Universitat
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FINAL DEGREE PROJECT

EFFECT OF EXCITATION/INHIBITION BALANCE ON THE DYNAMICS OF A NEURONAL POPULATION

Cristina Martí Solana

Degree in Physics

Faculty of Science

Academic year 2022-23

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Summary

Modelling neural networks allows us to understand some of the dynamics observed in brain regions. To achieve plausible results, it is necessary to understand the functioning of individual neurons in order to build a computational model and to be able to reproduce essential features of neural networks such as the balance between excitation and inhibition. By modelling cortical networks, we intend to investigate the formation of clusters of depolarized neurons in the visual cortex and the antiphase synchronization of some regions of the entorhinal cortex.

Resum

La modelització de xarxes neuronals permet entendre algunes de les dinàmiques observades a regions cerebrals. Per aconseguir resultats plausibles es necessita comprendre el funcionament individual de les neurones per elaborar un model computacional i poder reproduir les característiques essencials de les xarxes neuronals com el balanç entre excitació i inhibició. Mitjançant el modelatge de xarxes corticals es pretén profunditzar en la formació de clusters de neurones despolaritzades al còrtex visual i la sincronització en antifase d'algunes regions de l'escorça entorínica.

Resumen

La modelización de redes neuronales permite entender algunas de las dinámicas observadas a regiones cerebrales. Para conseguir resultados plausibles se necesita comprender el funcionamiento individual de las neuronas para elaborar un modelo computacional y poder reproducir las características esenciales de las redes neuronales como el balance entre excitación e inhibición. Mediante el modelado de redes corticales se pretende profundizar en la formación de clusters de neuronas despolarizadas en el córtex visual y la sincronización en antifase de algunas regiones dela corteza entorrinal.

Introduction

Neurons exhibit a variety of dynamic behaviours, including rhythmic oscillations, transient bursts of activity, and sustained firing. These behaviours are the result of the interaction between the biophysical properties of the neuron and the inputs it receives from other neurons and sensory systems. Mathematical models of neurons as dynamical systems can be used to simulate the behaviour of neurons and to study how neural circuits process information. To understand physiological effects of the brain, the most complex network we know, is required to model neuronal populations at a large scale which need to be computationally efficient and also biologically plausible. A simplified model that captures the essential dynamics of a wide range of neurons in the brain while being computationally efficient is the Izhikevich model of a spiking neuron, proposed by Eugene Izhikevich in 2003. This model is often used to study a wide range of phenomena in neuroscience, including synaptic plasticity, oscillations, and spike-timing-dependent plasticity. It has also been used in machine learning and robotics as a building block for spiking neural networks.

Real neuronal population main characteristic is the E-I balance. It refers to the delicate balance between excitatory (E) and inhibitory (I) signals that regulate the activity of neurons in the network. Excitatory signals promote neural activity, while inhibitory signals reduce it. Maintaining a proper balance of E-I signals is crucial for the normal functioning of neural networks, as an imbalance can lead to a variety of neurological disorders such as epilepsy, autism, and schizophrenia. In healthy neural networks, the balance between E-I signals is maintained through a variety of mechanisms, including the regulation of neurotransmitter release, the expression of specific ion channels, and the coordination of network activity by local inhibitory neurons. Researchers have found that the E-I balance can be disrupted by various factors, including genetic mutations, environmental toxins, and ageing. Understanding the mechanisms that regulate the E-I balance in neural networks is a key area of research in neuroscience, and may lead to the development of new treatments for neurological disorders.

The main objective of this work is to explain and reproduce some features emerging of the E-I balance that take place in cortical networks such as the clustering activity on error neurons of the visual cortex and the role of modular organization in anti-phase oscillations of the layers 2/3

of the entorhinal cortex, by building computational cortical networks using Izhikevich model.

The first section is an introduction of some basic concepts of neuron modelling, its relation with dynamical systems and a mathematical analysis of Izhikevich model. The next section presents the necessary tools to build a computational cortical network in order to achieve the objective of this work in the two following sections. At the end there is an appendix chapter explaining the computational methods used and some complementary results.

Contents

1 Single neuron modelling

1.1 General structure of a neuron

A neuron is a specialised cell in the nervous system that is responsible for transmitting electrical and chemical signals. It is easily recognisable by its elongated and asymmetric structure (figure 1). The general structure of a neuron can be divided into three main parts: the dendrites, the cell body (also called the soma), and the axon:

- Dendrites: These are tree-like structures that extend from the cell body and receive signals from other neurons or sensory receptors. Dendrites are covered in tiny protrusions called dendritic spines that increase the surface area for receiving signals.
- Cell Body (Soma): The cell body is the main part of the neuron that contains the nucleus and other cellular machinery that keeps the neuron functioning. The cell body also integrates the signals received from the dendrites to determine whether the neuron should fire its own electrical signal.
- Axon: The axon is a long, thin structure that extends from the cell body and transmits electrical signals, called action potentials, away from the cell body to other neurons or muscles. Axons are covered in a fatty substance called myelin that helps to speed up the transmission of electrical signals.

At the end of the axon, there are specialized structures called axon terminals that communicate with other neurons or muscles through the release of chemical messengers called neurotransmitters. The point of contact between the axon terminal and the receiving neuron or muscle is called a *synapse*.

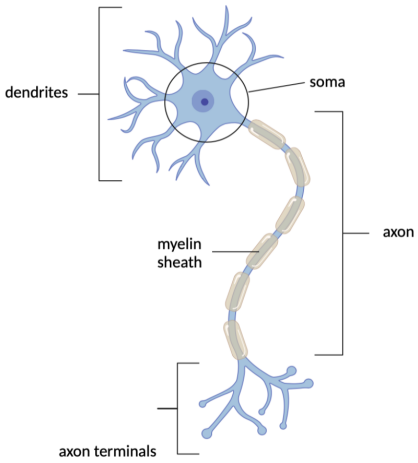


Figure 1: **Basic structure of a motor neuron.**

1.2 Membrane electrophysiology

The plasmatic membrane defines the cell and separates it form the exterior. Neurons are eukaryote cells with a phos-

pholipid bilayer membrane with embedded protein molecules that work as ionic channels between the interior and the exterior of the cell [1]. This channels create ionic currents through the membrane generating electrical activity and propagating it. Most of this currents involve sodium (Na^+), potassium (K^+), calcium (Ca^{2+}) and chloride (Cl^-) ions that have different concentrations inside and outside of the cell and create electrochemical gradients. On the extracellular medium there is a large concentration of Na^+, Cl^- and Ca^{2+} compared with the interior, where there is a high concentration of K^+ and negatively charged molecules.

In spite of the ion flow through ionic channels there are other kinds of ion transport that maintain the concentration asymmetry. The active transport of ionic pumps draw ions in and out of the cell, like the Na^+/K^+ pump that draws out three Na^+ for every two K^+ pumped in, maintaining the concentration gradient. There is also an effect of passive redistribution of charges, the negatively charged molecules attract K^+ into the cell and repel Cl^- favouring the concentration gradient.

Due to the concentration asymmetry through the membrane there is a charge asymmetry creating a voltage difference between the inside and the outside of the membrane called *membrane potential*. The membrane potential on a regular neuron with no signal in transit is called *resting potential* and is generated due to the expulsion of inside K^+ ions to the extracellular environment through non regulated K^+ channels in the plasmatic membrane powered by the concentration gradient of K^+. The entrance of Na^+ ions to the cytosol is thermodynamically favourable driven by the concentration gradient and also by the negative potential membrane inside the cell, nevertheless most part of the Na^+ channels in the plasmatic membrane are closed when cells are on rest. During an *action potential* some of these channels open allowing Na+ ions to move into the cell and depolarise the membrane [1]. As the cell membrane depolarizes, the voltage-gated sodium channels eventually reach a threshold level, triggering a sudden and massive influx of sodium ions into the neuron. This influx of positively charged ions rapidly increases the voltage inside the neuron, causing a rapid *spike* in electrical activity. After the action potential has been triggered, the voltage-gated sodium channels quickly close, and voltage-gated potassium channels open, causing potassium (K+) ions to flow out of the neuron. This outflow of positively charged ions repolarizes the cell membrane, restoring the negative charge inside the neuron and bringing the neuron back to its resting state. In some cases, the efflux of potassium ions

may briefly overshoot the resting state causing an hyperpolarization of the membrane potential, when this happens the neuron enters a *refractory period*, during which it is temporarily unable to generate another action potential.

The action potential then travels along the axon, jumping from node to node if the axon is myelinated, until it reaches the axon terminals. At the axon terminals, the action potential triggers the release of neurotransmitters, which communicate with other neurons or muscles.

1.3 Dynamics of two dimensional neuronal models

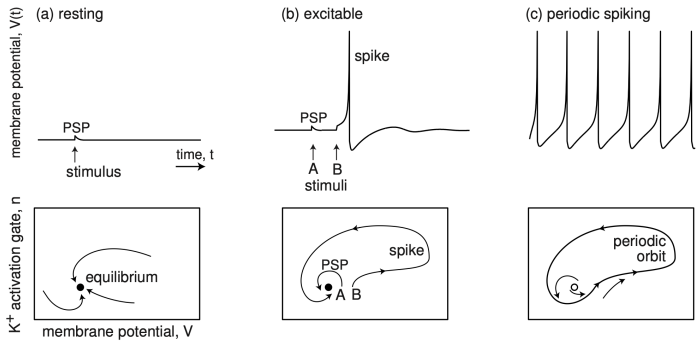
A dynamical system consists of a system described by a set of variables whose state changes with time. In the case of neurons those variables are the membrane potential, excitation and recovery variables such as currents activation or inactivation, and adaptation variables like activation of voltage-dependent currents. With these variables we can make qualitative predictions of the system evolution without attempting to mathematical equations. To simplify the understanding is useful to consider a geometrical approach of the neuron dynamics. In order to do so we consider a two dimensional system so it can be represented by vector fields that allow to understand the neuronal dynamics behaviour analysing their geometrical properties. A common variable choise are the membrane potential and a membrane recovery variable accounting for the activation of sodium channels and the inactivation of potassium channels which provides negative feedback to the membrane potential.

In figure 2a there is a representation of the possible behaviours of the neuron as a two-dimensional system: at the resting potential there are no changes in the neuron dynamics, so it is at its equilibrium state, if we perturbate this state with a stimulus the response of the neuron depends on the stability of that state of equilibrium. If the equilibrium point is stable the neuron remains at rest after a small perturbation called postsynaptic potential (PSP) but if the perturbation continues after the PSP the equilibrium is not stable anymore and the neuron amplifies the perturbation generating a spike. If the excitation variable is strong enough the neuron falls into a periodic spiking activity, that from the dynamical point of view the neuron is said to describe a stable periodic orbit or limit cycle. The evolution of trajectories near the equilibrium point is what makes it stable or unstable. A point is said to be *stable* if perturbations of trajectories

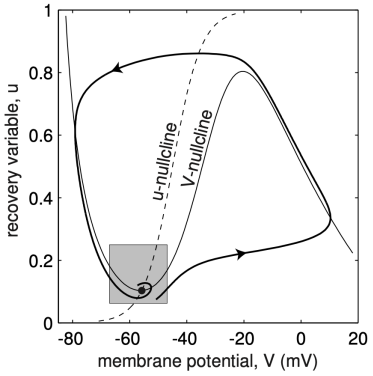
nearby result in localised motions like small oscillations and *unstable* points are those where small perturbations of trajectories lead to bigger amplitude motions that can or cannot converge to the initial point.

1.3.1 Limit cycle dynamics

Limit cycles represent stable patterns of activity that arise due to the interaction between the neuron's membrane potential and the opening and closing of ion channels that control the flow of ions across the membrane, generating a periodic train of action potentials with oscillatory behaviour repeating a pattern over time that is stable and resistant to perturbations. A representation of a typical neuron limit cycle in the phase plane is shown in figure 2b. The asymmetric form of the limit cycle is due to the nonlinearity of sigmoidal functions[1] in the neurons dynamics where the membrane potential undergoes a slow rise and a rapid fall, followed by a period of rest. This typical trajectory is called relaxation oscillation and emerges from the interplay between different types of ion channels [2].



(a) Qualitative analysis of the three possible behaviours of a neuron when receiving an input at its equilibrium state. [2]



(b) Limit cycle in neuronal systems. The main feature is the left-knee equilibrium point due to sigmoidal nullclines. [3]

Figure 2

[1] A sigmoidal function is a mathematical function that exhibits a characteristic S-shaped curve. It is often used to model processes that exhibit saturation or gradual transitions between different states.

1.3.2 Excitability classes and bifurcations

We've described three different behaviours of the neuron depending on the dynamics near the equilibrium point, where the neuron goes through a phase transition between a stable periodic orbit and the equilibrium state with the intensity of the stimulus as the order parameter. This phase transition is called *bifurcation* of the neuron dynamics and occurs when a neuron undergoes a sudden change in its firing pattern or behaviour due to changes in its intrinsic properties or input from other neurons. Bifurcation is related to *excitability*: to be near a bifurcation makes the neuron excitable. The bifurcation analysis can characterise the stability of the set of solutions that arise from that bifurcation and, for instance, helps to understand the dynamics of networks. Each type of bifurcation leads to different excitability properties, Hodgking [4] studied bifurcations and made a classification of excitability types depending on the neuron's response. The qualitative distinction between classes is the frequency-current curve:

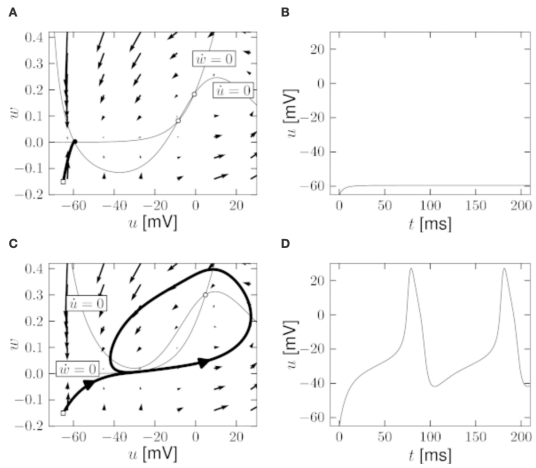
- *Class 1 neurons* are neurons that have a linear or sublinear response to input, meaning that their firing rate increases in proportion to the magnitude of the input. In other words, the more input they receive, the more they will fire, but at a rate that is proportional to the input, so the current-frequency curve is continuous.

- *Class 2 neurons*, on the other hand, have a supralinear response to input, meaning that their firing rate increases more rapidly than the magnitude of the input, meaning that the current-frequency relation is not continuous.[2]

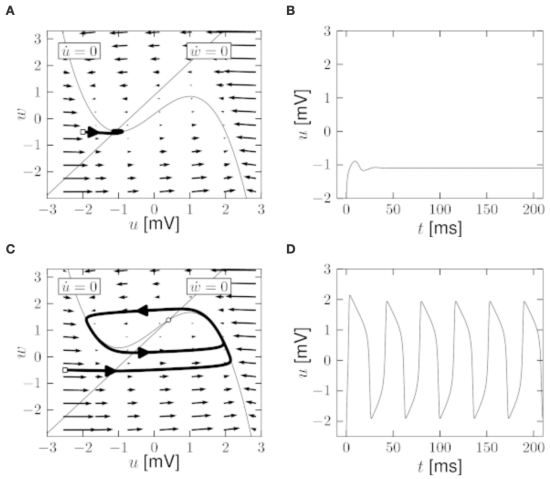
The main bifurcations that transition from the resting state to the spiking state in Class I and Class II neurons are the saddle-node and the subcritical Andronov-Hopf bifurcations. Before this bifurcations a stable equilibrium state coexists with a limit cycle attractor.

Saddle node bifurcation In a two-dimensional system, the saddle node bifurcation occurs when two fixed points, one stable and one unstable, collide and annihilate each other. As the parameter of the system is varied, the stable and unstable fixed points move towards each other, until they merge and disappear at a critical value of the parameter. At this point, the system

[2]There is a Class 3 type where the relation is not well defined.



(a) SNIC on the Morris-Lecar model. **A** For zero input the u and w nullclines intersect in three points, one stable (black dot) and two unstable (white dots). A trajectory starting at (-65,-0.15) converges into the stable point. **B** Time course of the trajectory shown in **A**. **C** The same situation of **A** but with a positive input. The stable fix point has merged with the saddle and disappeared leaving a limit cycle around the other unstable fixed point. **D** Time course of the limit cycle in **C**. [5]



(b) Subcritical Hopf bifurcation on FitzHugh-Nagumo. **A** For zero input the u and w nullclines intersect in a stable fixed point. A trajectory starting at (-1.1,-0.5) converges at the stable point. **B** Time course of the membrane potential of A. **C** With a positive input the fixed point is replaced by a limit cycle. **D** Time course of the limit cycle of **C**.[5]

undergoes a sudden change in behaviour. Before the bifurcation, the stable fixed point attracts trajectories that are near it, while the unstable fixed point repels trajectories that are near it. After the bifurcation, the stable fixed point disappears, and the unstable fixed point becomes the only equilibrium point in the system. This means that trajectories that were previously attracted to the stable fixed point are now repelled by the unstable fixed point.

In figure 3a there is a representation of a saddle-node on an invariant circle bifurcation (SNIC). This bifurcation is a particular case of the saddle-node in which the trajectory that emerges is a stable periodic orbit called a limit cycle. Firstly the neuron is at its resting state but when a external current is send to the neuron the eigenvalues of the equilibrium state change to the point that it collides with an unstable fixed point and the neurons activity changes to a periodic spiking or limit cycle.

The SNIC bifurcation is characteristic of Class I neurons, but the saddle-node bifurcation is not always related to a limit cycle. In a two-dimensional system limit cycles can exist for other reasons than the bifurcation and the saddle-node bifurcation can emerge into other behaviours

like in the Class II neurons, where the limit cycle occurs before the bifurcation point leading to a saddle-node off limit cycle.

Hopf bifurcation One bifurcation that explains the discontinuity in Class 2 current-frequency relation is the Hopf bifurcation, related to the loss of stability of the stable fixed point. In this case the stable fixed point is a focus, with negative real part. As the external current (or the bifurcation parameter) is increased the focus turns less stable and reaches the bifurcation point, where the real part of the eigenvalue is negative. Focuses are related to oscillatory behaviours, so in the bifurcation point the oscillatory activity changes. If the new oscillatory solution is unstable we are talking about a subcritical Hopf bifurcation, illustrated on figure 3b . In this bifurcations the instability of the oscillatory solution near the bifurcation point makes the system approach a large amplitude limit cycle.

1.4 Izhikevich spiking model

The simplest way to model neurons is by a point neuron model which considers that all the activity occurs in the axon, so the model has no spatial distribution. All this models are based on an equivalent electrical circuit where the cell membrane is represented by a capacitor, which stores charge and separates the electrical charges inside and outside of the cell; the ion channels are represented by resistors, which control the flow of ions into and out of the cell and the synapses are represented by a variable resistor, which changes the strength of the synaptic connection between neurons. The corresponding equation is of the form:

$$C\frac{dV}{dt} = I_{ion} + I_{ext} + I_{sin}$$

The equivalent circuit model of a neuron also includes a battery or voltage source, which represents the resting potential of the neuron. This voltage source maintains a constant voltage across the cell membrane.

There exist arround 1760 point neuron models, many of them used for modelling specific parts of the brain like the hippocampus or the cortex and some of them which are more general. Eugene

M. Izhikevich proposes a two-dimensional spiking neuron model as a reduction of multidimensional conductance-base models. The behaviour of such models has a strong dependence on the relationship between activation and inactivation curves and the time constants rather than the ionic currents, so they can be reduced to minimal models by removing gating variables (through establishing a dependence between them). All conductance-based models can be reduced to a system with one fast voltage variable and a slow recovery variable with sigmoidal nullclines.

1.4.1 Derivation of the model

We consider an approximation of the dynamics near the resting state. Looking at the dynamics of a limit cycle near the resting state marked with a gray box on figure 2b the V-nullcline describes a parabolic function with its minimum at (V_{min}, u_{min}):

$$u = u_{min} + p(V - V_{min})^2$$

where p is an scaling factor, and the u-nullcline follows a straight line with offset V_0 and slope s:

$$u = s(V - V_0)$$

The nullcline of a variable x is defined by $\dot{x} = 0$. By applying this condition to both variables we determine the dynamics for the shaded region:

$$\dot{V} = \tau_f[p(V - V_{min})^2 - (u - u_{min})] \tag{1}$$

$$\dot{u} = \tau_s[s(V - V_0) - u] \tag{2}$$

τ_f and τ_s are the fast and slow time scales that determine the slow dynamics of the recovery variable and the faster dynamics of the membrane potential. As we said before, the perturbation of the equilibrium state of the neuron leads to different patterns on the neurons activity so the dynamics near the resting potential (or equilibrium state) determine the spiking configuration of the neuron.

Equations 1 and 2 only represent the upstroke of the neurons activity so we need to reset the

system at the peak of the action potential V_{max} to simulate the downstroke:

$$(V, u) \rightarrow (V_{reset}, u + u_{reset}) \quad \text{when} \quad V = V_{max} \tag{3}$$

With a proper rescaling of parameters the system can be described with four adimensional parameters [6]:

$$\dot{v} = v^2 - u + I \tag{4}$$

$$\dot{u} = a(bv - u) \tag{5}$$

$$\text{if} \quad v \geq 1 \quad v \rightarrow c \quad u \rightarrow u + d \tag{6}$$

where I represents the current signal arriving at the neuron. Parameters a and b take account in the subthreshold behaviour determining the excitability class of the neuron (Class I or Class II) while values of c and d act before the spike, resetting the neuron. a and b regulate the time scale and the sensitivity to the membrane potential subthreshold oscillations of the recovery variable u in a way where $b < a$ ($b > a$) corresponds to saddle-node (Hopf) bifurcation of the resting state [7]. The reset value after the spike for v is c (typically $-65\,mV$).

1.4.2 Cortical neuron modelling

By fitting the model to the spike initiation dynamics of a cortical neuron so the membrane potential units are mV and the time scale is ms the equations turn into [7]:

$$\dot{v} = 0.04v^2 + 5v + 140 - u + I \tag{7}$$

$$\dot{u} = a(bv - u) \tag{8}$$

$$\text{if} \quad v \geq 30\,mV \;: \quad v \rightarrow c \quad u \rightarrow u + d \tag{9}$$

The parameter configuration result in many firing patterns observed in neocortical and thalamic neurons (figure 4). Since the neurons behaviour is described by action potentials, they can be classified by their firing patterns. The most common pattern observed in cortex cells is the *regular spiking* (RS), for a prolongated input the neuron fires a set of action potentials

with a interspike frequency which increases with the input's intensity. A similar pattern is the *intrinsically bursting* (IB) in which the neuron exhibits a initial burst of spikes followed by a RS. The *chattering* (CH) is a series of high frequency spikes separated by an adaptation period which can reach 40Hz of interspike frequency. The adapation period does not appear in the *fast spiking* pattern (FS), where the neuron exhibits a set of spikes with a fast recovery. The *low-threshold spiking* pattern (LTS) is also a high frequency spiking pattern but with a larger adaptation period and it's observed in neurons with a low firing threshold.

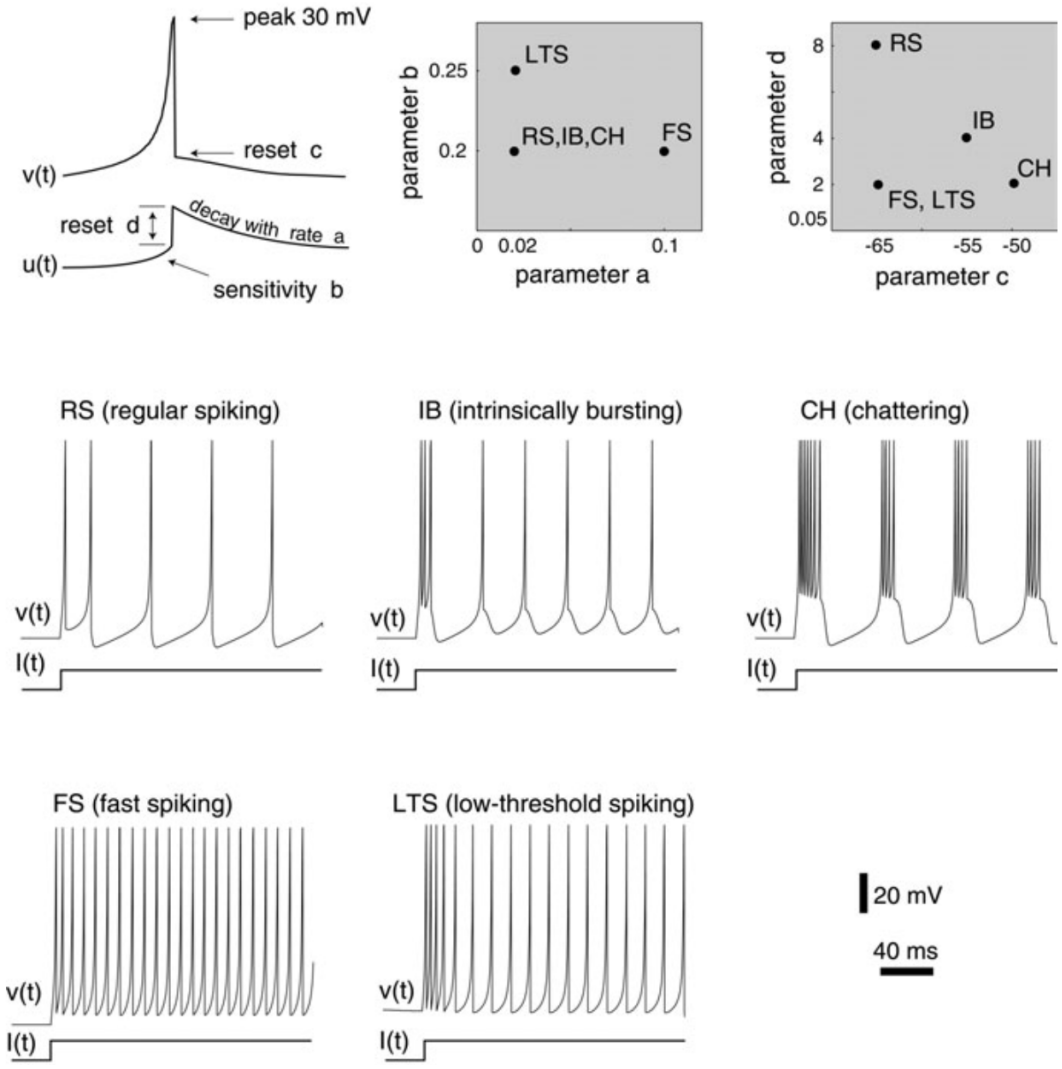


Figure 4: **Firing patterns of cortical neurons**. Made with Izhikevich model [8]

2 Cortical network modelling

The complexity of the brain allows to consider different scales of comprehension, since a macroscopic view dividing the brain in different areas, to the understanding of the biophysical properties and dynamics of a single neuron. Between this two scales there is a mesoscopic scale consisting on interactions between neurons and the formation of neuronal populations. Interacting populations are useful to explain responses to stimulus in specific regions of the brain and their activity.

2.1 Population neurocomputational properties

2.1.1 Synaptic coupling

In the brain the majority of neurons are connected by chemical synapses and can be excitatory or inhibitory, facilitating or preventing the postsynaptic neurons action potential respectively. Each neuron has only one kind of chemical synapse, so we can classify them on excitatory or inhibitory neurons. Common firing patterns of cortical excitatory neurons are RS, IB and CH whereas FS and LTS are inhibitory cortical patterns. Looking at the parametrization of neocortical firing patterns on figure 4 the parameters combination of excitatory neurons could be $(a, b) = (0.02, 0.2)$ and $(c, d) = (-65, 8)+(15, -6)\sigma^2$ being σ a random variable distributed between $[0, 1]$, so different neurons have different dynamics in order to achieve heterogeneity [8]. Following same goal, parametrization of inhibitory neurons is of the form $(a, b) = (0.02, 0.25)+(0.08, -0.05)\sigma$ and $(c, d) = (-65, 2)$. σ^2 is used to tilt the distribution towards RS, so the majority of mammalian neocortex neurons are of the RS type [9].

The synaptic transmission is mediated with the depolarising (excitatory) and hiperpolarising (inhibitory) amino acid neurotransmitters AMPA and GABA which regulate the synaptic current conductance. Macroscopic behaviour of synaptic currents follows the Ohm's law [10]:

$$I^{(i)} = g_i r^{(i)}(V - E_i) \tag{10}$$

where $i = \text{AMPA}, \text{GABA}$, g is the maximal conductance, V the postsynaptic membrane potential

and E the revesal potential being $E_{\text{AMPA}} = 0\,mV$ and $E_{\text{GABA}} = -65\,mV$. r is the fraction of bound synaptic receptors modeled with equation [10]:

$$\tau_i \frac{dr_i}{dt} = -r_i + \alpha \sum_k \delta(t - t_k) \tag{11}$$

with time decays $\tau_A = 5,26$ ms and $\tau_G = 5,6$ ms. The summatory adds the contribution of presynaptic spikes, so it refers to the spike time of all presynaptic neurons connected and has a constant amplitude of α.

2.1.2 External noise

Cortical networks generally sustain some degree of electrical activity representing the brain's noisy internal state in absence of sensory stimulation. This noisy firing pattern present irregularities on the spiking activity similar to Poisson-like time sequences consequence of the cancellation of excitatory and inhibitory inputs in a slow time scale without correlation [11]. The probability of an event k to ocurr on a Poisson distibution given a rate R is

$$P(k; R) = \frac{(Rt)^k e^{-Rt}}{k!} \tag{12}$$

When simulating a brief population each neuron recives by excitatory synapse a Poisson-distributed spike-train of a certain rate to approximate the activity external to the population.

2.2 E-I balance

E-I balance is omnipresent in neuronal systems so it increases coding efficiency (maximal information transmission with as few neurons and action potentials as possible). It maintains an optimal signal-to-noise ratio within the population allowing the accurate processing and transmission of information. From a global perspective, the E-I balance in a neuronal network is the proper regulation of inhibitory and excitatory signals activity, for example, if a neuronal population receives more excitation than inhibition the activity of the population increases, also taking into account inhibitory neurons, which increase inhibition leading to a balanced state. The set of active neurons in a balanced network will likely evolve over time, giving rise to many

possible configurations that all represent different forms of E-I balance that change the relative activity of different sub-types of excitatory or inhibitory neurons giving it multidimensionality, rather than changes in the overall level of excitation or inhibition [12]. This adaptability allows the network to respond to varying demands and stimuli while maintaining overall balance.

To achieve an E-I balance we must consider some conditions so the average of the excitatory and inhibitory synaptic currents could be well-balanced [11]: (a) the number of connections per neurons should be random and much less than the total neurons in the population so the network connection ratio is low (b) the excitation activity should be cancelled with the inhibitory feedback, so inhibitory connections intensity need to be much higher than the excitatory.

2.2.1 Functions of balance in cortical networks

The study of E-I balance sheds light on the dynamic properties of cortical networks, such as oscillations and synchronization. These network-level phenomena are linked to various cognitive functions and are essential for information integration and coordination across different brain regions.

Cortical networks often display rhythmic oscillations in their activity, such as gamma (30-80 Hz) and theta (4-8 Hz) oscillations. The balance between excitatory and inhibitory currents plays a critical role in generating and maintaining these oscillatory patterns. For example, gamma oscillations are thought to arise from the precise timing of excitatory and inhibitory inputs, enhancing information processing and coordination among neurons. Also, proper balance ensures that networks can synchronize when necessary for functions like attention, perception, and memory consolidation.

The coordination of excitatory and inhibitory inputs enables the integration of information across different cortical regions. This integration is essential for higher-order cognitive processes, allowing the brain to combine sensory inputs, make decisions, and generate complex behaviors which ensures the stability of network activity while allowing it to adapt to changing sensory inputs and cognitive demands.

2.3 Information routing

Routing is the process of determining the path for information flow within a network, and it can be categorized as either static or dynamic. Static routing involves establishing a fixed pathway, ensuring that a signal originating from a specific node consistently reaches its destination nodes connected to it. In the context of the brain, stimulating a particular region results in the activation of structurally linked areas, those reachable via successive synapses from the initial site. However, in reality, information flow only reaches a subset of potential target regions. In other words, effective connectivity doesn't align perfectly with structural connectivity. Effective connectivity is adaptable and influenced by context and tasks, meaning that the route through which information can be directed changes according to circumstances, a process referred to as *dynamic routing*.

Researchers have found that for every collective dynamic state within the entire system, there exists a distinct pattern governing the distribution and transfer of information among its components [13]. If the dynamic state undergoes a qualitative change, the entire routing pattern undergoes modification, making the routing pattern inherently dynamic. Moreover, recent advancements in computational neuroscience have proposed potential mechanisms underlying this phenomenon. These insights have emerged from the analysis of a system consisting of multiple circuits operating below the threshold for developing synchronized oscillations. These circuits exhibit brief and weakly synchronized collective oscillations with frequencies that drift stochastically. However, when linked by long-range excitatory connections, they produce spontaneous bursts of synchrony that impact the entire system. Specifically, during these high-frequency (gamma) bursts, the drifting frequencies synchronize temporarily and result in transient phase-locking. This phenomenon can control the flow of information, selectively augmenting or reducing information transfer along specific routes depending on the transient phase pattern.

3 Formation of depolarized clusters

Predictive coding is a theoretical framework used in neuroscience based on the idea that the brain constantly generates predictions about incoming sensory information and compares these predictions to the actual sensory input. When there is a mismatch between the prediction and the actual input, an error signal is generated. This error signal is thought to be carried by specific neurons, often referred to as "error neurons" whose generation is poorly understood. Excitatory neurons in layer 2/3 of the primary visual cortex are ideal candidates to act as error neurons. It has been found that these neurons response is divided into depolarized clusters [14] so the arrival of an external input does not activate all the members of the network.

Neurons in the brain can depolarize and hyperpolarize as part of their normal electrical activity. The process of depolarization refers to a change in the neuron's membrane potential where it becomes less negative, potentially leading to an action potential or neural firing while hyperpolarized neurons have a more negative membrane potential restricting their firing. To understand how depolarization and hyperpolarization work, a network of 500 neurons has been considered with 80% of excitatory neurons and 20% inhibitory as seen in figure 5.

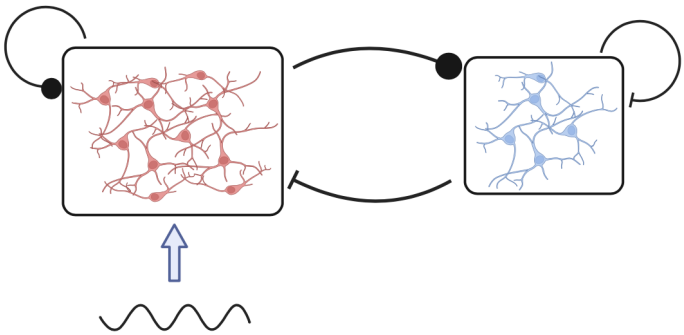


Figure 5: **Connection scheme of the network**. A sinusoidal signal is added to the excitatory population in order to mimic the oscillatory activity of external networks.

Excitatory neurons recive a sinusoidal input of 5Hz and the simulation has been run for different amplitudes of the input signal and for different densities of connexion to the input signal (see appendix A for more details). Without input the network's activity is in a substreshold regime feed by an external noisy activity. In figure 6 there is a representation of the number of

depolarized neurons and the mean firing rate of the population through all configurations.

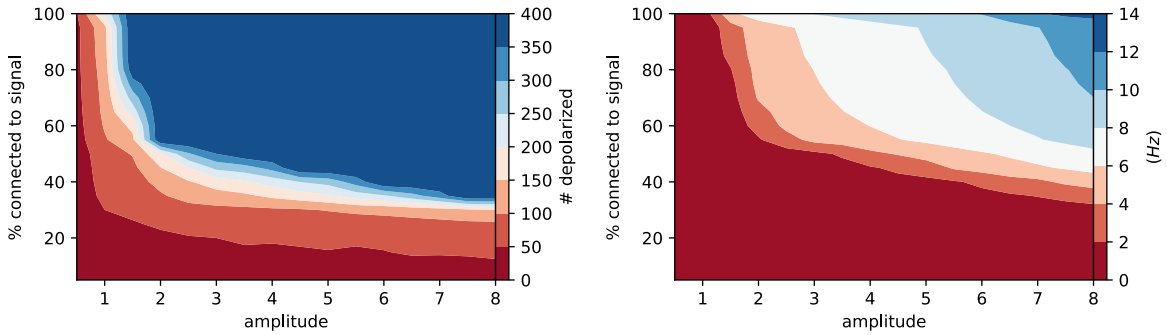


Figure 6: **Evolution of the number of depolarized neurons (right) and mean firing rate (left)**. Both variables depend on the amplitude of the external signal and the number of connections to it.

The number of depolarized neurons increases with the amplitude of the signal and also with the density of connection as it does the mean firing rate of the excitatory population, that goes up to 14Hz for 8mA of amplitude and with all neurons connected to the signal. For high densities of connection ($55\% - 100\%$) to the input the number of depolarized neurons has a fast growth with amplitude until all the population is depolarized, for densities up to 80% this threshold appears to be constant at 1.5mA of amplitude. For lower connection densities the depolarized neurons number decreases its growth with amplitude, being practically constant for big amplitudes ($7\text{mA} - 8\text{mA}$). The mean firing rate has also a fast increase with amplitude for high densities and a slower one for low densities while the growth of firing rate for a constant amplitude is faster for big amplitudes. For every frequency range there is an evolution change for 90% of the population connected to the signal where there is a displacement of higher frequencies through lower amplitudes.

The mean firing rate map shows a big region of parameter combinations with low spiking activity with frequencies between 0 and 2Hz which matches with the opposite region of all neurons being depolarized. This feature sets a relation between these two magnitudes meaning that the number of depolarized neurons in the population gives information about the evolution of its firing rate or viceversa and establishes that in order to increase firing rate all population needs to be depolarized.

4 Anti-phase synchronization by modular organization

Cortical networks exhibit rhythmic neural oscillations at various frequencies, these oscillations synchronize the activity of neurons within and between brain regions facilitating communication and coordination. One of the patterns that emerge from this synchrony are anti-phase oscillations, usually explained by the finite propagation velocity of spikes that produce a time delay in coupling between different regions of the brain. When distances between regions are short other structural factors should be considered, such as the connection density of the network or the type of synapsis.

Layer 2 and layer 3 of the entorhinal cortex are mainly cortical input targeted layers within the hippocampus that interact through a potential anti-phase synchornization [15] refering to a coordination of activity where the two layers exhibit opposite phases of neuronal firing or oscillations facilitating the precise processing and transmission of sensory information. This two layers are two consecutive regions in the cortical column so the propagation of information within these two layers is fast and they have a strong inhibitory connection.

4.1 Inhibitory coupling

The inhibitory coupling between neurons inhibits the firing of one neuron while the other one is active. This occurs through inhibitory synapses, where the release of neurotransmitters like gamma-aminobutyric acid (GABA) leads to hyperpolarization of the postsynaptic neuron, making it less likely to generate an action potential. This coupling can lead to synchronizations and oscillations of the system by modulating the excitability of neurons. When one inhibitory neuron becomes active and inhibits its target neuron, the target neuron becomes less active, this can create an anti-phase relationship where one neuron's increased inhibition corresponds to the other's decreased activity. The dynamics of an anti-phase synchronization between two coupled neurons with inhibitory synapse is ilustrated on figure 7, when one neuron is at its peak activity, the other is at its trough in a stable state forming a limit cycle with a left-knee equilibrium point.

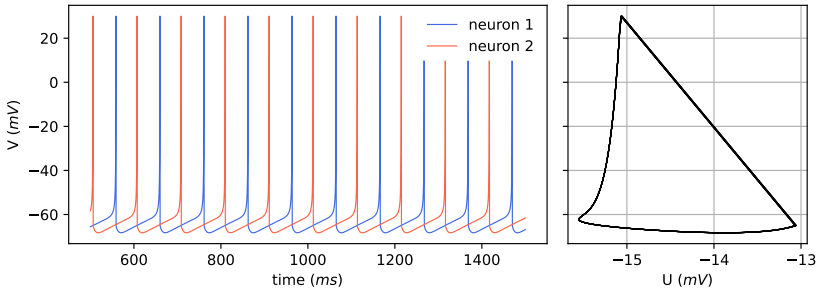


Figure 7: **Anti-phase synchronization of two inhibitory neurons**. (left) Evolution of the membrane potential (right) Phase plane trajectory of the neuron.

4.2 Modular organization network

Studies prove that connection densities have impacts on the synchronization properties of a network and its stability [16] [17], meaning that phase and anti-phase oscillatory patterns depend on the connectivity of the network. To see how connection density affects network's synchronization we consider a cortical network of two populations with 250 neurons each connected by inhibitory synapse and with bidirecctional coupling (see appendix A for more details). As ilustrated in figure 8 each population has an intern density connection α and both receive an inhibitory input from the other population with connection density β. The model has been run for different values of α mantainig the extrapopulation input constant with $\beta = 0.05$.

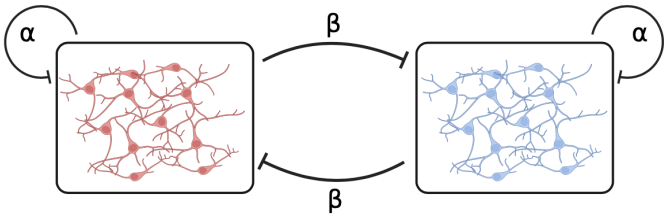


Figure 8: **Connection scheme for inhibitory network**. Each population has a intrapopulation connection density α and is connected to the other population with a connection density β

Through the change of connection density the emergent pattern changes, until it reaches anti-phase oscillation for densities of $\alpha \geq 0.9$ (see rasterplots on B.2). Mean firing rates on different dimensions are represented on figure 9.

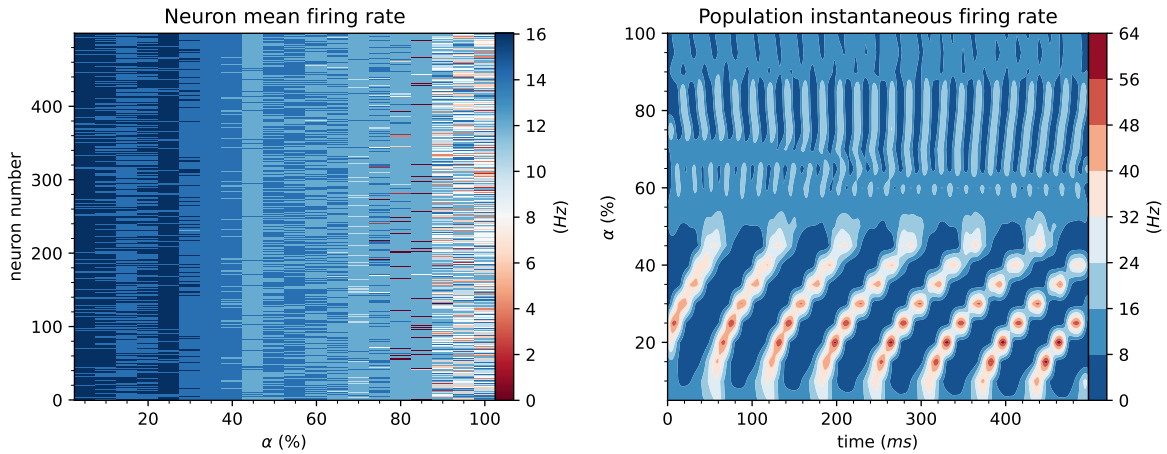


Figure 9: **Evolution of firing rates through the change on intrapopulation density** α, (left) Mean firing rate for each neuron (right) Temporal evolution of population's mean firing rate.

Neuron's mean firing rates decrease as the connection density increases showing the inhibitory feedback on the population's activity, which looses homogeneity for higher densities, specially for the anti-phase sychronization patterns ($\alpha = 90\% - 100\%$). The evolution of the population's mean firing rate has two clear behaviours linked by a diffuse state of transition: from $\alpha = 5\% - 40\%$ there is a synchronized patterned activity with high firing peaks that are displaced through time as the density increases, until these firing peaks lose synchronization and start a change of behaviour at $\alpha = 45\% - 60\%$ range increasing the frequency pattern and the mean firing rate of the population as seen for densities $\alpha = 65\% - 85\%$. For densities $\alpha = 90\% - 100\%$ the population mean firing rate decreases and appears a higher frequency pattern corresponding to the anti-phase synchronization.

While the change on intrapopulation connection density leads to a continuous transition between two frequency patterns, the anti-phase synchronization relates to a first order transition to a state of lower population mean firing rate and a higher patterned frequency breaking the bias of the population's evolution. The connection configuration for anti-phase synchronization has two strong coupled populations with a weak interaction between each other, this type of scheme is called *modular organization* and is a common configuration between populations of different regions of the brain.

The basis for information transmission in a neuronal network is the integration of incoming signals from multiple synapses (if the summed input reaches a certain threshold the neuron generates an action potential) and the information routing pattern is set by the network's collective dynamics, but in oscillatory modular networks local properties can regulate information routing across the whole network [18]: altering the connection density leads to a coordinated restructuring of equilibrium leading to reciprocal adjustments in the way individual neurons within the two populations exchange information as seen in figure 10.

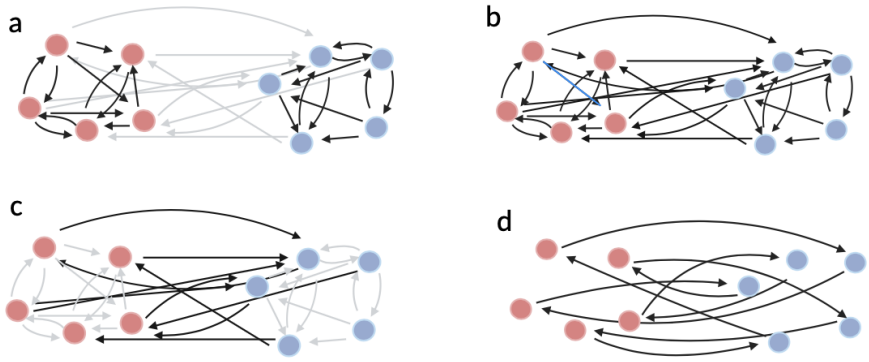


Figure 10: **Routing information patterns in modular network**. For low densities ($\alpha = 0.05 - 0.40$) the information exchange it's higher within populations (**a**) and for higher values of α ($\alpha = 0.65 - 0.85$) more information is exchanged between populations (**c**). This two states are linked with an homogeneous information exchange in the whole network (**b**) explaning the continuous phase transition ($\alpha = 0.45 - 0.60$). For anti-phase synchronization ($\alpha = 0.90 - 1$) the routing pattern changes (**d**) leading to systems of two coupled neurons.

The first order transition observed in the firing pattern which corresponds to the anti-phase synchronization organization is explained by a restructuring of the information routing so information is exchanged between populations but not within them and the network behaves like a pair of coupled inhibitory neurons. The information routings should not be conceptualized merely as physical connections between neurons. Instead, they represent effective information pathways that profoundly influence the network's behavior and functioning. These pathways govern how information is channeled, processed, and utilized within the system, playing a pivotal role in shaping its overall dynamics and response to various stimuli and conditions.

5 Conclusions

The Izhikevich model of spiking neuron is a plausible model for modelling observed behaviours in cortical networks and helps to understand the organization and dynamics of cortical areas such as the entorhinal cortex or the visual cortex.

Neuronal depolarization appears to have a strong relationship with the number of neurons receiving the external input and also with the strength of it. The mean firing rate of the population is related with the number of depolarized neurons of the population, so in order to change population's firing rate a large percentage of neurons need to be depolarized. This information suggests that for depolarized clusters of layers 2/3 of the entorhinal cortex, the mean firing rate of the region can not increase by adding an external signal with constant frequency. To do so, the majority of the cells of the region should be depolarized.

Anti-phase oscillations can emerge from modular organized inhibitory networks because of a reorganization of the information routing, so dynamics resemble a system of two coupled inhibitory neurons. Also, the anti-phase pattern transition is not continuous, contrary to what was observed in the transition between two patterns in phase with different frequencies. These facts build a possible explanation of the anti-phase synchronization observed between layers 2 and 3 of the entorhinal cortex, where the hypothesis of delayed interactions is not applicable due to the short distance between layers.

These two features of cortical networks emerge from the regulated activity of the E-I balance condition, which allows information transmission and network's dynamic behaviour.

A Computational properties and methods

A.1 Model and parameters

All results were obtained with computational models of cortical networks of spiking neurons following Izhikevich equations on section 1.4.2 with a chemical synaptic coupling between neurons modeled with equations from section 2.1.1. Every modeled network has an added external noise following Poisson distribution, explained in section 2.1.2. Parameters were adjusted following references [8],[10] and [19], listed on table

	Section 3	Section 4
N	500	500
g_{AMPA}	0.20	
g_{GABA}	0.80	0.20
g_{noise}	0.10	0.25
Noise frequency (Hz)	600	600

Table 1: Parameters used in simulations

A total of 285 simulations have been run for section 3 counting for changes in amplitude of the external signal from 0.5mA to 8mA in jumps of 0.5mA and in connection density to the signal from 5% to 100% in jumps of 5%. For section 4 the intraconnection density is changed from 5% to 100% in jumps of 5% in a total of 19 simulations.

A.2 Integration method and data management

The model was integrated in a Python environment following Euler's method with a timestep of 0.5ms and considering a starting running period of 1000ms in every simulation in order to achieve a stationary state. The obtained data was stored in numpy arrays format to maximize the compatibility with the electrophysiology analysis toolkit *Elephant* [20] used after every simulation to extract spike times and rates. The main magnitudes extracted from simulations were:

- Membrane potential: stored as a two-dimensional numpy array.

- Local field potential: is the mean value of the membrane potentials of all neurons of the population. It is useful to extract global magnitudes of the population such has its evolution through time.
- Spike times: list of times in which every neuron fires an action potential. Their data is saved into Neo objects [21].
- Mean firing rate: is the mean of all neuron's firing rate. It can be calculated through time or as a global parameter of the simulation.
- Instantaneous firing rate: calculated by kernel convolution. The kernel is used for convolution with the spike train and its standard deviation determines the time resolution of the instantaneous rate estimation. According to [19] a Gaussian kernel with standard deviation of 4ms has been used.

Graphical representations were done under the enviroments of *Matplotlib* and *Viziphant*, a Python module for easy visualization of Neo objects and *Elephant* results [22].

B Complementary results

B.1 Results for adding the external signal at both populations

In section 3 the external signal was added only to the excitatory population, results considering the external input in all the network does not have any appreciable difference has seen in figure 11.

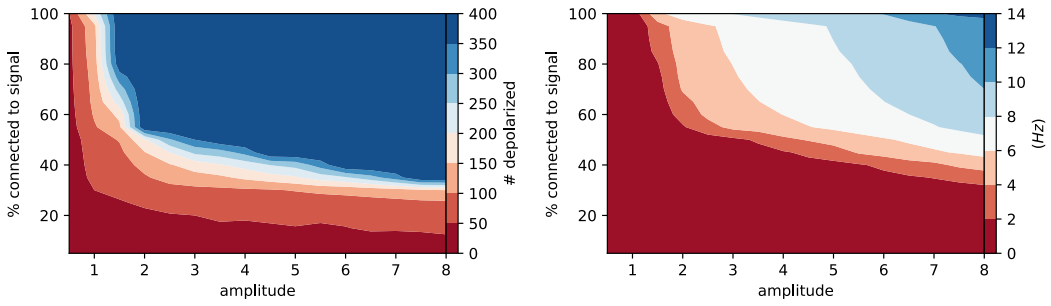


Figure 11: **Evolution of the number of depolarized neurons (right) and mean firing rate (left)**. In this case, external signal has been added to all the network.

B.2 Rasterplots for modular organization

For a better understanding of the results showed in section 4.2 on figure 12 there is a comparative view of the spiking dynamics of the two inhibitory populations through the change of its intrapopulation connection density. The anti-phase synchronization appears at $\alpha = 0.9$ and it is maintained for higher densities of connection.

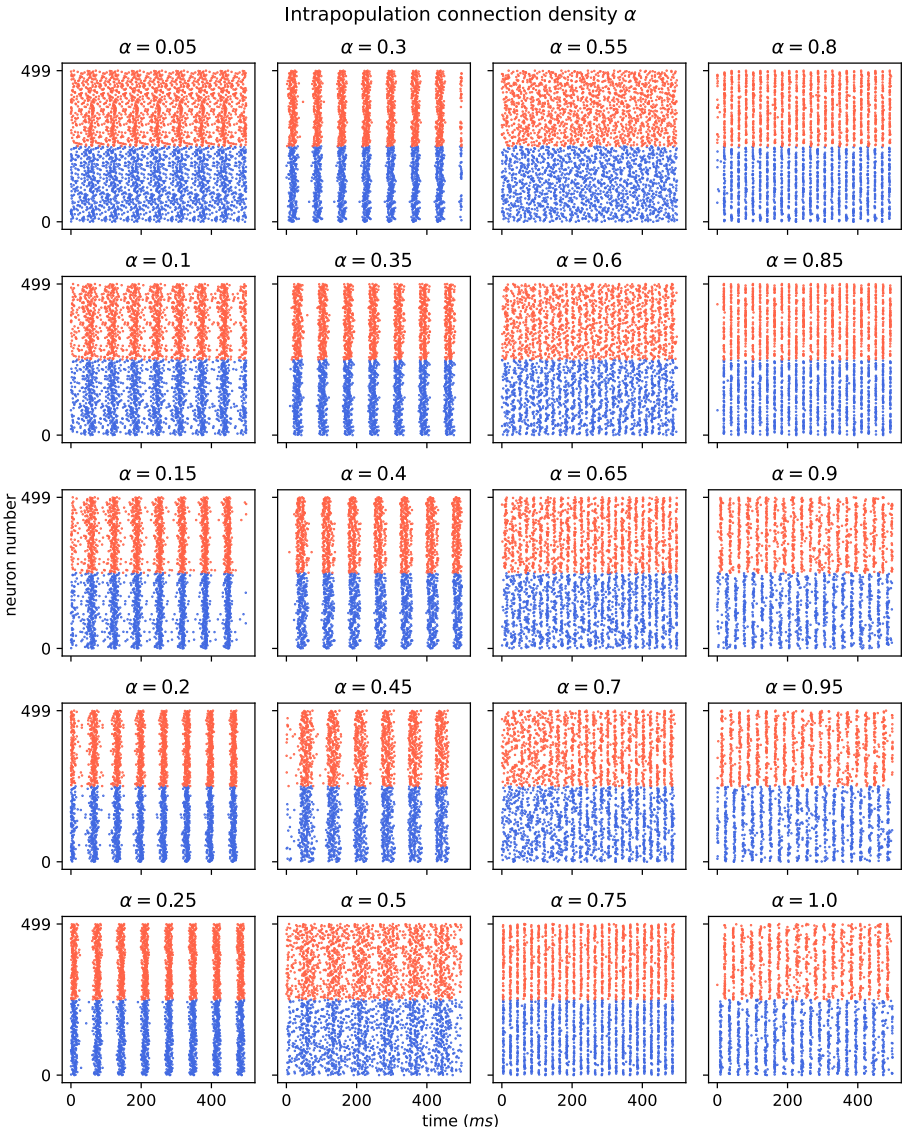


Figure 12: **Rasterplots of two inhibitory populations (red and blue) for different intrapopulation connection densities**. The extrapopulation connection density is constant for all rasterplots.

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