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The SYMBIONT Project: Symbolic Methods for Biological Networks

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www.symbiont-project.org

SYMBIONT PROJECT

Overview

SYMBIONT 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 some existing results.

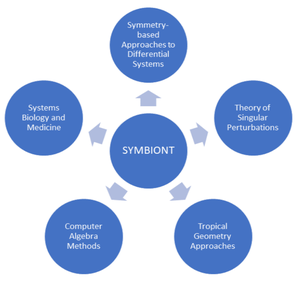

Figure 1: SYMBIONT project overview

Main Objectives

1. Solving high dimensional parametric models for fixed points
2. Order reduction of ordinary differential equations
3. Improved techniques for parameter fitting with respect to observed data
4. Applications in systems biology and medicine

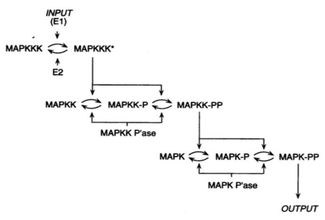

Figure 2: MAPK is an important signalling network. Reduced models serve as test cases.

Methods and Results

Computer algebra methods for solving systems of equations and inequalities

For polynomial or rational vector fields, classical topics in the qualitative theory of ordinary differential equations such as the existence and stability of periodic solutions and equilibria can be reduced to real quantifier elimination problems. These questions are important for chemical reaction networks (CRN). However, they turn out difficult for medium size and large networks when using generic methods. Based on ideas from Stoichiometric Network Analysis (SNA) specifically virtual substitution and regular chain techniques allow the symbolic computation of Hopf bifurcation fixed points. Some crucial structural features of CRN are used to derive corresponding heuristics for quantifier elimination [2]. "Complex Balancing," which is frequently encountered in CRNs, leads to parameterized binomial systems. For solving such systems, we are using polynomial time solution methods [4].

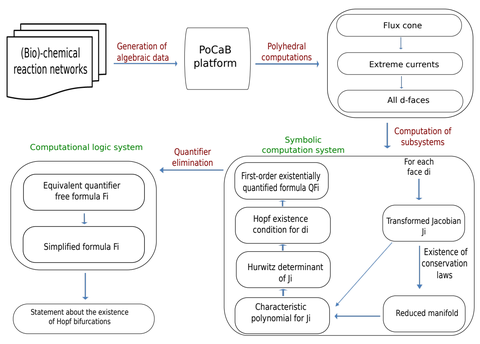

Figure 3: Schematic view of HoCoQ—an algorithm for computing Hopf bifurcations using convex coordinates and quantifier elimination.

Model order reduction and qualitative dynamics

Model order reduction often relies on quasi-steady state phenomena that lead to slow-fast variable decomposition. This is related to the classical singular perturbation scheme due to Tikhonov and Fenichel [3]. The aim is to determine critical manifolds, i.e., parameter values resulting in stationary points with positive dimension. Figure 4 illustrates typical results. In addition, we use scaling and more generally Lie symmetries for variable and parameter nondimensionalisation and identification of small parameters.

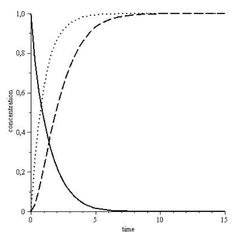

Figure 4: An instance where quasi-steady state reduction provides incorrect results (Michaelis-Menten system with small parameter k_{-1}). The dashed line represents the concentration of product correctly, the dotted line represents the quasi-steady state approximation.

Tropical geometry offers an alternative framework. For polynomial ODEs, we use tropical methods to rank monomial terms according to their orders of magnitude and to identify 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 call a solution to the latter problem a tropical equilibration, which we can compute automatically (cf. [5] and Fig. 5). We show that tropical equilibrations can be algorithmically grouped into branches and put into correspondence with metastable dynamic regimes of chemical reaction networks (cf. Fig. 6a). Each tropical equilibration branch leads to a different reduced model.

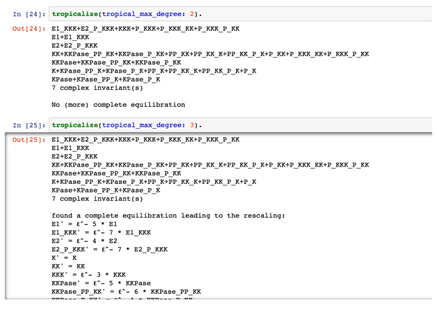

Figure 5: Computation of tropical equilibrations using Constraint Logic Programming in BIOCHAM-4.

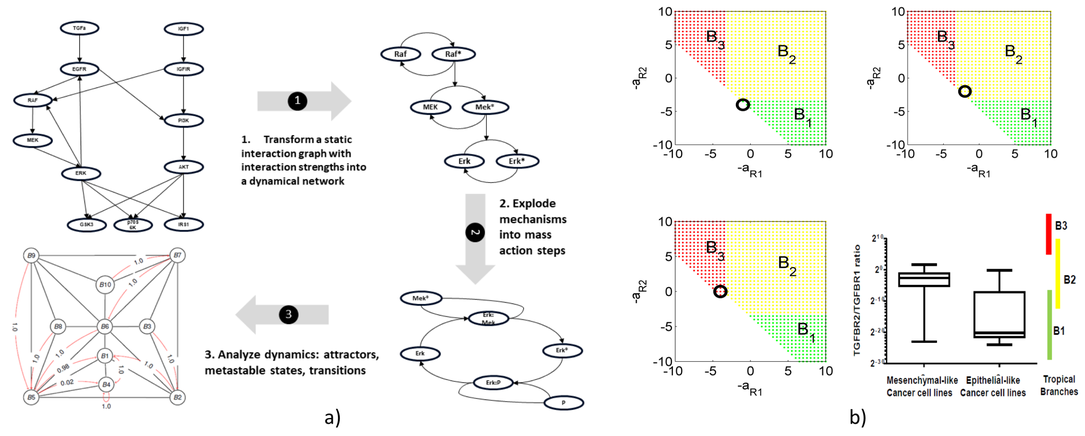

Figure 6: a) Flowchart indicating reconstruction and analysis of dynamical networks used as models for cell processes. Static networks are directed graphs; Dynamic networks are systems of polynomial ODEs; Branches B1, …, B10 of tropical equilibrations indicate metastable regimes; Transitions between metastable regimes form a non-deterministic automaton. b) Tropical equilibration branches provide proxys for metastable regimes of large biochemical networks.

Parameter fitting

We aim to develop symbolic and numeric methods dedicated to the parameter estimation problem for models formulated by means of nonlinear integro-differential equations (IDE). In particular, we address the computation of the model input-output equation and the numerical integration of IDE systems (cf. [1] and Fig. 7).

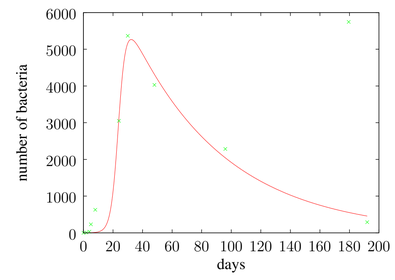

Figure 7: Fitting of parameters (coefficients) of the Volterra–Kostitzin integro-differential model, described as $\dot{p}(t) = \varepsilon p(t) - hp^2(t) - cp(t)\int_o^t K(t-\tau)p(\tau)\,\mathrm{d}\tau$ where $p(t)$ denotes the number of bacteria.

Applications in systems biology and medicine

SYMBIONT eventually aims at investigating challenging models for systems biology and medicine applying the various methods described here. It will compute attractors, dominant subsystems, and metastable regimes as well as tipping points and transitions between such regimes (cf. Fig. 6b, Fig. 8). Our analysis could provide hints about the onset of a disease and support the mechanistic understanding of the disease process. For instance, network dynamic regimes are related to tumor cell phenotypes in the case of TGF-β signalling [6].

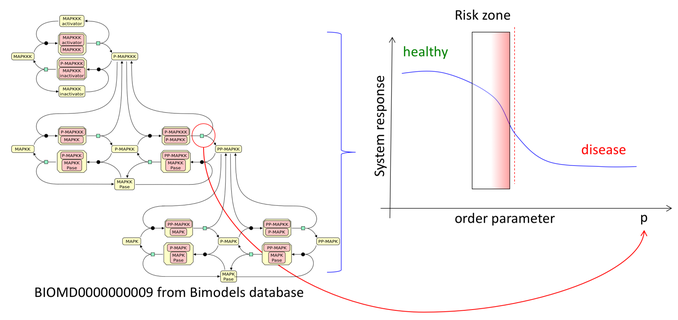

Figure 8: A representation of critical transitions in biological systems. The deviation of few "critical" parameters in the network (left) can shift the system's response resulting in the transition from "healthy" to "disease" state (right).

Challenges

- A rigorous proof of the appearance of Hopf bifurcations, e.g., in the MAPK cascade
- Using hidden toric structures of steady states in combination with linear conservation constraints
- Model reduction for ODEs with sums of fractions
- Additional constraints (e.g. stability constraints) to the tropical equilibration branches
- Tipping points and dynamical regimes of large biological networks symbolically

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We are seeking PhD students and postdoctoral researchers for our project. We also organize regular workshops open for external researchers fostering collaborations. Find information on our website.

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