Chapter IV
Deterministic Modeling in Medicine

Elisabeth Maschke-Dutz
Max Planck Institute for Molecular Genetics, Germany

ABSTRACT

In this chapter basic mathematical methods for the deterministic kinetic modeling of biochemical systems are described. Mathematical analysis methods, the respective algorithms, and appropriate tools and resources, as well as established standards for data exchange, model representations and definitions are presented. The methods comprise time-course simulations, steady state search, parameter scanning, and metabolic control analysis among others. An application is demonstrated using a test case model that describes parts of the extrinsic apoptosis pathway and a small example network demonstrates an implementation of metabolic control analysis.

INTRODUCTION

We can observe the molecular background of complex disease processes with systems biology. Today, drug development plays a central role in the interdisciplinary area of systems biology. Scientists from various disciplines, such as biology, bioinformatics, medical research, chemistry, physics, computer science and mathematics, work together to analyze complex disease processes by studying molecular interaction networks. The aim is to understand and analyze the complex behavior of human diseases. Through this collaborative research we can obtain specific methods and results that can lead to new predictions and assumptions about the observed diseases and processes.

Metabolic pathways like the citric acid cycle and glycolysis, for example, are important processes that may be used to analyze the complex mechanism in living biological systems. The modeling of these pathways provides appropriate structures for observing the behavior of metabolic diseases, i.e. diabetes. Gene regulatory networks describe protein-DNA interactions or indirectly as the interaction

between DNA and DNA. Here, we can also examine the regulation of the activity of single genes and the behavior of single molecules, as well as observe the interaction and regulation between different genes and proteins in complex structures. The normal function of single genes is affected in several diseases. A lot of information is available about the functionality of single genes in different diseases and also the roles of mutations in these genes are comprehensively described (Weinberg 1994). Many project studies about this topic are currently underway, and we expect more interesting results in the future (Futreal *et al.* 2004). Multiprotein complexes are the result of numerous protein-protein interactions. These interactions are essential for physiological processes. In biological networks, diffusion and the molecular transport across cell membranes are also important physiological processes. In different compartments of the cell the function of a protein can change, because the functionality of a protein depends also on the existing targets in the appropriate compartments. For example the p53 protein acts in the nucleus as a transcription factor of apoptosis. The protein Mdm2 in turn can bind to p53 and initiates its ubiquitination and subsequent degradation in the cytoplasm. In the cytoplasm p53 can not act as a transcription factor and instead the degradation of p53 is initialized in this compartment. Signaling pathways play an important role in many diseases. For example the cell signaling mechanism regulates cell proliferation and cell differentiation. The main structures that are responsible for the progression of cancer are interferences in signaling pathways (Cui *et al.* 2007). The reasons for these inferences in turn are founded in mutated proteins.

Using mathematical models we can describe complex cellular processes. This chapter gives an overview of the possibilities available to analyze these molecular, cellular and physiological processes with mathematical modeling, and outlines how we can integrate experimental data. We demonstrate the utilization of the mathematical model analysis in two examples. Time-course simulation and parameter scanning are applied to a model for the extrinsic apoptosis pathways and metabolic control analysis is applied to a small sample network.

MATHEMATICAL MODELING

We can describe biological systems with Boolean models, stochastic models and deterministic models. Boolean networks are based on the Boolean logic (Kaufmann 1993) and can be used to describe gene regulatory interactions. There are two Boolean states: expressed and not expressed. The expression level of a gene is represented in one of the two binary states, ‘0’ and ‘1’. In 1977 Gillespie introduced the exact stochastic simulation algorithms called direct method and first reaction method (Gillespie 1977). The stochastic modeling process deals with discrete variables that are numbers of molecules. Up to now, the stochastic modeling methods are improved and extended (Gibson & Bruck 2000).This chapter will point out the deterministic, kinetic modeling of biochemical reaction networks. This kind of modeling uses continuous variables and allows the representation of the structure and behavior of the modeling system in a very detailed and arbitrarily complex way. The knowledge of complex diseases according to their molecular background, and the use of drugs and predictions resulting from the interpretation of experimental data, provides information about the constitution of the mathematical model. We can include this information into the model structure in analogous mathematical terms and equations. The introduced deterministic approach is based on a system of ordinary differential equations (ODE system).