Parallel parameter synthesis from hybrid logic HUCTL formulas

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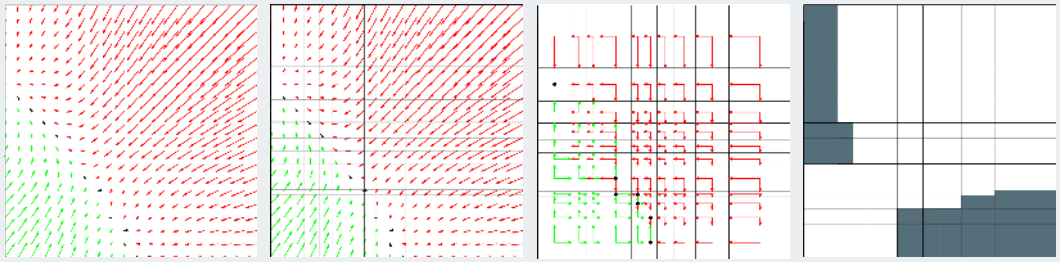
Motivation and Problem Statement

- When studying *complex systems* ocurring in the real world, many researchers in biology, physics, economy, and other scientific fields rely on **formal models**.
- Such models often contain **parameters** which influence the model behaviour. Exact values of the parameters are usually hard to measure or completely unknown.
- To determine the exact influence of parameter values on the model behaviour is crucial to our understanding of these models and to the evaluation of their soundness.
- **Parameter Synthesis Problem:** For a given *model* and a given *property*, compute *parameter valuations* under which the model satisfies the property.

Parameter Synthesis by Model Checking

- We focus on models developed in **systems biology** based on *ordinary differential equations (ODE)* and properties given in the *hybrid computation tree logic (HUCTL)* developed at our laboratory.
- Our algorithm [1] is based on *model checking*, which is a common verification technique. However, to deal with the parameter uncertainty, we work with a **symbolic parameter space representation**, which exploits the similarities between close parameter valuations while still allowing effective parallelisation.
- The decisions about the symbolic parameter sets are translated to **SMT queries** and delegated to an appropriate solver.

1. The vector field of the ODEs
2. A multi-affine approximation
3. A semi-symbolic transition system
4. Property validity regions



HUCTL: Temporal Logic for Bifurcation Analysis

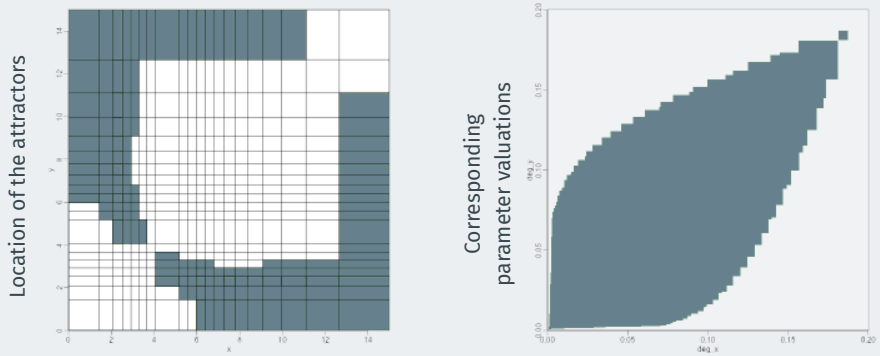
Temporal logics are a common framework for expressing properties of transition systems. However, these logics usually rely on quantitative information to express behavioural properties (*Is there an attractor where x > 3?*). In [2] we extended the *computation tree logic* with hybrid operators in order to reason about **general behavioural patterns** (*Is there an attractor anywhere in the system?*). Such properties are often investigated in *bifurcation analysis* of the original ODEs, which is a hard analytical problem. Here, we provide a way to achieve comparable results **algorithmically** on the discretised models.

Stable steady state pattern:	↓ x: **AX** x
Unstable steady state pattern:	↓ x: **EX** x
General attractor pattern:	↓ x: **AG EF** x
Two instances of *pattern*:	∃ x ∈ *pattern* : *pattern* ∧ ¬ **EF** *pattern*

PITHYA: Parameter Investigation Tool

We implement our method in an open-source tool Pithya [3]. This tool (at various stages of development) was used for analysis of several real biological models, specifically a model of **biodegradation of 1,2,3-trichloropropane** using a synthetic pathway in [4], various **cell singalling pathway** models in [5], and a **G1/S transition cycle** model in [6].

Two attractors discovered in a bi-stable repressilator model:



Try Pithya online at: `http://pithya.ics.muni.cz`

Publications: [1] Beneš, Brim, Demko, Pastva, Šafránek: *Parallel SMT-Based Parameter Synthesis with Application to Piecewise Multi-affine Systems*, ATVA 2016. [2] Beneš, Brim, Demko, Pastva, Šafránek: A Model Checking Approach to Discrete Bifurcation Analysis, FM 2016. [3] Beneš, Brim, Demko, Pastva, Šafránek: *Pithya: A Parallel Tool for Parameter Synthesis of Piecewise Multi-Affine Dynamical Systems*, CAV 2017. [4] Demko, Beneš, Brim, Pastva, Šafránek: *High-Performance Symbolic Parameter Synthesis of Biological Models: A Case Study*, CMSB 2016. [5] Hajnal, Šafránek, Demko, Pastva, Krejci, Brim: *Toward Modelling and Analysis of Transient and Sustained Behaviour of Signalling Pathways*, HSB 2016. [6] Brim, Češka, Demko, Pastva, Šafránek: *Parameter Synthesis by Parallel Coloured CTL Model Checking*, CMSB 2015.

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