Capturing and Reducing Dynamics of Large-scale Automata Networks

Loïc Paulevé

LRI, CNRS / Université Paris-Sud, Orsay, France – BioInfo team

loic.pauleve@lri.fr

http://loicpauleve.name

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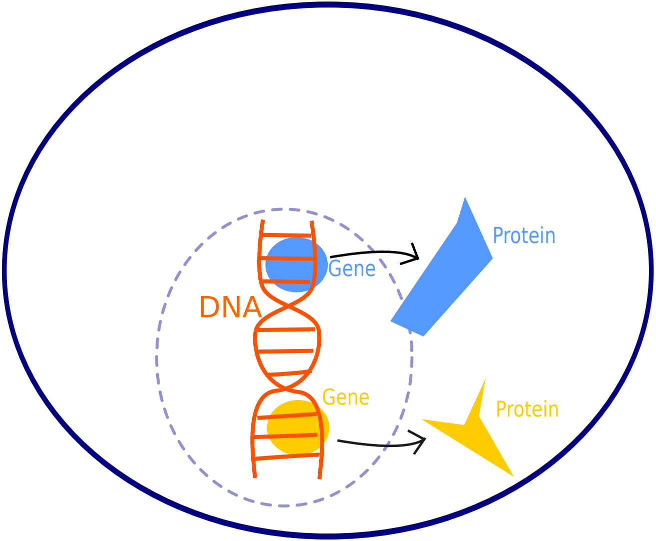
Biological Interaction Networks



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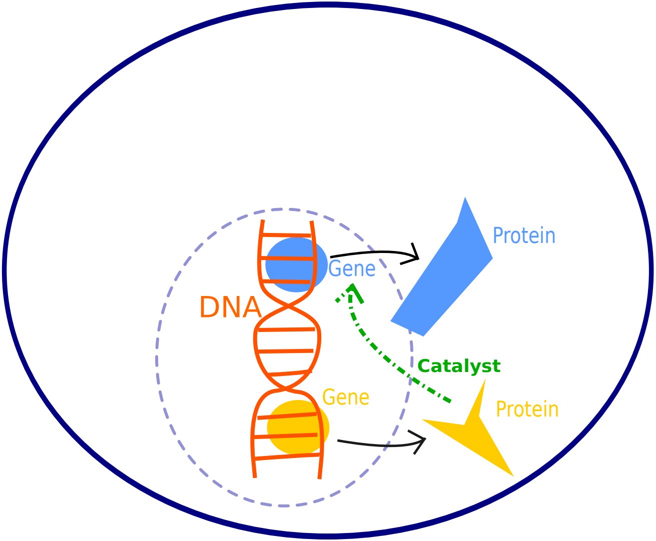

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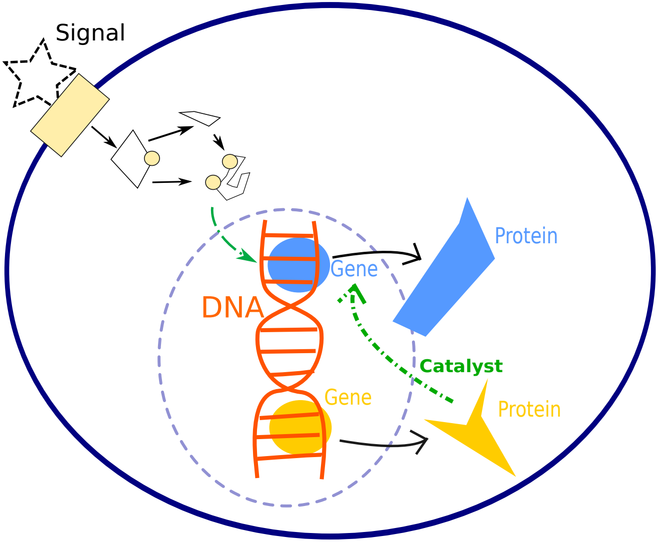
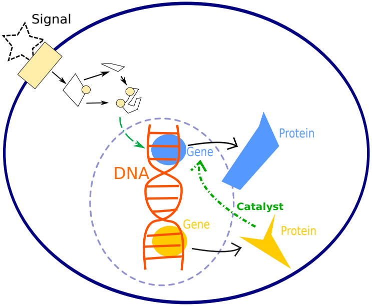


Biological Motivations



Prediction

- Cell response w.r.t. signal+environment
- Long-term behaviours (differentiation)

Control

- Mutations for modifying cell response
- Re-differentiation

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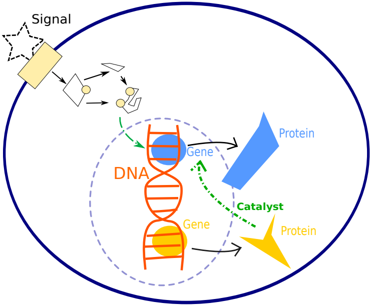

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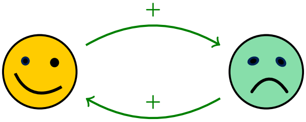
$\Rightarrow$ **Models** of the system **dynamics**
- Formal verification
- Synthesis

Interaction Networks

Qualitative approach

- Interacting Entities having simplistic behaviour (e.g.: happy/sad)
- Positive or negative influences
- Dynamical system: state of entities evolve with time
- Complex system: locally simple, emerging properties hard to predict



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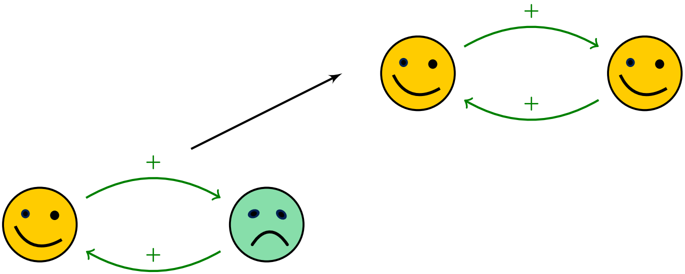

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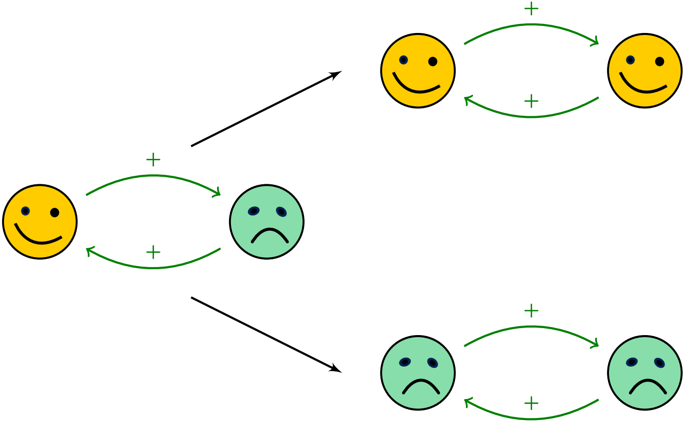

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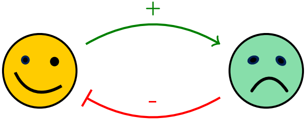

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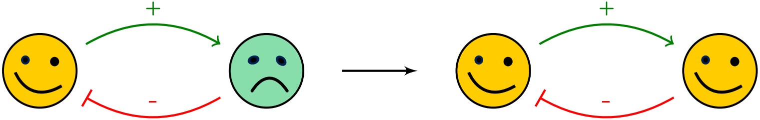

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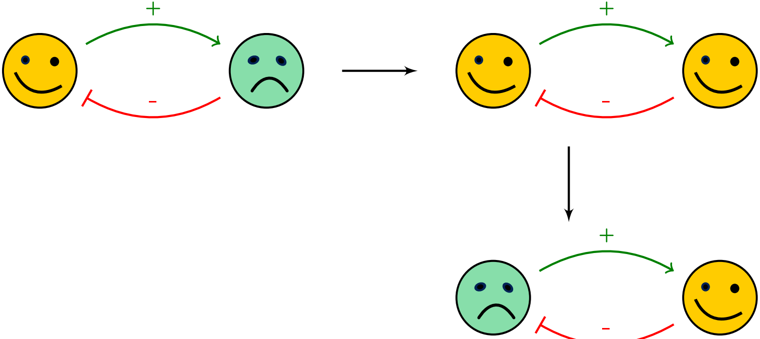

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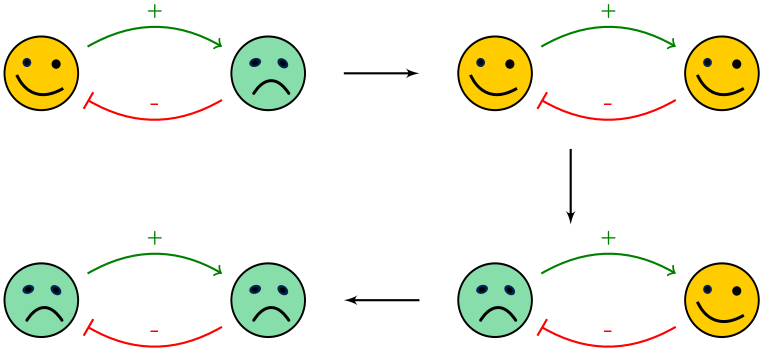

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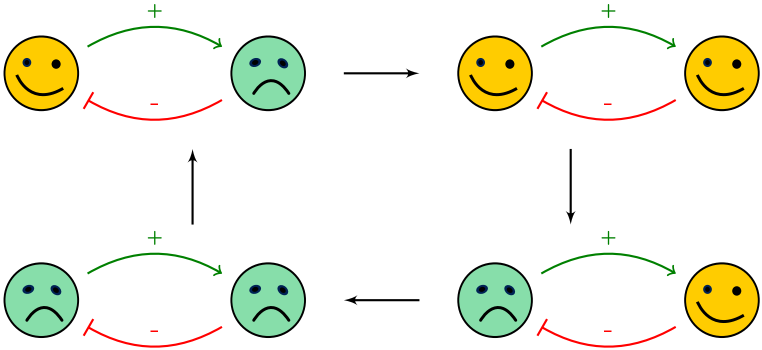
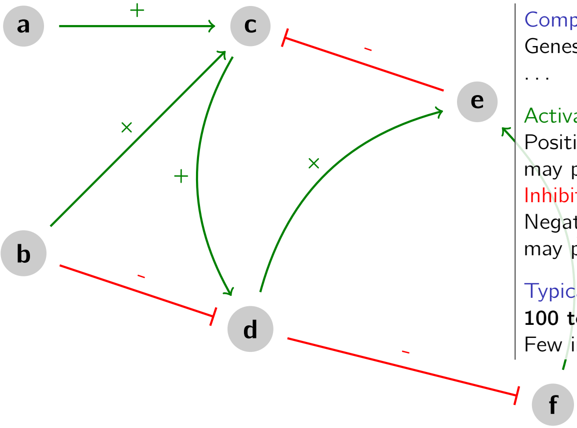


Interaction Networks

E.g., Signalling Networks, Gene Regulatory Networks



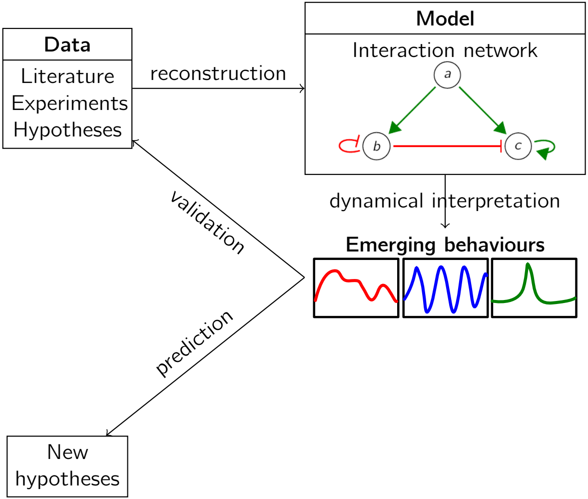
Components
Genes, proteins, complexes, ...

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

Formal Methods for Systems Biology

Aim: **understand, analyse, control** emerging dynamics.



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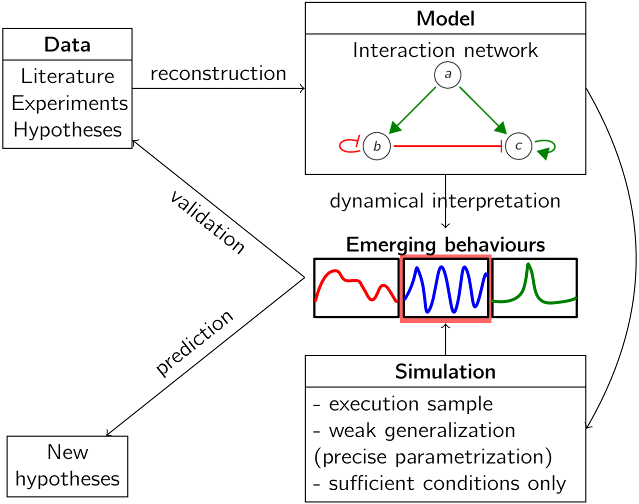

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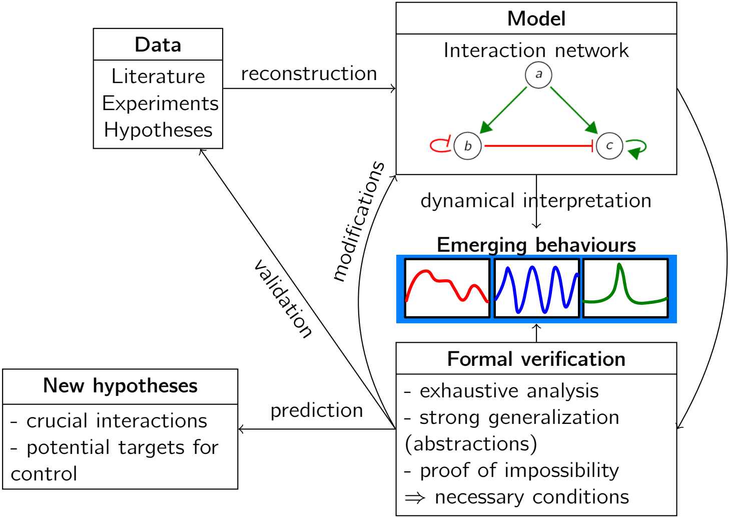
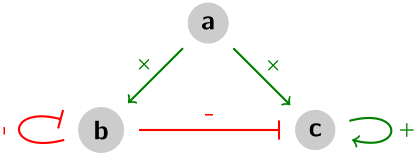


Dynamics of Qualitative Networks

Example in Boolean case



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$f^b(x) = x[a] \wedge \neg x[b]$

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$\langle a, b, c \rangle$ $\langle 1, 0, 0 \rangle$

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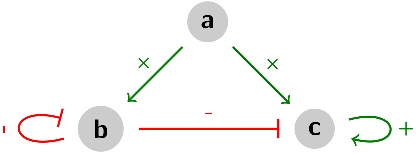

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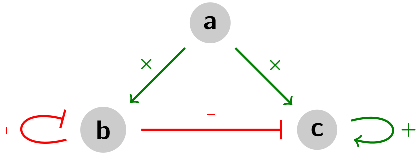

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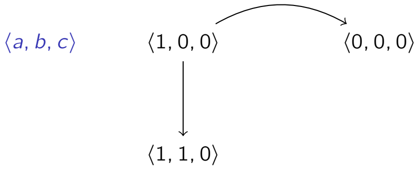

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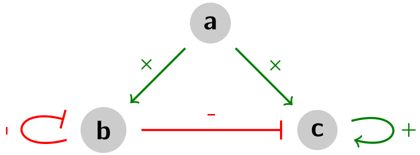

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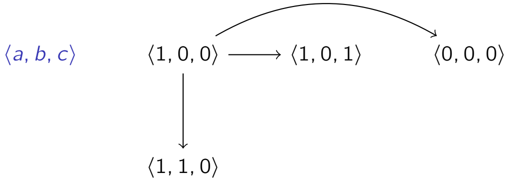

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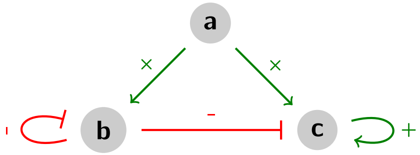

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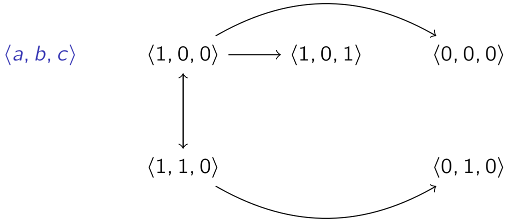

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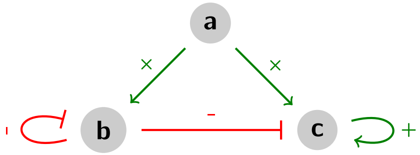

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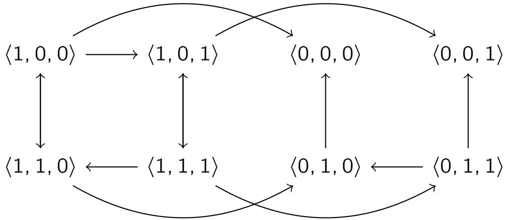

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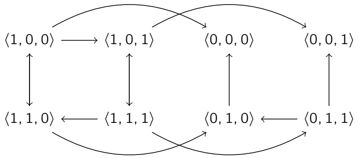
Formal Analysis of Dynamics



Reachability

- From given initial condition(s) (e.g. $\langle 1, 0, 0\rangle$),
- is it possible to activate component b and then c?

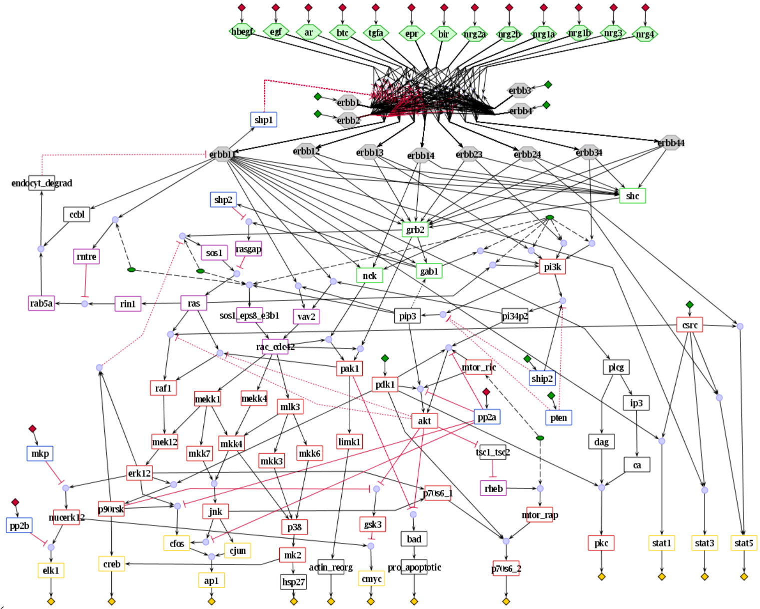
Control

- From given initial condition(s) (e.g. $\langle 1, 0, 0\rangle$),
- how to prevent the activation of component c?

Attractors

- What are the reachable long-term behaviours?
- How to jump from one attractor to another?

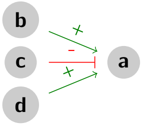
Issues with Large Interaction Networks



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} - 10^{30} to $2^{10\,000}$ - 10^{3000} states).
- Large range of initial conditions to consider.
- Difficult to extract comprehensive proofs of (im)possibility.

Contributions

Scalable analysis of **transient dynamics** of automata networks

Static analysis

Model $\longrightarrow$ Abstraction $\longrightarrow$ Decision (possibly incomplete)

Key ingredients

- Concurrent systems
- Transition-centered specification
- Causality analysis and abstraction

Results

- Prevent raw model-checking (PSPACE-complete)
- Derive necessary or sufficient conditions from abstractions
- Allow coupling with exhaustive analysis

Outline

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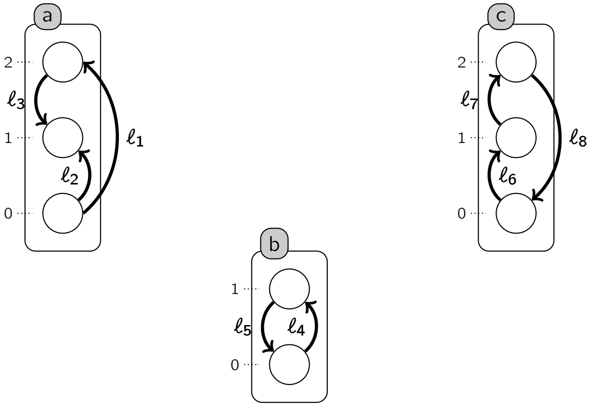
Asynchronous Finite Automata Networks



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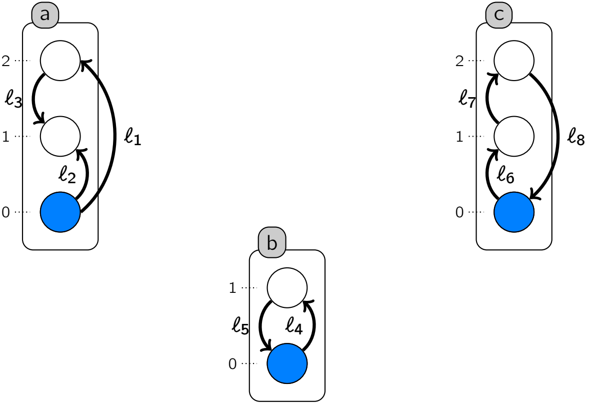

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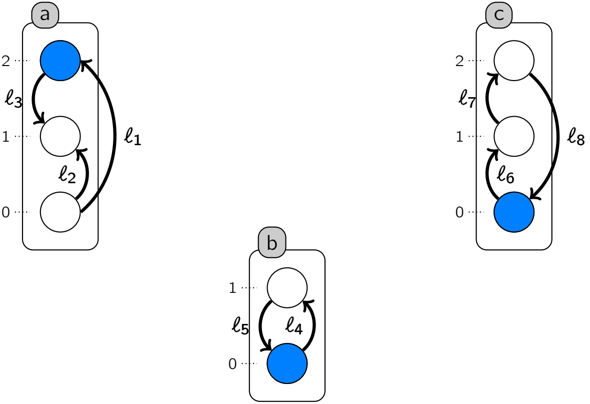

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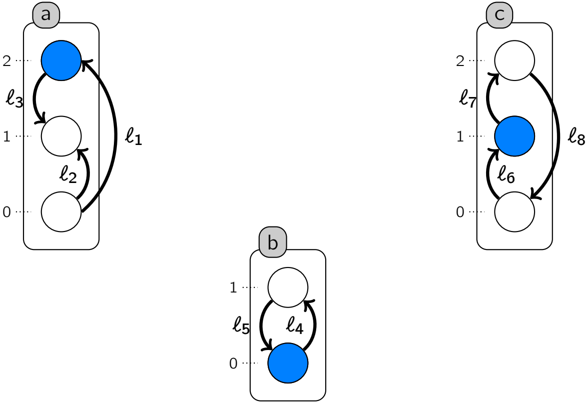

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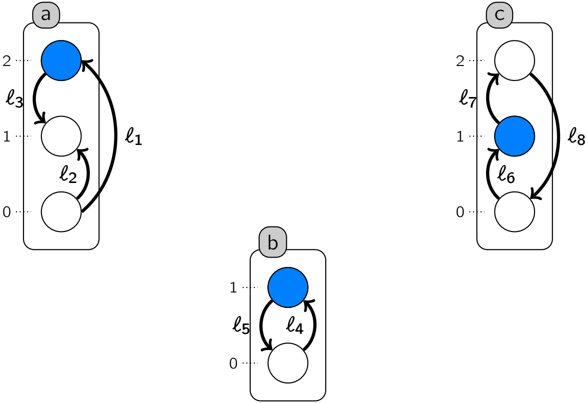

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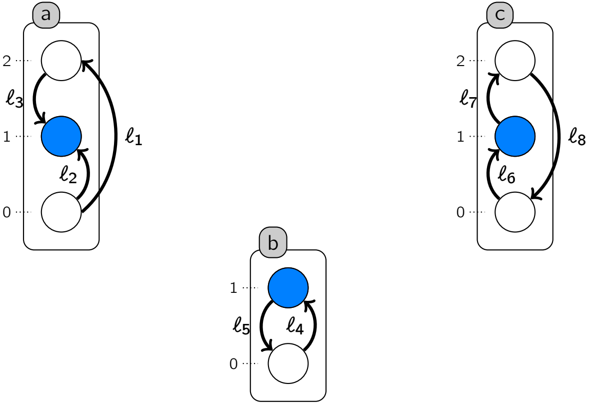

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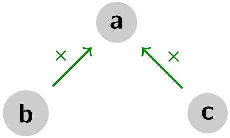

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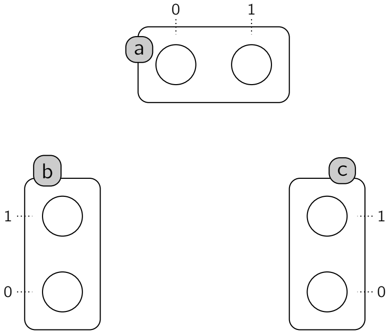

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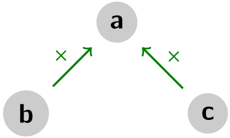

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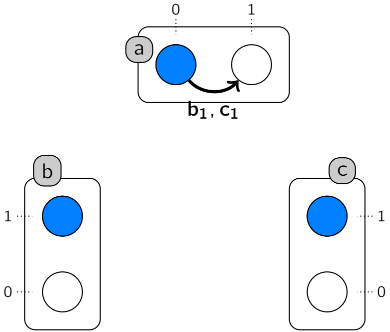

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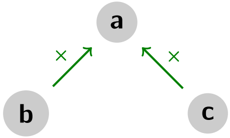

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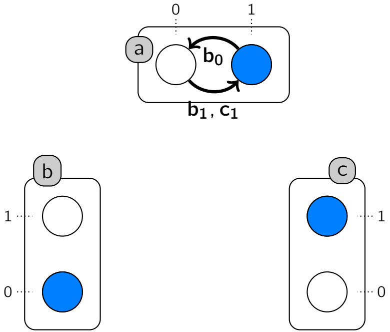

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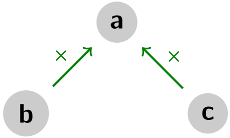

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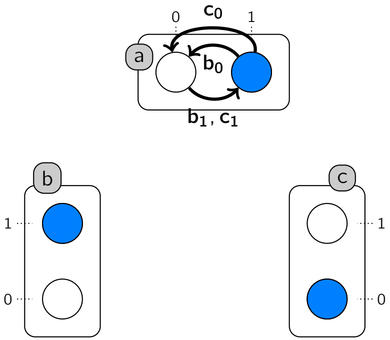

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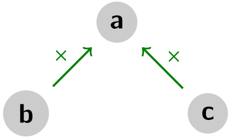

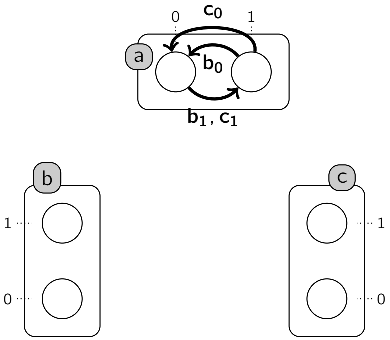

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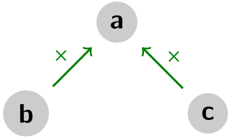

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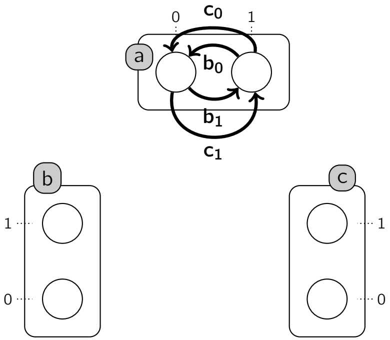
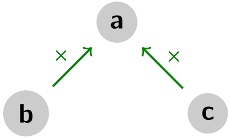
$a_0 \rightarrow a_1$: $b_1 \vee c_1$

$a_1 \rightarrow a_0$: $b_0 \vee c_0$



Transition-centered specification



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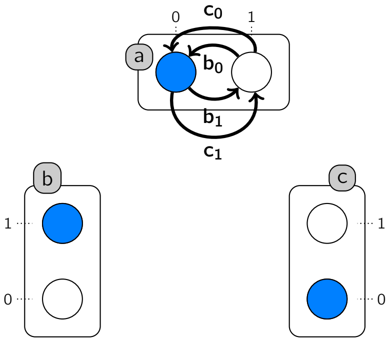

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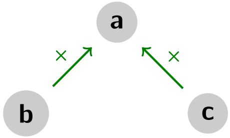

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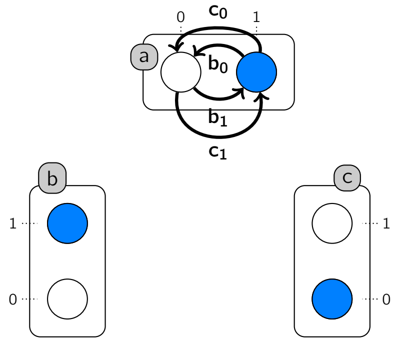

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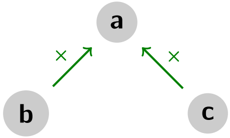

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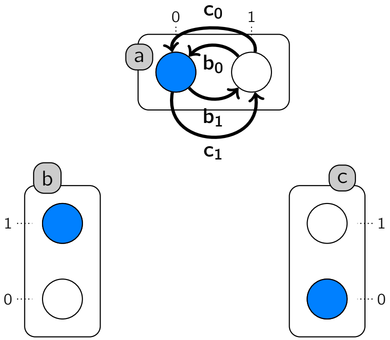
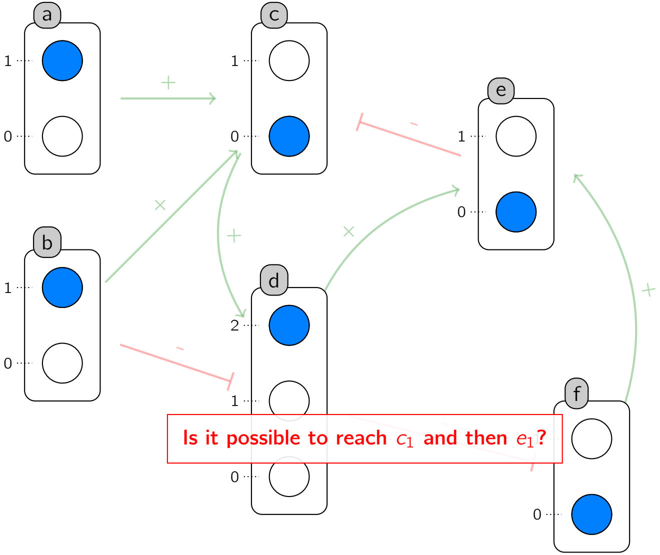


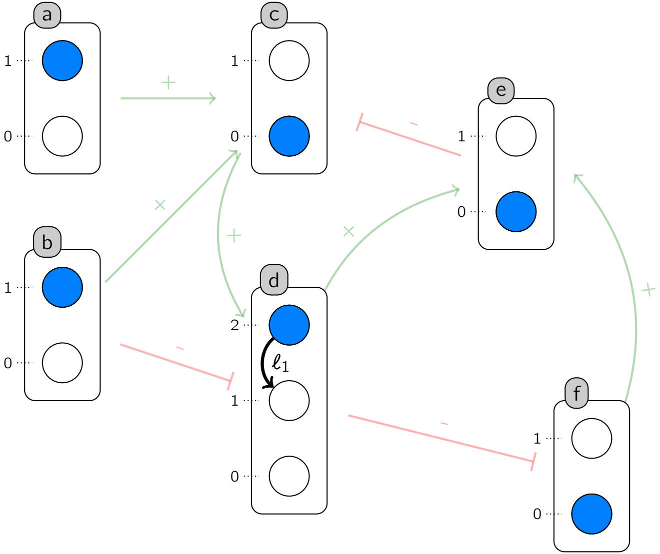
Outline

Reachability



Is it possible to reach c_1 and then e_1?

Reachability



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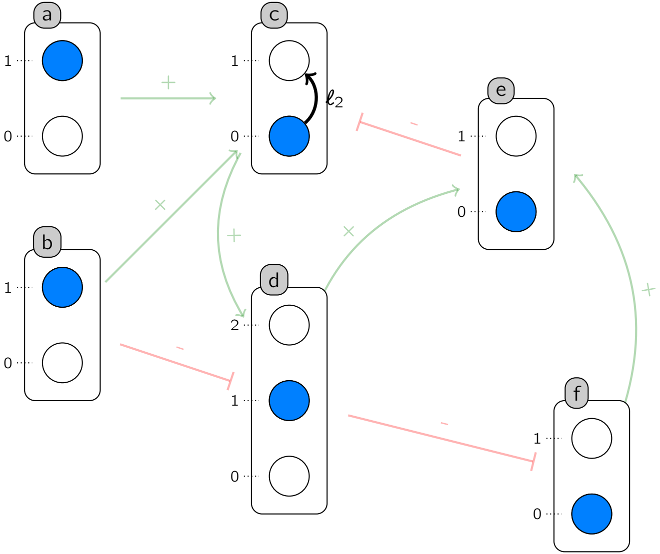

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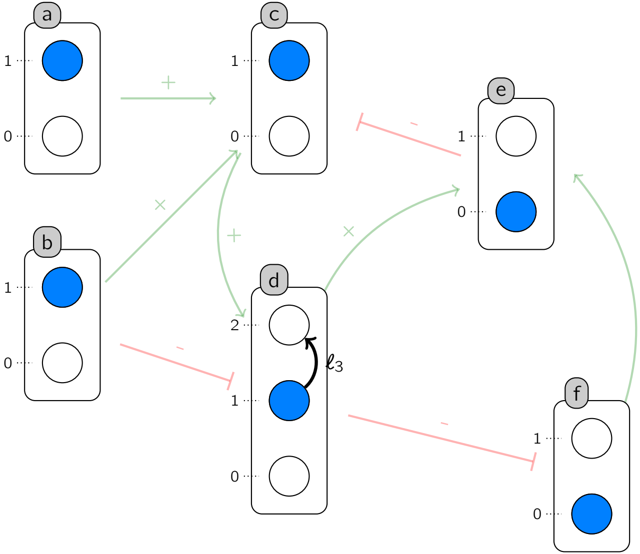

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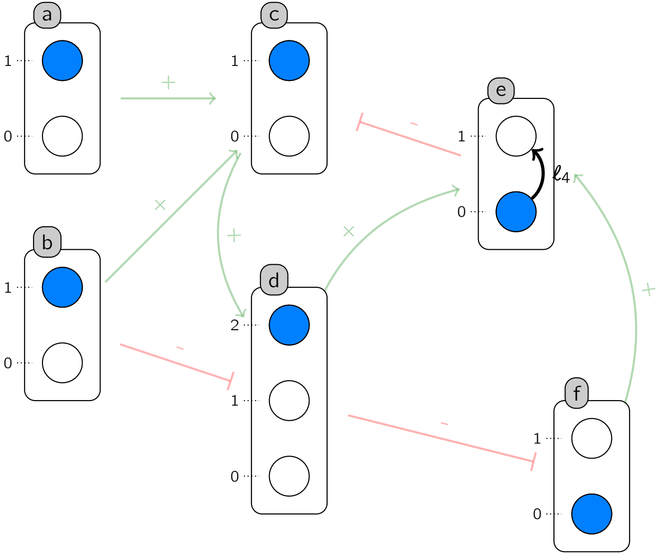

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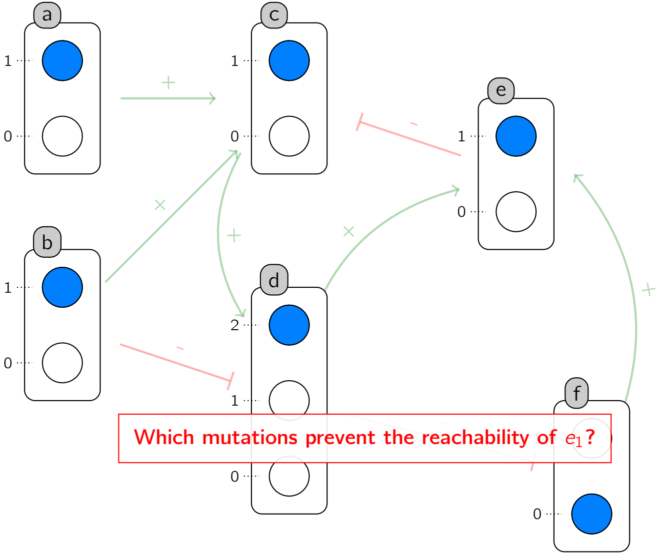
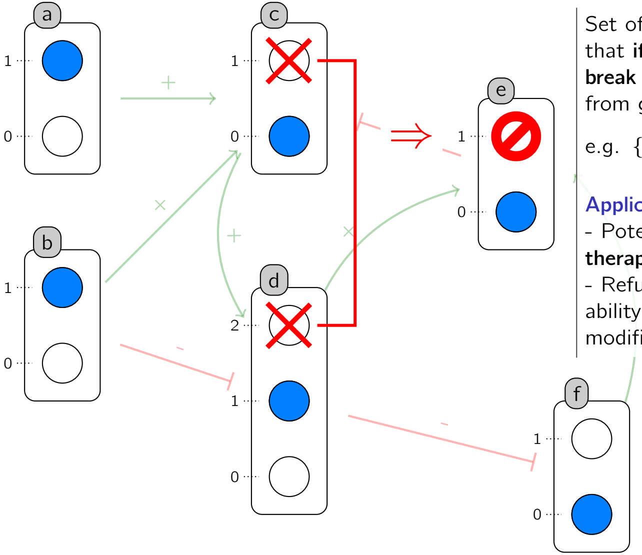


Which mutations prevent the reachability of e_1?

Cut Sets for Reachability



Set of **local states** that **if all disabled break reachability** from given initial states

e.g. $\{c_1, d_2\}$

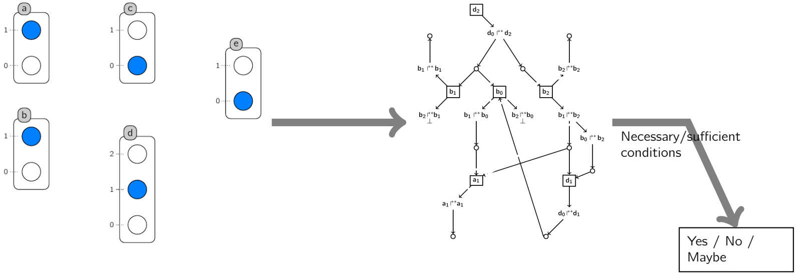
Applications

- Potential **therapeutic targets**
- Refute model if reachability still occurs in the modified (real) system

Reachability Analysis with Abstract Interpretation

Automata Network
+ reachability prop.

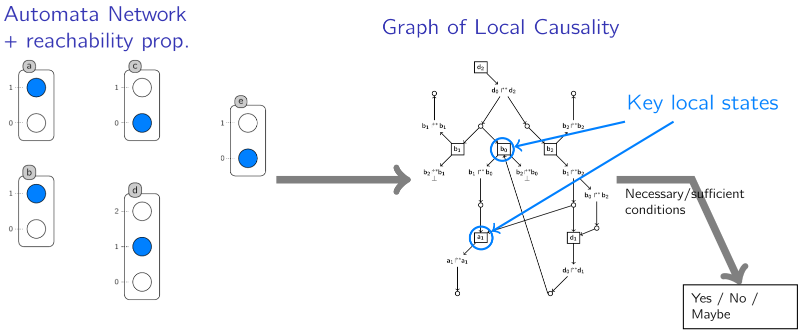
Graph of Local Causality



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

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

Reachability Analysis with Abstract Interpretation



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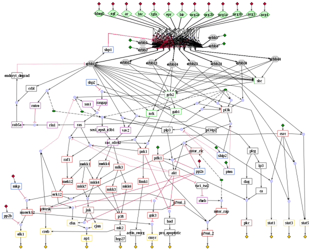
- Low complexity: poly(nb. automata) $\times$ exp(nb of procs in one automaton)
  $\Longrightarrow$ efficient with a small number of processes per automaton, while a very large number of automata can be handled.
- Key local states: necessary for reachability satisfiability (control).

Applications

Large signalling networks - reachability

Model	NuSMV	ITS	**PINT**
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	[9mn-KO]	**0.050s**

- Range over initial states / reachability prop.
- In those cases: always conclusive.



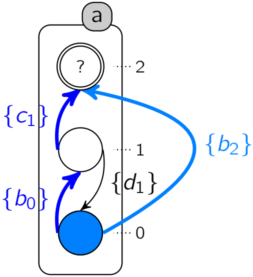
TGF-β signalling - ANR BioTempo, N. Theret (INSERM), G. Andrieux (IRISA)

- 9,000 interaction components
- Identification of key processes for a particular activation
- Dynamics: 2^{9000} states, PINT: reachability $< 1s$, key components $< 10min$

$\Rightarrow$ first formal analysis of dynamics at such a large scale

Outline

Local Causality



$$\text{local-cause}(a_0 \rightarrow^* a_2) = \{a_0 \xrightarrow{b_0} a_1 \xrightarrow{c_1} a_2,\ a_0 \xrightarrow{b_2} a_2\}$$

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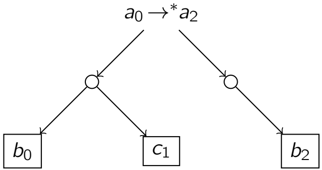

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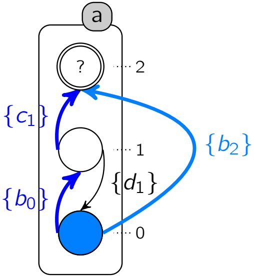

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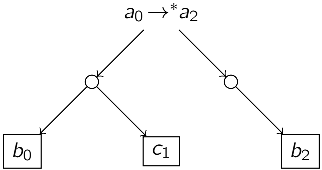
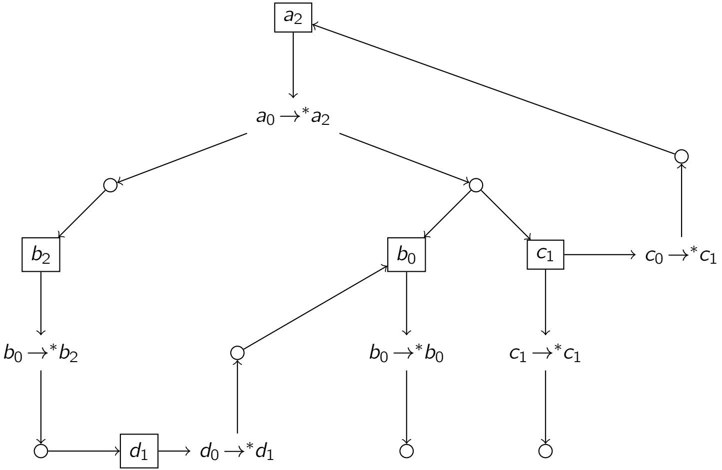


For any trace π starting at some global state s with $a_0 \in s$ and reaching a_2:

- either $a_0 \xrightarrow{b_0} a_1 \xrightarrow{c_1} a_2$ or $a_0 \xrightarrow{b_2} a_2$ is a sub-trace of π;
- either b_1 and c_0, or b_2 are reached before a_2 in π.

Local Causality Graph

- Causality of a_2.
- Initial context $\varsigma = \{a \mapsto \{0\}; b \mapsto \{0\}; c \mapsto \{0, 1\}; d \mapsto \{0\}\}$.



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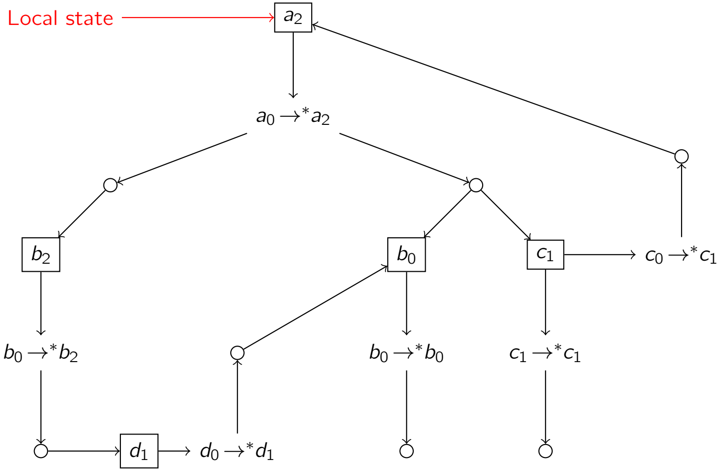

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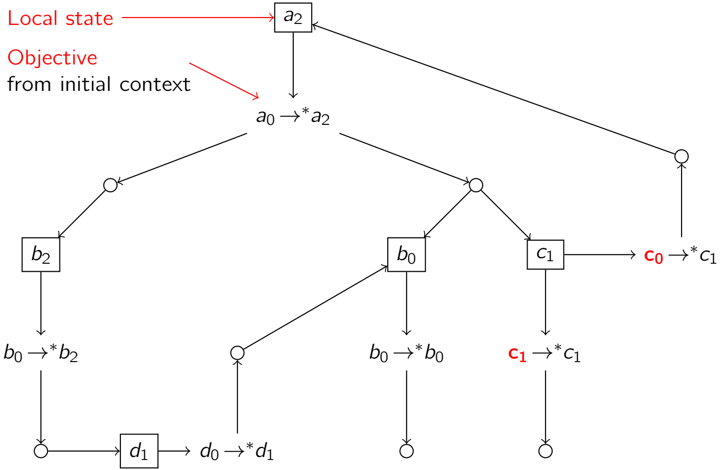

Local Causality Graph

- Causality of a_2.
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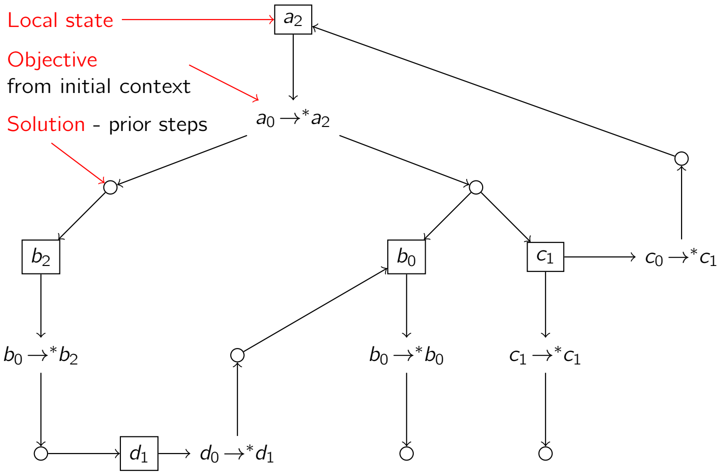

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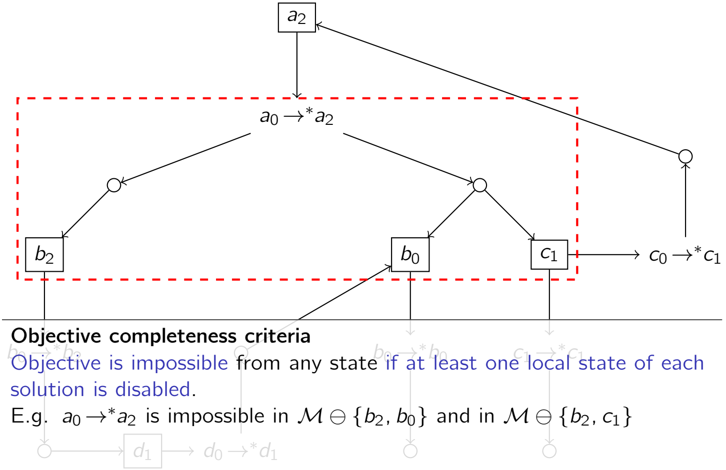


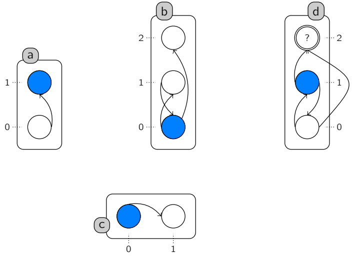
Objective completeness criteria

Objective is impossible from any state if at least one local state of each solution is disabled.

E.g. $a_0 \to^* a_2$ is impossible in $\mathcal{M} \ominus \{b_2, b_0\}$ and in $\mathcal{M} \ominus \{b_2, c_1\}$

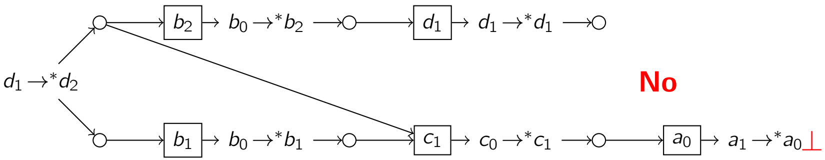
Necessary conditions for reachability

Example



Necessary condition for d_2 reachability from ς:
There exists a traversal of the LCG s.t.:

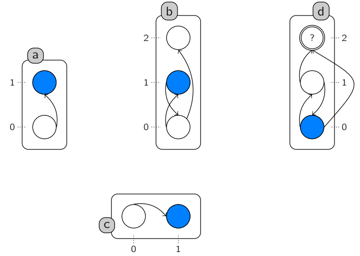
- objective → follow at least one solution;
- local state → follow all objectives;
- no cycle.



(Complexity: poly(nb. autotomata) + exp(nb. local states per automaton))

Necessary conditions for reachability

Example



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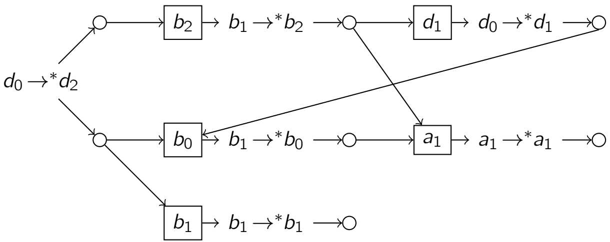

Inconc

(Complexity: poly(nb. autotomata) + exp(nb. local states per automaton))

Outline

Goal-oriented reduction

Motivations

Local causality analysis in previous work...

- ...decide efficiently reachability properties (and cut sets)
- ...but can be inconclusive (abstractions).

We may still want to do **exhaustive explorations** of the state space...

- ...to ensure conclusiveness
- ...to ensure that we are not missing cut-sets for reachability
- ...to do any more precise analysis.

Can local causality analysis drives exhaustive analysis of the state space?

Model reduction

Model reductions

- merge/remove components/transitions,
- try to preserve some properties.

Goal-oriented reduction of automata networks

- dedicated to a given reachability property (reach a_i, then b_j, ...);
- reduction by removing transitions;
- conserve all minimal traces satisfying a reachability property.

Minimal traces (sequences of transitions)
A trace $\pi \models P$ is minimal w.r.t. P iff there is no sub-trace $\pi' \subsetneq \pi$ s.t. $\pi' \models P$.

Examples for $P =$ reach a_i:

- $b_0 \xrightarrow{c_0} b_1, c_0 \xrightarrow{b_1} c_1, a_0 \xrightarrow{b_1, c_1} a_i$ (YES)
- $b_0 \xrightarrow{c_0} b_1, c_0 \xrightarrow{b_1} c_1, d_0 \xrightarrow{c_1} d_1, a_0 \xrightarrow{b_1, c_1} a_i$ (NO)
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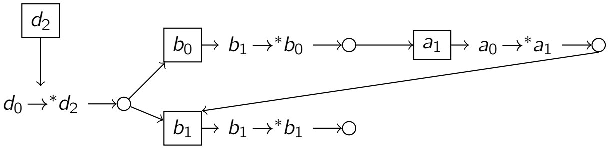
Reduction for single local reachability

Sketch

1. Compute LCG $\mathcal{G}$ from initial context for given local reachability property
2. Remove impossible objectives
3. Extends its context with local states nodes + intermediates given by local-cause
4. Repeat until fixpoint $\rightarrow \lceil\mathcal{G}\rceil$

$\Rightarrow$ keep only transitions in $\bigcup\{\text{tr}(\text{local-cause}(a_i \rightarrow^* a_j)) \mid a_i \rightarrow^* a_j \in \lceil\mathcal{G}\rceil\}$



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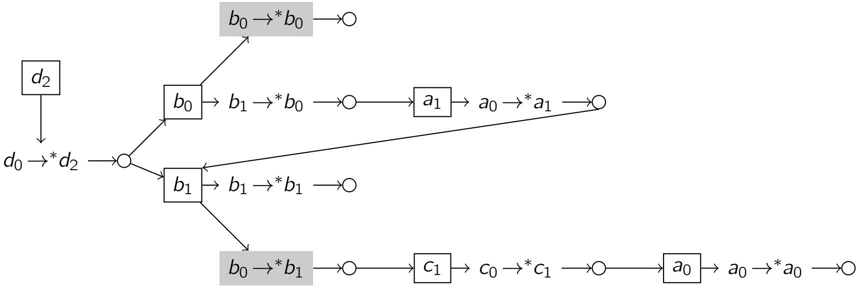

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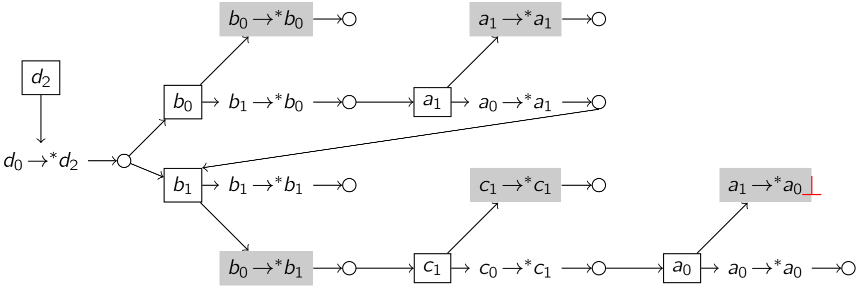


Goal-oriented reduction

Theorem

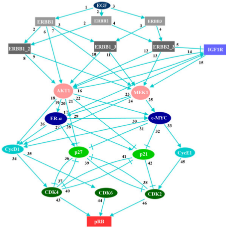
Given an AN $\mathcal{A} = (\Sigma, S, T)$, a global state $s \in S$, and one automaton local state a_i, for all minimal trace π from s to a_i, $\text{tr}(\pi) \subset \text{tr}(\lceil \mathcal{G} \rceil)$.

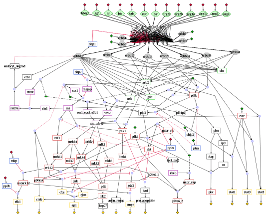
Consequence

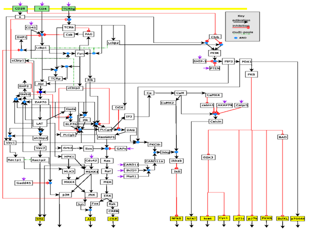
The AN $\mathcal{A} = (\Sigma, S, \text{tr}(\lceil \mathcal{G} \rceil))$ conserves all minimal traces for reaching a_i from s.

Results

Preliminary benchmarks with single reachability







Model		# tr	NuSMV time	NuSMV mem	ITS time	ITS mem	# states
Egf-r (20)	normal	68	0.1s	15Mb	0.35s	19Mb	4.200
	reduced	43	0.03s	11Mb	0.13s	8Mb	722
Egf-r (104) profile 1	normal	378	75s	2.1Gb	0.8s	750Mb	$\approx 10^7$
	reduced	0	-	-	-	-	1
Egf-r (104) profile 2	normal	378	KO	KO	540s	1.5Gb	$> 8.10^{14}$
	reduced	211	52s	100Mb	3.4s	100Mb	$\approx 6.10^7$
TCell-r (94)	normal	217	KO	KO	KO	KO	?
	reduced	42	10s	190Mb	0.25s	15Mb	60.000

For all cases, reduction step took between 0.01 and 0.1s.

Conclusion

Analysis of transient dynamics

- Understand what is reachable from particular states
- Necessary for capturing key intermediate components
- Difficult: model-checking is PSPACE-complete

Local causality abstractions in Automata Networks

- Exploit concurrency in transition-centered models
- Low complexity - tractable on very large networks
- Most analyses applies to any updating schedule

Goal-oriented reduction

- Intertwining between static and dynamics analysis
- Drives the exploration of the state space
- More to come: on-the-fly reduction, application for model identification, etc.

SASB'15

6th International Workshop on Static Analysis and Systems Biology

8 September 2015 - Saint-Malo (France)

https://www.lri.fr/sasb2015/

Scope:

- Quantitative and qualitative models
- Topology vs dynamics
- Model reduction
- Abstract interpreration frameworks
- Practical methods for tackling biological models..

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- Nathalie Théret, INSERM, Rennes, France

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- Sylvain Sené, Aix-Marseille Université, France
- Andrei Zinovyev, Institut Curie, France
- Paolo Zuliani, Newcastle University, UK

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Questions?