Journées du GT Bioss 2024 — 2024-05-27

Modeling, Analysis and Parameter Inference of a Class of Hybrid Regulatory Networks

Maxime FOLSCHETTE

maxime.folschette@centralelille.fr
http://maxime.folschette.fr/

CRIStAL
Centre de Recherche en Informatique, Signal et Automatique de Lille

Université de Lille
cnrs
centralelille
BioComputing

Introduction

- **Centrale Nantes** — PhD thesis — 2011–2014
- **Univ Kassel** — postdoc — 2014–2015
- **Univ Nice** — ATER — 2015–2016
- **Univ Nantes** — ATER — 2016–2017
- **Univ Rennes** — postdoc — 2017–2018
- **CNRS/LS2N** — postdoc — 2018–2019
- **Centrale Lille** — **maître de conférences** — 2019 ⋮

Analysis of the Dynamics

→ Efficient reachability analysis on large networks

→ Dynamical patterns enumeration with answer set programming

→ Complex patterns enumeration with polyadic μ-calculus

Learning Models from Data

→ **Inference of constraints on hybrid parameters**

→ Learning models from time series data

Learning New Knowledge from Models

→ Static computational model to study hepatocellular carcinoma progression

→ Integrate heterogeneous data with semantic web

Today

→ Understand the role of glucose absorption in diabetes

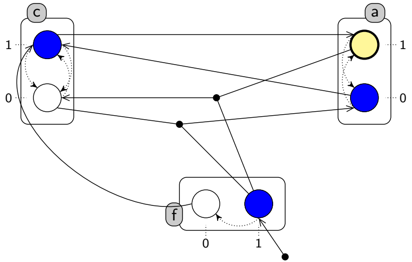
→ Learn plankton food chains from measurments

→ **Formal verification of hybrid models**

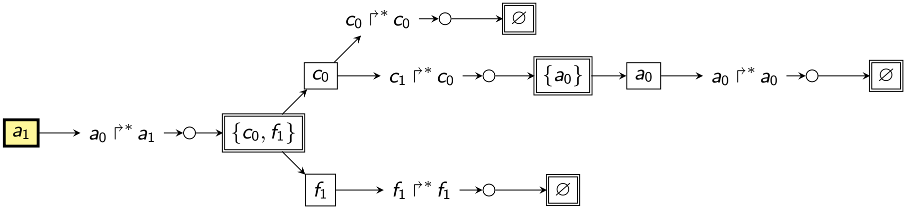
Other Works

Abstract Interpretation

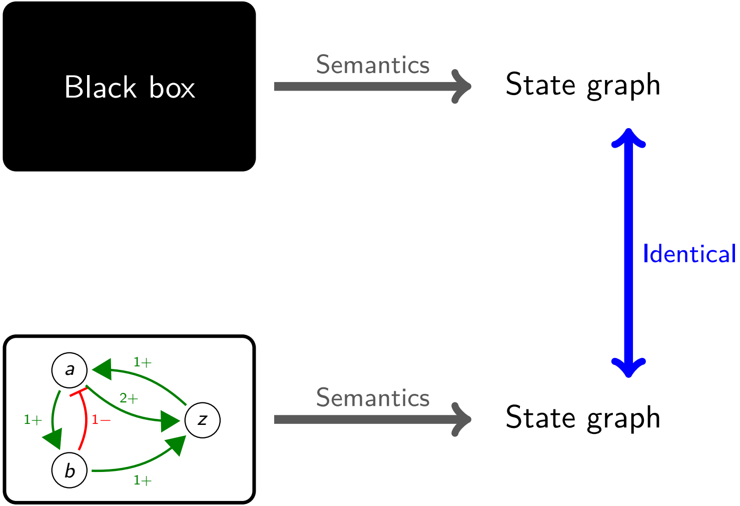
[Folschette *et al.*, *Theoretical Computer Science*, 2015b]



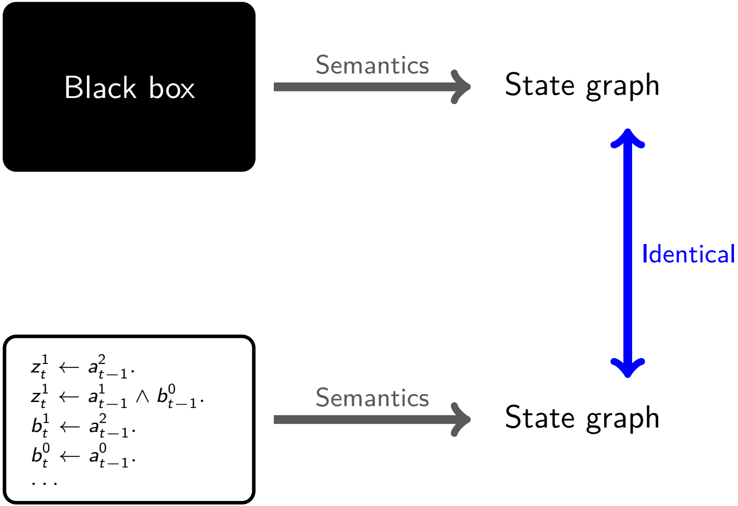
- No cycle
- No conflict
- All leaves are $\boxed{\varnothing}$



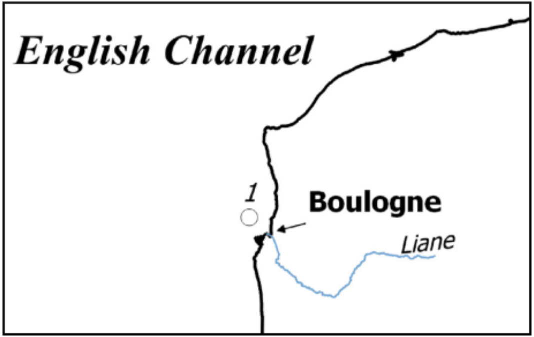
Learning Logic Programs for Explainability



Learning Logic Programs for Explainability



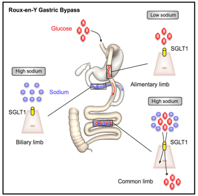
Long-term Datasets of Phytoplankton Populations

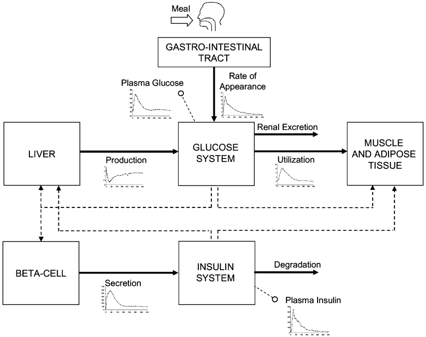


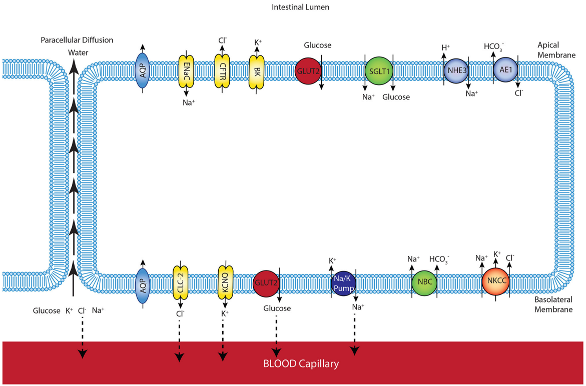
https://www.seanoe.org/data/00397/50832/

Sampling location	Sampling date	Taxon	Value	Sampling depth
001-P-015	1992-05-18	CHLOROA	6.0	Surface (0-1m)
006-P-001	2019-12-02	Chaetoceros	1000.0	Surface (0-1m)
002-P-007	1994-05-25	Pleurosigma	100.0	Surface (0-1m)
002-P-030	2005-10-19	SALI	34.83	Surface (0-1m)
006-P-007	2015-09-28	Guinardia delicatula	11400.0	Surface (0-1m)

Studying Glucose Dynamics at Body and Cell Levels





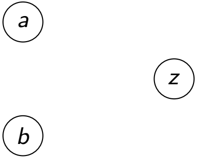


Discrete Models

Discrete Networks / Thomas Modeling

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

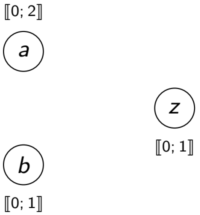
- A set of components $N = \{a, b, z\}$



Discrete Networks / Thomas Modeling

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

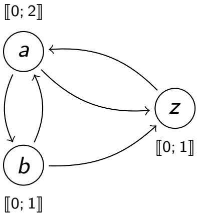
- A set of components $N = \{a, b, z\}$
- A discrete domain for each component $\mathrm{dom}(a) = [\![0; 2]\!]$



Discrete Networks / Thomas Modeling

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

- A set of components $N = \{a, b, z\}$
- A discrete domain for each component $\mathrm{dom}(a) = [\![0; 2]\!]$
- Discrete parameters / evolution functions $K_{a,\omega}$



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

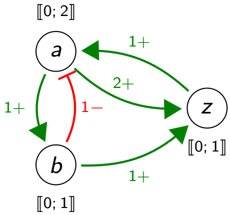
z	b	$K_{a,\omega}$
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

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

Discrete Networks / Thomas Modeling

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

- A set of components $N = \{a, b, z\}$
- A discrete domain for each component $\mathrm{dom}(a) = [\![0; 2]\!]$
- Discrete parameters / evolution functions $K_{a,\omega}$
- Signs & thresholds on the edges (redundant) $a \xrightarrow{2+} z$



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

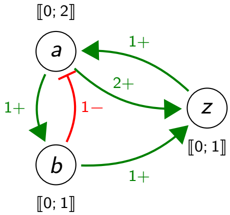
z	b	$K_{a,\omega}$
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

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

Discrete Networks / Thomas Modeling

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

- A set of components $N = \{a, b, z\}$
- A discrete domain for each component $\mathrm{dom}(a) = [\![0; 2]\!]$
- Discrete parameters / evolution functions $K_{a,\omega}$
- Signs & thresholds on the edges (redundant) $a \xrightarrow{2+} z$



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**

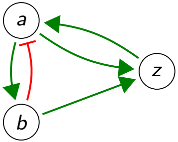
a	b	$K_{z,\omega}$
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

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

State Graph

The state-graph depicts explicitly the whole dynamics

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



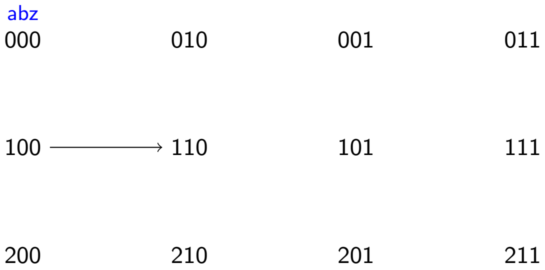
z	b	f_a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

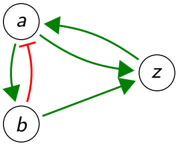
a	b	f_z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

a	f_b
0	**0**
1	**1**
2	**1**

State Graph

The state-graph depicts explicitly the whole dynamics





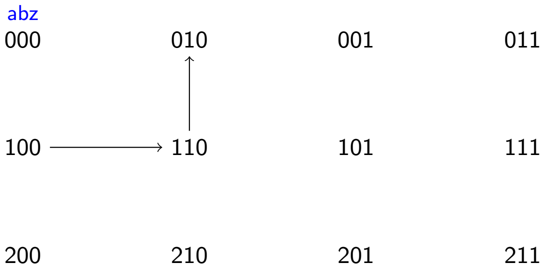
z	b	f_a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

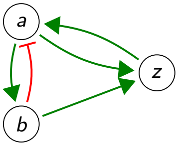
a	b	f_z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

a	f_b
0	**0**
1	**1**
2	**1**

State Graph

The state-graph depicts explicitly the whole dynamics





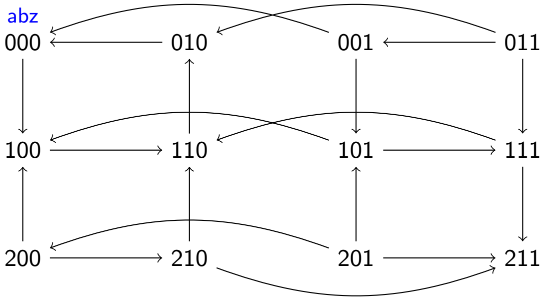
z	b	f_a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

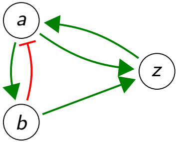
a	b	f_z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

a	f_b
0	**0**
1	**1**
2	**1**

State Graph

The state-graph depicts explicitly the whole dynamics





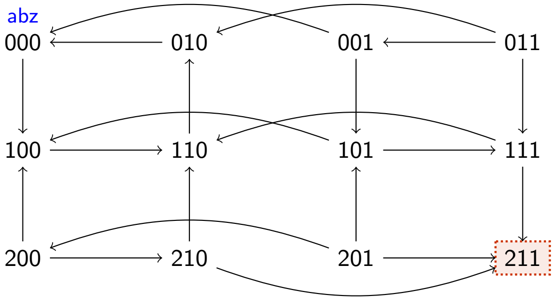
z	b	f_a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

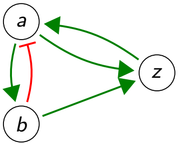
a	b	f_z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

a	f_b
0	**0**
1	**1**
2	**1**

State Graph

The state-graph depicts explicitly the whole dynamics





z	b	f_a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

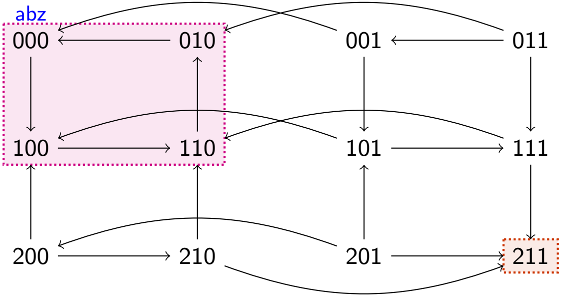
a	b	f_z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

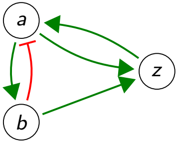
a	f_b
0	**0**
1	**1**
2	**1**

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

State Graph

The state-graph depicts explicitly the whole dynamics





z	b	f_a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

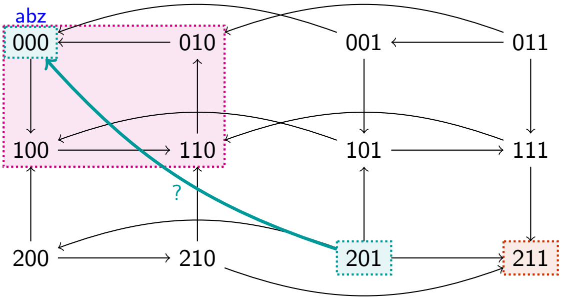
a	b	f_z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

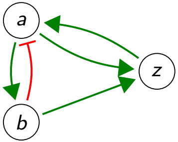
a	f_b
0	**0**
1	**1**
2	**1**

- **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 explicitly the whole dynamics





z	b	f_a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

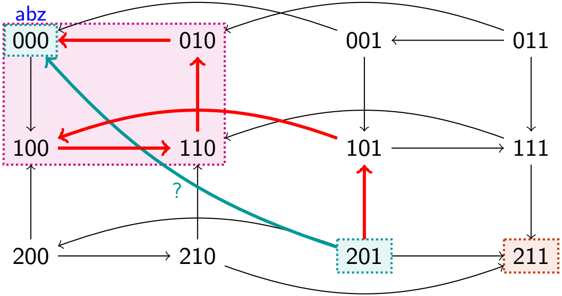
a	b	f_z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

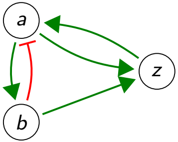
a	f_b
0	**0**
1	**1**
2	**1**

- **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**?

State Graph

The state-graph depicts explicitly the whole dynamics





z	b	f_a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

a	b	f_z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

a	f_b
0	**0**
1	**1**
2	**1**

- **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**?

Discrete Parameter Identification

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

With Boolean variables, $|\text{dom}(v)| = 2$: $\left(2^{\left(2^{|\text{pred}(v)|}\right)}\right)^{|N|}$

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

Discrete Hoare Logic on Discrete Thomas Modeling

[Hoare, *Communications of the ACM*, 1969]
[Dijkstra, *Communications of the ACM*, 1975]

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"

Example: $\{\ a = 0 \land b = 0\ \}\ a{+}{+}\ ;\ b{+}{+}\ \{\ a = 1 \land b > 0\ \}$

Discrete Hoare Logic on Discrete Thomas Modeling

[Hoare, *Communications of the ACM*, 1969]
[Dijkstra, *Communications of the ACM*, 1975]

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"

Example: $\{\ a = 0 \wedge b = 0\ \}\ a{+}{+}\ ;\ \ b{+}{+}\ \{\ a = 1 \wedge b > 0\ \}$

Weakest precondition calculus:
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

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

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 (known biological 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"

Example: $\{ \ a = 0 \land b = 0 \ \} \ a{+}{+} \ ; \ b{+}{+} \ \{ \ a = 1 \land b > 0 \ \}$

Weakest precondition calculus:
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

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

Hybrid Models

Comparison of Frameworks

Discrete models

- \+ Abstraction: Simple to compute
- − Abstraction: No continuous time/levels

Comparison of Frameworks

Differential equations

+ Very precise simulations
– Difficult to tune (equations/parameters)
– Sometimes too complex to check simple properties

Discrete models

+ Abstraction: Simple to compute
– Abstraction: No continuous time/levels

Comparison of Frameworks

Differential equations

+ Very precise simulations
– Difficult to tune (equations/parameters)
– Sometimes too complex to check simple properties

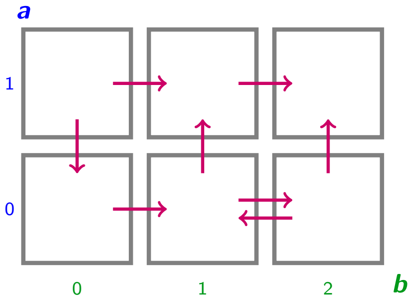
Hybrid models

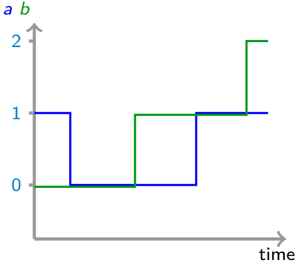
+ Middle-ground: continuous time/levels
+ Not too complex in terms of parameters/simulation
– New formalism: requires new tools
  - To find parameters
  - To check dynamical properties

Discrete models

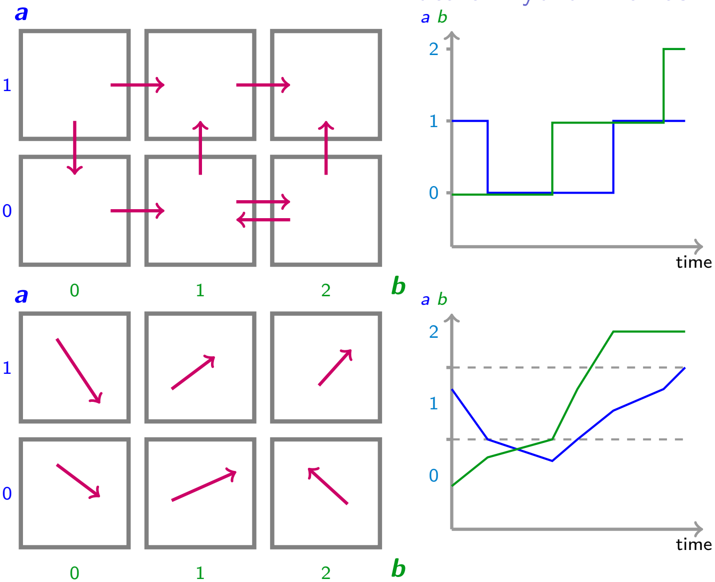
+ Abstraction: Simple to compute
– Abstraction: No continuous time/levels

Idea of Hybrid Thomas Modeling





Idea of Hybrid Thomas Modeling



Definitions

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

Discrete state:

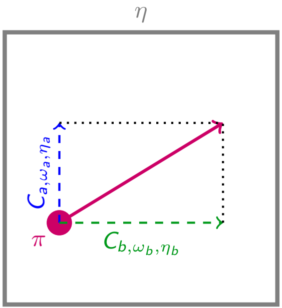
$$\eta = (\eta_a, \eta_b)$$

$\eta \in \times_{u \in N} \mathrm{dom}(u)$

Fractional part in discrete state:

$$\pi = (\pi_a, \pi_b)$$

$\pi \in [0, 1]^{|N|}$



Celerity:

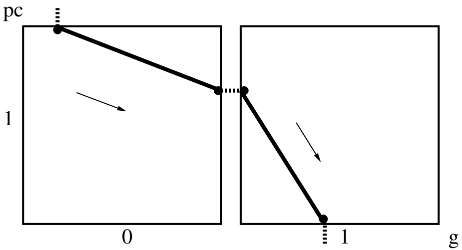
$$C_{a,\omega_a,\eta_a}$$

Variable (a)

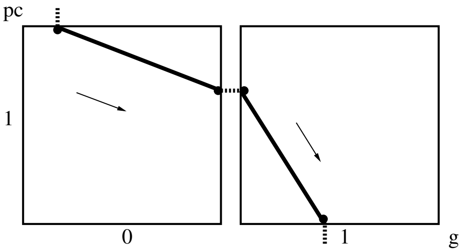
Set of activating resources of a (ω_a)

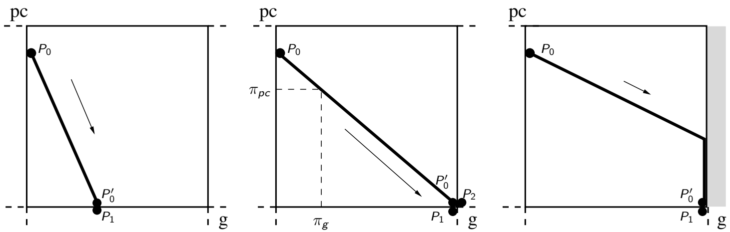
Level of a (η_a)

Semantics



Semantics

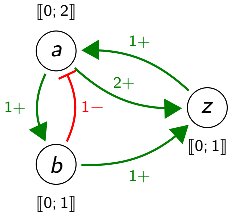




Hybrid Gene Regulatory Network (HGRN)

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

- A set of components $N = \{a, b, z\}$
- A discrete domain for each component $\text{dom}(a) = [\![0; 2]\!]$
- Real parameters C_{a,ω_a,η_a}



a	b	C_{b,ω_b,η_b}
0	0	$C_{b,\varnothing,0}$
0	1	$C_{b,\varnothing,1}$
1, 2	0	$C_{b,\{a\},0}$
1, 2	1	$C_{b,\{a\},1}$

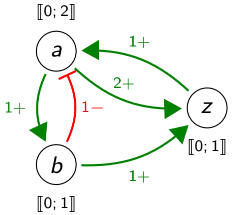
a	b	z	C_{a,ω_a,η_a}
0	0	0	$C_{a,\{b\},0}$
1	0	0	$C_{a,\{b\},1}$
2	0	0	$C_{a,\{b\},2}$
0	0	1	$C_{a,\{b,z\},0}$
1	0	1	$C_{a,\{b,z\},1}$
2	0	1	$C_{a,\{b,z\},2}$
0	1	0	$C_{a,\varnothing,0}$
1	1	0	$C_{a,\varnothing,1}$
2	1	0	$C_{a,\varnothing,2}$
0	1	1	$C_{a,\{z\},0}$
1	1	1	$C_{a,\{z\},1}$
2	1	1	$C_{a,\{z\},2}$

z	a	b	C_{z,ω_z,η_z}
0	0, 1	0	$C_{z,\varnothing,0}$
1	0, 1	0	$C_{z,\varnothing,1}$
0	2	0	$C_{z,\{a\},0}$
1	2	0	$C_{z,\{a\},1}$
0	0, 1	1	$C_{z,\{b\},0}$
1	0, 1	1	$C_{z,\{b\},1}$
0	2	1	$C_{z,\{a,b\},0}$
1	2	1	$C_{z,\{a,b\},1}$

Hybrid Gene Regulatory Network (HGRN)

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

- A set of components $N = \{a, b, z\}$
- A discrete domain for each component $\mathrm{dom}(a) = [\![0; 2]\!]$
- Real parameters C_{a,ω_a,η_a}



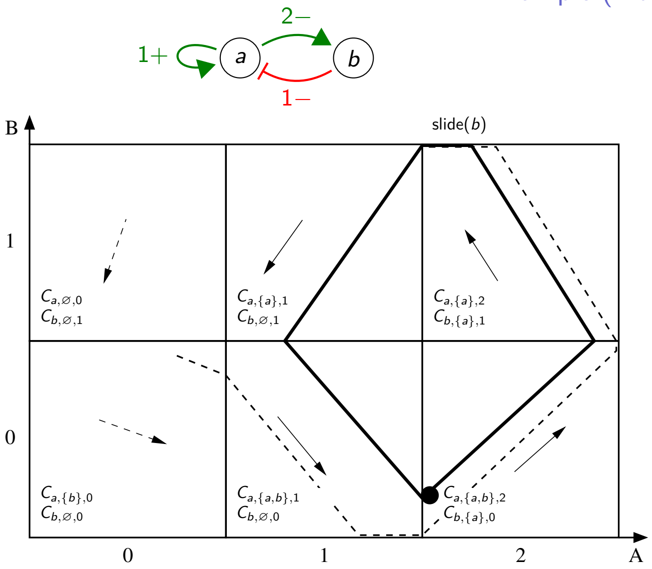
a	b	C_{b,ω_b,η_b}
0	0	$C_{b,\varnothing,0}$
0	1	$C_{b,\varnothing,1}$
1, 2	0	$C_{b,\{a\},0}$
1, 2	1	$C_{b,\{a\},1}$

a	b	z	C_{a,ω_a,η_a}
0	0	0	$C_{a,\{b\},0}$
1	0	0	$C_{a,\{b\},1}$
2	0	0	$C_{a,\{b\},2}$
0	0	1	$C_{a,\{b,z\},0}$
1	0	1	$C_{a,\{b,z\},1}$
2	0	1	$C_{a,\{b,z\},2}$
0	1	0	$C_{a,\varnothing,0}$
1	1	0	$C_{a,\varnothing,1}$
2	1	0	$C_{a,\varnothing,2}$
0	1	1	$C_{a,\{z\},0}$
1	1	1	$C_{a,\{z\},1}$
2	1	1	$C_{a,\{z\},2}$

z	a	b	C_{z,ω_z,η_z}
0	0, 1	0	$C_{z,\varnothing,0}$
1	0, 1	0	$C_{z,\varnothing,1}$
0	2	0	$C_{z,\{a\},0}$
1	2	0	$C_{z,\{a\},1}$
0	0, 1	1	$C_{z,\{b\},0}$
1	0, 1	1	$C_{z,\{b\},1}$
0	2	1	$C_{z,\{a,b\},0}$
1	2	1	$C_{z,\{a,b\},1}$

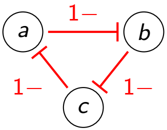
$$C_{a,\omega_a,\eta_a} \in \mathbb{R}$$

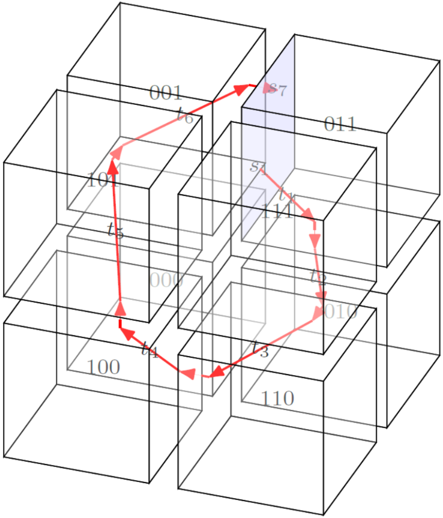
Example (2 dimensions)



Example (3 dimensions)

[Honglu Sun *et al.*, *BIOINFORMATICS*, 2023]





Hybrid Hoare Logic

Possible Parametrizations

$$C_{a,\omega_a,\eta_a} \in \mathbb{R}$$

Possible Parametrizations

$$C_{a,\omega_a,\eta_a} \in \mathbb{R}$$

Possible parametrizations $= \infty$

Hybrid Hoare Logic

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

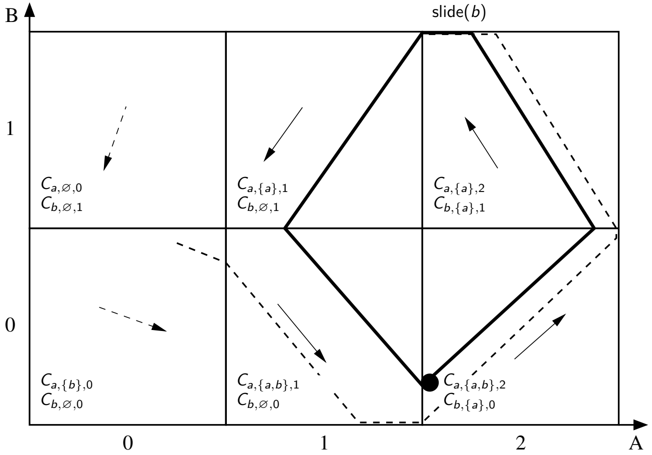
Hoare triple: $\begin{Bmatrix} D' \\ H' \end{Bmatrix} \begin{pmatrix} \Delta t \\ \mathit{assert} \\ v\pm \end{pmatrix} \begin{Bmatrix} D \\ H \end{Bmatrix}$

Weakest precondition calculus: $\begin{Bmatrix} \mathrm{WPre}(D) \\ \mathrm{WPre}(H) \end{Bmatrix} \begin{pmatrix} \Delta t \\ \mathit{assert} \\ v\pm \end{pmatrix} \begin{Bmatrix} D \\ H \end{Bmatrix}$

. . . Where $\mathrm{WPre}(H)$ is a very complicated expression

Hybrid Hoare Logic to Infer Parameters

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



Inference with Optimization

Optimization with Evolutionnary Algorithm

Learning dynamic model

⇕

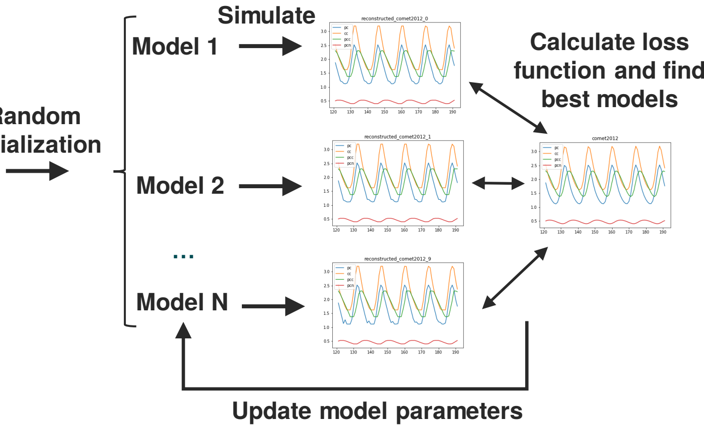
Minimise the loss function

$$\underset{Parameters}{\text{Min}} \; Distance(data_{real}, data_{simu})$$

Two bio-inspired optimization algorithms used in current works:

- **Genetic algorithm**
- **Particle swarm optimization**

Random initialization



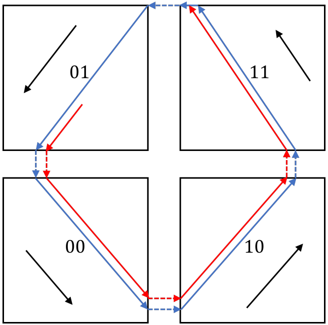
Main idea of Particle swarm optimization

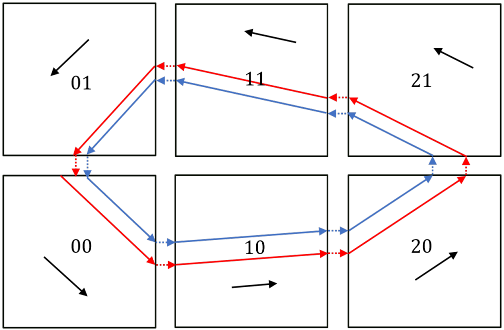
Dynamical Analysis

Limit Cycles

Given a hybrid model with given parameters, does this model feature a limit cycle?

Two possible patterns for limit cycles:



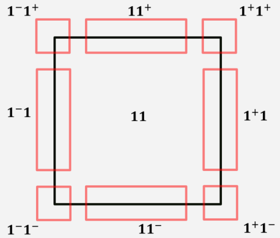


Limit Cycle Enumeration (1)

1. Abstraction of the model with discrete domain. ➡ 2. Find cycles of discrete domains which contain continuous trajectories. ➡ 3. Search for limit cycle(s) inside cycles found in step 2.

Limit Cycle Enumeration (1)

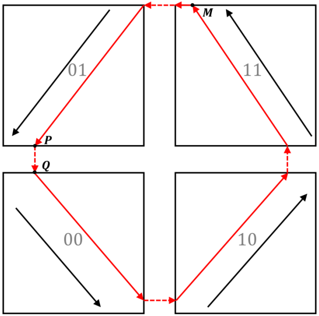
1. Abstraction of the model with discrete domain. → 2. Find cycles of discrete domains which contain continuous trajectories. → 3. Search for limit cycle(s) inside cycles found in step 2.



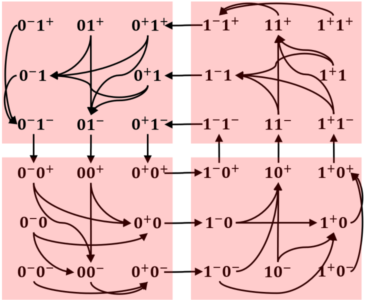
$$(1^+,1^+) = \{(\pi,11) |\ \pi^1 = 1, \pi^2 = 1\}$$

$$(1,1^+) = \{(\pi,11) |\ \pi^1 \in]0,1[, \pi^2 = 1\}$$

Examples of **discrete domain**



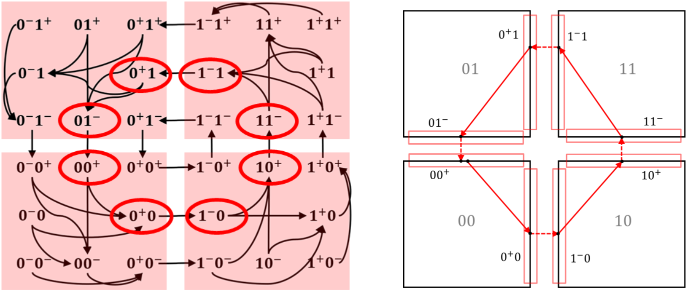
Original system



Graph of discrete domains

Limit Cycle Enumeration (2)

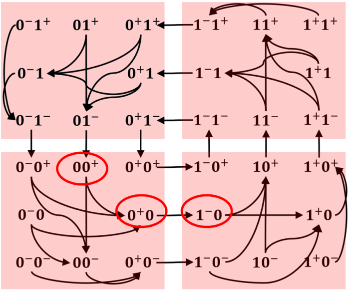
1. Abstraction of the model with discrete domain. ➡ **2. Find cycles of discrete domains which contain continuous trajectories.** ➡ 3. Search for limit cycle(s) inside cycles found in step 2.

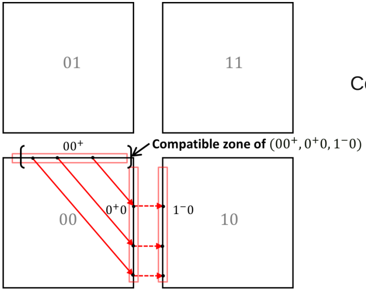


Example of a cycle of discrete domains which contains continuous trajectories

Limit Cycle Enumeration (3)

1. Abstraction of the model with discrete domain. → **2. Find cycles of discrete domains which contain continuous trajectories.** → 3. Search for limit cycle(s) inside cycles found in step 2.





Compatible zone S of $(00^+, 0^+0, 1^-0)$:
$S \subseteq 00^+$ s.t. $\forall h \in S$, any trajectory from h stays inside $(00^+, 0^+0, 1^-0)$.

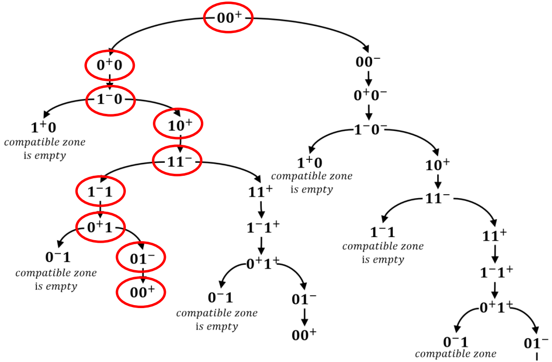
Example of **compatible zone**

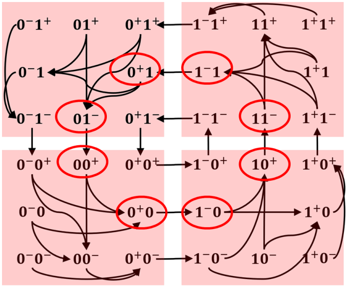
Limit Cycle Enumeration (4)

1. Abstraction of the model with discrete domain. ➡ **2. Find cycles of discrete domains which contain continuous trajectories.** ➡ 3. Search for limit cycle(s) inside cycles found in step 2.

⬍

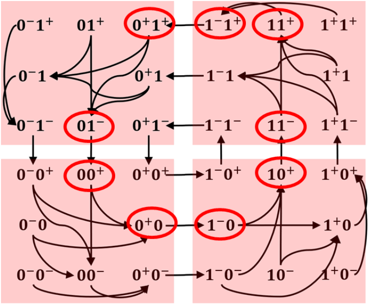
Find cycles of discrete domains of which the **compatible zones** are **not empty**.

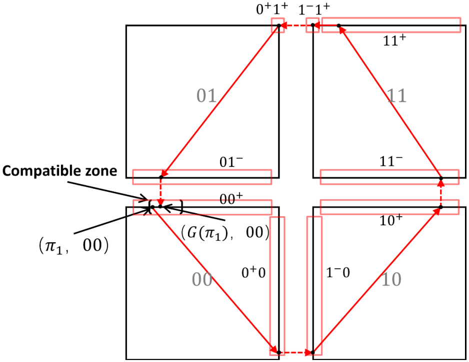




Limit Cycle Enumeration (5)

1. Abstraction of the model with discrete domain. ➡ 2. Find cycles of discrete domains which contain continuous trajectories. ➡ **3. Search for limit cycle(s) inside cycles found in step 2.**



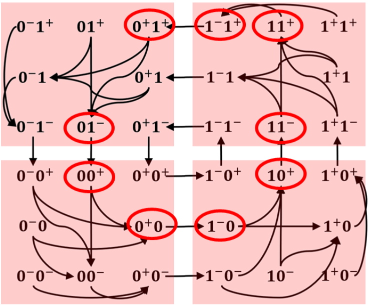


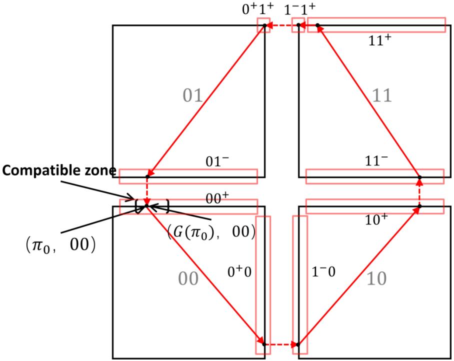
$$G(\pi_1) = M \times \pi_1 + b$$

G: Poincaré map

Limit Cycle Enumeration (5)

1. Abstraction of the model with discrete domain. ➡ 2. Find cycles of discrete domains which contain continuous trajectories. ➡ **3. Search for limit cycle(s) inside cycles found in step 2.**





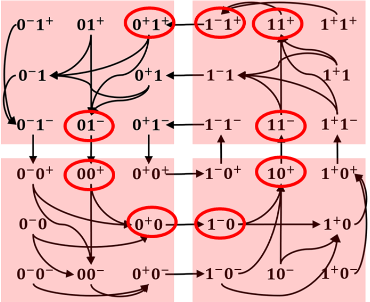
$$G(\pi_0) = M \times \pi_0 + b$$

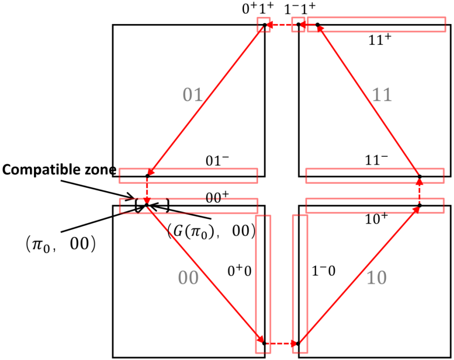
G: Poincaré map

Cycle $\Leftrightarrow G(\pi_0) = \pi_0$

Limit Cycle Enumeration (5)

1. Abstraction of the model with discrete domain. ➡ 2. Find cycles of discrete domains which contain continuous trajectories. ➡ **3. Search for limit cycle(s) inside cycles found in step 2.**



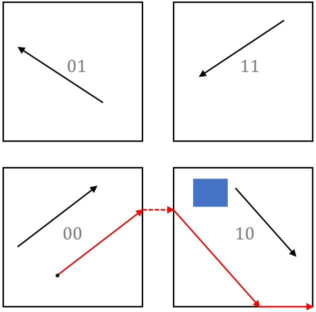


$G(\pi_0) = M \times \pi_0 + b$
G: Poincaré map

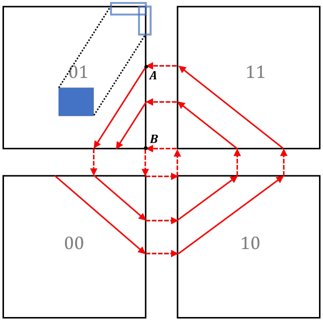
Cycle $\Leftrightarrow$ $G(\pi_0) = \pi_0$

Limit cycle $\Leftrightarrow$ all eigenvalues of M are in $[0, 1]$

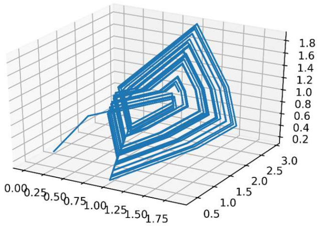
Reachability Analysis



Finite trajectory



Cyclic trajectory



(Potentially) chaotic trajectory

Conclusion

Conclusion

State of the art

- Hybrid formalism: between discrete networks and ODEs
- How to find the parameters?
- How to formally analyze the dynamics?

Parameters inference

- Hybrid Hoare logic with hybrid Dijkstra predicate calculus
- Optimization algorithm (parameters and thresholds)

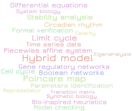
Formal analysis of the dynamics

- The Poincaré map is very useful
- Enumeration of limit cycles
- Reachability analysis

Thanks

Jonathan BEHAEGEL

Jean-Paul COMET



Honglu SUN

Morgan MAGNIN

Bibliography (mine)

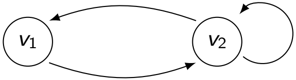
- Jonathan Behaegel, Jean-Paul Comet, Maxime Folschette. Constraint Identification Using Modified Hoare Logic on Hybrid Models of Gene Networks. *International Symposium on Temporal Representation and Reasoning (TIME'17)*, 2017.
- Honglu Sun, Maxime Folschette, Morgan Magnin. Limit cycle analysis of a class of hybrid gene regulatory networks. 20th International Conference on Computational Methods in Systems Biology (CMSB'22), *Lecture Notes in Computer Science*, vol. 13447, 2022.
- Honglu Sun, Jean-Paul Comet, Maxime Folschette, Morgan Magnin. Condition for sustained oscillations in repressilator based on a hybrid modeling of gene regulatory networks. *International Conference on Bioinformatics Models, Methods and Algorithms (BIOINFORMATICS 2023)*, 2023.

Bibliography

- Charles A. R. Hoare. An axiomatic basis for computer programming. *Communications of the ACM* 12 (10), 1969.
- René Thomas. Boolean formalization of genetic control circuits. *Journal of Theoretical Biology* 42 (3), 1973.
- Edsger W. Dijkstra. Guarded commands, nondeterminacy and formal derivation of programs. *Communications of the ACM* 18, 1975.
- Émilien Cornillon, Jean-Paul Comet, Gilles Bernot, Gilles Énée. Hybrid gene network: a new formalism and a software environment. *Modelling Complex Biological Systems in the Context of Genomics*, 2016.
- Jonathan Behaegel. *Modèles hybrides de réseaux de régulation : étude du couplage des cycles cellulaire et circadien*. PhD thesis, Université Côte d'Azur, 2018.
- Gilles Bernot, Jean-Paul Comet, Zohra Khalis, Adrien Richard, Olivier Roux. A genetically modified Hoare logic. *Theoretical Computer Science*, volume 765, 2019.
- Marie Pelleau, Antoine Miné, Charlotte Truchet, Frédéric Benhamou. A Constraint Solver based on Abstract Domains. 14th International Conference on Verification, Model Checking, and Abstract Interpretation (VMCAI'13), *Lecture Notes in Computer Science*, volume 7737, 2013.

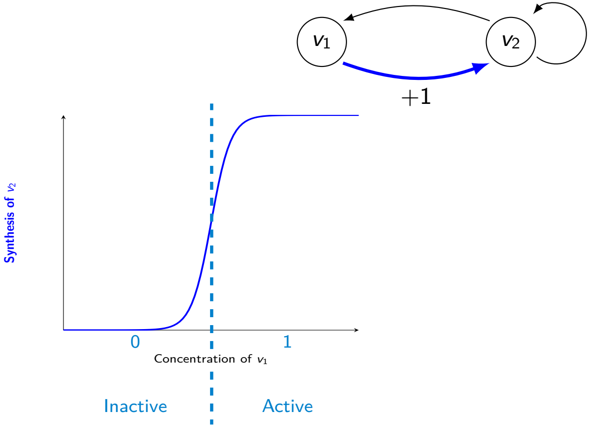
Origin of René Thomas Modeling

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



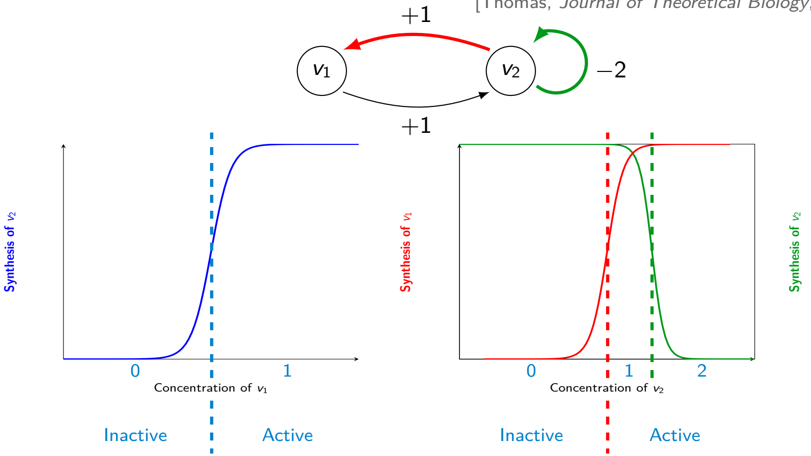
Origin of René Thomas Modeling

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



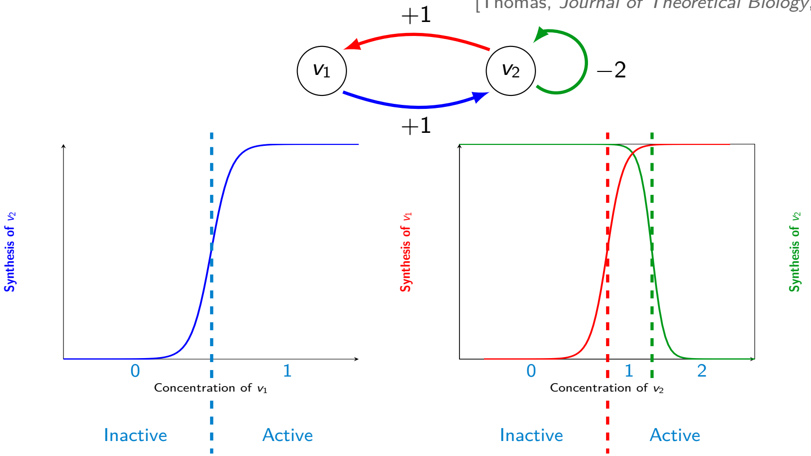
Origin of René Thomas Modeling

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



Origin of René Thomas Modeling

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



Inactive | Active | Inactive | Active

v_1 has no effect on v_2

v_1 triggers synthesis of v_2

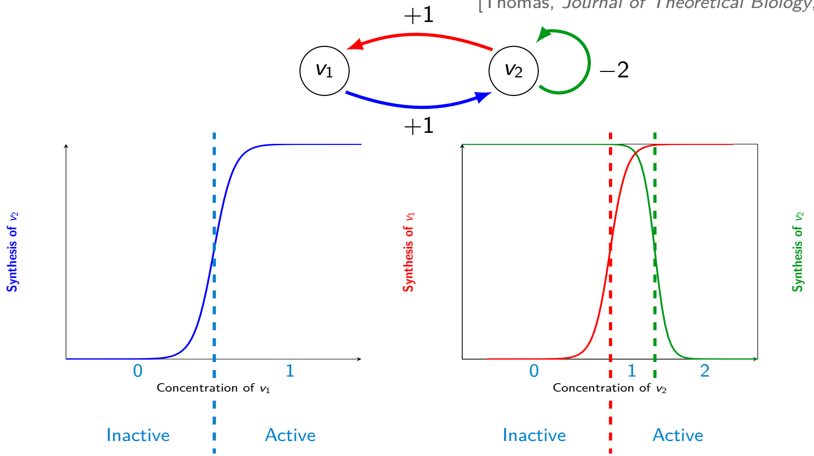
v_2 has no effect on v_1 or itself

v_2 triggers synthesis of v_1

v_2 triggers self-degradation

Origin of René Thomas Modeling

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



v_1 has no effect on v_2

v_1 triggers synthesis of v_2

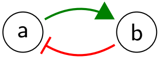
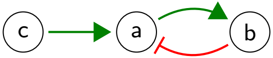
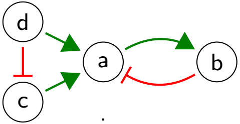
v_2 has no effect on v_1 or itself

v_2 triggers synthesis of v_1

v_2 triggers self-degradation

Relative strength of $v_1 \xrightarrow{+1} v_2$ and $v_2 \xrightarrow{-2} v_2$? $\Longrightarrow$ Parameters!

Discrete Parameter 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}	

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

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

Hybrid Hoare Logic

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

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

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

Properties (pre- and post-conditions): $\begin{Bmatrix} D \\ H \end{Bmatrix}$ $\leftarrow$ 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: $\begin{Bmatrix} \mathrm{WPre}(D) \\ \mathrm{WPre}(H) \end{Bmatrix} \begin{pmatrix} \Delta t \\ assert \\ v\pm \end{pmatrix} \begin{Bmatrix} D \\ H \end{Bmatrix}$

$$\mathrm{WPre}(D) \equiv D[\eta_v \setminus \eta_v \pm 1]$$

$$\mathrm{WPre}(H) \equiv H[\eta_v \setminus \eta_v \pm 1] \wedge \Phi_v^{\pm}(\Delta t) \wedge \mathcal{F}_v(\Delta t) \wedge \neg \mathcal{W}_v^{\pm} \wedge \mathcal{A}(\Delta t, assert) \wedge \mathcal{J}_v$$

Weakest Precondition in Hybrid Hoare Logic

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

Hoare triple: $\left\{\begin{matrix}\mathrm{WPre}(D)\\ \mathrm{WPre}(H)\end{matrix}\right\} \begin{pmatrix}\Delta t\\ \mathit{assert}\\ v\pm\end{pmatrix} \left\{\begin{matrix}D\\ H\end{matrix}\right\}$

$$\mathrm{WPre}(D) \equiv D[\eta_v \setminus \eta_v \pm 1]$$

$$\mathrm{WPre}(H) \equiv H[\eta_v \setminus \eta_v \pm 1] \wedge \Phi_v^{\pm}(\Delta t) \\ \wedge \mathcal{F}_v(\Delta t) \wedge \neg \mathcal{W}_v^{\pm} \wedge \mathcal{A}(\Delta t, \mathit{assert}) \wedge \mathcal{J}_v$$

- $H[\eta_v \setminus \eta_v \pm 1]$ ← Final hybrid state with substitutions
- $\Phi_v^{\pm}(\Delta t)$ ← Current celerity of v makes it change discrete state
- $\mathcal{F}_v(\Delta t)$ ← v is the first variable to change discrete state
- $\mathcal{W}_v^{\pm}$ ← v does not face a black wall (opposing celerity)
- $\mathcal{A}(\Delta t, \mathit{assert})$ ← Δt and *assert* must be true in current state
- $\mathcal{J}_v$ ← Connect successive steps (if several instructions)

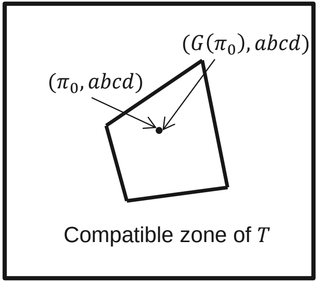
Constraints

$$((((((((((\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}))))))) \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})))))))$$

Limit Cycle Enumeration (6)

A cycle of discrete domains T: $a^+b^+cd \rightarrow \cdots \rightarrow a^+b^+cd$

Discrete domain a^+b^+cd



$$\pi_0 = \begin{pmatrix} 1 \\ 1 \\ x_0 \\ y_0 \end{pmatrix}$$

$$G(\pi_0) = \pi_0 \Leftrightarrow \binom{x_0}{y_0} = A \binom{x_0}{y_0} + b$$

Two eigenvalues of A: λ_1, λ_2

It is a stable limit cycle $\Leftrightarrow |\lambda_i| < 1, i \in \{1,2\}$