Workshop for Computational Techniques for Sustainability and Resilience, Ishigaki, Okinawa

Overview of the benefits of logic programming to check dynamics properties in the Process Hitting framework

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Context and Aims

MeForBio team:
Algebric modelling to study
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   Predicting the **evolutions** of the network.

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3) What for?

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

Plan

1) Answer set programming (ASP)
   - 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 :

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

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:
A clique in a graph is a set of pairwise adjacent vertices.

$vertex(1..99)$. % 1,...,99 are vertices
$edge(3, 7)$. % 3 is adjacent to 7
...

$edge(X, Y) : -edge(Y, X), vertex(X; Y)$.

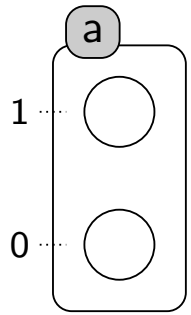
% GENERATE
$5\{in(X) : vertex(X)\}$.

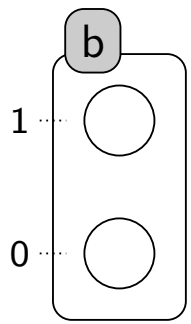
% TEST
$: -in(X), in(Y), vertex(X), vertex(Y), X! = Y,\ not\ edge(X, Y)$.

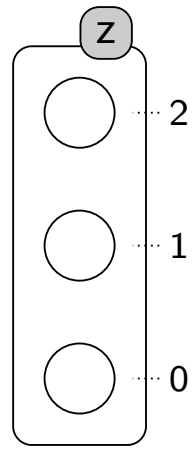
The Process Hitting modeling

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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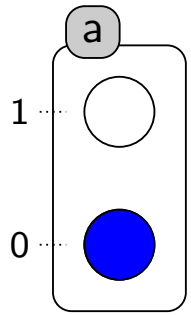

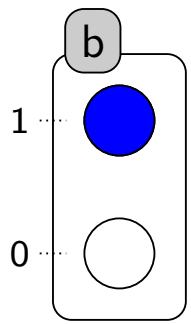

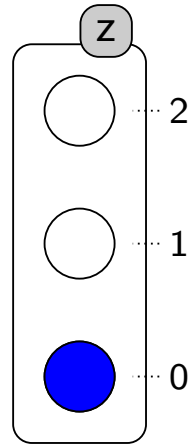

Sorts: components $a,\ b,\ z$

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

States: sets of active processes $\langle a_0, b_1, z_0 \rangle$

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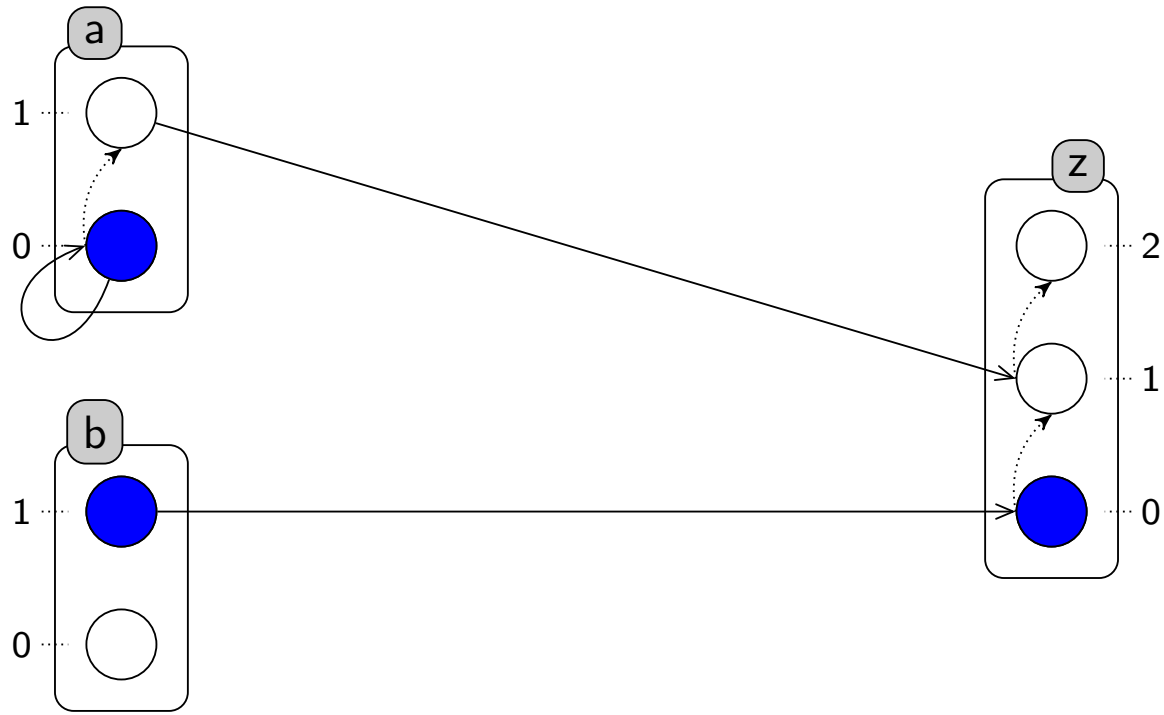

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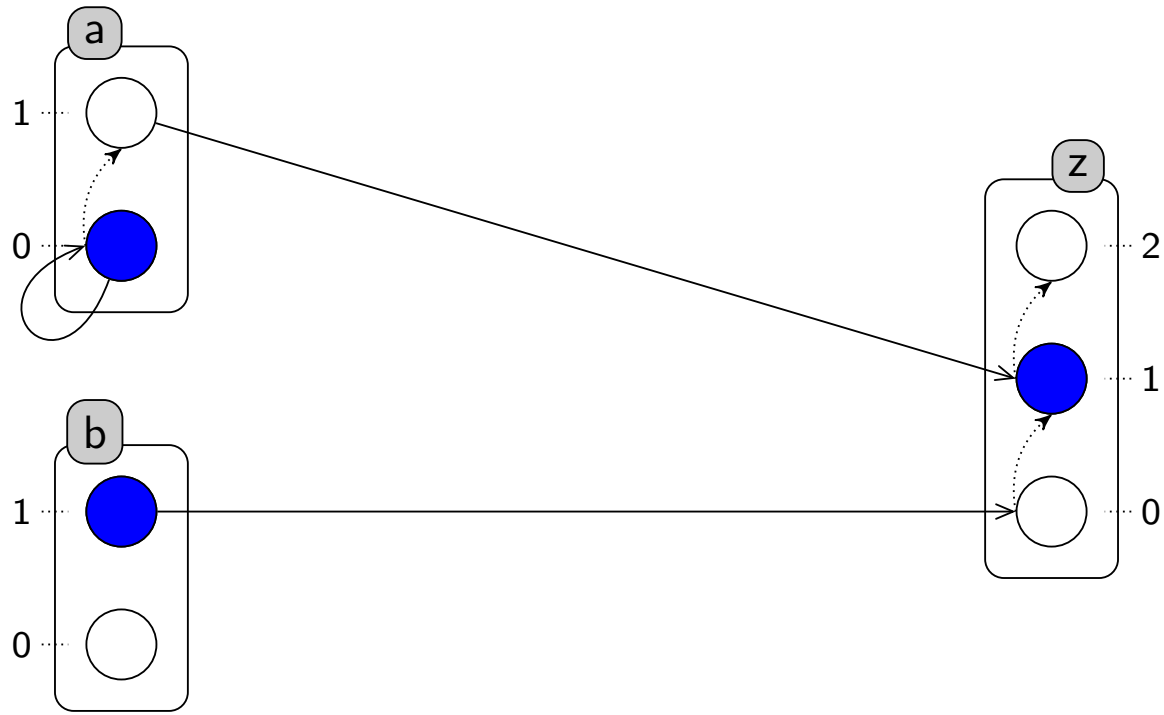

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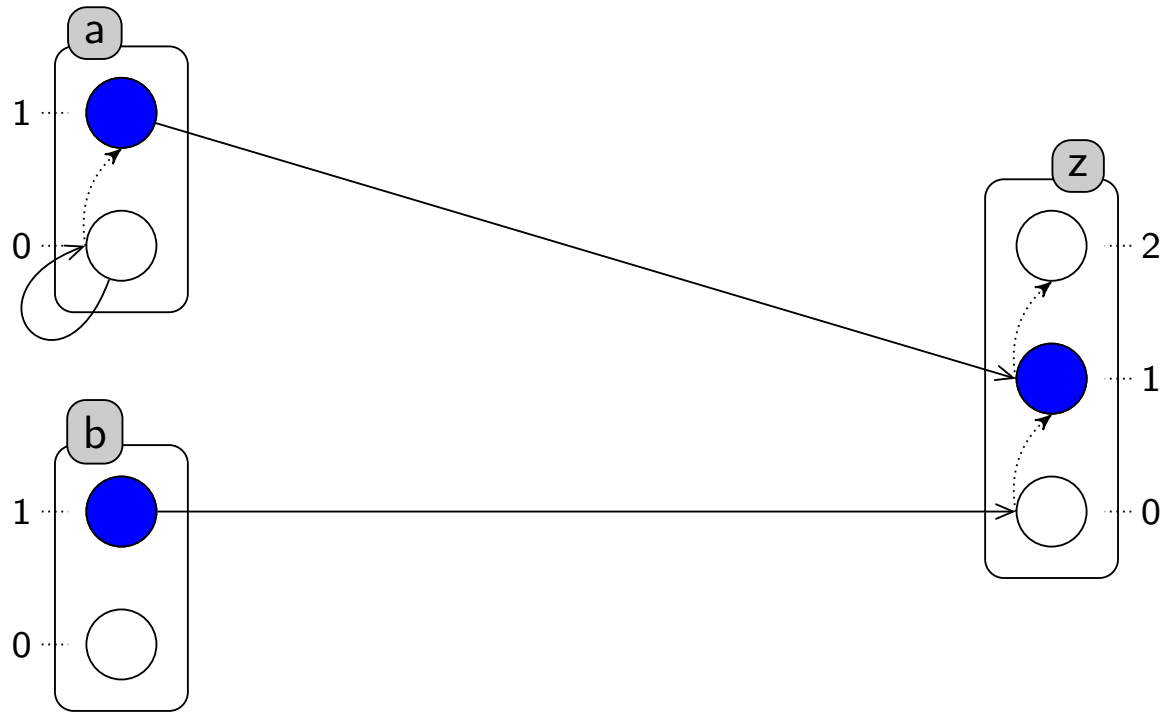

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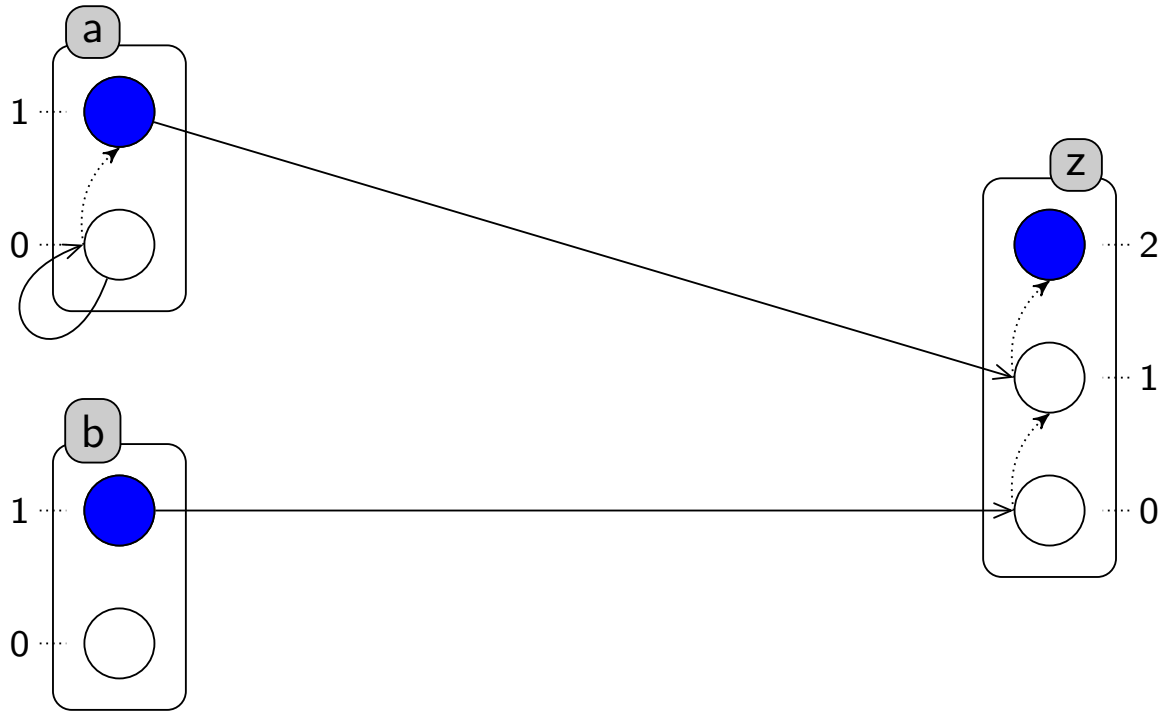

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PH through ASP

Network translation:

- **Sort**: `sort(A)` .
- **Process**: `process(A,I).`
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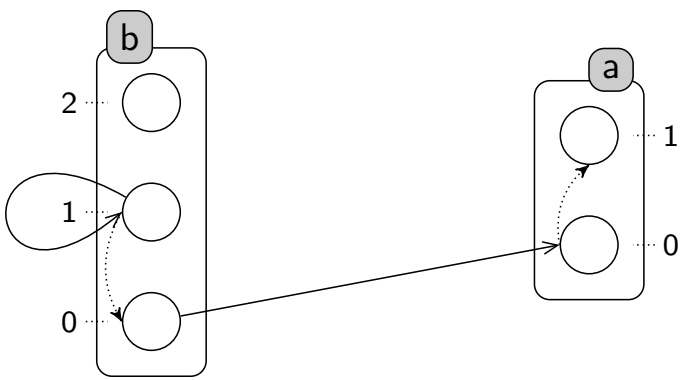

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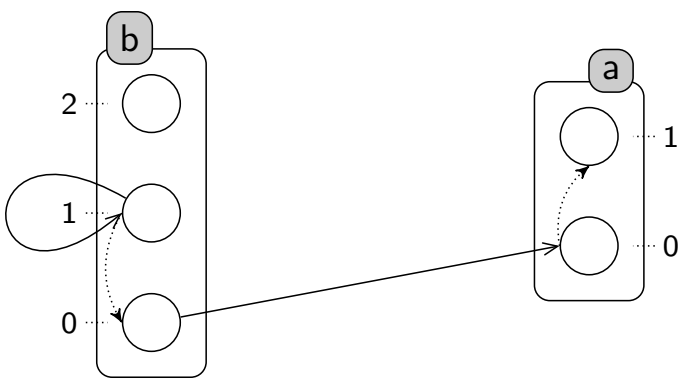


```
process("a", 0..1).
process("b", 0..2).
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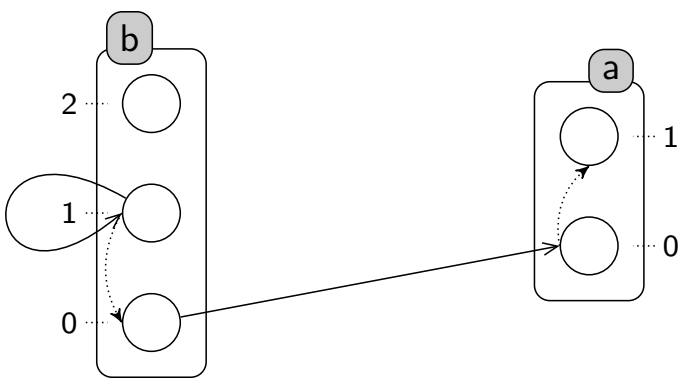


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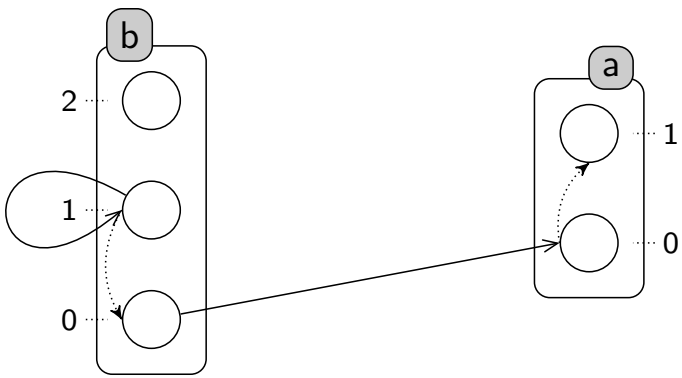


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process("a", 0..1).
process("b", 0..2).
sort(X) :- process(X,I).
action("b",0,"a",0,1).
action("b",1,"b",1,0).
```
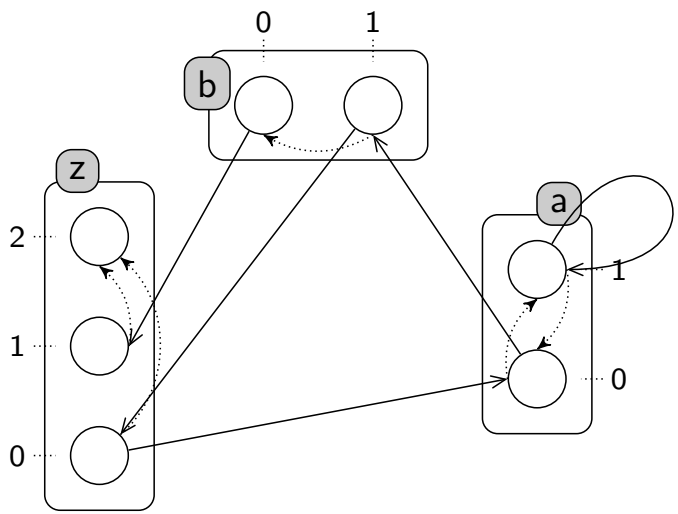

Fixed Points

Fixed point = state where no action can be played



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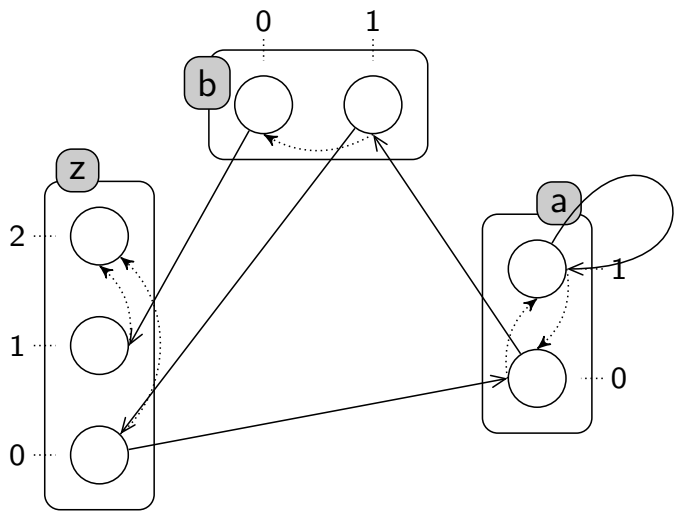
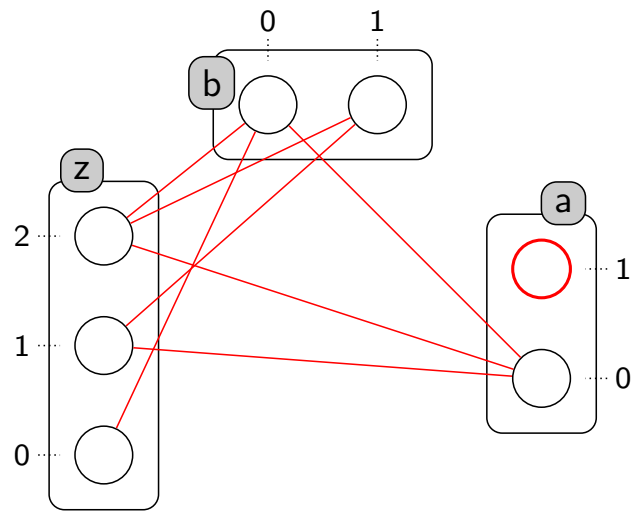
→ Hitless Graph





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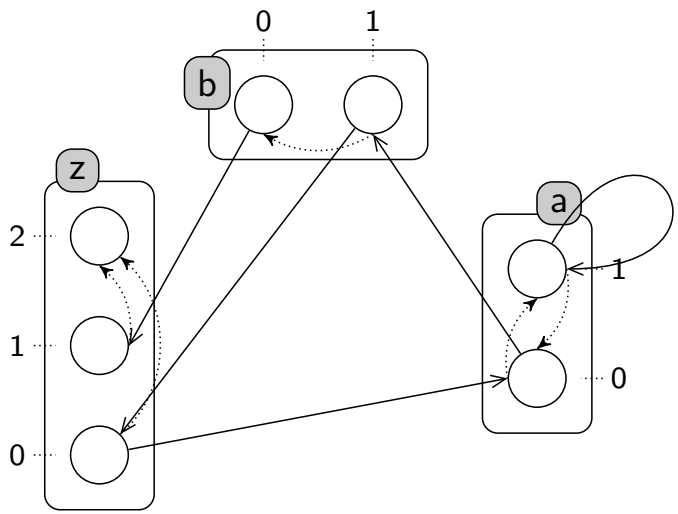
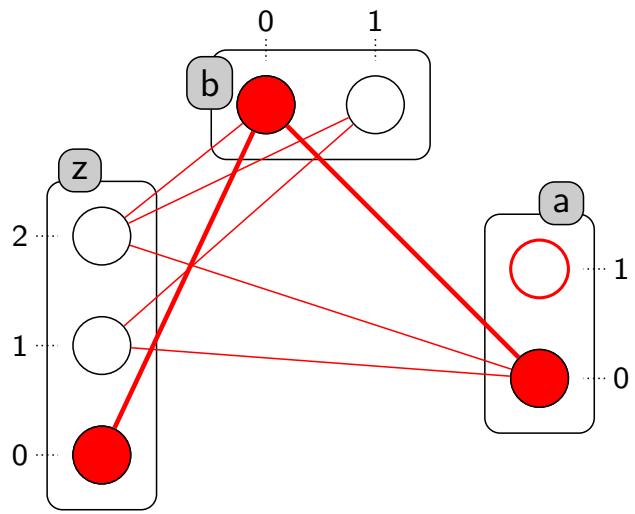
→ Hitless Graph → **n-cliques** = fixed points





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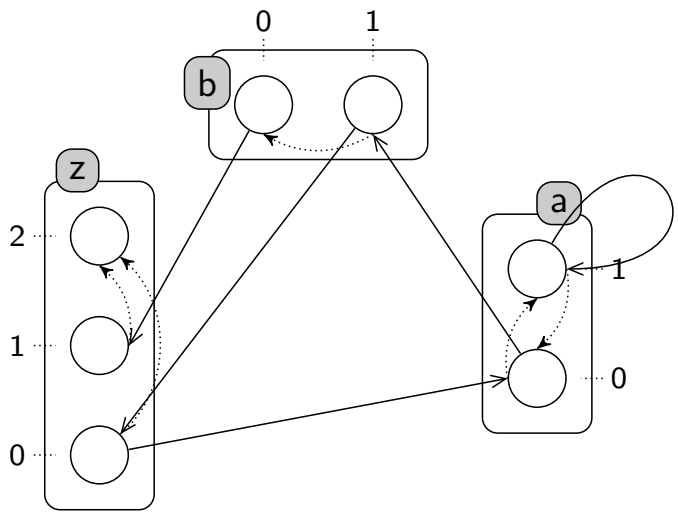
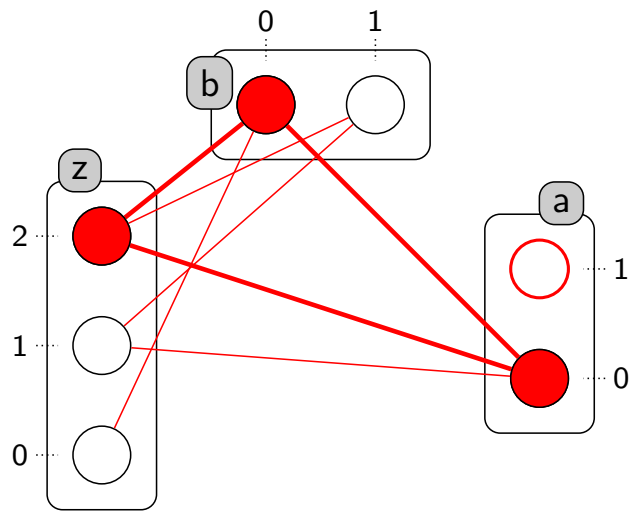


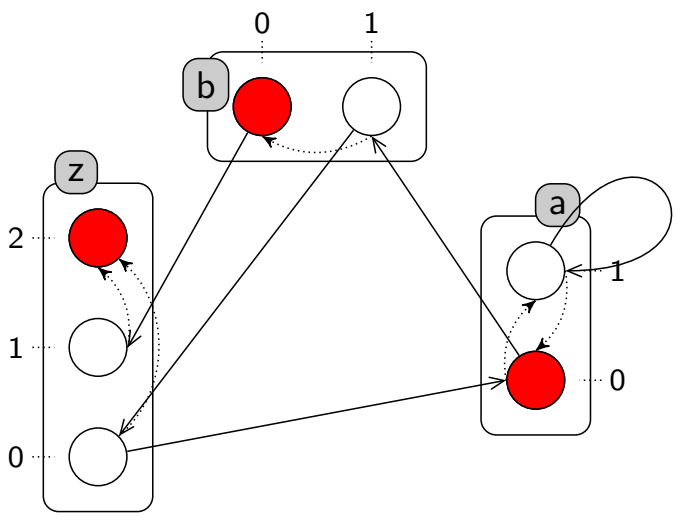


Static analysis

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.
```

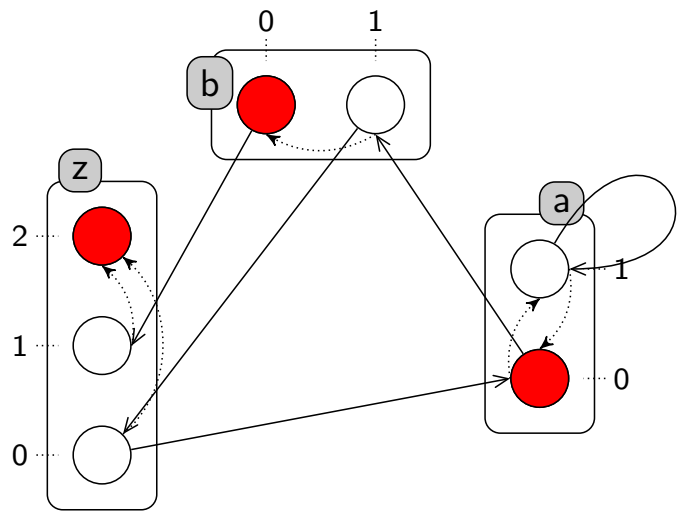


Static analysis

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

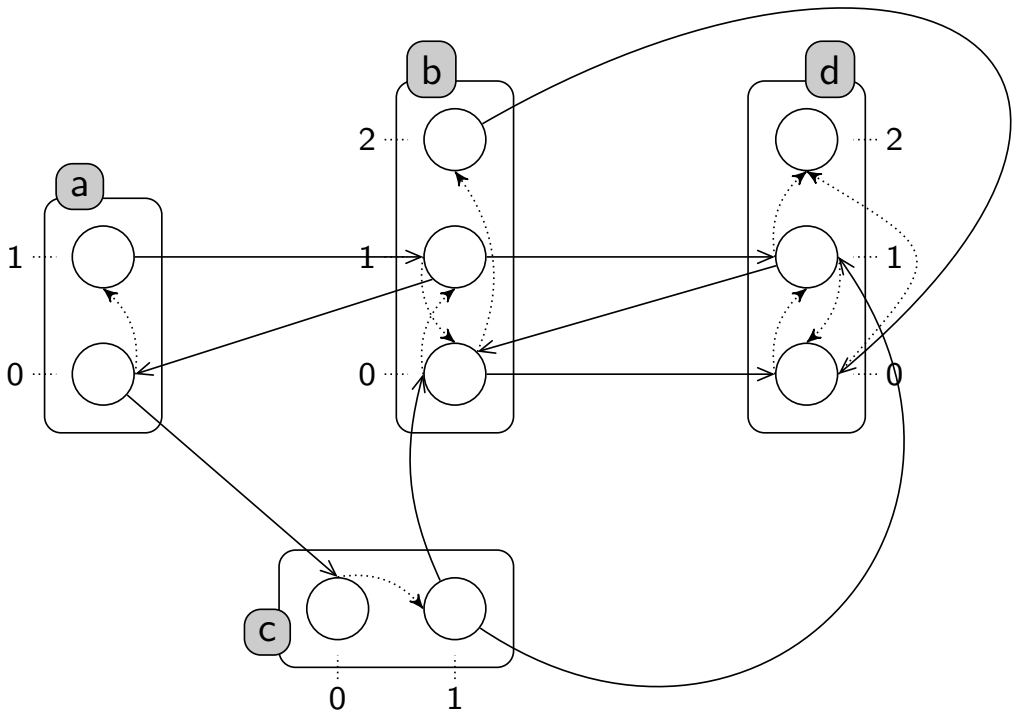
Figure: Execution time of ASP metod and PINT applied for biological networks with a desktop computer (core i5 and 4GB RAM).

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

Dynamic analysis

Reachability

Reachability of processes for PH networks:



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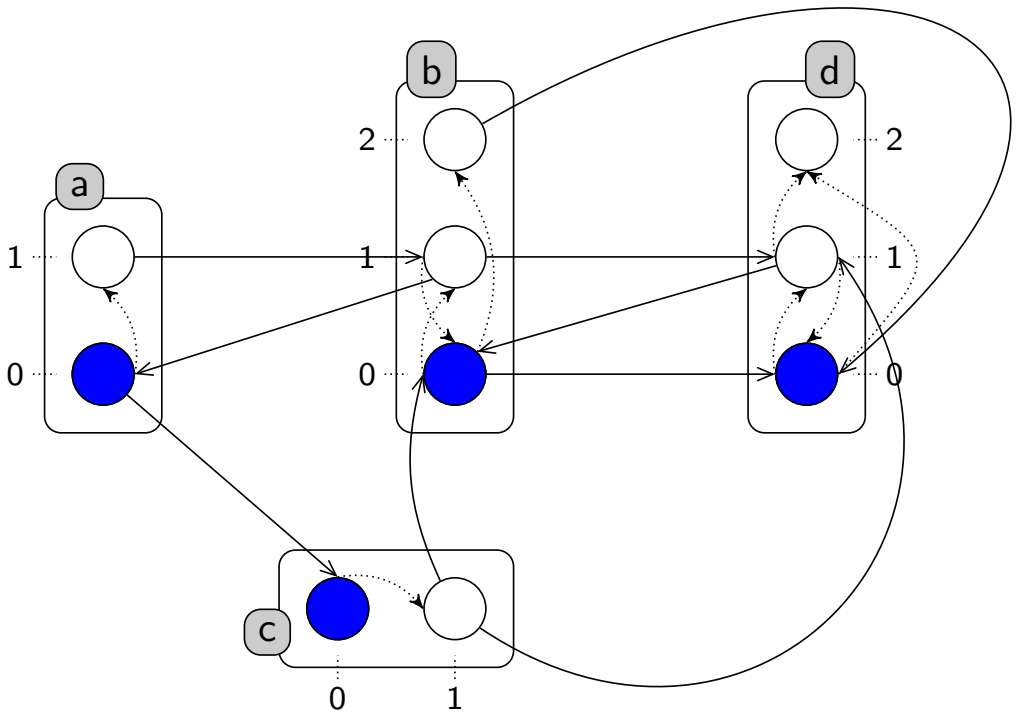

- Initial context

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

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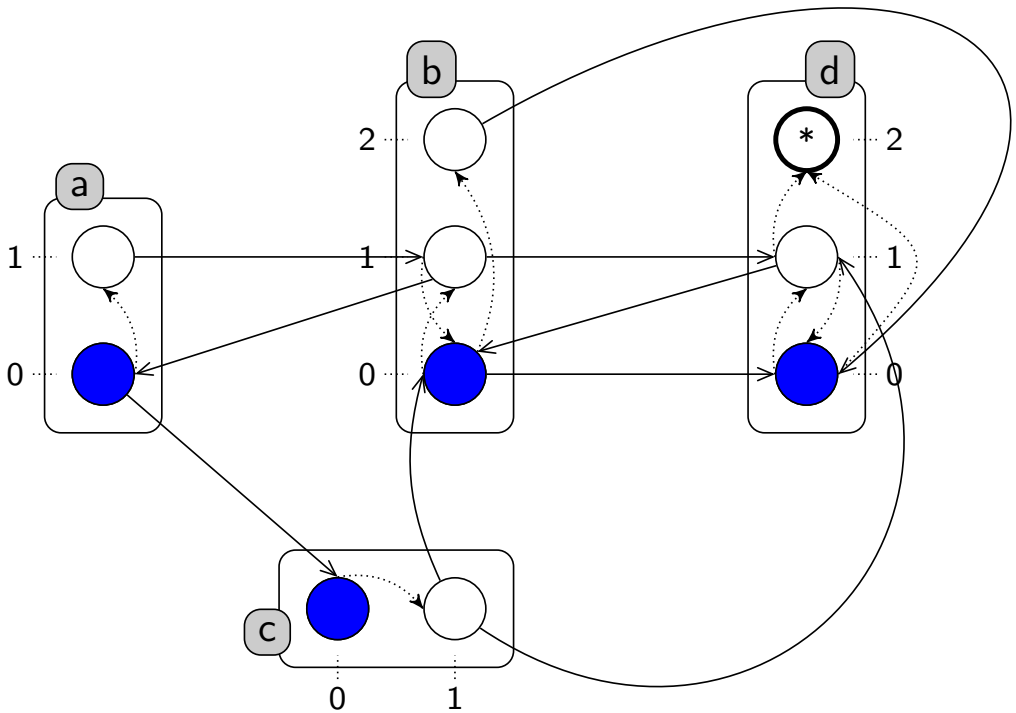

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$$[\ \Rsh\ d_2\ ]$$

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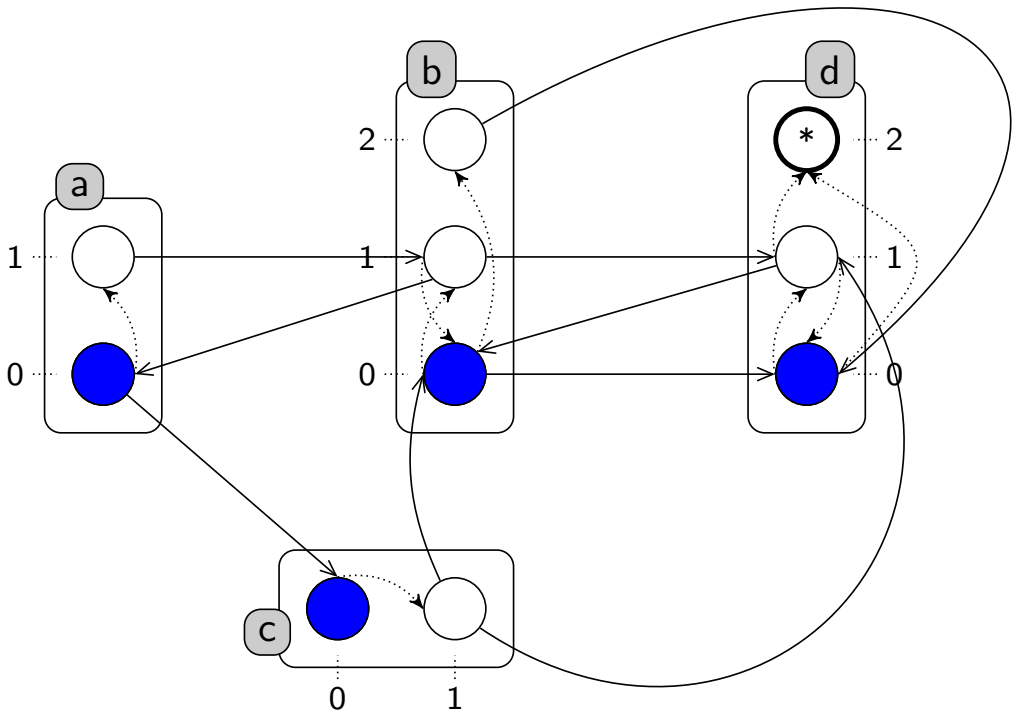

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$\rightarrow$ Concretization of the objective = scenario

$$a_0 \rightarrow c_0 \lceil^{\uparrow}\ c_1 :: \quad b_0 \rightarrow d_0 \lceil^{\uparrow}\ d_1 :: \quad c_1 \rightarrow b_0 \lceil^{\uparrow}\ b_1 :: \quad b_1 \rightarrow d_1 \lceil^{\uparrow}\ d_2$$

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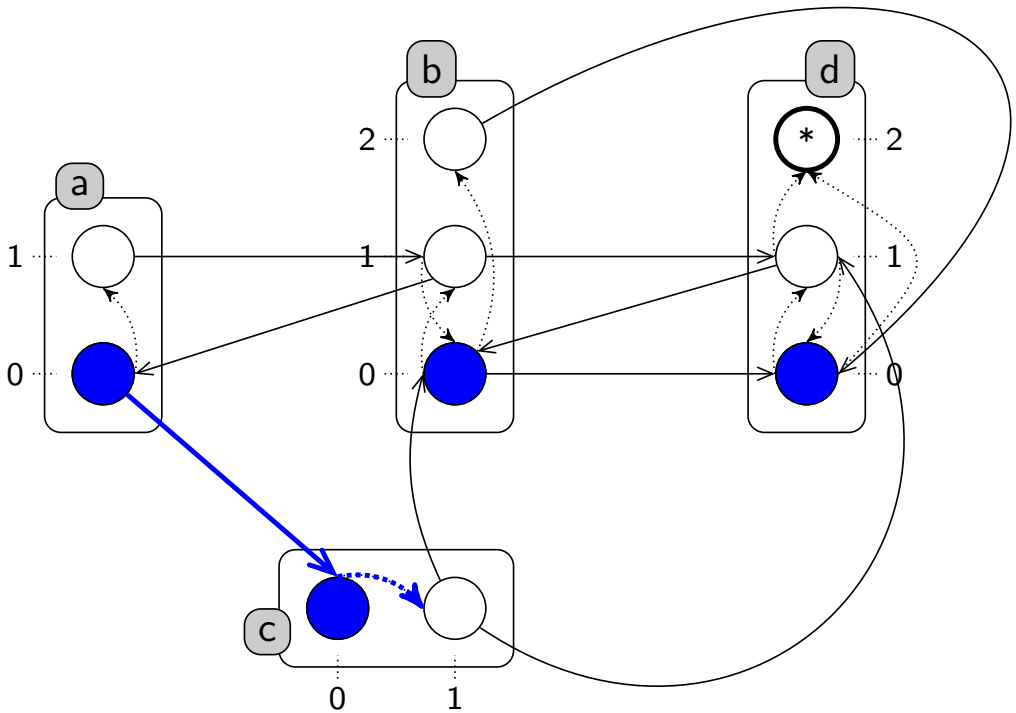

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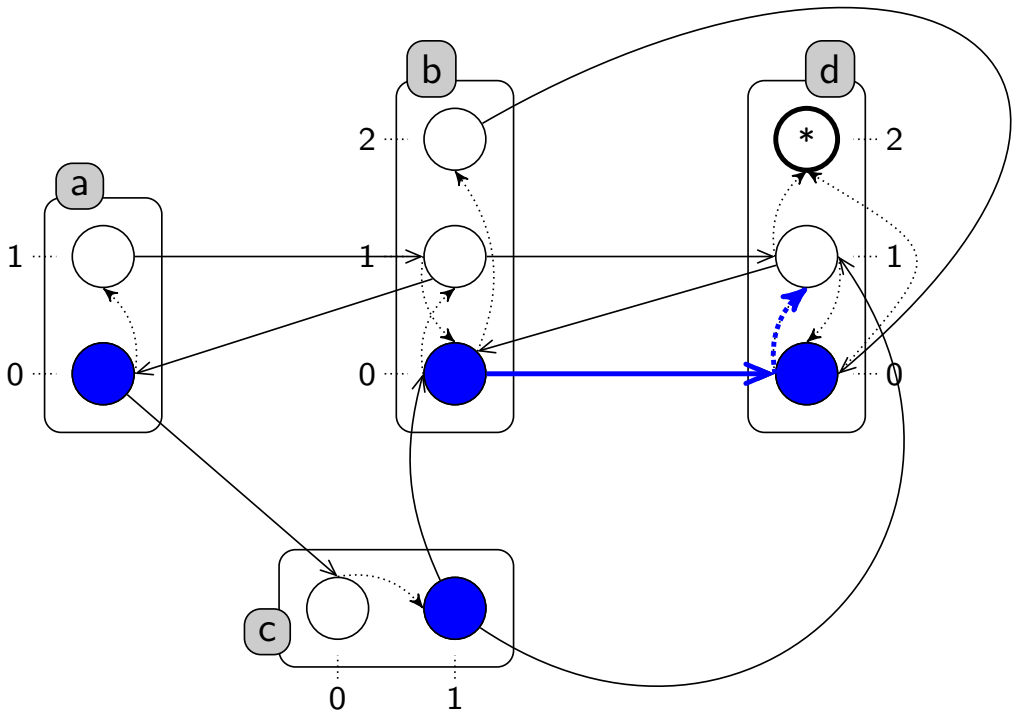

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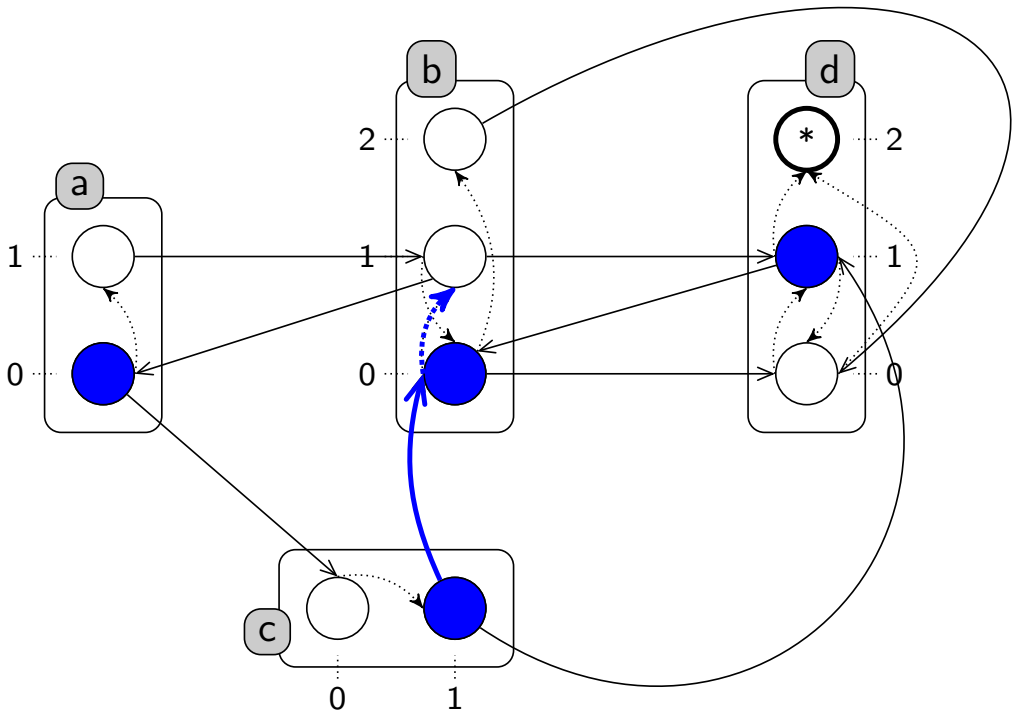

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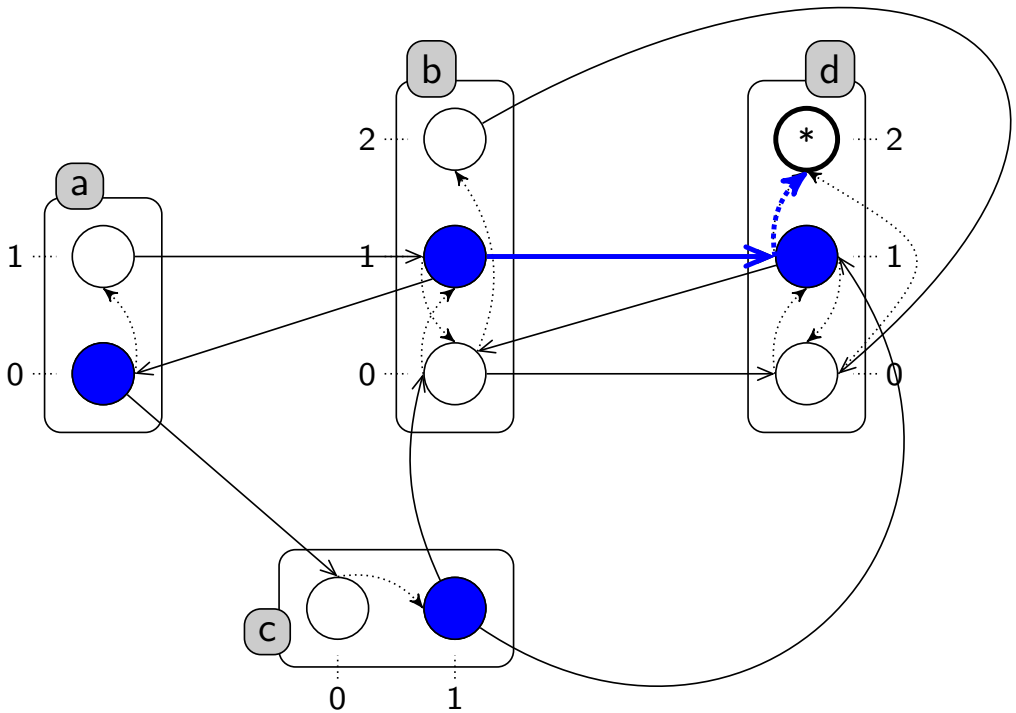

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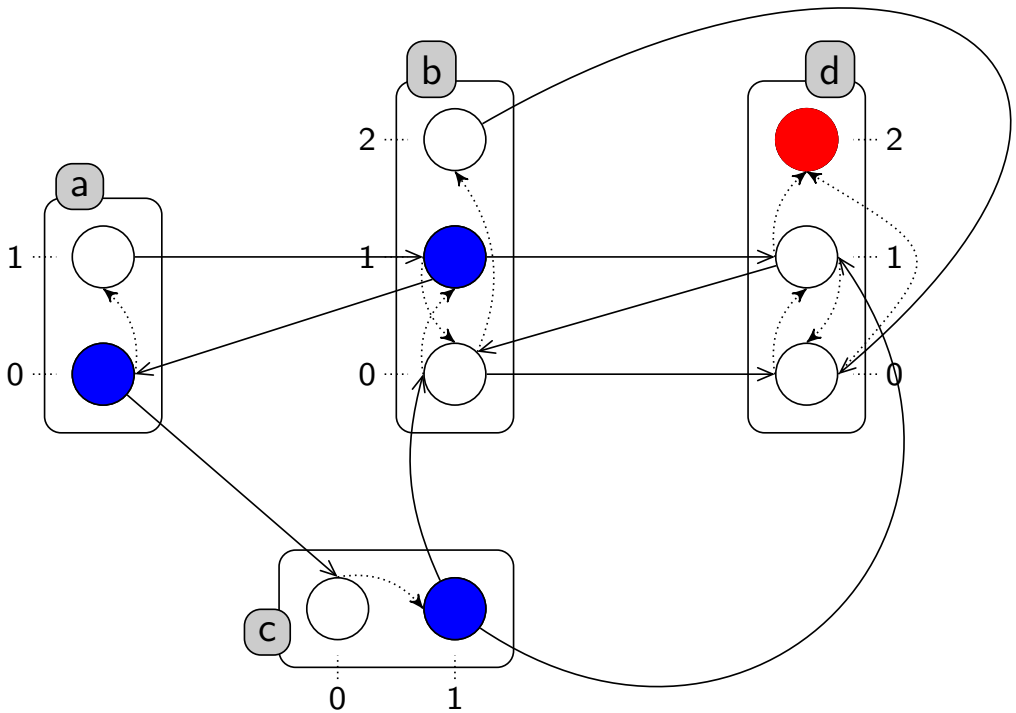

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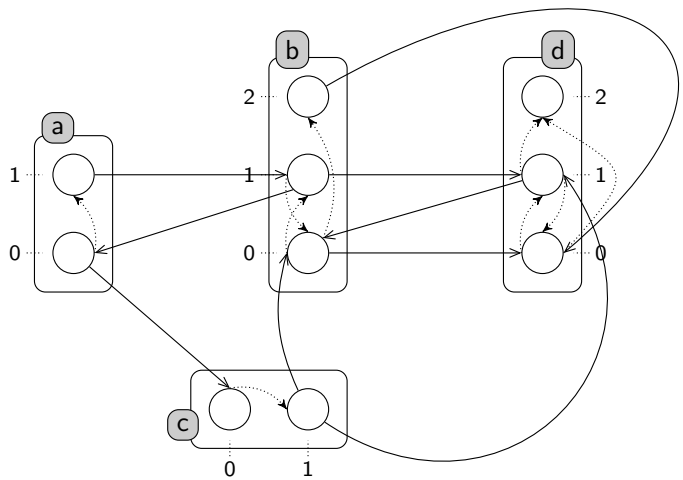
Dynamic analysis

Evolution through ASP

Network evolution through ASP



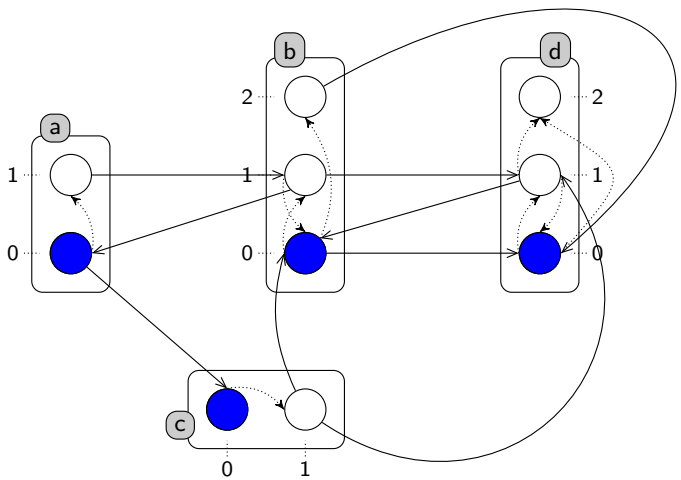
Dynamic analysis

Evolution through ASP

Network evolution through ASP

Initializing :

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



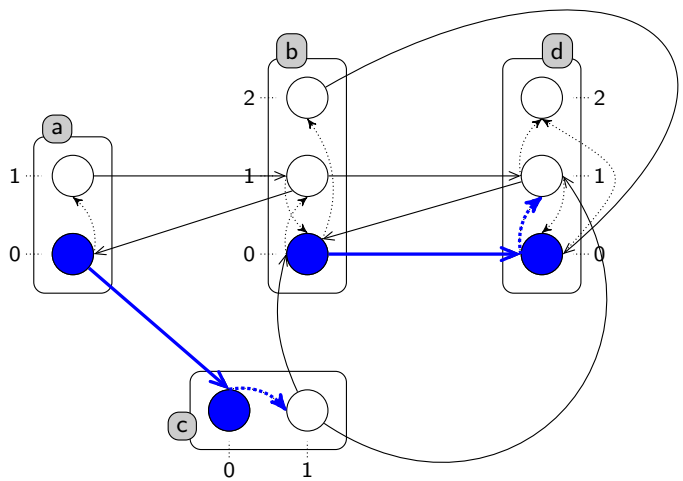
Dynamic analysis

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).
```



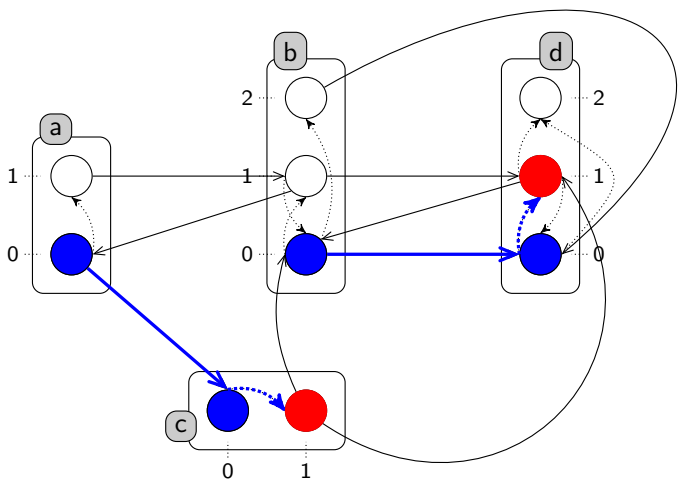
Dynamic analysis

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).
```



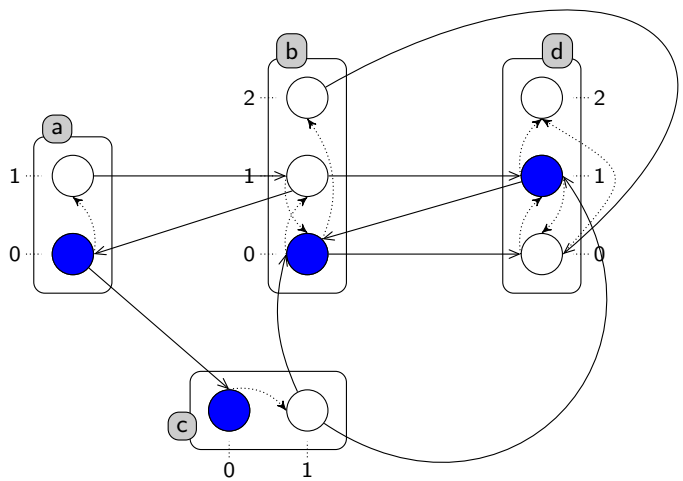
Dynamic analysis

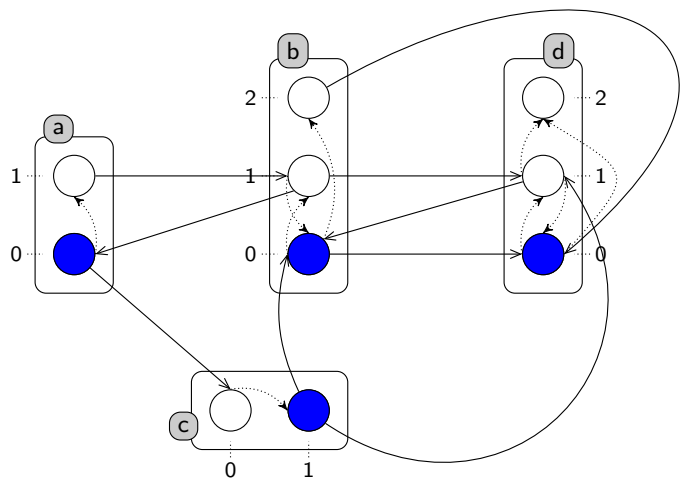
Evolution through ASP

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 ($N = 3$) :

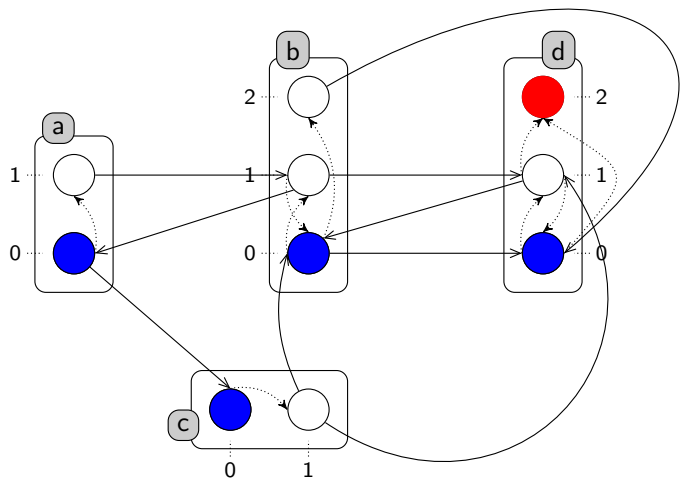
Answer 1: activeFromTo("d",0,1,0) activeFromTo("c",0,1,1)
actifFromTo("b",0,1,2).
Answer 2: activeFromTo("d",0,1,0) activeFromTo("b",0,2,1)
Answer 3: activeFromTo("c",0,1,0) activeFromTo("d",0,1,1)
activeFromTo("d",1,0,2) activeFromTo("b",0,1,3)
...
Answer 29: activeFromTo("c",0,1,0) activeFromTo("b",0,1,1)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

Dynamic analysis

Reachability through ASP

Success reachability through ASP:

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

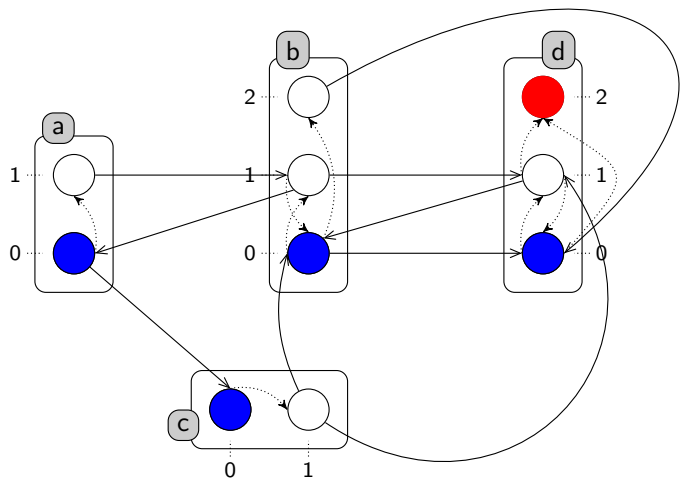


Dynamic analysis

Reachability through ASP

Success reachability through ASP:

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

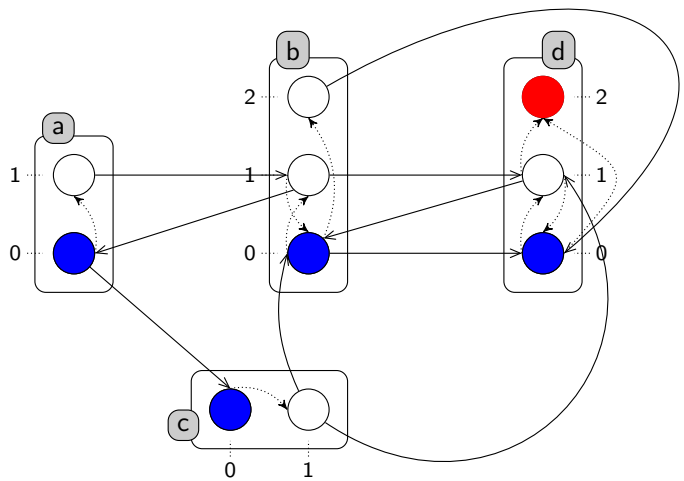


Dynamic analysis

Reachability through ASP

Success reachability through ASP:

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



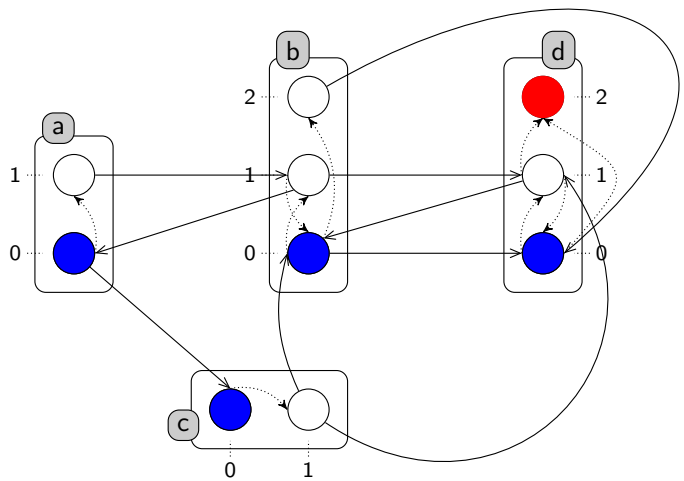
Dynamic analysis

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).`

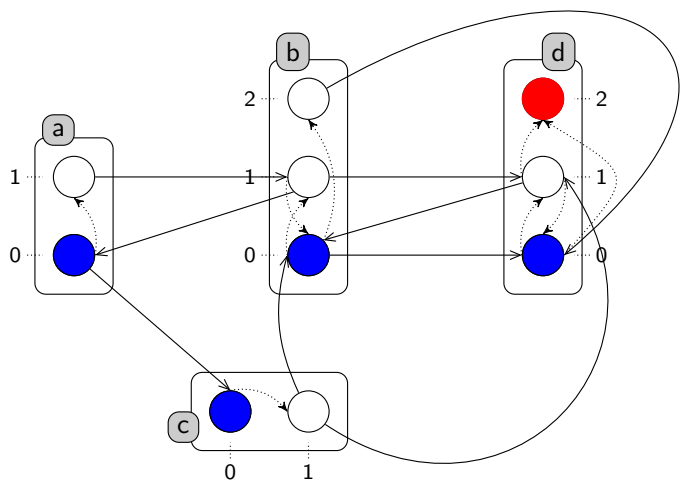
Answer 2: `activeFromTo("d",0,1,0) activeFromTo("c",0,1,1) activeFromTo("b",0,1,2) activeFromTo("d",1,2,3)`

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

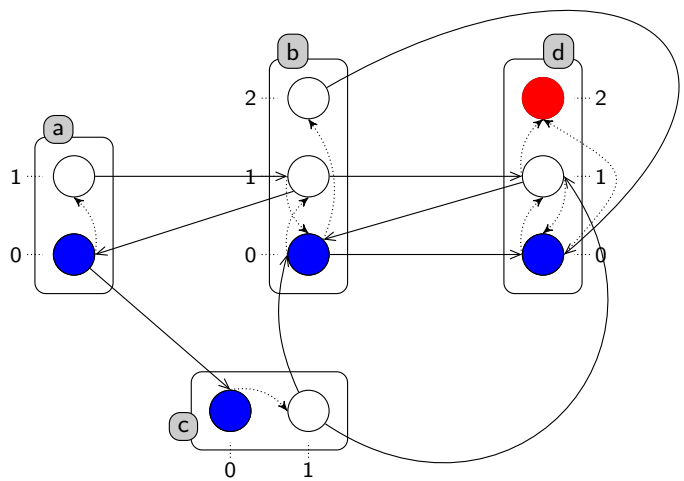
Reachability through ASP

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 iterative method ASP-PH.

General setting of the problem

Limits of discrete modeling

Quantitative information about the delays between two events is abstracted . . . but this information may be crucial in some dynamics.

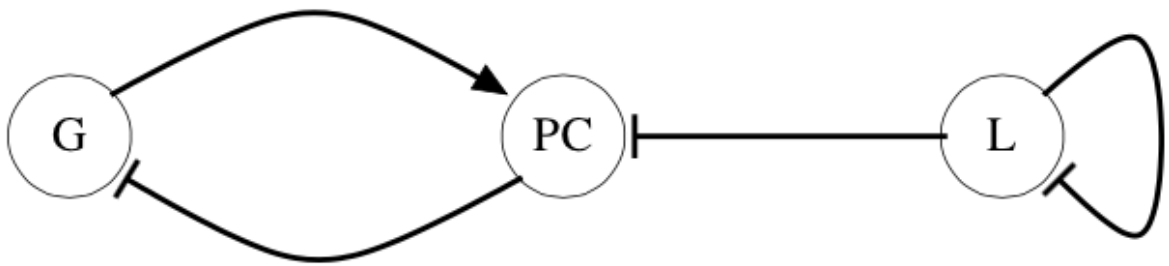
Issues related to the introduction of delays

- Discrete time vs dense time
- How to capture delays in the ASP modeling?

Towards model-cheking timed models using ASP

Circadian clock

– Simplified discrete model introduced by (Comet et al., 2012)
– nondeterministic and asynchronous model

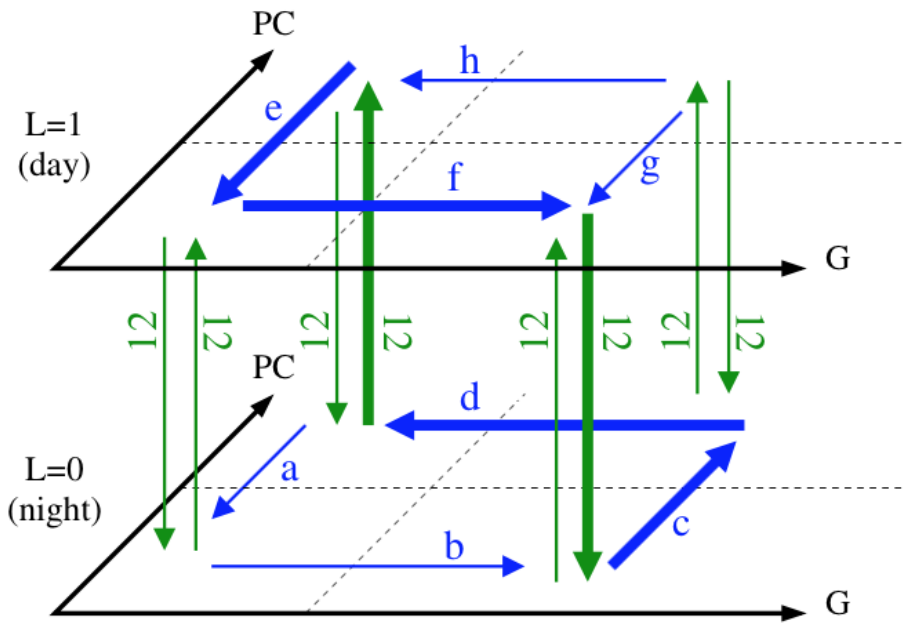


– **PC**: PER-CRY complex
– **G**: set of genes having a positive action on the complex PER-CRY
– **L**: Light

Towards model-cheking timed models using ASP

Circadian clock

– Simplified discrete model introduced by (Comet et al., 2012)
– nondeterministic and asynchronous model



Implementation using ASP

Circadian clock

Nodes:

```
process("L",0..1).
process("PC",0..1).
process("G",0..1).
```

Execution time of actions:

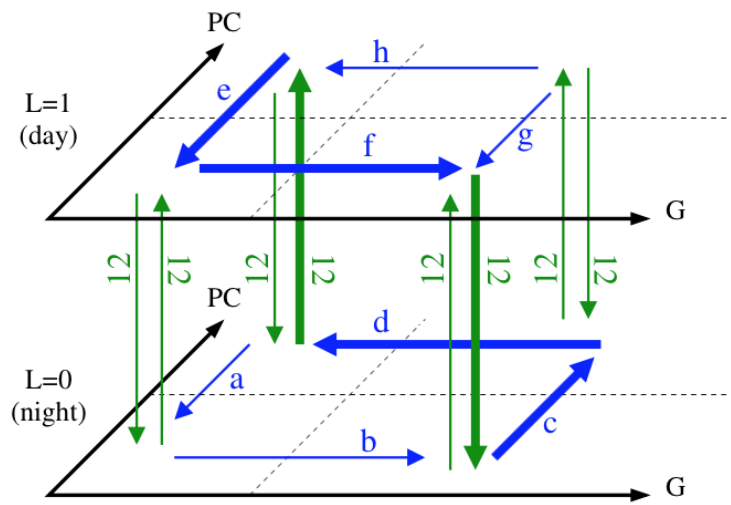
```
equalTo("a",7).  equalTo("b",5)...
```

Number of hours for day and night:

```
hoursDay(12).  hoursNight(12).
```

Actions:

```
action("G",0, "L",1, "PC",1,0, I):-
equalTo("e",I).
```



Implementation using ASP

Circadian clock

Timer for Light :

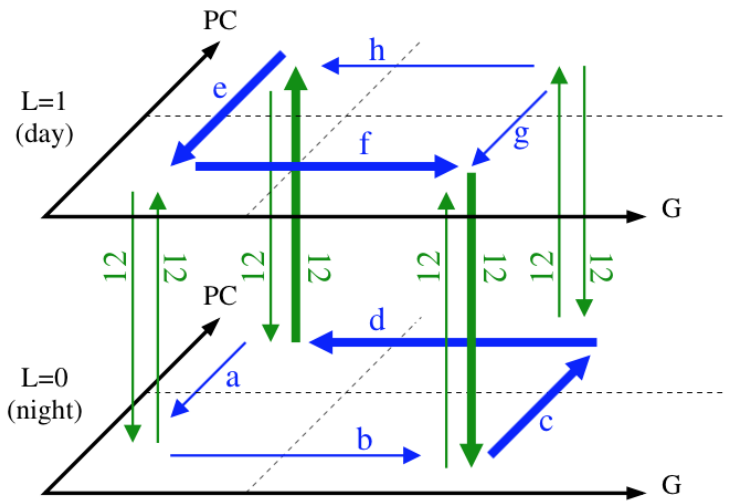
```
timerL(X,T).
```

Timer for component now changing :

```
timerComp(U,T).
```

Reaction is playing or component is changed at T :

```
processingActiveFromTo(B,J,K,U, X,
T).
activeFromTo(B,J,K, T).
```

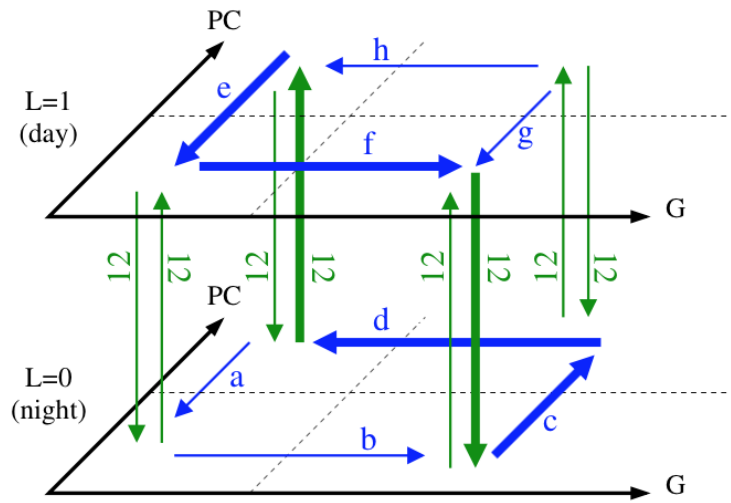


Implementation using ASP

Circadian clock

Result of the evolution of this oscillation after 40 hours:

```
Answer:  1
activeFromTo("PC",0,1,7)
activeFromTo("G",1,0,12)
activeFromTo("PC",1,0,14)
activeFromTo("G",0,1,19)
activeFromTo("PC",0,1,31)
activeFromTo("G",1,0,36))
activeFromTo("PC",1,0,38)
activeFromTo("G",0,1,43)
```



Conclusion & Prospects

- New dynamic analysis of Process Hitting models:
  - Fixed point
  - Network evolution
  - Reachability
- Representation of timed automata models through Process Hitting: Circadian clock

- **Prospects:**
  - Model-checking of for circadian clock
  - Estimation of new action parameters when duration for day/night cycle changes
  - Connecting dynamic properties with resilience
  - Adaptation on other models (PN, Boolean networks, Thomas' models,...)
  - Search of attractors
  - Reverse reachability ($goal \rightarrow I_0$?)...

Bibliography

[1]Christian Anger, Kathrin Konczak, Thomas Linke, and Torsten Schaub. A glimpse of answer set programming. KI, 19(1) :12, 2005.

[2] Chitta Baral. Knowledge representation, reasoning and declarative problem solving. *Cambridge university press*, 2003.

[3] Martin Gebser, Roland Kaminski, Benjamin Kaufmann, Max Ostrowski, Torsten Schaub, and Sven Thiele. A user's guide to gringo, clasp, clingo, and iclingo, 2008.

[4] Zohra Khalis, Jean-Paul Comet, Adrien Richard, and Gilles Bernot. The smbionet method for discovering models of gene regulatory networks. Genes, Genomes and Genomics, 3(1) :15-22, 2009.

[5] Steffen Klamt, Julio Saez-Rodriguez, Jonathan Lindquist, Luca Simeoni, and Ernst Gilles. A methodology for the structural and functional analysis of signaling and regulatory networks. BMC Bioinformatics, 7(1) :56, 2006.

[6] Vladimir Lifschitz. Answer set programming and plan generation. Artificial Intelligence, 138(1) :39-54, 2002.

Bibliography

[7] Loïc Paulevé, Morgan Magnin, Olivier Roux. Modelisation, Simulation et Verification des Grands Reseaux de Regulation Biologique.PhD thesis at École centrale de nantes, 2011.

[8] Loïc Paulevé, Morgan Magnin, and Olivier Roux. Static analysis of biological regulatory net-works dynamics using abstract interpretation. Mathematical Structures in Computer Science, 2012.

[9] Alexandre Rocca, Nicolas Mobilia, Éric Fanchon, Tony Ribeiro, Laurent Trilling, and Katsumi Inoue. Asp for construction and validation of regulatory biological networks. In Luis Fariñas del Cerro and Katsumi Inoue, editors, *Logical Modeling of Biological Systems*, pages 167-206. Wiley-ISTE, 2014.

[10] Regina Samaga, Julio Saez-Rodriguez, Leonidas G Alexopoulos, Peter K. Sorger, and Stef-fen Klamt. The logic of egfr/erbb signaling : Theoretical properties and analysis of high-throughput data. PLoS Computational Biology, 5(8) :e1000438, 2009.

[11] Comet, Jean-Paul, et al. Simplified models for the mammalian circadian clock. Procedia Computer Science 11 (2012): 127-138.

Thanks for your attention