Séminaire d'équipe MeForBio — 2021-02-08

Identifying Hybrid Parameters of a Hybrid Thomas Modeling with a Hybrid Hoare Logic and a Hybrid Dijkstra Predicate Calculus

Identification de paramètres hybrides sur un formalisme de Thomas hybride à l'aide d'une logique de Hoare hybride et d'un calcul des prédicats de Dijkstra hybride

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BioComputing

Introduction & Résumé

Analysis of the Dynamics

Centrale Nantes, PhD thesis — 2011–2014
→ Efficient reachability analysis on large networks
→ Dynamical patterns enumeration with answer set programming

Univ Kassel, postdoc — 2014–2015
→ Complex patterns enumeration with polyadic μ-calculus

Learning Models from Data

Univ Nice, ATER — 2015–2016
→ **Inference of constraints on hybrid parameters**

Univ Nantes, ATER — 2016–2017
→ Learning models from time series data

Learning New Knowledge from Models

Univ Rennes, postdoc — 2017–2018
→ Computational model to study hepatocellular carcinoma progression

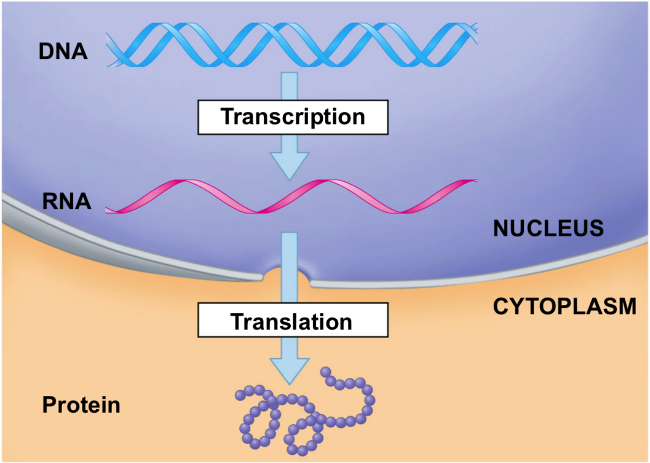
CNRS/LS2N, postdoc — 2018–2019
→ Integrate heterogeneous clinical, genetic, imaging data with semantic web in order to learn variables of interest

Today

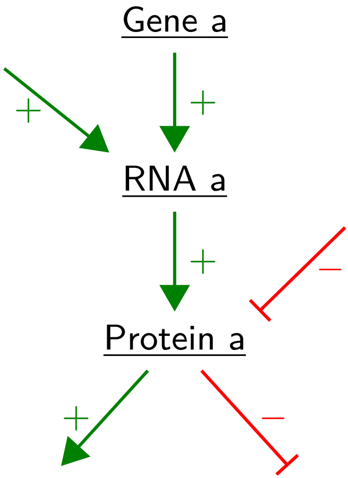
Centrale Lille, maître de conférences — 2019 ⋮
→ Understand the role of glucose absorption in diabetes
→ Learn plankton food chains from measurments

Discrete

Preliminary Abstraction



Preliminary Abstraction



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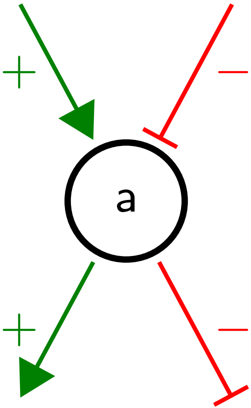

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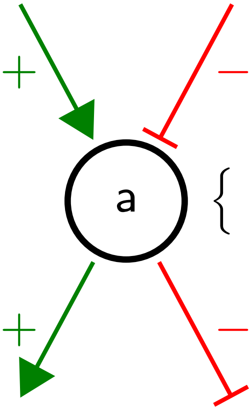
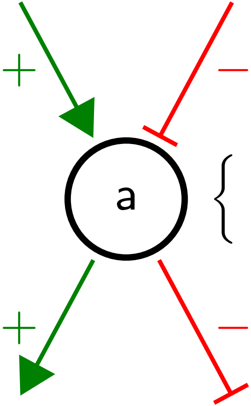


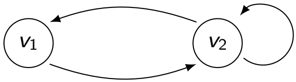
$$\left\{ \begin{array}{l} 0 = \text{inactive} \\ 1 = \text{active} \end{array} \right\}$$

Preliminary Abstraction



$$\left\{ \begin{array}{l} 0 = \text{complete degradation} \\ 1 = \text{traces} \\ 2 = \text{saturation} \end{array} \right\}$$

René Thomas Modeling



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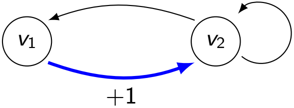

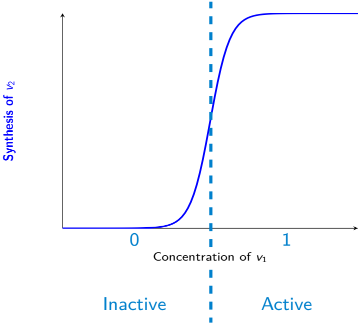

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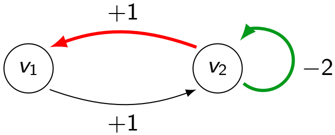

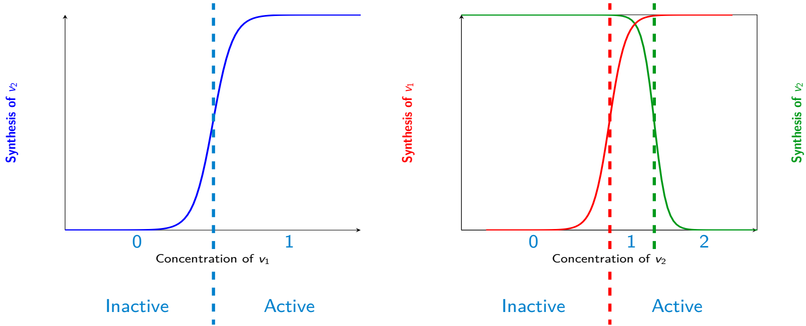

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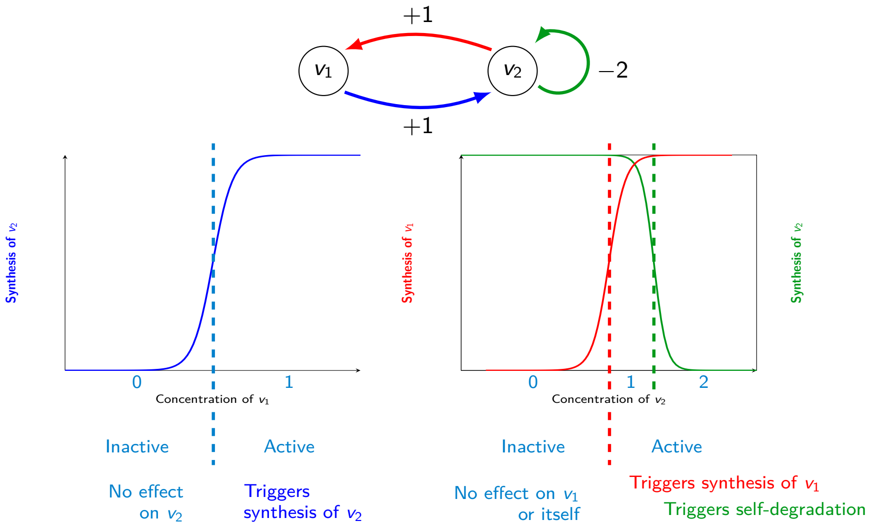
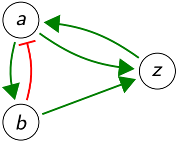


State Graph

The state-graph depicts explicitly the whole dynamics

abz

000	010	001	011
100	110	101	111
200	210	201	211



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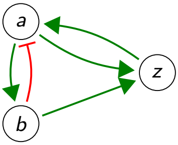

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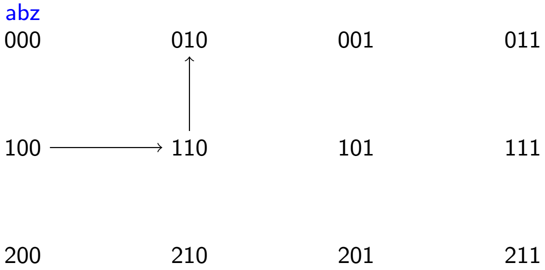

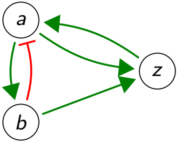

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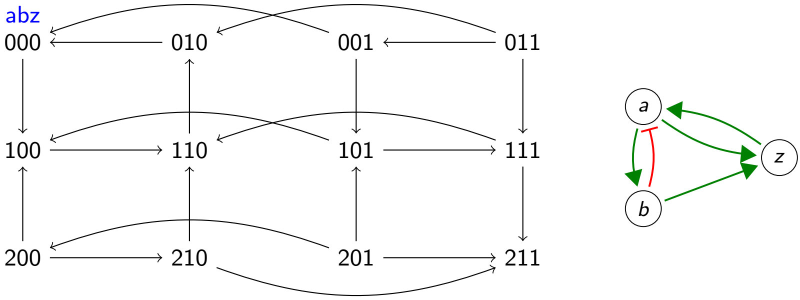

State Graph

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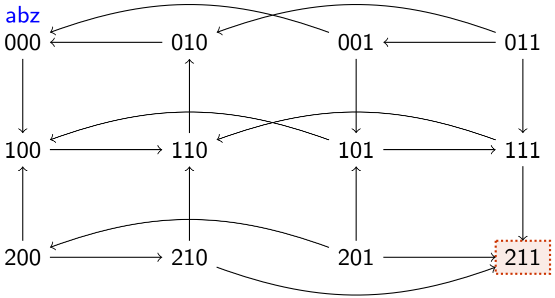
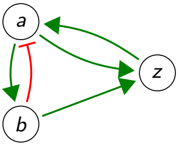
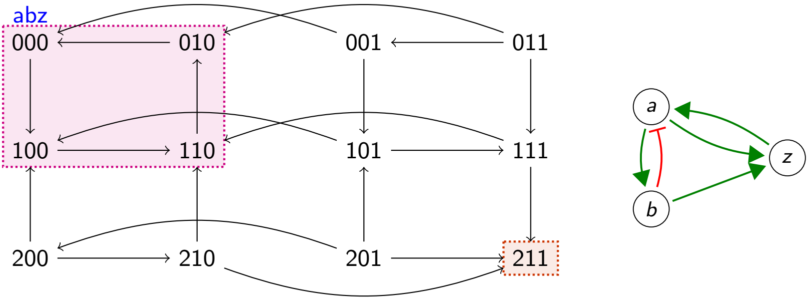




- **Stable state** = state with no successors

State Graph

The state-graph depicts explicitly the whole dynamics



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

State Graph

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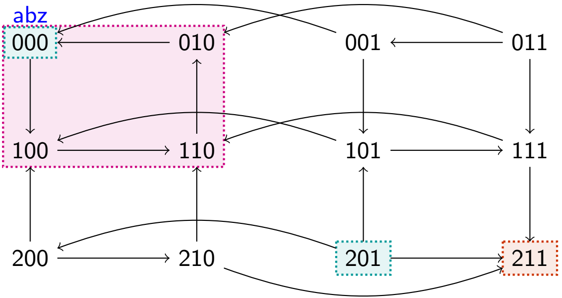
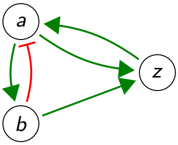


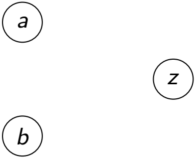


- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape
- **Reachability** = from **201**, can I reach **000**?

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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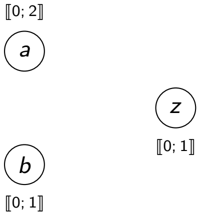

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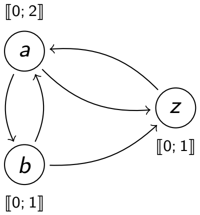

a	$K_{b,\omega}$
0	**0**
1	**1**
2	**1**

z	b	$K_{a,\omega}$
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

a	b	$K_{z,\omega}$
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

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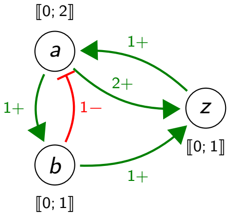
- Signs & thresholds on the edges (redundant) $a \xrightarrow{2+} z$



a	$K_{b,\omega}$
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1	**1**
2	**1**

z	b	$K_{a,\omega}$
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

a	b	$K_{z,\omega}$
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

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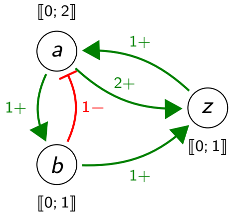

a	$K_{b,\omega}$
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2	**1**

z	b	$K_{a,\omega}$
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

a	b	$K_{z,\omega}$
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

$$K_{v,\omega} \in \mathbb{N}$$

Parameters Identification

$$\text{Possible parametrizations} = \prod_{v \in N} |\mathrm{dom}(v)|^{\left(\prod_{u \in \mathrm{pred}(v)} |\mathrm{dom}(u)|\right)}$$

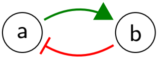
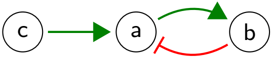
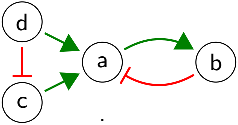
With $\forall v \in N, |\mathrm{dom}(v)| = 2$: $\left(2^{\left(2^{|\mathrm{pred}(v)|}\right)}\right)^{|N|}$

- Exponential in the number of nodes
- Double-exponential in the number of predecessors

To exhaustively and naively try out all parametrizations:

1. Assign one parametrization to the model
2. Compute the whole state-space (exponential !)
3. Test relevant properties (with model-checking)
4. Keep or discard this parametrization

Parameters Identification

Model	**Possible parametrizations**	**Hypotheses**
		$\lvert \mathrm{dom}(v) \rvert = 2$
	16	
	128	
	8192	
⋮	⋮	$\lvert \mathrm{pred}(v) \rvert = 1$
(10)	1048576	
(20)	1.1×10^{12}	
(100)	1.6×10^{60}	

Discrete Hoare Logic on Discrete Thomas Modeling

[Hoare, *Communications of the ACM*, 1969]
[Dijkstra, *Communications of the ACM*, 1975]
[Bernot *et al.*, *Theoretical Computer Science*, 2015]

Hoare triple: $\{\ Pre\ \}\ \ p\ \ \{\ Post\ \}$

- p is an imperative program
- Pre and $Post$ are properties (pre- and postcondition)

Meaning:
"If Pre holds, then p can execute and $Post$ will hold after execution"

Weakest precondition:
Given p and $Post$, one can compute the weakest (most general) precondition $WPre$ so that $\{\ WPre\ \}\ p\ \{\ Post\ \}$ holds
$WPre$ constrains the initial state of the system

Exemple : $\{\ WPre\ \}\ a+\ ;\ b+\ \{\ a = 1 \wedge b = 1\ \}$
$WPre \equiv a = 0 \wedge b = 0$

Discrete Hoare Logic on Discrete Thomas Modeling

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[Bernot *et al.*, *Theoretical Computer Science*, 2015]

Hoare triple: $\{ \; Pre \; \} \quad p \quad \{ \; Post \; \}$

- p is an imperative program (known dynamical path from literature)
- Pre and $Post$ are properties (pre- and postcondition)

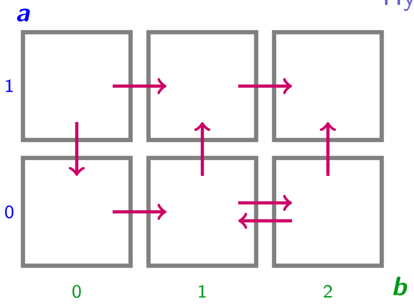
Meaning:
"If Pre holds, then p can execute and $Post$ will hold after execution"

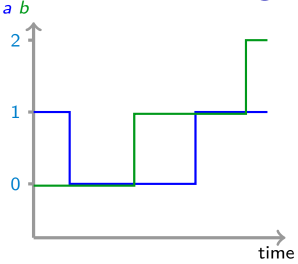
Weakest precondition:
Given p and $Post$, one can compute the weakest (most general) precondition $WPre$ so that $\{ \; WPre \; \} \; p \; \{ \; Post \; \}$ holds
$WPre$ constrains the initial state of the system and the parameters

Exemple : $\{ \; WPre \; \} \; a+ \; ; \; b+ \; \{ \; a = 1 \land b = 1 \; \}$
$WPre \equiv a = 0 \land b = 0 \land K_{a,\{a=0,b=0\}} = 1 \land K_{b,\{a=1,b=0\}} = 1$

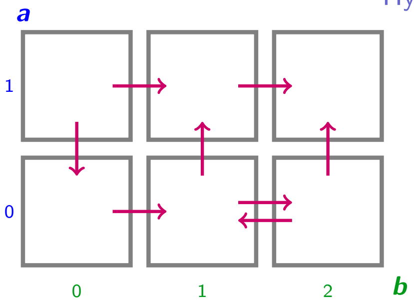
Hybrid

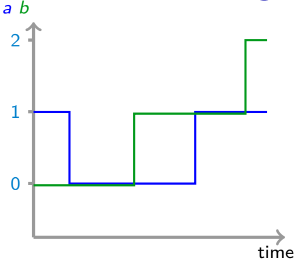
Hybrid Thomas Modeling

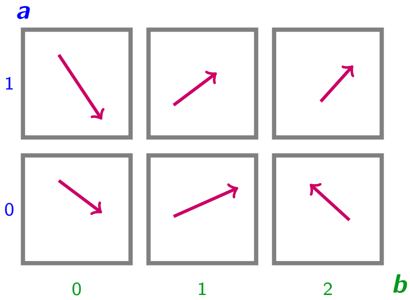


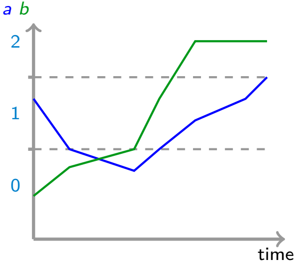


Hybrid Thomas Modeling









Hybrid Thomas Modeling

[Cornillon *et al.*, *Mod. Complex Biol. Syst. in the Context of Genomics*, 2016]

$$C_{a,\omega,n}$$

Hybrid Thomas Modeling

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$$C_{a,\omega,n} \in \mathbb{R}$$

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$$C_{a,\omega,n} \in \mathbb{R}$$

Possible parametrizations =

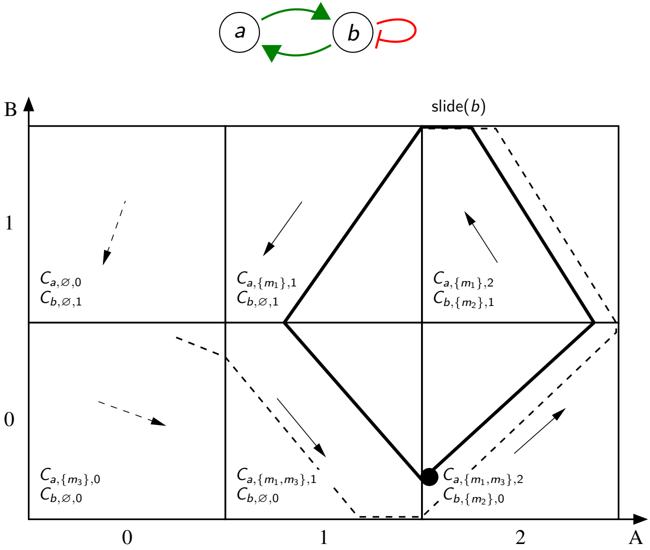
Hybrid Thomas Modeling

[Cornillon *et al.*, *Mod. Complex Biol. Syst. in the Context of Genomics*, 2016]

$$C_{a,\omega,n} \in \mathbb{R}$$

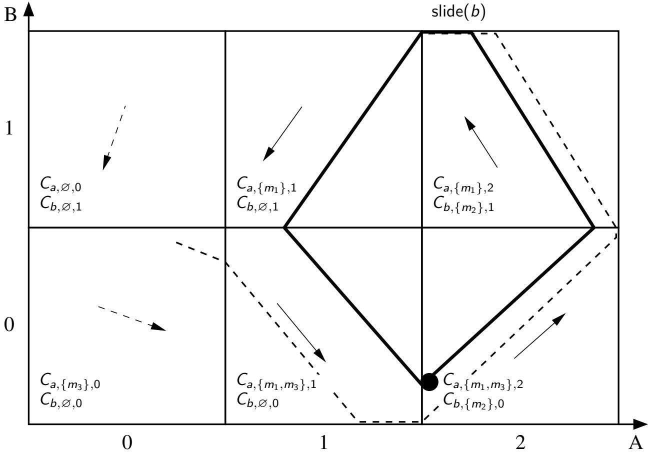
Possible parametrizations $= \infty$

Hybrid Thomas Modeling



Hybrid Hoare Logic to Infer Parameters

$$\left\{\begin{matrix} ??? \\ ??? \end{matrix}\right\} \begin{pmatrix} T_4 \\ \top \\ b+ \end{pmatrix} ; \begin{pmatrix} T_3 \\ \text{slide}^+(b) \\ a- \end{pmatrix} ; \begin{pmatrix} T_2 \\ \top \\ b- \end{pmatrix} ; \begin{pmatrix} T_1 \\ \top \\ a+ \end{pmatrix} \left\{\begin{matrix} D_0 \equiv (\eta_a = 2 \land \eta_b = 0) \\ H_0 \equiv (\pi_{\text{initial}} = \pi_{\text{final}}) \end{matrix}\right\}$$



Hybrid Hoare Logic

[Behaegel *et al.*, *TIME'17*, 2017]

Hoare triple: $\left\{\begin{matrix} D' \\ H' \end{matrix}\right\} \begin{pmatrix} \Delta t \\ assert \\ v\pm \end{pmatrix} \left\{\begin{matrix} D \\ H \end{matrix}\right\}$

Hybrid Hoare Logic

[Behaegel *et al.*, *TIME'17*, 2017]

Hoare triple: $\begin{Bmatrix} D' \\ H' \end{Bmatrix} \begin{pmatrix} \Delta t \\ assert \\ v\pm \end{pmatrix} \begin{Bmatrix} D \\ H \end{Bmatrix}$

Instruction:

$\begin{pmatrix} \Delta t \\ assert \\ v\pm \end{pmatrix}$
$\leftarrow$ Time spent in the qualitative state
$\leftarrow$ Biological knowledge (saturation, celerity, ...)
$\leftarrow$ Qualitative instruction ($v+$ ou $v-$)

- $\Delta t \in \mathbb{R}^+$
- *assert* is a property using the following predicates:
  - $\text{slide}^{\pm}(u)$ $\leftarrow$ Variable u "slides" on a border (e.g., saturation)
  - $\text{noslide}^{\pm}(u)$ $\leftarrow$ Variable u does not "slide"
  - $C_u > 0$ $\leftarrow$ Constraints on the celerities of the current qualitative state

Hybrid Hoare Logic

[Behaegel *et al.*, *TIME'17*, 2017]

Hoare triple: $\begin{Bmatrix} D' \\ H' \end{Bmatrix} \begin{pmatrix} \Delta t \\ assert \\ v\pm \end{pmatrix} \begin{Bmatrix} D \\ H \end{Bmatrix}$

Propriétés (pré- et postcondition) : $\begin{Bmatrix} D \\ H \end{Bmatrix}$ $\leftarrow$ Qualitative/discrete part; $\leftarrow$ Hybrid/real part

D and H are properties on:

- $\eta_u \in \mathbb{N}$ $\leftarrow$ Qualitative states of the variables
- $\pi_u \in [0..1]$ $\leftarrow$ Fractional parts (position in the hybrid state)
- $C_{u,\omega,n}$ $\leftarrow$ Celerities
- Δt $\leftarrow$ Time

Weakest Precondition in Hybrid Hoare Logic

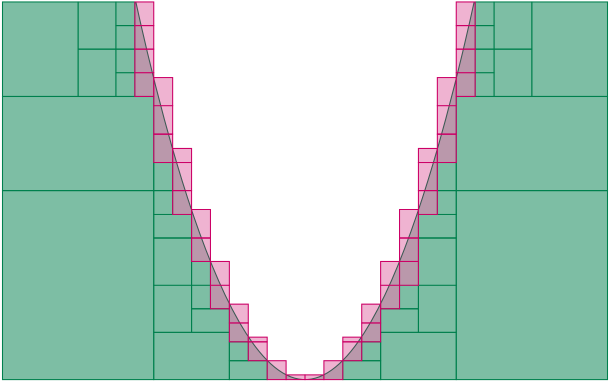
[Behaegel *et al.*, *TIME'17*, 2017]

Hoare triple: $\begin{Bmatrix} D' \\ H' \end{Bmatrix} \begin{pmatrix} \Delta t \\ assert \\ v\pm \end{pmatrix} \begin{Bmatrix} D \\ H \end{Bmatrix}$

$$H' \equiv H \land \Phi_v^+(\Delta t) \land \mathcal{F}_v(\Delta t) \land \neg \mathcal{W}_v^+ \land \mathcal{A}(\Delta t, assert) \land \mathcal{J}_v$$

The AbSolute Solver

[Pelleau *et al.*, *VMCAI*, 2013]

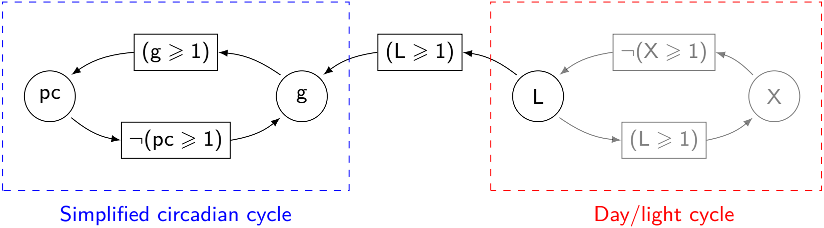


Solving the constraint: $y \leqslant x^2$

Application: Circadian Clock

A Simplified Circadian Cycle Model

[Behaegel *et al.*, *TIME'17*, 2017]



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

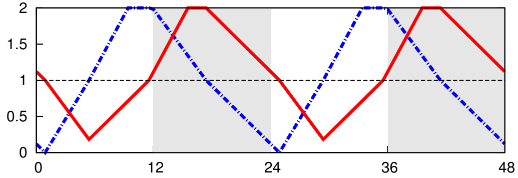
L = light of the day
X = Modeling artifact (clock)

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

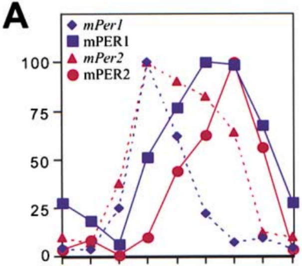
$$((((((((((\pi_g^{0\prime} = 0.12) \land ((\pi_{pc}^{0\prime} = 0.12) \land (\pi_L^{0\prime} = 0))) \land (((\pi_L^1 = 1) \land ((C_{L,\{m5\},0} > 0) \land (\pi_L^{1\prime} =$$
$$(\pi_L^1 - (C_{L,\{m5\},0} \times 6.6))))) \land ((\neg((C_{g,\varnothing,0} > 0) \land (\pi_g^{1\prime} > (\pi_g^1 - (C_{g,\varnothing,0}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

Results

- **Simplifications** of the constraints → Not very effective
- Using a non-linear solver: **AbSolute** → We obtain solutions
- Results checked with a simulation:



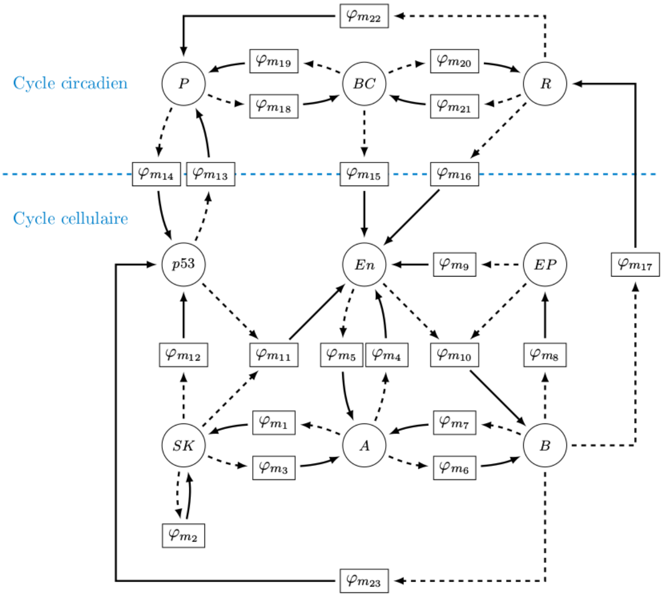
Simulation with 1 set of compatible values



Experiments

Application: Cell Cycle & Circadian Clock

Coupling of Cell and Circadian Cycles



Coupling of Cell and Circadian Cycles

$$\begin{pmatrix} 0.59 \\ \top \\ BC+ \end{pmatrix} ; \begin{pmatrix} 2.44 \\ \text{slide}^+(BC) \wedge \text{slide}^-(P) \\ R+ \end{pmatrix} ; \begin{pmatrix} 0.52 \\ \text{slide}^-(EP) \\ SK+ \end{pmatrix} ; \begin{pmatrix} 1.77 \\ \top \\ p53+ \end{pmatrix} ; \begin{pmatrix} 1.78 \\ \top \\ SK+ \end{pmatrix} ; \begin{pmatrix} 2.05 \\ \text{slide}^+(R) \\ P+ \end{pmatrix} ;$$

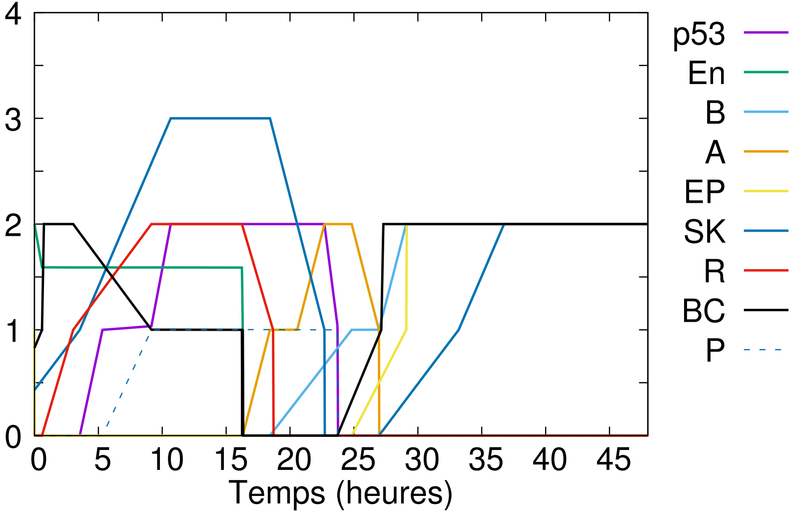
$$\begin{pmatrix} 1.51 \\ \text{slide}^+(SK) \\ En- \end{pmatrix} ; \begin{pmatrix} 1.93 \\ \top \\ BC- \end{pmatrix} ; \begin{pmatrix} 0.20 \\ \text{slide}^-(En) \\ A+ \end{pmatrix} ; \begin{pmatrix} 2.13 \\ \top \\ SK- \end{pmatrix} ; \begin{pmatrix} 0.11 \\ \begin{pmatrix} (\text{slide}^-(BC) \wedge \\ \text{slide}^+(P) \end{pmatrix} \\ R- \end{pmatrix} ; \begin{pmatrix} 2.02 \\ \text{slide}^+(A) \\ SK- \end{pmatrix} ;$$

$$\begin{pmatrix} 1.06 \\ \top \\ p53- \end{pmatrix} ; \begin{pmatrix} 1.07 \\ \text{slide}^-(SK) \\ B+ \end{pmatrix} ; \begin{pmatrix} 1.97 \\ \top \\ P- \end{pmatrix} ; \begin{pmatrix} 0.16 \\ \top \\ A- \end{pmatrix} ; \begin{pmatrix} 2.14 \\ \text{slide}^+(B) \\ EP+ \end{pmatrix} ; \begin{pmatrix} 0.18 \\ \text{slide}^+(EP) \\ En+ \end{pmatrix} ;$$

$$\begin{pmatrix} 0.18 \\ \text{slide}^-(A) \wedge \text{slide}^+(En) \\ B- \end{pmatrix} ; \begin{pmatrix} 0.19 \\ \text{slide}^-(B) \\ EP- \end{pmatrix} \left\{ \begin{pmatrix} (\eta_P = 0) \wedge (\eta_{BC} = 0) \wedge \\ (\eta_R = 0) \wedge (\eta_{SK} = 0) \wedge \\ (\eta_{EP} = 0) \wedge (\eta_A = 0) \wedge \\ (\eta_B = 0) \wedge (\eta_{En} = 1) \wedge \\ (\eta_{PP} = 0) \end{pmatrix} \\ \top \right\}$$

152 celerities, 378 fractional parts, 1536 constraints

Coupling of Cell and Circadian Cycles



Conclusion

Conclusion

Summary

- Hybrid formalism between discrete networks and ODEs
- Hybrid Hoare logic to reason about dynamical paths
- Hybrid Dijkstra predicate calculus to infer constraints on parameters
- Using a nonlinear constraint solver to find solutions: AbSolute
- Application to a simplified model of the circadian cycle

Outlook

- Generalize to other types of continuous functions
- Other applications
- Learn hybrid models!

Collaboration & Bibliography

Jonathan BEHAEGEL

Jean-Paul COMET

- 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'17), 2017.

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