

# The SYMBIONT Project: Symbolic Methods for Biological Networks

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## Abstract

The international interdisciplinary SYMBIONT project ranges from mathematics via computer science to systems biology, with a balanced team of researchers from those fields. At the present stage the project has a clear focus on fundamental research on mathematical methods, and prototypes in software. Results are systematically benchmarked against models from computational biology databases. We summarize the motivation and aims for the project, and report on existing results by the consortium and first activities. The project website can be found at [www.symbiont-project.org](http://www.symbiont-project.org).

## 1 Introduction

Unprecedented information accumulation in biology and medicine in the last 20 years has led to a situation where any new progress in these fields is dependent on the capacity to model and make sense of large data. Only yesterday, simple models with two to five ordinary differential equations were used to illustrate fundamental ideas such as multi-stationarity or biological rhythms sustained by biological cells. Already such simple models asked for involved analysis justifying one or several scientific publications for a single model. Today, even much larger models are built to represent cell processes, explain and predict the origin and evolution of complex diseases, or the differences between patients in precision and personalized medicine. For instance, the BIOMODELS repository contains thousands of hand-built models of up to several hundreds of variables. Much quicker analysis is also needed. In precision medicine one aims at moving from hypotheses to their verification within only minutes.

Numerical analysis of large models often fails to meet these desiderata because it implies either exhaustive scan of the parameter space or the identification of the numerical parameters from data. Both tasks are impossible for large biological systems because parameters are largely unknown and because of the curse of dimensionality: Data, even rich, become rapidly sparse when the dimensionality of the problem increases. An alternative to numerical methods is the use of symbolic methods, which can be used, e.g., to compute bifurcation and phase diagrams of biological models, which are in turn very useful tools for decision. In spite of important progress in the last years, symbolic methods also have their limitations. They cannot be applied directly to models of hundreds of variables as needed for precision medicine. In order to make this possible, the models need first be approximated and reduced to their essential features.

The breakthrough objective targeted by the SYMBIONT project<sup>1</sup> is to establish new paradigms in computational biology based on symbolic methods of sufficient power. This objective will be achieved by

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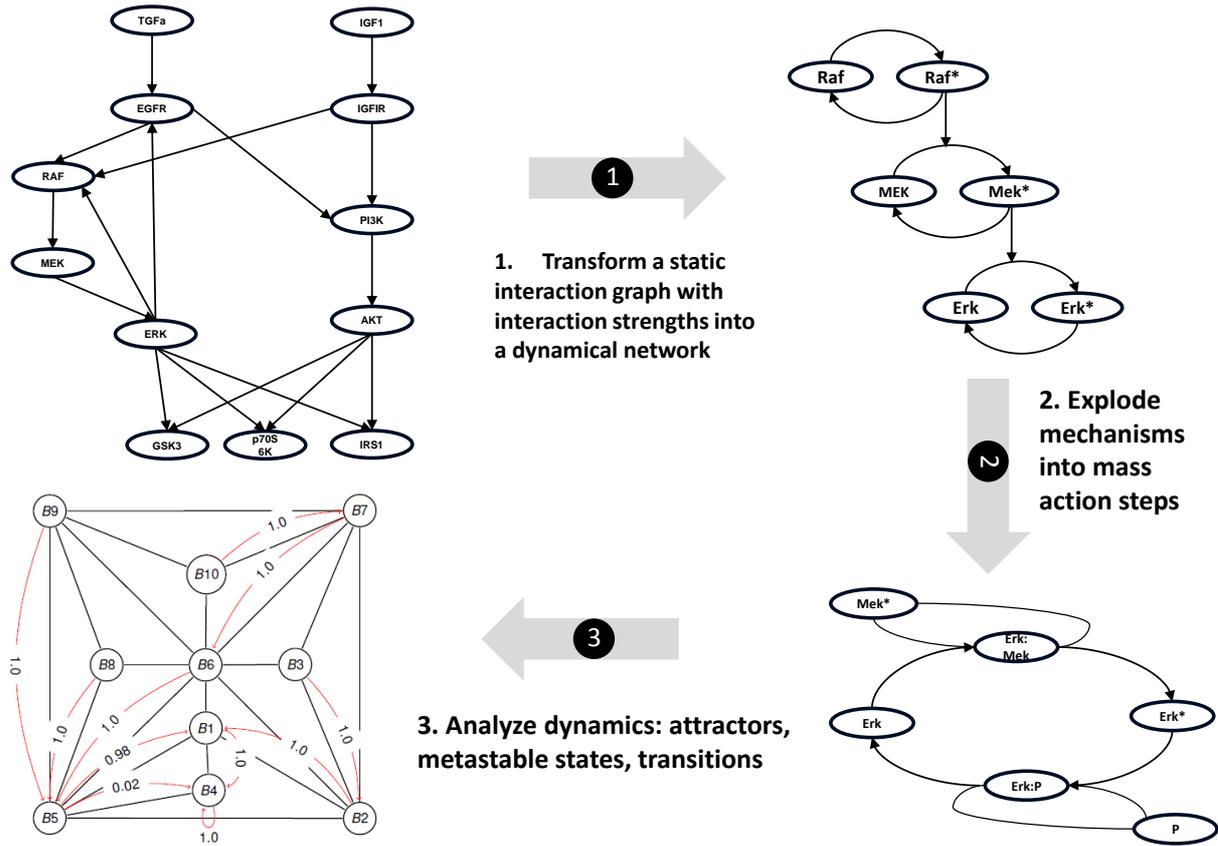


Figure 1: Flowchart indicating reconstruction and analysis of dynamical networks used as models for cell processes. Static networks are directed graphs; Dynamic networks are systems of polynomial ODEs; Branches B1, . . . , B10 of tropical equilibrations indicate metastable regimes; Transitions between metastable regimes form a non-deterministic automaton.

combining symbolic methods with model reduction methods.

## 2 Tropical Analysis of Biological Networks

Tropical methods, also known as idempotent or max-plus algebras, due their name to the fact that one of the pioneers of the field, Imre Simon, was Brazilian. These methods found numerous applications to computer science, physics, statistics, and also engineering, e.g., railway traffic. SYMBIONT is working towards the development of tropical approximations of biochemical networks. These approximations will be used for model order reduction and for qualitative analysis of the model dynamics; see Figure 1.

We have already used tropical methods to rank monomial terms into rate vectors according to their orders of magnitude and to identify lowest order, dominant terms. When there is only one dominant term or when the dominant terms all have the same sign, the dynamics is fast and the system tends rapidly towards a region in phase space, where at least two dominant terms of opposite signs are equilibrated. We have called this tropical equilibrations and developed methods to compute them automatically [5]. We have shown that tropical equilibrations can be grouped into branches that were put into correspondence with metastable dynamic regimes of chemical reaction networks. Furthermore, qualitative network dynamics can be described as a sequence of transitions from one branch to another. Each tropical equilibration branch can lead to a distinct reduced model that can be obtained and justified algorithmically; see [3] and the

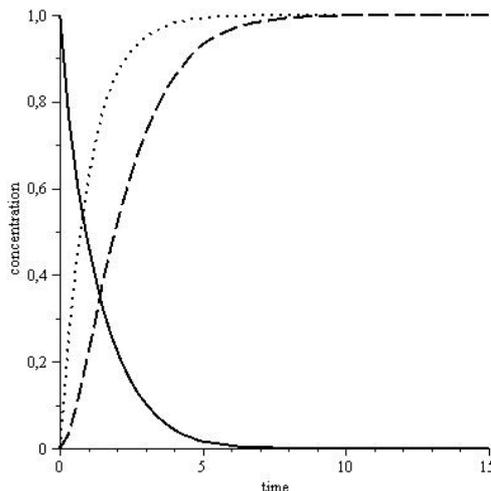


Figure 2: An instance where quasi-steady state reduction provides incorrect results (Michaelis-Menten system with small parameter  $k_{-1}$ ). The dashed line represents the concentration of product correctly, the dotted line represents the quasi-steady state approximation. One goal of SYMBIONT is to provide reliable criteria for dimension reduction.

references there.

Within the SYMBIONT project, we will further improve tropical approximation methods. We will furthermore study the parametric dependence of tropical solutions. We will define stability conditions and use these to filter the tropical solutions. The algorithms and the validity of the tropical approximations will be justified rigorously, and the methods will be tested on case studies and biological applications.

### 3 Algebraic, Differential Algebraic, and Analytic Methods

Classical topics in the qualitative theory of ordinary differential equations are the existence and stability of periodic solutions, equilibria and invariant manifolds or the determination of bifurcation diagrams. These questions are important in relation with chemical reaction networks (CRN), but difficult for medium size and large networks. Applied to computing equilibria of CRN and their bifurcations, numerical solvers based on homotopy continuation work well for medium size networks but can be submitted to instability for larger networks. SYMBIONT employs methods from algorithmic commutative algebra, effective quantifier elimination, and symmetry analysis, building on results from bifurcation theory and singular perturbation theory. The goal is to investigate and justify heuristic approaches, and to lay the groundwork for further approaches in the study of reaction equations as well as related parameter dependent systems.

In order to handle not only equational constraints for systems of polynomials or rational functions but also inequality conditions arising in CRN theory, we have already successfully applied real quantifier elimination methods to biological systems of modest size [1, and the references there], specifically virtual substitution and, more recently, also regular chain techniques. It will be important to identify crucial structural features of CRN and to develop corresponding heuristics for quantifier elimination.

Recent results of our consortium on Hopf bifurcations in CRN are important preliminary steps towards understanding dynamical behavior of large networks. On the one hand, we combine stoichiometric network analysis (SNA method) and real computer algebra for computing critical parameter values. On the other hand, we use normal form theory and symmetry reduction to determine the nature of the bifurcations. It is an ambitious long-term goal of SYMBIONT to finally arrive at methods and tools for symbolic bifurcation analysis, with the idea that parametric phenomena are key factors for explaining phenotypes and disease

in biology and medicine.

From a general perspective, symmetry methods are a central tool for the investigation of differential equations. Many reduction methods may be seen as symmetry reductions, and group invariant solutions often describe the asymptotic behavior of systems. There exist some approaches to adapt symmetry theory for parameter-dependent systems, and SYMBIONT will develop a rigorous theory of approximate symmetries for systems on multiple time scales that is consistent with perturbation theory, and apply it to model reductions in reaction networks.

Our consortium has already contributed to symbolic and algebraic approaches to singular perturbations and singular perturbation reductions. Thus, a coordinate-free reduction method for polynomial and rational systems was developed. Moreover, for parameter dependent systems a universal approach to detecting and computing critical parameter values, from which singular perturbations emanate, via methods of algorithmic algebra was established. Finally, the validity of the familiar quasi-steady state reduction heuristic was investigated, with positive and negative results; see Figure 2. SYMBIONT aims at efficient computations involving methods from real algebra, carefully balancing between efficiency and reliability. Goals include further investigation of the relation between degenerate scalings and singular perturbation reductions and, furthermore, the development a theory of approximate symmetries of systems on multiple time scales that is consistent with perturbation theory and its application to model reductions in biochemical networks [2, and the references there].

## 4 Challenging Models for Systems Biology and Medicine

SYMBIONT eventually aims at investigating challenging models for systems biology and medicine applying methods as described in Sections 2 and 3 above. The main paradigm here is the intrinsic hybrid nature of large networks dynamics. We will compute attractors, dominant subsystems, and metastable regimes as well as tipping points and transitions between such regimes; see Figure 1. We were already able to relate network dynamic regimes to tumor cell phenotypes in the case of TGF- $\beta$  signaling [4]. It is believed that tipping points can be associated with human diseases and often occur prior to the onset of the disease. Our analysis could provide hints about the onset of the disease as well as about the mechanistic understanding of the disease process.

We will address three fundamental questions: First, can we compute tipping points and dynamical regimes of large biological networks symbolically? Second, to which extent can attractors, dynamical regimes, and tipping points of these networks be related to disease phenotypes? Third, can we make testable predictions?

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