

# Abstract Interpretation of Qualitative Biological Networks

IRCCyN, Nantes - 18th February 2013

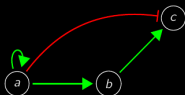
Loïc Paulevé

ETH Zürich, Institut für Automatik (BISON group)

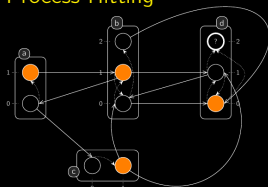
<http://loicpauleve.name>

## Overview

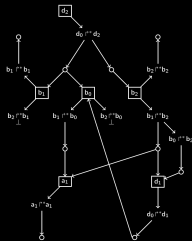
Biological network



Qualitative modelling with  
Process Hitting



Graph of Local Causality



Reachability analysis

Necessary processes

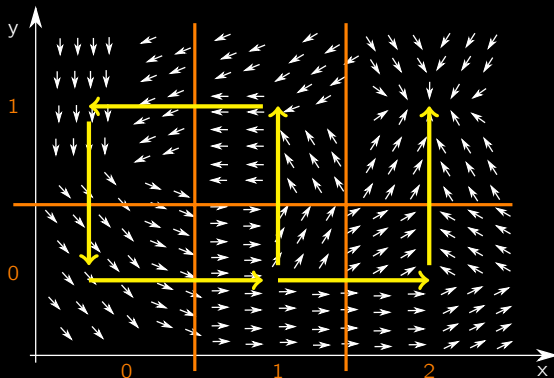
+ tractable for large-scale networks

- 1 Introduction
- 2 Qualitative Modelling with the Process Hitting
  - Generalised Dynamics of Interaction Graph
  - Refinement with Cooperation
- 3 Causality Analysis: Reachability and Cut Sets
  - Graph of Local Causality
  - Process Reachability
  - Key Processes
- 4 Conclusion and Future Work

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## Qualitative models

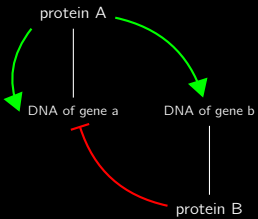
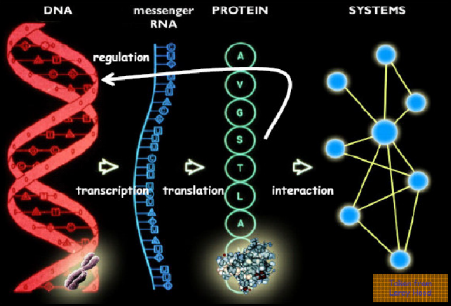
- Assume a **quantization of the species population/concentration**.
- Have a **finite discrete state space** (typically  $2^n$  states).



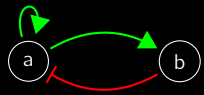
- We focus on **Regulatory Networks**. . .
- . . . but the methods can be applied to **any qualitative models**.

# Biological Regulatory Networks (BRNs)

The Interaction Graph



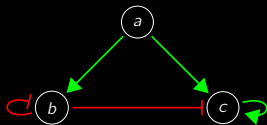
Interaction graph



## Qualitative Networks

- Each component has a finite set of **qualitative levels** ( $\{0, 1, 2\}$ ).
- Functions associate the **next level** given the state of the regulators.

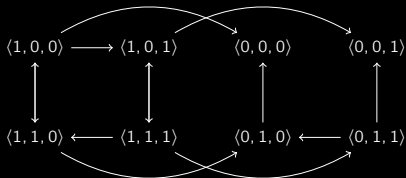
## Boolean network example



$$f^a(a, b, c) = 0$$

$$f^b(a, b, c) = \begin{cases} 1 & \text{if } a = 1 \text{ and } b = 0 \\ 0 & \text{otherwise} \end{cases}$$

$$f^c(a, b, c) = \begin{cases} 1 & \text{if } b = 0 \text{ and } (a = 1 \text{ or } c = 1); \\ 0 & \text{otherwise} \end{cases}$$



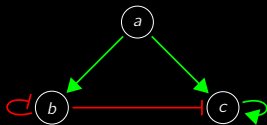
[René Thomas in *Journal of Theoretical Biology*, 1973]

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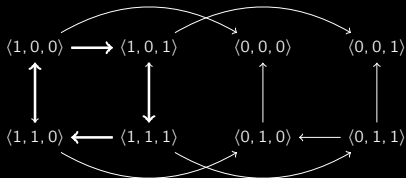
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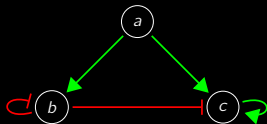
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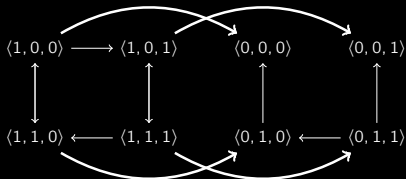
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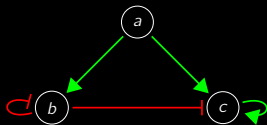
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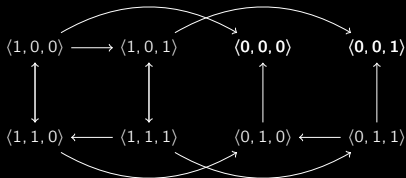
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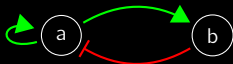


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## Dynamical properties from the Interaction Graph

An interaction graph can describe a **large set of different dynamics**.



Relationships between the interaction graph and dynamical properties:

- Multi-stationnarity **requires a positive circuit** (René Thomas conjecture) [Soule in ComPlexUs, 2003] [Richard, Comet in Discrete Appl. Math., 2007].
- Sustained oscillations **require a negative circuit** (René Thomas conjecture) [Remy, *et al.* in Adv. Appl. Math., 2008] [Richard in Adv. Appl. Math., 2010].
- The maximum number of fixed points can be characterized [Aracena in Bul. of Mathematical Biology, 2008]; [Richard in Discrete Appl. Math., 2009].
- Topological Fixed Points [Paulevé, Richard in CRAS 2010].
- etc.

(See [Paulevé, Richard at SASB'11] for a short survey).

## Motivation and Challenges

Prove dynamical properties      Validate/Refute a model

- Fixed points (steady states) analysis;
- Reachability properties;
- Attractors characterisation.

Control dynamical properties      Therapeutic targets

- Necessary or sufficient conditions.
- Key components/influences/parameters.

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Large-scale models

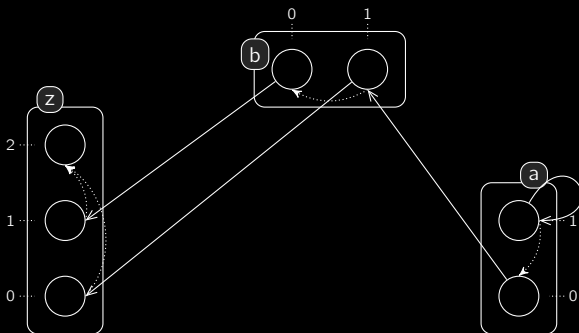
- Lack of details (knowledge) for some interactions  
→ avoid model/parameters enumeration.
- Numerous environment inputs: uncertainty for the initial conditions  
→ handle multiple initial states at once.
- Work around the state-space combinatoric explosion  
→ abstraction techniques.

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## The Process Hitting Framework

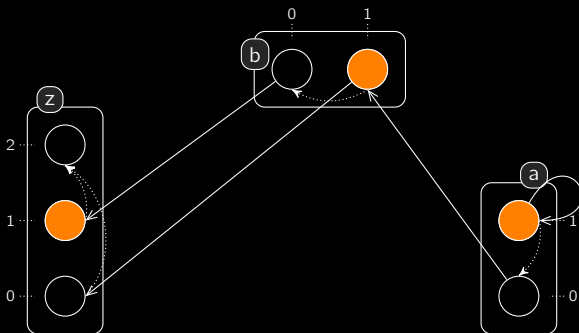
[Paulevé, Magnin, Roux in TCSB 2011]



- **Sorts:**  $a, b, z$ ; **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:**  $\langle a_1, b_1, z_1 \rangle, \langle a_0, b_1, z_1 \rangle, \langle a_0, b_0, z_1 \rangle, \dots$ ;
- Restriction of Automata Networks.

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[Paulevé, Magnin, Roux in TCSB 2011]

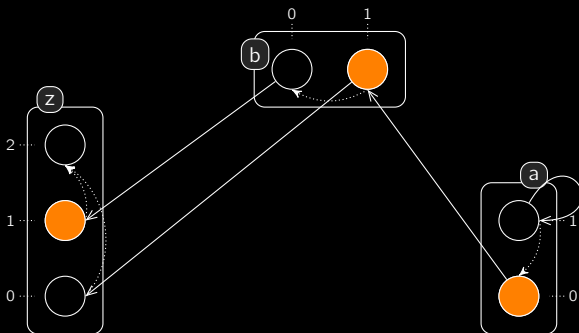


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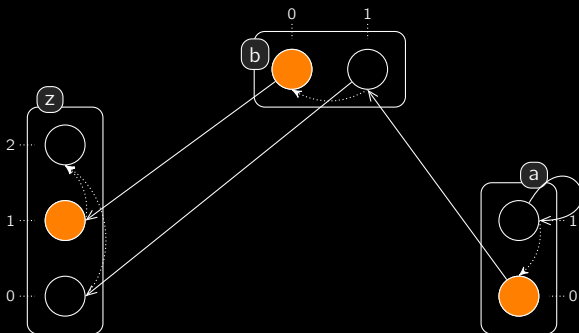
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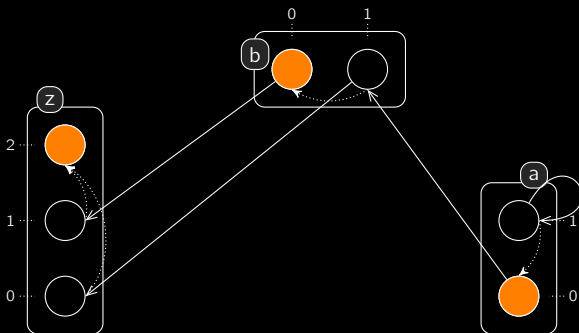
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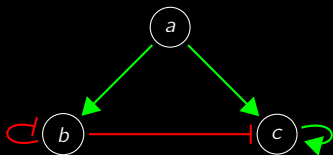
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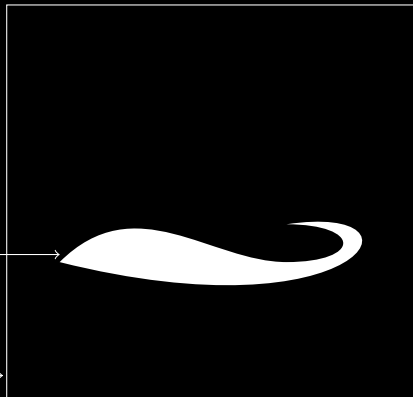
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## Generalised Dynamics of Regulatory Networks



Dynamics of the  
real system

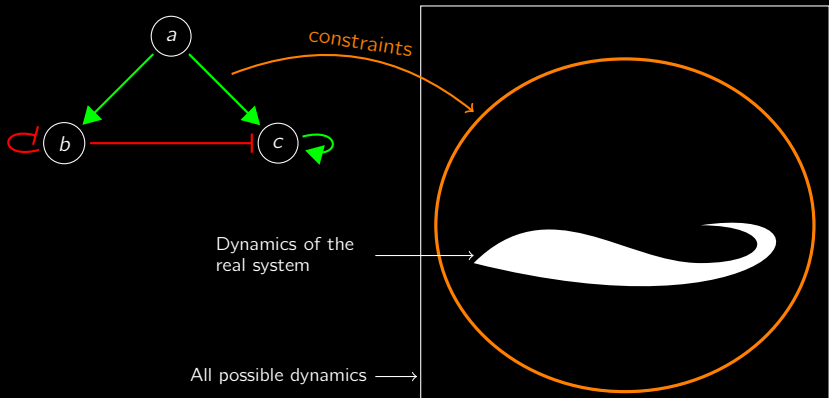
All possible dynamics



### Dynamics over-approximation

- A component **can not increase** if none effective activator is present.
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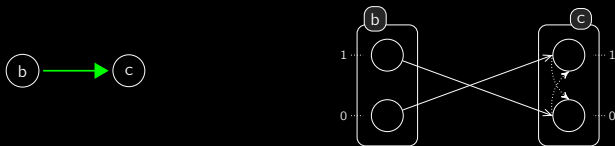
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- Idea: the **most permissive** dynamics [Paulevé, Magnin, Roux in TCSB 2011].
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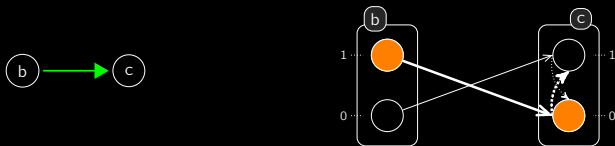
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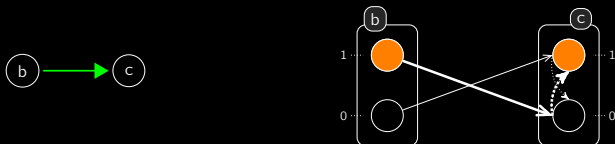
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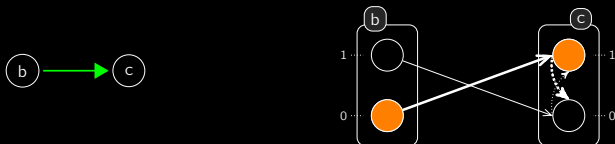




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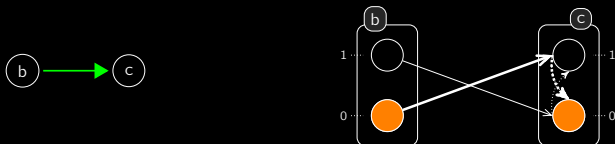
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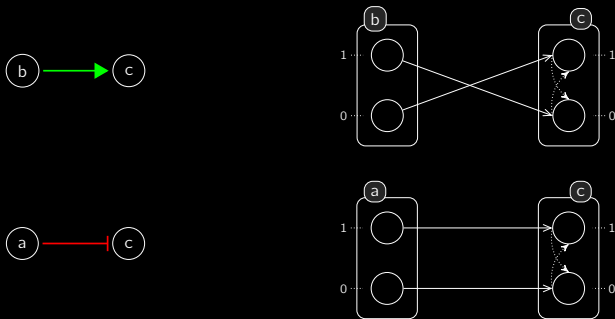
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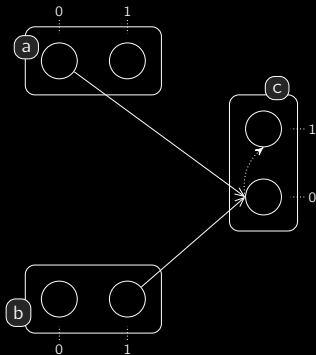
Boolean case:



Note: this construction can be easily extended to multi-valued components.

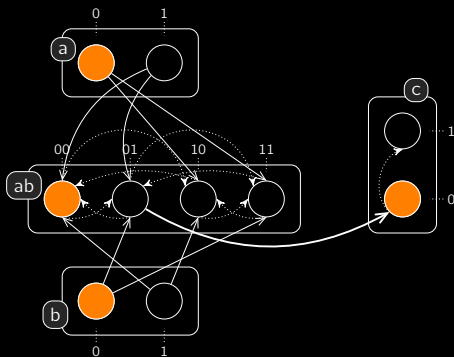
## Refining with Cooperation

- Idea:  $c_0 \rightarrow c_1$  when  $a_0$  and  $b_1$  are present.
- Introduction of a **cooperative sort** reflecting the state of the sorts  $a$  and  $b$ .



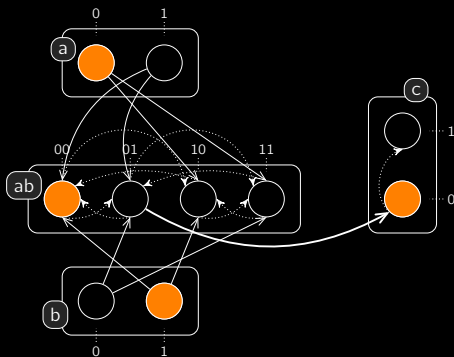
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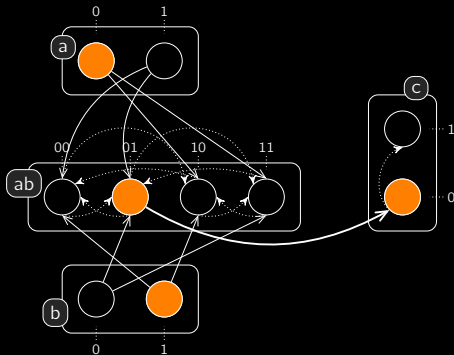
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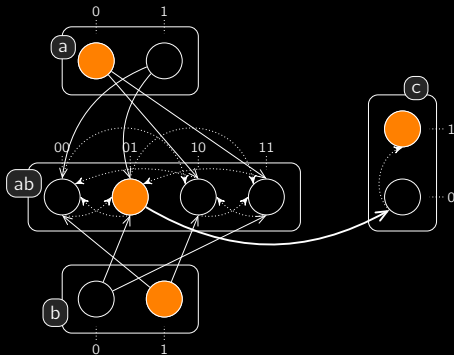
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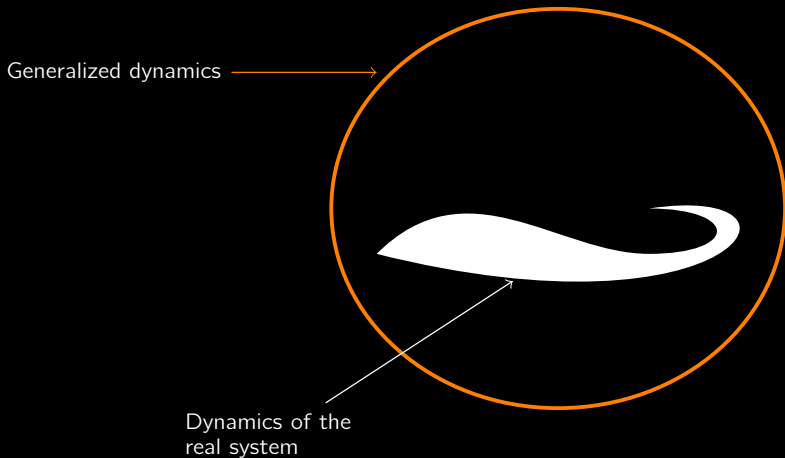
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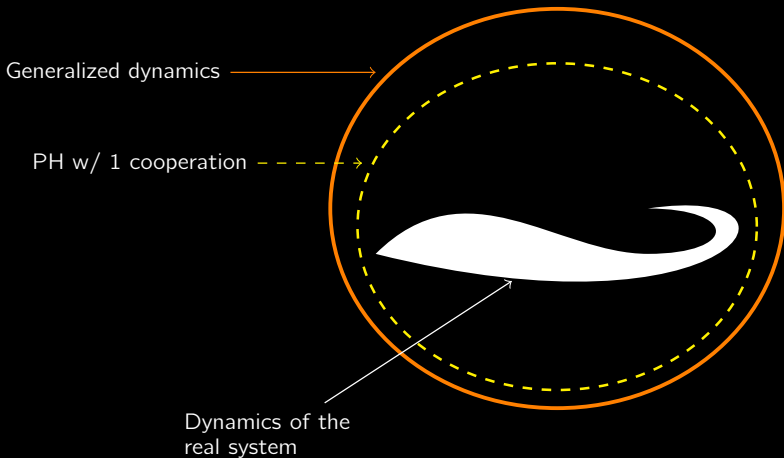
⇒ introduce a temporal shift; **similar to complexes**.



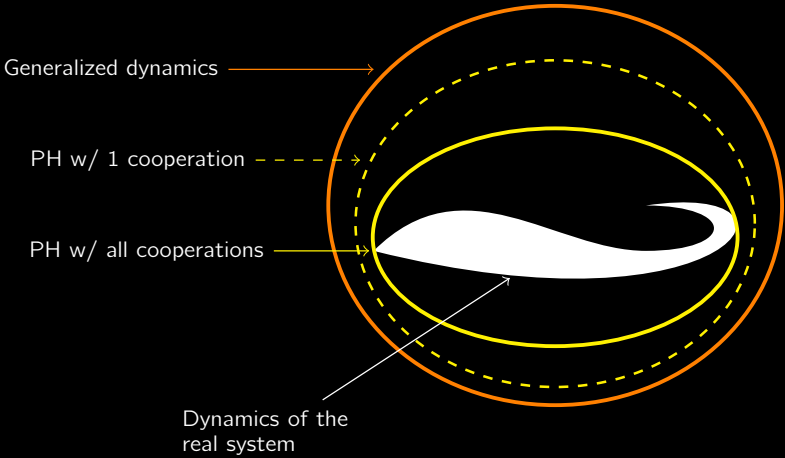
## Abstraction Relationships



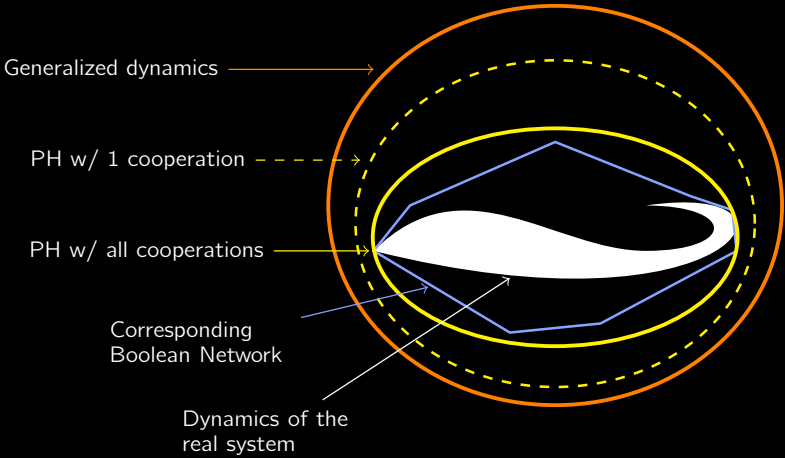
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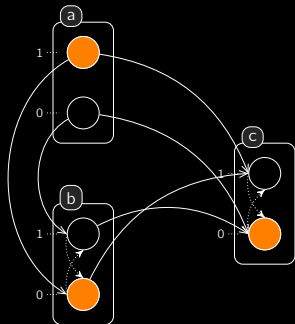
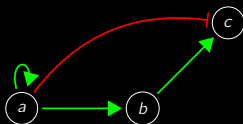


# Abstraction Relationships



## Toy example

Incoherent feed-forward loop



$\langle a_1, b_0, c_0 \rangle$



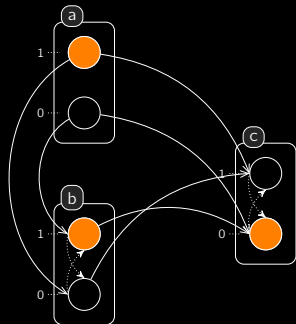
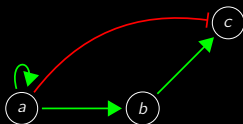
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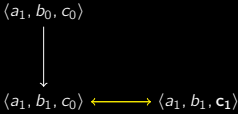
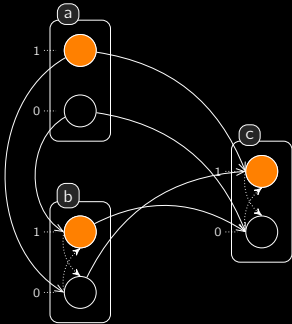
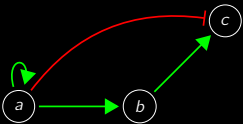
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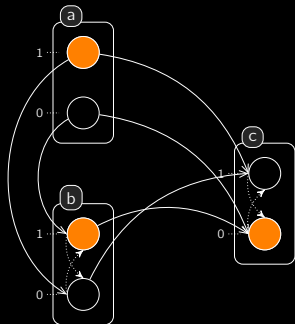
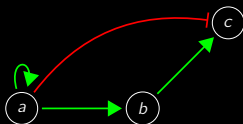
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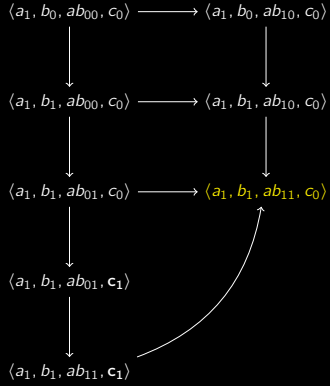
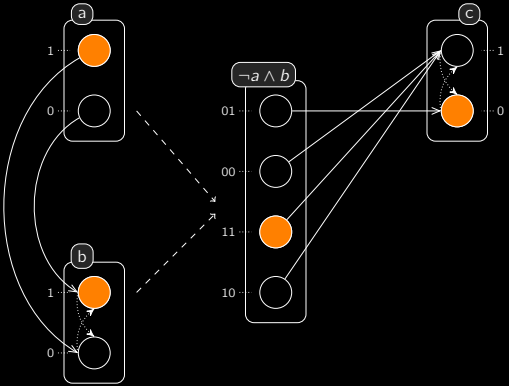
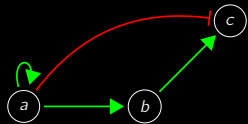
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## Other work around the Process Hitting

### Stochastic and time dimension

[Paulevé et al. in TCSB 2011] [Paulevé, PhD thesis]

- Markovian and non-Markovian **stochastic semantics**.
- Simulation, probabilistic **model-checking**.

### Process Hitting to Boolean Networks

[Folschette, Paulevé, Inoue, Magnin, Roux at CMSB'12]

- Inference of the Interaction Graph from a Process Hitting.
- **A Process Hitting can abstract at once different Boolean Networks.**

### Static analysis of fixed points (steady states)

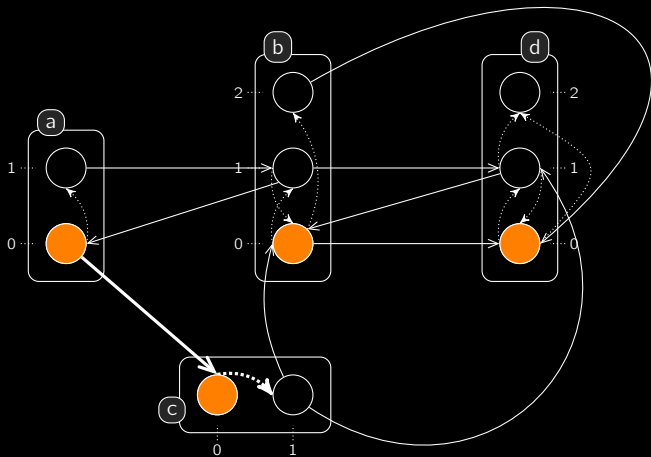
[Paulevé et al. in TCSB 2011]

- Reduction to the search for  $N$ -cliques in  $N$ -partite graphs.
- Efficient enumeration.

## Outline

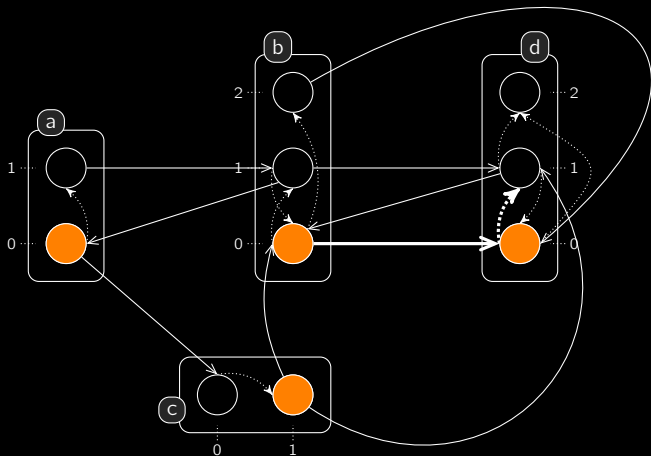
- 1 Introduction
- 2 Qualitative Modelling with the Process Hitting
  - Generalised Dynamics of Interaction Graph
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- 3 **Causality Analysis: Reachability and Cut Sets**
  - Graph of Local Causality
  - Process Reachability
  - Key Processes
- 4 Conclusion and Future Work

## Scenarios



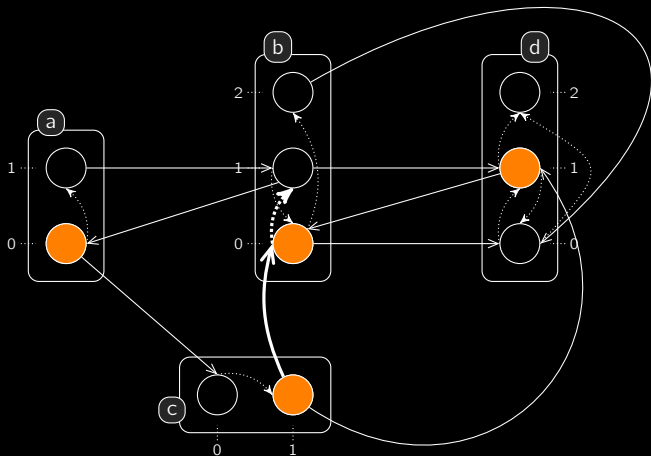
$$a_0 \rightarrow c_0 \uparrow c_1 :: b_0 \rightarrow d_0 \uparrow d_1 :: c_1 \rightarrow b_0 \uparrow b_1 :: b_1 \rightarrow d_1 \uparrow d_2$$

## Scenarios



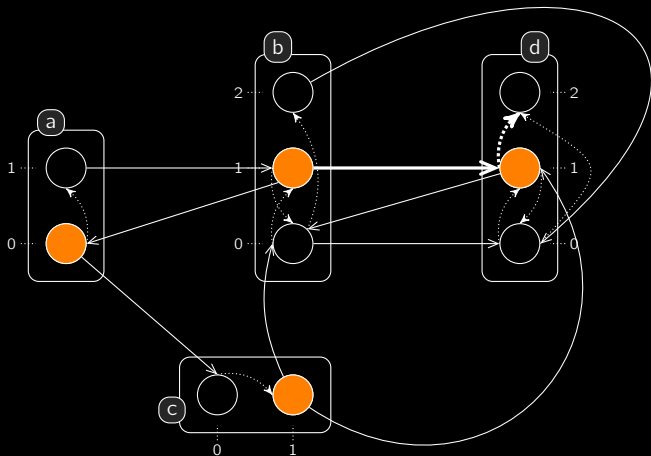
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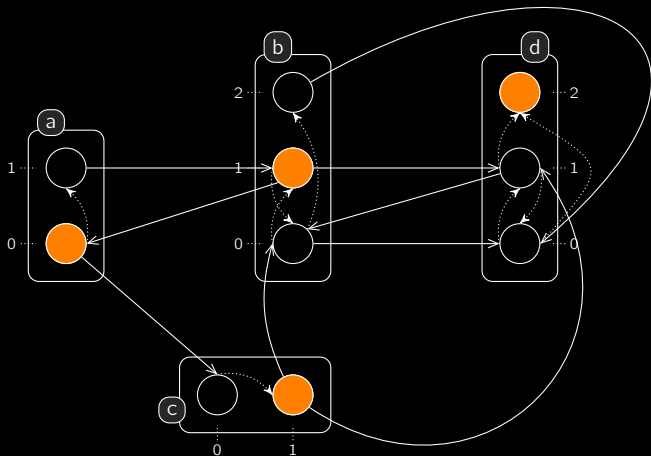
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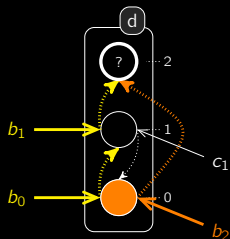
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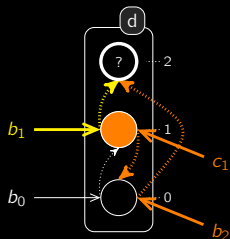


## Local Causality

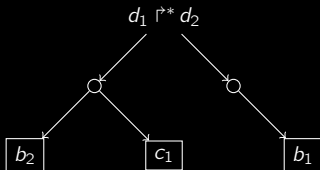


- $\text{sol}(d_0 \uparrow^* d_2) = \{b_0 \rightarrow d_0 \uparrow d_1 :: b_1 \rightarrow d_1 \uparrow d_2, b_2 \rightarrow d_0 \uparrow d_2\};$
- $\text{sol}^\wedge(d_0 \uparrow^* d_2) = \{\{b_0, b_1\}, \{b_2\}\}.$

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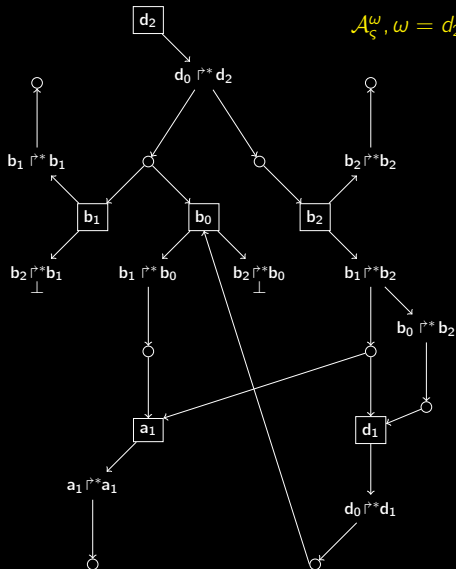


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## Graph of Local Causality

$$\mathcal{A}_\zeta^\omega, \omega = d_2, \zeta = \langle a_1, \{b_1, b_2\}, c_1, d_0 \rangle$$



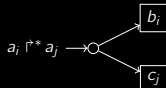
### Legend

Requirement

$$\boxed{a_j} \longrightarrow a_i \overset{*}{\rightarrow} a_j$$

Solution

$$(\{b_i, c_j\} \in \text{sol}^\wedge(a_i \overset{*}{\rightarrow} a_j))$$



Continuity

$$a_i \overset{*}{\rightarrow} a_j \longrightarrow a_k \overset{*}{\rightarrow} a_j$$

Trivial solution

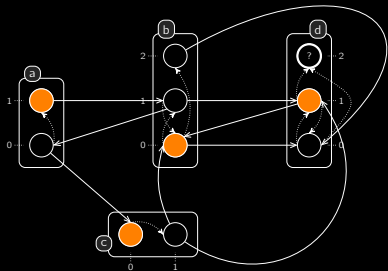
$$a_i \overset{*}{\rightarrow} a_j \longrightarrow \bigcirc$$

No solution

$$a_i \overset{*}{\rightarrow} a_j \perp$$

## Un-ordered Over-approximation

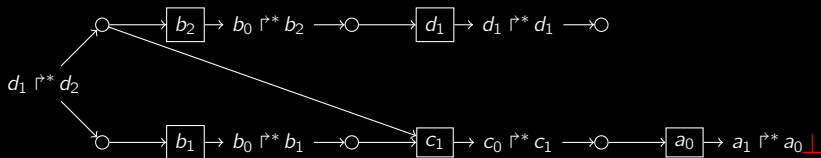
Example



Necessary condition for reaching  $d_2$ :

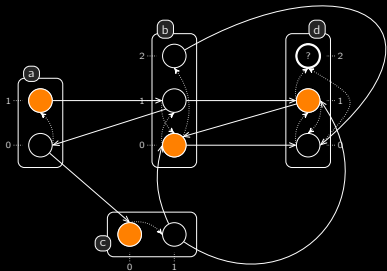
There exists a traversal of  $\mathcal{A}_\xi^\omega$  such that:

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



## Un-ordered Over-approximation

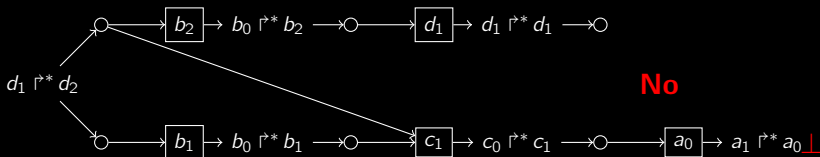
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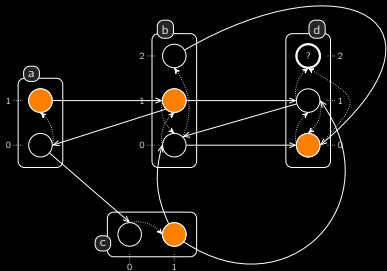
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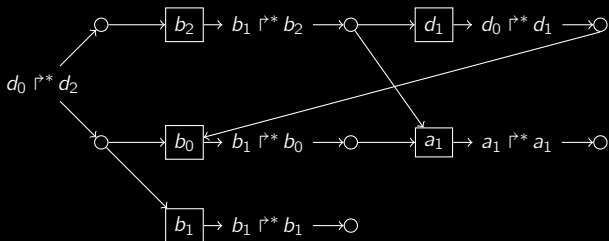
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Inconc

## Static Analysis of Successive Reachability

Over-  
approximations

- Un-ordered approximation.
- Ordered approximation.
- Ordered approximation with occurrences order constraints.

No / Inconc



Successive Process Reachability (reach  $a_i$ , then  $b_k$ , etc.)



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⇕

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### Complexity

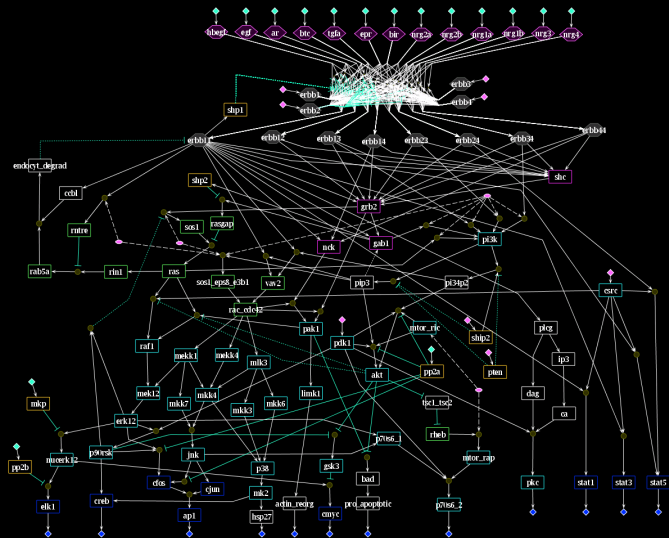
⇒ efficient with a **small number of processes per sort**, while a **very large number of sorts** can be handled.

[Paulevé, Magnin, Roux in *Mathematical Structures in Computer Science*, 2012]



# EGFR/ErbB Signalling Network

(104 components)



[Samaga, *et al.* in PLoS Comput Biol, 2009]

**Process Hitting**  
 193 sorts,  
 748 processes,  
 2356 actions:  
 $\approx 2 \cdot 10^{96}$  states.

## Execution times

- Real biological models.
- Wide-range of biological/arbitrary reachability analysis.
- **Always conclusive.**

Model	sorts	procs	actions	states	Biocham <sup>1</sup>	libDDD <sup>2</sup>	PINT <sup>3</sup>
egfr20	35	196	670	$2^{64}$	[3s-KO]	[1s-150s]	<b>0.007s</b>
tcrsig40	54	156	301	$2^{73}$	[1s-KO]	[0.6s-KO]	<b>0.004s</b>
tcrsig94	133	448	1124	$2^{194}$	KO	KO	<b>0.030s</b>
egfr104	193	748	2356	$2^{320}$	KO	KO	<b>0.050s</b>

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

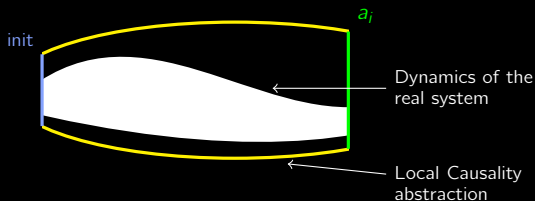
<sup>2</sup> <http://move.lip6.fr/software/DDD>

<sup>3</sup> <http://process.hitting.free.fr>

## Necessary Sets of Processes for Reachability

### Settings

- reachability of  $a_i$  (level  $i$  of component  $a$ );
- from partially-determined initial condition (set of initial states).



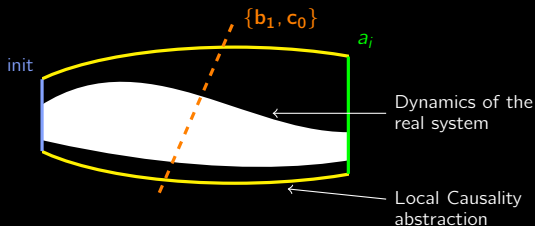
- All traces use, at one point, at least one process of a cut set.
- Disabling all processes of a cut set should prevent reachability in the real system.
- Otherwise, the model is not an over-approximation.

We restrict ourselves to necessary  $N$ -sets of processes.

## Necessary Sets of Processes for Reachability

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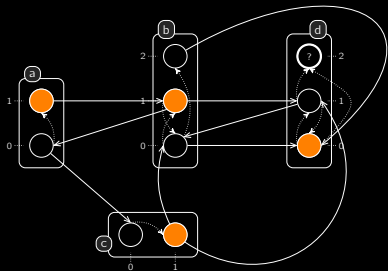
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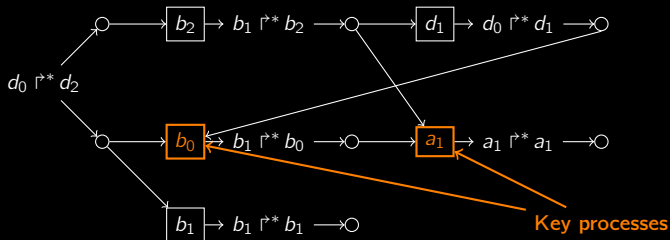
## Extraction of Key Processes



Necessary condition for reaching  $d_2$ :

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- no cycle.



## 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, p15INK4b, p21CIP1.
- 20 000 nodes, including 5600 processes (biological or cooperative).

### Cut $N$ -sets

N	Exec. time	SNAIL <sub>1</sub>	p15INK4b <sub>1</sub>	p21CIP1 <sub>1</sub>
1	0.9s	1	1	1
2	1.6s	+6	+6	+0
3	5.4s	+0	+92	+0
4	39s	+30	+60	+0
5	8.3m	+90	+80	+0
6	2.6h	+930	+208	+0

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## Conclusion

### The Process Hitting framework

- Qualitative asynchronous modelling.
- Different levels of dynamics abstractions (partial knowledge on cooperations).
- Automatic encoding of Boolean Networks (over-approximation).

### Abstract causality analysis

- Local causality reasoning.
- Over- and under-approximation of reachability properties.
- Extract necessary sets of processes (potential therapeutic targets).
- Tractable on very large networks.

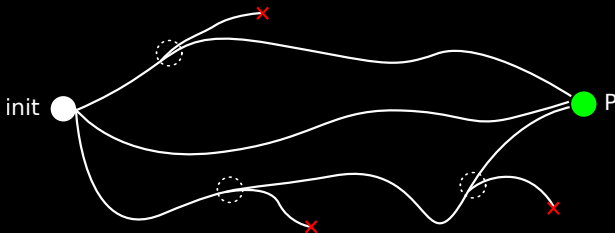
Implementation: PINT software - <http://process.hitting.free.fr>



## Future work

## Process Hitting with Priorities

- Static split of actions into **priority classes**.
- An action can be played only if none action with higher priority can be played.
- $\implies$  **different time-scales**;
- $\implies$  **enhanced expressivity** (with 3 classes: Petri Nets).



## Link with continuous and stochastic models

- From quantitative to qualitative models.

## Acknowledgement

IRCCyN, Nantes MeForBio

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IRISA, Rennes Dyliss

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ETH Zürich BISON

- Heinz Koeppl

ANR BioTempo.