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Tutorial 3: Executable Models of Gene Regulatory Networks

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Summary

Systems biology studies complex interactions in biological systems, with the aim to understand better the entirety of processes that happen in such a system, as well as to grasp the emergent properties of such a system as a whole. This can for instance be at the level of metabolic or interaction networks, signal transduction, genetic regulatory networks, multi-cellular development, or social behaviour of insects. The last decade has seen a rapid development in the collaboration between biologists and computer scientists in the area of systems biology and bioinformatics. Formal modelling and analysis techniques that have been developed for distributed computer systems, are applicable to biological systems as well. Biological systems are built from separate components that communicate with each other and thus influence each other's behaviour. Notably, signal transduction within a cell consists of cascades of biochemical reactions, by which for instance genes are activated or down-regulated. The genes themselves produce the proteins that drive signal transduction, and cells can be connected in a multicellular organism, making this basically one large, complex distributed system.

Two different kinds of models for biological systems are operational versus denotational.
Operational models (such as Petri nets) are executable and mimic biological processes.
Denotational models (such as differential equations) express mathematical relationships between quantities and how they change over time. Operational models are generally at a higher abstraction level and easier to analyse. Moreover, operational models explain the mechanisms behind a biological system in a more intuitive fashion than a denotational model. Metaphorically one can ask the question whether molecules in a cell, or cells themselves, solve differential equations to decide what to do in a particular situation, or rather when they encounter one another follow simple sets of rules derived from their physical interactions.

Formal models can be an excellent way to store and share knowledge on biological systems, and to reason about such systems. Furthermore, in vivo experiments in the lab tend to take a long time, and are labour intensive. In comparison, in silicon experiments can take relatively little time and effort. And for instance genetic

perturbations can be difficult (or unethical) to perform in the lab, while they may require trivial adaptations of a formal model.

In this tutorial, we will give an introduction to what is phrased executable biology, and the role that formal methods in this context. We will focus on Petri nets, which constitute an excellent formalism for modelling biological systems, in particular gene regulatory networks. We will explain the basic formalism, the analysis method based on Monte Carlo simulations and on state space exploration. The framework will be explained on the basis of three different case studies. The first case study is vulval development of C. elegans, where the Petri net simulations turn out to be in line with in vitro experiments, and moreover new predictions can be made. Next we will explain how to use Petri nets to build the gene regulatory network that captures the hematopoiesis process in mice and how is possible to infer, check, and predict biological properties exploring the generated state space. Furthermore, we will show how we applied the same approach to derive insightful predictions on Yeast behavior during starvation. Moreover, we will present a proof-of-concepts tool used to design and analyze our models. Finally, we will discuss future perspectives, especially with regard to model checking analysis.

Structure
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1. Introduction on executable biology, and the role of formal methods
2. Introduction on Petri nets, and how they can be used for modeling biological systems
3. Monte Carlo model checking and simulation-based analysis of Petri net models (of biological systems)
4. C.elegans vulval development case study
5. Hematopoiesis case study
6. Demo of the new prototype tool to design Petri nets for biological systems
7. Yeast case study
8. Future perspectives