Kyoto University

Exhaustive analysis of dynamics of Process Hitting through Answer Set Programming

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joint work with: Maxime FOLSCHETTE & 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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3) What for?

   Searching of PH **properties** through ASP (fixed points, reachability).

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5) Conclusion & prospect

Answer Set Programming

ASP:

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

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

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

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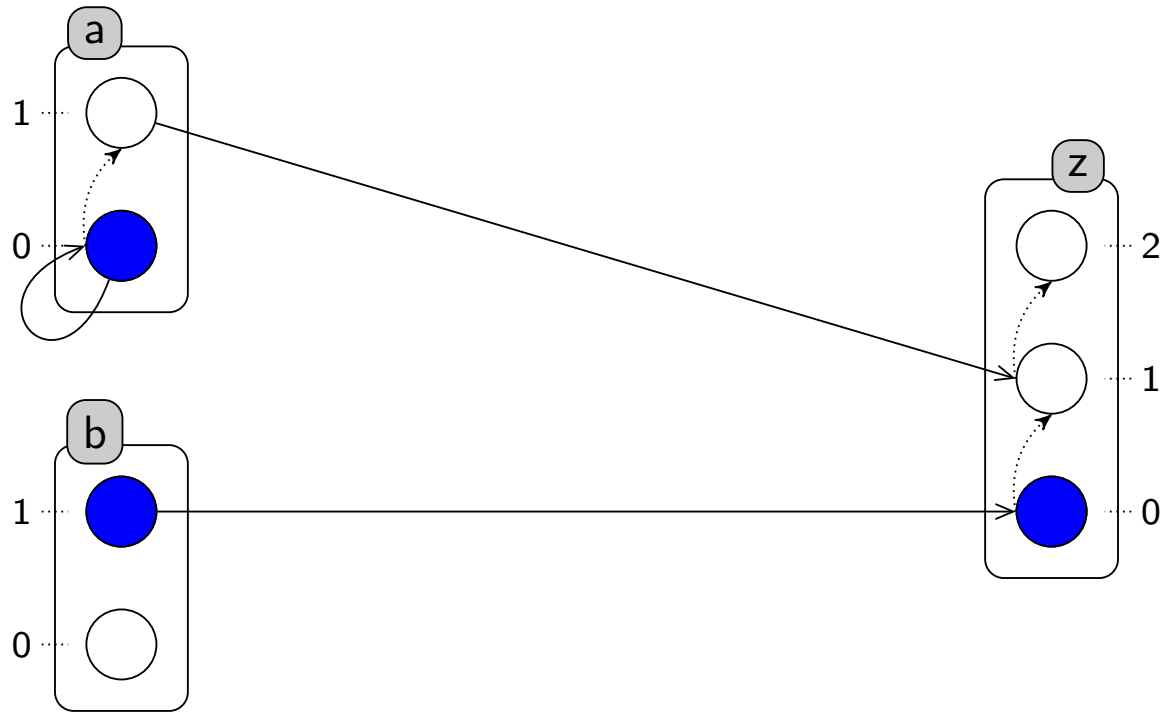

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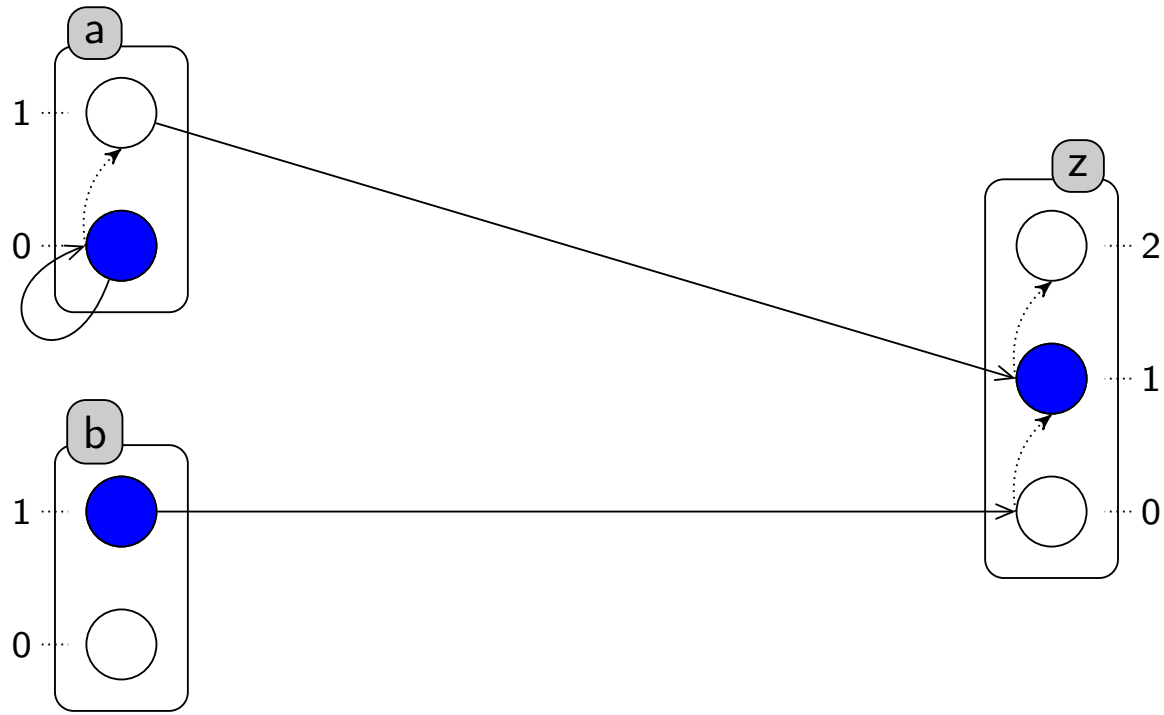

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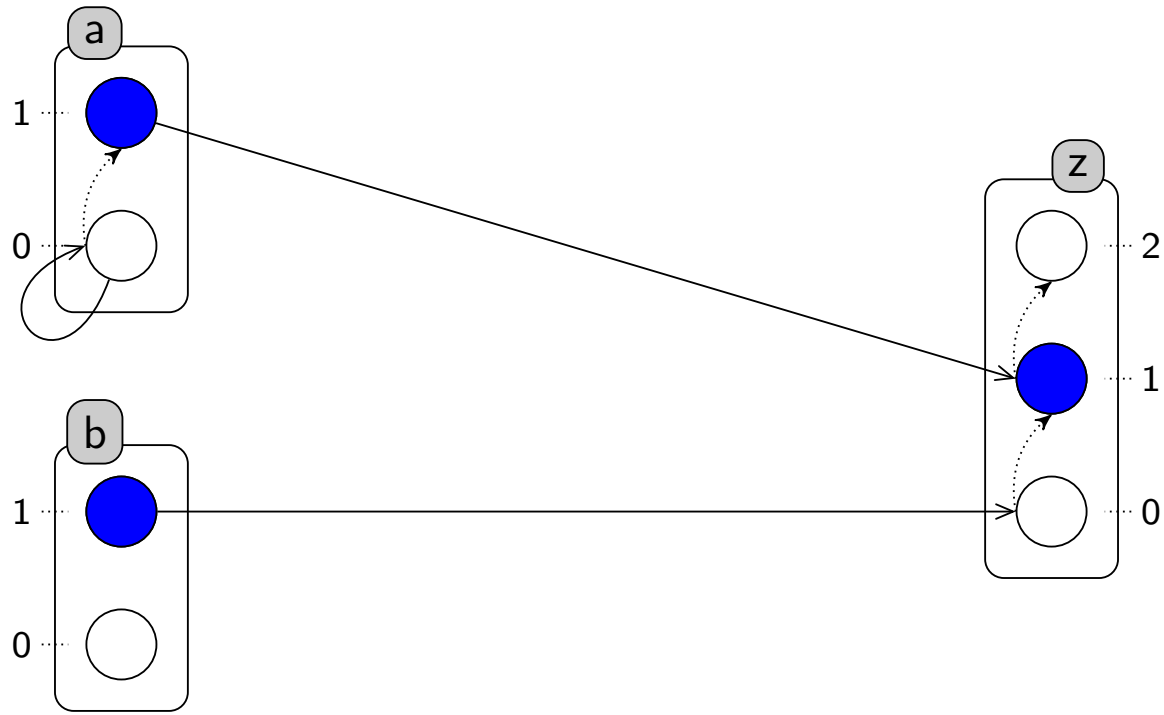

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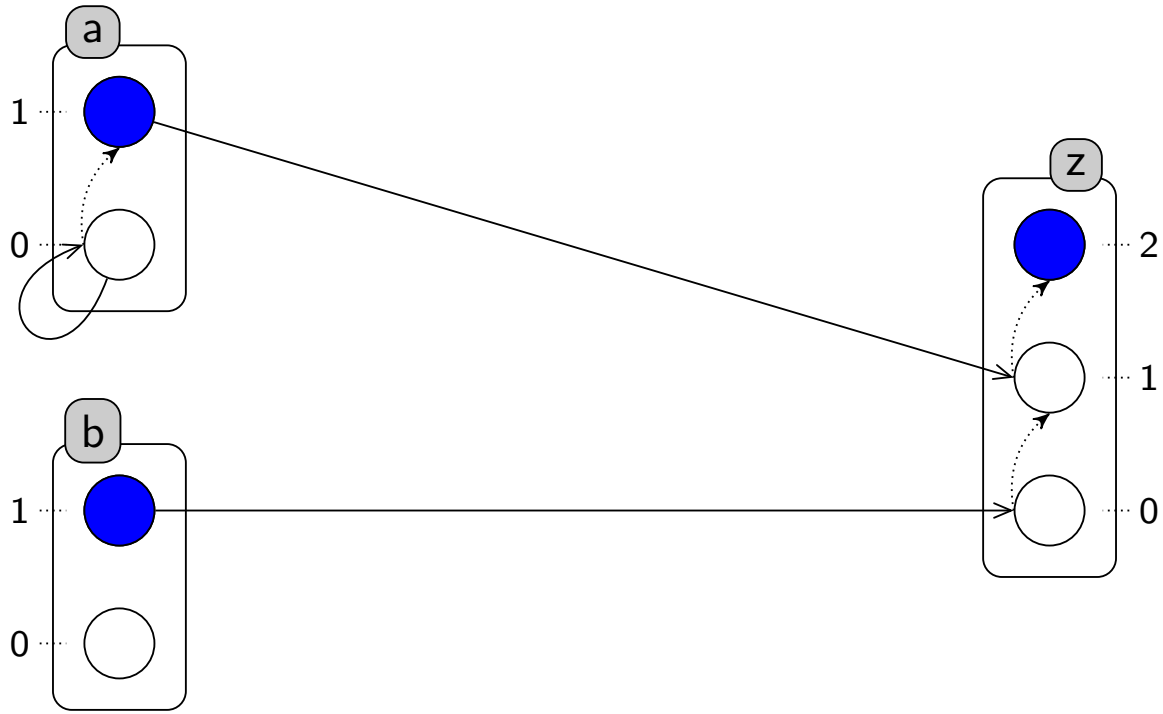

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PH through ASP

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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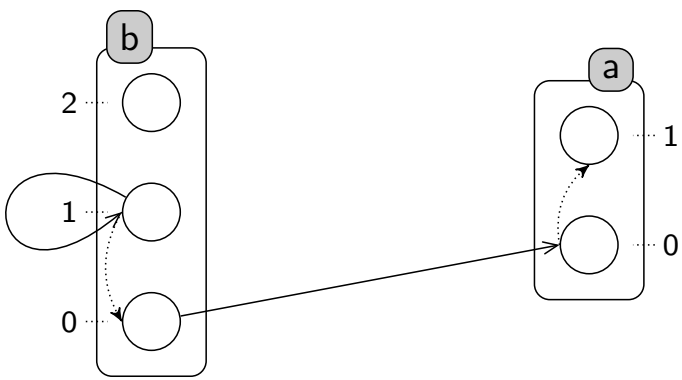

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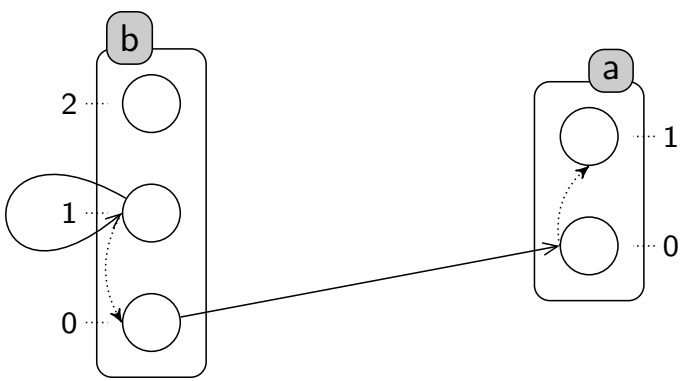


```
process("a", 0..1).
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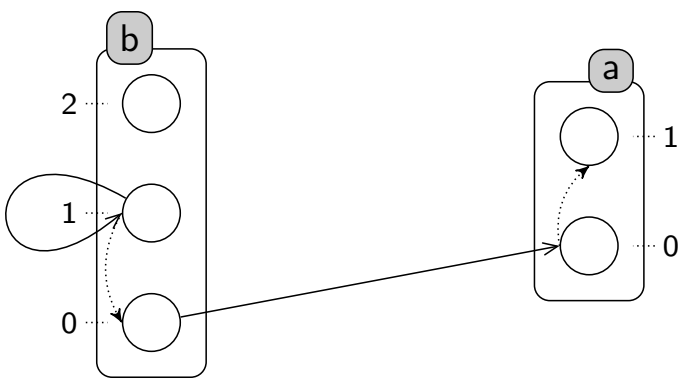


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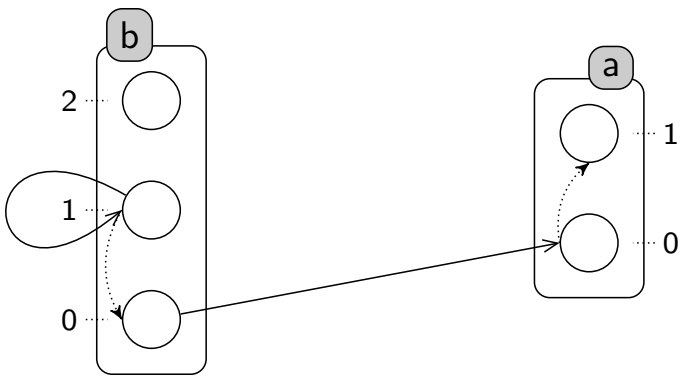


```
process("a", 0..1).
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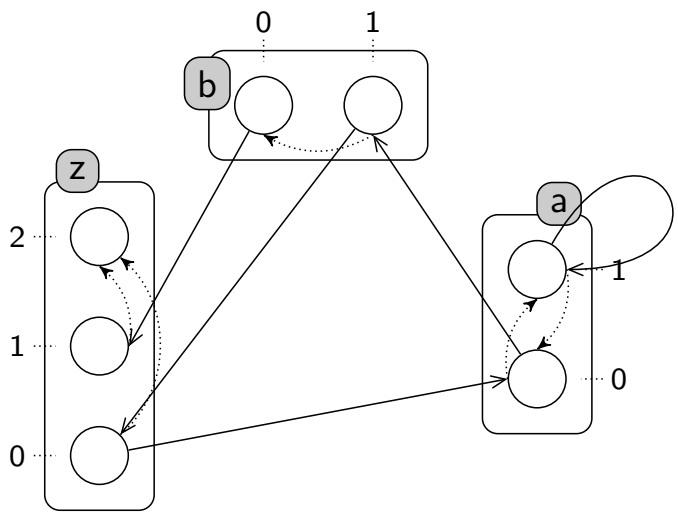
sort(X) :- process(X,I).
action("b",0,"a",0,1).
action("b",1,"b",1,0).
```

Fixed Points

Fixed point = state where no action can be played



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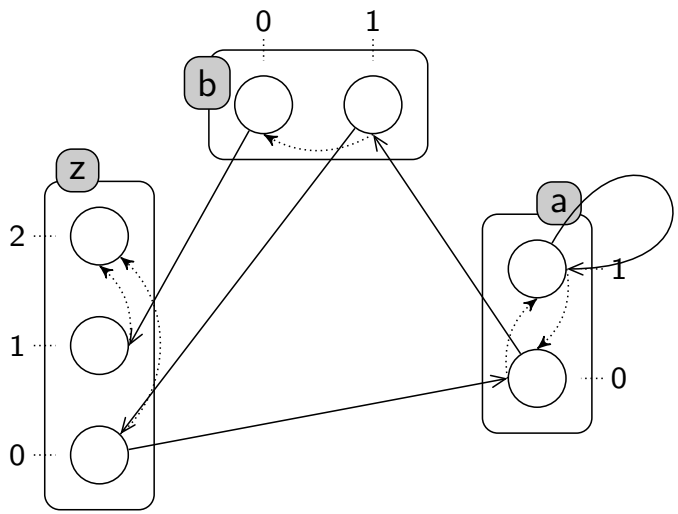
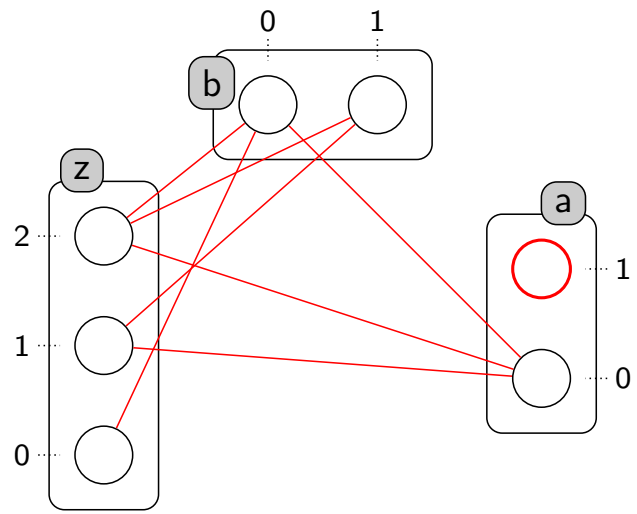
→ Hitless Graph





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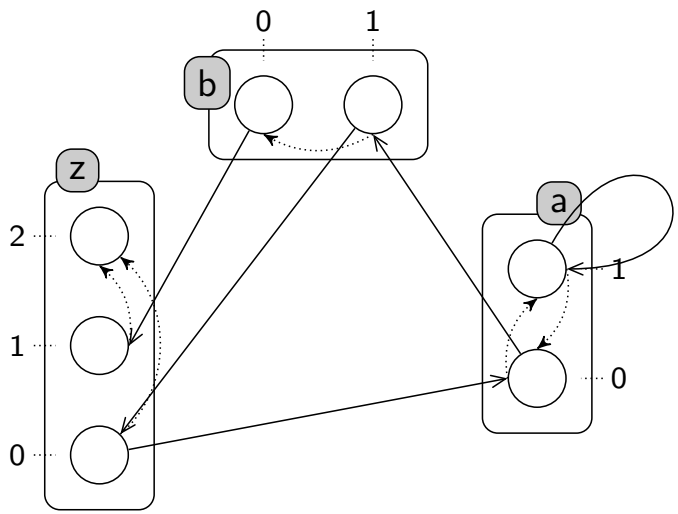
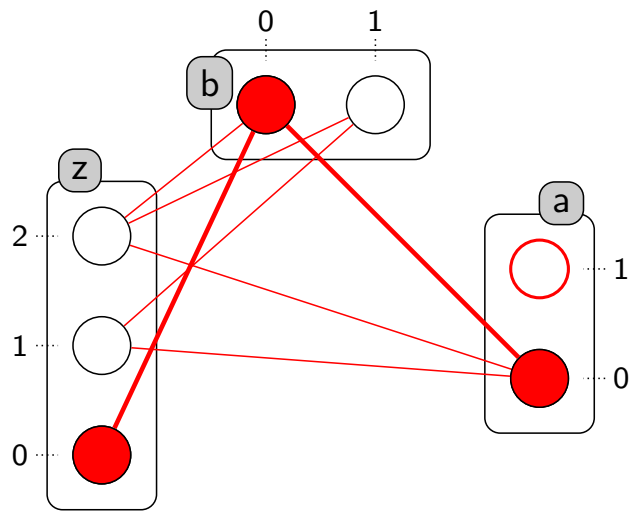
→ Hitless Graph → **n-cliques** = fixed points





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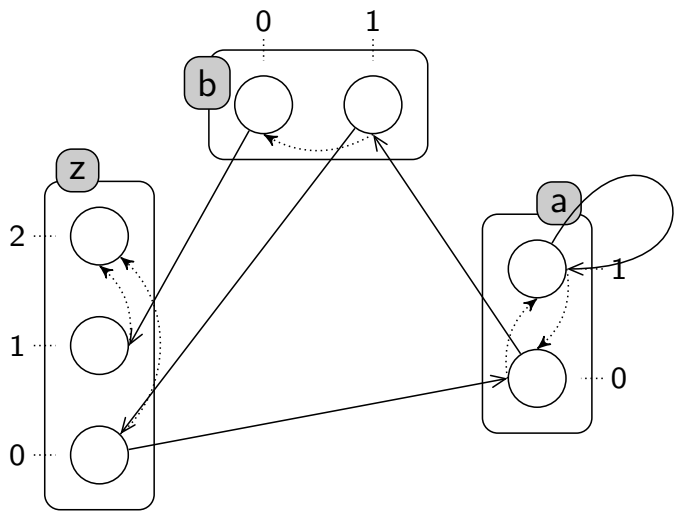
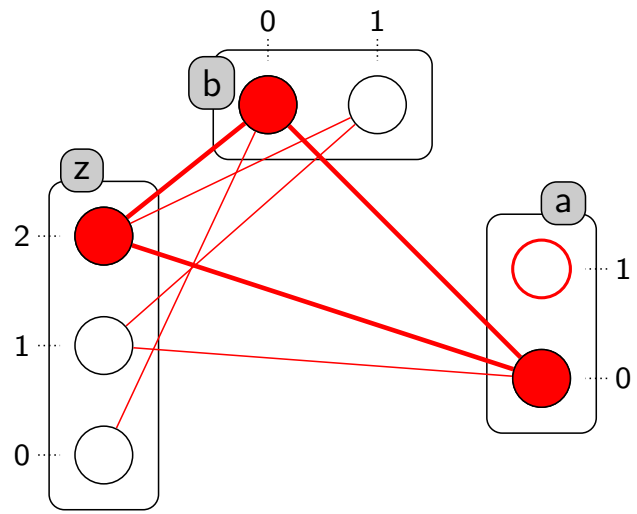


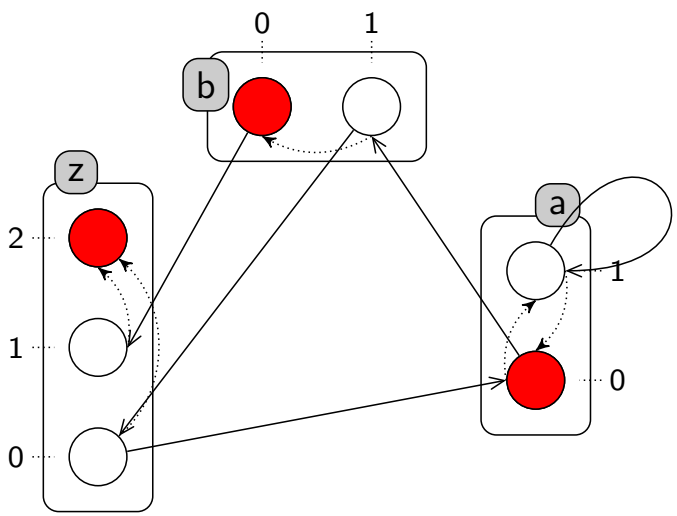


Static analysis

Fixed point through ASP

Implementation:

```
1 {selectProcess(A,I) : shownProcess(A,I) } 1 :- sort(A).
:- hit(A,I,B,J), selectProcess(A,I), selectProcess(B,J), A!=B.
```

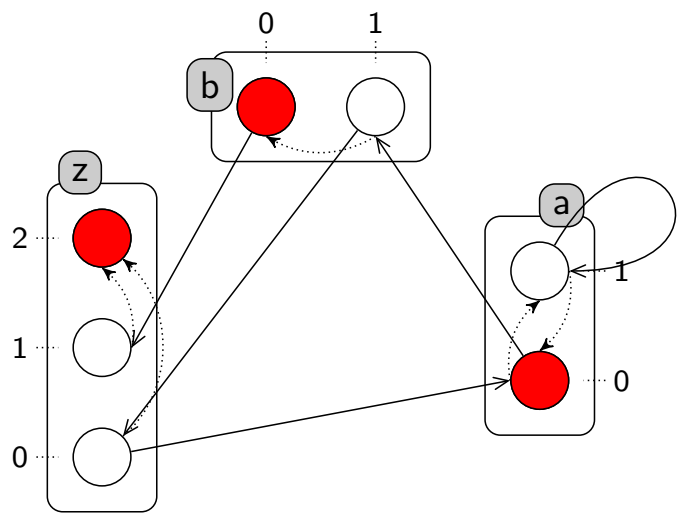


Static analysis

Fixed point through ASP

ASP program result:

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



Static analysis

Fixed Point

Comparison

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

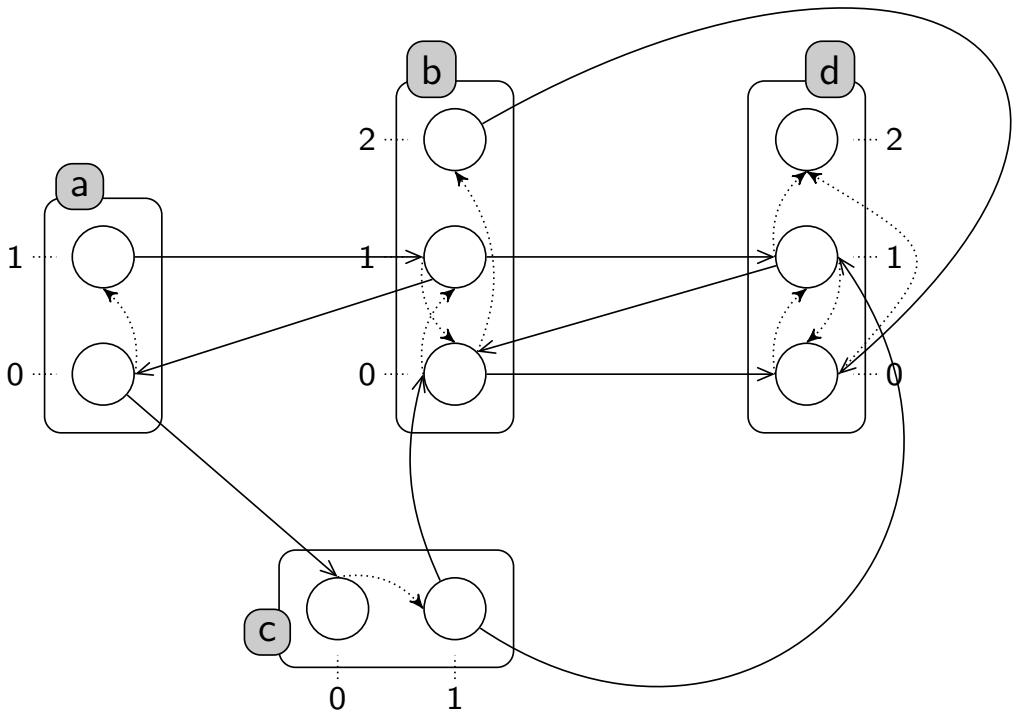
Figure: Excecution time of ASP metod and PINT applied for biological networks with a desktop computer (core i5 and 4GB RAM).

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

Dynamic analysis

Reachability

Reachability of processes for PH networks:



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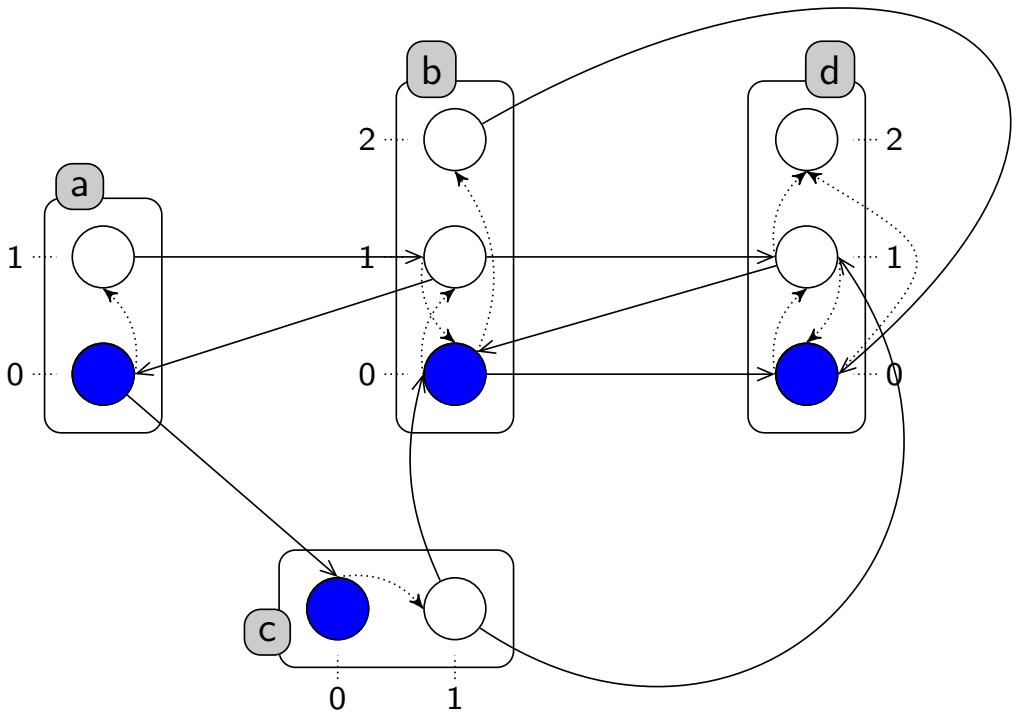

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$\langle a_0, b_0, c_0, z_0 \rangle$

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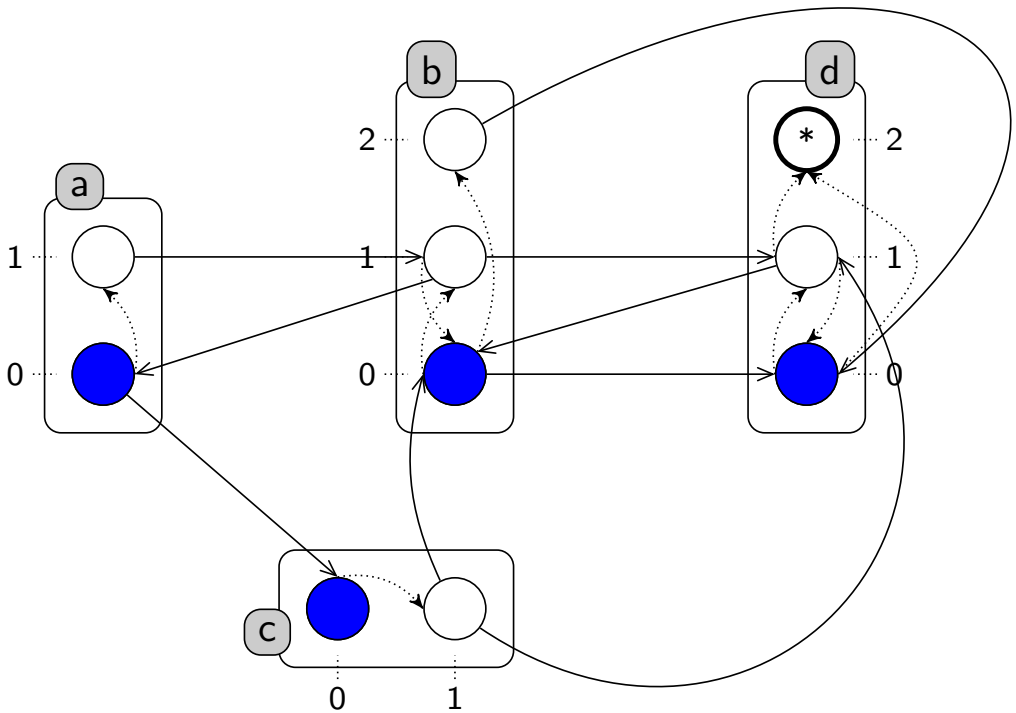

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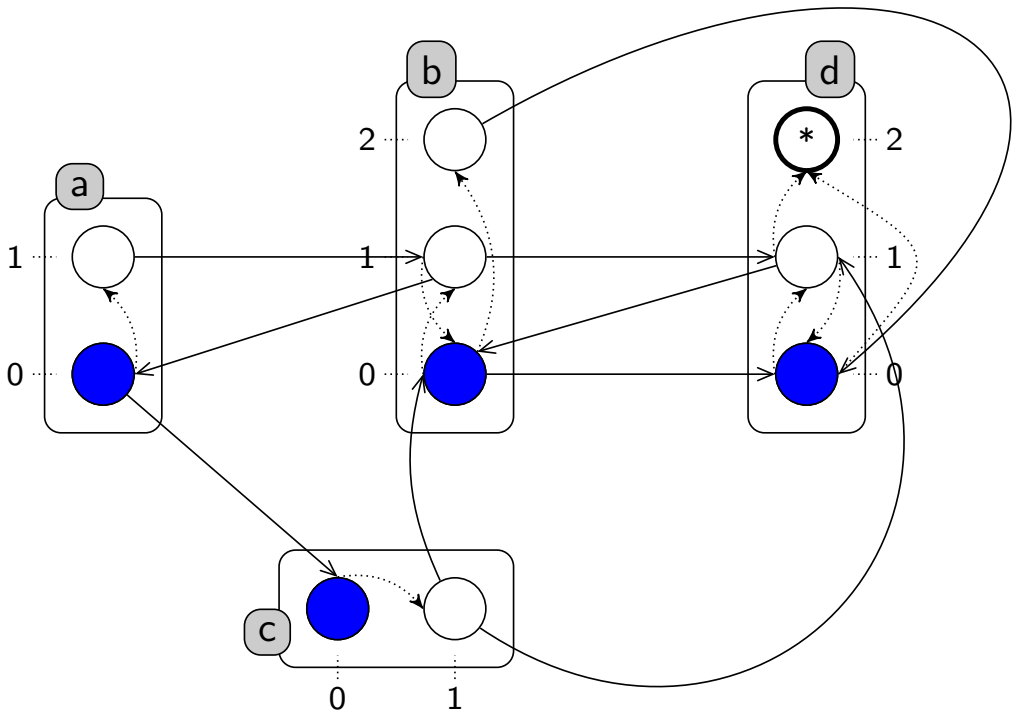

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$\rightarrow$ Concretization of the objective = scenario

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

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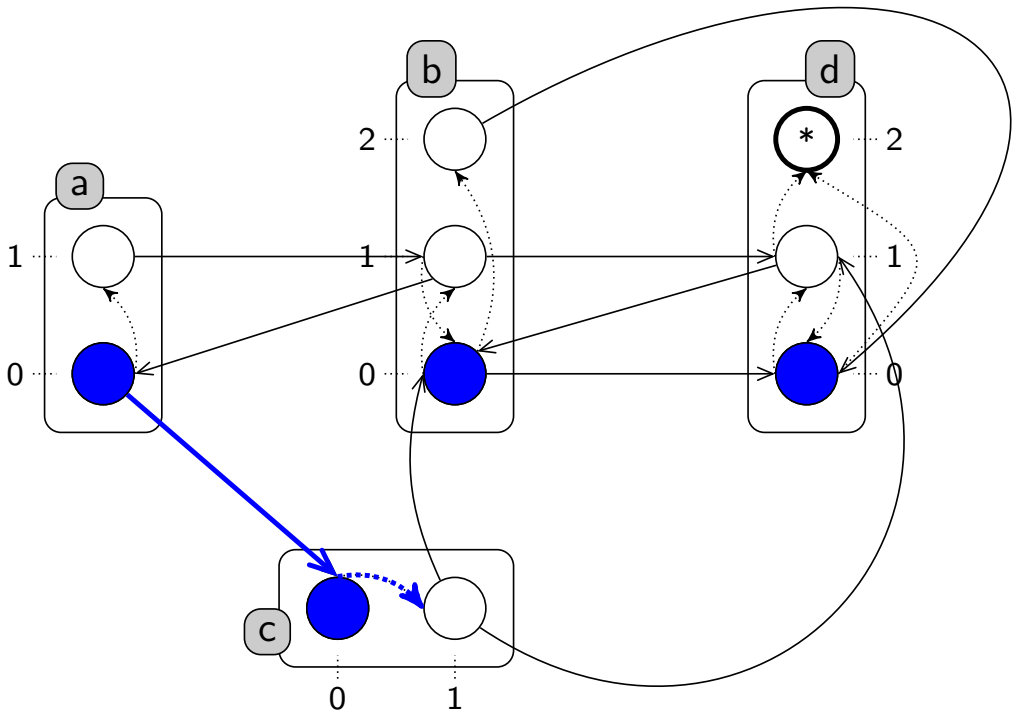

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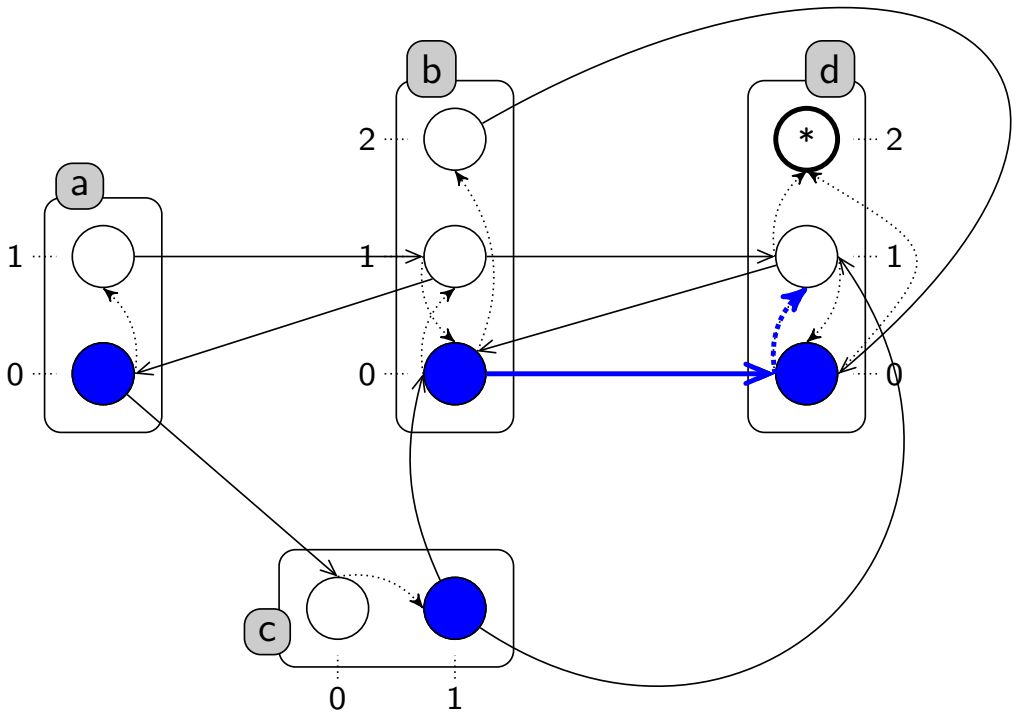

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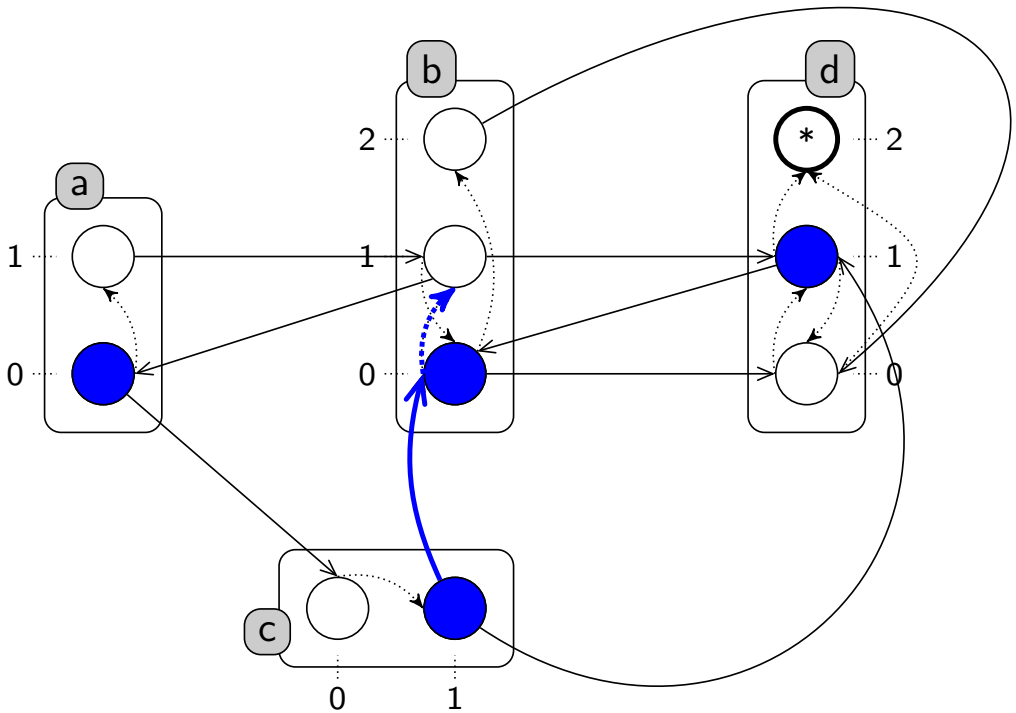

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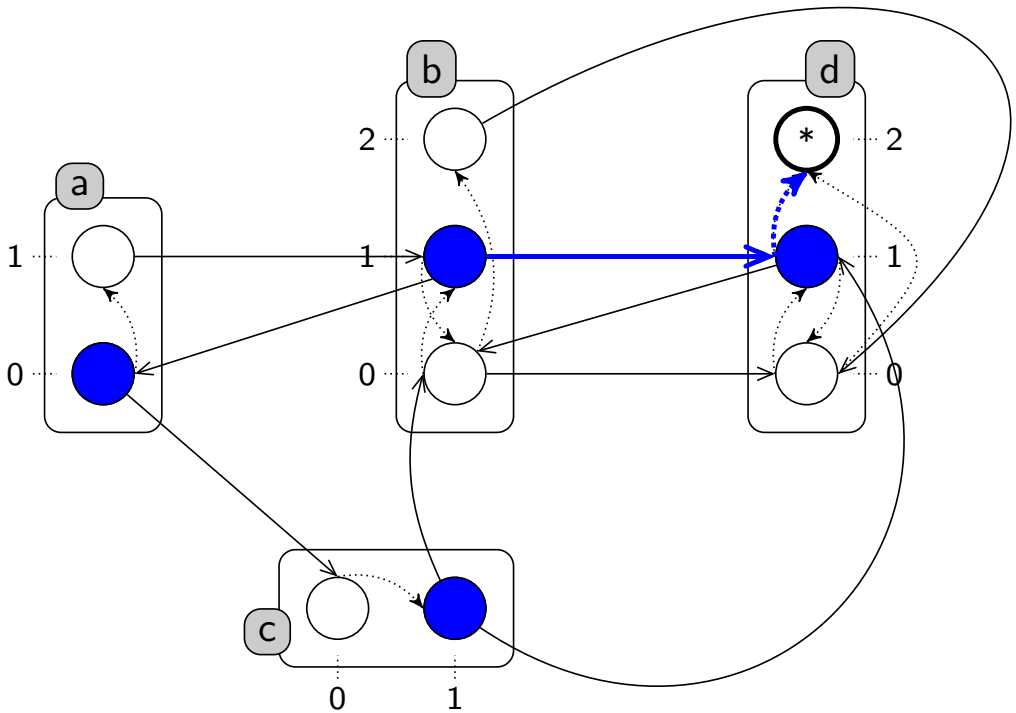

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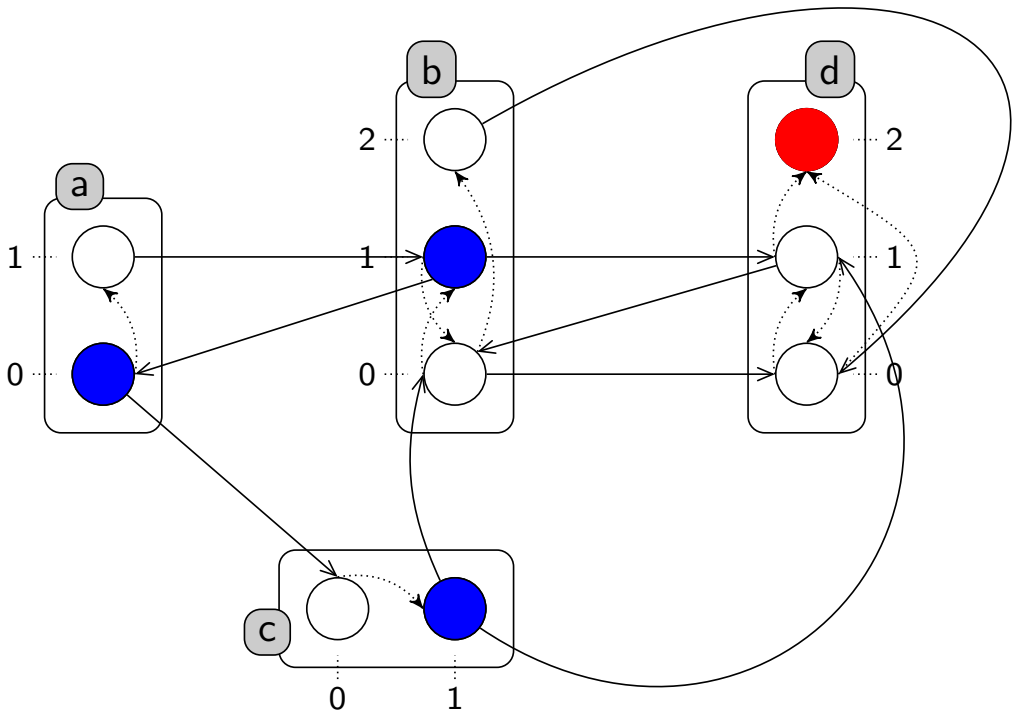

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$$[\ \Rsh\ d_2\ ]$$

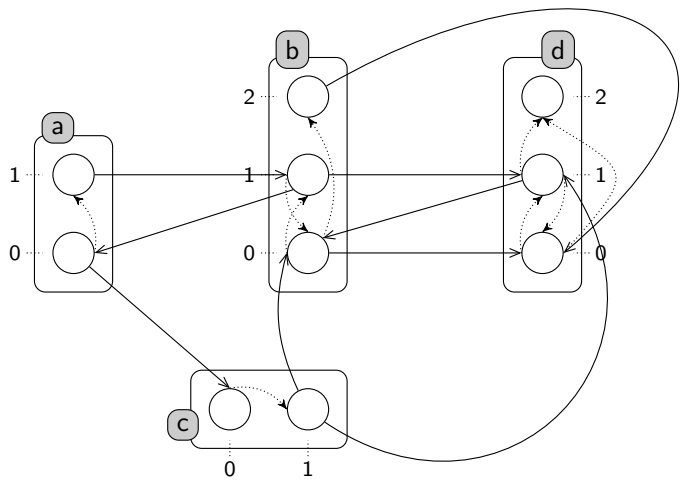
$\rightarrow$ Concretization of the objective = scenario

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

Dynamic analysis

Evolution through ASP

Network evolution through ASP



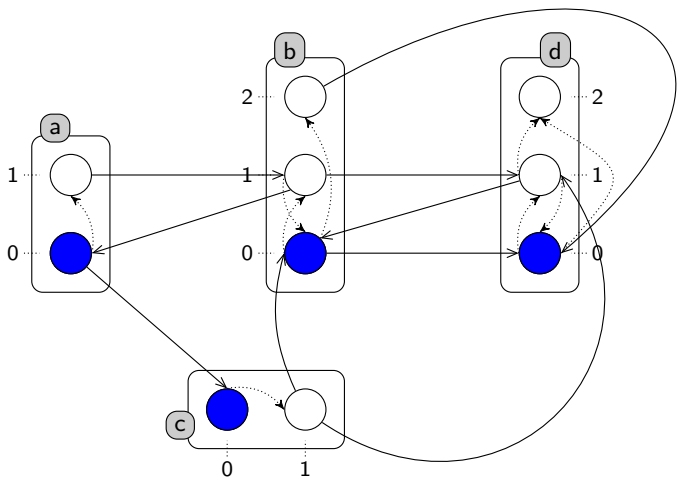
Dynamic analysis

Evolution through ASP

Network evolution through ASP

Initializing :

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



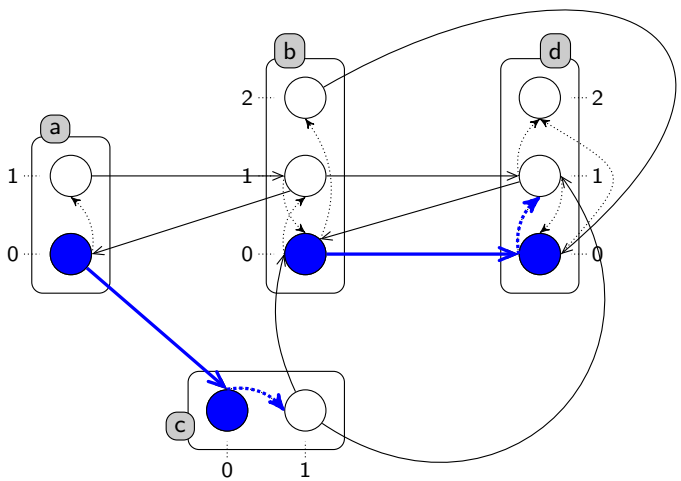
Dynamic analysis

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).
```



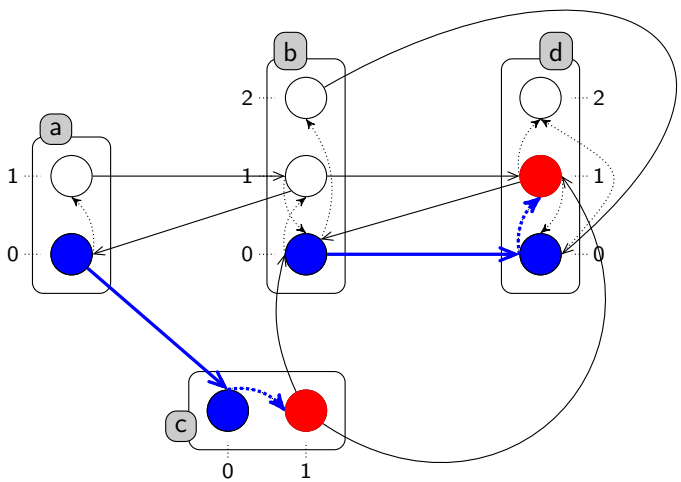
Dynamic analysis

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).
```



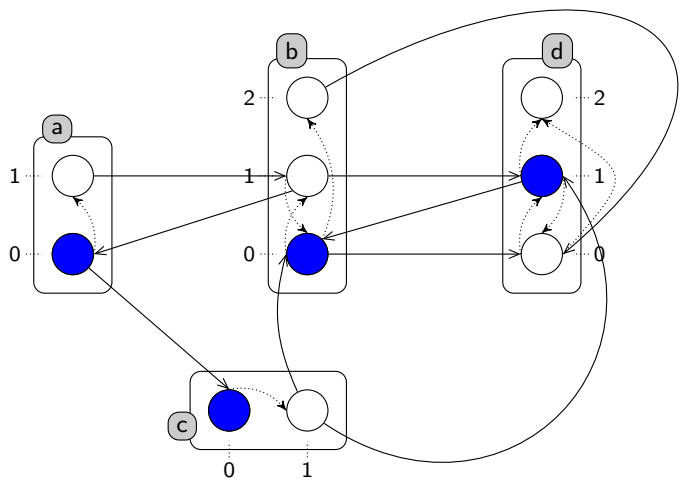
Dynamic analysis

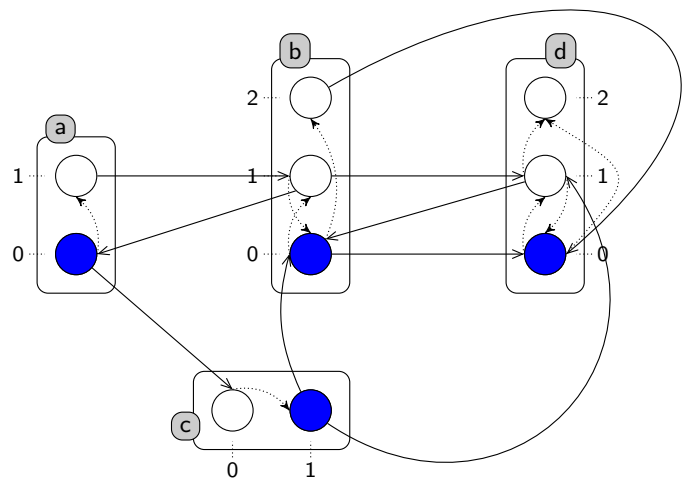
Evolution through ASP

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)`

...

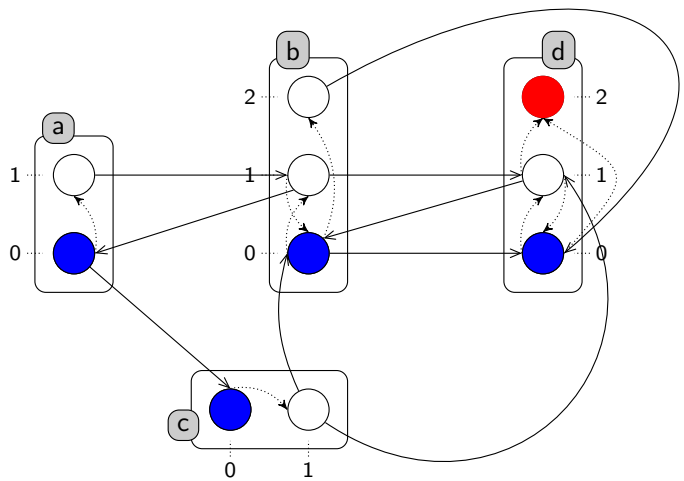
Answer 29: `activeFromTo("c",0,1,0) activeFromTo("b",0,1,1) activeFromTo("a",0,1,2)`

Dynamic analysis

Reachability through ASP

Success reachability through ASP:

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

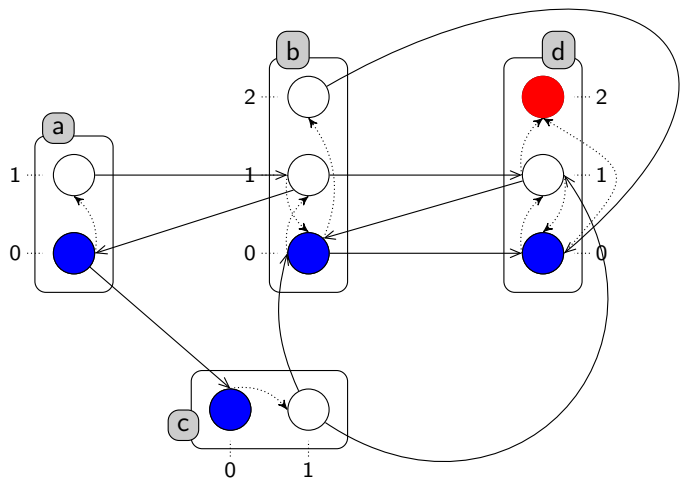


Dynamic analysis

Reachability through ASP

Success reachability through ASP:

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

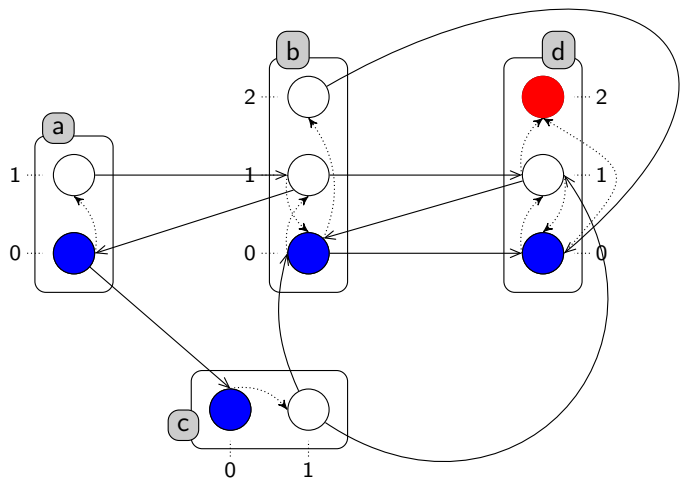


Dynamic analysis

Reachability through ASP

Success reachability through ASP:

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



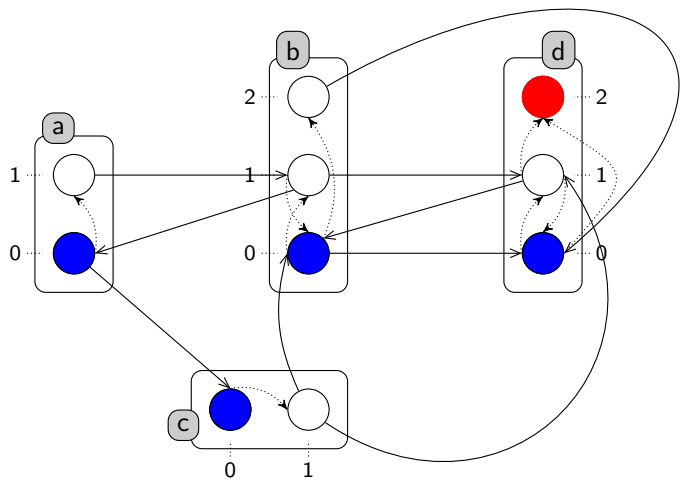
Dynamic analysis

Reachability through ASP

Success reachability through ASP:

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

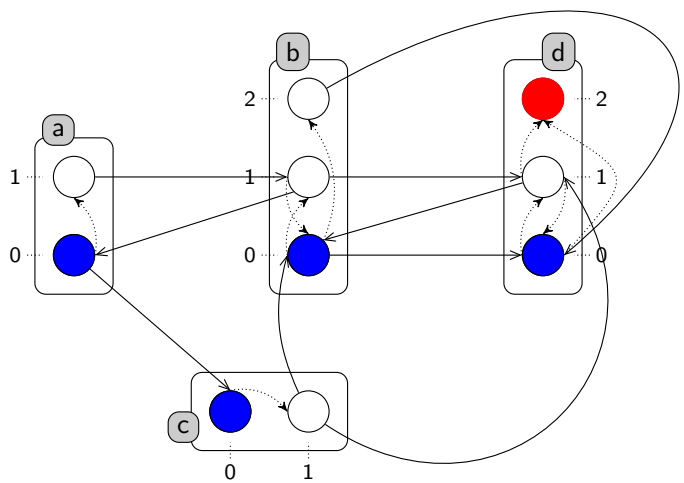
Answer 2: `activeFromTo("d",0,1,0) activeFromTo("c",0,1,1) activeFromTo("b",0,1,2) activeFromTo("d",1,2,3)`

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

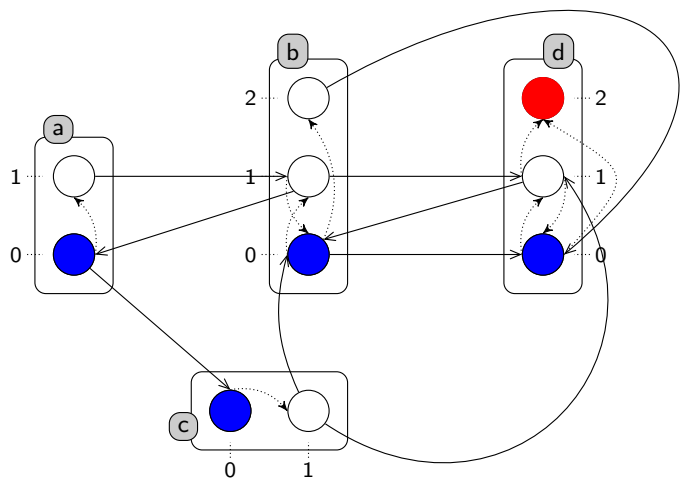
Reachability through ASP

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-target	#sorts	ASP-TH	PINT	LIBDDD	GINSIM	ASPI-PH
ERBB-whole	20	0m2.44s	out	1m55.38s	2m31.64s	0m11.84s
ERBB-sub	20	0m2.61s	0m0.03s	1m54.96s	-	0m5.02s
TCR-whole	40	-	Inconc	out	out	4m27.93s
TCR-sub	40	-	0m0.02s	out	-	1m35.08s

Figure: Compared performances of Rocca et al. method denoted by ASP-TH, PINT, LIBDDD, GINSIM and our new itirative method ASP-PH.

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