Parameter Synthesis by Parallel Coloured CTL Model Checking

David Šafránek

with Luboš Brim, Martin Demko, Samuel Pastva

sybila
systems biology laboratory

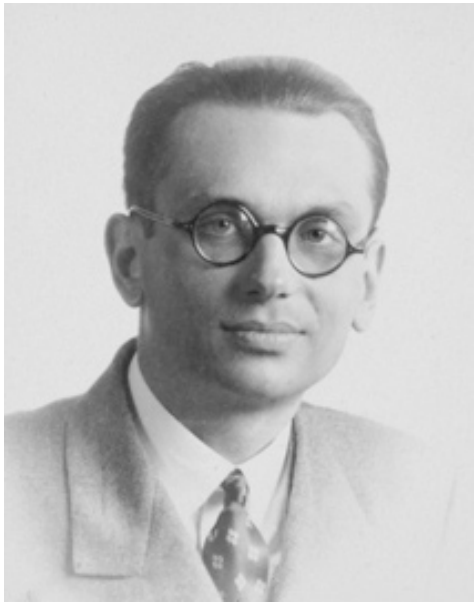
Masaryk University
Czech Republic

Biological and Formal Systems

Two famous men from Brno, two interesting results of the past centuries...

J. G. Mendel
1822–1884

biology
genetics
no rigour



Kurt Gödel
1906–1978

math
formal systems
incompletness

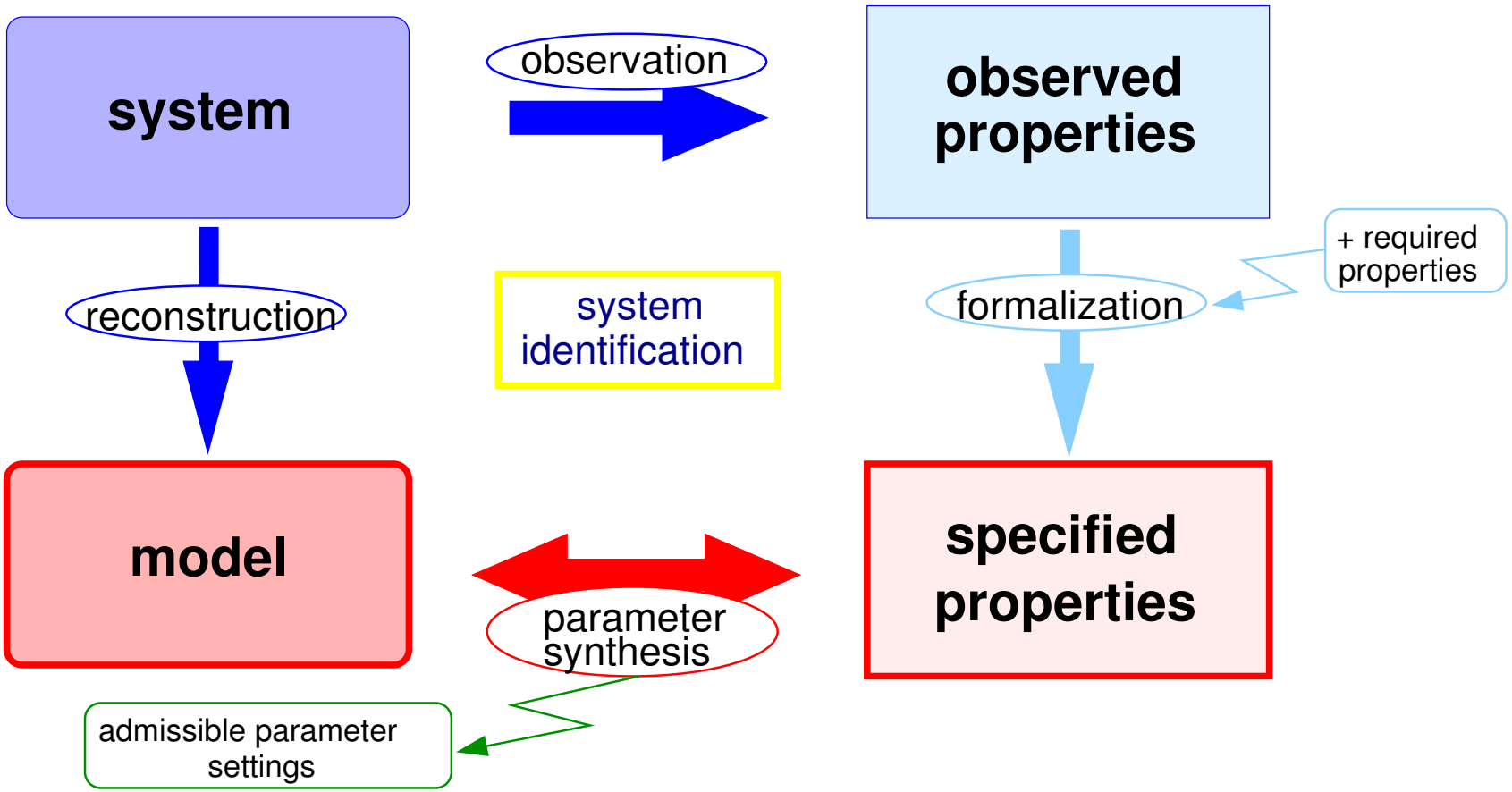
Lets imagine they worked together...

Motivation: Approaching the Model-Based Biology
Collecting Constraints on Systems Dynamics

- *biophysics*: still most usual are continuous (ODE) models
  $\Rightarrow$ based on first-principles and mathematical approximation
- *biology*: wet-lab measurements to understand the natural molecular mechanisms $\Rightarrow$ **time-series data**
- literature provides general **biological constraints** on systems dynamics
- *computer science*: turn all known constraints into **formal specification** and find admissible model **parameters**
- a suitable formal language is provided by **temporal logics**
- if the model has a form of a state-transition system we can employ **model checking**
  $\Rightarrow$ **guarantees** on model-based prediction
  $\Rightarrow$ **exhaustive – much more than simulation!**

Parameter Synthesis by Model Checking

Approaches Developed for ODE Models



Batt et al. 2007 [RoVerGene, BDD-based approach]
Barnat et al. 2010 [BioDiVinE, coloured model checking heuristics]
Batt et al. 2010 [GNA, symbolic approach]

Parameter Synthesis: Problem Formulation

Parameter Synthesis Problem

Assume $\mathcal{P}$ is the admissible **parameter space**. Given a temporal property φ and a parameterized model $\mathcal{M}$ **find the maximal set** $P \subseteq \mathcal{P}$ **of parameterizations** such that $\mathcal{M}(p) \models \varphi$ for all $p \in P$.

Relative Robustness w.r.t $\mathcal{P}$

Given a temporal property φ and a parameterized model $\mathcal{M}$ check if $\mathcal{M}(p) \models \varphi$ **holds for all possible parameterizations** $p \in \mathcal{P}$ (valuations of parameters).

Problem Reduction

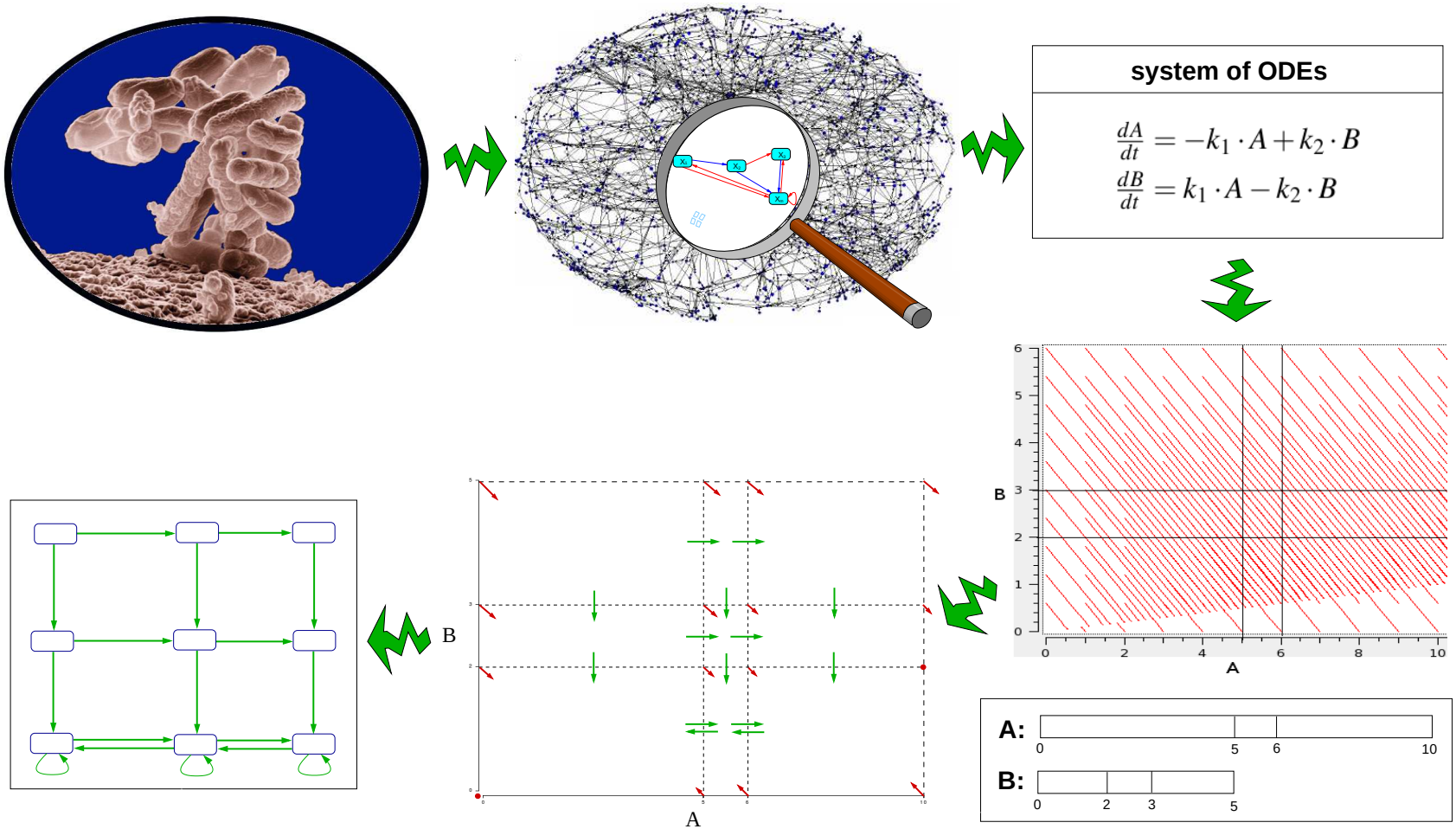
Robustness is reduced to Parameter Synthesis Problem by taking the set $\mathcal{P}$ of all possible parameterizations as P.

Temporal Logics and Biological Systems

- qualitative (untimed) properties (LTL, CTL)
  - modalities (possibilities/necessities in future behaviour)
  - reachability of particular (sets of) states
  - temporal ordering of events, monotonicity
  - temporal correlations of model variables
  - stability (attractors, basins of attraction)
- some examples:
  - oscillation
    LTL: $(\mathbf{G}[(A \leq 3) \Rightarrow \mathbf{F}(A > 3)]) \wedge (\mathbf{G}[(A > 3) \Rightarrow \mathbf{F}(A \leq 3)])$
  - bistability and reachability of two stable states
    (non-deterministic models or qualitative abstractions)
    CTL: $\mathbf{EFAG}(A \leq 5) \wedge \mathbf{EFAG}(A > 5)$
- model checking is undecidable for continuous systems
  - either simulation/monitoring [Fages (LTL), Donzé (STL)]
  - our approach: abstraction by means of finite automata

Rectangular Abstraction: The Big Picture

From a Continuous System to its Qualitative Quotient



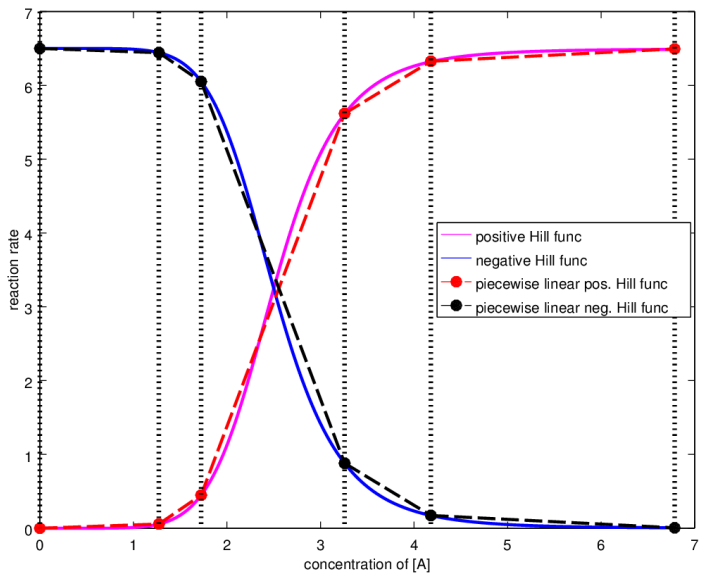
P. Collins, L. Habets, J.H. van Schuppen, I. Černá, J. Fabriková, and D. Šafránek. Abstraction of Biochemical Reaction Systems on Polytopes. In Proceedings of 18th IFAC World Congress, 2011.

related work: EC-MOAN project (de Jong, van Schuppen), also Batt, Belta, Yordanov

Discretisable Continuous (ODE) Models

model	abstraction	kinetics
piece-wise multi-affine	transient over-approximated steady state over-approximated	sigmoidal kinetics mass action
piece-wise affine	transient over-approximated steady state exact	first-order sigmoidal kinetics

- a large class of molecular devices modeled at abstract level (e.g., signalling pathways, gene regulatory circuits, ...)
- optimal approximation of sigmoid functions by piece-wise affine functions (ramps) [Bartocci et al. CAV 2011]



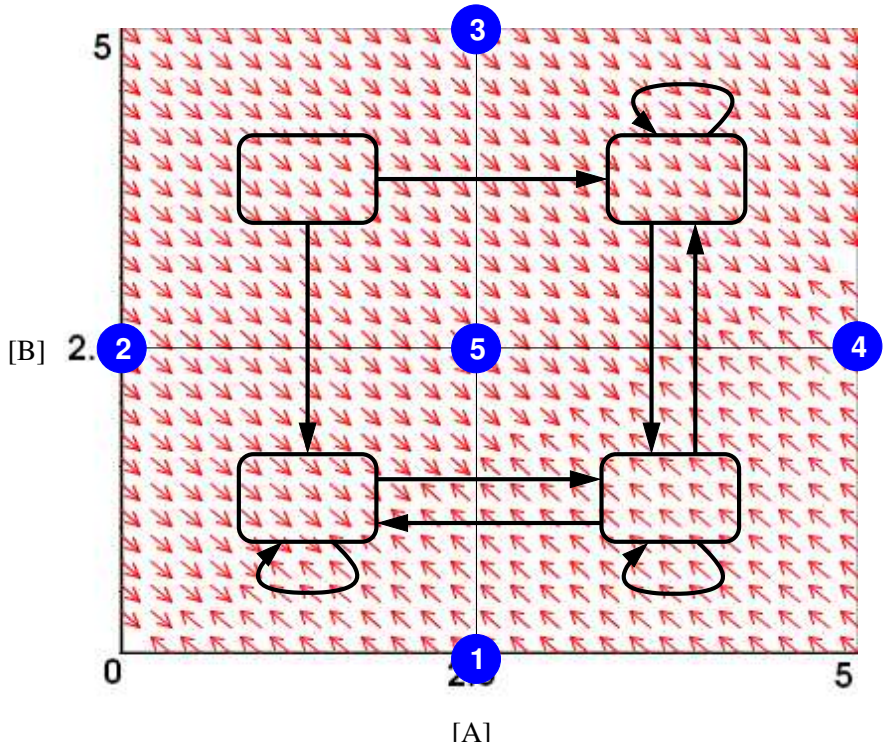
Synthesising the Parameters

Phase Space Discretisation Leads to Parameter Space Discretisation

$$\frac{dA}{dt} = -k_1 \cdot A + k_2 \cdot B$$
$$\frac{dB}{dt} = k_1 \cdot A - k_2 \cdot B$$

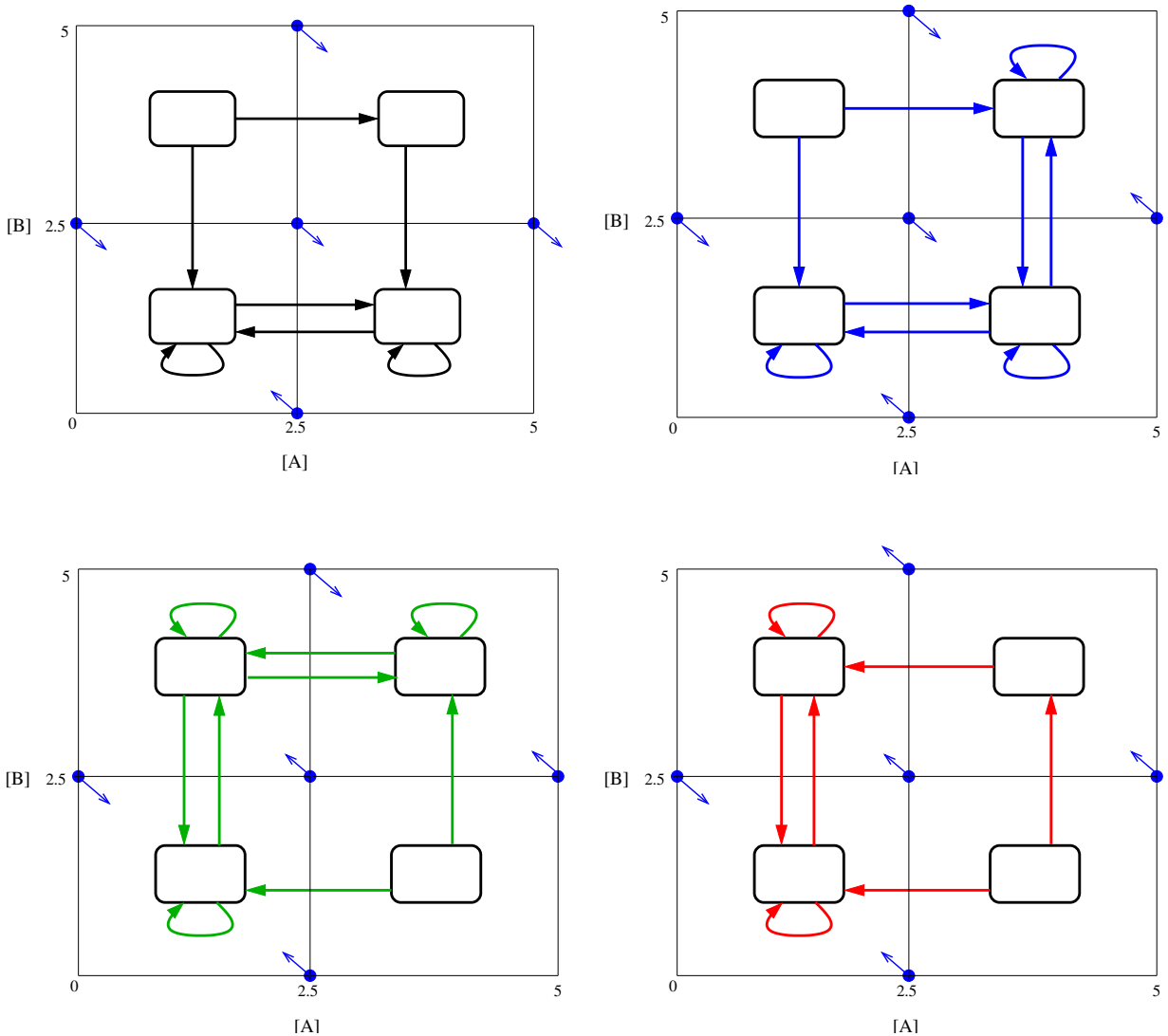
$k_2 = 0.8$

$k_1 = ?$

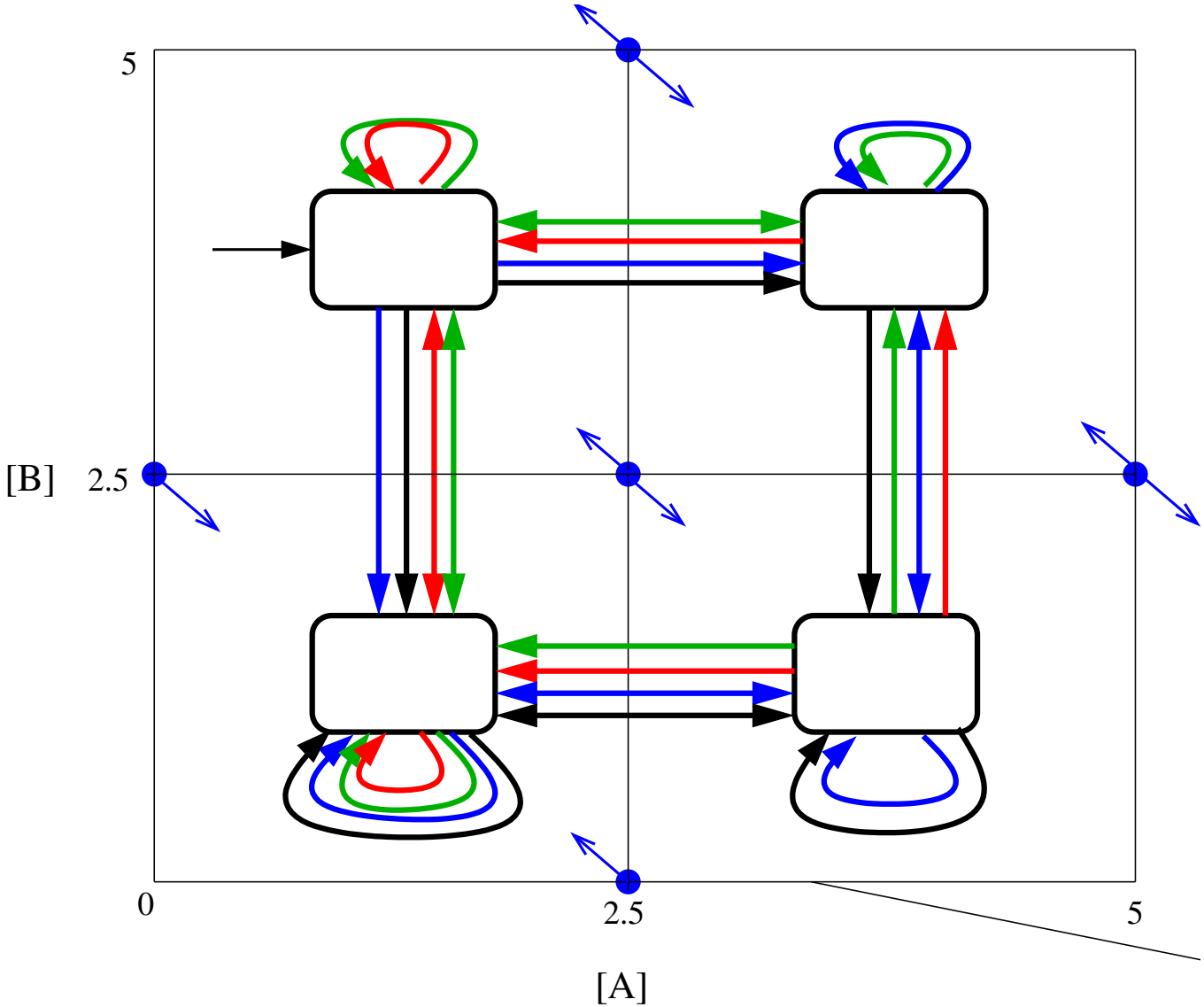


	value of k1: (0,0.4)	(0.4,0.8)	(0.8,1.6)	(1.6,max)
1	↖	↖	↖	↖
2	↘	↘	↘	↘
3	↘	↘	↘	↖
4	↘	↖	↖	↖
5	↘	↘	↖	↖

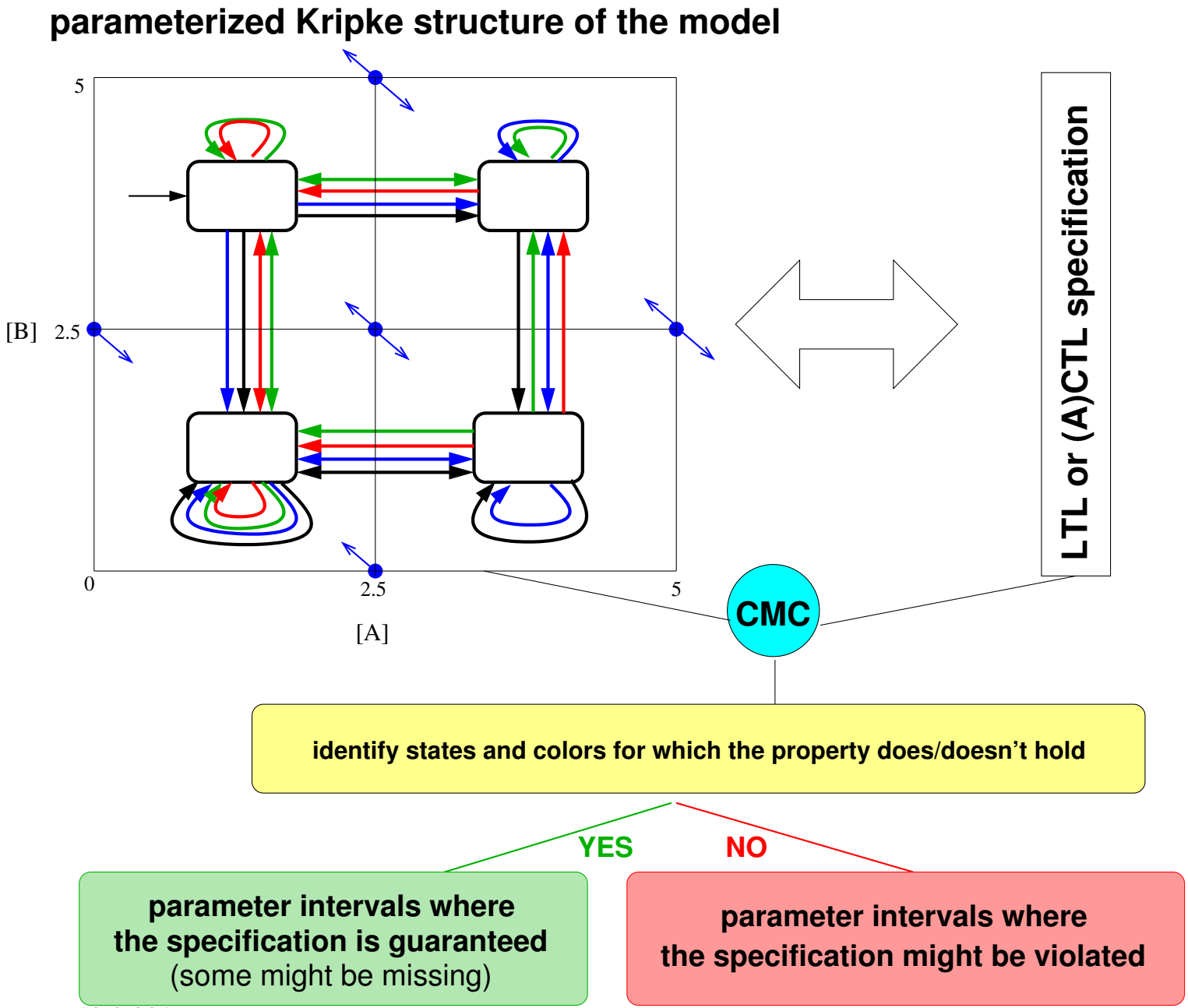
Effect of Parameters on Abstraction Automaton



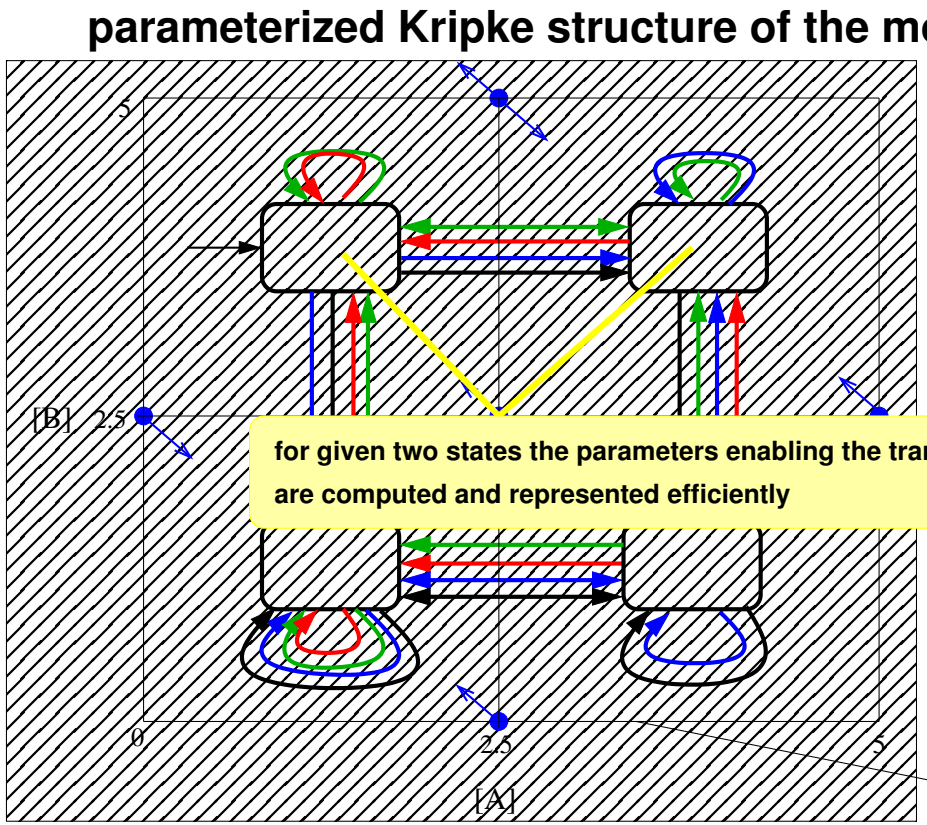
Parametrized Kripke Structure



Parameter Synthesis by Coloured Model Checking



Parameter Synthesis by Coloured Model Checking



Overall Analysis Workflow

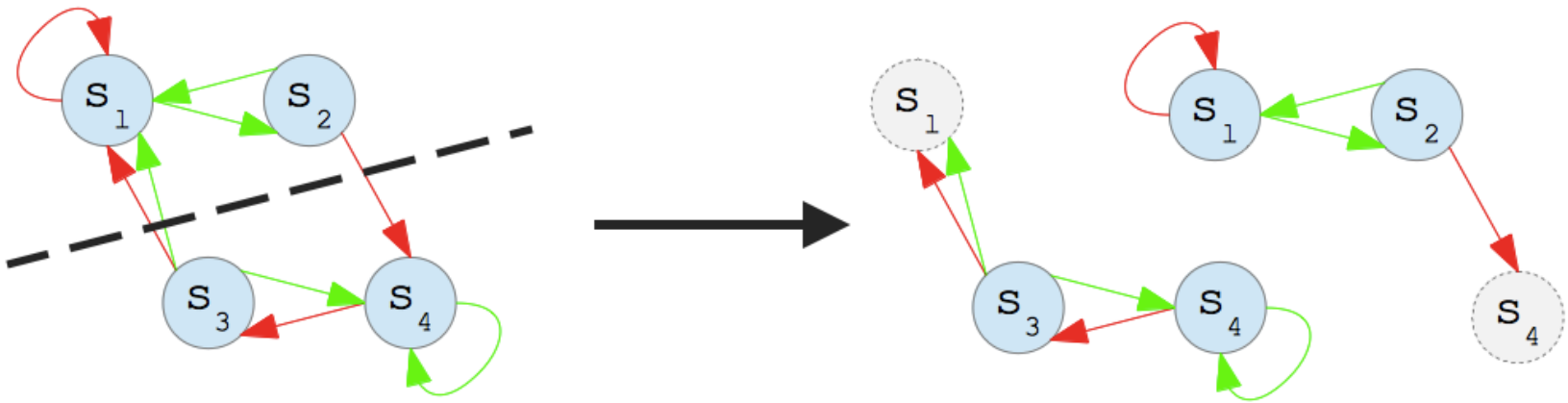
1. formulate the CTL property φ
2. approximate a parametrised ODE model by means of a (parameterised) piece-wise (multi)affine model (PWA)
3. discretise a PWA model into a finite state-transition system (parametrised Kripke structure)
4. employ coloured CTL model checking to identify (for each state) parameter sets satisfying φ
5. insterpret and visualise the results

Parallel Coloured CTL Model Checking

adapting the enumerative **distributed** CTL model checking algorithm [Brim etal. 2005]:

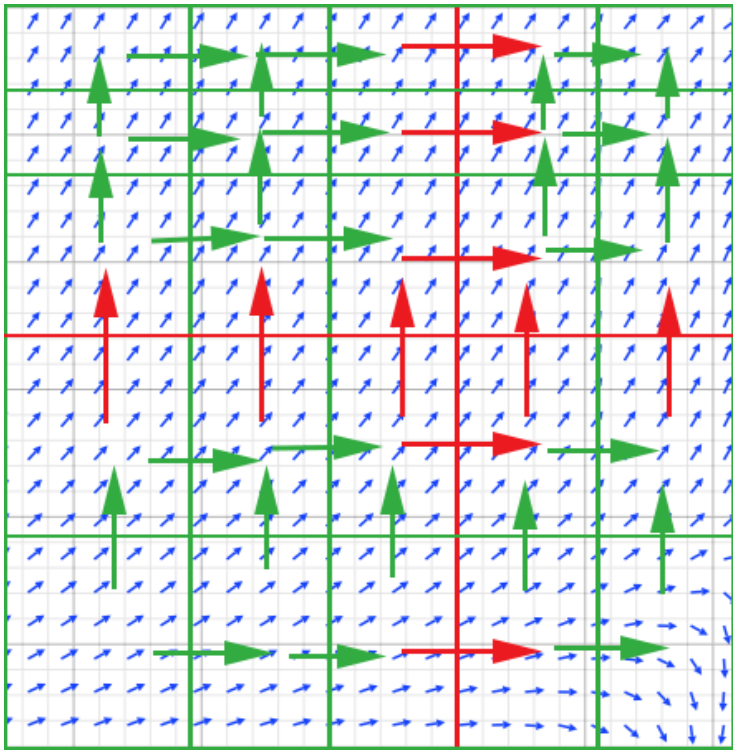
- traverse the states backwards while unfolding the formula and label every reached state with a subformula satisfied there (do until fixpoint is reached)
- each worker computes inside its own part of state space
- when new relevant information is computed locally it is dispatched to all other workers for which it is relevant
- satisfation of every subformula is decided for all parameter sets at once

State Space Distribution – Main Idea



- state space divided using a partition function (mapping from states to workers)
- direct successors belonging to neighbouring partitions (**border states**) are duplicated locally
- a border state represents the missing part of the state space

State Space Distribution – Rectangular Partitioning



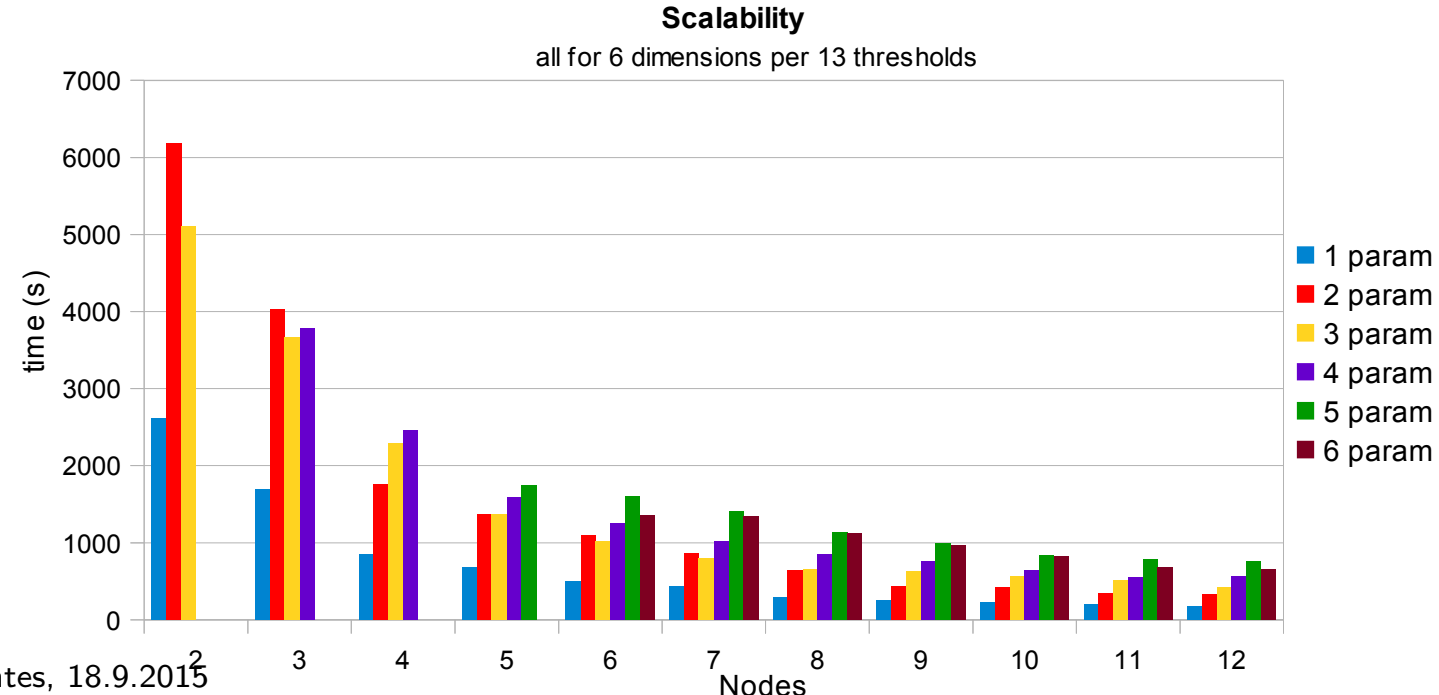
- rectangular abstraction ensures there are only transitions between adjacent states
- we use this fact to create a partitioning that minimises number of cross edges (adjacent states are placed into the same partition if possible)

Implementation

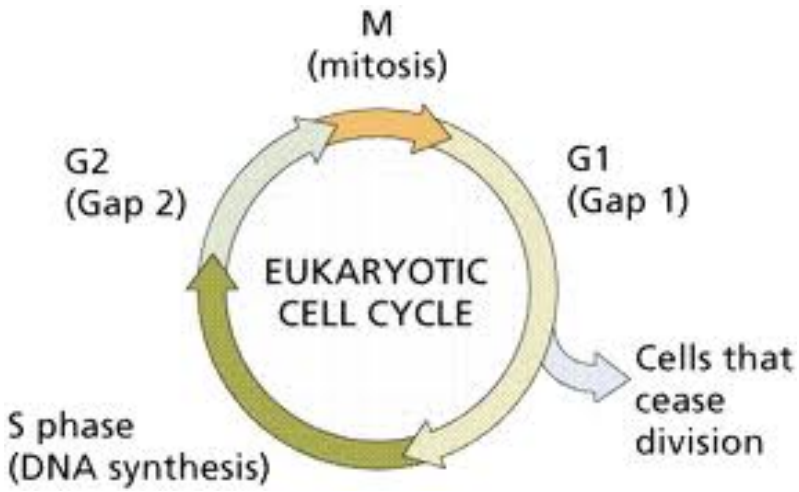
- prototype implementation is available on GitHub:
  `https://github.com/sybila/Distributed-CTL-Model-Checker`
- **input:** a CTL property φ and a model specified as a set of parametrised ODEs with upper and lower bounds for parameters and variables
- **procedure:** approximation $\rightarrow$ discretisation $\rightarrow$ CMC
- **output:** for every state a set of parameter intervals where φ satisfied (can be later visualized by third-party tools)
- experimental feature: Boolean and Thomas' networks are also partially supported

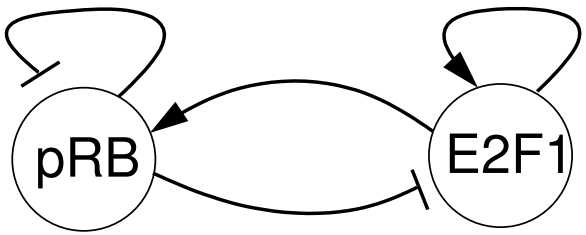
Performance Evaluation and Scalability
Enzymatic Chain Reaction Mass Action as a Benchmark

$$\frac{S + E \rightleftharpoons ES_1 \rightleftharpoons \cdots \rightleftharpoons ES_k \rightleftharpoons P + E}{\dot{S} = 0.1 \cdot ES_1 - p_1 \cdot E \cdot S}$$
$$\dot{E} = 0.1 \cdot ES_1 - p_2 \cdot E \cdot S + 0.1 \cdot ES_k - p_2 \cdot E \cdot P$$
$$\dot{ES_1} = 0.01 \cdot E \cdot S - p_3 \cdot ES_1 + 0.05 \cdot ES_2$$
$$\vdots$$
$$\dot{ES_k} = 0.1 \cdot ES_{k-1} - p_k \cdot ES_k + 0.01 \cdot E \cdot P$$
$$\frac{\dot{P} = 0.1 \cdot ES_k - p_{k+1} \cdot E \cdot P - 0.1 \cdot P}{p_1 = 0.01, p_2 = 0.01, p_3 = 0.2,}$$
$$p_k = 0.15, p_{k+1} = 0.01$$



Case Study: Regulation of G_1/S Cell Cycle Transition





[Swat et al. 2004]

$$\frac{d[pRB]}{dt} = k_1 \frac{[E2F1]}{K_{m1}+[E2F1]} \frac{J_{11}}{J_{11}+[pRB]} - \phi_{pRB}[pRB]$$

$$\frac{d[E2F1]}{dt} = k_p + k_2 \frac{a^2+[E2F1]^2}{K_{m2}^2+[E2F1]^2} \frac{J_{12}}{J_{12}+[pRB]} - \phi_{E2F1}[E2F1]$$

$a = 0.04,\ k_1 = 1,\ k_2 = 1.6,\ k_p = 0.05,\ \phi_{E2F1} = 0.1$
$J_{11} = 0.5,\ J_{12} = 5,\ K_{m1} = 0.5,\ K_{m2} = 4, \phi_{pRB} = ?$

- *pRB* – tumor suppressor protein
- *E2F1* – central transcription factor
- bistable switch: either low or high stable *E2F1*

Case Study: Bistability in G_1/S Transition

- approximate each sigmoid by a sum of piece-wise affine ramps
- resulting approximated system is piece-wise multi-affine:

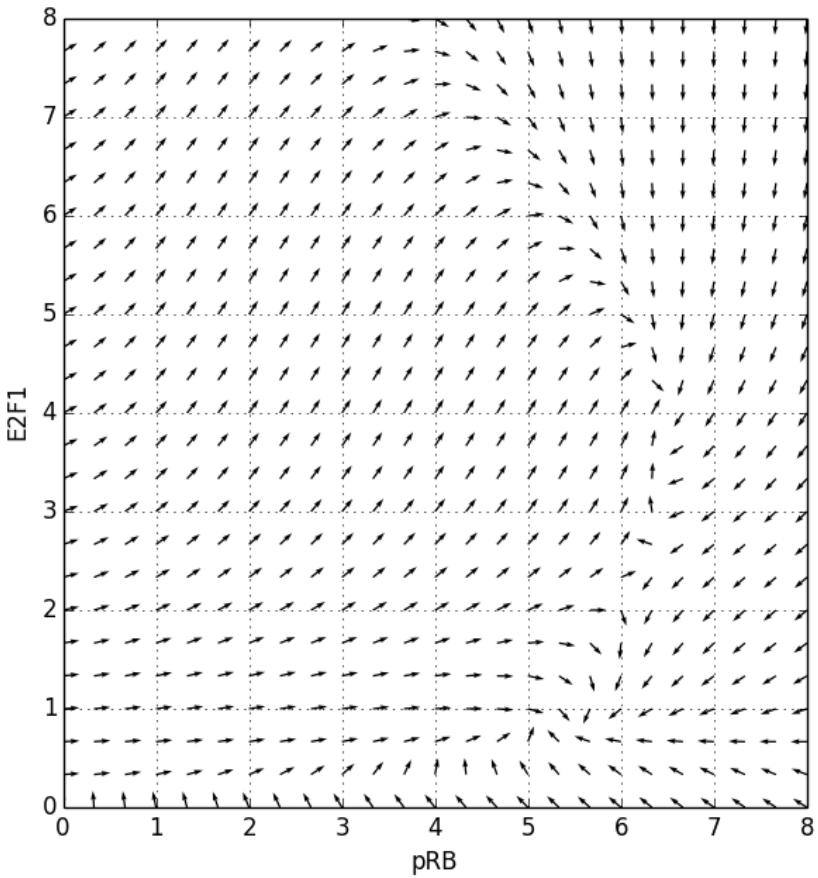
$$\begin{aligned}
\frac{d[E2F1]}{dt} = \; & k_p + \frac{k_2 \cdot a^2}{K_{m2}^2} \cdot [\textstyle\sum_{i=2}^{|\sigma_{E2F1}|} R^-(E2F1, \sigma_{E2F1}^{i-1}, \sigma_{E2F1}^{i}, Hill^-(\sigma_{E2F1}^{i-1}, K_{m2}, 2), Hill^-(\sigma_{E2F1}^{i}, K_{m2}, 2))] \cdot \\
& \cdot [\textstyle\sum_{j=2}^{|\sigma_{pRB}|} R^-(pRB, \sigma_{pRB}^{j-1}, \sigma_{pRB}^{j}, Hill^-(\sigma_{pRB}^{j-1}, J_{12}, 1), Hill^-(\sigma_{pRB}^{j}, J_{12}, 1))] + \\
& + k_2 \cdot [\textstyle\sum_{i=2}^{|\sigma_{E2F1}|} R^+(E2F1, \sigma_{E2F1}^{i-1}, \sigma_{E2F1}^{i}, Hill^+(\sigma_{E2F1}^{i-1}, K_{m2}, 2), Hill^+(\sigma_{E2F1}^{i}, K_{m2}, 2))] \cdot \\
& \cdot [\textstyle\sum_{j=2}^{|\sigma_{pRB}|} R^-(pRB, \sigma_{pRB}^{j-1}, \sigma_{pRB}^{j}, Hill^-(\sigma_{pRB}^{j-1}, J_{12}, 1), Hill^-(\sigma_{pRB}^{j}, J_{12}, 1))] - \phi_{E2F1}[E2F1]
\end{aligned}$$

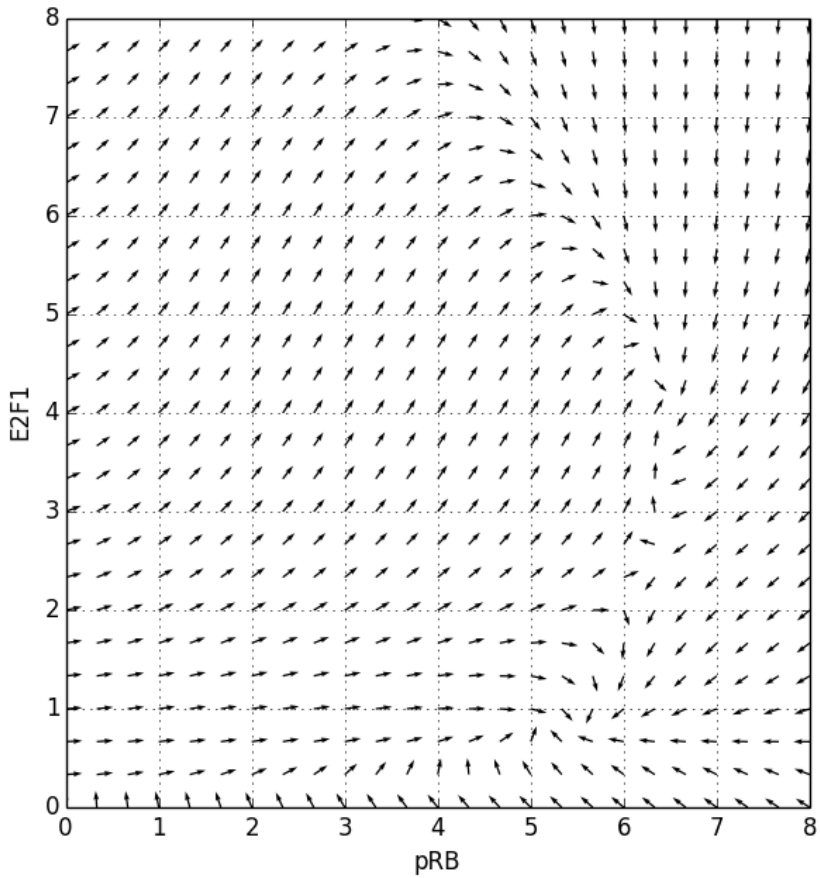
$$\begin{aligned}
\frac{d[pRB]}{dt} = \; & k_1 \cdot [\textstyle\sum_{i=2}^{|\sigma_{E2F1}|} R^+(E2F1, \sigma_{E2F1}^{i-1}, \sigma_{E2F1}^{i}, Hill^+(\sigma_{E2F1}^{i-1}, K_{m1}, 1), Hill^+(\sigma_{E2F1}^{i}, K_{m1}, 1))] \cdot \\
& \cdot [\textstyle\sum_{j=2}^{|\sigma_{pRB}|} R^-(pRB, \sigma_{pRB}^{j-1}, \sigma_{pRB}^{j}, Hill^-(\sigma_{pRB}^{j-1}, J_{11}, 1), Hill^-(\sigma_{pRB}^{j}, J_{11}, 1))] - \phi_{pRB}[pRB]
\end{aligned}$$

$|\sigma_{E2F1}| = |\sigma_{pRB}| = 70$ ... number of piece-wise affine segments

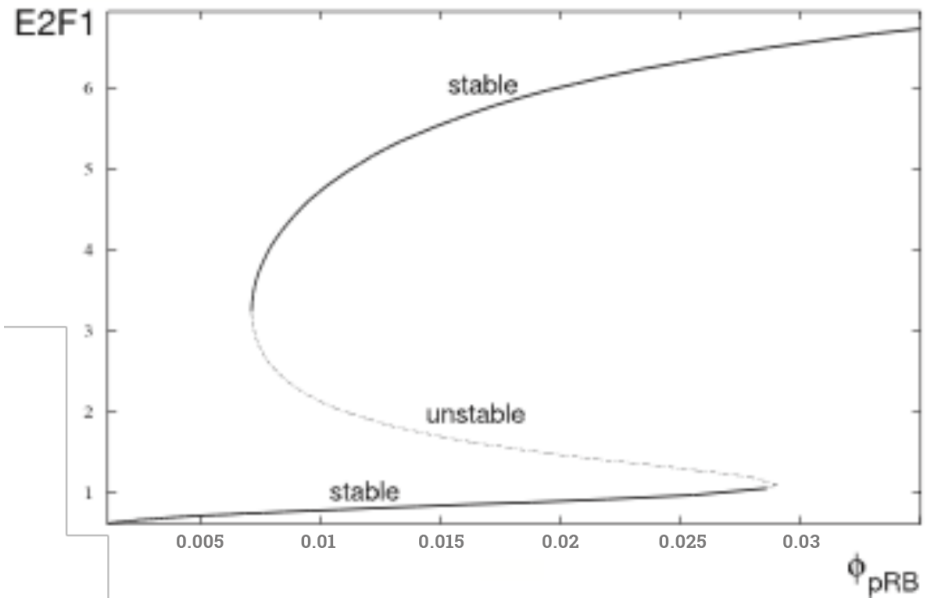
Case Study: Bistability in G_1/S Transition

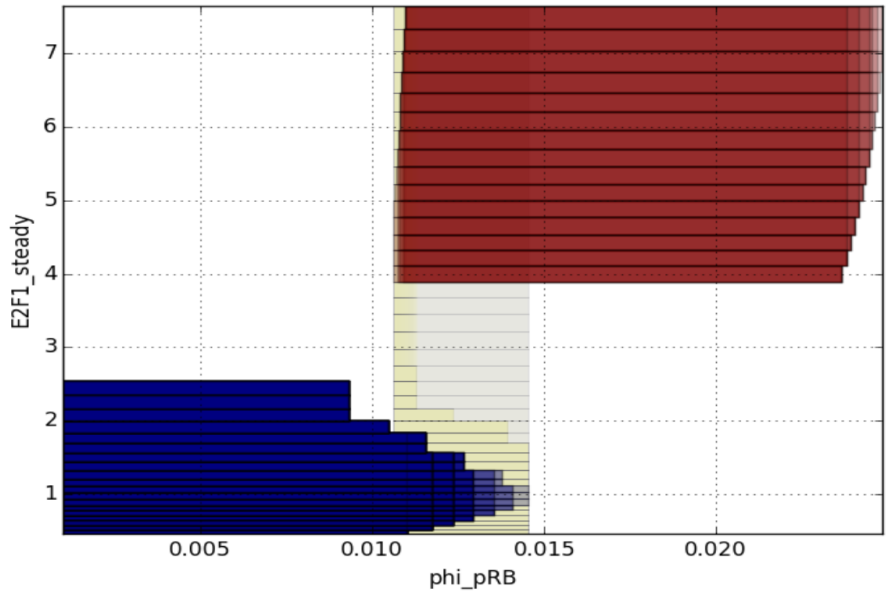
Original ODE Model vs. Piece-wise Multi-Affine Model Vectorfield





Case Study: Regulation of G_1/S Cell Cycle Transition



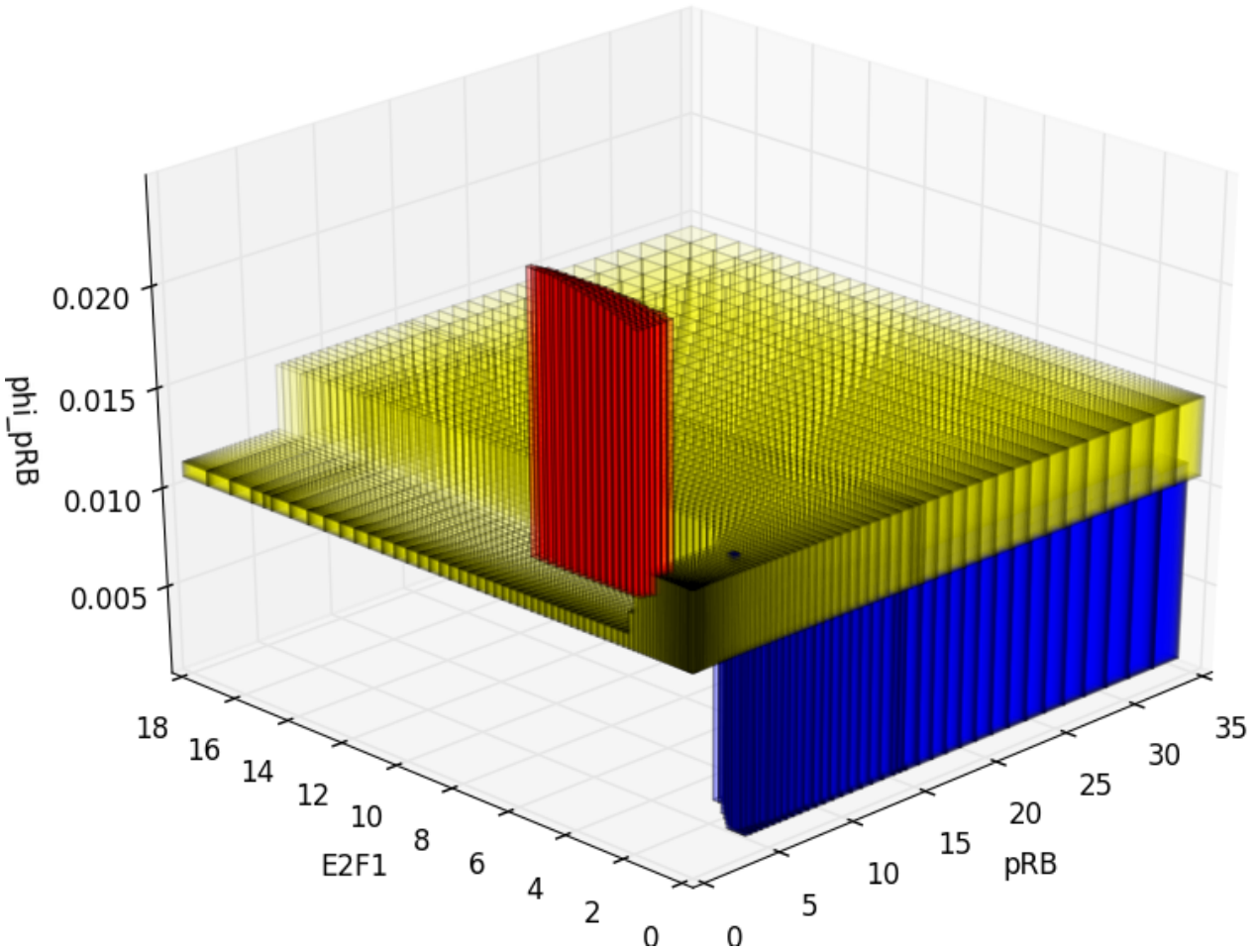


`high`	$4 < E2F1 < 7.5$
`low`	$0.5 < E2F1 < 2.5$

- red: **AG** `high` (GUARANTEED)
- blue: **AG** `low` (GUARANTEED)
- yellow: **EFAG** `high` $\wedge$ **EFAG** `low` (NON-GUARANTEED)

Case Study: Bistability in G_1/S Transition

CTL CMC Analysis Results



GUARANTEED: Red and blue parts correspond to **AG** `high` and **AG** `low`, respectivelly.

NON-GUARANTEED: Yellow are the states where $\varphi \equiv$ **EFAG** `high` $\wedge$ **EFAG** `low` holds.

Conclusions

- we have put together advantages of enumerative CTL model checking with the features of rectangular abstraction
- we have lifted CTL model checking to colouted model checking to enable property-driven parameter synthesis
- CTL MC allows global analysis of the system and for suitable formulas gives guarantees (depends on the format of ODE model)
- we gain from advantages of parallel algorithm to obtain scalability
- the algorithm is universal – can be applied to any transition-parametrised state-transition system (e.g., multi-valued boolean networks)
- we plan to incororate the technique in the general toolbox BioDiVinE for parameter synthesis

The End

Thank You for your attention.

The Lab and its Networking

- `http://sybila.fi.muni.cz`
- Faculty of Informatics, Masaryk University Brno
- external collaborations with:
  - Marta Kwiatkowska, Louis Mahadevan, University of Oxford
  - Loïc Paulevé, Université Paris-Sud
  - Jean-Marie Jacquet, University of Namur
  - Heike Siebert, Freie Universität Berlin
  - Ion Petre, ABO Akademi Turku
  - Ezio Bartocci, TU Vienna
  - Luca Bortolussi, University of Trieste
  - Christoph Flamm, University of Vienna
  - Ralf Steuer, Humboldt University Berlin
  - Pieter Collins, Maastricht University
  - Jan van Schuppen, Delft University
  - Ilka Axmann, Univeristät Düsseldorf
  - Frank Bruggeman, Free University Amsterdam
  - Jane Hilston, University of Edinburgh