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Synchronization between populations of neurons

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by

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“There may be nothing new under the sun,
but permutation of the old within complex systems can do wonders.”

– Stephen Jay Gould

Abstract

In order to execute cognitive functions the brain must bind features and information which occurs at different cortical areas. The most accepted hypothesis to underlie such integration of information is the binding by synchrony. Accordingly to it: two brain regions interact with each other whenever they have coherent activity. The mechanism of this phenomenon has been subject of controversial debate for many years: how can two distant dynamical elements synchronize at zero lag even in the presence of non-negligible delays in the transfer of information between them? So far, complex mechanisms and neural architectures have been proposed to answer this question. However, a simple and robust mechanism has been proposed recently. Zero-lag synchronization between two elements is achieved by relaying the dynamics via a third mediating element. The synchronization thus obtained is robust over a considerable parameter range. In this work we study the dynamical relay phenomenon in complex networks of chemically coupled neurons, specifically the capacity to provide the basis for the binding by synchrony process. We show that three identical neuronal populations satisfy the minimum conditions to produce lag-free synchrony among delayed populations reciprocally connected to a central relay population. We also investigate the dynamical behavior of the thalamocortical circuit whose relay station role is played by the thalamus. We found that the thalamocortical circuit supports the dynamical relay mechanism. More importantly, we report the identification of a variable that might be responsible to control the on-off synchronization of the cortical populations depending only on the ratio of dorsal over ventral thalamus external activity. The simplicity of the key controlling element in the model also suggests that both bottom-up and top-down incoming stimulus to thalamic region share responsibilities in the cortical synchronization phenomenon, in contrast to previous hypothesis. This work supports the binding by synchrony theory and helps to establish solid bases for this phenomenon.

Keywords: synchronization, delay, thalamus, binding by synchrony, synchronization control.

Contents

Chapter 1

Introduction

"One never notices what has been done; one can only see what remains to be done."

– Marie Curie

Even primitive men have felt the need to seek something fundamental to their own existence. For simple observations, they realized that living beings needed breathing, and if not do so for a short period of time, say a few minutes, they would lose their lives in an irreversible way, without any other damage. To complete the description, it was mysterious and invisible as volatile as the own life. Subsequently already noticed the interpretation of blood as the key, because only the living bleed. The ancient Greeks shared these ideas: Aristotle, one of the most famous ancient thinkers believed that the purpose of the brain was only cool the heated blood that circulated the inside [1]. The Bible indicates that blood is essential to life and is therefore prohibited to eat it as living matter. Namely, the book Geneses, chapter nine, verse four, says: "But flesh with the life thereof, which is the blood thereof, shall ye not eat".

Until the seventeenth century, it was believed that the organ responsible for passions was the liver, the largest one of the organs and the more irrigated viscera. While the love was the heart, such as this, for example, in the comedy "Twelfth Night" or "What You Willnight at Kings" of William Shakespeare.

Only in the nineteenth century it was acknowledged the importance of nerves. By analogy with electric circuits, it was realized that the act of cutting the nerves that connect one eye, for example, cause blindness of the eye. However only at the end of the nineteenth century after the invention of the microscope, using the method of silver staining developed by Golgi (published in 1885), Ramón y Cajal showed that the nervous system was not formed by a continuous reticulum but by different neural cells [2] .

Today we believe, through advances in neuroscience, that the brain is responsible for the thoughts, feelings, wishes and decisions rather than some other non-physical element. This means that there is no soul that falls in love, although there is still this feeling, and passion remains as true as ever was. Now we believe that these important events happen physically in the brain [3]. Thus, probably due to its crucial importance in the life and behavior of each of us this, which is probably the most complex system known, attracts the attention of scientists and researchers from many areas of knowledge.

In this chapter we discuss some fundamental concepts of neuronal behavior. Afterwards a brief comment on the background knowledge necessary to understand the key ideas developed by our study is given, and finally the results are released shortly after.

1.1 Computation neuroscience

In general, the biological systems are very complex and far from equilibrium. This tends to create gaps between both approaches of descriptive biological details, always in greater quantity, and the more abstract models that define our level of understanding. The physicist point of view seeks to select only the essential factors to obtain the desired basic behaviors. And thus, help in the construction of general theories that describe the desired systems.

Neuroscience is a vast field of knowledge, which was traditionally studied from characterization of patterns and rules that determine the understanding of living systems. However since the area have expanded by the increasing introduction of computational methods moreover the fact of to attract attention of researchers of different backgrounds. Computation neuroscience[1] brings together researches from several different background areas including: biology, chemistry, physics, computer science, math, psychology, physiology, anatomy, engineering, philosophy.

It emphasizes descriptions of functional and biologically realistic neurons (and neural systems) and their physiology and dynamics. These models intents to capture the essential features of the biological system at multiple spatial-temporal scales, from membrane currents, protein and chemical coupling to network oscillations, columnar architecture, learning and memory. These computational models are used to test hypotheses that can be directly verified by current or future biological experiments.

Computation neuroscience attacks problems from a wide scope, from subcellular systems, say synapses behavior to the most far consciousness states which involves the whole central nervous system (CNS). In between, we can also include: single neuron model, development of neurons and its parts (e.g. axon development of patterning and guidance), sensory processing, memory and synaptic plasticity, behaviors of networks, cognition and learning. Our own contribution in this particular work aims to call attention to a traditional cognition problem which we come up with a new solution using large networks of neurons coupled. It may turn out to be an important mechanism used by natural systems or at least could motivate the creation of artificial ones. Interpreting our result, we were also able to speculate about attention and how could sensory processes influence this particular cognitive function called binding problem (section 1.4).

1.2 Neuronal activity

The cell theory propose that cells are the basic unit of structure in all living things. This idea is credit to Schwann and Schleiden who in 1839 suggested that cells were the basic unit of life and all organisms are made up of one or more cells. Afterward, in 1858, Rudolf Virchow concluded that all cells come from pre-existing cells thus completing the classical cell theory.

However the nervous system was still considered to be an exception. The nervous tissue was thought to be a continuous reticulum system due to nerve observations that mimics a wire. This idea persisted until the development of the histological stained technique with a silver chromate solution by Camillo Golgi which allowed Ramón y Cajal to perform his experiments. This technique is able to paint only a few % of the cells [2] which allows the single neuron observation. Therefore Cajal concluded that the neurons were the fundamental elements of the nervous system [5].

Beyond what has been stated Cajal also proposed the polarized principle [2] which says that the activity coming from the dendrites are somehow processed and pass to the neighbors neurons throw the axon. Nowdays it is known that such principle is not always valid because of some exceptions, as will be commented next. Accordingly, we follow by describing some fundamental

[1] For a recent review we refer the reader to the paper of Erik De Schutter [4]

neuronal properties, namely its anatomical parts and the dynamical states process. We also explain how the excitability leads to neuron to neuron communication and the main causes of delay in the transmission of information.

1.2.1 The neuron

There are about 10^{10} neurons in CNS organized in a multilevel hierarchical system [6]. The nervous system provides a lot of diversity of neuron type, connectivity, functionality, etc. Therefore pretty much all of what is said refers to the most commun behavior despite the whole variability present. In this topic we describe the neuron first by its anatomical structure followed by a bit of its dynamical equilibrium state. At last we comment the other dynamical states of a typical neuron, namely the excited and the refractory period and how they are reached.

1.2.1..1 morphology Some of the general morphological characteristics satisfied by most neurons [2] are displayed in fig 1.1.

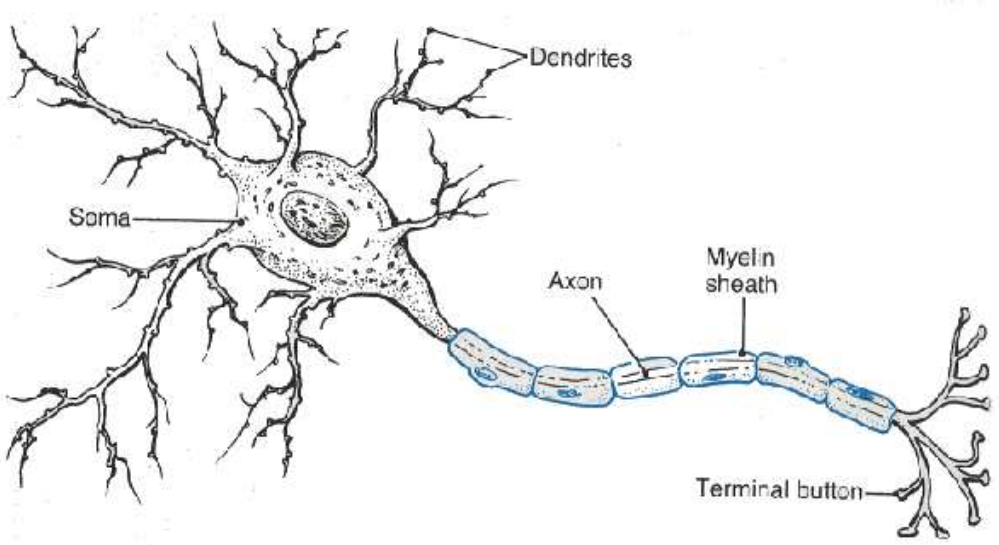

Figure 1.1. A typical motor neuron myelin-covered sketch. Figure adapted from the web site http://www.mindcreators.com/Images/NB_Neuron.gif .

The three main parts of a neuron are the dendrites, the soma (cell body) and the axon. Most of the incoming current to a neuron comes from the dendrites. Probably the great distinctive features of neurons is the presence of large dendritic trees. They are responsible for most of the variety in neuron size, shape and types (there are about 10^4 different morphological classes of neurons [7]), see for instance two cerebral cortex cells in fig 1.2 .

The dendrict tree also contains many post synaptic terminals of chemical synapses. A lot of functions [8] have also been claimed to be performed by dendritic arbors such as biological gates and coincidence detectors [9], learning signaling by dendritic spikes [10], to increase the learning capacity of the neuron [11] or to increase the ability to differ incoming stimulus intensity into a neuron (or enhance the dynamic [12]). However such dendritic computation properties are still far away form been clearly understood.

The cell body (soma) contains the nucleus and most of the cytoplasmic organelles. It is mainly where the metabolic process occur.

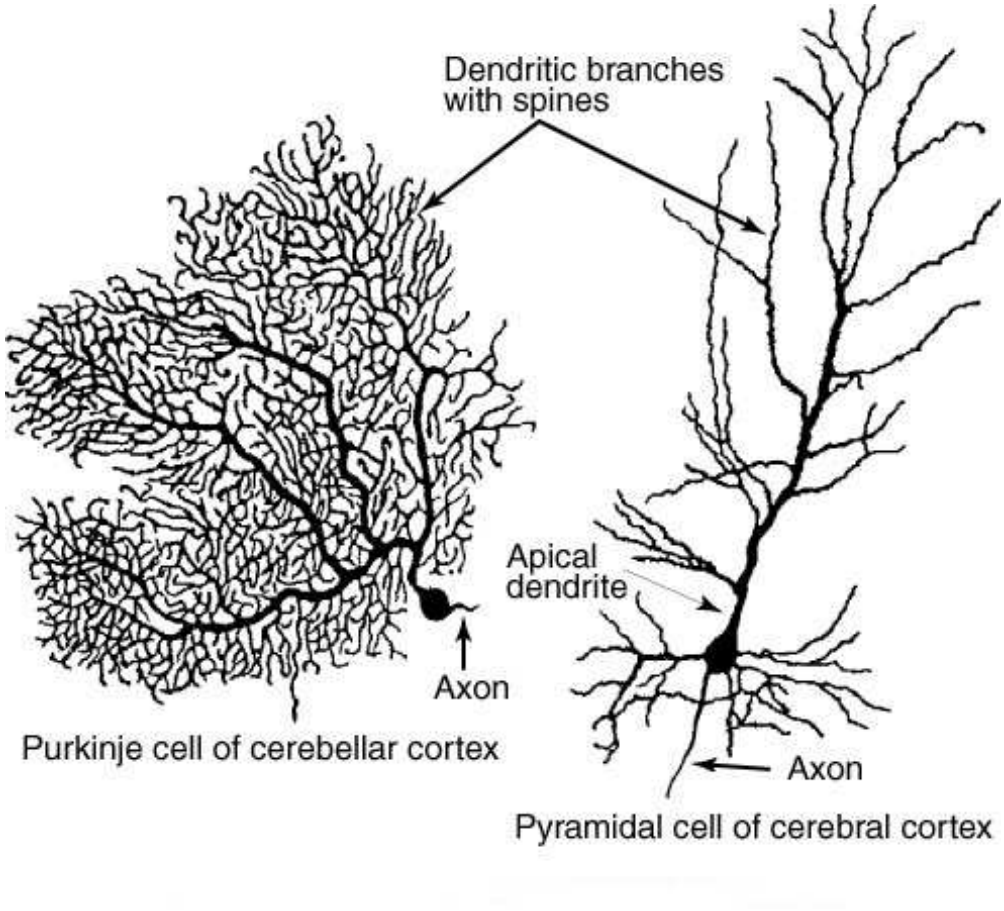

Figure 1.2: Examples of different types of neurons. Figure adapted from [5].

In general, the axon goes very far away from the soma. It might have different size (from 0.1 to 2.000 mm) depending on its functionality [2]. It starts at the axon hillock where the action potential is generated and present ramifications at the extremities. From those terminal buttons come out most of the pre synaptic terminals. It might be involved by myelin to protect and control some properties as the propagation velocity.

Due to its specialization the axon is the main conducting unit of action potential. Such propagation occurs without distortion, moreover, the information carried by an action potential is considered to be given by the particular path taken [2]. This is the way the brain interpret electrical signals to construct our perception of the exterior world coming throw the sensory systems.

1.2.1..2 equilibrium state. The neurons are, as well as all other living cells, enclosed by a membrane. It separates the extracellular space from the interior of the neuron. The membrane is a lipid bi-layer of 3 to 4 nm thick which acts as a capacitor by separating the ions lying along its interior and exterior surface [13, 14], see fig. 1.3. The variation of the ionic concentration gives rise to the potential difference maintained by the cell membrane which is called the membrane potential. It is under normal conditions around -90 to 50 mV. The membrane potential also defines the rest potential, a dynamical equilibrium state of ions coming back and forth. The ions might go throw a specialized structure (pore-forming proteins) called ionic channel or active selective pumps since the lipid bi-layer is impermeable in natural conditions. There are a large variety of

different types ionic channels, each neuron has more than ten types. Each one of the channels have its own properties, in particular, some of them are highly selective to a specific ion.

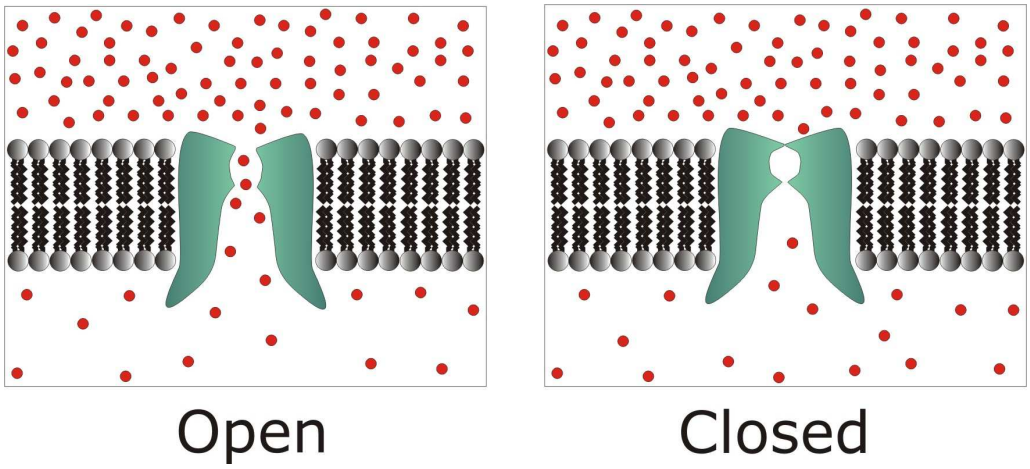

Figure 1.3. The dynamical equilibrium state involves a small ($\sim$ 10mV) potential difference from the intraneuronal medium to the extracellular region. It can be changed by the flux of ions (red dots) throw the opened ionic channels distributed across the lipid bi-layer membrane. Figure adapted from the web site http://www.sophion.dk/sophion/Open-close2.jpg .

1.2.1..3 action potential. The neurons are nonlinear excitable elements, i.e., they generate a spike when its membrane potential goes above a defined threshold (about 20-30 mV above the rest potential [13]). This excitation is also called action potential. When the membrane potential of a given neuron is perturbated, for instance via the incoming activity from a neighbor, it relaxes back to its rest potential in a time scale determined by the membrane time (τ_m) if it doesn't exceed the threshold.

The spike is generated in a particular region called axon hillock located in between the soma and the axon. The pulse propagates [15] mainly throw the axon (forward propagation) but may also propagate in the other direction (backpropagating spike [16, 17]).

The spike occurs in a very narrow time window followed by a fall of the membrane potential bellow the rest state. At that point the neuron is said to be hyperpolarized and its potential difference is greater with respect to the exterior region (arbitrarily defined as 0 mV). This stage is called refractory period and the neuron is typically not allowed to reach the threshold and consequently to spike. Typically, the membrane potential relaxes to the rest potential before another cycle happens. We refer the interested reader to fig 1.3 for a whole microelectrodo recorder cycle.

1.2.2 Neuronal communication

Charles Sherrington, in 1897, suggested that neurons perform functional contacts with other neurons and other types of cells through synapses. Meanwhile the existence of such structures was demonstrated by electron microscopy, 50 years later [5].

Nowadays, we define the synapse as the specialized junctions through which cells of the nervous system signal to one another and to non-neuronal cells such as muscles or glands. It is also the region in which two neurons are closest to each other. The cell transmitting a signal is known as pre-synaptic cell while the cell that receives the signal is the post-synaptic cell. These regions may be present throughout the neuron.

The CNS is a highly connected tissue. Each neurons exchange information with about 10^4 other neurons [2]. There are at least three different ways of communication among neurons: chemical synapses, electrical synapses and ephaptic interaction.

1.2.2..4 Chemical synapses. The predominant form of communication between neurons brain of vertebrates is the chemical synapse [13]. In this type of synapse there is a separation of the order of few tens of nanometers called synaptic cleft, see figure 1.4. In the pre-synaptic terminals, there are collections of synaptic vesicles, each containing thousands of molecules of neurotransmitters. The vesicles release neurotransmitters in the synaptic cleft when the pre-synaptic neuron fires. In this case the neurotransmitters suffer a diffusion process in the extra cell synaptic cleft space. The molecules of neurotransmitters may well be linked to the cell receptors post-synaptic causing the opening of ionic channels. Thus the membrane potential changes, and if it exceeds a certain threshold the post-synaptic neuron will fire in response to a stimulation, concluding the communication. Note that in this case there is an anatomical difference between two well-defined cells, which makes this type of communication unidirectional.

The resulting variation of the post synaptic neuron membrane potential depends on the number of channels opened due to the neurotransmitters binding and the type of neurotransmitter. There are a huge number of different neurotransmitter some of them act [18] in order to excite (increase its membrane potential or depolarize) the post synaptic neuron while other inhibit its activity (decrease the membrane potential or hyperpolarize) [19–21]. We are going to focus on the chemical synapse mainly because it is the most commun type of interaction present in CNS. Since the chemical synapse is an intrinsically source of delay we describe next, section 1.2.3, an estimation of the causes an how long it does take.

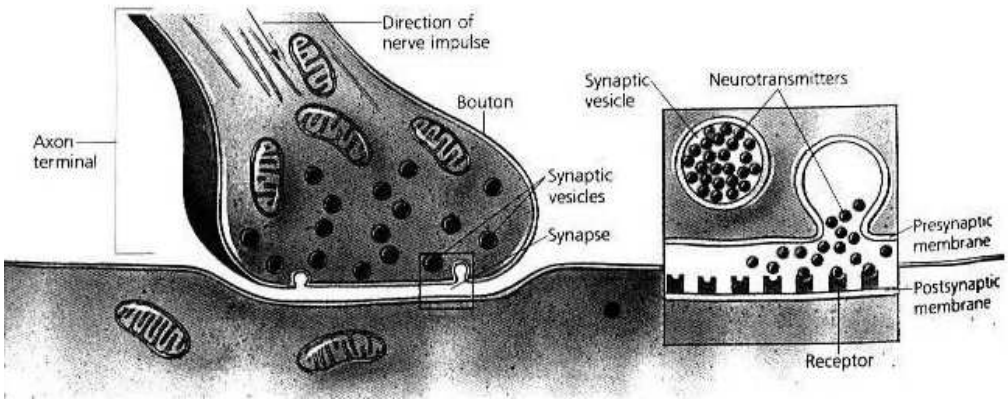

Figure 1.4. Chemical synapse action. A typical sketch of the main elements involved in a chemical synaptic transmission. When an action potential invades the presynaptic terminal and activates voltage-dependent Ca^{2+} channels it raises this ion concentration in such terminal. The phenomenon produces a release of neurotransmitter molecules of the synaptic vesicles. Subsequently, the neurotransmitters diffuse across the cleft (synaptic extra-cellular region) all the way throw the postsynaptic receptor where they may bind. Therefore it opens the ionic channels of the postsynaptic neuron and causes the variation of its membrane potential, concluding the process. Figure adapted form http://www.benet.org/teachers/meraci/Neuron_Synapse.jpg .

1.2.2..5 Gap junctions. The electrical synapses occur through the electrical interaction between cells. In this case, the membranes of neurons are located very near to each other and connect up through channels specialized called gap junctions, see fig 1.5. These are proteins that have more larger channels than the pores of the ionic channels: thus, various substances are simply

free to spread by these channels. Moreover, there is also a flow of current between the neurons, which means that these connections are more bidirectional.

They have also been involved in explaining spread neuronal synchrony [22, 23]. Evidence for gap junctions role in giving rise to fast rhythmic activity has been put forward by observations that fast oscillations can be generated in conditions where chemical synaptic transmission was blocked [24]. Gap junctions also present two clear advantages over chemical synapses for the induction of zero-lag synchrony. First, they are not affected by synaptic delays since no neurotransmitters are used. Second, the electronic coupling between cells mainly acts via diffusion mechanisms and therefore, it tends to homogenize the membrane potential of the cells involved. Thus, gap junctions can be considered of synchronizing nature rather than excitatory or inhibitory class [23]. Electrical synapses are believed to underlie homogenization of firing among neurons and to foster synchrony in moderately distributed networks [23, 25–28].

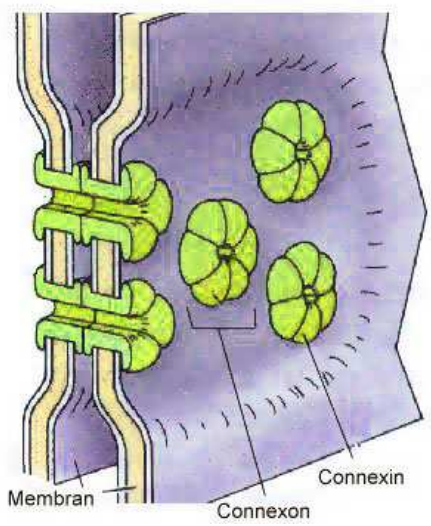

Figure 1.5. Gap Junction. Two neurons get very closed together separated by an uniform gap, roughly 2-3 nm in width. The connexin proteins joint together an hexagonal shape called connexon which link the two neurons of the electrical synapse. Figure adapted from http://www.ferienhaus-baumann.de/incentive-hp/biochemie/bilder/!gapjun0.jpg .

1.2.2..6 Ephatic interaction. It is another type of neuronal communication which is sometimes present. Formally ephaptic coupling is the process by which neighboring neurons affect each other by current spread through the extracellular space [29–31]. Typically it is allowed to cause neuron activity when the unmyelinated axons gather into densely packed fascicles in some convergence cases, for instance from olfactory epithelium to bulb.

1.2.3 Conduction delay

It is possible to dissect in at least five different contributions the latency in the communication between two neurons via a prototypical axo-dendritic chemical synapse. For illustration purposes here we follow the time excursion of an action potential generated in a presynaptic cell up to becoming a triggering source for a new spike in a postsynaptic cell.

- The first component is due to the propagation of an action potential from the axon hillock to the synaptic terminal. The limited axonal conduction velocity imposes a delay ranging from

a few to tens of milliseconds depending on the caliber, myelination, internodal distance, length of the axonal process, and even the past history of impulse conduction along the axon [32–34].

- A second element of brief latency occurs due to the synaptic transmission. After the action potential has reached the presynaptic ending several processes contribute to different degree to the so-called synaptic delay. These include the exocytosis of neurotransmitters triggered by calcium influx, the diffusion of the transmitters across the synaptic cleft, and their binding to the postsynaptic specializations. Altogether the complete process from the release to the binding to specialized channels can typically span from 0.3 ms to even 4 ms [35].
- Another source of delay is the rise time of the postsynaptic potential. Different ionic channels show different time-scales in producing a change in the membrane conductance which eventually induces the building-up of a significant potential. For fast ionotropic AMPA or $GABA_A$ receptors it can take a time of the order of half a millisecond for such a process to rise a postsynaptic potential [6].
- Dendritic propagation toward the soma by either passive or active conduction is also a source of a small lag which value depends on the dendritic morphology.
- Finally, the postsynaptic neuron can exploit several mechanisms, such as membrane potential fluctuations, to control to some degree an intrinsic latency in triggering a new action potential [36].

For long-distance fibers the most important contribution of delay typically comes from the axonal conduction. In human, an averaged-sized callosal axon connecting the temporal lobes of both hemispheres is reported to accumulate a delay of 25 milliseconds [37]. Definitely not a negligible quantity for systems working with an internal dynamics of less than 10 ms in many cases.

1.3 Neuron model

The neuronal dynamics is mainly modeled by differential equations. One of the earliest models is the integrate and fire (I&F) neuron model [38–41]. It is given by only one linear differential equation which adds up the external input contributions and simultaneously relax exponentially to the rest state. Eventually the membrane potential reaches a threshold value and the membrane potential is set at the rest state during a fixed interval called refractory period. New features (say calcium channel dependence) were add to this model to generate for instance the integrate-and-fire-or-burst one [42].

Some mathematical models based on detailed biophysical equation for dynamics of ionic channel appeared ,e.g., the Hodgkin-Huxley (HH) [43]. It motivated the study of many alternatively models. For instance the HH model inspired a simplified two coupled differential equations system called FitzHugh-Nagumo model [44,45]. Subsequently both FitzHugh-Nagumo and HH were combined into a voltage-gated calcium channel model with a delayed-rectifier potassium channel called Morris-Lecar [46]. In order to describe different types of neuron with a better precision, some other models were developed, namely Hindmarsh-Rose [47] or the Izhikevich model which reproduce several observed features also by a set of coupled differential equations [48,49].

All of those previously commented models were done with an assumption that the neuron has no spatial structure, that is, a punctual element. The cable theory was then developed to study further geometry of a cable itself [50], its ramifications [51] or to understand the pulse propagation

activity throw small buttons placed into the membrane called spines [52]. This motivated the two compartmental model [53] and later the multicompartmental model [28, 54–56].

The spatial structure could be formulated as biophysically detailed description which include the dynamics of several elements and channels or by simplified models as coupled maps [57] or even simpler dynamics with cellular automaton [12, 31, 58, 59]. The greater the elemental simplicity the better the topological description is allowed to be. This line of research aims to find out the possibility that extensive neuronal regions could be the stage for some kind of "dendritic computation" [12, 60].

Nevertheless since our goal deals with the study of the behavior of large networks of interacting neurons we will use a simple, traditional and well diffused model: integrate and fire. Next, we describe a little better such model as well as another pioneer model, the HH. It was also used into a few works which inspired our own which introduce an important motif made of only three neurons, we reserve it to a latter discussion at section 1.5.

1.3.1 Integrate and Fire

The integrate and fire model has over 100 years old [41]. It was first proposed long before the mechanisms responsible for the generation of neuronal action potentials were known [39, 40]. Yet the I&F is widely used nowdays [61, 62]. One of the most important features of such model is the simplicity, it becomes specially usefull to build large network of neurons. Since we are interested in large populations we introduce next the I&F model driven by external Poissonian synaptic input for populations [63]:

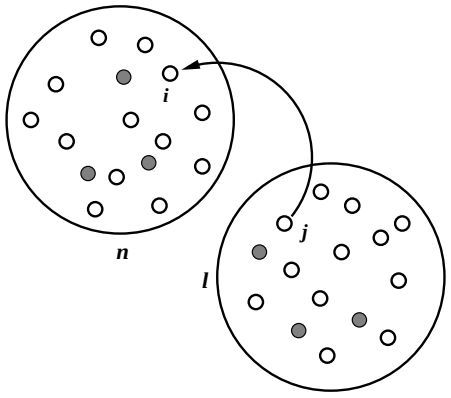

Figure 1.6. Network model synapse example. An unidirectional synapse depicts an innervation coming from neuron j belonging to population l to neuron i of population n such as referred to in equation 1.2.

Each neuron i satisfies the following dynamical equation for the membrane potential ($V_i(t)$):

$$\tau_{m(i)} \frac{dV_i(t)}{dt} = -V_i(t) + RI_i(t) \ . \tag{1.1}$$

Where $\tau_{m(i)}$ is the membrane time constant and (it depends on the populations, as we can see in fig 1.3); $I_i(t)$ is the total voltage arriving to the soma. The last term in the above equation is given by the sum of all postsynaptic potentials (PSP) of neurons belonging to the network plus the total postsynaptic potentials of all external neurons, which is modeled as a Poisson process:

$$RI_i(t) = \tau_{m(i)} \sum_j J_{l(j)} \sum_k \delta(t - t_j^k - \tau_{l(j)}^{n(i)}) + J_{ext} \xi_{n(i)} \ . \tag{1.2}$$

The first sum is taken over the presynaptic neuron j and it depends on the population l which it belongs, see the schematic draw in figure 1.6. t_j^k is the time of the $k-th$ spike received by neuron i from neuron j. The axonal conduction delay from a neuron j in population l to a neuron i belonging to population n is given by $\tau_{m(j)}^{n(i)}$. $J_{l(j)}$ stands for the PSP and depends on the population which the presynaptic neuron belongs to; J_{ext} is the PSP coming from neurons outside the network. Finally, $\xi_{n(i)}$ stands for a Poisson process and is fully described by the mean rate of incoming activity $\nu_{n(i)}$ in a neuron i of population n. Note that in such model the synaptic contributions are considered as simple delta functions.

The dynamics of the neurons can be described as following: the integrate-and-fire neurons start at a reset potential V_r which can be changed by the synaptic current, if the potential $V_i(t)$ of the i-th neuron reaches the threshold θ this neuron fires and its potential comes back to V_r where stays without any change until the ens of the refractory period τ_{rp}.

1.3.2 Hodgkin and Huxley

The Hodgkin-Huxley model is due to the pioneer work of Alan Lloyd Hodgkin and Andrew Huxley in 1952 [43] which explains the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon. Such axon is very wide (up to 1 mm in diameter) and controls part of the water jet propulsion system in squid. The huge size allowed the researches to insert a microelectrode inside it in order to make the membrane potential measure as a function of time, see figure 1.7.

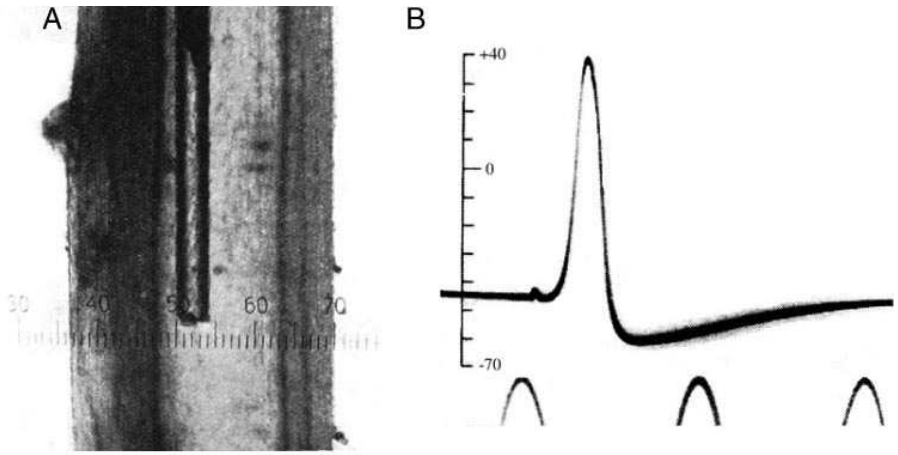

Figure 1.7. Squid giant axon. At left (A) there is a microelectrode of 100 μm of diameter inserted into the interior of a squid giant axon of about 1 mm. At right (B) shows an action potential dynamics, the y axis refers to the membrane potential while the x axis is the time. The time interval between two peaks below equals to 2 ms. Figure adapted from original work of Hodkin and Huxley [64].

The model is given by a set of nonlinear differential equations for the membrane potential and its dynamical ionic channels. The temporal evolution of the voltage across the membrane potential of each neuron plus the inclusion of the appropriate synaptic currents (I_{syn}) coming from the neighbors interactions and an external current (I_{ext}) is given by:

$$C\frac{dV}{dt} = -g_{Na}m^3h(V-E_{Na}) - g_K n^4(V-E_K) - g_L(V-E_L) + I_{ext} + I_{syn}\ ; \qquad (1.3)$$

where $C = 1\ \mu$F/cm^2 is the membrane capacitance, the constants $g_{Na} = 120$ mS/cm^2, $g_K = 36$ mS/cm^2, and $g_L = 0.3$ mS/cm^2 are the maximal conductance of the sodium, potassium, and leakage channels, and $E_{Na} = 50$ mV, $E_K = -77$ mV, and $E_L = -54.5$ mV stand for the corresponding reversal potentials. According to Hodgkin and Huxley formulation the voltage-gated ion channels are described by the following set of differential equations:

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m\ ; \tag{1.4}$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h\ ; \tag{1.5}$$

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n\ ; \tag{1.6}$$

where the gating variables m(t), h(t), and n(t) represent the activation and inactivation of the sodium channels and the activation of the potassium channels, respectively. The experimentally fitted voltage-dependent transition rates are:

$$\alpha_m(V) = \frac{0.1(V+40)}{1 - exp(-0.1(V+40))}\ ; \tag{1.7}$$

$$\beta_m(V) = 4exp(\frac{-(V+65)}{18})\ ; \tag{1.8}$$

$$\alpha_h(V) = 0.07exp(\frac{-(V+65)}{20})\ ; \tag{1.9}$$

$$\beta_h(V) = [1 + exp(\frac{-(V+35)}{10})]^{-1}\ ; \tag{1.10}$$

$$\alpha_n(V) = \frac{0.1(V+55)}{1 - exp(-0.1(V+55))}\ ; \tag{1.11}$$

$$\beta_n(V) = 0.125exp(\frac{-(V+65)}{80})\ . \tag{1.12}$$

The Hodgkin-Huxley model describes how action potentials in neurons are initiated and propagated with great precision. Nevertheless its calculations needs are much heavier which limits the study of networks of neurons to only a few of them, as we are going to describe with more detail latter in section 1.5.

1.4 The Binding problem

There are few places in the nervous system where all the information needed to carry out a particular task is localized. Sensory, cognitive and motor processes involves essentially interactions among large populations of neurons within different brain regions which somehow transfer information from one to another. The bind problem arises whenever information from distinct populations must be exchanged. In summary, it is about how are combined the stimulus features? A solid base to understand how information variously distributed in patterns of neuronal firing results in coherent representation is still need [65]. In summary it arises whenever information from

distinct populations must be exchanged. The binding problem was originally stated as a theoretical problem when the experimental study couldn't provide much information since the realization that none of the localized parts of the brain could generate some aspects of mind's function like consciousness or reason [66]. Such studies raise hopes that allows one to ask for instance the following question: Will the solution of the binding problem be the solution to the mystery of consciousness?

The most popular hypothesis involves temporal correlation of firing patterns, namely that features should be bound via firing synchronization of different neurons. Which is called binding by synchrony theory and still needs to be proven.

1.4.1 Binding by synchrony

Neuronal synchronization has been hypothesized to underlie the emergence of cell assemblies and to provide an important mechanism for the large-scale integration of distributed brain activity [22, 67, 68]. One of the basic ideas in the field is called the binding by synchrony theory which exploits the dimension that temporal domain offers for coding [66, 67, 69–71]. Essentially, it states that synchrony can be instrumental for temporally bringing together the processing output of different functionally specialized areas in order to give rise to coherent percepts and behavior. The differential effect that synchronous versus temporally dispersed inputs can exert onto a downstream neuron indicates how the temporal coherence of a set of neurons can become a flexible and potentially information-carrier variable that can modulate subsequent stages of processing [67, 72, 73]. Despite an ongoing debate about its functional role in neuronal processing is still open, the last two decades have seen the accumulation of large amount of data which shows evidence, at least in a correlative manner, for a role of synchrony and the oscillatory activity that often accompanies it in a variety of cognitive processes ranging from perceptual grouping or stimulus salience to selective attention or working memory [70, 74–77].

Interestingly, neuronal synchrony is not restricted to the local environment of a single cortical column or area. Rather, long-range synchrony across multiple brain regions, even across inter-hemispheric domains, has been reported in several species including the cat and primate cortex [78–83]. However, the zero-lag correlated activity of remote neuronal populations seems to challenge a basic intuition. Namely, one tends to tacitly assume that since the interaction among distant systems is retarded by the conduction delays (and therefore, that it is the past dynamics of one system what is influencing the other one at present) it is not possible that such interaction alone can induce the isochronous covariation of the dynamics of two remote systems. Actually, the latencies associated with conducting nerve impulses down axonal processes can amount to several tens of milliseconds for a typical long-range fiber in species with medium or large sized brains [32, 84, 85]. These ranges of conduction delays are comparable with the time-scale in which neuronal processing unfolds and therefore they cannot be simply discarded without further justification. Furthermore, profound effects in the structure and dynamics of the nervous system might have arisen just as a consequence of the communication conditions imposed by the time delays [86, 87]. As an example, several proposals of the origin of the lateralization of brain functions are based on the temporal penalty to maintaining information transferring across both hemispheres [37, 88].

Next we present an appropriate motif of excitable elements capable to generate zero-lag synchrony despite of conduction delays. It is illustrated in chronological order, i.e., first to semiconductor lasers and then to neurons. This exposition concludes our brief review and allow us to introduce (next chapter) the dynamical relay of neuron populations which we believe to provide an explanation for how could the binding by synchrony arises in large neuronal networks. At last,

we propose a more specific topology which we believe could control such synchrony mechanism, chapter 3 .

1.5 Dynamical Relay

The dynamical relay was originally formulated for oscillators semiconductor lasers systems bidirectionally coupled and further extended to other nonlinear systems such as neuronal elements. In the following we describe the synchronization mechanism and the minimum elements needed to provide zero-lag synchronization of delayed coupled elements. We review what have been done into this topic, how it motivates our own work and the connections to the binding problem in a much more general concept which include the whole CNS instead of only few elements.

1.5.1 Laser

In lasers systems (solid-state and semiconductors [89, 90]) investigations over three instantaneously coupled elements showed an interesting behavior in which the first and the third lasers synchronized their activity. It motivated a deeper study in similar systems coupled with delay. Surprisingly, this configuration appeared to support the same isochronous activity [91, 92]. This first result was obtained in delayed systems experimentally and numerically in semiconductors laser. Delay in coupled semiconductor lasers occurs even for short separation distance because of the fast internal time scale involved in such lasers. Moreover, Fischer et al. also considered thermoreceptor neuron simulation modeled by Hodgkin Huxley equations which already showed a great generality.

The phenomenon generated much interest both theoretically and experimentally. In the theoretical framework we could highlight the explanation of partial synchronization [93] and the motif structure [94]. The coupling architecture was also classified experimentally and numerically [91,92,95]. Besides, it was latter verified in many other oscillators systems, lasers, electronic circuit [96] in coupled quadratic maps, Kuramoto and Rösler oscillators [97]. In particular, we are mainly interest in neuronal applications which we describe in detail next [22, 98].

1.5.2 Neuron

The most simple configuration to illustrate the effects of dynamical relaying corresponds to three neurons connected to form the “V” motif, that is, two neurons that interact by mutually relaying their dynamics onto a third one. We would like to comment the pioneer results [22, 91, 92] using the Hodgkin & Huxley (HH) cells with reciprocal delayed synaptic connections (see top panel in figure 1.8 for an schematic representation of the network architecture). Consider the case in which the isolated neurons already operate in an intrinsic spiking state, say by an external constant current, therefore the synaptic activity modifies the timing of their action potentials until it reaches a stable configuration of isochronous activity of the outer neurons. Further details about the methodology used in the following simulations can be found at Refs. [98, 99].

In figure 1.8 shows the evolution of the membrane potentials under such conditions before and after an excitatory synaptic coupling among the cells is activated. Previously to the switch-on of the synaptic coupling between the cells we can observe how the three neurons fire out of phase as indicated by the left vertical guide to the eye in figure 1.8. However, once the interaction becomes effective at $t = 0$ and synaptic activity is allowed to propagate, a self-organized process, in which the outer neurons synchronize their periodic spikes at zero-phase even in the presence of long

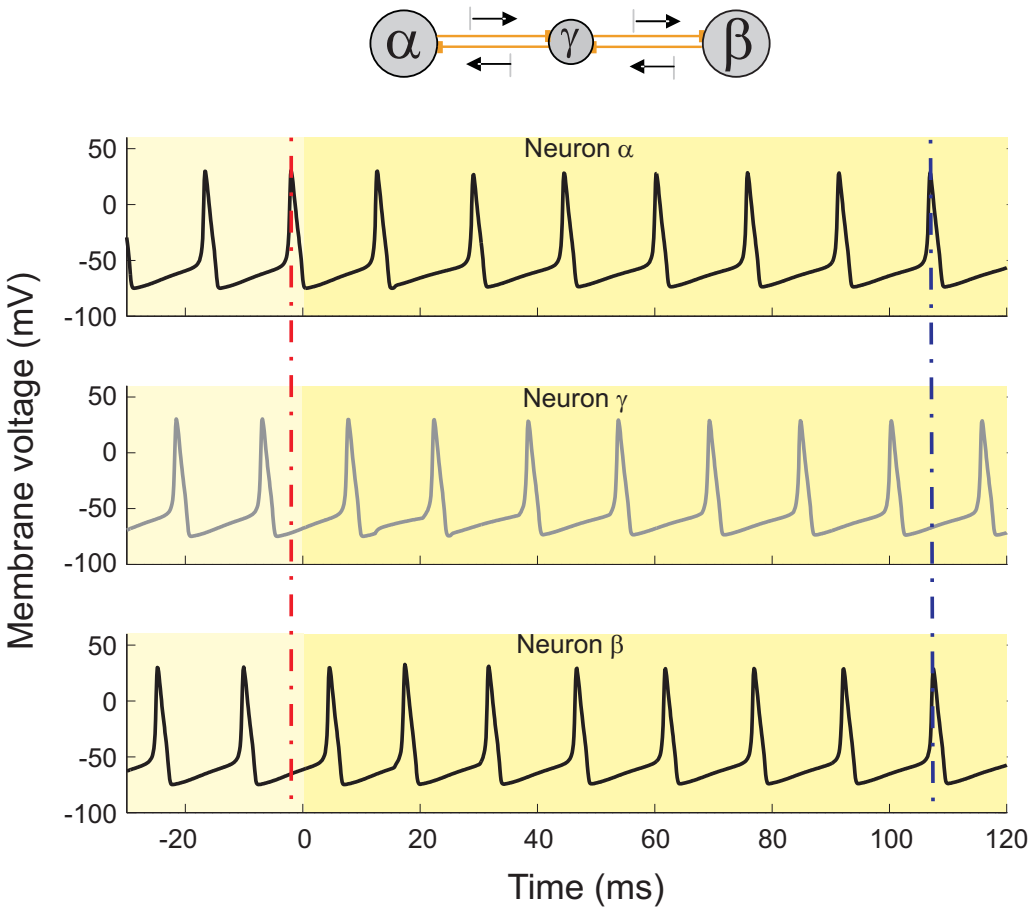

Figure 1.8. Time series of the membrane voltage of three coupled HH cells $N_\alpha - N_\gamma - N_\beta$. At time $t = 0$ the excitatory synapses were activated. Conduction delay $\tau = 8$ ms. Vertical lines help the eye to compare the spike coherence before and after the interaction takes place. Figure adapted from [22].

conducting delays, is observed. Notice that no external agent or influence is responsible for the setting of the synchronous state but this is entirely negotiated by the network itself.

It was also checked that the present synchrony is not just a phase condition between purely periodic oscillators. When independent noise sources were added as membrane fluctuations, to each neuron, a non-perfectly deterministic firing of the three neurons happened. Furthermore, the circuit maintained an approximated zero-lag synchrony between the outer neurons, reflecting both the robustness of the synchrony mechanism to moderate noise perturbations and showing that the synchronization process can be generalized beyond a phase relation.

The mechanism responsible for synchronization was explained to depends on the ability of an excitatory postsynaptic potential (EPSP) to modify the firing latencies of a postsynaptic neuron in a consistent manner. It further relies on the symmetric relay that the central neuron provides for the indirect communication between the outer neurons. The key idea is that the network motif under study allows for the outer neurons to exert an influence on each other via the intermediate relay cell. Thus, the reciprocal connections from the relay cell assure that the same influence that is propagating from one extreme of the network to the other is also fed-back into the neuron which originated the perturbation and therefore, promoting the synchronous state.

It must be noticed, however, that the effect of a postsynaptic potential on a neuron strongly depends on the internal state of the receiving cell, and more specifically on the phase of its spiking cycle at which a postsynaptic potential (PSP) arrives [100, 101]. Since the neurons of the module are in general at different phases of their oscillatory cycles (at least initially) the effects of the PSPs are different for the three cells. The magnitude and direction of the phase-shifts induced by PSPs can be characterized by phase response curves. The important point here is that the accumulation of such corrections to the interspike intervals of the outer neurons is such that after receiving a few PSPs they compensate the initial phase difference and both cells end up discharging isochronously, representing a stable state. Simulations predict that a millisecond-precise locking of spikes can be achieved already after the exchange of only a few spikes in the network (in a period as short as 100 ms). This value is found to be a function of the maximal synaptic conductivity and can be even shorter for stronger synapses connections.

A key issue of the synchronization properties exhibited by such network architecture is whether the zero-lag correlation can be maintained for different axonal lengths or whether it is specific to a narrow range of axonal delays. To resolve this issue it was tested the robustness of the synchronous solution for other values of the conduction delays. Figure 1.9 displays the quality of the zero-lag synchronization for two HH cells as a function of the conduction delay. In that graph the results for two different scenarios were plotted: one in which the neurons are directly coupled via excitatory synapses (dashed line) and a second one in which the two neurons interact through a relay cell also in an excitatory manner (solid line). A quick comparison already reveals that while the direct excitatory coupling exhibits large regions of axonal conduction delays where the zero-lag synchrony is not achieved, the relay-mediated interaction leads to zero time-lag synchrony in 28 out of the 30 delay values explored, $(1-30)$ ms. Only for the cases of $\tau = 3$ ms and $\tau = 10$ ms the network motif under study does not converge to the isochronous discharge for the outer neurons. For such latencies the three cells entered into a chaotic firing mode in which the neurons neither oscillate with a stable frequency nor exhibit a consistent relative lag between their respective spike trains.

Robust zero-lag synchrony among the outer neurons is also observed when the synaptic interaction between the cells is inhibitory instead of excitatory. Different synaptic rise and decay times within the typical range (of fast AMPA and $GABA_A$ mediated transmission) were also tested with identical results. Moreover simulations to test the robustness of this type of synchrony with respect to the nature of the relay cell were conducted. It indicates that when a relay cell is operating in a parameter regime different from the outer ones (such as different firing rate or conductance), the zero-lag synchrony is not disturbed. Remarkably, even in the case where the relay cell is operating in a subthreshold regime, and thus only spiking due to the excitatory input from any of the outer neurons, the process of self-organization toward the zero-lag synchrony is still observed. It is also worth mentioning that in all cases such firing coherence is achieved through small shifts in the spiking latencies which leave the mean frequency of discharges (or rate) almost unchanged. These results indicate that the network motif of two neurons relaying their activities through a third neuron leads to a robust zero-lag synchrony almost independently of the delay times and type of synaptic interactions.

1.5.2.a broad distribution of conducting delays

Axons show a significant dispersion in properties such as diameter, myelin thickness, internodal distance, and past history of nerve conduction. Within a fiber bundle the variability from one axon

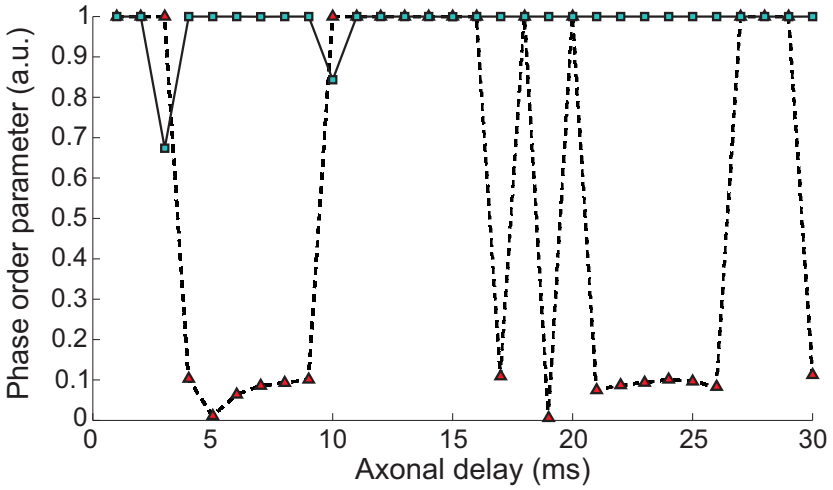

Figure 1.9. Dependence of zero time-lag synchronization as a function of the axonal delay for a scheme of two coupled cells (dashed line) and three coupled cells (solid line). In the case of the three interacting cells only the synchrony between the outer neurons is plotted here. Figure adapted from [22].

to another of these characteristics is directly related to the speed of propagation of action potentials along them and eventually translates into the existence of a whole range of latencies in the neuronal communication between two separated brain areas. Thus, conduction times along fibers are more suitably considered as a spectrum or distribution rather than a single latency value [37, 102].

A crucial question is therefore whether the synchronization transition that have been described in the former section is restricted to single latency synaptic pathways or preserved also for broad distributions of axonal delays. Since data about axonal distributions of conduction velocities in long-range fibers is limited, specially in the case of humans [37, 102], and there is probably not a unique prototypical form of such distributions we explore a whole family of gamma distributions with different shapes.

The left panels shown in figure 1.10 illustrate different gamma distributions of axonal delays for three different shape factors. The numerical simulations indicates that for a large region of mean delays (between 3 and 10 ms) the outer neurons synchronize independently of the shape of the distribution. The right panel of figure 1.10 displays the zero-lag synchronization index of the outer neurons of the network motif as a function of the shape of the gamma distribution of axonal delays and its mean value. Only distributions with unrealistic small shape factor (i.e., exponentially decaying distributions) prevent synchrony irrespective of the average delay of the synaptic connections. For more realistic distributions, there is a large region of axonal delays that gives rise to the zero-lag synchrony among the outer neurons. As in the case of single latencies, there is a drop in the synchrony quality for distributions with a mean value around $\hat{\tau} \sim (10-12)$ ms, where chaotic firing is observed. The isochronous spiking coherence is in general recovered for larger mean delay values.

So far a rather symmetric situation in which similar distributions of axonal delays are present in each of the two branches that connect the relay neuron to the outer units have been considered. This assumption can only hold when the relay cell is approximately equidistant from the outer ones. In the final section of this chapter we refer to several results pointing to the thalamic nuclei

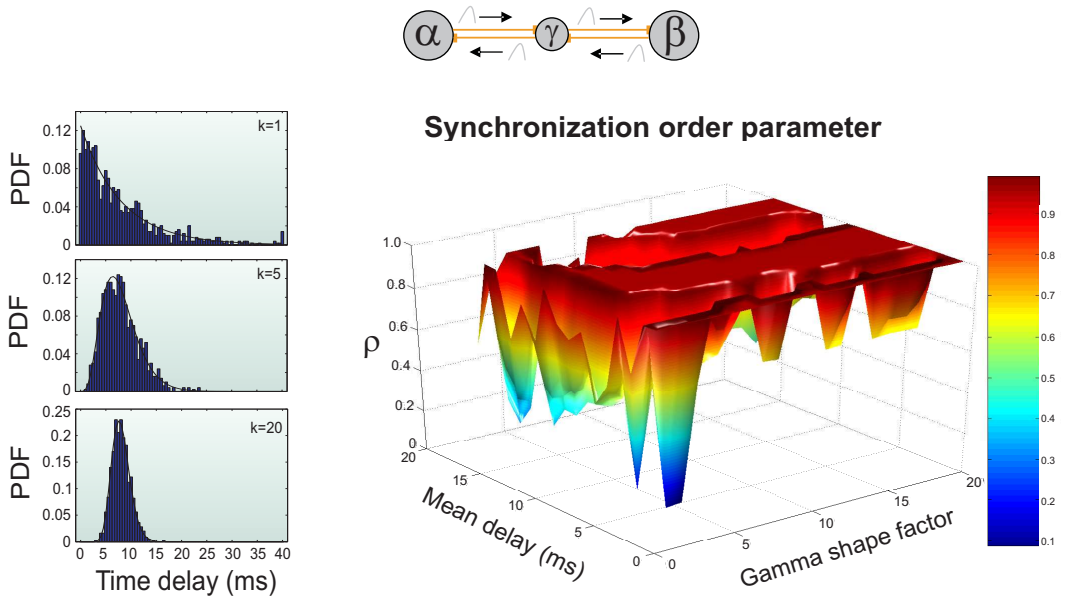

Figure 1.10. Left panels: gamma distribution of delays with different shape factors (k=1, 5, and 20) and the same mean ($\tau = 8$ ms). Right panel: synchronization index at zero-lag of the outer neurons as a function of the shape factor and mean of the distribution of delays. Figure adapted from [22].

and their circuitry as ideal relay centers of cortical communication which approximately satisfy this condition. The situation in which the axonal delays of each of the two pathways of the network motif are described by dissimilar distributions is shown in figure 1.11. In this case, the distributions of delays for each branch have different mean values then a nonzero phase-lag appears between the dynamics of the outer neurons. This effect is illustrated for gamma distributions of different shape factors in figure 1.11. For delta distributions of delays (which is equivalent to the single latency case) the lag amounts to the difference in mean values. Thus, if one of the pathways is described by a delta distribution of delays centered at τ_a = 5 ms while the other is represented by a latency of τ_b = 7 ms, then after some transient the neuron closer to the relay cell consistently fires 2 ms (i.e., $\tau_b - \tau_a$) in advance to the other outer neuron. It is worth to note that such value it is still much smaller than the total delay accumulated to communicate both neurons ($\tau_a + \tau_b = 12$ ms). The study of broader distributions effects of delays has outer cells that tend to fire with a lag even smaller than the difference in the mean values of the distributions. Therefore it suggests that broader distributions of delays can help distant neurons to fire almost isochronously.

In conclusion, three neurons in a oscillatory regime connected as the “V” motif show isochronouly fire of the outer elements. Furthermore the mechanism is robust regarding to the type of synapse connection, small noise perturbation, broad distribution of delays and works even when the relay cell operates in a subthreshold regime. Moreover occurs in a neurophysiology acceptable time scale. All of those desirable properties make one wonder whether dynamical should occur in a large neuronal population system. The study of synchronization between delayed coupled populations of neurons is described in next chapter.

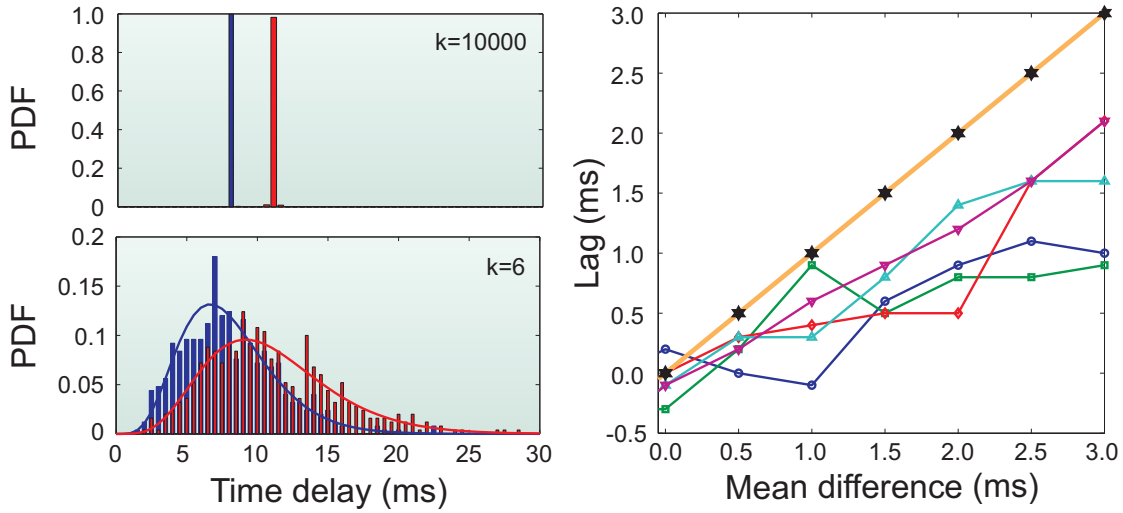

Figure 1.11. Left panels: different gamma distributions of delays used for the two dissimilar branches of the network module. Upper left panel shows distributions with shape factor k=10000 (quasi-delta) and means of 8 and 11 ms. Bottom left panel shows distributions with shape factor k=6 and means of 8 and 11 ms. Right panel: lag between the discharges of the outer neurons as a function of the difference in the mean of the distributions of delays for the two branches. Shape factors k=6 (squares), k=8 (circles), k=10 (diamonds), k=12 (up-triangles), k=14 (down-triangles), and k=10000 (stars) were tested. Figure adapted from [22].

1.6 General Organization

In the previous sections we introduced the main concepts involved in the following chapters. In particular a biophysical description of neurons activity and the way they communicate was given. We also introduced some important neuronal models such as the pioneer Hodgkin Huxley and the Integrate and Fire which involved a very extended literature due to its simplicity.

Those basic elements can be put together in order to provide new explanations to the binding problem, i.e., to use the dynamical relay approach to show how it could induce synchronization of the separated brain areas. It is done in the next chapter where we study a generalization of the "V" motif, which had been shown to work from the single neuron level, to the population level. Hence we create three populations of neurons and connected them in a simple way inspired by central nervous system (CNS) architecture. In fact we present results to display the dynamical relay as a roboust way to induce lag-free synchronization of distant brain areas.

Chapter 3 develops further the neuronal network to provide a better description of the thalamocortical circuit since it is believe that the thalamus could play the central relay station role. In this case we show that it could also provide zero-lag synchrony plus to control whether or not it is supposed to occur as a function of the external driving input to the thalamic region.

Finally we end up with the general conclusions of the present studies, in the last chapter, followed by a perspective discussion.

Chapter 2

Three Random Populations

> "More is different".
>
> P. W. Anderson [103]

The first task we would like to face is to simulate the same three element open chain bidirectionally connected (see section 1.5) exchanging each individual neuron by one population of neurons, see figure 2.1. Our goal is to check whether the three populations are also able to produce zero-lag synchrony of the two outer populations. It is an attempt to explain the binding problem (introduced in section 1.4) by bottom up approach. Such synchronization mechanism of separated brain areas is mainly found in cortical regions during cognitive tasks involving attention.

The cortical populations of neurons are probably the most studied since the cortex [37, 70, 104–108] is the brain area believed to be mainly responsible for the difference between human being brains and other species. It is well known that the cortex is built of excitatory and inhibitory neurons (see section 1.2.2). The proportion is about 4 excitatory neurons for each inhibitory one. In order to somehow contain the self sustained activity in those populations, it is currently believed that the brain regions should be close to the balanced case to compensate the different number of neurons of each type. A balanced population satisfies the following relation: $J_{inh} = -4J_{exc}$, where the postsynaptic potential (PSP) amplitude of the excitatory neuron is J_{exc} and the PSP amplitude of the inhibitory neuron is J_{inh}.

Our attempt to generalize the previous result in single neurons to populations of neurons is not so straightforward. It involves different types of neurons, connections strengths and delays. Some new variables had to be introduced which we set in physiological accepted range of values. Furthermore the simplest and symmetric choices where taken when possible. The model description with its variables and parameters are going to be described in the following section.

Next we compare the simulations outcomes in networks of balanced and unbalanced populations and discuss about the robustness of such results. Any possible explanation of the synchronization effects observed should be very roboust in several variables because it is found in many animals with wide difference in brain size and age (development stage). Finally we compare the dynamical relay model with other proposals and infer about its relevance.

2.1 Network description

The network is made of three neuronal populations bidirectionally connected. Inasmuch as the number of neurons have to be considerably high ($\sim 1.2 \cdot 10^4$) we used the simple integrate and fire

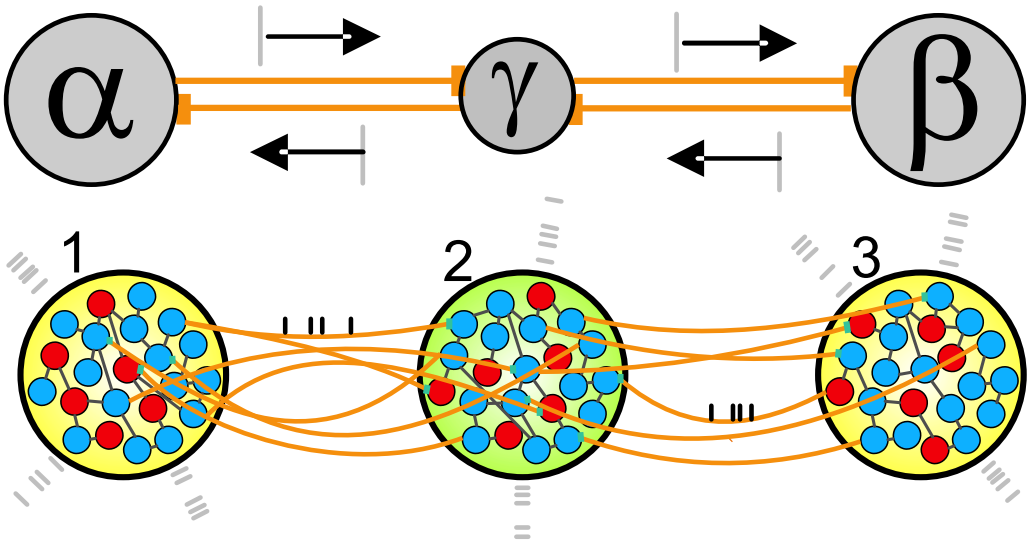

Figure 2.1. To generalize the results for three neurons (top) to three populations (bottom) is the goal of the chapter. Figure adapted from [99].

neuron model, previously described in section 1.3.1 . Each population has 4175 neurons of which 80% are excitatory and 20% are inhibitory.

The dynamics of each neuron evolved from the reset potential of Vr = 10 mV by means of the synaptic currents up to the time when the potential of the i-th neurons reached a threshold of 20 mV, value at which the neuron fires and its potential relaxes to Vr . The potential is clamped then to this quantity for a refractory period of 2 ms during which no event can perturb this neuron.

The populations are randomly connected with the neurons of the same population, i.e., each neuron receives synaptic inputs from 10% of other neurons randomly chosen of the same population. Therefore, the populations are said to be sparsely connected. The internal connection has a small delay of 1.5 ms and the PSP amplitude is modeled as a delta function with amplitude set to be $J_{exc} = 0.1$ mV and $J_{inh} = -gJ_{exc}$, the populations are balanced when $g = 4$

In addition, the populations are also randomly connected with each other, in this case each neuron receive synaptic input from C excitatory neurons of other populations. We kept the extra population connectivity C about one order of magnitude lower than the internal population connectivity. Those interpopulation connection are supposed to be long distance with longer conduction delay, which we take to be $\tau = 12$ ms.

We connected each neuron of the network with 1000 external excitatory neurons, The external activity is modeled as a Poisson process with rate ν_{ext} and the synaptic efficacy is $J_{ext} = J_{exc} = 0.1$ mV. Notice that a neuron will fire if it receives at least 100 synaptic inputs since the membrane potential should be raised 10 mV and each spike contributes with 0.1 mV.

The simulations were performed with the neuronal simulator package NEST [109–112]. Next, we show the simulation results of the network in a few different conditions to highlight the ”V” motif ability against the direct connection topology.

2.2 Results

We would like to stress two different cases in the results next: the balanced and the unbalanced cases. The main difference between them appears spontaneously in a given population when it

is not coupled with the other ones. A balanced population shows an asynchronous and irregular firing pattern while the unbalanced case can has synchronous and regular behavior. The dynamical relay provides the sufficient conditions to generate synchronization of the populations located at the extremes of the motif in both cases. However the mechanism happens to have distinct nature. In order to show the effects of the topology we also compare the "V" motif with a simpler structure in which the two outer populations are directed connected and the central one is isolated.

Next, we show how the three populations bidirectionally connected quickly fall in a stable activity pattern in which the two outer populations synchronize their spikes. It suggests an explanation for how could the binding mechanism take place despite long delays involved in their communication.

2.2.1 The balanced case

The balanced case consists of each one of the populations internally balanced, with $g = 4$. This specific choice allows the sparsely connected network to be in a very complex case because it is close to a transition between asynchronous to synchronous transition. We refer the interested reader to reference [63].

Therefore, we set this parameter and perform simulations for three populations each one in a different initial condition. Each neuron is subjected to an independent Poisson process with a fixed rate of $\nu_{ext} = 5.4$ Hz. The interpopulation connectivity C was set to be $C = 0.8\%$, what means that each neuron receive synapses from 0.8% of the excitatory neurons in the neighboring population.

In order to show how the synchronization mechanism takes place in a small time window we plot the simulation results in figure 2.2. First we set different initial conditions for each populations which starts unconnected. At 100 ms we connect the populations throw the interpopulations connections. About 100 ms after the connections between populations are on, the outer populations (1 and 3) are already synchronized while the activity of the central population (2) is completely out of phase with respect to the other two populations. This result can be seen in the raster plot (panel a) of fig. 2.2 or in the Peri-Stimulus Time Histogram (PSTH) (panel b). In the raster plot each point represent a spike of one of the of 100 neurons randomly chosen, 80 of which are excitatory and 20 inhibitory, as a function of time and the PSTH is the firing histogram of those 100 selected neurons randomly chosen.

Another way to see the synchronization effect is to look at the cross-correlogram between neurons of the different populations (panels c,d and e of figure 2.2). The cross-correlogram is measured as the mean number of coincidences per second (in a bin of 2 ms) of 300 pairs of neurons from different populations within the time window ranging from 300 to 500 ms.

We compare the "V" motif with a simpler motif in which the outer populations are directly connected. Accordingly to the simulations of the direct connected populations, figure 2.3, the "V" motif is the simplest motif to induce lag-free synchrony. The direct connected case has the outer populations (1 and 3) as neighbors and the central population (2) is isolated. As we can see in fig. 2.3, meanwhile the two connected populations do synchronize the activity, it happen to be completely out of phase.

Specifically, if the populations are unconnected the activity remains asynchronous. Nevertheless the connections allows the system to quickly synchronize each of the involved populations internally and in respect to each other with a defined frequency of oscillation. The period is typically given by multiples of the interpopulation connection delay τ. Namely in the results of fig. 2.2 the average period of oscillation is twice the delay, that is, 24 ms.

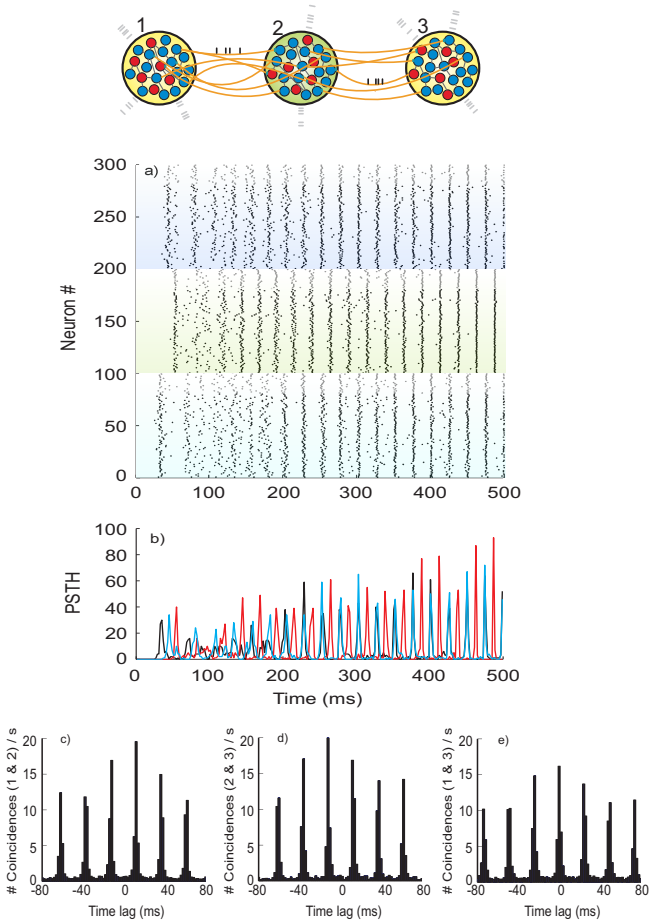

Figure 2.2. Dynamics of three balanced large-scale networks interacting through dynamical relaying. Panel a): raster plot of 300 neurons randomly selected among the three populations (Neurons 1-100 are from Pop. 1, 101-200 from Pop. 2, and 201-300 from Pop. 3). The top 20 neurons of each subpopulation (plotted in gray) are inhibitory, and the rest excitatory (black). Panel b): firing histogram of each subpopulation of 100 randomly selected neurons (black, red, and blue colors code for populations 1, 2, and 3, respectively). Panel c): averaged cross-correlogram between neurons of Pop. 1 and Pop. 2. Panel d): averaged cross-correlogram between neurons of Pop. 2 and Pop. 3. Panel e): averaged cross-correlogram between neurons of Pop. 1 and Pop. 3. At t=100 ms the external interpopulation synapses become active. Bin sizes for the histogram and correlograms is set to 2 ms. Inter-population axonal delays are set to 12 ms.

2.2.2 The unbalanced case

In opposition to the previous case, an unbalanced population may be set in a synchronized region of parameters, typically for $g < 4$. The interpopulation connectivity allows the neurons in the population to couple their phase of oscillation. In the unbalanced case we have studied, we assumed $g = 3.5$. Besides the parameter g, we also changed two other parameters (ν_{ext} and C) with respect to the previous case discussed in section 2.2.1. The external stimulus was set as $\nu_{ext} = 5$ Hz and the interpopulation connectivity C was set to be $C = 0.025\%$.

With these parameters set as above each populations present self sustained activity. So, the populations oscillate even without interpopulation connections. We proceed in the same way as before to give an example of how the interpopulation connections induces the phase couping. We have observed that in less than 200 ms the outer populations synchronize their firing. Accordingly we display first the "V" motif which allows a fast synchrony of the outer population (figure 2.4)

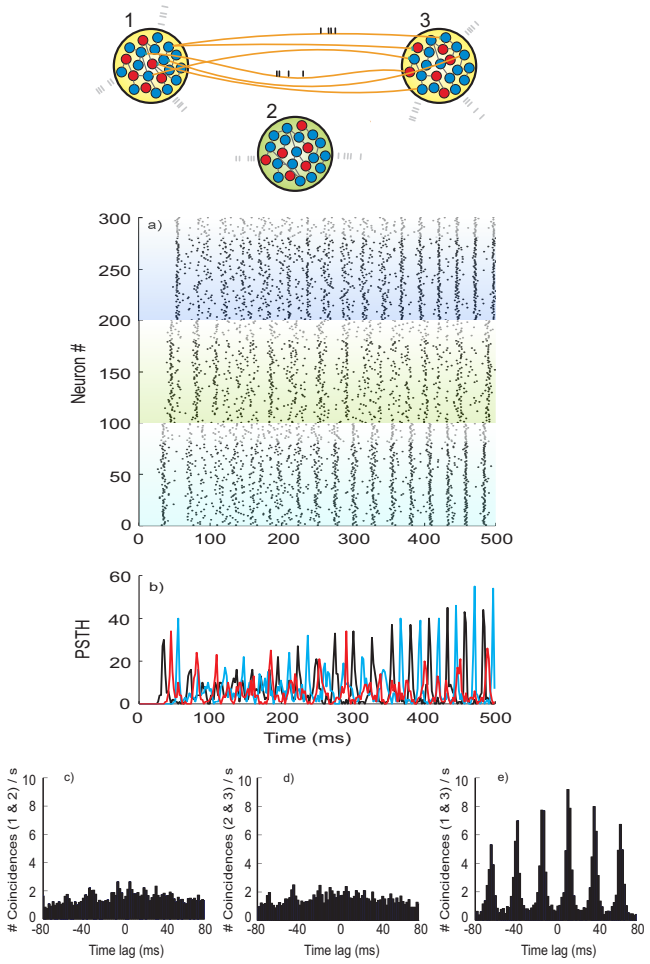

Figure 2.3. Dynamics of two balanced large-scale networks interacting directly. Population 2 is disconnected from other populations. Panel a): raster plot of 300 neurons randomly selected among the three populations (Neurons 1-100 are from Pop. 1, 101-200 from Pop. 2, and 201-300 from Pop. 3). The top 20 neurons of each subpopulation (plotted in gray) are inhibitory, and the rest excitatory (black). Panel b): firing histogram of each subpopulation of 100 randomly selected neurons (black, red, and blue colors code for populations 1, 2, and 3, respectively). Panel c): averaged cross-correlogram between neurons of Pop. 1 and Pop. 2. Panel d): averaged cross-correlogram between neurons of Pop. 2 and Pop. 3. Panel e): averaged cross-correlogram between neurons of Pop. 1 and Pop. 3. At t=100 ms the external inter-population synapses become active. Bin sizes for the histogram and correlograms is set to 2 ms. Inter-population axonal delays are set to 12 ms.

and compare it with another motif where the central population is not connected and the two outer population are directed connected (figure 2.5). Analogous to the balanced case previously described, the dynamical relay helps the system to synchronize while the latter case only produces out of phase synchronization of the populations involved. The main difference of the final pattern of oscillations among the unbalanced case with respect to the balanced case is that the period of oscillation in the first case is not a multiple of the interpopulation connection delay τ. The period of oscillation of the connected populations happen to be shorter than when the populations are unconnected but longer than twice the connection delay τ. Consequently, it releases the system of the constrains of the periods of oscillations with respect to the delay.

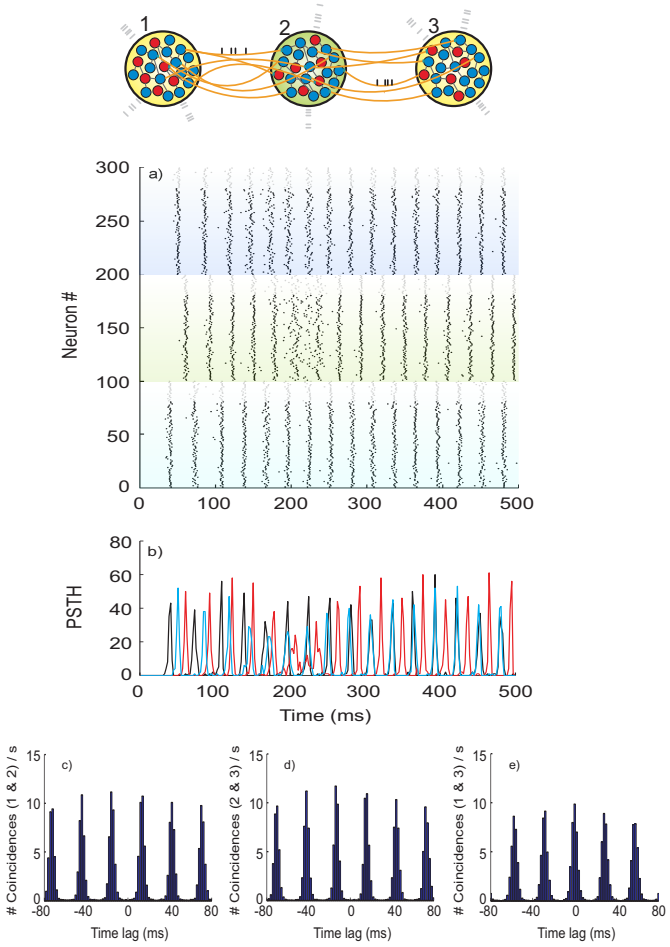

Figure 2.4. Dynamics of three unbalanced ($g = 3.5$) large-scale networks interacting through dynamical relaying. Panel a): raster plot of 300 neurons randomly selected among the three populations (Neurons 1-100 are from Pop. 1, 101-200 from Pop. 2, and 201-300 from Pop. 3). The top 20 neurons of each subpopulation (plotted in gray) are inhibitory, and the rest excitatory (black). Panel b): firing histogram of each subpopulation of 100 randomly selected neurons (black, red, and blue colors code for populations 1, 2, and 3, respectively). Panel c): averaged cross-correlogram between neurons of Pop. 1 and Pop. 2. Panel d): averaged cross-correlogram between neurons of Pop. 2 and Pop. 3. Panel e): averaged cross-correlogram between neurons of Pop. 1 and Pop. 3. At t=100 ms the external interpopulation synapses become active. Bin sizes for the histogram and correlograms is set to 2 ms. Inter-population axonal delays are set to 12 ms. Figure adapted from [99].

2.3 Robustness

Previously, we have shown the robustness of the system with respect to the balance of excitation-inhibition synaptic efficacy of the populations. Another feature of relevance is the interpopulation delay. In all of the dynamical relay studies of three random populations the mechanism showed to be valid for a wide range of possible physiological values from 2 to 20 ms. Insofar as the synchronization is observed to take place across many species (different amount of delay) and several development states (besides many possible other conditions) consequently the system of interest should also present robustness in respct to many factors. In particular, in the next section we present two main features which remains stable under controlled perturbations. One concerns to the network topology and the other takes into account a dynamical external input over the populations in a even more realistic case.

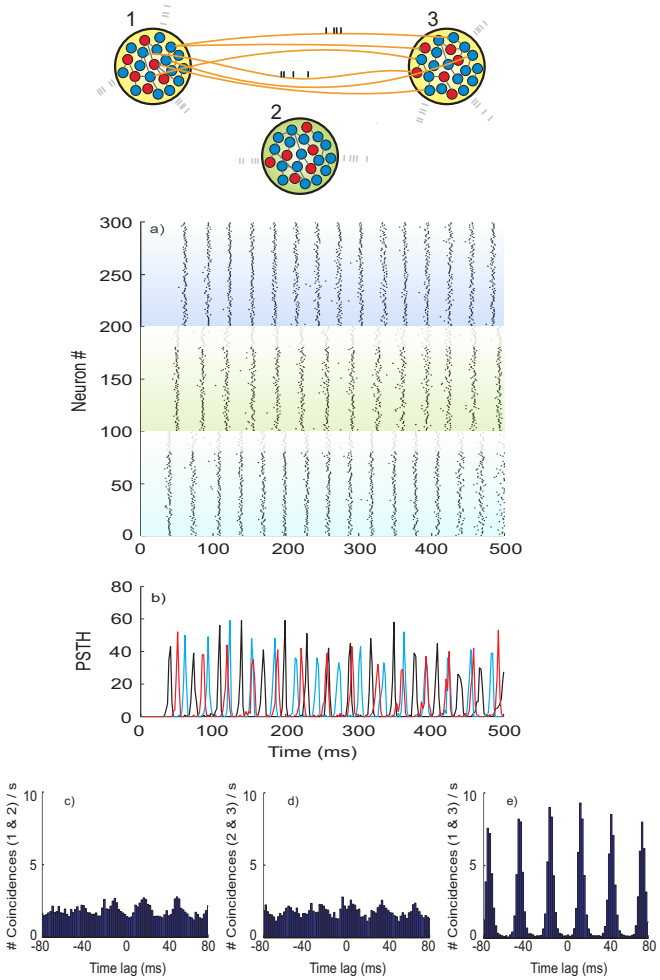

Figure 2.5. Dynamics of two unbalanced ($g = 3.5$) large-scale networks interacting directly. Population 2 is disconnected from other populations. Panel a): raster plot of 300 neurons randomly selected among the three populations (Neurons 1-100 are from Pop. 1, 101-200 from Pop. 2, and 201-300 from Pop. 3). The top 20 neurons of each subpopulation (plotted in gray) are inhibitory, and the rest excitatory (black). Panel b): firing histogram of each subpopulation of 100 randomly selected neurons (black, red, and blue colors code for populations 1, 2, and 3, respectively). Panel c): averaged cross-correlogram between neurons of Pop. 1 and Pop. 2. Panel d): averaged cross-correlogram between neurons of Pop. 2 and Pop. 3. Panel e): averaged cross-correlogram between neurons of Pop. 1 and Pop. 3. At t=100 ms the external inter-population synapses become active. Bin sizes for the histogram and correlograms is set to 2 ms. Inter-population axonal delays are set to 12 ms. Figure adapted from [99].

2.3.1 Closed motif

The Closed motif is build by connecting populations 1 to 3 of figure 2.1. It introduces a directed connection between populations (1,3) with variable strength (measured as the number of synaptic input received by both population). Such study is justified since many of the cortical populations happen to be connected. In fact, there exists much more cortico-cortical connections than connections with other subcortical parts. Therefore it would be useful to understand the dynamics when all the populations belong to the cortex.

The results we find were very similar for both the balanced and the unbalanced cases. In general, we expect to see synchronization of populations 1 and 3 for synaptic strength of the direct

connection (1-3) less than the other ones (1-2 and 2-3).

2.3.2 Asymmetric input

In natural condition we don't expect the external incoming activity over the involved populations to be equivalent. Rather an asymmetric amount of stimulus may drive the populations of neurons. Therefore we check whether the results previously described maintain in such asymmetric cases. Moreover we looked for how much asymmetry is allowed in order to guarantee the dynamical relay effect to occur.

In opposition to the closed motif case, the asymmetric input have very different robustness for the balanced and the unbalanced populations. In particular the former displays more robustness, i.e., the dynamical relay do synchronize the outer populations for almost any asymmetry. The only condition which must be satisfied is that the three population should be active, in a sense that each neurons should spike at least some times per second. Due to the interpopulation connections the populations activity couple themselves which generate lag free synchrony of populations 1 and 3.

On the other hand, the unbalanced case is much more sensible to the input asymmetry. Accordingly we found the dynamical relay to be effective for asymmetries smaller than 10% of the input in the outer populations. Even when they are not on phase, the neurons in any of the populations are synchronized.

2.4 Zero-lag synchrony discussion

In this chapter we presented a network topology that enhances zero-lag synchronization of distant populations of neurons. We showed that the generalization of three neurons to three populations of neurons is possible to occur. Two populations of neurons can became synchronized if instead of been directed connected, they are coupled reciprocally to a third central population. We compare two different population dynamics. One involves the balanced population, which does not go into an oscillating regime until the full interpopulation connections take place. It produce an interesting effect of population synchrony out of disordered activity. The second case already deals with oscillating populations which are conduced to an isochronous phase relation of the outer populations. Our results suggests that such topology may contribute to the large-scale synchronization phenomena reported in several experiments as described in the introduction, see section 1.4.1.

The network motif highlighted here has the characteristic of naturally inducing zero-lag synchrony among the firing of two separated neuronal populations. Interestingly, such property is found to hold for a wide range of conduction delays, a highly convenient trait not easily reproduced by other proposed mechanisms, which have a more restricted functionality in terms of axonal latencies. Regarding its physiological substrate, the associative thalamic nuclei have the cortex as their main input and output sources and seems to represent active relay centers of cortical activity with properties well suitable for enhancing cortical coherence [113]. The advantage of this approach in terms of axonal economy, specially compared to an extensive network of fast long-range cortical links, is overwhelming. Ongoing research is being directed to a detailed modeling of the interaction between cortex and such nuclei with an emphasis in investigating the role of axonal limited conduction velocity. From the experimental side the relatively well controlled conditions of thalamocortical slice experiments, allowing for the identification of synaptically coupled neurons and cell class, might be a first step for testing whether the topology investigated here provides a significant substrate for coherent spiking activity. Another important issue is how the dynamic selection of the areas that engage and disengage into synchrony is achieved. It has

been hypothesized that a dynamically changing coherent activity pattern may ride on top of the anatomical structure to provide flexible neuronal communication pathways [114]. Based on the properties formerly reviewed subcortical structures such as some thalamic nuclei might be promising candidates to play a role in regulating such coherence and contribute to the large-scale cortical communication.

In order to test the efficacy of the thalamus as the relay population in the thalamocortical circuit we create another network topology which include several elements of such network. Our goal is to extend the zero-lag population synchrony presented in this chapter to a more physiological faithfully system. The thalamocortical study is discussed in the next chapter.

Chapter 3

Thalamo-Cortical Circuit

"Only those who attempt the absurd will achieve the impossible."

– M. C. Escher

The Thalamus receive all sensorial information and has a fundamental interaction with many cortical regions. Such interaction happens in the thalamo-cortical circuit. From the study exposed in the previous chapter one wonders whether the central population could be the thalamus itself. It is placed in a central region and has an almost constant temporal latency between thalamic nuclei irrespectively of the distances. The different distance is compensated by different velocity conductions due to myelination of axon fibers [115]. Therefore it reproduces the ideal conditions to allow zero-lag synchronization of different cortical areas even in the presence of large conduction delays.

The two brain areas of interest here (Thalamus and Cortex) have been subjected to an extensive study [6, 104, 107]. In order to build a thalamocortical circuit we included several physiological known properties and maintained the whole system in an acceptable parameter space region. We build a large neuronal network to reproduce faithfully a small piece of the thalamocortical circuit.

The three populations structure was shown to be able to induce lag-free synchronization which is found in several experimental conditions. However, the synchrony effect is not necessary a blessing. Indeed it is currently in research ways to reduce generalized synchronization, which is one of the challenges for epileptic patients. It is important to clarify the difference between synchronous and asynchronous states. The first have been noticed to give rise to communication of separated brain areas but it has to be somehow dissolved into asynchronous states. Consequently it becomes necessary to control the dynamical brain state. In this chapter we present a thalamocortical model which is not only capable to generate zero-lag synchronization of separated brain areas but also controls the transition between on-off dynamical synchronized states.

The next section describes the thalamocortical circuit we used. It has many variables, so analogous to the previous chapter study, any result must be sufficiently robust to make sense. Moreover those synchronization properties are found to be independent of many elements such as brain size or age. We continue describing the results and the analysis developed to find more information in a very noise situation. Finally, we discuss the results highlighting the most important features along with suitable explanation.

3.1 Network description

The thalamus has a complex structure. In this model we consider it as been made of two parts. Each one is a population of I&F neurons in our model (section 1.3.1). Therefore, now we have two populations to play the central relay station role in the thalamocortical dynamical relay. One is the dorsal thalamus, from now on we are going to call it as thalamocortical (TC). It is modeled as a random network of only excitatory neurons. The second part of Thalamus stands for ventral thalamus, here we are going to call it nuclei reticularis (RT). It has only inhibitory neurons which is also modeled as a random network. Both cortical populations (CO_1, CO_2) are also random networks themselves.

All neurons obey the following dynamics: starting from the reset potential of $V_r = 10$ mV the membrane potential V evolves by means of the synaptic currents up to the time when the potential of the i-th neurons reaches a threshold of 20 mV, value at which the neuron fires and its potential relaxes to V_r . The potential is clamped then to this quantity for a refractory period of 2 ms during which no event can perturb this neuron.

The two central populations are bidirectionally connected with two cortical populations. The network is built like the scheme displayed in fig 3.1. Once more we numerically simulated the whole system using the neuronal simulator NEST [109–112].

The circuit has many different parameters involved, so we are going to describe them in two parts: one for the populations construction and the other to describe the way the populations interact with each other.

Intra-populations description. The intrapopulation elements are those which depend only of the parameters of the population itself.

- **cortexes (CO_1 and CO_2):** Each one of the cortical populations is composed of $N = 1000$ elements with 80% of excitatory and 20% of inhibitory neurons. They are sparsely connected, i.e., the connectivity is of 10%, which means that each neuron contribute with PSP of 100 randomly chosen neurons of the same population. The populations are internally balanced what means that each neurons receive the same amount of excitatory $j_e = 0.05$ mV and inhibitory $j_i = -0.2$ mV current from other neurons of the same population, i.e., $g = 4$. The membrane time constant is $\tau_{mem} = 20$ ms and the delay of each internal synapse is $\tau = 1.5$ ms.
- **TC:** There are 200 neurons in TC, sparsely connected with connectivity of 10%. They are all excitatory with $j_e = 0.05$ mV and delay of $\tau = 1$ ms. Their membrane time constant is $\tau_{mem} = 15$ ms.
- **RT:** There are 40 neurons in RT, with connectivity of 60%. They are all inhibitory with $j_i = -0.0735$ mV and delay of $\tau = 2$ ms and their membrane time constant is $\tau_{mem} = 25$ ms.

Different parameters of neurons properties such as τ_{mem}, τ and j as well as the number of neurons belonging to each population were taken to mimic physiological properties and values.

Extra-populations connectivity. Those are the parameters to describe the way neighbor populations connect and the intensity of the contacts.

- **COs to TC and RT (c_1):** 1% connectivity, delay of $\tau_1 = 8$ ms and synaptic efficacy of $j_1 = 0.05$ mV.

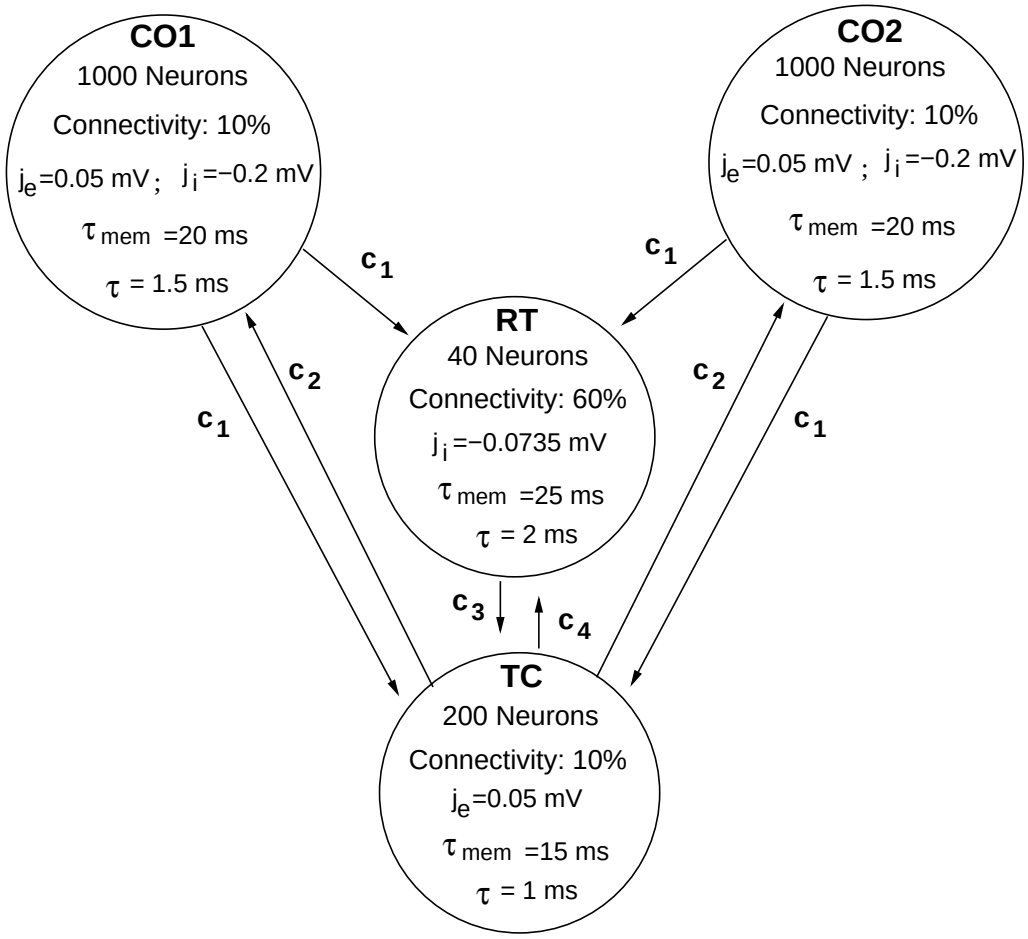

Figure 3.1. Thalamocortical network. The populations are randomly connected with physiology faithfullness parameters, topology and connectivity. The two cortical ones are balanced with both excitatory (80%) and inhibitory (20%) neurons. All of them are sparse with exception of RT. The thalamus can be considered as both RT and TC together, which is also balanced when considered as a whole. The extra populations connectivity are described by the following parameters: c_1 with 1% connectivity, delay of $\tau_1 = 8$ ms and synaptic efficacy of $j_1 = 0.05$ mV; c_2 has 10% connectivity, delay of $\tau_2 = 5$ ms and $j_2 = 0.05$ mV; c_3 has 80% connectivity, delay of $\tau_3 = 2$ ms and $j_3 = -0.0735$ mV; c_4 has 1% connectivity, delay of $\tau_4 = 2$ ms and $j_4 = 0.05$ mV. The interpopulation connectivity is defined as the ratio of the number of postsynaptic connections each neuron of the first population has in the second by the number of neurons in the second population.

- **TC to COs (c_2):** 10% connectivity, delay of $\tau_2 = 5$ ms and $j_2 = 0.05$ mV.
- **RT to TC (c_3):** 80% connectivity, delay of $\tau_3 = 2$ ms and $j_3 = -0.0735$ mV.
- **TC to RT (c_4):** 1% connectivity, delay of $\tau_4 = 2$ ms and $j_4 = 0.05$ mV.

3.2 Results

The On-off dynamical control of synchronization states is done with only one variable, the external stimulus received by one of the central population. Next we show simulation results in some runs for different values of external stimulus to exemplify the mechanism. In addition, we generalize the results via statistical studies of cross-correlogram analysis over 100 different realizations. Therefore we were able to classify the patterns found for the different conditions. Our

results suggest that high frequency oscillations (beta and gamma ranges) commonly present in awake cognitive tasks could be induced by dynamical relay of the thalamocortical interactions.

3.2.1 Single trial experiment

This section presents the results of a few trials of simulations. In order to realize the behavior of the system we show in figure 3.2 the raster plot of 25 neurons of each population randomly chosen. The activity of excitatory neurons of the cortical regions (CO_1, CO_2) are in pink while the inhibitory neurons are in blue. The activity of RT region is displayed in green and the spikes of TC are in red. The external stimulus over the cortexes (CO_1, CO_2) and RT populations are fixed at $\nu_0 = 4.5$ Hz and the external stimulus over TC is specified in each case. The internal connectivity starts at an early negative time in the graphic scale of fig 3.2 while the interpopulation connectivity is turned on only at time 0 ms to avoid trivial initial conditions. We keep the network and all parameters fixed as in the previous description, section 3.1 and fig. 3.1. For $\nu_{TC} = \nu_0$ (top left panel) the number of coincidences of activity of neurons in CO_1 with respect to neurons of CO_2 is the same as expected by chance, i.e., the two cortical areas are not synchronized. However, for values of $\nu_{TC} > \nu_0$ synchronization of the two cortical areas appears, see the other panels. Indeed the number of coincidences seems to increases for higher values of external input over TC population (ν_{TC}).

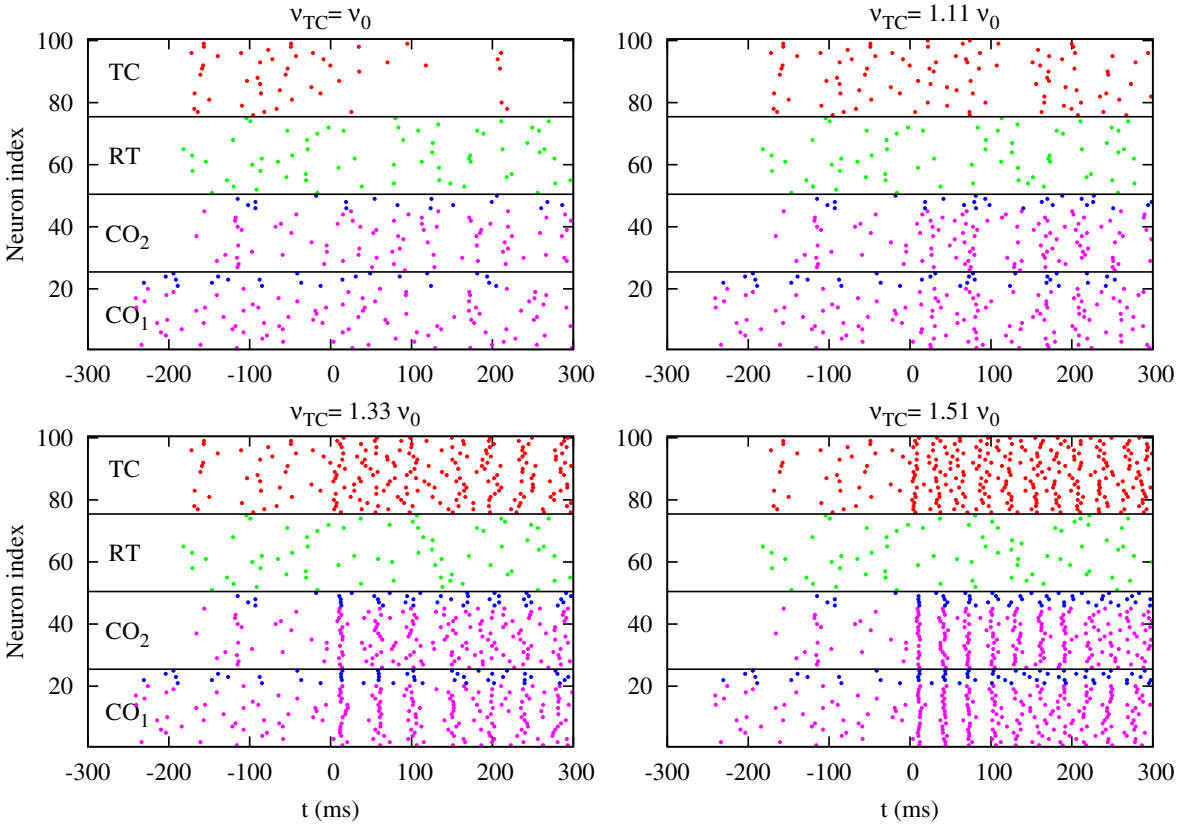

Figure 3.2. Raster plots of 100 neurons randomly chosen with 25 of each population. The network is built like the scheme of fig. 3.1 in a case that RT and the cortexes populations receive external stimulus of $\nu_0 = 4.5$ Hz while the rate in TC is shown on top of each graphic. The interpopulation connectivity is turned on at time 0 ms. The activity of excitatory neurons of the cortical regions (CO_1, CO_2) are displayed in pink while the inhibitory neurons are shown in blue. The activity of RT is plotted in green and the spikes of TC appear in red.

The following section describes a way to quantify the lag-free synchronization intensity of the two cortical areas. It was done by taking into account similarities in the activity patterns of many simulation with different networks and noise realizations.

3.2.2 Crosscorrelogram analysis over several realizations

Here we describe the way used to measure the synchronization quality of the cortical populations via the crosscorrelogram averaged over 100 different realizations. Hence it is possible to get smooth graphics of very noise variables such as the number of spike coincidences of two random neurons, one of each cortical population.

The crosscorrelogram corresponds to the mean number of spike coincidences of 300 pairs of neurons randomly chosen located at different cortical areas during the time period ranging from 1 s to 2 s of simulations to avoid transient period influence. It is measured as a function of the time difference of the coincidences. Subsequently, it pass throw another average process over the 100 realizations giving rise to the average crosscorrelogram.

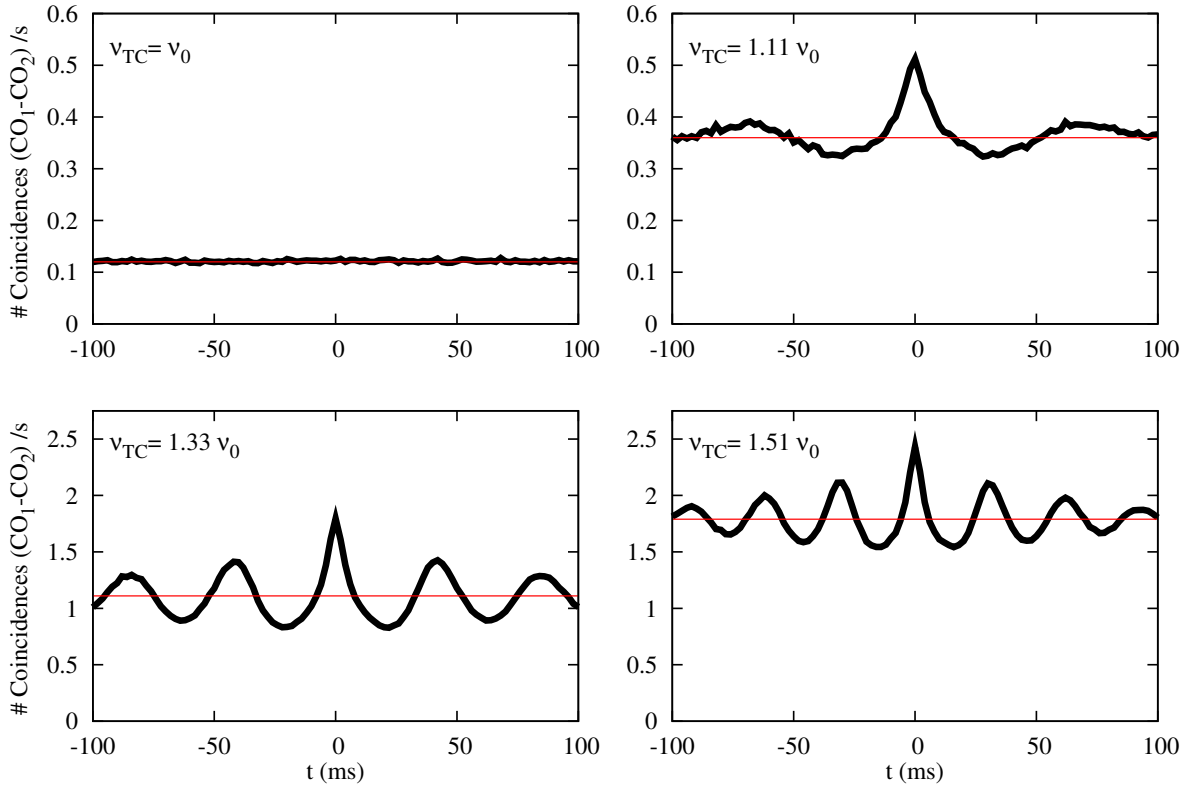

Figure 3.3. Crosscorrelogram average over 100 runs. Each crosscorrelogram corresponds to the mean number of coincidences of 300 pairs of neurons located at different cortical areas. The measure was done from 1 s to 2 s of simulations to avoid transient period influence. The red line stands for the mean value of the coincidences, which is defined as the noise of the signal-noise ratio. The first panel (top-left) shows no signal at all. A little increase of 11% produce a well defined peak at zero-lag (top-right). When TC receives 33% more external activity than the others populations (bottom-left): the maximun value (at time zero) is extremely larger than the mean value. For even greater values of ν_{TC} the periods of the oscillations shrink (bottom-right). The curves were obtained for $\nu_0 = 4.5$.

Figure 3.3 presents the average crosscorrelogram for the system described in sec. 3.1 with the

same external stimulus of the previous raster plots of fig. 3.2. The red line stands for the mean value of the coincidences or the value expected by chance. As we said before, the first panel (top left) shows no signal at all of synchronization, there is no more coincidences than what is expected by chance.

However a small raise (about 11%) of the external stimulus incoming on the TC population already produces an interesting shape for the crosscorrelogram curve with a sharp maximum value at $t = 0$. It means that most of the coincidences detected in neurons of the two cortical populations corresponds to simultaneous spikes of this pair of neurons located at different cortical areas.

For even higher values of the external activity incoming to the TC population, say $\nu_{TC} = 1.33\ \nu_0$, the average crosscorrelogram becomes even smother with periodic activity which was very difficulty to detect in the raster plot. More importantly, the peak at zero-lag is well pronounced.

At last, the bottom right graphic has a larger input over TC and the period happen to be clearly shorter than in the previous case (note that ν_{TC} exceeds ν_0 by more than 50% in this case).

Next we proceed taking more information of the average crosscorrelogram of fig. 3.3. Up to this point we have only considered the same external stimulus ν_0 incoming into RT and the cortical population. Nevertheless the following features of fig. 3.4 show a structurally similar behavior for other values of ν_0. Hence it can be interpreted as a robust result of this thalamo-cortical model.

In the top left panel of figure 3.4 it can be sen that the number of lag-free coincidences of the two cortical regions per second is a monotonic function which increases as a function of the TC external activity ν_{TC}. This happens because TC sends more excitatory synapses to the cortical areas. Therefore there are more cortical activity which gives rise to a larger number of coincidences.

Although the number of coincidences increases it can be noticed that the signal to noise ratio does not behave in the same way, top right graphic of fig. 3.4. To quantify the efficacy of the extra activy reaching TC population to induce lag-free synchronization into the cortical populations we use the $\frac{signal - noise}{noise}$ where the two variables are defined as following:

- signal: the number of coincidences at zero-lag in the average crosscorrelogram (the peak in the synchronous crosscorrelograms of fig. 3.3);
- noise: The mean number of coincidence taking into account all delays of the average crosscorrelogram (red line of fig. 3.3) .

In this case, see fig. 3.4 top right panel, we do not find a monotonic function neither a pronounced peak but instead we see a plateau, or a considerable region in which ν_{TC} exceeds ν_0 in a range from 10% to 80% independently of the external stimulus ν_0.

A careful look of the average crosscorrelograms shows the periodic behavior of the cortical populations. This allows us compute the period of the oscillations as a function of ν_{TC}. This result is shown in the bottom left panel of figure 3.4 which shows an exponential decay. Despite the fact that different curves represent different systems, for large values of ν_{TC} all of them colapse into the same curve.

Once we have the period of oscillation it is straightforward to make the same picture for the frequencies, as in figure 3.4 (bottom right panel). Now, we can compare the frequency of oscillations of the two cortical regions with the natural frequencies of oscillations which have been since a long time already characterize. The range stated before in which ν_{TC} exceeds ν_0 in a range from 10% to 80% allows the cortexes regions to oscillate in a large frequency band, from high beta to gamma values. Those are the same as the ones found in cat experiments which involve attention in awake individuals in high cognitive tasks.

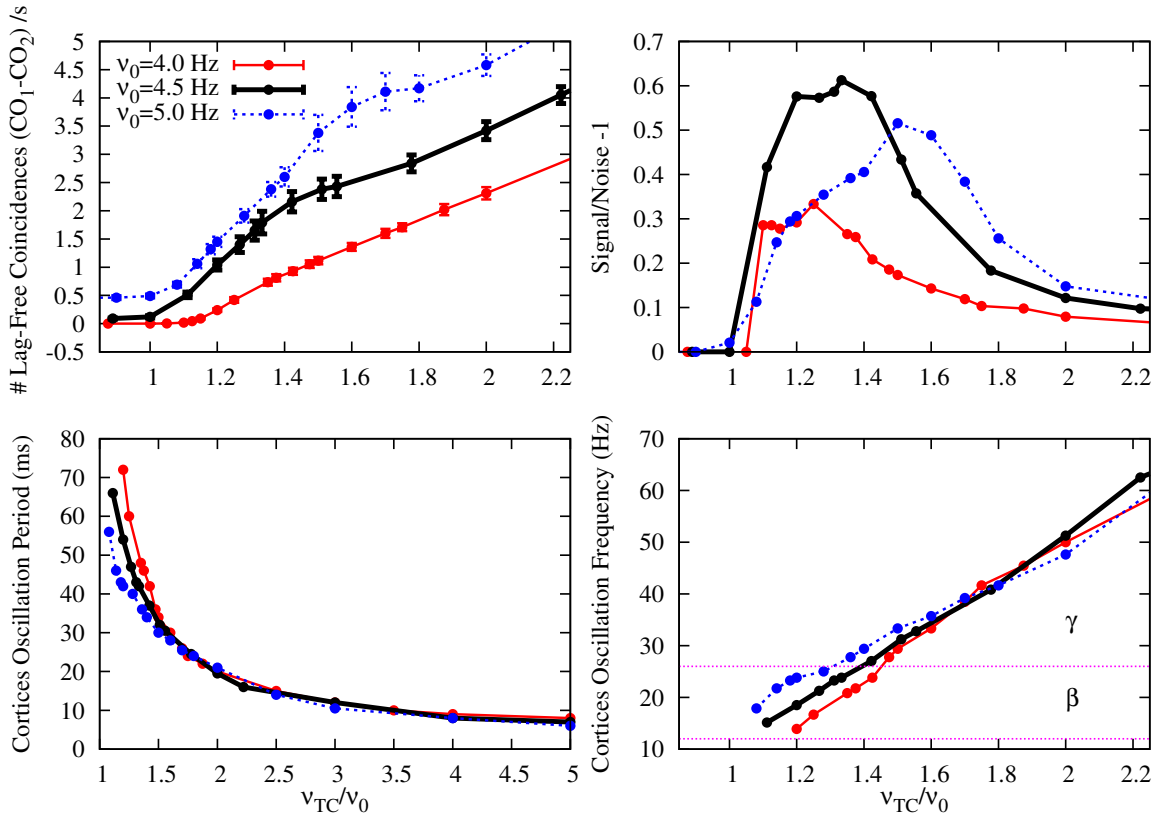

Figure 3.4. Average crosscorrelogram analysis. Top-left: the number of lag-free coincidences between the cortical populations as a function of the external input $\frac{\nu_{TC}}{\nu_0}$ incoming into TC population appears as a monotonous increasing curve. Top-right: the $\frac{signal-noise}{noise}$ shows a region of maximun values rather than a simple increasing function. Bottom-left: The mean period between next peaks of the crosscorrelogram as a function of $\frac{\nu_{TC}}{\nu_0}$ converge to the same curve for all values of ν_0 tested. Bottom-right: The frequency of oscillation of the cortical areas fits in the beta and gamma natural frequency ranges of oscillation.

3.3 On-off synchronization of separated cortical areas

We have described the simulation results involved in a simple but biophysically realistic thalamocortical model. Otherwise from the simpler network motif studied in the previous chapter (2) the thalamocortical network ,described in figure 3.1, is not only able to synchronize the cortical regions but also control whether or not it is supposed to occur.

An example of transitions between synchronized-desynchronized states under external modulation of the TC activity are shown in figure 3.5. Only by varying ν_{TC}, as shown in the top panel, it was possible to generate synchronous and asynchronous patterns. The raster plot is analogous to that of figure 3.2 which represent the activity of 25 neurons randomly chosen of each population. Correspondingly, the synchronous activity of the cortex regions occur during higher input in TC regions while the asynchronous activity can be induced when $\nu_{TC} \lesssim \nu_0$. This is an extreme case in which the synchrony is switched from zero to its maximal signal to noise value. Indeed, the system supports several intermediate situations.

Immediately after the reduction of ν_{TC} (for instance at 400 ms) TC happens to have very few activity. The reason for the phenomenon is because TC was previously (say from 200 ms to 400 ms) receiving more activity and causing more spikes which also excites more RT population. In

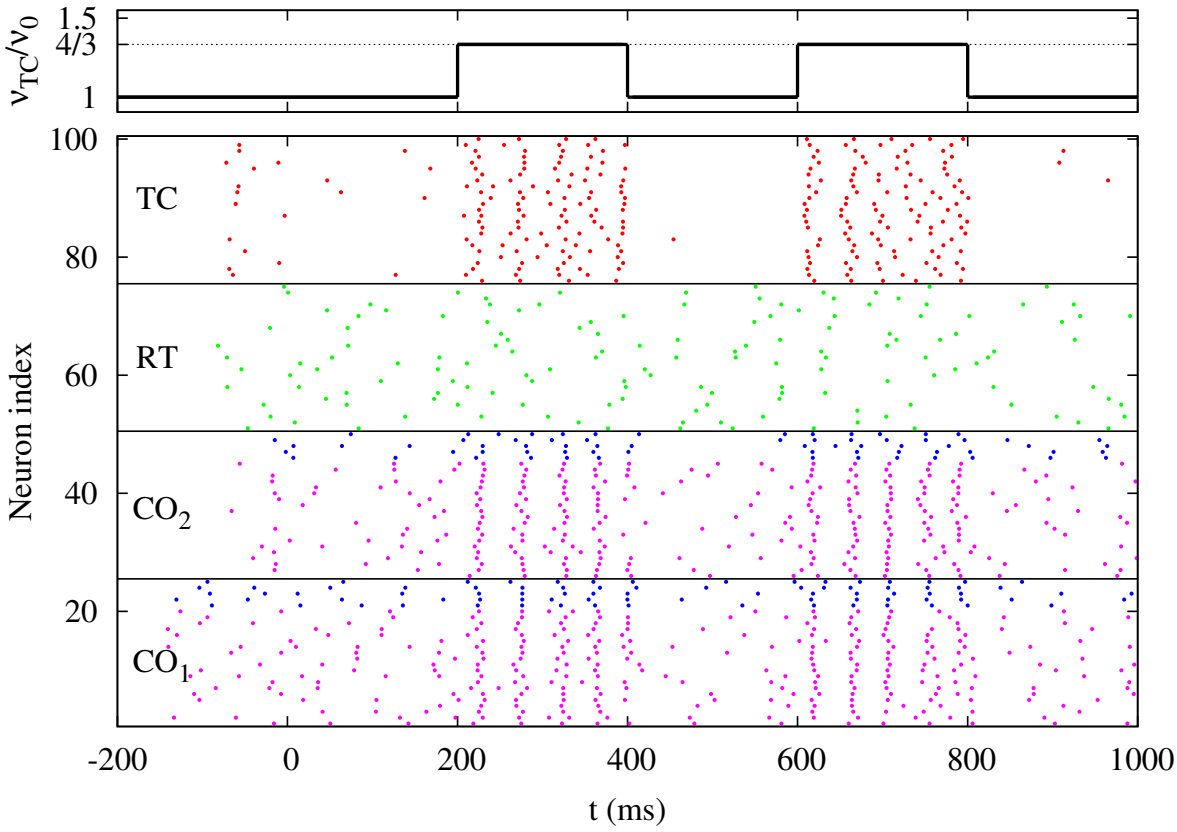

Figure 3.5. On-off synchronization example. The synchronization of the cortical regions responds according to the external input over TC (top picture). The synchrony is not allowed in the system for low values of input ν_{TC} over the input to rest of the populations ν_0, for instance $\frac{\nu_{TC}}{\nu_0} = 1$ from 0 ms (when the extrapopulations connections are started) to 200 ms or (400 ms -600 ms) or (800 ms-1 s). However the synchrony does take place for higher values of input, say $\frac{\nu_{TC}}{\nu_0} = \frac{4}{3}$. Therefore it corresponds to a possible case of On-off synchronization control of the cortical regions via switching the external input over TC. Since such innervation comes from both bottom (sensorial areas) and top regions (cortical areas), our result suggests that both of them play an important rule in the task of controlling cortical synchrony.

their turn, the neurons of RT inhibit even more the TC population. Therefore when the external driving over TC falls the inhibition is still high and consequently the firing rate of TC neurons decrease.

Once the network is constructed a switching of the external input over one of the two central populations may turn on and off the communication between the cortical populations. In particular, the case $\nu_{TC} = \nu_0$ happens to induce no synchrony among cortical populations. But for higher values of ν_{TC}, say for instance $\nu_{TC} = \frac{4}{3}\nu_0$, the central population is allowed to play a very effective role in the thalamocortical network whose consequence is the phase coupled cortical synchronization.

The dynamical relay showed previously, chapter 2, has a very special feature that could be noticed by a careful reader. The central population (2) is out of phase with respect to the other two in both the balanced and the unbalanced cases. However, in the thalamocortical circuit we see the TC oscillating activity is delayed but a time which exactly amounts the delay coupling. This result can be seen in figure 3.6. Where it is shown the crosscorrelogram of TC with respect to one of the cortical populations, in this case CO_1. In particular the maximun number of coincidences occur around 5 ms which is the delay of connections c_2 from TC to cortex population.

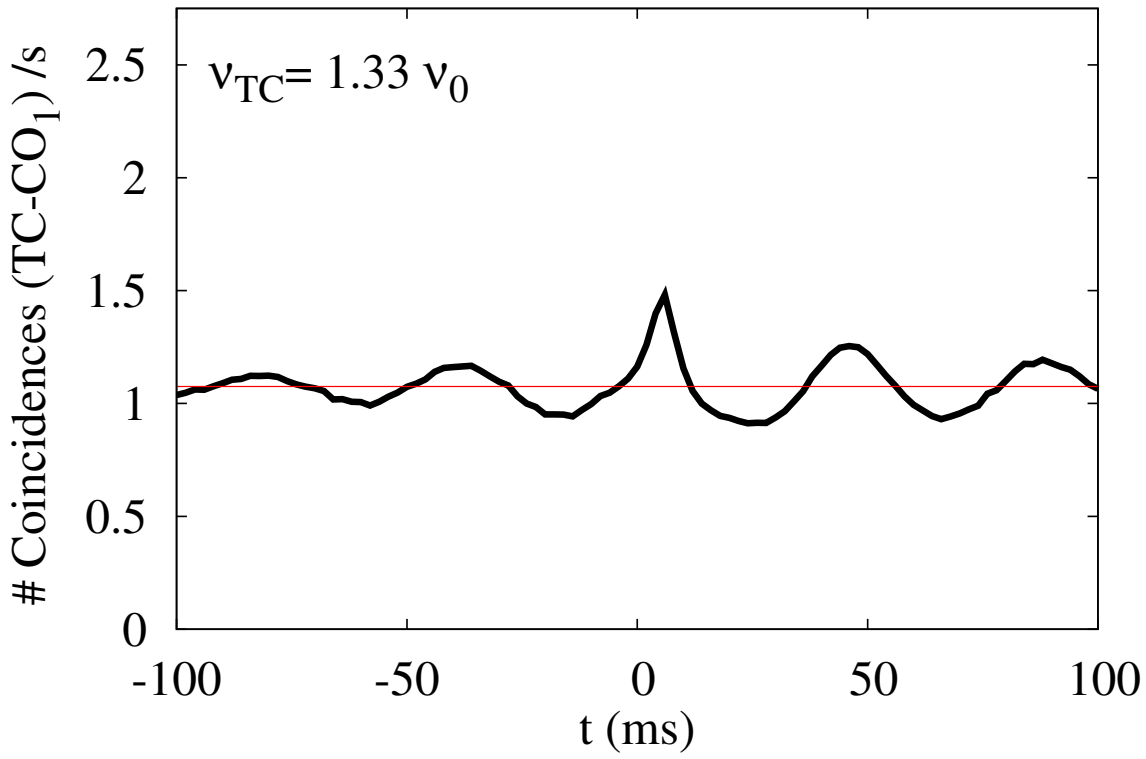

Figure 3.6. Crosscorrelogram average over 100 runs among TC and CO_1 regions. The maximun number of correlations between neurons of TC and CO_1 populations occurs around the delay of that connectivity, ($c_2 = 5$ ms), see fig. 3.1. The curve present an asymmetric shape which means that the TC activity influences more CO region than the other way around.

One condition to the dynamic relay to occur is that the elements involved must be in the oscillatory regime. In the thalamocortical circuit, the role of the relay station is mainly played by the TC population (because it sends back the synapses to the cortical populations), so the system goes throw an excitable-oscillatory phase transition depending on the external driving ν_{TC} over it. Therefore such transition induce the system to go into the synchronous-asynchronous states instantaneously because the dynamical relay only works for oscillatory elements.

In conclusion, we have presented a thalamocortical network with the thalamus as the central dynamical relay station. It can be very effective to control the cortical synchrony in a realistic time scale without any dependence of slower dynamic elements such as plasticity. The TC region is innervated by both bottom-up (ν_{bu}) and top-down (ν_{td}) excitation. Namely, from sensory systems or activity coming from cortical areas respectively. Since both types of stimulus contribute to the change the control variable ($\nu_{TC} = \nu_{bu} + \nu_{td}$) we conjecture that the two of them are important. It is worth mention that our simple argument is against a previous speculation of P. Fries [114] who stated that only top-down activity should control the cortical coherence in the context of the binding problem. Moreover we provide an explanation, throw identification of the probable mechanism, for a phenomenon that have been already seen experimentally, and reported recently in a paper called "Synaptic background activity controls spike transfer from thalamus to cortex" of Jakob Wolfart et al. [107]: *"these findings support the idea that corticothalamic synapses have a powerful role in controlling information transfer by the thalamus. It is known that corticothalamic*

feedback constitutes the primary source of synapses in the thalamus, one order of magnitude larger than synapses from peripheric axons. Despite this anatomical fact, the feedforward view is still prominent: the thalamus is often considered as a 'relay' of information to cortex. By regulating the intensity of background activity, the cortex could exert a fast and efficient control of the thalamic relay, through instantaneous adjustment of gain and of bursting probability, which may be related to focused attention mechanisms".

In summary, here we presented a thalamic-cortical model to show that cortical lag-free oscillations can be obtained throw thalamic relay despite of the transmition delays among distant regions. More importantly, we found a control to turn on and off such synchronization mechanism depending only on external input activity innervated into dorsal and ventral thalamus populations. Correspondingly, it suggest that both bottom-up and top-down incoming activity to thalamus play an important role into the attention process involved in the binding problem.

Chapter 4

Conclusions and Perspectives

"One never notices what has been done; one can only see what remains to be done."

– Marie Curie

We have studied the dynamical relay phenomenon in neuronal population. It was a generalization of the minimun three neuron system originally formulated. We modeled large neuronal populations by random networks of integrate and fire neuron. For these identical populations, we also checked that the minimun motif to produce dynamical relay involves three elements. We have also modeled the thalamocortical circuit with the thalamus playing the role of the relay population. Our goal was to come closer to real CNS architecture and see how far can the dynamical relay sustain when we include more physiological details.

4.1 Conclusions

We have shown a successful bottom-up approach in which extremely simple structures (introduced into section 1.5) provides inspiring motivations. Our goal is to bring this message to the neuroscience community with our answer to a possible mechanism to guarantee zero-lag synchronization. We believe this methodology should be more explored specifically in the study of very complex systems such as those found in neuroscience.

The population synchrony problem has many nonlinear elements which involves multiple time scale interaction and two types of connections (excitation and inhibition). Nevertheless it was shown to allow a generalization of the dynamical relay from the three neurons motif to the population structure for a wide range of parameters. This result validates the dynamical relay mechanism as a possible way to induce zero-lag synchrony of separated neuronal populations. Several proposals have been made based on inhibitory connections, gap junctions, canonical circuits or synaptic plasticity however none of them were sufficiently robust to mediate zero-phase synchrony for long transmission delays involving only excitatory connections.

The minimal condition to produce lag-free synchrony among two distant regions throw the dynamic relay is to have another central population connecting the other two. Such coupling can be effective even for large delays systems or when the isolated populations present an isochronous activity.

We also studied carefully a thalamocortical circuit. It was beforehand a promissing candidate which has the thalamus region as the central relay population. The model is able to describe the complex thalamocortical interactions in a faithfully way. We believe to have found an optimal

level of description which allowed us to detect some of the main aspects of the thalamocortical network.

Contrary to what has been previously hypothesized [114], the great simplicity of such an important key control tells us that both top-down and bottom-up activity have important functions in this dynamical mechanism. Namely, this attention command satisfy our intuition on the cocktail party effect, i.e., one expect to be able to keep a conversation even when many other noise and external stimulus are impinging on herself or himself. Nevertheless, either an internal decision (top-down), for instance to go for another drink, or an incoming activity due to an external noise or some light effect (bottom-up) may act to switch from the previous synchronous state to an asynchronous one that might, eventually, goes back again to the synchronous state. The ability to come back to the asynchronous state even despite the fact that anatomical connections are constant at this time scale is of fundamental importance to prevent a catastrophically fail of recurrent inhibitions which might drive the whole system to a generalized epileptic oscillatory dynamical phase [116].

Our study also provides a specifically phase relation, that is to say, the thalamus (central node) appear out of phase comparing to the two cortical in phase synchronized populations. Such phase difference is due to the delay in the connections. Remarkably, the study of the simpler network of three populations also shows in many situations different phases in the relay population. It is in many situations a signature of the dynamical relay which can be compared with experiments. Moreover, some reports have already been made concerning this phase relation property of the thalamocortical circuit.

We hope these results will guide new experiments. It would mark a great step forward to understand the very important and always present cognitive function of attention. Consequently, to consolidate the function of distant populations synchronization into the binding problem.

4.2 Perspectives

While for the physics community the thalamocortical study presented here already is of a high complexity with many variables and parameters it is still considered a toy model for the neuroscience community, specially those interested in this circuit.

For that reason we believe it could be interesting a study which includes even more characteristics. In particular, more regions could be described focusing on whether or not some of the cortical regions connected to the thalamus are going to synchronize

In order to check how much of the binding problem is due to the dynamical relay many experimental verifications are still needed. In particular, the phase relation of the different synchronized areas might be one of the features of interest, research on simpler models such as artificial neuronal plates that might also help in understanding their activity and possibly its synchrony states and causes.

An important point not included in this work and that we would like to elucidate is to investigate deeper the parallel between the synchronous to asynchronous states of the cortical regions connected with the thalamus and another transition already described which involves only the thalamic dynamical state of tonic or bursting modes. The former is supposed to transmite the incoming information in a “more linear way” thus providing good precision. It also involves more excitatory activity in the thalamus than the bursting mode. This latter is characterized by the thalamic activity in bursts mode. Essentially it happens in the thalamus when the neuron is inhibited, with the membrane potential below the rest state, and then receive enough excitatory input to generate spikes. In certain conditions, because of the dynamics of the ionic channels which depends

on the membrane potential, bursts are generated. In such state, the thalamus is believed to communicate in a less precised way with the cortex. The last difference between them concerns to when the modes are expect to occur. In general, the tonic mode happens for awake and attention states of the brain which can also be related with the high frequencies of oscillation in high beta and gamma ranges, as those we got for the frequencies of oscillation of the cortical areas induced by high signal to noise ratio of TC region (figure 3.6). On the other hand a bursting state occurs more often in sleep animals. For this purpose, one possible way is to change the I&F model to another one, for instance the integrate, fire and burst model (IFB) [42], or others [47, 48, 117, 118].

A different point of view is also possible. Specifically, our success in such complex system was only possible after the previous study on simpler models. It is a bottom-up approach traditionally used in physics. So, to search for new interesting behavior on the few neurons level could provide more successful generalizations.

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