A Model Checking Approach to Dynamical Systems Analysis

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Outline

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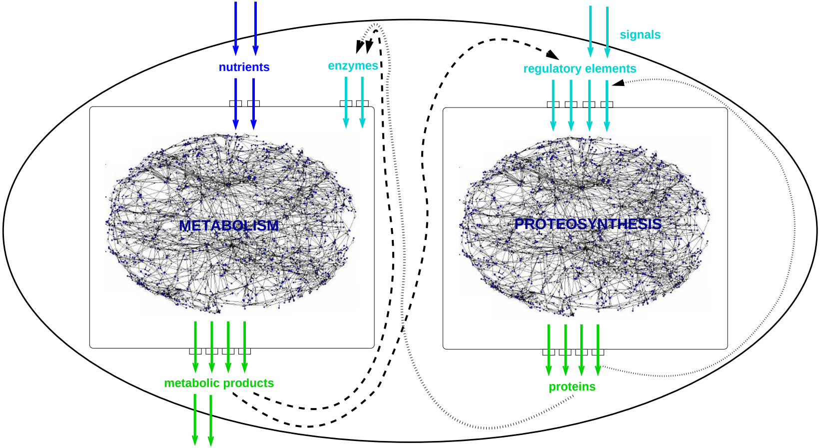
1. Motivation

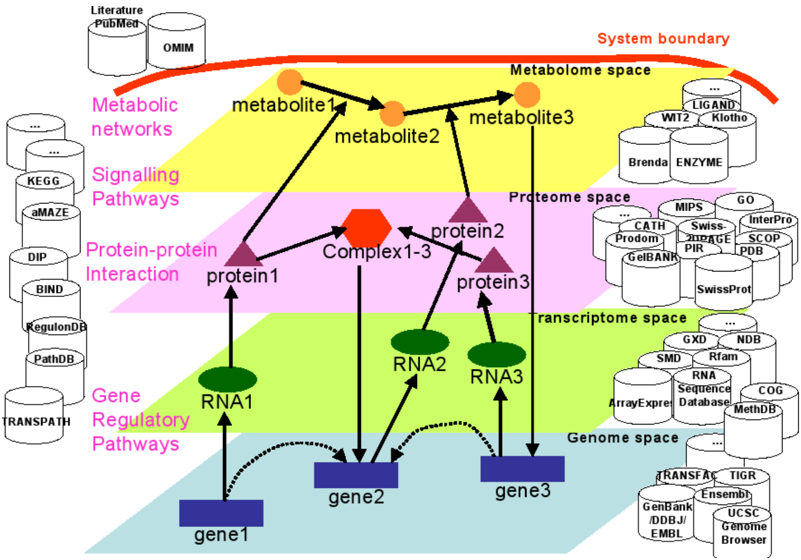
2. Parameter Synthesis by Coloured Model Checking
   - Case Study using Parameter Synthesis

3. Discrete Bifurcation Analysis
   - Case Study using Discrete Bifurcation Analysis

Motivation: Complex Real-World Systems
Systems View of Processes Driving the Cell



Motivation: Complex Dynamics of a Cell



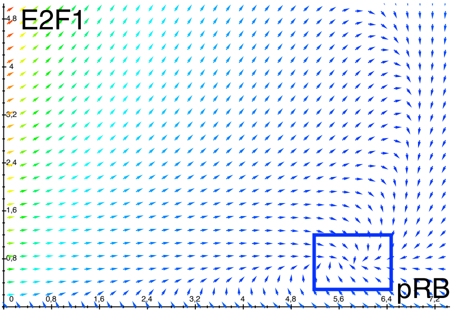
- continuous-time models of dynamical systems:

$$\dot{x} = f(x(t), p)$$

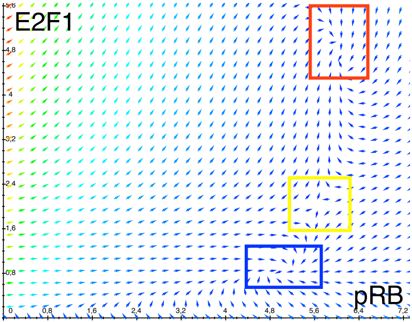
f … phase space (vector field), $f : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$

x … state vector ($\mathbb{R}^n$)

p … parameter vector ($\mathbb{R}^m$)



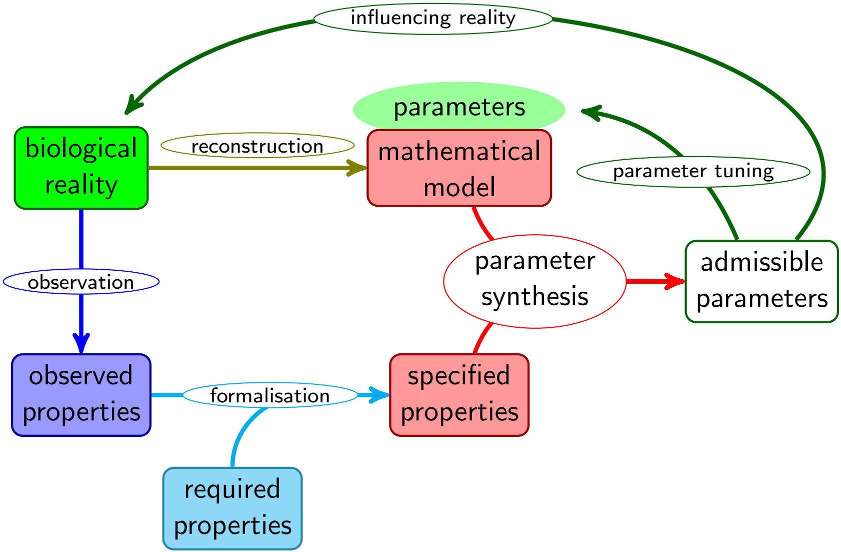
$p = 0.006$



$p = 0.012$

- *biophysics*: often use **parameterised** continuous-time models (ODEs), typically analysed by **local** methods (simulation)
- *biology*: observations in the form of **time-series data**
- literature provides further **constraints** on systems dynamics
- *computer science*: turn all known facts into **formal specification** and find admissible model **parameters**
- a suitable formal language is provided by **temporal logics**
- if the model is given as a state-transition system we can employ **model checking**
  $\Rightarrow$ **exhaustive** – global view wrt parameters and initial conditions, different than simulation

Motivation: Dynamical Systems with Parameters



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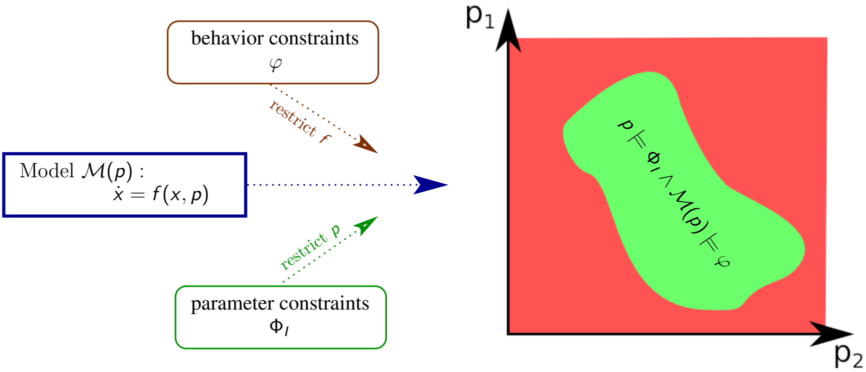
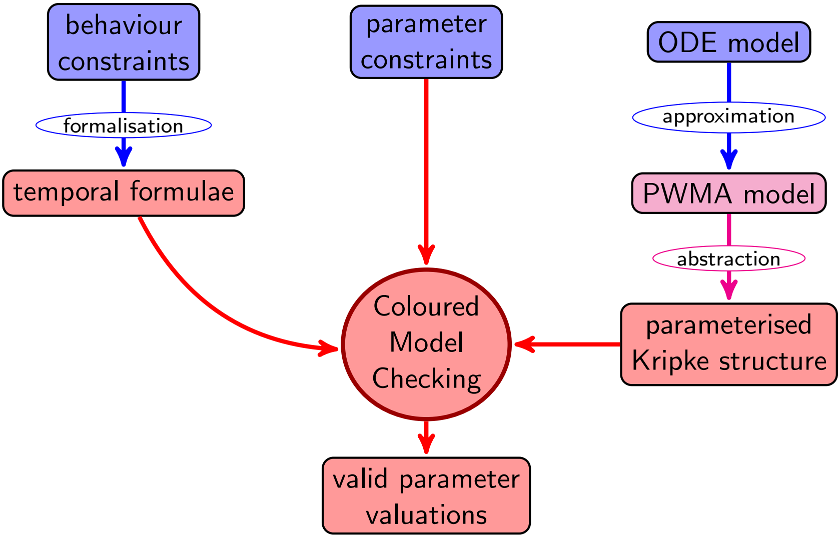


Parameter Synthesis Problem

Assume $\mathcal{P}$ is the admissible **parameter space**. Given a *behaviour constraint* φ, *parameter constraint* Φ_I, and a *parameterised model* $\mathcal{M}$, **find the maximal set** $P \subseteq \mathcal{P}$ **of parameterisations** such that $p \models \Phi_I$ and $\mathcal{M}(p) \models \varphi$ for all $p \in P$.

Workflow


behaviour constraints
formalisation
temporal formulae
parameter constraints
ODE model
approximation
PWMA model
abstraction
parameterised Kripke structure
Coloured Model Checking
valid parameter valuations

Work Chronology

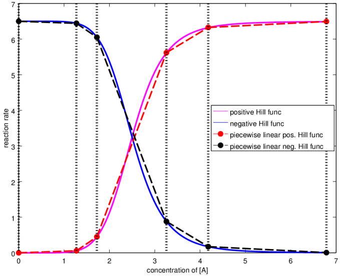
Related Work

- Batt et al. 2007: *RoverGene*, BDD/Polytopes-based approach
- Batt et al. 2010: *GNA*, symbolic approach, piecewise affine
- Grosu et al. 2011: *RoverGene* revisited, approximation improved
- Bogomolov et al. 2015, *SpaceEx*, multi-affine hybrid automata

Our Contribution

- HIBI 2010, TCCB 2012: coloured LTL model checking, piecewise multi-affine, parallel algorithm
- CMSB 2015: coloured CTL model checking, piecewise multi-affine, parallel algorithm
  - parameters represented as intervals
  - limitation: **independent parameters** only
- ATVA 2016, CMSB 2016: parameters represented in first order logic, SMT solver employed, **interdependent parameters**
- HSB 2015, FM 2016: discrete bifurcation analysis by coloured CTL model checking

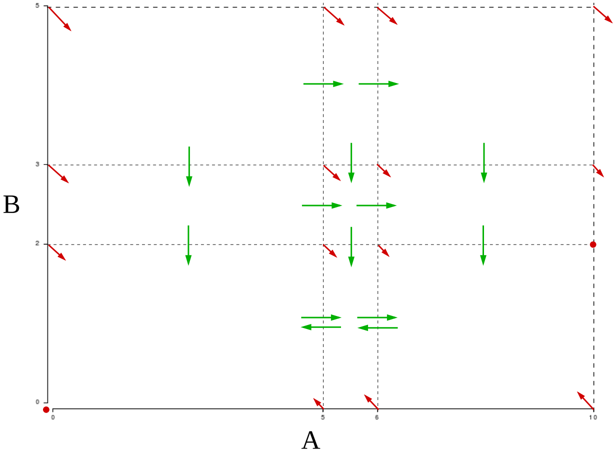
- a large class of molecular mechanisms modeled at activity-flow level (e.g., signalling pathways, gene regulatory circuits, ...)
- optimal approximation of sigmoid functions by piece-wise affine functions (ramps) [Grosu et al. CAV 2011]



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

Step 2: Rectangular Abstraction

- approach originates in [Batt, Belta, Habets, van Schuppen]
- continuous phase-space is partitioned into (hypher)rectangles
- **no diagonal transitions**, overapproximation

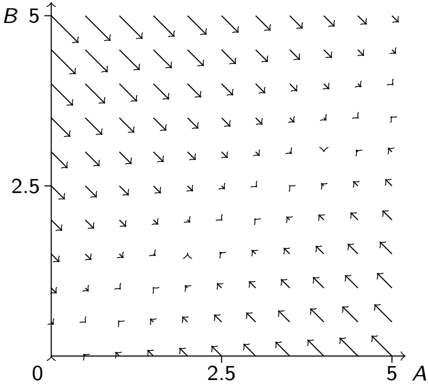


$$\frac{dA}{dt} = -k_1 \cdot A + k_2 \cdot B$$

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

$$k_2 = 0.8$$

$$k_1 = 0.6$$



Phase Space Discretisation Leads to Parameter Space Discretisation

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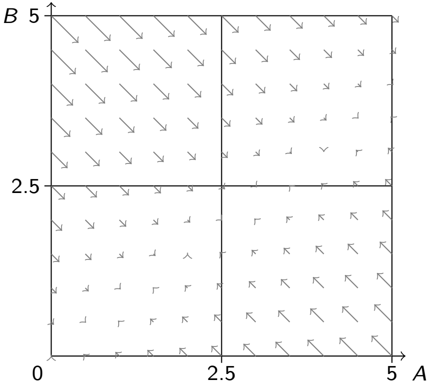

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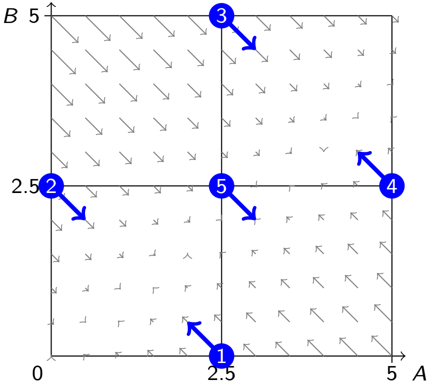

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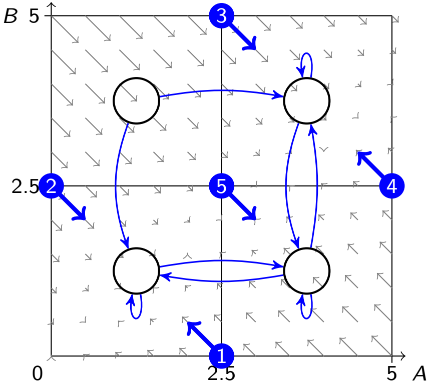


Step 3: Parameter Synthesis

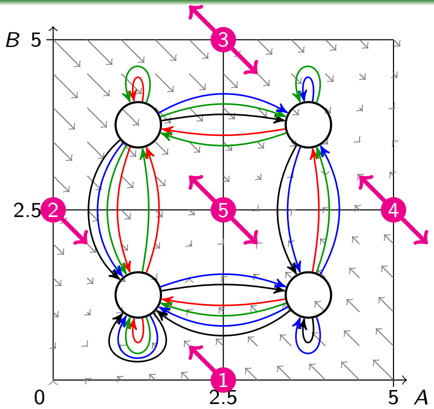
Phase Space Discretisation Leads to Parameter Space Discretisation

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

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

$$k_2 = 0.8$$

$$k_1 = ?$$



	(0,0.4)	(0.4,0.8)	(0.8,1.6)	(1.6,max)
1	↖	↖	↖	↖
2	↘	↘	↘	↘
3	↘	↘	↘	↖
4	↘	↖	↖	↖
5	↘	↘	↖	↖

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

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$$k_2 = 0.8$$

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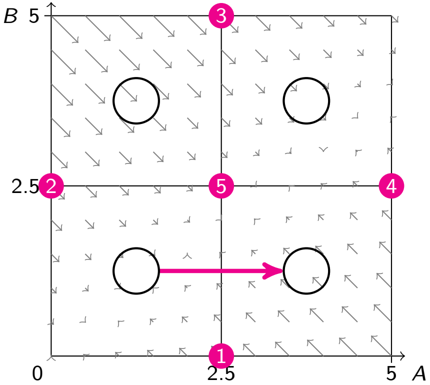

	(0,0.4)	(0.4,0.8)	(0.8,1.6)	(1.6,max)	
1	↖	↖	↖	↖	$-2.5 \cdot k_1 > 0$
2	↘	↘	↘	↘	
3	↘	↘	↘	↖	
4	↘	↖	↖	↖	
5	↘	↘	↖	↖	$-2.5 \cdot k_1 + 2.5 \cdot k_2 > 0$

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

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$$k_2 = 0.8$$

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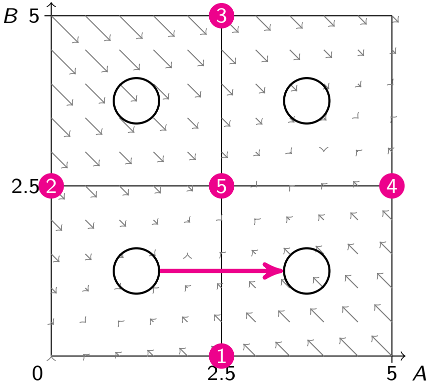
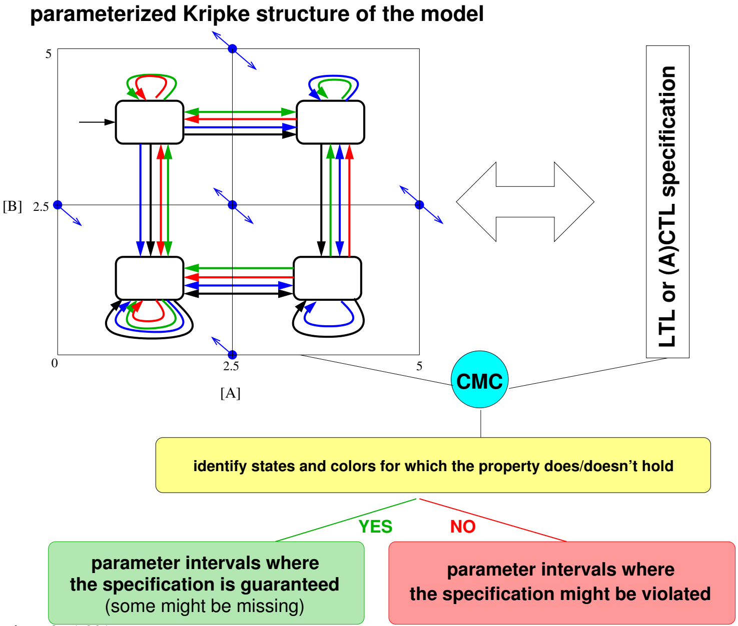


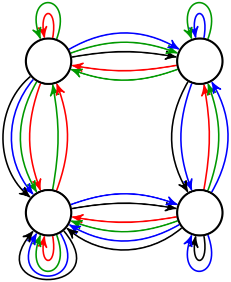
$$\Phi_{\text{state00}\to\text{state10}} := -2.5 \cdot k_1 > 0 \lor -2.5 \cdot k_1 + 2.5 \cdot k_2 > 0$$

The transition exists if and only if the formula is **satisfiable**.
Local parameter constraints are **predicates over reals**.

Parameter Synthesis by Coloured Model Checking

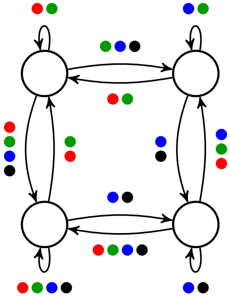


Transitions with Parameters (coloured transitions)



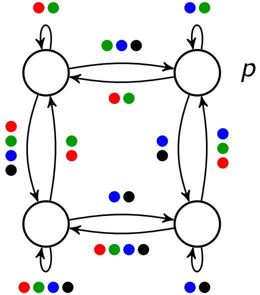
- each parameter valuation represents one Kripke structure
- shared state space, different transition space

Transitions with Parameters (coloured transitions)



- each parameter valuation represents one Kripke structure
- shared state space, different transition space
- we assume symbolic representation of parameters
- symbolic PKS: every transition is associated with a formula

- enumerative approach
- CTL model checking: dynamic programming, back propagation
- coloured CTL model checking: back propagation of colours



CTL formula: **EF** p

- **intersection** of colour sets: state + transition
- **union** of colour sets: inside state

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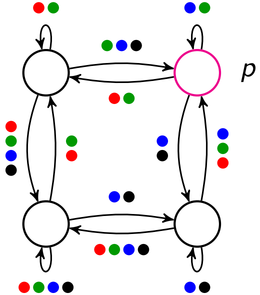

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Coloured CTL Model Checking

Basic Idea

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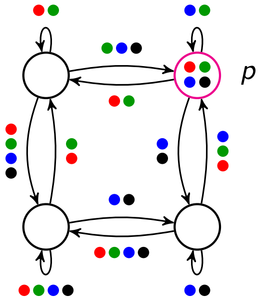

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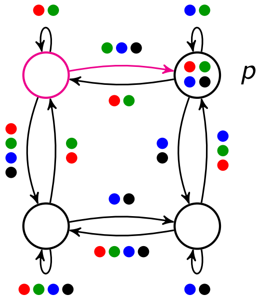

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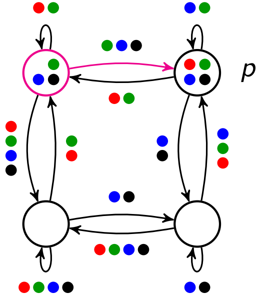

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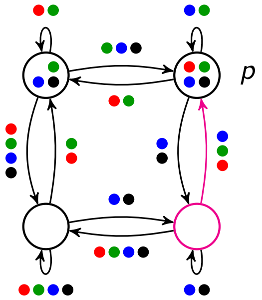

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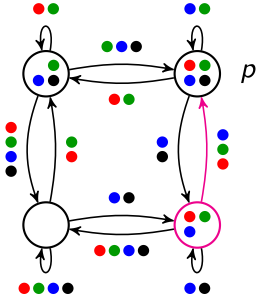

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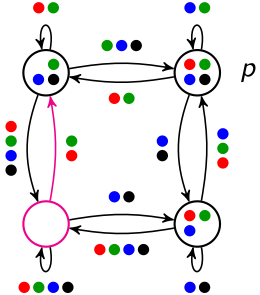

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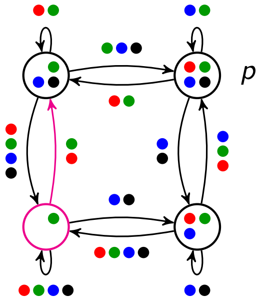

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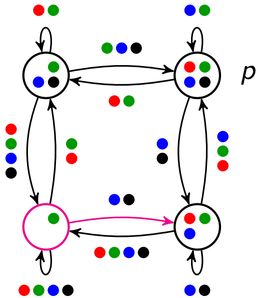

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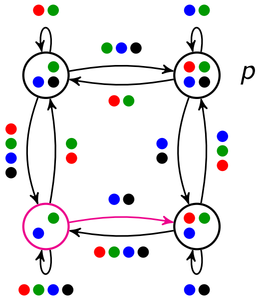

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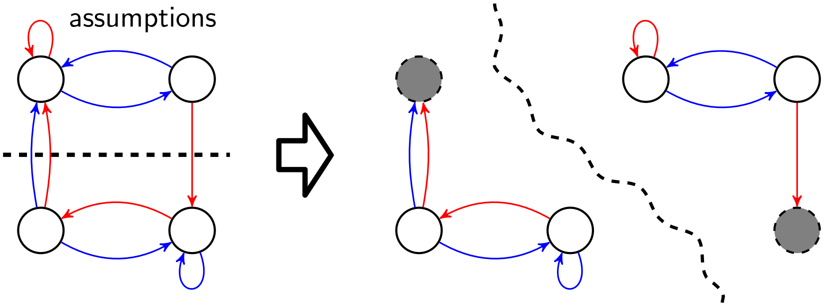
Kripke Fragments

- each worker owns a part of the whole state space
- extended with *border states*
- assumption-based approach, three-valued (*true*/*false*/*unknown*)
- after everything is computed locally, exchange border state assumptions



Idea based on:
Brim, Yorav, Žídková 2005: parallel CTL model checking

Encoding

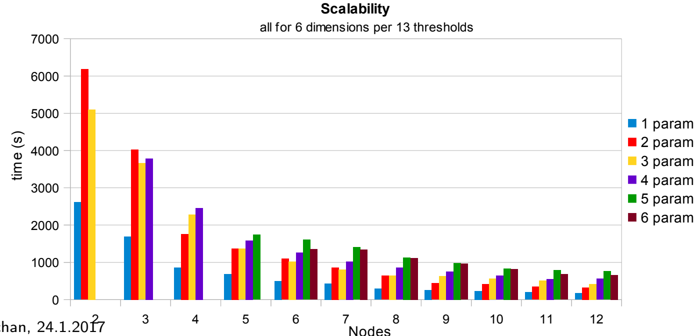
- every set of parameters (on transitions, inside states) represented by a formula with free variables: satisfying assignments are set elements
- union is disjunction, intersection is conjunction
- call SMT solver to check whether a formula is satisifiable (i.e. whether the set is nonempty)
- call SMT solver to check whether two formulae are equivalent (i.e. whether the set has changed)
- optimisation: delay SMT solver calls, cache SMT results

This work: linear arithmetic over reals
Generally: anything an SMT solver can handle

$$S + E \rightleftharpoons ES_1 \rightleftharpoons \cdots \rightleftharpoons ES_k \rightleftharpoons P + E$$

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

$$p_1 = 0.01, p_2 = 0.01, p_3 = 0.2,$$
$$p_k = 0.15, p_{k+1} = 0.01$$



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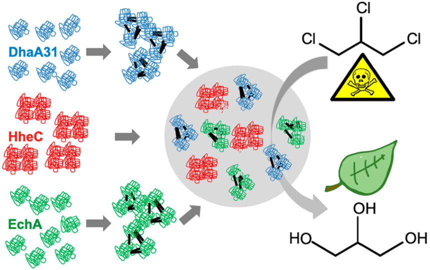
Case study: Biodegradation of Trichloropropane in *E. coli*

$$\textbf{TCP} \xrightarrow{\text{DhaA}} \textbf{DCP} \xrightarrow{\text{HheC}} \textbf{ECH} \xrightarrow{\text{EchA}} \textbf{CPD} \xrightarrow{\text{HheC}} \textbf{GDL} \xrightarrow{\text{EchA}} \textbf{GLY}$$



$$\frac{d[TCP]}{dt} = -\frac{k_1 \cdot DhaA \cdot [TCP]}{K_{m,1} + [TCP]}$$

$$\frac{d[DCP]}{dt} = \frac{k_1 \cdot DhaA \cdot \cdot [TCP]}{K_{m,1} + [TCP]} - \frac{k_2 \cdot HheC \cdot [DCP]}{K_{m,2} + [DCP]}$$

$$\frac{d[ECH]}{dt} = \frac{k_2 \cdot HheC \cdot [DCP]}{K_{m,2} + [DCP]} - \frac{k_3 \cdot EchA \cdot [ECH]}{K_{m,3} + [ECH]}$$

$$\frac{d[CPD]}{dt} = \frac{k_3 \cdot EchA \cdot [ECH]}{K_{m,3} + [ECH]} - \frac{k_4 \cdot HheC \cdot [CPD]}{K_{m,4} + [CPD]}$$

$$\frac{d[GDL]}{dt} = \frac{k_4 \cdot HheC \cdot [CPD]}{K_{m,4} + [CPD]} - \frac{k_5 \cdot HheC \cdot [GDL]}{K_{m,5} + [GDL]}$$

$$\frac{d[GLY]}{dt} = \frac{k_5 \cdot HheC \cdot [GDL]}{K_{m,5} + [GDL]}$$

- biodegradation of toxic substrate and intermediates
- synthetic pathway utilising enzymes from two other bacteria

  Rhodococcus rhodochrous NCIMB 13064; *Agrobacterium radiobacter* AD1
- find optimal enzymes concentration balancing *metabolic burden* and *toxicity*

Case study: Biodegradation of Trichloropropane in *E. coli*

Desired behaviour:

"*TCP is finally completely degraded and the concentration of intermediates does not exceed given bounds*"

Formally:

$$\varphi_1 = (\mathbf{A}([TCP] > x)\mathbf{U}(\mathbf{AF}(\mathbf{AG}\ [TCP] < y))),$$

$$\varphi_2 = (\mathbf{A}([GLY] < y)\mathbf{U}(\mathbf{AF}(\mathbf{AG}\ [GLY] > x))),$$

$$\varphi_3 = (\mathbf{AG}\ [DCP] < v) \wedge (\mathbf{AG}\ [GDL] < w),$$

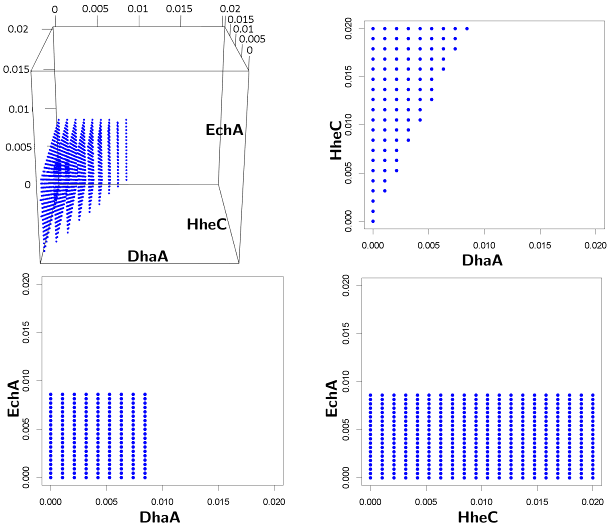
$$\varphi = (\varphi_1 \wedge \varphi_2 \wedge \varphi_3),$$

where x, y, v and w are estimated values making an instance of this property:

- $x = 1.9$ (according to authors[1] using the value 2 mM),
- $y = 0.01$ (obviously, cannot be zero),
- $v \in \{0.5, 0.3, 0.1\}$ (variations based on experimental data observation)
- $w \in \{0.5, 0.25, 0.1\}$ (variations based on experimental data observation)

[1] Kurumbang et al., ACS Synthetic Biology, 2013

Case study: Biodegradation of Trichloropropane in *E. coli*

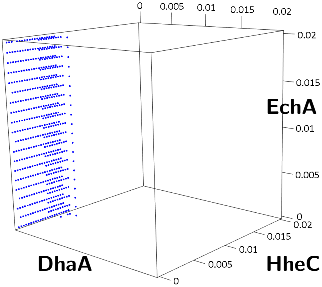


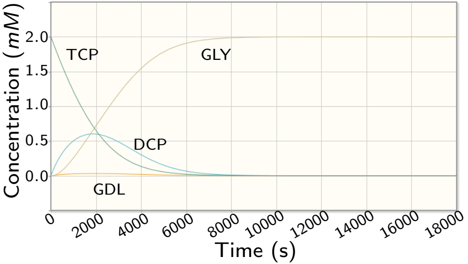
A sample of the resulting parameter space for a particular initial state:
TCP $\in [1.9, 1.9586]$, DCP $\in [0.448898, 0.5]$, GDL $\in [0.0, 0.0669138]$, GLY $\in [0.0, 0.01]$

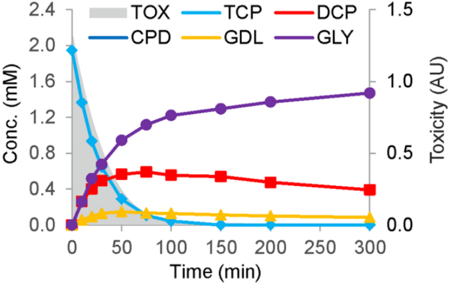
Dotted area corresponds to φ ($v = 0.5$, $w = 0.25$).

Case study: Biodegradation of Trichloropropane in *E. coli*

Preliminary Biological Validation





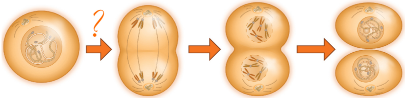


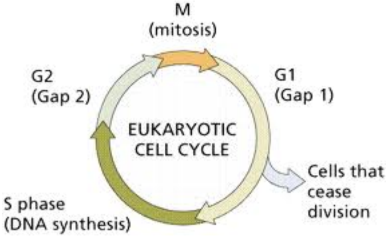
Outline

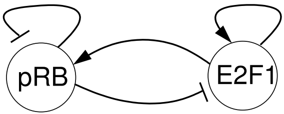
Motivation: How Parameters Influence Systems Dynamics?

Example: decision making in living cells

— *to divide or not to divide?*



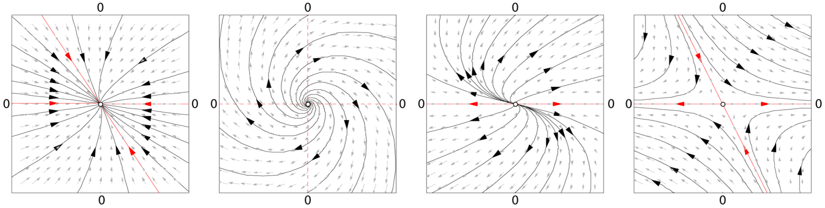




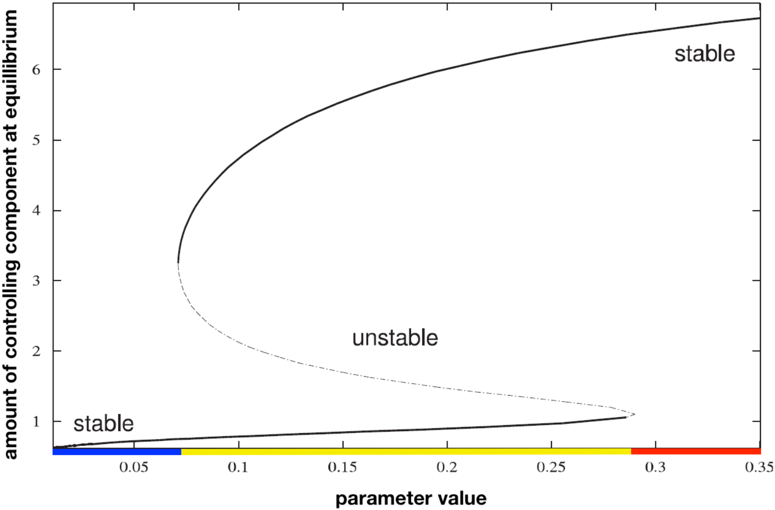
[Swat et al. 2004]

decisions implemented by circuits of positive and negative interactions
modelling of cell cycle since 1970 [Goldbetter et al.]

typical **phase portraits** around equilibria:



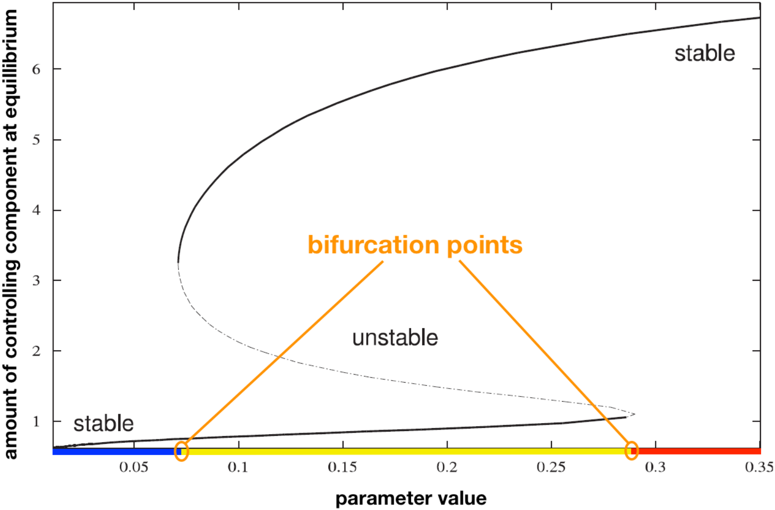
- bifurcation is defined as a topological change in phase space
  - small change in parameter $\Longrightarrow$ qualitative change in dynamics
  - the goal of bifurcation analysis is to **identify bifurcation points**



cannot divide can decide for division must divide

Motivation: How Parameters Influence Systems Dynamics?

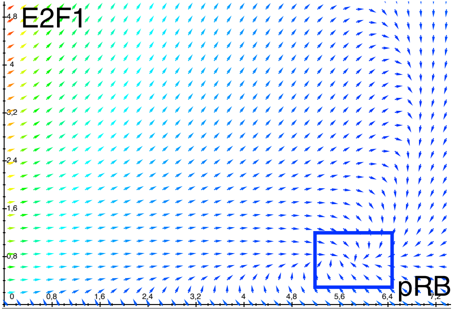
Bifurcation Analysis in Systems Theory



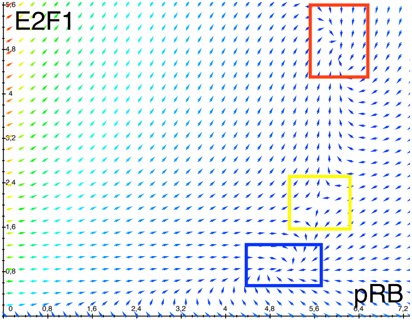
cannot divide | can decide for division | must divide

Motivation: Models of Complex Dynamical Systems
Understanding Role of Parameters

- in the vector field the equilbria have certain patterns
- the patterns change with parameters (appear, disappear, change shape)

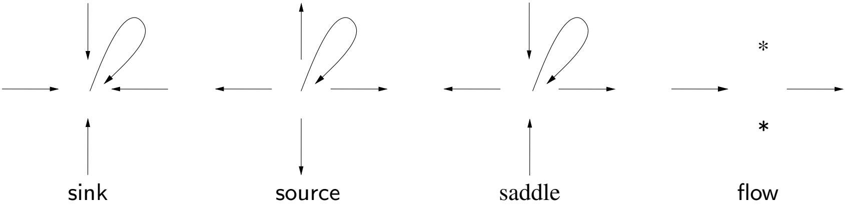


$p = 0.006$

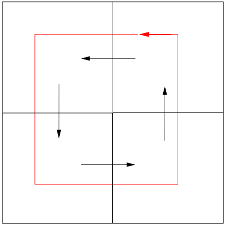


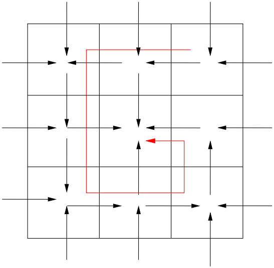
$p = 0.012$

Single-state patterns



Multi-state patterns





Phase Portrait Specification

- elementary patterns describe temporal behaviour in states
  - (in)stability, stabilisation, flow direction, ...
  - in non-deterministic system: possibility or inevitability
- employ **temporal logics** to formalise the patterns
- need to express branching over labeled transitions, future and past, state variables
  - stability (sink)
    there is a state with no outgoing transition (only a self-loop)
  - instability (source)
    there is a state with no incoming transition (only a self-loop)
  - increasing flow
    only transitions in particular direction
- some work done – UCTL [ter Beek et al.], hybrid logics [Arellano et al. 2011], ...

we combine all of these – introduce HUCTL_P

Phase Portrait Specification: HUCTL_P

- HUCTL_P — hybrid UCTL with past
- in addition to AP there are **direction formulae**:

$$\chi ::= \mathit{true} \mid d \mid \neg\chi \mid \chi \wedge \chi \text{ where } d \in \mathit{Dir}$$

- state formulae

$$\varphi ::= \mathit{true} \mid p \mid \neg\varphi \mid \varphi \wedge \varphi \mid \mathbf{E}\,\psi \mid \mathbf{A}\,\psi \mid \hat{\mathbf{E}}\,\psi \mid \hat{\mathbf{A}}\,\psi \mid x \mid \downarrow x.\varphi \mid @x.\varphi \mid \exists x.\varphi$$

- path formulae

$$\psi ::= \mathbf{X}_\chi\,\varphi \mid \varphi\,{}_\chi\mathbf{U}\,\varphi \mid \varphi\,{}_\chi\mathbf{U}_\chi\,\varphi \mid \varphi\,{}_\chi\mathbf{W}\,\varphi \mid \varphi\,{}_\chi\mathbf{W}_\chi\,\varphi$$

Phase Portrait Specification: HUCTL$_P$

Single-state patterns

- sink (stable steady state): $\downarrow s.\, \mathbf{AX}\, s$
- source (only self-loops, no other incoming): $\downarrow s.\, \hat{\mathbf{A}}\mathbf{X}\, s$
- 2d-saddle (nort-south outgoing, west-east incoming):

$$\mathbf{AX}_{N\vee S}\, \mathit{true} \wedge \mathbf{EX}_N\, \mathit{true} \wedge \mathbf{EX}_S\, \mathit{true} \wedge$$
$$\hat{\mathbf{A}}\mathbf{X}_{E\vee W}\, \mathit{true} \wedge \hat{\mathbf{E}}\mathbf{X}_E\, \mathit{true} \wedge \hat{\mathbf{E}}\mathbf{X}_W\, \mathit{true}$$

Multi-state patterns

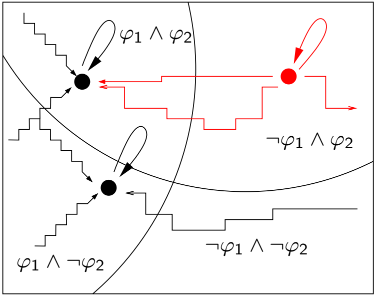
- state in a nontrivial SCC: $\downarrow s.\, \mathbf{EX}\, \mathbf{EF}\, s$
- state in a final SCC (generalised sink): $\downarrow s.\, \mathbf{AG}\, \mathbf{EF}\, s$

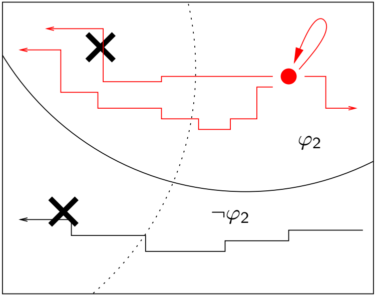
Relations among patterns

- at least two sinks in the whole system:
  $\exists s. \exists t. (@s. \neg t \wedge \mathbf{AX}\, s) \wedge (@t.\, \mathbf{AX}\, t)$

phase portrait specification $\phi = \{\varphi_1, \varphi_2\}$
phase portrait pattern $X_\phi = \{\varphi_1 \wedge \varphi_2, \varphi_1 \wedge \neg\varphi_2, \neg\varphi_1 \wedge \varphi_2, \neg\varphi_1 \wedge \neg\varphi_2\}$

subpatterns, e.g., $X' = \{\neg\varphi_1 \wedge \varphi_2, \neg\varphi_1 \wedge \neg\varphi_2\} \subset X_\phi$





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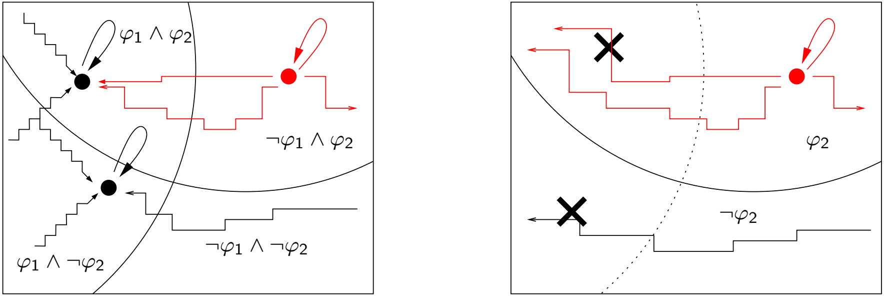


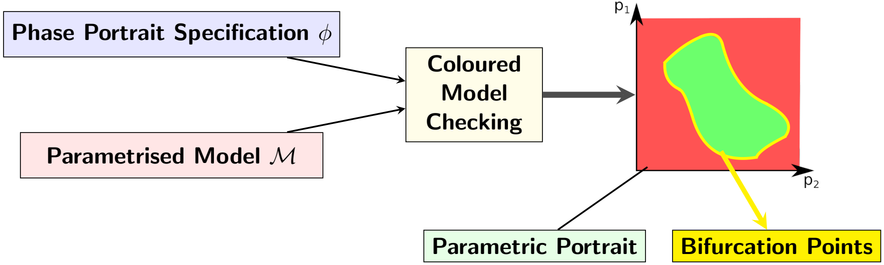
Parametric Phase Portrait

- parameter space $\mathcal{P}$
- $\mathcal{P}(\varphi) \subseteq \mathcal{P}$ all parameters for which there is a state satisfying φ
- **stratum**: $\Gamma_{X_\phi} = \bigcap_{\varphi \in X_\phi} \mathcal{P}(\varphi)$, $\Gamma_{X'} = \bigcap_{\varphi \in X'} \mathcal{P}(\varphi)$, ...
- $p \in \mathcal{P}$ is a **bifurcation point** if it is a *boundary point of some stratum*

Discrete Bifurcation Analysis Problem

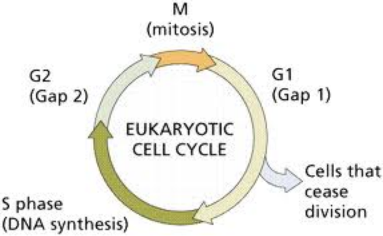
Problem Definition

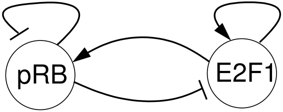
Assume $\mathcal{P}$ is a finite partially ordered domain representing the *m*-dimensional **parameter space**. Given a *parameterised model* $\mathcal{M}$ and a *phase portrait specification* ϕ, **compute the parametric portrait** of $\mathcal{M}$ wrt ϕ and **identify all bifurcation points** in $\mathcal{P}$ wrt $\mathcal{M}$ and ϕ.



Outline

Case Study: Regulation of G_1/S Cell Cycle Transition





[Swat et al. 2004]

$$\frac{d[pRB]}{dt} = k_1 \frac{[E2F1]}{K_{m1}+[E2F1]} \frac{J_{11}}{J_{11}+[pRB]} - \phi_{pRB}[pRB]$$
$$\frac{d[E2F1]}{dt} = k_p + k_2 \frac{a^2+[E2F1]^2}{K_{m2}^2+[E2F1]^2} \frac{J_{12}}{J_{12}+[pRB]} - \phi_{E2F1}[E2F1]$$

bifurcation analysis wrt ϕ_{pRB}

Analysed phase portrait pattern:

- $\varphi_1 := \exists s.\exists t.(@s.\,\mathbf{AG}\,\mathbf{EF}\,s) \wedge (@t.\neg\,\mathbf{EF}\,s \wedge \mathbf{AG}\,\mathbf{EF}\,t) \wedge \mathbf{E}_{\neg\mathrm{N}}\mathbf{F}\,s \wedge \mathbf{E}_{\neg\mathrm{S}}\mathbf{F}\,t$
- $\varphi_2 := \neg\varphi_1 \wedge {\downarrow} s.\,\mathbf{AG}\,\mathbf{EF}\,s \wedge E2F1 < 4$
- $\varphi_3 := \neg\varphi_1 \wedge {\downarrow} s.\,\mathbf{AG}\,\mathbf{EF}\,s \wedge E2F1 > 4$

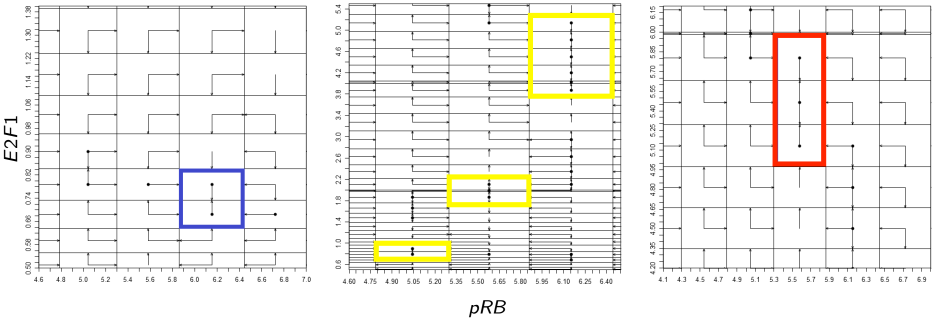
Case Study: Workflow

INPUT: phase portrait specification $\{\varphi_1, \varphi_2, \varphi_3\}$
ODE model

1. approximate the ODE model by a piece-wise multi-affine model
2. construct $\mathcal{M}$ by discretisation of the approximate model
3. run discrete bifurcation analysis procedure

OUTPUT: parametric phase portrait
bifurcation points

Case Study: Results



φ_2 $\qquad$ φ_1 $\qquad$ φ_3

$\phi_{pRB} = 0.0075$ $[0.002, 0.011]$

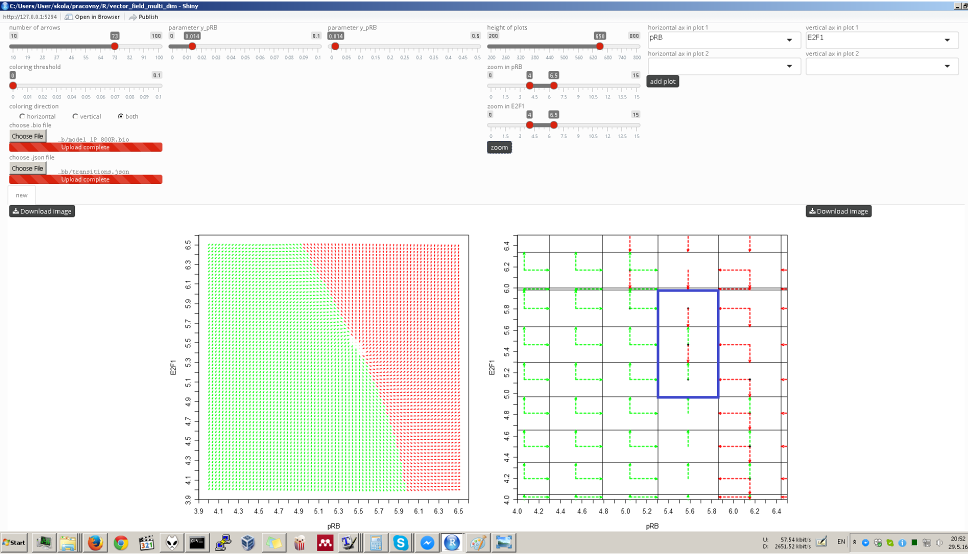
$\phi_{pRB} = 0.0115$ $[0.011, 0.0136]$

$\phi_{pRB} = 0.014$ $[0.0136, 0.5]$

bifurcation points: $\{0.011, 0.0136\}$

results agree with numerical methods up-to precision of approximation/discretisation

Coming Soon


C:/Users/User/skola/pracovny/R/vector_field_multi_dim - Shiny
http://127.0.0.1:5294
Open in Browser
Publish
number of arrows
parameter y_pRB
parameter y_pRB
height of plots
horizontal ax in plot 1
pRB
vertical ax in plot 1
E2F1
horizontal ax in plot 2
vertical ax in plot 2
add plot
coloring threshold
zoom in pRB
zoom in E2F1
zoom
coloring direction
horizontal
vertical
both
choose .bio file
Choose File
b/model_1P_800R.bio
Upload complete
choose .json file
Choose File
bb/transitions.json
Upload complete
new
Download image
Download image
E2F1
pRB
E2F1
pRB
Start

Conclusions

- exploiting dynamical systems under parameter uncertainty by model checking
- scalability achieved for number of parameters
- remaining challenges:
  - approximation: explore errors, what can be guaranteed?
  - abstraction: narrow the extent of overapproximation – can Darboux polynomials or barrier certificates help?
  - improve scalability w.r.t. systems dimensionality
  - is it possible to combine model checking with simulation? [TCSB XIV, 2012]

Other Contributions

Those worth mentioning

- specific for deterministic models:
  - STL* – value-freezing logic, monitoring, parameter exploration and robustness analysis

L. Brim, P. Dluhoš, D. Šafránek, T. Vejpustek. STL*: Extending signal temporal logic with signal-value freezing operator. Information and Computation, Volume 236, pp. 52-67, 2014

- specific for stochastic models:
  - parametric uniformisation for CTMC and CSL

L Brim, M Ceska, S Drazan, and D.Safranek. Exploring parameter space of stochastic biochemical systems using quantitative model checking. In CAV 2013. Lecture Notes in Computer Science, Volume 8044, 2013, pp 107-123.

M. Ceska, D. Safranek, S. Drazan, L. Brim: Robustness Analysis of Stochastic Biochemical Systems, (2014) Robustness Analysis of Stochastic Biochemical Systems. PLoS ONE 9(4): e94553.

- universally applicable methods:
  - formal language for biochemical space [SASB 2014, 2015]
  - parameter synthesis by coloured model checking
    $\rightarrow$ applied to boolean networks [CMSB 2012, 2013]
    $\rightarrow$ applied to qualitative abstractions of ODE models [HSB 2015, CMSB 2015, this talk]