Chapter 2
Introduction to GRNs

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ABSTRACT

The post-genomic era shifted the main biological focus from 'single-gene' to 'genome-wide' approaches. High throughput data available from new technologies allowed to get inside main features of gene expression and its regulation and, at the same time, to discover a more complex level of organization. Analysis of this complexity demonstrated the existence of nonrandom and well-defined structures that determine a network of interactions. In the first part of the chapter, we present a functional introduction to mechanisms involved in genes expression regulation, an overview of network theory, and main technologies developed in recent years to analyze biological processes are discussed. In the second part, we review genes regulatory networks and their importance in system biology.

INTRODUCTION

In the last two decades, biologists have drastically changed their approach to the study of the cell. In the literature, several works describe functional and biochemical analysis focusing on a single gene (Menasche et al., 2003; Miles et al., 2005) or a protein family (Logan et al., 2004; Sasaki et al., 2005). This "single-gene" approach led to a comprehensive knowledge about how or where a single gene of interest works. Recently, some innovative technologies are generating a great amount of biological data and represent a fertile source of knowledge. The most significant of these techniques, described in the *Technology Background* section of this chapter, are DNA microarrays, serial analysis of gene expression (SAGE) and chromatin immunoprecipitation chips (ChIP-chip). The availability of high-throughput data on the role of biological molecules allows a more exhaustive analysis of biological processes, that is the main focus of system biology.

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The need for a tool to integrate high-throughput biological data attracted the attention of the scientific community to the network paradigm as one of the most powerful and versatile theory for the study of complex systems (Albert et al., 2002).

In particular, the network approach offers a theoretical picture that can be used to explain and analyze the structure of biological systems and their evolution. Many theoretical studies on networks have demonstrated their application to model metabolic networks (Fiehn et al., 2003), neuronal networks (Kullander, 2005), gene regulatory networks (GRNs) (Olson, 2006), and other biological networks (Hollenberg, 2007).

What are networks? Networks are simply sets of items, called nodes, joined by specific types of relationships called links.

At the level of gene regulation, the nodes represent genes, proteins, mRNA and biological molecules in general, depending on which molecular products are considered. The links represent molecular interactions such as protein-protein interactions (Vidal et al., 1996), protein-DNA interactions (Gao et al., 2008), gene co-expression (Ala et al., 2008) and others.

Many different kinds of gene networks can be obtained, depending on which particular biological target is considered. Transcriptional regulation is a complex process that involves a great amount of elements and network theory helps to construct a comprehensive view about this process. However, a precise and commonly accepted definition of Gene Regulatory Network (GRN) does not yet exist (Brazma et al., 2003; Dewey et al., 2002). Under this label, it is possible to define various complementary models describing regulatory processes and functional relationships. The most common models are Coexpression Networks (CNs) based on similar expression profiles, Transcription Factors Networks (TFNs) centred on transcription factors activity, Signal Transduction Networks (STNs) that explore gene-activities and causal-effect relationships among genes and proteins under different environmental conditions (as defined in Galperin, 2004; Martelli et al., 2006; Tran et al., 2007) and Genetic Interaction Networks (GINs) that define logical relationships between genes, as defined in (Beyer et al., 2007; Tong et al., 2004), by comparing observed phenotypes of wild-type and mutant individuals of a species. In this chapter, we will focus on CNs and TFNs.

Biological networks can be constructed in different ways: from differential equations (Climescu-Haulica et al., 2007) to statistical correlation integrated by other biological information, such as phylogenetic conservation or gene function (Stuart et al., 2003), to minimize false positives among the inferred interactions, from Bayesian (Mukerjee et al., 2008) to Boolean networks (Martin et al., 2007).

Although the widespread use of experimental data provides an opportunity to investigate GRNs from another point of view, some limitations exist: it is not possible to analyze all genes and evaluate every biological status, information about the variability of expression profiles is lost, and experimental noise decreases data quality.

Some global properties of abstract network models can be used to analyze GRNs: mapping a real network to an abstract model allows the application of statistical inference to detect specific network fetaures. GRNs often display characteristic network features such as short path lengths and high cluster coefficient, typical of highly connected graphs, as described in Barabasi et al. (2004). The degree distribution of a typical GRN is often scale-free and described by a power-law (Albert, 2005), but GRNs could also show small world networks features (Watts et al., 1998). At a smaller scale, GRNs display typical structures as highly connected nodes (hubs), communities and their organization into hierarchical modules (Ravasz et al., 2003).

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