Simulation of synaptic plasticity and its contribution to the dynamics in a cortical microcircuit

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In this paper it is studied whether synaptic plasticity (change of the connection strength between two cells) is crucial for the dynamic oscillatory behavior in a pair of reciprocally connected cells in neocortex. More specifically the cell loop consists of an inhibitory interneuron (cell with a depressing effect) and a pyramidal cell (cell with an exciting effect). Computer simulations show that the plasticity increases the excitability of the cell. Due to interaction between the adaptation (the signaling from a cell does normally decrease with time) and the inhibitory conductance (strength of the depressing connection) the increased excitability is frequency dependent. In order to perform these simulations a computer model of each cell type was constructed. The cell models are based on cell pair recordings, done in Dr. Zilberter's-lab at KI, in a neocortical slice as well as on literature data.

Simulering av synaptisk plasticitet och dess bidrag till dynamiken i en kortikal mikrokrets

I denna rapport studeras hurvida plasticiteten (förändring hos kopplingsstyrkan mellan två celler) är viktig för dynamiken i ett par av ömsesidigt kopplade celler i neokortex. Mer specifikt består cellparet av ett interneuron (cell med nedtryckande effekt) och en pyramidcell (cell med exciterande effekt). Datorsimuleringar visar att plasticiteten ökar excitabiliteten hos cellparet. På grund av samverkan mellan adaptationen (signaleringen från en cell minskar normalt med tiden) och den inhibitoriska konduktansen (den nedtryckande cellens kopplingsstyrka) är den ökade excitabiliteten frekvensberoende. För att utföra dessa simuleringar konstruerades en datormodell av båda celltyperna. Cellmodellerna är baserade på mätningar hos cellpar i en skiva från neokortex, utförda i Zilberters lab på Karolinska Institutet, samt på data från litteratur.
Foreword

This Master Thesis is, as intended to be, the culmination of my education at KTH. The work is commissioned by SANS at NADA and is based on experiments performed by Yuri Zilberter at the Karolinska Institute.

First of all I would like to thank my supervisor Erik Fransén. He has not only answered all my questions, but also been there supporting when things have turned against me. I would also like to thank Anders Lansner for valuable hints. My room mates Christopher and Joacim also earns a thank for making the work a lot happier. Last but not least I would like to thank Yuri Zilberter and his PhD student Carl D. Holmgren for demonstrating their laboratory and making the data available.
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1 Problem definition

In the brain of Wistar rats it has been found that 75 percent of the cell pairs form reciprocal connections with each other. The exact location is in the layer 2/3 in neocortex. Since these cells form reciprocal loops they could be a part of an oscillatory mechanism. Moreover, the cell pair consists of one inhibitory and one excitatory neuron. The synapse from the inhibitory to the excitatory neuron is plastic. In general a plastic synapse can increase or reduce its strength due to the firing of the two cells. However, in this case, the plasticity is only controlled by the receiving neuron, i.e. after the synapse. This is made possible by the fact that some effect of the fired pulse (action potential) in the receiving neuron will be returned (back propagating action potential) to the synapse where it will alter the efficacy of the synapse.

My task is to examine if the plasticity is crucial for the dynamical behavior in the cell loop. Dynamical behavior could be oscillations due to external input etc. To be able to study this a computer model of each cell was constructed (see Appendix for the content overview of the files). These models were based on brain slice experiments performed by Dr. Zilberter at the Karolinska Institute (see chapter 4). After that, simulations with external input such as an oscillation were performed. Then the task was to examine the oscillatory behavior with and without plasticity (see chapter 5).

2 Introduction

2.1 In vivo and in vitro

First an explanation of two important concepts when working with biological experiments: in vitro and in vivo. In vitro means that an experiment is performed in an artificial environment such as a brain slice to which nourishment and oxygen is supplied. On the other hand in vivo is an experiment done during more natural conditions, with a natural environment, such as measurements done on living organisms.

2.2 Neocortex

In this thesis the focus will be on the neocortex (see figure 1). The neocortex provides the basis to identify, order, and act meaningfully in response to external stimuli or internal motivation, in other words the basis for cognition. Now, the neocortex collects data from different modalities in order to have something to operate on. Each modality has its own region in the brain, where for example the olfactory bulb is the center for smell while the hindbrain collects information from the brain stem, which can be signals from touch sensors. When the neocortex has determined what to do with a given input it sends signals to different regions. Such regions can be the thalamus, which is a kind of switchboard for incoming and outgoing signals. Another target region is the motor cortex where motor commands are initiated.
The neocortex is composed of different sheets of cell types, figure 2. This anatomical observation has led to the definition of six layers or laminae. Cells in different layers connect with cells in other layers. Cells in layer six send output to the thalamus. Signals from the thalamus project to layer four. Cells in layer five project to subcortical areas. The cells that will be studied are located in the layer two and three and receive, via layer four, input from thalamus and layer one. They build formations where there typically are 1000 pyramidal cells connected to one inhibitory interneuron and back and pyramidal cells are also connected to each other through weak connections. This could be interpreted as a kind of normalization, since if there are many pyramidal cells that are spiking then the interneuron will fire very strongly and as a result depresses the pyramidal cells. On the other hand if there are only a few pyramidal cells that are signaling then the resulting inhibition from the interneuron will be smaller, hence keeping the mean signaling at an approximately constant level.
2.3 The neuron

The neuron is the main functional element for storing, processing and retrieving data in the brain. Neurons are composed of, like all cells, a cell membrane encapsulating organelles and a nucleus. They connect to each other forming networks, figure 3a. A neuron generally has many inputs and outputs. The connection between two neurons is called a synapse, figure 3b. The information is transmitted through these synapses with chemical substances called neurotransmitters. These are released from the first neuron when it becomes activated. This activation origin from a electric pulse in the first neuron and due to its nature it is called action potential. So, when this action potential have triggered a burst of transmitters, they in turn bind to receptors on the second cell, which result in a electric pulse (not an action potential which will be explained soon) in the second neuron. This is because the receptors open ion channels that allow charged particles through the membrane.
So what happens between the input and output of a neuron? As mentioned above a neuron has many inputs. A neuron manages this by having a tree of inputs, called dendrites, connected to the cell body, also called soma. When transmitters from surrounding neurons reach this dendritic tree (neurotransmitter receptors are placed on small extensions from the dendrites called spines) a local electric pulse is generated. This electric pulse propagates down the tree to the cell body. As there are many input pulses that propagate down the tree the summation becomes larger than the individual pulses. This is crucial for the next step. If the summed pulse is large enough it can trigger an action potential. This action potential (AP) is triggered in an extension of the soma, called axon, which connect to other cells with synapses. To conclude, if the cell receives sufficient amount of input, it can be triggered and as a result signaling to other cells. Also, as in this thesis, the AP will be reflected as a back propagating action potential (BAP) to the dendrites. The BAP is crucial in this thesis in order to control the plasticity.

2.3.1 Action potential

How come that the action potential is triggered at a certain threshold? This is due to a interaction between two ion channels, i.e. sodium and potassium, figure 3c. As mentioned above the sodium makes the cell depolarized while the potassium makes the cell hyperpolarized since positive ions flow out from the cell. When a electric pulse arrives at the
axon the sodium channels open, while the potassium channels are delayed. When the positive sodium ions flow inside the cell it gets even more positive (which is also called depolarized) which in turn opens the channels even more. The potassium current controls this depolarization, because it makes the cell more negative (which is called hyperpolarized). The crucial part is that at a certain depolarization the inflow of positive ions is slightly larger than the outflow of positive ions, which is enough to start a positive feedback loop which in turn results in an action potential. When the action potential has reached a certain depolarization the sodium channels inactivate and the potassium channels is fully open which results in a large hyperpolarization. This is necessary in order to make the sodium channels operable again. Since the potassium channels are voltage controlled they will close due to the hyperpolarization.

Some special considerations are necessary for the interneuron since it does normally fire with a high frequency. Rapid firing can be accomplished by making the AP reach the threshold as fast as possible and then make it hyperpolarize as fast as possible. This can be accomplished by adjusting the conductance for the potassium and sodium channels, i.e. the channels that creates the AP.

So far only action potential in the soma or axon has been considered. But, as in this thesis, when the dendrites have mechanisms controlled by the BAP, the BAP must be not decay as it travels through the dendrites. If the dendrites are passive, the leakage of the cell will dampen the BAP. Therefore the dendrites should have some sodium and potassium channels in order to conserve the BAP.

2.3.2 Leakage channels and the input resistance of the cell

When an action potential has been fired the voltage converges to the resting potential. This step is called repolarization and is due to passive leakage channels. The density of these channels and concentration and type of ions on both sides of the membrane (inside and outside the cell) determines the resting potential. More theoretically this can be split into two forces, i.e. the diffusion and electric force. The electric force is due to different amounts of charge on both sides of the membrane, which results in an electric field that prevents ions from going in one direction. Different amounts of concentration of both sides of the membrane (no matter what electric charge) create the diffusion force. To illustrate the diffusion force you can imagine a drop of ink in a glass of water and the ink spreads out. The same thing applies to the cell, i.e. if there is a higher concentration, of some ion, inside the cell rather than outside then the ions want to flow out from the cell. These forces have been used to derive a quantitative description of the resting potential based on ion concentration and membrane permeability [1].

The density of the leakage channels also contributes to the input resistance of the cell. The cellular resistance is important since if the input resistance would be to low then all injected currents would diffuse out from the cell again and as a result the dynamics would be smoothed.
2.3.3 Adaptation

There are other channels such as calcium dependent potassium channels. Their task is to make the cell fire less frequent the longer it has been active. As the name implies the channel is controlled with calcium. The higher the calcium concentration is inside the cell the more potassium flows out from the cell. When a cell fires its calcium channels open, which increases the internal calcium concentration. This in turn lets more potassium inside which makes the repolarization slower and the cell fires less frequent [1].

2.4 Synapses and transmitter release

There are two main classes of cells, i.e. inhibitory and excitatory, where a typical excitatory cell is described above. Typically, an excitatory cell releases a neurotransmitter called glutamate that in turn attaches to a receptor called AMPA. The AMPA receptor is excitatory because it is permeable to sodium and potassium ions. The inhibitory cell releases a neurotransmitter called GABA that in turn connects to its receptor. Since the GABA-receptor opens and enables an influx of chloride ions the cell gets negative [2]. This is a sort of clamping of the potential below threshold, of the post cell, that makes it more difficult to trigger the cell. This can be formulated using the equilibrium potential of the synapse ($E_s$) and the threshold for an action potential ($V_{th}$):

Inhibitory

\[ E_s < V_{th} \]

Excitatory

\[ E_s > V_{th} \]

When an action potential triggers, neurotransmitter is being released. This is thought to be due to calcium channel. Experiments have revealed that when an action potential arrives, the internal calcium concentration is increased. The idea is that the internal calcium is required for the vesicles (containers for neurotransmitters) to fuse with the membrane in order to release neurotransmitters. As a result a cell that doesn't get enough calcium can't stimulate another cell.

3 General modeling methods

3.1 Passive membranes and the cable equation

In order to analyse, for example the dendritic tree, a physical model has to be setup. Since the dendrites consist of many tube or cable like sections it is natural to also analytically treat them like cables. These cables are assumed to have a continuous resistance inside and to the environment. Therefore they can be thought of as many small iso-potential units linked after each other. Through each of these units there flows an axial current inside the cell and also one outside the cell. There is also a radial surface current, or membrane current, which for simplicity is assumed to be passive. From this model an attribute called the electrotonic length can be derived. This is a measure of how effective such a cable is in terms of how much current escapes from the cable versus the amount of current injected. Later, in section 3.4.1,
the electronic length will be used as one of the simplification attributes used when reducing complex neuronal models [3].

3.2 Channel nonlinearities in the membrane and the Hodgkin-Huxley formalism

Since ion channels lie between two different concentrations of ions, the flux of ions has to overcome the electric field. This property makes the current-voltage relation non linear, which is called rectification [4]. This rectification has two extremes, i.e. inward and outward rectification. As inward-rectification implies, it is easier for ions to flow inside the cell and vice versa for the outward rectification. The Goldman-Hodgkin-Katz (GHK) model [5] captures this property. The GHK current equation:

\[
I = \frac{P_z^2F^2}{RT} \left[ \frac{[C]_{in} - [C]_{out} e^{-\frac{zFV}{RT}}}{1 - e^{-\frac{zFV}{RT}}} \right]
\]

Where \( P \) is the permeability (density of ion channel across the membrane), \( z \) is the ionic valence, \( R \) is the gas constant, \( F \) is the Faraday constant, \( l \) is the membrane width and \( T \) the temperature. The GHK voltage equation:

\[
V_{rest} = \frac{RT}{F} \ln \left( \frac{P_k \left[ K^+ \right]_{out} + P_{Na} \left[ Na^+ \right]_{out}}{P_k \left[ K^+ \right]_{in} + P_{Na} \left[ Na^+ \right]_{in}} \right)
\]

The problem with this model is that the type of rectification is dependent of the concentration gradient and therefore also the reversal potential. However, due to the chemical nature of ion channels this is not necessarily true. The mechanisms that control channels rely on the free energy, which is a kind of threshold for a chemical reaction to occur. This was taken into account when the next model, the energy barrier model, was evaluated. It explained a variety of behavior such as the multistage property (which is when many energy barriers have to be overcome), which was modeled with a number of energy barriers. Now the problem was the description of the time dependency. The time dependency is problematic due to the statistical nature of individual channels. The breakthrough came when Hodgkin and Huxley (1952) proposed a model that they called the gating particle model [6]. This model assumed that a channel had discreet states, which were defined by the gating particles. From one state there also was a probability to jump to another. By summing many such channels it could be shown that the current dynamic had astonishing similarities with the measured current. This idea was later confirmed by measurement of single channels with a method called patch clamp. For example, the sodium channel has three activation particles (m) and one inactivation particle (h). The activation particle goes to 1.0 when the channel is depolarized. In contrast the inactivation particle goes to 0.0 and a bit slower. Together these particles defines the membrane current:

\[
I_m = g_{max} m^3 h(V - E_{Na})
\]

Where \( g_{max} \) is the maximal conductance and \( E_{Na} \) is the equilibrium potential for sodium
defined with the GHK voltage equation.

A natural theoretical formulation and generalization of this model is the Markov model. This enables macroscopic descriptions that can be used to experimentally confirm different state transition schemes. The Markov model is defined by a probability, at a given time, to jump from one state to another state \( P(t) \) and the probability to jump to a state known that you are in a particular state \( Q \). The relation between these can be formulated with the Chapman-Kolmogorov equation [7]:

\[
\frac{dP(t)}{dt} = P(t)Q
\]

As this is a first order differential equation system, the time constants for the different transitions can be extracted from the eigenvalues. The power spectrum of the transition scheme can also be derived from the eigenvalues. This enables us to justify a transition scheme from the power spectrum of experimental data.

### 3.3 Synaptic transmission

When a synapse is activated the effect (EPSP or IPSP) on the postsynaptic site can be modeled as a time dependent conductance increase that is dependent of the activation at the pre site. This can be modeled as a sudden, when the AP reaches the pre site terminal, increase of the conductance at the post site and then letting the conductance to decay exponentially. The conductance in turn then triggers a electric pulse (EPSP or IPSP). A more accurate model of the change of the conductance, which is called alpha synapse, is to sum two exponentials with different time constants. In the following section we will look at different mechanisms that alters the amplitude of such postsynaptic pulse will be discussed.

#### 3.3.1 Short term plasticity

When a pre-cell is repetitively stimulating another cell (post cell), the post cells EPSP gradually changes. The EPSP can become smaller (depressed) or larger (facilitated). Often an intensive stimulation of a synapse first results in facilitation but after a while the depression becomes overwhelming. Currently this behavior is explained by calcium dependent transmitter release. First the calcium increases due to the influx of calcium with each action potential, which results in a burst of an amount of neurotransmitters proportional to \([Ca]_i^4\) [8]. After a while when the vesicles is getting depleted the synapse is being depressed. The EPSP amplitude after a 300 impulse conditioning train has been measured [9] and those measurements reveal that there are four distinct time constants of synaptic facilitation. First there are two relatively fast facilitations (with a decay of a few hundred milliseconds) followed by augmentation (few seconds) and potentation (100s). For the depression there seem to be two time constants, a fast (5s) and a slow that lasts several minutes [10]. The change of each of these processes is described by the following differential equation [11]:
Where $A$ constitutes depression if it is smaller than 1.0 and facilitation if it is bigger than 1.0. When an action potential stimulates the synapse, $A$ must be increased in the case of facilitation and decreased in the case of depression. This can be done either additive $A = A + (1 - \Delta A)$ or multiplicative $A = A \cdot \Delta A$. It can be shown that the multiplicative form is suitable for depression, while the facilitation needs the additive [12].

Another form of plasticity is the long-term potentiation (LTP) and depression (LTD) that last for hours and longer. However, this will not be included here.

3.3.2 The conditioning dependent plasticity

The special plasticity studied in this paper is the conditioning dependent plasticity. As mentioned above its effect is controlled by the back propagating action potential that is returned when an AP is triggered in the soma. The BAP opens calcium channels in the dendrites, which results in an increase in the internal calcium concentration. Calcium enables vesicles filled with neurotransmitters to fuse with the membrane. Since the BAP travels in the dendrites of the pyramidal cell, which is excitatory, vesicles filled with glutamatergic neurotransmitters will fuse with the membrane. As these excitatory neurotransmitters travels to the interneuron they will dampen the effect of the gabaergic (inhibitory) interneuron. The exact underlying mechanism is not understood, but it is indeed intuitive that the excitatory neurotransmitters will have an opposite effect for the inhibitory interneuron, figure 4.

![Figure 4: The location of the conditioned plasticity in the loop. The BAP opens calcium channels that in turn increase the calcium concentration that enables the glutamate travel to the inhibitory synapse and as a result decreasing its efficacy.](image)

To build an empiric model of the plasticity, Zilberter [13] used a protocol that consisted of three phases, figure 14. First the fast spiking inter neuron was stimulated in order to find the control IPSP amplitude. Then the pyramidal cell was stimulated with ten action potentials at 50Hz, i.e. the conditioning phase. These APs then generated BAPs that in turn increased the
calcium concentration in the dendrites. The increased calcium concentration then increased the effect of the plasticity, i.e. the depression. Directly after the last AP the calcium concentration and the amount of depression was measured. The amount of depression was simply measured by comparing the amplitude of the IPSP before and after the conditioning.

This test revealed a relation, see figure 5, between the calcium concentration in the dendrites and the amount of depression of the IPSP. Zilberter found that the relation may be described with a Michaelis Menten formula.

![Figure 5: Relation between the calcium concentration and the amount of depression.](image)

### 3.4 Simulation theory

#### 3.4.1 Model reduction and the compartment model

The models used in simulations cannot be too detailed due to two reasons. First it is impossible to know every detail of a cell and second, a detailed model takes longer time to simulate. Additionally it is good to have a low detailed model because that allows us to isolate and understand an interesting property. When talking about different details of cell models, there are basically two parallel kinds of simplification. The physical category, or morphology, captures physical attributes like number of dendrites and spines. The functional category handles type of channels and their distribution over the cell membrane.

To reduce the cell morphology, the common way is to cut up the cell in small compartments. Each compartment is then treated as an isopotential element that exchange currents axially, to neighbouring compartments, and radially through the membrane. The membrane current is the summation of all the currents from different ion channels, like sodium and potassium, plus the capacitive current through the membrane. As a result a compartment can be treated like an electric circuit where for example the voltage dependent channels corresponds to voltage dependent resistances.

The model can even be reduced by means of complexity of the dendritic tree, i.e. to collapse many small compartments to one bigger. There has been many algorithms to manage this, some which do direct simulations in order to find which parts are not necessary [14] and some which conserve various attributes such as the above discussed electrotonic length in order collapse compartments [15]. However this approach is only exact if the diameters, at the branch where dendrites will be collapsed, follow Rall’s rule: \( d^{3/2} = d_1^{3/2} + d_2^{3/2} + \ldots + d_N^{3/2} \), where \( d \) is the diameter of the father and \( d_i \) is the diameter of child \( i \) (there are \( N \) children).
Another property that can be modeled is the diffusion of calcium. Since the calcium concentration is important for many channels, we have to spread out the injected calcium that has entered through calcium channels, in a calcium buffer, whose volume is defined. These calcium buffers are geometrically complex and therefore some degree of simplification has to be made. A first approximation is accomplished by simply measure the entered number of calcium ions and distribute them over the defined volume.

3.4.2 Numerical accuracy

When the compartments have been setup and channels has been added it is time to perform the simulation. Usually the model is initiated with a membrane potential and then the emerged current is calculated. The currents in turn update the ionic concentrations, which in turn update the potential at the various compartments. Because the channel kinetics etc is defined by differential equations, we need a robust way to update the values based on derivatives. The simplest approach is to add the derivative, in the current time, during a short time to the old value, i.e. Euler forward. Unfortunate this approach is not stable. A stable but not so accurate way is to use the derivative at the next time step. The best approach from stability vs. accuracy point of view is the Crank and Nicholson (1947) method, which uses a mix between the Euler backward and forward –method [15].

Just to get a hint of the processing power required; a simulation of one second, with booth cells, a noise source and a frequency source took 30 second on a 1.5GHz P4 with 256Mb ram. When the plasticity was examined, two versions of the above simulation, with and without plasticity, were repeated 2000 times for different parameters resulting in a simulation time of approximately two days.

3.5 Simulation environment and tools

When simulating cells there are two freeware simulation packages that are widely used, NEURON and Genesis. NEURON was chosen since it can be run on UNIX, LINUX, Mac OS, and Windows, while Genesis can be run only on Unix and Linux.

NEURON is composed of two parts or languages. First there is an interpreted language that is used to setup NEURON’s internal data structures that in turn are used as the base for a differential equation solver. NEURON’s internal data structures define the simulation parameters, the morphology of the cell and the location of the ion channels and synapses as well as their properties (se 3.4.1). The other language is compiled and used to describe the differential equations of synapses and channels (se 3.4.2). The interpreted language is thought to enable a better interactivity while the compiled code, for the sake of performance, is used for repetitively called structures/components.

NEURON produces results that are common for experimentalists, for example current or voltage as a function of time. You can even scan a real cell and then let NEURON translate it into it’s own description language. Then by applying the same simulation setup as in the corresponding electrophysiological experiment NEURON could produce similar results (however generally not in real time).
NEURON is optimized for cell assemblies with few cells and for cells that are described with differential equations and cables (compartments).

NEURON has common functionality such as a library for manipulating vectors and libraries for file input and output. This functionality has been used for preliminary analysis of data as well as storage of data for figures.

Matlab has been used to generate figures from the data stored with NEURON. Microsoft Word has been used to write the report.

4 Models used in this project

The basic part of this project was to model the two cells individually (source code for the pyramidal cell and the fast spiking interneuron: RedPyr.hoc and RedFSN.hoc). After this the synapses (source code for the synapse with the interesting plasticity: Fsn2Pyr.mod) were modeled based on experiments performed by Zilberter [16]. The network as well as noise and frequency sources were connected (source code for the two reciprocally connected cells: LoopNet.hoc) and simulated finally (source code for the setup of the simulations parameters: Main.hoc).

4.1 Individual cells

First the morphology of the cell body had to be set up. Since a complex morphology of the cell body increases the simulation time a reduced version was needed. For the pyramidal cell an eight-compartment model was found [14], figure 6. Since it was difficult to get a model for a fast spiking neuron, the morphology of the pyramidal cell was used for that one as well. This was acceptable since “fast spiking interneuron” only says something about the firing characteristics.

![Figure 6: eight-compartment model.](image)

Typically the input resistance is 150 Mohm and the time constant is around 12 ms. These are adjusted by varying the conductance of the leakage channels and the resulting leakage conductance was set to $10^{-5}$ µS and the steady state potential was set to –70 mV. Specifically a hyperpolarizing current is injected and the time constant and amplitude of the resulting
voltage time course is measured. The resistance is extracted from ohms law; the relative voltage amplitude divided by the amplitude of the inputted current. The time constant is the decay time of the voltage course, i.e. the time it takes for the voltage to reach 1-1/e of the maximum amplitude.

Sodium and potassium currents were added to the soma in order to get an action potential. Parameters for the Hodgkin-Huxley model were taken from [17]. The width of each action potential, at the potential between threshold (-50 mV) and spike top, was adjusted to 1.0 ms and the resulting sodium and potassium channels became, 0.8 µS and 0.55 µS.

Since the plasticity is triggered by a back-propagating action potential in the dendrites, these dendrites should not damp the BAP too much. In order to conserve the amplitude in the dendrites a smaller density of sodium and potassium channels has been added to the dendrites. With a conductance that is 16-times smaller than in the soma the decay of the BAP is adjusted to 80 percent of the AP in the soma.

The pyramidal cell is different from FSN in that it’s frequency decreases with time. To get this effect I introduced calcium dependent potassium channels (conductance = 4*10^{-3} µS), calcium channels (conductance = 0.9*10^{-6} µS) and a diffusion buffer (tau=100 ms and steady state concentration = 0.25*10^{-5} µM) in the soma. The Hodgkin Huxley parameters were borrowed from [18] and the diffusion buffer had only one shell, whose depth was set to 0.1 µm. As guide lines for the adjustment I have used [19], figure 7. The amplitude of the current was not considered. Instead only the position and corresponding curvature were fitted.

This adaptation however lowered the resting potential of the cell and that resulted in a decrease of the resistance and time constant of the cell. This occurred due to a continuous output of potassium ions from calcium dependent potassium channels due to a nonzero calcium concentration level. To get rid of this the steady state calcium level was lowered (steady state concentration = 0.25*10^{-5} µM) and adjusted the adaptation accordingly. Though this might sound simple this adjustment took several weeks; first to locate the error source (calcium concentration) and then readjusting the adaptation.
4.2 Synapses

As the synapses in the circuit both show short-term plasticity, the synapses were based on Varela’s short time facilitation and depression model [11]. According to [13], both synapses will have short time depression and no facilitation. For both synapses the time constant for the short time depression were set to 200 ms, while the strength of the depression were set to 70 percent when the two pulses are separated by 200 ms (the time constant).

4.2.1 Conditioning dependent plasticity

The plasticity was modeled with one calcium pool in the dendrites of the pyramidal cell. The calcium pool was modeled with one shell and with a steady state concentration of 50 nM. According to [20] the time constant of the calcium buffer was set to 100 ms. Calcium influx was mediated by an L-channel, the channel that opens when the BAP reached the dendrites. The conductance of the L-channel (conductance = 8*10^{-5} µS) was set according to the calcium transient after a single AP according to [20]. Then according to [16] the Michaelis-Menten function was used to relate the concentration of calcium to the depression of the synapse.

$$D = \frac{K_{\text{max}}}{1 + \frac{Ca_{\text{half}}}{Ca^{2+}}}$$

$K_{\text{max}}$ and $Ca_{\text{half}}$ were derived from the relation between number of action potentials (the conditioning) and the amount of depression [13]. More specifically after four action potentials the calcium concentration was measured in the simulation. Then in Zilberter’s paper [13] the dependence between the number of APs and the amount of depression is specified. These two results gave the correspondence between calcium concentration and amount of depression. According to Zilberter $K_{\text{max}}$ is set to 0.5. From this the $Ca_{\text{half}}$ could be extracted (218 nM):

$$Ca_{\text{half}} = \frac{[Ca^{2+}]_4 (K_{\text{max}} - D_4)}{D_4}$$

The subscript (4) in the formula above stands for the number of action potentials before the corresponding variable is measured. There were also indications that the amount of paired pulse depression was dependent of the conditioning, but in the sake of simplicity this was omitted.

4.3 Microcircuit

Between the two cells the EPSP- and IPSP-amplitudes are about 1 mV according to [16]. Naturally a cell recieves many input and therefore the summed contribution will be larger. This requires that a complete model of the signals from the surrounding pyramidal cells and interneurons should be modeled. However it is not possible to set up all the surrounding cells due to two reasons. First the complexity of the simulation will increase (with two cells a typical plasticity evaluation takes two days) and second, there is currently no detailed model of the connections between the surrounding cells. Due to the complexity of the real network
some approximations had to be made. First the individual EPSPs and IPSPs are made larger, which is managed by increasing the conductance of both synapses, in order to enable one EPSP to fire an AP. Second the signals from the surrounding pyramidal cells and interneurons is substituted with a Poisson generated (alpha synapses to generate the EPSPs) noise source in order to raise the background firing level such that it is easier for smaller EPSPs and IPSPs to trigger an AP. The mean frequency of the Poisson [21] noise was set to 300Hz and the conductance to $2.5 \times 10^{-4} \mu S$ for the FSN and $5 \times 10^{-4} \mu S$ for the pyramidal cell. The amplitude of each poisson EPSP/IPSP were set such that the mean background potential was raised from $-75 \text{ mV}$ to $-65 \text{ mV}$ [22].

### 4.4 Evaluating the effect of the plasticity

Information in the brain is transmitted via the spatio-temporal pattern of spikes, i.e. via the rate and synchrony. As only pyramidal cells have long axons that project onto the local circuit, the output of the pyramidal cell when the pair was stimulated was chosen as the focus of intensity. Then by testing how this intensity depended on different parameter sets with and without the plasticity, the function of the plasticity could be evaluated.

Now, which parameters should be varied in order to discover the properties of the plasticity? Since the plasticity decays with time it could be interesting to see how the dynamic depends of the time between two successive EPSP or the frequency in a train of EPSPs. Therefore two EPSP-generators were added, one for each cell, which generated a variable but deterministic frequency (alpha synapses with conductance $0.5 \times 10^{-2} \mu S$ for the FSN and $1.5 \times 10^{-2} \mu S$ for the pyramidal cell). Also, the conductance of the synapse where the plasticity is located is an interesting parameter. Like the conductance, which changes the excitability of the cell loop, the adaptation time constant will be varied as well.

First the parameter space (which I will refer to as point space) was scanned for the most interesting points, i.e. where the plasticity made most difference. The algorithm that was used was to begin in one random point and then randomize a new point based on the first one. The variance of the translation to the new point was set proportional to the values of the old point. This is reasonable since a large value requires larger steps to scan a corresponding area.

When an interesting point has been found an area surrounding that point has to be examined. Here the choice was between generating points randomly or uniformly distributed on a grid. The random variant was chosen since it does automatically increase resolution with time (in the uniform variant the point grid has to be subdivided when all points in the grid has been examined).

To determine the effect of the short-term plasticity one second were simulated with different model parameters, with and without the plasticity. The plasticity was turned off, by setting $K_{\text{max}}$ to zero. Two different groups of measures were set up to measure the change that the plasticity gave rise to. The simplest group of measures was based on the number of action potentials in both cases. First this was used to calculate the change in number of action potentials. A version of this was to measure the relative difference, i.e. to divide the spike difference with the total number of spikes. The other group of measures was based on histograms of the inter spike interval, figure 8. The inter spike interval is defined as the time between two successive action potentials. Then each bar in the histogram indicates how many pairs of action potentials that were a certain time from each other. Now the histogram could
be seen as a vector with each dimension corresponding to a certain inter spike interval and the value corresponding to the number of AP-pairs that were in such interval. Since two measurements are made, with and without plasticity, there are two vectors. The difference between these two vectors was measured in three ways, the scalar dotproduct, the normalized scalar product and the Euclidian distance, see figure 16.

![Figure 8: Histogram of the inter spike interval. Here we can see that there are most action potentials with a distance of 25 ms between each other](image)

### 5 Results

The basic part of this thesis was to model the two cells individually. After this the synapses was modeled based on experiments performed by Zilberter [16]. Last, the two reciprocally connected cells were simulated with additional input such as background noise and the function of the plasticity was evaluated.

#### 5.1 Individual cells

To test that the time constant (12 ms) of the cell membrane and the input resistance (150 Mohm) is correct, the hyperpolarizing current step for both cells is plotted, figure 9. Here it can be seen that the resistance is -70 - (-83) mV/0.1 nA = 130 Mohm for the FSN and -76-(-91) mV/0.1 nA=150 Mohm for the pyramidal cell, which is good for both cells. However, the time constant is a bit too low, for instance 12 ms is reported by [12], for both cells; 56-50 ms = 6 ms for the FSN and 58-50 ms = 8 ms for the pyramidal cell.
Figure 9: Hyperpolarizing current step, that reveals the membrane capacitance and input resistance. The short bar, at 50 ms, indicates where the hyperpolarized current step is onset. The other two lines indicates the where the voltage has reached 1/e of the steady state voltage, which is used to calculate the time constant of the cell.

The decay (80 percent between resting potential and the top in the soma) of the BAP when it has reached the farthest dendrite can be seen in figure 10.
Figure 10: Depolarization current step into the soma. Left: Potential in the soma. Right: Potential in the dendrite.

Below the adaptation in the adjusted cell model and in the visual cortex of a rat is plotted, figure 11. The goal of the adjustments for the cell model has been to mimic the lower current (initial frequency less than 100 Hz) of the rat data. This includes the conservation of the curvature and the inter spike interval where the last AP is fired.
Figure 11: Adaptation plots. Left (a): Each curve is a constant current. The first inter spike interval generally is shorter (higher frequency) than the successive. Right (b): Recordings from visual cortex in a rat in layer 2/3 pyramidal cell. Notice the logarithmic scale.

The steady state frequency is plotted in figure 12. In the figure it can be seen that the FSN fires at lower currents than the pyramidal cell. The FSN do also have a higher stabilization frequency than the pyramidal cell due to the adaptation in the pyramidal cell.

![Figure 12: Steady state frequency as a function of the injected current.](image)

5.2 Synaptic transmission

5.2.1 Short term synaptic depression

The paired pulse depression of 70 percent, when the pulses are separated by 200 ms, is verified in figure 13.
5.2.2 The conditioning dependent plasticity

Below, in figure 14, the conditioning is plotted. In figure d) the first IPSPs (synaptic conductance) are larger than the IPSPs after the conditioning phase and therefore it can be concluded that the plasticity model works. The depression is about 25 percent, which is acceptable according to [13].
5.3 Activity of the microcircuit

When the individual cells were modeled they were connected to each other in order to create the microcircuit. Both cells in the microcircuit were stimulated with a synchronized frequency and the result can be seen in the figure 15. At lower frequencies every EPSP has become an AP. However at higher frequencies some APs is blocked. This in turn can depend on many factors, but there are probably two main contributors. First the inhibitory cell in its nature does decrease the excitability of the cell loop, which can result in the blocking of some APs. Second the calcium dependent potassium channel does reduce the excitability as well. This is due to the positive potassium ions that flow out from the cell, therefore hyperpolarizing the cell. The effect of the adaptation can be seen in the 50 Hz stimulation were all pulses are triggered in the beginning (150 ms, approx the 100 ms time constant of the calcium buffer that controls the adaptation), but as the adaptation has converged some pulses are being blocked.

5.4 Evaluation of the plasticity

In order to discover the properties of the plasticity a number of simulations were performed with a number of combinations of different parameters. These included varying the conductance and frequency, the adaptation time constant and the frequency and finally the dendritic calcium time constant and the frequency.

5.4.1 Conductance and frequency

First the conductance of each synapse was varied as well as the stimulation frequency. The range of these parameters are 0.0 - 0.1 µS for both synapses and the frequency was varied between 0 and 100 Hz. In this setup the plasticity had a noticeable effect above 40 Hz independent of the conductance and measuring method, figure 16. However, the position of the border was sensitive to the simulation accuracy and was stabilized at a step size of 0.005 ms. Above 40 Hz the frequency is being increased more than below. But for the vector based measurements there were some additional peaks. However these peaks could be explained by looking at the histogram of the inter spike intervals. The histogram, figure 8, shows that most
APs are 35 ms from each other (the inter spike interval). Since the plasticity increases the frequency, the mean inter spike interval will decrease. This in turn decreases the position of the maximum. The point is that if this maximum, without plasticity is within but very near the lower border of one bin, then the addition of plasticity will move the maximum into the neighboring bin. In terms of vector direction this causes a switch of two dimensions and that results in a big change in all three vectors measurements. This can be further understood by looking at what happens when the number of bins is increased. Then the probability that “near border but inside” is satisfied would increase, i.e. the number of such peaks would increase, which was experimentally verified.

Figure 16: Different measures of the contribution of plasticity at different frequencies (n=2000). a) Increase in number of spikes. b) Relative increase in number of spikes. c) Dot product. d) Normalized dot product. e) Euclidian distance.
To understand the border at 40 Hz the potential during 1 s (the same kind of simulation that underlies the measure described above) in the soma of the pyramidal cell, with and without plasticity, for two cases below (30 Hz) and above (50 Hz) 40 Hz, were plotted, figure 17. At 30 Hz all EPSP generates one AP with and without the plasticity. However at 50 Hz with and without plasticity some EPSP have not become APs! But when the plasticity is added, the excitability is also increased, which in turn unblocks some of the APs.

Figure 17: Samples of the simulation result with and without plasticity for two different stimulation frequencies.
Now the location of the border could be translated by changing the conductance between the fast spiking and the pyramidal cell. The border should be translated to lower frequency if the conductance is increased, since then there should be more blocked APs that could be unblocked when the plasticity is added. This was experimentally verified as the border with a slope (figure 18 and white line 2). Second when the inhibitory synapse is too strong in comparison to the plasticity the plasticity cannot unblock any APs. This behavior can be seen in right to the border (figure 18 and white line 3) at 0.25 µS. Last, the area (figure 18 and white line 1) left to 0.1 µS is due to that the inhibitory synapse is too weak and therefore every pulse gets through and as a result every EPSPs becomes APs.

![Figure 18. The contribution of the plasticity (darker color indicates that the plasticity makes a difference) as a function of stimulation frequency as well as conductance (n=2000, measure=increase in number of APs). b) is a) but with switched axis. c) and e) is the upper and lower horizontal cross sections of respectively a) (black lines). d) and f) are the upper and lower horizontal cross sections respectively of b) (black lines). The white lines mark borders where the plasticity becomes important and the corresponding numbers indicates different such borders.](image)

### 5.4.2 Adaptation time constant and frequency

Another experiment was to vary the time constant of the calcium buffer for the calcium dependent potassium channel, figure 19. Since the calcium dependent potassium channel decreases the excitability this could also translate the border. As can be seen the border
decreases in frequency when the time constant increases. This can be understood by remembering that a big time constant generates a larger mean calcium concentration. And a larger mean concentration reduces the excitability of the cell, i.e. more blocked APs, which in turn makes the plasticity contribute at even lower frequencies.

Figure 19: Contribution of plasticity as a function of frequency and the time constant of the adaptation calcium buffer (n=2000, measure=dot product of the histograms). Above the solid line (drawn by hand) the plasticity makes a larger difference, i.e. lighter color. The un-normalized dot product has been used.

5.4.3 Dendritic calcium time constant and frequency

First it was thought that the border at 40 Hz depended on the time constant of the dendritic calcium that in turn controlled the effect of the plasticity. However simulations revealed that increasing the time constant only increase the effect of the plasticity and not for which frequency it becomes important. This can be understood in the light of the “unblocking APs” described above. Namely, the location of the border is still determined by the amount of blocked APs. However, since the increased calcium time constant increases the mean effect of the plasticity, also the mean excitability of the cell loop increases. But at time constants that are less than the period of the stimulation frequency one can see that the effect of the plasticity decreases, figure 20.
6 Conclusion

The newly discovered plasticity reduces the inhibitory effect induced by the fast spiking interneuron. As a result the overall excitability of the loop increases. Due to interaction between the adaptation and the inhibitory conductance the increased excitability is frequency dependent.

Below summarize the effect of various parameters in the model will be summarized. The effect is measured in terms of the increase in number of APs when the plasticity is added. Increased effect means that the amplitude increases while the position of the border is fixed. Translated effect mean that the amplitude is fixed while the position of the border is translated.

- Increased dendritic calcium time constant: Increased effect.
- Increased maximal depression of the plasticity ($K_{\text{max}}$): Increased effect.
- Increased half activation of plasticity ($C_{\text{half}}$): No effect.
- Frequency of Poisson noise: Increased effect.
- Changed time constant of somatic calcium: Translated effect.
- Increased soma membrane time constant: Translated effect (to lower frequency).
- Increased time constant of the EPSP: Smeared out the border.
7 Discussion

A new type of plasticity has been simulated and its effect has been analyzed. However there are things in the model of the cells and synapses that could be better. First, the dynamics of the plasticity is only based on two parameters (section 4.2.1). For example it would be good to have experimental data of different number of action potentials as conditioning, which could make the relation between the calcium concentration and the amount of depression more accurate.

Another point is that a pyramidal-type compartment model is used for the interneuron, which most certainly has impact on the dynamical behavior. This is due to that the morphology has impact of the area and therefore resistance and time constant.

Finally as stated earlier the EPSP is too large. To correct this, more cells can be included in the network in order to reduce each individual EPSP/IPSP. However, when there are many cells that stimulate one cell, the synchronization between these input cells is important for how large the total contribution will be. At the extreme case where the cells are perfectly synchronized, i.e. were all EPSPs are summed to one big EPSP, my approach with two cells is identical to the multi cell model. Therefore one could test the network with varying degree of synchrony between the input cells. However many researchers including Zilberter believe that effective signaling occurs with strong synchrony.

7.1 A possible functional role of the plasticity

The described plasticity is controlled by the calcium concentration. The calcium concentration in turn is integrative. As a result, given a burst of action potentials, the calcium and therefore also the plasticity will increase with time. Since the plasticity increases the excitability of the loop, the frequency will first be low but gradually increase as the calcium concentration increases. The increase in frequency will probably stabilize at the maximum driving frequency, since the plasticity only unblocks already inputted APs. As a result this will correspond to an integration of the input frequency, leading to blocking of short trains of APs and allowing longer trains to pass. This could be taken further such that the first pulses don’t get through at all and only the last pulses will be restored. Now, imagine a process where a burst triggers a new successive burst. If the studied plasticity is introduced in this process only the last EPSPs in the first burst will be triggered. As a result the successive burst will be triggered slightly later and therefore the studied plasticity introduces a delay. The production of long delays is poorly understood and this may be one such mechanism.

8 References

[1]


9 Appendix

Main.hoc

The main program that runs the simulations

LoopNet.hoc

Definition of the reciprocally connected cells and the different stimulation types.

RedPyr.hoc

Definition of the pyramidal cell.

RedFSN.hoc

Definition of the fast spiking interneuron.

Fsn2Pyr.mod

The plastic synapse from the FSN- to the pyramidal cell.