

Model checking in biology and health care

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Abstract

Model checking is a useful technique for analyzing models in biology and health care. Here we point out several research topics concerning the modeling of various networks in biology, and modeling of diagnostic and treatment protocols in health care.

1 Introduction

Many complex biological phenomena can be modeled as networks. Prominent examples within biological cells are metabolic networks, signaling networks, and gene regulatory networks. Understanding the quantitative and qualitative behavior of such networks is an important prerequisite for curing various diseases. Modeling these networks within a framework that allows model checking is an attractive way of gaining such understanding [Brim et al. 2013; David et al. 2015].

In Twente the contribution of computer science to this research has concentrated on the use of UPPAAL [UPPAAL website 2018]. UPPAAL is attractive as it is a mature tool allowing a compositional approach, and with a graphical interface that facilitates communication with non-experts in formal methods.

Kinase signaling networks have been modeled in the context of osteoarthritis [Scholma et al. 2013, 2014]. A tool called ANIMO has been created [ANIMO 2018] that makes use of UPPAAL and is intended to be used by molecular biologists. ANIMO has been successfully used to model realistically sized biological networks [Schivo et al. 2014; Schivo et al. 2016, 2013; Schivo et al. 2012; Scholma et al. 2014]. Below we list several research topics for the modeling and analysis of biological networks.

Another line of research is modeling protocols for diagnosis and treatment, and then using model checking for analysing these protocols for effectiveness, efficiency, and costs. In Twente such analysis has been performed using UPPAAL for prostate cancer [Degeling et al. 2017; Schivo et al. 2015] and tooth wear [Choudry 2018; van Rooijen 2018] (in collaboration with the Academic Centre for Dentistry Amsterdam). Below we list several research topic for the modeling and analysis of diagnosis and treatment protocols.

2 Research topics for modeling and analysis of biological networks

Tools Modeling and analysis techniques should be offered to biologists and medical researchers via tools that hide as much as possible the technical complexities of the underlying computer science models. One way of achieving this is to try to stick as close as possible to user interfaces of the mostly informal network tools that have been developed already in biology.

Model generation Creating a model can be a time consuming task. Often the information needed for constructing a model can be found in literature or databases. Therefore we need to investigate techniques for building initial models from information that is extracted from heterogeneous sources. It is important to be able to deal with missing or incomplete information.

Parameter fitting and sensitivity Much of the effort in creating a model goes into providing the right parameters for a model. This is related to the issue of parameter sensitivity and robustness. Especially for parameters that vary from patient to patient it is important to establish that model properties are not critically dependent on such parameters.

Simulation and visualization Simulations are needed initially to gain confidence in the correctness of a model. Once confidence has been gained in the correctness, a model can be explored by simulating it with various stimuli. In this way hypotheses can be checked by in-silico experimentations. Challenges are the efficiency of such simulations, especially if reactions may take place at different timescales. In addition, the way results are visually and graphically presented to researchers of medical practitioners is of crucial importance.

Relating models and experiments Experiments will always form an indispensable component of biological research, and modeling can greatly enhance the effectiveness and efficiency of experiments. Models can be of great help in suggesting experiments and thereby pruning the large amount of possible experiments. Models are also important in interpreting the (often very large) amount of experimental data - just indicating which data is in accordance with the model so far, and which data is not, is already extremely useful. And more research should be performed on automatic

suggestions for model improvement in the light of new experimental data.

Using model checking for drug synthesis For some goal in a network model, model checking can provide the stimuli that have to be offered to a network in order to reach that goal, by analyzing the trace leading to the goal. In this way model checking is a powerful technique supporting drug synthesis. Since network models may have an enormous state space, the challenge is to find abstraction and high performance computing techniques that enable to check large scale network models.

3 Research topics for modeling and analysis of treatment protocols

Tools The ambition is to create a tool that enables health practitioners to create their own treatment protocols, and analyze them. This asks for a domain specific language that is both easy to use and sufficiently flexible and expressive to deal with many different scenarios.

Educated guesses for parameters Usually when modeling a treatment protocol many parameters are unknown or not known precisely, and it would be too costly or time consuming to establish such parameters by clinical trials. What is needed is a framework to deal with such educated guesses; by sensitivity analysis or parameter sweeps it could be established which parameters need to be established with more precision, and which parameters are not so crucial for the analysis outcomes.

Optimization It would be very useful to establish the optimal protocol under some constraint. What is the most effective protocol given a certain budget, or what is the most economic protocol that is able to obtain a given level of effectiveness? This asks for a theory of optimization of timed stochastic processes with costs.

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