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Complexity, synchronization and network structure inference: an application to neural dynamics

Doctoral Thesis

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Resumen

La combinación de redes complejas y dinámica no-lineal ha proporcionado un marco sólido para el estudio de un gran número de sistemas reales que pueden analizarse como grandes conjuntos de unidades dinámicas conectados entre sí de maneras altamente no triviales, como las redes sociales, las redes eléctricas, las interacciones genéticas o la dinámica neuronal. Entre todos los posibles fenómenos colectivos que pueden surgir en este contexto, la sincronización es el más estudiado, ya que se ha revelado como el mecanismo fundamental de transmisión de información en todo tipo de sistemas dinámicos.

Se sabe que los nodos de una red desempeñan diferentes papeles en la dinámica de las mismas según su posición topológica y su dinámica intrínseca. El hecho de que la sincronización esté mediada por la interacción entre nodos implica que la dinámica individual de cada unidad es susceptible de cambiar debido a la presencia del conjunto. En esta Tesis, hemos revertido la lógica habitual de esta forma de ver la interacción dinámica-estructura: así como la dinámica de cada nodo influye en el conjunto, el conjunto imprime sus huellas estructurales en la dinámica de cada nodo individual. Suponemos que, mucho antes de que la intensidad del acoplo sea lo suficientemente alta como para inducir la sincronización global del sistema, los cambios dinámicos a nivel de nodo están codificando las características de su papel estructural. Así pues, exploramos cómo estas leves variaciones en la dinámica de cada integrante de la red podrían utilizarse para extraer información sobre toda ella, sin necesidad de hacer referencia a las correlaciones por pares, incluso en aquellas situaciones en las que se desconoce la estructura. Es decir, proponemos investigar la correlación entre el rango topológico, medido por el grado del nodo, y los cambios en la dinámica de un solo nodo, medidos en términos de su complejidad -definida utilizando teoría de la información. Esta última cantidad combina la entropía de permutación y el desequilibrio -o desviación estadística de la aleatoriedad- para proporcionar una única medida del contenido de la complejidad de la serie temporal.

Desde el punto de vista analítico, mostramos que en el régimen de acoplamiento débil la solución de las ecuaciones variacionales está regulada por un fuerte término de auto-retroalimentación negativa proporcional a la centralidad del grado. Probamos nuestra predicción analítica en varios ejemplos de modelos de osciladores caóticos, neuronas acopladas por pulsos y redes experimentales de circuitos electrónicos no lineales que evidencian un comportamiento jerárquico -es decir, que la centralidad de grado se correlaciona con la complejidad estadística- mediante el uso de esta novedosa perspectiva de análisis de señales. Después, consideramos redes neuronales cultivadas experimentalmente. Monitoreamos el crecimiento y desarrollo de estas redes para caracterizar la evolución de su conectividad. Luego, exploramos la relación estructura-dinámica simulando un modelo dinámico biofísicamente plausible en los nodos de la red.

Nuestros resultados en todos estos sistemas implican que es posible inferir la distribución de grado de la conectividad de la red sólo a partir de medidas dinámicas individuales.

Exploramos las consecuencias de introducir interacciones de alto orden en una red compleja geométrica de neuronas Morris-Lecar. Nos centramos en el régimen en el que se observan las ondas de sincronización viajeras, comenzando por un acoplamiento basado en los primeros vecinos, para evaluar los cambios inducidos en la coordinación entre las unidades cuando se incluyen interacciones dinámicas de orden superior. La principal motivación para ello es que, aunque la sincronización es un mecanismo clave que interviene en la coordinación del conjunto neuronal, se sabe que los niveles excesivamente altos de sincronización pueden destruir la complejidad general del sistema, reduciendo su capacidad para procesar información. Un mecanismo plausible de regulación son los astrocitos, cuyo papel en el funcionamiento del cerebro es un problema abierto desde hace tiempo en la neurociencia. Aunque se han hecho varios intentos de modelar la interacción neurona-glía, esos modelos son, sin embargo, matemática y computacionalmente costosos, por lo que es útil introducir un modelo fenomenológico capaz de reproducir los efectos del conjunto glial observados en la red neuronal, de modo que, a la vez que conserve los aspectos fisiológicos más pertinentes, permita al mismo tiempo pasar a redes más grandes. Inspirándonos en el marco recientemente introducido de interacciones de alto orden en redes complejas, desarrollamos una variación del mismo; concretamente, utilizamos las interacciones de alto orden para modelar el efecto de la modulación sináptica de los astrocitos en la respuesta neural. Observamos que el fenómeno de las ondas viajeras se ve potenciado por estas interacciones, lo que permite que la actividad viaje más lejos a través del sistema sin generar estados patológicos de sincronización completa. Este esquema podría ser un paso hacia una simple modelización fenomenológica de las redes neurológicas incluyendo los astrocitos.

Aunque el enfoque de esta Tesis ha sido eminentemente teórico-computacional, se ha beneficiado de las contribuciones experimentales de dos grupos de colaboradores que nos han permitido complementar la perspectiva global de los resultados aquí recogidos. De esta manera, ha sido posible encontrar evidencia tanto desde el punto de vista computacional como experimental para apoyar las conclusiones extraídas de esta Tesis.

Abstract

The combination of complex networks and nonlinear dynamics has provided a solid framework for the study of a large number of very different real systems that can be analyzed as large ensembles of dynamical units with nontrivial connectivity patterns, such as social networks, power grids, genetic interactions or neural dynamics. Among all the possible collective features that can emerge in this context, synchronization is the most extensively studied, since it has been revealed as the fundamental mechanism in the transmission of information in all kinds of dynamical ensembles.

It is known that nodes play different roles in the ensemble dynamics depending on their topological position and intrinsic dynamics. The fact that synchronization is mediated through the interaction among nodes implies that the single dynamics of each unit is susceptible to change due to the presence of the ensemble. In this Thesis, we have reverted the usual logic of this insight about the dynamics-structure interplay: just as the dynamics of each node influences the ensemble, the ensemble imprints its structural marks into the dynamics of each individual node. We make the assumption that, long before the coupling strength is high enough to induce synchronisation, the dynamical changes at the node level are encoding the imprint of its structural role. Thus, we explore how this prominent feature could be used to extract information about the network, without having the need to make any reference to pairwise correlations, even in those situations where the structure is unknown. That is, we propose to investigate this correlation between the topological rank, measured by the node degree, and the changes in the single node dynamics, measured in terms of its information-theoretic complexity. The latter quantity combines the permutation entropy and the disequilibrium -or statistical departure from randomness- to provide a single measure of the time series complexity content.

From the analytical point of view, we show that in the weak coupling regime the solution to the variational equations is regulated by a strong negative self-feedback term proportional to the degree centrality. We test our analytical prediction in various examples of models of chaotic oscillators, pulse-coupled neurons, and experimental networks of nonlinear electronic circuits evidencing a hierarchical behavior -i.e., that degree centrality correlates with statistical complexity- through the use of this novel perspective of signal analysis. After, we consider experimental cultured neuronal networks. We monitor the growth and development of these networks to characterise the evolution of their connectivity. Then, we explore the structure-dynamics relationship by simulating a biophysically plausible dynamical model on top of each networks' nodes.

Our results in all of these systems imply that it is possible to infer the degree distribution of the network connectivity only from individual dynamical measurements.

We explore the consequences of introducing higher-order interactions in a geometric complex network of Morris-Lecar neurons. We focus on the regime where traveling synchronization waves are observed from a first-neighbors-based coupling to evaluate the changes induced in the coordination among units when higher-order dynamical interactions are included. The main motivation for this is that even if synchronization is a key mechanism involved in the coordination of the neural ensemble, it is well known that exceedingly high levels of synchronization can destroy the overall complexity of the system, reducing its ability to process information. A plausible regulating mechanism is the astrocytes ensemble, whose role in brain performance is a long-standing problem in neuroscience. Although several attempts have been made to model the neuroglial interaction, these models are, however, mathematically and computationally costly, and therefore it will be useful to introduce a phenomenological model which is able to reproduce the observed effects of the glial ensemble over the neural network such that, while retaining the more relevant physiological aspects, it allows at the same time to move on to larger networks. Inspired by the recently introduced framework of high-order interactions in complex networks, we developed a variation of it; specifically, we used high-order interactions to model the effect of the synaptic modulation of astrocytes in the neural output. We observe that the traveling-wave phenomenon gets enhanced by these interactions, allowing the activity to travel further in the system without generating pathological full synchronization states. This scheme could be a step toward a simple phenomenological modelization of neuroglial networks.

Although the focus of this Thesis has been eminently theoretical-computational, it has benefited from the experimental contributions of two groups of collaborators that have allowed us to complement the global perspective of the results gathered here. In this way, it has been possible to find evidence both from the computational and experimental point of view to support the conclusions drawn from this Thesis.

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*Livet må forstås baglæns,
men må leves forlæns.*

—

*Life can only be
understood backwards,
but it must be
lived forwards.*

—

*La vida solo se puede entender
mirando hacia atrás,
pero se debe vivir
mirando hacia delante.*

Søren Kierkegaard

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Chapter 1

Introduction

1.1 Motivation

One of the major open questions in Complex Networks poses how structure and dynamics are related. More specifically, what route of analysis would one take if there is just access to measures of the dynamical evolution of the individual elements and only partial knowledge of how the underlying structure is? Is it enough to consider first-order interactions when modelling the propagation of synchronization in complex networks?

Apart from being a theoretically appealing question, the relationship between structure and dynamics in Complex Networks is also of great interest in more applied backgrounds. For example, in Clinical Neuroscience they only have a functional measure: for obvious ethical reasons -apart from the technological ones- they cannot have access to a patient's *structural neural network* and would like to learn about the corresponding wiring architecture in order to know where to perform surgery. Another example would be criminalistics, where one might observe a set of crimes associated with a diversity of gangs and tries to predict which of those are more likely going to cause retaliation from rival gangs [1].

Our approach to the problem of structure inference from the individual dynamics relies on the fact that, when considering a system on the route to synchronization, its global states are mediated through the interaction among nodes. This implies that the single dynamics of each unit is susceptible to change due to the presence of the ensemble. If the connectivity is bidirectional, this perturbation will be stronger the more relevant is the topological position of the node in the network [2, 3]. Therefore, long before the coupling strength is high enough to synchronize the system, each coupled unit is encoding in its own dynamical changes the signature of its role in the structure. While there is a rich body of literature exploring how global quantities can guide the local activity of individual nodes to end up in a synchronized state or to understand local dynamics through a mean-field approximation, there is much less work done in the other direction. And that is what we are interested in and have developed in this Thesis: when considering an intermediate level of synchronization, is there anything that can be said about global structural quantities when only having access to local dynamical measurements?

In Chapter 3, we explore how this relevant feature could be used to extract information about the network structure, without having the need to make any reference to pairwise correlations, even in those cases where the topology is unknown. We propose to investigate this correlation between the topological rank, measured by the node degree, and the changes in the single node dynamics, measured in terms of its information-based complexity.

Moreover, in Chapter 4, after having investigated synthetic networks using this approach, we shifted our focus into real ones, more specifically, cultured neural networks coming from locust (*Schistocerca gregaria*) brain. As the real structure of these cultured networks is fully available, we simulated a neuronal model on top of each node to check whether our approach -developed in Chapter 3- still holds in more realistic scenarios.

Once a fairly solid ground regarding this approach was attained, we started to consider a more refined scenario. In Chapter 5, we present a phenomenological model that we carried out for the neuroglial modulation of synapses: apart from the most obvious neuronal interactions, we permitted more subtle ones to be present. These indirect or modulatory interactions represent the astrocytocal influence over the neuronal network and are modelled by high-order interactions. We wanted to understand the synchronization phenomenology that this theoretical framework opens up. Specifically, a question captured our attention: are there any novel features that appear when considering high-order interactions?

1.2 State of the art

Since the beginning of the scientific enterprise, even before the advent of the scientific method, Humankind has explored Nature with a reductionistic philosophy: an understanding about the whole *complicated* system will be attained if it is divided into a lot of simpler parts and these are studied separately. Conversely, the constructionistic approach -which consists in assuming that the whole can be pictured in terms of the fundamental laws governing its components- provided the common knowledge that there was a hierarchy in the sciences and that, for example, condensed matter physics was merely applied particle physics, biochemistry just a consequence of quantum mechanics and so forth. And, certainly, up to a point, it worked, at least until last century. It was then when it was evidenced that there were some natural domains in which constructivism simply proved to be useless. To put this paradigm shift into perspective, one has to realise that while reductionism was already present in the Diagnostic Handbook (a Babylonian medical text, dating about 1050 B.C.), the first complex systems center (The Santa Fe Institute) was founded in 1984. Being this so, it is evident that we are just starting to scratch the surface of what complex systems are, how to characterize them and, as it ultimately happens with any scientific discovery, how to take advantage of them (i.e., how to produce technology with these kind of systems).

To give an introductory notion about complex systems and what their main features are, we refer the reader to Fig. 1.1. A complex system -for example, the brain- differs from a complicated one -for example, a plane- in that the latter can be well understood as the sum of its parts, even if these are thoroughly non-trivial subsys-

1.2. State of the art

tems (engine, wings, etc), while the former is only approachable if both its elements and their interactions are taken into account. This non-separable interdependence between elements is known as *emergence*, and one of the best-known examples is that of viscosity in a drop of water: while no particular atom shows this property, when the interaction among billions of them occurs, this feature makes sense. One of the oldest examples showing the calculation of emergent properties is due to the work by Douglas R. Hartree [4] and Vladimir A. Fock [5], where they independently arrived to a method of approximation for the wave function of a quantum N -body system in the stationary state. This is regarded as an example of emergence because, although the equation of motion (i.e., the Schrödinger equation) can be solved independently for each of the N particles of the system, the solution one finds following the approximation is not the superposition of the individual solutions.

Another key feature of complex systems is that of self-organization, meaning there is no global ruler that dictates the evolution of the system; on the contrary, the dynamical behavior of the whole ensemble is given by the individual -and autonomous- response of interactions among components. We would say that from a *self-organized* behavior, these *emergent* phenomena take place. The pioneering work by Ilya Prigogine [6] in dissipative structures -that is, an open thermodynamical system which is far from equilibrium- opened the doors to the modern notion of self-organization. Continuing with this tradition, in 1987, Per Bak, Chao Tang and Kurt Wiesenfeld [7] coined the term *self-organized criticality*, which is defined to be the mechanism by which systems spontaneously -via the interactions among their components- set their dynamical regime to be near the transition point -also referred to as the critical point- between different phases. A great variety of examples (see [8, 9], among many others) of this phenomenon has been provided even before its conceptualization ([10, 11]). We refer the interested reader to Appendix A for further conceptual discussions on features of complex systems.

Complexity Science comprises a vast corpus of fields. In order to give an idea of what the principal areas are, with an emphasis on years and authors that have led the advances in each subdomain, in Fig. 1.2 we present a schematic visualization of the chronogram of the field (originally found in [13]).

In the next Chapter we will give a brief overview of the state of art of different relevant areas which are directly related to the investigations developed in this Thesis. The first important field for this Thesis is that of Complex Networks, a scientific stream that arises from the merging of Graph Theory and Complex Systems. The general idea of treating physical systems as networks comes from the basic assumption that, given the proper conditions, they can be conceptualized as nodes -which represent the elements of the system- and edges -representing a correlation or interaction between the nodes. As this is a high level of abstraction, a wide variety of systems can be studied under this formalism.

The underlying mathematical tool for analyzing them is the same: independently of the field concerned (sociology, physics, biology, economy, etc), the description, characterization and understanding of the properties of the networks is found in mathematical graph theory. Being this so, it is worth introducing some basic concepts for the sake of concreteness (see Section 2.1).

As we have already mentioned, emergent properties are one of the key features of

Figure 1.1: Illustration of what complex systems consist of. The key difference between complicated and complex systems is that the former can be understood as a sum of their parts, while the latter cannot. To comprehend the behavior of complex systems, one has to include the interactions among elements that compose the whole. (Reproduced with permission from [12]).

Figure 1.2: Visual scheme of some of the main subdomains that Complexity Science is partitioned in. (Original work due to Brian Castellani [13]).

1.2. State of the art

any complex system. Synchronization, defined as the coordinated activity among interacting dynamical elements of a system, is a prime example of these properties. During the past decades, it has been one of the most studied phenomena in complex systems and, particularly, in complex networks [14]. It is frequently said that the first direct mention to the idea of synchronization as we know it today was due to Christiaan Huygens, in 1665. The scientific folklore says that, while Huygens was lying in his bed, he noticed there was "a kind of sympathy" between two clocks swinging next to each other. Furthermore, he noticed that, unperturbed, they swang in anti-phase with the same frequency; when disturbed, they converged to that state again after half an hour and persisted in that oscillatory anti-phase. He correctly hypothesized that the crucial part was the common frame supporting both clocks; this is what we nowadays would call an interaction between dynamical elements. Another crucial observation was made by Lord Rayleigh in his book *The Theory of Sound* [15], in 1894. He described how organ pipes seemed to work in a coordinated fashion, well before the current synchronization paradigm was established. This phenomenon was first systematically studied (both theoretically and experimentally) by Appleton [16] and Van der Pol [17], respectively, in the decade of 1920. They both dealt with the synchronization of triode electronic generators.

From then on, the setup of two interacting oscillators gained more and more attention and, over time, it became a well studied problem. However, it was not until 1958 when the oscillator ensemble case got into the spotlight. Although this pioneering work, carried out by Wiener [18], turned out to be a dead end -because of the mathematical focus, placed on Fourier integrals-, it was a milestone due to the fact that it was the first recognition of the ubiquity of synchronization throughout natural processes. In contrast, Winfree took what became a more valuable route: in 1967, he formulated the problem [19] for a huge ensemble of oscillators connected in an all-to-all fashion -as described in Section 2.1.2; he simplified the problem by considering the weak coupling scenario and nearly-identical oscillations. He found out that this system could exhibit an analog of a phase-transition, regarding frequencies: when the variability among the individual oscillator frequencies is high (compared with the coupling strength), there is no coherence; as frequencies are made more and more homogeneous, this situation stays the same up until a certain threshold is crossed and a small group of oscillators starts showing a coordinated dynamics. The Winfree approach led Kuramoto to study the problem in 1975 [20] and, ultimately, to propose its paradigmatic model, which we sketch in Section 2.3.1.

In spite of its undeniable successes at the mathematical realm, this approach looks implausible in real-world scenarios. Specifically, the all-to-all pattern invoked to solve this problem would rather be a gross simplification of the real underlying structure where nodes would be embedded in. Moreover, apart from that, this all-to-all topology discards any potentially preferred local architecture or interaction -since every node would have an equally important interplay at all scales. Here it is where the Watts-Strogatz model, described in Section 2.1.2, came into play. In 1998, they started [21] the study of synchronization in networked systems as we know it.

Since the beginning of the research on the dynamics of complex networks, the deep relationship between topology and dynamics has been thoroughly explored with regard to its effect in the collective state, particularly in the synchronization between the nodes' dynamics [14, 22–24]. A huge effort has been devoted to understand this

phenomenon, and the knowledge gathered so far has driven the advances in crucial applications, such as in brain dynamics [25], power grids [26], and many others where synchronization is relevant [27, 28]. In most of them, the focus is placed on a state where all the network units reach the same dynamical state [14]. However, there are cases in which the system performs its activity in a partial or weakly synchronous state [29–31] to preserve a sort of balance between functional integration and segregation [32–34], whereas full synchronization is found to be pathological. As a product of those investigations, it was found that the underlying structure can be inferred from the dynamical correlations among the coupled units in the asynchronous regime [35–37]. Indeed, the nowadays very active field of functional brain networks -more on this in Appendix B- relies on the hypothesis that the observed dynamical correlations are strongly constrained by the anatomical structure [25], in some cases with a very high correlation between functional and topological networks [38].

One of the fields where this perspective of merging complex networks and non-linear dynamics has led to new research lines is that of neuro-scientific applications. We are particularly interested in this domain because we have access to cultured neural networks against which we can confront our theoretical-computational hypothesis. The neural system can be considered as a dynamical complex network in all its relevant scales, ranging from the microscopic one, where the networked elements are single neurons [39, 40], through the cortical column mesoscale [41] -see Appendix B for some mesoscale dynamical models-, to the entire brain [25, 42], with brain areas acting as nodes of a functional network defined in terms of correlation levels, using measures such as those defined in Appendix C. A fruitful alternative approach to this same problem of network inference is to make use of the Maximum Likelihood Estimate (MLE) technique: when dealing with spike trains (that is, the recorded output coming from neural activity), one can inspect their statistical dependencies *in a pairwise way* to potentially group them in an networked structure [43, 44]. We have to remark that while this route has provided some profound insights [45, 46], we have not taken it because it still comprises a pairwise framework, and we are interested in inspecting the nodes dynamics through an individual prism.

However, even if synchronization is a key mechanism involved in the coordination of the neural ensemble, it is well known that exceedingly high levels of synchronization can destroy the overall complexity of the system, reducing its ability to process information and, eventually, leading to pathological states as epilepsy [47]. Therefore, a healthy synchronous functioning in the brain needs the existence of mechanisms of regulation, both structural and dynamical, to ensure the proper equilibrium between coordination and function segregation. Further details can be found both in Section 2.2.2 and Appendix B.

A plausible regulating mechanism is the *astrocytes* -a cell type that belongs to a group called *glial cells*- ensemble [48, 49], whose role in the brain performance is a long-standing problem in neuroscience. It is now known that astrocytes are involved in early synapse formation [50]. Several attempts have been made to model the neuroglial interaction [51, 52], most of them focusing on the neuron-astrocyte pair or, more commonly, a triade of two neurons and an astrocyte [53, 54]. Recent studies have gone further to consider the networked context, using detailed conductivity models [55–57], similar to those introduced in Chapter 2.2.2. They coincide in

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showing how the interaction of the astrocytes ensemble with the neuron network can induce robust spatial synchronization in the neuronal ensemble surrounding the astrocytes [56–58], and in particular to enhance the propagation of activity waves [55]. These models are however mathematically and computationally costly [56], and therefore it will be useful to introduce a phenomenological model which is able to reproduce the observed effects of the glial ensemble over the neural network such that, while retaining the more relevant physiological aspects, allows at the same time to move on to larger networks. That is precisely what we do in Chapter 6, previously having presented the appropriate tools in Section 2.2, which were the result of adapting those developed in Refs [59–61]. As it has already been shown in other applications of this framework [62–64], the introduction of the high-order connectivity formalism to a complex network of synaptically connected neurons can provide insights about how introducing not only first but also second-neighbors interactions might be useful to comprehend further details of the neuronal dynamics in a simple and mathematically well-defined way.

Chapter 2

Methodology

In this Chapter we will introduce and explain the mathematical tools and experimental setups used along this Thesis. We will also give a brief overview of some related content that we have not explicitly used in this work but conforms an important part of the context in which this Thesis has been developed. For a more detailed -and somewhat less technical- discussion of these panoramic parts, we refer the reader to Appendices A -for a short discussion on conceptual issues when dealing with complex systems-, B -where we give a brief overview about Network Neuroscience-, C -in order to read a bit more about some other synchronization measures used today in Neuroscientific applications- and D -for a survey of complexity measures and the problems they entail.

2.1 Basic concepts in graph theory

Although this is by no means a thorough walkthrough of Graph Theory, it can be regarded as a first contact with the basic tools needed to tackle various concepts of complex networks. There are numerous and great sources which can be consulted for a complete description of this field, like Refs [65–67].

We define an undirected graph G as a pair of sets $G = (\mathbb{V}, \mathcal{E})$, where $\mathbb{V}$ is a non-empty countable set of N elements called *vertices* or *nodes*, and $\mathcal{E}$ is a set of *unordered* pairs of vertices, called *edges* or *links*. For example, the edge (i, j) means that the vertices i and j are *adjacent* or *connected*. Undirected graphs are depicted graphically as a set of dots, which represent the nodes, joined by lines between pairs of vertices, representing the corresponding links.

On the other hand, a directed graph D or digraph, is defined by a non-empty countable set of vertices $\mathbb{V}$ and a set of *ordered* pairs of different vertices $\mathcal{E}$ that are called directed edges. In a graphical representation, these links are depicted by means of an arrow, indicating the directionality of each edge (see Fig. 2.1, bottom row).

From a mathematical point of view, a graph is defined by means of the *adjacency matrix* $\mathbf{A} = \{a_{ij}\}$, that is a $N \times N$ matrix defined such that

2.1. Basic concepts in graph theory

$$a_{ij} = \begin{cases} w_{ij} & \text{if } (i, j) \in \mathcal{E} \\ 0 & \text{if } (i, j) \notin \mathcal{E} \end{cases} \quad (2.1)$$

where w_{ij} is the *weight* of the (i, j) link.

Here we have defined the adjacency matrix in the most general way. If we were to choose every $w_{ij} = 1$, we would be dealing with an unweighted network (meaning every link is equally important). In the case of undirected graphs (see Fig. 2.1, top row), this matrix is symmetric and therefore we can take only into account the upper triangular part. For digraphs, the adjacency matrix is not symmetric. It is worth noting that each choice has its own advantages and drawbacks: generally, a greater level of detail (weighted vs unweighted or directed vs undirected) leads to an spectacular increase in the difficulty of computations. In some cases of study, it can be more than enough to just consider undirected and unweighted graphs, while in others it may be radically relevant to include either feature or even both of them, like in prey-predator interaction networks [68] or in hyperlinks networks [69].

Figure 2.1: Adjacency matrix and graphical representation of different graphs. The dots represent the nodes and the lines -either directed or not- represent the edges. Reproduced and modified from [70].

A central concept when working with networks is that of measuring the *importance* of different nodes. The study of different ways of measuring the relevance of a node is interesting from various points of view: from attacking a network -the internet, an electric grid, a terrorist group, etc- to protecting it, or even to have a fundamental understanding of the basic phenomenon that is taking place -from learning about the origin of epileptic seizures to the optimization of vaccination campaigns in an epidemic disease.

When defining a measure of importance or *centrality*, it will depend on the characteristics or specific properties we are interested in. We will only give a brief overview of the most used ones.

- Degree centrality: it is the most basic and immediate one. It takes into account the number of edges in the graph incident on a vertex [65]. Although the

degree k_i of a vertex i is the number of connections of that node in the case of undirected networks, we have to be more careful in the case of directed networks. We can distinguish the *in-degree* $k_{in,i}$ of the vertex i as the number of edges arriving at i , while its *out-degree* $k_{out,i}$ is defined as the number of edges departing from i . Therefore, in a directed graph, the degree (k_i) of a node is defined by the sum of both. In terms of the adjacency matrix:

$$k_{in,i} = \sum_j a_{ji}, \quad k_{out,i} = \sum_j a_{ij} \quad (2.2)$$

This centrality measure has a direct interpretation in terms of how well an element is connected to other elements in the graph. From now on, we will be dealing exclusively with undirected and unweighted graphs, except explicitly said otherwise.

- Closeness centrality: it measures the average topological distance of a vertex to all others [65, 71]. Mathematically:

$$g_i = \frac{1}{\sum_{j \neq i} l_{ij}} \quad (2.3)$$

where l_{ij} is the *shortest path length* between nodes i and j : the number of edges in the shortest path connecting i to j . This measure gives a large importance to nodes which have small shortest path distances to the other nodes.

- Betweenness centrality: unlike the previous measures (which focus on how well a node is connected to determine its importance), this one accounts [72] quantitatively for the relevance of nodes which act as bridges, meaning that a node can have a small number of connections yet be crucial for the communication between regions of the network [66]. Precisely, if σ_{hj} is defined as the total number of shortest paths from h to j and $\sigma_{hj}(i)$ is the number of these shortest paths that pass through the node i , the betweenness of i is defined as:

$$b_i = \sum_{h \neq j \neq i} \frac{\sigma_{hj}(i)}{\sigma_{hj}} \quad (2.4)$$

- Eigenvector centrality: this measure classifies a node's importance based on the relevance of its neighbors: a node is important if it is linked to other important nodes [66]. The precise mathematical definition is:

$$x_i = \frac{1}{\lambda} \sum_{j=1}^N a_{ij} x_j \quad (2.5)$$

where λ is a constant and a_{ij} are the entries of the aforementioned adjacency matrix. Defining the vector of centralities $\mathbf{x} = (x_1, x_2, \dots)$, we can rewrite this equation in matricial form as:

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$$\lambda \mathbf{x} = \mathbf{A} \mathbf{x} \quad (2.6)$$

which is an eigenvector problem, with λ as the eigenvalue corresponding to the eigenvector $\mathbf{x}$.

In general, there will be N eigenvalues λ for which a non-zero eigenvector solution exists. However, the additional requirement that all the entries in the eigenvector be non-negative implies (by the Perron -Frobenius theorem) that only the largest eigenvalue results in the desired centrality measure.

To illustrate the different importance measures, we portray an example in Fig. 2.2, where nodes with the highest corresponding centrality are marked.

Figure 2.2: Illustration of the different centrality measures for a specific example of a network. Figure retrieved from [73].

2.1.1 Statistical characterization of networks

With the recent possibility of systematic gathering and handling of datasets on large-scale networks, Network Science (NS) has been in the need for statistical methods that could provide a solid foundation for the analysis of this data. The main motivation for the formulation of NS in statistical terms is that, in large systems, one cannot detect asymptotic regularities by looking at local elements or properties (just as the ones we have previously introduced). Subsequently, it is mandatory to focus on statistical measures that take into account the global behavior of these features.

- Degree distribution: it is defined [65] as the probability $P(k)$ that any randomly chosen node has degree k . It is obtained by constructing the normalized histogram of the degree of the nodes in a network. The average degree of a graph is, defined as in any probability distribution, the first moment of the distribution. Mathematically:

$$\langle k \rangle = \frac{1}{N} \sum_i k_i = \sum_k k P(k) \equiv \frac{2m}{N} \quad (2.7)$$

with m being the total number of edges, since each link end contributes to the degree of a node. Analogously to the average degree, we can take the n^{th} moment of the degree distribution:

$$\langle k^n \rangle = \sum_k k^n P(k) \quad (2.8)$$

- **Clustering Coefficient:** it gives a broad measure of how nodes in a graph tend to assemble together [66]; in other words, it is useful to find communities by identifying high density of links in particular areas of the network. It is defined as:

$$C = \frac{\text{no. of closed triplets}}{\text{no. of triplets}} \quad (2.9)$$

It is also sometimes referred to as *transitivity*.

2.1.2 Theoretical models of complex networks

These theoretical models are the mathematical rules to build different types of networks. The rationale beneath the elaboration of these models is that if we understand how different types of networks are constructed and developed, we may also get an intuition about the real system they have been designed to replicate. While theoretically there are almost up to a hundred different network models, in this Thesis we will make use of four of them. Being this so, we found interesting to describe those four and a few extra ones, for the sake of completeness. To characterize each of the models, we will either describe their construction (in the simplest cases) or just show their degree distributions, although that is far from a full description.

Deterministic networks: simple recipes for non-complex topologies. As in every domain of science, the first step to model a system is to start by considering only the simplest cases. And that is what deterministic networks are: toy models upon which we can lay the foundations for more complicated (and *complex!*) scenarios.

Some examples of deterministic models include the star, the all-to-all connectivity and regular networks (see Fig. 2.3 for an illustration of them).

Figure 2.3: Illustration of star (A) -a central node connected to the other $N - 1$ elements-, regular (B) -every node has the same degree- and all-to-all (C) networks -where each node is connected to every other vertex. All of them have the same size ($N = 20$), for comparison purposes.

The three cases we have briefly introduced have the same advantage and suffer from the same drawback: they are extremely easy to implement but are utterly unrealistic. We will see, next, that they will in some cases literally be the first step to implement more realistic ways of constructing the topology.

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A key aspect that is missing in these models is that of uncertainty. Being this so, we will move towards probabilistic graphs, instead of deterministic ones.

Probabilistic graphs. As it usually happens with Complex Systems, it is often the case that different processes -generated from a common mechanism- can lead the system to end up in the same state. That is precisely what happens in network formation: as far as we know, there are several mechanisms that explain how different network topologies can form, but fluctuations cannot be avoided. What this implies is that two realizations of the same connectivity scheme are subtly different in some aspects and equivalent in others.

Some of the most important examples (both because their ubiquity and their historical transcendence) are $\mathcal{G}(N, p)$ -also known as Erdős-Rényi- [74] and Watts-Strogatz [21] networks:

- **$\mathcal{G}(N, p)$ graphs:** Although they are commonly known as Erdős-Rényi graphs, they were actually firstly studied by Solomonoff and Rapoport [75], although popularized by a series of papers by Paul Erdős and Alfred Rényi [74]. Also, sometimes they are known as the "Poisson random graph" or the "Bernoulli random graph". In general, these graphs are theoretical networks in which some specific set parameters take fixed values, but the network is random in other respects (for example, we fix the number of vertices N and the number of edges m but we permit random connections with probability p).

This model is not defined by a single randomly generated graph but as an ensemble of them, that is, a probability distribution over possible networks.

In order to characterize this model, we will just give a brief calculation of its expected number of edges: the number of graphs with exactly N vertices and m edges equals the number of ways of picking the positions of the edges from the $\binom{N}{2}$ distinct vertex pairs. Therefore, the total probability of drawing a graph with m edges from the ensemble of networks is:

$$P(m) = \binom{\binom{N}{2}}{m} p^m (1-p)^{\binom{N}{2}-m} \quad (2.10)$$

which is the standard binomial distribution. Its mean value is therefore given by:

$$\langle m \rangle = \sum_{m=0}^{\binom{N}{2}} m P(m) = \binom{N}{2} p \quad (2.11)$$

As it can be seen, the meaning of Eq. (2.11) is that the expected total number of edges in the graph is equal to the expected number p between any pair of vertices, times the number of pairs. Using this expression, the mean degree in a graph with exactly m edges is $\langle k \rangle = 2m/N$ and therefore the mean degree in $\mathcal{G}(N, p)$ is:

$$\langle k \rangle = \sum_{m=0}^{\binom{N}{2}} \frac{2m}{N} P(m) = \frac{2}{N} \binom{N}{2} p = (N-1)p \quad (2.12)$$

Once we have these results, we can calculate its degree distribution.

In this case, a given node in the network is connected with independent probability p to each of the $N-1$ other nodes. Thus, the probability of being connected to a particular other k vertices and not to any of the others is $p^k(1-p)^{N-1-k}$. There are $\binom{N-1}{k}$ ways to choose those other k vertices, and therefore the total probability of k being connected to exactly k others is:

$$P(k) = \binom{N-1}{k} p^k (1-p)^{N-1-k} \quad (2.13)$$

which is a binomial distribution again. As we are in many cases interested in what properties large networks possess, we can safely assume $N \rightarrow \infty$. Thus

$$\begin{aligned} \ln [(1-p)^{N-1-k}] &= (N-1-k) \ln \left(1 - \frac{\langle k \rangle}{N-1} \right) \\ &\simeq -(N-1-k) \frac{\langle k \rangle}{N-1} \simeq -\langle k \rangle \end{aligned} \quad (2.14)$$

where the logarithm has been expanded to a Taylor series, and the equalities become strict for $N \rightarrow \infty$. Taking exponentials in both sides, we have $(1-p)^{N-1-k} = e^{-\langle k \rangle}$. Also, for large N :

$$\binom{N-1}{k} = \frac{(N-1)!}{(N-1-k)!k!} \simeq \frac{(N-1)^k}{k!} \quad (2.15)$$

Taking everything together, the degree distribution in the case of $N \rightarrow \infty$ will result in

$$P(k) = \frac{(N-1)^k}{k!} p^k e^{-\langle k \rangle} = \frac{(N-1)^k}{k!} \left(\frac{\langle k \rangle}{N-1} \right)^k e^{-\langle k \rangle} = e^{-\langle k \rangle} \frac{\langle k \rangle^k}{k!} \quad (2.16)$$

usually referred to as the Poisson random graph. We have portrayed in Fig. 2.5 (left) an example of this class of network's degree distribution for different values of the wiring parameter p .

- **Watts-Strogatz model:** Real-world networks tend to present a large value of transitivity [21, 76, 77]. This is a crucial nuance, as $\mathcal{G}(N, p)$ networks present no significant levels of clustering -although they do exhibit a low value of shortest-path length. In 1998, motivated by this question (i.e., is it possible to construct a network with a low shortest-path length but a high clustering coefficient?), Watts and Strogatz [21] proposed what is nowadays considered the birth of the modern theory of Complex Networks. In their model, the network construction process is:

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- We start from a ring model of N nodes, in which the degree of all of them is $k = 2c$.
- Going through each node, without repetition, with some probability β , we remove an existing link.
- With the same probability β , we create a new edge with *any of the nodes*.

Figure 2.4: Illustration of how Watts-Strogatz networks look based on changing the rewiring probability parameter (β). From left to right: $\beta = 0$ (or ring network), $\beta = 0.3$ (network showing the small-world property) and $\beta = 1$ (random network). It can be seen that as we increase β we lose short-range links in favor of long-range ones. At the end of this process, it is a completely random pattern of connections but for lower values of β , we see that there is a small number of long-range connections (low shortest-path length) at the expense of losing some short-ranged ones (thus still maintaining a high clustering coefficient).

It is straightforward to see that the relevant parameter in the construction of this topology is the rewiring probability β , check out Fig. 2.4 for a visual example of its importance. If $\beta = 0$, we are left with a regular network (the aforementioned ring); on the contrary, if $\beta = 1$, we end up with a random network, of the Erdős-Rényi kind, regardless of the initial c . There is a range of rewiring probabilities ($0.01 \lesssim \beta \lesssim 1$) for which we arrive to a class of networks that exhibit the so-called *small-world property*: a low shortest-path length -due to the rewired edges- and a high clustering coefficient -because of the underlying regular structure.

As we create the aforementioned shortcuts to the regular architecture to construct the small-world model, the average degree of each node will be $2c$. We find the probability of a node to have a certain degree k :

$$P(k) = \begin{cases} 0 & \text{if } k < c \\ \sum_{n=0}^{\min(k-c, c)} \binom{c}{n} (1-\beta)^n \beta^{c-n} \frac{(\beta c)^{k-c-n}}{(k-c-n)!} e^{-\beta c} & \text{if } k \geq c \end{cases} \quad (2.17)$$

We have portrayed an example (Fig. 2.5) of how this degree distribution looks like for a fixed set of parameters: $k = 2c = 4$ and $N = 10^4$ (while we varied the rewiring probability parameter β). For further details, we refer the interested reader to [78].

Figure 2.5: Plot of the degree distributions of Erdős-Rényi (left) and Watts-Strogatz networks (right). For the sake of comparison between these two classes of probabilistic networks, we have fixed the same size ($N = 10^4$). Also, for the ER network we chose $p = 0.2$; for the WS $\beta = 0.2$ and $c = 2$.

- **Spatial growth model:** These models [79, 80] are based on the idea that in many physical scenarios, distance is a key factor when trying to understand the structure adopted by the elements of that system. Furthermore, we are interested in this kind of models because, as we will see in Chapter 4, our neuronal cultures exhibit degree distributions that resemble this class of probabilistic networks, as it will become evident in Chapter 4 (Fig. 3 therein).

Let us consider a collection of N nodes distributed uniformly (with density ρ) over a d -dimensional space of linear size L . Let us further suppose that these vertices can be attached to one another via a finite range probability function (p) that decays sharply with distance (r):

$$p(r) = p_0 e^{-r/l_c} \quad (2.18)$$

where l_c is the interaction range, the quantity inducing a scale in the system and $p_0 = 1/(l_c \cdot (1 - e^{-L/l_c}))$ is the normalization parameter -which, in turn, varies with the interaction range so that $p(r)$ converges appropriately to be considered a probability. Therefore, it is to be expected that the degree distribution $P(k)$ follows an exponential shape, which is what we show -for different values of l_c in Fig. 2.6.

Up until now, every theoretical network type that we have introduced, despite their obvious differences, share a common feature: they do not provide any insight about the *network formation process*. That is, they just assume that nodes coexist and then they establish connections following the mathematical rules we have been discussing. There are, however a class of models which do not directly assume this:

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Figure 2.6: Plot of the degree distribution of a spatial network for different correlation length (l_c) values. The lower the value of l_c , the less dense and more modular the network is. For the sake of comparison between the spatial network and the other two classes of probabilistic networks, we have fixed the same network size ($N = 10^4$).

generative network models.

Generative network models. While the previously studied random models just dealt with an *a priori* given number of nodes and edges, it did not provide any insight about which mechanisms dictate how new nodes aggregate to create the network. In this case, the idea behind generative models is to propose network growing mechanisms to see what structures they produce and to compare these with real-world networks; if the two are similar to one another, it would suggest -not prove- that similar mechanisms may be responsible for the formation of real networks. Although the field of generative mechanisms has been really fruitful and has a wide spectrum of network construction philosophies (vertex copying models, models based on optimization, among many others), we will just overview the *preferential attachment model*, as this is the only generative model that we will make use of in this Thesis.

It has been evidenced that many real-life networks have degree distributions that are power-law-like [81–84] and in Ref. [85], authors provide a thorough review of empirical networks showing this property, although in [86] they recently revised this idea. It is somewhat surprising that networks so different in origin (the Internet, scientific citations or biological networks, to just name a few) have such a common feature; therefore, it seems appropriate to seek an underlying mechanism for their generation.

- **The Barabási-Albert model:** The crucial and central assumption of the preferential attachment model is that *the probability of acquiring a new con-*

nection is proportional to the number of connections each node already has. This certainly is plausible in the case of scientific citations, but it has been shown to also work in a wide variety of real-world cases. It should be clarified that, in order to make this a viable model, one has to start with a seed (that is, a starting state of the network), because strictly speaking, there are no connections in the beginning and therefore (due to the proportionality rule), no new connections would be made. To illustrate an example of this kind of networks, we will give a brief description of the Barabási-Albert model (which, apart from being one of the best studied ones, is of special interest of this Thesis).

At every step, the number of connections made by each new node is exactly c . Thus, the smallest degree in the network is always $k = c$ [66]. It can be shown that this model comes from the Price one [66, 87], which was proposed in the context of bibliographic citations.

For a formal derivation of this model's degree distribution, we refer the reader to [88], where this path is taken. For convenience, we will just present the degree distribution $P(k)$, given by:

$$P(k) = \frac{2c(c+1)}{k(k+1)(k+2)} \quad (2.19)$$

for $k \geq c$. If we take the $k \gg 1$ limit, we get:

$$P(k) \approx k^{-3} \quad (2.20)$$

which is why the Barabási-Albert model generates a degree distribution with a power-law shape that always has an exponent $\gamma = 3$. We have portrayed the degree distribution for various connectivities (varying the average degree of the network) in Fig. 2.7.

An exhaustive discussion of different generative models and their applications can be found in [66].

2.2 Dynamics in Complex Networks

At this point, we have just dealt with the Complex Networks part -that is, the structural part of our problems. However, as we said in Chapter 1, we are trying to understand the relationship between structure and dynamics in complex networked systems and to inspect how high-order interactions affect the propagation of synchronized activity in this class of systems. Moreover, as we want to explore the possibility that single-node dynamical measures inform us about the general network structure, we are going to introduce some dynamical models which, when networked and coupled, will undertake different routes to *synchrony*. We are going to introduce the dynamical models we have used (two examples of chaotic oscillators and a neuron model) and we will discuss a variety of them in Appendix B. We have to stress the fact that, as we already stated in Chapter 1, we use a neuronal model and the Rössler oscillator because we have access to an experimental implementation of both systems and, therefore, we will have the opportunity to test our hypothesis.

Figure 2.7: Plot of the degree distributions of Barabási-Albert. For the sake of comparison between this generative model and probabilistic networks -see Fig. 2.5-, we have fixed the same size ($N = 10^4$) and varied their corresponding connectivity parameters ($\langle k \rangle$ in the B-A case). As a guide for the eye, we also include the theoretical $\gamma = 3$ line.

Throughout this Thesis, we have worked with two main classes of dynamical models: *chaotic systems* and *spiking neuron models*. Therefore, although there exists a rich and interesting body of literature in the frame of nonlinear dynamics, we are only going to focus on contextualizing these two types of systems. We refer the interested reader to Refs [89, 90] for a basic theoretical overview of the literature in nonlinear dynamics and to the recent book by Strogatz [91] for an updated perspective and applications. Another remark that has to be done before we can continue is that networked neuronal dynamics is a *non-linearly coupled and time-pulsed* problem and, thus, it cannot be inspected with the general framework that we are equipped with to study the non-biological models that we will introduce next.

In this Thesis we have used the *Lorenz* and the *Rössler* oscillators as examples of systems exhibiting chaotic dynamics. Nevertheless, it is also undeniable that there is a historically-missing piece: the Kuramoto oscillator. Based on context completeness and on its historical relevance for the study of synchronization, we are going to briefly introduce it in Section 2.3.1.

2.2.1 Chaotic oscillators

In order to address if individual dynamics can be informative about global structure - via a restriction on potential degree distributions, we initiated our studies with chaotic attractors. We did so because there are some well-established ground-truths and they are much simpler systems (at least regarding interpretation and parameter-fixation) than biologically-inspired neuron models -which we also have experimental access to.

In order to inspect the whole dynamical evolution of a system composed by N dynamical units, we draw on the following expression:

$$\dot{\mathbf{x}}_i = \mathbf{f}(\mathbf{x}_i, \tau_i) - \sigma \sum_j \mathcal{L}_{ij} \mathbf{h}(\mathbf{x}_j) \quad (2.21)$$

where $\mathbf{x}_i$ is the vector of state variables of the i th dynamical unit, τ_i is the parameter heterogeneity vector that different nodes might present and $\mathbf{f}$ is the autonomous function -how a node would behave like if it did not interact. We have implicitly assumed that, parameter heterogeneity aside, every node is dynamically identical to the rest. Regarding the interaction term, σ is the *coupling strength* (that is, how intensely nodes interact) and $\mathbf{h}(\mathbf{x}_j)$ is the output function, which indicates how different variables are coupled with the ensemble.

If we deal with a diffusive process taking place in a linearly coupled networked system, we can specify its topology, whatever it may be, by a *Laplacian matrix* ($\mathcal{L}$), constructed from the *adjacency matrix*, which encodes the crucial ingredient -i.e., the interaction among dynamical units- to form a Complex System and the *degree matrix* ($\mathbf{K} = k\mathbf{I}$) -a diagonal matrix which contains the degree of each node- via the simple relation $\mathcal{L} = \mathbf{K} - \mathbf{A}$.

By varying $\mathcal{L}$, we specify distinct topologies -just as those which have already been introduced in Section 2.1.2. By changing $\mathbf{f}$, we may consider entirely different processes, like chaotic maps [92] or chaotic flows (examples of this class of dynamics are epidemic spreading [93] or electrical circuits [94]).

In the nonlinear dynamics context, a chaotic system is regarded to be one that, while being deterministic, is *extremely* sensitive to initial conditions and thus, unpredictable. This incapability of predicting the behavior of these systems is due to the fact that there is no way in which an *infinite* precision can be attained when sampling values from any system -be it experimentally or computationally- and, because of the very definition of chaos, an infinitesimal discrepancy can magnify in a qualitatively different behavior than the expected. This is the reason that, often, these systems are studied in terms of their stability or their asymptotic dynamics. It is remarkable that there is no general consensus about a definition of what attractors are -as discussed in [95] or [96]. We subscribe the following intuitive definition, found in [97], of what an attractors is: it is a *set* of numerical values toward which a system tends to evolve, for a wide variety of starting conditions of the system. And, a strange attractor version can be thought to be one that has a stable, nonperiodic behavior, that can be represented as a nonrepeating pattern in the system's phase space. So far, every strange attractor that has been found has zero measure and fractal dimension in the embedding phase space [98].

The Rössler system. This system is one of the most relevant and studied ones in the field of nonlinear dynamics (which provides us with a well explored parameter space and even some theorems to guide our search). It is taken as a paradigmatic example of a dynamics exhibiting phase coherence and chaotic amplitude; the other main reason to use this model is that we had access to experimental data generated

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with electrical circuits (as it will be detailed in Chapter 3) that implement this type of chaos.

This model is due to Otto E. Rössler [99], who proposed it in the context of seeking the model that possessed the minimum ingredients for continuous-time chaos. Although he developed a series of systems, the most famous is given by the set of equations:

$$\begin{aligned}\dot{x} &= -y - z \\ \dot{y} &= x + ay \\ \dot{z} &= b + z(x - c)\end{aligned}\tag{2.22}$$

where a , b and c are parameters. According to the notation used in Eq.(2.21), we can rewrite Eq.(2.22) as, with $\mathbf{f}(\mathbf{x}) = (-y - z, x + ay, b + z(x - c))$. Particularly, for the investigations carried out in this Thesis we chose $(a, b, c) = (0.2, 0.2, 9.0)$ and $\mathbf{h}(\mathbf{x}) = (0, y, 0)$. The expression for the networked case thus reads:

$$\dot{\mathbf{x}}_i = (-y_i - z_i, x_i + 0.2y_i, 0.2 + z_i(x_i - 9.0)) - \sigma \sum_j \mathcal{L}_{ij}(0, y_i, 0)\tag{2.23}$$

It can be shown, via the use of the Master Stability Function (MSF) formalism [100], that this is a Class II model: provided the coupling strength is high enough, a network of these oscillators can synchronize for any kind of topology.

There are at least three reasons why this system is minimal for continuous chaos:

- As its phase space has the minimal dimension three, the Poincaré-Bendixson theorem precludes the existence of other than steady, periodic, or quasiperiodic attractors in autonomous systems defined in one- or two-dimensional manifolds [101].
- Its nonlinearity is minimal because there is a single quadratic term.
- For a broad range of parameters, it generates a chaotic attractor with just one lobe -which allows to univocally define a phase-, in contrast to the Lorenz attractor -which, as we will see next, has two lobes.

The Lorenz oscillator. The rationale beneath choosing to work with this chaotic oscillator is, again, twofold: on one hand, it is historically one of the most relevant advances in chaos theory and, on the other hand, we wanted to provide a more robust evidence when exploring the central hypothesis of the Thesis -as stated in Chapter 1: we are interested in inspecting if individual dynamical measures can be informative about global structural quantities.

This chaotic dynamical model was the pioneering work developed by Lorenz in 1963 [102], deriving it in the context of a model in Earth's atmosphere convection dynamics (noteworthy, it also naturally arises in models of lasers and dynamos). In this case, we deal with a double-lobed attractor -because of the set of parameters we chose, which is detailed below-, this probably being the most iconic element of nonlinear dynamics. The equations are:

$$\begin{aligned}
\dot{x} &= a(y - x) \\
\dot{y} &= x(b - z) - y \\
\dot{z} &= xy - cz
\end{aligned} \tag{2.24}$$

where, again, a , b and c are parameters, whose typical values -and the ones we used- are $(a, b, c) = (10, 28, 8/3)$. We chose to couple the oscillators through the output function $\mathbf{h}(\mathbf{x}) = (0, y, 0)$. Just as in the Rössler case, we can also rewrite Eqs. (2.24) to refer to the networked scenario, using Eq. (2.21) as:

$$\dot{\mathbf{x}}_i = (10(y_i - x_i), x_i(28 - z_i) - y_i, x_i y_i - 8z_i/3) - \sigma \sum_j \mathcal{L}_{ij}(0, y_i, 0) \tag{2.25}$$

As we pointed out in the previous case, via the use of the MSF formalism [100], one can show that this is also a Class II model, so it can synchronize.

2.2.2 Spiking neuron models

Apart from studying chaotic dynamics, we have also inspected a biologically-inspired neuron model. The main reason beneath this exploration resides in the fact that we have access to an experimental setup that permits us to contrast our numerical results out with cultured neural networks coming from a locust, as it will be described in Chapter 4.

As the brain is arguably the primer example of a hierarchical multiscale complex system, one would be tempted to abandon every modellization effort that has the aim of understanding this system. Fortunately, many things can be learnt from a diversity of perspectives that have been deployed over the years and from the intersection of disciplines -psychology, medicine, physics, computer science, mathematics, ...-. We are going to sketch a broad scheme of different dynamical models (more on this in Appendix B) that have been carried out in parallel to the structural or correlational descriptions.

It is important to understand that each level of description will have a different focus and, thus, there will be a diversity of advantages and constraints that each of these will pose. A common conceptual framework that can be useful to understand the theoretical balance that these models have to achieve is that of *transparency vs accuracy*. Transparency refers to the physiological interpretability of a mathematical model (be it capturing neuronal spiking response or entire brain dynamical evolution); on the other hand, we understand accuracy as how similar the mathematical output and the empirical results are. And, on top of both, there is the constraint on *feasibility*, meaning that if a model fulfills both conditions (i.e., it is easily interpretable and accurate), it also has to be simple enough to either be analytically treated (this is almost never the case) or numerically integrated. For further discussions about this and for reading about other models other than the Morris-Lecar neuron, we refer the reader to Appendix B.

Since the dawn of Neuroscience, it is known that neurons are capable of producing sudden increases in their membrane voltage. These signals are more commonly known as action potentials or spikes, which are the consequence of the difference

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in ionic concentration (due to the fact that the neuronal membrane has gates susceptible to open and close to let ions in or out [103]). Even before the discovery of what was causing these spikes to exist, it was hypothesized (see [104, 105] or, more recently [106], among many other examples) that the purpose of these electrical variations was that of transmitting information. Not too long ago, neurological research [107–109] pointed towards the timing of single spikes as the way of neurons to encode information, not only in their average firing frequency.

One of the most fruitful approaches when modeling the dynamical behavior of real-world neurons has been the introduction of *compartmental models*. These consider neurons and their parts -axon, dendritic tree, soma, etc- as electrical circuits consisting on small portions of uniform membrane potential which can be described by two quantities: a capacity and a transversal conductance. The compartments would be coupled together through a resistance that is determined by geometrical properties of the cell.

Although there are many compartments that *ought to be* considered (the fast inactivating and persistent Na^+ currents, the non-specific cation current, the muscarinic K^+ current, the fast non-activating K^+ current, among many others [110]), in practice much simpler versions are used. The prime example of compartmental models is the Hodgkin-Huxley neuron.

The Hodgkin-Huxley model. It is considered to be the founding stone of modern neuronal models. It is even used nowadays, due to its biological plausibility and to the phenomenological richness it offers. It was the first compartmental model and also the pioneering work in conductance-based models (neurons' protein molecule ion channels are represented by conductances and their lipid bilayer by a capacitor) to be developed. Introduced in 1952 by Hodgkin and Huxley [111] in the context of a mathematical effort to explain the physiological evidence of hyperpolarization of the squid's giant axon. Although the model has a quite limited behavior for original values of parameters, it can actually exhibit all properties in Fig. B.1, if the parameters are tuned. In general, all conductance-based models are referred to as being of the *Hodgkin-Huxley-type*. Such models are important not only because their parameters are biophysically meaningful and measurable, but also because they allow us to investigate questions related to synaptic integration, dendritic cable filtering, effects of dendritic morphology, the interplay between ionic currents, and other issues related to single cell dynamics. For further details about these models and other simpler ones, see Appendix B.

This model is expensive to implement. Thus, one can use it only to simulate a small number of neurons or when simulation time is not an issue. Alternatively, one can look for simpler-but-still biologically plausible models, the primer example of this being the Morris-Lecar neuron.

The Morris-Lecar model. In order to compare with the data coming from cultured networks that our collaborators provided us with, we implemented the bio-inspired Morris-Lecar (ML) model, introduced in 1981 by Catherine Morris and her then supervisor Harold Lecar [112]. They proposed this set of equations in the context of reproducing the variety of oscillations that experimental recordings

showed for the Ca^{2+} and K^+ conductances. The equations describing the membrane potential behavior for this mathematical neuron read:

$$\begin{aligned} C\dot{V} &= -g_{\text{Ca}}M_{\infty}(V - V_{\text{Ca}}) - g_{\text{K}}W(V - V_{\text{K}}) \\ &\quad - g_{\text{l}}(V - V_{\text{l}}) + q\xi + I^{\text{ext}} \\ \dot{W} &= \phi\tau_W(W_{\infty} - W) \end{aligned} \quad (2.26)$$

where V and W are, respectively, the active variable (that is, the neuron's membrane potential) and the recovery variable (the fraction of open K^+ channels of the neuron) and M_{∞} , W_{∞} and τ_W are hyperbolic functions dependent on V , detailed below; ϕ is a reference frequency and $q\xi$ is a Gaussian white noise of zero mean and intensity q . The parameters g_X and V_X account for the electric conductance and equilibrium potentials of the $X = \{\text{K}, \text{Ca}, \text{leaky}\}$ channels. Additionally, the channel voltage-dependent saturation values respond to the dynamics:

$$\begin{aligned} M_{\infty}(V) &= \frac{1}{2} \left[1 + \tanh \left(\frac{V - V_1}{V_2} \right) \right] \\ W_{\infty}(V) &= \frac{1}{2} \left[1 + \tanh \left(\frac{V - V_3}{V_4} \right) \right] \\ \tau_W(V) &= \cosh \left(\frac{V - V_3}{2V_4} \right) \end{aligned} \quad (2.27)$$

The values of the parameters we used throughout this Thesis when simulating this model are given in Table 2.1.

C	$20.0 \mu\text{F}/\text{cm}^2$
g_{Ca}	$4.0 \mu\text{S}/\text{cm}^2$
g_{K}	$8.0 \mu\text{S}/\text{cm}^2$
g_{l}	$2.0 \mu\text{S}/\text{cm}^2$
V_{Ca}	120.0 mV
V_{K}	-80.0 mV
V_{l}	-60.0 mV
V_1	-1.2 mV
V_2	18.0 mV
V_3	12.0 mV (for type I), 2.0 mV (for type II)
V_4	17.4 mV
ϕ	$1/15$

Table 2.1: Parameters used for the Morris-Lecar simulations.

The typical neuronal dynamics exhibited by Eq. (2.26) consists of a sequence of L spikes produced at random times t_l , with $l = 1, 2, \dots, L$, whose amplitude variability is negligible (or, as in physiological terms, the neuron has a *stereotypical spiking profile*).

First of all, we studied the single noiseless neuron scenario - that is, before delving into networked dynamical cases, we study the individual behavior of each unit and to begin with this process, we set $q = 0$. We explored the *characteristic curve* of the neuronal firing rate when we varied the external current I^{ext} for the two types of excitability regimes that the Morris-Lecar model allows, by choosing adequately

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V_3 in Eq.(2.26), in order to be able to fix -when we move to the networked case- the external current for both neuronal types. These excitability regimes, type I and type II, respectively show a continuous or discrete transition in its spiking frequency when increasing the external current I^{ext} . Results are shown in Fig. 2.8.

Figure 2.8: Characteristic response curve for the two types of excitability regimes that the Morris-Lecar model allows, by varying V_3 in Eq. 2.26. In (black) dots, type I neuron ($V_3 = 12.0$ mV): it exhibits a continuous curve. In (red) triangles, type II neuron ($V_3 = 2.0$ mV): when increasing I^{ext} , its spiking rate undergoes a discontinuous transition. The I threshold values are marked as vertical lines, respectively: $I_{thr}^I = 40.0$ mA (black dashed line) and $I_{thr}^{II} = 51.0$ mA (red dot-dashed line).

We decided to work with neurons displaying a type II excitability regime, which, as seen in Fig. 2.8, exhibit a discontinuous transition from silency to the spiking regime. We set the external current $I^{ext} = 50.0$ mA such that the neuron is sub-threshold ($I_{thr}^{II} = 51.0$ mA) to neuronal firing, which is induced by the white Gaussian noise -we provide an example of how a time series of this model, with the selected parameters, looks like in Fig. 2.9 (left plot).

Thus, we now have to explore the role that the noise intensity has in the spiking activity of the neuron. To do so, we firstly inspected how the time series and the ISI distribution looked like for different noise intensities -calculating them for time series with 2000 spikes-, a process which has been summarized in Fig. 2.9. After that preliminary characterization, we investigated the relation between the activity and the noisy input via the *signal to noise ratio* [113, 114] $SNR = \mu/v$, where μ is the mean of the distribution of interspike interval (ISI) times and v is the variance of the same distribution. We portray the results in Fig. 2.10.

We selected $q = 0.5$ as the noise intensity we would be using further on, due to the fact that it makes the ISI distribution narrow while still providing enough input to make the neuron spike. Furthermore, the spiking activity induced by the noise is not too close to coherence [115].

The next question that naturally arises then is, once we have the basic characteriza-

Figure 2.9: (Right) Illustration of how the time series looks like for different noise amplitude values. We see that for $q = 0.2$, there almost no spikes and for $q = 3.0$ the neuron is basically a noisy oscillator; therefore, we already have the first constraint: we should select an intermediate value of q if we want a frequent but non-coherent spiking behavior. (Left) Visualization of the ISI distributions for the noise amplitudes depicted in the previous panel. We calculated these distributions with 2000 spikes. As it can be seen, we here show that $q = 0.5$ makes the distribution as least as narrow as greater values of noise (as that of $q = 3.0$, for example) while keeping the spiking behavior.

Figure 2.10: Signal to noise ratio (SNR) of the type II Morris-Lecar neuron when varying the intensity (q) of the noisy input. We have marked with a vertical (red) dotted line the value that we have selected from this analysis and the one shown in Fig. 2.9.

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tion for the individual neuron, how to couple them in a networked fashion. There are multiple options attending to physiology [116]: electrically -via gap junctions-, chemically -through neurotransmitters released in chemical synapses- or electrochemically -that is, considering both aspects. The advantage for taking the first option is that it can be modelled as a *Laplacian* interaction and, thus, we could make use of Eq. (2.21); nevertheless, from the biological point of view it is a non-realistic scenario because, although it is being evidenced that there are more gap junctions than previously thought [117], currently, it is considered that the main neural communication is through chemical synapses [116]. Thus, we take the second route, which means that the coupling of the neuron i th with the neuron ensemble is described by the injected synaptic current; while there are multiple ways of modelling these chemical synapses [118–120], we take one of the simplest ones:

$$I_i = \frac{\sigma}{K} \sum_{j \in \mathcal{N}} I_{ij} = \frac{\sigma}{K} \sum_j a_{ij} e^{-2(t-t_j)} (V_0 - V_j) \quad (2.28)$$

given by the superposition of all the post-synaptic potentials emitted by the neighbours of node i in the past, being $t_j < t$ the time of the last spike of neighbour j (that is what we mean by $j \in \mathcal{N}$). The synaptic conductance σ , normalized by the largest node degree present in the network $K = \max(k_i)$, plays the role of coupling intensity. V_0 is the voltage the neuron membrane would have in absence of external input or spontaneous activity, also known as the rest potential; following physiological evidence [121], we set it to be $V_0 = 59.0$ mV.

Although we exploited this scheme to provide a variety of insights (see Chapters 3 and 4), it can be refined even further. That is, instead of just describing first-neighbors synaptical interactions, we allow high-order interactions to be present in the network.

High-order interactions. In Chapter 6 we are interested in introducing glial effects in neural networks. Ultimately, we would like to develop a computationally cheap and mathematically simple model that accounts for the neuro-glial interaction. The first step towards fulfilling this challenge is to model the effect of astrocytes in the synchronization route of a neural ensemble. To do so, we modified our approach inspired in a mathematical tool recently developed by E. Estrada et al. in [59–62].

A known fact of the brain is that it contains, at least, as many neurons as glial cells, some studies even pointing towards a more favorable ratio for the latter type of cells [122]. If one takes this into account, it may not be obvious to find out why neurons have occupied the spotlight for such a long time.

The classical view regarding glial cells is that they fulfil a variety of *support roles*. They have been extensively studied from different angles: as metabolic regulators [123], as neuroprotectors (via the blood-brain barrier) [124], debris removers [125], myelin producers (to enhance neuronal electrical signal transmission) [126] or as synaptic growth factor releasers [127].

While all this roles are essential for the correct functioning of the brain, there is also a growing corpus of evidence that suggests the implication of a type of glial cells (namely, *astrocytes*) in the synaptical modulation [128–130]. Furthermore, even

the traditional idea of synapses is being challenged, with some authors introducing the term *tripartite synapsis* [131]. It is known that astrocytes can establish up to 10^5 synapses, meaning that they might be responsible for the modulation of the electrical response of neurons sharing no anatomical connection at all and, therefore, they could be the source of high-order interactions supporting coordination levels that overcome the outreach of direct neural connectivity.

Several attempts have been made to model the neuroglial interaction [51], most of them focusing on the neuron-astrocyte pair or, more commonly, a triade of two neurons and an astrocyte [53, 54]. However, few studies have considered the networked context, which is usually mathematically and computationally costly [55]. In this work we model the neural-glial ensemble as a geometrical network with synaptic coupling, where the synaptic modulation of astrocytes is introduced using a high-order interaction formalism inspired in that developed in Refs. [59–61] and [62]. It provides a solid quantitative mean to simulate and analyze the dynamics of a system in which these higher-order interactions are present. These effects are susceptible of revealing themselves particularly important in space embedded systems, where the Euclidean distances shape not only the probability of connection but also their weights. The high-order connectivity operator allows us to extend the usual first-neighbour interaction scheme, that disregards higher-order interactions under the implicit assumption that if two nodes are not topologically connected they do not dynamically interact; such an assumption is no longer valid in a network of neurons whose communication is mediated by astrocytes.

After having constructed the network, one would have to choose the form of interaction, that means that the rule of decay -exponential, log-normal, geometrical, among others- of high-order interactions is a key ingredient of this whole process. Finally, once the decay rule has been chosen, another parameter that can be fixed -depending on the precise system we are dealing with- is the *maximum interaction distance*: that is, which would be the furthest (in the network sense) interacting neighbour. For example, are third-neighbours (nodes whose shortest path length is equal to three) relevant for the system we want to model? Or is it enough with second-neighbors? These questions are the last that have to be answered.

We present a visual example of the idea beneath this high-order interactions framework in Fig. 2.11, where a spatial network of $N = 150$ nodes is presented, highlighting first and second-neighbours.

For a more thorough and detailed discussion and description of this novel framework, we refer the reader to [59–61] and for an application of this tool, check [62].

Some mathematical notions. Let $\mathcal{G} = (V, E)$ be a simple, loopless, connected, unweighted and undirected graph with N nodes and m edges. The usual way to proceed when considering first-neighbour interactions only is to define the adjacency matrix $\mathbf{A}$ (as we did in Section 2.1) and to express the networked dynamics in terms of Eq. (2.21). This extension of high-order interactions in general reads as follows:

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Figure 2.11: Spatial network ($N = 150$) visualization in which first and second-neighbours are highlighted.

$$\begin{aligned} \dot{x}_i = & f(x_i) + \sigma_1 \sum_{(i,j) \in \mathcal{N}} (H(x_j) - H(x_i)) + \sigma_2 \sum_{d(i,k)=2} (H(x_k) - H(x_i)) + \dots \\ & \dots + \sigma_{d_{\max}} \sum_{d(i,r)=d_{\max}} (H(x_r) - H(x_i)) \end{aligned} \quad (2.29)$$

where σ_d are the coupling strengths with which each distance of order d is considered to interact, $\mathcal{N}$ means the neighborhood of a certain node -that is, nodes that share a connection with it- and the summation over $d(i, j) = \tilde{d}$ means to only consider those nodes i and j separated a network distance of $\tilde{d}$. If we assume that $\sigma_1 = \sigma$ and that the rest are just a fraction of it, decaying with the topological distance:

$$\begin{aligned} \dot{x}_i = & f(x_i) + \sigma \sum_{(i,j) \in \mathcal{N}} (H(x_j) - H(x_i)) + \sigma 2^{-\alpha} \sum_{d(i,k)=2} (H(x_k) - H(x_i)) + \dots \\ & \dots + \sigma d_{\max}^{-\alpha} \sum_{d(i,r)=D} (H(x_r) - H(x_i)) \end{aligned} \quad (2.30)$$

Although we did not take this route directly because the interactions we are interested in modelling are not Laplacian, we certainly took inspiration from this approach, as it will be seen nextly.

An example: geometrical neuro-glial networks. For the structural part, we follow the spatial generative model described in Section 2.1.2. We used $l_c = 0.075$ and $L = 89$; this particular choice of parameters is such that these synthetic networks resemble the ones our collaborators found in the neural cultures experiments -see Chapter 4 for details. We used the aforementioned Morris-Lecar model, with a capital modification: we include non-structural synaptic currents as valid inputs, that is, high-order interactions are permitted.

In spatial, highly clustered networks with reduced link range l_c , the coupling configuration generally used (that is, only permitting first-neighbour interactions) favors travelling wave synchronization, as long as the coupling strength is high enough [132]. On the contrary, in the mean field approximation limit, $l_c \rightarrow L$, only globally incoherent/coherent states are accessible [133]. In our model, as a balance between these two extrema, we intend to explore the potential enhancement effect of higher-order connectivity at the local spatial scale, as for example the glial ensemble has in the neural circuits that are not directly connected among them [130]. Therefore, we allow that the injection current I_i accounts for the contribution not only from neurons $j \in \mathcal{N}_i$ whose topological distance is $d(i, j) = 1$, but also from neighbors at higher topological distances $d(i, j) > 1$, that is:

$$I_i = \frac{\sigma}{K} \sum_{d=1}^D d^{-\alpha} \left(\sum_{j|d(i,j)=d} I_{ij} \right) \quad (2.31)$$

where I_{ij} is defined as in Eq. (2.28), D is the maximal allowed topological distance. The successively distant contributions to the injection synaptic current I_i are modulated by a geometrically decaying term, $d^{-\alpha}$, where the constant α is a suppression parameter for the distance-dependent coupling strength. Notice that when the summation is limited to the first order $D = 1$, the usual first-neighbours interaction is recovered.

2.3 Synchronization

One of the main focuses of modern Complex Networks Science, and of this Thesis, is to provide a reliable way of relating the dynamics taking place in a network with the structure it is embedded in. A common way of characterizing the global activity of the nodes of a network is by means of the *synchronization* level. The main interest of developing precise synchronization measures is that often the functionality of the system is related to the synchronization level. Furthermore, it is possible that the structural network is partially (or completely) unknown and the major idea beneath this Thesis is to inspect the relationship between the dynamical node measures and the structural features of the network.

We will firstly present a model in which many quantities can be analytically calculated, in order to provide some insights and exemplifications.

2.3.1 The Kuramoto model: a paradigmatic system

As it was said in Chapter 1, Winfree [19] carried out the first calculations on what today is regarded as the birth of the study of *collective synchronization*. One of the most successful strategies to confront this problem was introduced by him and later developed by Y. Kuramoto [20]. He realized that *phase oscillators* permitted an analytical treatment when some assumptions were made (detailed shortly), so he got rid of the amplitude variable and the equations describing each dynamical unit are given by:

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$$\dot{\theta}_i = \omega_i + \frac{K}{N} \sum_{j=1}^N \sin(\theta_j - \theta_i) \quad (i = 1, \dots, N) \quad (2.32)$$

where θ_i is the phase of oscillator i , $\dot{\theta}_i$ is the instantaneous frequency that oscillator i exhibits at a given timestep, ω_i stands for the natural frequency of the oscillator i and K is the coupling strength. The normalization factor $1/N$ in the coupling term guarantees a smooth behavior in the thermodynamic limit ($N \rightarrow \infty$). One greatly simplifies the problem if the following assumptions [134–136] are made:

- The population is big enough (namely, $N \rightarrow \infty$).
- We can wait for a sufficiently long time (to ensure the stationary state).
- Every oscillator is nearly identical to the rest.
- We are interested in macrostates (i.e., an order parameter is useful to characterize this problem).

At first sight, these may seem like a lot of rigid requisites to study the problem. Regardless of that impression, it cannot be disputed that many insights have come out of this theoretical framework. The major advance using this perspective, on this specific model, was that of understanding the *synchronization route as a dynamical parallelism to an equilibrium phase transition*.

In an equilibrium phase transition, the system has a disruptive change from a *low order parameter* to a *high order parameter* (this being literally order or other magnitudes to characterize the system), passing through a *threshold value* of this order parameter where the transition happens, as the *control parameter* increases. The equivalent narrative in the synchronization route would be that of considering the *frequency variance* as the order parameter and the *coupling strength* as the control one. Then, exactly like in the aforementioned phase transition, one has a scenario of high frequency variance -asynchronous phase-, passes through a threshold -onset of synchronization- and ends up with low frequency variance -synchronous phase.

Kuramoto [20] realized that the most suitable case for analytical treatment should be the mean field approach. He worked on an all-to-all (as described in Section 2.1.2), sinusoidal coupling. This system is an excellent example of the need of numerical approaches in our systems, as we mention in Section 2.5. Even in the simplest case in which nodes interact with the ensemble via a single mean field interaction, there are still open questions that have evaded every analytical attempt.

As it can be shown [14], calculations are simplified if we introduce the *global* complex order parameter:

$$r(t)e^{i\phi(t)} = \frac{1}{N} \sum_{j=1}^N e^{i\theta_j(t)} \quad (2.33)$$

with the modulus $0 \leq r(t) \leq 1$ measuring the phase coherence the population exhibits, which is bounded between 0 -complete asynchrony, each phase evolves according to its own internal dynamics- and 1 -totally synchronous state, all oscillators

possess the same phase at all times when in this state; $\phi(t)$ is the average phase. Using these newly defined quantities, Eq.(2.32) can be rewritten as:

$$\dot{\theta}_i = \omega_i + Kr \sin(\phi - \theta_i), \quad (i = 1, \dots, N) \quad (2.34)$$

Even from a conceptual point of view, before delving into mathematical details, one can see that the second term, as it is proportional to r , will impose a positive feedback loop to the whole network's oscillation. Without loss of generality, let us set $\phi = 0$ -that is, to use a rotating frame of reference. Then, Eq.(2.34) would be modified to:

$$\dot{\theta}_i = \omega_i - Kr \sin \theta_i, \quad (i = 1, \dots, N) \quad (2.35)$$

If one demands some conditions [14, 134] for the stationary distribution of drifting oscillators -namely, $\langle e^{i\theta} \rangle_{\text{lock}} = \langle \cos \theta \rangle_{\text{lock}} = \int_{-Kr}^{Kr} \cos \theta(\omega) g(\omega) d\omega$ -, and taking the $N \rightarrow \infty$ limit -thus moving onto the continuous case-, a self-consistent equation for r would read:

$$r = \sigma r \int_{-\frac{\pi}{2}}^{\frac{\pi}{2}} (\cos^2 \theta) g(\omega) d\theta \quad (2.36)$$

where $\omega = Kr \sin(\theta)$ and $g(\omega)$ is the distribution of frequencies that is usually assumed to be unimodal and symmetric around 0. A non-trivial solution that this equation admits is:

$$K_c = \frac{2}{\pi g(0)} \quad (2.37)$$

For larger values, $r > 0$. This expression is the mean-field one for the critical value of the coupling strength at the onset of synchronization.

Networked Kuramoto oscillators. We can think about the networked version of the previous scenario if we reformulate Eq. (2.32) as:

$$\dot{\theta}_i = \omega_i + \sigma \sum_j a_{ij} \sin(\theta_j - \theta_i) \quad (i = 1, \dots, N) \quad (2.38)$$

which is independent of the topology [14] in which we embed the oscillators, allowing thus to inspect the onset of synchronization independently of the structure. If we consider a symmetric adjacency matrix, a local order parameter r_i can be defined as:

$$r_i e^{i\phi_i} = \sum_{j=1}^N a_{ij} \langle e^{i\theta_j} \rangle_t \quad (2.39)$$

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where $\langle \dots \rangle_t$ denotes the time average. A global order parameter will be then given by:

$$r = \frac{\sum_{i=1}^N r_i}{\sum_{i=1}^N k_i} \quad (2.40)$$

Therefore, we can rewrite Eq. (2.38) as:

$$\dot{\theta}_i = \omega_i - \sigma r_i \sin(\theta_i - \phi_i) - \sigma h_i(t) \quad (2.41)$$

We have set $h_i(t) = \text{Im} \left\{ e^{-i\theta_i} \sum_{j=1}^N a_{ij} (\langle e^{i\theta_j} \rangle_t - e^{i\theta_j}) \right\}$. We can ignore this term if we assume $k_i \gg 1$ (and, therefore, the upcoming results will not be applicable to *an arbitrary* real case; if one wants to use this approach, it will have to be ensured that this assumption holds).

After some more mathematical manipulation, rewriting and simplification [14], one arrives to the critical coupling strength in the networked case:

$$\sigma_c = \frac{K_c}{\lambda_{max}} \quad (2.42)$$

where λ_{max} is the largest eigenvalue of the adjacency matrix. This expression shows the strong dependence between structure and the dynamical collective state attained by the system.

We refer the interested reader to [14, 135] for a deeper discussion of this system and its importance.

2.3.2 Synchronization measures

Although there is a vast literature regarding synchronization measures, attending to the systems we dealt with in this Thesis, we decided to work with phase synchronization (when there was a phase-coherent oscillation), global amplitude synchronization (if the system presented amplitude variability) and event synchronization (for point-like processes). It has to be explicitly mentioned that, up until now, every system that has been found firstly attains phase synchronization and then, in some cases, the global one. We succinctly introduce other synchronization measures in Appendix C, mainly the most used in neuroscientific applications.

Phase synchronization. It is defined as the global entrainment of the phases while the amplitudes may remain uncorrelated [137]. The concept of phase synchronization can be generalized via that of *lag synchronization*, that opens the possibility to considering time shifts when addressing the coordination of two time series; in the case of the lag being null, we would be dealing with standard phase synchronization. In this Thesis, when we worked with phase-coherent Rössler oscillators (see Section 2.2.1), we reconstructed their phase via the following simple relation between two of their amplitude variables $x(t)$ and $y(t)$ [138]:

$$\theta(t) = \text{atan}\left(\frac{y(t)}{x(t)}\right) \quad (2.43)$$

An alternative approach, often followed in point-like dynamics, is to use a process known as *phase reconstruction* [138]. The idea beneath it is to define some constraints in the phase space, therefore creating a fixed region often referred to as *Poincaré section* or *Poincaré map*. Once this section is set, we define τ_k as the k th time in which the trajectory of the system in the phase space crosses it. The phase $\theta(t)$ then is reconstructed as follows:

$$\theta(t) = 2\pi k + 2\pi \frac{t - \tau_k}{\tau_{k+1} - \tau_k} \quad (\tau_k < t < \tau_{k+1}) \quad (2.44)$$

As it can be checked from this expression, a linear interpolation is performed between crossings of the particular Poincaré section. This implies that instead of employing the whole dynamical evolution of the system, in order to reconstruct the phase, it is enough to consider these particular points in the phase space. A geometrical example of how these two processes look like can be found in Fig. 2.12: the blue lines correspond to the first method (and, thus, $\theta(t)$ has explicitly been marked) and the red one is an example of a Poincaré section.

Figure 2.12: A projection of the Rössler attractor in the $x - y$ plane. The two blue lines that form an angle in the right part show how $\theta(t)$ is calculated from $x(t)$ and $y(t)$. This can be done because, in this regime, the Rössler oscillator has a proper rotation around a reference point. The horizontal red line marked in the left part illustrates an example of a Poincaré section, and each time τ_k would denote a crossing between this line and the system's trajectory. Figure retrieved from [138].

The reason to use the first approach instead of the phase reconstruction one was that the former requires the system to be phase-coherent, while the latter is often used with event-like dynamics -or one that is suitable of being described in that way. Also, phase reconstruction is much slower and computationally costly than the former.

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After having obtained the phase with either of the methods, to calculate the global value of the network phase synchronization, we used the Kuramoto order parameter (r) that we introduced in Eq.(2.33).

Global synchronization. In both examples of chaotic oscillators, Lorenz and Rössler, we used a global measure of synchronization known as the time-averaged amplitude error E . In the Lorenz case, this will be our only criteria to assess the synchronization state because its attractor is double-lobed and, thus, we cannot define a phase; on the other hand, for the latter case, apart from characterizing the synchronization regarding the system's phase, we also kept track of E as a way of providing complementary information of the synchronization route. The precise definition of this measure is given by:

$$E = \frac{2}{N(N-1)} \left\langle \sum_{i \neq j} \|\mathbf{x}_i - \mathbf{x}_j\| \right\rangle \quad (2.45)$$

Thus, for the chaotic oscillators explained in Section 2.2.1, we keep track of both the amplitude and the phase synchronization, as a way to ensure that the route to synchrony when we increase the coupling strength between interacting dynamical units is achieved.

Event synchronization. Of particular interest for this Thesis is the concept of Event Synchronization (ES). Up to now, we have defined synchronization measures for continuous signals (whether we studied amplitude values, phases or frequencies). However, many systems in nature express themselves as point-like processes and, in this case, previous measures may be non-applicable.

It is the case with spiking neurons systems. These events are indeed discrete, because one assumes the time in which the membrane potential increases to be narrow enough, when compared to the typical interspike interval, that it can be taken as point-like. A different and suitable synchronization measure is needed for analyzing this kind of data.

The essential definition of ES is to count the fraction of event pairs matching in time, and count how often each time series leads in these matches. It is not convenient to define synchronization as the *exact* coincidence of events (because their times are discrete in this case); therefore, we have to allow a time window Δt in which we will consider the events to have happened synchronously. The only condition that should be *a priori* imposed is that Δt should be smaller than half the minimum inter-event distance, to avoid double counting.

The most interesting ES measure for us is defined as follows [139]: the synchronization between nodes i and j is calculated as the correlation between the binarized time series of spikes at zero delay B_i , within a time bin Δt . The system is evolved for a long time T and then divided in Γ small time bins of size Δt (i.e., $T = \Gamma \Delta t$). The binarization process works as: if, at the τ^{th} bin, neuron i has produced a spike, $B_i(\tau) = 1$; otherwise, $B_i(\tau) = 0$. Mathematically, we can obtain the synchronization between nodes i and j as:

$$s_{ij} = \frac{\sum_{\tau=1}^{\Gamma} B_i(\tau) B_j(\tau)}{\sqrt{\sum_{\tau=1}^{\Gamma} B_i(\tau) \sum_{\tau=1}^{\Gamma} B_j(\tau)}} \quad (2.46)$$

The global synchronization measure S can be therefore calculated as the ensemble average of the pairwise synchronization measure s_{ij} :

$$S = \langle s_{ij} \rangle = \frac{1}{N(N-1)} \sum_{i \neq j}^N s_{ij} \quad (2.47)$$

In this case, $0 \leq S \leq 1$, the limiting cases being complete absence of synchronization and perfect coordination. We have plotted a visual example of how this measure would be computed for the case of a network of $N = 500$ neurons in Fig. 2.13.

Figure 2.13: Visual example of how the synchronization measure described by Eqs. (2.46-2.47) is calculated. We present the raster plot -spikes (as black lines) of all the neurons over time- for a network of $N = 500$ neurons. We have marked the spikes that belong to the time bin τ , also marked in red. Those would compute as $B_i(\tau) = 1$, as described in the main text.

There are some situations -such as when working with spatial networks- in which it will be interesting to consider not only global but also local -in the Euclidean sense- synchronization. Thus, Eq. (2.47) can be modified to take into account the existence of groups of synchronized nodes whose distance is less than a given parameter ρ (denoted as $r_{ij} < \rho$), with the appropriate modification so it would be a *local synchronization measure* S_ρ :

$$S_\rho = \langle s_{ij} \rangle, \quad \forall \{i, j\} | r_{ij} < \rho \quad (2.48)$$

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We would like to stress that in this case, we are referring to an Euclidean notion of locality, rather than the usual topological one, because we will be using this measure in cultured -and, therefore, spatial- networks, in which space is a key factor.

In order to learn more about other synchronization measures and to have a more panoramic view of the different techniques that are nowadays used in the literature -specially in the Neuroscience community- check out Appendix C.

2.4 Ordinal patterns and the complexity measure

Now that we have already introduced some concepts to understand the architecture of our system, the dynamics that we simulated on top of that and the synchronization measures we used to make sure that we explored a variety of dynamical regimes, the last piece we have to mention is that of the *complexity measure* we have employed. In this section we will describe the statistical complexity measure we have chosen from the many that can be found in the literature [140], therefore, we refer the reader to Appendix D for a more detailed overview of complexity measures and some more conceptual aspects of this part of the Thesis.

The ordinal patterns formalism [141] associates a symbolic sequence to a time series, transforming the actual values of the measure into a set of natural numbers. In the following explanation, we will refer to the different stages outlined in Fig. 2.14. We first have to choose what is the right feature of the time series for us to focus on (A) -be it timestamps, maxima, etc. Then, we extract the attained values of these "special points" (B), which are then stored in an array while conserving the corresponding time order (C,D). After that, this array is divided in sequences of length d -we have to make sure that these sizes are not too big, more on this next- and consecutive points in each sequence are compared and classified based on their relative values (E) -meaning, instead of considering their actual values, we order them relative to each other. After doing so, a natural number is assigned to each sequence of length d (F) and the probability of the realization of each possible d -symbols sequence is computed. Finally, the probabilities are then used to construct the complexity measure. This is a broad-field, well-established and known method, statistically reliable and robust to noise and extremely fast in computation [142–146]. It is derived from two also well-established measures (divergence and entropy), also easily interpretable when analyzing non linear dynamical systems. In addition, it only requires soft criteria, namely that the time series must be pseudo-stationary (further developed below) and that $N_p \gg d!$ (where N_p is the number of points of the entire time series), both of them being easily checkable. We proceed in the following way:

1. We count how many times a certain symbolic order sequence (or *pattern* π) of size d appears (N_π).
2. We then define a probability of occurrence for each pattern: $p_\pi = \frac{N_\pi}{N_T}$, where N_T is the total number of patterns in which we divide the time series, i.e. $N_T = N_p/d$.
3. We construct an *empirical probability distribution*, which we call P_π from now on, from the pool of p_π .

This procedure is illustrated in Fig. 2.14 using a short time series coming from a chaotic Rössler oscillator. In the following, we describe in detail how to obtain the ordinal patterns, to construct their distribution and, ultimately, the complexity measure from a time series.

2.4. Ordinal patterns and the complexity measure

Figure 2.14: Illustration of the ordinal patterns formalism. (A) Detection of the maxima of the simulated (Rössler oscillator) signal. (B) Extraction of the attained values of these maxima -in the case of this type of system, for the M-L neuron we will work with Inter-Spike Intervals, as explained in Chapter 4-, which are then stored in an array (D) in the appropriate time order. After, this array is divided in sequences of length d ($d = 3$ in this example), and consecutive points in each sequence are compared and classified based on their relative values (E). Each sequence of length d is given a natural number and the probability of the realization of each possible d -symbols sequence is computed (F). The probabilities are then used to construct the complexity measure.

Mathematical definition of statistical complexity. Let $\Pi_d = \{0, 1, \dots, d-1\}$. Here $d \in \mathcal{P}$ is the total set of possible permutations of a sequence of numeric values (i.e., a time series or a vector) $v = (v_0, v_1, \dots, v_d) \in \mathcal{R}^{d+1}$, we then say that v has *ordinal pattern* $\pi = (r_0, r_1, \dots, r_d) \in \Pi_d$ if it fullfils the following constraint:

$$v_{r_0} > v_{r_1} > \dots > v_{r_{d-1}} > v_{r_d} \quad (2.49)$$

and

$$r_{l-1} > r_l \quad \text{if} \quad v_{l-1} > v_l \quad (2.50)$$

Once we have set the definition of ordinal patterns, we define the probability distribution of the ordinal patterns coming from the time series via the relative frequency of appearance (p_π) of a certain pattern π :

$$p_\pi = \frac{\#\{d | 0 \leq d \leq N_p - d!, (x_{d+1}, \dots, x_{d+d!}) \text{ has type } \pi\}}{d! - N_p + 1} = \frac{N_\pi}{N_T} \quad (2.51)$$

Once the probability distribution P_π is obtained using the relative frequencies p_π , we can define the statistical complexity (C), a measure that should be minimal both for pure noise and absolute regularity (in contrast to others like Kolmogorov Entropy or Lempel-Ziv Complexity, defined in Appendix D), and provide a bounded value. We choose the conventional normalization such that C is capped at 1 for other regimes. Being this so, we need to characterize the disorder and a correcting term, i.e. a way of comparing known probability distributions with the actual one. Following the traditional way [147–149], we define the statistical complexity as:

$$C[P_\pi] = H[P_\pi] \cdot Q[P_\pi] \quad (2.52)$$

that is, as the product of the Permutation Entropy (H) and the Disequilibrium (Q). The permutation entropy H is computed using the Shannon entropy (introduced in Appendix D), that gives an idea of the *unpredictability* of the series:

$$S[P_\pi] = - \sum_{j=1}^{d!} p_j \cdot \log(p_j) \quad (2.53)$$

where, by definition, we set $p_\pi(0) = 0 \ln(0) = 0$. The permutation entropy H corresponds to the normalization of S with respect to the entropy of the uniform probability distribution, S_{max} :

$$H = \frac{S}{S_{max}}, \quad S_{max} = S[P_e], \quad (2.54)$$

$$P_e \equiv \{1/d!\}_{1, \dots, d!} \implies 0 \leq H \leq 1$$

2.4. Ordinal patterns and the complexity measure

We have to explicitly mention that this measure can be applied to *any* time series whose underlying stochastic process verifies the following *weak* stationarity constraint:

$$\text{for } k \leq d, \quad p(x_t < x_{t+k}, t) = p(x_t < x_{t+k}) \quad (2.55)$$

that is, the time series has to be stationary for sufficiently small times (points not separated longer than d).

We recall that the other main ingredient necessary to construct the statistical complexity measure involves *Disequilibrium*. This quantity is a way of measuring the departure of our *empirical* probability distribution P_π (obtained from our data) from the uniform probability distribution P_e . This notion of *departure* can be acquired by several means; in this text, we adopt the statistical metric (it is not a proper measure of distance) given by the Kullback-Leibler [150] divergence (D_{KL} or, for lighter notation, K):

$$\begin{aligned} K[P_\pi|P_e] &= - \sum_{j=1}^{d!} p_j \cdot \log(p_e) + \sum_{j=1}^{d!} p_j \cdot \log(p_j) = \\ &= S[P_\pi|P_e] - S[P_\pi] \end{aligned} \quad (2.56)$$

where $S[P_\pi|P_e]$ is the Shannon cross entropy. We find it interesting and useful to give an intuitive idea about what this quantity measures: if we think of it in general $K(P_{true}, P_{param})$ (where P_{true} is the actual probability distribution and P_{param} is a parametrization of it), we can understand it as the "expected information loss when parametrizing P_{true} as if it was P_{param} ".

As this measure will not fulfill the triangle inequality [151] and is not symmetric, it cannot be regarded as a proper distance; thus, we symmetrize Eq.(2.56) to get a metric -actually, it can be shown [151, 152] that its square root is the proper metric. When doing this, we get the Jensen-Shannon divergence (J):

$$J[P_\pi|P_e] = (K[P_\pi|P_e] + K[P_e|P_\pi])/2 \quad (2.57)$$

It is highly convenient to write Eq.(2.57) in terms of the already introduced Shannon entropy solely:

$$J[P_\pi|P_e] = S[(P_\pi + P_e)/2] - S[P_\pi]/2 - S[P_e]/2 \quad (2.58)$$

Finally, we can write the disequilibrium Q as the normalized version of J as:

$$Q = Q_0 J[P|P_e] \quad (2.59)$$

with $Q_0 = \frac{N_p+1}{N_p} \log(N_p + 1) - 2 \log(2N_p) + \log(N_p)^{-1}$, implying again $0 \leq Q \leq 1$.

In order to get a qualitative idea of how these quantities behave, we have reproduced (with permission) a figure (see Fig. 2.15) from [153]. There, we have marked the three regimes that we will be detailing in Fig. 2.16. We consider a fairly regular time series (coming from an uncoupled phase-coherent Rössler oscillator), a more dynamically rich one (coming from the same oscillator but coupled with others) and from pure white noise.

Each of the factors in Eq.(2.52) captures a different aspect of the time series. While H encodes *how varied* the ordinal patterns probability distribution is, the disequilibrium encapsulates *how uniformly populated* are the different patterns that are non-zero. As a consequence, a time series can have a high value of this statistical complexity measure if it is either very varied (a lot of different patterns exist), that is $H \approx 1$ or if its empirical probability distribution is highly non-uniformly populated (those patterns that exist, have greatly diverse probabilities of appearance), which is equivalent to $Q \approx 1$. We present a graphical visualization of these different possibilities in Fig. 2.16.

Figure 2.15: The complexity measure $C = H \cdot Q$ is defined in such a way that it is maximum when both of its constituents are not close to zero; that is, in the regime which lies in between pure order and complete disorder. Dashed and labeled [(A), (B), (C)] vertical lines mark the three regimes considered in Fig. 2.16. Figure reproduced and modified with permission from [153].

This field is highly active, and some of the variations of this measure that have been recently proposed are: fine-grained PE [154], weighted PE [144] or robust PE [155], to name a few.

2.5. Integration methods

Figure 2.16: We have chosen $d = 4$ in every case we present now; therefore, there will be $d! = 24$ different types of ordinal patterns (OP) and we use the maxima to compute how these OP are distributed. In (A), we portray a situation in which there are very few populated ordinal patterns (that is, $H \approx 0$) and pretty unevenly distributed ($Q \approx 1$), due to a very regular dynamical evolution -in this case coming from an uncoupled phase-coherent Rössler oscillator; (B) shows a complex situation -extracted from the simulation of a coupled Rössler oscillator- in which both H and Q will be non-small and thus $C > 0$. In (C) every pattern is populated ($H \approx 1$) but with approximately the same probability ($Q \approx 0$), coming from a highly noisy output. From top to bottom, this figure is the quantitative analog of Fig. 2.15 read from left to right; qualitatively, there are three regimes that we have marked with vertical lines in Fig. 2.15 and that we quantify here.

2.5 Integration methods

As we are either dealing with chaotic attractors or with stochastic systems, the possibility of analytically tackling this problem is a challenging one. If we also consider the fact that we work with these kind of elements but networked in a complex fashion, the numerical perspective seems to be the most feasible one.

Therefore, we have to choose an integration method for the set of differential equations that we use as our dynamical system in each scenario. This is where numerical integration becomes necessary.

2.5.1 Deterministic dynamics

In the case of the Lorenz and Rössler oscillators (see Section 2.2.1), we employed a fourth order Runge-Kutta (RK4) method, which belongs to the Runge-Kutta [156, 157] family of iterative methods. The RK4 method is used for solving first order differential equations, which take the general form:

$$\dot{y} = f(t, y), \quad y(t_0) = y_0 \quad (2.60)$$

where t_0, y_0 are known initial conditions and $f(t, y)$ is also specified. Then, a step parameter $h > 0$ is chosen ($h = 0.0025$ for both chaotic oscillators) and the following quantities are defined:

$$\begin{aligned} y_{n+1} &= y_n + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4) \\ t_{n+1} &= t_n + h \end{aligned} \quad (2.61)$$

for $n = 0, 1, 2, \dots$, taking:

$$\begin{aligned} k_1 &= hf(t_n, y_n) \\ k_2 &= hf\left(t_n + \frac{h}{2}, y_n + \frac{k_1}{2}\right) \\ k_3 &= hf\left(t_n + \frac{h}{2}, y_n + \frac{k_2}{2}\right) \\ k_4 &= hf(t_n + h, y_n + k_3) \end{aligned} \quad (2.62)$$

The name of the method is due to the fact that its local truncation error is $\mathcal{O}(h^4)$. The meaning of each increment k_i is as follows:

- k_1 is based on the slope at the beginning of the interval, using y .
- k_2 takes the slope at the midpoint of the interval, making use of y and k_1 .
- k_3 exactly the same as k_2 but instead of taking y and k_1 , we take y and k_2 instead.
- k_4 encodes the slope at the end of the interval, using y and k_3 .

It is worth mentioning that the greatest weight when averaging these increments is given to k_2 and k_3 .

2.5.2 Stochastic integration scheme

When dealing with the Morris-Lecar neuron, we used the stochastic second order Runge-Kutta (sRK2) method, due to the fact that, using the RK4 we just introduced, we will not be able to compute equations that have a noisy part, as the RK4 is a deterministic algorithm that is not able to deal with stochastic terms. There also exists the corresponding stochastic fourth order Runge-Kutta (sRK4) algorithm, but it is not worth for us using it.

In this case, while the scheme is more cumbersome and has more parts, it is more general and actually includes the deterministic RK version [158]. The general problem that this method can solve is a d -dimensional Stochastic Differential Equation with a one-dimensional Wiener process -with the Stratonovich interpretation. The corresponding SDE [159] takes the form:

$$\dot{y}(t) = f(t, y) + g(t, y)\xi_w(t) \quad (2.63)$$

where $\xi_w(t)$ denotes a white noise with time dependence -in general- and $f(x, t)$ is the deterministic part of the problem. In the same spirit as explained before -for RK4- the deterministic RK2 method can be written [159] as:

$$\begin{aligned} k_1 &= hf(t, y(t)) \\ y(t+h) &= y(t) + \frac{h}{2}[f(t, y(t)) + f(t+h, y(t) + k_1)] \end{aligned} \quad (2.64)$$

2.5. Integration methods

where, as before, h is the integration step. If we now replace $y(t+h)$ with the predictor of the Euler method, given by $y(t+h) = x(t) + hf(y(t)) + g(y(t))h^{1/2}u(t) + O[h^{3/2}]$ [159], where $u(t)$ is a normal distribution with zero mean and $\text{var}(u) = 1$, $\text{var}(\xi_w(t)) = h$. Plugging this into the previous expression we arrive to the stochastic Runge-Kutta of order 2 method:

$$\begin{aligned} k_1 &= hf(t, y(t)) \\ k_2 &= h^{1/2}u(t)g(t, y(t)) \\ y(t+h) &= x(t) + \frac{h}{2}[f(t, y(t)) + f(t+h, y(t) + k_1 + k_2)] + \\ &\quad \frac{h^{1/2}u(t)}{2}[g(t, y(t)) + g(t+h, y(t) + k_1 + k_2)] \end{aligned} \quad (2.65)$$

Our stochastic problem is the noisy Morris-Lecar neuron, where the noise is additive and thus $g(y, t) = 1$. Therefore, in our case:

$$y(t+h) = y(t) + \frac{h}{2} \left[f(t, y(t)) + f(t+h, y(t) + k_1 + k_2) + h^{1/2}u(t) \right] \quad (2.66)$$

This method is also known as the Heun method [160]. For a full discussion of this method and some examples of its use, we refer the reader to [158–160].

2.6 Experimental implementation

Undoubtedly, the spirit of this Thesis is a theoretical and computational one. Nevertheless, as we are fully aware of the capital importance of the experimental side of the scientific enterprise, our collaborators implemented various experimental setups to explore whether our theoretical hypothesis were accurate.

As we already mentioned, there are two kinds of theoretical contexts that we have worked with, and thus, there will be correspondingly another two experimental setups we will be dealing with: one for the chaotic oscillators -via a electrical circuit that behaves in a chaotic manner (see Chapter 3)- and another for the neural model -through culturing networks of neurons *in silico*, check out Chapter 4 for more details.

Chapter 3

Complexity and structure in synthetic networks

Dynamical complexity as a proxy for the network degree distributionA. Tlaie,^{1,2,3} I. Leyva,^{1,2} R. Sevilla-Escoboza,⁴ V. P. Vera-Avila,⁴ and I. Sendiña-Nadal^{1,2}¹*Complex Systems Group & GISC, Universidad Rey Juan Carlos, 28933 Móstoles, Madrid, Spain*²*Center for Biomedical Technology, Universidad Politécnica de Madrid, 28223 Pozuelo de Alarcón, Madrid, Spain*³*Department of Applied Mathematics and Statistics, ETSIT Aeronáuticos, Universidad Politécnica de Madrid, 28040 Madrid, Spain*⁴*Centro Universitario de los Lagos, Universidad de Guadalajara, Jalisco 47460, México*

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We explore the relation between the topological relevance of a node in a complex network and the individual dynamics it exhibits. When the system is weakly coupled, the effect of the coupling strength against the dynamical complexity of the nodes is found to be a function of their topological roles, with nodes of higher degree displaying lower levels of complexity. We provide several examples of theoretical models of chaotic oscillators, pulse-coupled neurons, and experimental networks of nonlinear electronic circuits evidencing such a hierarchical behavior. Importantly, our results imply that it is possible to infer the degree distribution of a network only from individual dynamical measurements.

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Since the beginning of the research on the dynamics of complex networks, the deep relationship between topology and dynamics has been thoroughly explored with regard to its effect in the collective state, particularly in the synchronization between the nodes' dynamics [1–4]. A huge effort has been devoted to understand this phenomenon, and the knowledge gathered so far has driven the advance in crucial applications, such as in brain dynamics [5], power grids [6], and many others where synchronization plays a relevant [7,8] role. In most of them, the focus is placed on a state where all the network units reach a global common behavior [4]. However, there are cases in which the system performs its activity in a partial or weakly synchronization regime [9–11] to preserve a sort of balance between functional integration and segregation [12–14], whereas full synchronization is found to be pathological. As a by-product of those investigations, it was found that the underlying structure can be inferred from the dynamical correlations among the coupled units in the unsynchronous regime [15–17]. Indeed, the nowadays very active field of functional brain networks relies on the hypothesis that the observed dynamical correlations are strongly constrained by the anatomical structure [5], in some cases with a very high correlation between the functional and topological networks [18].

It is well known that, in the path to synchrony, the role of the nodes differs as a result of their various topological positions within the network [16,19] as well as of their own intrinsic dynamics [20]. Thus, the role of the highly connected nodes (hubs) as coordinators of the dynamics of the whole system has been very often considered [21–24]. It has been also reported that the hubs are prone to synchronize to each other [25] and to the mean field [26] in a weak coupling regime, while the rest of the nodes follow a hierarchical route to synchronization in the process of joining the hubs.

The fact that synchronization is mediated through the interaction among nodes implies that the single dynamics of

each unit is susceptible to change due to the presence of the ensemble. If the connectivity is bidirectional, this perturbation will be stronger the more relevant is the topological position of the node in the network [25,26]. Therefore, long before the coupling is enough to synchronize the system, each coupled unit is encoding in its own dynamical features the signature of its structural relevance. In this work, we explore how this prominent feature could be used to extract information about the network, without having the need to make any reference to pairwise correlations, even in those situations where the structure is unknown. Therefore, in this work, we propose to explore this correlation between the topological rank, measured by the node degree, and the changes in the single node dynamics, measured in terms of its information-based complexity.

II. MODEL

Let us consider a network of N dynamical units whose m dimensional real state vector $\mathbf{x}_i$ ($i = 1, \dots, N$) evolves according to

$$\dot{\mathbf{x}}_i = \mathbf{f}(\mathbf{x}_i, \tau_i) - d \sum_j \mathcal{L}_{ij} \mathbf{h}(\mathbf{x}_j), \quad (1)$$

where $\mathbf{f}(\mathbf{x}_i, \tau_i)$ is the function governing the node dynamics with τ_i accounting for some parameter heterogeneity and d is the coupling strength. $\mathcal{L} = \{\mathcal{L}_{ij}\}$ is the Laplacian matrix describing the coupling structure, whose coefficients are given by $\mathcal{L}_{ij} = k_i \delta_{ij} - a_{ij}$, where k_i is the node degree, and $\mathbf{A} = \{a_{ij}\}$ the adjacency matrix, such that $a_{ij} = 1$ if there is a link between nodes i, j , and $a_{ij} = 0$ otherwise. The number N_k of nodes having the same degree k is given by the degree probability distribution $P(k)$ as $N_k = N P(k)$.

In order to address our hypothesis about the relationship between the changes in the dynamical properties of each single unit and the number of neighbors it has, we measure the Martín-Plastino-Rosso (MPR) statistical complexity [27–29]

of ordinal patterns extracted from the signal produced by each dynamical unit, as a function of the node degree k_i and the coupling strength d . The methods of analysis of time series based on statistical complexity are gaining relevance in recent years as they provide an easily computable way to quantify the information carried by a signal [30–32], and have been applied to a wide variety of systems: from brain data [31,33], to climate data [34], or financial analysis [35]. Most of them are based on the *permutation entropy* of the ordinal patterns probability distribution $P_\pi(D)$, where D is the embedding dimension [30]. In this study we use the statistical complexity measure defined as $C = HQ$ [27], where $H = S/S_{\max}$ is the normalized permutation entropy [with $S = -\sum_\pi P_\pi \log(P_\pi)$ the Shannon entropy and $S_{\max}$ the entropy of the equilibrium probability distribution $P_e = 1/D!$] and Q is the disequilibrium measuring the distance between the two probability distributions P_e and P_π by means of the Jensen-Shannon divergence [36] (see details in the Appendix).

In the following sections, we check the generality of our hypothesis using several numerical models (Sec. III) and provide some theoretical insight (Sec. IV) as well as experimental evidence (Sec. V). Finally, the results are discussed in Sec. VI.

III. NUMERICAL RESULTS

A. Chaotic dynamics

We first check our conjecture by investigating a network of N bidirectionally coupled identical Rössler oscillators [37] whose time evolution is governed by Eq. (1), with $\mathbf{x} = (x, y, z)$ as the state vector, $\mathbf{f}(\mathbf{x}) = (-y - z, x + ay, b + z(x - c))$, and $\mathbf{h}(\mathbf{x}) = (0, y, 0)$ the vector field and output functions, respectively. The coupling strength d is normalized by the maximum node degree of the network $K = \max(k_i)$. The chosen parameters $a = b = 0.2$ and $c = 9.0$ are such that each Rössler unit develops a phase coherent chaotic attractor when it is isolated. From each time series of the scalar x_i , we extracted the corresponding sequences of 10^4 maxima. From these data, we measured the *amplitude complexity* C_i of each node as defined in Sec. II associated with the probability distribution of all $D!$ permutations π of order $D = 4$. As we expect that nodes having the same degree k will play equivalent dynamical roles in the ensemble, we computed the evolution of $\langle C \rangle_k$ within a degree class k by averaging over the N_k nodes having identical degree k , i.e., $\langle C \rangle_k = \sum_{[i|k_i=k]} C_i / N_k$.

In addition, we monitor the change in the collective state as the coupling strength d is increased by calculating both the time averaged phase order parameter $R = \frac{1}{N} \langle |\sum_{j=1}^N e^{i\theta_j}| \rangle$, where the phase of the dynamical unit is defined as $\theta_j = \arctan(y_j/x_j)$, and the time averaged synchronization error $E = \frac{2}{N(N-1)} \langle \sum_{i \neq j} \|\mathbf{x}_i - \mathbf{x}_j\| \rangle$, which account for the phase and complete synchronization states, respectively. Throughout the paper, the results are averaged over 10 different networks and initial condition realizations.

We begin our study with a very simple network configuration, a star of $N = 30$ nodes, to grasp the evolution of the dynamical complexity and the role of hubs in heterogeneous networks. In Fig. 1(a) we report the degree of phase synchronization (R , solid line) and the synchronization error

FIG. 1. (a) Phase order parameter R and synchronization error E vs d for a star of $N = 30$ identical Rössler oscillators (see the main text for the parameter values). (b) Dynamical complexity C for the hub and one of the leaves vs d . All the measures are averaged over 10 initial conditions, storing sequences of maxima of length 10^4 per node, using $D = 4$ as the embedding length for the permutation patterns.

(E normalized to its maximum value, dashed line) vs the coupling strength d , observing the two expected transitions that any network of identical phase coherent chaotic oscillators undergoes, namely, a first phase synchronization (PS) transition when $R \sim 1$ and, later, for larger coupling strength, a complete synchronization (CS) transition when $E = 0$. As a star only has two kinds of nodes, $N - 1$ leaves and one hub, we plot in Fig. 1(b) the dynamical complexities C_i of the hub (red solid line) and that of one of the leaves (blue dashed-dotted line) as a function of the coupling strength. Note that those values coincide at $d = 0$ since the nodes are identical. For small values of the coupling, when the system is still far from achieving PS, the hub suffers a strong depletion of C indicating that the leaves are pulling the hub's trajectory out of the original chaotic attractor to a much simpler dynamics, whereas the C value of the leaves remains almost unchanged. As the coupling increases, and the system passes through PS, the C values of leaves and hub get closer up to the point in which CS is achieved and all nodes follow the same original chaotic state and the initial value of dynamical complexity is recovered.

After this preliminary analysis showing a clear dependence of the evolution of the dynamical complexity of each node on its topological role, we checked whether this correlation is still observable in more complex topologies. We chose to couple ensembles of $N = 150$ Rössler oscillators on top of scale-free (SF) networks generated according to [38], with $\langle k \rangle = 4$. In Fig. 2(a) we plot the synchronization measures E (dashed line, values properly rescaled for better comparison) and R (solid line) along with the $\langle C \rangle_k$ values for several values of k . As in the case of the star configuration, there is a clear reduction of $\langle C \rangle_k$ for weak coupling featuring also a strong hierarchical

FIG. 2. Dependence of the dynamical complexity at the node level and its topological role in a SF network of $N = 150$ Rössler oscillators. (a) Complexity values C_i vs d for different values of the node degree k_i in a network with $\langle k \rangle = 4$. For the sake of comparison, the complete (E , black dashed line) and phase (R , black continuous line) synchronization curves are shown, rescaled for a better visualization. (b) $\langle C \rangle_k$ vs k for the two coupling values d marked in (a) with vertical dashed lines, located before ($d = 0.02$) and after ($d = 0.29$) the phase synchronization transition. (c) $\langle C \rangle_k$ vs the rescaled coupling $d\langle k \rangle$ for the highest (filled markers) and lowest (void markers) node degree classes for three different mean degrees $\langle k \rangle$ of the networks (see legend). Each point is the average of 10 network realizations.

dependence on k that is lost when the network is clearly phase synchronized. This dependence is much more evident in Fig. 2(b) where the $\langle C \rangle_k$ trends for two different coupling regimes are plotted as a function of k . At low coupling regime and still far from reaching full PS [vertical dashed line at $d = 0.02$ in Fig. 2(a)], there is an anticorrelation (blue circles) between k and the dynamical complexity. This behavior is suggesting an application to structurally rank the nodes in a network according to the complexity of their time series and, therefore, to potentially use this anticorrelation as a proxy for the degree sequence. The fact that this correlation between $\langle C \rangle_k$ and k holds for a wide range of the coupling strength indicates that the method could be still applied in natural systems where, in general, the coupling is not an accessible parameter and, in addition, it could be different for different areas of the system. Note that, at values of the coupling within the full PS regime [vertical dashed line at $d = 0.29$ in Fig. 2(a)], the dependence is lost, with $\langle C \rangle_k$ almost invariant with k .

To further explore the scaling properties of this correlation, we varied the mean degree of the $P(k)$ while preserving the rest of the properties. We found that it scales with $\langle k \rangle$ as shown in Fig. 2(c) for ensembles of SF networks ($N = 150$) with three different mean degrees, where the $\langle C \rangle_k$ is plotted vs the rescaled coupling $d\langle k \rangle$. It can be seen that the three curves of $\langle C \rangle_k$ for the nodes with the highest degree (filled markers)

FIG. 3. Dependence of the dynamical complexity at the node level and its topological role in a SF network of $N = 150$ chaotic Lorenz oscillators and $\langle k \rangle = 4$. (a) Complexity values $\langle C \rangle_k$ vs d for different values of the node degree k_i . (b) $\langle C \rangle_k$ vs k for the two coupling values $d = 0.17$ marked in (a) with a vertical dashed line.

collapse up to exhibiting the same behavior with $d\langle k \rangle$, as well as those for the nodes with the lowest degree (void markers), whose decreasing trends are much less pronounced.

In order to test the generality of our results, we repeated the study for an ensemble of identical Lorenz oscillators [39] whose chaotic dynamics is far from being phase coherent. In Eqs. (1), the node dynamics is now replaced by $\mathbf{f}(\mathbf{x}) = (10(y - x), x(28 - z) - y, xy - (8/3)z)$ and the coupling function is $\mathbf{h}(\mathbf{x}) = (0, y, 0)$, with the same network parameters, SF networks of $N = 150$ ($\langle k \rangle = 4$). Figure 3 shows that the main feature described above is here preserved in this case, with a strong correlation between the dynamical complexity $\langle C \rangle_k$ and the degree, and therefore the possibility to rank the topological relevance of a node only based on individual dynamical measurements.

The observed negative correlation between $\langle C \rangle_k$ and k featured by networks of chaotic oscillators is not restricted to ensembles of identical units. In the spirit of evidencing this, the robustness of this relationship is tested by considering an ensemble of slightly different Rössler oscillators. To do that, we introduced some variability in the Rössler natural frequencies considering $\mathbf{f}(\mathbf{x}) = (-\omega y - z, \omega x + ay, b + z(x - c))$ in Eq. (1) where the individual node frequencies ω are set as $\omega_i = 1 \pm \delta\omega_i$ with $\delta\omega_i$ a random value uniformly drawn from the interval $[-0.05, 0.05]$. The results are portrayed in Fig. 4, showing that some level of node heterogeneity does not affect the negative correlation between the dynamical complexity and the node degree.

B. Stochastic dynamics: The Morris-Lecar neuron

So far, we have considered the node dynamics to be continuous and deterministic, which is a strong limitation in

FIG. 4. Dependence of the dynamical complexity at the node level and its topological role in a SF network of $N = 150$ Rössler nonidentical oscillators with frequency heterogeneity. (a) Complexity values $\langle C \rangle_k$ vs d for different values of the node degree k_i in a network with $\langle k \rangle = 4$. (b) $\langle C \rangle_k$ vs k for the two coupling values d marked in (a) with vertical dashed lines, located before ($d = 0.03$) and after ($d = 0.07$) the phase synchronization transition.

the potential application to real systems with more complicated dynamics and where the presence of intrinsic noise is unavoidable. Therefore, we investigated whether the relationship between structure and dynamics described in previous sections can be extended to stochastic dynamics, in particular to neural dynamics. We implemented the bioinspired Morris-Lecar (ML) model [40] for type II excitatory neurons (with a discontinuous frequency-current response curve), whose equations describing the membrane potential behavior for each unit read as [19,41]

$$\begin{aligned} C\dot{V}_i &= -g_{Ca}M_\infty(V_i - V_{Ca}) - g_KW_i(V_i - V_K) \\ &\quad - g_l(V_i - V_l) + q\xi_i + I_i + I_i^{\text{ext}}, \\ \dot{W}_i &= \phi \tau_W(W_\infty - W_i), \end{aligned} \quad (2)$$

where V_i and W_i are, respectively, the membrane potential and the fraction of open K^+ channels of the i th neuron and M_∞ , W_∞ , and τ_W are hyperbolic functions dependent on V_i and ϕ is a reference frequency. The parameters g_X and V_X account for the electric conductance and equilibrium potentials of the $X = \{K, Ca, \text{leaky}\}$ channels. The external current $I_i^{\text{ext}} = 50.0$ nA is the same for all the neurons and is chosen such that neurons are subthreshold to neuronal firing which is induced by the white Gaussian noise $q\xi_i$ of zero mean and intensity q . The coupling of the neuron i th with the neuron ensemble is described by the injected synaptic current

$$I_i = \frac{d}{K} \sum_j a_{ij} e^{-2(t-t_j)} (V_0 - V_i) \quad (3)$$

given by the superposition of all the post-synaptic potentials emitted by the neighbors of node i in the past, being t_j the time of the last spike of node j . The synaptic conductance d , normalized by the largest node degree present in the network K , plays the role of coupling intensity.

Additionally, the channel voltage-dependent saturation values respond to the dynamics:

$$M_\infty(V_i) = \frac{1}{2} \left[1 + \tanh \left(\frac{V_i - V_l}{V_2} \right) \right], \quad (4)$$

TABLE I. Parameters used in the numerical simulations of the Morris-Lecar network in Eqs. (2).

C	$20.0 \mu\text{F}/\text{cm}^2$
g_{Ca}	$4.0 \mu\text{S}/\text{cm}^2$
g_K	$8.0 \mu\text{S}/\text{cm}^2$
g_l	$2.0 \mu\text{S}/\text{cm}^2$
V_{Ca}	120.0 mV
V_K	-80.0 mV
V_l	-60.0 mV
V_1	-1.2 mV
V_2	18.0 mV
V_3	2.0 mV
V_4	17.4 mV
ϕ	$1/15$

$$W_\infty(V_i) = \frac{1}{2} \left[1 + \tanh \left(\frac{V_i - V_3}{V_4} \right) \right], \quad (5)$$

$$\tau_W(V_i) = \cosh \left(\frac{V_i - V_3}{2V_4} \right). \quad (6)$$

In Table I we detail the values of the parameters used in the simulations, corresponding to type II class excitability for the neuron dynamics which means that a discontinuous transition is found in the dependence of the spiking frequency on the external current.

The typical neuronal dynamics exhibited by Eqs. (2) when $d = 0$ consists of a sequence of L spikes produced at random times t_l , $l = 1, 2, \dots, L$, whose amplitude variability is negligible. Therefore, we focused on the complexity C_i of the sequence of interspike times $(t_l - t_{l-1})$ patterns of each neuron. Additionally, in order to quantify the level of synchronization, we counted how many neurons fire within the same time window [19]. The total simulation time T is divided in $n = 1, \dots, N_b$ bins of a convenient size τ , such that $T = N_b \tau$, and the binary quantity $B_i(n)$ is defined such that $B_i(n) = 1$ if the i th neuron spiked within the n th interval and 0 otherwise. The coherence between the spiking sequences of neurons i and j is therefore characterized with the quantity $s_{ij} \in [0, 1]$:

$$s_{ij} = \frac{\sum_{n=1}^{N_b} B_i(n) B_j(n)}{\sum_{n=1}^{N_b} B_i(n) \sum_{n=1}^{N_b} B_j(n)}, \quad (7)$$

where the term in the denominator is a normalization factor and $s_{ij} = 1$ corresponds to full coincidence between the two spiking series. The ensemble average of s_{ij} , $S = \langle s_{ij} \rangle = \frac{2}{N(N-1)} \sum_{i,j=1, i \neq j}^N s_{ij}$, is conveniently rescaled and reported in Fig. 5 as a dotted line, indicating a transition from an asynchronous to an almost synchronous firing as the synaptic conductance d is increased. Superimposed to this curve are the complexities C_i of nodes with low ($k = 2$, blue dashed-dotted line) and high ($k = 32$, red solid line) degrees for 10 realizations of a SF network of $N = 150$ ML neurons.

We observe that, as the coupling increases, the complexity of the highly connected nodes peaks at incipient levels of synchronization, as well as for the low degree nodes, which occurs later. For small coupling, this is due to the fact that the hubs are cross talking with many nodes receiving

FIG. 5. Dependence of the dynamical complexity at the node level and its topological role in a SF network of $N = 150$ Morris-Lecar neurons. (a) Complexity values $\langle C \rangle_k$ vs d for low ($k = 2$) and high ($k = 32$) degree node values in a network with $\langle k \rangle = 4$. For the sake of comparison, the phase synchronization curve (S , black dotted line) is shown, rescaled for a better visualization. (b) $\langle C \rangle_k$ vs k for the two coupling values d marked in (a) with vertical dashed lines. Each point is the average of 10 network realizations.

incoherent, noise-induced signals contributing to an increase its own complexity. For larger values of the coupling strength ($d = 300$), still far from PS, the hubs' complexity lowers because the increasing number of inputs pushes the neuron towards the periodic transition. In the bottom panel of Fig. 5, we show the correlation between the complexity $\langle C \rangle_k$ and the node degree at the two coupling strengths marked with dashed lines in the upper plot. Again, as in the case of deterministic dynamics, a negative correlation of the complexity values with the number of synapses appears for intermediate values of the synchronization level. This suggests that, indeed, there is a region close to full synchronization where the complexity of a node can tell us about its degree.

IV. AN ANALYTICAL INSIGHT

The behavior can be understood analytically by performing a mean field approximation and a linear stability analysis of the actual state of each oscillator in the weak coupling regime where the system is still far from reaching the same collective state [25,26]. The local mean field that oscillator i is receiving is $\bar{\mathbf{x}}_i = k_i^{-1} \sum_{j=1}^N a_{ij} \mathbf{h}(\mathbf{x}_j)$. In the case of a highly connected node ($k_i \gg 1$), its mean field can be well approximated by the global mean field $\mathbf{X} = N^{-1} \sum_{j=1}^N \mathbf{h}(\mathbf{x}_j)$, i.e., $\bar{\mathbf{x}}_i \sim \mathbf{X}$, whose variance is, below the onset of synchronization, very small [25,42]. Under this assumption, the contribution from the coupling term to the time evolution of the hubs in Eq. (1) is simply $N\mathbf{X}$ that can be neglected since it is either zero or a constant depending whether the attractor has a symmetry with respect to the origin. Therefore, the governing equations for the hubs [25] are given by

$$\dot{\mathbf{x}}_i \simeq \mathbf{f}(\mathbf{x}_i) + dN\mathbf{X} - dk_i \mathbf{h}(\mathbf{x}_i), \quad (8)$$

that is, the hub's dynamics is being modulated by a strong negative self-feedback term $[-dk_i \mathbf{h}(\mathbf{x}_i)]$ that stabilizes the

TABLE II. Values of the electronic components and constants used for the construction of the Rössler-type oscillator.

$C_1 = 1 \text{ nF}$	$C_2 = 1 \text{ nF}$	$C_3 = 1 \text{ nF}$	$V_{ee} = 15 \text{ V}$
$R_1 = 2 \text{ M}\Omega$	$R_2 = 200 \text{ k}\Omega$	$R_3 = 10 \text{ k}\Omega$	$R_4 = 100 \text{ k}\Omega$
$R_5 = 50 \text{ k}\Omega$	$R_6 = 5 \text{ M}\Omega$	$R_7 = 100 \text{ k}\Omega$	$R_8 = 10 \text{ k}\Omega$
$R_9 = 10 \text{ k}\Omega$	$R_{10} = 100 \text{ k}\Omega$	$R_{11} = 100 \text{ k}\Omega$	$R_{12} = 150 \text{ k}\Omega$
$R_{13} = 68 \text{ k}\Omega$	$R_{14} = 10 \text{ k}\Omega$	$R_{15} = 100 \text{ k}\Omega$	$V_d = 0.7 \text{ V}$

unstable periodic orbits resulting in a more stable trajectory than the original uncoupled one [43]. To prove this, let us consider all the infinitesimal displacements $\delta \mathbf{x}$ from a given trajectory $\mathbf{x}_i$ of a hub. The time evolution of the tangent vector $\delta \mathbf{x}_i$ obtained as the linearization of Eq. (8) is

$$\delta \dot{\mathbf{x}}_i = [\mathbf{J}\mathbf{f}(\mathbf{x}_i) - dk_i \mathbf{J}\mathbf{h}(\mathbf{x}_i)] \delta \mathbf{x}_i, \quad (9)$$

where $\mathbf{J}$ stands for the Jacobian matrix. Without loss of generality, assuming that the coupling function $\mathbf{h}$ is linear, the solution to the variational equations of the perturbations results in an exponential growth at a rate given by the Lyapunov exponents, whose maximum is given by $\Lambda(k) = \Lambda_0 - dk_i$ where Λ_0 is the maximum positive Lyapunov exponent corresponding to the chaotic uncoupled oscillator. As a consequence, the trajectory will become dynamically less complex as a linear function of k , as observed in Fig. 2(b). Eventually, if the original node is chaotic and highly connected, it can become periodic with the consequent loss of statistical complexity. On the contrary, for the less connected nodes $k_i \sim 1$, in the weak coupling regime, the diffusive term is too small as to modify the trajectory, and the node dynamics retains most of its original complexity.

V. EXPERIMENTAL IMPLEMENTATION

In order to provide some experimental evidence, we designed a star network with eight bidirectionally coupled Rössler-type chaotic electronic circuits. We implemented a setup consisting on an electronic version of the Rössler-type system [44] described by the following equations:

$$\dot{v}_{1i} = -\frac{1}{R_1 C_1} \left(v_{1i} + \frac{R_1}{R_2} v_{2i} + \frac{R_1}{R_4} v_{3i} \right), \quad (10)$$

$$\begin{aligned} \dot{v}_{2i} = & -\frac{1}{R_6 C_2} \left[-\frac{R_6 R_8}{R_9 R_7} v_{1i} + \left(1 - \frac{R_6 R_8}{R_c R_7} \right) v_{2i} \right] \\ & + \frac{d}{R_{15} C_2} \sum_{j=1}^N a_{ij} [v_{2j} - v_{2i}], \end{aligned} \quad (11)$$

$$\dot{v}_{3i} = -\frac{1}{R_{10} C_3} \left(-\frac{R_{10}}{R_{11}} G_{v_{1i}} + v_{3i} \right), \quad (12)$$

and the piecewise function $G_{v_{1i}}$ as

$$G_{v_{1i}} = \begin{cases} 0 & \text{if } v_{1i} \leq v_{\text{ref}}, \\ G_0 & \text{if } v_{1i} > v_{\text{ref}}, \end{cases} \quad (13)$$

where $v_{\text{ref}} = V_d(1 + \frac{R_{14}}{R_{13}}) + V_{ee} \frac{R_{14}}{R_{13}}$ and $G_0 = \frac{R_{12}}{R_{14}} v_{1i} - V_{ee} \frac{R_{12}}{R_{13}} - V_d(\frac{R_{12}}{R_{13}} + \frac{R_{12}}{R_{14}})$. All parameter values are listed in Table II and a schematic representation of the experimental

FIG. 6. Schematic representation of the experimental setup of a star network with eight Rössler-type oscillators. Using ADCs, signals are measured and stored by a DAQ card and a PC, while DO ports change the value of the coupling strength d through a digital potentiometer (XDCP).

setup is shown in Fig. 6. We refer the interested reader to Ref. [45] for the visualization of the electronic and coupling circuits and to Refs. [46–49] for a detailed description of the experimental implementation of the circuits and previous realizations of different network configurations. The analog-to-digital cards (ADCs) (AI0...AI7) ports from the data acquisition (DAQ) card are used for sampling the variable v_2 of each circuit. A coupler is introduced between the circuits. The coupling circuit is based on a differential operational amplifier (Op-Amp) where the v_{2j} and v_{2i} signals are introduced. A digital potentiometer (XDCP) is used to vary the gain of the amplifier, which is adjusted by digital pulses from digital ports (DO). Here, P00 is used to increase or decrease the resistance of the voltage divisor (d), while P01 sets the value of the resistance (100 discretized steps,

1 step = 100 Ω). The entire experimental process is controlled by a virtual interface in LabVIEW 2016 (PC).

The experiment works in the following way: first, d is set to zero and digital pulses (P00 and P01) are sent to the digital potentiometer (X9C103) until the value of maximum resistance is reached. After waiting 500 ms, d is varied from 0 to 10 k Ω in 100 steps and at each step, the measure is repeated for 30 different initial conditions. For each coupling value, the variables v_{2i} of the circuits are acquired by the analog ports (AI0...AI7), and the synchronization error is calculated and stored in the PC. The local maxima of each oscillator (5000 maxima) are located and stored to perform the corresponding complexity measures, as explained in Sec. II.

The results are presented in Fig. 7, where the synchronization state [Fig. 7(a)] and dynamical complexity of the hub and of one of the leaves [Fig. 7(b)] are to be compared with their numerical counterparts in Figs. 1(a) and 1(b). Despite the natural parameter mismatch and environmental noise affecting our experimental setup, the two markedly different paths of the dynamical complexities of both the hub and the leaves, a large loss in the hub, and an almost constant level of complexity in the leaves, largely agree with those obtained in the numerical simulation, confirming the generality of the observation.

VI. CONCLUSIONS

In this work, we have inspected the relationship between the topological role of a node in a complex network and its dynamical behavior, represented by its statistical complexity. We show, both numerically and experimentally, that in a simple star of identical chaotic oscillators, the hub exhibits a minimum of complexity in the route to synchronization while the leaves almost keep unperturbed their initial complex behavior. When considering more heterogeneous degree distributions, the same behavior is observed in the route to synchronization, with higher degree nodes exhibiting lower values of complexity. Importantly, when comparing the complexity of each node and its degree, we found a distinctive linear correlation with higher degree nodes exhibiting less complexity and that is generally observed in networks of other types of chaotic oscillators or pulse-coupled neurons. The reported results could explain recent observations about the low complexity of the hubs in functional brain networks [33] but, beyond that, they suggest that the role played by the topology of a network could be unveiled by just computing the dynamical complexity associated with the time series sampled at each node. The fact that structural information of a network can be inferred without computing pairwise correlations like those commonly performed in functional networks could be exploited in diverse fields as neuroscience, econophysics, or power grids.

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FIG. 7. (a) Phase order parameter R and synchronization error E vs d for a star of $N = 8$ almost identical (within the 5% experimental tolerance) Rössler-type electronic circuits for the system experimental description. (b) Dynamical complexity of the hub and of one of the leaves vs d . Complexity measures are averaged over 30 different initial conditions and calculated over sequences of 5000 maxima with embedding length $D = 3$.

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APPENDIX: ORDINAL PATTERNS AND COMPLEXITY MEASURE

The ordinal patterns' formalism [30] associates a symbolic sequence to a time series, transforming the actual values of the measure into a set of natural numbers. To do that, the time series is divided in bins of size D . In each bin, the D data values are ordered in terms of its relative amplitudes [13], which provides the correspondent symbolic sequence. The information content of these sequences is then evaluated as a function of the complexity measure. This is a broad-field, well-established, and known method, statistically reliable and robust to noise, extremely fast in computation and with a clear definition and interpretation in physical terms. It is derived from two also well-established measures (divergence and entropy), also easily interpretable when analyzing nonlinear dynamical systems. In addition, it only requires soft criteria, namely, that the time series must be pseudostationary and that $M \gg D!$ (where M is the number of points of the entire time series), which are easily checkable. We proceed in the following way:

(1) We count how many times a certain symbolic order sequence (or *pattern*) of size D appears (N_π).

(2) We then define a probability of occurrence for each pattern: $P_\pi = \frac{N_\pi}{N_T}$, where N_T is the total number of patterns in which we divide the time series, i.e., $N_T = N/D$.

(3) We construct an *empirical probability distribution*, which we call P from now on, from the pool of P_π .

Once the probability distribution P is obtained, we can now define the dynamical complexity, a measure that should be minimal both for pure noise and absolute regularity, and provide a bounded value for other regimes. This being so, we need to characterize the disorder and a correcting term (i.e., a way of comparing known probability distributions with the actual one). In the main text, we define the dynamical complexity ($C = HQ$) as the product of the permutation entropy (H) and the disequilibrium (Q).

To define the permutation entropy H , the first step is the evaluation of the Shannon entropy, that gives an idea of the

disorder of the series:

$$S[P] = - \sum_{j=1}^{D!} p_j \log(p_j). \quad (A1)$$

The permutation entropy corresponds to the normalization of S with respect to the entropy of the uniform probability distribution $S_{\max}$:

$$H = \frac{S}{S_{\max}}, \quad S_{\max} = S[P_e],$$

$$P_e \equiv \{1/D!\}_{1,\dots,D!} \Rightarrow 0 \leq H \leq 1. \quad (A2)$$

Regarding the disequilibrium Q , it is a way of measuring the distance of the actual probability distribution P with the equilibrium probability distribution P_e . This notion of *distance* can be acquired by several means; in this text, we adopt the statistical distance given by the Kullback-Leibler [50] relative entropy (K):

$$K[P|P_e] = - \sum_{j=1}^{D!} p_j \log(p_e) + \sum_{j=1}^{D!} p_j \log(p_j)$$

$$= S[P|P_e] - S[P], \quad (A3)$$

where $S[P|P_e]$ is the Shannon cross entropy. If we now make symmetric Eq. (A3), we get the Jensen-Shannon divergence (J):

$$J[P|P_e] = (K[P|P_e] + K[P_e|P])/2. \quad (A4)$$

For our purposes, it is highly convenient to write (A4) in terms of S solely:

$$J[P|P_e] = S[(P + P_e)/2] - S[P]/2 - S[P_e]/2. \quad (A5)$$

Finally, we can write the disequilibrium Q as the normalized version of J as

$$Q = Q_0 J[P|P_e] \quad (A6)$$

with $Q_0 = \frac{N+1}{N} \log(N+1) - 2 \log(2N) + \log(N)^{-1}$, implying again $0 \leq Q \leq 1$.

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- [1] L. M. Pecora, *Phys. Rev. E* **58**, 347 (1998).
 - [2] M. Barahona and L. M. Pecora, *Phys. Rev. Lett.* **89**, 054101 (2002).
 - [3] S. Boccaletti, V. Latora, Y. Moreno, M. Chavez, and D.-U. Hwang, *Phys. Rep.* **424**, 175 (2006).
 - [4] A. Arenas, A. Díaz-Guilera, J. Kurths, Y. Moreno, and C. Zhou, *Phys. Rep.* **469**, 93 (2008).
 - [5] E. Bullmore and O. Sporns, *Nat. Rev. Neurosci.* **10**, 186 (2009).
 - [6] M. Rohden, A. Sorge, M. Timme, and D. Witthaut, *Phys. Rev. Lett.* **109**, 064101 (2012).
 - [7] A. Pluchino, V. Latora, and A. Rapisarda, *Int. J. Mod. Phys. C* **16**, 515 (2005).
 - [8] N. Fujiwara, J. Kurths, and A. Díaz-Guilera, *Phys. Rev. E* **83**, 025101 (2011).
 - [9] E. Rodriguez, N. George, J. P. Lachaux, J. Martinerie, B. Renault, and F. J. Varela, *Nature (London)* **397**, 430 (1999).
 - [10] J.-P. Lachaux, E. Rodriguez, J. Martinerie, and F. J. Varela, *Human Brain Mapping* **8**, 194 (1999).
 - [11] L. M. Pecora, F. Sorrentino, A. M. Hagerstrom, T. E. Murphy, and R. Roy, *Nat. Commun.* **5**, 4079 (2014).
 - [12] G. Tononi, O. Sporns, and G. M. Edelman, *Proc. Natl. Acad. Sci. USA* **91**, 5033 (1994).
 - [13] A. A. Rad, I. Sendiña-Nadal, D. Papo, M. Zanin, J. M. Buldú, F. del Pozo, and S. Boccaletti, *Phys. Rev. Lett.* **108**, 228701 (2012).
 - [14] O. Sporns, *Curr. Opinion Neurobiol.* **23**, 162 (2013).
 - [15] A. Arenas, A. Díaz-Guilera, and C. J. Pérez-Vicente, *Phys. Rev. Lett.* **96**, 114102 (2006).

- [16] J. Gómez-Gardeñes, Y. Moreno, and A. Arenas, *Phys. Rev. Lett.* **98**, 034101 (2007).
- [17] D. Li, I. Leyva, J. A. Almendral, I. Sendiña-Nadal, J. M. Buldú, S. Havlin, and S. Boccaletti, *Phys. Rev. Lett.* **101**, 168701 (2008).
- [18] C. Honey, O. Sporns, L. Cammoun, X. Gigandet, J.-P. Thiran, R. Meuli, and P. Hagmann, *Proc. Natl. Acad. Sci. USA* **106**, 2035 (2009).
- [19] A. Navas, J. A. Villacorta-Atienza, I. Leyva, J. A. Almendral, I. Sendiña-Nadal, and S. Boccaletti, *Phys. Rev. E* **92**, 062820 (2015).
- [20] P. S. Skardal, D. Taylor, and J. Sun, *Phys. Rev. Lett.* **113**, 144101 (2014).
- [21] M. P. Van Den Heuvel and O. Sporns, *Trends Cogn. Sci.* **17**, 683 (2013).
- [22] D. Papo, M. Zanin, J. A. Pineda-Pardo, S. Boccaletti, J. M. Buldu, and J. M. Buldú, *Philos. Trans. R. Soc. B* **369**, 20130525 (2014).
- [23] G. Zamora-López, Y. Chen, G. Deco, M. L. Kringelbach, and C. Zhou, *Sci. Rep.* **6**, 38424 (2016).
- [24] G. Deco, T. J. Van Hartevelt, H. M. Fernandes, A. Stevner, and M. L. Kringelbach, *NeuroImage* **146**, 197 (2017).
- [25] T. Pereira, *Phys. Rev. E* **82**, 036201 (2010).
- [26] C. Zhou and J. Kurths, *Chaos* **16**, 015104 (2006).
- [27] R. López-Ruiz, H. L. Mancini, and X. Calbet, *Phys. Lett. A* **209**, 321 (1995).
- [28] M. T. Martin, A. Plastino, and O. A. Rosso, *Phys. Lett. A* **311**, 126 (2003).
- [29] P. W. Lamberti, M. T. Martin, A. Plastino, and O. A. Rosso, *Phys. A (Amsterdam)* **334**, 119 (2004).
- [30] C. Bandt and B. Pompe, *Phys. Rev. Lett.* **88**, 174102 (2002).
- [31] J. M. Amigó, K. Keller, and V. A. Unakafova, *Philos. Trans. R. Soc. A* **373**, 20140091 (2018).
- [32] A. Politi, *Phys. Rev. Lett.* **118**, 144101 (2017).
- [33] J. H. Martínez, M. E. López, P. Ariza, M. Chavez, J. Pineda-Pardo, D. López-Sanz, P. Gil, F. Maestú, and J. M. Buldú, *Sci. Rep.* **8**, 10525 (2018).
- [34] M. Barreiro, A. C. Marti, and C. Masoller, *Chaos* **21**, 013101 (2011).
- [35] A. Schnurr, *Stat. Papers* **55**, 919 (2014).
- [36] M. Zanin, L. Zunino, O. A. Rosso, and D. Papo, *Entropy* **14**, 1553 (2012).
- [37] O. E. Rössler, *Phys. Lett. A* **57**, 397 (1976).
- [38] R. Albert and A.-L. Barabási, *Rev. Mod. Phys.* **74**, 47 (2002).
- [39] E. N. Lorenz, *J. Atmos. Sci.* **20**, 130 (1963).
- [40] C. Morris and H. Lecar, *Biophys. J.* **35**, 193 (1981).
- [41] B. Sancristóbal, R. Vicente, J. M. Sancho, and J. García-Ojalvo, *Front. Comput. Neurosci.* **7**, 1 (2013).
- [42] M. G. Rosenblum and A. S. Pikovsky, *Phys. Rev. Lett.* **92**, 114102 (2004).
- [43] S. Boccaletti, C. Grebogi, Y.-C. Lai, H. Mancini, and D. Maza, *Phys. Rep.* **329**, 103 (2000).
- [44] T. L. Carroll, *Am. J. Phys.* **63**, 377 (1995).
- [45] R. Sevilla-Escoboza and J. M. Buldú, *Data Brief* **7**, 1185 (2016).
- [46] R. Sevilla-Escoboza, R. Gutiérrez, G. Huerta-Cuellar, S. Boccaletti, J. Gómez-Gardeñes, A. Arenas, and J. M. Buldú, *Phys. Rev. E* **92**, 032804 (2015).
- [47] R. Sevilla-Escoboza, I. Sendiña-Nadal, I. Leyva, R. Gutiérrez, J. M. Buldú, and S. Boccaletti, *Chaos* **26**, 065304 (2016).
- [48] I. Leyva, R. Sevilla-Escoboza, I. Sendiña-Nadal, R. Gutiérrez, J. M. Buldú, and S. Boccaletti, *Sci. Rep.* **7**, 45475 (2017).
- [49] I. Leyva, I. Sendiña-Nadal, R. Sevilla-Escoboza, V. P. Vera-Avila, P. Chholak, and S. Boccaletti, *Sci. Rep.* **8**, 8629 (2018).
- [50] S. Kullback and R. A. Leibler, *Ann. Math. Stat.* **22**, 79 (1951).

Chapter 4

An application to cultured neuronal networks

Statistical complexity and connectivity relationship in cultured neural networks

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ABSTRACT

We explore the interplay between the topological relevance of a neuron and its dynamical traces in experimental cultured neuronal networks. We monitor the growth and development of these networks to characterise the evolution of their connectivity. Then, we explore the structure-dynamics relationship by simulating a biophysically plausible dynamical model on top of each networks' nodes. In the weakly coupling regime, the statistical complexity of each single node dynamics is found to be anti-correlated with their degree centrality, with nodes of higher degree displaying lower complexity levels. Our results imply that it is possible to infer the degree distribution of the network connectivity only from individual dynamical measurements.

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1. Introduction

One of the main research lines in the study of the dynamics of complex networks has been the deep relationship between the connectivity and the dynamics of the nodes, and how this interaction shapes the emergence of a collective state such as synchronisation [1–4]. An enormous effort has been devoted to the understanding of this phenomenon, and the knowledge gathered so far has driven the advance in crucial applications in brain dynamics [5], power grids [6], and in many other fields where synchronisation is essential [7,8] for the system's proper functioning.

Commonly, studies have focused in states of full synchronisation [4]. Nevertheless, there are very relevant cases in which only a partial or weak synchronisation level is achieved [9–11], and often this state becomes optimal to balance functional integration and segregation in the system [12–14] while a complete coordination is evidencing the existence of a pathological condition.

Several investigations [15–17] have shown that nodes play different roles in the ensemble dynamics depending on their topological position and intrinsic dynamics [18]. One of the most explored situation is that of the hubs acting as coordinators of the dynamics of the whole system [19–22], being the first nodes to synchronise among them [23] and to the mean field [24], while the rest of the nodes progressively locks the hubs dynamics.

This effect of the topology on the dynamics in the weakly synchronised regime opens the question of whether it is possible to infer the network architecture from statistical correlations among the coupled units [15,25]. Currently, a great amount of the research is being conducted in this sense. In particular, the computational neuroscience field roots in the hypothesis that dynamical correlations (which can be recorded in non-invasive ways) are greatly constrained and induced by the anatomical structure of the brain [5]. From these site-to-site correlation maps, the *functional brain networks*, it is often possible to obtain information about the underlying topological networks [26].

However, it has been less explored the fact that this structural-dynamical interaction also plays in the other way around: just as the dynamics of each node influences the ensemble, the ensemble imprints its structural marks into the dynamics of each individual node [23,24]. We make the assumption that, long before the coupling strength is high enough to induce synchronisation, the dynamical changes at the node level are encoding the imprint of its structural role. This relevant feature could be used to extract information about the network without making any reference to pairwise correlations, particularly in those cases where the structure is unknown or unreliable, as we showed in a previous work [27].

Here, we extend our study of the influence that the ensemble has over the node dynamics to an experimental case. We culture networks of neurons coming from *Schistocerca gregaria* and study the potential relationship between a simulated dynamical model (the Morris-Lecar neuron) and the anatomical network structure of a neuronal culture. The main motivation for this study is that in cultured neuronal networks the simultaneous obtention of

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Fig. 1. Image segmentation processing steps and extraction of the network graph. (a) Red layer of a RGB cut of a culture 6 DIV old. (b) Output of the segmentation algorithm of the region of interest. Single neurons and aggregates of neurons are highlighted in red while the neurites are marked in green. (c) Mapping of the segmentation objects in (b) into a full graph where circles (neurons and neuronal clusters) and diamonds (branching and end points of neurites, with no neurons) are the nodes, these being connected with green lines, representing the neurites. (d) Graph representing the projection of the full graph into the cluster graph with only neuronal clusters (red) and neurites (green), where the links represent the existence of a path between cluster nodes through junction nodes in the full graph in (c). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

structural and dynamical information is not possible, either because one recording technique influences the other measurement or mainly because the culture is not able to survive to both measurements.

2. Experimental setup: culturing the network

To analyse the spatial structure of a real network, we focus on the study of cultured neuronal networks (CNNs), considered as a simplified version of a more complex network of the central nervous system [28–30]. For this purpose, we analyse the network structure in this CNN model by means of optical microscopy techniques, extracting the detailed connectivity and its statistical topological properties.

Our CNNs were obtained from *Schistocerca gregaria* specimens, also known as desert locusts. As they share basic neuronal features with vertebrates, this invertebrate model has been recently used in neuroscience as an easier approach for the understanding of more complex neural systems [31]. The large size of its neurons makes it ideal for observing the structure of the network, as an alternative to the mammals.

In our experiments we follow the protocol described in [32]. Each locust is dissected to extract its frontal ganglion, formed by approximately 100 neurons [33]. To obtain an intermediate neuron density that allows us to study a complex network morphology we extracted 12 ganglia per culture. After the dissection, the frontal ganglia endure a chemical and mechanical procedure to remove all the connections and dissociate the neurons. The neuronal somata are cultured in a Petri dish, in an enriched environment to allow the neurites to regrowth and form a new connectivity network. The cultures are monitored *in vitro* from day 0 (DIV0, DIV=days *in vitro*) to day 14 (DIV14). The data used in this work correspond to 6 cultures grown in the same conditions. We inspected the morphological features of the cultured networks using a phase contrast inverted microscope (Eclipse Ti-S, Nikon) with a 10x air objective (Achromat, ADL, NA 0.25) and an automated motorised XYZ stage controller. High resolution images were obtained in a daily basis.

In order to analyse the spatial network, we need to extract the corresponding mathematical graph. To do so, we process the culture images by means of an image segmentation algorithm [34,35]. In Fig. 1 we portray the whole process, starting from a typical microscope image of the culture (Fig. 1(a) shows just a small area) and ending up with the output of the segmentation detecting

neurons (and aggregates of neurons) and the neuronal processes connecting them Fig. 1(a). The algorithm is summarised in the following steps:

1. The red layer of a RGB high-resolution image of the recorded cultured network is processed (Fig. 1(a)).
2. The image is segmented and thresholded to separate background from foreground areas. Then neurons and aggregates of neurons (red areas in Fig. 1(b)) and neurites (green paths in Fig. 1(b)) are identified separately.
3. Both neurons and neurites are connected and coded in the adjacency matrix where single and clustered neurons are the nodes and neurites are the links between them. Branching and end points of the neurites are also registered as junction nodes in the graph, even when there is no neuron on them. This provides a complete version of the graph that we call the *full graph* (Fig. 1(c)) with two types of nodes, those corresponding to neurons and the ones denoting a branching point in the neuronal process path connecting two neurons.
4. The previous data is used to build a reduced version of the graph, where only neurons (or neuronal clusters) are the nodes, and the links represent the existence of a path between neuronal clusters, eventually through branching points. In this graph, junction nodes have been removed and we observe a more direct path between neuronal clusters, obtaining a simple version of the matrix, the *cluster graph* (Fig. 1(d)).

We analyse the morphological and topological properties of the cultured network using both full and cluster graphs, where the links are unweighted. With the purpose of characterising the segregation and integration of the cultured neuronal network along the experiment, in Fig. 2 we measure the longitudinal progression of the averaged clustering coefficient (C) and shortest path length L , normalised by the size of the largest connected component S_1 [3], resulting L/S_1 . The relationship between C and L is often used as an indicator of the balance between the local and long-distance connectivity in the network. These aforementioned parameters were measured in both the full graph (with neuronal clusters and junction nodes) and in the cluster graph (with only neuronal clusters nodes).

In the full graph (Fig. 2(a)), the normalised shortest path L/S_1 shows a high mean value at the early days of the culturing, where the connectivity is still not fully developed. Between DIV3 and DIV6 there is a significant decrease and showed no significant

Fig. 2. Results of the cultured network analysis. Mean value of the clustering coefficient C and mean path length L normalised by the size of the largest connected component S_1 (a) in a full graph, where clusters and junctions are the nodes, and (b) in a cluster graph, where the only nodes are clusters of neurons. Each point is the average over 6 experiments.

change thereafter, meaning a high integration degree in the mature culture network. The clustering coefficient was characterised by a very low mean value, showing a slight increase between DIV3 and DIV6, when the network development occurs. The low mean values of C are due to the fact that both neurons and branching points are considered nodes meaning that the probability of forming triangles is reduced (see Fig. 1(b)).

In the case of the cluster graphs (Fig. 2(d)) we observe a similar trend in L/S_1 (see Fig. 2(b)) as the one described for the full graph. On the contrary, C exhibits higher mean values, with a more acute increase between DIV 3 and DIV 6, that coincides with the most intense developmental phase. As neuronal aggregates are the only nodes in this cluster graph and junctions are not represented as nodes, the mean values of C are more accurate with the connected structure. After that point, in the mature neuronal network these two parameters keep constant values [34,35].

The analysis of these parameters in both types of graphs concludes with the emergence of a mature cultured neuronal network from an initial random stage. This evolved structure is characterised by high clustering coefficients and low mean path values, indicating the presence of a mature network with high segregation (favored by high clustering values) and integration (facilitated by the existence of small shortest paths) levels. These are the characteristics of a small world structure, where the high tendency to form clusters of nodes in highly interconnected subgroups and short distance between them contribute to an optimal functionality in the network [34].

We also analyzed the degree distribution $P(k)$ of these networks, being k the number of links that each node has. In Fig. 3 we plot an example of the cumulative degree distribution $P_c(k)$ of an in-vitro clustered network at DIV7 (black squares), compared to equivalent simulated networks (same number of nodes and links) obtained from usual generative models: random Erdős–Renyi (ER, blue diamonds), scale-free obtained by Barabasi–Albert algorithm (SF, red dots) and a spatial network with a distance-dependence linkage pattern (spatial-ER green diamonds). As described in [34], the cultured networks belong to the single-scale type as they show a well defined k . The study of $P_{cum}(k)$ reveals a fast decay with a large number of nodes with similar number of connections, and a few ones with a different and large node degrees. As it can be seen, the experimental connectivity largely differs from the pure random ER, showing instead shared features between SF and spatial networks.

3. Dynamical model

Once we have extracted the connectivity of real neuronal cultures, we can provide a dynamical behavior to their nodes, in order to enable the exploration of the potential interplay between structure and dynamics. For this study we implemented

Fig. 3. Comparative plot of the cumulative degree distribution $P_c(k)$ of an experimental clustered neuronal network at DIV7 (black squares) and equivalent synthetic networks: random Erdős–Renyi (ER, blue diamonds), scale-free obtained with the Barabási–Albert algorithm (SF, red dots) and a spatial network where distance-dependence linkage pattern (spatial-ER green diamonds). We see that the cultured network's distribution shows a similar behavior, for low degrees, as the SF one, and there is a region in which it is similar to the spatial network (namely, the decay for large values of k is almost identical). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the bio-inspired Morris–Lecar (ML) model [27,36], whose equations describing the membrane potential behavior for each unit read [17,37]:

$$C\dot{V}_i = -\overbrace{g_X M_\infty (V_i - V_X)}^{\text{Ionic channels}} + q\xi_i + \underbrace{\frac{\sigma}{K} \sum_j a_{ij} e^{-2(t-t_j)} (V_0 - V_i)}_{I_i} + I_i^{\text{ext}}, \quad (1)$$

$$\dot{W}_i = \phi \tau_W (W_\infty - W_i)$$

where V_i and W_i are, respectively, the membrane potential and the fraction of open K^+ channels of the i th neuron and M_∞ , W_∞ , and τ_W are hyperbolic functions dependent on V_i and ϕ is a reference frequency. The parameters g_X and V_X account for the electric conductance and equilibrium potentials of the $X = \{K, Ca, \text{leaky}\}$ channels. The external current $I_i^{\text{ext}} = 50.0$ mA is the same for all the neurons and is chosen such that neurons are sub-threshold to neuronal firing which is induced by the white Gaussian noise $q\xi_i$ of zero mean and intensity q . The coupling of the neuron i th with the neuron ensemble is described by the injected synaptic current I_i , given by the superposition of all the post-synaptic potentials emitted by the neighbours of node i in the past, being t_j the time of the last spike of node j , and the corresponding element of the adjacency matrix is $a_{ij} = 1$ if there is a link between nodes i, j and $a_{ij} = 0$ otherwise. The synaptic conductance σ , normalised by the largest node degree present in the network K , plays the role of coupling intensity.

Additionally, the channel voltage-dependent saturation values are given by the following functions:

$$M_\infty(V_i) = \frac{1}{2} \left[1 + \tanh \left(\frac{V_i - V_1}{V_2} \right) \right],$$

$$W_\infty(V_i) = \frac{1}{2} \left[1 + \tanh \left(\frac{V_i - V_3}{V_4} \right) \right], \quad (2)$$

$$\tau_W(V_i) = \cosh \left(\frac{V_i - V_3}{2V_4} \right).$$

We chose the parameters such that the neurons in the simulations corresponded to type II class excitability for the neuron dynamics, which means that a discontinuous transition is found in

Fig. 4. Illustration of the Ordinal Patterns formalism. (a) Detection of the maxima of the simulated (Morris–Lecar neuron) signal. (b) Extraction of the timestamps at which these maxima have been attained. Consecutive timestamps are subtracted (c) and their differences (ISIs) are stored in an array (d). The time series of ISIs is divided in sequences of length D ($D = 3$ in this example), and consecutive points in each sequence are compared and classified based on their relative values (e). Each sequence of length D is given a natural number and the probability of the realization of each possible D -symbols sequence is computed (f). The probabilities are then used to construct the complexity measure.

the dependence of the spiking frequency on the external current. The values for all the parameters can be found in Refs. [27,38].

We have to remark, however, that this model was originally conceived for a single neuron and in this work we are dealing with aggregates of 20 of them as our individual nodes. Although this quantity is not enough for employing a *neural mass model*, it should be noted that, strictly, it is not a single neuron either.

4. Statistical characterisation of the dynamics

With the purpose of providing a solid description of the system, we use two different quantities: a global and a local one. The global measure is the *synchronisation level* of the network, i.e. how similar are the dynamical outputs of our units, while the local one is an individual measure of the *complexity* of a node's time series.

4.1. Synchronization measure

In order to quantify the level of synchronization we estimate how many neurons fire within the same time window. The total simulation time T is divided in $n = 1, \dots, N_b$ bins of a convenient size τ , such that $T = N_b \tau$, and the binary quantity $B_i(n)$ is defined such that $B_i(n) = 1$ if the i th neuron spiked within n th interval and

0 otherwise. The synchronisation between the spiking sequences of neurons i and j is therefore characterised with the pairwise correlation matrix $s_{ij} \in [0, 1]$

$$s_{ij} = \frac{\sum_{n=1}^{N_b} B_i(n) B_j(n)}{\sum_{n=1}^{N_b} B_i(n) \sum_{n=1}^{N_b} B_j(n)}, \quad (3)$$

where the term in the denominator is a normalisation factor and $s_{ij} = 1$ means full coincidence between the two spiking series. The ensemble average of s_{ij} , $S = \langle s_{ij} \rangle = \frac{2}{N(N-1)} \sum_{i,j=1, i \neq j}^N s_{ij}$ is a measure of the global synchronisation in the network. In Fig. 5(a) we plot an example of the averaged value of S as a function of σ for an experimental CNN clustered network with $N = 246$ nodes, obtained at DIV7 as explained in Section 2. A transition from an asynchronous to an almost synchronous firing is observed as the synaptic conductance σ is increased, which confirms that the structure is suitable for inducing synchronisation in the system.

4.2. Statistical complexity

Once we know the effect that the relationship between network topology and dynamics has on the global state, we explore the effect that the presence of the ensemble has on the single node

Fig. 5. Dependence of the statistical complexity at the node level and its topological role in an experimental neuronal network 7 days in vitro old with $N = 246$ Morris–Lecar neurons. (a) Synchronisation curve for the explored values of the synaptic conductance. (b) Complexity values $(C)_k$ vs. d for low ($k = 3$) and high ($k = 20$) degree node values. (c) $(C)_k$ vs. k for the conductance value ($\sigma = 950$) marked in (b) with a vertical dashed line. Each point is the average of 6 network realisations.

dynamics by measuring the *statistical complexity* of the single nodes along the synchronisation process. As the typical neuronal dynamics exhibited by Eq. (1) consists of a sequence of L spikes whose amplitude variability is negligible, we focused on the complexity C_i of the sequence of inter-spike intervals ($t_i - t_{i-1}$) (ISI) of each neuron.

The ordinal patterns formalism [39] associates a symbolic sequence to a series [40], transforming the actual values of the data series into a set of natural numbers. To do that, the ISI series of each neuron is divided in sequences of length D . In each sequence, the data values are ordered in terms of their relative magnitudes [13], which provides the corresponding symbolic sequence. The information content of these sequences is then evaluated as a function of the complexity measure. The complete process is illustrated in Fig. 4.

This is a broad-field, well-established and known method, statistically reliable and robust to noise, extremely fast in computation and with a clear definition and interpretation in physical terms. It is derived from two also well-established measures (divergence and entropy), also easily interpretable when analysing non linear dynamical systems. In addition, it only requires soft criteria, namely that the time series must be weakly-stationary, i.e., for $k \leq D$, the probability for $ISI_t < ISI_{t+k}$ should not depend on time [39], and that $M \gg D!$ (where M is the number of points

of the entire time series of ISIs), which are easily checkable. We proceed in the following way, as shown in Fig. 4:

- From each single node time series in the simulated (Morris–Lecar neuron) signal, we detect the spikes (a) and extract the duration between two consecutive spikes (b).
- We compute series of the inter-spike time intervals ISI (c) and save them in an array (d), which will be our object of study.
- The ISI series is divided in sequences of length D ($D = 3$ in this illustration, (e)). We compare consecutive points in each sequence and associate a natural number to each of them (f), ranking them based on their relative size.
- We count how many times a certain symbolic sequence (or *pattern*) π of length D appears (N_π).
- Then, we define a probability of occurrence for each pattern: $P_\pi = \frac{N_\pi}{N_T}$, where N_T is the total number of sequences of length D in which the time series is divided, i.e. $N_T = (L - 1)/D$, being L the total number of spikes.
- We construct a *probability distribution*, which we call P from now on, from all possible symbolic sequences of length D with probability P_π .

Once the probability distribution P is obtained, the statistical complexity is defined. It is a measure that should be minimal both for pure noise and absolute regularity, and provide a bounded value for other regimes. Being this so, we need to characterise the disorder and a correcting term (i.e., a way of comparing known probability distributions with the actual one). The statistical complexity (C), as defined in Ref. [41], is the product of the Permutation Entropy (H) and the Disequilibrium (Q).

To define the permutation entropy H , the first step is the evaluation of the Shannon entropy, that gives an idea of the *predictability* of the series:

$$S[P] = - \sum_{j=1}^{D!} p_j \cdot \log(p_j) \quad (4)$$

The permutation entropy corresponds to the normalisation of S with respect to the entropy of the uniform probability distribution, S_{max} :

$$H = \frac{S}{S_{max}}, \quad S_{max} = S[P_e], \quad P_e \equiv \{p_i = 1/D!\}_{i=1, \dots, D!} \Rightarrow 0 \leq H \leq 1 \quad (5)$$

Regarding the disequilibrium Q , it is a way of measuring the distance of the actual probability distribution P with the equilibrium probability distribution P_e . This notion of *distance* can be acquired by several means; in this work, we adopt the statistical distance given by the Kullback–Leibler [42] relative entropy (K):

$$\begin{aligned} K[P|P_e] &= - \sum_{j=1}^{D!} p_j \cdot \log(p_e) + \sum_{j=1}^{D!} p_j \cdot \log(p_j) \\ &= S[P|P_e] - S[P] \end{aligned} \quad (6)$$

where $S[P|P_e]$ is the Shannon cross entropy. If we now symmetrise Eq. (6), we get the Jensen–Shannon divergence (J):

$$\begin{aligned} J[P|P_e] &= (K[P|P_e] + K[P_e|P])/2 \stackrel{(*)}{=} J[P|P_e] \\ &= S[(P + P_e)/2] - S[P]/2 - S[P_e]/2 \end{aligned} \quad (7)$$

where $(*)$ is simply the rewritten version in terms of S . Finally, we can write the disequilibrium Q as the normalised version of J as:

$$Q = Q_0 J[P|P_e] \quad (8)$$

with $Q_0 = \frac{N+1}{N} \log(N+1) - 2 \log(2N) + \log(N)^{-1}$, implying again $0 \leq Q \leq 1$. We then just have to multiply H and Q to obtain the *Complexity measure*:

$$C = H \cdot Q \quad (9)$$

5. Results

We summarise our results for the statistical complexity in a cultured neuronal network in Fig. 5. As commented above, in panel (a) we show as a reference the synchronisation level vs the synaptic conductance σ for the dynamics simulated on top of a DIV7 experimental network. In panel Fig. 5(b) we plot the value of $\langle C \rangle_k$ as a function of the conductance σ for two nodes with high ($k = 30$) and poor ($k = 3$) connectivity, being $\langle C \rangle_k = \sum_{i|k_i=k} C_i / N_k$, with N_k the number of nodes with degree k . The results evidences that, on that same route to synchronisation, there exists differences between how hubs and peripheral nodes behave due to the presence of the ensemble, even when the global synchronisation level is still very low.

The main detail that catches our attention is that the peripheral nodes show a greater complexity than the hubs ($\sigma = 950$). To further explore this finding, in the third panel we depict the statistical complexity vs the degree, for this value of σ . We can extract an interesting result here: for $\sigma = 950$, there exists an anti-correlation between $\langle C \rangle_k$ and k .

This anti-correlation observed in cultured neuronal cultures is not as evident as the one reported in Ref. [27] in SF networks, but taking into account that the structure, which has grown in a limited spatial domain, does not belong to the class of power-law networks (as it was already discussed) and that the model (Morris-Lecar) was not originally designed for this kind of neuronal aggregates, one can conclude that the anti-correlation between the statistical complexity C and the degree k is a quite robust feature.

6. Conclusions

In Ref. [27] we investigated the relationship between the statistical complexity and topology in synthetically generated networks. Here, we focused on the study of real-world topologies, as the ones exhibited by self-organised neuronal cultures. The longitudinal study of the morphology of these networks shows an evolution in the topology from isolated neurons to a percolated heterogeneous topology with small-world properties.

In order to study the structure-dynamics interaction in these networks, we simulated a dynamical model (the Morris-Lecar neuron) on top of experimental neuronal networks at the mature developmental stage. We evidenced that, in the weakly coupled regime, it is possible to anti-correlate the individual node statistical complexity of the series of the neuronal inter-spike intervals with the degree of a node. Therefore, it would be possible to infer the degree distribution of the network from node dynamical measurements, which confirms the result obtained for synthetic networks [27]. This approach based on the computation of complexity values retrieved from single node dynamics, provides a different perspective than the usual methods of network inference, since it does not imply node-to-node calculations. Additionally, our method does not impose the need of measuring the dynamics of every node: it can be an incomplete measure, an still it will provide their relative roles. We hope this approach will be useful in applications where the knowledge of the degree distribution, instead of the detailed connectome, provides a sufficient insight over an unknown topology and about the functioning of the underlying system.

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References

- [1] Pecora LM. Synchronization conditions and desynchronizing patterns in coupled limit-cycle and chaotic systems. *Phys Rev E* 1998;58(1):347–60.
- [2] Barahona M, Pecora LM. Synchronization in small-world systems. *Phys Rev Lett* 2002;89:054101.
- [3] Boccaletti S, Latora V, Moreno Y, Chavez M, Hwang D-U. Complex networks: structure and dynamics. *Phys Rep* 2006;424(4–5):175–308.
- [4] Arenas A, Díaz-Guilera A, Kurths J, Moreno Y, Zhou C. Synchronization in complex networks. *Phys Rep* 2008;469(3):93–153.
- [5] Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 2009;10(3):186–98.
- [6] Rohden M, Sorge A, Timme M, Witthaut D. Self-organized synchronization in decentralized power grids. *Phys Rev Lett* 2012;109:064101.
- [7] Pluchino A, Latora V, Rapisarda A. Changing opinions in a changing world: a new perspective in sociophysics. *Int J Mod Phys C* 2005;16(04):515–31.
- [8] Fujiwara N, Kurths J, Díaz-Guilera A. Synchronization in networks of mobile oscillators. *Phys Rev E* 2011;83:025101.
- [9] Rodríguez E, George N, Lachaux JP, Martinerie J, Renault B, Varela FJ. Perception's shadow: long-distance synchronization of human brain activity. *Nature* 1999;397(6718):430–3.
- [10] Jean-Philippe L, Eugenio R, Jacques M, J VF. Measuring phase synchrony in brain signals. *Hum Brain Mapp* 1999;8(4):194–208.
- [11] Pecora LM, Sorrentino F, Hagerstrom AM, Murphy TE, Roy R. Cluster synchronization and isolated desynchronization in complex networks with symmetries. *Nat Commun* 2014;5:4079.
- [12] Tononi G, Sporns O, Edelman GM. A measure for brain complexity: relating functional segregation and integration in the nervous system. *Proc Natl Acad Sci* 1994;91(11):5033–7. doi:10.1073/pnas.91.11.5033.
- [13] Rad AA, Sendiña Nadal I, Papo D, Zanin M, Buldú JM, del Pozo F, et al. Topological measure locating the effective crossover between segregation and integration in a modular network. *Phys Rev Lett* 2012;108:228701.
- [14] Sporns O. Network attributes for segregation and integration in the human brain. *Curr Opin Neurobiol* 2013;23:162–71. doi:10.1016/j.conb.2012.11.015.
- [15] Gómez-Gardeñes J, Moreno Y, Arenas A. Paths to synchronization on complex networks. *Phys Rev Lett* 2007;98(3):034101. doi:10.1103/PhysRevLett.98.034101.
- [16] Li D, Leyva I, Almendral JA, Sendiña Nadal I, Buldú JM, Havlin S, et al. Synchronization interfaces and overlapping communities in complex networks. *Phys Rev Lett* 2008;101:168701.
- [17] Navas A, Villacorta-Atienza JA, Leyva I, Almendral JA, Sendiña Nadal I, Boccaletti S. Effective centrality and explosive synchronization in complex networks. *Phys Rev E* 2015;92:062820.
- [18] Skardal PS, Taylor D, Sun J. Optimal synchronization of complex networks. *Phys Rev Lett* 2014;113(14):144101.
- [19] Van Den Heuvel MP, Sporns O. Network hubs in the human brain. *Trends Cogn Sci* 2013;17:683–96.
- [20] Papo D, Zanin M, Pineda-Pardo JA, Boccaletti S, Buldú JM, Buldú JM. Functional brain networks: great expectations, hard times and the big leap forward. *Phil Trans R Soc B* 2014;369(1653). 20130525–20130525.
- [21] Zamora-López G, Chen Y, Deco G, Kringelbach ML, Zhou C. Functional complexity emerging from anatomical constraints in the brain: the significance of network modularity and rich-clubs. *Sci Rep* 2016;6(1):38424.
- [22] Deco G, Van Hatervelt TJ, Fernandes HM, Stevner A, Kringelbach ML. The most relevant human brain regions for functional connectivity: evidence for a dynamical workspace of binding nodes from whole-brain computational modelling. *Neuroimage* 2017;146:197–210.
- [23] Pereira T. Hub synchronization in scale-free networks. *Phys Rev E* 2010;82:036201.
- [24] Zhou C, Kurths J. Hierarchical synchronization in complex networks with heterogeneous degrees. *Chaos* 2006;16(1):015104.
- [25] Arenas A, Díaz-Guilera A, Pérez-Vicente CJ. Synchronization reveals topological scales in complex networks. *Phys Rev Lett* 2006;96:114102.
- [26] Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, et al. Predicting human resting-state functional connectivity from structural connectivity. *Proc Natl Acad Sci* 2009;106(6):2035–40.
- [27] Tlaie A, Leyva I, Sevilla-Escoboza R, Vera-Avila V, Sendiña-Nadal I. Dynamical complexity as a proxy for the network degree distribution. *arXiv:1807.09629* 2018.
- [28] Eckmann J-P, Feinerman O, Gruendlinger L, Moses E, Soriano J, Tlusty T. The physics of living neural networks. *Phys Rep* 2007;449:54–76.
- [29] Fuchs E, Ayali A, Robinson A, Hulata E, Ben-Jacob E. Coemergence of regularity and complexity during neural network development. *Dev Neurobiol* 2007;67:1802–14.
- [30] van Pelt J, Vadjia I, Wolters PS, Corner M, Ramakers GJA. Dynamics and plasticity in developing neuronal networks in vitro. *Prog Brain Res* 2005;147:173–88.
- [31] Burrows M. The neurobiology of an insect brain. Oxford University Press; 1996.
- [32] Anava S, Saad I, Ayali A. The role of gap junction proteins in the development of neural network functional topology. *Mol Insect Biol* 2013;22:457–72.
- [33] Ayali A, Zilberstein Y, N C. The role of gap junction proteins in the development of neural network functional topology. *J Exp Biol* 2002;205:2825–32.
- [34] de Santos-Sierra D, Sendiña Nadal I, Leyva I, Almendral J, Anava S, Ayali A, et al. Emergence of small-world anatomical networks in self-organizing clustered neuronal cultures. *PLoS ONE* 2014;9:E85828.

- [35] de Santos-Sierra D, Sendiña Nadal I, Leyva I, Almendral J, Ayali A, Anava S, Sánchez-Ávila C, et al. Graph-based unsupervised segmentation algorithm for cultured neuronal networks' structure characterization and modeling. *Citometry A* 2015;87:513–23.
- [36] Morris C, Lécarré H. Voltage oscillations in the barnacle giant muscle fiber. *Biophys J* 1981;35(1):193–213.
- [37] Sancristóbal B, Vicente R, Sancho JM, García-Ojalvo J. Emergent bimodal firing patterns implement different encoding strategies during gamma-band oscillations. *Front Comput Neurosci* 2013;7:18.
- [38] Leyva I, Navas A, Sendiña-Nadal I, Buldu JM, Almendral JA, Boccaletti S. Synchronization waves in geometric networks. *Phys Rev E* 2011;84(6):065101.
- [39] Bandt C, Pompe B. Permutation entropy: a natural complexity measure for time series. *Phys Rev Lett* 2002;88:174102.
- [40] Letellier C. Symbolic sequence analysis using approximated partition. *Chaos Solitons Fractals* 2008;36(1):32–41. doi:10.1016/j.chaos.2006.06.025.
- [41] Martin M, Plastino A, Rosso O. Statistical complexity and disequilibrium. *Phys Lett A* 2003;311(2–3):126–32.
- [42] Kullback S, Leibler RA. On information and sufficiency. *Ann Math Stat* 1951;22(1):79–86.

Chapter 5

High-order interactions in neural networks

High-order couplings in geometric complex networks of neurons

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We explore the consequences of introducing higher-order interactions in a geometric complex network of Morris-Lecar neurons. We focus on the regime where traveling synchronization waves are observed from a first-neighbors-based coupling to evaluate the changes induced when higher-order dynamical interactions are included. We observe that the traveling-wave phenomenon gets enhanced by these interactions, allowing the activity to travel further in the system without generating pathological full synchronization states. This scheme could be a step toward a simple phenomenological modelization of neuroglial networks.

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I. INTRODUCTION

The combination of complex networks and nonlinear dynamics has provided a solid framework for the study of a large number of very different real systems that can be analyzed as large ensembles of dynamical units with nontrivial connectivity patterns; these systems are as diverse as economics [1], genetics [2], social dynamics [3], and neuroscience [4].

Among all the possible collective features that can emerge in this context, synchronization is the most extensively studied, since it has been revealed as the fundamental mechanism in the transmission of information in all kinds of dynamical ensembles [5]. One of the fields where this perspective has led to new research lines is in neuroscientific applications. The neural system can be considered as a dynamical complex network in all its relevant scales, ranging from the microscopic, where the networked elements are single neurons [6,7], through the cortical column mesoscale [8], to the entire brain [4,9], with the brain areas acting as nodes of a functional network defined in terms of correlation levels.

However, even if synchronization is a key mechanism involved in the coordination of the neural ensemble, it is well known that exceedingly high levels of synchronization can destroy the overall complexity of the system, reducing its ability to process information and, eventually, leading to pathological states as epilepsy [10]. Therefore, a healthy synchronous functioning in the brain needs the existence of mechanisms of regulation, both structural and dynamical, to ensure the proper equilibrium between coordination and function segregation.

A plausible regulating mechanism is the astrocytes ensemble [11], whose role in brain performance is a long-standing problem in neuroscience. It is now known that astrocytes are involved in early synapse formation [12]. At the microscale, it is known that a single astrocyte can contact up to 10^5 synapses, meaning that these cells might be responsible for the modulation [13,14] of the electrical response of neurons sharing no anatomical connection at all [15–18] and, therefore, they could be the source of high-order interactions

supporting coordination levels that overcome the outreach of direct neural connectivity. Several attempts have been made to model the neuroglial interaction [19,20], most of them focusing on the neuron-astrocyte pair or, more commonly, a triad of two neurons and an astrocyte [21,22]. Recent studies have gone further to consider the networked context, using detailed conductivity models [23–25]. They coincide in showing how the interaction of the astrocytes ensemble with the neuron network can induce robust spatial synchronization in the neuronal ensemble surrounding the astrocytes [24–26] and in particular to enhance the propagation of activity waves [23]. These models are, however, mathematically and computationally costly [24], and therefore it will be useful to introduce a phenomenological model which is able to reproduce the observed effects of the glial ensemble over the neural network such that, while retaining the more relevant physiological aspects, it allows at the same time to move on to larger networks.

In this work we model the neural-glial ensemble as a geometrical network (similarly to those studied in Refs. [27–29]) with synaptic coupling, where the effect of the synaptic modulation of astrocytes is introduced using a high-order interaction formalism developed by Estrada *et al.* in Refs. [30–33]. It provides a solid quantitative mean to simulate and analyze the dynamics of a system in which these higher-order interactions are present. These effects are susceptible of revealing themselves particularly important in space embedded systems, where the Euclidean distances shape not only the probability of connection but also their weights. The high-order connectivity operator allows us to extend the usual first-neighbor interaction scheme that disregards higher-order interactions under the implicit assumption that if two nodes are not topologically connected they do not dynamically interact; such an assumption is no longer valid in a network of neurons whose communication is mediated by astrocytes.

The application of the high-order connectivity formalism to a complex network of synaptically connected neurons can provide insights about how introducing not only first but also second-neighbors interactions might be useful to comprehend

further details of the neuronal dynamics in a simple and mathematically well-defined way. We show how it enhances the appearance of synchronization waves, a mean for transmitting a dynamical activation throughout the system in a coherent way, but avoiding the neuronal hyper-synchronization disorder that would result from increasing a direct neural connectivity.

II. MODEL

The network consists of an ensemble of N neurons that are randomly seeded in a two-dimensional (2D) Euclidean square area of size $L \times L$. The nodes are connected following a distance-dependent geometric rule (we refer the reader to Refs. [34–36] for further discussion of the experimental relevance of these topologies), such that neuron i has a probability of establishing a link with neuron j [37–39]:

$$p_{ij} = p_0 e^{-\left(\frac{r_{ij}}{l_c}\right)}, \quad (1)$$

where p_0 is a normalization constant, r_{ij} is the Euclidean distance between i and j , and l_c the correlation length parameter that controls the typical outreach of the connections when constructing the network; low values of this parameter yield highly clustered, short-ranged networks, while standard Erdős-Rényi networks are obtained in the limit of large l_c . The neural connectivity is encoded in the correspondent adjacency matrix $A = \{a_{ij}\}$ such that $a_{ij} = 1$ means a physical connection between neurons i and j and $a_{ij} = 0$ otherwise. In this case, we used a symmetrical adjacency matrix, $a_{ij} = a_{ji}$, with a_{ij} structurally supporting a chemical synapse. We chose a_{ij} to be symmetrical because, although experimentally it has been evidenced that chemical interactions are unidirectional, the fact that the number of synapses is so enormous implies that the probability that the dendritic trees of two neurons can contact each other is not negligible. In addition, as we intend to model in a phenomenological way the effect of the glia-neuron interaction, the symmetrical form of the adjacency matrix will take into account that activity information flows in both directions. Furthermore, as we will show later, the synaptic conductance is modeled to be asymmetrical, so when both structure and dynamics are considered, the interaction is effectively directed.

Single-node dynamics is implemented as a Morris-Lecar neuron [40]:

$$\begin{aligned} C\dot{V}_i &= -g_{Ca}M_\infty(V_i - V_{Ca}) - g_KW_i(V_i - V_K) \\ &\quad - g_l(V_i - V_l) + I_i + I_i^{\text{ext}} \\ \dot{W}_i &= \phi \tau_W(W_\infty - W_i), \end{aligned} \quad (2)$$

where V_i and W_i are, respectively, the membrane potential (or active variable) and the fraction of open K^+ channels of the i th neuron, also known as the recovery variable; ϕ is a reference frequency, namely the inverse of the timescale for the recovery process. The parameters g_X and V_X account for the electric conductance and equilibrium potentials of the $X = \{K, \text{Ca}, \text{leaky}\}$ channels. An external current $I_i^{\text{ext}} = I_0 + Q\xi_i$ is added, with $I_0 = 50$ mA chosen such that neurons are subthreshold to their natural firing regime, which, in this case, will be induced by the additive white Gaussian noise $Q\xi_i$ of zero mean and intensity Q . The injected current I_i is the total amount of current coming from network inputs that neuron

TABLE I. Parameters used for the Morris-Lecar simulations.

C	20.0 $\mu\text{F}/\text{cm}^2$
g_{Ca}	4.0 $\mu\text{S}/\text{cm}^2$
g_K	8.0 $\mu\text{S}/\text{cm}^2$
g_l	2.0 $\mu\text{S}/\text{cm}^2$
V_{Ca}	120.0 mV
V_K	−80.0 mV
V_l	−60.0 mV
V_1	−1.2 mV
V_2	18.0 mV
V_3	2.0 mV
V_4	17.4 mV
ϕ	1/15
Q	0.5 mA
V_0	−59.0 mV

i gets; mathematically, in the local coupling approximation, first-order neighbors contribute to the synaptic coupling, and therefore $I_i = \sum_{j \in \mathcal{N}_i} I_{ij}$, where $\mathcal{N}_i$ is the neighborhood of node i , that is, nodes j such that $a_{ij} = 1$.

The direct synaptic interaction between presynaptic j neuron and excitatory postsynaptic i neuron is captured by the injected current I_{ij} [41–43]:

$$I_{ij} = \frac{\sigma}{K} [e^{-2(t-t_j)}(V_0 - V_i)], \quad (3)$$

with $t_j < t$ being the time of the last spike of node j . The synaptic conductance σ , normalized by the largest node degree K (number of connections that a given node has) present in the network, plays the role of coupling strength. This normalization is introduced in order to compare the dynamics of Eq. (3) independently of the specific connectivity density of the network. To have more details about this prescription, we refer the reader to Ref. [44].

Additionally, the channel voltage-dependent saturation values M_∞ , W_∞ , τ_W respond to hyperbolic functions dependent on V_i :

$$M_\infty(V_i) = \frac{1}{2} \left[1 + \tanh \left(\frac{V_i - V_1}{V_2} \right) \right], \quad (4)$$

$$W_\infty(V_i) = \frac{1}{2} \left[1 + \tanh \left(\frac{V_i - V_3}{V_4} \right) \right], \quad (5)$$

$$\tau_W(V_i) = \cosh \left(\frac{V_i - V_3}{2V_4} \right). \quad (6)$$

The explicit value of every parameter can be found in Table I.

In spatial, highly clustered homogeneous networks with reduced link range l_c , the coupling configuration described in Eq. (3) favors traveling-wave synchronization, as long as σ is high enough [39], a well-established feature of the spatially extended neural ensembles [20]. On the contrary, in the mean-field approximation limit, $l_c \rightarrow L$, only globally incoherent or coherent states are accessible [45]. In our model, as a balance between these two extrema, we intend to explore the potential enhancement effect of higher-order connectivity at the local spatial scale in the wave regime, as for example the glial ensemble has in the neural circuits that are not directly connected among them [18]. Therefore, following the same mathematical framework developed in Refs. [30–32],

we allow that the injection current I_i accounts for the contribution not only from neurons $j \in \mathcal{N}_i$ whose topological distance (also referred to as network distance, that is, the shortest-path length) is $d_{ij} = 1$, but also from neighbors at higher topological distances $d_{ij} > 1$, that is,

$$I_i = \sum_{d=1}^D d^{-\alpha} \left(\sum_{j|d_{ij}=d} I_{ij} \right), \quad (7)$$

where D is the maximal topological distance considered. The successively distant contributions to the injection synaptic current I_i are modulated by a geometrically decaying term, $d^{-\alpha}$, where the constant α is a suppression parameter for the distance-dependent coupling strength. Notice that when the summation is limited to the first order $D = 1$, the usual first-neighbors interaction is recovered.

III. SYNCHRONIZATION MEASURES

In order to quantify the level of coordination among the network firing events we count how many neurons fire within the same time window. First, the total simulation time T is divided in N_b bins of a convenient size τ , longer than the time duration of each individual spike but much shorter than the average interspike interval. Then the total simulation time is discretized as $T = N_b \tau$ and the time series of the dynamics of neuron i th is replaced by the binary series B_i , where $B_i(n) = 1$ if the i th neuron spiked within the n th time bin, and 0 otherwise, with $n = 1, \dots, N_b$. This simplification of the dynamics ensures a fast and precise calculation of the ensemble statistics. Finally, the coherence between the spiking sequence of neurons i and j can be characterized with the quantity $s_{ij} \in [0, 1]$

$$s_{ij} = \frac{\sum_{n=1}^{N_b} B_i(n) B_j(n)}{\sqrt{\sum_{n=1}^{N_b} B_i(n) \sum_{n=1}^{N_b} B_j(n)}}, \quad (8)$$

where the term in the denominator is a normalization factor, such that $s_{ij} = 1$ implies full coincidence between the spike trains of neurons i and j . The ensemble average of s_{ij} is the global synchronization measure S , given by:

$$S = \langle s_{ij} \rangle = \frac{1}{N(N-1)} \sum_{i \neq j}^N s_{ij}. \quad (9)$$

However, as we are interested not only in global but also spatial local effects in the ensemble coherence from the high-order couplings, we use the coherence matrix s_{ij} to compute also the Euclidean local synchronization S_ρ , where only the correlation values s_{ij} of those neurons pairs which are closer to each other than a given distance ρ are taken into account, that is [39]:

$$S_\rho = \langle s_{ij} \rangle, \quad \forall \{i, j\} | r_{ij} < \rho. \quad (10)$$

In our computations, all measures are averaged over five different realizations of networks.

It is expected that in the limit $\rho \rightarrow L$, $S_\rho \sim S$. High values of S_ρ would indicate that there are areas of size ρ firing synchronously. In the following, we use the difference $S_\rho - S$ as an indicator of the existence of either a traveling wave

FIG. 1. Successive snapshots of the neurons' spiking activity in the traveling-wave synchronization mode. Filled dots represent spiking neurons while empty dots represent silent neurons. In the example the wave is propagating from the left to the right in a network of $N = 150$ Morris-Lecar neurons. Other parameters: $p_0 = 1.0$, $L = 50$, $l_c = 0.15$, $\sigma = 150$, $D = 1$.

front (when $S_\rho - S$ is large) or global or null synchronization ($S_\rho \sim S$) otherwise. It should be noted that, in general, the difference $S_\rho - S$ is not *designed* as to solely detect wavelike activity. There can be cases (such as in strongly modular networks) in which a high discrepancy between S_ρ and S are due to a clustered but globally incoherent neuronal firing (that is, each module fires in a coherent fashion but the modular activity does not propagate to the rest of the network). In our particular case, neurons are in spatially embedded networks with homogeneous connectivity which is distance regulated and thus strong modularity can be discarded.

IV. RESULTS

When just first-order interactions are present, this geometrical arrangement of neurons favors the propagation of traveling waves of neurons' spiking activity, supported by a highly clustered structure with a typically low link outreach [39]. To illustrate such propagation, in Fig. 1 we show two successive snapshots of an example where $l_c = 0.15$ and $\sigma = 150$. Here black dots represent spiking neurons while void dots portray those which are silent. The links between nodes are not included for clarity. This feature is quantified in Fig. 2, showing that this wavelike phenomenon is characterized by a local synchronization S_ρ (circles) larger than the global synchronization S (crosses), as it can be observed. The low value of the link outreach l_c prevents the system to reach full synchronization even when the coupling strength σ increases, whereas the local synchronization S_ρ grows much faster, indicating a reinforcement of the wave activity.

We now evaluate the effect of introducing higher-order contributions in the synaptic coupling in Eq. (7) received from neighbors at topological distance up to $D = 2$.

Results are collected in Fig. 3, where $S_\rho - S$ is plotted as a function of the conductance σ for different values of the suppression constant α , ranging between 0 and 3. For the sake of comparison, the curve for $D = 1$ is included (red circles). When $D > 1$, the higher the value of the suppression α , the weaker the influence from $D = 2$ neighbors. Therefore, we observe that for the higher suppression $\alpha = 3$ (purple squares), the behavior approaches the $D = 1$, and both curves overlap in almost the whole range of explored couplings up to $\sigma \sim 200$.

FIG. 2. Synchronization route as a function of the coupling strength σ for $l_c = 0.15$ and $D = 1$. Local synchronization S_ρ (black circles) computed with $\rho = 10$ and global synchronization (red crosses). Both series of data are averages over five $N = 150$ network realizations, with the connectivity scheme outlined in Sec. II.

However, as high-order effects become stronger for smaller values of α in Fig. 3, the S_ρ - S curves exhibit a maximum, located at lower values of the conductance σ . For instance, the curve for $D = 2$, $\alpha = 0$ (black triangles) peaks at $\sigma \sim 50$, while for the case $D = 1$ the S_ρ - S difference is very small. The conclusion is that the introduction of another layer of interacting neighbors allows the propagation of traveling waves for coupling strengths where first-order interactions only supports incoherent activity. It can be deduced that this critical value of σ is related to the best communication efficiency of the spiking activity, given the constraints of a

FIG. 3. Difference between local S_ρ and global S synchronization as a function of the coupling strength σ for different values of the suppression constant α and maximal topological distances $D = 1$ and $D = 2$. The gray circle highlights the intersection between the curves $D = 1$ and $(D = 2, \alpha = 0)$. Each point is an average over five network realizations. Same parameters as in Fig. 2.

FIG. 4. Normalized local synchronization ($\bar{S}_\rho$) values as a function of ρ/L for the two sets of parameter conditions defined by the gray circle in Fig. 3. Horizontal dashed lines mark the normalized values of the corresponding global synchronization. Vertical dashed lines mark the point defining the width of the traveling front. Each point is averaged over 10 network realizations.

fixed topology and dynamical parameters. Notice that the traveling-wave feature implies a temporal ordering of the network's activity, as opposed to global synchronization (no temporal order) or incoherent activity (random spikes) and, therefore, this dynamical regime ensures a robust encoding of activity.

To further explore the network activity and traveling-wave features, we focused on the coupling strength at which the two previously mentioned curves intersect (gray circle in Fig. 3, $\sigma \sim 100$), corresponding in both cases to wave propagation. However, we can observe that the wave-front features are also modified by the high-order effects. We analyzed these differences by varying the scale ρ at which the local synchronization S_ρ is measured for both cases at the crossing point. Figure 4 compares S_ρ for $D = 1$ (red circles) and $D = 2$, $\alpha = 0$ (blue triangles), normalized to their respective maxima, $\bar{S}_\rho = S_\rho / \max(S_\rho)$, as a function of ρ/L , such that when ρ is of the same size L as the surface in which the network is seeded, the local synchronization statistically converges to the normalized global synchronization level [$\bar{S} = S / \max(S)$] observed for each case (horizontal dashed lines). As expected, there is an optimal length scale ρ at which the local synchronization measure is maximum: Smaller scales undervalue the cluster of neurons spiking synchronously, while larger scales average neurons which are in different dynamical states. Therefore, the value of ρ at which S_ρ peaks is an estimation of the wave-front width. Thus, as Fig. 4 indicates, higher-order interactions, for the same conductance value, allow the propagation of wider spiking waves, almost doubling the size with respect to $D = 1$. This could lead us to conclude that taking into account the direct influence of neighbors at larger topological distance allows the activity to be transmitted faster throughout the network, as more neurons are active in each wave front (while preserving the locality feature) and thus the wave front needs less time to cross the entire network.

V. CONCLUSIONS

In this work we have evidenced that the introduction of higher-order dynamical interactions in an ensemble of neurons with geometrical connectivity patterns leads to a faster and much more robust propagation of the activity through this spatially embedded system. This is so, due to the fact that, if at a given wave front there are more active neurons involved in the firing transmission, then it is more probable that the wave front will traverse the whole network, even if some of the neurons fail to transmit the signal. Thus, the transmission is more resistant to failures and, therefore, more robust. The propagation occurs as a traveling wave, whose wave front gets enhanced thanks to recruiting more neurons in the transmission. In addition, we have shown that higher-order dynamical interactions allow this kind of time-ordered synchronization for much lower coupling values than the case where only first-order neighbors are involved.

We hypothesize that this could be an innovative way of modeling the effects of neuroglial interaction, among other physical systems in which higher-order interactions need to be taken into account. Specifically, we argue that this mechanism of higher-order interactions could be a potent and computationally cheaper phenomenological approach to the detailed physiological models that can be found nowadays in the lit-

erature [23,25]. The central foundation for having chosen this particular mathematical formalism comes from a biological insight: Astrocytes have been evidenced to modulate up to $\approx 10^5$ synapses [46], while the majority of the neurons they interact with do not share an anatomical connection. This would imply that, while there is a given number of topological links in the network, some indirect ones would be present in the form of dynamical modulation, this role being played by astrocytes. As this is only a first step toward modeling the interplay between astrocytes and neurons in a network, we focused on establishing a solid base on which we will continue the research.

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- [1] W. Souma, Y. Fujiwara, and H. Aoyama, *Physica A* **324**, 396 (2003).
 - [2] S. K. Sieberts and E. E. Schadt, *Mamm. Gen.* **18**, 389 (2007).
 - [3] P. V. Fellman, in *Unifying Themes in Complex Systems*, edited by A. Minai, D. Braha, and Y. Bar-Yam (Springer, Berlin, Heidelberg, 2010).
 - [4] E. Bullmore and O. Sporns, *Nat. Rev. Neurosci.* **10**, 186 (2009).
 - [5] A. Arenas, A. Díaz-Guilera, J. Kurths, Y. Moreno, and C. Zhou, *Phys. Rep.* **469**, 93 (2008).
 - [6] J.-P. Eckmann, O. Feinerman, L. Gruendlinger, E. Moses, J. Soriano, and T. Tlusty, *Phys. Rep.* **449**, 54 (2007).
 - [7] A. Kumar, S. Rotter, and A. Aertsen, *Nat. Rev. Neurosci.* **11**, 615 (2010).
 - [8] H. Zeng, *Curr. Opin. Neurobiol.* **50**, 154 (2018).
 - [9] V. M. Eguiluz, D. R. Chialvo, G. A. Cecchi, M. Baliki, and A. V. Apkarian, *Phys. Rev. Lett.* **94**, 018102 (2005).
 - [10] P. Jiruska, M. De Curtis, J. G. Jefferys, C. A. Schevon, S. J. Schiff, and K. Schindler, *J. Physiol.* **591**, 787 (2013).
 - [11] T. Fellin, O. Pascual, S. Gobbo, T. Pozzan, P. G. Haydon, and G. Carmignoto, *Neuron* **43**, 729 (2004).
 - [12] M. M. Bolton and C. Eroglu, *Curr. Opin. Neurobiol.* **19**, 491 (2009).
 - [13] W. J. Nett, S. H. Oloff, and K. D. McCarthy, *J. Neurophysiol.* **87**, 528 (2002).
 - [14] M. C. Angulo, A. S. Kozlov, S. Charkpak, and E. Audinat, *J. Neurosci.* **24**, 6920 (2004).
 - [15] G. Perea, M. Navarrete, and A. Araque, *Trends Neurosci.* **32**, 421 (2009).
 - [16] N. J. Allen and B. A. Barres, *Nature (London)* **457**, 675 (2009).
 - [17] F. Oschmann, H. Berry, K. Obermayer, and K. Lenk, *Brain Res. Bull.* **136**, 76 (2018).
 - [18] M. De Pittà, N. Brunel, and A. Volterra, *Neuroscience* **323**, 43 (2016).
 - [19] M. De Pitta and H. E. Berry, *Computational Glioscience* (Springer, Berlin, 2019).
 - [20] M. Santello, N. Toni, and A. Volterra, *Nat. Neurosci.* **22**, 154 (2019).
 - [21] Z. Sajedinia and S. Hélie, *Comput. Intell. Neurosci.* **2018**, 3689487 (2018).
 - [22] J.-J. Li, M.-M. Du, R. Wang, J.-Z. Lei, and Y. Wu, *Int. J. Bifurcat. Chaos* **26**, 1650138 (2016).
 - [23] M. Amiri, F. Bahrani, and M. Janahmadi, *J. Theor. Biol.* **292**, 60 (2012).
 - [24] O. Kanakov, S. Gordileeva, A. Ermolaeva, S. Jalan, and A. Zaikin, *Phys. Rev. E* **99**, 012418 (2019).
 - [25] S. Y. Gordileeva, A. V. Ermolaeva, I. A. Kastalskiy, and V. B. Kazantsev, *Front. Physiol.* **10**, 294 (2019).
 - [26] A. B. Porto-Pazos, N. Veiguela, P. Mesejo, M. Navarrete, A. Alvarellos, O. Ibáñez, A. Pazos, and A. Araque, *PLoS one* **6**, e19109 (2011).
 - [27] M. Perc, *New J. Phys.* **7**, 252 (2005).
 - [28] X. Sun, M. Perc, Q. Lu, and J. Kurths, *Chaos* **18**, 023102 (2008).
 - [29] W.-J. Yuan, J.-F. Zhou, and C. Zhou, *PLoS One* **8**, e84644 (2013).
 - [30] E. Estrada and G. Silver, *J. Math. Anal. Appl.* **449**, 1581 (2017).
 - [31] E. Estrada, E. Hameed, N. Hatano, and M. Langer, *Lin. Algeb. Appl.* **523**, 307 (2017).
 - [32] E. Estrada, L. V. Gambuzza, and M. Frasca, *SIAM J. Appl. Dynam. Syst.* **17**, 672 (2018).
 - [33] J. H. Arias, J. Gómez-Gardeñes, S. Meloni, and E. Estrada, *J. Theor. Biol.* **453**, 1 (2018).

- [34] D. de Santos-Sierra, I. Sendiña-Nadal, I. Leyva, J. A. Almendral, S. Anava, A. Ayali, D. Papo, and S. Boccaletti, [PloS one](#) **9**, e85828 (2014).
- [35] O. Shefi, I. Golding, R. Segev, E. Ben-Jacob, and A. Ayali, [Phys. Rev. E](#) **66**, 021905 (2002).
- [36] O. Stetter, D. Battaglia, J. Soriano, and T. Geisel, [PLoS Comput. Biol.](#) **8**, e1002653 (2012).
- [37] M. Kaiser and C. C. Hilgetag, [Phys. Rev. E](#) **69**, 036103 (2004).
- [38] M. Barthélemy, [Phys. Rep.](#) **499**, 1 (2011).
- [39] I. Leyva, A. Navas, I. Sendiña-Nadal, J. M. Buldu, J. A. Almendral, and S. Boccaletti, [Phys. Rev. E](#) **84**, 065101(R) (2011).
- [40] C. Morris and H. Lecar, [Biophys. J.](#) **35**, 193 (1981).
- [41] M. J. Leone, B. N. Schurter, B. Letson, V. Booth, M. Zochowski, and C. G. Fink, [Phys. Rev. E](#) **91**, 032813 (2015).
- [42] S. Mofakham, C. G. Fink, V. Booth, and M. R. Zochowski, [Phys. Rev. E](#) **94**, 042427 (2016).
- [43] Z. G. Esfahani, L. L. Gollo, and A. Valizadeh, [Sci. Rep.](#) **6**, 23471 (2016).
- [44] J. Gómez-Gardeñes, Y. Moreno, and A. Arenas, [Phys. Rev. E](#) **75**, 066106 (2007).
- [45] R. Rosenbaum and B. Doiron, [Phys. Rev. X](#) **4**, 021039 (2014).
- [46] E. A. Bushong, M. E. Martone, Y. Z. Jones, and M. H. Ellisman, [J. Neurosci.](#) **22**, 183 (2002).

Chapter 6

General discussion

6.1 General discussion and conclusions

After having presented the main results of this Thesis, we are now in the position to expose the conclusions one can extract from this work.

As our guiding research question, we have inspected the relationship between the topological role of a node in a diversity of complex network structures and the dynamical behavior that node exhibits, represented by its statistical complexity. We have shown, both numerically and experimentally, that in the route to synchronization, higher degree nodes exhibit lower values of complexity. Importantly, when comparing the complexity of each node and its degree, we found a distinctive linear correlation, for various types of chaotic oscillators and for a biologically plausible neuron model. Thus, these results seem to be general enough to consider this approach as a viable path to inspect the problem of network structure inference. A crucial nuance of this insight is that structural information can be inferred *without computing pairwise correlations* like those commonly performed in brain functional networks and this could be exploited in diverse fields as neuroscience, econophysics, or power grids.

After having gained some insights, supported by the explorations just described, we considered *real-world* topologies instead of synthetic ones -specifically, self-organised neuronal cultures. We reported that in the weakly coupled regime it is possible to inversely correlate the individual node statistical complexity -coming from the simulated time series of the Morris-Lecar model we chose- with its degree. Therefore, a larger corpus of evidence that suggests the generality of the intuition beneath this approach is piling up.

Hence, we provide experimental support to the suggestion that this approach based on the computation of complexity values retrieved from single node dynamics is solid enough to be applied in other contexts. As it was mentioned earlier, it provides a different perspective than the usual methods of network inference, since it does not imply node-to-node calculations. Furthermore, our method does not impose the need of measuring the dynamics of every node: it can be an incomplete measure, and still it will provide information about their relative roles.

Nextly, we focused our attention into a refinement of the neuronal dynamics we

were considering. Specifically, we introduced high-order dynamical interactions in an ensemble of neurons with geometrical connectivity patterns. We highlight the importance of the novelty of this approach, as it was a demand both by experimentalists working on synapses modulated by astrocytes and by theoreticians trying to capture the essence of this modulation in a computationally cheap way. Apart from reproducing previously known results -that is, those obtained when only considering first neighbors interactions- we found that this interaction scheme leads to a faster and much more robust propagation of the activity through this spatially embedded system. The rationale beneath this phenomenon would be that -comparing both dynamical scenarios- since at every timestep there are more neurons involved in the information transmission when including high-order interactions, if a fixed quantity of them fails, it is more probable that the wave keeps on traveling through the network. Thus, the transmission is more resistant to failures and, therefore, more robust. Crucially, the propagation occurs as a traveling wave, whose wave front gets enhanced thanks to recruiting more neurons in the transmission. It has been hypothesized that some of the information in the neural activity is encoded in the timing of spikes. If this was the way in which the brain operates, our finding could be of capital importance to provide a solid mathematical ground to understand this phenomenon. In addition, we have shown that higher-order dynamical interactions allow this kind of time-ordered synchronization for much lower coupling values than the case where only first-order neighbors are involved.

We suggest that this phenomenological view could be an innovative way of modeling the effects of neuroglial interaction, among other physical systems in which higher-order interactions need to be taken into account. We also argue that this higher-order interactions framework could be a potent and computationally cheaper approach to the detailed physiological models that can be found nowadays in the literature. We believe that this way of modeling the problem is physiologically well justified: Astrocytes have been evidenced to modulate up to $\approx 10^5$ synapses, while the majority of the neurons they interact with do not share an anatomical connection. This would imply that, while there is a given number of topological links in the network, some indirect ones would be present in the form of a dynamical modulation. Thus, this role would be played by astrocytes from the physiological perspective and, computationally, by high-order interactions.

All of the results can be thought as preliminary ones, as we are opening the gates towards new research directions that will lead to novel research questions, which we will detail in the next section.

6.2 Future directions

We have only started scratching the surface of the potential applications of the new perspective we have developed in this Thesis, regarding network structure inference. As suggestive as our results might be, a lot of work has yet to be carried out. Of particular interest is to use this method in the context of Neuroscience, when dealing with animal models. This is so because, in some of them, researchers have access to both structural and dynamical measures -specially when considering simpler animals. Then, it would be a perfect scenario to try this approach out and to give further reasons to support the believe that retrieving global structural features of the network from local dynamical measures is a feature shared by many systems.

Another utterly interesting problem -in which we are actually working on- would be the natural next step in cultured networks domain: to directly record both the activity exhibited by neurons and the structural network they form, to check whether our approach holds in that case, as we would expect. Related to this, it is compelling to compare our approach with the more used Maximum Likelihood Estimate for network structure inference, to inspect whether the results transcend the inference method we choose.

To end up, the immediate issues to be explored regarding high-order interactions would be to explore other dynamical models, to increase the network size, to increase the interaction distance and to try other spatial rules when constructing the topology. When this process has provided some well-grounded results, it could be interesting to mix the approach just described (that is, how the topology of partially unknown networks can be constrained via the individual dynamics) with this further refinement in the interactions. Ultimately, we would like to design an experiment in which high-order interactions effects can be shown to be present, to add up this dynamical empirical evidence to the structural insight -that is, astrocytes being anatomically present in a great deal of brain synapses- provided by others.

Appendix A

Some concepts on Complex Systems

In this Appendix we will deal with some conceptual features of Complex Systems, as this is the framework in which the Thesis has been developed. The actual connection with the Thesis will be detailed in the next section, where we show how these theoretical aspects are realised in our particular cases of study.

As Bak and others discussed repeatedly [161, 162], one of the most interesting aspects of self-organized criticality is that of *universality*. This means that wildly different systems (ranging from a sandpile [161] to History itself [163], through neuronal avalanches [164]) can be understood by the same means. The underlying rationale beneath this is that these systems share the common feature of being poised around their critical point, thus they all can be understood by the same statistical characterization. Fundamentally, this means that while some small-scale, local or fine-grained details might change in realizations of systems that are near their critical point, the gross statistical structure will stay the same.

The paradigmatic example used to show these abstract concepts is the sandpile model. It has the advantage of being simple enough to understand the mechanics of its inner workings and to have an intuitive notion of the results, that are powerful and suggestive. It consists on a grid in which we deposit, one by one, sand grains that progressively form a pile. It can be shown [161] that this system has a critical state. Once the sandpile model reaches it *there is no correlation between the details of a perturbation and the system's response to it*. Generally this means that dropping another grain of sand onto the pile may cause nothing to happen, or it may cause the entire pile to collapse into a massive slide. If we plot the number of occurrences of avalanches of a certain size s , we encounter a power-law distribution (see Fig. A.1). This is a feature common to many complex systems in nature: ranging from the distribution of earthquakes' magnitudes [165] to the rates of species extinction in Earth history [166], through the water level of the Nile river [167] or the variability of financial assets in the market [168].

It is crucial to state the relevance of the appearance of this power-law distribution and what it implies if a physical system exhibits it:

- It points out to the strong necessity of questioning *gradualism* -i.e., the idea

Figure A.1: Power-law behavior of the occurrence of avalanches in the sandpile model. We call s the size of the avalanche and $D(s)$ the number of times it has taken place. The line appears as the result of choosing a log-log plot, so that the power-law exponent emerges as $\gamma = 1.37$ in this particular realization. The dotted line represents the exact power-law fit. Extracted from [161].

that small changes are continuously happening and that those are what shape our reality, provided enough time- and to start considering shifting the epistemological focus into catastrophism -that is, a philosophical view of the world in which some major and disruptive events take place and are the cause for change. This evidence is found in the power-law behavior of a great diversity of systems, because it suggests that the same mechanism that operates to produce imperceptible events -which are the most likely to happen- are the ones that create cataclysmic phenomena -that may occur with a non-null probability.

- It challenges the usual characterizations given traditionally in science: there are no average or characteristic events in a system with this kind of distributions. Also, at least theoretically, the variance of such a distribution is infinite: this implies that there is an absolute loss of predictability and an infinite amount of memory is needed in order to understand the present state of the system. Obviously, as physical systems are constrained (this is, there are no fjords in Norway which are larger than Norway or smaller than a grain of sand), to understand the present state of complex systems displaying a power-law-like distribution, we will need a huge amount of memory and the predictability will be insignificant -at least when compared with those of equilibrium systems, for example.
- The existence of power-law distributions is the statistical hint of the underlying complexity of the system. Thus, it could be argued that explaining the statistical features of complex systems is, mathematically, just a matter of understanding where the exponent of the power-law comes from.

As a general rule: if a power-law distribution exists for a given system, it cannot be a closed one in equilibrium -intuitively, a system is said to be in equilibrium if minor perturbations yield minor disturbances (that is, equilibrium systems are linear ones). The only known exception to this rule is found if the closed equilibrium system has a phase transition and its dynamical state is poised right at its critical point. This is suggestive, as it may appear like a fine-tuning has taken place and everything we see around us is very accurately tailored such that a wild variety of natural systems are close to their critical point. This is where Self-Organized Criticality comes into play.

This general framework states that self-organized critical systems evolve to the critical state as a consequence of the interactions among their constituents over a very long transient period. In this sense, although there would exist a fine-tuning, there is no need for an external *fine-tuner*, because it is a property that would emerge from the system's dynamics. Following this line of thinking, catastrophes are inevitable: they are just a magnified version of the same dynamical procedure that creates small events -for which we do not seek an specific reason to occur (for example, the daily extinctions of species when compared to the dinosaurs one).

A.1 General features of a Complex System

It is interesting to note that there are some features present in complex systems that are contrary to the usual ones considered in Physics, for example [169]:

- I **Downward causation:** this is one of the most fundamental characteristics of complex systems. It states that not only the parts give rise to the whole but that also the whole influence its parts -that is, again, the whole cannot be understood in terms of its constituents. This is the basic feature that explains *emergence*. For example, human habits shape cells as much as cellular function dictates what behaviors (thus, habits) we will display. In this Thesis, the example can be found in the route to synchronization of networked Rössler oscillators (see Chapter 3 for details): the global dynamical output (global and phase synchronization) is shaped by the individual behavior (how each oscillator responds) and viceversa (because the oscillators will progressively adhere to the mean-field evolution).
- II **Autonomous and non-uniform agents:** the parts that form the whole system do not evolve according to the same rules -i.e., there is no global rule governing the dynamics- and they are heterogeneous. Therefore, any controlling structure must emerge from the self-organization of the elements forming the system. We can see an example of these properties in the case of synchronization waves (see Chapter 5), as there is no global forcing of activity, but a mix of noisy background that induces a spatiotemporal pattern dictated only by the interactions of the nodes.
- III **Nonlinearity:** the outputs that one gets from complex systems are not proportional to the inputs that it receives. As there is mutual interference between the parts, the linear superposition of their features will not be enough to explain the properties exhibited by the whole. A clear example of this can be

found in Fig. 2.8, where the neuron response is nonproportional to the input charge.

IV Instability and sudden changes: as it was already mentioned when discussing power-law distributions, there will be catastrophes and stepped evolution, opposed to the gradual changes usually supposed in science. Just like in the previous case, we evidenced this characteristic for the examples shown in Fig. 2.8: for the type I neuron, there seems to occur a *second order phase transition*, where its order parameter (firing frequency) undergoes a continuous change when varying the control parameter (the externally input current); it is a sort of *first order phase transition* in the case of type II neurons, for which there is a discontinuity in the firing frequency.

We want to stress the fact that, while these concepts can be found in the Thesis, the value they offer is an epistemological one: every feature introduced here points towards the necessity of a new scientific paradigm when dealing with complex systems. Obviously, this Appendix is merely an introduction for those interested in the philosophical-conceptual part of Complex Systems and the features that we have just mentioned can be further developed, but as this is not the main focus of the Thesis, we refer the interested reader to Refs. [163, 169, 170] -and to the references therein- for a well-grounded starting point in tackling these concepts.

Appendix B

A succinct and biased overview of modern Network Neuroscience

As part of our research lies in the field of Network Neuroscience, we found it pertinent to give a brief overview of the state of the art in this matter, to give a panoramic idea of what research questions are being posed nowadays and to fit our work therein. We will divide these investigations in the different levels of description of the brain (micro, meso and macro), always in the context of Network Science. For example we will not delve into the overview of biochemical processes at synapses nor behavioral studies, among many other areas which are relevant to Neuroscience, because these cannot be studied using the Complex Networks formalism.

B.1 Models in Network Neuroscience

We can distinguish the topological network from the functional one: while the former is derived *somewhat* directly from anatomical data, the latter is constructed via statistical correlations between recorded activities (whether the recorded units are neurons, neuron groups or brain areas).

A crucial step for deeply understanding the biological processes that lie beneath the mental ones is achieving a greater comprehension of structure-function relationships. Therefore, there exists an obvious motivation for identifying the relation of connectome networks to functional connectivity.

Microscale There are three main model organisms that nowadays are yielding significant microscale connectivity data at the cellular level. These organisms are: *Caenorhabditis Elegans*, *Drosophila Melanogaster* and *Mus Musculus*.

- *C. Elegans*: there have been recent studies [171] that have dealt with the wiring architecture of the posterior nervous system of adult males of this species. Other studies [172] had available two different nematode species (specially in terms of feeding behaviors) and compared the synaptic connectivity of the pharyngeal nervous system of them. Analyzing their connectivities via Graph Theory, they could determine that different synaptic rewiring lead to divergent roles of various neurons involved in regulating predatory feeding.

- *D. Melanogaster*: studies of microscale wiring patterns in this animal have suggested that the architecture of specific subcircuits can be understood in terms of wiring length minimization and volume exclusion [173]. Recently [174], a microscale circuit involved in a visual motion detection task was reconstructed with electron microscopy. This procedure unveiled certain patterns of inter-neuronal connectivity that were aligned with the idea of individual neurons promoting privileges in directionality.
- *Mus Musculus*: detection of directed visual motion was also studied in circuits of its retina [175]. In subsequent work, dense reconstruction of a significant portion of the mouse retina was carried out in [176]. Microscale connection motifs in this matrix revealed circuit mechanisms underlying motion detection and other aspects of visual function.

It is not that common to find straightforward applications of graph theory methods to microscale connectivity data because there are very few datasets which deal with more than just tens of neurons. Therefore, one can think that the use of network science’s quantitative analysis has only begun to provide insights to microscale connectivity investigations.

Important open questions in this field involve the specificity of certain connectivity patterns between individual neurons, the relation (or not) between certain network motifs and particular types of local computations or the question of whether particular architectures favor robustness at this scale.

There is still a lot of room for researching the connection between circuit architecture, computation (at the neuronal level) and behavior. Probably the most common approach has been to characterize the structural network of specific subareas of the *C. elegans* nervous system and the potential relation to certain behaviors.

Relevant advances have been achieved from microscale investigations that are based on a combined structure-function approach. An example is a study of a subset of neurons (located in the mouse primary visual cortex), carried out in [177]. A thorough analysis of the final connectivity map unveiled some specific structural features such as convergence of inputs from multiple pyramidal cells with diverse orientation preference onto inhibitory neurons. This study provides an example of how the combination of anatomy and physiology analyses can show how neural activity and organization can relate to behavioral tasks.

Large-scale recording techniques applied to organisms such as the zebrafish larva (*Danio rerio*) can result in whole-brain recordings with a great resolution, even in neural population (of the order of tens of neurons) activity [178]. This activity is susceptible of being analyzed with time series techniques, and there exists some evidence of functionally correlated circuits organizing in modules [179]. An objective for the short term is to link related neural events with structural connections that may delimit how whole-brain functional connectivity can be organized.

A new possibility has become relevant: to interact with a neuronal circuit’s activity, thanks to the use of optogenetics [180, 181]. This technology exploits an essential finding: when genetically mutated, neurons can express a protein that allows them to electrically respond to light pulses. What is remarkable, aside from the spatiotemporal precision of this technique, is the fact that it can be used *in vivo*, while the

animal is performing a task (and, thus, behavioral information can be linked with physiological one). Furthermore, it has been utilized to modify (via stimulation of certain neuronal groups) an animal’s abilities [182] or decisions [183], among many other applications. Some even propose that it is used in human epileptic patients, because of the potentially precise inhibition it can induce: an ultra-localized light beam could be targeted to an epileptic focus [184].

Mesoscale Current efforts to construct mesoscale connectivity maps for large portions of (or, for some simple animals, even complete) nervous systems are being conducted in a number of organisms, with the most important results coming from *D. Melanogaster* and *Mus Musculus*; in this case, *C. Elegans* does not come in handy because it does not have enough neurons (≈ 300) to consider it *mesoscale*.

- *D. Melanogaster*: in [185], they were able to record high-resolution 3D images of approximately 16.000 individual neurons in this fly’s brain and were then employed to construct a whole-brain adjacency matrix. They then subdivided this matrix according to functional criteria and subsequently aggregated single-neurons into local processing units, resulting in a mesoscale connectome of 41 nodes and their weighted interconnections. Moreover, when cluster analysis was carried out, there appeared communities whose integrants were functionally specialized to put through visual, olfactory, auditory and motor processing. More recent work has started to unveil additional network features such as submodules and small-world organization [186, 187], among others.
- *Mus musculus*: simultaneous studies in the rat cerebral cortex [188] have resulted in resemblant understandings as those of *Drosophila*. In [189], they quantitatively analyzed the anatomical connections of ten areas of mouse visual cortex. Zingg et al. [190] developed an adjacency matrix for mouse neocortex by combining data from hundreds of tracer injections into a single network representation (i.e., exclusively based in the connectivity data). The resulting directed network happened to contain ”several modules corresponding to subdivisions involved in various sensory, motor and integrative functions”. A simultaneous effort [191] has lead to the development of another mouse connectome chart that maps the (directed and weighted) anatomical connections among 295 gray-matter regions. When approaching this network from graph-theoretical analysis, high clustering as well as a number of highly connected network hubs are found.

Recurrent results in connectomics at the mesoscale, across species, are: a tendency towards networks of high clustering (due to the presence of modules) [192], a powerful correlation of these modules with different functional or behavioral tasks [193], and the use of connection features of local areas to build an understanding of their potential functional global contributions [41]. A feature that seems to be shared among a lot of species (from invertebrates to mammals, through birds) is that their mesoscale network architectures are interconnected by hubs [194].

The increasing accessibility of mesoscale connectome data [191], as well as high-resolution (Functional Magnetic Resonance Imaging) fMRI recordings [195], might offer a way to investigate this topic in the mouse (*Mus Musculus*) brain.

Some relevant research in this field has been performed in the macaque monkey.

Wang et al. [196] studied the potential relation between topological and functional connectivity at high spatial resolution within the monkey somatosensory cortex. The remarkable contribution of this study was that it permitted a straightforward identification from topological data (anatomical connectivity patterns observed after injections of anatomical tracers) into a functional response (specific digit representations), both being experimentally measured.

Macroscale The boundary between meso- and macroscales is, at least at present, somewhat arbitrary. Mesoscale maps usually are related to connectivity data that report on brain areas and their projections, just as most macroscale studies that deploy tract tracing methods, in non-human primates, or noninvasive imaging in human brain.

- *Primate cerebral cortex*: tract tracing has played a relevant role for the study of anatomical connections in animal models, particularly in non-human primates. An extensive set of investigations performed by Henry Kennedy and colleagues [197–200] have shown the structural network anatomy of the macaque cerebral cortex in a whole new level of detail. The general connectivity outline for each module was best approximated by a lognormal distribution [199], with a few strong projections and a huge mixture of medium and weak pathways.

Graph-theoretical analyses supported the ideas of: a relatively high prevalence of unidirectional links [198], an important contribution of long-distance projections towards areal specificity [201], significant distance-dependence of connection densities [200], and hierarchical dispositions of modules into counter-streams [198]. Various of these characteristic structural features are also found in other mammalian species, (the cat or rodent brain, among others).

- *Humans*: their connectomics nowadays relies mainly on noninvasive techniques, such as imaging and reconstructing structural connections using diffusion Magnetic Resonance Imaging (MRI) and tractography. This approach benefits from the use of signals that report the diffusion anisotropy of water within biological tissue. Different methods then infer statistical models of fiber anatomy.

Network studies of human structural connectivity architectures have persistently reported broad degree distributions, with a “heavy tail” of well-connected nodes [42]. The precise profile of this distribution remains somewhat elusive, mainly because of resolution limits and issues like node parcellation. Nevertheless, the majority of studies tend to point towards exponential or exponentially truncated power-law distributions for node degree. There is another ubiquitous feature reported across most, if not all, network studies of the human connectome: *small-worldness*, i.e., the fact that the network has a high clustering while having a short path length [202] when compared with random topologies. This is remarkable, as the presence of small-world arrangement suggests a balance between anatomical and functional segregation on the one side -as pointed out by high clustering- and a parallel capacity for global integration on the other side -as indicated by short communication paths [203]. While there was a time in which small-worldness was to be seen in almost every network neuroscience paper (see [204–206], among many others), this

idea has been recently challenged [207] and the debate is still an ongoing one.

At the whole-brain level, there have been numerous relevant studies: one of them [208] showed that patterns of coordinated spontaneous blood oxygenation level dependent (BOLD) fluctuations were similar to those of structural connectivity derived from tract tracing studies; another group [209] carried out a similar analysis, comparing anatomical and functional connectivity across 39 different regions of macaque cortex and evidencing a significant statistical relationship.

When considered as cumulative evidence, these results further suggest a mechanistic role of structural architecture in generating specific patterns of neural dynamics. At this level of analysis, relationships of structural and functional connectivities have largely focused on spontaneous neural activity (i.e., resting state). In humans, a lot of the emphasis over the latest years has been made on variations in BOLD activity acquired during a “task-free” or resting state. In spite of its unconstrained character (by definition), there are various studies which have shown that both spatial and temporal patterns of resting brain activity appear to be highly informative about the brain’s functional arrangement [210, 211]. Resting-state functional connectivity is generally constructed by means of the synchronization measures we presented previously, trying to compare the time series of BOLD signals measured with fMRI across the entire brain.

The notion that anatomical connections shape functional connectivity has gained strength when comparing resting-state functional connectivity networks and the corresponding structural connectomes, due to the revelation of robust and reproducible statistical relationships. In [192], Hagmann and colleagues showed robust correlations between the strengths of anatomical and functional connectivities across the entire cortical surface. Later on, it was evidenced [212] that these correlations were still present even after potential confounds (such as spatial proximity between regions) were considered. This result strongly pointed to functional connectivity being (at least partially) caused by the passing on of indirect influence along multi-step paths in the connectome [209]. A parallel study [213] also showed robust anatomical connectivity-functional connectivity correlations based on a voxel-by-voxel contrast across the cerebral cortex.

Following these pioneering studies, several independent analyses have further increased the confidence in the existence of statistical relationships between structural and functional connectivity (at least when studying resting state recordings) in the human brain [214]. Numerous studies have concentrated on the role of *spatial embedding* (that is, the distance dependence) for shaping the topology of anatomical and functional networks [215, 216]. Other analyses have studied structure-function relations and compared them across species [217].

The idea of anatomical connections shaping and/or constraining functional connections is not only based on comparisons of structural and functional architectures but is also supported by interventional studies that have shown changes in functional connectivity resulting from manipulations of the anatomical counterpart [218, 219]. As an immediate extension of this notion to brain and mental disorders, numerous analyses have tried to relate misbehaviour of functional connectivity patterns to potential disturbances of structural connectivity [220].

B.2 Dynamical models in Neuroscience

It is important to note that the brain is the perfect example of a multiscale model, because the different processes that take place in it are intertwined: from genes to cognition, through dendrites or cortical columns, every part of it affects the correct functioning of the whole. Furthermore, apart from the spatial aspect, the temporal scales that are involved are enormously different: they range from the microseconds scale of neurotransmitter release to that of a behavioral output, of the order of seconds, or the psychological state of the person, which can be modulated during the scale of years.

Being this so, it is important to note that we will be describing only a tiny part of what dynamical phenomena take place in the brain. Specifically, we will shed some light on neuronal models -thus, via the network architectures we have already explained in Section 2.1.2, potentially neuronal networks are also studied using this approach- and on neuronal aggregates, making use of population models. We will briefly describe the latter because of the popularity they have in the Neuroscience community, but they are not a networked example -although they can be, as it has recently been seen in [221].

Neuronal population models If we want to account for the neural aggregated response without giving a detailed description of the individual behavior of each of them, we would work with population dynamics. This class of models ignore specific spike times and network structural heterogeneity and, thanks to their low dimensionality, can provide analytical insights about steady states and bifurcation landscapes of neuronal populations.

The Wilson-Cowan model It was introduced in 1972 by H. R. Wilson and J. D. Cowan [222], trying to simplify biophysically detailed neuron models that were the most common way to emulate the activity of a neuronal ensemble. As they suggested in their original work, although it is certainly interesting to have a single-cell level detailed description of the nervous system, it is also probably not insightful (when pondering the cost of developing such a model) for those parts related to higher functions like pattern recognition or memory storage. They also pointed out that these brain tasks were primarily global and, thus, could be understood from such a perspective (with a coarse-grained description of the detailed neuronal activity). In this spirit, the model focuses on accounting for population features, employing just two differential equations. The two crucial parameters in the model are the strength of connectivity between each subtype of population (excitatory and inhibitory) and the strength of input to each subpopulation. Varying these generates a diversity of dynamical behaviors that are representative of observed activity in the brain, like multistability, oscillations, traveling waves, and spatial patterns.

The two equations that govern this model's dynamics are:

$$\begin{aligned}\tau_e \dot{a}_e &= -a_e(t) + [1 - r_e a_e(t)] F_e(w_{ee} a_e(t) - w_{ei} a_i(t) + I_e(t)) \\ \tau_i \dot{a}_i &= -a_i(t) + [1 - r_i a_i(t)] F_i(w_{ie} a_e(t) - w_{ii} a_i(t) + I_i(t))\end{aligned}\tag{B.1}$$

where $a_j(t)$ is the proportion of neurons of the j -th population that are active per

unit time and

$$F_j(x) = \frac{1}{1 + e^{-\gamma_j(x - \theta_j)}}, \quad j = e, i \quad (\text{B.2})$$

are the typically selected nonlinearities, where the gain γ_j and threshold σ_j can depend on the population type $j = e, i$. The argument of this F_j is a weighted sum (noted by $w_{kl} > 0$) of the connection strength between the number of neurons belonging to the k population and those to the l one. The terms $[1 - r_j a_j(t)]$ in Eq. (B.1) capture the refractory time that there exists after an activation (meaning they cannot respond an infinite number of times per unit of time).

As there have been further refinements in this model, we refer the interested reader to [223] for applications and a detailed description of it.

The Jansen-Rit model It is a neural population model of a local cortical circuit introduced in 1995 [224] as the result of generating a plausible mathematical explanation of experimentally recorded EEG signals. The single area model contains three interconnected neural populations: one for the pyramidal neurons and two for excitatory and inhibitory interneurons forming feedback loops -physiologically, these would represent neighbouring cortical units and subcortical structures like the thalamus.

Each of these populations will have an average membrane potential -which will be the state variable- as the result of different inputs (average pulse densities). There are different elements that will have to be dealt with: three populations of neurons and their synaptical interactions. The so-called *post-synaptic systems* P_i ($i = 1, 2, 3$) convert the average firing rate describing the input to a population into an average excitatory or inhibitory post-synaptic potential (EPSP or IPSP). The impulse response function takes the form:

$$h(t) = \begin{cases} \alpha \beta t e^{-\beta t} & \text{if } t \geq 0 \\ 0 & \text{else} \end{cases} \quad (\text{B.3})$$

where α and β are constants that differ in the excitatory ($\alpha = A, \beta = a$) and inhibitory ($\alpha = B, \beta = b$) cases. The former expresses the maximal amplitude that post-synaptic potentials can attain, while the latter lumps together characteristic delays of the synaptic transmission and sets the timescale of the problem. The system of six first-order differential equations that describes this model is:

$$\begin{cases} \dot{y}_0(t) = y_3(t) & \dot{y}_3(t) = Aa \text{Sigm}[y_1(t) - y_2(t)] - 2ay_3(t) - a^2 y_0(t) \\ \dot{y}_1(t) = y_4(t) & \dot{y}_4(t) = Aa \{p(t) + C_2 \text{Sigm}[C_1 y_0(t)]\} - 2ay_4(t) - a^2 y_1(t) \\ \dot{y}_2(t) = y_5(t) & \dot{y}_5(t) = BbC_4 \text{Sigm}[C_3 y_0(t)] - 2by_5(t) - b^2 y_2(t) \end{cases} \quad (\text{B.4})$$

where y_0, y_1 and y_2 are the three main variables: the output of the post-synaptic systems; the connectivity is captured by constants C_i and $\text{Sigm}(v)$ is given by:

$$\text{Sigm}(v) = \frac{\nu_{\max}}{1 + e^{r(v_0 - v)}} \quad (\text{B.5})$$

where $\nu_{\max}$ is the maximum firing rate of the families of neurons, v_0 is the value of the potential for which a 50% firing rate is achieved and r is the slope of the sigmoid at v_0 .

It is remarkable that, based on purely neuroanatomical studies [225], Jansen and Rit showed not only that it was possible to collapse C_i into a single parameter C (and express each C_i as a fraction of this C), but also that, for a certain set of parameters, alpha-like activity and EEG-like signals were observed to come out of the model.

This model can be extended further into multiple area ones, which include interactions between multiples neural masses; in order to delve into refinements of this model, check out [226].

A conductance-based neural field model The main difference between this model and other population ones is that in this case there is a combination between neural field equations (as in other models dealing with aggregated dynamics) and *biologically realistic synaptic dynamics*. It was introduced in 2013 by Friston et al [227] and, as the authors claim in their original work, it allows for realistic inter and intra-laminar intrinsic connections that underlie spatiotemporal neuronal dynamics. Opposite to what happens with mass models (in which population dynamics is expressed in terms of average currents and post-synaptic potentials), this model allows the geometrical structure and topography of neural interactions to be present. After an exhaustive analysis, they conclude that conductance-based field models may be important in empirical studies of cortical gain control or pharmacological manipulations.

The equations that dictate this system's dynamics are:

$$\dot{q}(x, t) = \begin{bmatrix} \dot{v} \\ \dot{g}_k \\ \dot{\mu}_k \\ \dot{\mu}'_k \end{bmatrix} = \begin{bmatrix} \frac{1}{C} \sum_k g_k (v_k - v(x, t)) \\ \lambda_k (\mu_k(x, t) - g_k(x, t)) \\ \mu'_k(x, t) \\ \mu'_k(x, t) \\ -2sc\mu'_k(x, t) + s^2 (\partial_{xx}\mu_k(x, t)) \\ -c^2\mu_k(x, t) + as^2c\sigma(v(x, t)) + u \end{bmatrix} \quad (\text{B.6})$$

where $q(x, t) = \{v(x, t), g_k(x, t), \mu_k(x, t)\}$ is the state variable, $v(x, t)$ is the trans-membrane potential, $g_k(x, t)$ is a set of synaptic conductances that model distinct channel types and $\mu_k(x, t)$ is the pre-synaptic input to which neurons are exposed. Furthermore, λ_k are rate constants that characterize the response of each channel type to afferent input. The last equation reflects the usual assumption that the number of synaptic connections decays exponentially ($d(x, t) = ae^{-c|x|}\delta(t - |x|/s)$) with some characteristic spatial scale c , a speed (s) of neural spike propagation and a connection strength scaling factor (a).

We could now couple different populations -each of their dynamics being governed by Eq. (B.6)- and include connectivity terms and excitation/inhibition between

them. For that kind of discussion, results and further comparisons, we refer the reader to [227].

General considerations of neuronal population dynamics

Conductance-based models consider neurons to be an electrical circuit: the membrane is interesting because of its response to the inflow (or outflow) of currents through the channels it possesses. Those, through which ions diffuse, are associated with conductances that are a function of gradients throughout the membrane and of receptors.

The canonical view about conductance dynamical models involves two categories of expressions:

- An equation that captures the rate of change of the potential as a current flow (components that follow Ohm’s law).
- Equations for the conductances that are dependent on pre-synaptical neuron spikes and of the ratio of open ionic channels.

When approaching the problem in this manner, we will forcefully involve non-linear terms (as post-synaptic potential changes will invoke the product of conductances and voltage differences related to the variety of channel types). To put it in an alternative phrasing: the equations that dictate neural dynamics *have to be second-order and non-linear*, if we relay on the electromagnetic framework of modelling them.

The contrast is then evident with neural mass and mean field models, which are rooted on convolution operators. In this case, the mathematical equivalent of post-synaptic depolarization is a linear convolution of pre-synaptic spikes. As it is known, a convolution operation can be expressed as linear differential equations.

Thus, to sum up, the crucial difference between conductance-based models and mass models is that the former have to be expressed in a non-linear way and therefore, in principle, they provide a certain biological realism, at the cost of being perhaps too detailed and difficulting the task of scalating these dynamics cross a certain threshold (nowadays, with the current computational power, it is around $10^4 \approx 10^5$ neurons).

B.2.1 Features of neuron models

Spiking Neurons can be simulated via different dynamical systems [228]. These models, as it will be seen nextly, differ in the various neuronal behaviors they can exhibit; fig. B.1 shows some of these features. The size of the network (that is, the number of constituents it has) can vary wildly: from about 100 up to 10^5 neurons and over 10^7 synaptic connections. There are different factors that can characterize each spiking neuron model:

1. Biological plausibility: this is the central point of modelling. If our simulated system does not resemble the experimental one, everything else will be worthless. In this context, this implies that the spiking neuronal model will be able to produce a set of behaviors exhibited by real biological neurons; some examples are portrayed in fig. B.1.

2. Spiking: a spike is an abrupt and transient change of membrane voltage that propagates to other neurons via a long protrusion called an axon. The relevant part (as neurons tend to be modelled as point-like objects) is that of a spike being both *sudden* and *transient*. This, for modellization purposes, means that spikes can be regarded as timestamps with no duration.
3. Frequency adaptation: a reduction in the firing frequency of a neuron spike response following an initial increase. [229]
4. Excitability class: If a neuron is in the excitability class I, it means it can continuously encode the strength of an input into the frequency of spiking. If it belongs to class II, this encoding is discontinuous.
5. Integrator or resonator: we refer to neurons with damped subthreshold oscillations as resonators and to those that do not have this property as integrators. [229]
6. Bistability: coexistence of two firing modes (for example, firing and silence) in the same experimental condition. [230]

To graphically encapsulate these model features, we have adapted a figure found in [229]. This adaptation can be seen in Fig. B.1.

Figure B.1: Summary of the neuro-computational properties of biological spiking neurons. Each horizontal bar denotes a 20-ms time interval. The MATLAB file generating the figure and containing all the parameters, as well as interactive MATLAB tutorial program, as well as an e-version of the figure, can be downloaded from www.izhikevich.com.

B.2.2 Spiking neuron models

The Hodgkin-Huxley model Although we have briefly mentioned it in Section 2.2.2, we did not delve into any type of mathematical description, so we complement that qualitative description in this subsection. As we mentioned previously, the computational cost of this model is virtually unbounded: one can work with tens of different compartments, each of one consisting at least on a coupled differential equation. The original version [111] consists of four equations and tens of parameters, namely:

$$\begin{aligned} C\dot{V}_m + I_{ion} &= I_{ext} \\ \dot{n} &= \frac{n_\infty(V) - n}{\tau_n(V)} \\ \dot{m} &= \frac{m_\infty(V) - m}{\tau_m(V)} \\ \dot{h} &= \frac{h_\infty(V) - h}{\tau_h(V)} \end{aligned} \tag{B.7}$$

where $I_{ion} = \bar{g}_{Na}m^3h(V_m - E_{Na}) + \bar{g}_K n^4(V_m - E_K) + g_L(V_m - E_L)$ and

$$\begin{aligned} n_\infty &= \frac{\alpha_n}{\alpha_n + \beta_n}, & \tau_n &= \frac{1}{\alpha_n + \beta_n} \\ m_\infty &= \frac{\alpha_m}{\alpha_m + \beta_m}, & \tau_m &= \frac{1}{\alpha_m + \beta_m} \\ h_\infty &= \frac{\alpha_h}{\alpha_h + \beta_h}, & \tau_h &= \frac{1}{\alpha_h + \beta_h} \end{aligned} \tag{B.8}$$

where

$$\begin{aligned} \alpha_n(V) &= 0.01 \frac{10-V}{\exp(\frac{10-V}{10})-1}, & \beta_n(V) &= 0.125 \exp\left(\frac{-V}{80}\right) \\ \alpha_m(V) &= 0.1 \frac{25-V}{\exp(\frac{25-V}{10})-1}, & \beta_m(V) &= 4 \exp\left(\frac{-V}{18}\right) \\ \alpha_h(V) &= 0.07 \exp\left(\frac{-V}{20}\right), & \beta_h(V) &= \frac{-V}{\exp(\frac{30-V}{10})+1} \end{aligned} \tag{B.9}$$

α_x models the rate at which gate x transitions to being open while the corresponding closing counterpart is captured by β_x .

In the spirit of simplifying the computation even more than the Morris-Lecar neuron -described in Sec. 2.2.2-, we will present the Integrate-and-Fire neuronal models, as the ultimate example of a cheap yet somewhat biophysically meaningful model.

Integrate-and-Fire models This is actually a class of models [110], that build on the fact that, to a first and rough approximation, neuronal dynamics can be conceived as a summation process (we will actually describe neurons nextly as *integrators*, see Fig. B.1) combined with a mechanism that triggers action potentials above some critical voltage.

B.2. Dynamical models in Neuroscience

These models make use of the fact that neuronal action potentials of a given neuron always have roughly the same shape. If the form of an action potential is always similar, then this aspect cannot be used to transmit information: rather information is contained in the presence or absence of a spike. Therefore action potentials are reduced to *events* that happen at a precise instant. In these cases, no attempt is made to describe the shape of an action potential.

The equation governing the most basic of these models is given by:

$$\dot{v} = \begin{cases} I + a - bv & \text{if } v \geq v_{thr} \\ c & \text{else} \end{cases} \quad (\text{B.10})$$

where v is the membrane potential, I is the input current and a, b, c and the threshold potential v_{thr} are parameters of the model. It is important to explicitly mention that, once v crosses v_{thr} , the neuron is said to spike and the membrane potential is *immediately reset* to $v = c$.

For further refinements of this model, we found interesting the book by Gerstner et. al [110]. As an example of a mathematically and computationally cheap model, that is barely used due to the lack of biological relevance, we will introduce the Izhikevich model.

Izhikevich model Although this model has no intent to model the biophysical aspect of real neurons, it does have a physiological interpretation. It is very rarely used, even though it is efficient and displays a lot of desirable features, as it will be shown in Tab. B.2.

The equations which describe this dynamical system are [228, 229]:

$$\begin{aligned} \dot{v} &= 0.04v^2 + 5v + 140 - u + I \\ \dot{u} &= a(bv - u) \end{aligned} \quad (\text{B.11})$$

with the auxiliary after-spike resetting:

$$\text{if } v \geq +30\text{mV}, \quad \text{then } \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} \quad (\text{B.12})$$

Here v is the active variable of the neuron and u is a recovery variable, which provides negative feedback to v . The parameters a, b and c can be tuned and numeric values (the $0.04v^2 + 5v + 140$ term) have been chosen so that v has mV scale and time ms units. After the spike reaches its apex (+30mV), the active variable and the recovery one are reset according to the scheme presented in Eq. (B.12). If v skips over 30, then it first is reset to 30, and then to c , so that all spikes have equal magnitudes.

Ideally, one would like a model to show every property that a biological neuron exhibits, while being computationally tractable. As this is never the case, at least until the moment this is being written, one has two options: to choose between microscale models attending to some feature that looks interesting for a particular issue or coarse-grain the dynamics, as it was explained with population models. In table B.2, it has been summarized whether the different neuronal models we have just presented are able to express that behavior or not.

	IF	Izhikevich	ML	HH
Biophys meaningful	0	0	1	1
Tonic spiking	1	1	1	1
Phasic spiking	0	1	1	1
Spike freq adapt	0	1	0	1
Class I excitable	1	1	1	1
Class II excitable	0	1	1	1
Sub-thresh osc	0	1	1	1
Resonator	0	1	1	1
Integrator	1	1	1	1
Bistability	0	1	1	1

Figure B.2: Comparison of different neuronal models regarding different neuronal properties. In blue, the model we used in this Thesis (Morris-Lecar) has been emphasized. Table adapted from [228]. (Electronic version of the figure and reproduction permissions are freely available at www.izhikevich.org)

B.2.3 The role of noise in modelling

Whenever a mathematical model is set forth to capture a natural phenomenon, there is a part that is left out those patterns or rules; the part that we cannot -or do not want to- model is what we refer to as *noise*. This uncertainty is a large -the notion of large varies depending on the specific scientific context- collection of dynamical variables that induces a subtle and non-crucial effect on the phenomenon we want to understand; it can also be regarded as the 'higher-order corrections' or fluctuations that exist in every natural domain, be it because our lack of experimental precision -spatial resolution, for example- or due to our ignorance - as in the case of gas particles moving in a box.

In the neuronal context, for example, we can illustrate (following Ref. [231]) different sources for noise as:

- Internal: resulting from stochastic opening (and closing) of membrane ion channels.
- Synaptic: as a consequence of the probabilistic vesicle (neurotransmitter) release.
- Cross-talk responses from indirectly stimulated neurons (the current propagates through the medium they are embedded in).
- An input with many frequency components.
- The resulting current from integrating many independent synaptic events.

As it can be already seen with this particular example, there can be a high number of noise sources, wildly different in origin and, thus, requiring to be careful when interpreting the role that noise plays in our problem and to realize that it is an inherent part of the mathematical inspection of nature.

In our particular case of study -that is, the noisy Morris-Lecar neuron- noise is of vital importance: as we work with a set of parameters that set the dynamical configuration of this model to be an excitable one, there would be no activity if it was not because of the noisy input. Therefore, the fact that this contribution is small does not necessarily imply that it is irrelevant or negligible.

Appendix C

Extra remarks and synchronization measures

We understand the phenomenon of synchronization as one in which *coupled* dynamical elements of a system behave in a similar way. In the case of coupled oscillators, synchronization can be found as an amplitude, phase or complete (both amplitude and phase) synchronization. It is remarkable that, depending on the coupling's nature, the node dynamics and the underlying structure, the route to synchronization is completely different [14].

Thus, the problem here is to characterize *how intensely* nodes in a network interact by means of comparing the similarity between their dynamical outputs -that is, their time series. The issue with this characterization is that, once one has the time series of every node of the network, there are virtually infinite ways of relating them. Specifically, thinking pairwise, one can define essentially an endless amount of distances between two time series. Therefore, the usual route chosen nowadays is to pick the easiest (non-oversimplified) and most straightforward synchronization measure which is available. For example, when dealing with a system in which only the phase oscillates, it makes no sense to construct a measure of synchronization that takes into account the amplitude. Another possible source of conflict is the actual difficulty for computation (not even meaning the analytical one). For example, it has been long known that one of the most unbiased ways of statistically characterizing the distance between two time series has been the *mutual information*, although it is not generally used nowadays mainly due to its computational cost.

We will give an overview of different synchronization measures used in today's neuroscientific contexts. We have to specify this because the general notion of synchronization might have some different nuances than this rather specific one: in Neuroscience, scientists seek to check how time series (be it BOLD signals, fMRI data, electrophysiological recordings of two neurons, evoked potentials, etc) are related rather than studying the collective phenomenon as such -this is specially evident when Granger Causality or Mutual Information are used as synchronization measures.

- Cross-Correlation function: it measures the linear correlation between two variables X and Y as a function of their delay time (τ) [232]; this is of interest

because there may exist a causal relationship between the signals (and some delay because of the time it takes for chemo-electrical signals to travel along the brain). If $x(t)$ and $y(t)$ are signals normalized to have zero mean and unit variance, their cross-correlation function is:

$$C_{xy} = \int_{-\infty}^{+\infty} x^*(t)y(t + \tau)dt \quad (\text{C.1})$$

where $x^*(t)$ is the complex conjugate of $x(t)$ and τ the time lag between signals. It is always true that C_{xy} is bounded from +1 (complete linear direct correlation) to -1 (complete linear inverse correlation), where $C_{xy} = 0$ would suggest the lack of linear interdependence for a given time lag τ . The value of τ that maximizes this function is an estimation of the delay between the signals, under the implicit assumption that they are linearly related. It must be stressed again, however, that this delay cannot be directly regarded as a measure of the propagation time of, say, the electrical signal in the cerebral cortex.

- Coherence: it gives a linear correlation between two signals as a function of the frequency [233]. It is also known as *magnitude squared coherence* or *coherence spectrum*. It is the cross-spectral density function (actually, the Fourier transform of eq C.1) normalized by the product of the individual auto-spectral density functions. The main limitations of this measure are: as neural data is of finite size, one can only have an estimate of the true spectrum; moreover, it assumes a linear coupling in the spectrum and stationarity. In practice, a signal f is usually subdivided into M epochs of equal length (and then averaging each spectrum $S_{--}(f)$ over these epochs). Mathematically:

$$\kappa_{xy}^2(f) = \frac{|\langle S_{xy}(f) \rangle|^2}{|\langle S_{xx}(f) \rangle| |\langle S_{yy}(f) \rangle|} \quad (\text{C.2})$$

where $\langle \cdot \rangle$ indicates averaging over the M segments in which we divide the signal.

This measure is bounded between 0 (the activities of the signals in the particular frequency in which $\kappa = 0$ are linearly independent) and 1 (the signals are maximally correlated in the frequency domain for that particular frequency).

- Granger causality: this measure is of particular interest in neuroscience. It tries to answer the question of whether there exists a causal relation between two brain regions, without any specific information on directionality [234]. The main difference between this measure and the cross-correlation function is that in the latter we are able to extract a delay but not the specific causality (at least in a straightforward way). The idea beneath this measure is the following: if, for two simultaneously measured signals X and Y , one can predict X better by incorporating the past information from Y than if it does not get incorporated, then Y can be called causal to X . This can be assessed by comparing the univariate and bivariate fitting of the autorregressive models to the signals. In the univariate case:

$$X(n) = \sum_{k=1}^p a_{xk} x(n-k) + u_x(n) \quad (\text{C.3})$$

$$Y(n) = \sum_{k=1}^p a_{yk} y(n-k) + u_y(n) \quad (\text{C.4})$$

where $a_x k$ is the x model parameter, p the model order and u_x the uncertainty of the x model. The prediction error in this case depends only on the past values of the own signal. We also rename the variance of u_x as $\text{var}(u_x) = V_{X|X_-}$ for simplicity in our notation.

For bivariate autorregressive modeling, mathematically we have:

$$x(n) = \sum_{k=1}^p a_{xyk} x(n-k) + \sum_{k=1}^p b_{xyk} y(n-k) + u_{xy}(n) \quad (\text{C.5})$$

$$y(n) = \sum_{k=1}^p a_{yxk} y(n-k) + \sum_{k=1}^p b_{yxk} x(n-k) + u_{yx}(n) \quad (\text{C.6})$$

where the prediction error for each individual signal depends on the past values of both signals. Again, for the sake of simplifying the notation $\text{var}(u_{xy}) = V_{X|X_-,Y_-}$.

Then, the Granger causality of Y to X can be quantified as:

$$G_{Y \rightarrow X} = \ln \left(\frac{V_{X|X_-}}{V_{X|X_-,Y_-}} \right) \quad (\text{C.7})$$

This measure will be close to zero if the past of Y does not improve the prediction of X . Any improvement leads to increase the causality measure (because the decrease of $V_{X|X_-,Y_-}$). If both $G_{X \rightarrow Y}$ and $G_{Y \rightarrow X}$ are high, there is a high chance of a bidirectional coupling (or feedback) between the signals.

The main limitation of this measure is that it can only be truly assessed if both time series contain all possible relevant information and sources of activities for the problem. As this is virtually never the case, one has to be cautious when interpreting causality claims.

- Mutual information: if we consider a pair of variables X and Y , the mutual information between them is [235]:

$$MI_{xy} = \sum_{i,j} p_{ij} \log \left(\frac{p_{ij}}{p_i p_j} \right) \quad (\text{C.8})$$

where p_{ij} is the joint probability of $X = X_i$ and $Y = Y_j$, meaning that the variables X and Y attain the value X_i and Y_i , respectively. The calculation

of p_i is based on a counting process: the number of times (N_i) the variable X attains the value X_i , over the whole set of values N it has attained. Mathematically: $p_i = N_i/N$. The joint probability p_{ij} is calculated as $p_{ij} = p_i \cdot p_j$ if X and Y are independent variables. If not, one has to use the proper definition: $p_{ij} = p_j \cdot p(X = X_i | Y = Y_j)$, where $p(X = X_i | Y = Y_j)$ is a conditional probability (the likelihood of event $X = X_i$ occurring given that $Y = Y_j$ is true).

The basic idea beneath this measure is how much *extra* information one gets from one signal by knowing the outcomes of the other one. The lower bound is attained for independent processes ($p_{ij} = p_i p_j$ and therefore $MI = 0$) and the upper one is achieved for identical signals ($MI = I$, where I is the Shannon entropy). We see in its structure that this measure is symmetric and thus we can not say anything about the direction of the interaction.

Phase Synchronization There are two main measures of Phase Synchronization (PS) when using phase reconstruction -see Section 2.3.2 for details-. We hereby detail two alternative ones that are sometimes used in the literature:

- Stroboscopic index: the phase of one of the oscillators is observed for every t_j in which the other oscillator attains a certain phase value ϕ_0 . Then, it is averaged over all the possible phase values. The mathematical definition [137] is:

$$\lambda_{n,m} = \frac{1}{L} \sum_{l=1}^L |r_l(t_j)| \quad (\text{C.9})$$

where the index j corresponds to time, $r_l(t_j) = (1/M_l) \sum_{\gamma} e^{i\phi_{\gamma}(t_j)}$ for all j -such that $\phi_x(t_j)$ belongs to bin l and M_l is the number of points in this bin.

- Phase Locking Value (PLV): it can be seen [236] as the intensity of the first mode of the distribution of $\psi'_{n,m}(t)$ (i.e., it measures how the relative phase is distributed over the unit circle). The precise definition is given by:

$$\gamma_{n,m} = \sqrt{|\langle e^{i\phi(t)} \rangle|^2} = \sqrt{\langle \cos \phi(t) \rangle^2 + \langle \sin \phi(t) \rangle^2} \quad (\text{C.10})$$

where $\langle \cdot \rangle$ denotes average over time.

Both indexes have the same range of variation: they are close to 0 for uncorrelated signals and to 1 if there is a strong PS. However, there are some differences which can be exploited depending on which one we would like to use. On one hand, PLV presents the greatest sensibility to the transition from weak coupling to PS state. On the other hand, the stroboscopic index is non-zero even in cases where no PS but only very weak interactions are present. Additionally, it has a straightforward way of determining its significance threshold from the data, which may be very useful to avoid spurious detection of PS in uncoupled signals. It can be then concluded that PLV is suitable for situations in which our purpose is to cluster a number of time series into groups, while the stroboscopic index is great at assessing weak phase coupling.

Point-process synchronization We cannot finish this Appendix without mentioning that there is a slight variation of the event synchronization measure we used -see Section 2.3.2 for details-, introduced in [237]. If we denote by $c^\tau(x|y)$ the number of times an event appears in x shortly after it appears in y , they defined

$$c^\tau(x|y) = \sum_{i=1}^{m_x} \sum_{j=1}^{m_y} J_{ij}^\tau \quad (\text{C.11})$$

as the basic quantity to construct the synchronization measure. In this expression m_x is the total number of events in the time series X and J_{ij}^τ :

$$J_{ij}^\tau = \begin{cases} 1 & \text{if } 0 < t_i^x - t_j^y \leq \tau \\ 1/2 & \text{if } t_i^x = t_j^y \\ 0 & \text{else} \end{cases} \quad (\text{C.12})$$

which, as we can see, is a similar quantifier as the one introduced in Section 2.3.2, noted by $B_i(\tau)$ in that case. Then, they distinguish two different measures to capture the relationship between time series:

$$Q_\tau = \frac{c^\tau(y|x) + c^\tau(x|y)}{\sqrt{m_x m_y}}, \quad 0 \leq Q_\tau \leq 1 \quad q_\tau = \frac{c^\tau(y|x) - c^\tau(x|y)}{\sqrt{m_x m_y}}, \quad -1 \leq q_\tau \leq 1 \quad (\text{C.13})$$

which are, respectively, the symmetrical and antisymmetrical combinations of $c^\tau(x|y)$. Correspondingly, Q_τ measures the synchronization of the events and q_τ captures their delay behavior. The saturating values of $Q_\tau = 1$ and $q_\tau = 1$ mean that the events are fully synchronized and that those in x always precede to those in y .

In order to read more about this measure, we recommend directly consulting the original paper [237].

Appendix D

A survey of complexity measures

Even before the advent of Complexity Sciences, there was an interest to quantify *how complex* different systems were. It is in fact said that the concept of complexity, at least in its origin and in the context of Computer Science, is a disguised consequence of Gödel's theorem. The rationale supporting this statement would be the following: the first proposal to measure complexity, due to Kolmogorov [238], equates it to the shortest computer program capable of generating a given string; it is known that this quantity is uncomputable (because there is no algorithm that can compute it), commonly referred to as the *halting problem* [239]; this halting problem is a computer-science flavor of the Gödel's incompleteness theorem [240]. An interesting and extensive discussion is given in [241].

Other scientific stream in the study of complexity comes from telecommunication theory, or, as it is nowadays known, *information theory*. The seed for this fruitful framework was Shannon's seminal proposal [235] on how to quantify the *entropy* of a message.

However, in Complexity Sciences, there are some known general precepts. For example, according to [242], there are some broad features that one has to take into account in order to *properly define* a complexity measure that is meaningful:

- Observer-dependence: It makes no sense to define (or even to think about doing so) the complexity of a natural phenomenon, because it has, presumably, infinite detail. Therefore only when observations are made, according to an acquisition model, is when the question of complexity becomes relevant. This would suggest that complexity refers to the way measurements are made and not to the natural process as such.
- Emergent levels of complexity: A defining feature of complexity is the existence of a hierarchy regarding description levels, that is: characteristics in the *coarser level* emerge from finer constituents interacting in a finer level.
- Modularization with interdependencies: Complex systems are partially decomposable, their modules dependent on each other. In this sense, some authors [242] conclude that the more modules or interactions among them a system has, the more complex it is (because it cannot be divided into independent simple sub-systems).

Having these guidelines in mind, we will now proceed to present different proposals on how to quantify and measure complexity.

D.1 Algorithmic measures

Kolmogorov Complexity: consider three strings of numbers: a regular one (for example, 666666), another coming from an irrational number (for example, π 's first six digits, 314159) and a sequence truly extracted from a random process (for example, 843542). The question now is: how long will it take us to describe each of the sequences? And what if we had strings of thousands of characters? It is obvious that to characterize the first sequence it will just take a simple recipe: "repeat number 6 for the entire sequence". In the second case, something similar to "take as many digits of π as the size of your sequence and drop the comma out" will serve. The key now is... What about the third one?

To characterize how long these instructions have to be in order to reproduce the desired sequence of characters, Kolmogorov [238] proposed a definition of the form: the complexity of a sequence x is the length of its shortest description. As we are not really interested in defining Turing Machines, recursive functions, etc., we recommend the interested reader to check [243] for an introductory discussion on this complexity measure.

There are two crucial criticisms this measure always faces: its uncomputability (as we already mentioned in the foreword of this section, relating this impossibility to Gödel incompleteness theorems) and the fact that it is maximum whenever the sequence is truly random (that is, with no regularities). Many authors argue that it is therefore a measure of ignorance, not of complexity.

Crude and Effective Complexity Murray Gell-Man proposed to think about capturing complexity via a measure called Crude Complexity [244]: The length of the shortest message that will describe a system, *at a given level of coarse graining*, to someone at a distance, employing language, knowledge, and understanding that both parties share (and know they share) beforehand. That is, he rethought Kolmogorov Complexity and added a subjective component to it (as the sum of the level of study, background of the person describing, etc.). Here we explicitly see one of the general features that a well-behaved complexity measure should have, as we mentioned in the foreword of this Section (namely, emergent levels of complexity).

As a further refinement, the same author (and S. Lloyd) introduced the notion of Effective Complexity. The main idea [245] is to split the algorithmic information content of some string sequence into two parts: its random characteristics and its regularities. Then, Effective Complexity is defined as the Kolmogorov Complexity of the regularities alone.

Lempel-Ziv Complexity Interestingly enough, this measure is nowadays more used as a compression algorithm (for example in GIF or PDF files) than as an actual complexity quantifier (eventhough it is one of the most algorithm-based used measures). It was proposed by Lempel and Ziv [246] in 1976 and it is related to Kolmogorov complexity but only making use of the shallow copy process (and

D.2. Dynamics-based measures

not a generic Turing Machine as we mentioned in that case). More precisely, this measure states that the complexity of a sequence of strings is the number of steps in a self-delimiting production process by which such a sequence is presumed to be generated. Equivalently, this complexity measure can be thought as the number of “new” substrings found as the sequence evolves. It has to be explicitly mentioned that this measure excels in characterizing long sequences and behaves poorly for very short ones.

Logical depth Bennett introduced [247] this measure as the computational resources (usually time) taken to calculate the results of a program of minimal length. It is thus a combination of computational complexity (the amount of computational resource (normally time or memory) that it takes to solve a class of problem) and Kolmogorov complexity.

The major difference with Kolmogorov’s measure is that instead of taking the program *length* as the interesting complexity quantifier, it focuses on its *computation time*. It has been suggested that this measure defies Occam’s Razor: if we observe a certain sequence, is it safe to assume that it is the result of the simplest program execution? If the simplest program is too slow, this may not be the case. A longer program, perhaps with a tiny probability relative to the first one, but much faster, might be responsible. As Grassberger points out: “life emerged spontaneously, i.e. with a randomly assembled ‘algorithm’ which had to be very short. But it has taken approximately 10^9 years to work with this program until life has assumed its present forms.” [248].

There are undoubtedly other interesting algorithmic measures of complexity that we have not included (sophistication, effective measure complexity, forecasting complexity, etc.) for an extensive (and somewhat obscure) literature review on this respect, we suggest reading [249].

D.2 Dynamics-based measures

This subset of complexity measures follows a radically different viewpoint: instead of characterizing a sequence of symbols (as we explained in Sec. D.1), the central object of study is the time series that results from the evolution of a chaotic system. Although this subdomain of Complexity Sciences is relatively younger than its algorithmic sibling, it is also true that its origin (lying in nonlinear dynamics) dates at least back to Poincaré [250] (at around 1895) and, thus, the literature is very rich. We are going to give a succinct overview of the most commonly used complexity quantifiers.

Lyapunov exponents They are conceptually defined [251] as the rate of divergence of nearby trajectories in the phase space of a system. As it was proven by Lyapunov, it is enough to calculate the greatest exponent (instead of the whole spectrum), because (apart from the Perron effect [252]), its behavior is predictive of the system’s behavior. Thus, the common practice is to just work with the so-called Maximal Lyapunov Exponent (MLE).

Let us be more precise in its definition. Let $\delta x(X_0, t)$ be the separation of two orbits

which come from the equations governing the system of interest. The MLE is then defined as:

$$\lambda = \lim_{\substack{t \rightarrow \infty \\ \delta x_0 \rightarrow 0}} \frac{1}{t} \ln \left| \frac{\delta x(X_0, t)}{\delta x_0} \right| \quad (\text{D.1})$$

One can then distinguish three scenarios regarding types of orbits, based on the value of λ :

- 1 **Stable fixed point** or stable periodic orbit: in this case, $\lambda < 0$. This is a common feature of dissipative or non-conservative systems, as it tends to equilibrium (the more negative λ is, the faster it reaches it). A simple physical example of this would be a damped oscillator.
- 2 **Neutral fixed point** or an eventually fixed point: we encounter this scenario when $\lambda = 0$; if this is so, the system is in some sort of steady state mode. Conservative systems exhibit this Lyapunov exponent. The physical example now would be a simple harmonic oscillator. As the frequency is unrelated to the amplitude, a phase portrait of the different scenarios when varying the amplitude would be concentric circles (and thus the orbits would show a constant separations, i.e., $\lambda = 0$).
- 3 **Unstable and chaotic orbit**: $\lambda > 0$; this means that nearby points, no matter how close, will diverge to any arbitrary separation (which is equivalent to say that the entire phase space will eventually be visited). These points are said to be unstable. A physical example can be found in Brownian motion (deterministic rules, no order in its orbit).

Within dynamical systems, this measure is the most used to characterize chaotic dynamics in a very detailed and well-defined fashion.

Correlation dimension This measure came from the idea of determining whether the process we are analyzing is a chaotic or a stochastic one [253]. It belongs to the bigger family of *fractal dimensions*, which is a general way of characterizing a great variety of mathematical objects (from fractals, i.e., geometrical entities, to time series, that is, dynamical elements). As it was the case with the *Maximal Lyapunov Exponent*, the object of interest when applying this measure is not the time series *per se* but, rather, the attractor that we can construct via the Takens' theorem [254]. This theorem states that any state variable can be used to calculate the invariants of the dynamics. This means that, as we cannot probe the entire state space, we can *reconstruct* the attractor using the dynamics that we have available.

Mathematically, the definition the *correlation dimension* (referred to as D_2) involves the prior calculation of the *correlation integral*, noted as $C(\epsilon)$. Let N be a set of points in an m -dimensional space $\vec{x}_i = [x_1(i), \dots, x_m(i)]$, $i = 1, \dots, N$. Then $C(\epsilon)$ is calculated as:

$$C(\epsilon) = \lim_{N \rightarrow \infty} \frac{g}{N^2} \quad (\text{D.2})$$

D.3. Information-theoretical measures

where g is the total number of pairs of points which are separated distance less than ϵ . As we take the limit for the number of points N , and the distance between them tends to zero ($\epsilon \rightarrow 0$), the correlation dimension D_2 , for small values of ϵ , will take the form

$$D_2 = \lim_{\epsilon \rightarrow 0} \frac{\log C(\epsilon)}{\log \epsilon} \quad (\text{D.3})$$

Although this measure is one of the most used ones, it has to be noted that there has been criticism regarding its ability to distinguish low-dimensional chaos from stochastic processes (see [255], for example).

In order to deepen the discussion on this class of measures, both in the number of practical methods and in their meaning, we recommend the extensive review found in [256].

D.3 Information-theoretical measures

This approach is, together with the algorithmic approach, the most fruitful and currently used one. In fact, as it is the route we took, we are going to describe it with a bit more of detail than the previous two. If the reader wants to overcome this bias and is interested in a quite complete and equidistant bibliography to Complexity measures, we cannot recommend enough the effort made in [140], with over 380 references in which authors introduced a complexity measure. The fact that such an extensive bibliography exists *just on complexity measures*, already talks about the lack of consensus that we are going to explicitly discuss next.

As it happened in the two previous subdomains of Complexity Sciences we discussed, there is a myriad of measures that are available to use. In this case, the criteria we have used to decide which ones to include here have been diverse: be it due to historical relevance (Shannon entropy), mathematical definiteness and non-ambiguity (Excess entropy), by reason of it ubiquitous for a long time (Rényi entropy) or because it is a cutting-edge promising framework being developed nowadays (Partial Information Decomposition).

Shannon entropy This is the founding contribution upon which the entire field of Information Theory (IT) has been built. As its own name indicates, IT deals with *information*; although it may sound obvious, it really is not. To begin with: what is understood by information?

As a first answer, we can stick with the definition of *pairwise information*: we say that one variable provides information about another if knowledge in the former reduces uncertainty in the latter. An alternative definition of information is: that which partially, or totally, contributes to getting rid of uncertainty. We see that, in both cases, this fundamental quantity is intimately related to that of *uncertainty*. And here is where Shannon's contribution comes into play.

Let us begin by stating some properties we want our *uncertainty measure* to have:

- 1 **It has to be maximum for a uniform distribution.**

- 2 **It should be a continuous function of the probabilities:** an arbitrarily small changes in the probabilities should be reflected as an accordingly small difference in our measure.
- 3 **It ought to be independent on how we group variables:** requiring this is the same as saying that we want our measure to depend on the probability distribution itself, not on the individual probabilities of each outcome constituting that distribution.

Shockingly enough, these constraints are enough to uniquely determine the form of the *entropy* H , up to a multiplicative constant (which, by convention, can be fixed). This is what Shannon proved [257] back in 1948. Without going into the proof, we reproduce the resulting mathematical definition of H :

$$H = - \sum_i p_i \log(p_i) \quad (\text{D.4})$$

where the summation index i goes all over possible outcomes, p_i is the probability of occurrence of event i and the logarithm can be taken to be in any base (conventionally, for historical reasons, it is taken to be in base 2, so that the resulting units are *bits*). It is straightforward to check that a fair coin ($p_i = 0.5$) yields the maximum entropy that can be attained (i.e., $H = 1$, because our choice of the normalization constant).

As we defined H in an axiomatic way, one can say that it is *the* quantitative measure of uncertainty associated with a given probability distribution. The counterargument is that there are a lot of different ways in which Eq. (D.4) can be understood; for a deeper discussion of these complementary views, we suggest taking a look at [258].

Rényi entropy It is a generalization of its Shannon sibling, due to Alfred Rényi [259] -the same author who co-authored the popularization of the random network modelization, or Erdős-Rényi, that we described in Sec. 2.1.2) in 1961. It is crucial in various fields ranging from ecology (understood as the *index of diversity*) to quantum computing (where it is useful for estimating the *entanglement* strength).

Let us consider a discrete random variable X that can take on different outcomes $1, 2, \dots, n$ with corresponding probabilities $p_i(X = i)$ for $i = 1, \dots, n$. We then define the Rényi entropy of order α (where $\alpha \geq 0$ and $\alpha \neq 1$) as:

$$H_\alpha(X) = \frac{1}{1 - \alpha} \log \left(\sum_{i=1}^n p_i^\alpha \right) \quad (\text{D.5})$$

Just like in the case of Shannon entropy, the logarithm is usually taken as base 2, to use *bits* as units. It is straightforward to see that the limiting case $\alpha \rightarrow 1$ is the usual Shannon entropy. We therefore remark that this measure should strictly be referred to as a *family* of measures. If the reader is interested in applications of this quantifier, we recommend visiting [260].

Mutual information We say that one variable X provides information $I[X; Y]$ about another variable Y if knowledge in the former reduces uncertainty in the later. The difference, of course, is that now we have a mathematical tool to quantify uncertainty (namely, Eq.(D.4)). Thus, we can put forward a quantifier based on Shannon entropy.

The mathematical relation between $I[X; Y]$ and probability distributions is given by the expression:

$$I[X; Y] \equiv \sum_{x \in \mathcal{X}} \sum_{y \in \mathcal{Y}} \Pr(x, y) \log_2 \left[\frac{\Pr(x, y)}{\Pr(x) \Pr(y)} \right] \quad (\text{D.6})$$

which, after some rewriting and reordering yields:

$$I[X; Y] = H[Y] + H[X] - H[X, Y] \quad (\text{D.7})$$

which is expressed in terms of the Shannon entropy, and immediately implies the symmetry property $I[X; Y] = I[Y; X]$. It is also worth noting that if variables X and Y are independently distributed, $I[X, Y] = 0$.

Eq. (D.6) allows yet another interpretation of information: it can be viewed as the Kullback–Leibler distance [261] (expectation of the log difference between two probability distributions) between the true joint distribution $p(x, y)$ and the joint distribution under the assumption the data are independent $p(x), p(y)$.

This measure is one of the most popular in the context of Neuroimages, due to its model-free nature and its lack of assumptions about what caused the correlations (or lack of them) between data-generated probability distributions. Its major drawback is its heavy computational burden, compared to simpler measures. We have to stress that it can be regarded as a complexity measure -in the sense of providing insights on the statistical structure of two dynamical processes- or as a synchronization measure -as explained in Appendix C.

Partial Information Decomposition Although PID is a formalism and it is not a measure *per se*, it is a framework [262] that facilitates the introduction of finer information-quantifiers. That is, instead of characterizing the information (or uncertainty) content of a system using a single scalar (as *every measure we have presented so far*, be it computational or chaos-based complexity measures), it further atomizes contributions to it, and distinguishes between different sources of uncertainty.

If we extend Eqs. D.6 and D.7 to the three-variables (namely, X, Y, Z) case

$$\begin{aligned} I(Z : X, Y) &= \sum_{\substack{x \in \mathcal{X}, y \in \mathcal{Y} \\ z \in \mathcal{Z}}} p(x, y, z) \log_2 \left(\frac{p(z|x, y)}{p(z)} \right) \\ &= H(Z) - H(Z|X, Y), \end{aligned} \quad (\text{D.8})$$

we can illustrate why PID is a powerful and interesting tool by decomposing this expression. We are actually going to do that through answering the following questions:

- 1 What is the amount of information that *just* X holds about Z ? Alternatively we can ask it as: what is the information that cannot be retrieved in any other way than learning about X ? This is the *unique information* of X about Z , noted by $I_{unq}(Z : X \setminus Y)$.
- 2 What information does considering $\{X, Y\}$ as a whole variable have about Z that we cannot possibly get from observing them separately? This is called *synergy* or *complementary information* of $\{X, Y\}$ about Z , noted by $I_{syn}(Z : X; Y)$.
- 3 What about the information that one of the variables, say X have about Z that could also be retrieved by looking at the other variable Y alone? This part of information is *redundancy* or *shared information* of X and Y about Z , noted by $I_{red}(Z : X; Y)$.

To illustrate the measure, we reproduced (with permission) a figure (Fig. D.1) originally found in [263].

Figure D.1: Illustration of how the Partial Information Decomposition scheme allows us to give finer details about Mutual Information in the three-variables case. Notation is as follows: I is the whole Mutual Information, CI , UI and SI stand for Complementary, Unique and Shared Information, respectively. Their corresponding definitions can be found in the text. Reproduced with permission from [263].

Although this is only the first refinement level that this formalism allows, we are not going to fully delve into all its depth. We recommend consulting Refs. [263–265] for further details, applications and finer methods.

D.4 Controversy and difficulties

As it is discussed in [266], even the precise definition of complexity is challenging. There have been multiple proposals [140] but all of them have suffered from at least

one of these problems: either they fail to recognize simple processes as such -maybe, correspondingly they classify complex phenomena as simple- or they are extremely context-specific -that is, they may be only applied to genomes or computer algorithms. If they do not exhibit these conflicts, they are so vague that are practically meaningless.

There have been recent attempts to formalize a generalized complexity measure (see [267, 268]), which were based on the fundamental hypothesis that in any system, complexity can be separated in two parts:

- Objective component: it is a function of the number of components, their variety and interrelatedness. This part can be thought of as the entropy we described previously (see Sec. 2.4)
- Subjective component: it captures the departure from a subject's reference simplicity. This is context-dependent and can be regarded as something similar to the disequilibrium we introduced in Sec. 2.4.

The fundamental nuance introduced in this Reference [267] is that of distinguishing a richer variety of reference simplicity frames. Thus, instead of considering pure randomness as the universal simplicity, they argue that, in order to measure complexity, a subjective reference for simplicity that tells about what is simple is to the viewer or to a given context is needed.

To our understanding, one central issue regarding Complexity is that there is not even a consensus on *what Complexity is*. There are intuitions or informal ideas that often lead to misinterpretations and contradictions. Apart from an aesthetic criterion or a *normality* one -that is, those measures which are more used tend to be more respected- there are many cases in which there exists no justification of why using a certain measure over others. Disregarding that, another problem that is perhaps more severe is that of interpretation: *what is the complexity measure capturing?* As an illustrative example, check out [269], where the authors dissect a popular complexity measure and digress in general about the need for concreteness and preciseness when talking about quantifying complexity.

We argue that, although a precise and rigorous definition might not be obtained in some time, these issues have to be taken into account by researchers working on problems that require the use of complexity measures. Specially, the interpretation of results has to be carefully done, to avoid overstatements or misunderstandings.

For a more conceptual and philosophical discussion, we recommend the reader to consult [270].

Bibliography

- [1] B. Mark, G. Raskutti, and R. Willett, “Estimating Network Structure from Incomplete Event Data”, arXiv preprint arXiv:1811.02979 (2018).
- [2] C. Zhou and J. Kurths, “Hierarchical synchronization in complex networks with heterogeneous degrees”, *Chaos* **16**, 015104 (2006).
- [3] T. Pereira, “Hub synchronization in scale-free networks”, *Phys. Rev. E* **82**, 036201 (2010).
- [4] D. R. Hartree, “The wave mechanics of an atom with a non-Coulomb central field. Part I. Theory and methods”, in *Mathematical Proceedings of the Cambridge Philosophical Society*, Vol. 24, 1 (Cambridge University Press, 1928), pp. 89–110.
- [5] V. Fock, “Näherungsmethode zur Lösung des quantenmechanischen Mehrkörperproblems”, *Zeitschrift für Physik* **61**, 126–148 (1930).
- [6] I. Prigogine, “Modération et transformation irréversible des systèmes ouverts”, *Bulletin de la Classe des sciences. Académie royale de Belgique* **31**, 600–606 (1945).
- [7] P. Bak, C. Tang, and K. Wiesenfeld, “Self-organized criticality: An explanation of the $1/f$ noise”, *Physical review letters* **59**, 381 (1987).
- [8] K. Linkenkaer-Hansen, V. V. Nikouline, J. M. Palva, and R. J. Ilmoniemi, “Long-range temporal correlations and scaling behavior in human brain oscillations”, *Journal of Neuroscience* **21**, 1370–1377 (2001).
- [9] D. R. Chialvo, “Critical brain networks”, *Physica A: Statistical Mechanics and its Applications* **340**, 756–765 (2004).
- [10] R. Smalley Jr, D. L. Turcotte, and S. A. Solla, “A renormalization group approach to the stick-slip behavior of faults”, *Journal of Geophysical Research: Solid Earth* **90**, 1894–1900 (1985).
- [11] D. Turcotte, R. Smalley, and S. A. Solla, “Collapse of loaded fractal trees”, *Nature* **313**, 671–672 (1985).
- [12] M. W. Chaffee and M. Mcneill, “A model of nursing as a complex adaptive system.”, *Nursing outlook* **55**, 232–241 (2007).
- [13] B. Castellani, *Map of the Complexity Sciences*, (2018) https://www.art-sciencefactory.com/images/complexity-map_Jan2018.jpg (visited on 10/19/2019).
- [14] A. Arenas, A. Díaz-Guilera, J. Kurths, Y. Moreno, and C. Zhou, “Synchronization in complex networks”, *Phys. Rep.* **469**, 93 –153 (2008).
- [15] J. W. S. Rayleigh, *The theory of sound* (London:Macmillan, 1896).
- [16] E. V. Appleton, “Automatic synchronization of triode oscillators”, in *Proc. Cambridge Phil. Soc.*, Vol. 21, 231 (1922), p. 1923.

- [17] B. van der Pol, “Forced oscillations in a circuit with non-linear resistance. (Reception with reactive triode)”, *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science* **3**, 65–80 (1927).
- [18] N. Wiener, 1958.
- [19] A. Winfree, “Biological rhythms and the behavior of populations of coupled oscillators”, *Journal of Theoretical Biology* **16**, 15–42 (1967).
- [20] Y. Kuramoto and H. Araki, 1975.
- [21] D. J. Watts and S. H. Strogatz, “Collective dynamics of ‘small-world’ networks”, *nature* **393**, 440 (1998).
- [22] L. M. Pecora, “Synchronization conditions and desynchronizing patterns in coupled limit-cycle and chaotic systems”, *Phys. Rev. E* **58**, 347–360 (1998).
- [23] M. Barahona and L. M. Pecora, “Synchronization in Small-World Systems”, *Phys. Rev. Lett.* **89**, 054101 (2002).
- [24] S Boccaletti, V Latora, Y Moreno, M Chavez, and D.-U. Hwang, “Complex networks: Structure and dynamics”, *Phys. Rep.* **424**, 175–308 (2006).
- [25] E. Bullmore and O. Sporns, “Complex brain networks: graph theoretical analysis of structural and functional systems”, *Nat. Rev. Neurosci.* **10**, 186–198 (2009).
- [26] M. Rohden, A. Sorge, M. Timme, and D. Witthaut, “Self-Organized Synchronization in Decentralized Power Grids”, *Phys. Rev. Lett.* **109**, 064101 (2012).
- [27] A. Pluchino, V. Latora, and A. Rapisarda, “Changing opinions in a changing world: a new perspective in sociophysics”, *Int. J. Mod. Phys. C* **16**, 515–531 (2005).
- [28] N. Fujiwara, J. Kurths, and A. Díaz-Guilera, “Synchronization in networks of mobile oscillators”, *Phys. Rev. E* **83**, 025101 (2011).
- [29] E. Rodriguez, N. George, J. P. Lachaux, J. Martinerie, B. Renault, and F. J. Varela, “Perception’s shadow: Long-distance synchronization of human brain activity”, *Nature* **397**, 430–433 (1999).
- [30] L. Jean-Philippe, R. Eugenio, M. Jacques, and V. F. J., “Measuring phase synchrony in brain signals”, *Human Brain Mapping* **8**, 194–208 (1999).
- [31] L. M. Pecora, F. Sorrentino, A. M. Hagerstrom, T. E. Murphy, and R. Roy, “Cluster synchronization and isolated desynchronization in complex networks with symmetries”, *Nature Communications* **5**, 4079 (2014).
- [32] G Tononi, O Sporns, and G. M. Edelman, “A measure for brain complexity: relating functional segregation and integration in the nervous system.”, *Proc. Natl. Acad. Sci.* **91**, 5033–5037 (1994).
- [33] A. A. Rad, I. Sendiña Nadal, D. Papo, M. Zanin, J. M. Buldú, F. del Pozo, and S. Boccaletti, “Topological Measure Locating the Effective Crossover between Segregation and Integration in a Modular Network”, *Phys. Rev. Lett.* **108**, 228701 (2012).
- [34] O. Sporns, “Network attributes for segregation and integration in the human brain”, *Curr. Opinion Neurobiol.* **23**, 162–171 (2013).
- [35] A. Arenas, A. Díaz-Guilera, and C. J. Pérez-Vicente, “Synchronization Reveals Topological Scales in Complex Networks”, *Phys. Rev. Lett.* **96**, 114102 (2006).
- [36] J. Gómez-Gardeñes, Y. Moreno, and A. Arenas, “Paths to synchronization on complex networks”, *Phys. Rev. Lett.* **98**, 034101 (2007).

- [37] D. Li, I. Leyva, J. A. Almendral, I. Sendiña Nadal, J. M. Buldú, S. Havlin, and S. Boccaletti, “Synchronization Interfaces and Overlapping Communities in Complex Networks”, *Phys. Rev. Lett.* **101**, 168701 (2008).
- [38] C. J. Honey, O. Sporns, L. Cammoun, X. Gigandet, J. P. Thiran, R. Meuli, and P. Hagmann, “Predicting human resting-state functional connectivity from structural connectivity”, *Proceedings of the National Academy of Sciences* **106**, 2035–2040 (2009).
- [39] J.-P. Eckmann, O. Feinerman, L. Gruendlinger, E. Moses, J. Soriano, and T. Thlusty, “The physics of living neural networks”, *Physics Reports* **449**, 54–76 (2007).
- [40] A. Kumar, S. Rotter, and A. Aertsen, “Spiking activity propagation in neuronal networks: reconciling different perspectives on neural coding”, *Nature reviews neuroscience* **11**, 615 (2010).
- [41] H. Zeng, “Mesoscale connectomics”, *Current opinion in neurobiology* **50**, 154–162 (2018).
- [42] V. M. Eguiluz, D. R. Chialvo, G. A. Cecchi, M. Baliki, and A. V. Apkarian, “Scale-free brain functional networks”, *Physical review letters* **94**, 018102 (2005).
- [43] M. Okatan, M. A. Wilson, and E. N. Brown, “Analyzing functional connectivity using a network likelihood model of ensemble neural spiking activity”, *Neural computation* **17**, 1927–1961 (2005).
- [44] Y. V. Zaytsev, A. Morrison, and M. Deger, “Reconstruction of recurrent synaptic connectivity of thousands of neurons from simulated spiking activity”, *Journal of computational neuroscience* **39**, 77–103 (2015).
- [45] W. Taouali and B. Cessac, “A maximum likelihood estimator of neural network synaptic weights”, *BMC neuroscience* **14**, P59 (2013).
- [46] J. W. Pillow and P. E. Latham, “Neural characterization in partially observed populations of spiking neurons”, in *Advances in Neural Information Processing Systems* (2008), pp. 1161–1168.
- [47] P. Jiruska, M. De Curtis, J. G. Jefferys, C. A. Schevon, S. J. Schiff, and K. Schindler, “Synchronization and desynchronization in epilepsy: controversies and hypotheses”, *The Journal of physiology* **591**, 787–797 (2013).
- [48] T. Fellin, O. Pascual, S. Gobbo, T. Pozzan, P. G. Haydon, and G. Carmignoto, “Neuronal synchrony mediated by astrocytic glutamate through activation of extrasynaptic NMDA receptors”, *Neuron* **43**, 729–743 (2004).
- [49] S. Jäkel and L. Dimou, “Glial cells and their function in the adult brain: a journey through the history of their ablation”, *Frontiers in cellular neuroscience* **11**, 24 (2017).
- [50] M. M. Bolton and C. Eroglu, “Look who is weaving the neural web: glial control of synapse formation”, *Current opinion in neurobiology* **19**, 491–497 (2009).
- [51] M. De Pitta and H. E. Berry, *Computational Glioscience* (Springer, 2019).
- [52] M. Santello, N. Toni, and A. Volterra, “Astrocyte function from information processing to cognition and cognitive impairment”, *Nature neuroscience*, 1 (2019).
- [53] Z. Sajedinia and S. Hélie, “A New Computational Model for Astrocytes and Their Role in Biologically Realistic Neural Networks”, *Computational Intelligence and Neuroscience* **2018**, 3689487 (2018).

- [54] J.-J. Li, M.-M. Du, R. Wang, J.-Z. Lei, and Y. Wu, “Astrocytic gliotransmitter: diffusion dynamics and induction of information processing on tripartite synapses”, *International Journal of Bifurcation and Chaos* **26**, 1650138 (2016).
- [55] M. Amiri, F. Bahrami, and M. Janahmadi, “Functional contributions of astrocytes in synchronization of a neuronal network model”, *Journal of Theoretical Biology* **292**, 60–70 (2012).
- [56] O. Kanakov, S. Gordleeva, A. Ermolaeva, S. Jalan, and A. Zaikin, “Astrocyte-induced positive integrated information in neuron-astrocyte ensembles”, *Physical Review E* **99**, 012418 (2019).
- [57] S. Y. Gordleeva, A. V. Ermolaeva, I. A. Kastalskiy, and V. B. Kazantsev, “Astrocyte as spatiotemporal integrating detector of neuronal activity”, *Frontiers in physiology* **10**, 294 (2019).
- [58] A. B. Porto-Pazos, N. Veiguela, P. Mesejo, M. Navarrete, A. Alvarellos, O. Ibáñez, A. Pazos, and A. Araque, “Artificial astrocytes improve neural network performance”, *PloS one* **6**, e19109 (2011).
- [59] E. Estrada and G. Silver, “Accounting for the role of long walks on networks via a new matrix function”, *Journal of Mathematical Analysis and Applications* **449**, 1581–1600 (2017).
- [60] E. Estrada, E. Hameed, N. Hatano, and M. Langer, “Path Laplacian operators and superdiffusive processes on graphs. I. One-dimensional case”, *Linear Algebra and its Applications* **523**, 307–334 (2017).
- [61] E. Estrada, L. V. Gambuzza, and M. Frasca, “Long-range interactions and network synchronization”, *SIAM Journal on Applied Dynamical Systems* **17**, 672–693 (2018).
- [62] J. H. Arias, J. Gómez-Gardeñes, S. Meloni, and E. Estrada, “Epidemics on plants: Modeling long-range dispersal on spatially embedded networks”, *Journal of Theoretical Biology* **453**, 1–13 (2018).
- [63] G. Silver, M. Akbarzadeh, and E. Estrada, “Tuned communicability metrics in networks. The case of alternative routes for urban traffic”, *Chaos, Solitons & Fractals* **116**, 402–413 (2018).
- [64] Y. Tsuji and E. Estrada, “Influence of long-range interactions on quantum interference in molecular conduction. A tight-binding (Hückel) approach”, *The Journal of chemical physics* **150**, 204123 (2019).
- [65] E. Estrada and P. A. Knight, *A first course in network theory* (Oxford University Press, USA, 2015).
- [66] M. Newman, *Networks* (Oxford university press, 2018).
- [67] J. A. Bondy, U. S. R. Murty, et al., *Graph theory with applications*, Vol. 290 (Macmillan London, 1976).
- [68] K. E. Fussmann, F. Schwarzmüller, U. Brose, A. Jousset, and B. C. Rall, “Ecological stability in response to warming”, *Nature Climate Change* **4**, 206 (2014).
- [69] L. A. Adamic and N. Glance, “The political blogosphere and the 2004 US election: divided they blog”, in *Proceedings of the 3rd international workshop on Link discovery (ACM, 2005)*, pp. 36–43.
- [70] K. Börner, S. Sanyal, and A. Vespignani, “Network science”, *Annual review of information science and technology* **41**, 537–607 (2007).

- [71] A. Bavelas, “Communication patterns in task-oriented groups”, The Journal of the Acoustical Society of America **22**, 725–730 (1950).
- [72] L. C. Freeman, “A set of measures of centrality based on betweenness”, Sociometry, 35–41 (1977).
- [73] D. Ortiz-Arroyo, “Discovering sets of key players in social networks”, in *Computational social network analysis* (Springer, 2010), pp. 27–47.
- [74] P. Erdős and A. Rényi, “On the evolution of random graphs”, Publ. Math. Inst. Hung. Acad. Sci **5**, 17–60 (1960).
- [75] R. Solomonoff and A. Rapoport, “Connectivity of random nets”, The bulletin of mathematical biophysics **13**, 107–117 (1951).
- [76] P. W. Holland and S. Leinhardt, “Transitivity in structural models of small groups”, Comparative group studies **2**, 107–124 (1971).
- [77] O. Richters and T. P. Peixoto, “Trust transitivity in social networks”, PloS one **6**, e18384 (2011).
- [78] M. Newman, “Models of the Small World”, Journal of Statistical Physics **101**, 819–841 (2000).
- [79] M Barthélemy, “Crossover from spatial to scale-free networks”, Europhys. lett **63**, 915–921 (2003).
- [80] M. Kaiser and C. C. Hilgetag, “Spatial growth of real-world networks”, Physical Review E **69**, 036103 (2004).
- [81] R. Albert, H. Jeong, and A.-L. Barabási, “Internet: Diameter of the worldwide web”, nature **401**, 130 (1999).
- [82] S. Redner, “How popular is your paper? An empirical study of the citation distribution”, The European Physical Journal B-Condensed Matter and Complex Systems **4**, 131–134 (1998).
- [83] M. E. Newman, “The structure of scientific collaboration networks”, Proceedings of the national academy of sciences **98**, 404–409 (2001).
- [84] H. Ebel, L.-I. Mielsch, and S. Bornholdt, “Scale-free topology of e-mail networks”, Physical review E **66**, 035103 (2002).
- [85] A. Clauset, C. R. Shalizi, and M. E. Newman, “Power-law distributions in empirical data”, SIAM review **51**, 661–703 (2009).
- [86] A. D. Broido and A. Clauset, “Scale-free networks are rare”, Nature communications **10**, 1017 (2019).
- [87] D. d. S. Price, “A general theory of bibliometric and other cumulative advantage processes”, Journal of the American society for Information science **27**, 292–306 (1976).
- [88] A.-L. Barabási, “Network science”, Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences **371**, 20120375 (2013).
- [89] J. M. T. Thompson and H. B. Stewart, *Nonlinear dynamics and chaos* (John Wiley & Sons, 2002).
- [90] D. Kaplan and L. Glass, *Understanding nonlinear dynamics* (Springer Science & Business Media, 2012).
- [91] S. H. Strogatz, *Nonlinear dynamics and chaos: with applications to physics, biology, chemistry, and engineering* (CRC Press, 2018).
- [92] S. Jalan and R. Amritkar, “Self-organized and driven phase synchronization in coupled maps”, Physical review letters **90**, 014101 (2003).

- [93] K. Li, X. Fu, M. Small, and Z. Ma, “Adaptive mechanism between dynamical synchronization and epidemic behavior on complex networks”, *Chaos: An Interdisciplinary Journal of Nonlinear Science* **21**, 033111 (2011).
- [94] X. F. Wang and G. Chen, “Synchronization in scale-free dynamical networks: robustness and fragility”, *IEEE Transactions on Circuits and Systems I: Fundamental Theory and Applications* **49**, 54–62 (2002).
- [95] M. W. Hirsch, S. Smale, and R. L. Devaney, *Differential equations, dynamical systems, and an introduction to chaos* (Academic press, 2012).
- [96] D. Ruelle, “What is a strange attractor”, *Notices of the AMS* **53**, 764–765 (2006).
- [97] G. Boeing, “Visual analysis of nonlinear dynamical systems: chaos, fractals, self-similarity and the limits of prediction”, *Systems* **4**, 37 (2016).
- [98] J. D. Farmer, E. Ott, and J. A. Yorke, “The dimension of chaotic attractors”, *Physica D: Nonlinear Phenomena* **7**, 153–180 (1983).
- [99] O. E. Rössler, “An equation for continuous chaos”, *Phys. Lett. A* **57**, 397–398 (1976).
- [100] L. M. Pecora and T. L. Carroll, “Master Stability Functions for Synchronized Coupled Systems”, *Phys. Rev. Lett.* **80**, 2109–2112 (1998).
- [101] E. Coddington and N. Levinson, *Theory of Ordinary Differential Equations* (Krieger Publishing Company, 1984), pp. 391–398.
- [102] E. N. Lorenz, “Deterministic Nonperiodic Flow”, *Journal of the Atmospheric Sciences* (1963).
- [103] E. Neher and B. Sakmann, “Single-channel currents recorded from membrane of denervated frog muscle fibres”, *Nature* **260**, 799 (1976).
- [104] E. D. Adrian, “The impulses produced by sensory nerve endings: Part I”, *The Journal of physiology* **61**, 49 (1926).
- [105] G. Werner and V. B. Mountcastle, “Neural activity in mechanoreceptive cutaneous afferents: stimulus-response relations, Weber functions, and information transmission”, *Journal of neurophysiology* **28**, 359–397 (1965).
- [106] R. S. Petersen and M. E. Diamond, “Spatial–temporal distribution of whisker-evoked activity in rat somatosensory cortex and the coding of stimulus location”, *Journal of Neuroscience* **20**, 6135–6143 (2000).
- [107] W. Bialek, F. Rieke, R. D. R. Van Steveninck, and D. Warland, “Reading a neural code”, *Science* **252**, 1854–1857 (1991).
- [108] F. Rieke, D. Warland, R. de Ruyter van Steveninck, and W. Bialek, “Spikes: Exploring the neural code MIT Press”, Cambridge MA (1997).
- [109] E. Ahissar, R. Sosnik, and S. Haidarliu, “Transformation from temporal to rate coding in a somatosensory thalamocortical pathway”, *Nature* **406**, 302 (2000).
- [110] W. Gerstner, W. M. Kistler, R. Naud, and L. Paninski, *Neuronal dynamics: From single neurons to networks and models of cognition* (Cambridge University Press, 2014).
- [111] A. L. Hodgkin and A. F. Huxley, “A quantitative description of membrane current and its application to conduction and excitation in nerve”, *The Journal of physiology* **117**, 500–544 (1952).
- [112] C. Morris and H. Lecar, “Voltage oscillations in the barnacle giant muscle fiber”, *Biophys. J.* **35**, 193–213 (1981).

- [113] J. Sijbers, P. Scheunders, N. Bonnet, D. Van Dyck, and E. Raman, “Quantification and improvement of the signal-to-noise ratio in a magnetic resonance image acquisition procedure”, *Magnetic resonance imaging* **14**, 1157–1163 (1996).
- [114] W. Gragido, J. Pirc, N. Selby, and D. Molina, “Chapter 4 - Signal-to-Noise Ratio”, in *Blackhatonomics*, edited by W. Gragido, J. Pirc, N. Selby, and D. Molina (Syngress, Boston, 2013), pp. 45–55.
- [115] A. S. Pikovsky and J. Kurths, “Coherence resonance in a noise-driven excitable system”, *Physical Review Letters* **78**, 775 (1997).
- [116] E. R. Kandel, J. H. Schwartz, T. M. Jessell, D. of Biochemistry, M. B. T. Jessell, S. Siegelbaum, and A. Hudspeth, *Principles of neural science*, Vol. 4 (McGraw-hill New York, 2000).
- [117] B. W. Connors and M. A. Long, “Electrical synapses in the mammalian brain”, *Annu. Rev. Neurosci.* **27**, 393–418 (2004).
- [118] T. Wang, L. Yin, X. Zou, Y. Shu, M. J. Rasch, and S. Wu, “A Phenomenological Synapse Model for Asynchronous Neurotransmitter Release”, *Frontiers in computational neuroscience* **9**, 153 (2016).
- [119] P. Wallisch, “Chapter 26 - Synaptic Transmission”, in *MATLAB for Neuroscientists (Second Edition)*, edited by P. Wallisch, M. E. Lusignan, M. D. Benayoun, T. I. Baker, A. S. Dickey, and N. G. Hatsopoulos, Second Edition (Academic Press, San Diego, 2014), pp. 395–402.
- [120] T. C. Südhof and R. C. Malenka, “Understanding synapses: past, present, and future”, *Neuron* **60**, 469–476 (2008).
- [121] A Raes, Z Wang, R. Van Den Berg, M Goethals, G Van de Vijver, and P. Van Bogaert, “Effect of cAMP and ATP on the hyperpolarization-activated current in mouse dorsal root ganglion neurons”, *Pflügers Archiv* **434**, 543–550 (1997).
- [122] C. S. von Bartheld, J. Bahney, and S. Herculano-Houzel, “The search for true numbers of neurons and glial cells in the human brain: A review of 150 years of cell counting”, *Journal of Comparative Neurology* **524**, 3865–3895 (2016).
- [123] U. Fünfschilling, L. M. Supplie, D. Mahad, S. Boretius, A. S. Saab, J. Edgar, B. G. Brinkmann, C. M. Kassmann, I. D. Tzvetanova, W. Möbius, et al., “Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity”, *Nature* **485**, 517 (2012).
- [124] S. Liebner, R. M. Dijkhuizen, Y. Reiss, K. H. Plate, D. Agalliu, and G. Constantin, “Functional morphology of the blood–brain barrier in health and disease”, *Acta Neuropathologica* **135**, 311–336 (2018).
- [125] Y.-J. Jung and W.-S. Chung, “Phagocytic roles of glial cells in healthy and diseased brains”, *Biomolecules & therapeutics* **26**, 350 (2018).
- [126] P. Rea, *Essential clinically applied anatomy of the peripheral nervous system in the head and neck* (Academic Press, 2016).
- [127] N. J. Allen and B. A. Barres, “Signaling between glia and neurons: focus on synaptic plasticity”, *Current opinion in neurobiology* **15**, 542–548 (2005).
- [128] N. J. Allen and B. A. Barres, “Neuroscience: glia—more than just brain glue”, *Nature* **457**, 675 (2009).
- [129] F. Oschmann, H. Berry, K. Obermayer, and K. Lenk, “From in silico astrocyte cell models to neuron-astrocyte network models: A review”, *Brain Research Bulletin* **136**, 76–84 (2018).

- [130] M. De Pittà, N. Brunel, and A. Volterra, “Astrocytes: orchestrating synaptic plasticity?”, *Neuroscience* **323**, 43–61 (2016).
- [131] G. Perea, M. Navarrete, and A. Araque, “Tripartite synapses: astrocytes process and control synaptic information”, *Trends in Neurosciences* **32**, 421–431 (2009).
- [132] I. Leyva, A. Navas, I. Sendiña-Nadal, J. M. Buldu, J. A. Almendral, and S. Boccaletti, “Synchronization waves in geometric networks”, *Physical Review E* **84**, 065101 (2011).
- [133] R. Rosenbaum and B. Doiron, “Balanced Networks of Spiking Neurons with Spatially Dependent Recurrent Connections”, *Phys. Rev. X* **4**, 021039 (2014).
- [134] S. H. Strogatz, “From Kuramoto to Crawford: exploring the onset of synchronization in populations of coupled oscillators”, *Physica D: Nonlinear Phenomena* **143**, 1–20 (2000).
- [135] J. A. Acebrón, L. L. Bonilla, C. J. P. Vicente, F. Ritort, and R. Spigler, “The Kuramoto model: A simple paradigm for synchronization phenomena”, *Reviews of modern physics* **77**, 137 (2005).
- [136] J. D. da Fonseca and C. V. Abud, “The Kuramoto model revisited”, *Journal of Statistical Mechanics: Theory and Experiment* **2018**, 103204 (2018).
- [137] M. G. Rosenblum, A. S. Pikovsky, and J. Kurths, “Phase synchronization of chaotic oscillators”, *Physical review letters* **76**, 1804 (1996).
- [138] S. Boccaletti, J. Kurths, G. Osipov, D. Valladares, and C. Zhou, “The synchronization of chaotic systems”, *Phys. Rep.* **366**, 1–101 (2002).
- [139] S. Kochubey and L. Savtchenko, “Geometrical size of the neuronal network plays a key role in synchronization of its activity”, *Neurophysiology* **40**, 224 (2008).
- [140] B. Edmonds, *Bibliography of Measures of Complexity*, (1997) <http://bruce.edmonds.name/combib/> (visited on 09/21/2019).
- [141] C. Bandt and B. Pompe, “Permutation Entropy: A Natural Complexity Measure for Time Series”, *Phys. Rev. Lett.* **88**, 174102 (2002).
- [142] J. Amigó, *Permutation complexity in dynamical systems: ordinal patterns, permutation entropy and all that* (Springer Science & Business Media, 2010).
- [143] C. S. Daw, C. E. A. Finney, and E. R. Tracy, “A review of symbolic analysis of experimental data”, *Review of Scientific instruments* **74**, 915–930 (2003).
- [144] K. Keller, A. Unakafov, and V. Unakafova, “Ordinal patterns, entropy, and EEG”, *Entropy* **16**, 6212–6239 (2014).
- [145] O. A. Rosso, L. C. Carpi, P. M. Saco, M. G. Ravetti, A. Plastino, and H. A. Larrondo, “Causality and the entropy–complexity plane: Robustness and missing ordinal patterns”, *Physica A: Statistical Mechanics and its Applications* **391**, 42–55 (2012).
- [146] J. L. Herrera-Diestra, J. M. Buldú, M. Chávez, and J. H. Martínez, “Using symbolic networks to analyse dynamical properties of disease outbreaks”, *arXiv preprint arXiv:1911.05646* (2019).
- [147] R. López-Ruiz, H. Mancini, and X. Calbet, “A statistical measure of complexity”, *Phys. Lett. A* **209**, 321–326 (1995).
- [148] M. Martin, A. Plastino, and O. Rosso, “Statistical complexity and disequilibrium”, *Phys. Lett. A* **311**, 126–132 (2003).
- [149] P. Lamberti, M. Martin, A. Plastino, and O. Rosso, “Intensive entropic non-triviality measure”, *Physica A* **334**, 119–131 (2004).

- [150] S. Kullback and R. A. Leibler, *On Information and Sufficiency*.
- [151] F. Osterreicher and I. Vajda, “A new class of metric divergences on probability spaces and its applicability in statistics”, *Annals of the Institute of Statistical Mathematics* **55**, 639–653 (2003).
- [152] D. M. Endres and J. E. Schindelin, “A new metric for probability distributions”, *IEEE Transactions on Information theory* (2003).
- [153] J. H. Martínez, M. E. López, P. Ariza, M. Chavez, J. A. Pineda-Pardo, D. López-Sanz, P. Gil, F. Maestú, and J. M. Buldú, “Functional brain networks reveal the existence of cognitive reserve and the interplay between network topology and dynamics”, *Scientific reports* **8**, 10525 (2018).
- [154] L. Xiao-Feng and W. Yue, “Fine-grained permutation entropy as a measure of natural complexity for time series”, *Chinese Physics B* **18**, 2690 (2009).
- [155] C. Bian, C. Qin, Q. D. Ma, and Q. Shen, “Modified permutation-entropy analysis of heartbeat dynamics”, *Physical Review E* **85**, 021906 (2012).
- [156] C. Runge, “Über die numerische Auflösung von Differentialgleichungen”, *Mathematische Annalen* **46**, 167–178 (1895).
- [157] W. Kutta, “Beitrag zur näherungsweise Integration totaler Differentialgleichungen”, *Z. Math. Phys.* **46**, 435–453 (1901).
- [158] A. Rößler, “Runge–Kutta methods for Itô stochastic differential equations with scalar noise”, *BIT Numerical Mathematics* **46**, 97–110 (2006).
- [159] M. San Miguel and R. Toral, “Stochastic effects in physical systems”, in *Instabilities and nonequilibrium structures VI* (Springer, 2000), pp. 35–127.
- [160] T. C. Gard, “Introduction to Stochastic Differential Equations”, *Journal of Applied Mathematics and Mechanics* **69**, 258–258 (1989).
- [161] P. Bak, C. Tang, and K. Wiesenfeld, “Self-organized criticality”, *Physical review A* **38**, 364 (1988).
- [162] D. L. Turcotte, “Self-organized criticality”, *Reports on progress in physics* **62**, 1377 (1999).
- [163] P. Bak and M. Paczuski, “Complexity, contingency, and criticality”, *Proceedings of the National Academy of Sciences* **92**, 6689–6696 (1995).
- [164] J. M. Beggs and D. Plenz, “Neuronal avalanches in neocortical circuits”, *Journal of neuroscience* **23**, 11167–11177 (2003).
- [165] F. Meng, L. N. Y. Wong, and H. Zhou, “Power law relations in earthquakes from microscopic to macroscopic scales”, *Scientific reports* **9**, 10705 (2019).
- [166] D. M. Raup, “Biological extinction in earth history”, *Science* **231**, 1528–1533 (1986).
- [167] R. Black, H. Hurst, and Y. Simaika, *Long-term storage: an experimental study* (Constable, 1965).
- [168] B. B. Mandelbrot, “Scaling in financial prices: II. Multifractals and the star equation”, (2001).
- [169] C. Lucas, *The Philosophy of Complexity*, (2005) <http://www.calresco.org/lucas/philos.htm> (visited on 10/28/2019).
- [170] F. Heylighen, P. Cilliers, and C. Gershenson, “Complexity and philosophy”, *arXiv preprint cs/0604072* (2006).
- [171] Q. Wang, O. Sporns, and A. Burkhalter, “Network analysis of corticocortical connections reveals ventral and dorsal processing streams in mouse visual cortex”, *Journal of Neuroscience* **32**, 4386–4399 (2012).

- [172] D. Bumbarger, M. Riebesell, R. Sommer, et al., “System-wide rewiring underlies behavioral differences in predatory and bacterial-feeding nematodes”, *Cell* **152**, 109–119 (2013).
- [173] M. Rivera-Alba, S. N. Vitaladevuni, Y. Mishchenko, Z. Lu, S.-y. Takemura, L. Scheffer, I. A. Meinertzhagen, D. B. Chklovskii, and G. G. de Polavieja, “Wiring economy and volume exclusion determine neuronal placement in the *Drosophila* brain”, *Current Biology* **21**, 2000–2005 (2011).
- [174] S.-y. Takemura, A. Bharioke, Z. Lu, A. Nern, S. Vitaladevuni, P. K. Rivlin, W. T. Katz, D. J. Olbris, S. M. Plaza, P. Winston, et al., “A visual motion detection circuit suggested by *Drosophila* connectomics”, *Nature* **500**, 175 (2013).
- [175] K. L. Briggman, M. Helmstaedter, and W. Denk, “Wiring specificity in the direction-selectivity circuit of the retina”, *Nature* **471**, 183 (2011).
- [176] M. Helmstaedter, “Cellular-resolution connectomics: challenges of dense neural circuit reconstruction”, *Nature methods* **10**, 501 (2013).
- [177] D. D. Bock, W.-C. A. Lee, A. M. Kerlin, M. L. Andermann, G. Hood, A. W. Wetzell, S. Yurgenson, E. R. Soucy, H. S. Kim, and R. C. Reid, “Network anatomy and in vivo physiology of visual cortical neurons”, *Nature* **471**, 177 (2011).
- [178] M. B. Ahrens, M. B. Orger, D. N. Robson, J. M. Li, and P. J. Keller, “Whole-brain functional imaging at cellular resolution using light-sheet microscopy”, *Nature methods* **10**, 413 (2013).
- [179] R. Portugues, C. E. Feierstein, F. Engert, and M. B. Orger, “Whole-brain activity maps reveal stereotyped, distributed networks for visuomotor behavior”, *Neuron* **81**, 1328–1343 (2014).
- [180] R. Portugues, K. E. Severi, C. Wyart, and M. B. Ahrens, “Optogenetics in a transparent animal: circuit function in the larval zebrafish”, *Current opinion in neurobiology* **23**, 119–126 (2013).
- [181] K. Deisseroth, “Optogenetics”, *Nature methods* **8**, 26 (2011).
- [182] A. Claridge-Chang, R. D. Roorda, E. Vrontou, L. Sjulson, H. Li, J. Hirsh, and G. Miesenböck, “Writing memories with light-addressable reinforcement circuitry”, *Cell* **139**, 405–415 (2009).
- [183] S. E. Maze, “How Neural Activity Shapes Decision Making: An Optogenetic Investigation of the Neural Basis of Mate Choice in Female Songbirds”, (2017).
- [184] Z. C. Wick and E. Krook-Magnuson, “Specificity, versatility, and continual development: the power of optogenetics for epilepsy research”, *Frontiers in cellular neuroscience* **12** (2018).
- [185] A.-S. Chiang, C.-Y. Lin, C.-C. Chuang, H.-M. Chang, C.-H. Hsieh, C.-W. Yeh, C.-T. Shih, J.-J. Wu, G.-T. Wang, Y.-C. Chen, et al., “Three-dimensional reconstruction of brain-wide wiring networks in *Drosophila* at single-cell resolution”, *Current Biology* **21**, 1–11 (2011).
- [186] C.-T. Shih, O. Sporns, and A.-S. Chiang, “Toward the *Drosophila* connectome: structural analysis of the brain network”, *BMC neuroscience* **14**, P63 (2013).
- [187] C.-T. Shih, O. Sporns, S.-L. Yuan, T.-S. Su, Y.-J. Lin, C.-C. Chuang, T.-Y. Wang, C.-C. Lo, R. J. Greenspan, and A.-S. Chiang, “Connectomics-based

- analysis of information flow in the *Drosophila* brain”, *Current Biology* **25**, 1249–1258 (2015).
- [188] M. Bota, O. Sporns, and L. W. Swanson, “Architecture of the cerebral cortical association connectome underlying cognition”, *Proceedings of the National Academy of Sciences* **112**, E2093–E2101 (2015).
 - [189] T. A. Jarrell, Y. Wang, A. E. Bloniarz, C. A. Brittin, M. Xu, J. N. Thomson, D. G. Albertson, D. H. Hall, and S. W. Emmons, “The connectome of a decision-making neural network”, *Science* **337**, 437–444 (2012).
 - [190] B. Zingg, H. Hintiryan, L. Gou, M. Y. Song, M. Bay, M. S. Bienkowski, N. N. Foster, S. Yamashita, I. Bowman, A. W. Toga, et al., “Neural networks of the mouse neocortex”, *Cell* **156**, 1096–1111 (2014).
 - [191] S. W. Oh, J. A. Harris, L. Ng, B. Winslow, N. Cain, S. Mihalas, Q. Wang, C. Lau, L. Kuan, A. M. Henry, et al., “A mesoscale connectome of the mouse brain”, *Nature* **508**, 207 (2014).
 - [192] P. Hagmann, L. Cammoun, X. Gigandet, R. Meuli, C. J. Honey, V. J. Wedeen, and O. Sporns, “Mapping the structural core of human cerebral cortex”, *PLoS biology* **6**, e159 (2008).
 - [193] B. Mišić and O. Sporns, “From regions to connections and networks: new bridges between brain and behavior”, *Current opinion in neurobiology* **40**, 1–7 (2016).
 - [194] M. Shanahan, V. P. Bingman, T. Shimizu, M. Wild, and O. Güntürkün, “Large-scale network organization in the avian forebrain: a connectivity matrix and theoretical analysis”, *Frontiers in computational neuroscience* **7**, 89 (2013).
 - [195] A. E. Mechling, N. S. Hübner, H.-L. Lee, J. Hennig, D. von Elverfeldt, and L.-A. Harsan, “Fine-grained mapping of mouse brain functional connectivity with resting-state fMRI”, *Neuroimage* **96**, 203–215 (2014).
 - [196] Z. Wang, L. M. Chen, L. Négyessy, R. M. Friedman, A. Mishra, J. C. Gore, and A. W. Roe, “The relationship of anatomical and functional connectivity to resting-state connectivity in primate somatosensory cortex”, *Neuron* **78**, 1116–1126 (2013).
 - [197] N. T. Markov, M. Ercsey-Ravasz, A. Ribeiro Gomes, C. Lamy, L. Magrou, J. Vezoli, P. Misery, A. Falchier, R. Quilodran, M. Gariel, et al., “A weighted and directed interareal connectivity matrix for macaque cerebral cortex”, *Cerebral cortex* **24**, 17–36 (2012).
 - [198] N. T. Markov, J. Vezoli, P. Chameau, A. Falchier, R. Quilodran, C. Huissoud, C. Lamy, P. Misery, P. Giroud, S. Ullman, et al., “Anatomy of hierarchy: feedforward and feedback pathways in macaque visual cortex”, *Journal of Comparative Neurology* **522**, 225–259 (2014).
 - [199] M. Ercsey-Ravasz, N. T. Markov, C. Lamy, D. C. Van Essen, K. Knoblauch, Z. Toroczkai, and H. Kennedy, “A predictive network model of cerebral cortical connectivity based on a distance rule”, *Neuron* **80**, 184–197 (2013).
 - [200] N. T. Markov, M. Ercsey-Ravasz, D. C. Van Essen, K. Knoblauch, Z. Toroczkai, and H. Kennedy, “Cortical high-density counterstream architectures”, *Science* **342**, 1238406 (2013).
 - [201] N. T. Markov, M. Ercsey-Ravasz, C. Lamy, A. R. R. Gomes, L. Magrou, P. Misery, P. Giroud, P. Barone, C. Dehay, Z. Toroczkai, et al., “The role of long-range connections on the specificity of the macaque interareal cortical

- network”, *Proceedings of the National Academy of Sciences* **110**, 5187–5192 (2013).
- [202] D. S. Bassett and E. Bullmore, “Small-world brain networks”, *The neuroscientist* **12**, 512–523 (2006).
 - [203] L.-D. Lord, A. B. Stevner, G. Deco, and M. L. Kringelbach, “Understanding principles of integration and segregation using whole-brain computational connectomics: implications for neuropsychiatric disorders”, *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* **375**, 20160283 (2017).
 - [204] O. Sporns and J. D. Zwi, “The small world of the cerebral cortex”, *Neuroinformatics* **2**, 145–162 (2004).
 - [205] L. Wang, C. Zhu, Y. He, Y. Zang, Q. Cao, H. Zhang, Q. Zhong, and Y. Wang, “Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder”, *Human brain mapping* **30**, 638–649 (2009).
 - [206] Q. K. Telesford, K. E. Joyce, S. Hayasaka, J. H. Burdette, and P. J. Laurienti, “The ubiquity of small-world networks”, *Brain connectivity* **1**, 367–375 (2011).
 - [207] D. Papo, M. Zanin, J. H. Martínez, and J. M. Buldú, “Beware of the small-world neuroscientist!”, *Frontiers in human neuroscience* **10**, 96 (2016).
 - [208] J. L. Vincent, G. H. Patel, M. D. Fox, A. Z. Snyder, J. T. Baker, D. C. Van Essen, J. M. Zempel, L. H. Snyder, M. Corbetta, and M. E. Raichle, “Intrinsic functional architecture in the anaesthetized monkey brain”, *Nature* **447**, 83 (2007).
 - [209] T. Matsui, K. W. Koyano, K. Tamura, T. Osada, Y. Adachi, K. Miyamoto, J. Chikazoe, T. Kamigaki, and Y. Miyashita, “fMRI activity in the macaque cerebellum evoked by intracortical microstimulation of the primary somatosensory cortex: evidence for polysynaptic propagation”, *PloS one* **7**, e47515 (2012).
 - [210] B. J. Shannon, M. E. Raichle, A. Z. Snyder, D. A. Fair, K. L. Mills, D. Zhang, K. Bache, V. D. Calhoun, J. T. Nigg, B. J. Nagel, et al., “Premotor functional connectivity predicts impulsivity in juvenile offenders”, *Proceedings of the National Academy of Sciences* **108**, 11241–11245 (2011).
 - [211] R. L. Buckner, F. M. Krienen, and B. T. Yeo, “Opportunities and limitations of intrinsic functional connectivity MRI”, *Nature neuroscience* **16**, 832 (2013).
 - [212] C. Honey, O. Sporns, L. Cammoun, X. Gigandet, J.-P. Thiran, R. Meuli, and P. Hagmann, “Predicting human resting-state functional connectivity from structural connectivity”, *Proceedings of the National Academy of Sciences* **106**, 2035–2040 (2009).
 - [213] P. Skudlarski, K. Jagannathan, V. D. Calhoun, M. Hampson, B. A. Skudlarska, and G. Pearlson, “Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations”, *Neuroimage* **43**, 554–561 (2008).
 - [214] A. M. Hermundstad, D. S. Bassett, K. S. Brown, E. M. Aminoff, D. Clewett, S. Freeman, A. Frithsen, A. Johnson, C. M. Tipper, M. B. Miller, et al., “Structural foundations of resting-state and task-based functional connectivity in the human brain”, *Proceedings of the National Academy of Sciences* **110**, 6169–6174 (2013).

- [215] P. E. Vértes, A. F. Alexander-Bloch, N. Gogtay, J. N. Giedd, J. L. Rapoport, and E. T. Bullmore, “Simple models of human brain functional networks”, *Proceedings of the National Academy of Sciences* **109**, 5868–5873 (2012).
- [216] S. A. Nastase, V. Iacovella, B. Davis, and U. Hasson, “Connectivity in the human brain dissociates entropy and complexity of auditory inputs”, *Neuroimage* **108**, 292–300 (2015).
- [217] O. Miranda-Dominguez, B. D. Mills, D. Grayson, A. Woodall, K. A. Grant, C. D. Kroenke, and D. A. Fair, “Bridging the gap between the human and macaque connectome: a quantitative comparison of global interspecies structure-function relationships and network topology”, *Journal of Neuroscience* **34**, 5552–5563 (2014).
- [218] B. N. Routh, D. Johnston, K. Harris, and R. A. Chitwood, “Anatomical and electrophysiological comparison of CA1 pyramidal neurons of the rat and mouse”, *Journal of neurophysiology* **102**, 2288–2302 (2009).
- [219] R. C. O’Reilly and M. J. Frank, “Making working memory work: a computational model of learning in the prefrontal cortex and basal ganglia”, *Neural computation* **18**, 283–328 (2006).
- [220] M. P. van den Heuvel and O. Sporns, “Network hubs in the human brain”, *Trends in cognitive sciences* **17**, 683–696 (2013).
- [221] A. Gomez-Villa, M. Bertalmío, and J. Malo, “Visual Information flow in Wilson-Cowan networks”, *arXiv preprint arXiv:1907.13046* (2019).
- [222] H. R. Wilson and J. D. Cowan, “Excitatory and inhibitory interactions in localized populations of model neurons”, *Biophysical journal* **12**, 1–24 (1972).
- [223] Z. P. Kilpatrick, “Wilson-cowan model”, *Encyclopedia of Computational Neuroscience*, 3159–3163 (2015).
- [224] B. H. Jansen and V. G. Rit, “Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns”, *Biological cybernetics* **73**, 357–366 (1995).
- [225] V. Braitenberg and A. Schüz, *Cortex: statistics and geometry of neuronal connectivity* (Springer Science & Business Media, 2013).
- [226] F. Grimbert and O. Faugeras, “Bifurcation analysis of Jansen’s neural mass model”, *Neural computation* **18**, 3052–3068 (2006).
- [227] D. Pinotsis, M. Leite, and K. Friston, “On conductance-based neural field models”, *Frontiers in computational neuroscience* **7**, 158 (2013).
- [228] E. M. Izhikevich, “Which model to use for cortical spiking neurons?”, *IEEE transactions on neural networks* **15**, 1063–1070 (2004).
- [229] E. Izhikevich, *Dynamical Systems in Neuroscience* (MIT Press, 2007).
- [230] A. Shilnikov, R. L. Calabrese, and G. Cymbalyuk, “Mechanism of bistability: tonic spiking and bursting in a neuron model”, *Physical Review E* **71**, 056214 (2005).
- [231] J. P. Segundo, J.-F. Vibert, K. Pakdaman, M. Stiber, and O. D. Martínez, “Noise and the neurosciences: a long history, a recent revival and some theory”, in (1994).
- [232] E. Pereda, R. Q. Quiroga, and J. Bhattacharya, “Nonlinear multivariate analysis of neurophysiological signals”, *Progress in neurobiology* **77**, 1–37 (2005).
- [233] J. S. Bendat and A. G. Piersol, *Random data: analysis and measurement procedures*, Vol. 729 (John Wiley & Sons, 2011).

- [234] C. W. Granger, “Investigating causal relations by econometric models and cross-spectral methods”, *Econometrica: Journal of the Econometric Society*, 424–438 (1969).
- [235] C. E. Shannon and W. Weaver, *The mathematical theory of communication* (University of Illinois press, 1998).
- [236] J.-P. Lachaux, E. Rodriguez, J. Martinerie, and F. J. Varela, “Measuring phase synchrony in brain signals”, *Human brain mapping* **8**, 194–208 (1999).
- [237] R. Q. Quiroga, T. Kreuz, and P. Grassberger, “Event synchronization: a simple and fast method to measure synchronicity and time delay patterns”, *Physical review E* **66**, 041904 (2002).
- [238] A. N. Kolmogorov, “Three approaches to the quantitative definition of information”, *International journal of computer mathematics* **2**, 157–168 (1968).
- [239] M. Davis, *The undecidable: Basic papers on undecidable propositions, unsolvable problems and computable functions* (Courier Corporation, 2004).
- [240] K. Gödel, “Über formal unentscheidbare Sätze der Principia Mathematica und verwandter Systeme I”, *Monatshefte für mathematik und physik* **38**, 173–198 (1931).
- [241] R. Badii and A. Politi, *Complexity: Hierarchical structures and scaling in physics*, Vol. 6 (Cambridge University Press, 1999).
- [242] B Edmonds, “Syntactic Measures of Complexity PhD Thesis”, Centre for Policy Modelling, University of Manchester (1999).
- [243] M. Koucký, “A brief introduction to kolmogorov complexity”, MÚ AV ČR, Praha, 4 (2006).
- [244] M. Gell-Mann and S. Lloyd, “Information measures, effective complexity, and total information”, *Complexity* **2**, 44–52 (1996).
- [245] M. Gell-Mann and S. Lloyd, “Effective complexity”, in *Murray Gell-Mann: Selected Papers* (World Scientific, 2010), pp. 391–402.
- [246] A. Lempel and J. Ziv, “On the complexity of finite sequences”, *IEEE Transactions on information theory* **22**, 75–81 (1976).
- [247] C. H. Bennett, “On the nature and origin of complexity in discrete, homogeneous, locally-interacting systems”, *Foundations of physics* **16**, 585–592 (1986).
- [248] P. Grassberger, “Problems in quantifying self-generated complexity”, *Helvetica Physica Acta* **62**, 489–511 (1989).
- [249] R. Wackerbauer, A. Witt, H. Atmanspacher, J. Kurths, and H. Scheingraber, “A comparative classification of complexity measures”, *Chaos, Solitons & Fractals* **4**, 133–173 (1994).
- [250] H. Poincaré, *New methods of celestial mechanics*, Vol. 13 (Springer Science & Business Media, 1992).
- [251] C. Skokos, “The Lyapunov characteristic exponents and their computation”, in *Dynamics of Small Solar System Bodies and Exoplanets* (Springer, 2010), pp. 63–135.
- [252] O. Perron, “Die stabilitätsfrage bei differentialgleichungen”, *Mathematische Zeitschrift* **32**, 703–728 (1930).
- [253] P. Grassberger and I. Procaccia, “Measuring the strangeness of strange attractors”, *Physica D: Nonlinear Phenomena* **9**, 189–208 (1983).
- [254] F. Takens, “Detecting strange attractors in turbulence”, in *Dynamical systems and turbulence, Warwick 1980* (Springer, 1981), pp. 366–381.

- [255] G. P. DeCoster and D. W. Mitchell, “The efficacy of the correlation dimension technique in detecting determinism in small samples”, *Journal of Statistical Computation and Simulation* **39**, 221–229 (1991).
- [256] N. B. Abraham, A. M. Albano, A. Passamante, and P. E. Rapp, *Measures of complexity and chaos*, Vol. 208 (Springer Science & Business Media, 2013).
- [257] C. E. Shannon, “A mathematical theory of communication”, *Bell system technical journal* **27**, 379–423 (1948).
- [258] D. Feldman, “A Brief Introduction to: Information Theory,...”, (2002).
- [259] A. Rényi et al., “On measures of entropy and information”, in *Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability, Volume 1: Contributions to the Theory of Statistics* (The Regents of the University of California, 1961).
- [260] E. Beadle, J. Schroeder, B. Moran, and S. Suvorova, “An overview of Renyi Entropy and some potential applications”, in *2008 42nd Asilomar Conference on Signals, Systems and Computers* (IEEE, 2008), pp. 1698–1704.
- [261] S. Kullback and R. A. Leibler, “On information and sufficiency”, *The annals of mathematical statistics* **22**, 79–86 (1951).
- [262] P. L. Williams and R. D. Beer, “Generalized measures of information transfer”, *arXiv preprint arXiv:1102.1507* (2011).
- [263] G. Pica, E. Piasini, D. Chicharro, and S. Panzeri, “Invariant components of synergy, redundancy, and unique information among three variables”, *Entropy* **19**, 451 (2017).
- [264] D. Chicharro and S. Panzeri, “Synergy and redundancy in dual decompositions of mutual information gain and information loss”, *Entropy* **19**, 71 (2017).
- [265] M. Wibral, V. Priesemann, J. W. Kay, J. T. Lizier, and W. A. Phillips, “Partial information decomposition as a unified approach to the specification of neural goal functions”, *Brain and cognition* **112**, 25–38 (2017).
- [266] F. Heylighen, “The growth of structural and functional complexity during evolution”, *The evolution of complexity*, 17–44 (1999).
- [267] M. Efatmaneshnik and M. J. Ryan, “Fundamentals of System Complexity Measures for Systems Design”, in *INCOSE International Symposium*, Vol. 25, 1 (Wiley Online Library, 2015), pp. 876–890.
- [268] M. Efatmaneshnik and M. J. Ryan, “A general framework for measuring system complexity”, *Complexity* **21**, 533–546 (2016).
- [269] D. P. Feldman and J. P. Crutchfield, “Measures of statistical complexity: Why?”, *Physics Letters A* **238**, 244–252 (1998).
- [270] B. Edmonds, “What is Complexity?-The philosophy of complexity per se with application to some examples in evolution”, in *The evolution of complexity* (Kluwer, Dordrecht, 1995).
- [271] M. Gosak, A. Stožer, R. Markovič, J. Dolenšek, M. Marhl, M. S. Rupnik, and M. Perc, “The relationship between node degree and dissipation rate in networks of diffusively coupled oscillators and its significance for pancreatic beta cells”, *Chaos* **25** (2015).
- [272] R. G. Bettinardi, G. Deco, V. M. Karlaftis, T. J. Van Hartevelt, H. M. Fernandes, Z. Kourtzi, M. L. Kringelbach, and G. Zamora-López, “How structure sculpts function: Unveiling the contribution of anatomical connectivity to the brain’s spontaneous correlation structure”, *Chaos* **27**, 047409 (2017).

- [273] M. Gosak, A. Stožer, R. Markovič, J. Dolensek, M. Marhl, M. Slak Rupnik, and M. Perc, “The relationship between node degree and dissipation rate in networks of diffusively coupled oscillators and its significance for pancreatic beta cells”, *Chaos: An Interdisciplinary Journal of Nonlinear Science* **25**, 073115 (2015).
- [274] M. Schröder, M. Mannattil, D. Dutta, S. Chakraborty, and M. Timme, “Transient Uncoupling Induces Synchronization”,
- [275] L. M. Pecora, T. L. Carroll, G. A. Johnson, D. J. Mar, J. F. Heagy, L. M. Pecora, T. L. Carroll, G. A. Johnson, and D. J. Mar, “Fundamentals of synchronization in chaotic systems , concepts , and applications and applications”, **520**, 520–543 (2012).
- [276] M. S. Baptista, J. X. de Carvalho, and M. S. Hussein, “Finding quasi-optimal network topologies for information transmission in active networks”, *PLoS ONE* **3** (2008).
- [277] K. Rajan, L. F. Abbott, and H. Sompolinsky, “Stimulus-dependent suppression of chaos in recurrent neural networks”,
- [278] C. Fu, W. Lin, L. Huang, and X. Wang, “Synchronization transition in networked chaotic oscillators: The viewpoint from partial synchronization”, *Phys. Rev. E* **89**, 052908 (2014).
- [279] M. Schröder, M. Mannattil, D. Dutta, S. Chakraborty, and M. Timme, “Transient Uncoupling Induces Synchronization”, *Phys. Rev. Lett.* **115**, 054101 (2015).
- [280] G. Saxena, A. Prasad, R. Ramaswamy, and D. K. Campbell, “Amplitude death: The emergence of stationarity in coupled nonlinear systems”, *Phys. Rep.* **521**, 205–228 (2012).
- [281] K. Kaneko, “Clustering, coding, switching, hierarchical ordering, and control in a network of chaotic elements”, *Physica D: Nonlinear Phenomena* **41**, 137–172 (1990).
- [282] J Bragard, G Vidal, H Mancini, C Mendoza, and S Boccaletti, “Chaos suppression through asymmetric coupling”, *Chaos* **17** (2007).
- [283] A. N. Pisarchik, I. Bashkirtseva, and L. Ryashko, “Chaos can imply periodicity in coupled oscillators”, *EPL (Europhysics Letters)* **117**, 40005 (2017).
- [284] A.-L. Cheng and Y.-Y. Chen, “Analytical study of funnel type Rössler attractor”, *Chaos: An Interdisciplinary Journal of Nonlinear Science* **27**, 073117 (2017).
- [285] A. Schnurr, “An ordinal pattern approach to detect and to model leverage effects and dependence structures between financial time series”, *Stat. Papers* **55**, 919–931 (2014).
- [286] S. Berger, G. Schneider, E. Kochs, and D. Jordan, “Permutation Entropy: Too Complex a Measure for EEG Time Series?”, *Entropy* **19**, 692 (2017).
- [287] J. M. Amigó, K. Keller, and V. A. Unakafova, “Ordinal symbolic analysis and its application to biomedical recordings.”, *Phil. Trans. R. Soc. A* **373**, 20140091 (2018).
- [288] G. Zamora-López, Y. Chen, G. Deco, M. L. Kringelbach, and C. Zhou, “Functional complexity emerging from anatomical constraints in the brain: the significance of network modularity and rich-clubs”, *Sci. Rep.* **6**, 38424 (2016).

- [289] M. Pedersen, A. Omidvarnia, J. M. Walz, A. Zalesky, and G. D. Jackson, “Spontaneous brain network activity: Analysis of its temporal complexity”, *Network Neuroscience* **1**, 100 (2016).
- [290] M. Zhao, C. Zhou, Y. Chen, B. Hu, and B.-H. Wang, “Complexity versus modularity and heterogeneity in oscillatory networks: Combining segregation and integration in neural systems”, *Phys. Rev. E* **82**, 046225 (2010).
- [291] A. Politi, “Quantifying the Dynamical Complexity of Chaotic Time Series”, *Phys. Rev. Lett.* **118**, 144101 (2017).
- [292] A. Avena-Koenigsberger, B. Misic, and O. Sporns, “Communication dynamics in complex brain networks”, *Nature Reviews Neuroscience* **19**, 17–33 (2017).
- [293] M. Wiedermann, J. F. Donges, J. Kurths, and R. V. Donner, “Mapping and discrimination of networks in the complexity-entropy plane”, *Phys. Rev. E* **96**, 042304 (2017).
- [294] J. Diaz, D. Mateos, and C. Boyallian, “Complexity-Entropy Maps as a Tool for the Characterization of the Clinical Electrophysiological Evolution of Patients under Pharmacological Treatment with Psychotropic Drugs”, *Entropy* **19**, 540 (2017).
- [295] C. Masoller, Y. Hong, S. Ayad, F. Gustave, S. Barland, A. J. Pons, S. Gómez, and A. Arenas, “Quantifying sudden changes in dynamical systems using symbolic networks”, *New J. Phys.* **17**, 023068 (2015).
- [296] D. Papo, M. Zanin, J. A. Pineda-Pardo, S. Boccaletti, J. M. Buldu, and J. M. Buldú, “Functional brain networks: great expectations, hard times and the big leap forward”, *Phil. Trans. R. Soc. B* **369**, 20130525–20130525 (2014).
- [297] F. Montani, E. B. Deleglise, and O. A. Rosso, “Efficiency characterization of a large neuronal network: A causal information approach”, *Physica A: Statistical Mechanics and its Applications* **401**, 58–70 (2014).
- [298] T. Watanabe, S. Hirose, H. Wada, Y. Imai, T. Machida, I. Shirouzu, S. Konishi, Y. Miyashita, and N. Masuda, “A pairwise maximum entropy model accurately describes resting-state human brain networks”, *Nature Communications* **4**, 1370 (2013).
- [299] A. C. Yang and S.-J. Tsai, “Is mental illness complex? From behavior to brain”, *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **45**, 253–257 (2013).
- [300] Y. Jia, H. Gu, and Q. Luo, “Sample entropy reveals an age-related reduction in the complexity of dynamic brain”, *Scientific Reports* **7**, 7990 (2017).
- [301] E. Shumbayawonda, A. Fernández, M. Hughes, and D. Abásolo, “Permutation Entropy for the Characterisation of Brain Activity Recorded with Magnetoencephalograms in Healthy Ageing”, *Entropy* **19**, 141 (2017).
- [302] M. Pedersen, A. Omidvarnia, J. M. Walz, A. Zalesky, and G. D. Jackson, “Spontaneous brain network activity: Analysis of its temporal complexity”, *Network Neuroscience* **1**, 100–115 (2017).
- [303] G. Deco, T. J. Van Hartevelt, H. M. Fernandes, A. Stevner, and M. L. Kringelbach, “The most relevant human brain regions for functional connectivity: Evidence for a dynamical workspace of binding nodes from whole-brain computational modelling”, *NeuroImage* **146**, 197–210 (2017).
- [304] D. M. Mateos, R. Guevara Erra, R. Wennberg, and J. L. Perez Velazquez, “Measures of entropy and complexity in altered states of consciousness”, *Cognitive Neurodynamics* **12**, 73–84 (2018).

- [305] S. A. Nastase, V. Iacovella, B. Davis, and U. Hasson, “Connectivity in the human brain dissociates entropy and complexity of auditory inputs”, *NeuroImage* **108**, 292–300 (2015).
- [306] Z. Wang, Y. Li, A. R. Childress, and J. A. Detre, “Brain Entropy Mapping Using fMRI”, *PLoS ONE* **9**, edited by S. Hayasaka, e89948 (2014).
- [307] M. Bola and B. A. Sabel, “Dynamic reorganization of brain functional networks during cognition”, *NeuroImage* **114**, 398–413 (2015).
- [308] M. Zanin and D. Papo, “Characterizing Motif Dynamics of Electric Brain Activity Using Symbolic Analysis”, *Entropy* **16**, 5654–5667 (2014).
- [309] F. Zubler, H. Gast, E. Abela, C. Rummel, M. Hauf, R. Wiest, C. Pollo, and K. Schindler, “Detecting Functional Hubs of Ictogenic Networks”, *Brain Topography* **28**, 305–317 (2015).
- [310] A. Aragonese, S. Perrone, T. Sorrentino, M. C. Torrent, and C. Masoller, “Unveiling the complex organization of recurrent patterns in spiking dynamical systems”, *Sci. Rep.* **4**, 4696 (2015).
- [311] M. McCullough, M. Small, T. Stemler, and H. H.-C. Iu, “Time lagged ordinal partition networks for capturing dynamics of continuous dynamical systems”, *Chaos: An Interdisciplinary Journal of Nonlinear Science* **25**, 053101 (2015).
- [312] M. Zanin, L. Zunino, O. A. Rosso, and D. Papo, “Permutation entropy and its main biomedical and econophysics applications: A review”, *Entropy* **14**, 1553–1577 (2012).
- [313] J. H. Martínez Huartos, “Analysing Brain Dynamics by Means of Networks Science”, 183 (2015).
- [314] O. A. Rosso, L. C. Carpi, P. M. Saco, M. Gómez Ravetti, A. Plastino, and H. A. Larrondo, “Causality and the entropy-complexity plane: Robustness and missing ordinal patterns”, *Physica A* **391**, 42–55 (2012).
- [315] H. Liang and H. Wang, “Structure-Function Network Mapping and Its Assessment via Persistent Homology”, *PLoS Computational Biology* **13**, 1–19 (2017).
- [316] D. Bussandri, L. G. Linck, R. Miguel, and P. Lamberti, “Estadística No Extensiva Para El Analisis De Secuencias Nonextensive Generalization of the Jensen Shannon Divergence for Sequence Annalysis”, **24**, 113–118 (2012).
- [317] A. M. Kowalski, M. T. Martín, A. Plastino, O. A. Rosso, and M. Casas, “Distances in probability space and the statistical complexity setup”, *Entropy* **13**, 1055–1075 (2011).
- [318] B. Corominas-Murtra, J. Goñi, R. V. Solé, and C. Rodríguez-Caso, “On the Origins of Hierarchy in Complex Networks”, *PNAS* **110**, 13316 (2013).
- [319] M. P. Van Den Heuvel and O. Sporns, “Network hubs in the human brain”, *Trends Cogn. Sci.* **17**, 683–696 (2013).
- [320] P. S. Skardal, D. Taylor, and J. Sun, “Optimal synchronization of complex networks”, *Phys. Rev. Lett.* **113**, 144101 (2014).
- [321] S. Boccaletti, C. Grebogi, Y.-C. Lai, H. Mancini, and D. Maza, “The control of chaos: theory and applications”, *Phys. Rep.* **329**, 103–197 (2000).
- [322] M. Barreiro, A. C. Marti, and C. Masoller, “Inferring long memory processes in the climate network via ordinal pattern analysis”, *Chaos* **21**, 013101 (2011).
- [323] R. Albert and A.-L. Barabási, “Statistical mechanics of complex networks”, *Rev. Mod. Phys.* **74**, 47 (2002).

- [324] R. Sevilla-Escoboza, R. Gutiérrez, G. Huerta-Cuellar, S. Boccaletti, J. Gómez-Gardeñes, A. Arenas, and J. M. Buldú, “Enhancing the stability of the synchronization of multivariable coupled oscillators”, *Phys. Rev. E* **92**, 032804 (2015).
- [325] R. Sevilla-Escoboza, I. Sendiña Nadal, I. Leyva, R. Gutiérrez, J. M. Buldú, and S. Boccaletti, “Inter-layer synchronization in multiplex networks of identical layers”, *Chaos* **26**, 065304 (2016).
- [326] I. Leyva, R. Sevilla-Escoboza, I. Sendiña Nadal, R. Gutiérrez, J. Buldú, and S. Boccaletti, “Inter-layer synchronization in non-identical multi-layer networks”, *Sci. Rep.* **7**, 45475 (2017).
- [327] I. Leyva, I. Sendiña-Nadal, R. Sevilla-Escoboza, V. P. Vera-Avila, P. Chholak, and S. Boccaletti, “Relay synchronization in multiplex networks”, *Sci. Rep.* **8**, 8629 (2018).
- [328] B. Sancristóbal, R. Vicente, J. M. Sancho, and J. García-Ojalvo, “Emergent bimodal firing patterns implement different encoding strategies during gamma-band oscillations.”, *Front. Comput. Neurosci.* **7**, 18 (2013).
- [329] A. Navas, J. A. Villacorta-Atienza, I. Leyva, J. A. Almendral, I. Sendiña Nadal, and S. Boccaletti, “Effective centrality and explosive synchronization in complex networks”, *Phys. Rev. E* **92**, 062820 (2015).
- [330] M. G. Rosenblum and A. S. Pikovsky, “Controlling Synchronization in an Ensemble of Globally Coupled Oscillators”, *Phys. Rev. Lett.* **92**, 114102 (2004).
- [331] Y. B. Pesin, *Sov. Math. Dokl.* **17** (1976).
- [332] R. Sevilla-Escoboza and J. M. Buldú, “Synchronization of networks of chaotic oscillators: Structural and dynamical datasets”, *Data in Brief* **7**, 1185–1189 (2016).
- [333] T. L. Carroll, “A simple circuit for demonstrating regular and synchronized chaos”, *American Journal of Physics* **63**, 377–379 (1995).
- [334] E. V. Appleton, “The automatic synchronization of triode oscillators”, *Proc. Camb. Phil. Soc.* **21** (1922).
- [335] B. van der Pol, “A theory of the amplitude of free and forced triode vibrations”, *Radio Review (later Wireless World)* **1**, 701–710 (1920).
- [336] W. Maass, “Networks of spiking neurons: the third generation of neural network models”, *Neural networks* **10**, 1659–1671 (1997).
- [337] S. Ghosh-Dastidar and H. Adeli, “Third generation neural networks: Spiking neural networks”, in *Advances in Computational Intelligence* (Springer, 2009), pp. 167–178.
- [338] S. Ghosh-Dastidar and H. Adeli, “Spiking neural networks”, *International journal of neural systems* **19**, 295–308 (2009).
- [339] S. M. Bohte and J. N. Kok, “Applications of spiking neural networks”, *Information Processing Letters* **6**, 519–520 (2005).
- [340] F. Ponulak and A. Kasinski, “Introduction to spiking neural networks: Information processing, learning and applications.”, *Acta neurobiologiae experimentalis* **71**, 409–433 (2011).
- [341] D. Sterratt, B. Graham, A. Gillies, and D. Willshaw, *Principles of computational modelling in neuroscience* (Cambridge University Press, 2011).
- [342] X.-F. Jiang, “An effective decision support system based on neural networks and its application”, *International Journal of Advancements in Computing Technology* **5** (2013).

- [343] X. Wei, “Robot path planning based on simulated annealing and artificial neural networks”, *Res. J. Appl. Sci. Eng. Technol* **6**, 149–155 (2013).
- [344] R. FitzHugh, “Impulses and physiological states in theoretical models of nerve membrane”, *Biophysical journal* **1**, 445–466 (1961).
- [345] M. Burrows, *The neurobiology of an insect brain* (Oxford University Press on Demand, 1996).
- [346] S Anava, Y Saad, and A Ayali, “The role of gap junction proteins in the development of neural network functional topology”, *Insect molecular biology* **22**, 457–472 (2013).
- [347] G. Boyan and B. Niederleitner, “Patterns of dye coupling involving serotonergic neurons provide insights into the cellular organization of a central complex lineage of the embryonic grasshopper *Schistocerca gregaria*”, *Development genes and evolution* **220**, 297–313 (2011).
- [348] D. de Santos-Sierra, I. Sendiña-Nadal, I. Leyva, J. A. Almendral, S. Anava, A. Ayali, D. Papo, and S. Boccaletti, “Emergence of small-world anatomical networks in self-organizing clustered neuronal cultures”, *PloS one* **9**, e55828 (2014).
- [349] D. de Santos-Sierra, I. Sendiña-Nadal, I. Leyva, J. A. Almendral, A. Ayali, S. Anava, C. Sánchez-Ávila, and S. Boccaletti, “Graph-based unsupervised segmentation algorithm for cultured neuronal networks’ structure characterization and modeling”, *Cytometry Part A* **87**, 513–523 (2015).
- [350] W. S. McCulloch and W. Pitts, “A logical calculus of the ideas immanent in nervous activity”, *The bulletin of mathematical biophysics* **5**, 115–133 (1943).
- [351] E. B. Falk, L. W. Hyde, C. Mitchell, J. Faul, R. Gonzalez, M. M. Heitzeg, D. P. Keating, K. M. Langa, M. E. Martz, J. Maslowsky, et al., “What is a representative brain? Neuroscience meets population science”, *Proceedings of the National Academy of Sciences* **110**, 17615–17622 (2013).
- [352] A. Borst and T. Euler, “Seeing things in motion: models, circuits, and mechanisms”, *Neuron* **71**, 974–994 (2011).
- [353] M. Barthélemy, “Spatial networks”, *Physics Reports* **499**, 1–101 (2011).
- [354] T. L. Carroll, “A simple circuit for demonstrating regular and synchronized chaos”, *American Journal of Physics* **63**, 377–379 (1995).
- [355] J. Milnor, “On the concept of attractor”, in *The theory of chaotic attractors* (Springer, 1985), pp. 243–264.
- [356] R. Pastor-Satorras, C. Castellano, P. Van Mieghem, and A. Vespignani, “Epidemic processes in complex networks”, *Rev. Mod. Phys.* **87**, 925–979 (2015).
- [357] A. V. Proskurnikov and R. Tempo, “A tutorial on modeling and analysis of dynamic social networks. Part I”, *Annual Reviews in Control* **43**, 65–79 (2017).
- [358] T. Nishikawa and A. E. Motter, “Comparative analysis of existing models for power-grid synchronization”, *New Journal of Physics* **17**, 015012 (2015).
- [359] C. Dugas, Y. Bengio, F. Bélisle, C. Nadeau, and R. Garcia, “Incorporating second-order functional knowledge for better option pricing”, in *Advances in neural information processing systems* (2001), pp. 472–478.
- [360] F. Rosenblatt, “The perceptron: a probabilistic model for information storage and organization in the brain.”, *Psychological review* **65**, 386 (1958).

- [361] D. S. Callaway, J. E. Hopcroft, J. M. Kleinberg, M. E. Newman, and S. H. Strogatz, “Are randomly grown graphs really random?”, *Physical Review E* **64**, 041902 (2001).
- [362] M. Barahona and L. M. Pecora, “Synchronization in small-world systems”, *Physical review letters* **89**, 054101 (2002).
- [363] V. N. Belykh, I. V. Belykh, and M. Hasler, “Connection graph stability method for synchronized coupled chaotic systems”, *Physica D: nonlinear phenomena* **195**, 159–187 (2004).
- [364] M. Faggian, F. Ginelli, F. Rosas, and Z. Levnajić, “Synchronization in time-varying random networks with vanishing connectivity”, *Scientific reports* **9**, 10207 (2019).
- [365] G. Yan, Z.-Q. Fu, J. Ren, and W.-X. Wang, “Collective synchronization induced by epidemic dynamics on complex networks with communities”, *Physical Review E* **75**, 016108 (2007).
- [366] S. Y. Kim, E. Pareda-Delgado, and S. E. Alger, “Enhancing memory consolidation through slow oscillation and spindle synchronization”, *Journal of Neuroscience* **37**, 11517–11519 (2017).
- [367] J. H. Martínez Huartos, “Analysing Brain Dynamics by Means of Networks Science”, PhD thesis (Technical University of Madrid, 2015).
- [368] R. M. May, “Simple mathematical models with very complicated dynamics”, *Nature* **261**, 459–467 (1976).
- [369] L. Minati, H. Ito, A. Perinelli, L. Ricci, L. Faes, N. Yoshimura, Y. Koike, and M. Frasca, “Connectivity Influences on Nonlinear Dynamics in Weakly-Synchronized Networks: Insights From Rössler Systems, Electronic Chaotic Oscillators, Model and Biological Neurons”, *IEEE Access* **7**, 174793–174821 (2019).