Chapter 1

Introduction

The book is organized in three main parts. *Part I* deals with *networks at the level of the cell*, the basic unit of any living organism. In the cell, all kinds of structural and functional processes are ruled by the intricate interaction of genes, proteins and other molecules. It is then easy to understand why the complex network approach has become a common and useful paradigm to investigate, model and understand cellular processes. The first part of the book covers various kinds of cellular networks such as: gene networks, protein networks, metabolic networks, protein-folding networks, as well as signaling networks.

The first Chapter, by *Brilli and Lió*, is a general overview on the structure and function of regulatory networks, gene coexpression networks and protein-protein interaction networks. Here, the reader will find a review of the main properties of a network, and the basic measures to characterize its topology, such as degree distributions, average shortest path lengths, clustering coefficient, assortativity and network motifs.

The first step to understand the behavior of gene regulatory systems, is to study the dynamics of small gene networks. Historically, one of the first examples of artificial gene circuits to be investigated was the repressilator, a synthetic network of three genes whose products inhibit the transcription of each other cyclically. In the second Chapter, *Ullner et al.* show how to describe the dynamics of coupled small synthetic gene networks through a set of ordinary differential equations. In particular, two different types of genetic oscillators, the repressilator and a relaxator oscillator, with two different types of coupling (namely a phase-attractive and a phase-repulsive coupling) are considered. This is enough to produce rich dynamical scenarios that include multistability, oscillation death, and quantized cycling.

The drawback of the differential equation-based approach is the necessity to know the kinetic details of molecular and cellular interactions, an information that is rarely available. There is increasing evidence, however, that the input-output curves of many regulatory relationships are strongly sigmoidal and can be approximated by step functions. In addition to this, regulatory networks often maintain their function even when faced with fluctuations in components and reaction rates. This explains the diffusion of coarse-grained methods, such as Boolean models. In a Boolean network the state of each node can assume one of two possible values, and the interaction between nodes is ruled by a set of Boolean functions. The Chapter by *Thakar and Albert* introduces the reader to Boolean modeling methods, showing how these can be used to infer causal relationships from expression data, and also to analyze the dynamics of systems whose network of interactions is known.

The global dynamics of gene regulatory networks must be robust in order to guarantee their stability under a broad range of external conditions. The effect of noise on the dynamics of Boolean networks is investigated in the Chapter by *Dìaz-Guilera and Alvarez-Buylla*. In this case, the noise simulates errors and external stimuli affecting the transmission of signals in real living processes. The authors focus on an experimentally grounded gene regulatory network that describes the interactions required for primordial cell fate determination during early stages of flower development. This is a very instructive example, since it shows how the noise maximizes the capacity of the system to explore the state space, while at the same time the network is able to retain the observed steady states under different noisy regimes.

The Chapter by *Bongini and Casetti* is about protein folding, one of the most fundamental and challenging open questions in molecular biology. The core of the protein folding is to understand how the information contained in a sequence of aminoacids is translated into the three-dimensional native structure of a protein. And to clarify why all the natural selected sequences of aminoacids fold to a uniquely determined native state, while a generic polypeptide does not. With these questions in mind, the authors describe two different strategies to analyze the high-dimensional energy landscape of model proteins. The first approach is essentially topological in character, and amounts to define a network whose nodes are the minima of the potential energy and whose edges are the saddles connecting them. The second approach is based on the definition of global geometric quantities that characterize the folding landscape as a whole. The reader will lear that both methods can give interesting information on the differences between the landscapes of protein-like systems and those of generic polymers.

A simplified representation of the potential energy function of a protein near equilibrium can be obtained, at low computational cost, by using the so-called elastic network models (ENMs). In ENMs, the aminoacids are the nodes of the network, represented as point particles in three dimensions (3D), while the edges of the network are springs joining the nodes, representing harmonic restraints on displacements from the equilibrium structure. The attractive feature of ENMs is that they provide an intuitive and quantitative description of the behavior near equilibrium. Furthermore, the few parameters used in ENMs can be easily adjusted, giving uncommon adaptability to the method. There are, however, some limitations. Although ENMs robustly predict collective global motions, they do not provide reliable descriptions of local motions. Also, the harmonic approximation requires a potential minimum, limiting the utility of ENMs for modeling non-equilibrium dynamics. In the Chapter by *Lezon et al.* the theory behind the ENM and some of its extensions are reviewed. Finally, some recent applications, mainly focusing on two groups of proteins, membrane proteins and viruses, are presented. Those are among the most ubiquitous classes of proteins, and are difficult to examine by all-atom simulations due to their large sizes.

In the final Chapter of Part I, *Palumbo et al.* focus on metabolic networks. The Chapter try to answer the question: "how far can we go by knowing only the wiring diagram of metabolic networks?". For such a reason the authors compare purely topological information with physiological and kinetic information, highlighting the particular relations holding between the static and the dynamic approach in the biochemical regulation of cells.

Neuroscience is another field of biology and medicine where the complex networks approach has found wide applications. *Brain networks* ar the subject of *Part II* of the book. On one hand, scientists are indeed interested in disclosing the main structure at the basis of the functioning of the human brain network, in both modeling and analysis of high resolution data. On the other hand, laboratory experiments on cultured neural networks make today possible to closely investigate the basic response in the network's dynamics and organization to controlled external stimulations. This part of the book offers a review of the current state of the art on both these approaches.

In the first Chapter of Part II, *Sporns* reviews what is currently known on the human brain connectivity structure, and on how the latter plays an essential role in some functional brain dynamics. The Chapter reports a series of recent results, based on which scientists are now able to furnish a first description of the architecture of the human brain in terms of a network of small-world type, including the presence of modules and hub regions that shape the brain endogenous dynamics as well as its responses to external stimuli.

The brain network analysis from high resolution data is the subject, instead, of the Chapter by *De Vico Fallani and Babiloni*, in which it is pointed out that brain networks have no precise anatomical support, but they can be represented as functional networks, which could change in topology and properties according to a specific subject's behavior or task. The Chapter highlights how some of the peculiar features of these functional networks can be estimated from high-resolution EEG signals.

The Chapter by *Arenas et al.* reviews a recent approach to unravel the wiring connectivity in the nematode Caenorhabditis Elegans, which in biology is nowadays considered the benchmark to understand the mechanisms underlying a whole animal's behavior, at the molecular and cellular levels. The Chapter discusses the validity of an optimization approach with the actual neuronal layout data, and remarks how the current approach to optimization of neuronal layouts is still far from being conclusive.

The Chapter by *Raichman et al.* reviews extensively how complex patterns of activity and morphological memory are expressed in cultured neural networks cultivated on micro-electrode arrays. These cultures, indeed, are widely used as a tool for laboratory controlled non invasive investigations of network neuronal systems' organization and dynamics, allowing for chemical and electrical manipulations. The series of experiments described in this Chapter allows to look at cultured neuronal networks as complex dynamical biophysical systems that have some forms of intrinsic memory, information coding and self-regulation, and that further show repeating activity motifs and long term adaptation processes to changing environment, in response to different external stimuli, such as morphology constrains and thermal stimulations.

The second part of the book ends with the Chapter by *Memmesheimer and Timme*, presenting the state of the art on how patterns of precisely timed and synchronized spikes emerge in neural circuits. In this Chapter the reader will find an overview of a series of recent results on synchrony and spatio-temporal patterns in recurrent networks. Two classes of hypothesis that might be at the basis of the emergence of such precisely timed spikes are discussed: the possibility that some feed-forward anatomical structures are embedded in the cortical circuit supporting the propagation of synchronous spiking activity, and the alternative possibility that recurrent networks may collectively organize synchronous spikes without the need of a specific feed-forward anatomy.

Part III of the book is devoted to *networks at the individual and population levels*. The first Chapter of this part, by *Stouffer et al.* addresses ecological systems as made up of highly interconnected and complex networks of interactions between species, and not as independent patches. Although food webs, mutualistic networks and spatial ones are well described by their structural properties, nowadays little is known about these networks' dynamics. Given the importance of understanding as many aspects as possible of the complex interplay between the networks of interacting species with the spatial context in which they live, further developments along the lines exposed in this Chapter will prove crucial in the future.

The Chapter by *Bagnoli* discusses evolutionary models in simple biosystems. The Chapter deals with theoretical approaches to self-organization in evolutionary population dynamics, including evolution on a fitness landscape, dynamic ecosystems, and game theoretical models. Noticeable, the Chapter put into evidence the role and the emergence of network structure in systems that range several orders of magnitude, from the elementary constituents to whole ecosystems, with the aim of showing how macro-evolutionary patterns may arise from a simplified individual-based dynamics.

The Chapter by *Pacheco et al* focuses on the evolution of cooperation in adaptive social networks. The tools used are those of evolutionary game dynamics, coupled to recent advances in network modeling. Specifically the authors discuss the problem of how cooperation arises in networks that are adaptive and dynamic in nature. They start from the observation that the structure of many modern networks of interactions are not stable in the long term and develop a two-player dilemmalike model, to account for the influence of a changing topology on the level of cooperation achieved by the system. The conclusions point out that such a modeling approach might be an important ingredient towards more realistic models of cultural dynamics.

The Chapter by *Frasca et al.* deals with models of collective behaviors in animal groups. The social complex organization of an animal group undergoes many shape and structural changes over time and space, and has been the subject of study from many years as a way to learn from natural systems how motion of different units can be coordinated. The Chapter address recent findings about both the structure and the dynamics of coordination models. The Chapter concludes with a discussion about the applications of the models treated and their usefulness in many contexts such as distributed sensing, search and rescue, environmental modeling and surveillance and what should be the minimum ingredients needed to design decentralized coordination and control strategies in engineering systems.

The last Chapter of the book, contributed by *T. Gross*, addresses one of the first problems in which the influence of the network topology was evidenced – the spreading of a disease. The author discusses the role of state-topology interplay in epidemics dynamics by working out a model in which not only the structure affects the way the epidemics spread but also the dynamics induce topological changes. In particular, the conceptual model introduced incorporates a mechanism of rewiring that depends on the dynamical states of the network nodes and produces an increase of the invasion threshold concurrent to a persistence threshold which is below the former. The author concludes the Chapter by discussing several aspects of the model analyzed and many open questions on the epidemiology of adaptive networks.