The NII-Yamanashi-LRI Workshop

Exhaustive analysis of the dynamics of Process Hitting through Answer Set Programming

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joint work Olivier ROUX & Morgan MAGNIN

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Context and Aims

MeForBio team:
Algebric modelling to study
complex dynamical biological systems

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   Biological Regulatory Networks (BRNs): Studying **gene interactions** with mathematical tools;

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3) What for?

   searching of PH **properties** through ASP (Fixed points, reachability).

Plan

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   - Definition
   - Example of an ASP program

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5) Conclusion & prospect

Answer Set Programming

ASP:

- Logic program written in language of AnsProlog*
- Form of rules :

$$\textit{head} \leftarrow \textit{body}.$$
$$L_0 \leftarrow L_1, ..., L_m, \textbf{not } L_{m+1},..., \textbf{not } L_n.$$

with each L_i : literal in the sense of classical logic.

Rule's meaning:

If L_1,...,L_m are **true** and if L_{m+1},..., L_n are **false**
then L_0 is **true**.

Answer Set Programming

Special types of rules:

- **Constraint** :

$$\leftarrow L_1, ..., L_m, \textbf{not } L_{m+1}, ..., \textbf{not } L_n.$$

- **Fact** :

$$L_0.$$

- **Cardinality** :

$$min\{L_0, ..., L_j\}max \leftarrow L_1, ..., L_m, \textbf{not } L_{m+1}, ..., \textbf{not } L_n.$$

Answer Set Programming

Example:

$bird(X) \leftarrow lays\_egg(X).$
$mammal(X) \leftarrow engender(X).$
$fly(X) \leftarrow bird(X),$ **not** $mammal(X).$
$lays\_egg(tweety).$

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$fly(tweety) \leftarrow True, True.$

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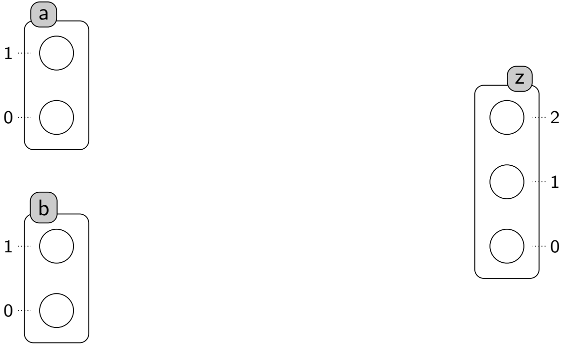
Answer: `fly(tweety), bird(tweety).`

The Process Hitting modeling

Sorts: components *a*, *b*, *z*

The Process Hitting modeling



Sorts: components a, b, z

Processes: local states / levels of expression z_0, z_1, z_2

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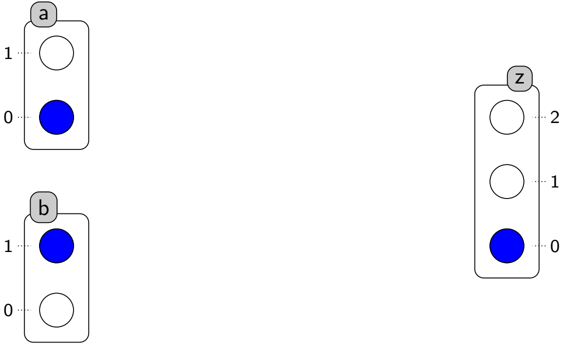

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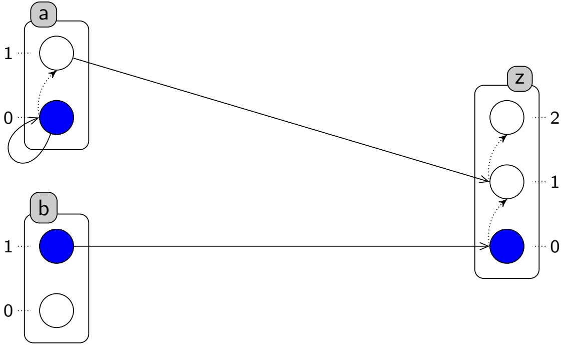

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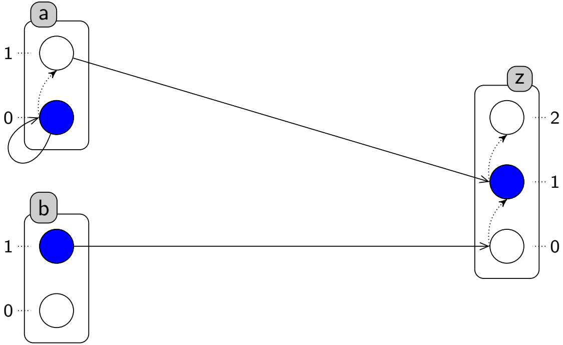

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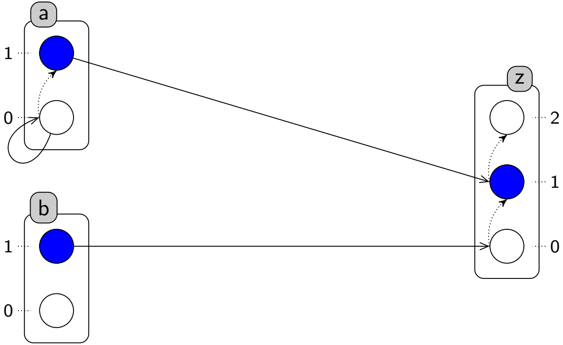

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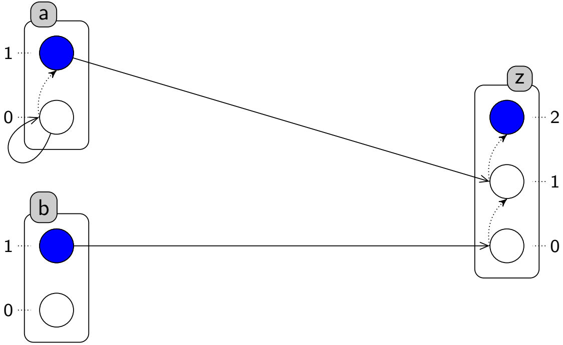

Sorts: components $a,\ b,\ z$

Processes: local states / levels of expression $z_0,\ z_1,\ z_2$

States: sets of active processes $\langle a_1, b_1, z_2 \rangle$

Actions: dynamics $b_1 \rightarrow z_0 \Rsh z_1,\ a_0 \rightarrow a_0 \Rsh a_1,\ a_1 \rightarrow z_1 \Rsh z_2$

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PH through ASP

Network traduction:

- **Sort**: `sort(A) .`
- **Process**: `process(A,I).`
- **Action** $a_i \rightarrow b_j \Rsh b_k$: `action(A,I,B,J,K).`

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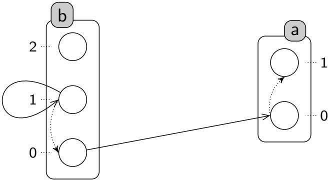

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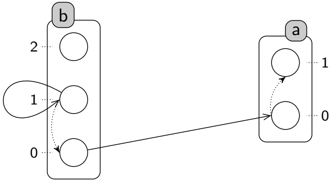

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sort("a").  sort("b").
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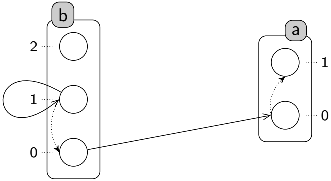

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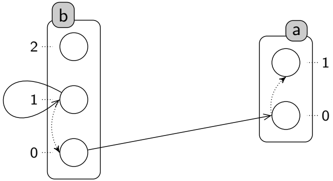

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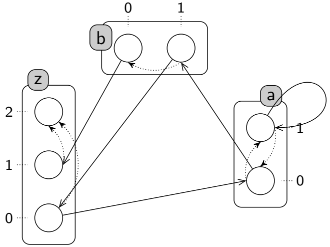
process("b", 0..2).
action("b",0,"a",0,1).
action("b",1,"b",1,0).
```

Fixed Points

Fixed point = state where no action can be played



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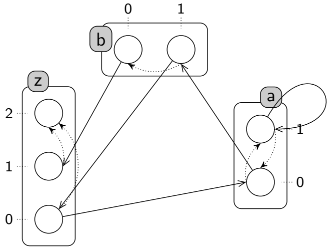
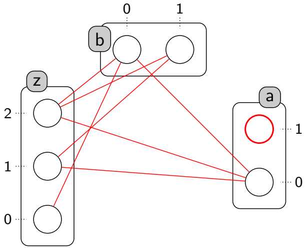
→ Hitless Graph





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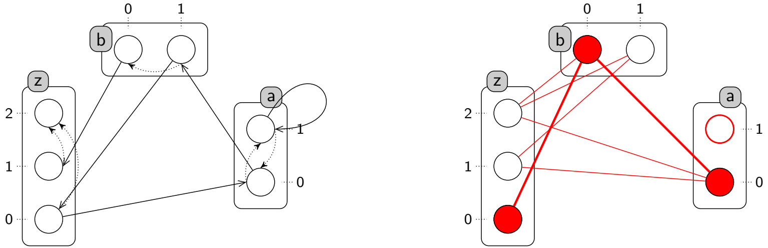

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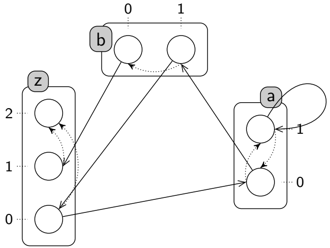
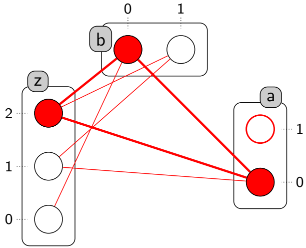
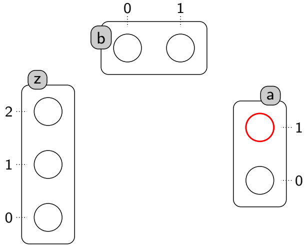




Implementation of the algorithm (N-Cliques)

Definition of hitless graph :

```
noAction(A,I,B,J) :- not hit(A,I,B,J), not hit(B,J,A,I), A!=B,
                     shownProcess(A,I), shownProcess(B,J).
```



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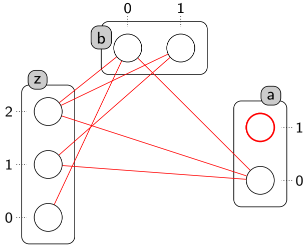

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Select processes :

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1 {selectProcess(A,I) : shownProcess(A,I) } 1 :- sort(A).
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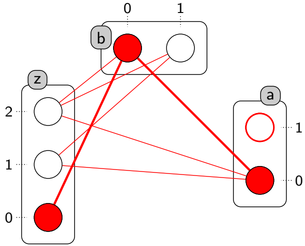

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Find Fixed points :

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noHit(A,I,B,J) :- noAction(A,I,B,J),
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noExistFixPoint :- 0 {noHit(A,I,B,J)} 0, selectProcess(A,I),
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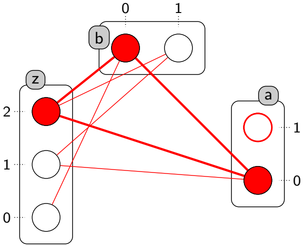

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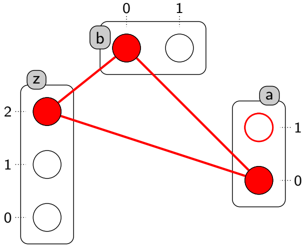
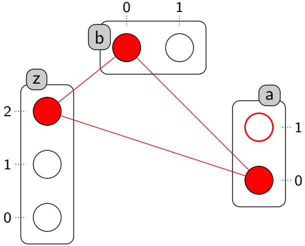


Static analysis

Fixed point through ASP

ASP program result:

```
Answer 1:  fixProcess(a,0), fixProcess(b,0), fixProcess(z,2).
```



Static analysis

Fixed point through ASP

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                     ~~selectProcess(B,J), A!=B.~~
~~noExistFixPoint :- 0 {noHit(A,I,B,J)} 0, selectProcess(A,I),~~
                     ~~selectProcess(B,J).~~
              ~~:- noExistFixPoint.~~
fixProcess(A,I) :- selectProcess(A,I).
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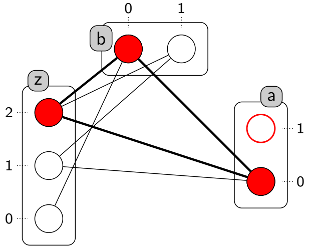

Static analysis

Fixed point through ASP

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1 {selectProcess(A,I) : shownProcess(A,I) } 1 :- sort(A).
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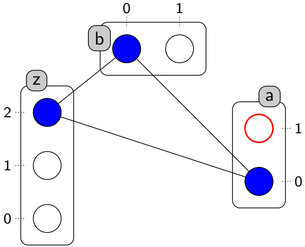


Static analysis

Fixed Point

Comparison

Model	#sorts	#states	#fix-point	mthd1	mthd2	PINT
mvbrn	3	12	1	0.000s	0.000s	0.006s
ERBB	42	2^{70}	3	0.220s	0.000s	0.017s
tcrsig40	54	2^{73}	1	0.220s	0.020s	0.021s
tcrsig94	133	2^{194}	0	2.540s	0.060s	0.027s
egfr104	193	2^{320}	0	8.220s	0.140s	0.074s

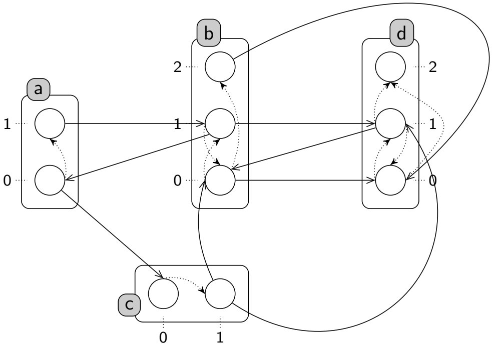
Figure : Excecution time of ASP metods and PINT applied for biological networks with a desktop computer (core i5 and 4GB RAM).

PINT : a library developed to parse and study PH models.

Dynamic analysis

Reachability

Reachability of processes:



Dynamic analysis

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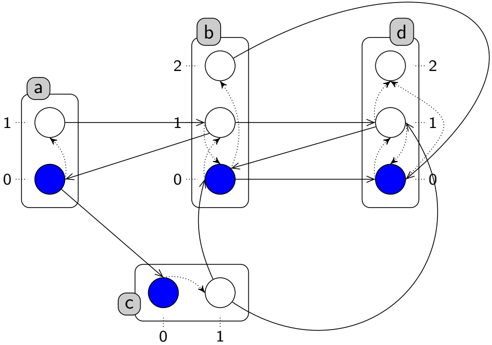

- Initial context

$\langle a_0, b_0, c_0, z_0 \rangle$

Dynamic analysis

Reachability

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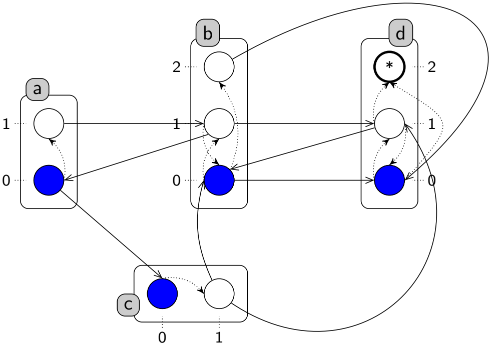

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- Objectives

  $[\ \Rsh d_2\ ]$

Dynamic analysis

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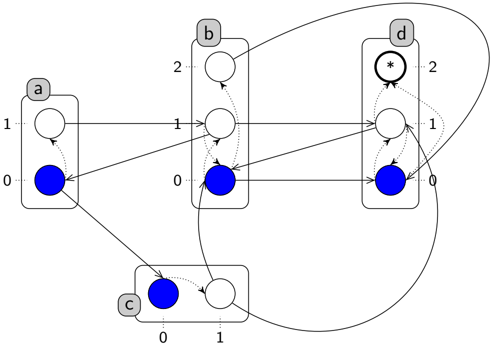

- Initial context

  $\langle a_0, b_0, c_0, z_0 \rangle$

- Objectives

  $[\ \Rsh d_2\ ]$

$\rightarrow$ Concretization of the objective = scenario

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

Dynamic analysis

Reachability

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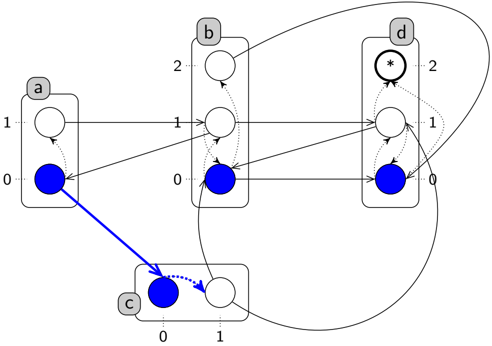


- Initial context

  $\langle a_0, b_0, c_0, z_0 \rangle$

- Objectives

  $[\Rsh d_2]$

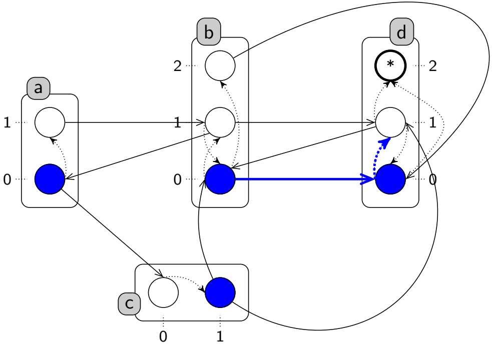
$\rightarrow$ Concretization of the objective = scenario

$\underline{a_0 \rightarrow c_0 \Rsh c_1} :: \; b_0 \rightarrow d_0 \Rsh d_1 :: \; c_1 \rightarrow b_0 \Rsh b_1 :: \; b_1 \rightarrow d_1 \Rsh d_2$

Dynamic analysis

Reachability

Reachability of processes:



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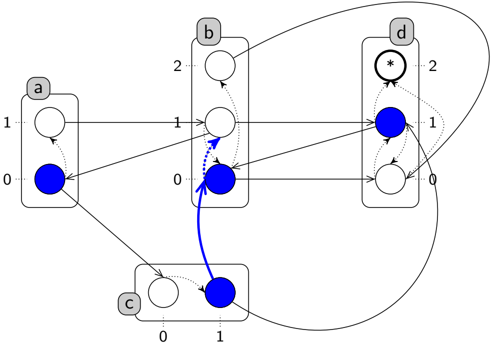
Dynamic analysis

Reachability

Reachability of processes:



- Initial context

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$\rightarrow$ Concretization of the objective = scenario

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Dynamic analysis

Reachability

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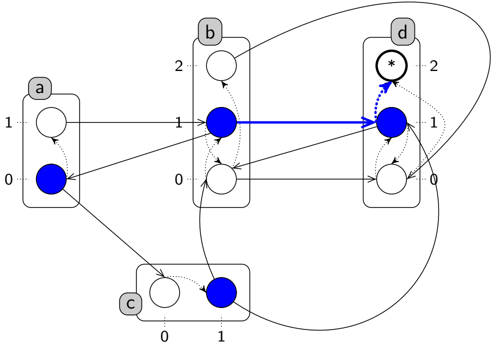


- Initial context

  $\langle a_0, b_0, c_0, z_0 \rangle$

- Objectives

  $[\ \upharpoonleft d_2\ ]$

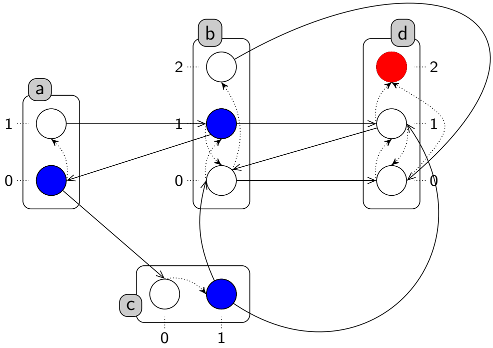
$\rightarrow$ Concretization of the objective = scenario

$a_0 \rightarrow c_0 \upharpoonright c_1 :: \ b_0 \rightarrow d_0 \upharpoonright d_1 :: \ c_1 \rightarrow b_0 \upharpoonright b_1 :: \ \underline{b_1 \rightarrow d_1 \upharpoonright d_2}$

Dynamic analysis

Reachability

Reachability of processes:



- Initial context

$\langle a_0, b_0, c_0, z_0 \rangle$

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$[\ \Rsh d_2\ ]$

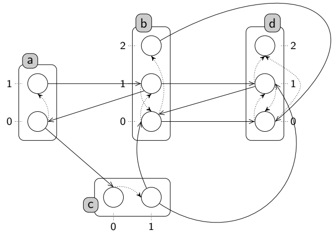
→ Concretization of the objective = scenario

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

Dynamic analysis

Evolution through ASP

Network evolution through ASP



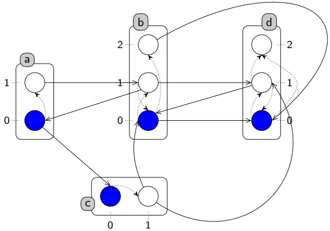
Dynamic analysis

Evolution through ASP

Network evolution through ASP

Initializing :

`init(activeProcess("a",0)).` avec `a:` sorte, `0:` indice du processus



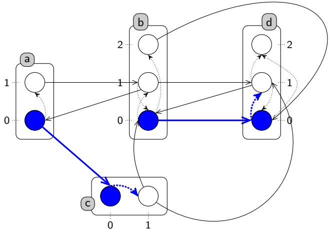
Dynamic analysis

Evolution through ASP

Network evolution through ASP

Playable actions at step T :

```
playableAction(A,I,B,J,K,T) :- action(A,I,B,J,K),
                    instate(activeProcess(A,I),T),
                    instate(activeProcess(B,J),T), time(T).
```



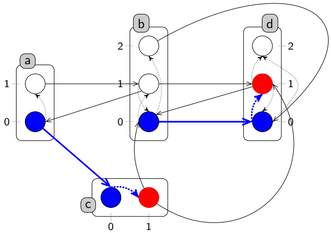
Dynamic analysis

Evolution through ASP

Network evolution through ASP

Change active processes :

```
{activeFromTo(B,J,K,T)} :- playableAction(A,I,B,J,K,T),
                           J!=K, time(T).
                           :- 2{ activeFromTo(B,J,K,T)}, time(T).
```



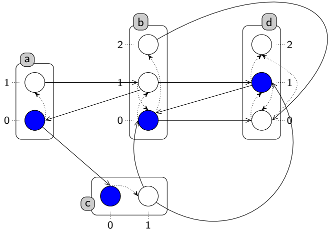
Dynamic analysis

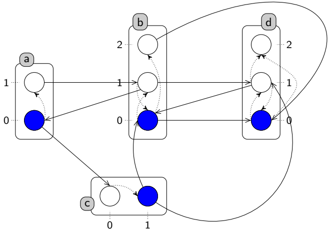
Evolution through ASP

Network evolution through ASP

Active processes at next step (T+1) :

```
instate(activeProcess(B,K),T+1) :- activeFromTo(B,J,K,T), time(T).
instate(activeProcess(A,I),T+1) :- instate(activeProcess(A,I),T),
                                   activeFromTo(B,J,K,T), A!=B, time(T).
```





Dynamic analysis

Evolution through ASP

Network evolution through ASP

```
time(0..N).
```

Results ($N = 3$) :

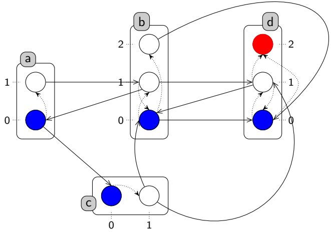
```
Answer 1:   activeFromTo("d",0,1,0) activeFromTo("c",0,1,1)
actifFromTo("b",0,1,2).
Answer 2:   activeFromTo("d",0,1,0) activeFromTo("b",0,2,1)
Answer 3:   activeFromTo("c",0,1,0) activeFromTo("d",0,1,1)
activeFromTo("d",1,0,2) activeFromTo("b",0,1,3)
...
Answer 29:   activeFromTo("c",0,1,0) activeFromTo("b",0,1,1)
activeFromTo("a",0,1,2)
```

Dynamic analysis

Reachability through ASP

Success reachability through ASP:

```
goal(activeProcess("d",2)).
```

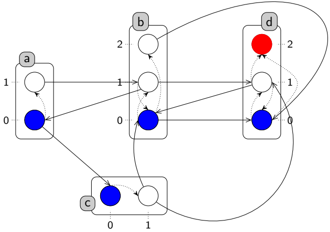


Dynamic analysis

Reachability through ASP

Success reachability through ASP:

```
goal(activeProcess("d",2)).
satisfaible(F,T) :- goal(F), instate(F,T).
:- not satisfaibleTot.
```



Dynamic analysis

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:- not satisfaibleTot.
time(0..N).
```
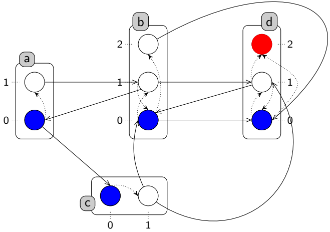



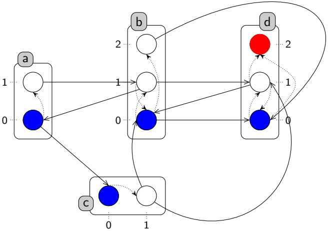
Dynamic analysis

Reachability through ASP

Success reachability through ASP:

```
goal(activeProcess("d",2)).
satisfaible(F,T) :- goal(F), instate(F,T).
:- not satisfaibleTot.
time(0..N).
```

predict N −> Inconvenient



Dynamic analysis

Reachability through ASP

Results for ($N = 2$) :

```
UNSATISFIABLE
```

Results for ($N = 3$) :

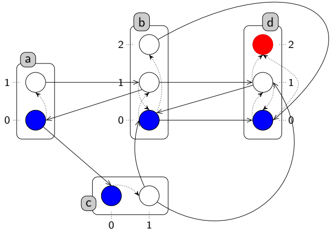
```
Answer 1:   activeFromTo(c,0,1,0), activeFromTo(d,0,1,1),
activeFromTo(b,0,1,2), activeFromTo(d,1,2,3).
Answer 2:   activeFromTo("d",0,1,0) activeFromTo("c",0,1,1)
activeFromTo("b",0,1,2) activeFromTo("d",1,2,3)
```

Dynamic analysis

Reachability through ASP

Success reachability through ASP iterative:

```
goal(activeProcess("d",2)).
#base
instate(F,0) :- init(F).
#cumulative t
playableAction(A, I, B, J, K,t), activeFromTo(B, J, K,t),
instate(activeProcess(A, I),t + 1)...
#volatile t
notSatisfaible(t) :- goal(F), not instate(F,t).
:- notSatisfaible(t).
```



Dynamic analysis

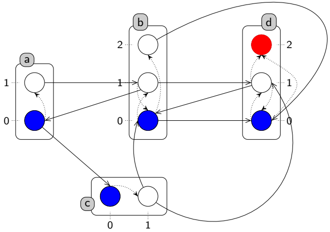
Reachability through ASP

Success reachability through ASP iterative:

Results:

Answer 1: `activeFromTo(c,0,1,0), activeFromTo(d,0,1,1), activeFromTo(b,0,1,2), activeFromTo(d,1,2,3).`

Answer 2: `activeFromTo("d",0,1,0) activeFromTo("c",0,1,1) activeFromTo("b",0,1,2) activeFromTo("d",1,2,3)`



Dynamic analysis

Reachability through ASP

Comparison:

Initializing biological models components and the objectives.

Model	#sorts	#states	#steps	ASP	ASPi	PINT
Exemple	4	36	4	0.000s	0.000s	0.000s
ERBB	42	2^{70}	18	10.620s	5.020s	0.022s
tcrsig40	54	2^{73}	26	156.500s	127.250s	0.012s

Figure : Excecution time of ASP metods (CLINGO et ICLINGO) and PINT applied for biological networks with a desktop computer (core i5 and 4GB RAM)

Dynamic analysis

Reachability through ASP

Comparison:

Method of Rocca et al.:

- ASP
- CTL properties with model cheking (AF, EF, AG...)
- Transitions graph

Dynamic analysis

Reachability through ASP

Comparison:

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Comparaison of the property EF

$$\texttt{prop = EF } (I_0, goal)$$

Dynamic analysis

Reachability through ASP

Comparaison:

Example: Tail resorption of tadpole :
12 sorts, 42 process, 139 actions and 524.288 states.

$$\texttt{prop = EF(}I_0, goal\texttt{)}$$

Dynamic analysis

Reachability through ASP

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$$\texttt{prop = EF(}I_0, goal\texttt{)}$$

Network traduction :

- Transition graph: $3min6s$
- Process Hitting : $0.346s$

Dynamic analysis

Reachability through ASP

Comparaison:

Example: Tail resorption of tadpole :
12 sorts, 42 process, 139 actions and 524.288 states.

$$\texttt{prop = EF(}I_0, goal\texttt{)}$$

Network traduction :

- Transition graph: $3min6s$
- Process Hitting : $0.346s$

Property verification :

- Rocca et al. method : $7min17s$
- our itirative method : $1.9s$

Conclusion & Prospects

- New dynamic analysis of Process Hitting models:
  - Fixed point
  - Network evolution
  - Reachability

- Prospects:
  - Adaptation on other models (PN, model of Thomas...)
  - Eliminating cycles
  - Search attractors
  - Reverse reachability ($goal \rightarrow I_0$?)

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Thanks for your attention