ is the voltage response from the STP model for $i = 1 \ldots N$ runs, which correspond to the data points in the pulse train, while the noise $\sigma_i$ is independent for each pulse and is extracted from the data. For more details on the exact sampling method and maximum a-posteriori estimators see Chapter 2.

For model selection we varied the number of parameters that can change from the first parameter set $\tilde{\theta}_b$ to the second one $\tilde{\theta}_a$ – i.e. $D$, $U$ or both, and then used the Akaike Information Criterion (AIC) for model comparison (as in Chapter 2).

$^6$Also called Lambert W function, omega function or product logarithm.
3.2. Presynaptic NMDAR's control of the release machinery

3.2.1.2 PreNMDAR phenomenological model

Our model is based on the Tsodyks-Markram model (Markram et al., 1998) without facilitation (see also Chapter 2):

\[
\frac{dR(t)}{dt} = \frac{1 - R(t)}{D} - UR(t)\delta(t - t_{AP})
\]  
(3.11)

This equation models the vesicle depletion process, where the number of vesicles \( R(t) \) is decreased with \( UR(t) \) after release due to a presynaptic spike at time \( t_{AP} \), modeled by a Dirac delta distribution \( \delta(t) \). Between spikes \( R(t) \) recovers to 1 with a depression timeconstant \( D \). \( U \) represents the usage of the presynaptic vesicles, which here we interpreted as being equivalent to the release probability.

We then integrated the above equations between spikes \( n \) and \( n + 1 \), a time \( \Delta t_n \) apart, yielding

\[
R_{n+1} = 1 - [1 - R_n(U)] \exp\left(-\frac{\Delta t_n}{D}\right)
\]  
(3.12)

As we assumed that at time zero the synapse has not been recently activated, we set \( R_0 = 1 \).

The postsynaptic potential \( PSP_n \) is given by

\[
PSP_n = AR_nU
\]  
(3.13)

where \( A \) is an amplitude factor that includes the number of release sites, the properties and number of postsynaptic receptors, and cable filtering, and is set to the maximum a-posteriori as specific in Chapter 2.

When applying the Bayesian inference framework described above to this STP model and RRP analysis of the data we show that preNMDARs regulate both the depression time-constant (\( D \)) and the release probability (\( U \)) (see results section). The most parsimonious explanation is that the latter is a consequence of the former — a slower RRP recovery time-constant yields a smaller RRP, which in turn changes \( U \).

In our model the depression time-constant \( D \) (related to refilling rate) is controlled by preNMDAR activation as

\[
D = \beta D_{\text{fast}} - (1 - \beta)D_{\text{slow}}
\]  
(3.14)

where \( \beta \) represents the preNMDAR activation. \( D \) can be shifted between the parameters \( D_{\text{fast}} \) and \( D_{\text{slow}} \) by varying \( \beta \), where \( \beta = [0, 1] \) — note that \( \text{fast} \) and \( \text{slow} \) represent before and after preNMDAR blockade in our inference framework, respectively. This allows us to model the changes in \( D \) in a similar fashion to what is done in experiments.
and also capture the frequency-dependence effect (see below). At any given moment $\beta$ can be set to 0, which models the preNMDAR blockade (similar to the antagonist drug wash-in). Similarly, preNMDAR activation also regulates $U$ through $\beta$

$$U = \beta U_{\text{high}} - (1 - \beta) U_{\text{low}}$$  \hspace{1cm} (3.15)

Although our and previous work (McGuinness et al., 2010; Buchanan et al., 2012) shows that Calcium influx is crucial for preNMDAR-mediated regulation of synaptic dynamics, we still lack a clear understanding of the exact mechanisms. Therefore, we modelled a instantaneous link between preNMDAR current and $\beta$.

The activation of preNMDARs is modelled by the joint effect of voltage-dependent removal of the $Mg^{2+}$ block and the glutamate binding. By setting $\beta$ depending on the preNMDARs current after a few spikes we capture the frequency-dependence found experimentally. The presynaptic voltage is modelled using the adaptive exponential integrate-and-fire model, which as been shown to be a good model of pyramidal cells spiking properties (Clopath et al., 2010; Brette and Gerstner, 2005) and the parameters are the same as ones used in Clopath et al. (2010). The output of this model is then fed onto the voltage-dependent equation for the NMDAR $Mg^{2+}$ block (Jahr and Stevens, 1990) defined as

$$o_{Mg^{2+}}(V) = \frac{1}{1 + \exp(-0.062V C/3.57)} \hspace{1cm} (3.16)$$

where $V$ is the presynaptic voltage in mV and $C$ is the extracellular magnesium concentration in mM (here we use 1mM, which corresponds to the concentration used in our experimental preparation). Note that such a voltage-dependence has recently been shown for presynaptic NMDA receptors as well (Rossi and Collin, 2013). We then model the glutamate release and binding with one simple equation

$$\frac{d\text{Glu}(t)}{dt} = \frac{-\text{Glu}(t)}{\tau_{\text{off}}} + L\delta(t-t_{\text{AP}})(1 - \text{Glu}(t)) \hspace{1cm} (3.17)$$

this equation captures the NMDA activation upon release of glutamate $L = 0.7$ (similar to the release probability of PC-PC connections) following a presynaptic spike modelled by a Dirac delta distribution $\delta(t)$. After glutamate release and binding the receptor recovers to baseline 0 with a time-constant $\tau_{\text{off}} = 40\text{ms}$ and saturates at 1 — bounding the receptor activation between 0 and 1. More complicated models of NMDA activation exist (Destexhe et al., 1994, 1998), in particular it is common to have a dual exponential model with a finite rise time. However, we found that this did not make a qualitative difference, thus we used this simpler formulation. Finally, the
preNMDAR conductance is the product of the $Mg^{2+}$ and receptor activation as

$$g_{\text{preNMDAR}}(V,t) = o_{Mg^{2+}}(V)\text{Glu}(t)$$  \hspace{1cm} (3.18)

The final effect is modelled using the preNMDAR current, which is defined as

$$I_{\text{preNMDAR}}(V,t) = g_{\text{preNMDAR}}(V,t)(V - E_{\text{rev}})$$  \hspace{1cm} (3.19)

where $E_{\text{rev}} = 0$ is the NMDAR reversal potential. We use the maximum current to link the preNMDAR current with the regulation of the STP parameters.

$$\beta = (\min(max(I_{\text{preNMDAR}}(V,t)), C_{10Hz}) - C_{0.1Hz})/C_{10Hz}$$  \hspace{1cm} (3.20)

Therefore, $\beta$ represents the normalized preNMDAR activation (as described above), where $C_{0.1Hz}$ and $C_{10Hz}$ are the maximal currents achieved when the presynaptic neuron fires at 0.1Hz and 10Hz, respectively. This normalization assumes that at very low frequencies (0.1Hz) the current is not strong enough to trigger any effect and that the effect is maximal at frequencies equal or higher than 10Hz (with five presynaptic spikes), which is consistent with our data.

In order to mimic the experimental setup we inject current in the presynaptic neuron to evoke five spikes. The frequency-dependence effect of preNMDARs is mostly dependent on the time-constant $\tau_{\text{off}}$ and this was adjusted to fit our own experimental results (see Fig. 3.7). Our results suggest a faster timeconstant than the deactivation timeconstant of preNMDARs found in previous studies (Bidoret et al., 2009). This is in part due to the relatively abstract model we consider here. For example, we do not model the biophysics of the preNMDAR activation and the mechanistic link between preNMDAR activation and the regulation of the vesicle dynamics. However, we predict that if short-term depression of the glutamate release is also taken into account, this would require a deactivation timeconstant closer to the one found experimentally. Finally, we model preNMDAR activation blockade $\beta_{\text{blockade}}$ by setting $\beta_{\text{blockade}} = 1 - \beta$.

### 3.2.1.3 Properties of stochastic synaptic responses

To study the impact of preNMDARs on the stochastic release, we use the Binomial release model (Del Castillo and Katz, 1954)

$$P(X = k) = \binom{N}{k} U^k (1-U)^{N-k}$$  \hspace{1cm} (3.21)

which defines the probability of having $k$ successful events (neurotransmitter release) given $N$ trials (release sites) with equal probability $U$. 
The mean synaptic response is scaled by a postsynaptic amplitude $A$, which can be related to the quantal amplitude

$$\mu_{\text{syn}} = ANU$$

and the variance is given by

$$\sigma^2_{\text{syn}} = A^2NU(1-U)$$

Next, we calculated the Signal-to-Noise Ratio (SNR) between the synaptic responses defined here by a random variable $s$ and additive background noise by the random variable $n$ as follows

$$\text{SNR}_{\text{syn}} = 2\frac{(\langle s \rangle - \langle n \rangle)^2}{\sigma^2_s + \sigma^2_n}$$

It is assumed that $n \sim \mathcal{N}(0, \sigma^2_n)$ and we also use the Gaussian approximation to the Binomial release model specified above, $s \sim \mathcal{N}(NUA,A^2NU(1-U))$, from which follows

$$\text{SNR}_{\text{syn}} = 2\frac{(NUA)^2}{A^2NU(1-U) + \sigma^2_n}$$

As our results suggest mostly changes in release probability mediated by preNMDARs, in our analysis we set $N = 6.3$ based on Markram et al. (1997a) and $A = 1$, and both remain fixed after preNMDAR blockade.

### 3.2.1.4 Experiments

Whole-cell recordings from visual cortical layer-5 pyramidal cells in 300-$\mu$m-thick acute slices from postnatal day 11-18 mice (C57/Bl6) were performed. Patch pipettes (4-6 M) filled with (in mM) K-Gluconate 115, KCl 5, K-HEPES 10, Mg-ATP 4, Na-GTP 0.3, Na-phosphocreatine 10, Alexa 594 15 were used. Neurons were visualized using Dodt contrast imaging. Fluorescent images were obtained with custom-built 2-photon systems. Miniature EPSC recordings were performed in voltage clamp at -80 mV in the presence of TTX (0.5 $\mu$M) and BMI (5 $\mu$M). Some EPSPs and EPSCs were evoked by extracellular stimulation using a theta glass electrode (tip size $\sim$2-10 $\mu$m), positioned in layer-5. To find connected cells, quadruple whole-cell recordings were performed.

Presynaptic action potentials were evoked while holding the cells in current-clamp mode. To investigate the RRP size, 14 action potentials were evoked in the presynaptic neuron at 30 Hz every 80 sec, while the postsynaptic cell was held in voltage-
3.2. Presynaptic NMDAR’s control of the release machinery

clamp mode at a hyperpolarized potential (∼−90 mV). To investigate the frequency-
dependence of preNMDARs, 5 action potentials were evoked in the presynaptic neu-
ron at 30 Hz every 40 sec in current-clamp mode. For calcium imaging experiments,
individual pyramidal cells were filled with calcium-sensitive and morphological dyes
(200 µM Fluo-5F and 40 µM Alexa 594) and visualized by 2-photon microscopy at
820 nm. Calcium responses due to five action potentials evoked at 30 Hz were aquired
as frame scans (64x8 pixels) with ScanImage v3.5. Basal calcium level was measured
100 ms prior to the spike train.

The NMDA receptor antagonist D/L AP5 and Ro 25-6981 was bath applied at a
concentration of 200 µM and at 0.5 µM, respectively. Stability criteria were applied
to all recordings: the change in input resistance was < 30%, membrane potential < 8
mV, series resistance < 20% and that the initial baseline period was stable; otherwise
recordings were omitted or truncated. Statistical significance was assessed by Stu-
dent’s t-test at the 0.05 level, unless otherwise stated. Means are reported as ±SEM,
one, two, and three asterisks indicate $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively.

3.2.2 Results

There is wide evidence that preNMDARs regulate neurotransmitter release across dif-
ferent brain areas (Berretta and Jones, 1996; MacDermott et al., 1999; Woodhall et al.,
2001; Liu et al., 1997; MacDermott et al., 1999; Sjöström et al., 2003). However, ex-
actly how they regulate the release machinery is not clear. Here we present results that
suggest that preNMDARs regulate the baseline release probability indirectly.

3.2.2.1 PreNMDAR blockade in layer-5 PCs decreases mEPSCs frequency and
basal calcium levels

Spontaneous release of neurotransmitter — known as minis — are triggered by spon-
taneous vesicle fusion. A change in frequency, but not amplitude of events recorded
postsynaptically is considered as an indication of modification in presynaptic release
probability. Therefore, we started out by studying miniEPSCs (mEPSCs) after block-
ade of preNMDARs using AP5 (see methods). We observed that the frequency of
mEPSCs, but not their amplitude was diminished when compared to baseline levels
(Fig. 3.3).

These results suggested a change in release probability mediated by preNMDARs,
potentially through changes in internal calcium levels. In order to test this hypothesis
Figure 3.3: AP5 washin decreases mEPSCs frequency, but not their amplitude. (a-b) Sample mEPSC experiment with AP5 washin experiment. (a) mEPSC frequency decreases (top), but their amplitude does not change (bottom) after AP5 washin (red solid line) and recovers to baseline (before: black solid line, wash out: blue solid line). (b) Same data but represented as a cumulative probability as a function of mEPSC frequency (top) and amplitude (bottom). (c) mEPSC frequency decreases after AP5 washin (red solid line) across multiple experiments, but not the control experiments (blue solid line). (d) Ensemble plot reveals a consistent decrease in mEPSC frequency but not amplitude after AP5 washin.
we performed calcium imaging of pyramidal cell boutons. We have shown previously that preNMDARs expression at excitatory connections in layer-5 visual cortex is target specific (Buchanan et al., 2012). Consistent with these findings after AP5 washin we found two possible outcomes: boutons with (Type 1) and without suppression (Type 2) of calcium levels (Fig. 3.4a,b). This suppression was consistent across several recordings in only a subset of boutons (Fig. 3.4c) of the basal calcium (Fig. 3.4e), but not on the peak calcium (Fig. 3.4d). These results suggested that preNMDARs regulate baseline release probability rather than just instantaneously increasing release probability through calcium influx.

3.2.2.2 Model inference and selection shows that both release probability and depression time-constant are regulated

The Tsodyks-Markram phenomenological model of STP provides a good description of STP and can be related to properties of the release machinery (Markram et al., 1998) (see Chapter 2). Here we infer the two parameter version of the model, which is sufficient to capture STP at PC-PC layer-5 connections in young mice (see Chapter 2). For the inference process we apply the novel Bayesian framework introduced here, where we infer before and after preNMDAR blockade simultaneously for each experiment (see Methods).

Our inference framework successfully captures the 14-pulse STP before and after preNMDAR blockade using Ro. We demonstrate this with the maximum a-posteriori solutions, which yield a very good overlap with the model (Fig. 3.5a). When comparing the posterior probabilities before and after blockade we observe an increase in the depression timeconstant, $D$, and a reduction in the release probability, $U$ (Fig. 3.5b,d).

We then performed model selection, where we allowed different parameters to change after preNMDAR blockade: $D$ and $U$, or only $D$ and $U$ (Fig. 3.5c). The model selection shows that both changes in $U$ alone and both $D$ and $U$ capture the data, even though our model selection criteria penalises model complexity. This together with the model inference suggests that both $D$ and $U$ are being regulated by preNMDARs at layer-5 PC-PC connections.
Figure 3.4: Differential reduction by AP5 washin of basal bouton calcium signals. (a) An axon collateral branched off the main axon of a PC filled with Alexa 594 and extended into the basal dendritic tree. Calcium imaging was performed in two boutons in this branch. (b) While the first bouton showed a suppression of basal calcium signal after AP5 washin, the other remained unchanged. (c) Clustering analysis of AP5 washin dataset reveals two clusters, with and without changes in the basal calcium levels. (d) Ensemble data shows no changes in the peak calcium signal, but a strong suppression of the basal calcium after AP5 washin (e).
3.2. Presynaptic NMDAR’s control of the release machinery

Figure 3.5: PreNMDAR blockade regulates both release probability and depression time-constant in PC-PC connections. (a) STP two parameter model fits data before (red circles: data, red diamonds: maximum a posteriori solution) and after (blue circles: data, blue diamonds: maximum a posteriori solution) Ro washin using a 14-pulse train at 30Hz. (b-d) Probabilistic inference shows that Ro washin decreases release probability \( U \) while increasing the depression time-constant \( D \). (b) Posterior distributions before and after Ro washin for \( D \) (left) and \( U \) (right). (c) PreNMDAR model selection between: changes only in \( D \), \( U \) or in both parameters. (d) Maximum a-posterior solutions before and after Ro washin for \( D \) (left) and \( U \) (right).
3.2.2.3 Readily-releasable pool size and replenishment rate are regulated by preNMDARs

The readily-releasable pool is a key component in the presynaptic release machinery (Schneggenburger et al., 1999). In particular Thanawala and Regehr (2013) showed that presynaptic \( \text{Ca}^{2+} \) influx regulates the RRP size. Therefore, we wondered whether the regulation of release probability suggested by our data could be a consequence of changes in the RRP from the \( \text{Ca}^{2+} \) influx through the preNMDARs. To test this we used a high-frequency protocol (30Hz) to estimate the RRP size and respective replenishment rates (Fig. 3.6a). A regression analysis suggested that both RRP size and the replenishment rate are affected by preNMDAR blockade — as measured by the y-intercept and the slope of the linear regression, respectively (Fig. 3.6b). In this analysis it is assumed that depression is due to a decrease in the readily releasable quanta, so that RRP can be estimated from the cumulative plot at steady-state with a high-frequency protocol (Schneggenburger et al., 1999). We used the TM model to derive the same RRP measures, and although one can use the RRP analysis to determine these parameters, we show that this relationship is nonlinear (see Appendix A). When comparing the estimated RRP size and replenishment rates across multiple recordings we observed a reduction in RRP size and in the replenishment rate after Ro wash-in (Fig. 3.6c,d). Interestingly, we observed a reduction in RRP size in a low extracellular \( \text{Ca}^{2+} \) condition, but no changes in the replenishment rate. Note that we also observe that the replenishment rate increases in the control case (Fig. 3.6d), which might, in part, be a consequence of presynaptic NMDAR’s activation. This suggests that preNMDARs play a special role in regulating the replenishment rate, supposedly mediated by the activation of a signalling cascade rather than through calcium influx per se. Moreover, these results are consistent with the STP model inference results in that changes in \( U \) and \( D \) can be related to changes in RRP size and replenishment rate, respectively. Because RRP size is one of the key determinants in release probability (Thanawala and Regehr, 2013) these results are also consistent with both mEPSCs and \( \text{Ca}^{2+} \) imaging experiments.

3.2.2.4 PreNMDAR increase high-frequency synaptic transmission

Next we developed a mathematical model of how preNMDARs regulate the presynaptic terminal (see Methods). This model is based on the dual requirement of \( \text{Mg}^{2+} \) unblocking and receptor activation through glutamate. Because at low frequencies the
3.2. Presynaptic NMDAR's control of the release machinery

Figure 3.6: Blocking preNMDARs decreases both the readily-releasable pool size and replenishment rate. (a-b) Sample experiment with RRP analysis. (a) Amplitude changes of the first EPSC with a 14-pulse protocol after Ro washin (left) and of the remaining EPSCs (right). (b) Both the slope (RRP replenishment rate) of a linear fit to the 14-pulse train and the y-intercept (RRP size) change after Ro washin. (c) RRP size decreases after Ro washin or when reducing the extracellular calcium concentration. Control is not significant ($p = 0.18$) (d) Replenishment rate decreases after Ro washin but not when reducing the extracellular calcium concentration. Control shows a significant change ($p < 0.05$). In (c) and (d) percentages are calculated as $(1 - \text{after} / \text{before}) \times 100$, where after in the control case corresponds to mock wash-in.
preNMDAR activation does not accumulate we predicted that the effect of preNMDARs should be only observed at high frequencies, when using a protocol with five presynaptic spikes (Fig. 3.7a). Note that the model captures the frequency-dependence by using the peak positive current and that we discarded the brief negative current caused by the presynaptic action potential as this is unlikely to be significant at the presynaptic bouton due to its distance from the soma.

In order to find the exact frequency at which preNMDAR effect is fully expressed, we performed current-clamp recordings of PC-PC connections using a 5-pulse protocol at different frequencies. A sigmoidal fit to the data revealed that the preNMDAR effect starts at frequencies higher than 5 Hz and is fully expressed by 10 Hz (Fig. 3.7b,c). These data allowed us to further tune the model and extract the deactivation timeconstant $\tau_{\text{off}} = 40$ ms of the preNDMAR effect on the release machinery.

This shows that preNMDARs boost high-frequency ($>5$ Hz) synaptic transmission in the young mouse visual cortex.

3.2.2.5 PreNMDARs do not reduce synaptic variability, but increase signal-to-noise ratio at high-frequencies

High frequency signals in the cortex are likely to contain important information (Lisman, 1997). Therefore synapses should guarantee that such signals are transmitted with high fidelity.

By assuming a Binomial release model we calculated synaptic variability and the signal-to-noise ratio (SNR) (see Methods). We then studied how preNMDAR blockade affects both synaptic variability and SNR. Interestingly, blockade of preNMDARs does not appear to change synaptic variability (Fig. 3.8a,b). However, preNMDAR blockade reduces SNR (Fig. 3.8c,d).

Combined with the results above this shows that preNMDARs help to sustain reliable synaptic information transmission at high frequencies.

3.2.3 Discussion and conclusions

MiniEPSP analysis and $Ca^{2+}$ imaging suggested that release probability are being regulated through $Ca^{2+}$ influx. STP model inference indicated that $U$ (release probability) as well as $D$ (depression timeconstant) are being regulated when using a steady-state protocol at 30 Hz. Moreover, RRP analysis of the same dataset suggested that the RRP size and its replenishment rate are being regulated. It is well established that $Ca^{2+}$ influx
3.2. Presynaptic NMDAR’s control of the release machinery

Figure 3.7: PreNMDAR increase high-frequency synaptic transmission. (a) Schematic of preNMDAR model (left). Presynaptic action potentials (blue solid line, top) remove the $Mg^{2+}$ block (black solid line), and release glutamate into the synaptic cleft (red solid line). The removal of the $Mg^{2+}$ block together with the glutamate binding leads to the activation of preNMDARs (green solid line), which in turn triggers preNMDAR-mediated current that can modify the synaptic dynamics (blue solid line, bottom). (b) AP5 washin with evoked EPSPs at different frequencies reveals the exact shape of the frequency-dependent effect. Scatter plot represents EPSPs after AP5 washin normalized to before. We model preNMDAR activation using the peak current mediated by preNMDARs (see Methods) after simulating the model upon 5 presynaptic spikes (see (a)), which fits the data (green dashed line; solid black line is a sigmoidal fit given for comparison). Normalized synaptic responses in the model were also normalized to before (i.e. for $\beta = 1$). (c) PreNMDAR blockade decreases PPR at frequencies higher than 5 Hz (solid line represents the mean and open circles the individual data points), which is consistent with modification of the synaptic dynamics.
Figure 3.8: PreNMDARs do not reduce synaptic variability and improve signal-to-noise ratio at high-frequencies. (a-b) Ro washin does not impact the synaptic transmission variance (blue: before washin, red: after washin; \( p = 0.0582, n = 11 \)). (c-d) Ro washin moves synaptic transmission to a lower signal-to-noise region (blue: before washin, red: after washin; \( p < 0.001, n = 11 \)).
3.2. Presynaptic NMDAR’s control of the release machinery

Figure 3.9: Schematic of how preNMDARs regulate the release machinery. Our data supports the view that preNMDARs regulate release probability, but only indirectly through the regulation of the readily-releasable pool replenishment rate. Influx of \( \text{Ca}^{2+} \) through the activation of preNMDARs at frequencies higher than 5Hz speeds up the RRP replenishment rate (supposedly through the activation of a signalling cascade), which in turn increases RRP size. Changes in RRP size dictates the observed changes in release probability.  

increases the rate of replenishment (Wang and Kaczmarek, 1998). Moreover, recent work by Thanawala and Regehr (2013) demonstrated that the release probability at a synapse is directly correlated with the size of its RRP. Taken together these results suggest that RRP size is related to changes in the release probability \( U \), while changes in the replenishment to the depression timeconstant \( D \) in the model inference.

Therefore, the most parsimonious interpretation of the preNMDAR function based on our results is the following (see schematic in Fig. 3.9): (i) the \( Mg^{2+} \) unblocking and the binding of glutamate onto preNMDARs saturates at frequencies higher than \( \sim 10\text{Hz} \), (ii) the preNMDAR activation triggers \( Ca^{2+} \) influx that is well positioned to increase the RRP replenishment rate (supposedly through an unknown signalling cascade), which in turn increases the RRP size. These changes in the RRP size then lead to changes in the release probability observed in many studies of preNMDARs. We introduce a mathematical model that supports this interpretation of preNMDAR mechanistic activation.

These results also support the results presented in Chapter 2, which suggested that the variance of STP estimations should depend on how informative the protocol is. Here we used a 14-pulse protocol to infer short-term depressing synapses, which yields
a better inference than a standard 5-pulses protocol (compare with inference in Section 3.3).

Abbott et al. (1997) showed that STP implements a gain control at low frequencies. This property of short-term depression makes it hard for synapses to sustain high frequency information transmission. Using a mathematical model of preNMDARs activation we showed that through the combined requirement of $\text{Mg}^{2+}$ unblocking and ligand binding of preNMDARs, they increase synaptic transmission at frequencies higher than 5Hz. Therefore preNMDARs function as a gain control mechanism for high frequencies, helping sustain information flow at high frequencies through a synaptic history-dependent gain, consistent with previous findings in the hippocampus (McGuinness et al., 2010) and cerebellum (Bidoret et al., 2009).

### 3.3 Presynaptic NMDARs differentially regulate release probability at excitatory neocortical synapses

In the previous section we showed that preNMDARs regulate release probability at PC-PC connections. Here we inferred the STP model given data from excitatory connections onto different inhibitory cell-types: (i) Pyramidal Cells-onto-Basket Cells (PC-BC) and (ii) Pyramidal Cells-onto-Martinotti Cells (PC-MC) connections. Our results suggest that release probability is also being regulated at these excitatory connections. Moreover, the degree of the effect on the release probability appears to depend on the connection-type.

Given the importance of synaptic dynamics for neural information processing, this differential regulation of synaptic dynamics suggests that presynaptic NMDA receptors are well positioned to control information processing of excitatory and inhibitory signals in the brain.  

#### 3.3.1 Methods

**3.3.1.1 Inference and phenomenological model**

Here we use the same Bayesian inference framework described in Section 3.2. However, because here we consider STP data from connections that can not be fully captured by the two-parameter TM model – mostly due to PC-MC facilitating connections,
we infer the extended TM model (see Chapter 2). This model has four parameters: de-
pression timeconstant $D$, facilitation timeconstant $F$, baseline release probability $U$
and facilitation rate $f$.

3.3.2 Experiments

Quadruple whole-cell recordings of layer-5 cortical neurons were attempted in 300-
$\mu$m-thick slices cut from the primary visual cortex of P12-19 wild type mice (C57/Bl6)
and transgenic mice positive for parvalbumin (PV; Chattopadhyaya et al. (2004); JAX
007677) or somatostatin (SOM; Oliva Jr et al. (2000); JAX 003718) as previously
described (Sjöström et al., 2003). Patch pipettes (3-6 M) were filled with (in mM)
K-Gluconate 115, KCl 5, K-HEPES 10, Mg-ATP 4, Na-GTP 0.3, Na-phosphocreatine
10, Alexa 594 15, Biocytin 0.1%. Cells were visualized using Dodt contrast or oblique
illumination. Note that elsewhere we refer to PC-PV as PC-BC and PC-SOM con-
nections as PC-MC. Fluorescent images were obtained with a custom-built 2-photon
system. During current clamp recordings of monosynaptically connected cells, ac-
tion potentials were evoked in the presynaptic cells with 5-ms-long somatic current
injections (0.5-2 nA). During extracellular stimulation and paired recordings, 30-Hz
trains of five EPSPs were evoked every 15-20 seconds. Stability criteria were applied
to all recordings: the change in input resistance was $<30\%$, membrane potential $<8$
mV, series resistance $<20\%$ and that the initial baseline period was stable; otherwise
recordings were omitted or truncated. The NMDA receptor antagonist D/L AP5 was
bath applied at a concentration of 200 $\mu$M, while the NR2b-specific blocker Ro 25-
6981 was perfused at 0.5 $\mu$M. Statistical significance was assessed by Student’s t-test
for equal means at the 0.05 level.

3.3.2 Results

We first inferred the eTM STP model (four parameter version) using a 5-pulse pro-
tocol at 30Hz at all the three connections: PC-PC, PC-BC and PC-MC (before and
after APV washin). Inferring the full model at PC-PC connections shows that $U$ (base-
line release probability) is down-regulated with preNMDAR blockade (Fig. 3.10a,b),
which is consistent with our previous results. Note that PC-MC is a facilitating con-
nnection. However whether changes in the other parameters occur is not clear — the
posterior is broad — as the protocol here is not as informative as the 14-pulse protocol
used in the previous section or a Poisson-based protocol (see Chapter 2). At the other
two excitatory connection-types onto INs (BCs and MCs) the inference yields a similar result in that $U$ also appears to be down-regulated at these two connections after preNMDAR blockade (Fig. 3.10c-f), which is consistent with Buchanan et al. (2012).

Figure 3.10: Down regulation of release probability onto PCs, BC and MC INs by preNMDAR blockade. (a,b) Bayesian analysis suggests a decrease in release probability at PC-PC connections. (a) MAP solutions for PC-PC. (b) Marginalized posterior probability of the 4 parameters for PC-PC. (c,d) Bayesian analysis suggests a decrease in release probability at PC-BC connections. (c) MAP solutions for PC-BC. (d) Marginalized posterior probability of the 4 parameters for PC-BCs. (e,f) Bayesian analysis suggests a decrease in release probability at PC-MC connections. (e) MAP solutions for PC-MC. (f) Marginalized posterior probability of the 4 parameters for PC-MC.

Next, we performed model selection of potential preNMDAR models, where we allow for changes in: $D$, $F$, $U$, $f$, $UD$, $UF$ or $Uf$. The best model is the one that changes $U$, which gives the minimal evidence ratio across the three connection-types (Fig. 3.11a-c).

Using the maximum a-posterior solutions for $U$ before and after preNMDAR blockade ($U_{\text{High}}$ and $U_{\text{Low}}$) we compared the degree of change across the different connection-types (Fig. 3.12a). PC-PC connections are more strongly regulated by preNMDARs,
3.3. Presynaptic NMDARs differentially regulate release probability at excitatory neocortical synapses.

Figure 3.11: PreNMDAR model selection suggests changes in baseline release probability at PC-PC, PC-BC and PC-MC connections. (a) Model selection supports changes in U in PC-PC (top), PC-BC (middle) and PC-MC (bottom). (b) Posterior probability for high and low U (before: red lines, after: blue lines; solid lines presents mean and light lines individual recordings) for PC-PC (top), PC-BC (middle) and PC-MC (bottom). (c) MAP solutions for PC-PC (top), PC-BC (middle) and PC-MC (bottom) assuming changes in U alone.
but PC-MC connections are equally regulated in relative terms (Fig. 3.12b). This suggests that the degree of preNMDAR-mediated regulation of release probability depends on the postsynaptic cell type.

Figure 3.12: Degree of preNMDAR-mediated regulation of release probability depends on the postsynaptic cell type. (a) MAP solutions before (high) and after (low) preNMDAR blockade for three connection types. (b) Absolute effect is stronger at PC-PC connections, but relative effect is similar at both PC-PC and PC-MC, and weaker at PC-BC connections.

3.4 Discussion

Our results suggest that preNMDARs increase release probability indirectly by up-regulating the vesicle replenishment rate and that their differential expression in microcircuits can redirect high-frequency information flow. However, presynaptic NMDARs are clearly only one part of a complex network responsible for the interaction of short and long-term synaptic plasticity (Duguid and Sjöström, 2006).

For example, the joint activation of endocannabinoids and preNMDARs (Sjöström et al., 2003; Bender and Feldman, 2006) is known to be crucial for presynaptically expressed tLTD. Based on our results a possibility is that the activation of presynaptic endocannabinoid receptors inhibits the signalling pathway used by preNMDARs to up-
regulate release probability. However, this view does not appear to be consistent with the low-frequency pairing requirements for tLTD at layer-5 PC-PC synapses (Sjöström et al., 2001).

Moreover, our data shows that preNMDARs indirectly regulate release probability at PC-PC connections. We also found expression of preNMDARs at excitatory connections onto inhibitory neurons (BCs and MCs), but whether preNMDAR-mediated regulation of release probability relies on similar mechanisms is unclear and should be explored in future work.

On the other hand there are also receptors known to underlie LTP. For example, in the hippocampus LTP at excitatory connections onto interneurons is known to rely – at least in part – on postsynaptic Calcium-permeable AMPA Receptors (cpAMPA). My collaborators looked for cpAMPA expression in the layer-5 microcircuit and found that they are expressed in PC-BC, but not in PC-MC connections. Interestingly, computer modelling suggests the reversed effect we observed with preNMDARs (data not shown). While preNMDARs specifically impact on MC-mediated disynaptic inhibition, cpAMPARs may specifically impact on BC-mediated direct inhibition.

The field is moving towards a more mechanistic understanding of how and why synaptic dynamics are regulated by different factors. A behaviorally relevant factor is neuromodulation. Different neuromodulators have been shown to regulate synaptic dynamics (Kawai et al., 2012; Kerr et al., 2013; Nadim and Bucher, 2014). Understanding how the presynaptic terminal integrates different factors on a short and long-time scale will help clarify how synaptic dynamics are shaped during learning. Therefore it is important that future studies investigate not only the impact of neural activity but also other factors, such as neuromodulation and growth factors.

In the next chapter I present a novel model of synaptic plasticity that abstracts known synaptic physiology, such as endocannabinoid and preNMDAR’s regulation of synaptic dynamics, unifies some short and long-term synaptic plasticity experimental results and makes functional predictions.
Chapter 4

A unified model of pre and postsynaptic spike-timing-dependent plasticity

“Mental states of every kind – sensations, feelings, images – which were at one time present in consciousness and then have disappeared from it – have not with their disappearance absolutely ceased to exist.”
— Hermann Ebbinghaus, Memory: A contribution to experimental psychology

In the previous chapter I showed that presynaptic NMDARs, which are pivotal in presynaptic LTD (Sjöström et al., 2003; Bender and Feldman, 2006), also play a key role in the regulation of the presynaptic release machinery. However, presynaptic NMDARs constitute only a small part of a complex network responsible for the interaction of short and long-term synaptic plasticity. This complexity has contributed to the locus of expression of long-term synaptic plasticity been hotly debated for decades. It is now clear that synaptic plasticity can be both pre- and postsynaptically expressed (Padamsey and Emptage, 2014). Yet the functional role of this segregation remains entirely mysterious. In this chapter I study potential functional consequences of combined pre and postsynaptic locus of expression of synaptic plasticity based on a spike-based phenomenological model, and whether the model is consistent with slice and in vivo results. Together with collaborators I developed a novel phenomenological model of spike-timing-dependent plasticity (STDP) that abstracts and unifies pre- and postsynaptic plasticity components. Our unified STDP model captures the co-variation of short and long-term plasticity and reveals STDP as a presynaptic phenomenon, consis-
tent with a wide range of experimental results from rat visual cortex (Sjöström et al., 2001, 2003, 2007), as well as somatosensory cortex (Markram and Tsodyks, 1996). Functionally, this unified STDP rule develops receptive fields with improved reliability, as has been observed in rat auditory cortex in vivo (Froemke et al., 2013). In addition, this unified model enables fast relearning of previously stored information, in keeping with the memory savings theory Ebbinghaus (1885, 1913), which refers to rapid relearning through hidden storage of forgotten but previously acquired memories. Our results are also consistent with recent structural spine plasticity studies in mouse visual cortex in vivo (Hofer et al., 2008). Thus our work shows that unified pre- and postsynaptic STDP leads both to improved discriminability and more flexible learning.  

4.1 Introduction

Long-term synaptic plasticity is a widely favoured candidate mechanism for memory formation in the brain (Nabavi et al., 2014). Despite many decades of research, there is still an ongoing debate about whether long-term synaptic plasticity is pre or postsynaptically expressed, or both (Davies et al., 1989; Padamsey and Emptage, 2014). It is now becoming clear that synapses in many brain regions have both pre and postsynaptic expression to varying degrees, depending on factors such as connection type, synapse state, animal age, and activity pattern (Zakharenko et al., 2001; Bayazitov et al., 2007; Sjöström et al., 2007). In particular, experimental results have shown that time-dependent LTP (tLTP) between layer-5 pyramidal cells is both pre and postsynaptically expressed (Markram and Tsodyks, 1996; Sjöström et al., 2007). On the other hand time-dependent LTD (tLTD) appears to be mostly presynaptically expressed (Sjöström et al., 2003). Nevertheless, the vast majority of current theoretical treatments of information storage in the brain simplify the analysis by disregarding the locus of expression of long-term synaptic plasticity (Gerstner et al., 1996; van Rossum et al., 2000; Song et al., 2000; Senn et al., 2001; Shouval et al., 2002; Pfister and Gerstner, 2006; Clopath et al., 2008; Barrett et al., 2009; Clopath et al., 2010; Graupner and Brunel, 2012). Here, we investigate the possible functional roles of pre and postsynaptically expressed long-term plasticity. To do so, we developed a biologically tuned rate-sensitive spike-timing-dependent plasticity (STDP) model that includes both pre

\[ \text{The data from receptive field plasticity experiments was provided by Robert C. Froemke (New York University) and is partly published in Froemke et al. (2013).} \]
and postsynaptic expression. This model is tuned to data of layer-5 pyramidal-to-
pyramidal connections, from both tLTD and tLTP (Sjöström et al., 2001, 2003, 2007).

4.2 Material and Methods

Short and Long-term Synaptic Plasticity models

Short-term plasticity model

For the short-term synaptic plasticity we use a well established phenomenological model, the Tsodyks-Markram model with facilitation (Markram et al., 1998). This model is defined by the following ODEs

\[ \frac{dr(t)}{dt} = \frac{1 - r(t)}{D} - u(t^-)r(t^-)X(t) \]  
\[ \frac{du(t)}{dt} = \frac{U - u(t^-)}{F} + U[1 - u(t^-)]X(t) \]

The first equation models the vesicle depletion process, where the (normalized) number of vesicles \( r(t) \) is decreased with \( u(t^-)r(t^-) \) after a presynaptic spike from the train \( X(t) = \sum_{pre} \delta(t - t_{pre}) \). Between spikes \( r(t) \) recovers to 1 with a depression timeconstant \( D \). The second equation models the dynamics of the release probability \( u(t) \) which increases an amount \( U[1 - u(t^-)] \) after every presynaptic spike, decaying back to baseline release probability \( U \) with a facilitation timeconstant \( F \). The notation \( t^- \) indicates that these functions should be evaluated right before the spike occurs. By varying the parameters \( D, F, U \) one can obtain different synaptic dynamics. We use parameters that fit typical pyramidal-onto-pyramidal synapses \( D = 200\text{ms} \) and \( F = 50\text{ms} \) (Chapter 2), while \( U \) is modified by plasticity as described below. The average number of vesicles released per spike is \( r(t)u(t) \), which can be interpreted as the presynaptic strength.

Long-term plasticity model

In layer-5 (L5) pyramidal to pyramidal cell synapses, time-dependent long-term depression (tLTD) is presynaptically expressed. It is mediated by the coincidence activation of a postsynaptic signal (endocannabinoid (EC) release) and a presynaptic signal (presynaptic NMDA receptor activation) (Sjöström et al., 2003, 2004; Bender and Feldman, 2006; Yang and Calakos, 2013). Traditionally, LTP is governed by postsynaptic coincidence detection of the combined binding of glutamate and postsynaptic
depolarization (Bender and Feldman, 2006; Sjöström et al., 2007; Shouval et al., 2010),
promoting an increase in the number and/or properties of postsynaptic AMPA receptors
(Malinow and Malenka, 2002; Bredt and Nicoll, 2003; Malenka and Bear, 2004).
However, time-dependent long-term potentiation (tLTP) also has a presynaptic component,
mediated by postsynaptic diffusion of nitric oxide (NO) (Hardingham and Fox, 2006; Sjöström et al., 2007; Hardingham et al., 2013; Yang and Calakos, 2013).

Many models have been introduced (Froemke and Dan, 2002; Pfister and Gerstner, 2006; Clopath et al., 2010). However, these models often ignore the presynaptic contribution to the weight modification (but see Senn et al. (2001)).

Here we describe our phenomenological triplet model of long-term modification
of synaptic dynamics. This model has three synaptic traces, two postsynaptic ($y_+$ and
$y_-$) and one presynaptic ($x_+$), which increase upon a post or presynaptic spike ($Y(t)$
and $X(t)$), respectively. These traces are first-order filtered versions of the spike trains.
We define the postsynaptic depression trace as
\[
\frac{dy_-(t)}{dt} = \frac{-y_-(t)}{\tau_{y_-}} + Y(t)
\] (4.3)
the postsynaptic potentiation trace as
\[
\frac{dy_+(t)}{dt} = \frac{-y_+(t)}{\tau_{y_+}} + Y(t)
\] (4.4)
and the presynaptic potentiation trace as
\[
\frac{dx_+(t)}{dt} = \frac{-x_+(t)}{\tau_{x_+}} + u(t)r(t)X(t)
\] (4.5)

The long-term modification in the weight is achieved by modifying the postsynaptic amplitude $A(t)$ and the release probability $U(t)$. Note that any presynaptic information conveyed to the postsynapse should be constrained by the presynaptic release dynamics (Eqs. 4.1 and 4.2), we consider this by making the increase on $x_+$ upon a presynaptic spike reflect the short-term plasticity model as $u(t)r(t)X(t)$. The postsynaptic amplitude is modified with every postsynaptic spike according to
\[
\Delta A(t) = c_+ x_+(t)y_-(t)Y(t)
\] (4.6)
where $c_+$ is a constant that sets the amount of postsynaptic LTP. The triplet character
of this rule is expressed by the fact that it contains the presynaptic component once, but the postsynaptic activity twice ($Y(t)$ and filtered version $y(t)$). This ensures that LTP
only takes place when the postsynaptic spike follows not only the presynaptic one, but also occurs sufficiently soon after another post spike (Pfister and Gerstner, 2006). As a result, low pairing frequencies do not lead to LTP as $y_-$ will have decayed, consistent with data (Sjöström et al., 2001).

Similarly, the presynaptic release probability is modified whenever the presynaptic cell is active according to

$$
\Delta U(t) = -d_- y_-(t) y_+(t) X(t) + d_+ y_+(t) x_+(t^-) X(t) \tag{4.7}
$$

Triplet\textsubscript{LTD} Triplet\textsubscript{LTP}

For plasticity in $U$ to occur, the presynaptic spikes $X(t)$ “read-out” the postsynaptic traces (presynaptic coincidence detection), $y_-$ for presynaptic LTD and $x_+ y_+$ for presynaptic LTP. $d_-$ and $d_+$ are constants that set the amount of presynaptic LTD and LTP, respectively. As above, the notation $(t^-)$ (see Eq. 4.6 and 4.7) means that the value of the respective synaptic trace is “read-out” before being updated.

The total synaptic strength is a product of both pre and postsynaptic components

$$
w(t) = A(t) u(t) r(t) \tag{4.8}
$$

For a synapse which has not been stimulated recently this simplifies to $w(t) = A(t) U(t)$. Interestingly, our model makes explicit the distinction between the locus of both the induction and expression of long-term synaptic plasticity. As in previous models due to the Hebbian nature of the model, induction depends on both pre and postsynaptic activity, and on the exact correlation profile of pre-post spiking (Song et al., 2000; Pfister and Gerstner, 2006). However, in contrast to previous models which were agonist about the expression locus, in our model plasticity is both pre and postsynaptically expressed – through changes in the presynaptic release probability $U$ and the postsynaptic factor $A$. Being a release probability $U$ is hard-bounded between 0.1 and 1. Also $A$ is hard-bounded $A = [0.1, 3]$. As is, the postsynaptic amplitude $A$ in the model never goes down, which is obviously unrealistic. Therefore, for the network simulations we include a postsynaptic factor subtractive normalization as $\Delta A(t) = \Delta A(t) - \frac{1}{N} \sum_{i=1}^{N} \Delta A(t)$. Biologically, this might correspond to slow synaptic homeostasis (Turrigiano et al., 1998). To speed up the numerical implementations we integrate the synaptic traces
between the \( n_{\text{pre/post}} \) and \( n_{\text{pre+1/post+1}} \) spikes, yielding

\[
y_{n_{\text{post}}+1}^{n_{\text{post}}+1} = y_{n_{\text{post}}}^{n_{\text{post}}} \exp\left(-\frac{\Delta t_{\text{post}}}{\tau_{y^-}}\right) + 1 \tag{4.9}
\]
\[
y_{n_{\text{post}}+1}^{n_{\text{post}}} = y_{n_{\text{post}}}^{n_{\text{post}}} \exp\left(-\frac{\Delta t_{\text{post}}}{\tau_{y^+}}\right) + 1 \tag{4.10}
\]
\[
x_{n_{\text{pre}}+1}^{n_{\text{pre}}} = x_{n_{\text{pre}}}^{n_{\text{pre}}} \exp\left(-\frac{\Delta t_{\text{pre}}}{\tau_{x^+}}\right) + u_{n_{\text{pre}}} r_{n_{\text{pre}}} \tag{4.11}
\]

We subsequently integrated the model between pre and postsynaptic \( n \) spike

\[
A_{n_{\text{post}}+1} = A_{n_{\text{post}}} + c_+ x_{n_{\text{pre}}}^{n_{\text{pre}}} \exp\left(-\frac{\Delta t_{\text{post}}}{\tau_{x^+}}\right) y_{n_{\text{post}}}^{n_{\text{post}}} \exp\left(-\frac{\Delta t_{\text{post}}}{\tau_{y^-}}\right) \tag{4.12}
\]
\[
U_{n_{\text{pre}}+1} = U_{n_{\text{pre}}} + \left(-U_{n_{\text{pre}}}^{n_{\text{pre}}} + U_{n_{\text{pre}}}^{n_{\text{pre}}}^{n_{\text{pre}}}\right) \tag{4.13}
\]
\[
U_{n_{\text{pre}}} = d_- y_{n_{\text{post}}}^{n_{\text{post}}} \exp\left(-\frac{\Delta t_{\text{pre}}}{\tau_{y^-}}\right) y_{n_{\text{post}}}^{n_{\text{post}}} \exp\left(-\frac{\Delta t_{\text{pre}}}{\tau_{y^+}}\right) \tag{4.14}
\]
\[
U_{n_{\text{pre}}}^{n_{\text{pre}}} = d_+ y_{n_{\text{post}}}^{n_{\text{post}}} \exp\left(-\frac{\Delta t_{\text{pre}}}{\tau_{y^-}}\right) x_{n_{\text{pre}}}^{n_{\text{pre}}} \exp\left(-\frac{\Delta t_{\text{pre}}}{\tau_{y^+}}\right) \tag{4.15}
\]
\[
w_{n+1} = A_{n_{\text{post}}}^{n_{\text{post}}} + u_{n_{\text{pre}}}^{n_{\text{pre}}} + 1 r_{n_{\text{pre}}+1} \tag{4.16}
\]

where \( \Delta t_{\text{post}} = (t_{\text{post}} - t_{\text{pre}-1}) \), \( \Delta t_{\text{pre}} = (t_{\text{pre}} - t_{\text{post}-1}) \), \( \Delta t_{\text{post}} = (t_{\text{post}} - t_{\text{pre}-1}) \) and \( \Delta t_{\text{pre}} = (t_{\text{pre}} - t_{\text{post}-1}) \). The synaptic traces are “read-out” just before the spike-induced changes. Finally, we also integrated the STP equations (Eqs. ??3.2) between presynaptic spikes \( n_{\text{pre}} \) and \( n_{\text{pre}} + 1 \), a time \( \Delta t_{\text{pre}} \) apart, yielding

\[
r_{n_{\text{pre}}+1} = 1 - [1 - r_n (1 - u_n)] \exp\left(-\frac{\Delta t_{\text{pre}}}{D}\right) \tag{4.17}
\]
\[
u_{n_{\text{pre}}+1} = U + u_n [1 - U] \exp\left(-\frac{\Delta t_{\text{pre}}}{F}\right) \tag{4.18}
\]

with initial conditions \( r_0 = 1 \) and \( u_0 = U \).

**Receptive field development**

For the receptive field development simulations we used a feedforward network with 100 presynaptic neurons \( j \) with Poisson statistics and a single integrate-and-fire postsynaptic neuron (see details below). The firing rate of the presynaptic Poisson neurons is modelled using a Gaussian profile defined as

\[
\rho(j; p, \sigma) = \rho_{\text{min}} + (\rho_{\text{max}} - \rho_{\text{min}}) e^{-\frac{(j - p)^2}{2\sigma^2}} \tag{4.19}
\]

where \( \rho \) is the rate in the Poisson neuron model \( j \), \( p \) the input position for which the rate is maximal and \( \sigma = 5 \) Hz the distribution spread. \( \rho_{\text{max}} \) and \( \rho_{\text{min}} \) are the maximum
and minimum rates, and are set to \( \rho_{\text{max}} = 50 \text{ Hz} \) and \( \rho_{\text{min}} = 2 \text{ Hz} \). Note that for receptive field development we scaled \( d_{-}, d_{+} \) and \( c_{+} \) by 0.035, which yields a smoother receptive field development. \( A \) is scaled by 55 pA, so that the synaptic input is appropriately scaled for the neuron model parameters. The network was simulated for 300s, which was long enough to achieve convergence. For the savings experiment we interleave between two receptive field positions with \( d_{-}, d_{+} \) and \( c_{+} \) scaled by 0.3, which yields faster simulations. Results for both receptive development and memory savings were plotted based on 10 runs (see respective Figures).

### Properties of stochastic synaptic responses

The release of neurotransmitter was assumed to follow a Binomial model (Del Castillo and Katz, 1954)

\[
P(X = k) = \binom{N}{k} U^k (1 - U)^{N-k}
\]  

(4.20)

which defines the probability of having \( k \) successful events (neurotransmitter release) given \( N \) trials (release sites) with equal probability \( U \).

The mean synaptic response is scaled by a postsynaptic scaling factor \( A \), which can be related to the quantal amplitude

\[
\mu_{\text{syn}} = ANU
\]  

(4.21)

The variance is

\[
\sigma_{\text{syn}}^2 = A^2 NU (1 - U)
\]  

(4.22)

Note that in the standard notation of the Binomial release model \( U \) is \( p \) and \( A \) is \( q \). Here we adopted the former notation to keep consistency with the notation used in our synaptic plasticity model.

### \( U \) and \( A \) extraction from data

Following the Binomial release model (Eq. 4.20), \( \mu_{\text{syn}} \) (Eq. 4.21) and \( \sigma_{\text{syn}}^2 \) (Eq. 4.22), \( U \) is given as

\[
U = \frac{\mu_{\text{syn}}}{NA}
\]  

(4.23)

and \( A \) as

\[
A = \frac{\sigma_{\text{syn}}^2}{\mu_{\text{syn}}} + \frac{\mu_{\text{syn}}}{N}
\]  

(4.24)
The number of release sites $N$ is believed to change only after a few hours (Bolshakov et al., 1997). As the slice synaptic plasticity experiments analysed here lasted only up to 1.5 hours (Sjöström et al., 2001) and we are interested in the relative changes we assumed constant $N = 6.3$ in our analysis, as estimated by Markram et al. (1997a).

We also extracted $U$ and $A$ from the in vivo data obtained by Froemke et al. (2013). Again using a Binomial model we obtained estimators for their variability measure, which is given by $q = NA(1 - U)$ and the mean by $\mu = ANU$. Rearranging we get $A = \frac{q + |\mu|}{N}$ and $U = \frac{|\mu|}{NA}$. By setting $N = 6.3$ we used these estimators to extract $A$ and $U$ from Froemke et al. (2013) measurements for both the best (unpaired) receptive field position and for the paired position, which got depressed (referred to as off position) and potentiated (referred to as on position), respectively.

CV analysis

Using $\mu_{\text{syn}}$ and $\sigma_{\text{syn}}^2$ we can calculate the coefficient of variation

$$CV_{\text{syn}} = \frac{\sqrt{A^2NU(1-U)}}{ANU}$$

(4.25)

$$CV_{\text{syn}}^2 = \frac{A^2NU(1-U)}{(ANU)^2}$$

(4.26)

$$CV_{\text{syn}}^{-2} = \frac{NU}{(1-U)}$$

(4.27)

This shows that $CV_{\text{syn}}^{-2}$ does not depend on the postsynaptic component $A$. Furthermore, the locus of expression of synaptic modifications can be interpreted geometrically by plotting the normalized CV (or the more commonly used normalized $CV^{-2}$) against the normalized mean weight (Faber and Korn, 1991).

Synaptic signal detection

We calculate the Signal-to-Noise Ratio (SNR) between the synaptic responses defined here by a random variable $s$ and additive background noise defined by the random variable $n$ as follows

$$\text{SNR}_{\text{syn}} = 2 \frac{\langle s \rangle - \langle n \rangle}{\sigma_s^2 + \sigma_n^2}$$

(4.28)

It is assumed that $n \sim \mathcal{N}(0, \sigma_n^2)$ and we also use the Gaussian approximation to the Binomial release model specified above, $s \sim \mathcal{N}(NUA, A^2NU(1-U))$, from which follows

$$\text{SNR}_{\text{syn}} = 2 \frac{(ANU)^2}{A^2NU(1-U) + \sigma_n^2}$$

(4.29)
We use ROC analysis to compute the false alarm and detection probability

\[ P(\text{false alarm})_{\text{syn}} = \int_{T}^{+\infty} n(T; 0, \sigma_n^2) \]  

\[ P(\text{detection})_{\text{syn}} = \int_{T}^{+\infty} s(T; ANU, A^2NU(1-U)) \]  

\[ P(\text{false alarm})_{\text{syn}} = \frac{1}{2} \text{erfc} \left( \frac{T}{\sqrt{2\sigma_n^2}} \right) \]  

\[ P(\text{detection})_{\text{syn}} = \frac{1}{2} \text{erfc} \left( \frac{T - ANU}{\sqrt{2A^2NU(1-U)}} \right) \]

where \( T \) is the discrimination threshold, and \( \text{erfc} \) is the complementar error function defined as \( \text{erfc}(x) = \frac{2}{\sqrt{\pi}} \int_{x}^{\infty} e^{-t^2} dt \). To assess the overall discriminability we use \( P(\text{discriminability}) \), which is the area under the ROC curve (AUC). The AUC is computed by integrating over the ROC curve using the trapezoid method.

**Data fitting**

We fitted the free parameters of the plasticity model \( \vec{\theta} = \{d_-, \tau_y-, d_+, \tau_y+, c_+, \tau_x+ \} \) (6 in total) to the frequency-dependent slice data of Sjöström et al. (2001) (see Table 4.1). However, rather than fitting to changes in the weight \( w \), we fit directly to modifications in \( U \) and \( A \). This was done by minimizing the mean-squared error between the data and the experiments for both \( U \) and \( A \) (as shown in Fig. 4.1)

\[ \vec{\theta} = \arg\min_{\vec{\theta}} \frac{1}{N} \sum_{j} \left( \frac{U_{\text{after model}}}{U_{\text{before model}}} - \frac{U_{\text{after data}}}{U_{\text{before data}}} + \frac{A_{\text{after model}}}{A_{\text{before model}}} - \frac{A_{\text{after data}}}{A_{\text{before data}}} \right)^2 \]  

The fitting was further validated against the pharmacological blockade experiments reported in (Sjöström et al., 2007). The plasticity protocols used are identical to the ones used in the respective papers (Sjöström et al., 2001, 2007). For induction protocols at high frequencies (10 Hz and higher) pre and postsynaptic spike trains consisted of five spikes at a given frequency and were paired 15 times at 0.1 Hz (yielding a total of 75 spike pairings). While, low frequency pairings (0.1 Hz) were done with a single pre and postsynaptic spike, but repeated 50 times. The pairing timing was set as a delay between pre and postsynaptic spikes (Sjöström et al., 2001). To reproduce the pharmacological blockade experiments we used a high frequency pairing (50 Hz) with +10 ms delay, which is comparable with our frequency-dependent results and approximates the long depolarizing currents used by (Sjöström et al., 2007).
Table 4.1: Unified pre and postsynaptic STDP model parameters. The model was fitted to data from young rat visual cortex (Sjöström et al., 2001, 2007).

<table>
<thead>
<tr>
<th></th>
<th>$d_-$</th>
<th>$\tau_{y-}$ (ms)</th>
<th>$d_+$</th>
<th>$\tau_{y+}$ (ms)</th>
<th>$c_+$</th>
<th>$\tau_{x+}$ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best fit</td>
<td>0.227</td>
<td>3.29</td>
<td>0.85</td>
<td>108.9</td>
<td>0.289</td>
<td>5.8</td>
</tr>
</tbody>
</table>

With this model we also capture pharmacological blockade of the plasticity traces, which we simulate by blocking the effect of the synaptic traces. More specifically we simulate eCB blockade by setting $d_- = 0$. In our model this has the effect of eliminating the presynaptic LTD term, $y_-(t)y_+(t)X(t)$ which discloses presynaptic LTP, consistent with experimental evidence (Sjöström et al., 2007). Note that in this way we block the effect of eCB presynaptically (by discarding the term $d_-y_-(t)y_+(t)X(t)$), but not postsynaptically $c_+x_+(t)y_-(t)Y(t))$. This is consistent with the eCB blockade done in Sjöström et al. (2007) as the drugs used are likely to block the binding of presynaptic eCB receptors. We also capture Nitric Oxide (NO) blockade by setting $y_+ = 0$, so that both presynaptic components ($d_-y_-(t)y_+(t)X(t)$ and $d_+y_+(t)x_+(t)X(t)$) of our plasticity model are effectively removed. This captures the moderate decrease in LTP and the lack of changes in synaptic dynamics observed after NO blockade (Sjöström et al., 2007).

**Statistical comparison**

Results are reported as mean ± SEM. Statistical comparisons were made with Student’s t-test if data was normally distributed, or Mann-Whitney U non-parametric test otherwise. Significance levels are defined as $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$, respectively.

**Neuron models**

For the feedforward networks the presynaptic neurons follow a homogeneous Poisson distribution with rates given by the Gaussian profiles above-mentioned. While the postsynaptic neuron is an adaptive exponential integrate-and-fire neuron model (Brette and Gerstner, 2005). The model parameters used are the ones reported in (Brette and Gerstner, 2005). We model the synaptic input given by Eq. 4.8 as scaled input currents (see details above).
Comparison with Pfister et al. triplet model

Our model has arguably some similarities with the triplet-STDP model introduced by (Pfister and Gerstner, 2006). This triplet model is defined by the following components, presynaptic traces modelled by

$$\frac{dx_1(t)}{dt} = \frac{-x_1(t)}{\tau_+} + \delta_{\text{pre}}$$

(4.35)

and

$$\frac{dx_2(t)}{dt} = \frac{-x_2(t)}{\tau_+} + \delta_{\text{pre}}$$

(4.36)

, and postsynaptic traces modelled by

$$\frac{dy_1(t)}{dt} = \frac{-y_1(t)}{\tau_-} + \delta_{\text{post}}$$

(4.37)

and

$$\frac{dy_2(t)}{dt} = \frac{-y_2(t)}{\tau_-} + \delta_{\text{post}}$$

(4.38)

where the weight changes are modelled as a combination of pair and triplet components (full Triplet model) as follows

$$\Delta w^- = -X(t)y_1(t) [A_2^- + A_3^- x_2(t^-)]$$

(4.39)

$$\Delta w^+ = Y(t)x_1(t) [A_2^+ + A_3^+ y_2(t^-)]$$

(4.40)

Pfister and Gerstner (2006) showed that in order to fit the intra-pairing frequency observed in the young rat visual cortex (VC) (Sjöström et al., 2001) a reduced model ($A_3^- = 0$ and $A_2^+ = 0$) is enough (minimal VC Triplet)

$$\Delta w^- = -X(t)A_2^- y_1(t)$$

(4.41)

$$\Delta w^+ = Y(t)A_3^+ x_1(t) y_2(t^-)$$

(4.42)

Moreover, another slightly more complex model ($A_3^- = 0$) can also capture triplet and quadruplet experiments performed in the hippocampus (Wang et al., 2005) (minimal HC Triplet)

$$\Delta w^- = -X(t)A_2^- y_1$$

(4.43)

$$\Delta w^+ = Y(t)x_1 [A_2^+ + A_3^+ y_2(t^-)]$$

(4.44)

Interestingly, our model also has two tLTP and one tLTD components, that can be mapped onto the minimal HC Triplet (see Table 4.2). However, in our model we needed
three triplets, rather than one triplet and two douplets as in the minimal HC Triplet model. This is because we also capture the pharmacological blockade experiments reported in (Sjöström et al., 2007). We did not, however, attempt to fit the hippocampal data. Moreover, we did not attempt to fit the Pfister and Gerstner (2006) model to our novel data, as that model is not defined at the same level as ours (pre and postsynaptic expression), so that is not clear how to map the different components of the Pfister and Gerstner (2006) model onto pre and postsynaptic modifications.

Table 4.2: Comparison between unified pre-postSTDP model and the minimal Triplet models (for simplicity we removed the function arguments) (Pfister and Gerstner, 2006).

<table>
<thead>
<tr>
<th></th>
<th>tLTD</th>
<th>tLTP₁</th>
<th>tLTP₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-postSTDP</td>
<td>$X_d-\gamma\gamma_+$</td>
<td>$X_d+\gamma\gamma_+$</td>
<td>$Y_{c+\gamma\gamma}_-$</td>
</tr>
<tr>
<td>minimal HC Triplet</td>
<td>$X_A_2 \gamma_1$</td>
<td>$Y_A_2 ^+\gamma_1$</td>
<td>$Y_A_3 ^+\gamma_1\gamma_2$</td>
</tr>
<tr>
<td>minimal VC Triplet</td>
<td>$X_A_2 \gamma_1$</td>
<td>-</td>
<td>$Y_A_3 ^+\gamma_1\gamma_2$</td>
</tr>
</tbody>
</table>

4.3 Results

Inspired by earlier long-term plasticity models (Pfister and Gerstner, 2006), we use a phenomenological abstraction of synaptic plasticity using exponentially decaying traces of the pre- and postsynaptic spikes, $X(t)$ and $Y(t)$ respectively (Fig. 4.1a). There are three synaptic traces. $x_+(t)$ represents previous presynaptic activity and can be intuitively understood as glutamate binding to postsynaptic NMDA receptors. Postsynaptically expressed long-term potentiation (LTP) is triggered when presynaptic activity — represented by the trace $x_+(t)$ — is rapidly followed by postsynaptic depolarization — provided by the spikes $Y(t)$ — as this unblocks NMDA receptors (Sjöström, 2002). Conversely, the positive trace $y_+$ represents prior postsynaptic activity, and can be thought of as nitric oxide retrogradely diffusing from the postsynaptic side to elicit presynaptically expressed LTP (Sjöström et al., 2007). The negative trace $y_-$, on the other hand, analogous to postsynaptic endocannabinoid release, elicits presynaptically expressed long-term depression (LTD) when coincident with presynaptic spiking activity $X(t)$ (Sjöström et al., 2003). This mechanistic interpretation does not imply that this is true for all central synapse types, nor does it imply that these are the only mechanisms; it is merely meant to provide an intuitive understanding of how the synaptic traces $x_+, y_+$, and $y_-$ can plausibly be read out by the spikes.
4.3. Results

$X(t)$ and $Y(t)$ at the biological synapse (Fig. 4.1b). To account for long-term changes in neurotransmitter release, we relied on the Markram and Tsodyks’s (Markram et al., 1998) vesicle depletion model. In our implementation, the vesicle usage parameter $U$ was increased by presynaptic LTP (Sjöström et al., 2007; Markram and Tsodyks, 1996) and decreased by presynaptic LTD (Sjöström et al., 2003), while postsynaptic LTP was modelled by increasing the postsynaptic amplitude $A$ (see Methods).

The model was simultaneously tuned to the timing and frequency dependence of plasticity experiments (Fig. 4.1c, d), as well as to changes in the probability of release $U$ and in the quantal amplitude $A$ found experimentally by assuming that synaptic responses were binomially distributed (Fig. 4.1e, f and Methods). Because we model long-term plasticity in $U$, we also capture cross-scale interaction of short and long-term synaptic plasticity, so that after tLTD and tLTP induction short-term depression is weaker and stronger, respectively, as observed experimentally (Fig. 4.1g, h) (Sjöström et al., 2003, 2007). All data was obtained from monosynaptic connections between neocortical layer-5 pyramidal cells (L5 PCs) in developing rat visual cortex (Sjöström et al., 2001, 2007, 2003). Although we cannot preclude a contribution from changes in the number of release sites $N$ in any of our results, we assumed for simplicity’s sake that STDP did not affect $N$ by fixing it to 6.3, the average number of putative synaptic contacts found between connected neocortical L5 PCs (Markram et al., 1997a).

We verified our $U$ and $A$ extraction method by analysing short-term plasticity experiments with pharmacological manipulation of presynaptic release or of postsynaptic gain (Fig. 4.2a, Sjöström et al., 2003), and experiments with pharmacological blockade of pre or postsynaptic long-term plasticity (Fig. 4.2b, Sjöström et al., 2007). In addition, long-term changes in $U$ but not in $A$ were inversely correlated with changes in paired-pulse ratio, as expected (Fig. 4.2c). Taken together, these results lend solid experimental support to our binomial-distribution-based approach for extracting $U$ and $A$ (Fig. 4.2) to tune changes in the short-term dynamics of our unified STDP model (Fig. 4.1e,f).

We next validated our tuned STDP model by testing it against experiments in which presynaptic forms of depression or potentiation were pharmacologically blocked. Abolishing presynaptic LTP by nitric oxide production/release blockade reduces potentiation as only the postsynaptic component is left (Sjöström et al., 2007). In agreement, when we disabled presynaptic LTP by turning off $y_+$ (Fig. 4.3a), the model gave rise to postsynaptic LTP of overall lowered magnitude (Fig. 4.3c). This is consistent with blockade experiments performed by Sjöström et al. (2007) where the release
Figure 4.1: A biologically tuned phenomenological computational model with unified pre and postsynaptic expression of long-term synaptic plasticity. (a) The synaptic weight is determined by the presynaptic vesicle usage factor $U$ and the postsynaptic amplitude $A$. Changes in $U$ correspond to altering the probability of release, while increasing $A$ corresponds to LTP via AMPA receptor insertion. $U$ and $A$ are governed by interactions between the pre and postsynaptic spike trains $X$ and $Y$ with the synaptic traces $x_+, y_+$, and $y_-$, representing transsynaptic signalling. (b) In this example, the postsynaptic neuron spikes three times at 20 Hz ($Y$) $\Delta t=+10$ ms after the presynaptic neuron ($X$), leading to LTP by increasing both $A$ and $U$ simultaneously. The relative timing $\Delta t$ is subsequently reversed to -10 ms, and LTD results as $U$ weakens strongly, even though $A$ still weakly strengthens. LTD does thus not cancel out LTP, but leaves a trace of prior LTP. (c) The model (black line) captures the characteristic temporal asymmetry of experimental STDP (squares, (Sjöström et al., 2001)). Relative timing is defined as $\Delta t = t_{\text{spike}}^{\text{post}} - t_{\text{spike}}^{\text{pre}}$. (d) The model also fits the rate dependence of synaptic plasticity (squares, (Sjöström et al., 2001)) for both positive (blue) and negative timings (red). (e-f) Changes in presynaptic release $U$ and postsynaptic gain $A$ match experimental data (see Methods; (Sjöström et al., 2001)). (g,h) As in experiments, the model predicts that short-term depression is reduced after LTD induction (20 Hz, $\Delta t=-10$ ms) (g) and increased after LTP (50 Hz, $\Delta t=+10$ ms) (h). Insets show representative experimental data from (Sjöström et al., 2003) (g) and from (Sjöström et al., 2007) (h).
Figure 4.2: Control U and A extraction from synaptic plasticity slice paired recordings using pharmacology and high frequency pairing (using a long-step current injection plasticity protocol). (a) CNQX washin decreases the $U$ ($p < 0.01$), but not $A$ ($p = 0.32$; red symbols), while low calcium decreases $U$ ($p < 0.01$), but not in $A$ ($p = 0.48$; blue symbols). Control experiments do not yield changes in either component: $U$ ($p = 0.15$), but not $A$ ($p = 0.1$; black symbols)). (data reanalyzed from (Sjöström et al., 2003)) (b) Extraction of $U$ and $A$ after LTP induction and blockade of plasticity traces NO and eCB. LTP induction yields an increase in both $U$ ($p < 0.001$) and $A$ ($p < 0.001$). eCB blockade increases the presynaptic component $U$ ($p < 0.01$), but does not change $A$ ($p = 0.1$; blue symbols), while NO blockade increases $A$ ($p < 0.001$), but does not change $U$ ($p = 0.27$; red symbols) (data reanalyzed from (Sjöström et al., 2007)). (c,d) Changes in presynaptic release probability $U$ (c), but not postsynaptic factor $A$ (d) correlates with changes in paired-pulse ratio. Dashed line represents a linear regression on the individual data points (open circles). Data shown is normalized to baseline (before plasticity induction). Open symbols represent individual experiments, while solid symbols represent averages. Error bars represent SEM.
Figure 4.3: Model is consistent with pharmacological blockade of plasticity traces. (a-b) Schematic of pharmacological blockade simulation for both Nitric Oxide (NO) and Endocannabinoids (eCB) signalling. We block postsynaptic NO production/release by inhibiting the $y_+$ trace (a), while eCB is blocked by inhibiting presynaptic LTD (b, by setting $d_- = 0$, which models action of CB1 antagonist). Both manipulations are consistent with the role of pharmacological blockers used experimentally (Sjöström et al., 2007). (c-f) Simulation of pharmacological blockade of long-term potentiation signalling at 50Hz with +10ms (see methods). (c) Blockade of NO and EC decrease and increase potentiation, respectively (bars indicate simulated blockade, while squares represent data reproduced from (Sjöström et al., 2007)). (d) Coefficient of variation analysis upon NO and EC blockade. Squares represent data reproduced from (Sjöström et al., 2007) and open circles the model results. (e) No changes in synaptic dynamics are observed when blocking NO retrograde signalling. (f) Strong depression is revealed after EC blockade (insets represent data reproduced from (Sjöström et al., 2007)). Data shown is normalized to baseline (i.e. before plasticity induction).
and production of NO was inhibited. Blockade of presynaptic LTD by abolishing endocannabinoid signalling using CB1 antagonists during LTP induction gives rise to stronger presynaptic potentiation (Sjöström et al., 2007). We simulated this condition by setting $d_-$ = 0, which simulates the blockade of presynaptic eCB receptors performed experimentally (Fig. 4.3b) — as expected — the model gave rise to increased presynaptic LTP (Fig. 4.3c). Although some aspects of neocortical plasticity are certainly different at other excitatory synapses, e.g. the precise rate and timing requirements for layer-2/3 PCs (Froemke et al., 2006), this model unifying pre and postsynaptic forms of expression plasticity should to a first approximation capture the key features of neocortical excitatory synapse long-term plasticity (Sjöström et al., 2008).

Using unified STDP, we investigated the consequences of the locus of expression for the development of neocortical receptive fields (RFs). We modelled the development of a RF using a feedforward network with a single postsynaptic neuron and 100 synaptic inputs. Inputs had a Gaussian profile with Poisson firing statistics, and the plasticity of each synaptic input was governed by our unified STDP learning rule (see Methods). An RF develops as the input profile is presented to the network (Fig. 4.5a,b).

The synaptic variance depends on both the release probability $U$ and the postsynaptic factor $A$ (see Methods). The learning rule yields regions of low variance for both on (high $U$ and $A$) and off (low $U$ and $A$) the RF (Fig. 4.5c). This shows that in order to obtain reliable responses, solely increasing $A$ would increase the variance, instead $U$ has also to be modified. Therefore, in contrast to a learning rule with postsynaptic modifications only, our learning rule avoids regions of high variance (Fig. 4.5d). Note, however, that due to the different input firing rates (2-50Hz), with our unified STDP model the release probability does not necessarily reach its maximum value where the variance is minimal.

Interestingly, this change in variability is consistent with recent experimental results by Froemke et al. (2013) in which a auditory stimulus at a given frequency was paired with stimulation of the nucleus basalis (NB). A decrease in variability and an increase in the mean of the synaptic responses of the receptive fields that were paired with NB stimulation was observed (Fig. 4.4a). We extracted $U$ and $A$ from their experimental measurements (see Methods; Fig. 4.4b). When comparing the results before and after modifications in the receptive field that were paired (i.e. the ones that were potentiated, which we refer to as $On$) we obtained $A_{On}^{before} = 6.2$ pA, $A_{On}^{after} = 8$ pA (29%
increase; Fig. 4.4b-c), $U_{\text{before}}^{\text{On}} = 0.71$ and $U_{\text{after}}^{\text{On}} = 0.88$ (24% increase; Fig. 4.4b,d).

While for receptive fields that were unpaired and that got depressed (typically the best receptive field position, which we refer to as Off) we obtained $A_{\text{before}}^{\text{Off}} = 20.1 \pm 5.1$ pA, $A_{\text{after}}^{\text{Off}} = 17.7 \pm 5.5$ pA (14% decrease; Fig. 4.4b-c), $U_{\text{before}}^{\text{Off}} = 0.89 \pm 0.11$ and $U_{\text{after}}^{\text{Off}} = 0.79 \pm 0.05$ (12.7% decrease; Fig. 4.4b,d). Both results are consistent with our modelling predictions (Fig. 4.5d,f).

Next, we used the signal-to-noise ratio (SNR) as a measure of signal detection performed at the synaptic level with respect to background gaussian noise (see Methods). This analysis demonstrates that only on the developed RF the SNR is high (Fig. 4.5e). Although, both high and low $U$ yield low variance (Fig. 4.5d), only high $U$ yields high SNR (Fig. 4.5f). A classification analysis (see Methods) to assess the discriminability of the synaptic responses reveals that only the synaptic dynamics on the RF yields a near-perfect classifier (Fig. 4.5g). In order to assess the synaptic response discriminability we use the area under the classification curve as a measure of discriminability. This measure shows that the results hold for different levels of background noise (Fig. 4.5h).

These results suggest that pre and postsynaptic plasticity both change in RF development to yield more reliable and informative synaptic responses. Our findings are in agreement with in vivo neocortical RF plasticity experiments (Froemke et al., 2013) as well as with in vitro neocortical recordings showing reliable synaptic transmission (Silver, 2003).

Expression of neocortical L5 PC STDP is curiously asymmetric: potentiation has both pre and postsynaptic components (Sjöström et al., 2007), whereas depression only regulates the presynaptic compartment (Sjöström et al., 2003). This means that long-term depression per se cannot fully erase potentiation. We use our model to investigate the potential benefits of this asymmetric arrangement, by studying its effects on the development of two RFs in a single neuron. We used the same feedforward network as before, but activity from the two RFs were alternatingly presented on the 100 inputs to the single postsynaptic neuron. The neuron learned each RF by changes in the presynaptic release $U$ and the postsynaptic gain $A$ of the input synapses (Fig. 4.6a-b), while apparently forgetting previously learnt RFs – as assessed by the postsynaptic firing rate to that given input (Fig. 4.6c). However, because the postsynaptic component ($A$) outlasted the presynaptic one ($U$) (Fig. 4.6b), the neuron could more rapidly relearn information about a previous learnt RF (Fig. 4.6d). In addition, the improvement in discriminability was also faster after relearning (Fig. 4.6e). In conclusion, a neuron
4.3. Results

Figure 4.4: Extraction of $U$ and $A$ from in vivo receptive field plasticity experiments (data reanalyzed from Froemke et al. (2013)). (a) Modification of variability and mean as reported in Froemke et al. (2013), for unpaired (off) frequencies (mean: red filled circles, single experiments: light red circles) and paired (on) frequencies (mean: blue filled circles, single experiments: light blue circles) receptive fields. (b) Modification in $U$ and $A$ for on and off position, obtained assuming a Binomial release model (see Methods). (c) $A$ is downregulated and upregulated for off ($p < 0.05$) and on ($p < 0.001$) positions, respectively, after receptive field plasticity. (d) $U$ is also downregulated and upregulated for off ($p < 0.05$) and on ($p < 0.001$) positions, respectively, after receptive field plasticity.
Figure 4.5: Long-term pre and postsynaptic plasticity reduces variability and improves discriminability of receptive fields. (Continued on the following page.)
Figure 4.5: Long-term pre and postsynaptic plasticity reduces variability and improves discriminability of RFs. (a-b) Development of pre and postsynaptic RFs with 100 presynaptic neurons (inputs are defined using rate-coded a Gaussian profile – represented by the dashed grey line (a, top)) and a single postsynaptic neuron. (a) After convergence the simulation yields a distribution of release probabilities, $U$, and (b) postsynaptic factors, $A$ tuned to the input profile (before development: grey solid line, after development: black solid line). Dark and light red crosses represent a on and off RF position, respectively. (c-d) Modification of synaptic variance. (c) After RF development synaptic variance drops for both on and off neurons. (d) Synaptic variance map for different levels of $U$ and $A$ (grey colour map). As in (c) on and off neurons yield low synaptic variance (dark and light red arrows, respectively). In vivo plasticity results measuring synaptic responses from on and off RFs are in agreement with model (data from (Froemke et al., 2013) – orange arrows). For comparison is are also given the results for a learning rule where only the postsynaptic component is modified for on and off neurons (dark and light blue arrows, respectively). Black square represents initial condition. (e-f) Modification of signal-to-noise ratio (SNR). (e) After RF development the SNR increases for on, but drops for off neurons. (f) SNR map for different levels of $U$ and $A$ (grey colour map). Arrows representation as in (d). (g-h) Discriminability of synaptic responses. (g) Only on neurons yield a perfect classifier with both pre and postsynaptic plasticity (dark red line). For comparison are given the classification results before development (black line), after for off neurons (light red line) and after for a learning rule with only postsynaptic plasticity (blue line). (h) Discriminability (area under the curve in (g)) for different background noise levels. Grey dashed line represents a random classifier.
with unified STDP could learn about a new stimulus while simultaneously retaining trace information about a previously experience, which enabled more rapid relearning when the prior stimulus was re-encountered. These results are in keeping with Hermann Ebbinghaus’s memory savings concept (Ebbinghaus, 1885, 1913), which refers to the inaccessible storage of trace information of forgotten but previously experienced information that enables more rapid relearning.

**Discussion**

We investigated the functional implications of pre and postsynaptically expressed long-term plasticity using a phenomenological model of rate-sensitive STDP that includes pre and postsynaptic expression. This model was tuned to biological data from monosynaptic connections between neocortical L5 PCs, with $U$ and $A$ extracted by assuming a binomial distribution. We validated the model as well as the $U/A$ extraction approach with experimental data using pharmacological manipulations of short and long-term plasticity. When we applied our model to the development of RFs, we found that improved discriminability resulted from the combined pre and postsynaptic expression, and that this was consistent with RF plasticity in the intact brain. We next used the model to examine the consequence of the asymmetric localization of expression of depression and potentiation in L5 PC STDP, and we found that the incomplete reversal of LTP by LTD induction results in a memory trace of previously stored information. This trace improves relearning of the same information at a later stage, in keeping with Ebbinghaus’s memory savings theory (Ebbinghaus, 1885, 1913).

Our unified STDP model has similarities and differences with other influential models of plasticity. Senn et al. (2001) proposed a model of STDP that includes an increase in short-term plasticity upon induction of LTP (Markram and Tsodyks, 1996). This model did not, however, include any postsynaptic expression, nor were the functional consequences of expression locus explored extensively. Pfister and Gerstner (2006) introduced the first spike-triplet-based phenomenological model of STDP, which Clopath et al. (2010) extended to account for voltage dependence (Sjöström et al., 2001). We opted not to include more complex interactions such as voltage dependence, as the implications for our analysis are probably negligible. Our model does share some key features with that of Pfister and Gerstner (2006), e.g. triplet dependence and three synaptic traces, and is therefore likely to yield similar theoretical outcomes. A key difference, however, is that our model includes a description of the
Figure 4.6: The unified STDP model predicts rapid relearning of previously experienced stimuli in keeping with memory savings theory. (a) The presynaptic plasticity component $U$ follows the switching between two stimuli (red and blue Gaussian profiles on the top left, with arrows indicating switching timepoints). (b) The postsynaptic plasticity factor $A$, however, is not reversed by presentation of a new stimulus, so that a trace of previously learned information remains. (c) The neuron functionally changes its response between the two stimuli, as indicated by the alternating stimulus-specific firing rate. (d) The functional response of the neuron develops faster during relearning (black, represents postsynaptic firing rate for second presentation of the blue stimulus) than during learning (blue, represents postsynaptic firing rate for first presentation of the blue stimulus), in agreement with Ebbinghaus’s memory savings concept (Ebbinghaus, 1885, 1913). (e) Discriminability improves faster during relearning (black) than learning (blue).
expression of plasticity, which as we have shown here has interesting functional implications.

In our model, release probability is changed during learning, as inspired by biological findings (Sjöström et al., 2003, 2007; Markram and Tsodyks, 1996). Release probability is highly heterogeneous in the brain (Branco and Staras, 2009), and changes in synaptic dynamics have indeed been linked both to memory improvement (Tan et al., 2006) and to pathology (Abramov et al., 2009). Froemke et al. (2013) demonstrated that responses in auditory cortex became more reliable with learning, leading to improved perception. Our simulations suggested that this improved reliability could rely on a combination of pre and postsynaptic plasticity, but that postsynaptic plasticity alone does not suffice. Our findings thus lend additional support to the view that presynaptic plasticity is necessary for optimal performance in information storage and in perception (Tan et al., 2006; Abramov et al., 2009), and that postsynaptic AMPA receptor insertion alone does not afford synapses with the most favourable computational capacity.

Using monocular deprivation, Hofer et al. (2008) showed that spine changes in L5 PCs of visual cortex outlast sensorial experience, so that a trace of prior visual experience remains, thus providing a structural substrate for Ebbinghaus’s memory savings theory. With our model, we find analogous properties in that postsynaptic expression outlasts changes in the input statistics, which also provides memory savings (Fig. 4.6). It is well established that synapse size and weight are closely correlated (Sjöström et al., 2008), which suggests a link: the spine-mediated memory savings found by Hofer et al. (2008) is likely a reflection of the same long-term plasticity that we account for in our model.

Taken together, our results highlight how pre and postsynaptic forms of plasticity are tightly and differentially regulated by activity. Our theoretical treatment also suggests that pre and postsynaptic forms of long-term synaptic plasticity provide synapses in the brain with different features. On the one hand, the combination of pre and postsynaptic plasticity affords synapses with improved performance in both learning and perception. Unbalanced expression of synaptic plasticity, on the other hand, enables the formation of an information trace that could underlie memory savings. In conclusion, variable pre and postsynaptic expression of long-term plasticity is not haphazard but specific and performance enhancing.
Chapter 5

Conclusions

“Ideas do not last long. We must do something with them.”
— Santiago Ramón y Cajal

Throughout this thesis I have presented and discussed results on the analysis, mechanisms and function of multi time-scale interaction of synaptic plasticity, namely short-term and spike-timing-dependent plasticity. Despite growing evidence supporting this interaction, there are still only a few theoretical and experimental studies addressing this topic (Markram and Tsodyks, 1996; Senn et al., 2001; Sjöström et al., 2003; Carvalho and Buonomano, 2011).

I introduced a novel Bayesian inference framework of STP that should help clarify how STP is shaped under different conditions and how variable STP is across different neuronal connections and populations (see Chapter 2). In the present thesis I applied this framework to infer three different connection types in the canonical layer-5 microcircuit (pyramidal cell-to-pyramidal cell, pyramidal cell-to-basket cell and pyramidal cell-to-Martinotti cell connections). The results suggest that these three connections exhibit distinct synaptic dynamics. Future work should aim at confirming this clustering results by using a larger dataset. Using this formulation I have also shown that more informative stimulation protocols (Poisson based or by combining multiple frequencies) should greatly improve STP model estimations. This formulation assumes a Gaussian noise model, but a model with a more detailed noise description could allow the inference of the quantal parameters, which could in principle be combined with the Bayesian quantal analysis framework introduced by Bhumbra and Beato (2013). Overall, this inference framework provides a new toolset to reanalyse existing data and guide future experimental and theoretical work. For example, it has been known for a while that STP changes after STDP (Markram and Tsodyks, 1996) and with
development (Reyes and Sakmann, 1999). However, it is not clear exactly which components of the presynaptic release machinery are modified. The inference framework introduced here together with more informative protocols can be used to investigate these and related questions.

Presynaptic NMDARs are an important component in the interaction of short and long-term synaptic plasticity (Sjöström et al., 2003). In order to understand how exactly they regulate the release machinery I extended the Bayesian framework introduced in Chapter 2 to infer short-term plasticity from presynaptic NMDA receptor (preNMDAR) pharmacological blockade data at pyramidal cell-to-pyramidal cell connections (see Chapter 3). The inference results suggest that preNMDARs up-regulate baseline release probability and the depression timeconstant, which is consistent with experimental analysis. I have also shown that a preNMDAR mathematical model captures the frequency-dependence activation of preNMDARs, which show how preNMDARs implement a gain mechanism of synaptic transmission at high frequencies. Short-term depression makes it hard for synapses to sustain high frequency information transmission, preNMDARs are thus well positioned to help sustain high-frequency information flow (> 10Hz). Using a Binomial release model I demonstrated that preNMDAR’s regulation of release probability improves the signal-to-noise ratio of synaptic transmission.

Experimental data shows that preNMDARs also regulate synaptic dynamics at other connection types: namely pyramidal cell-to-Martinotti cell and pyramidal cell-to-basket cell (Buchanan et al., 2012). The inference of STP model parameters from this data suggest that the impact of preNMDARs on synaptic dynamics is connection-specific, potentially contributing to the connection-specificity of STP observed across different brain areas (Blackman et al., 2013).

In a parallel study and in close collaboration with experimental researchers we explored the functional consequences of target-specific expression of preNMDARs. This work shows that the differential expression of preNMDARs reroutes high frequency signalling in the canonical layer-5 microcircuit. This is caused by preNMDARs specifically impacting frequency-dependent disynaptic inhibition mediated by Martinotti cells.

These results and others (Bidoret et al., 2009; McGuinness et al., 2010; Larsen et al., 2014) are beginning to provide a better mechanistic and functional understanding of how and why synaptic dynamics are regulated by different factors, namely by presynaptic NMDARs. Understanding how the presynaptic terminal integrates differ-
ent factors on a short and long-time scale will help clarify how synaptic dynamics are shaped during learning. Therefore it is important that future studies investigate the impact of neural activity on synaptic dynamics other factors such as neuromodulation (Kawai et al., 2012; Kerr et al., 2013; Nadim and Bucher, 2014) and adhesion molecules (Blackman et al., 2013) are also likely to play important roles.

In an attempt to unify different scales of synaptic plasticity and explore its function I introduced a unified model of spike-timing-dependent synaptic plasticity with pre and postsynaptic components (see Chapter 4). I have shown that this unified model captures a wide range of short-term and long-term synaptic plasticity data (Sjöström et al., 2001, 2003, 2007). Functionally, I demonstrated that this segregation into pre and postsynaptic factors explains some observations on receptive field development (Froemke et al., 2013). Moreover this unified model enables faster relearning of previously stored information, in keeping with Ebbinghaus’s memory savings theory (Ebbinghaus, 1885, 1913).

Interestingly, these results also provide a potential explanation of monocular deprivation results by Hofer et al. (2008). Hofer et al. (2008) showed that spine changes in layer-5 PCs of visual cortex outlast sensorial experience, so that a trace of prior visual experience remains, thus providing a structural substrate for Ebbinghaus’s memory savings theory. With our model, we find analogous properties in that postsynaptic expression outlasts changes in the input statistics. It is well established that synapse size and weight are closely correlated (Sjöström et al., 2008), which suggests a link: the spine-mediated memory savings found by Hofer et al. (2008) is likely a reflection of pre and postsynaptic long-term plasticity. Based on the unified model I predict that the spines that outlast monocular deprivation become silent connections through presynaptic modifications, thus enabling neurons to become functionally active to the intact eye.

Unsupervised extraction of features present in naturalistic inputs is one of the most important problems solved by sensorial cortices (Olshausen and Field, 1996). Synaptic plasticity has been put forward as a potential explanation for the development of feature-specific receptive fields (Masquelier and Thorpe, 2007; Clopath et al., 2010; Gjorgjieva et al., 2011). The unified pre-post STDP learning rule presented here suggests that such feature-specificity would have particular modifications not only on the mean synaptic weight but also on its variability and dynamics. Future theoretical and experimental studies should explore this possibility.

Neuromodulation is believed to gate synaptic plasticity (Pawlak et al., 2010), pro-
viding an important third factor that links synaptic modification with behavioural outcomes. In particular it has been shown that STDP depends on neuromodulation (Pawlak et al., 2010; Cassenaer and Laurent, 2012), which has led to the development of theoretical models of reward-STDP (Izhikevich, 2007; Legenstein et al., 2008; Fremaux et al., 2010). It would be of interest to study the impact of reinforcement learning models of STDP with an explicit distinction between pre and postsynaptic components during learning.

Finally, based on my own and other’s work I argue that it is timely to start bringing different time scales together in an effort to develop a truly multi-time-scale model of synaptic plasticity: from short-term to early and late-phase long-term synaptic plasticity. By doing so it will be possible for the first time to understand how synaptic dynamics, learning and memory consolidation co-vary. Such a unified understanding of synaptic plasticity is also likely to yield important contributions to the development of treatments for disorders such as Alzheimers Disease (AD), Schizophrenia and Depression. Indeed, Lee et al. (2014) has recently shown that presenilins – the major gene products involved in familial AD – impair both short and long-term synaptic plasticity in the hippocampus. Many promising doors remain unexplored in this relatively new and exciting field.
Scientific communication

During my doctoral studies I have presented my research in different venues and formats, below I give a detailed list.

In preparation

- **Costa RP**, Froemke RC, Sjostrom PJ and van Rossum MCW - Memory savings through unified pre and postsynaptic STDP.

- Abrahamsson T*, **Costa RP***, Buchanan KA, Elgar D, Oyrer J, Blackman AV, van Rossum MCW and Sjostrom PJ - Control of vesicle release by cortical presynaptic NMDA receptors. (* equal contribution)

- Lalanne T, Oyrer J, **Costa RP**, Chung AJ, Sjostrom PJ and Farrant M - Synapse-specific plasticity in local circuits of mouse visual cortex

Journals


Posters


- **Costa RP**, Buchanan KA, Elgar D, Oyrer J, Blackman AV, van Rossum MC, Sjostrom PJ - Presynaptic NMDA Receptors Differentially Regulate Release


**Invited talks**


- Modelling memory traces of chronic pain, Computational Biology Seminar, *IBM T. J. Watson Research Center*, NY, USA, August 2013


- The role of STP and layer-5 motifs in spatiotemporal pattern recognition (with Dr. Stefan Hausler), *EU Brain-i-nets project meeting*, Graz, Austria, November 2012

- Towards a unified functional description of layer-5 local microcircuit of the neocortex, *Institute for Theoretical Computer Science, Graz University of Technology*, Graz, Austria, May 2012
• State-dependent modulation of STDP (Work Package 1) - together with Prof. Dan Shulz and Prof. Wolfgang Maass, Brain-i-Nets EU review meeting, EPFL, Lausanne, Switzerland, March 2012

• Modelling synaptic plasticity in local circuit motifs of the neocortex, Brain-i-Nets Workshop, Leysin, Switzerland, March 2012
Appendix A

Mapping RRP analysis to short-term synaptic plasticity models

The ready-release pool (RRP) plays a key role in determining the release dynamics on the presynaptic terminal, namely the probability of a given vesicle being released (Schneggenburger et al., 1999; Thanawala and Regehr, 2013). A linear regression analysis of short-term plasticity has been used to estimate the size and rate of the RRP (Thanawala and Regehr, 2013). However, it is not clear how this analysis relates to short-term synaptic plasticity (STP) models. Here we derive the RRP analysis as proposed by Schneggenburger et al. (1999) from the Tsodyks-Markram STP model (Markram et al., 1998), and show how the RRP analysis relates to different STP parameters.

A.1 Methods

A.1.1 Tsodyks-Markram model

The integrated form of the depression only Tsodyks-Markram model is given by (see Chapter 2 for more details)

$$ R_{n+1} = 1 - [1 - R_n(1 - U)] \exp \left( -\frac{\Delta t_n}{D} \right) $$

(A.1)

as we assumed that at time zero the synapse has not been recently activated, we set $R_0 = 1$. The postsynaptic potential $PSP_n$ is given by

$$ PSP_n = AR_n U $$

(A.2)
where $A$ is an amplitude factor that includes the number of release sites and the properties and number of postsynaptic receptors.

The steady-state values $R_\infty$ in response to prolonged periodic stimulation with rate $\rho$ is

$$R_\infty(\rho) = \frac{1 - \exp\left(-\frac{1}{\rho D}\right)}{1 - [1 - U] \exp\left(-\frac{1}{\rho D}\right)}$$

(A.3)

from which follows the steady-state postsynaptic potential $PSP_\infty$

$$PSP_\infty(\rho) = AR_\infty U$$

(A.4)

### A.1.2 RRP derivation from TM model

Following the linear equation form given by

$$y = mx + b$$

(A.5)

we formulate our problem based on the steady-state of the TM model (in the following we omit the dependence on the rate $\rho$)

$$PSP^n = r_{ref}n + RRP_{size}$$

(A.6)

where $PSP^n$ represents the linear regression based on the steady-state cumulative plot (Fig. A.1a), $n$ is the pulse number, $r_{ref}$ the rate of refilling calculated here as the steady-state increase given by the TM model

$$r_{ref} = PSP_\infty$$

(A.7)

and $RRP_{size}$ is the size of the readily available pool (as proposed by Schneggenburger et al. (1999)), obtained by computing the y-axis crossing value as

$$RRP_{size} = \sum_{i=0}^{Z} PSP_i - PSP_\infty Z$$

(A.8)

where $Z$ is the pulse number at which the steady-state response is achieved. $Z$ is calculated by simulating the model until the steady-state is achieved.

Therefore the linear regression of the postsynaptic response is given by

$$PSP^n = PSP_\infty n + \sum_{i=0}^{Z} PSP_i - PSP_\infty Z$$

(A.9)

$$PSP^n = PSP_\infty (n - Z) + \sum_{i=0}^{Z} PSP_i$$

(A.10)
As expected $PSP^n$ is equal to the cumulative PSP (before the steady-state PSP as specified by $Z$) plus the increase after the steady-state. Next we calculate $P_{\text{train}}$ as specified by Schneggenburger et al. (1999); Thanawala and Regehr (2013)

\[
P_{\text{train}} = \frac{PSP_0}{RRP} \\
P_{\text{train}} = \frac{PSP_0}{\sum_{i=0}^{Z} PSP_i - PSP_\infty Z}
\]  

$P_{\text{train}}$ was proposed by Schneggenburger et al. (1999); Thanawala and Regehr (2013) to provide a good estimator of release probability during the spike train. In the results I explore how these metrics $r_{\text{ref}}, RRP_{\text{size}}$ and $P_{\text{train}} (r_{\text{model}}^{\text{ref}}, RRP_{\text{model}}$ and $P_{\text{train model}}$ in Fig. A.1, respectively) relate to the depression timeconstant $D$ and release probability $U$ in the TM model.

### A.2 Results

In Fig. A.1a I illustrate the RRP linear regression analysis in the TM model. This shows that there is a positive correlation between $RRP_{\text{size}}$ and the $U$ parameter (release probability), and also a nonlinear dependence on the depression timeconstant $D$ (Fig. A.1b). While $D$ correlates better with the RRP rate of replenishment (Fig. A.1d). On the other hand the $P_{\text{train}}$ measure does not seem to provide a good estimation of either $U$ and $D$ (Fig. A.1c). Overall, these results support the RRP experimental data analysis for RRP size and rate of replenishment, and previous findings (Schneggenburger et al., 1999; Thanawala and Regehr, 2013). However, as shown here, even when using a simple STP model there is not a simple linear relationship between these measures and the model parameters, so these estimations have to be taken with care and better estimators should be developed in the future.
Figure A.1: Ready-release pool linear regression analysis at 30Hz. (a) Cumulative PSPs from simulation of the TM model for 14 pulses (scatter plot) with linear regression (black solid line, Eq. A.9). (b) Model RRP size (Eq. A.8), (c) $P_{\text{train}}$ (Eq. A.12) and (d) $r_{\text{ref}}$ (Eq. A.7) as a function of the TM parameters — $U$ (red solid line) and $D$ (blue solid line) were varied while the other one was kept fixed ($D = 0.2$ and $U = 0.7$).
Bibliography


