Groupe de travail Dyliss

Analysis of Biological Networks: A Summary of my Works

Analyse des réseaux biologiques: un résumé de mes travaux

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Overview of This Presentation

Frameworks: modeling biological processes

- **Thomas modeling** (historically widespread)
- **Asynchronous Automata Networks** (generalization)
- **Hybrid Thomas modeling** (generalization)

Model completion: inferring missing information on the model

- **Hybrid Hoare logic** (parameters/logical gates on Hybrid Thomas modeling)
- **Continuous transitions** (logical thresholds from expression profiles)

Dynamic analyses: explore the dynamics of a model

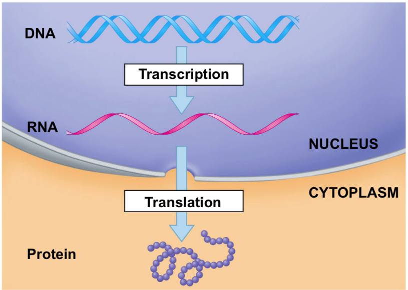
- **μ-calculus** & **Answer Set Programming** (exhaustive)
- **Abstract interpretation** (approximations)

TGF-β pathways project: my work here as a postdoc

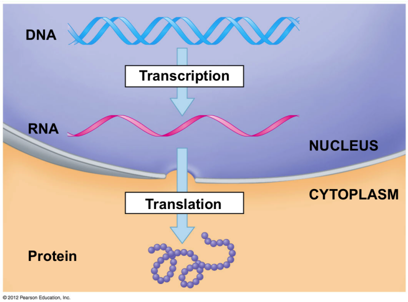
- Extract and build a big graph from databases
- Search for inconsistencies in cancerous types

Frameworks

Abstractions of the Representation



Abstractions of the Representation



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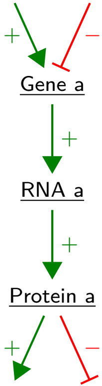

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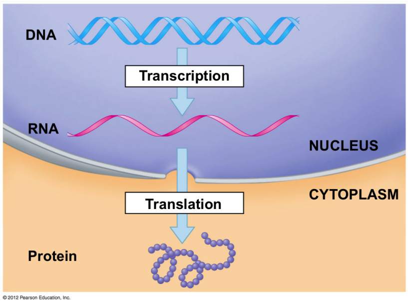
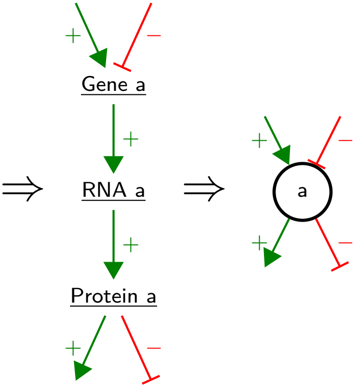
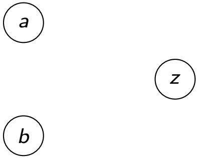




Discrete Networks / Thomas Modeling

[Kauffman, *Journal of Theoretical Biology*, 1969]
[Thomas, *Journal of Theoretical Biology*, 1973]

- A set of components $N = \{a, b, z\}$



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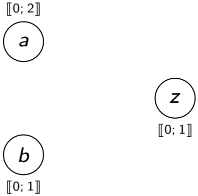
[Thomas, *Journal of Theoretical Biology*, 1973]

- A set of components $N = \{a, b, z\}$
- A set of discrete expression levels for each component $a \in \mathbb{F}^a = [\![0;2]\!]$
- The set of global states $\mathbb{F} = \mathbb{F}^a \times \mathbb{F}^b \times \mathbb{F}^z$



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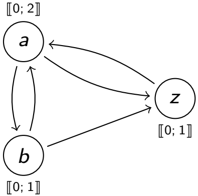
- The set of global states $\mathbb{F} = \mathbb{F}^a \times \mathbb{F}^b \times \mathbb{F}^z$
- An evolution function for each component $f^z : \mathbb{F} \to \mathbb{F}^z$

a	$f^b(a)$
0	**0**
1	**1**
2	**1**

z	b	$f^a(z, b)$
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

a	b	$f^z(a, b)$
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**



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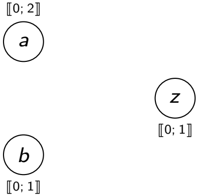

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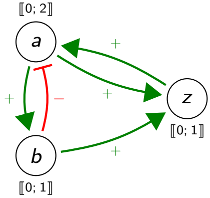
- Signs on the edges $a \xrightarrow{+} z$



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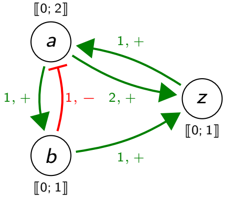
- Signs on the edges $a \xrightarrow{+} z$ or signs & thresholds $a \xrightarrow{2,+} z$



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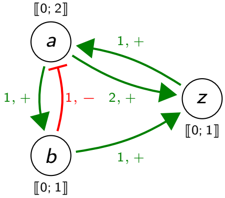
- A set of discrete expression levels for each component $a \in \mathbb{F}^a = [\![0; 2]\!]$
- The set of global states $\mathbb{F} = \mathbb{F}^a \times \mathbb{F}^b \times \mathbb{F}^z$
- Signs on the edges $a \xrightarrow{+} z$ or signs & thresholds $a \xrightarrow{2,+} z$
- Discrete parameters / evolution functions $f^a : \mathbb{F} \to \mathbb{F}^a$

a	$f^b(a)$
0	**0**
1	**1**
2	**1**

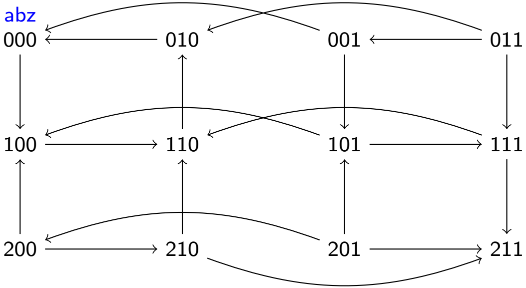
z	b	$f^a(z, b)$
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

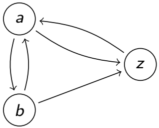
a	b	$f^z(a, b)$
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**



State-graph

The state-graph depicts the whole dynamics
Computation: **exponential** in the size of the model





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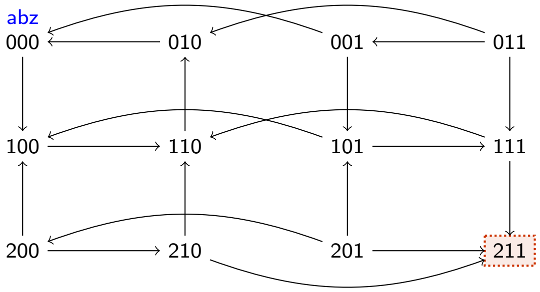

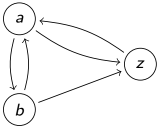

- **Stable state** = state with no successors

State-graph

The state-graph depicts the whole dynamics
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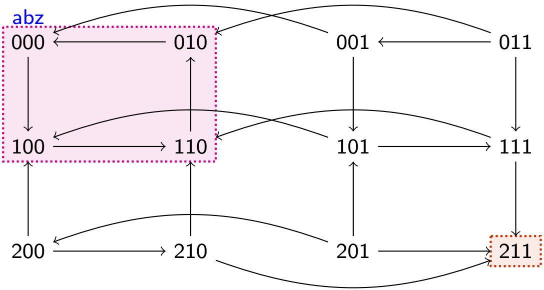
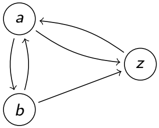
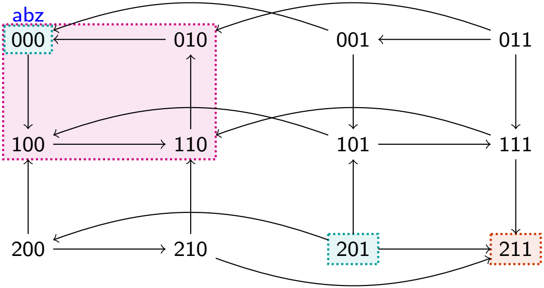


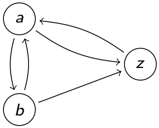


- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape

State-graph

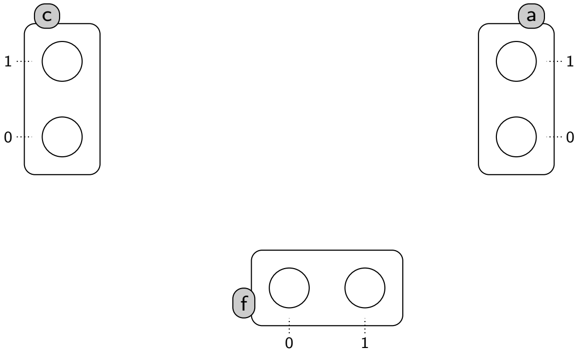
The state-graph depicts the whole dynamics
Computation: **exponential** in the size of the model





- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape
- **Reachability** = from **000**, can I reach **201**?

Asynchronous Automata Networks (AAN)
Enriched Process Hitting (PH)



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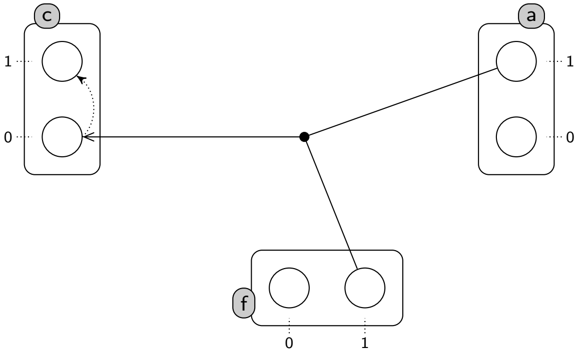

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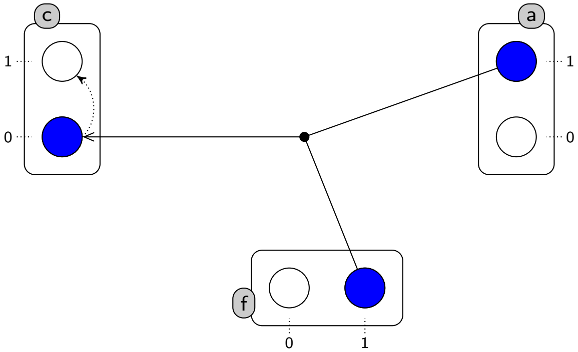

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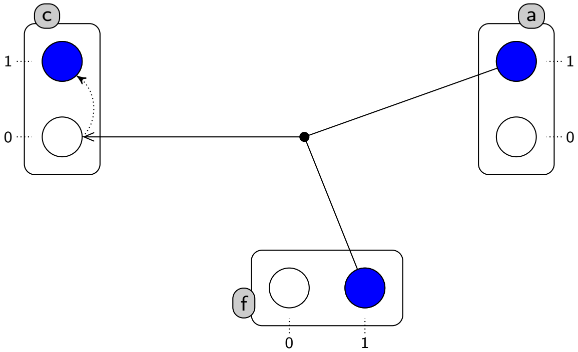
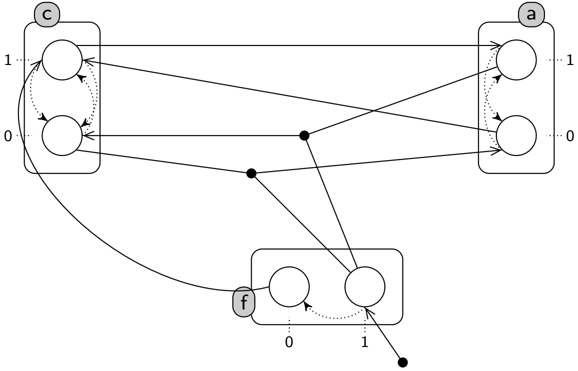


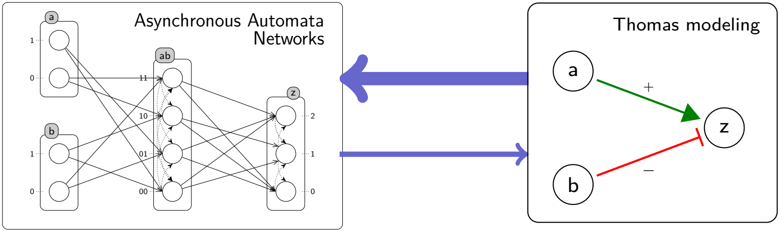
Asynchronous Automata Networks (AAN) Enriched Process Hitting (PH)

Model from [François *et al.*, *Molecular Systems Biology*, 2007]



Translations Between AAN and Thomas Modeling

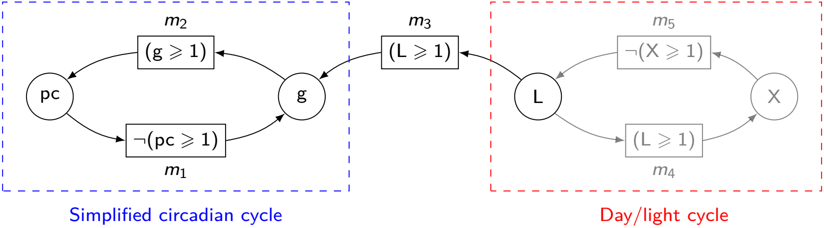
[Folschette *et al.*, *Theoretical Computer Science*, 2015a]
[Folschette *et al.*, *CS2Bio'13*, 2013]



- Asynchronous Automata Networks encompass Thomas modeling
- Mutual translations developed
- Results are also mutually applicable

Model Completion

A Simplified Circadian Cycle Model

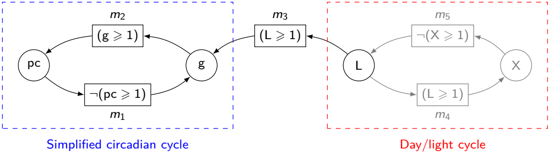


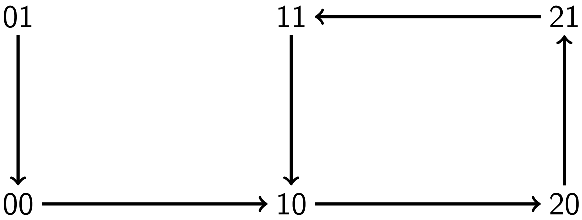
pc = PER/CRY complex
g = *per* and *cry* genes

L = light of the day
X = Modeling artifact (clock)

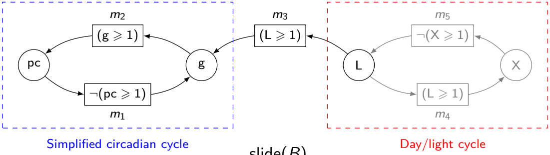
m_1 = PER/CRY complex inhibits *per* and *cry* genes
m_2 = transcription and complexation
m_3 = light makes BMAL1/CLOCK complex activate *per* and *cry* genes
m_4 & m_5 = 12h day/night oscillation

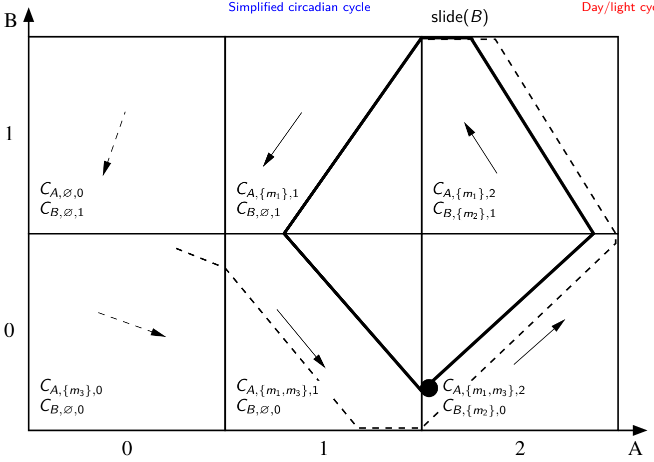
Hybrid Thomas Modeling





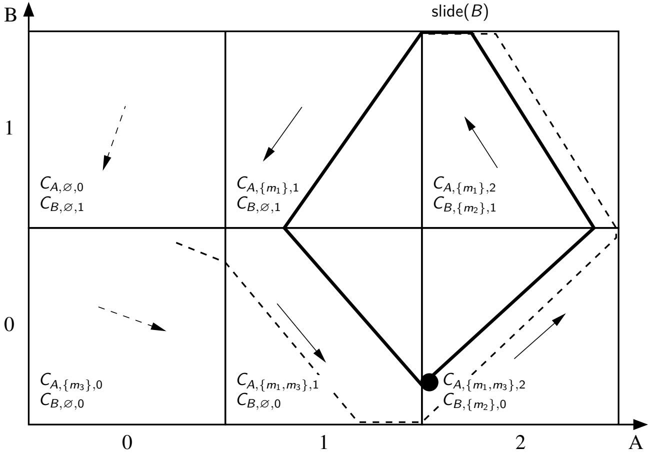
Hybrid Thomas Modeling





Hybrid Hoare Logic to Infer Parameters

$$\left\{\begin{matrix}???\\???\end{matrix}\right\}\begin{pmatrix}T_4\\\top\\B+\end{pmatrix};\begin{pmatrix}T_3\\\text{slide}^+(B)\\A-\end{pmatrix};\begin{pmatrix}T_2\\\top\\B-\end{pmatrix};\begin{pmatrix}T_1\\\top\\A+\end{pmatrix}\left\{\begin{matrix}D_0\equiv(\eta_A=2\wedge\eta_B=0)\\H_0\equiv(\pi_{\text{initial}}=\pi_{\text{final}})\end{matrix}\right\}$$

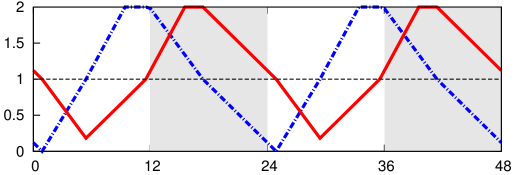


$((((((((((\pi_g^{0\prime} = 0.12) \wedge ((\pi_{pc}^{0\prime} = 0.12) \wedge (\pi_L^{0\prime} = 0))) \wedge (((\pi_L^1 = 1) \wedge ((C_{L,\{m5\},0} > 0) \wedge (\pi_L^{1\prime} =$
$(\pi_L^1 - (C_{L,\{m5\},0} \times 6.6))))) \wedge ((\neg((C_{g,\varnothing,0} > 0) \wedge (\pi_g^{1\prime} > (\pi_g^1 - (C_{g,\varnothing,0} \times 6.6)))) \wedge (\neg((C_{pc,\varnothing,1} < 0) \wedge (\pi_{pc}^{1\prime} <$
$(\pi_{pc}^1 - (C_{pc,\varnothing,1} \times 6.6)))) \wedge \neg((C_{X,\varnothing,0} > 0) \wedge (\pi_X^{1\prime} > (\pi_X^1 - (C_{X,\varnothing,0} \times 6.6)))))) \wedge ((\pi_L^1 = (1 - \pi_L^{0\prime})) \wedge ((\pi_g^1 = \pi_g^{0\prime}) \wedge$
$((\pi_{pc}^1 = \pi_{pc}^{0\prime}) \wedge (\pi_X^1 = \pi_X^{0\prime})))))))) \wedge (((\pi_X^2 = 0) \wedge ((C_{X,\varnothing,1} < 0) \wedge (\pi_X^{2\prime} = (\pi_X^2 - (C_{X,\varnothing,1} \times 0.6))))) \wedge ((\neg((C_{g,\varnothing,0} >$
$0) \wedge (\pi_g^{2\prime} > (\pi_g^2 - (C_{g,\varnothing,0} \times 0.6)))) \wedge (\neg((C_{pc,\varnothing,1} < 0) \wedge (\pi_{pc}^{2\prime} < (\pi_{pc}^2 - (C_{pc,\varnothing,1} \times 0.6)))) \wedge \neg((C_{L,\varnothing,0} >$
$0) \wedge (\pi_L^{2\prime} > (\pi_L^2 - (C_{L,\varnothing,0} \times 0.6)))))) \wedge (((\pi_L^2 = 0) \wedge ((C_{L,\varnothing,0} < 0) \Rightarrow (\pi_L^{2\prime} < (\pi_L^2 - (C_{L,\varnothing,0} \times 0.6))))) \wedge ((\pi_X^2 =$
$(1 - \pi_X^{1\prime})) \wedge ((\pi_g^2 = \pi_g^{1\prime}) \wedge ((\pi_{pc}^2 = \pi_{pc}^{1\prime}) \wedge (\pi_L^2 = \pi_L^{1\prime}))))))))\sphericalangle \wedge (((\pi_g^3 = 0) \wedge ((C_{g,\varnothing,1} < 0) \wedge (\pi_g^{3\prime} =$
$(\pi_g^3 - (C_{g,\varnothing,1} \times 5.4))))) \wedge ((\neg((C_{pc,\{m2\},1} < 0) \wedge (\pi_{pc}^{3\prime} < (\pi_{pc}^3 - (C_{pc,\{m2\},1} \times 5.4)))) \wedge (\neg((C_{L,\varnothing,0} > 0) \wedge (\pi_L^{3\prime} >$
$(\pi_L^3 - (C_{L,\varnothing,0} \times 5.4)))) \wedge \neg((C_{X,\varnothing,1} < 0) \wedge (\pi_X^{3\prime} < (\pi_X^3 - (C_{X,\varnothing,1} \times 5.4)))))) \wedge (((\pi_{pc}^3 = 1) \wedge ((C_{pc,\{m2\},1} >$
$0) \Rightarrow (\pi_{pc}^{3\prime} > (\pi_{pc}^3 - (C_{pc,\{m2\},1} \times 5.4))))) \wedge ((\pi_g^3 = (1 - \pi_g^{2\prime})) \wedge ((\pi_{pc}^3 = \pi_{pc}^{2\prime}) \wedge ((\pi_L^3 = \pi_L^{2\prime}) \wedge (\pi_X^3 =$
$\pi_X^{2\prime})))))))) \wedge (((\pi_L^4 = 0) \wedge ((C_{L,\varnothing,1} < 0) \wedge (\pi_L^{4\prime} = (\pi_L^4 - (C_{L,\varnothing,1} \times 0.47))))) \wedge ((\neg((C_{g,\{m3\},1} < 0) \wedge (\pi_g^{4\prime} <$
$(\pi_g^4 - (C_{g,\{m3\},1} \times 0.47)))) \wedge (\neg((C_{pc,\{m2\},1} < 0) \wedge (\pi_{pc}^{4\prime} < (\pi_{pc}^4 - (C_{pc,\{m2\},1} \times 0.47)))) \wedge \neg((C_{X,\{m4\},1} <$
$0) \wedge (\pi_X^{4\prime} < (\pi_X^4 - (C_{X,\{m4\},1} \times 0.47)))))) \wedge ((\pi_L^4 = (1 - \pi_L^{3\prime})) \wedge ((\pi_g^4 = \pi_g^{3\prime}) \wedge ((\pi_{pc}^4 = \pi_{pc}^{3\prime}) \wedge (\pi_X^4 =$
$\pi_X^{3\prime}))))))) \wedge (((\pi_{pc}^5 = 1) \wedge ((C_{pc,\{m2\},0} > 0) \wedge (\pi_{pc}^{5\prime} = (\pi_{pc}^5 - (C_{pc,\{m2\},0} \times 5.53))))) \wedge ((\neg((C_{g,\{m1,m3\},1} <$
$0) \wedge (\pi_g^{5\prime} < (\pi_g^5 - (C_{g,\{m1,m3\},1} \times 5.53)))) \wedge (\neg((C_{L,\varnothing,1} < 0) \wedge (\pi_L^{5\prime} < (\pi_L^5 - (C_{L,\varnothing,1} \times 5.53)))) \wedge \neg((C_{X,\{m4\},1} <$
$0) \wedge (\pi_X^{5\prime} < (\pi_X^5 - (C_{X,\{m4\},1} \times 5.53)))))) \wedge (((\pi_g^5 = 1) \wedge ((C_{g,\{m1,m3\},1} > 0) \Rightarrow (\pi_g^{5\prime} >$
$(\pi_g^5 - (C_{g,\{m1,m3\},1} \times 5.53))))) \wedge ((\pi_{pc}^5 = (1 - \pi_{pc}^{4\prime})) \wedge ((\pi_g^5 = \pi_g^{4\prime}) \wedge ((\pi_L^5 = \pi_L^{4\prime}) \wedge (\pi_X^5 = \pi_X^{4\prime})))))))) \wedge (((\pi_X^6 =$
$1) \wedge ((C_{X,\{m4\},0} > 0) \wedge (\pi_X^{6\prime} = (\pi_X^6 - (C_{X,\{m4\},0} \times 0.6))))) \wedge ((\neg((C_{g,\{m1,m3\},1} < 0) \wedge (\pi_g^{6\prime} <$
$(\pi_g^6 - (C_{g,\{m1,m3\},1} \times 0.6)))) \wedge (\neg((C_{pc,\{m2\},0} > 0) \wedge (\pi_{pc}^{6\prime} > (\pi_{pc}^6 - (C_{pc,\{m2\},0} \times 0.6)))) \wedge \neg((C_{L,\{m5\},1} <$
$0) \wedge (\pi_L^{6\prime} < (\pi_L^6 - (C_{L,\{m5\},1} \times 0.6)))))) \wedge ((\pi_X^6 = (1 - \pi_X^{5\prime})) \wedge ((\pi_g^6 = \pi_g^{5\prime}) \wedge ((\pi_{pc}^6 = \pi_{pc}^{5\prime}) \wedge (\pi_L^6 =$
$\pi_L^{5\prime}))))))) \wedge (((\pi_g^7 = 1) \wedge ((C_{g,\{m1,m3\},0} > 0) \wedge (\pi_g^{7\prime} = (\pi_g^7 - (C_{g,\{m1,m3\},0} \times 4.5))))) \wedge ((\neg((C_{pc,\varnothing,0} >$
$0) \wedge (\pi_{pc}^{7\prime} > (\pi_{pc}^7 - (C_{pc,\varnothing,0} \times 4.5)))) \wedge (\neg((C_{L,\{m5\},1} < 0) \wedge (\pi_L^{7\prime} < (\pi_L^7 - (C_{L,\{m5\},1} \times 4.5)))) \wedge \neg((C_{X,\{m4\},0} >$
$0) \wedge (\pi_X^{7\prime} > (\pi_X^7 - (C_{X,\{m4\},0} \times 4.5)))))) \wedge ((\pi_g^7 = (1 - \pi_g^{6\prime})) \wedge ((\pi_{pc}^7 = \pi_{pc}^{6\prime}) \wedge ((\pi_L^7 = \pi_L^{6\prime}) \wedge (\pi_X^7 =$
$\pi_X^{6\prime}))))))) \wedge (((\pi_{pc}^8 = 0) \wedge ((C_{pc,\varnothing,1} < 0) \wedge (\pi_{pc}^{8\prime} = (\pi_{pc}^8 - (C_{pc,\varnothing,1} \times 0.9))))) \wedge ((\neg((C_{g,\{m3\},0} > 0) \wedge (\pi_g^{8\prime} >$
$(\pi_g^8 - (C_{g,\{m3\},0} \times 0.9)))) \wedge (\neg((C_{L,\{m5\},1} < 0) \wedge (\pi_L^{8\prime} < (\pi_L^8 - (C_{L,\{m5\},1} \times 0.9)))) \wedge \neg((C_{X,\{m4\},0} >$
$0) \wedge (\pi_X^{8\prime} > (\pi_X^8 - (C_{X,\{m4\},0} \times 0.9)))))) \wedge ((\pi_{pc}^8 = (1 - \pi_{pc}^{7\prime})) \wedge ((\pi_g^8 = \pi_g^{7\prime}) \wedge ((\pi_L^8 = \pi_L^{7\prime}) \wedge (\pi_X^8 = \pi_X^{7\prime})))))))$

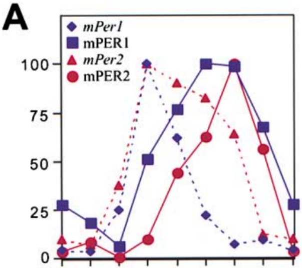
$$((((((((((\pi_g^{0\prime} = 0.12) \wedge ((\pi_{pc}^{0\prime} = 0.12) \wedge (\pi_L^{0\prime} = 0))) \wedge (((\pi_L^1 = 1) \wedge ((C_{L,\{m5\},0} > 0) \wedge (\pi_L^{1\prime} =$$
$$(\pi_L^1 - (C_{L,\{m5\},0} \times 6.6))))) \wedge ((\neg((C_{g,\varnothing,0} > 0) \wedge (\pi_g^{1\prime} > (\pi_g^1 - (C_{g,\varnothing,0} \times 6.6)))) \wedge (\neg((C_{pc,\varnothing,1} < 0) \wedge (\pi_{pc}^{1\prime} <$$
$$(\pi_{pc}^1 - (C_{pc,\varnothing,1} \times 6.6)))) \wedge \neg((C_{X,\varnothing,0} > 0) \wedge (\pi_X^{1\prime} > (\pi_X^1 - (C_{X,\varnothing,0} \times 6.6)))))) \wedge ((\pi_L^1 = (1 - \pi_L^{0\prime})) \wedge ((\pi_g^1 = \pi_g^{0\prime}) \wedge$$
$$((\pi_{pc}^1 = \pi_{pc}^{0\prime}) \wedge (\pi_X^1 = \pi_X^{0\prime})))))))) \wedge (((\pi_X^2 = 0) \wedge ((C_{X,\varnothing,1} < 0) \wedge (\pi_X^{2\prime} = (\pi_X^2 - (C_{X,\varnothing,1} \times 0.6))))) \wedge ((\neg((C_{g,\varnothing,0} >$$
$$0) \wedge (\pi_g^{2\prime} > (\pi_g^2 - (C_{g,\varnothing,0} \times 0.6)))) \wedge (\neg((C_{pc,\varnothing,1} < 0) \wedge (\pi_{pc}^{2\prime} < (\pi_{pc}^2 - (C_{pc,\varnothing,1} \times 0.6)))) \wedge \neg((C_{L,\varnothing,0} >$$
$$0) \wedge (\pi_L^{2\prime} > (\pi_L^2 - (C_{L,\varnothing,0} \times 0.6)))))) \wedge (((\pi_L^2 = 0) \wedge ((C_{L,\varnothing,0} < 0) \Rightarrow (\pi_L^{2\prime} < (\pi_L^2 - (C_{L,\varnothing,0} \times 0.6))))) \wedge ((\pi_X^2 =$$
$$(1 - \pi_X^{1\prime})) \wedge ((\pi_g^2 = \pi_g^{1\prime}) \wedge ((\pi_{pc}^2 = \pi_{pc}^{1\prime}) \wedge (\pi_L^2 = \pi_L^{1\prime}))))))))) \nless \wedge (((\pi_g^3 = 0) \wedge ((C_{g,\varnothing,1} < 0) \wedge (\pi_g^{3\prime} =$$
$$(\pi_g^3 - (C_{g,\varnothing,1} \times 5.4))))) \wedge ((\neg((C_{pc,\{m2\},1} < 0) \wedge (\pi_{pc}^{3\prime} < (\pi_{pc}^3 - (C_{pc,\{m2\},1} \times 5.4)))) \wedge (\neg((C_{L,\varnothing,0} > 0) \wedge (\pi_L^{3\prime} >$$
$$(\pi_L^3 - (C_{L,\varnothing,0} \times 5.4)))) \wedge \neg((C_{X,\varnothing,1} < 0) \wedge (\text{[illegible]} < (\pi_X^3 - (C_{X,\varnothing,1} \times 5.4)) \text{[illegible]} (((\pi_{pc}^3 = 1) \wedge ((C_{pc,\{m2\},1} >$$
$$0) \Rightarrow (\pi_{pc}^{3\prime} > (\pi_{pc}^3 - (C_{pc,\{m2\},1} \times 5.4))))) \wedge ((\pi_g^3 = (1 - \pi_g^{2\prime})) \wedge ((\pi_p \text{[illegible]} {}_{pc}^{\prime}) \wedge ((\pi_L^3 = \pi_L^{2\prime}) \wedge (\pi_X^3 =$$
$$\pi_X^{2\prime})))))))) \wedge (((\pi_L^4 = 0) \wedge ((C_{L,\varnothing,1} < 0) \wedge (\pi_L^{4\prime} = (\pi^4 \text{[illegible]} (C_{L,\varnothing,1} \times 0. \text{[illegible]}) \wedge ((\neg((C_{g,\{m3\},1} < 0) \wedge (\pi_g^{4\prime} <$$
$$(\pi_g^4 - (C_{g,\{m3\},1} \times 0.47)))) \wedge (\neg((C_{pc,\{m} \text{[illegible]} < 0) \wedge (\pi_{pc} \text{[illegible]} (\pi_{pc}^4 \text{[illegible]} {}_{pc,\{m2\},1} \times 0.47)))) \wedge \neg((C_{X,\{m4\},1} <$$
$$0) \wedge (\pi_X^{4\prime} < (\pi_X^4 - (C_{X,\{m4\},1} \times 0.47)))))) \wedge ((\pi_L^4 = (1 - \pi_L^{3\prime})) \wedge (\text{[illegible]} = \pi_g^{3\prime}) \wedge ((\pi_{pc}^4 = \pi_{pc}^{3\prime}) \wedge (\pi_X^4 =$$
$$\pi_X^{3\prime}))))))) \wedge (((\pi_{pc}^5 = 1) \wedge ((C_{pc,\{m2\},0} > 0) \wedge (\pi_{pc}^{5\prime} = (\pi_{pc}^5 - (C_p \text{[illegible]} 2\},0} \times 5.53))))) \wedge ((\neg((C_{g,\{m1,m3\},1} <$$
$$0) \wedge (\pi_g^{5\prime} < (\pi_g^5 - (C_{g,\{m1,m3\},1} \times 5.53)))) \wedge (\neg((C_{L,\varnothing,1} < 0) \wedge (\pi_L^5 \text{[illegible]} (\pi_L^5 - (C_{L,\varnothing,1} \times 5.53)))) \wedge \neg((C_{X,\{m4\},1} <$$
$$0) \wedge (\pi_X^{5\prime} < (\pi_X^5 - (C_{X,\{m4\},1} \times 5.53)))))) \wedge (((\pi_g^5 = 1) \wedge ((C_{g,\{m} \text{[illegible]} 3\},1} > 0) \Rightarrow (\pi_g^{5\prime} >$$
$$(\pi_g^5 - (C_{g,\{m1,m3\},1} \times 5.53))))) \wedge ((\pi_{pc}^5 = (1 - \pi_{pc}^{4\prime})) \wedge ((\pi_g^5 = \pi_g^{4\prime} \text{[illegible]} ((\pi_L^5 = \pi_L^{4\prime}) \wedge (\pi_X^5 = \pi_X^{4\prime})))))))) \wedge (((\pi_X^6 =$$
$$1) \wedge ((C_{X,\{m4\},0} > 0) \wedge (\pi_X^{6\prime} = (\pi_X^6 - (C_{X,\{m4\},0} \times 0.6))))) \wedge ((\neg((\text{[illegible]} {}_{g,\{m1,m3\},1} < 0) \wedge (\pi_g^{6\prime} <$$
$$(\pi_g^6 - (C_{g,\{m1,m3\},1} \times 0.6)))) \wedge (\neg((C_{pc,\{m2\},0} > 0) \wedge (\pi_{pc}^{6\prime} > (\pi_{pc}^6 - (C_{pc,\{m2\},0} \times 0.6)))) \wedge \neg((C_{L,\{m5\},1} <$$
$$0) \wedge (\pi_L^{6\prime} < (\pi_L^6 - (C_{L,\{m5\},1} \times 0.6)))))) \wedge ((\pi_X^6 = (1 - \pi_X^{5\prime})) \wedge ((\pi_g^6 = \pi_g^{5\prime}) \wedge ((\pi_{pc}^6 = \pi_{pc}^{5\prime}) \wedge (\pi_L^6 =$$
$$\pi_L^{5\prime}))))))) \wedge (((\pi_g^7 = 1) \wedge ((C_{g,\{m1,m3\},0} > 0) \wedge (\pi_g^{7\prime} = (\pi_g^7 - (C_{g,\{m1,m3\},0} \times 4.5))))) \wedge ((\neg((C_{pc,\varnothing,0} >$$
$$0) \wedge (\pi_{pc}^{7\prime} > (\pi_{pc}^7 - (C_{pc,\varnothing,0} \times 4.5)))) \wedge (\neg((C_{L,\{m5\},1} < 0) \wedge (\pi_L^{7\prime} < (\pi_L^7 - (C_{L,\{m5\},1} \times 4.5)))) \wedge \neg((C_{X,\{m4\},0} >$$
$$0) \wedge (\pi_X^{7\prime} > (\pi_X^7 - (C_{X,\{m4\},0} \times 4.5)))))) \wedge ((\pi_g^7 = (1 - \pi_g^{6\prime})) \wedge ((\pi_{pc}^7 = \pi_{pc}^{6\prime}) \wedge ((\pi_L^7 = \pi_L^{6\prime}) \wedge (\pi_X^7 =$$
$$\pi_X^{6\prime}))))))) \wedge (((\pi_{pc}^8 = 0) \wedge ((C_{pc,\varnothing,1} < 0) \wedge (\pi_{pc}^{8\prime} = (\pi_{pc}^8 - (C_{pc,\varnothing,1} \times 0.9))))) \wedge ((\neg((C_{g,\{m3\},0} > 0) \wedge (\pi_g^{8\prime} >$$
$$(\pi_g^8 - (C_{g,\{m3\},0} \times 0.9)))) \wedge (\neg((C_{L,\{m5\},1} < 0) \wedge (\pi_L^{8\prime} < (\pi_L^8 - (C_{L,\{m5\},1} \times 0.9)))) \wedge \neg((C_{X,\{m4\},0} >$$
$$0) \wedge (\pi_X^{8\prime} > (\pi_X^8 - (C_{X,\{m4\},0} \times 0.9)))))) \wedge ((\pi_{pc}^8 = (1 - \pi_{pc}^{7\prime})) \wedge ((\pi_g^8 = \pi_g^{7\prime}) \wedge ((\pi_L^8 = \pi_L^{7\prime}) \wedge (\pi_X^8 = \pi_X^{7\prime})))))))$$

Results

- **Simplifications** of the constraints
- Let's use a **solver**! :-)
- Results checked with a simulation:



Simulation with compatible values



Experiments

Modeling Gene Interactions

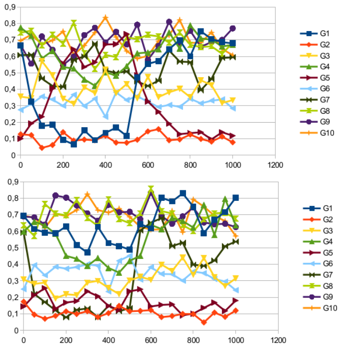
Goal: understand biological dynamics, i.e. gene interactions.

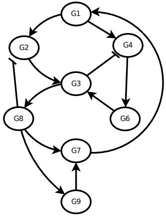
Data: time series

- discrete/regular time steps
- continuous value

Model: Boolean network

- discrete/regular time steps
- discrete values





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Goal: understand biological dynamics, i.e. gene interactions.

Data: time series

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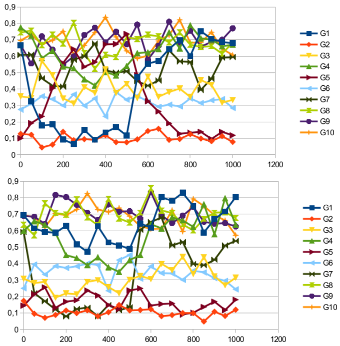
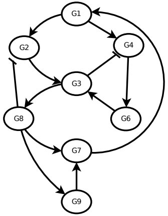
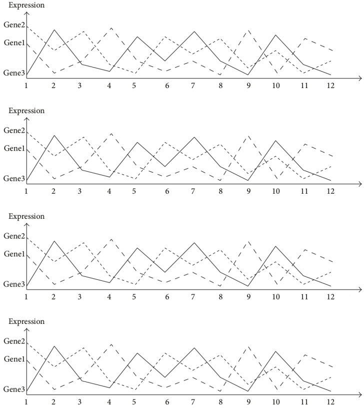
- discrete values





Continuum Logic Program

INPUT:
A set of time series data

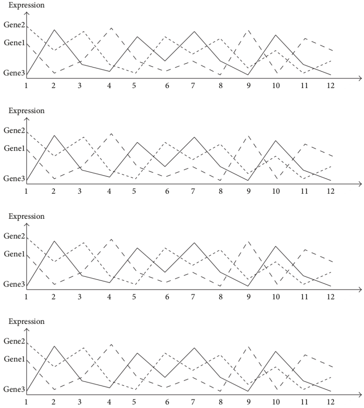


OUTPUT:
A continuum logic program

$$p([0,0.5],t) \leftarrow q([0,0.5],t-1).$$
$$p([0.5,1],t) \leftarrow q([0.5,1],t-1).$$
$$q([0,0.5],t) \leftarrow p([0,0.5],t-1) \wedge r([0.5,1],t-1).$$
$$q([0.5,1],t) \leftarrow p([0.5,1],t-1) \wedge r([0.5,1],t-1).$$
$$r([0,0.5],t) \leftarrow p([0.5,1],t-1).$$
$$r([0.5,1],t) \leftarrow p([0,0.5],t-1).$$

Continuum Logic Program

INPUT:
A set of time series data

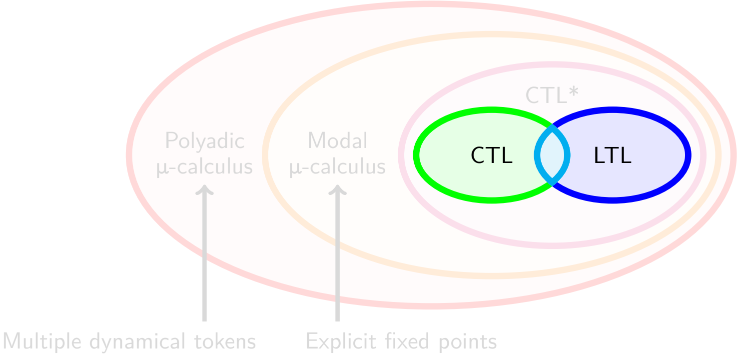


OUTPUT:
A continuum logic program

$$p([0,0.5],t) \leftarrow q([0,0.5],t-1).$$
$$p([0.5,1],t) \leftarrow q([0.5,1],t-1).$$
$$q([0,0.5],t) \leftarrow p([0,0.5],t-1) \wedge r([0.32,1],t-1).$$
$$q([0.5,1],t) \leftarrow p([0.5,1],t-1) \wedge r([0.32,1],t-1).$$
$$r([0,0.32],t) \leftarrow p([0.5,1],t-1).$$
$$r([0.32,1],t) \leftarrow p([0,0.5],t-1).$$

Dynamic Analysis

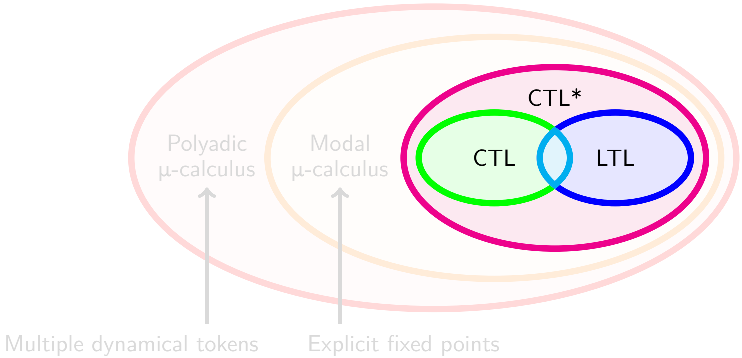
Polyadic μ-caculus



Aim: Unification of properties without quantifiers

- Enumeration of attractors & disruptions
- Bisimulation between two models (regarding some observables)
- Searching Zeno behaviors

Polyadic μ-caculus



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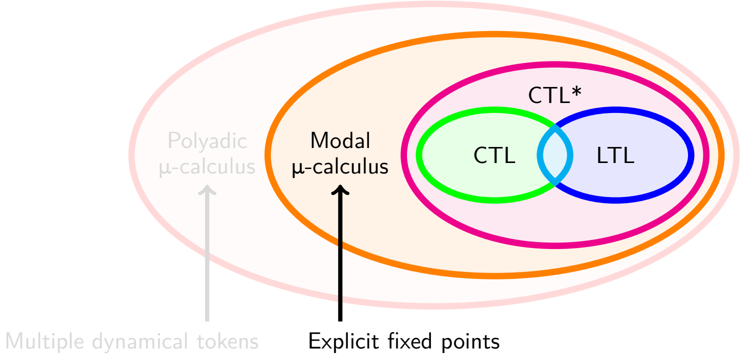
Polyadic μ-caculus



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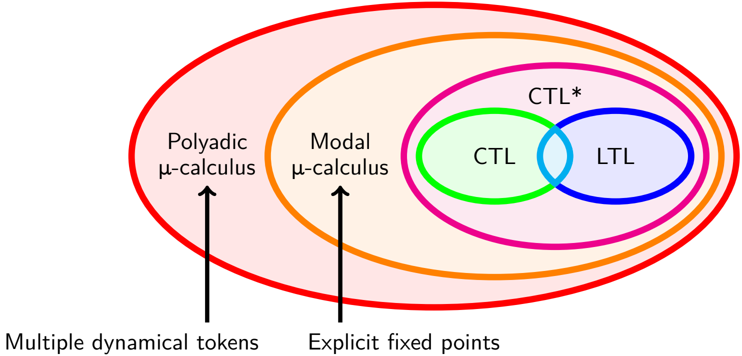
Polyadic μ-caculus



Aim: Unification of properties without quantifiers

- Enumeration of attractors & disruptions
- Bisimulation between two models (regarding some observables)
- Searching Zeno behaviors

Answer Set Programming

Answer Set Programming (ASP): Declarative & logic programming

Rule: $head \leftarrow body.$
"If *body* is true, then *head* must be true (usual logical consequence)"

Fact: $head.$
"*head* is always true"

Constraint: $\bot \leftarrow body.$
"If *body* is true, it invalidates the whole answer set"

Example:
$node(a).\ node(b).\ node(c).$
$edge(a,b).\ edge(b,c).\ edge(a,c).$
$edge(X,Y) \leftarrow edge(Y,X).$

Solving: Finding the minimal set of atoms satisfying the problem

```
node(a) node(c) node(b)
edge(a,b) edge(b,c) edge(a,c)
edge(b,a) edge(c,b) edge(c,a)
```

Answer Set Programming

Answer Set Programming (ASP): Declarative & logic programming

Rule: $head \leftarrow A_1, ..., A_n, \texttt{not } A_{n+1}, ..., \texttt{not } A_m.$
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Solving: Finding the minimal set of atoms satisfying the problem

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Solving: Finding the minimal set of atoms satisfying the problem

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edge(a,b) edge(b,c) edge(a,c)
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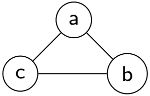

Solving: Finding the minimal set of atoms satisfying the problem

```
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```

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Rule: $\textit{head} \leftarrow A_1, \dots, A_n, \texttt{not}\ A_{n+1}, \dots, \texttt{not}\ A_m.$
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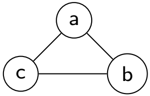
Fact: *head*.
"*head* is always true"

Constraint: $\bot \leftarrow \textit{body}.$
"If *body* is true, it invalidates the whole answer set"

Example:
node(*a*). *node*(*b*). *node*(*c*).
edge(*a*, *b*). *edge*(*b*, *c*). *edge*(*a*, *c*).
$\textit{edge}(X, Y) \leftarrow \textit{edge}(Y, X).$



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edge(a,b) edge(b,c) edge(a,c)
edge(b,a) edge(c,b) edge(c,a)
```

Answer Set Programming

Cardinalities: $min\ \{\ atom : enum\ \}\ max \leftarrow body.$

- Enumerates all atoms of the form *atom* according to the variables of *enum*
- Keep between *min* and *max* possibilities
- Creates as many answer sets as there are combinations

General method:

1) **Enumerate** of all candidate combinations using cardinalities

$color(red).\ color(green).\ color(blue).$

$1\ \{\ attrib(X, C) : color(C)\ \}\ 1 \leftarrow node(X).$

```
Answer set 1: attrib(b,red) attrib(c,red) attrib(a,red)
Answer set 2: attrib(b,red) attrib(c,red) attrib(a,blue)
Answer set 3: attrib(b,red) attrib(c,green) attrib(a,blue)
  ⋮ (27 answer sets)
```

2) **Filter out** the undesired candidates using constraints

$\bot \leftarrow attrib(X, C), attrib(Y, C), edge(X, Y).$

```
Answer set 1: attrib(b,green) attrib(c,blue) attrib(a,red)
Answer set 2: attrib(b,green) attrib(c,red) attrib(a,blue)
Answer set 3: attrib(b,blue) attrib(c,green) attrib(a,red)
  ⋮ (6 answer sets)
```

Answer Set Programming

Cardinalities: $min\ \{\ atom : enum\ \}\ max \leftarrow body.$

- Enumerates all atoms of the form *atom* according to the variables of *enum*
- Keep between *min* and *max* possibilities
- Creates as many answer sets as there are combinations

General method:

1) **Enumerate** of all candidate combinations using cardinalities

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$1\ \{\ attrib(X, C) : color(C)\ \}\ 1 \leftarrow node(X).$

```
Answer set 1: attrib(b,red) attrib(c,red) attrib(a,red)
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Answer set 3: attrib(b,red) attrib(c,green) attrib(a,blue)
   ⋮ (27 answer sets)
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```
Answer set 1: attrib(b,green) attrib(c,blue) attrib(a,red)
Answer set 2: attrib(b,green) attrib(c,red) attrib(a,blue)
Answer set 3: attrib(b,blue) attrib(c,green) attrib(a,red)
   ⋮ (6 answer sets)
```

Answer Set Programming

Cardinalities: $min\ \{\ atom : enum\ \}\ max \leftarrow body.$

- Enumerates all atoms of the form *atom* according to the variables of *enum*
- Keep between *min* and *max* possibilities
- Creates as many answer sets as there are combinations

General method:

1) **Enumerate** of all candidate combinations using cardinalities

$color(red).\ color(green).\ color(blue).$

$1\ \{\ attrib(X, C) : color(C)\ \}\ 1 \leftarrow node(X).$

```
Answer set 1: attrib(b,red) attrib(c,red) attrib(a,red)
Answer set 2: attrib(b,red) attrib(c,red) attrib(a,blue)
Answer set 3: attrib(b,red) attrib(c,green) attrib(a,blue)
   ⋮ (27 answer sets)
```

2) **Filter out** the undesired candidates using constraints

$\bot \leftarrow attrib(X, C), attrib(Y, C), edge(X, Y).$

```
Answer set 1: attrib(b,green) attrib(c,blue) attrib(a,red)
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   ⋮ (6 answer sets)
```

Conclusion on ASP for Model-checking

[Ben Abdallah, Folschette, Roux, Magnin, *BIBM'15*, 2015]
[Ben Abdallah, Folschette, Roux, Magnin, *AMB*, 2017]

- **General approach applied to dynamical analysis:**
  1) Describe the model with facts and rules (automata, actions, dynamics)
  2) Enumerate all states/all dynamics with cardinalities
  3) Filter out unwanted results
- Applications: **Stable states**, **Reachability** analysis, **Attractors** enumeration
- **Pros:** Very flexible (programming language) & Complexity handled by the solver
- **Cons:** Iterative approach (requires to cap the search) & Still computational

Models		**Stable states**	**Reachability analysis**		
Name	States	ASP	libddd[1]	GINsim[2]	ASP
egfr20	2^{64}	**0.017s**	1min 55s	2min 32s	**12s**
tcrsig40	2^{73}	**0.021s**	∞	∞	**4min 28s**

[1] LIP6/Move [Couvreur *et al.*, *Lecture Notes in Computer Science*, 2002]
[2] TAGC/IGC [Chaouiya, Naldi, Thieffry, *Methods in Molecular Biology*, 2012]

egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin *et al.*, 2009]

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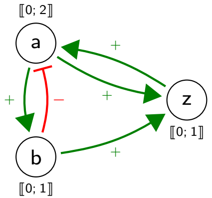
Static Analysis of Thomas Modeling

[Thomas, *Numerical Methods in the Study of Critical Phenomena*, 1981]

Conjectures of René Thomas:



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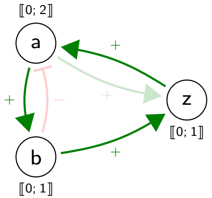
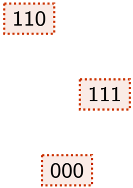
Conjectures of René Thomas:

- Multiple **stable states** ⇒ positive cycle in the graph





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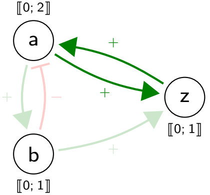

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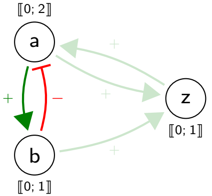
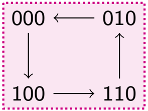
- Sustained oscillations (**complex attractor**) ⇒ negative cycle in the graph





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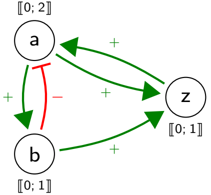

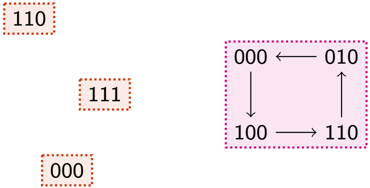

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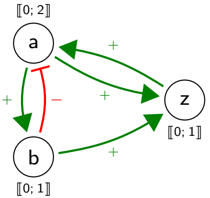

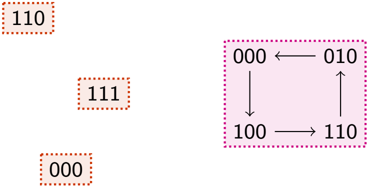

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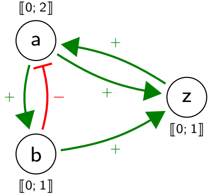

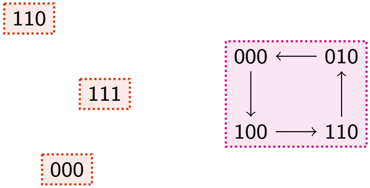

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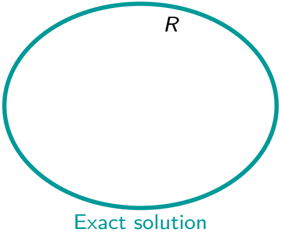
Over- and Under-approximations

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]

→ Directly checking R is hard (**exponential**)

→ Rather check **approximations** P and Q so that: $P \Rightarrow R \Rightarrow Q$
Computing P or Q is much simpler (roughly **polynomial**)



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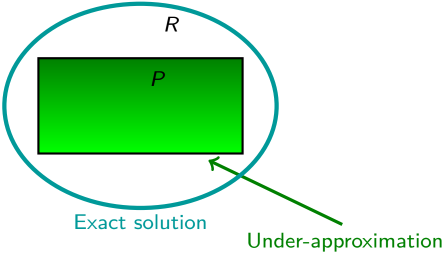

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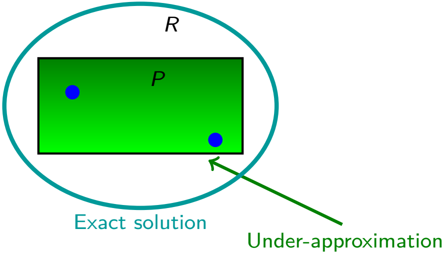

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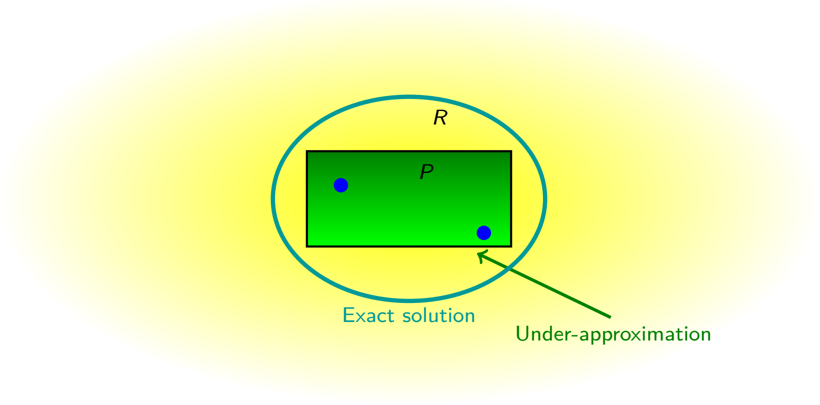

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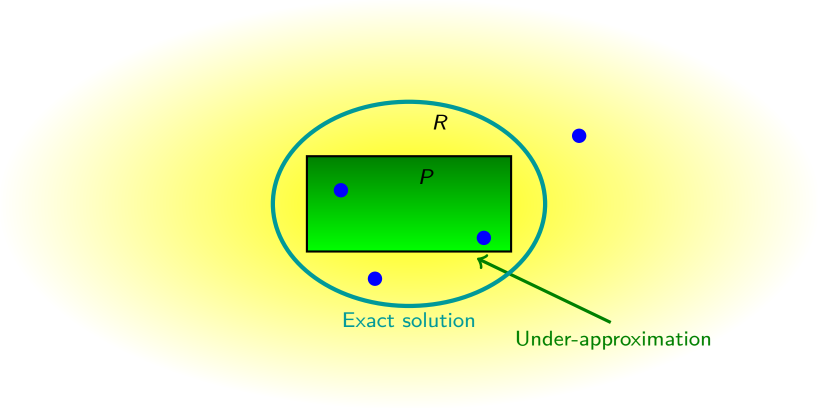
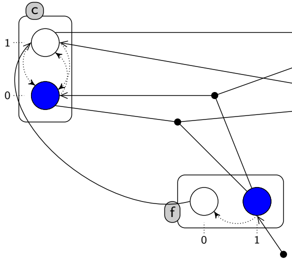
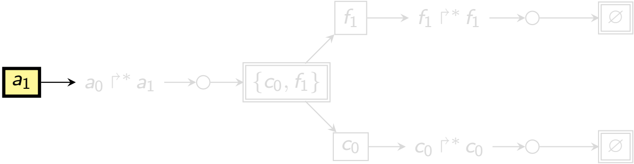


Abstract Interpretation (Under-approximation)

[Folschette *et al.*, *Theoretical Computer Science*, 2015b]



- No cycle
- No conflict
- All leaves are $\boxed{\varnothing}$



OK! :-) scenario $= \{c_0, f_1\} \rightarrow a_0 \upharpoonright a_1$

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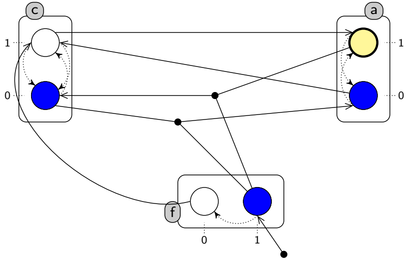

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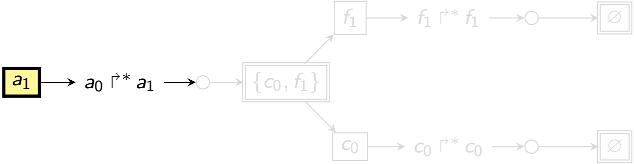

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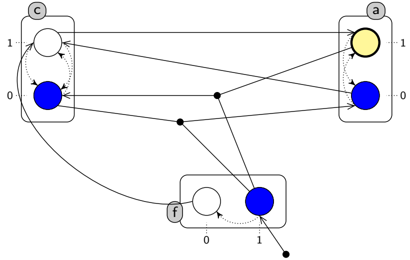

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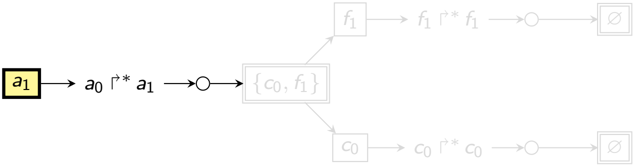

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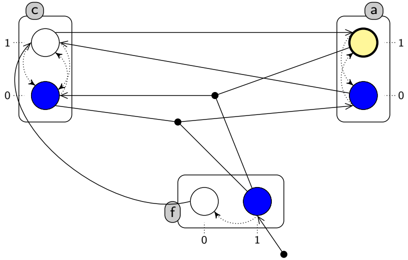

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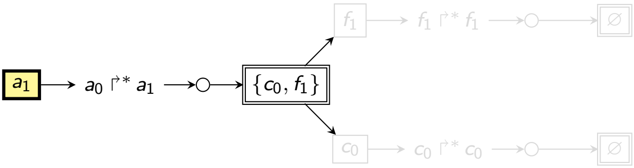

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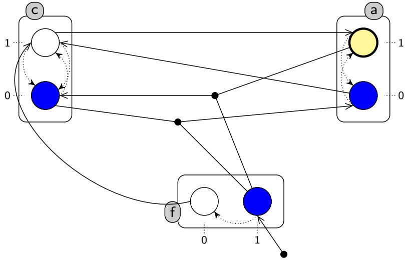

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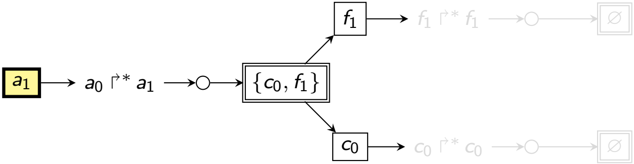

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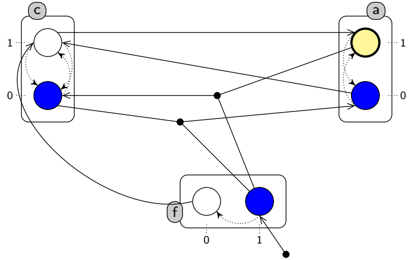

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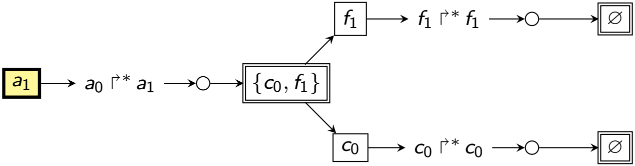

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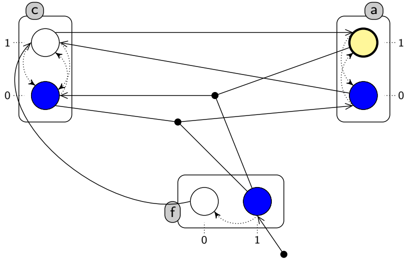

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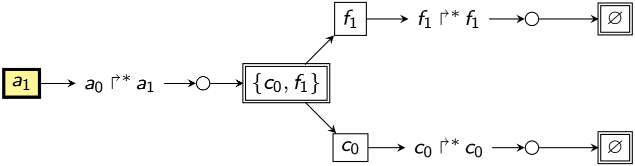

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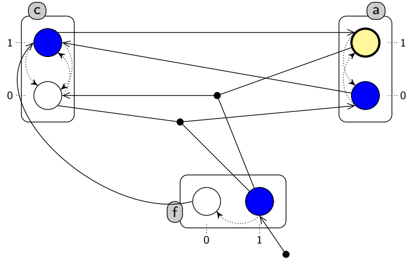

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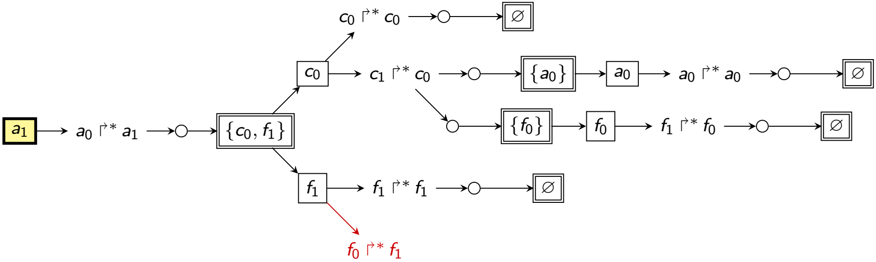

Cannot conclude... :-|

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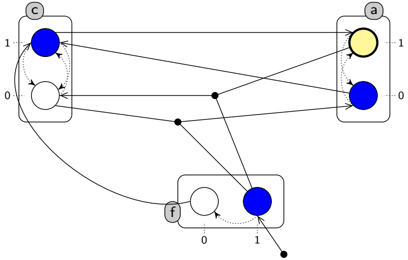

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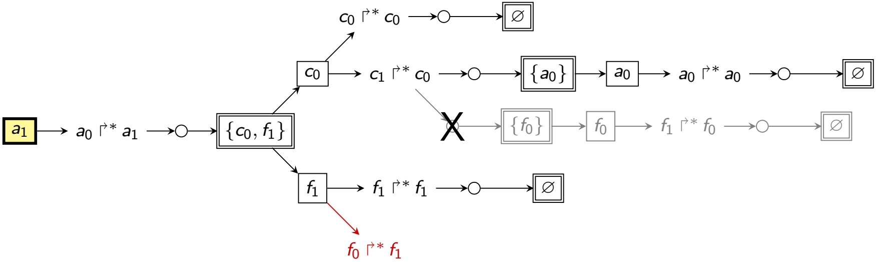

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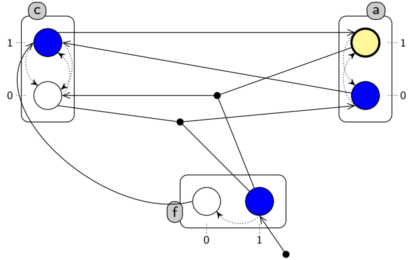

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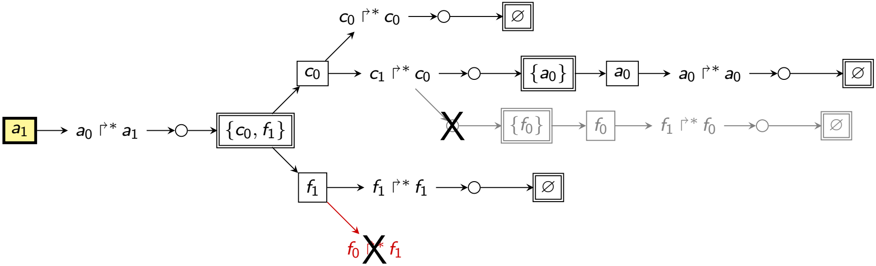

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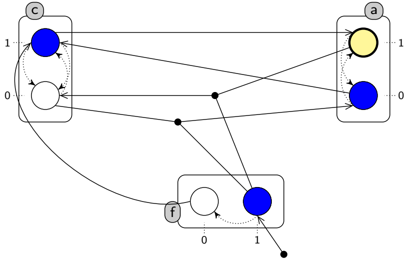

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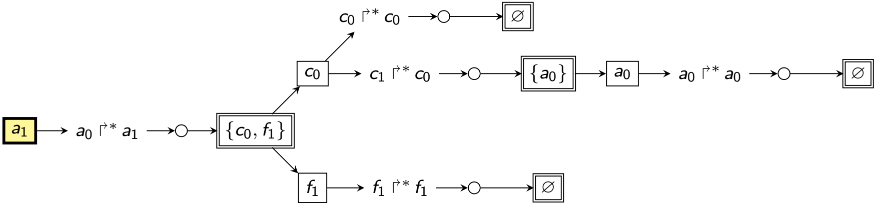

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Implementation of the Abstract Interpretation

Complexity:

- Computation of the local causality graph:
  - Polynomial in the number of automata
  - Exponential in the number of local states of each automata (usually very low, max. 4)
- Analysis of the graph (sufficient condition):
  - Polynomial in the size of the abstract graph
- Enumeration of the subsets of solutions (if needed):
  - Exponential in the size of the abstract graph

→ Very efficient on biological networks: **many components with few local states**

Model	Automata	Actions	States	libddd[1]	GINsim[2]	PINT[3]
egfr20	35	670	2^{64}		<1s	**0.02s**
tcrsig40	54	301	2^{73}		∞	**0.02s**
tcrsig94	133	1124	2^{194}	[>1min – ∞]		**0.03s**
egfr104	193	2356	2^{320}	[>1min – ∞]		**0.16s**

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egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin *et al.*, 2009]
egfr104 : Epithelial Growth Factor Receptor (104 components) [Samaga *et al.*, 2009]
tcrsig40 : T-Cell Receptor (40 components) [Klamt *et al.*, 2006]
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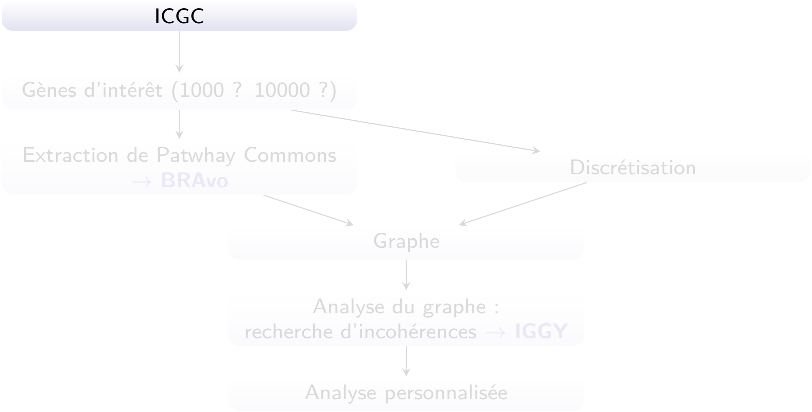
Ongoing Work

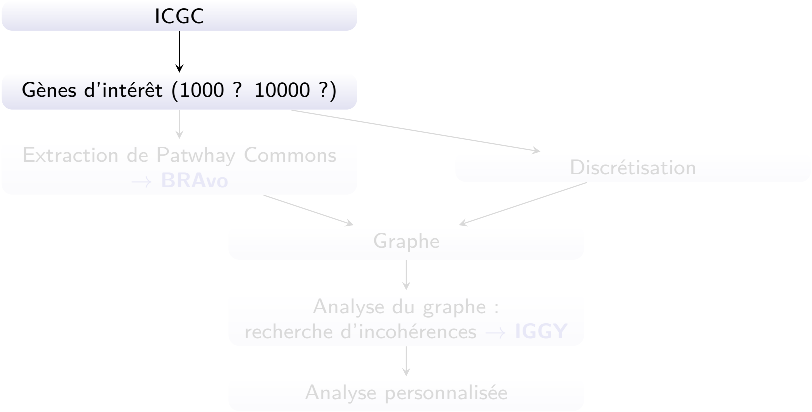
TGF-β Pathways Project

« Modélisation des réseaux d'influence du TGF-β lors de la progression tumorale pour l'identification de cibles thérapeutiques »



TGF-β Pathways Project

« Modélisation des réseaux d'influence du TGF-β lors de la progression tumorale pour l'identification de cibles thérapeutiques »



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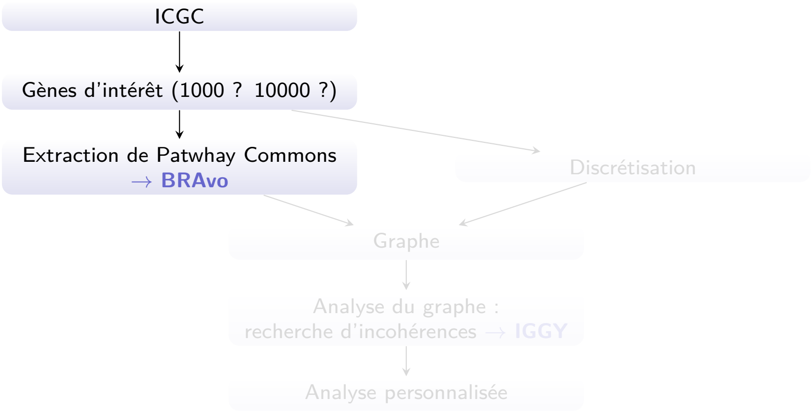

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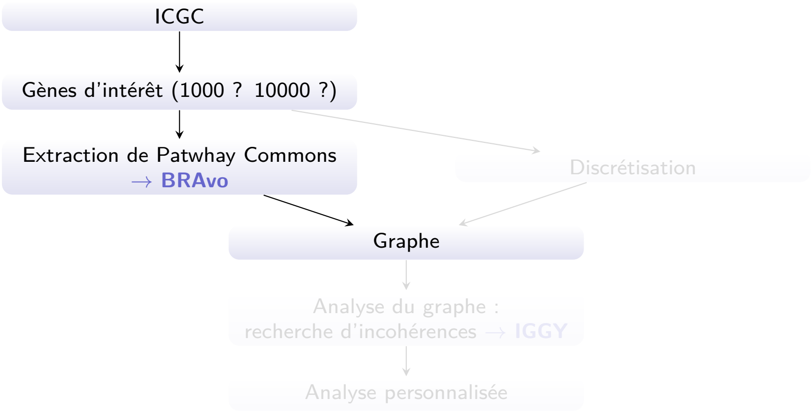

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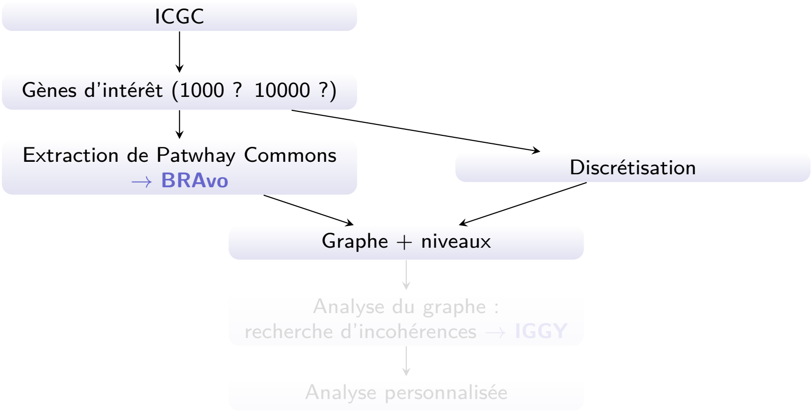

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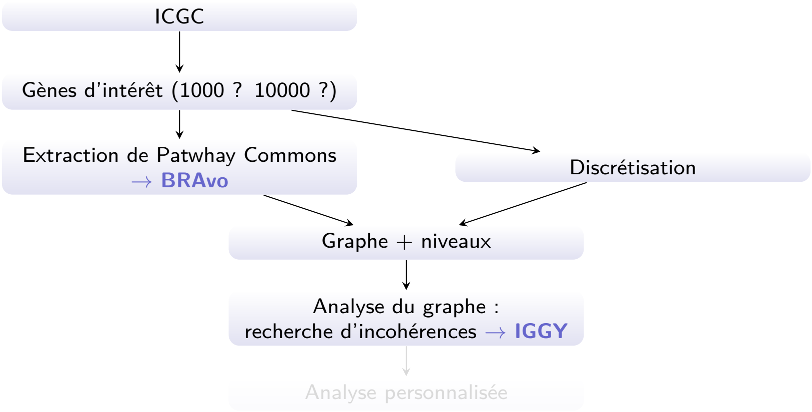

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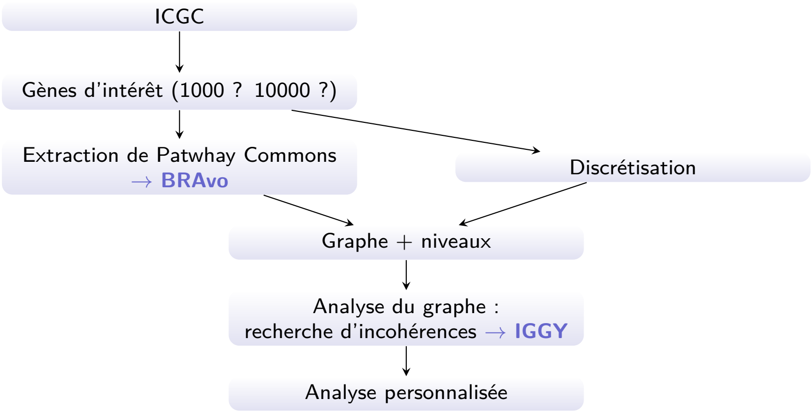
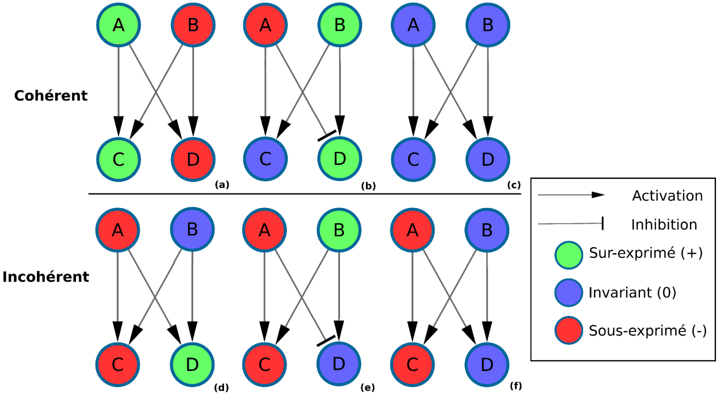


Inconsistency Search With Coloring

- Some **observations** from experiments give an initial coloring
- **Propagate** the coloring to neighbor nodes
- Minimize **inconsistencies**
- Minimize the **repairs** to fix the inconsistencies



Summary

Frameworks: modeling biological processes

- **Thomas modeling** (historically widespread)
- **Asynchronous Automata Networks** (generalization)
- **Hybrid Thomas modeling** (generalization)

Model completion: inferring missing information on the model

- **Hybrid Hoare logic** (parameters/logical gates on Hybrid Thomas modeling)
- **Continuous transitions** (logical thresholds from expression profiles)

Dynamic analyses: explore the dynamics of a model

- **μ-calculus** & **Answer Set Programming** (exhaustive)
- **Abstract interpretation** (approximations)

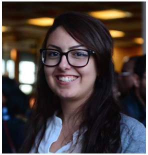
TGF-β pathways project: my work here as a postdoc

- Extract and build a big graph from databases
- Search for inconsistencies in cancerous types

Collaborations

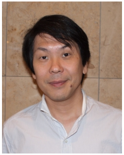
Olivier ROUX

Morgan MAGNIN



Emna BEN ABDALLAH

Tony RIBEIRO



Katsumi INOUE

Martin LANGE

Loïc PAULEVÉ

Jean-Paul COMET

Jonathan BEHAEGEL

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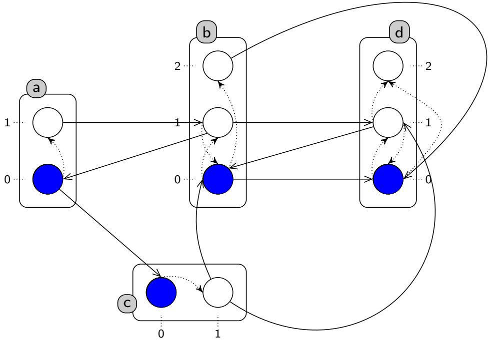
- Jonathan Behaegel, Jean-Paul Comet, **Maxime Folschette**. Constraint Identification Using Modified Hoare Logic on Hybrid Models of Gene Networks, *International Symposium on Temporal Representation and Reasoning (TIME)*. October 2017.

The Reachability Problem

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]

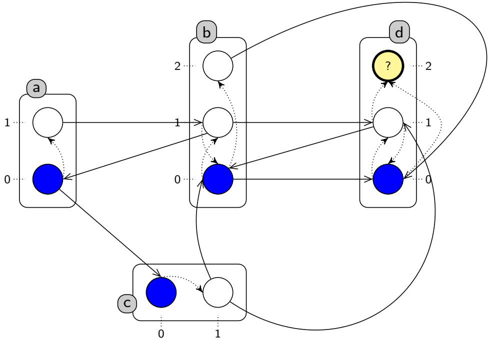


- Initial state

$\langle a_1, b_0, c_0, d_0 \rangle$

The Reachability Problem

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]



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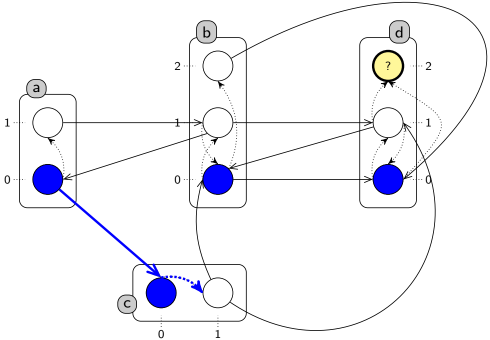

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$\underline{a_0 \rightarrow c_0 \upharpoonright c_1} :: b_0 \rightarrow d_0 \upharpoonright d_1 :: c_1 \rightarrow b_0 \upharpoonright b_1 :: b_1 \rightarrow d_1 \upharpoonright d_2$

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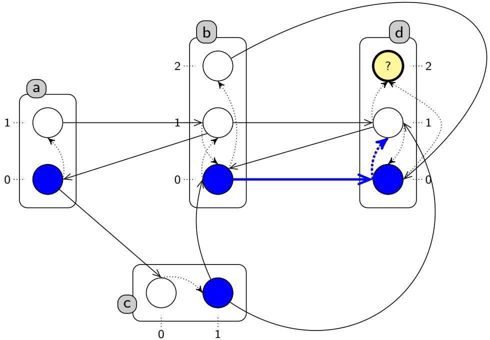

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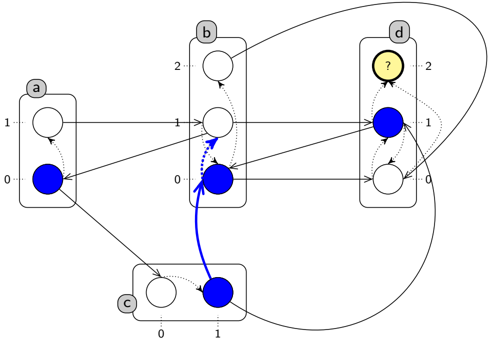

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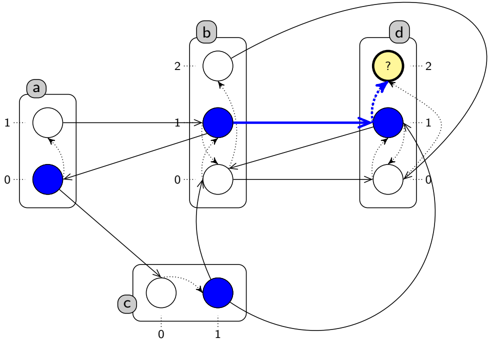

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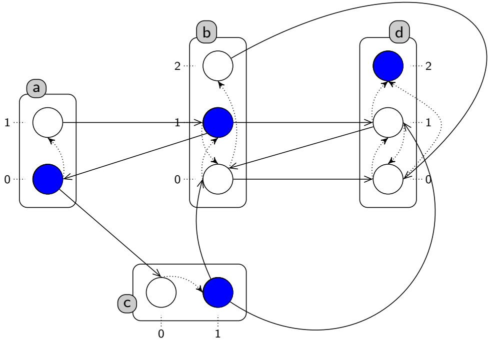

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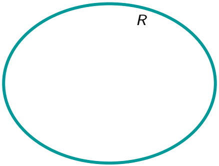
Over- and Under-approximations

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]

→ Directly checking R is hard (**exponential**)

→ Rather check **approximations** P and Q so that: $P \Rightarrow R \Rightarrow Q$
Computing P or Q is much simpler (roughly **polynomial**)



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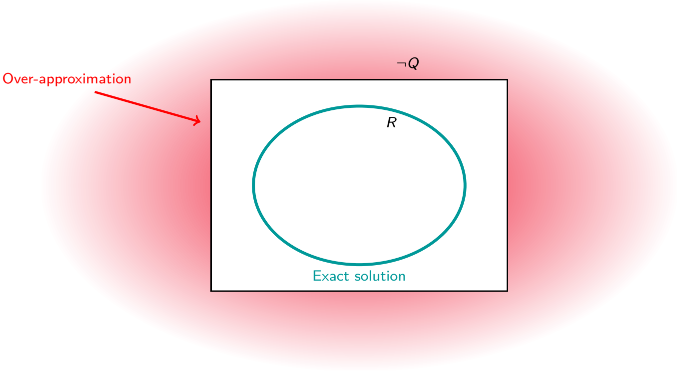

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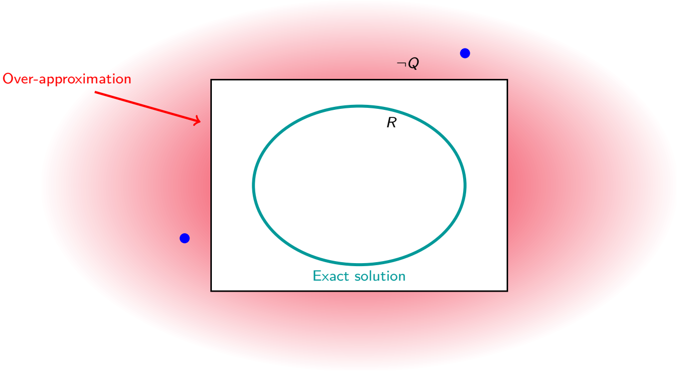

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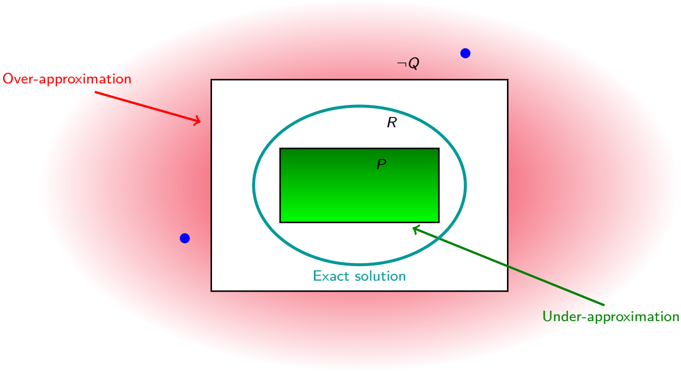

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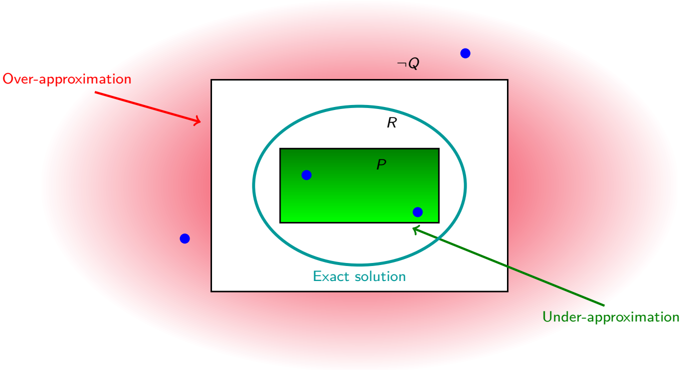

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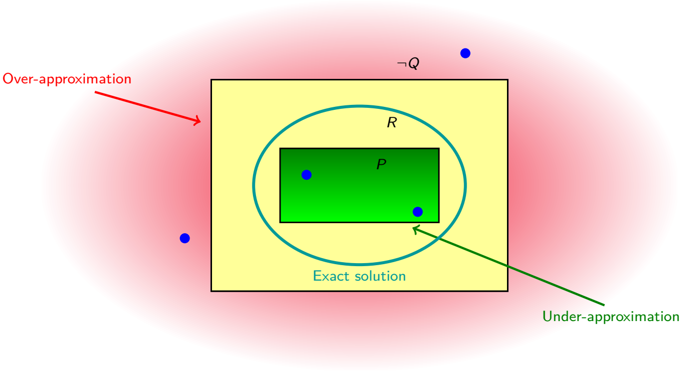

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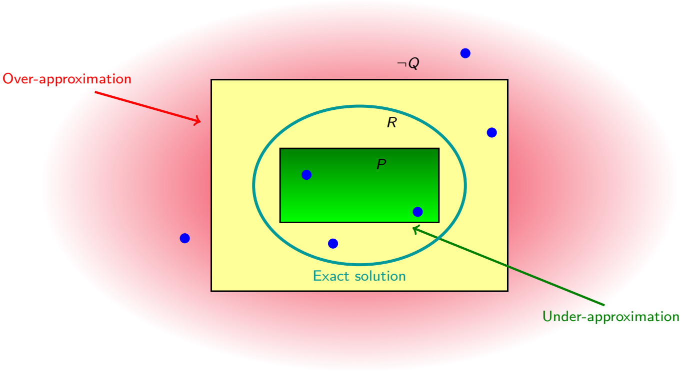
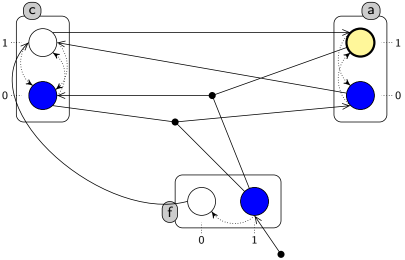


Abstract Interpretation (Under-approximation)

[Folschette *et al.*, *Theoretical Computer Science*, 2015b]



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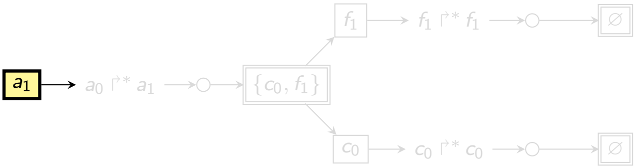

$$\{c_0, f_1\} \rightarrow a_0 \upharpoonright a_1$$

Abstract Interpretation (Under-approximation)

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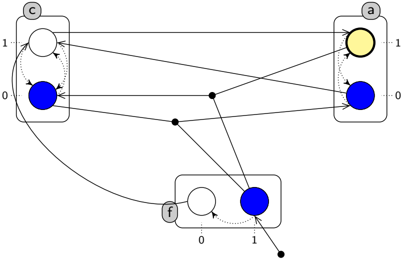

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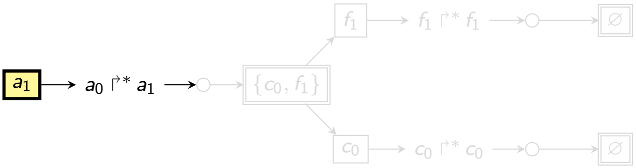

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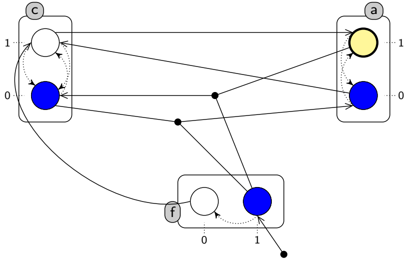

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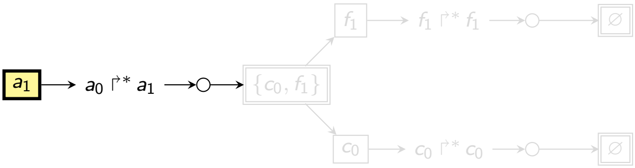

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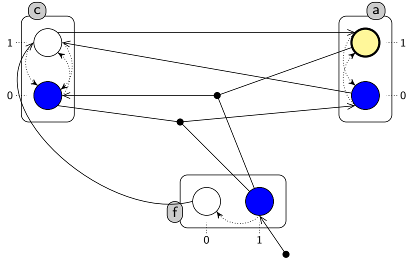

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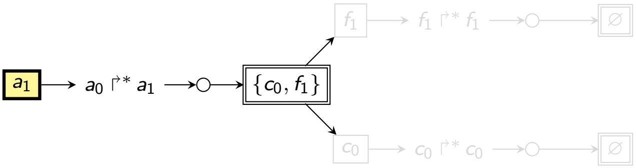

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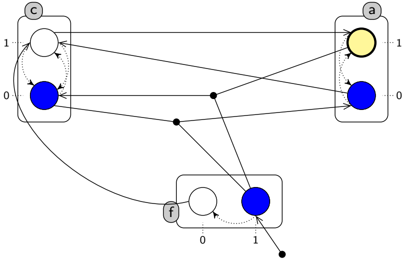

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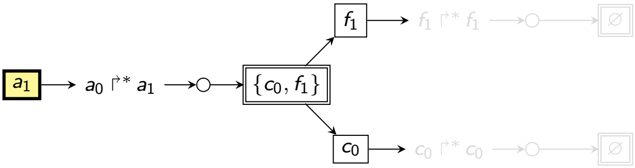

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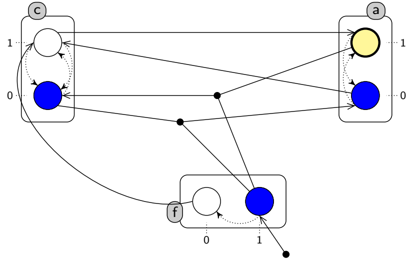

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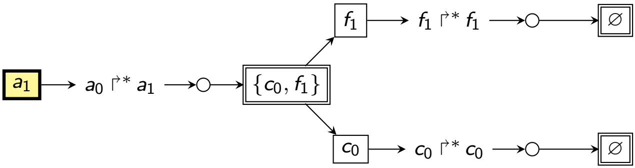

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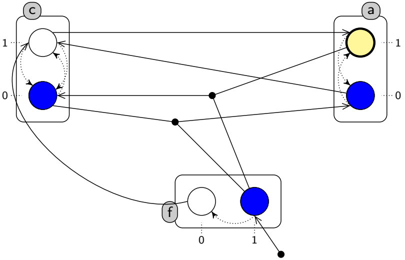

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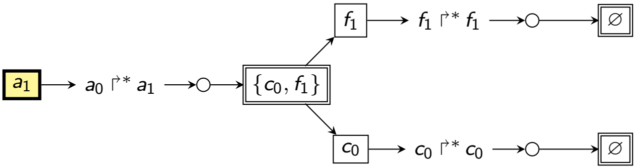

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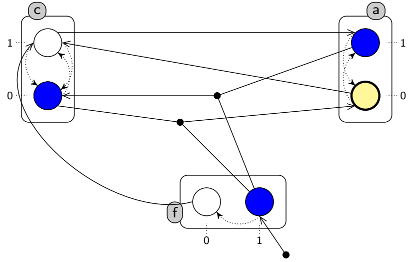

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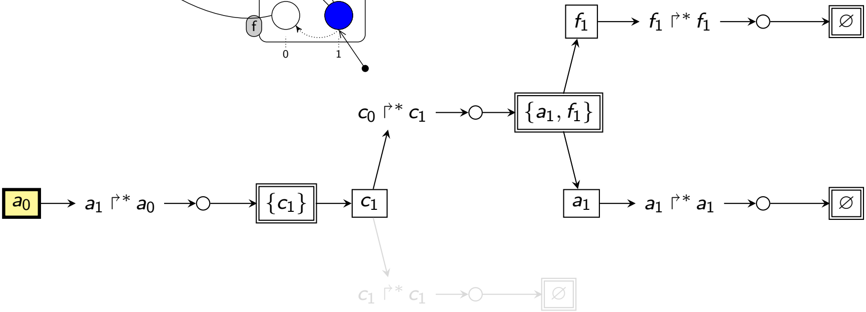

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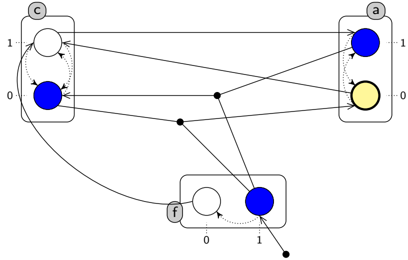

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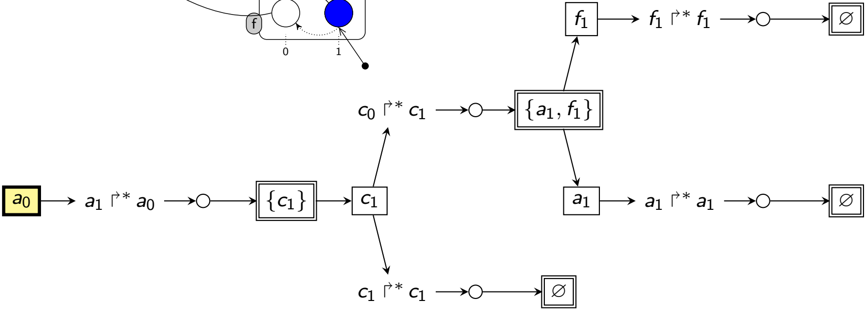
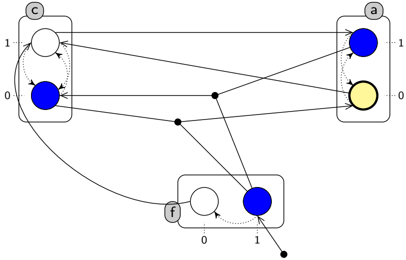


$$\{a_1, f_1\} \rightarrow c_0 \Rsh c_1 \;::\; \{c_1\} \rightarrow a_1 \Rsh a_0$$

Abstract Interpretation (Under-approximation)

[Folschette *et al.*, *Theoretical Computer Science*, 2015b]



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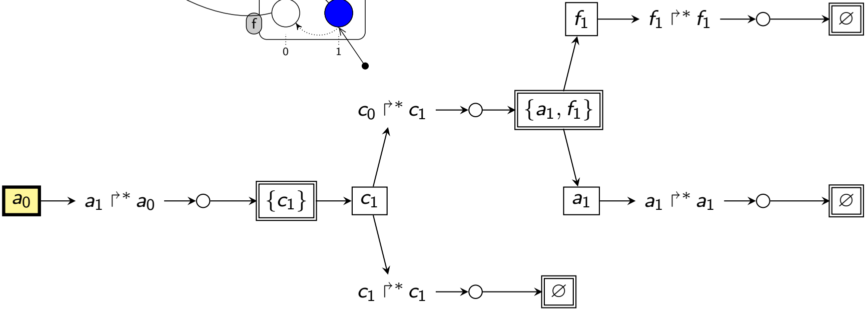

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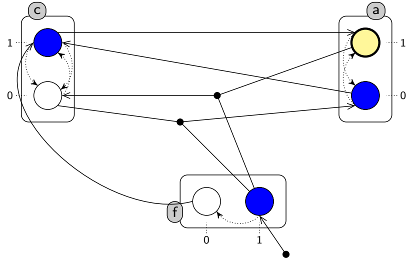

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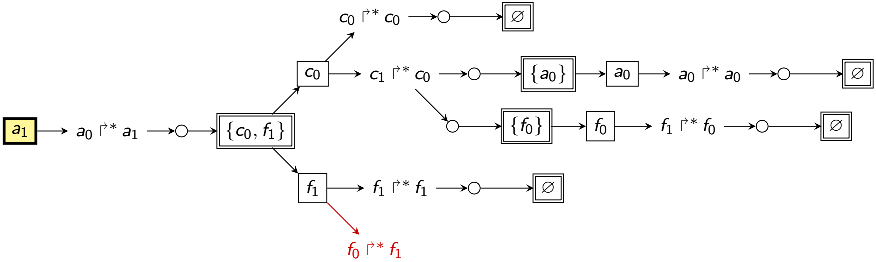

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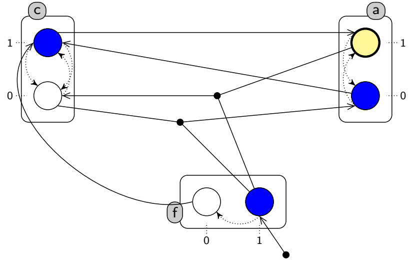

- No conflict
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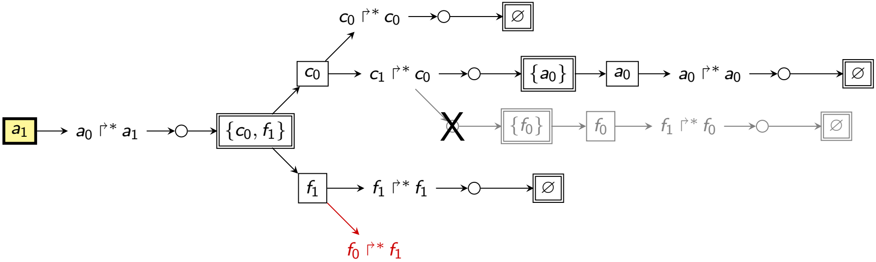

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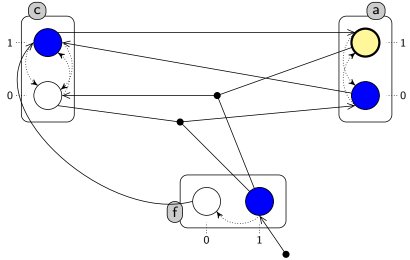

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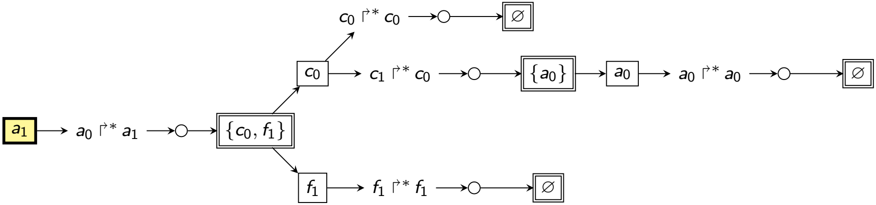

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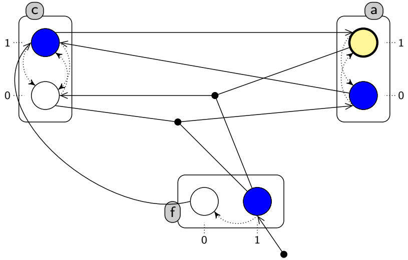

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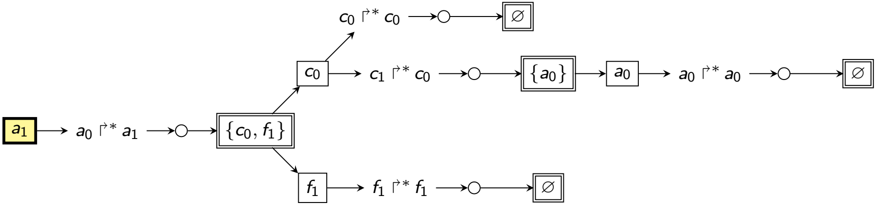

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Implementation of the Abstract Interpretation

Complexity:

- Computation of the local causality graph:
  - Polynomial in the number of automata
  - Exponential in the number of local states of each automata (usually very low, max. 4)
- Analysis of the graph (sufficient condition):
  - Polynomial in the size of the abstract graph
- Enumeration of the subsets of solutions (if needed):
  - Exponential in the size of the abstract graph

→ Very efficient on biological networks: **many components with few local states**

Model	Automata	Actions	States	libddd[1]	GINsim[2]	PINT[3]
egfr20	35	670	2^{64}		<1s	**0.02s**
tcrsig40	54	301	2^{73}		∞	**0.02s**
tcrsig94	133	1124	2^{194}	[>1min − ∞]		**0.03s**
egfr104	193	2356	2^{320}	[>1min − ∞]		**0.16s**

[1] LIP6/Move [Couvreur *et al.*, *Lecture Notes in Computer Science*, 2002]
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egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin *et al.*, 2009]
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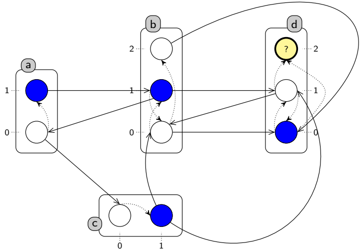
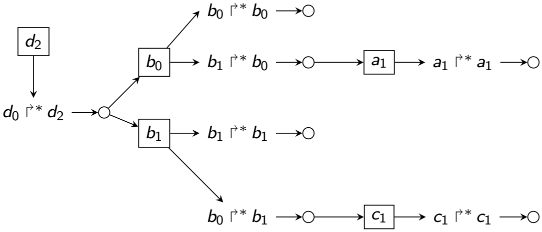
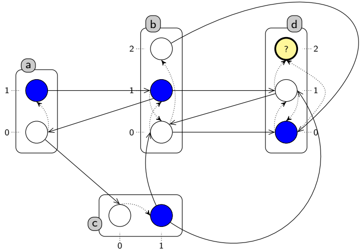




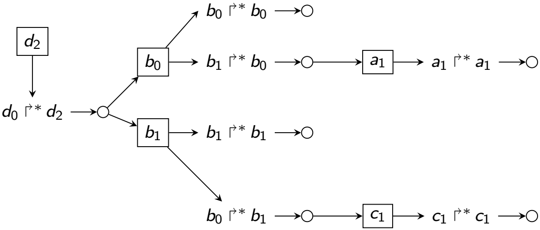
d_2	Required process
$d_0 \Rsh^* d_2$	Objective
○	Solution to an objective

Under-approximation



Sufficient condition:

- no cycle
- each objective has a solution



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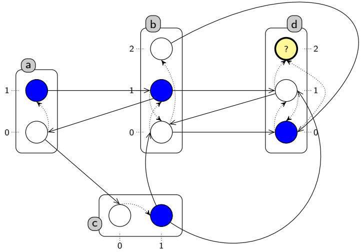

Under-approximation

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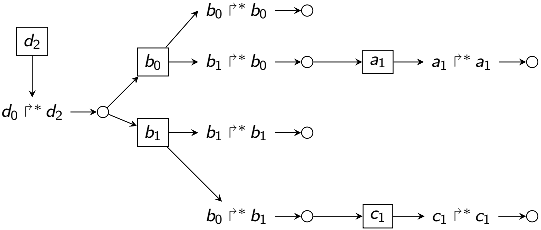
P is **true** $\Rightarrow$ R is **true**



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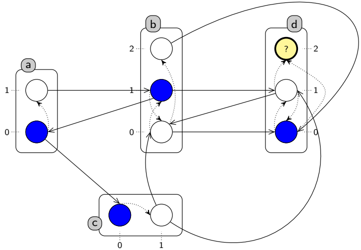

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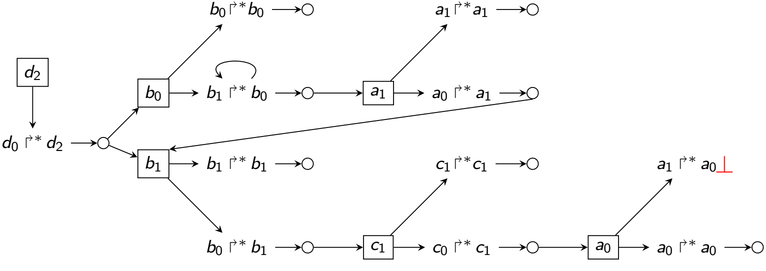

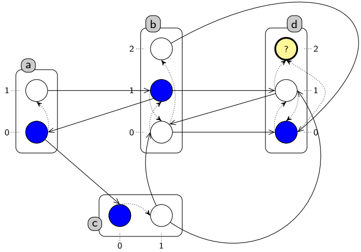

Under-approximation

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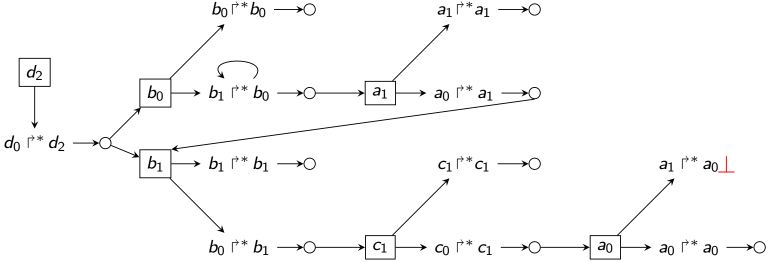
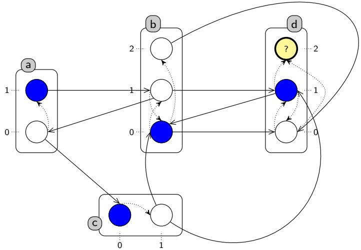
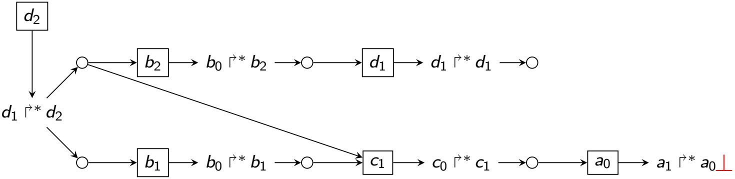
P is **false** ⇒ **Inconclusive**



Over-approximation



Necessary condition:



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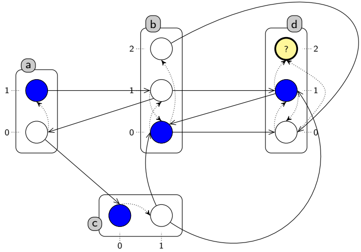
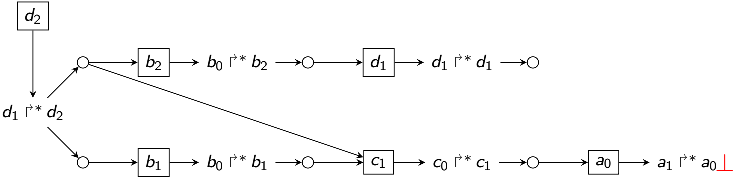


Necessary condition:

There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
- process → follow **all** objectives



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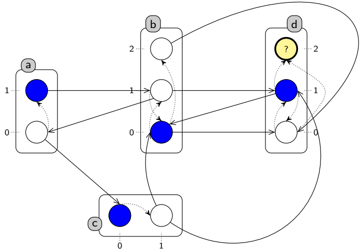

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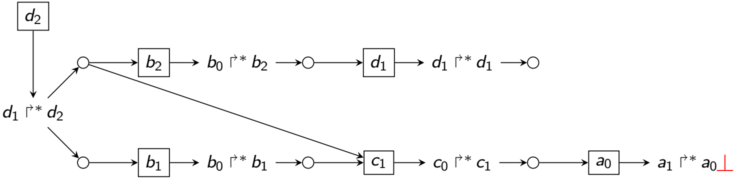

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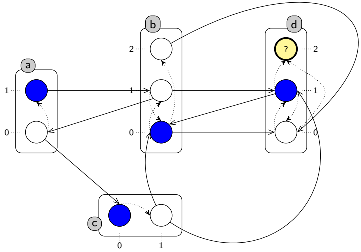

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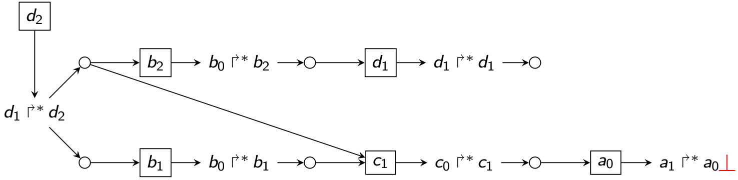
Q is **false** ⇒ R is **false**



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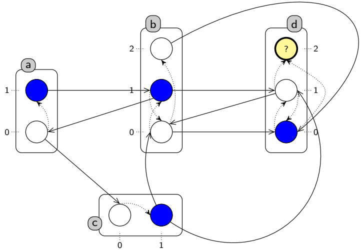

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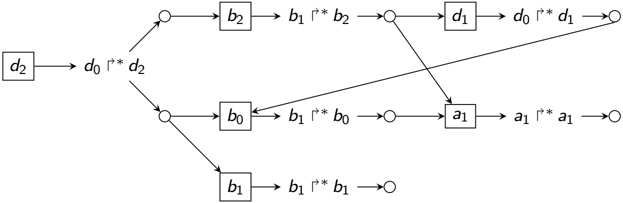

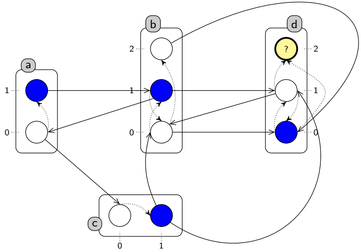

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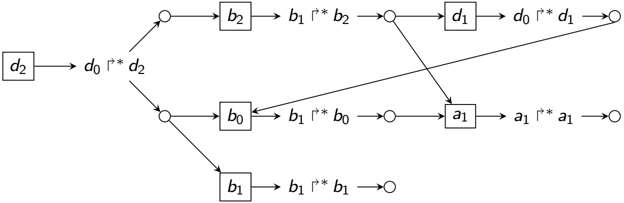
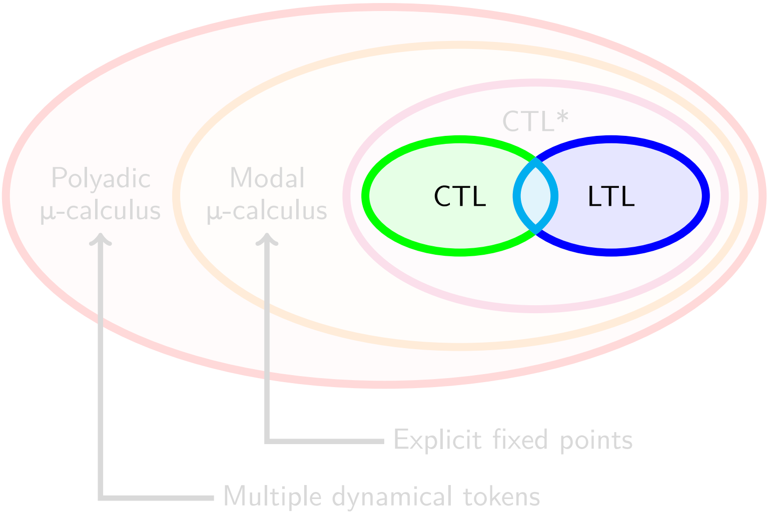
R is true ⇒ Inconclusive



The Polyadic μ-caculus



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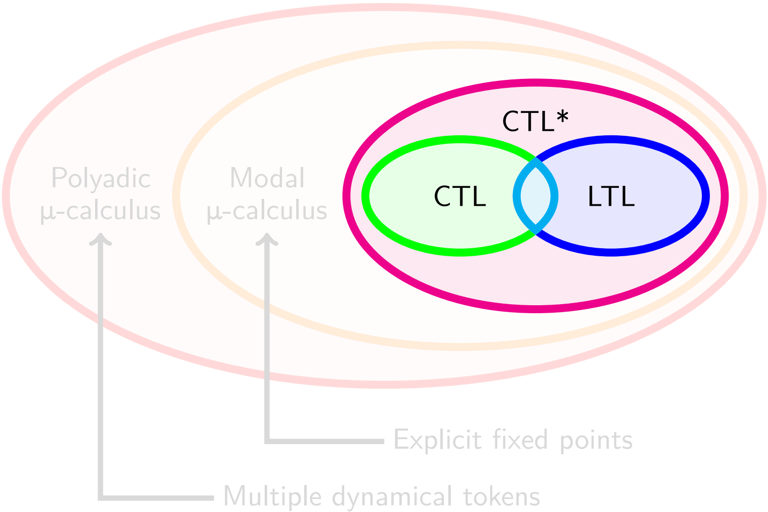

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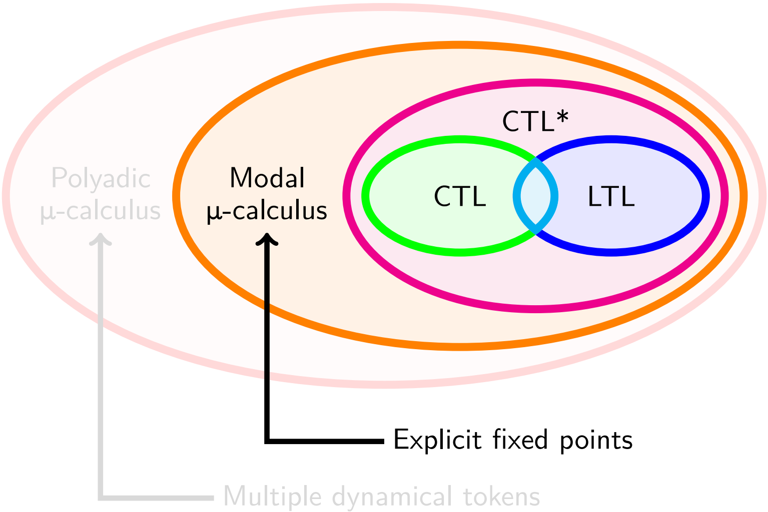

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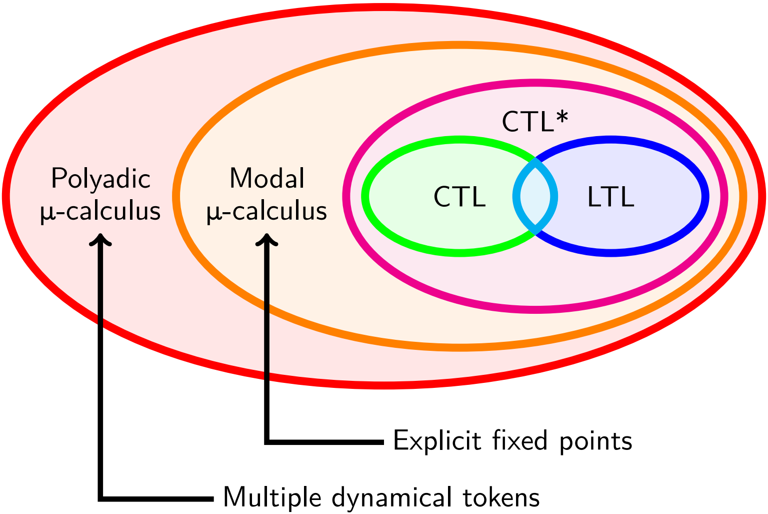

Modal and Polyadic μ-calculus

[Andersen, Technical report, 1994]

LTL: Implicit fixed point of the "Until" operator
$p\ U\ q \equiv$ "Either q, or p and the next state also verifies $p\ U\ q$"

(Modal) μ-calculus makes such fixed points explicit

$$\varphi = p \mid \neg\varphi \mid \varphi \wedge \varphi \mid \varphi \vee \varphi \mid \Diamond\varphi \mid \Box\varphi \mid \mu X.\varphi \mid \nu X.\varphi \mid X$$

- Basic property: p ("p is verified in this node")
- Modal operators: $\Box$ ("for all successors"), $\Diamond$ ("there exists a successor")
- Fixed points: μ (least fixed point), ν (greatest fixed point)

Polyadic (modal) μ-calculus allows to manipulate several tokens in parallel

$$\varphi = p_i \mid i \leftarrow j \mid i = j \mid \neg\varphi \mid \varphi \wedge \varphi \mid \varphi \vee \varphi \mid \Diamond_i\varphi \mid \Box_i\varphi \mid \mu X.\varphi \mid \nu X.\varphi \mid X$$

Token manipulations:
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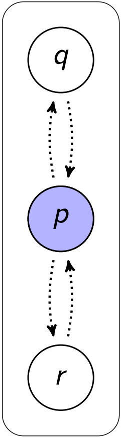

No tokens: only one evolution is studied

Atomic property (p, q, r)

$[\![p]\!] = \{p\}$

$[\![q \vee r]\!] = \{q; r\}$

Possible future ("may")

$[\![\Diamond\ q]\!] = \{p\}$

Necessary future ("must")

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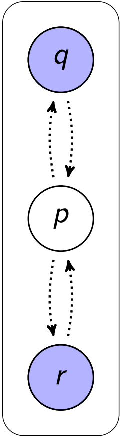

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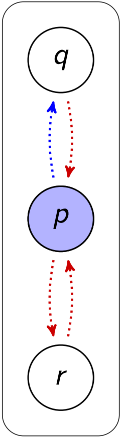

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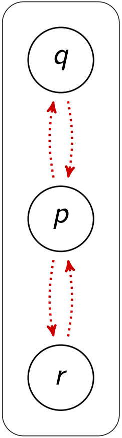

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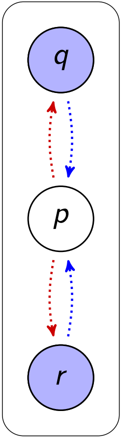

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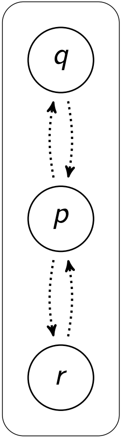
Examples with Polyadic µ-calculus



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Possible future ("may")

$[\![\Diamond_1\ q]\!] = \{(p, p); (p, q); (p, r)\}$

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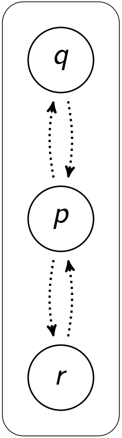

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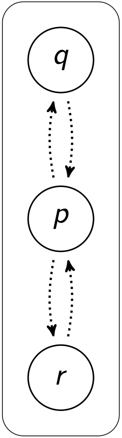

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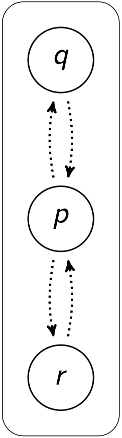

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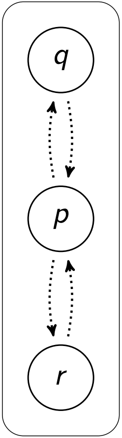

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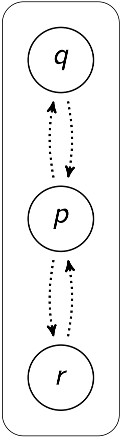

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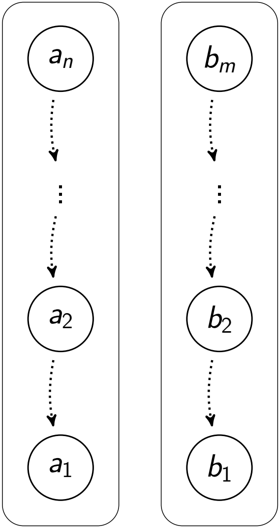

Least fixed point (μ)

$\phi = \mu X.(\Box_1 \bot \wedge \Box_2 \bot) \vee \Diamond_1 \Diamond_2 X$

Iterations:

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$[\![\phi]\!]_1 = \{(a_1, b_1)\}$
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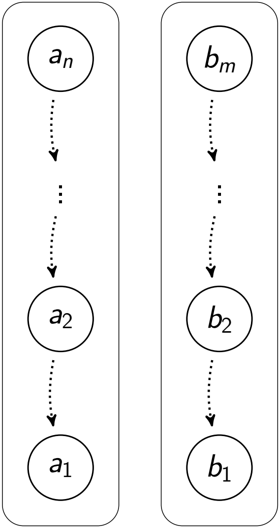
Generalization:

$[\![\phi]\!] = \{(a_i, b_i) \mid i \in [1; \min(m, n)]\}$

Idea: use one (or n) token per automata

Examples with Polyadic µ-calculus



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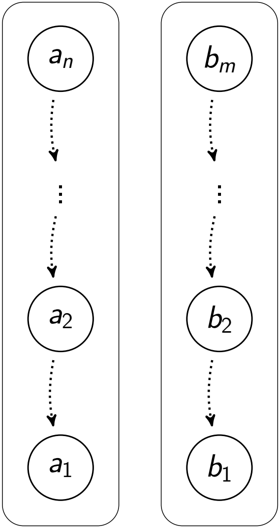

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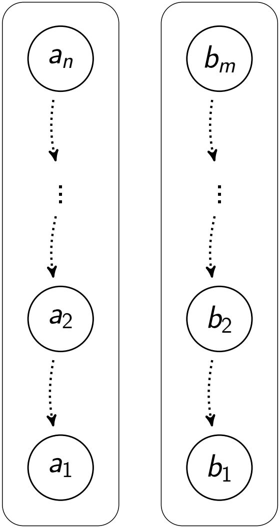

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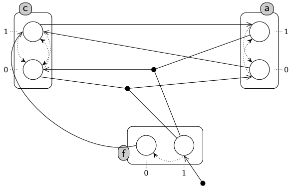
Applications of the Polyadic μ-calculus



Objective: Unify formulas for many dynamical problems

Not always possible with classical temporal logics (LTL, CTL, CTL*):

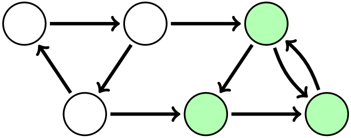
1) From the initial state $(a, b, z) = (0, 0, 0)$, is it possible to reach $z = 2$?
   $(a = 0 \wedge b = 0 \wedge z = 0) \Rightarrow \mathrm{EF}(z = 2)$

2) Does $(0, 0, 0)$ belong to an attractor?
   $(a = 0 \wedge b = 0 \wedge z = 0) \Rightarrow \mathrm{N}\bot \vee \mathrm{AG}(\mathrm{EF}(a = 0 \wedge b = 0 \wedge z = 0))$

3) What is the set of attractors of the model?
   ??? — Requires a quantification on the set of all states

Idea: Use polyadic μ-calculus with one token per automata

Search for Attractors with Polyadic μ-calculus



$= $ belongs to an attractor

$$\varphi_{\text{att}} = \{\boldsymbol{y} \leftarrow \boldsymbol{x}\}\nu W.\underbrace{\underbrace{(\mu Z.\,(\boldsymbol{x} = \boldsymbol{y}) \vee (\Diamond_{\boldsymbol{x}} Z))}_{\varphi_{\text{reach}}} \wedge (\Box_{\boldsymbol{x}} W)}_{\varphi_{\text{explore}}}$$

- $[\![\varphi_{\text{reach}}]\!] = \{(s; t) \mid s \rightarrow^* t\}$
  $\varphi_{\text{reach}} \equiv$ "There exists a path from $\boldsymbol{x}$ to $\boldsymbol{y}$"
- $[\![\varphi_{\text{explore}}]\!] = \{(s; t) \mid \forall s', s \rightarrow^* s' \Rightarrow s' \rightarrow^* t\}$
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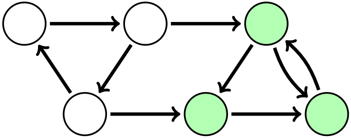

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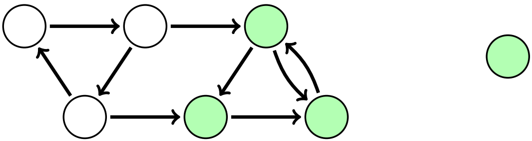

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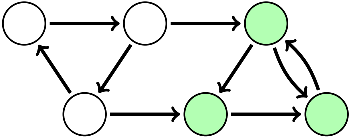

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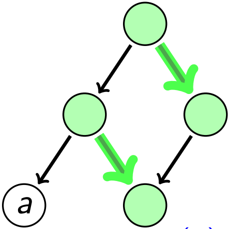
Search for Disruptions with Polyadic µ-calculus




= disruption regarding a

$$\varphi_{\text{disr}}(\boldsymbol{a}) = \overbrace{\Big(\mu W.(\boldsymbol{x} = \boldsymbol{a}) \vee (\Diamond_{\boldsymbol{x}} W)\Big)}^{\varphi_{\text{reach}}} \wedge$$
$$\Diamond_{\boldsymbol{x}}\{\boldsymbol{x} \leftarrow \boldsymbol{y}\} \underbrace{\Big(\nu Z.\neg(\boldsymbol{y} = \boldsymbol{a}) \wedge (\Box_{\boldsymbol{y}} Z)\Big)}_{\varphi_{\text{noreach}}}$$

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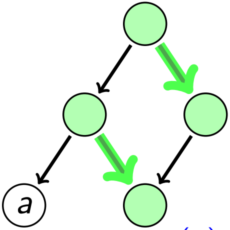
Search for Disruptions with Polyadic μ-calculus



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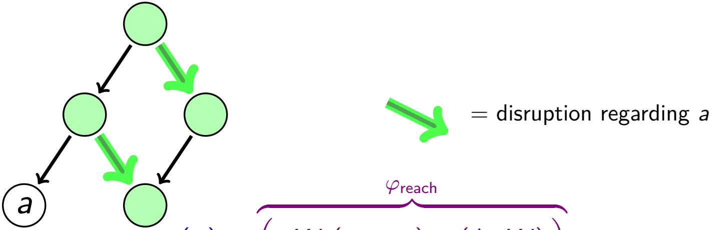

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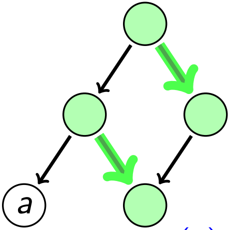

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Bisimulation with Polyadic µ-calculus

Generic **bisimulation** between two models:

$$\varphi_{\text{bisim}} = \nu X.(\bigwedge_{p \in P} p_1 \Leftrightarrow p_2) \wedge (\Box_1 \Diamond_2 X \wedge \Box_2 \Diamond_1 X)$$

Bisimulation only on two sets of **observable components** O and O':

$$\varphi_{\text{bisim-obs}} = \nu X.(\bigwedge_{p \in P} \bigwedge_{(i;j) \in C} p_i \Leftrightarrow p_j) \wedge (\Box^*_{\overline{O}} \Box_O \Diamond^*_{\overline{O'}} \Diamond_{O'} X)$$

where:

$$\Box_S \Psi = \bigwedge_{i \in S} \Box_i \Psi \qquad \Diamond_S \Psi = \bigvee_{i \in S} \Diamond_i \Psi$$

$$\Box^*_S \Psi = \nu Y.\Psi \wedge \Box_S Y \qquad \Diamond^*_S \Psi = \mu Y.\Psi \vee \Diamond_S \Psi$$

Conclusion on Polyadic μ-calculus

Properties expressed so far:

- Enumeration of attractors
- Enumeration of disruptions
- Bisimulation between two models (regarding a set of observables)
- Highlighting Zeno behaviors

Aim: Unification of properties without quantifiers

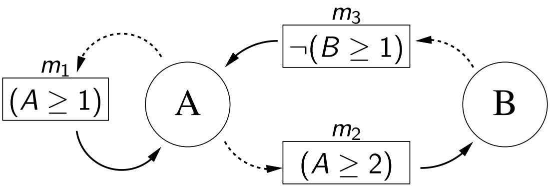
Complexity: Exponential (equivalent to building the state graph)

Outlooks:

- New formulas
- Implementation
- Generate μ-calculus formulas? (More readable interface)

Hybrid Thomas Modeling

[Cornillon *et al.*, *Modelling Complex Biological Systems in the Context of Genomics*, 2016]

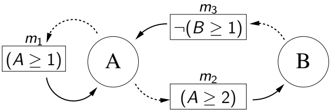


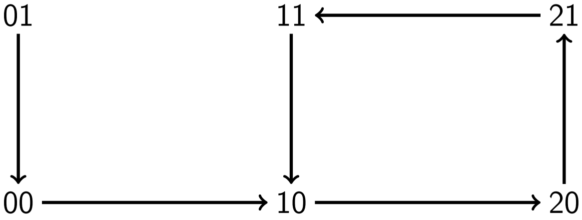
lacI repressor regulation of the lactose operon in E. Coli

$\mathrm{A} = \mathrm{NRI}$ protein $+$ glnG gene $+$ glnA promoter
$\mathrm{B} = \mathrm{lacI}$ gene repressor $+$ glnK promoter

$m_1 = \mathrm{glnA}$ promoter is regulated by phosphorylated NRI
$m_2 = \mathrm{glnA}$ promoter is also regulated by lacI
$m_3 = \mathrm{lacI}$ gene repressor is regulated by NRIp

Hybrid Thomas Modeling





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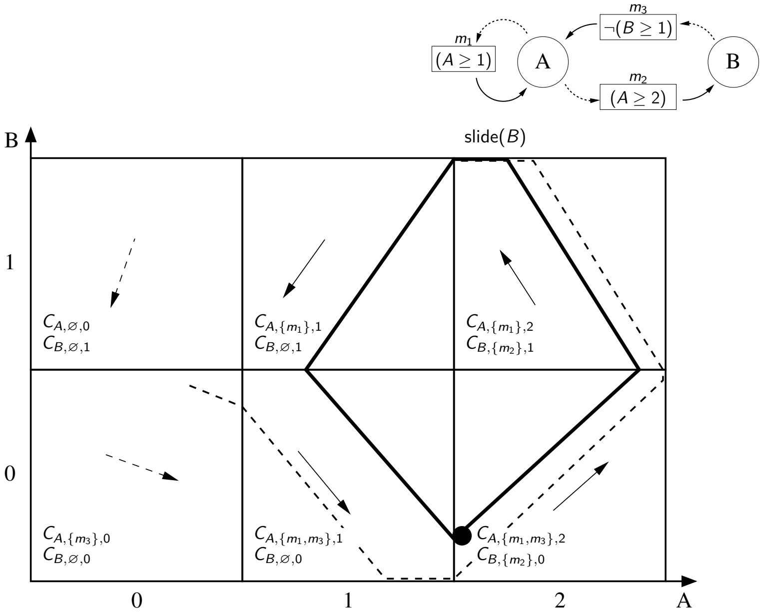
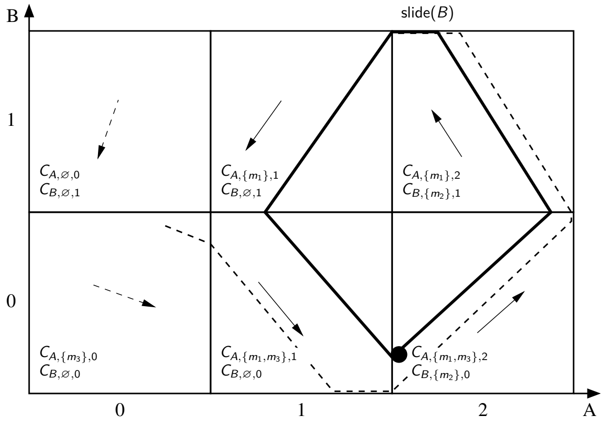


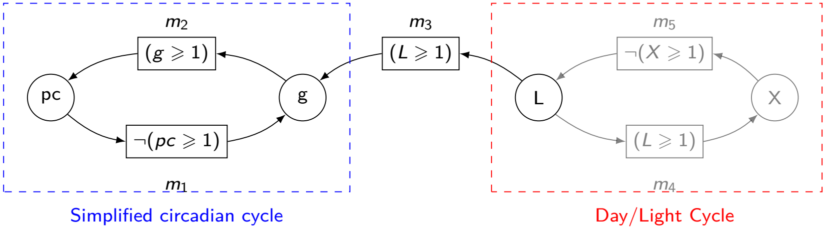
Hybrid Hoare Logic to Infer Parameters

$$\left\{\begin{matrix} D_4 \\ H_4 \end{matrix}\right\} \begin{pmatrix} T_4 \\ \top \\ B+ \end{pmatrix} ; \begin{pmatrix} T_3 \\ \text{slide}^{+}(B) \\ A- \end{pmatrix} ; \begin{pmatrix} T_2 \\ \top \\ B- \end{pmatrix} ; \begin{pmatrix} T_1 \\ \top \\ A+ \end{pmatrix} \left\{\begin{matrix} D_0 \equiv (\eta_A = 2 \wedge \eta_B = 0) \\ H_0 \equiv \top \end{matrix}\right\}$$



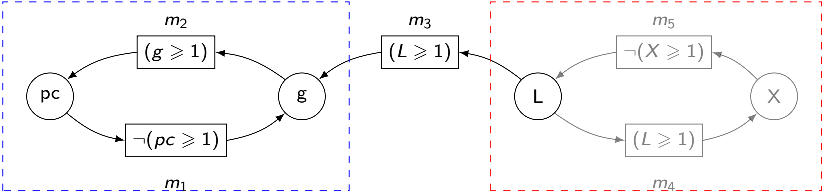
$$
\begin{aligned}
H_F \equiv\ & \big(\neg(C_{B,\varnothing,0} > 0) \vee \neg(1 > {\pi_B^0}' - C_{B,\varnothing,0} \cdot T_1)\big) \\
& \wedge (C_{A,\{m_1,m_3\},1} > 0) \wedge ({\pi_A^1}' = 1 - C_{A,\{m_1,m_3\},1} \cdot T_1) \\
& \wedge \big(\neg(C_{A,\{m_1\},1} > 0) \vee \neg(1 > {\pi_A^1}' - C_{A,\{m_1\},1} \cdot T_2)\big) \\
& \wedge \big((C_{A,\varnothing,0} > 0) \vee \neg(C_{A,\{m_1\},1} < 0) \vee \neg(1 < {\pi_A^1}' - C_{A,\{m_1\},1} \cdot T_2)\big) \\
& \wedge (C_{B,\varnothing,1} < 0) \wedge (1 = 0 - C_{B,\varnothing,1} \cdot T_2) \\
& \wedge \big(\neg(C_{B,\{m_2\},1} < 0) \vee \neg(0 < 1 - C_{B,\{m_2\},1} \cdot T_3)\big) \\
& \wedge \big(C_{A,\{m_1\},2} < 0 \wedge ({\pi_A^3}' = 0 - C_{A,\{m_1\},2} \cdot T_3)\big) \\
& \wedge \big(\neg(C_{B,\{m_2\},1} > 0) \vee (0 > 1 - C_{B,\{m_2\},1} \cdot T_3)\big) \\
& \wedge \big(\neg(C_{A,\{m_1,m_3\},2} < 0) \vee \neg(0 < {\pi_A^3}' - C_{A,\{m_1,m_3\},2} \cdot T_4)\big) \\
& \wedge (C_{B,\{m_2\},0} > 0) \wedge ({\pi_B^0}' = 1 - C_{B,\{m_2\},0} \cdot T_4)\ .
\end{aligned}
$$

A Simplified Circadian Cycle Model



$(((((((((((\pi_g^{0\prime} = 0.12) \wedge ((\pi_{pc}^{0\prime} = 0.12) \wedge (\pi_L^{0\prime} = 0))) \wedge (((\pi_L^1 = 1) \wedge ((C_{L,\{m5\},0} > 0) \wedge (\pi_L^{1\prime} =$
$(\pi_L^1 - (C_{L,\{m5\},0} \times 6.6))))) \wedge ((\neg((C_{g,\varnothing,0} > 0) \wedge (\pi_g^{1\prime} > (\pi_g^1 - (C_{g,\varnothing,0} \times 6.6)))) \wedge (\neg((C_{pc,\varnothing,1} < 0) \wedge (\pi_{pc}^{1\prime} <$
$(\pi_{pc}^1 - (C_{pc,\varnothing,1} \times 6.6)))) \wedge \neg((C_{X,\varnothing,0} > 0) \wedge (\pi_X^{1\prime} > (\pi_X^1 - (C_{X,\varnothing,0} \times 6.6)))))) \wedge ((\pi_L^1 = (1 - \pi_L^{0\prime})) \wedge ((\pi_g^1 = \pi_g^{0\prime}) \wedge$
$((\pi_{pc}^1 = \pi_{pc}^{0\prime}) \wedge (\pi_X^1 = \pi_X^{0\prime}))))))) \wedge (((\pi_X^2 = 0) \wedge ((C_{X,\varnothing,1} < 0) \wedge (\pi_X^{2\prime} = (\pi_X^2 - (C_{X,\varnothing,1} \times 0.6))))) \wedge ((\neg((C_{g,\varnothing,0} >$
$0) \wedge (\pi_g^{2\prime} > (\pi_g^2 - (C_{g,\varnothing,0} \times 0.6)))) \wedge (\neg((C_{pc,\varnothing,1} < 0) \wedge (\pi_{pc}^{2\prime} < (\pi_{pc}^2 - (C_{pc,\varnothing,1} \times 0.6)))) \wedge \neg((C_{L,\varnothing,0} >$
$0) \wedge (\pi_L^{2\prime} > (\pi_L^2 - (C_{L,\varnothing,0} \times 0.6)))))) \wedge (((\pi_L^2 = 0) \wedge ((C_{L,\varnothing,0} < 0) \Rightarrow (\pi_L^{2\prime} < (\pi_L^2 - (C_{L,\varnothing,0} \times 0.6))))) \wedge ((\pi_X^2 =$
$(1 - \pi_X^{1\prime})) \wedge ((\pi_g^2 = \pi_g^{1\prime}) \wedge ((\pi_{pc}^2 = \pi_{pc}^{1\prime}) \wedge (\pi_L^2 = \pi_L^{1\prime}))))))))\ntriangleleft \wedge (((\pi_g^3 = 0) \wedge ((C_{g,\varnothing,1} < 0) \wedge (\pi_g^{3\prime} =$
$(\pi_g^3 - (C_{g,\varnothing,1} \times 5.4))))) \wedge ((\neg((C_{pc,\{m2\},1} < 0) \wedge (\pi_{pc}^{3\prime} < (\pi_{pc}^3 - (C_{pc,\{m2\},1} \times 5.4)))) \wedge (\neg((C_{L,\varnothing,0} > 0) \wedge (\pi_L^{3\prime} >$
$(\pi_L^3 - (C_{L,\varnothing,0} \times 5.4)))) \wedge \neg((C_{X,\varnothing,1} < 0) \wedge (\pi_X^{3\prime} < (\pi_X^3 - (C_{X,\varnothing,1} \times 5.4)))))) \wedge (((\pi_{pc}^3 = 1) \wedge ((C_{pc,\{m2\},1} >$
$0) \Rightarrow (\pi_{pc}^{3\prime} > (\pi_{pc}^3 - (C_{pc,\{m2\},1} \times 5.4))))) \wedge ((\pi_g^3 = (1 - \pi_g^{2\prime})) \wedge ((\pi_{pc}^3 = \pi_{pc}^{2\prime}) \wedge ((\pi_L^3 = \pi_L^{2\prime}) \wedge (\pi_X^3 =$
$\pi_X^{2\prime})))))))) \wedge (((\pi_L^4 = 0) \wedge ((C_{L,\varnothing,1} < 0) \wedge (\pi_L^{4\prime} = (\pi_L^4 - (C_{L,\varnothing,1} \times 0.47))))) \wedge ((\neg((C_{g,\{m3\},1} < 0) \wedge (\pi_g^{4\prime} <$
$(\pi_g^4 - (C_{g,\{m3\},1} \times 0.47)))) \wedge (\neg((C_{pc,\{m2\},1} < 0) \wedge (\pi_{pc}^{4\prime} < (\pi_{pc}^4 - (C_{pc,\{m2\},1} \times 0.47)))) \wedge \neg((C_{X,\{m4\},1} <$
$0) \wedge (\pi_X^{4\prime} < (\pi_X^4 - (C_{X,\{m4\},1} \times 0.47)))))) \wedge ((\pi_L^4 = (1 - \pi_L^{3\prime})) \wedge ((\pi_g^4 = \pi_g^{3\prime}) \wedge ((\pi_{pc}^4 = \pi_{pc}^{3\prime}) \wedge (\pi_X^4 =$
$\pi_X^{3\prime}))))))) \wedge (((\pi_{pc}^5 = 1) \wedge ((C_{pc,\{m2\},0} > 0) \wedge (\pi_{pc}^{5\prime} = (\pi_{pc}^5 - (C_{pc,\{m2\},0} \times 5.53))))) \wedge ((\neg((C_{g,\{m1,m3\},1} <$
$0) \wedge (\pi_g^{5\prime} < (\pi_g^5 - (C_{g,\{m1,m3\},1} \times 5.53)))) \wedge (\neg((C_{L,\varnothing,1} < 0) \wedge (\pi_L^{5\prime} < (\pi_L^5 - (C_{L,\varnothing,1} \times 5.53)))) \wedge \neg((C_{X,\{m4\},1} <$
$0) \wedge (\pi_X^{5\prime} < (\pi_X^5 - (C_{X,\{m4\},1} \times 5.53)))))) \wedge (((\pi_g^5 = 1) \wedge ((C_{g,\{m1,m3\},1} > 0) \Rightarrow (\pi_g^{5\prime} >$
$(\pi_g^5 - (C_{g,\{m1,m3\},1} \times 5.53))))) \wedge ((\pi_{pc}^5 = (1 - \pi_{pc}^{4\prime})) \wedge ((\pi_g^5 = \pi_g^{4\prime}) \wedge ((\pi_L^5 = \pi_L^{4\prime}) \wedge (\pi_X^5 = \pi_X^{4\prime})))))))) \wedge (((\pi_X^6 =$
$1) \wedge ((C_{X,\{m4\},0} > 0) \wedge (\pi_X^{6\prime} = (\pi_X^6 - (C_{X,\{m4\},0} \times 0.6))))) \wedge ((\neg((C_{g,\{m1,m3\},1} < 0) \wedge (\pi_g^{6\prime} <$
$(\pi_g^6 - (C_{g,\{m1,m3\},1} \times 0.6)))) \wedge (\neg((C_{pc,\{m2\},0} > 0) \wedge (\pi_{pc}^{6\prime} > (\pi_{pc}^6 - (C_{pc,\{m2\},0} \times 0.6)))) \wedge \neg((C_{L,\{m5\},1} <$
$0) \wedge (\pi_L^{6\prime} < (\pi_L^6 - (C_{L,\{m5\},1} \times 0.6)))))) \wedge ((\pi_X^6 = (1 - \pi_X^{5\prime})) \wedge ((\pi_g^6 = \pi_g^{5\prime}) \wedge ((\pi_{pc}^6 = \pi_{pc}^{5\prime}) \wedge (\pi_L^6 =$
$\pi_L^{5\prime}))))))) \wedge (((\pi_g^7 = 1) \wedge ((C_{g,\{m1,m3\},0} > 0) \wedge (\pi_g^{7\prime} = (\pi_g^7 - (C_{g,\{m1,m3\},0} \times 4.5))))) \wedge ((\neg((C_{pc,\varnothing,0} >$
$0) \wedge (\pi_{pc}^{7\prime} > (\pi_{pc}^7 - (C_{pc,\varnothing,0} \times 4.5)))) \wedge (\neg((C_{L,\{m5\},1} < 0) \wedge (\pi_L^{7\prime} < (\pi_L^7 - (C_{L,\{m5\},1} \times 4.5)))) \wedge \neg((C_{X,\{m4\},0} >$
$0) \wedge (\pi_X^{7\prime} > (\pi_X^7 - (C_{X,\{m4\},0} \times 4.5)))))) \wedge ((\pi_g^7 = (1 - \pi_g^{6\prime})) \wedge ((\pi_{pc}^7 = \pi_{pc}^{6\prime}) \wedge ((\pi_L^7 = \pi_L^{6\prime}) \wedge (\pi_X^7 =$
$\pi_X^{6\prime}))))))) \wedge (((\pi_{pc}^8 = 0) \wedge ((C_{pc,\varnothing,1} < 0) \wedge (\pi_{pc}^{8\prime} = (\pi_{pc}^8 - (C_{pc,\varnothing,1} \times 0.9))))) \wedge ((\neg((C_{g,\{m3\},0} > 0) \wedge (\pi_g^{8\prime} >$
$(\pi_g^8 - (C_{g,\{m3\},0} \times 0.9)))) \wedge (\neg((C_{L,\{m5\},1} < 0) \wedge (\pi_L^{8\prime} < (\pi_L^8 - (C_{L,\{m5\},1} \times 0.9)))) \wedge \neg((C_{X,\{m4\},0} >$
$0) \wedge (\pi_X^{8\prime} > (\pi_X^8 - (C_{X,\{m4\},0} \times 0.9)))))) \wedge ((\pi_{pc}^8 = (1 - \pi_{pc}^{7\prime})) \wedge ((\pi_g^8 = \pi_g^{7\prime}) \wedge ((\pi_L^8 = \pi_L^{7\prime}) \wedge (\pi_X^8 = \pi_X^{7\prime})))))))$

Manually simplified constraints



Simplified circadian cycle

Day/Light Cycle

Célérités sur g et pc	
$C_{g,\varnothing,0} < 0$	$C_{g,\{pc,L\}_0} > 0$
$C_{g,\varnothing,1} < 0$	$0 < C_{g,\{pc,L\},1} < \frac{1}{5.53}$
$C_{g,\{L\},0} < 0$	$C_{pc,\varnothing,0} < 0$
$C_{g,\{L\},1} < 0$	$C_{pc,\varnothing,1} = -\frac{0.12}{0.9}$
$C_{g,\{pc\},0} > 0$	$0 < C_{pc,\{g\},0} < \frac{1}{6.13}$
$C_{g,\{pc\},1} > 0$	$0 < C_{pc,\{g\},1} < \frac{1}{5.4}$

Célérités sur L et X	
$-\frac{1}{0.6} < C_{L,\varnothing,0} < 0$	$C_{X,\varnothing,0} < 0$
$C_{L,\varnothing,1} < 0$	$-\frac{1}{6} \leqslant C_{X,\varnothing,1} < 0$
$C_{L,\{X\},0} > 0$	$0 < C_{X,\{L\},0} < \frac{1}{5.1}$
$C_{L,\{X\},1} > 0$	$C_{X,\{L\},1} > 0$

Results with compatible constraints from another work