

Chapter 21

Dynamic Links and Evolutionary History in Simulated Gene Regulatory Networks

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ABSTRACT

In this chapter, we describe the use of evolutionary methods for the in silico generation of artificial gene regulatory networks (GRNs). These usually serve as models for biological networks and can be used for enhancing analysis methods in biology. We clarify our motivation in adopting this strategy by showing the importance of detailed knowledge of all processes, especially the regulatory dynamics of interactions undertaken during gene expression. To illustrate how such a methodology works, two different approaches to the evolution of small-scale GRNs with specified functions, are briefly reviewed and discussed. Thereafter, we present an approach to evolve medium sized GRNs with the ability to produce stable multi-cellular growth. The computational method employed allows for a detailed analysis of the dynamics of the GRNs as well as their evolution. We have observed the emergence of negative feedback during the evolutionary process, and we suggest its implication to the mutational robustness of the regulatory network which is further supported by evidence observed in additional experiments.

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INTRODUCTION

In biology, organisms consist of large numbers of heterogeneous elements existing on many spatial scales that nonlinearly interact physically and chemically on various timescales. Such interactions are the result of natural selection, the outcome of evolutionary process as driven by genetic variation and environmental change. It is one of the aims of systems biology to understand the principles of these interactions holistically and thereby to clarify the relationship between the microscopic regulatory dynamics and the macroscopic phenotypic properties of organisms. Knowledge from evolutionary history alone is insufficient for this endeavor because on the one hand it is not available in sufficient detail, and on the other, we can only infer the dynamics from extant organisms. Consequently, our knowledge about evolutionary lineage with regard to the dynamic properties of organisms is principally incomplete. Computer simulations and especially simulations of the evolutionary development of organisms provide us with a powerful tool to address this problem. Although having the inherent drawback of substantial simplifications of the processes involved, computer simulations of development offer us the possibility to study the complete dynamics that evolve during the artificial phylogenetic and ontogenetic history of organisms. Furthermore, in addition to studying known biological systems and processes, we can also study possible alternatives that – at least to date – we do not see in nature, which has been nicely phrased as studying “life as it could be” (Forbes (2000)). Also the seemingly apparent drawback of simplification can actually help us to not get lost in too much biological detail and therefore allows us to see the broader “systems” picture more clearly.

Therefore, we should regard computer simulations as powerful tools to investigate facts that are not available from analysis of biological data alone. Of course, the connection between the computational model and the real biological system, i.e., the abstraction level of the model, needs to be taken into careful account when interpreting the results. For example, in a computational model of evolutionary development, it is possible to observe all dynamics that take place on a simulated GRN, and at the same time all simulated GRNs can be put into their evolutionary context. This is possible because the data of such an experiment is at the same time complete and limited with regard to its complexity, making it possible to perform a thorough analysis. However, these observations are coupled to the simulation environment and it will be very unlikely that the simulated processes will fully mirror those that evolved in nature. What can be found however, are principles, for example, the role of feedback. Possible reasons for the emergence of such principles can then be carefully deduced from the computational models.

This chapter will review approaches to the simulation of the evolution of GRNs for systems biology, and will present a method for the simulation of evolutionary multicellular development. We will show how models are chosen in a task specific manner, such as evolving GRNs for certain behaviors like cellular clocks/oscillators. We then discuss the scientific value of these approaches.

The chapter is organized as follows: Following this introduction, we will briefly describe standard methods in biology used to collect data about GRNs from organisms and how knowledge from the data is extracted. We will then discuss the limitations of these approaches to biological research in general and thereby elucidate the underlying motivation in using computational models, emphasizing especially the expected benefits. After a review of different models used for simulated evolution of GRNs, we will describe a model of evolutionary development that we focus on in our own research, with an emphasis on the choice of abstraction level. An analysis made on evolutionary runs yielded from this model producing stable cell growth, is given as an example. The importance of understanding the features of evolved individuals in terms of both the dynamic structure of GRNs and their evolutionary history will be highlighted.

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