Modelling, Simulation, and Model Checking of Large Biological Regulatory Networks

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IRCCyN / MeForBio team, Nantes (France)

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Morgan Magnin

Olivier Roux

Other people I work with

Andrew Phillips

Microsoft Research, Cambridge, UK

Stochastic simulation

Adrien Richard

I3S & CNRS, Nice, France

Biological Regulatory Networks

Overview

Computer science for systems biology

- Models for dynamical concurrent systems.
- Validation of the model / control of the system.
- We focus on Biological Regulatory Networks (BRNs).
- We introduce a new modelling framework: the Process Hitting.

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The Process Hitting [Paulevé, Magnin, Roux in TCSB 2011]

- *Elementary* framework for dynamical complex systems;
- Applied to BRNs; not limited to.
- Stochastic and Time dimensions (simulation + standard model checking).
- Software available (PINT - `http://process.hitting.free.fr`).

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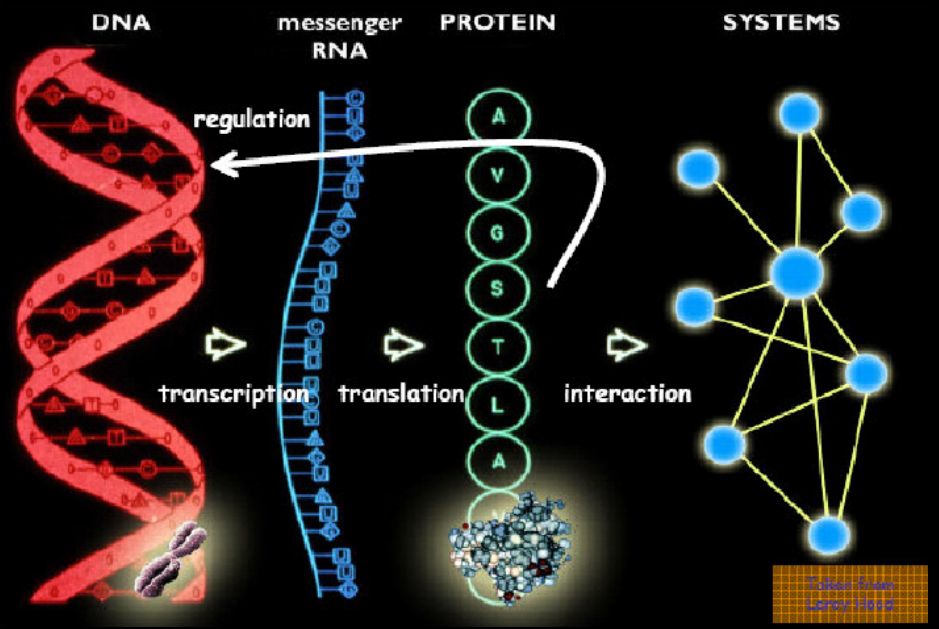
Large-scale model checking (dynamical properties)

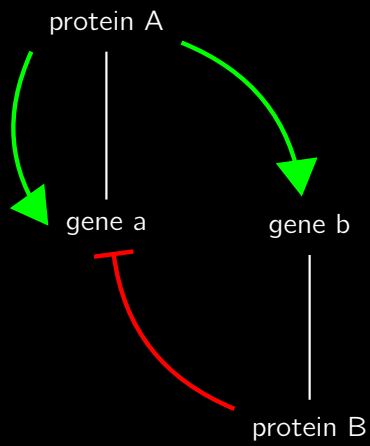
- Cope with state space explosion.
- Our approach: Static Analysis of the model.
- Static analysis by Abstract Interpretation.

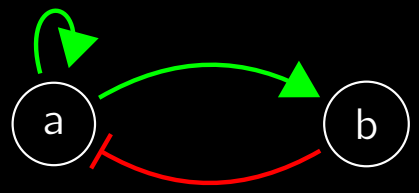
Outline

Biological Regulatory Networks (BRNs)

The interaction graph







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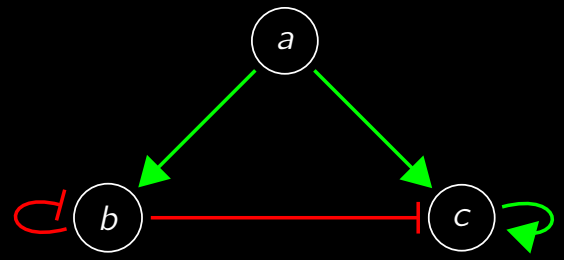
Discrete Networks (BRNs)

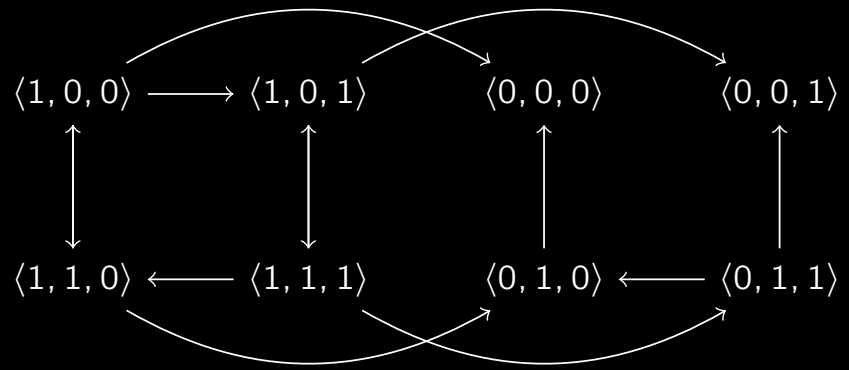
- Each component has a finite set of qualitative levels; e.g. $\{0, 1, 2\}$;
- may be seen as a quantization of the concentration of the component.

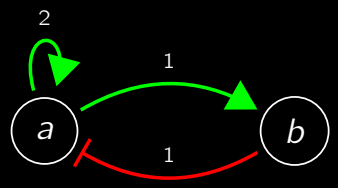


$f^a(x) = 0$

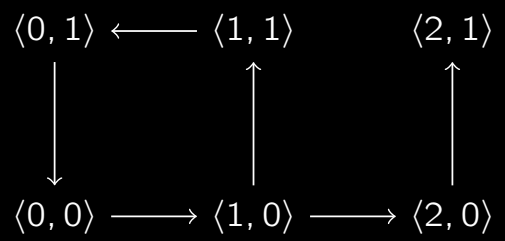
$f^b(x) = x[a] \wedge \neg x[b]$

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





+ K



[René Thomas in Journal of Theoritical Biology, 1973] [A. Richard, J.-P. Comet, G. Bernot in Modern Formal Methods and Applications, 2006]

Hybrid Modelling

Continuous features governing discrete transitions

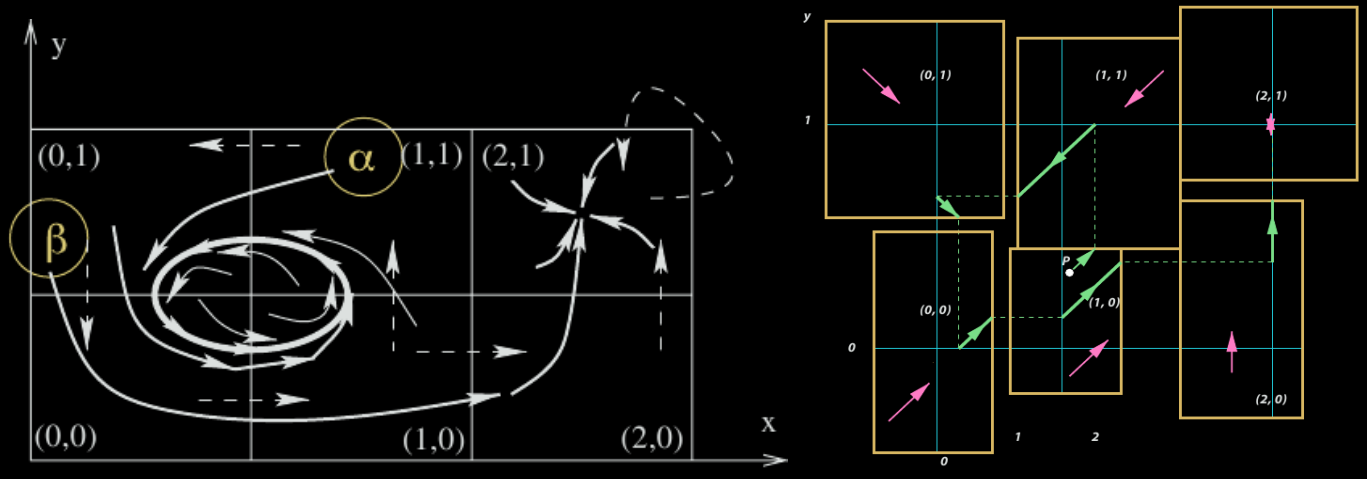
Introduce delays to actions

Stochastic Models

- Delays are random variables (generally exponential, i.e Markovian);
- $\Rightarrow$ compute probabilities for observing behaviours.

Stochastic Petri Nets / π-calculus, etc.

Timed Models



Timed / Hybrid Automata

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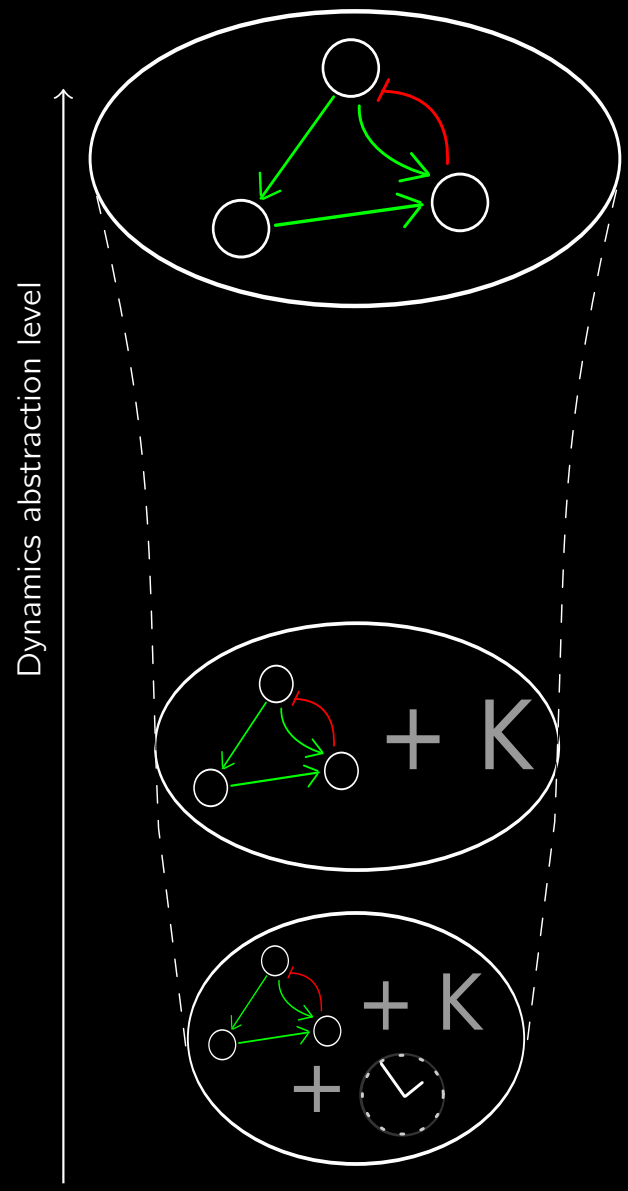
Summary and Contribution



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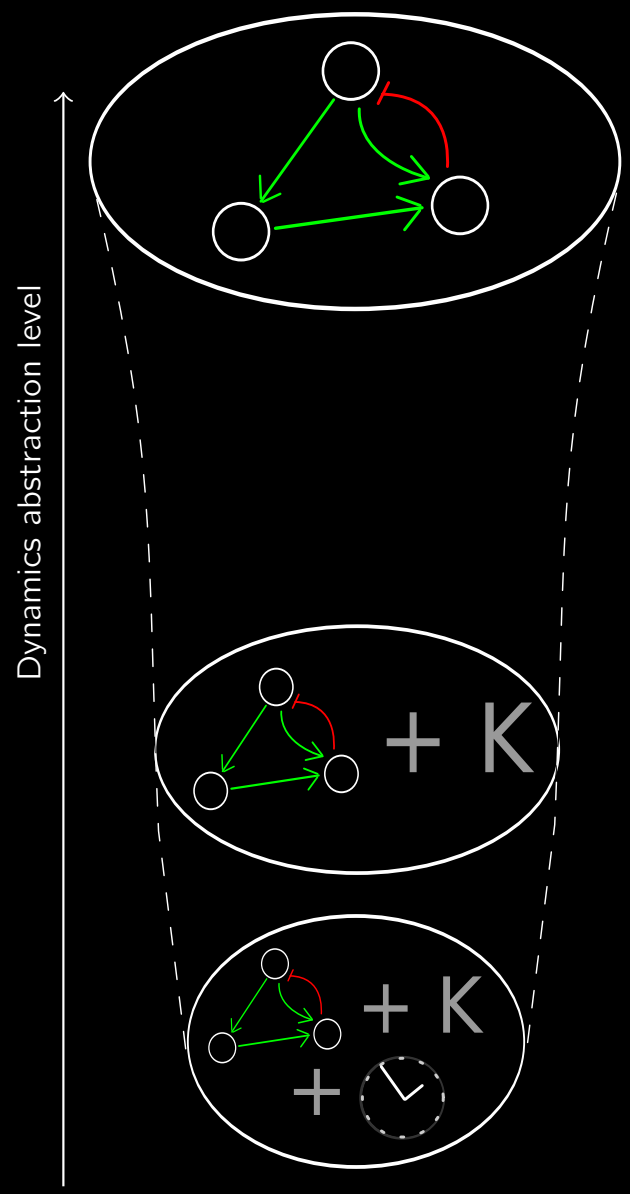

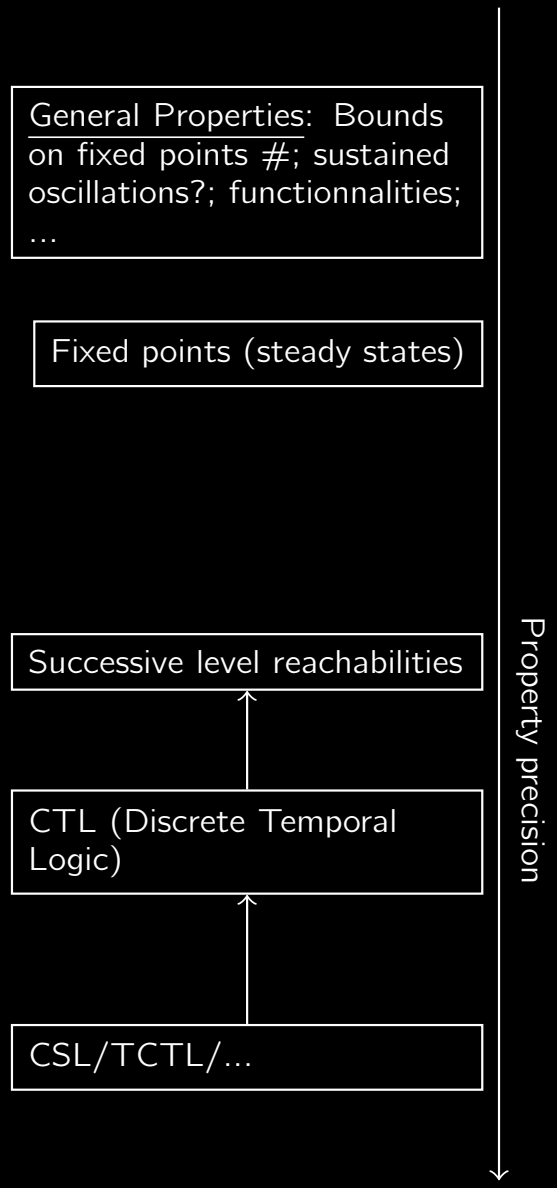

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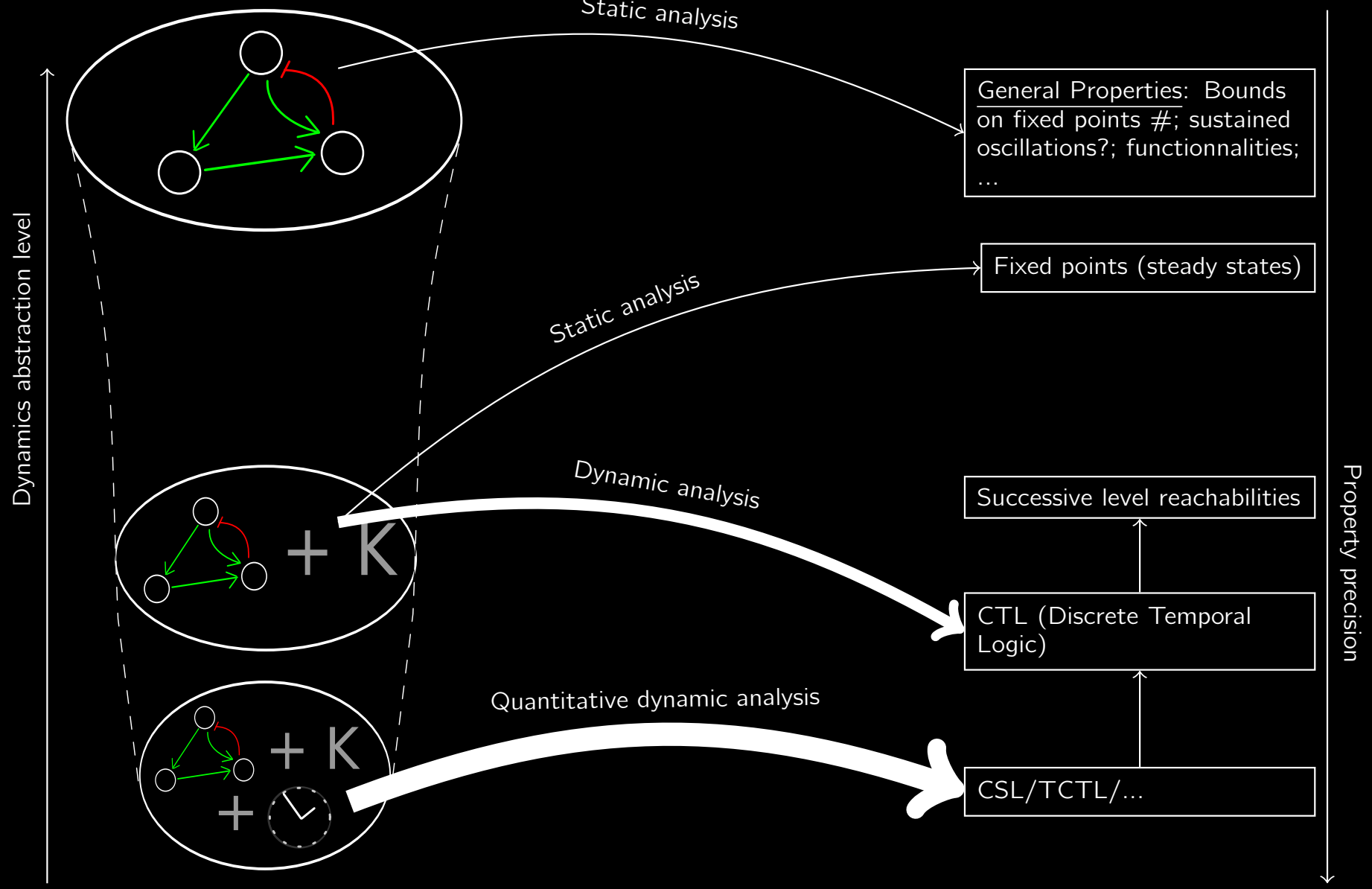

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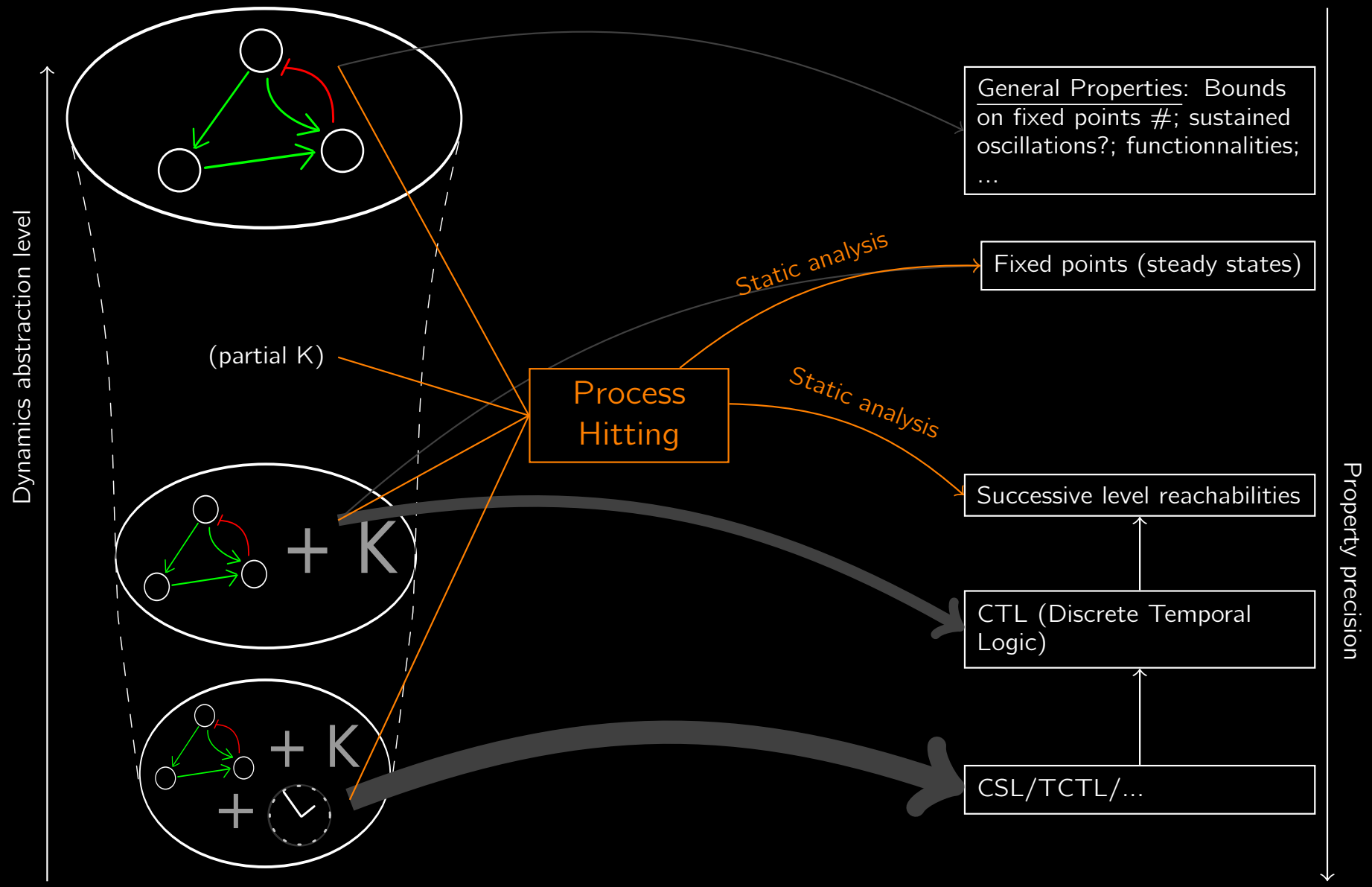

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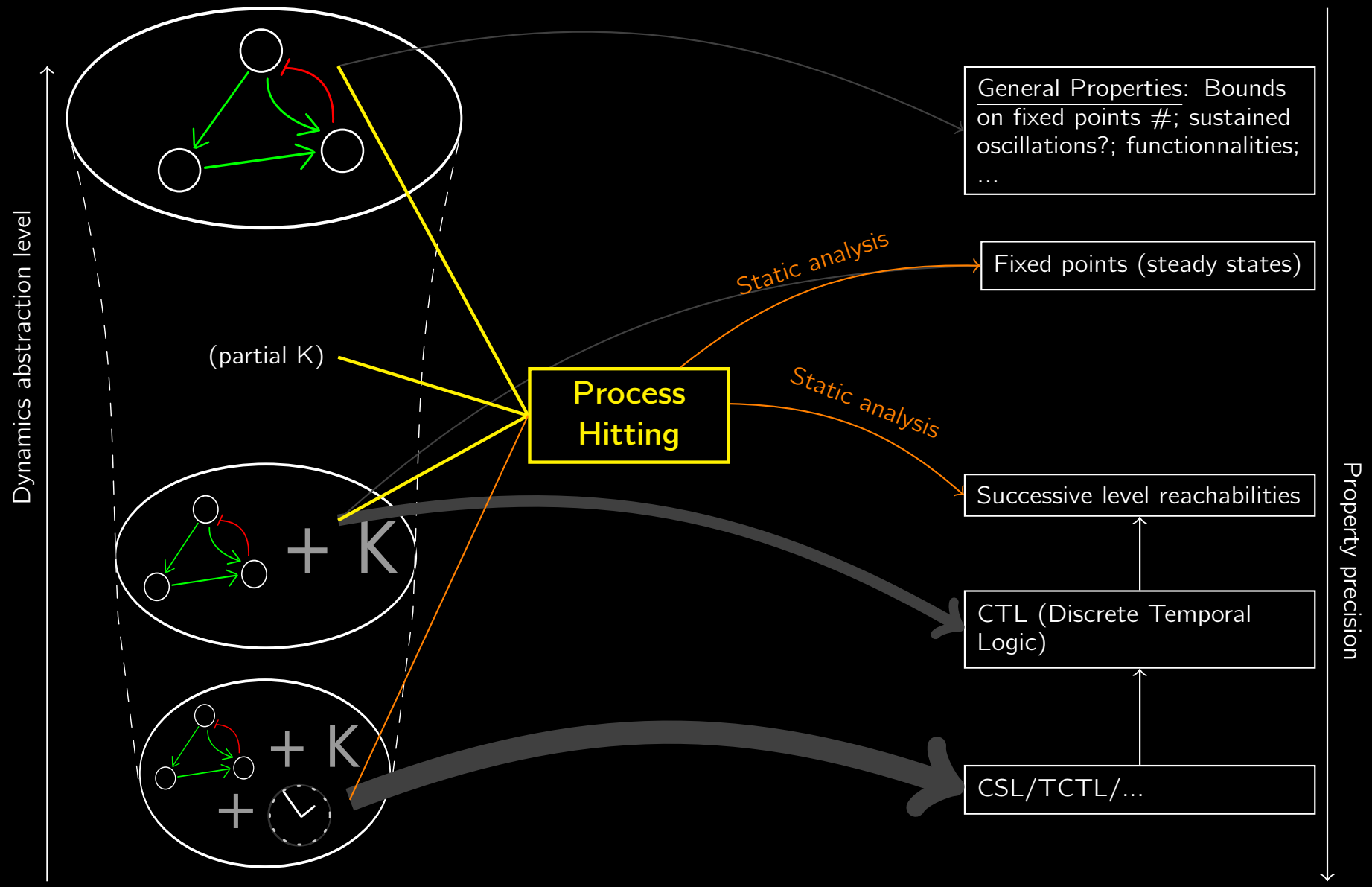
Outline



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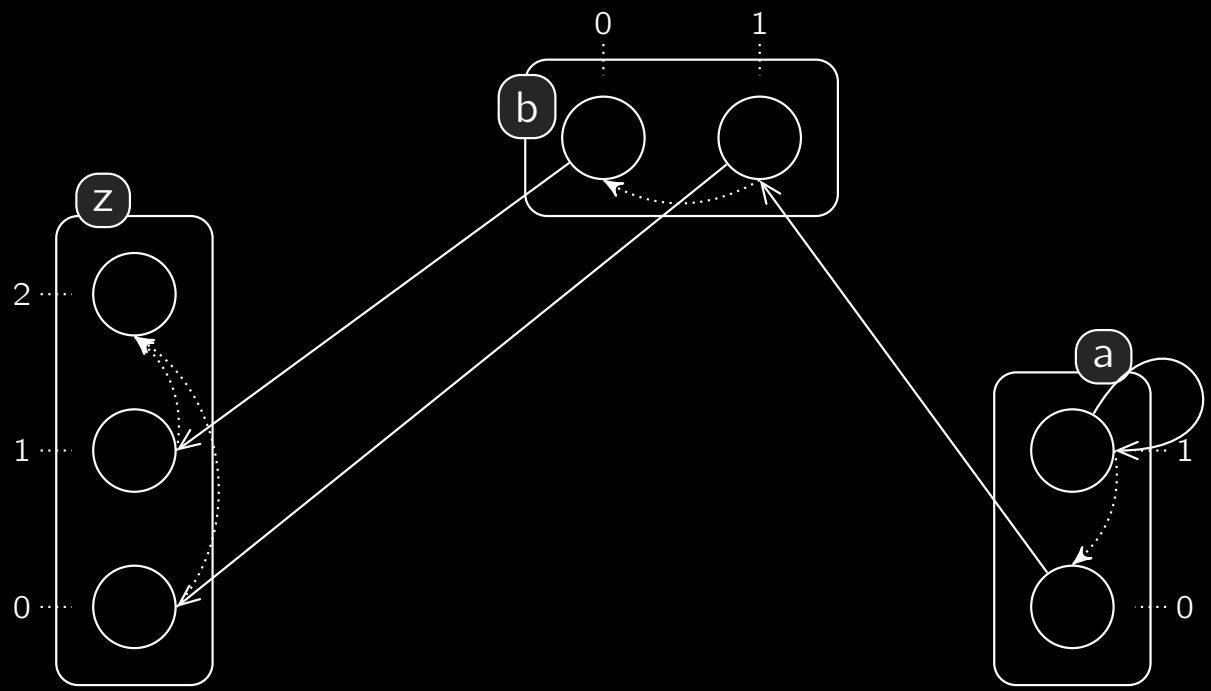
The Process Hitting Framework

[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, ...;
- States: $\langle a_1, b_1, z_1 \rangle$, $\langle a_0, b_1, z_1 \rangle$, $\langle a_0, b_0, z_1 \rangle$, ...;
- Restriction of Communicating Finite-State Machines (CFSM).

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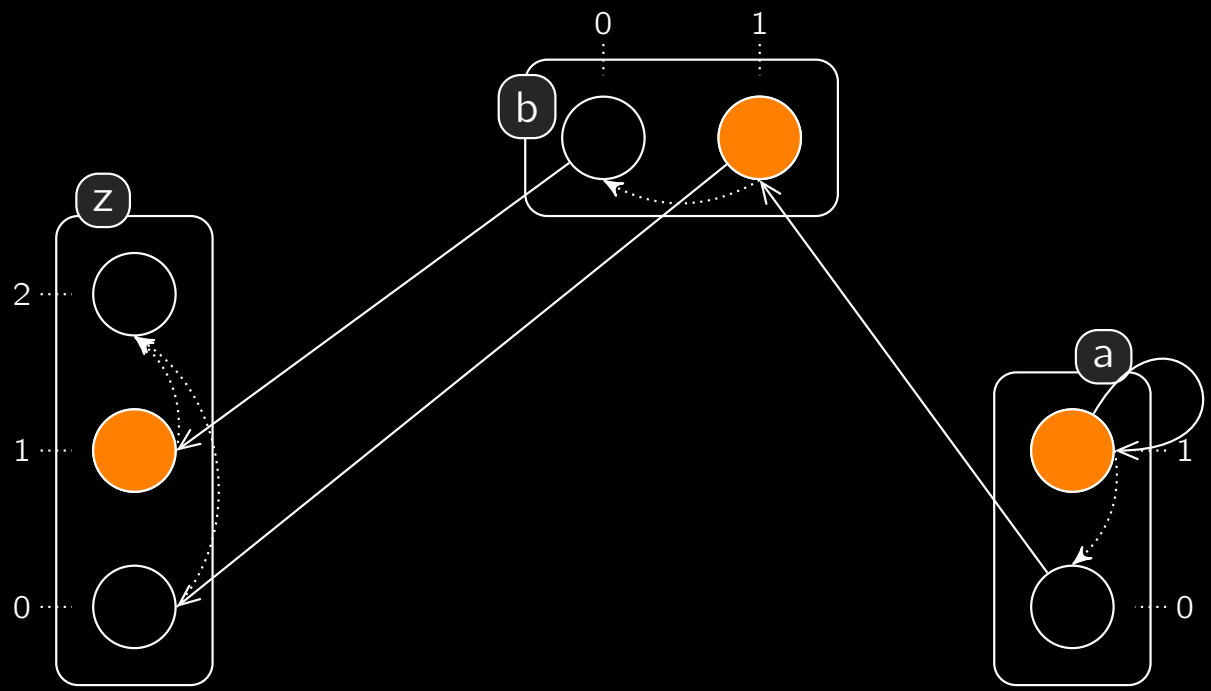

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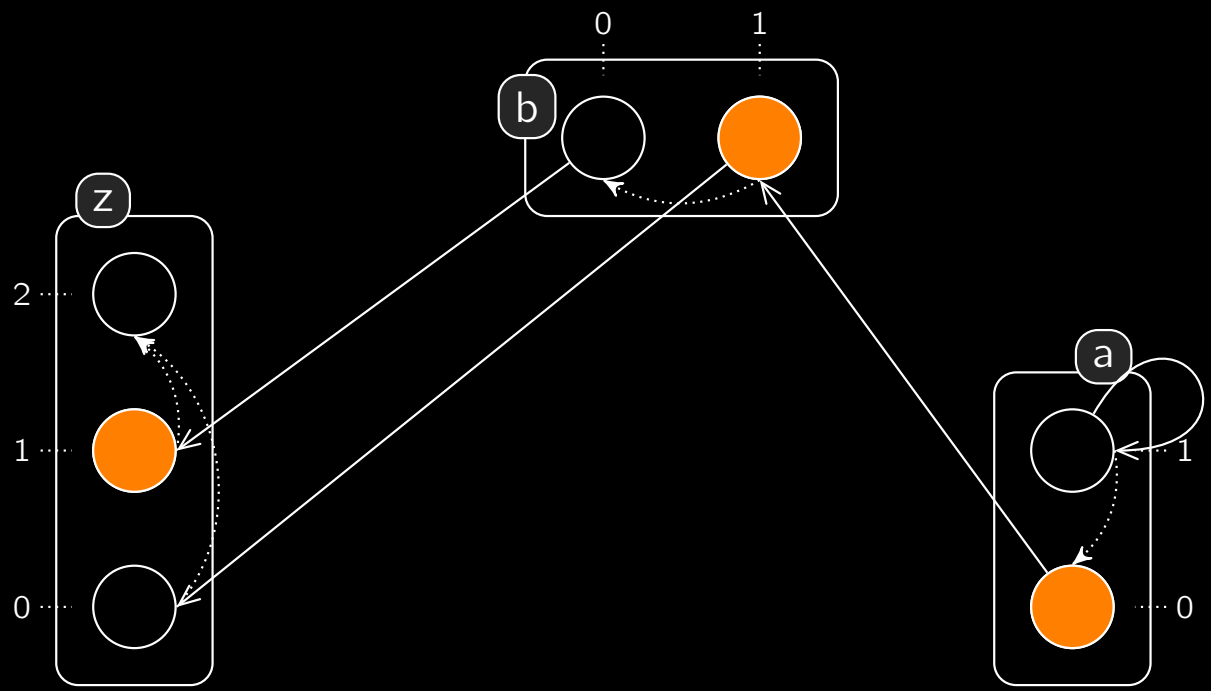

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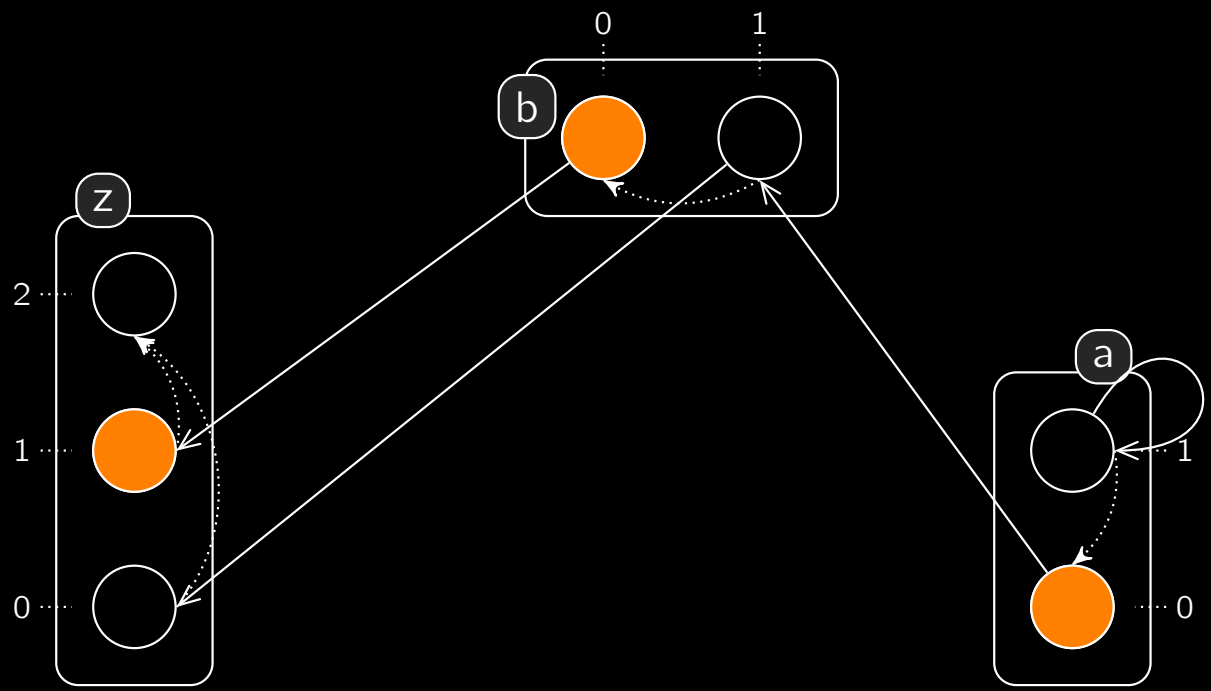

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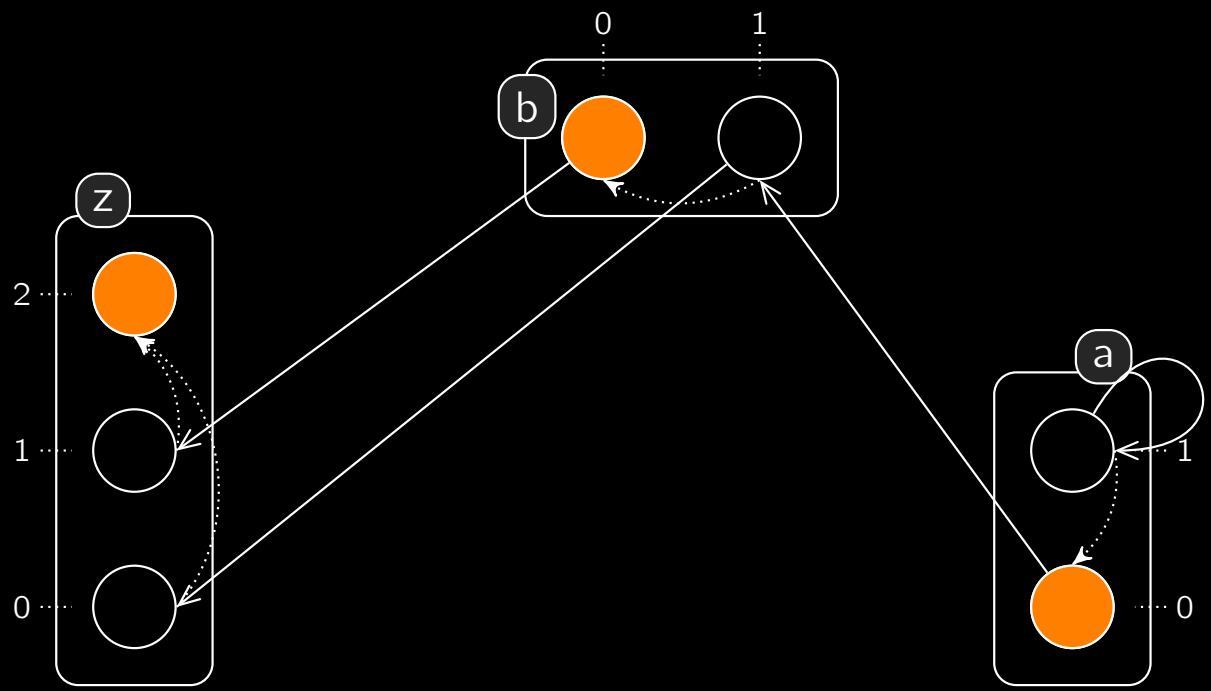

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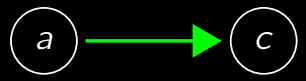
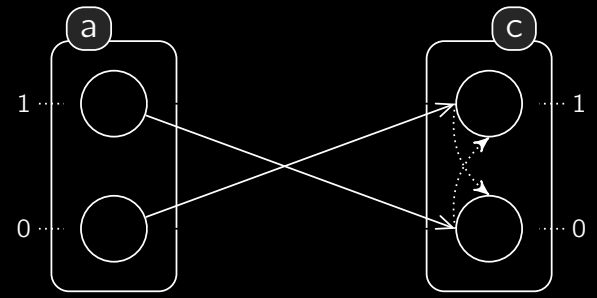
From BRNs to Process Hittings





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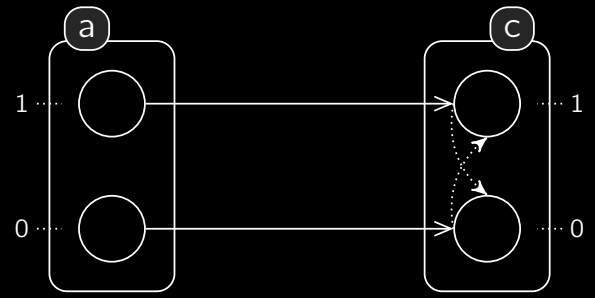

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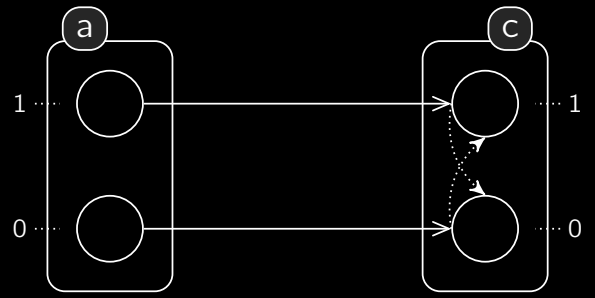
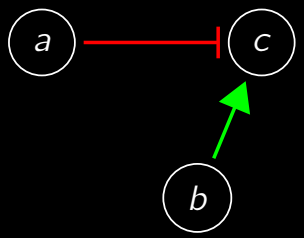
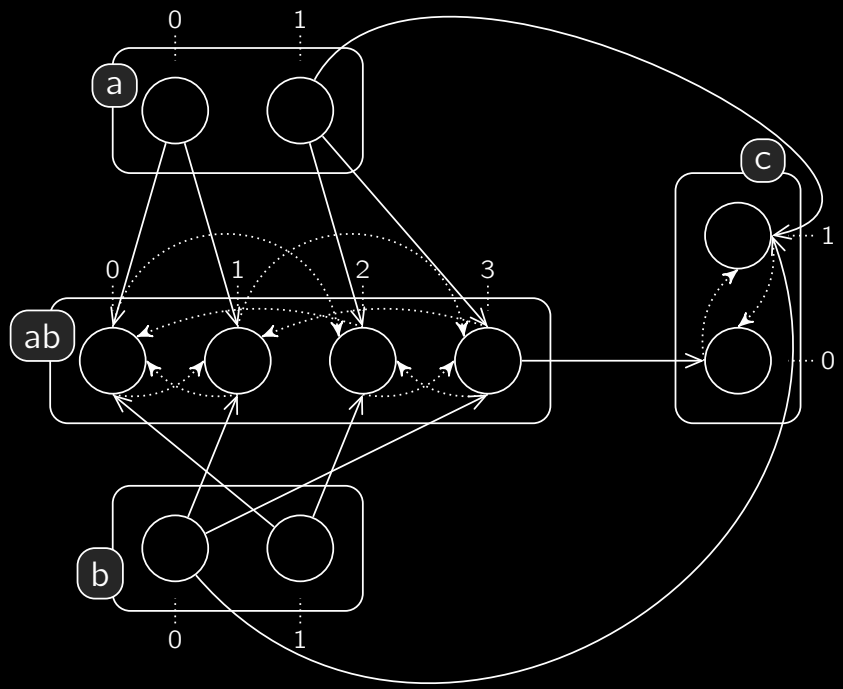




$c = \neg a \wedge b$



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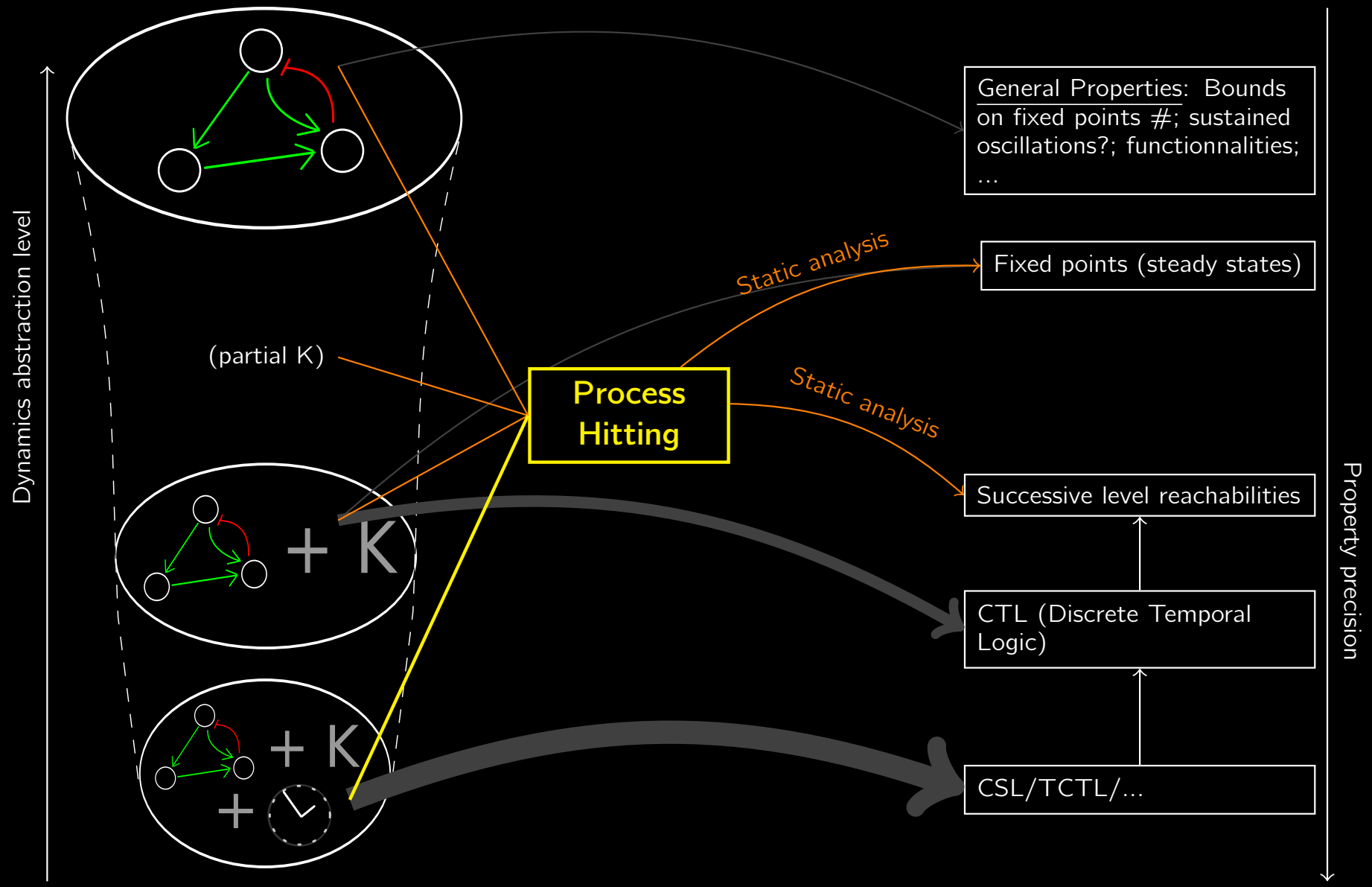

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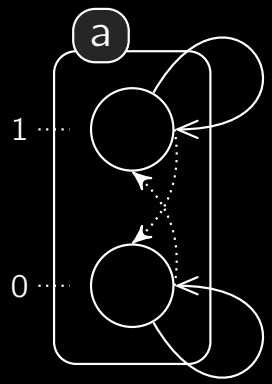
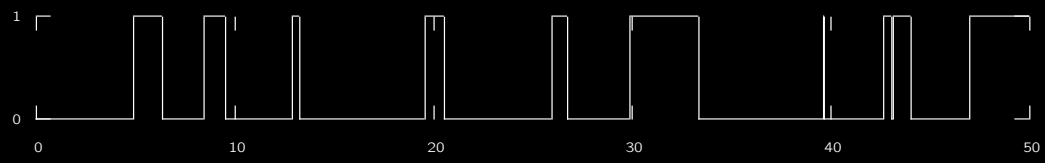
Stochasticity Absorption Factor

[Paulevé, Magnin, Roux in IEEE TSE, 2010]

- Stochastic dimension is prominent... but no precise time features:
- (Markov) Exponential distribution: mean r^{-1}; variance r^{-2}.
- At our level of abstraction, we need to tune time features.





sa=1

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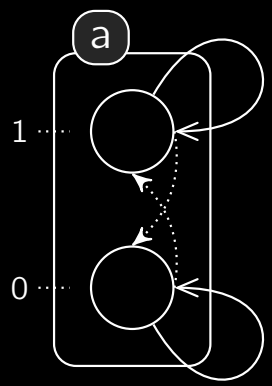
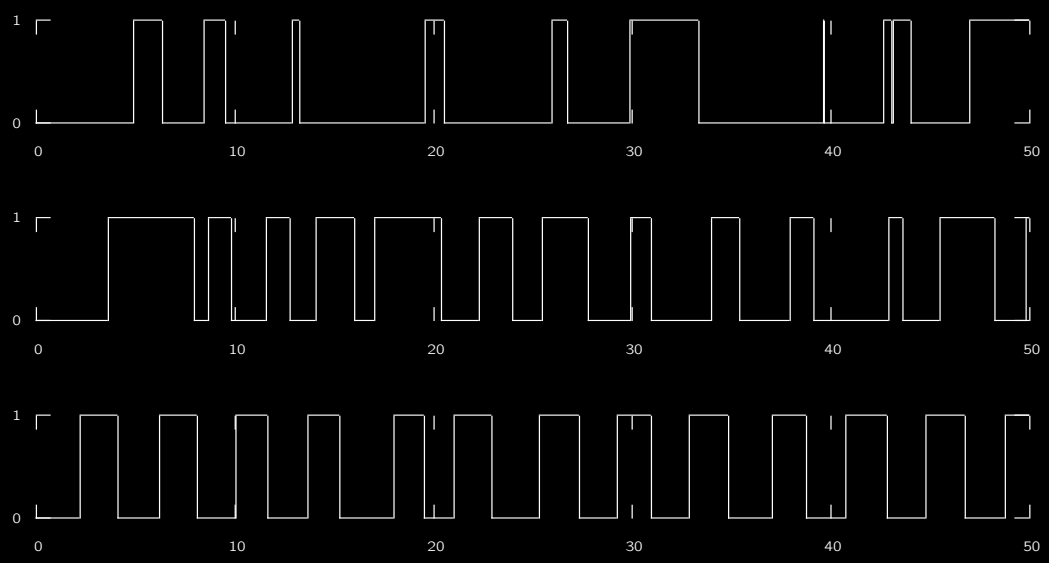
- At our level of abstraction, we need to tune time features.
- Provide a stochasticity absorption factor *sa*:
- duration follows the sum of *sa* exponentials of rate $r.sa$;
- mean r^{-1}; variance $r^{-2}sa^{-1}$ (Erlang distribution).

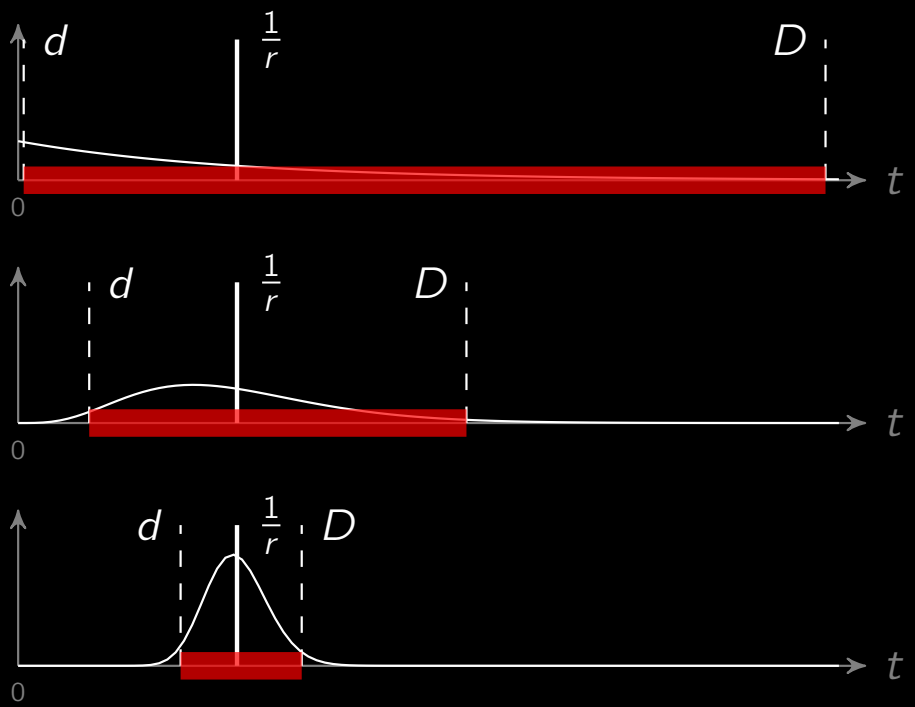




Stochastic and Time Parameters

[Paulevé, Magnin, Roux in IEEE TSE, 2010]

- Specify either (r, sa), or its firing interval $[d; D]$,
- which is the confidence interval at confidence coefficient $1 - \alpha$.
- We have estimators to translate $[d; D]$ to (r, sa).



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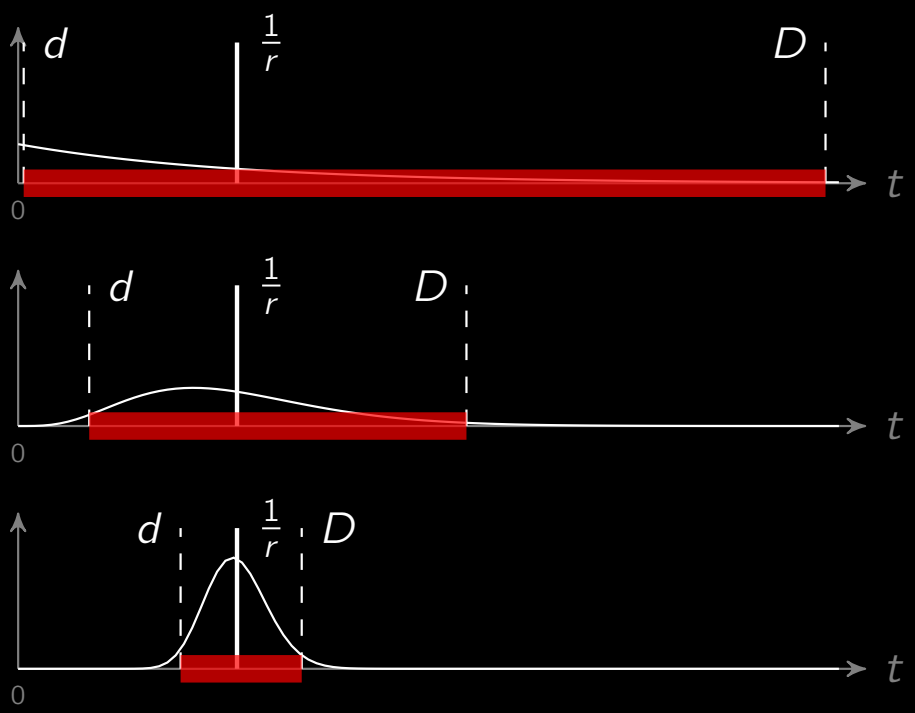
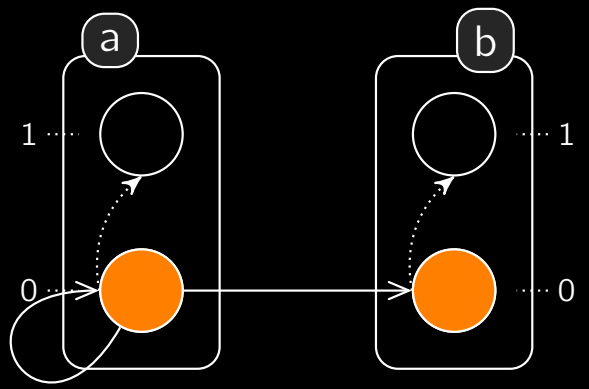


action duration



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

Simulation and Model Checking

Stochastic Model Checking

- Translation from the Erlang stochastic π-calculus to PRISM [Paulevé, Magnin, Roux in IEEE TSE, 2010].
- Applies to the Process Hitting as well.
- Not tractable with large stochasticiy absorption factors;
- but there is hope in symmetry reductions, or abstractions of sequences of transitions, or ...

Simulation

- Non-Markovian simulation using the
- Generic abstract machine for stochastic process calculi [Paulevé, Youssef, Lakin, Phillips at CMSB 2010].
- Process Hitting simulator implemented in PINT.

Challenge: scalable inference of stochastic and time parameters...

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Challenge: scalable inference of stochastic and time parameters...
... still open; prior need for scalable qualitative analyses.

Static Analysis of Process Hitting

Intuition

- Simplicity of Process Hitting $\Rightarrow$ simple structures.
- Efficient static derivation of dynamical features.

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- Reduction to the n-cliques of a n-partite graph.

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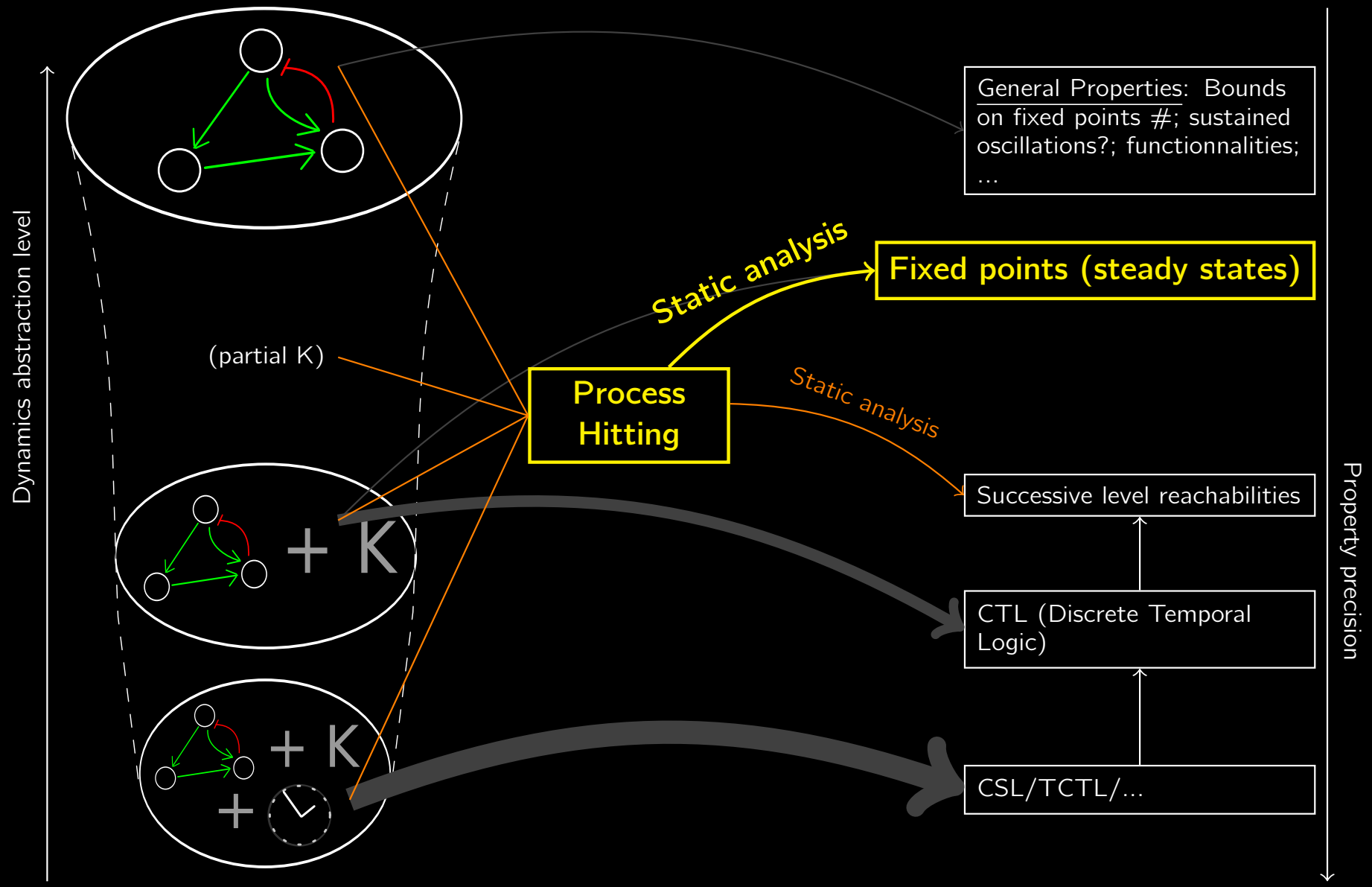
Reachability properties $\mathbf{EF}\ a_i \wedge (\mathbf{EF}\ b_j \wedge \dots)$

- Limited complexity: $\approx$ polynomial in #sorts; exponential in #processes per sort.
- May be inconclusive: Yes/No/Jocker.
- Abstract interpretation techniques.
- $\Rightarrow$ address very large systems.
- + extraction of key processes (towards control).

[Paulevé, Magnin, Roux in SASB'10 + Technical report]

Outline



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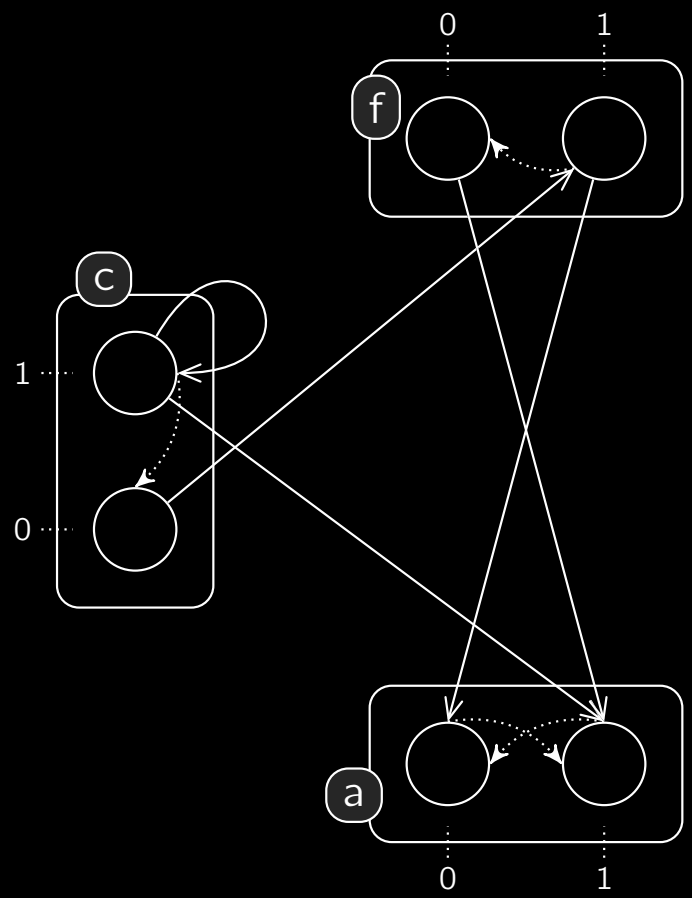
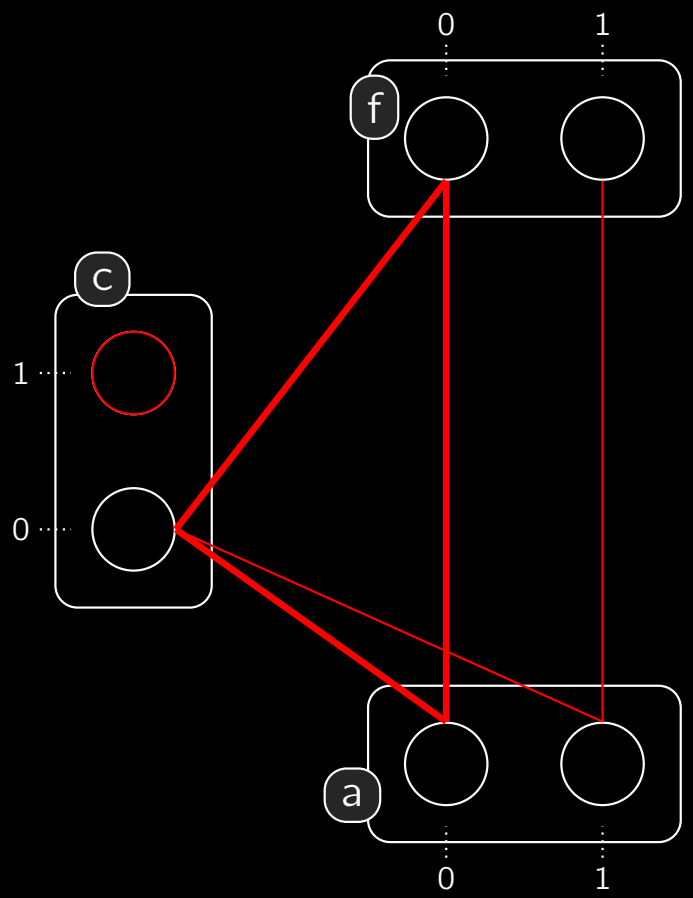
Fix Points

[Paulevé, Magnin, Roux in TCSB 2011]

Process Hitting



Hitless graph



n-cliques are fix points

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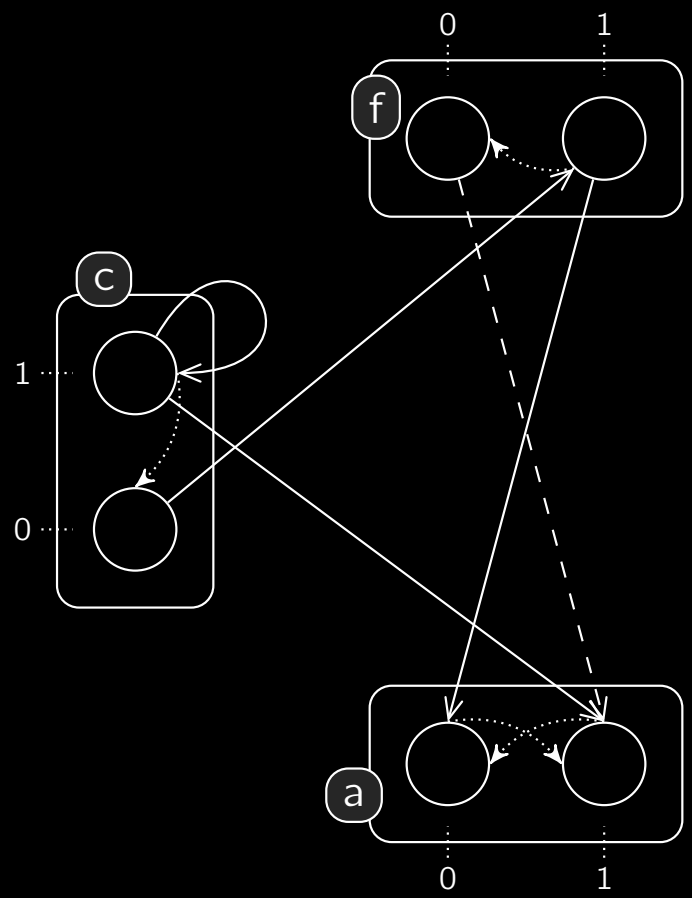

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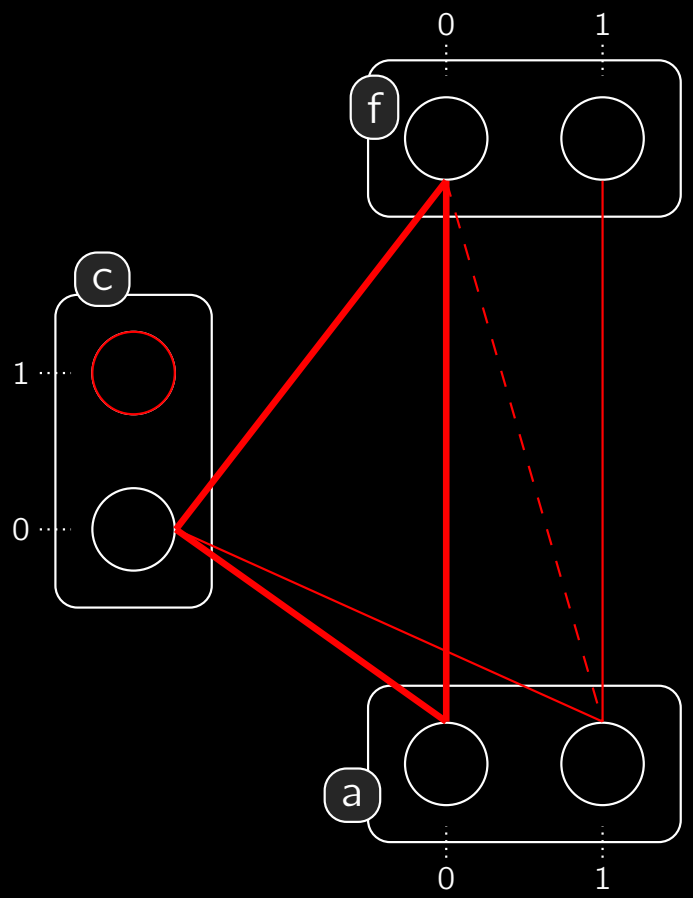

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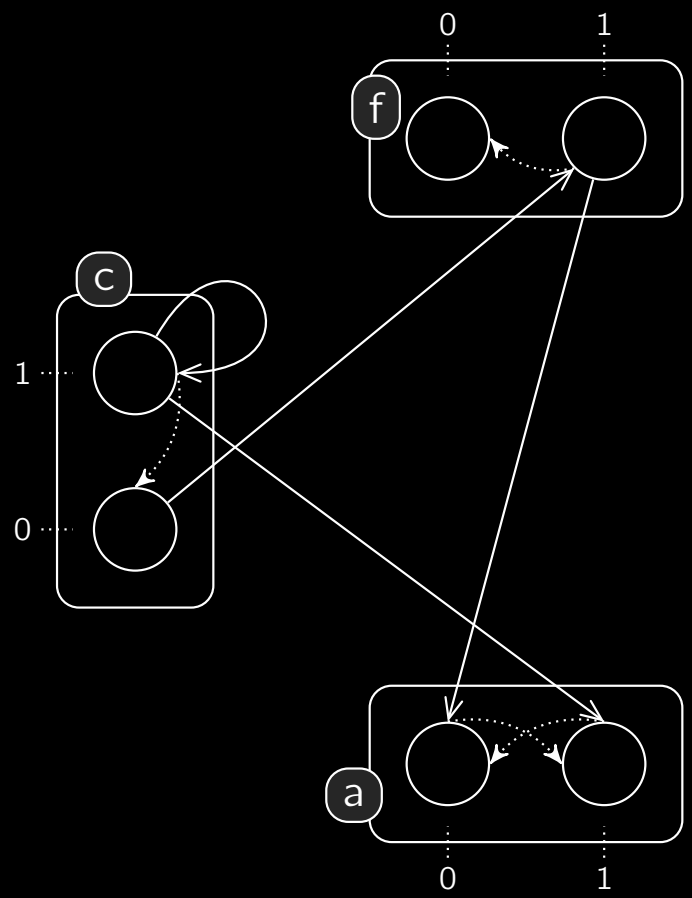
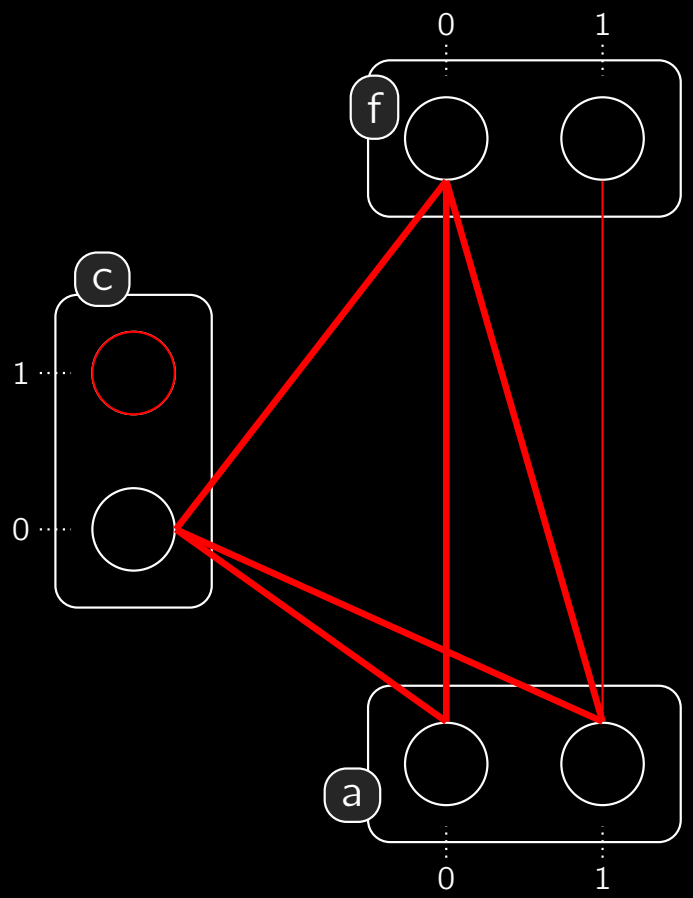
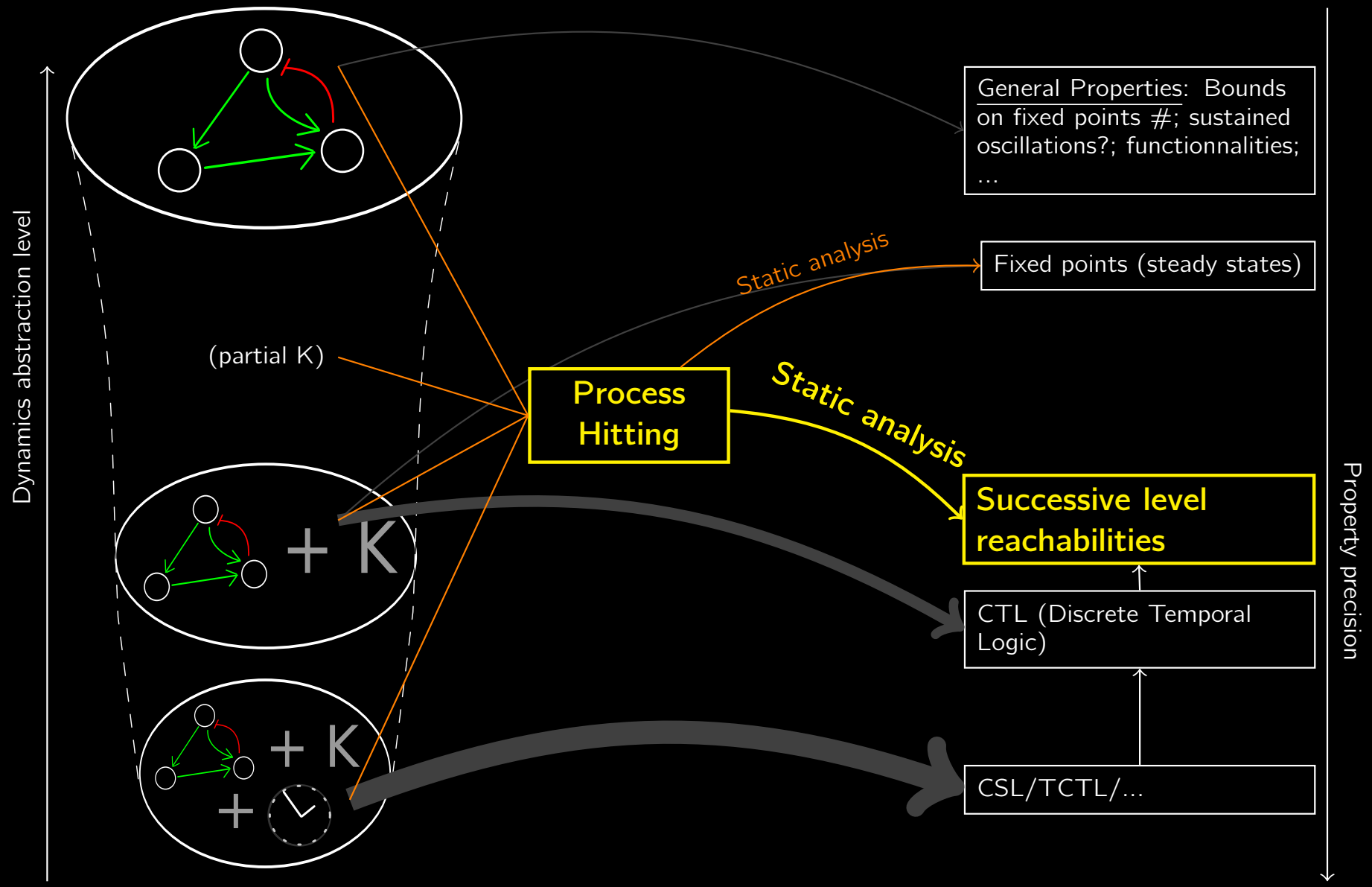


Hitless graph



n-cliques are fix points

Outline



Loïc Paulevé, Morgan Magnin, Olivier Roux

Approximation of Reachability Properties

- Successive reachability of processes (reach a_0 then b_1 then ...);
- Approach using abstract interpretation techniques;
- Results in both over- and under-approximations;
- Limited complexity at the cost of potentially being inconclusive.

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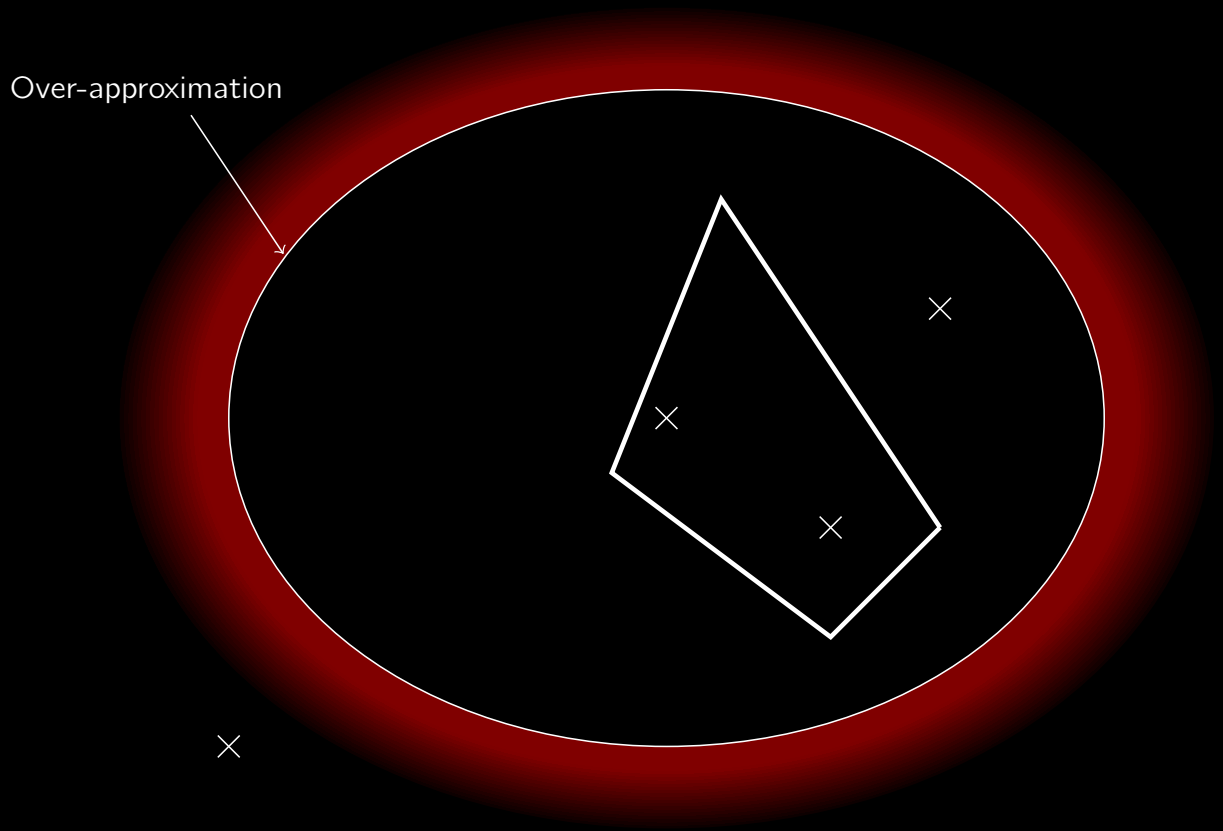

[Paulevé, Magnin, Roux at SASB 2010 + MSCS submitted]

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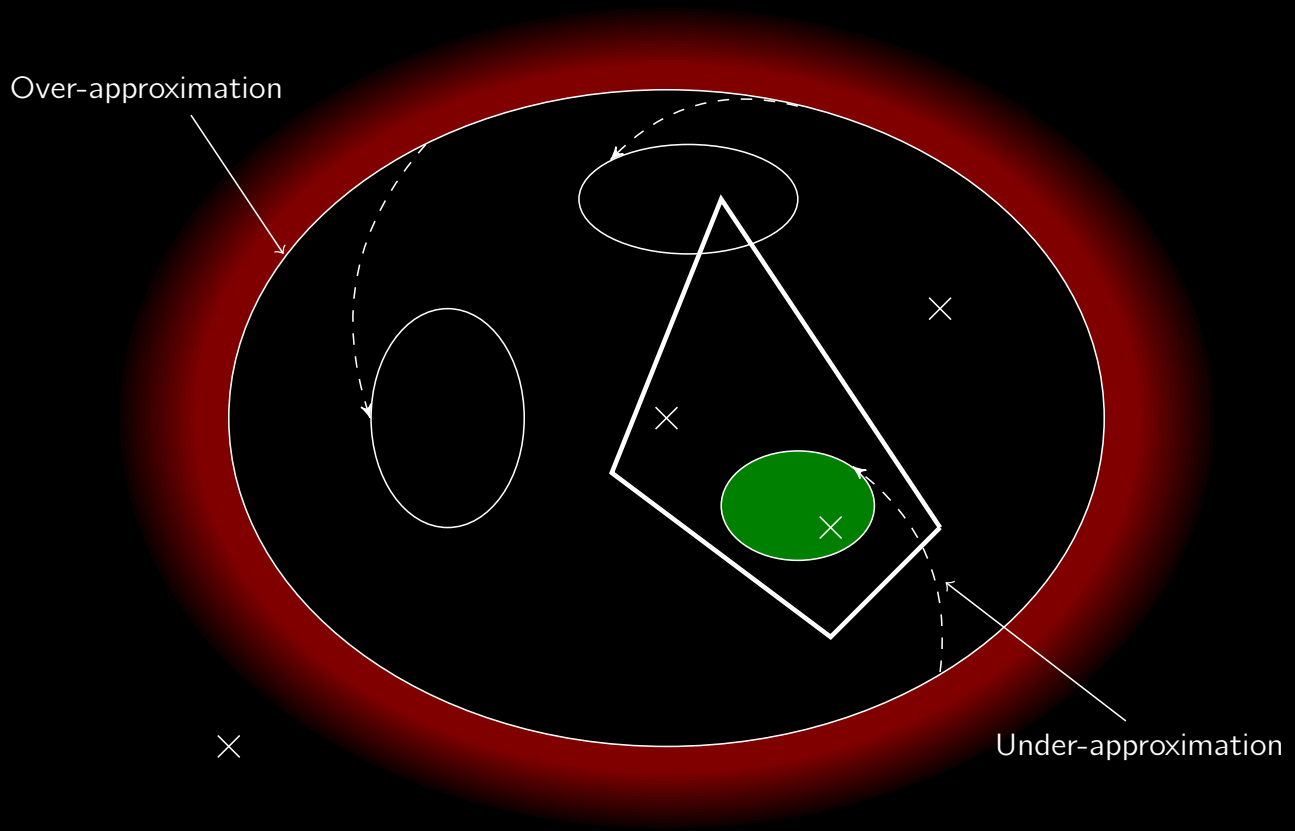

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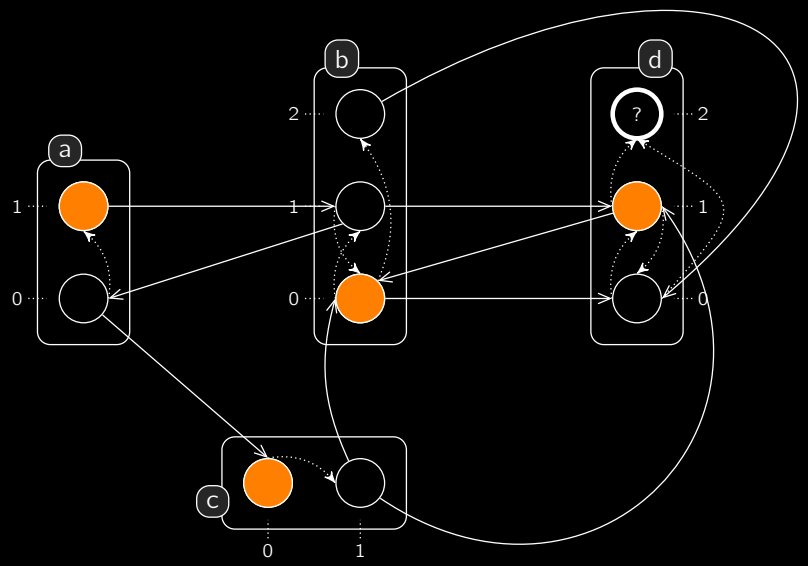
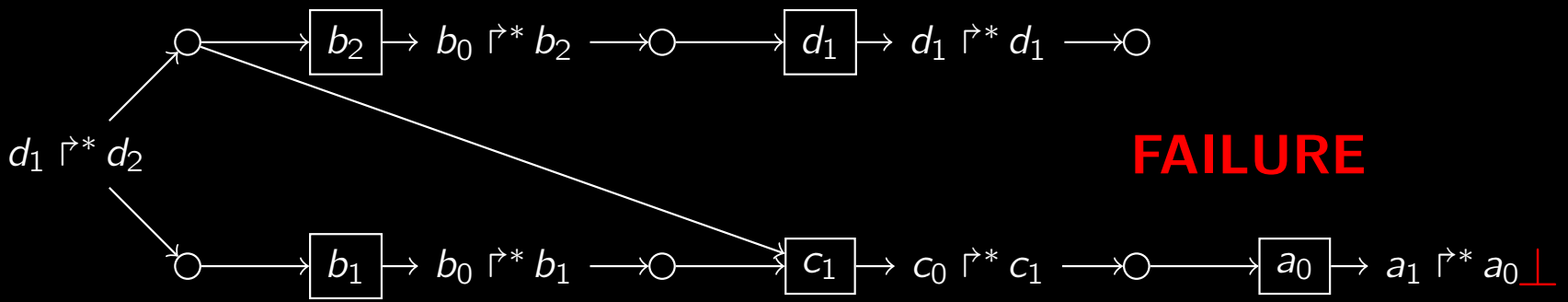
Un-ordered Over-approximation



- Necessary condition: there always exists a solution ending with a trivial objective.



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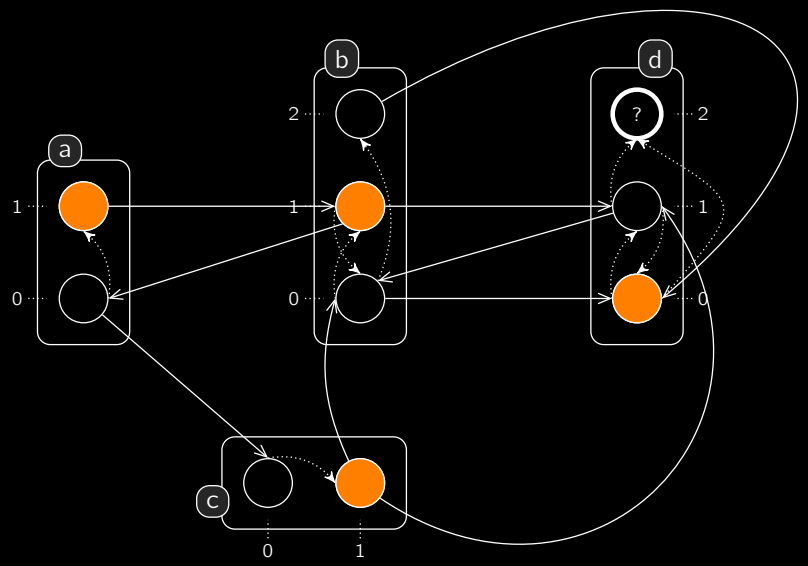

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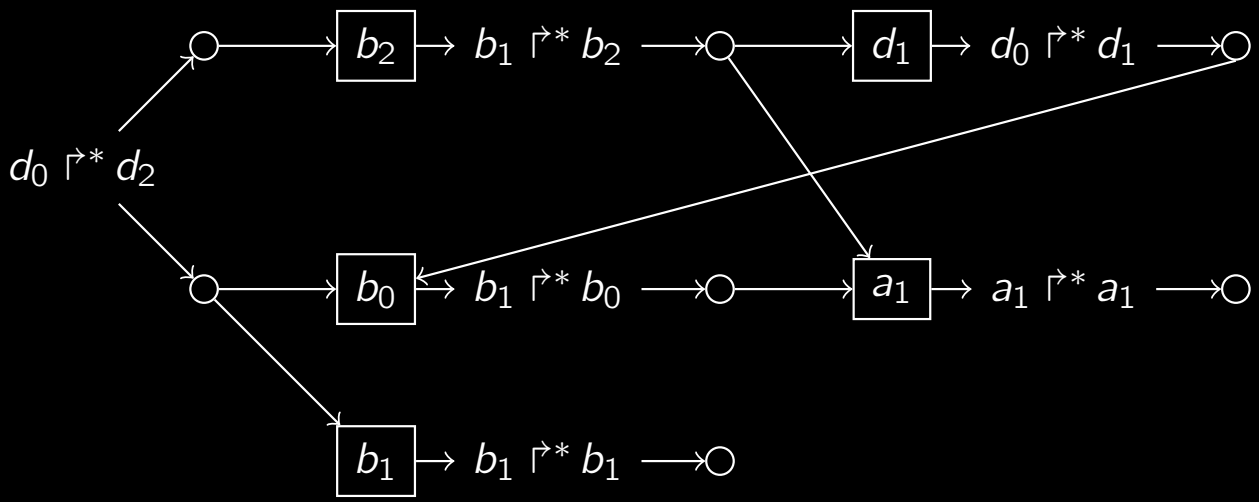
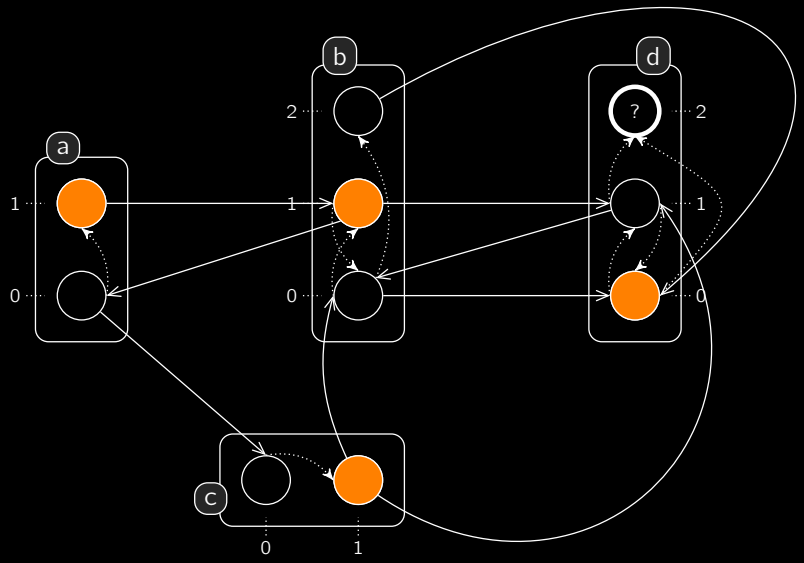


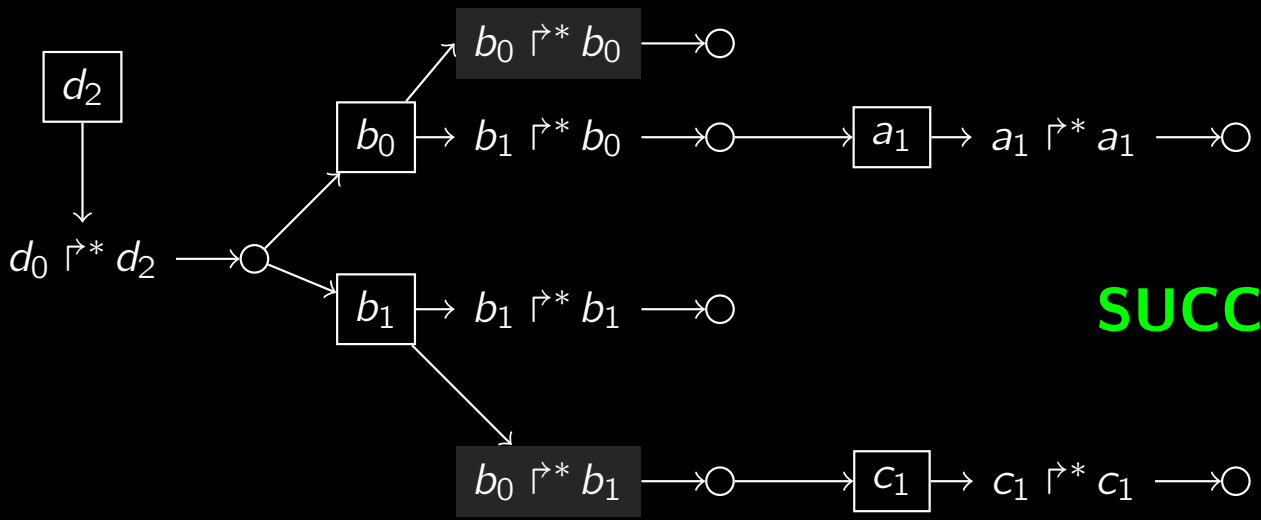
OK

Under-approximation



Sufficient condition:

- $\lceil \mathcal{B}_\varsigma^\omega \rceil$ has no cycle; and
- all referenced objectives have at least one solution.



SUCCESS

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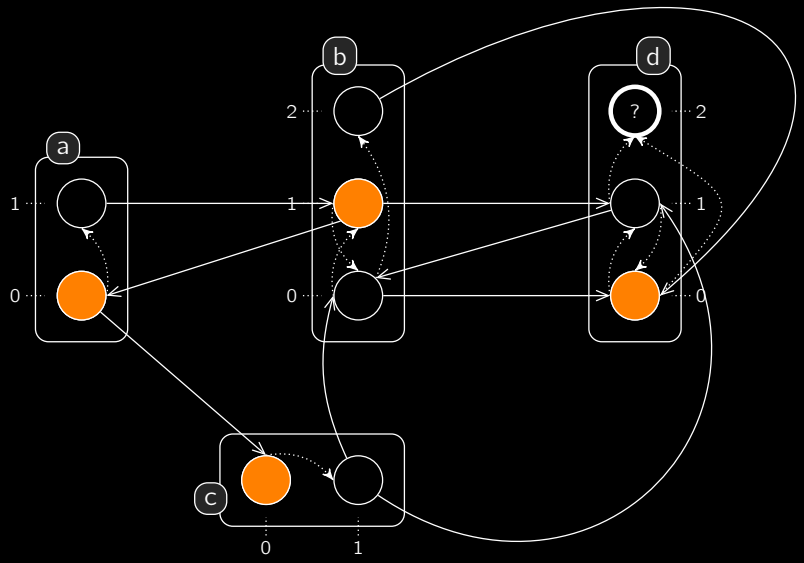

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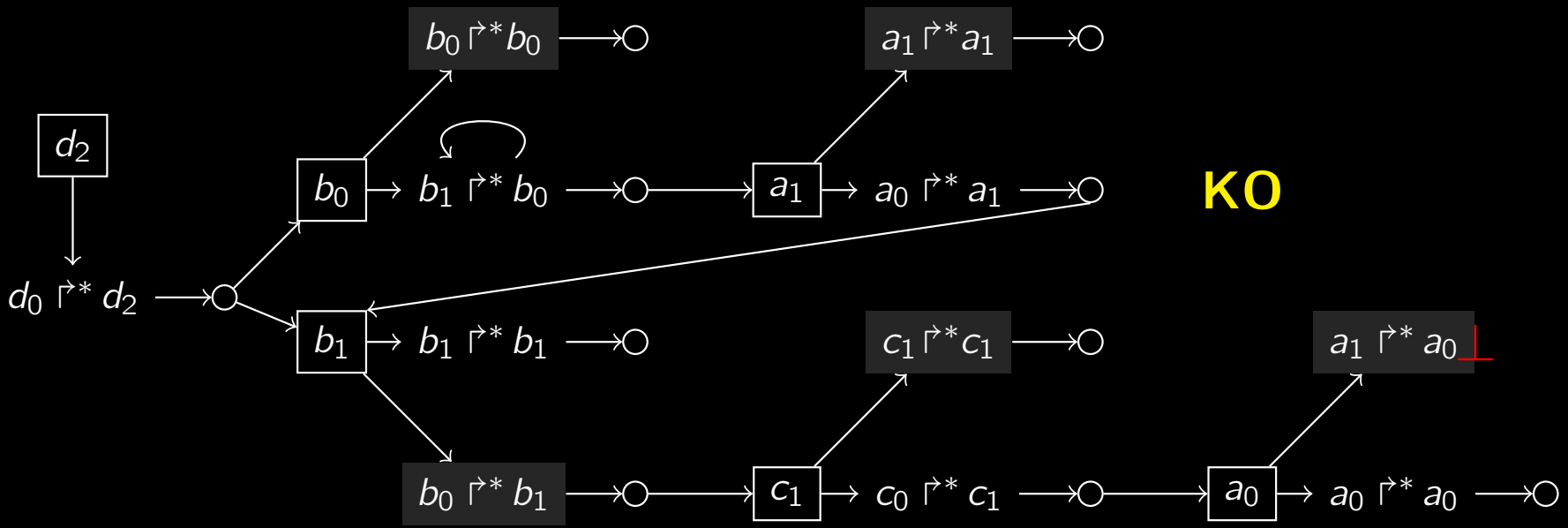


Abstract Interpretation of Process Hitting

Summary

- Reachability properties of the form $\mathrm{EF}\ a_i \wedge (\mathrm{EF}\ b_j \wedge \dots)$;
- Static computation of abstract structures from Process Hitting models.
- Recursive and iterative reasonments.
- Over- and under-approximations (Yes/No/Jocker).
- Extraction of key processes (that are necesssary): towards control.

Complexities

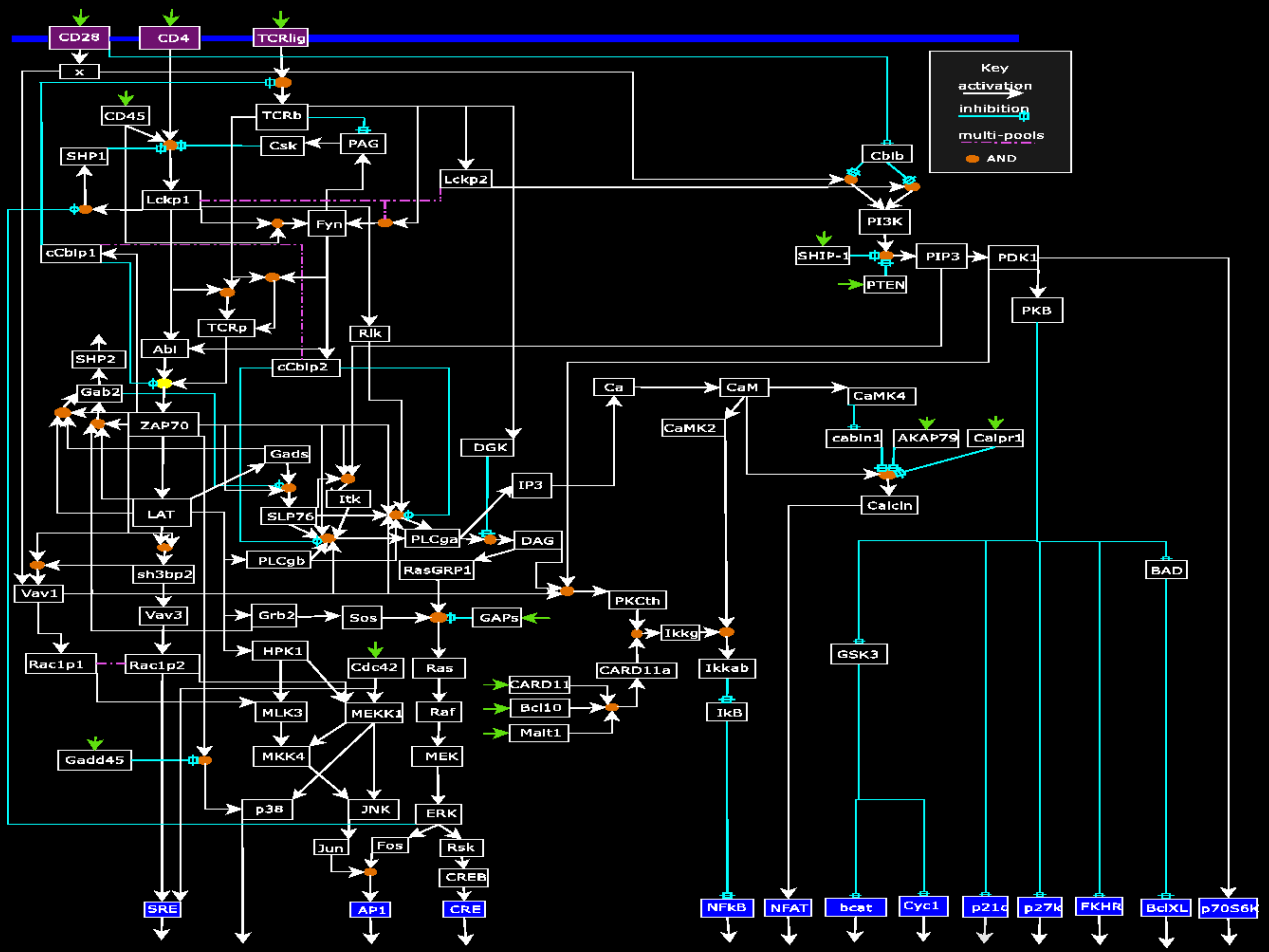
- $\approx$ polynomial in #sorts; exponential in #processes per sort.

$\Longrightarrow$ efficient with a small number of processes per sort; while a very large number of sorts can be handled.

Outline

T-Cell Receptor Signalling Pathway

(94 components)



[Saez-Rodriguez, *et al.* in PLoS Comput Biol, 07]

Process Hitting
133 sorts,
448 processes,
1124 actions:
$\approx 2 \cdot 10^{58}$ states.

Reachability analysis always conclusive; around 0.01*s* (compared to *libddd*: out of memory). [http://ddd.lip6.fr]

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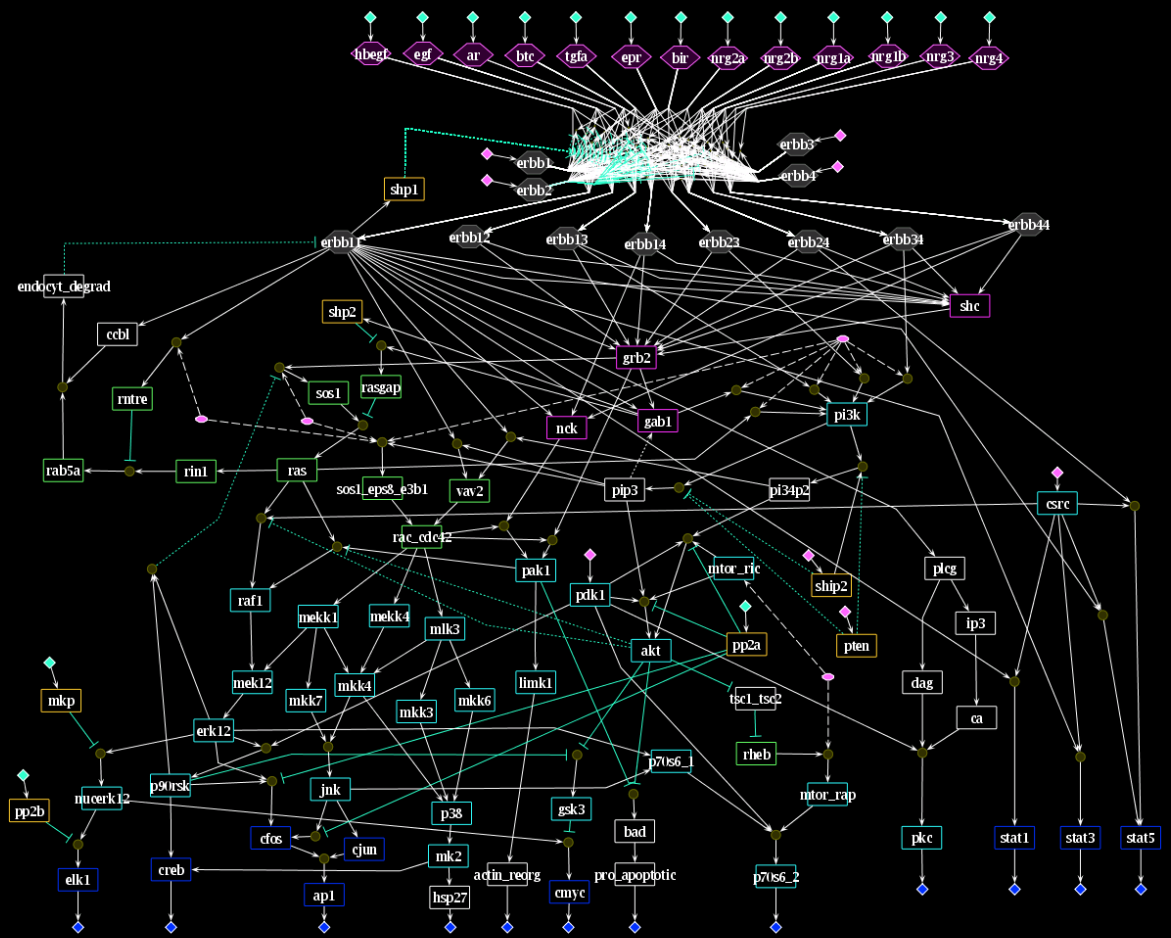
EGFR/ErbB Signalling

(104 components)



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

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

Reachability analysis always conclusive; around 0.05*s* (compared to *libddd*: out of memory). [http://ddd.lip6.fr]

Outline

Conclusion

The Process Hitting

- *Elementary* framework for dynamical complex systems;
- Applied to BRNs; not limited to.
- Generic tuning of time features within stochastic models (simulation + standard model checking).
- Software available (PINT - `http://process.hitting.free.fr`).

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BRNs Modelling using Process Hitting

- Approach by abstraction refinements: from the generalized dynamics of the interation graph to the construction of cooperations;
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Static Analysis of Process Hitting

- Fix points by topological analysis;
- Very efficient over- and under-approximations of process reachability;
- Extract necessary processes for achieving reachabilities: towards control.
- Brings new insight to derive precise dynamical properties from BRNs.

Outlook

Derive more properties

- Characterisation of attractors;
- Verification for sustained oscillations;
- etc.

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Motivation: impact of time features on dynamics.

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- Parameters inference (from properties, data, etc.);
- *Key* parameters (having a significant impact on dynamics).

Idea: detect key concurrencies leading to the satisfaction or non-satisfaction of a property.

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Application to BRNs

- Address bigger BRNs (E. Coli, etc.);
- Focus on properties of interest for BRNs analysis;
- Suggestions are very welcome.