Universitat
de les Illes Balears

Modeling the Entorhinal Cortex - Dentate Gyrus Circuit

Cristian Estarellas Martin

Master's Thesis

Master's degree in *Physics of Complex System*

at the

UNIVERSITAT DE LES ILLES BALEARS

Academic year *2015-2016*

Date: September 12, 2016

UIB Master's Thesis Supervisor Claudio R. Mirasso Santos

Abstract

Hippocampal formation is an structure of the brain localised in the temporal lobe. It has important functions related to the creation of memories, space memory, orientation and speech. In this work we propose a model to study the effect of a inhibition population in the dentate gyrus, one basic component of the hippocampus. The objective is based on the determination of plausible mechanisms to explain experimental results obtained by the group of Dr. Canals at the Instituto de Neurociencias de Alicante.

Acknowledgements

En primer lugar me gustaría agradecer a mi director, Claudio Mirasso, por la ayuda que me ha ofrecido, sus consejos y su apoyo en todo momento que me ha permitido mejorar en el ámbito científico y en el estudio de la neurociencia computacional. También agradecer al Dr. Santiago Canals por su amabilidad y permitirme visitar el Instituto de Neurociencias de Alicante. Agradecer a Lorena y a mi familia por todo el apoyo y ánimos que he tenido en los buenos y malos momentos.

Contents

List of Figures

Chapter 1

Introduction

1.1 A journey through the brain

Simple situations in your life as going to the job, talking with someone, studying or others that you can imagine are processed by an organ. You are using now the organ to read, to understand words that are you reading, or even to think in other subjects. Obviously, the organ I am talking about is the brain which we use without understanding much about it. In this work, it is my aim to analyse a simple, but important, circuit of the brain related to the memory and learning process, and that it is part of the hippocampus.

The brain have been studied in the field of neuroscience since Luigi Galvani observed, in dissected frogs, the role of electricity in nerves in 18th century and Santiago Ramón y Cajal created the neuron doctrine with the hypothesis that the elemental units of the brain were neurons [1]. Nowadays, neuroscience is a multidisciplinary field covering disciplines as biology, medicine, biochemistry, chemistry, physics and mathematics. These two fields, physics and mathematics, are gaining leadership in last years due to their contributions based on the dynamical system theory applied on brain and the use of mathematics models to represent neurons and build connections between them achieving neuron populations [2–4].

Models in the neuroscience world can be as important as experiments. The use of models helps us to understand the dynamical behaviour of the system and to analyse how information flows, sometimes difficult aspects to obtain from the experiments. Therefore, models allow us to mimic experiments, compare experi-

mental data with numerically simulated result, or even to contribute on ideas to design new experiments.

The brain is a complex organ responsible for making an enormous number of activities and functions, being one of the most complicated biological networks. The brain is divided in two hemispheres (left and right) and is structured in four lobes. The frontal lobe is related to executive functions and motivational components. The parietal lobe are responsible for receiving sensations and coordinate the equilibrium. The occipital lobe to the speech and the visual system. Finally, the temporal lobe are related to the speech, processing of information and memory.

The temporal lobe is the most interesting part for us because it contains the hippocampus and the introducing modelled in this work. Before introducing the motivation of, we do a brief presentation of the most important elements of the brain, i.e. neurons and synapses, and address the hippocampal structure and in particular the regions that I am going to model.

1.1.1 Neuron, the base of our brain.

Basic cells of the nervous system are called neurons [5]. They are distributed around all the body, nevertheless in this work we are going to focus on neurons of the brain. The quantity of neurons in the brain is approximatelly 10^9, and are connected between them through electrical and chemical synapses providing distinct dynamics. There are many kind of neurons which are classified depending on the size, the anatomical structure, their chemical connections or the quantity of connections per neuron [6].

Each neuron is composed by three basic parts (see Figure 1.1). The first is the soma, which contains the neural nucleus and is the body of the neuron. The second part are the dendrites. They are small branches that receive the inputs from pre-synaptic neurons. Finally, the axon is the largest part of the neuron and it transports the electrical signal from the soma to the axon terminals. Some axon are surrounded by Schwann cells, which relies the axon on the myelin sheath that prevent the conduction of the electrical signal through the membrane except at specific places cells known as nodes of Ranvier [7].

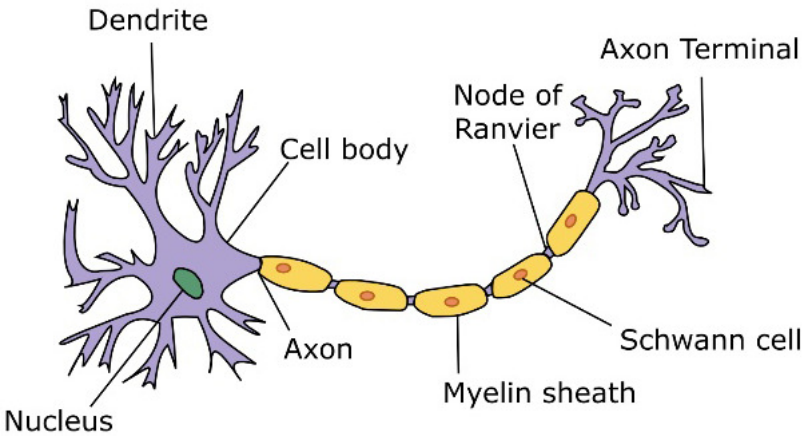


Figure 1.1: Scheme of a neuronal structure with its basic components.

The neuron is like an electronic device, which has a current, a potential, a certain capacitance and resistances. The current of the neuron is generate by exchanging ions. Specifically, a flow of Na^+ ions is driven from the external to the internal region of the neural membrane, while other flow of K^+ ions moves from inside the neuron to the external cellular part. A typical characteristic of the neuron, which is usually measured experimentally, is the voltage between the external and internal parts of the cell, called membrane potential.

Dynamically, neurons are considered excitable cells. Their membrane potential at the equilibrium, which is the stable state of an excitable system, is called resting potential and it is a negative voltage, indicating that the internal part of the cell is at a lower voltage than the external part. In this equilibrium state, it is said that the neuron is polarised. When the neuron is externally stimulated the membrane potential can increase (depolarization) until ir reaches a threshold, after which an *action potential*, or spike, is generated [8]. In that process, sodium channels are open increasing the Na^+ conductance, i.e. ions go into the neural membrane rising the internal potential to larger values. However in the maximum peak of the *action potential*the potassium channels are open and the K^+ conductance increases, i.e. the ion flows to the extra cellular medium decreasing the membrane potential until reaching a value after which the membrane recovers to its stationary condition. There is a refractory time where neurons cannot generate another spike until recovering its equilibrium state (Figure 1.2) [9].

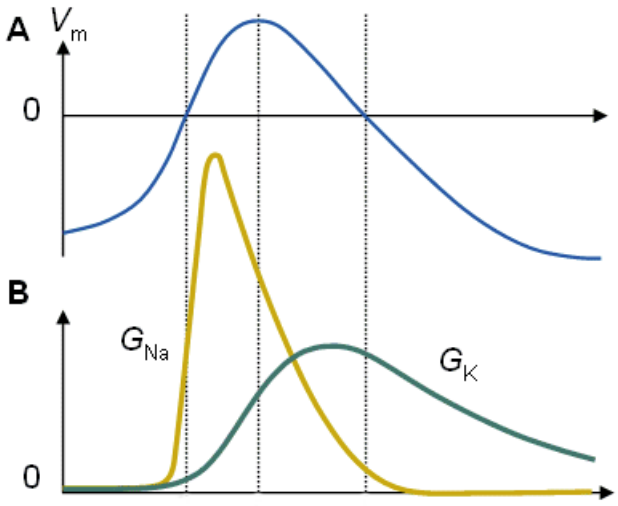


Figure 1.2: Dynamical process of an action potential indicating the membrane potential (A) and the conductance of the sodium (G_{Na}) and the potassium (G_K) which show an increment of their values at the moment of opening channels (B). Picture from Bioelectromagnetism book [9].

The process of the spike generation is a local effect, nevertheless the spike travels along the axon. The spike is usually propagates from the soma to the axon and arrives to neuron axon terminals of the neuron, where neurotransmitters are released, facilitating the communication with the postsynaptic neuron (see Figure 1.3) [7].

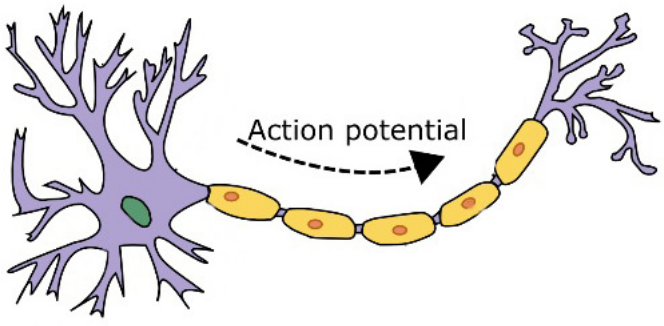


Figure 1.3: Representation of the spread direction of an action potential in a neuron.

1.1.2 Synapse, the bridge between neurons.

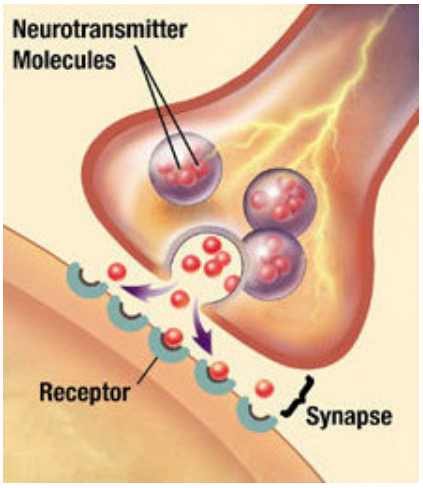


Figure 1.4: Scheme of the chemical synaptic process.

The synapse refers to the connection between neurons. There are two kinds of synapses. The electrical synapse where the signal propagates through a small gap between the neurons in a fast process and the chemical synapse, where the signal is transmitted due to the release of neurotransmitters from the presynaptic to the postsynaptic neuron. Chemical synapses are slower and the synaptic space larger than the one in the electrical synapse. The chemical synapses are more abundant and consequently are the most used in models. This synapse will be considered in this work and is explained in details in the next section.

Chemical connections are established by a synaptic space where there is an extracellular liquid between the pre- and postynaptic membranes. The performance in the connection is simple: the electrical impulse in the presynaptic neuron releases chemical neurotransmitters through the synaptic space which are captured by the receptors of the postsynaptic neuron (Figure 1.4). There are several factors that can change the response of the postsynaptic neuron [7]:

- The type of neurotransmitters. For instance, excitatory or inhibitory neurotransmitters generate different effects in the postsynaptic neuron depolarising or hyperpolarising it.
- The amount of neurotransmitters that are released, which modifies the strength of the connection and the signal transmission.
- The nature of the postsynaptical receptors influences the synaptic process.

Synapses can be of two type, depending on the kind of neurotransmitters that are released: i) an excitatory synapse, which depolarises the postsynaptic membrane and, ii) an inhibitory synapse that hyperpolarizes the postsynaptic membrane. In the excitatory process, the interaction of neurotransmitters with

receptors of the postsynaptic neuron open sodium (Na^+) and potassium (K^+) channels. The sodium goes into the membrane whereas the potassium tends to go out the membrane.The quantity of sodium, which penetrates into the internal region of the neuron, is far larger than potassium quantity drived to the external membrane, depolarising the membrane by increasing its membrane potential (see Figure 1.5.A) [7]. Neurotransmitters participating in inhibitory synapses interact with receptors opening channels of potassium (K^+) and chloride (Cl^-), where the potassium has the same behaviour than in the excitatory case and the chloride tends to penetrate inside the neuron hyperpolarising the membrane (see Figure 1.5.B) [7].

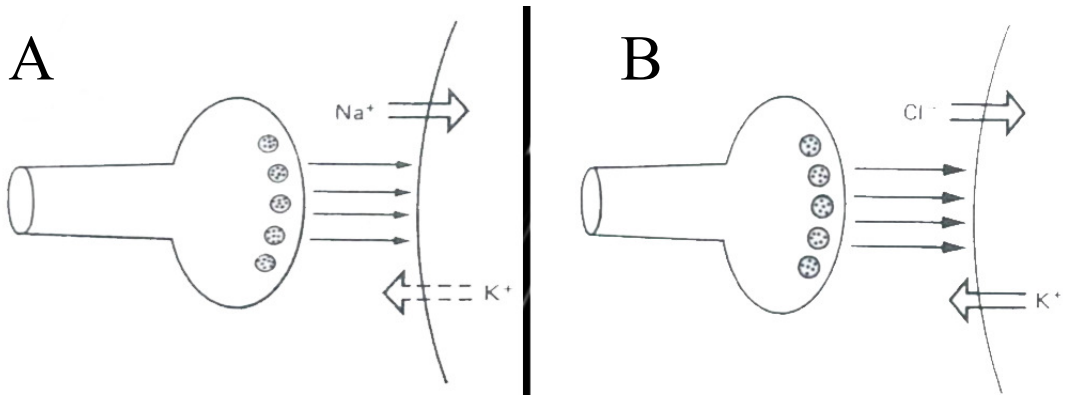


Figure 1.5: Scheme of the synaptic processes: the excitatory synapse (A) and inhibitory synapse(B). Both show transmissions of ions and their directions of propagation. The left element represents the presynaptic neuron whereas the right one is the postsynaptic neuron. In each type of synapse there is a diffusion of potassium (K^+) from the postsynaptic membrane to the external side but there is a flow of sodium (Na^+) in the excitatory synapse and chlorine (Cl^-) in the inhibitory synapse. Picture from Neurophysiology book [7].

The main excitatory neurotransmitter released from the presynaptic neuron is glutamate and the postsynaptic receptors are called AMPA (the *α-amino*-3-*hydroxy*-5-*methyl*-4-*isoxazolepropionic* acid receptor) and NMDA (the *N-methyl-D-aspartic* acid receptor), both with a reversal potential of 0 mV. The receptors are distinguished because the AMPA receptor is significantly faster than the NMDA in the activation and deactivation processes [10].

The main inhibitory neurotransmitter is the GABA (γ-*Aminobutyric* acid) and there are two receptors $GABA_A$ and $GABA_B$. The former is much faster than the later in the process of activation/deactivation [10].

1.1.3 The Hippocampus, your memory manager

The name hippocampus comes from the latin *hippo=hourse* and *kampos=monster* due to the similitude with the seahorse (see Figure 1.6). The hippocampus forms part of a group of structures called hippocampal formation. It is localised in the temporal lobule and as observed in Figure 1.7, is a part of the limbic system. The group is constituted by the: 1) dentate gyrus (DG), 2) the hippocampus (which is formed by different areas called cornu ammoni and know as CA1, CA2 and CA3 regions) 3) the subiculum (S) (Figure 1.8), 4) presubivulum (PrS) and parasubivulum (PaS), and 5)the entorhinal cortex (EC). In particular, the entorhinal cortex is the structure bridges the hippocampus with other cortical regions, becoming the major input of the dentate gyrus through projections known as perforant path (PP) [11].

Figure 1.6: Comparison between the hippocampus and the seahorse.

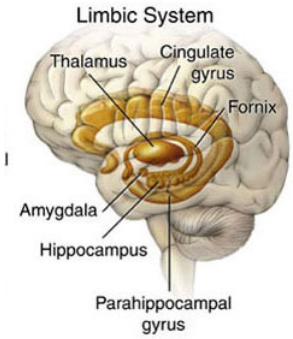


Figure 1.7: Scheme of the limbic system with their components labelled.

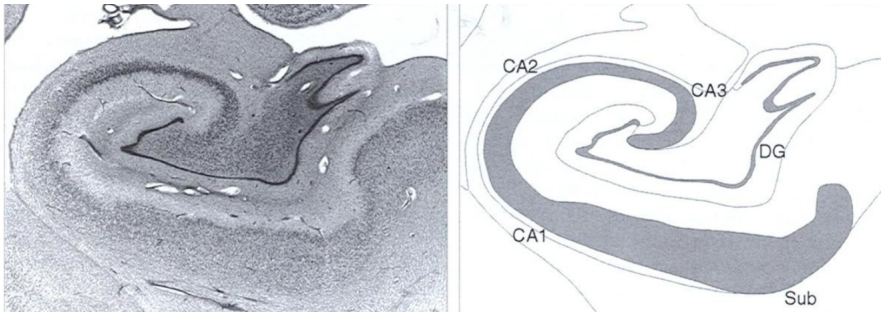


Figure 1.8: Hippocampus of a human brain in the left panel and its scheme with principal components (cornu ammoni regions, dentate gyrus and subiculum).

The information in the hippocampal region tends to spread unidirectionally, beginning and ending at the entorhinal cortex. The flux of information flows from the second layer of the entorhinal cortex through the perforant path to the dentate gyrus. Neurons from the dentate gyrus project their axons to CA3. However, CA3 does not project back to the dentate gyrus but it projects to CA1, which is the major excitatory input of the subiculum region. Finally, the subicumlum projects to the entorhinal cortex closing the neural circuit (see Figure 1.9). [12].

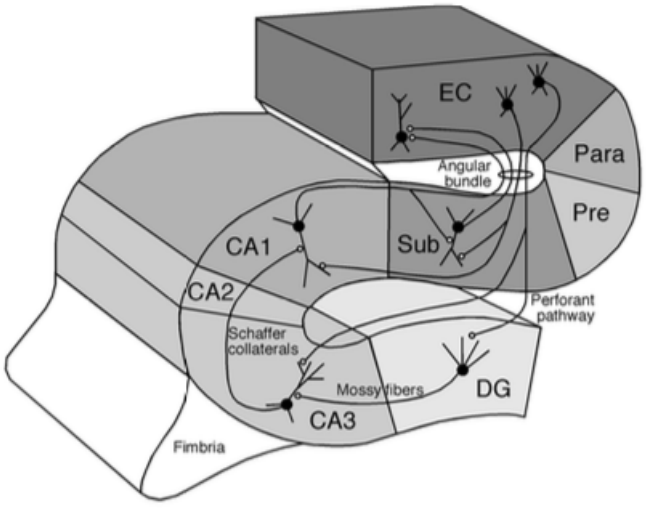


Figure 1.9: Neural circuit of the hippocampal formation with connections displayed on solid lines where the black point indicates the beginning of the connection and the white point its ending. The unidirectional trajectory can be appreciated it. Picture from The Hippocampus Book. [12]

The hippocampus structure has been studied for years because of its role in the process of memory, specifically, in the creation of memories as well as

the mechanism used to transfer information [13–15], although the function and mechanism are not fully understood. The role of the hippocampus started to be clearer after the article published by Scoville and Milner exlpaining the results of a failed surgery in that region, that finished with the destruction of the hippocampus [16]. The patient had problems to create spontaneous memories and suffered two cases of amnesia (anterograde and retrograde). Nevertheless, the patient was able to remember old memories giving the idea that the memories are transmitted to another structure after a certain time.

The hippocampus is also related with spatial memory and the ability to find new ways to arrive to the destiny in a familiar environment. One curious evidence is the study of the relation between the volume of the grey matter in the hippocampus and the ability to learn a large complex network of roads, streets, monuments and directions of a city and navigate within it (this ability is the typical task carried out by licensed London taxi drivers) [17]. Moreover, there is a kind of neurons called *place cells* founded in the rat and mouse hippocampus, that have the bility to generate an action potentials depending on the place that the animal is or the direction that they are seeing [18, 19]. These cells together with the grid cells from the entorhinal cortex constitute a circuit working as an internal GPS of the brain [20].

Due to the importance of the hippocampus there is a growing interest to understand the behaviour and mechanism that the hippocampus uses to achieve the different functions. This aim of this work is much less ambitious. The core structure is the dentate gyrus that exhibits a pattern separation function [21].In other words, the dentate gyrus can distinguish similar signals to avoid interferences when remembering memories. Probably, the reader will associate this function with the typical algorithm for classification in the machine learning field, which is a good association. Machine learning is inspired in the brain performance and this interesting function of the dentate gyrus is a perfect example of that inspiration. Hence, the study of the dentate gyrus is being a chance to understand the real performance that people are copying with information-processing models.

The major part of the dentate gyrus is composed by excitatory granule cells in a number of approximately 1.2×10^6 in rats [22]. But there is also a small

number of inhibitory neurons, the pyramidal basket cell, that interact with the granule cells.

The goal of this Master thesis is to make a model of a neural circuit of the hippocampal formation, in particular, the entorhinal cortex connected to the dentate gyrus. Our model will be the first step to check the dynamical behaviour of the dentate gyrus focused on the effect that inhibitory interneurons exert over the excitatory granule cells. It is the aim to suggest possible mechanisms that can clarify some experimental findings.

1.2 Neural Model: How a physicist draws a neuron on a paper

The brain is a complex system composed by millions of neurons connected between them. In order to understand the brain performance in the neuroscience field there is a cooperation between modelling and experimentation, which is needed to get consistent and reliable scientific results. A model can provide information about the system that is sometimes difficult to find in experiments. For instance, it is possible to determine the mechanism of certain dynamical behaviour or to study a particular population with a type of interneuron without adding external factors. In addition, studies of neural network features such as causality, spread of information or cluster formations are more manageable and less expensive by means of modelling than in the laboratory.

However, modelling the neurons is not an easy task due to their different dynamics, the amount of morphologically different cells and their corresponding role. For this reason, there are many models depending on the region of interest and different goals since models cannot reproduce all existent features, focusing only on particular neural properties.

The simplest model is the Integrate and Fire model ($I\&F$) that uses one equation to describe the behaviour of the neuron below the threshold potential. Nonetheless, the $I\&F$ model does not generate an action potential and cannot show different rhythms and many well-known spiking patterns [23]. However the model has been improved adding more parameters and equations to extend its

functionality . There are more biologically plausible, although more complicated, models as the Hodgink and Huxley model ($H.H.$), which simulates the dynamics of the potassium (K^+) and sodium (Na^+) currents and couples them with the membrane potential equation [24, 25]. This model provides more biological information since it is focused on the effects of the current to the membrane potential.

Unfortunately, modelling has a considerable compromise between the computational efficiency and the biological approximation to real neuronal behaviour. The two models mentioned above are two extremely contraries examples. On one hand, $I\&F$ model is fast and simple, then, there is not a computational cost although the biological features and dynamics are poor. On the contrary, the $H.H.$ model is biologically plausibile, but the computational cost much higher. Basically, the more the model approximates to real neurons, the higher the computational effort is needed [26].

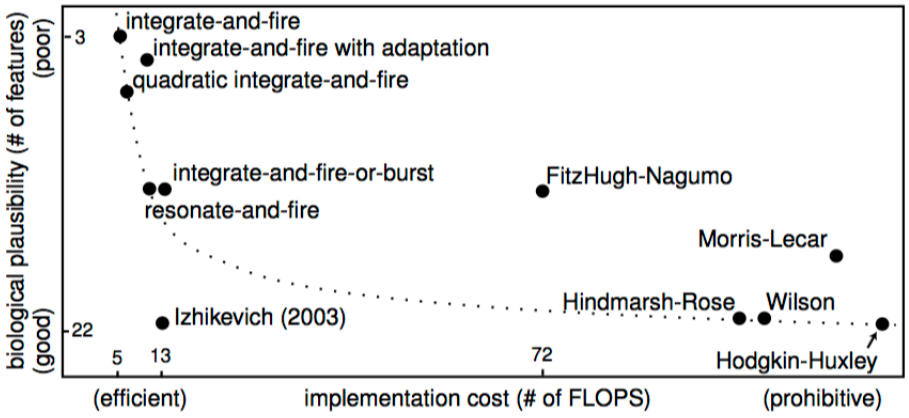


Figure 1.10: Classification of models by their biological plausibility (vertical axe) and computational cost (horizontal axe). Graphic from the Izhikevich work [26].

To get an equilibrium between computational cost and a rich dynamic many models with different properties have been developed, some of them focused on a biological representation, others showing a wide range of neural spiking. Figure 1.10 shows a classification of most popular models depending on their biological features and computational cost.

In Figure 1.10 the Izhikevich model appears, exhibiting the best relation between biological approximation and computational efficiency. This model was

proposed by Eugene M. Izhikevich in 2003 [27]. By simply changing few parameters, the model allows to represent a large range of particular spiking behaviours from the neural cortex (see Figure 1.11). Figure 1.11 shows different dynamics that appear in brain neurons. It is worth highlighting two particualr classes of neurons.The class I generates action potentials with low frequency for small injection currents and the frequency increases gradually as function of the current. Class II neurons generate action potentials in a certain range of frequencies, they start with high frequency right after the thresold and are relatively insensitive to the current [8].

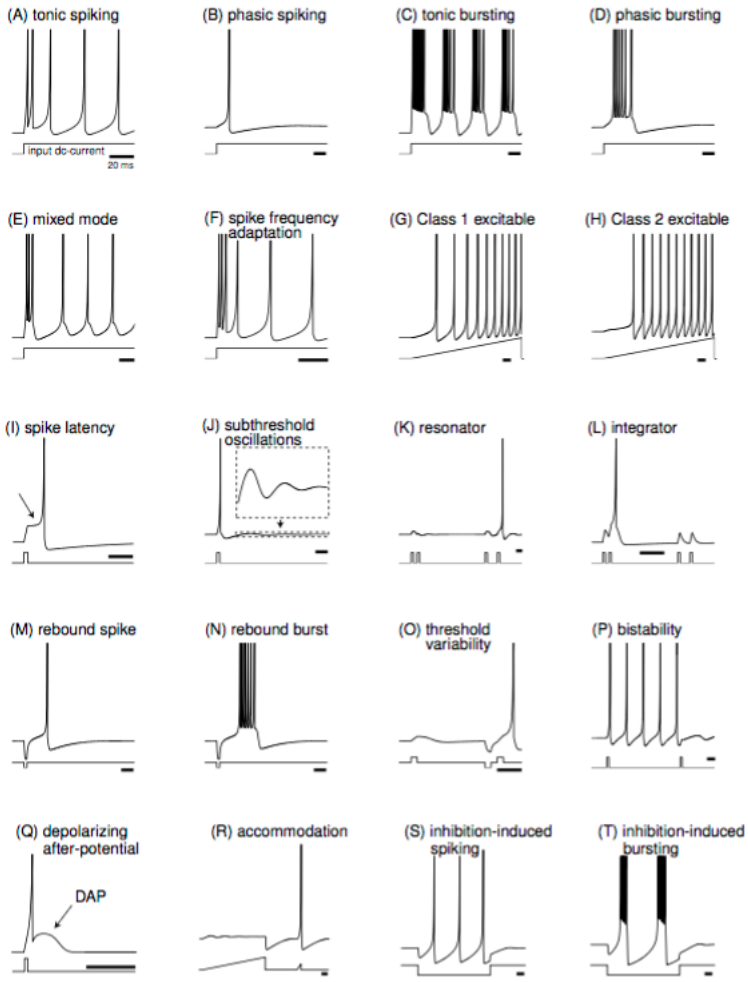


Figure 1.11: Dynamics of spiking from the Izhikevich model. Each plot shows the membrane potential of the neuron (top) stimulated by the input current (bottom). The different types of spiking represent recorded activity from cortex neurons. Graphic from Izhikevich work [26].

1.2.1 Excitability, the neural property.

One of the most important property of the neuron is the excitability. The spike is produced when the superthreshold synaptic input evokes a large postsinaptic potential, because the threshold of the membrane potential is crossed. Conversely, a subthreshold synaptic input produces a small postsynatic potential, therefore it is not strong enough to generate a spike.

A system can be classified as excitable as long as it fulfils the following three properties:

- A threshold value exists above which an excitation can occur.
- The form and size of the response of the excitation is invariant to the magnitude of the perturbation.
- A refractory time exists. Right after an excitation, the probability to generate another pulse is much smaller.

Neurons are considered excitable cells since they fulfil the previous requirements and for this reason they can be understood within the framework of the Dynamical System Theory. However, not all neurons have a well defined threshold, but they have a range of values of the membrane potential where the action potential takes place.

1.2.2 Izhikevich model, simple and brilliant.

The Izhikevich model offers particular spiking styles patterns as shown in Figure 1.11 using a two dimensional system (Equations (1.1) and (1.2)). The variable v is the membrane potential whereas the variable u represents a membrane recovery taking into account the activation and deactivation of ionic currents like sodium and potassium [27].

$$\dot{v} = 0.04v^2 + 5v + 140 - u + I, \tag{1.1}$$

$$\dot{u} = a(bv - u). \tag{1.2}$$

Numeric coefficients from the Equation (1.1) have been fitted to fit the spiking dynamics of a cortical neuron. The membrane potential scale is mV and the time

scale is ms. In addition, when the peak of the spike, i.e. the maximum value of the membrane potential (v), reaches 30 mV, the v and u variables are reset as,

$$if\ v \geq 30\ mV \rightarrow \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} . \tag{1.3}$$

Another important feature of the Izhikevich model is the absence of a fixed threshold. It has not a given value for the potential threshold else it changes according to the neuron simulated between $-70\ mV$ and $-50\ mV$. This variation of the threshold potential depends on the parameter b.

Parameters responsible for the neural dynamic shown in Figure 1.11 are known as Izhikevich parameters (a, b, c, d). The summary of parameter values and the type of spiking patterns is shown in Figure 1.12.

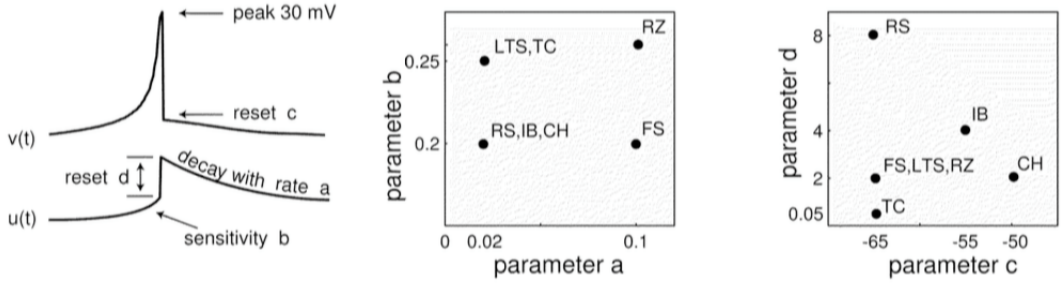


Figure 1.12: Effects of parameters a, b, c, d of the Izhikevich model. The left side shows their role in variables v and u. Others two plots are a summary of parameters values and the dynamics of spiking: Regular Spiking (RS), Intrinsically Bursting (IB), Chattering (CH), Fast Spiking (FS), Thalamo-Cortical (TC), Resonator (RZ), Low-Threshold Spiking (LTS). Graphic from the Izhikevich work [27].

Each parameter has an important function in the model for characterising the type of neuron (see Figure 1.12). Parameter a influences in the time scale of the recovery variable u, which becomes slower with smaller values of a. Parameter b controls the sensitivity of u to the subthreshold fluctuations of the membrane potential v. In other words, defines the strength of the coupling between both variables u and v, i.e. the larger the value of b, the stronger will be the influence of the membrane potential to the recovery variable. The third and fourth

variables, c and d, describes reset values for the membrane potential and recovery variable, respectively [27].

Interestingly, as previously mentioned, the model can exhibit two different kind of bifurcations depending on the parameters a and b. They are the Saddle node bifurcation if $b < a$ and the Andronov-Hopf bifurcation if $b > a$.

1.2.3 Synaptic model, our virtual bridge.

The synapse explained in the first chapter is an important ingredient in the recipe to make a realistic model. The synaptic process is characterised by the probability that neurotransmitters are released from the presynaptic neuron (P_{pr}) and the probability to be captured by the receptors in the postsynaptic cell (P_{po}), providing the probability for the process as $P = P_{pr}P_{po}$ [10].

It is possible to simplify the problem assuming a direct transmission of released neurotransmitters. Therefore, the synaptic process can be summarised in the probability that receptors gates in the postsynatic cell are opened or closed ($P_{po} \equiv P$). The temporal evolution of the probability relies on the open (α) and close (β) rates of the gates according to the Equation (1.4). Typically, the close rate is assumed to be constant whereas the open rate tends to depend on the neurotransmitter concentration [10].

$$\frac{dP(t)}{dt} = \alpha(1 - P(t)) - \beta P(t). \tag{1.4}$$

When the presynaptic neuron generates an action potential the parameter α grows rapidly increasing the probability to open channels of the postsynaptic neuron. During this process the parameter β is much smaller than α and it is ignored. A a consequence, the Equation (1.4) can be solved as,

$$P(t) = 1 + (P(0) - 1)e^{-\alpha t} \text{ for } 0 \leq t \leq T, \tag{1.5}$$

where T is the time at which the maximum probability occurs. Afterwards, the probability decays exponentially and is restricted by the close rate β, and the solution of Equation(1.4) becomes

$$P(t) = P(t)e^{-\beta(t-T)} \text{ for } t \geq T. \tag{1.6}$$

Experimental results were used to fit the α and β parameters. In addition, results show faster growing for AMPA and $GABA_A$ receptors in comparison with decaying process (see Figure 1.13). Due to this fact, it is possible to assume that the decaying part of the synaptic performance is the relevant one and therefore the Equation (1.5) can be disregarded. The assumption is fulfilled by Equation (1.7), whose time constant τ is $1/\beta$, with the condition $P \rightarrow P + P_{max}(1 - P)$ to reset the probability to the maximum value after the generation of an action potential in the presynaptic neuron [10].

$$\tau \frac{dP}{dt} = -P, \tag{1.7}$$

The synaptic model shown in the Equation (1.8) (where subindex i=AMPA, GABA) reproduces the same process than the Equation (1.7). The value of the time constant τ is chosen as 5.26 ms and 5.6 ms for the AMPA and GABA receptors, respectively. The second term of the Equation (1.8) expresses the reset condition of the probability, and the parameter, when a spike arrives att_k, γ is the maximum probability [28].

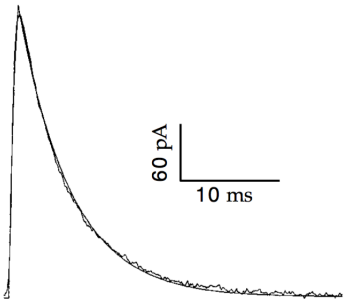


Figure 1.13: Experimental result of a excitatory postsynaptic current recorded from a mossy fiber input to a CA3 pyramidal cell in a hippocampal slice preparation.

$$\tau_i \frac{dP_i}{dt} = -P_i + \gamma_i \delta(t - t_k) \tag{1.8}$$

Finally, the synaptic current is computed using the Equation (1.9) where the g_i is the maximum conductance of the synapse, v the postsynaptic membrane potential and E_s the reversal potential, taking 0 mV for the excitatory postsynaptic potential (EPSP) and -65 mV for the inhibitory postsynapatic potential (IPSP).

$$I_{syn} = -g_i P_i (v - E_s) \tag{1.9}$$

Equations (1.8) and (1.9) together with the Izhikevich model (Equations (1.1) and (1.2)) are the basic components for making a reasonable model of three populations.

Chapter 2

Objectives of the Master thesis

The general objective of this work is to study the flux of information in a part of the hippocampus. In particular, the Master thesis is focused on the connection between the entorhinal cortex and the dentate gyrus and the performance of the inhibition in that region making a model of three neural populations. Two of them belong to the dentate gyrus (being one an excitatory population and the other one inhibitory). The final aim of the model is to explain the experimental results obtained by the group of Dr. Canals at the Instituto de Neurociencias de Alicante.

Since the experimental findings are not still published, we are going to only briefly summarise their initial results. The experiment is set by the three populations, but they can only record the information from granule cells, the excitatory cell of the dentate gyrus. In a typical process of learning or memory a long term potential (LTP) usually occurs, i.e. a series of impulses strong enough produce alterations in the connections, producing synaptic plasticity. LTP is generated in the connection from entorhinal cortex to dentate gyrus and as a consequence of those excitatory stimuli. The expected result is a rising of the excitatory and inhibitory currents from the entorhinal cortex and the interneurons neighbourhood, respectively.

Nevertheless, they have obtained an increment of the excitatory current and a decrease of the inhibitory current. In addition, the correlation between the excitatory and inhibitory signal decreases as well. The way to see the effect is generating an evoked stimulus (called *evoked*), which is strong enough to be visible but weak enough to not to produce changes in the system, before and after

the LTP. Then, the stimulus in the inhibitory current generated by the *evoked* is larger before the LTP.

To achieve these objective, the work is structured in two chapters described below, chapter 3 *Hippocampal model* and chapter 4 *Discussion: the model begins to speak* where we explain in detail the different results we obtain and the best mechanism for the experimental results recorded in the laboratory. The line of research proceeds as follow:

1) *Fitting of the individual model for each neuron*: in this part 1 focus is focused on the study of the model used to represent the neuron. In this project, we use the Izhikevich model explained before in the introduction. Therefore, we have searched the parameters of the Izhikevich model corresponding to the kind of neurons that composes the second layer of the entorhinal cortex and the dentate gyrus.

2) *Creation of neural populations*: the important key in this part is to determine the connectivity, the conductance of the synapses and the maximum probability of capturing neurotransmitters in the synaptic process for each population according to their features.

3) *Determining the external connections*: the connection between the three populations depends on the influence of the entorhinal cortex and the inhibitory population to the excitatory population of the dentate gyrus. Therefore, this part is focused on the parameters that are necessary to obtain the behaviour recorded at the dentate gyrus.

4) *Explanation of the experimental result*: this is the final part of the process where, we try to relate the theoretical results with the experimental results obtained bt Dr. Canals, with whom we were collaborating. To understand the results, we will briefly explain some experimental results and the possible mechanism that the theoretical model proposed in this master thesis offers.

Chapter 3

The Hippocampal model: The first step to remember

In this chapter we will focus on explaining the simulation that provides the dynamical behaviour of the three populations. In particular, we model the first part of the hippocampal circuit, i.e. projections from the entorhinal cortex, the perforant path, to the dentate gyrus. We would like to highlight that in this work we propose a model with the goal to observe the role of each population giving a plausible mechanism that explain experimental results and the effect of the inhibitory population in the dentate gyrus. Before building populations, the three types of neurons used in this work will be explained.

This section is a good example of the crucial relation between the experimental and simulated data. To start a model it is necessary to know biological properties like the connections between neurons, the conductances, the type of inhibition or excitation, the type of plasticity, among others. It would be perfect to have all this information. However, there is no an exact number of connections or details in the neural structure because getting that information is very difficult. Then, finding a set of model parameters that reproduce the behaviour shown in experiments is a complicated task. Moreover, the basic model, in our case the Izhikevich model, was developed for individual neurons, therefore we do not have many clues on how many coupled neurons will behave.

3.1 Individual neurons, the brick of the building.

There are three particular types of neurons in our model. The second layer of the entorhinal cortex is composed by excitatory stellate cells and a group of inhibitory interneurons [12]. The dentate gyrus is modelled by one population of excitatory granule cells and another one constituted by inhibitory pyramidal basket cells [29, 30].

Each kind of neurons is characterised by a dynamical spiking regime according to Izhikevich parameters (a, b, c, d). However, to fit them to the real neurons we have to take into account their biological features and external influences like a bias current or the noise generated by external connections caused by other regions of the brain.

A train of Poisson noise is usually used to model the noise in the brain. That noise mimics inputs of neurons from external regions following a Poisson distribution. There are two ways of simulating the noise from external neurons, by assuming temporal or spatial integration [7].

- The *spatial integration* generates a train of Poisson for each external neuron connected to cells of our system with a Poisson rate relatively slow, i.e. we will generate 1000 trains of Poisson for one neuron.Therefore, since our model would have 1300 neurons, it would be necessary to generate 1.3×10^6 trains of Poisson.

- The *temporal integration* reduces the computational cost because it is assumed only one train of Poisson for each neuron of our model. However, the rate of that train will be much larger than that used in the spatial integration simulating an amount of external neurons. If we have 1000 trains with a rate of 2 Hz with the spatial integration for one neuron, in the temporal integration it can be approximated by 1 train with a rate of 2000 Hz.

3.1.1 Stellate cell

Stellate cells are dominant neurons of the second layer of the entorhinal cortex. They are neurons with a star shape due to their numerous dendrites radiating out from the soma (see Figure 3.1) [12, 31]. Studies of stellate cell reported subthreshold oscillations with slow dynamics [8], i.e., generating groups of spikes in periods of time that depend on the current. In the simple model of Izhikevich we can simulate the dynamical behaviour shown in Figure 3.2 with parameters $a = 0.03$, $b = 0.15$, $c = -60$, $d = 4$. In Figure 3.3, different dynamical regimes, as a function of the parameter a for the same bias current and Poisson noise are shown. Therefore, to generate a population with diversity, the parameter a will be a good choice to create heterogeneous responses.

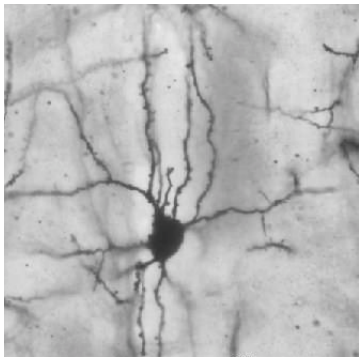


Figure 3.1: Photography of a Stellate cell.

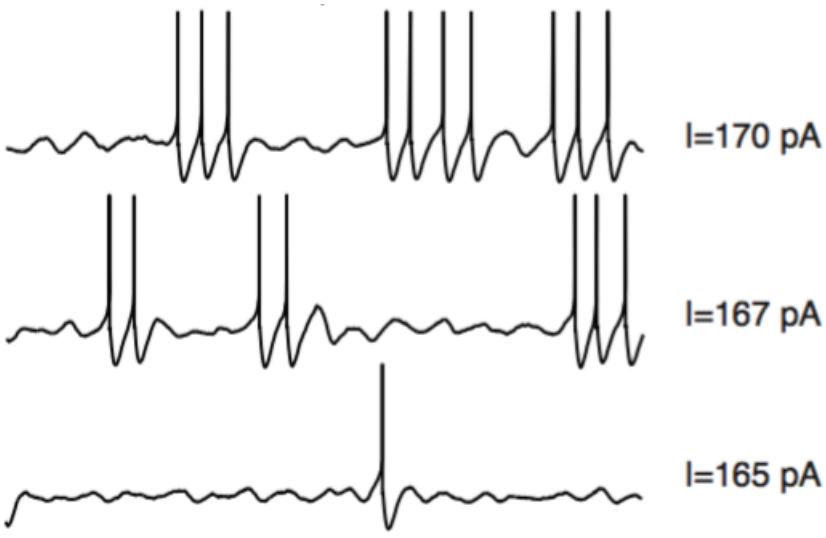


Figure 3.2: In vitro recording of a stellate cell of entorhinal cortex shows subthreshold oscillations and ocasional spikes for different values of input current. Graphic from Izhikevich book [8].

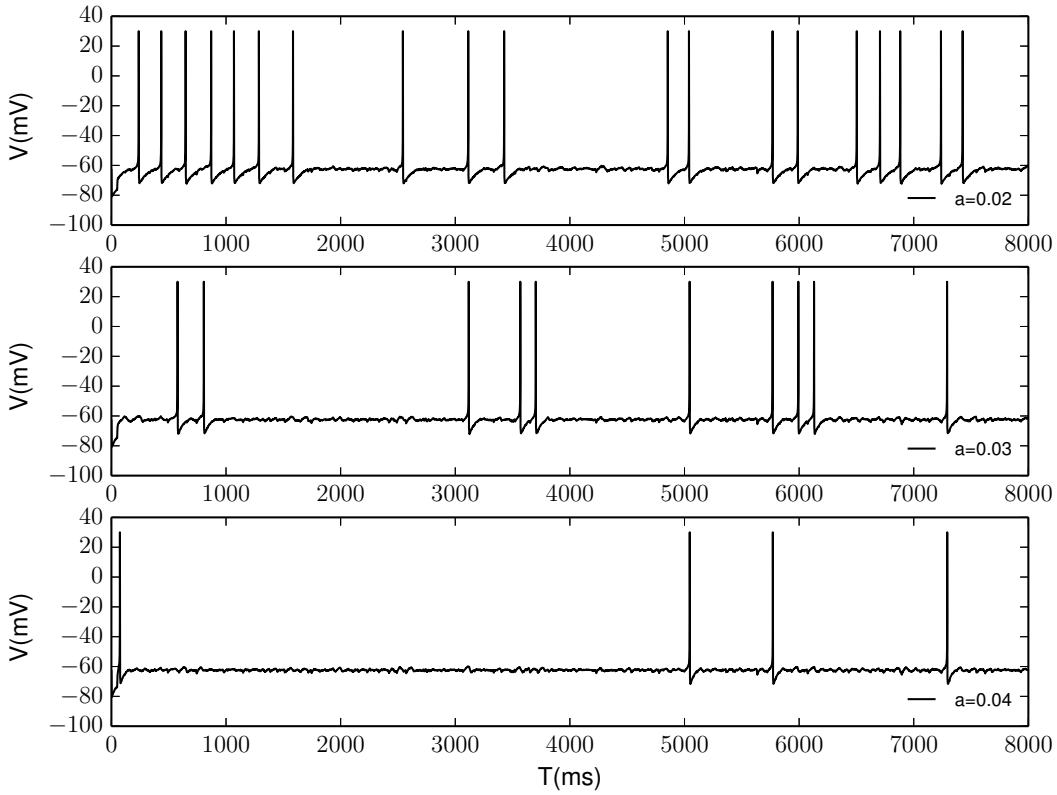
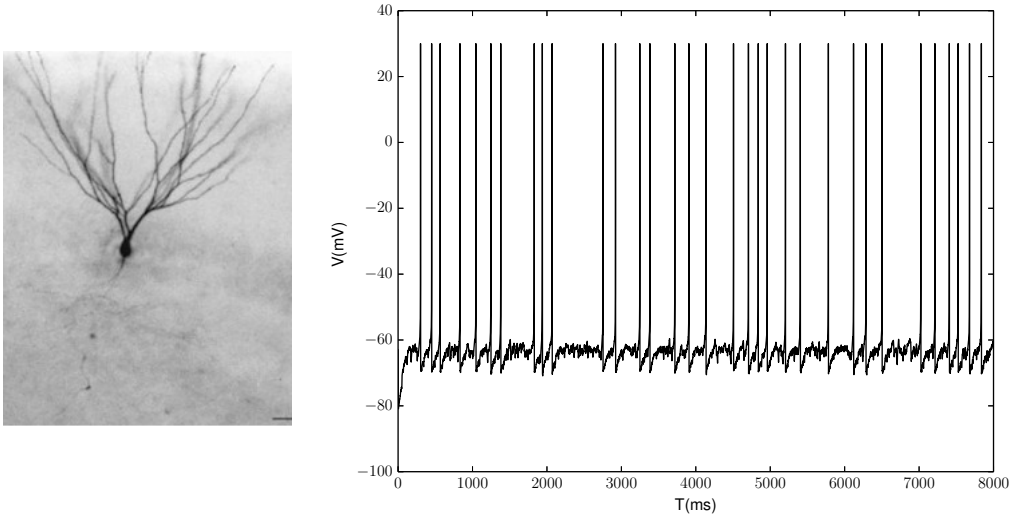


Figure 3.3: Simulation of a stellate cell through the Izhikevich model using the parameters $b = 0.15$, $c = -60$, $d = 4$ and $a = 0.02$ (top), $a = 0.03$ (middle), $a = 0.04$ (bottom). External conditions like the bias current or the Poisson noise is the same for three cases.

3.1.2 Dentate granule cell

Granule cells are the most abundant neuron in the dentate gyrus, as previously mentioned in the first chapter. They have a characteristic cone-shaped tree spiny apical dendrite whose length is, on average, 3500 μm (Figure 3.4a). The estimated number of spines in total is 9000, indicating the approximated number of excitatory synapses that granule cells receive from all sources, in particular the perforant paths that connects the second layer of the entorhinal cortex with them [12]. Granule cells show an excitatory regular spiking that we obtain by taking the parameters $a = 0.02$, $b = 0.2$, $c = -69$ and $d = 2$ [32].



(a) Ohtography of a granule cell

(b) Regular spiking dynamics

Figure 3.4: Granule cell picture at the left side of the figure and the its dynamics at the right side shows a regular spiking under a Poisson noise distribution obtained by the Izhikevich model.

3.1.3 Inhibitory interneuron

The name interneuron refers to neurons between cells which receives and transmit external inputs and outputs [6]. They involve a heterogeneous range of inhibitory and excitatory neurons, in particular, in this model there are two type of inhibitory interneurons. One of them is localised into the entorhinal cortex, in a minor quantity in comparison with stellate cells. They are fast spiking neurons and are modelled by Izhikevich parameters $a = 0.1$, $b = 0.2$, $c = -65$, $d = 2$. The second type is the basket cell of the dentate gyrus. Populations of these cells fire at the γ frequency, approximately 60 Hz. Then, Izhikevich parameters are in this case $a = 0.35$, $b = 0.25$, $c = -65$, $d = 2$. This allow us to achieve the frequency required from a small perturbation due to the Poisson trains.

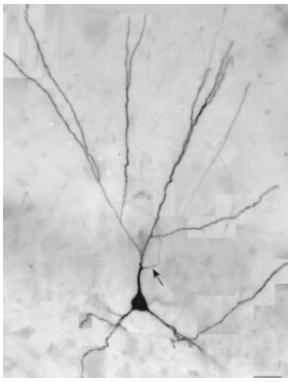
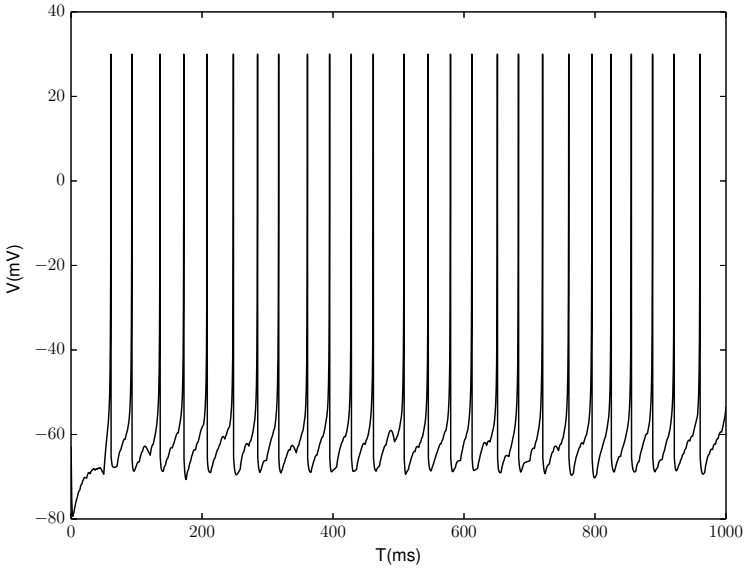
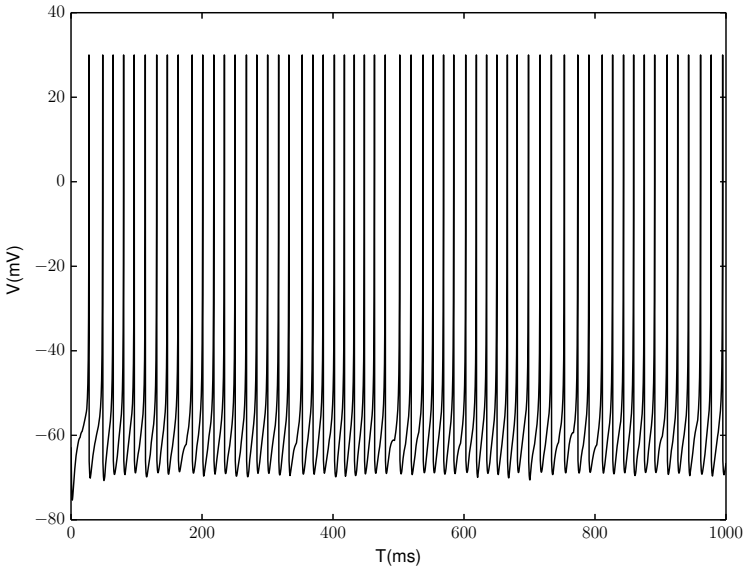


Figure 3.5: Photography of a pyramidal basket cell



(a) Interneuron from the entorhinal cortex



(b) Dentate Interneuron

Figure 3.6: Dynamics for different types of interneurons generate by the Izhikevich model. The first one (a) corresponds to a typical interneuron fast spiking in the entorhinal cortex. The second one (b) is a fast spiking with a high frequency according to interneurons from the dentate gyrus. The frequency is larger than 60 Hz, however due to their inhibition the population oscillates in the required frequency.

3.2 Neural population, the neighbourhood of neurons.

Separated populations do not exist in the brain. However, simulations of the brain or its structures with all their factors (the amount of neurons, connections, synapses...) is impossible to achieve due to the insufficient experimental information. However, with all the information it would be impossible due to the required computational cost. For this reason we assume a model composed by populations that contains an amount of neurons that represents the structure understudy. Evidently, the population fulfil neural structural requirements to produce the correct dynamic of each region.

When the model contains different populations, the number of components of each population has to be such that it reproduces the behaviour occurring in the brain. In this way, one can be sure that the results obtained by the model are most reliable.

The model developed here is constituted by three populations. They are the second layer of the entorhinal cortex and two populations of the dentate gyrus (the inhibitory population of basket cells and the excitatory population of granule cells). The entorhinal cortex population will act as the master population, i.e., it is the input to the other two populations. For this reason, the model is flexible with it since there is no a strict requirement. Instead the inhibitory population is a key ingredient for the model because it is only composed by inhibitory cells, as a consequence, the unique contribution of inhibition to granule cells.

The dentate granule population plays the role of the slave because it receives information from the entorhinal cortex and the interneurons. However, since the experimental data is recorded from granule cells, then, this population is our point of reference.

3.2.1 Entorhinal cortex: second layer

The second layer of the entorhinal cortex, where the perforant path stars, is mostly composed by stellate cells oscillating in a very precise θ frequency [33]. The population for our model is formed by stellate cells with Izhikevich parameters $a = 0.04 - 0.03\sigma$, $b = 0.15$, $c = -60$ and $d = 4$ and innhibitory interneurons with $a = 0.09 + 0.01\sigma$, $b = 0.25 - 0.05\sigma$, $c = -65$ and $d = 2$, where σ is a random number uniformly distributed between 0 and 1. We assume the usual amount of 80% excitatory and 20% inhibitory cells. . The total number of neurons is 200, consequently, 160 are excitatory stellate cells and 40 are inhibitory interneurons. For the population it is assumed a 6% connectivity, i.e., each pre-synaptic neuron is randomly connected, on average, with six post-synaptic neurons. The conductance used in the synapse is $g_{AMPA} = 0.025\ nS$ for stellate cells whereas the $g_{GABA} = 0.1\ nS$ for inhibitory cells.

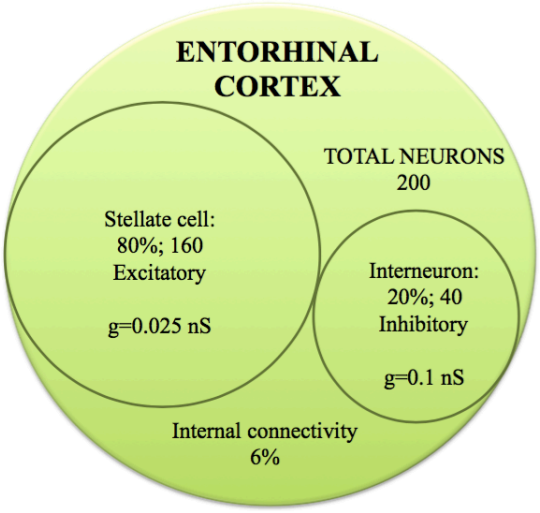


Figure 3.7: Population of the second layer of entorhinal cortex with a number of 200 neurons where 160 are excitatory stellate cells and 40 are inhibitory interneurons. The probability of connections is a 6% and conductances used are $g_{AMPA} = 0.025\ nS$ and $g_{GABA} = 0.1\ nS$.

3.2.2 Dentate pyramidal basket population

The role of inhibitory interneurons of the dentate gyrus is not fully understood. Nevertheless, its function is a key point in the behaviour of the granule cells, that recieve γ oscillatory inputs from the interneural neighbourhood and, as a result, a role in the separation pattern function of the dentate gyrus. The inhibitory population is formed by 100 inhibitory interneurons generating γ rythm using the parameters $a = 0.30 + 0.04\sigma$, $b = 0.25$, $c = -65$ and $d = 2$. Their neurotransmitters are GABA and the conductance of the interneuron is $g_{GABA} = 10\ nS$. The internal connection of the population is extremely low (2% [34]).

Interestingly, this population is completely inhibitory, hence one problem found in the model and explicitly explained in the next chapter is how it is possible to achieve a synchronization without excitatory neurons.

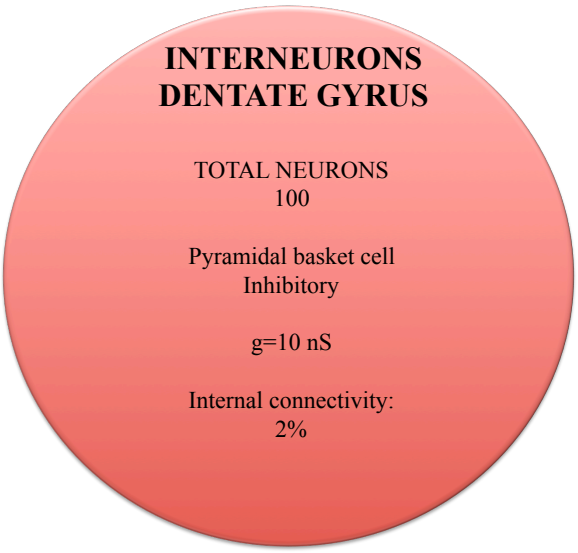


Figure 3.8: Population of interneurons localised in the dentate gyrus with a number of 100 which are inhibitory interneurons. The probability of connections is a 2% and the conductance used is $g_{GABA} = 10\ nS$.

3.2.3 Dentate granule population

This populations is the reference to fit external parameters of the model. I would like to remember that the dentate gyrus shows the electrical signal from granule cells that involve two types of frequency, θ and γ [35]. The external connection and conductance between populations are determined to achieve the dual behaviour in the granule population. The latter, in the model, is composed by 1000 excitatory neurons with parameters $a = 0.02 + 0.002\sigma$, $b = 0.2$, $c = -69$ and $d = 2$, a low internal connection (2%) and a conductance of $g_{AMPA} = 0.025\ nS$ [34].

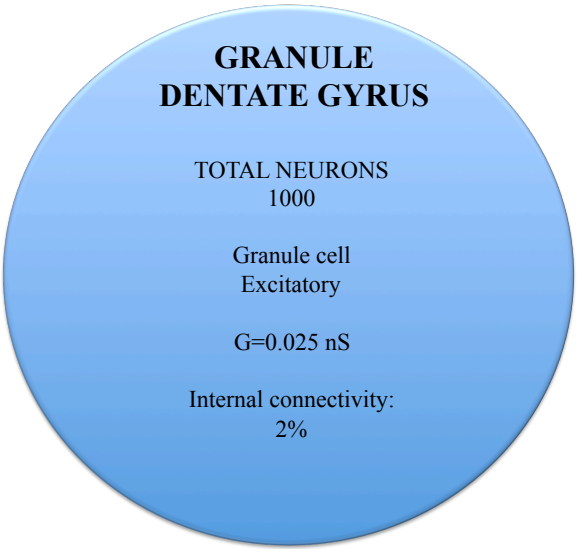


Figure 3.9: Population granule cells localised in the dentate gyrus with a number of 1000 which are excitatory neurons. The probability of connections is a 2% and the conductance used is $g_{AMPA} = 0.025\ nS$.

3.3 Simulation of the Dentate Gyrus

The model has three vertices where each vertex is a population (see Figure 3.10). The stellate cells from the entorhincal cortex (EC) are connected to the interneuron and granule population and there is an unidirectional connection from the interneuron group (IN) to the granule dentate gyrus (GC).

The perforant path has the same conductance ($g = 0.5\ nS$) and maximum probability of captured neurotransmitters ($P = 0.2$) for its external connections,

but axon terminals are connected to each population with particular connectivities, being 1% for EC-IN and 15% for EC-GC.

Dentate interneurons are connected to granule cells with a significant higher probability (20%), a conductance $g = 3\ nS$ and a probability of neurotransmitters captured in the synapse of $P = 0.5$. In this model there is no feedback between interneurons and granule and delays in connections are neglected because both populations are in the same structure (the dentate gyrus).

The way to get an accurate set of parameters for the model is checking the result of the spectrum, the temporal dynamics and raster plots with the experimental observations. This fit is not an easy task.

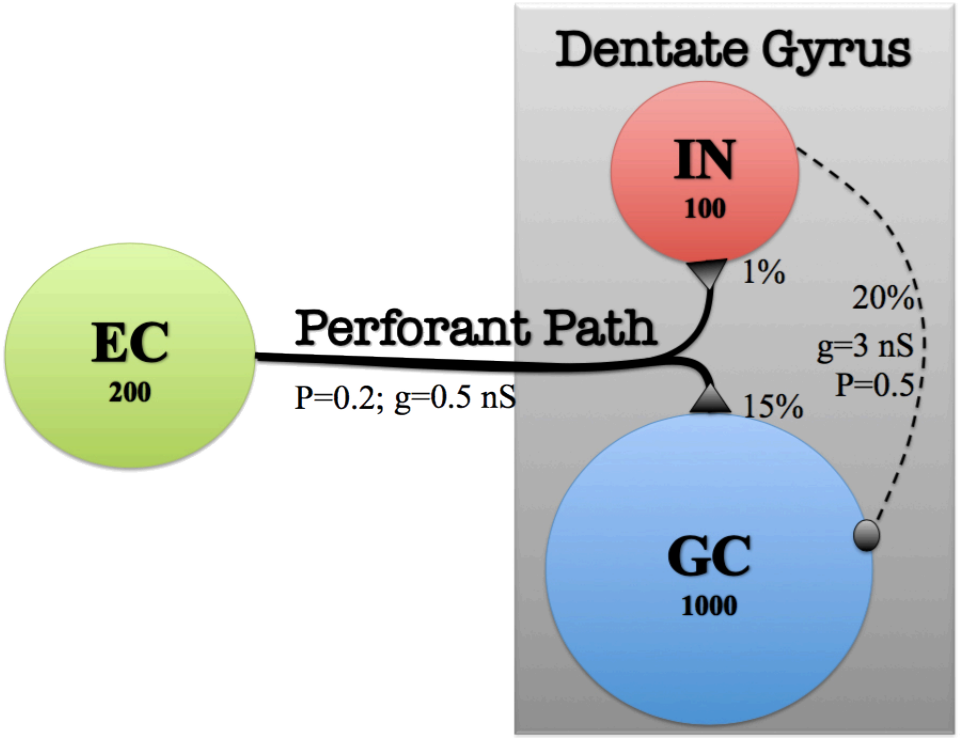


Figure 3.10: Scheme of the model of the neural circuit of the hippocampus. Concretely, the dentate gyrus formed by an interneuron population (IN) and a dentate granule population (GC) and the second layer of the entorhinal cortex (EC).

Chapter 4

Discussion: The model begins to speak

The model was written in Fortran and the Runge-Kutta method was used for computing the differential equations of the Izhikevich model (Equation (1.1) and (1.2)) with a step of integration of 0.01 ms. For the noise we have generated a Poisson train of 1.5 kHz for each neuron of our model with a excitatory synapse conductance of approximately 0.03 nS. Finally, we added a bias current in the stellate cells.

This section is organised in two parts. The first one focuses on the basic model and the comparison between the model and the publication of Andrade and Jonas, which is our guide for the model [36]. The second part of our results is targeted to explain four possible mechanisms explaining what happens in the experiment, commented in the *chapter 2*, carried out by Dr. Canals at the Instituto de Neurociencias de Alicante.

4.1 Reliability of the model

One of the most important objective of the model is to reproduce the main behaviour of the structure of interest before using it to search behind experiments. In order to accomplish our model two features have to fit the Andrade and Jonas study mentioned above. Those are a characteristic θ frequency in granule cells from the entorhinal cortex and a γ frequency from dentate interneurons. Conse-

quently, dentate granle cells generate a burst spiking (Figure 4.1).

Nevertheless, since dentate interneurons are complicated cells to measure, the experimental results from the guide study show the coherence between the inhibitory postsynaptic current (IPSC) coming from interneurons and the local field potential (LFP) of the granule population and the excitatory postsynaptic current (EPSC) coming from stellate cells and their LFP.

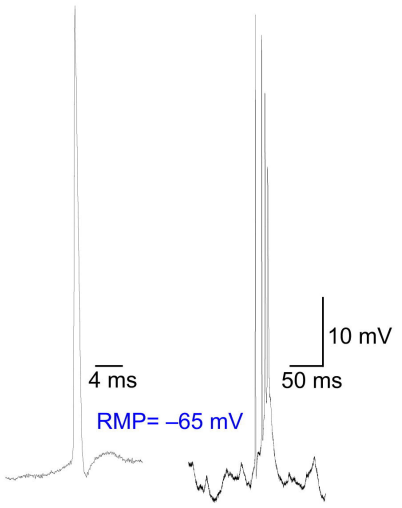
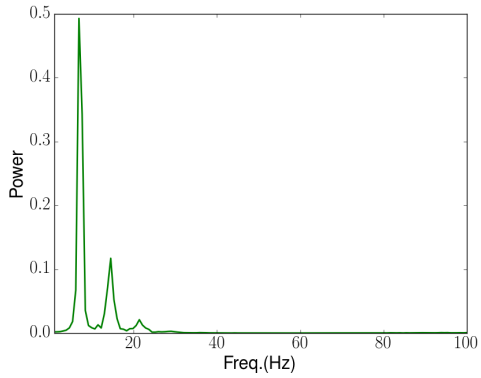


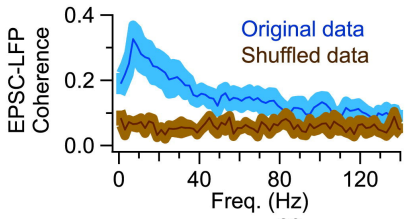
Figure 4.1: Single action potential and burst in awake rats. [36].

Parameters shown in the previous chapter are used to achieve an entorhinal and interneuron populations with frequencies at maximum peaks of coherence between EPSC/IPSC-LFP (Figure 4.2). As a result of the model we obtain from simulations the spectrum of granule cell population which suffers the combination of both frequencies, γ and θ (see Figure 4.2). In addition, the temporal dynamic of the granule population shown in Figure 4.3 (bottom) displays a sparse burst spiking.

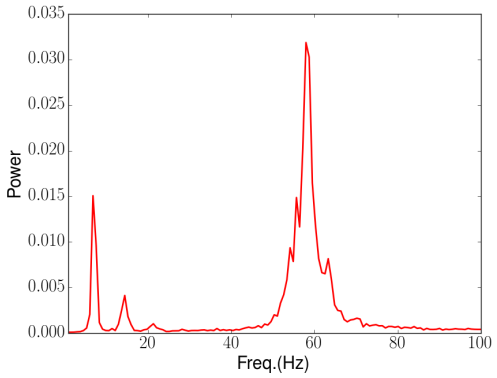
The result shown in Figure 4.2 is an average power spectrum over fifty iterations producing an insignificant error.



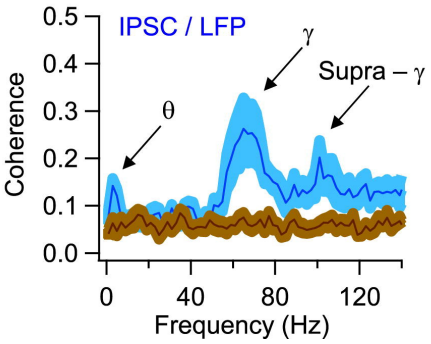
(a) Spectrum of entorhinal cortex population



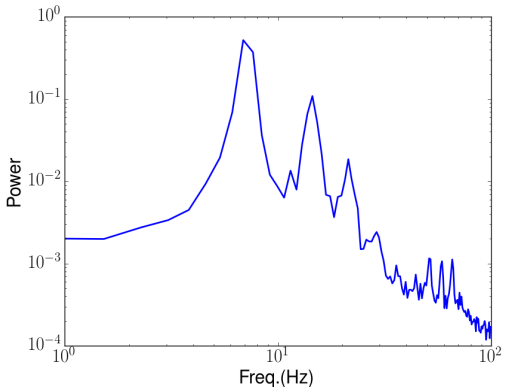
(b) Coherence between LFP from granule cells and EPSC.



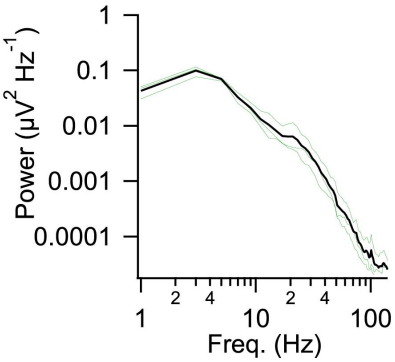
(c) Spectrum of interneuron population



(d) Coherence between LFP from granule cells and IPSC.



(e) Spectrum of granule population



(f) Spectrum of granule cells

Figure 4.2: Spectrum of each population simulated in the left column and their respective experimental indications from the study of Alejandro Javier and Peter Jonas. C) coherence between the LFP of granule cells and the EPSC. D) coherence between the LFP of granule cells and IPSC. The scale of the granule cells spectrum is logarithmic for a better comparison. F) spectrum of granule cells

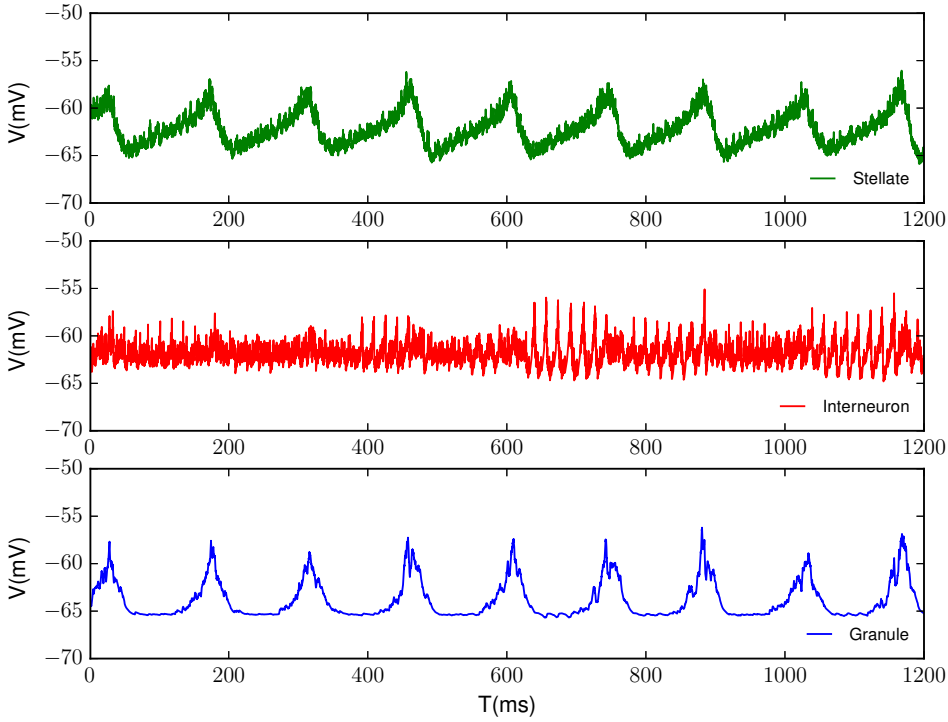


Figure 4.3: Temporal traces of the potential of each population of the model. The potential is an average on the membrane potential of all members of the population. The trace green is the entorhinal cortex, the red is the interneuron group and the blue is the dentate granule population.

4.2 What is doing the dentate gyrus?

We want to knows, through the model designed, which is the possible change produced by the LTP in the interneuron population. In our model, the dynamical variable related to the postsynaptic current is the probability of capturing the neurotransmitters (P) described by the Equation (1.8). Hence, the effect of the *evoked* influences its dynamic. We generate the evoked stimulus forcing an *action potential* into all neurons of the entorhinal cortex at a given time propagating a remarkable pulse to the interneuron population.

Our measurement is the size of the *evoked* in the dynamical postsynaptic probability of interneuron population, which is the average on the postsynaptic probability of all interneurons. That size is the difference between the signal with and without *evoked*. To reduce the noise effects we have done fifty iterations for both cases before subtracting them. Therefore, we have compared the *evoked* size

before and after the LTP, which produces a change in the system. There are four hypothesis of possible effects caused by the LTP (*Test 2-5*) compared with the original model, the system before LTP (*Test 1*).

- *Test 1*: Original structure before the LTP.
- *Test 2*: The maximum postsynaptic probability increases in the connections of EC-IN and EC-GC. The value raised from $P_{max} = 0.2 \rightarrow 0.5$.
- *Test 3*: The maximum postsynaptic probability reduces due to a depression in the IN-GC connections, $P_{max} = 0.5 \rightarrow 0.2$.
- *Test 4*: The connectivity inside the interneuron population increases ($2\% \rightarrow 10\%$), consequently, the inhibition of the population rises and changes the dynamical behaviour.
- *Test 5*: The conductance in the synapse of EC-IN and EC-GC increases from $g = 0.5\ nS$ to $g = 1.5\ nS$.

In Figure 4.4 we plot the size of the evoked for each *Test* explained before. It is observed that *Test 2* and *Test 5* have a significantly larger size and *Test 3* and *Test 4* have a much lower peak than *Test 1*. In addition, *Tests 2* and *Tests 5* have the same behaviour because both cases play the same role. From the Equation (1.9) $I_{syn} = -g_i P_i (v - E_s)$, i.e., increasing the conductance g or the maximum value of P produces a bigger influence from the entorhinal cortex to the dentate gyrus. However, that fact does not reduce the inhibitory postsynaptic current. Finally, *Tests 3* and *4* reduce the inhibition, nevertheless, the reasons are different. In *Test 3* the effect is forced by depressing in the axon, but in the *Test 4* is the dynamic of the interneuron population that produces the effect. In this last case, a larger number of interneurons couple producing a larger silence in the population due to the inhibition decreasing its projection to the granule cells.

Then, we have two possible mechanisms to explain the experimental results; *Test 4* and *Test 3*. However, in the experiment the correlation between the postsynaptic current from entorhinal cortex and interneurons to granule cells is lower after the LTP.

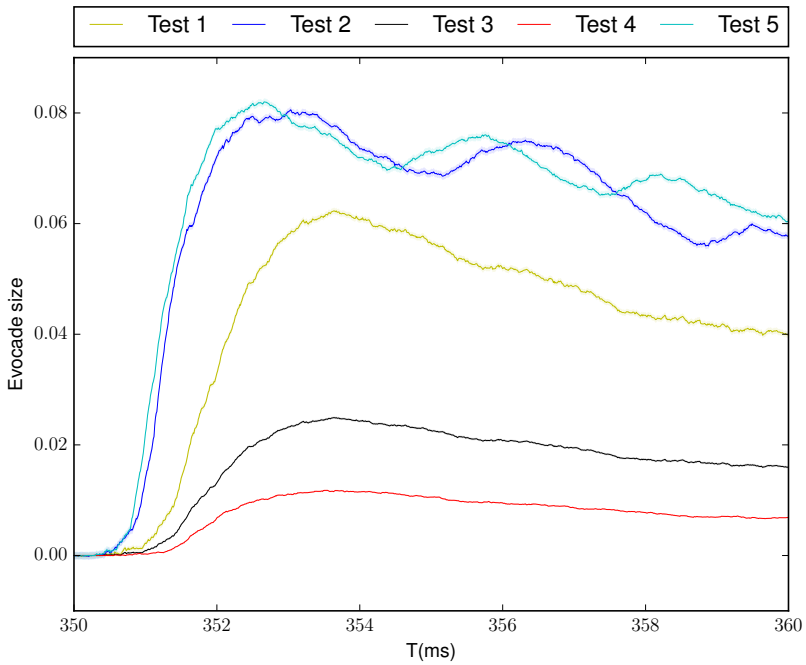


Figure 4.4: Size of the evoked signal in the dynamical variable of the inhibitory postsynaptic current. Tests correspond to different hypothesis of changing after the LTP and they are compared with the test 1 which shows the size of the evoked in the normal neural circuit simulated in the previous section. The vertical variable is a relative variable to compare the value between the tests and the horizontal variable is a temporal window of 10 *ms* which contains the evoked effect.

Figure 4.5 displays the correlation between the synaptic signal from the entorhinal cortex to granule cells and from inhibitory population to granule cells (maximum of the cross-correlation function). Basically, is the cross-correlation function between the inhibitory postsynaptic current from interneurons and the excitatory current from entorhinal cortex. It is observed that *Test 1* and *Test 3* are exactly equals due to the fact that *Test 3* only modifies the amplitude of the signal, not its dynamic. *Test 2* and *Test 5* have similar values as well, following their relation of increasing the entorhinal influence. Finally *Test 4* is the unique case where the correlation decays. This means, that the modification in the internal population changes the dynamical behaviour becoming the case closer to the experimental results.

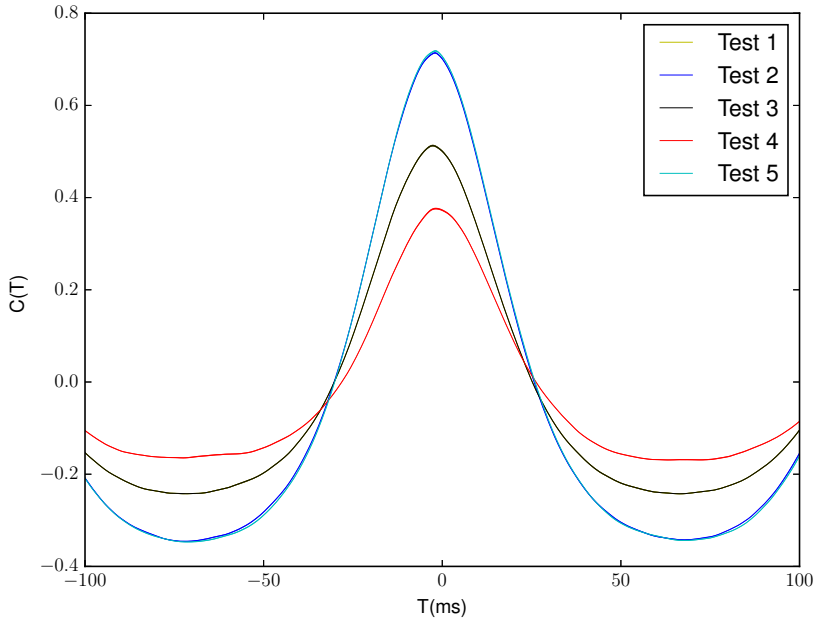


Figure 4.5: Cross-correlation function between the inhibitory signal from interneurons to granule cells and excitatory signal from entorhinal cortex to granule cells for each Test. Test 1 is hidden by the Test 3 because both have the same correlation.

Chapter 5

Conclusions: The ending is the new beginning

Finally, the results of this Master thesis can be summarized in two key statements. The first idea is that the study of the brain as a complex system is feasible despite of all the difficulties involved. Neuroscience is a multi-disciplinary field where physics and mathematics are starting new contributions gaining a place in that study. However, a good relation between physics/mathematics and the biomedical sciences is essential to improve our knowledge about the brain. The second idea is why we need a model, which are their advantages and how it works. In particular, this project is an example of the development of a model, the steps to follow, their setbacks and benefits. The model of the dentate gyrus with an input from the second layer of the entorhinal cortex shows a correct behaviour as compared with experimental results from Andrade and Perna studies, which show a θ frequency from entorhinal cortex and γ rhythm from interneurons in granule cells. In addition, we have benefited from this model to search possible mechanisms caused by a LTP in that region with the aim to explain the experimental results from the research group of Dr. Canals at the Institute of Neurosciences of Alicante (the hypothesis *Test 4*).

This hypothesis suggests that an increase in the connections inside of dentate interneuron population because of the LTP is the reason of the observed decay of the inhibition due to the evoked stimulus. This result gives an idea of a possible study focused on interneurons connections in dentate gyrus and their variations depending on the input.

5.1 What is the next step?

However, this is the beginning of new story. Although we were able to offer an explanation to the experimental results, still there are many questions to answer. Evidently, this is not a completed work, there are many aspects to improve. First of all, we could modify the Izhikevich model to an improved version adding more biological details, such as the capacitance of the neuron. This will increase the difficulty because there are more parameters to fit, however, the model would be more stable.

One question is, what happens with the interneurons? The result of this projects yields a reason to focus on the study of particular inhibitory population. How do they achieve a synchronization? or How does the synaptic plasticity affect in the connections of an inhibitory population?

Nevertheless, we believe that it is possible use the model developed in this Master thesis to study the spread of information or the performance of the neural circuit in the separation pattern function. What would be obtained in the granule population if we put a given input, like a letter, in the entorhinal cortex population?

All these questions open different ways to study the brain and to know more about the key organ, which is constantly developing and which we use without getting to know how.

Bibliography

[1] R. C., "Estructura de los centros nerviosos de las aves," *Revista Trimestral de Histologa Normal y Patolgica*, vol. 1, 1888.

[2] F. R., "Mathematical models of threshold phenomena in the nerve membrane," *Bulletin of Mathematical Biophysics*, vol. 17, pp. 257–278, 1955.

[3] H. J. L. and R. R.M., "A model of neural bursting using three coupled first order differential equations," *Proceedings of the Royal Society of London. Series B, Biological Sciences*, vol. 221, pp. 87–102, 1984.

[4] G. Buzsli and X.-J. Wang, "Mechanisms of gamma oscillations," *Annual review neuroscience*, vol. 35, pp. 203–225, 2012.

[5] F. S, *Origins of neuroscience: a history of explorations into brain function.* Oxford University Press, 2001.

[6] G. M. and J.-C. L., "Interneuron diversity series: Hippocampal interneuron classifications - making things as simple as possible, not simpler," *TRENDS in Neurosciences*, vol. 26, no. 10, pp. 564–569, 2003.

[7] D. B. Stratton, *Neurophysiology.* McGraw-Hill, 1981.

[8] E. M. Izhikevich, *Dynamical Systems in Neurosciece.* MIT Press, 2007.

[9] J. Malmivuo and R. Plonsey, *Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields.* Oxford University Press, 1995.

[10] P. Dayan and L.F.Abbot, *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems.* MIT Press, 2001.

[11] G. M. Shepherd, *The Synaptic Organization of the Brain.* Oxford University Press, 4 ed., 1998.

[12] P. Andersen, R. Morris, D. Amaral, T. Bliss, and J. O'Keefe, *The Hippocampus Book*. Oxford University Press, 2007.

[13] G. Riedel and J. Micheau, "Function of the hippocampus in memory formation: desperately seeking resolution," *Progress in neuro-psychopharmacology & biological psychiatry*, vol. 25, no. 4, pp. 835–853, 2001.

[14] H. Eichenbaum, P. Duchenko, E. Wood, M. Shapiro, and H. Tanila, "The hippocampus, memory, and place cells: Is it spatial memory or a memory space)," *Neuron*, vol. 23, no. 2, pp. 209–226, 1999.

[15] S. Ramirez, X. Liu, P.-A. Lin, J. Suh, M. Pignatelli, R. Roger L, J. R. Toms, and S. Tonegawa, "Creating a false memory in the hippocampus," *Science*, vol. 341, no. 6144, pp. 387–391, 2013.

[16] W. B. Scoville and B. Milner, "Loss of recent memory after bilateral hippocampal lesions," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 20, no. 1, pp. 11–21, 1957.

[17] M. E.A., W. K., and S. H.J., "London taxi drivers and bus drivers: a structural mri and neuropsychological analysis.," *Hippocampus*, vol. 16, no. 12, pp. 1091–101, 2006.

[18] O. J. and D. J., "The hippocampus as a spatial map: preliminary evidence from unit activity in the freely moving rat," *Brain Research*, vol. 31, pp. 573–590, 1971.

[19] O. J. and B. N., "Geometric determinants of the place fields of hippocampal neurons," *Nature*, vol. 381, pp. 425–428, 1996.

[20] H. T. Ito, S.-J. Zhang, M. P. Witter, E. I. Moser, and M.-B. Moser, "A prefrontal-thalamo-hippocampal circuit for goal-directed spatial navigation," *Nature*, vol. 522, pp. 50–55, 2015.

[21] J. K. Leutgeb, S. Leutgeb, M.-B. Moser, and E. I. Moser, "Pattern separation in the dentate gyrus and ca3 of the hippocampus," *Science*, vol. 315, no. 5814, pp. 961–966, 2007.

[22] A. David G, S. Helen E, and P. Lavanex, "The dentate gyrus: fundamental neuroanatomical organization (dentate gyrus for dummies)," *Progress in Brain Reserch*, vol. 163, pp. 3–22, 2007.

[23] A. L.F., "Lapique's introduction of the integrate-and-fire model neuron (1907)," *Brain Research Bulletin*, vol. 50, no. 5/6, pp. 303–304, 1999.

[24] H. A.L. and H. A.F., "A quantitative description of membrane current and its application to conduction and excitation in nerve," *The Journal of Physiology*, vol. 117, no. 4, pp. 500–544, 1952.

[25] H. A.L. and H. A.F., "Currents carried by sodium and potassium ions through the membrane of the giant axon of loligo," *The Journal of Physiology*, vol. 116, no. 4, pp. 449–472, 1952.

[26] E. M. Izhikevich, "Which model to use for cortical spiking neurons?," *IEEE Transactions on Neural Networks*, vol. 15, no. 5, 2004.

[27] E. M. Izhikevich, "Simple model of spiking neurons," *IEEE Transactions on Neural Networks*, vol. 14, no. 6, 2003.

[28] L. L. Gollo, C. R. Mirasso, M. Atienza, M. Crespo-Garcia, and J. L. Cantero, "Theta band zero-lag long-range cortical synchronization via hippocampal dynamical relaying," *PloS ONE*, vol. 6, no. 3, pp. 1–9, 2011.

[29] H. E. Scharfman and C. E. Myers, "Corruption of the dentate gyrus by 'dominant' granule cells: Implications for dentate gyrus function in health and disease," *Neurobiology of Learning and Memory*, vol. 129, pp. 69–82, 2016.

[30] D. M. Kullmann, "Interneuron networks in the hippocampus," *Current Opinion in Neurobiology*, vol. 21, pp. 709–716, 2011.

[31] D. Joshua T and N. Matthew F, "Stochastically gatin ion channels enable patterned spike firing through activity-dependent modulation of spike probability," *PLoS Computational Biology*, vol. 5, no. 2, pp. 1–19, 2009.

[32] N. Hananeia and L. Benuskova, "Computational simulation of dentate gyrus granule cell-the role of metaplasticity," *Neurocomputing*, vol. 175, pp. 300–309, 2016.

[33] H. Michel E, "Neural rebound spiking, resonance frequency and theta cycling spikking may contribute to grid cell firing in medial entorhinal cortex," *Philosophical transactions of the royal society B*, vol. 369, no. 1635:20120523, 2014.

[34] M. Robert J, V. Santhakumar, and Ivan, "Modeling the dentate gyrus," *Progress in Brain Research*, vol. 163, pp. 639–658.

[35] L. L. Colgin *Current Opinion in Neurobiology*, vol. 31, pp. 45–50, 2015.

[36] A. J. Perna-Andrade and P. Jonas, "Theta-gamma-modulated synaptic currents in hippocampal granule cells in vivo define a mechanism for network oscillations," *Neuron*, vol. 81, pp. 140–152, 2014.