Chapter 1

What are Gene Regulatory Networks?

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ABSTRACT

This book deals with algorithms for inferring and analyzing Gene Regulatory Networks using mainly gene expression data. What precisely are the Gene Regulatory Networks that are inferred by such algorithms from this type of data? There is still much confusion in the current literature and it is important to start a book about computational methods for Gene Regulatory Networks with a definition that is as unambiguous as possible. In this chapter, I provide a definition and try to clearly explain what Gene Regulatory Networks are in terms of the underlying biochemical processes. To do the latter in a formal way, I will use a linear approximation to the in general non-linear kinetics underlying interactions in biochemical systems and show how a biochemical system can be 'condensed' into the more compact description of Gene Regulatory Networks. Important differences between the defined Gene Regulatory Networks and other network models for gene regulation, such as Transcriptional Regulatory Networks and Co-Expression Networks, will be highlighted.

INTRODUCTION

Several terms have been used to indicate models of regulatory processes and functional relations between genes, such as Gene Regulatory Networks, Gene Networks, Gene Expression Networks, Co-Expression Networks, Genetic Regulatory Networks, Transcriptional Regulatory Networks and Genetic Interaction Networks. While often used as such in the literature, not all of the above terms are actually synonyms. I therefore will provide a precise definition of the 'Gene Regulatory Network' and point out the essen-

DOI: 10.4018/978-1-60566-685-3.ch001

tial differences with two other network models frequently used for gene regulation, i.e. Transcriptional Regulatory Networks and Co-Expression Networks.

Before a clear definition of Gene Regulatory Networks can be given, we first need to consider the abstract definition of a 'network', also formally called 'graph'. The mathematical theory of graphs is called graph theory (Bollobas, 1998; Erdös & Renyi, 1959), but recent advances in Complex Network Science go beyond graph theory alone and incorporate ideas from physics, sociology and biology (Barabasi & Oltvai, 2004; Dorogovtsev & Mendes, 2003; Newman, 2003; Pieroni et al., 2008; Watts & Strogatz, 1998). Three main types of graphs are essential in the context of Gene Regulatory Networks:

An undirected graph G is an ordered pair G: = (V, U) that is subject to the following conditions:

V is a set, whose elements are called vertices or nodes (the later will be used in the remainder of the chapter) and U is a set of unordered pairs of distinct vertices, called undirected edges, links or lines ('undirected edges' will be used in the remainder of the chapter). For each edge uij = {vi, vj} the nodes vi and vj are said to be connected, linked or adjacent to each other. Undirected graphs can be effectively used to represent the existence of associations or functional relationships (edges) between entities (nodes).

A directed graph or digraph G is an ordered pair G: = (V, D) with V being a set of nodes and D a set of ordered pairs of vertices, called directed edges, arcs, or arrows ('directed edges' will be used in the remainder of the chapter). A directed edge dij = {vi, vj} is considered to be directed from node vi to vj; vj is called the head or target and vi is called the tail or source; vj is said to be a direct successor, or child, of vi, and vi is said to be a direct predecessor, or parent, of vj. If a directed path leads from vi to vj, then vi is said to be an ancestor of vj. Directed graphs can be effectively used to represent causal influences or communication between the nodes.

A mixed graph G is a graph in which some edges may be directed and some may be undirected. It is written as an ordered triple G:= (V, U, D) with V, U, and D defined as above. Directed and undirected graphs are special cases of such mixed graphs. These graphs can thus represent associations as well as causal influences between the nodes. As we will see, Gene Regulatory Networks can most completely be represented as mixed graphs.

GENE REGULATORY NETWORKS

I start out by giving a possible formal definition for Gene Regulatory Networks. The remainder of the chapter is entirely dedicated to provide a detailed explanation of this definition.

Definition – Gene Regulatory Network (GRN): a Gene Regulatory Network is a mixed graph G:= (V, U, D) over a set V of nodes, corresponding to gene-activities, with unordered pairs U, the undirected edges, and ordered pairs D, the directed edges. A directed edge dij from vi to vj is present iff a causal effect runs from node vi to vj and there exist no nodes or subsets of nodes in V that are intermediating the causal influence (it may be mediated by hidden variables, i.e. variables not in V). An undirected edge uij between nodes vi and vj is present iff gene-activities vi and vj are associated by other means than a direct causal influence, and there exist no nodes or subsets of nodes in V that explain that association (it is caused by a variable hidden to V).

What do the nodes in GRNs precisely represent? The nodes in GRNs are often said to correspond to 'genes'. More precisely, they rather correspond to 'gene-activities' ('gene expression levels' or 'RNA concentrations') as these are the dynamical and quantitative variables that are related by the algorithms discussed in this book. Of course 'gene-activity' could be included in the definition of 'gene'. Therefore, there will be no need to adapt the name 'Gene-activity Regulatory Networks'.

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