

Parameter Synthesis and Robustness Analysis of Rule-Based Models

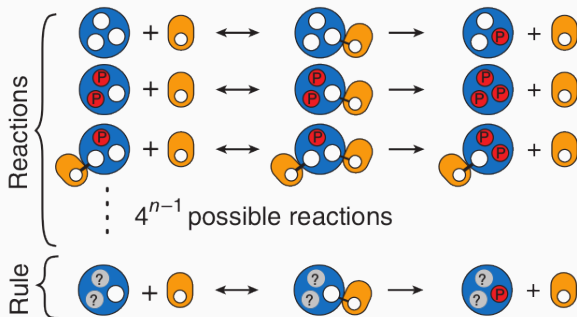
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- **systems biology** – understand the (biological) system of interest by building a model
- modelling dominated by *explicit* model formats such as ODEs, reaction-based systems, Petri nets, ...
- hard to organise, develop, and edit (e.g. extend by new information)
- scalability of the description

Rule-based modelling

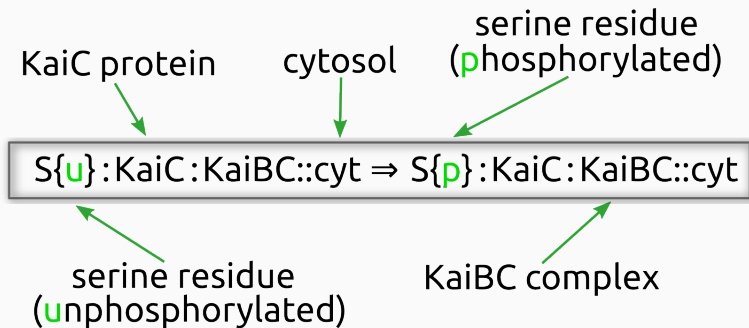
- compact extension of reaction-based systems
- suitable for the description of biological systems since the context/details are often not known



- there exist several representatives (Kappa, BNGL, Chromar, etc.)

BioChemical Space Language (BCSL)

- a high-level rule-based language for biochemical interactions
- focus on *human-readability* while preserving formal aspects
- part of an annotation format for *Comprehensive Modelling Platform*



- **State change**

1. $S\{u\}::\text{cell} \Rightarrow S\{p\}::\text{cell}$
2. $E.S\{u\}::\text{cell} \Rightarrow E.S\{p\}::\text{cell}$
3. $R(\text{active}\{\text{off}\})::\text{cyt} \Rightarrow R(\text{active}\{\text{on}\})::\text{cyt}$

- **Complex formation**

4. $E::\text{cell} + S\{u\}::\text{cell} \Rightarrow E.S\{u\}::\text{cell}$
5. $\alpha.\alpha::\text{out} + \beta.\beta::\text{out} \Rightarrow \alpha.\alpha.\beta.\beta::\text{out}$

- **Transport**

6. $\text{Prot}::\text{cell} \Rightarrow \text{Prot}::\text{out}$
7. $\Rightarrow \text{mRNA}::\text{nuc}$

- **Zooming inside the structure**

`act{off}:A():A().B()::cell` \Rightarrow `act{on}:A():A().B()::cell`

- **Define an alias for complex**

`AB = A().B()`

`AC = A().C()`

`AD = A().D()`

- **Usage of a variable**

`act{off}:A():?::cell` \Rightarrow `act{on}:A():?::cell` ; `? = {AB, AC, AD}`

- extension by quantitative dynamical aspects (in this paper)
- associating rules with rational *rate functions*
- quantifies the rule rate – how likely it is

$$S\{u\}::\text{cell} \Rightarrow S\{p\}::\text{cell} @ k1 \times [S\{u\}::\text{cell}]$$

BCSL model – example

```
#! rules
T(P{i})::cyt ⇒ T(P{m})::cyt @ a1×[T(P{i})::cyt]
T(P{m})::cyt ⇒ 2 T(P{i})::cyt @ a2×[T(P{m})::cyt]
T(P{i})::cyt ⇒ @ d1×[T(P{i})::cyt]
T(P{m})::cyt ⇒ @ d2×[T(P{m})::cyt]

#! inits
2 T(P{m})::cyt
1 T(P{i})::cyt

#! definitions
a2 = 0.5
d1 = 0.3
```


- a rule can be applied to a *state* by match–replace pair of actions
 1. appropriate agents are *matched* according to LHS of rule and rate function is evaluated
 2. matched agents are modified according to the RHS
 3. original agents are *replaced* by the modified ones
- given an initial state of the model, by transitive application of rules we obtain a labelled transition system
 - by normalisation of transition labels, the semantics of BCSL model is a **(parametrised) Discrete Time Markov Chain**

- probabilistic semantics \Rightarrow behavioural properties expressed in **Probabilistic CTL** (PCTL)

$$P \Rightarrow 0.3 \quad [F S\{u\}::cell > 0]$$

$$P =? \quad [F S\{u\}::cell > 0]$$

- model checking and local robustness in *non*-parametric case
- parameter synthesis and global robustness in parametric case
 - for PCTL analysis used external tool Storm model checker – method based on state elimination (finite state automaton \rightarrow regular expression)

- $P \bowtie n [\varphi]$ with $\bowtie \in \{\leq, <, >, \geq\}$ and $n \in [0, 1]$
→ boolean answer
- $P =? [\varphi]$
→ probability of satisfaction of path formula φ

- $P \bowtie n [\varphi]$ with $\bowtie \in \{\leq, <, >, \geq\}$ and $n \in [0, 1]$
→ partitioning of given parameter space (allowed intervals for unknown parameters) to SAT, UNSAT, and UNKNOWN regions (with defined precision)
- $P =? [\varphi]$
→ satisfiability function of parameters
(its evaluation for particular parametrisation – point in parameter space – provides the probability that the model satisfies path formula φ)

The *global robustness* of a system s is defined as

$$R_{a,P}^s = \int_P \psi(p) D_a^s(p) dp$$

- a is the property of the system under scrutiny,
- P is the set of all perturbations,
- $\psi(p)$ is the probability of the perturbation p ,
- *local robustness* $D_a^s(p)$ is a measure stating how much the property a is preserved in perturbation p .

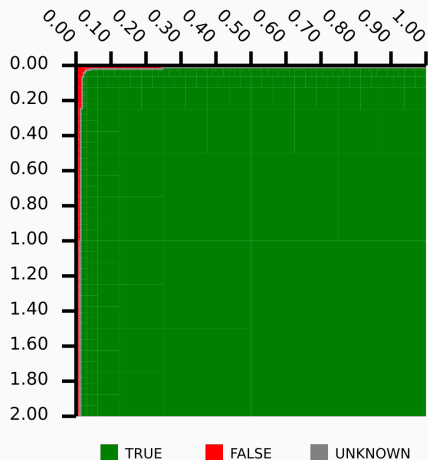
For a BCSL model \mathcal{M} , the *global robustness* can be computed as

$$R_{\phi, \mathbf{P}}^{\mathcal{M}} = \int_{\mathbf{P}} \frac{1}{|\mathbf{P}|} \mathfrak{f}(\mathbf{p}) d\mathbf{p}$$

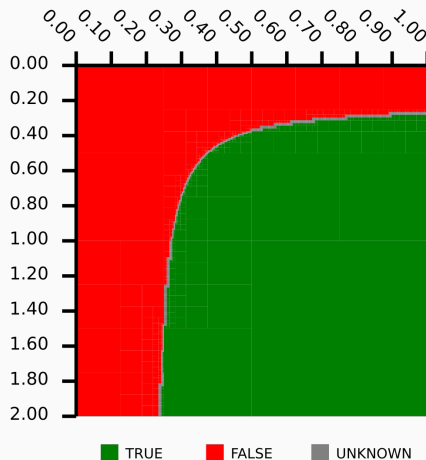
- ϕ is the property (with the outermost operator $P = ?$),
- \mathbf{P} is the parameter space,
- uniform probability $\psi(\mathbf{p}) = \frac{1}{|\mathbf{P}|}$ of parametrisation \mathbf{p} ,
- the *local robustness* can be computed as evaluation of satisfiability function of parameters $\mathfrak{f}(\mathbf{p})$ (obtained from parameter synthesis)

- an adopted (and simplified) version of Miyoshi et al. 2007 model describing circadian rhythms in cyanobacteria
- typical oscillatory behaviour of the model performed by repeated phosphorylation and de-phosphorylation of a protein complex KaiC
- two experiments to validate oscillatory behaviour of key product
 1. reach a *phosphorylated* form from an *unphosphorylated* one with **high probability**
 2. *vice versa*

Case studies – circadian clock



$P \geq 0.99 [F \text{ KaiC}(S\{p\}, T\{p\}) . \text{KaiC}(S\{p\}, T\{p\}) :: \text{cyt} > 0]$
global robustness ~ 0.995



$P \geq 0.99 [F \text{ KaiC}(S\{u\}, T\{u\}) . \text{KaiC}(S\{u\}, T\{u\}) :: \text{cyt} > 0]$
global robustness ~ 0.98

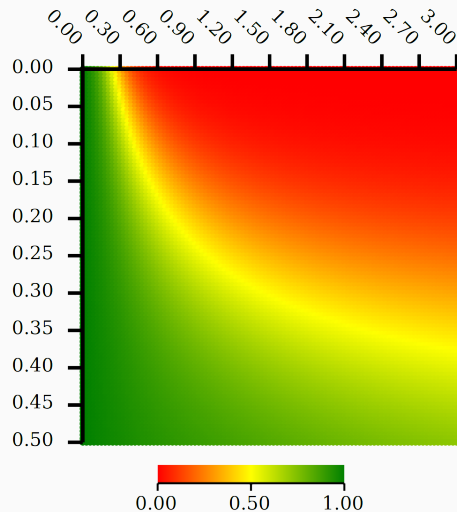
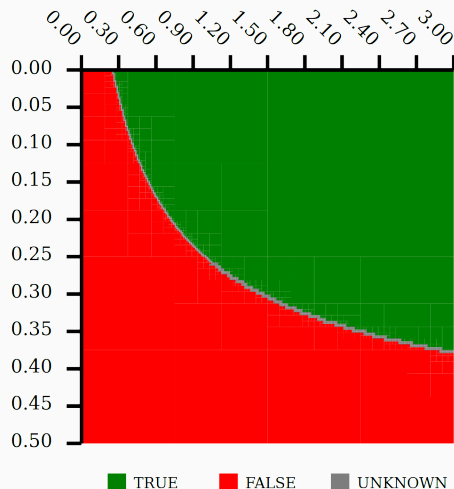
Case studies – tumour growth

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Case studies – tumour growth



property $P \geq 0.5$ [F T() :: cyt > 8]

- BioChemical Space Language with methods for exact analysis of probabilistic behaviour
- future steps are to focus on scalability issues – avoid explicit transition system enumeration using symbolic approaches and static analysis
- tool eBCSgen (submitted to CMSB'20)
 - available at <https://biodivine-vm.fi.muni.cz/galaxy>
 - all case-study data available in shared dataset
<https://biodivine-vm.fi.muni.cz/galaxy/u/xtrojak/h/ebcsgen-nfm-2020>