

Methods for Modelling and Analysing Dynamics of Very Large Interaction Networks

Loïc Paulevé

CNRS / LRI, Université Paris-Sud, France (Bioinfo team)

Associate member of INRIA AMIB project

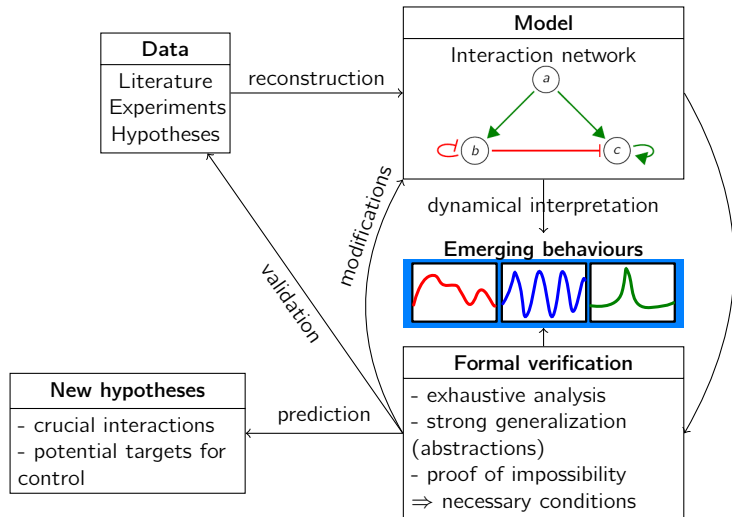
`loic.pauleve@lri.fr`

`http://loicpauleve.name`

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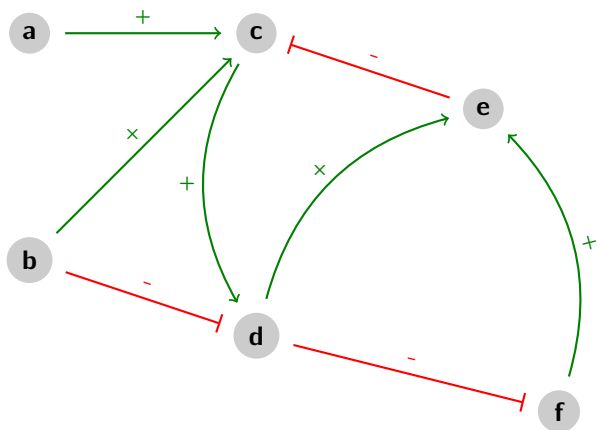
Formal Methods for Systems Biology

Aim: understand, analyse, control emerging dynamics.



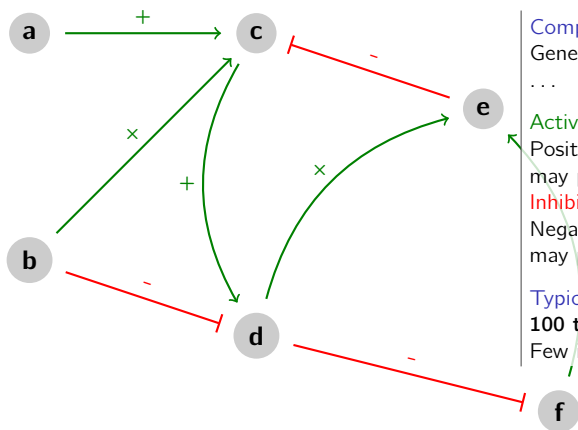
Interaction Networks

E.g., Signalling Networks



Interaction Networks

E.g., Signalling Networks



Components

Genes, proteins, complexes,
...

Activations

Positive influence (*a* increase may promote *c* increase).

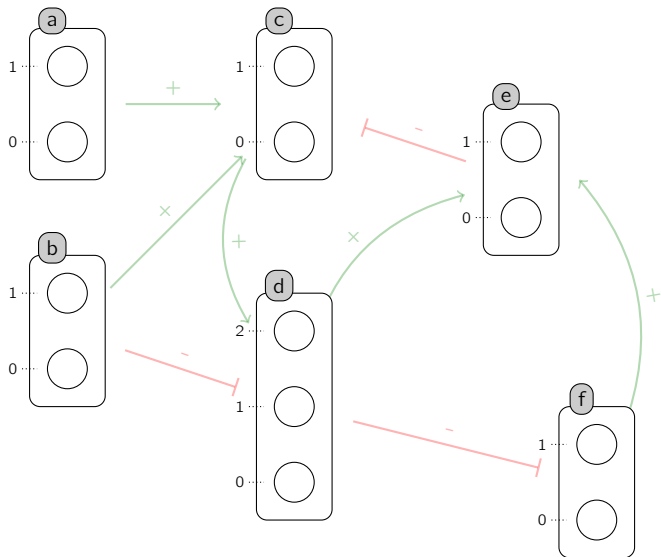
Inhibitions

Negative influence (*b* increase may promote *d* decrease).

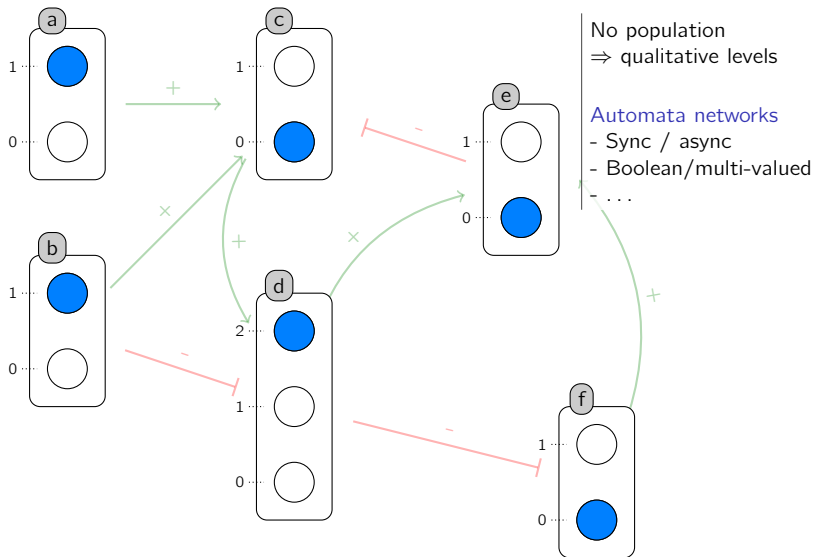
Typical settings

100 to +10,000 components
Few information on kinetics

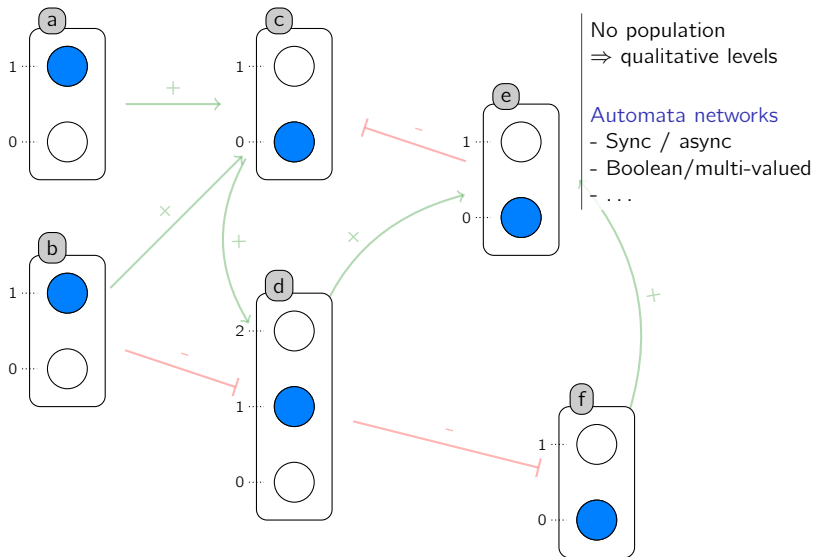
Qualitative Models for Interaction Networks



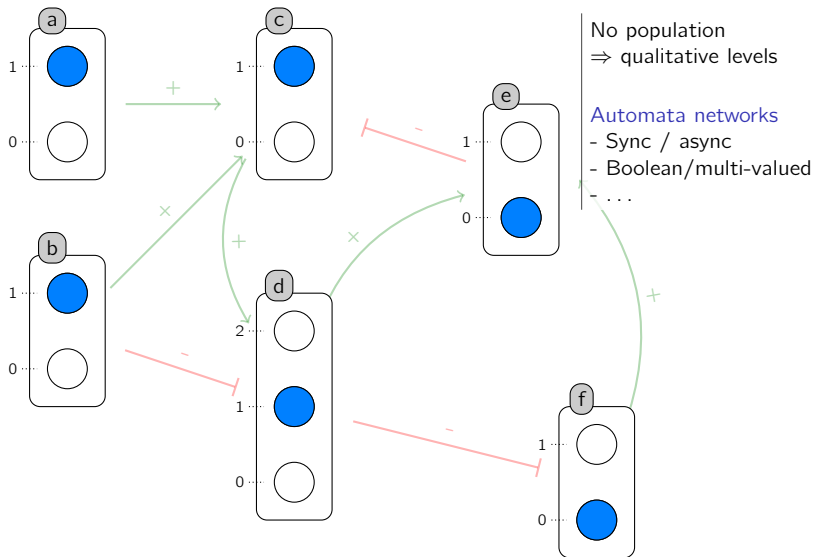
Qualitative Models for Interaction Networks



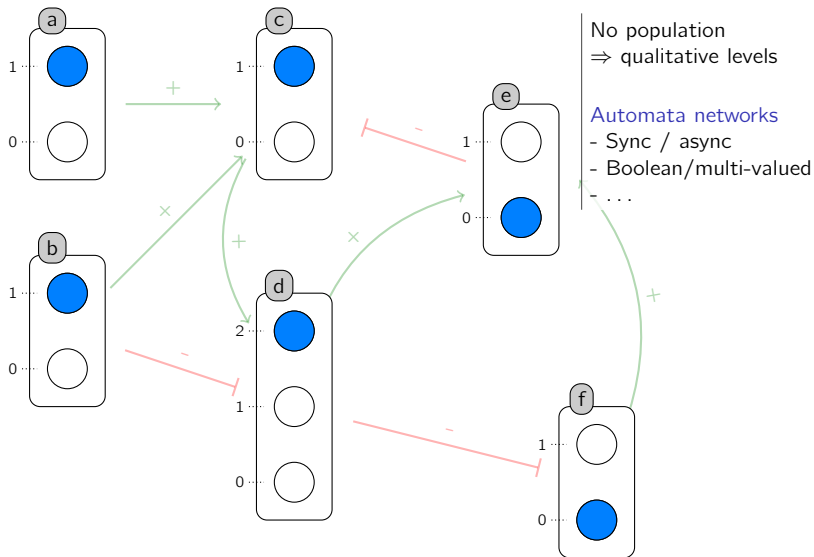
Qualitative Models for Interaction Networks



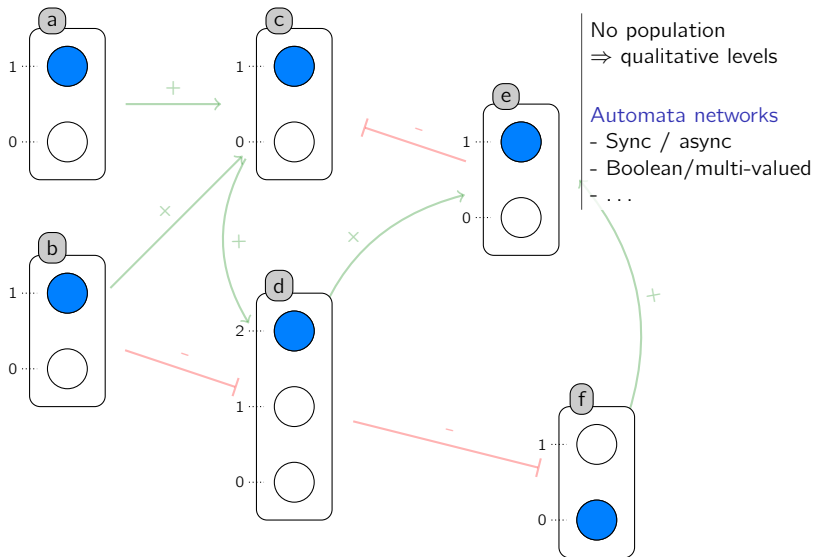
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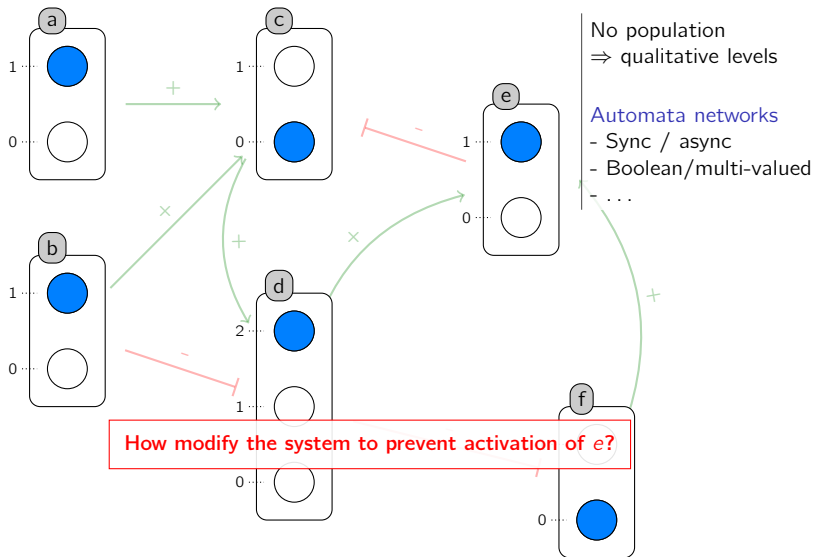
Qualitative Models for Interaction Networks



Qualitative Models for Interaction Networks



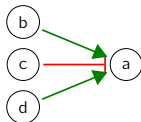
Qualitative Models for Interaction Networks



Issues with Large Interaction Networks

Modelling issues

- Partially-specified interactions.
- Boolean networks need to be fully specified (deterministic Boolean function f_a).
- Intractable enumeration of all models.



Analysis issues

- Combinatorial explosion of behaviours (e.g. 2^{100} to 2^{10000} states).
- Large range of initial conditions to consider.
- Difficult to extract comprehensive proofs of (im)possibility.

Failure of classical model-checking techniques,

Need **new formal approaches** to capture dynamics of large networks

① Discrete Modelling with the Process Hitting

② Analysing Dynamics

Graph of Local Causality

Reachability

Cut Sets for Reachability

③ Hybrid Modelling

1 Discrete Modelling with the Process Hitting

2 Analysing Dynamics

Graph of Local Causality

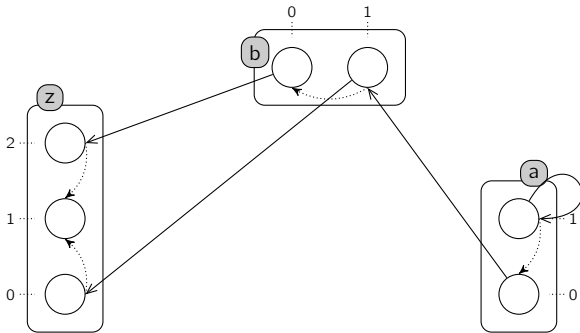
Reachability

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3 Hybrid Modelling

The Process Hitting Framework

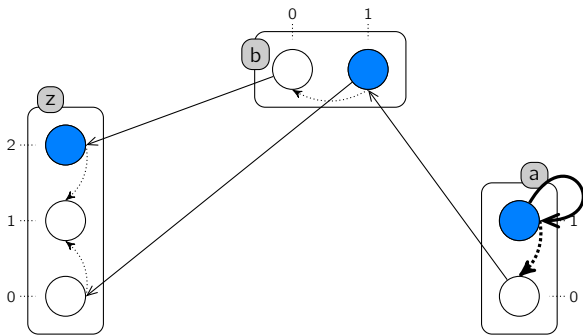
[Paulevé, Magnin, Roux in TCSB 2011]



- **Automata:** a, b, z ; **Processes:** $a_0, a_1, b_0, b_1, z_0, z_1, z_2$;
- **Actions:** a_0 hits b_1 to make it bounce to b_0, \dots ;
- **States:** $\langle a_1, b_1, z_2 \rangle, \langle a_0, b_1, z_2 \rangle, \langle a_0, b_0, z_2 \rangle, \dots$;

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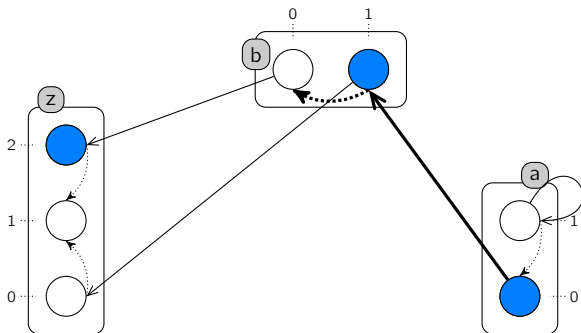
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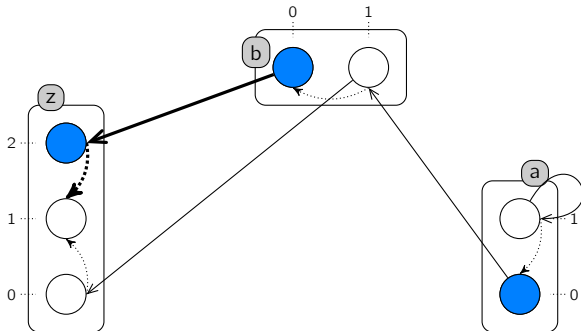
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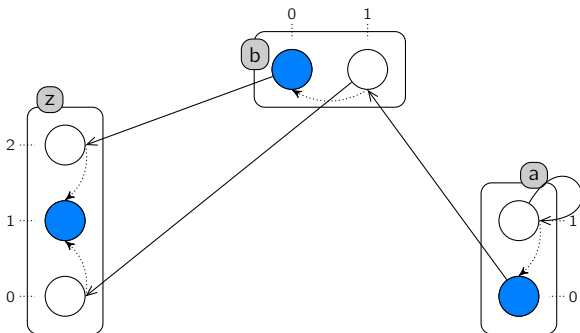
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The Process Hitting

Why a new framework?

Features of the Process Hitting

- Simple formalism; but enough to model networks dynamics.
- Special class of **Asynchronous Automata Networks** (or Petri Nets).
- A transition is **triggered by only one process** (biological or logical).

Advantages for Modelling

- **Atomic description** of transitions.
- Allows to model networks with **partial knowledge on cooperations**
 ⇒ encodes non-deterministic Boolean functions; e.g.:

$$f_a(x) = \begin{cases} 1 & \text{if } x_b = 1 \vee x_c = 1 \\ 0 & \text{if } x_b = 0 \vee x_c = 0 \end{cases}$$

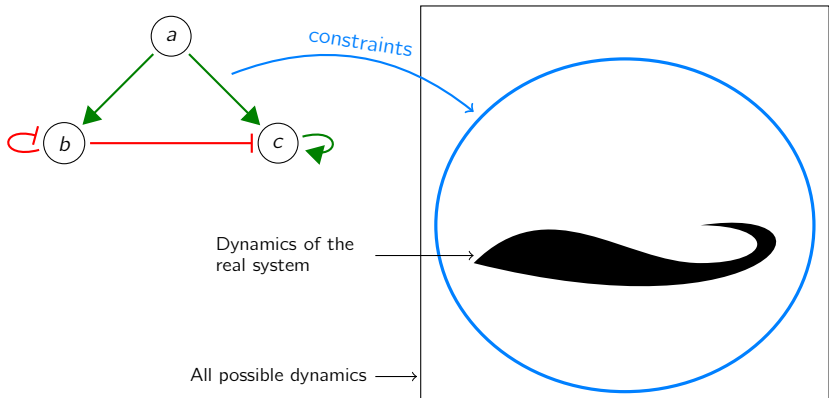
Advantages for Analysis

- Easy **fixed point derivation** (not shown in this talk).
- Very **efficient causality analysis**;
- allows **highly scalable reachability analysis**.

Limitations

- Synchronous update is complex to encode (but possible);
- Over-approximation approach: focus **mainly on necessary conditions** (but work in progress for the counterpart).

Generalised Dynamics of Interaction Networks

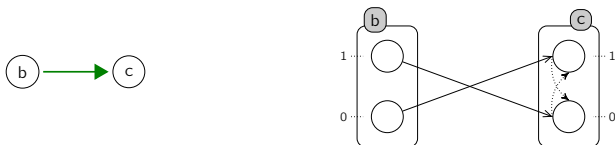


Dynamics over-approximation

- A component **can not increase** if none effective **activator** is present.
- A component **can not decrease** if none effective **inhibitor** is present.

Modelling Regulation with the Process Hitting

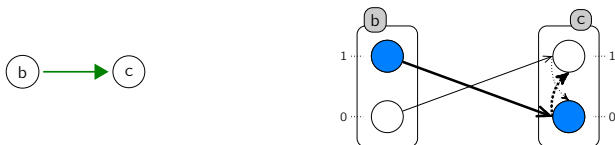
Boolean case:



- Independent regulations, automatic encoding of interaction graphs.
- Without knowledge of cooperation between regulators.
 ⇒ most permissive dynamics of the network.

Modelling Regulation with the Process Hitting

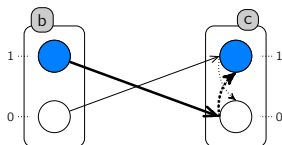
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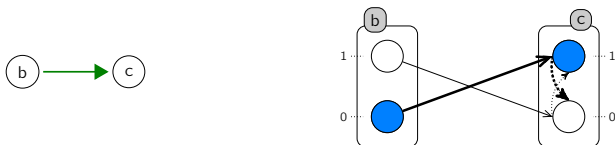
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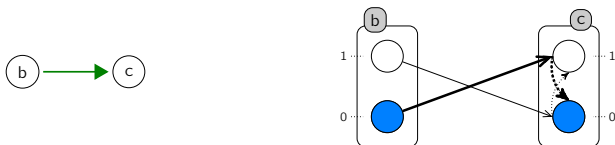
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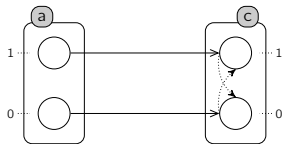
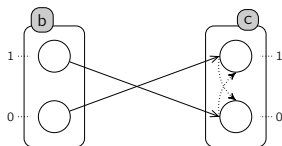
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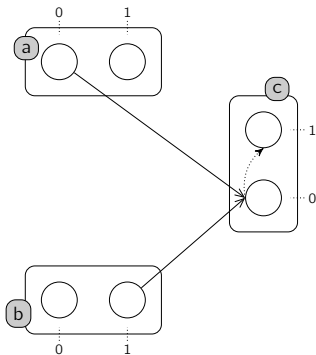
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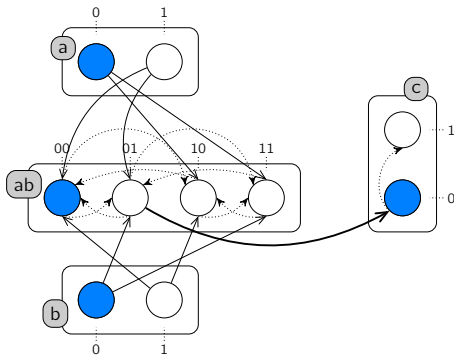
Refining with Cooperation

- Constraint: $c_0 \uparrow c_1$ when a_0 and b_1 are present.
- Introduction of a **cooperative automata** reflecting the state of a and b .



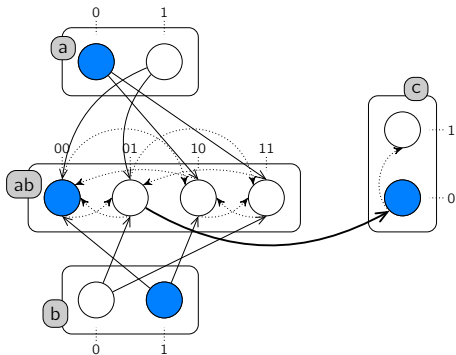
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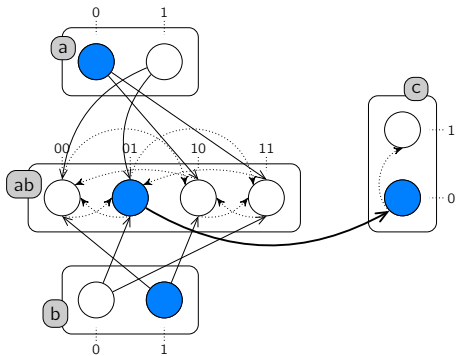
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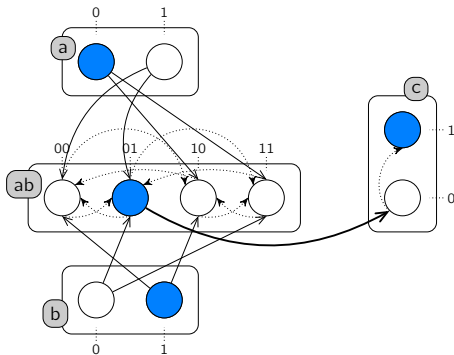
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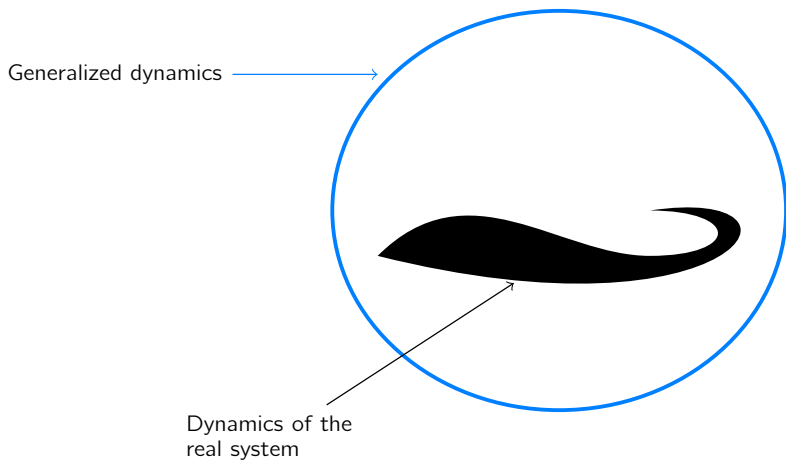
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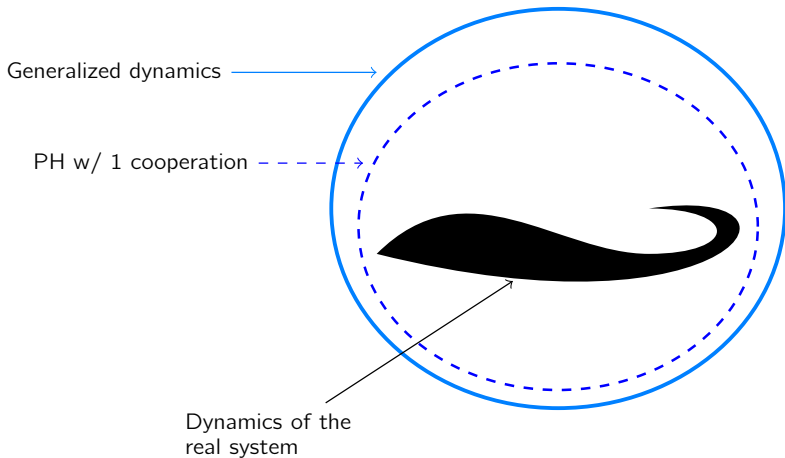


⇒ The Process Hitting can model **any interaction network** with **partial knowledge** on the cooperations (over-approximation of dynamics).

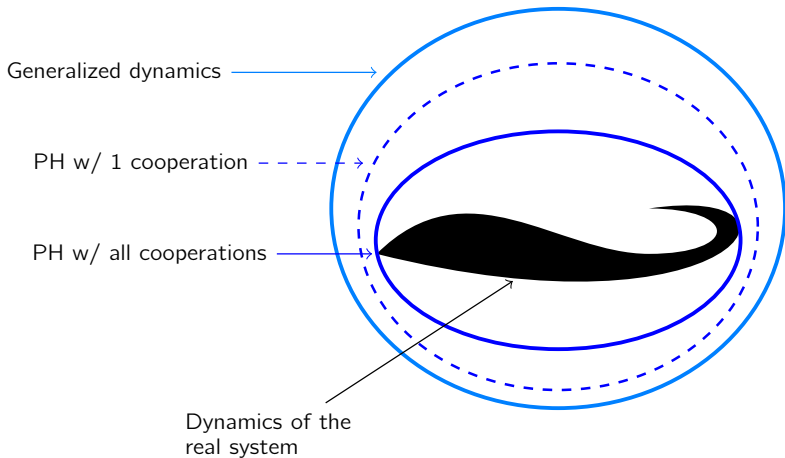
Abstraction Relationships



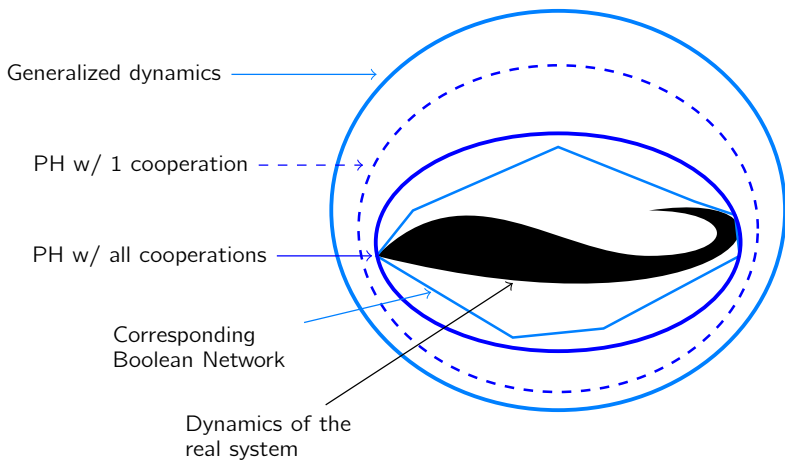
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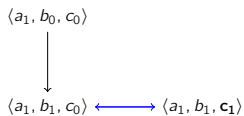
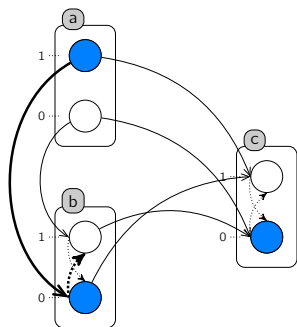
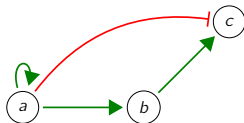
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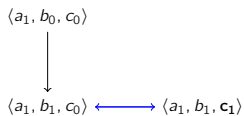
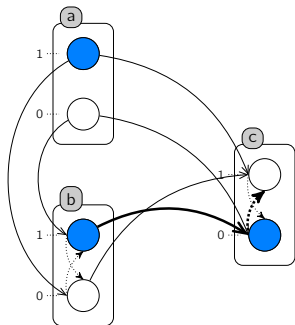
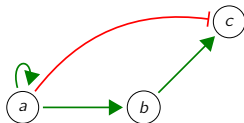
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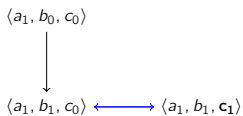
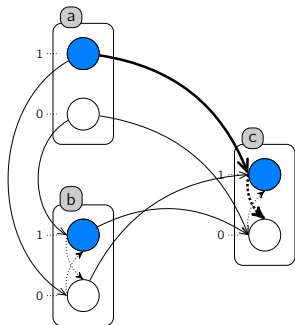
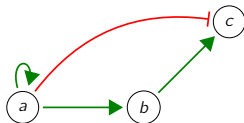
Toy example
Incoherent feed-forward loop



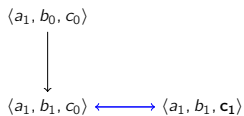
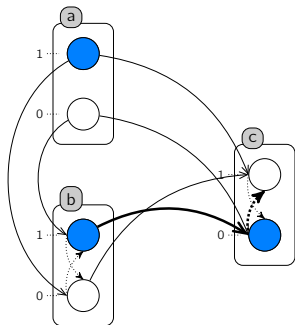
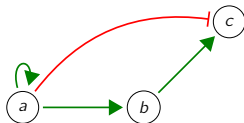
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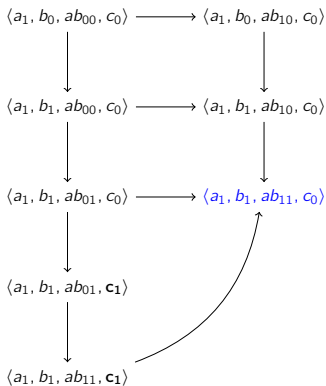
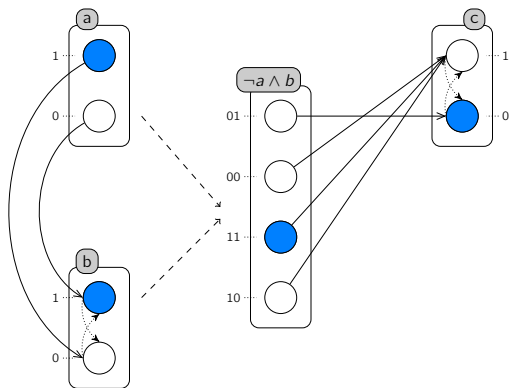
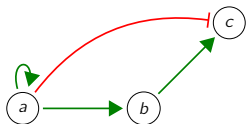


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1 Discrete Modelling with the Process Hitting

2 Analysing Dynamics

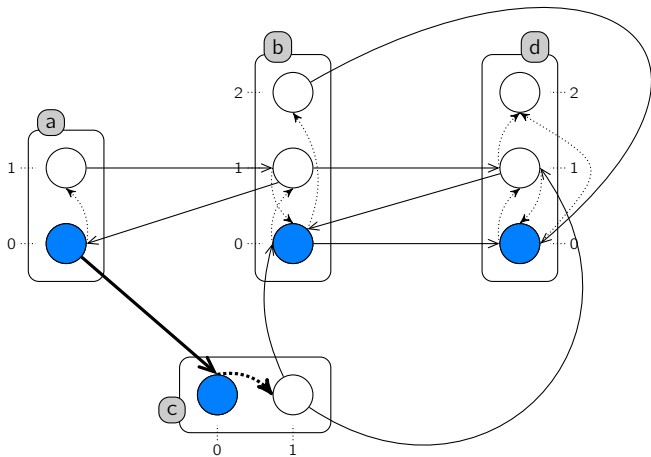
Graph of Local Causality

Reachability

Cut Sets for Reachability

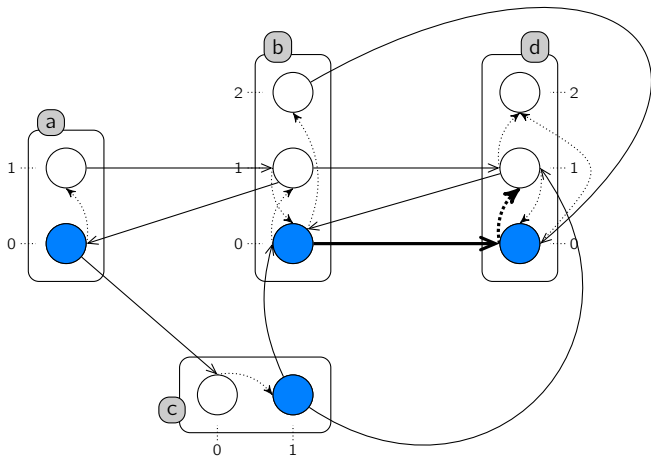
3 Hybrid Modelling

Looking for Scenarios



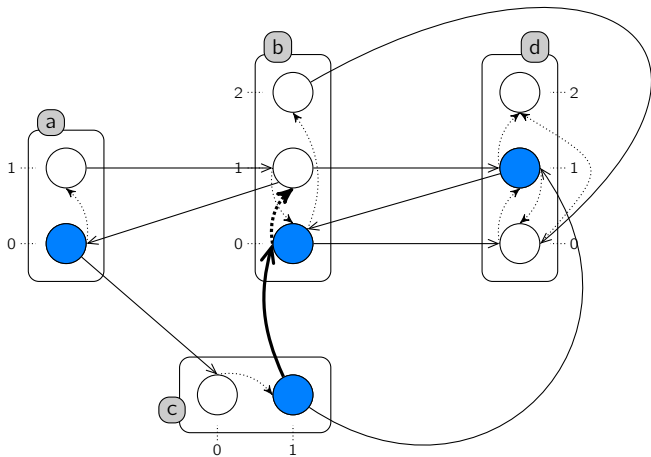
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Looking for Scenarios



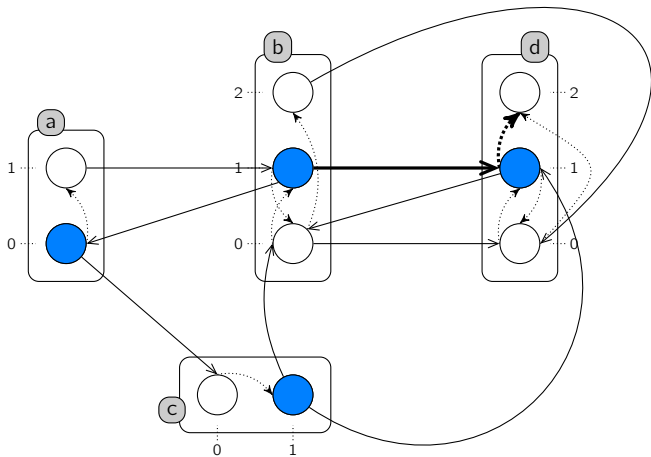
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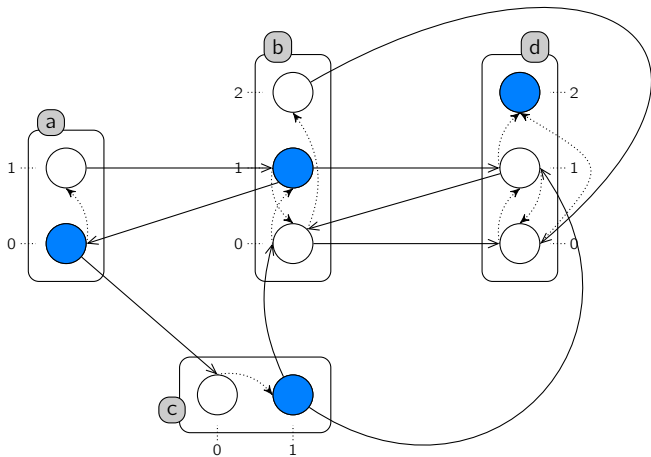
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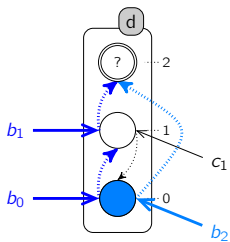
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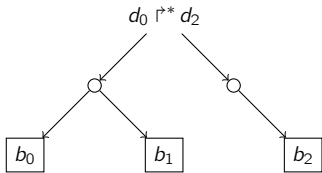
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Local Causality

Minimal solutions

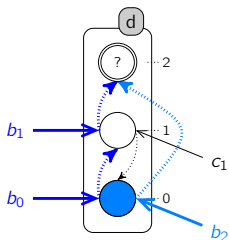


$$\text{sol}(d_0 \uparrow^* d_2) = \{\{b_0, b_1\}, \{b_2\}\}.$$

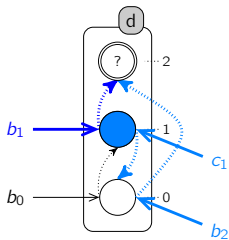
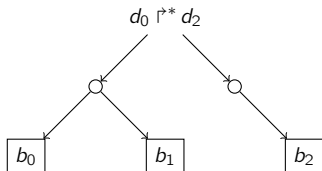


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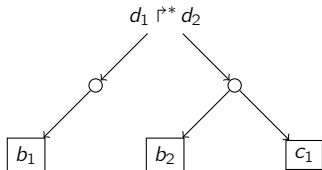
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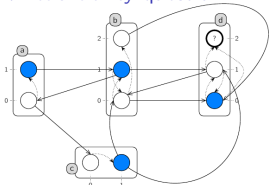
$$\text{sol}(d_1 \uparrow^* d_2) = \{\{b_1\}, \{b_2, c_1\}\}.$$



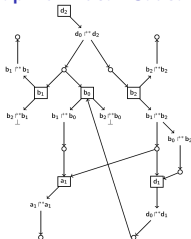
Efficient Reachability Analysis

Abstract interpretation of Process Hitting dynamics

Process Hitting
+ reachability question



Graph of Local Causality



Necessary/sufficient
conditions

Yes / No /
Maybe

Reach a_i , then b_j , etc.

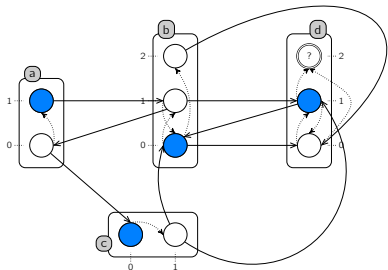
- Over- and under-approximations of local reachability properties.
- Low complexity: $\text{poly}(\text{nb. automata}) \times \exp(\text{nb of procs in one automaton})$

\implies efficient with a small number of processes per automaton, while a very large number of automata can be handled.

[Mathematical Structures in Computer Science (2012); workshop SASB'10]

Over-approximation of Reachability

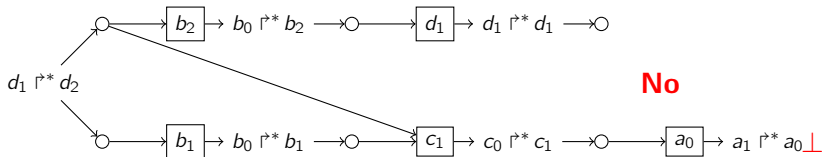
Example



Necessary condition for reaching d_2 :

There exists a traversal of the GLC s.t.:

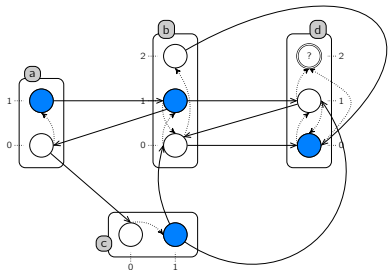
- objective \rightarrow follow at least one solution;
- process \rightarrow follow all objectives;
- no cycle.



No

Over-approximation of Reachability

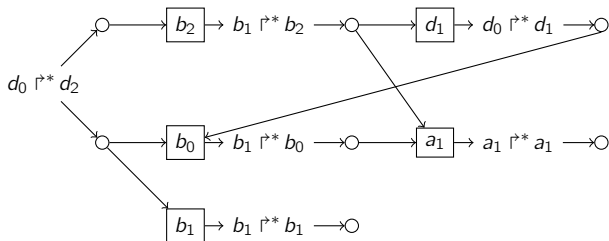
Example



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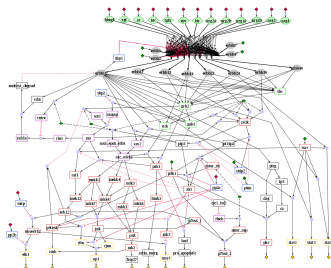


Inconc

Applications

- Signalling networks.
- Wide-range of biological/arbitrary reachability analysis.
- Always conclusive.

Model	Biocham ¹	libDDD ²	PINT ³
EGFR 20	[3s-KO]	[1s-150s]	0.007s
TCR 40	[1s-KO]	[0.6s-KO]	0.004s
TCR 94	KO	KO	0.030s
EGFR 104	KO	KO	0.050s



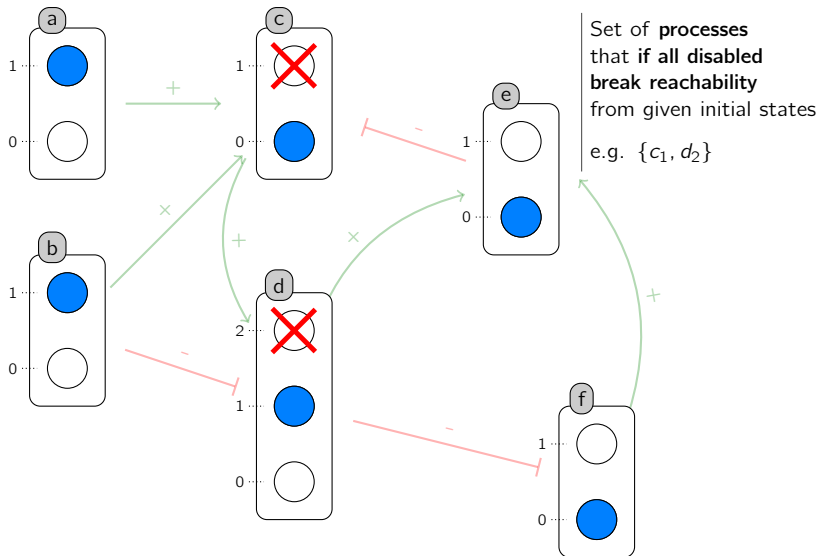
¹ <http://contraintes.inria.fr/biocham> (using NuSMV2)

² <http://move.lip6.fr/software/DDD>

³ <http://loicpauleve.name/pint>

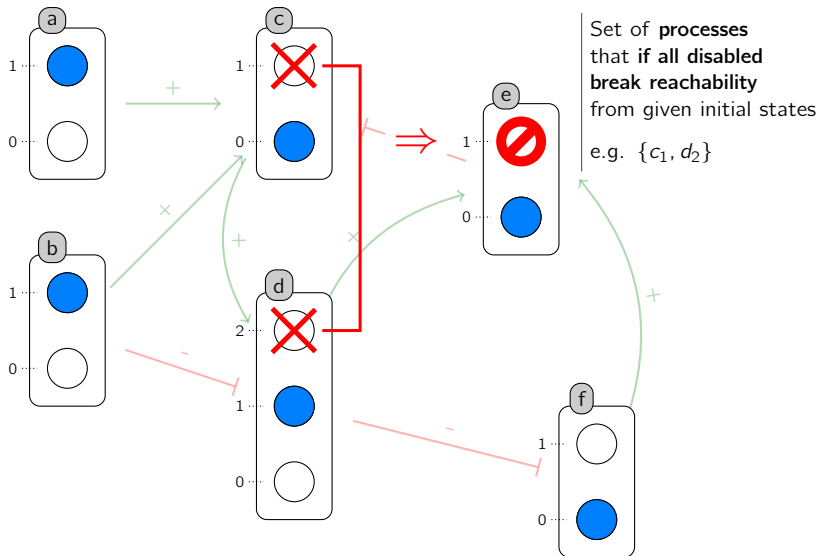
Cut Sets for Reachability

[Paulevé et al. at CAV'13]



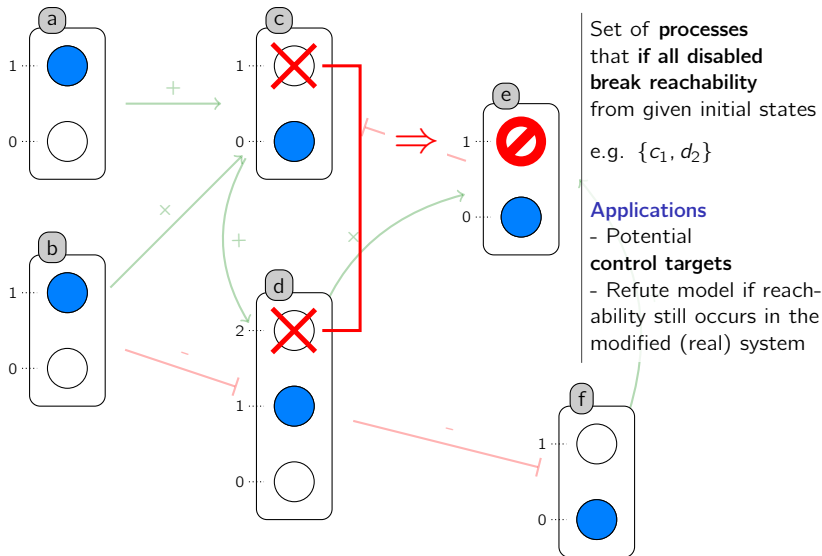
Cut Sets for Reachability

[Paulevé et al. at CAV'13]

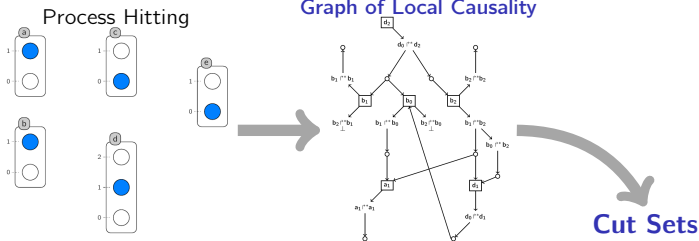


Cut Sets for Reachability

[Paulevé et al. at CAV'13]



Cut Sets for Reachability



Algorithm

- Graph flooding algorithm.
- Computes **all cut sets at once**: no enumeration of candidates.
- Very **efficient with large networks**.

Returned cut sets

- **All valid** (break the concerned reachability).
- Some may be missed, some may be non-minimal.

Formal analysis of the whole PID

Pathway Interaction Database

- Inductions, inhibitions, transcriptional regulation, complex formations, ...
- More than 9000 interacting components.
- Large environment (3000 entry-points).

Graph of Local Causality

- From Process Hitting model (Boolean interpretation).
- (Independent) reachability of active SNAIL, active p15INK4b.
- 20 000 nodes, including 5600 processes (biological or cooperative).

Cut N -sets computed

N	Exec. time	SNAIL ₁	p15INK4b ₁
1	0.9s	1	1
2	1.6s	+6	+6
3	5.4s	+0	+92
4	39s	+30	+60
5	8.3m	+90	+80
6	2.6h	+930	+208

1 Discrete Modelling with the Process Hitting

2 Analysing Dynamics

Graph of Local Causality

Reachability

Cut Sets for Reachability

3 Hybrid Modelling

Introducing Time and Probabilities

Motivations

- Quantifying probability of reachability properties.
- Quantifying time to reach a given state/attractor.

Related work

- Formal frameworks: hybrid automata, continuous-time Markov chains, etc.
- Tools: model-checkers (PRISM, UPPAAL); numerous simulations techniques.

Continuous-time Markov Chains (CTMCs)

- Each transition receives a rate (speed).
- Rates control the probability of taking transitions

$$P(s \rightarrow s') = \frac{\text{rate}(s \rightarrow s')}{\sum_{s''} \text{rate}(s \rightarrow s'')}$$

- Rates control the duration of transition

$$dt(s \rightarrow s') \sim \exp(-\sum_{s''} \text{rate}(s \rightarrow s''))$$

Suited for population-counting models, but issues with qualitative models!

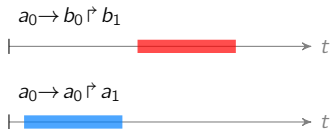
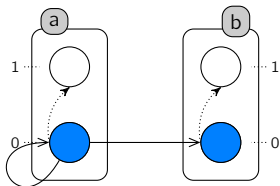
CTMCs for Qualitative Models

Issue

- Transition in qualitative models **hides multiple reactions**
- \Rightarrow some transitions may exhibit **very low duration variance**.
- **But the rate entirely controls the variance** (exponential distribution).

Proposed solution: Rate + **Stochasticity absorption factor** [Paulevé et al. IEEE TSE 11]

- Probability and duration can be independently tuned.
- Duration follows an **Erlang distribution** (non-Markovian setting).
- Allows to **encode any confidence interval for the duration**.
- Can still be converted to a regular CTMC at the end.



$\Rightarrow b_1$ is reached at a **very low probability**.

Ongoing-work: priorities and time-scales

Motivations

- Rates are difficult to estimate.
- Focus on time-scales (qualitative) rather than precise durations.

Approach

- Process Hitting with Priorities.
- Some actions are always taken first, when possible.
- Adapt previous abstract interpretations.

First results, research directions

- Scalable reachability analysis (under-approximation)
[Folschette et al. at CS2Bio'13].
- Take into account priorities for cut sets.

The Process Hitting framework

- Particular class of Asynchronous Automata Networks.
- Suited for modelling large interaction networks.
- Allows incomplete knowledge of cooperations (contrary to classical Boolean/multi-valued networks).

Formal analysis of dynamics

- Addressed in this talk: reachability and cut sets.
- Scalable thanks to abstract interpretation (potentially inconclusive).
- Graph of Local Causality provides comprehensive proofs.

Link with other formalisms

- Any Boolean network can be encoded in Process Hitting.
- Inference of Boolean networks from Process Hitting [Folschette et al. at CMSB'12].
- Automatic encoding of interaction databases in progress.

Pint Software

<http://loicpauleve.name/pint>

Pint

- Textual language for Process Hitting
- Command line utilities for analysis.

Main features

- **Reachability** analysis.
- **Cut set** analysis.
- Listing of **fixed points** (steady states).
- **Non-markovian simulator** for stochasticity absorption.
- **Importation** from various formats (CellNetAnalyser, SIF, ginML (partial), etc.)
- **Exportation** to various formats (PRISM, Biocham, Boolean networks, etc.)

Graphical interface in progress. . .

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