École thématique BioRegul : Modélisation Formelle de Réseaux de Régulation Biologique — 2023-06-06

Modélisation, analyse et inférence de paramètres pour les réseaux de régulation hybrides

Maxime FOLSCHETTE

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

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

Université de Lille
cnrs
centralelille
BioComputing

Introduction

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
→ Static computational model to study hepatocellular carcinoma progression

CNRS/LS2N — postdoc — 2018–2019
→ Integrate heterogeneous data with semantic web

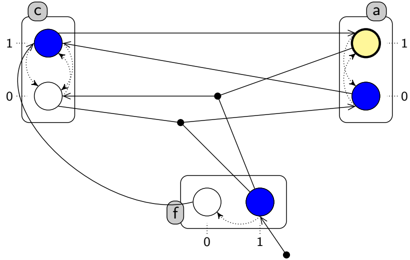
Today

Centrale Lille — **maître de conférences** — 2019 ⋮
→ Understand the role of glucose absorption in diabetes
→ Learn plankton food chains from measurments
→ **Formal verification of hybrid models**

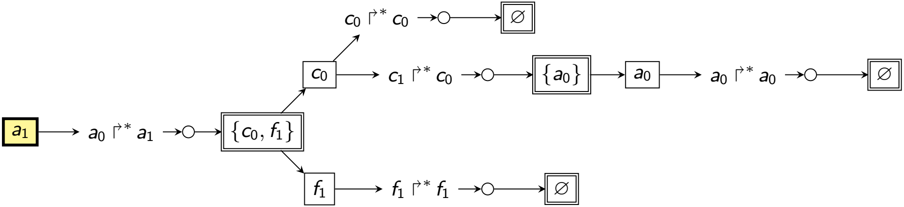
Other Works

Abstract Interpretation

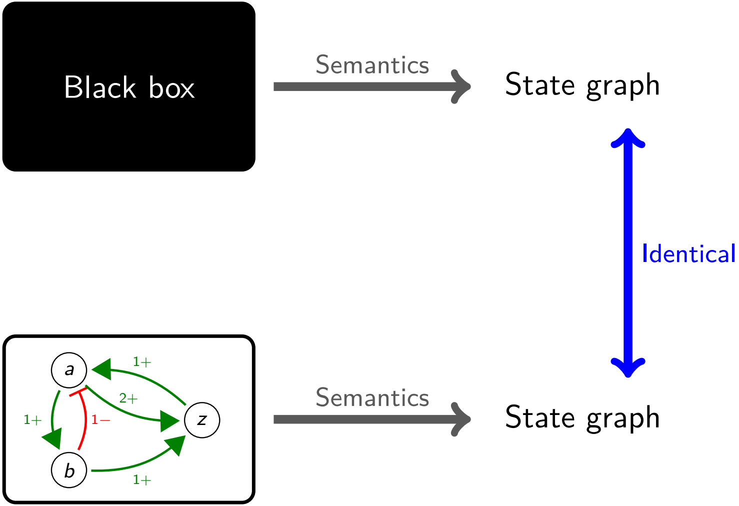
[Folschette *et al.*, *Theoretical Computer Science*, 2015b]



- No cycle
- No conflict
- All leaves are $\varnothing$



Learning Logic Programs for Explainability



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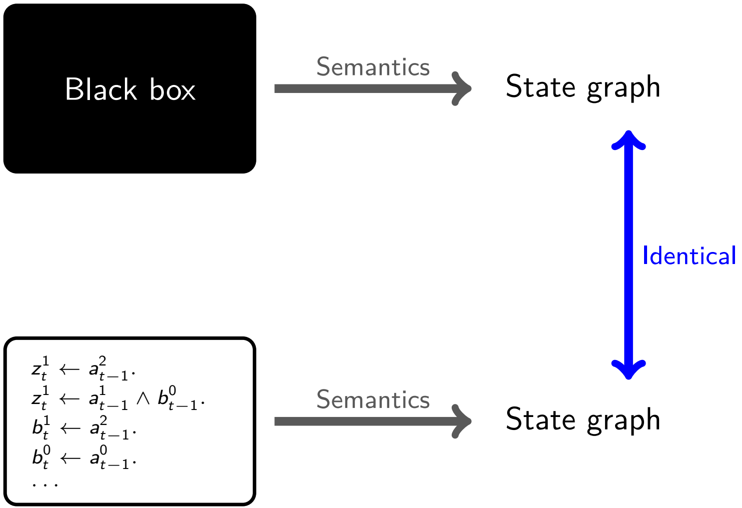
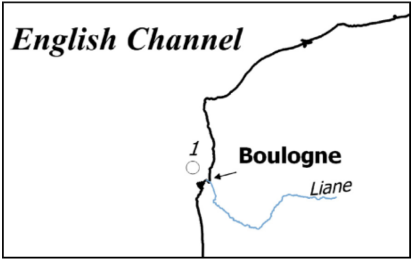


Long-term Datasets of Plankton Populations

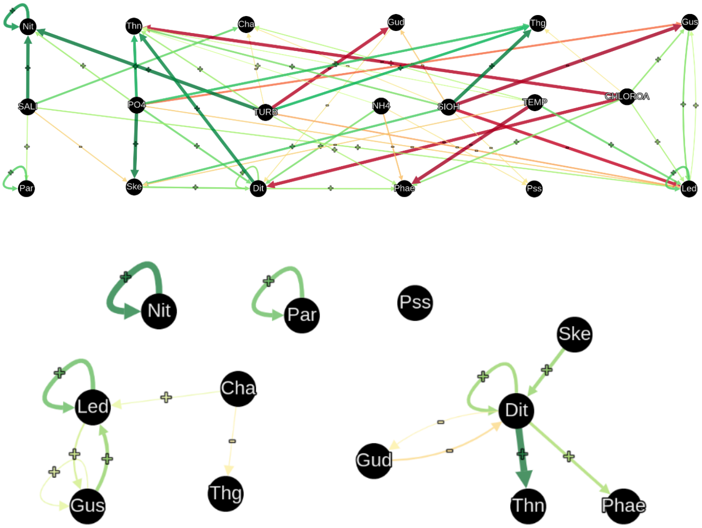


https://www.seanoe.org/data/00397/50832/

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)

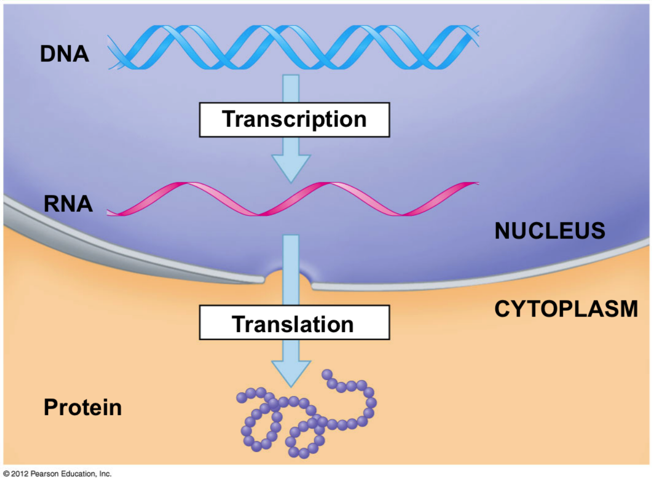
Environmental variables (7) Phytoplankton species (12)

Learning Biotic Interactions



Discrete Models

Preliminary Abstraction



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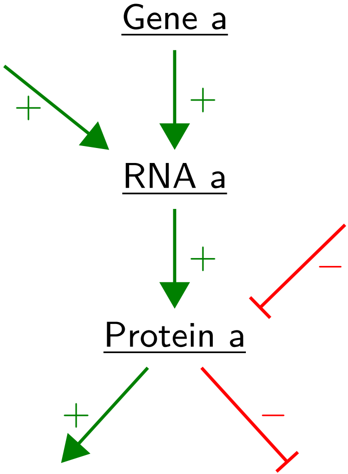

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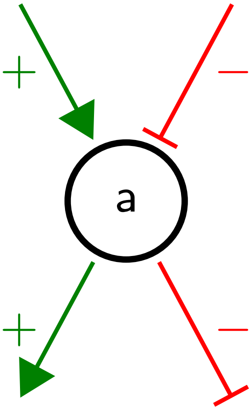

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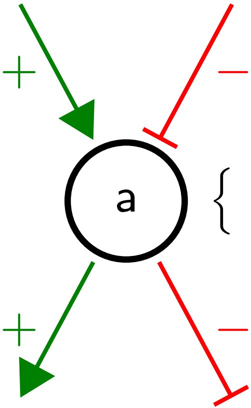
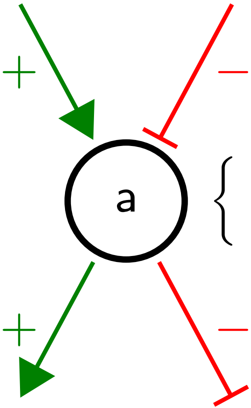


$$\left\{ \begin{array}{l} 0 = \text{inactive} \\ 1 = \text{active} \end{array} \right\}$$

Preliminary Abstraction

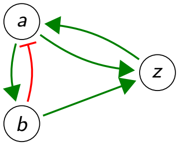


$$\left\{ \begin{array}{l} 0 = \text{complete degradation} \\ 1 = \text{traces} \\ 2 = \text{saturation} \end{array} \right\}$$

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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abz

000 010 001 011

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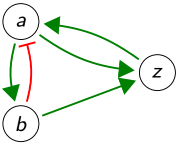

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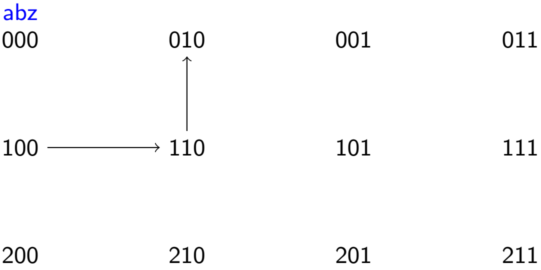

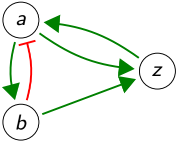

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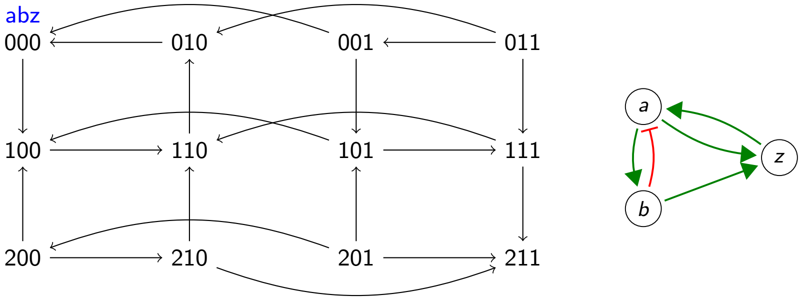

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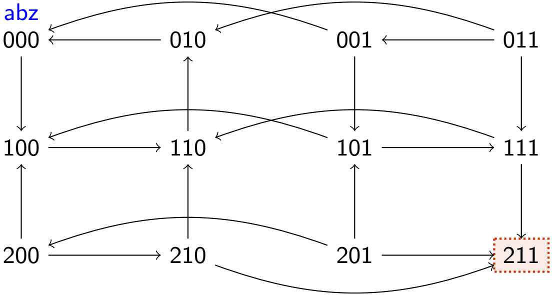

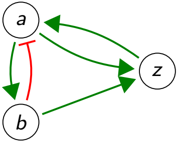

- **Stable state** = state with no successors

State Graph

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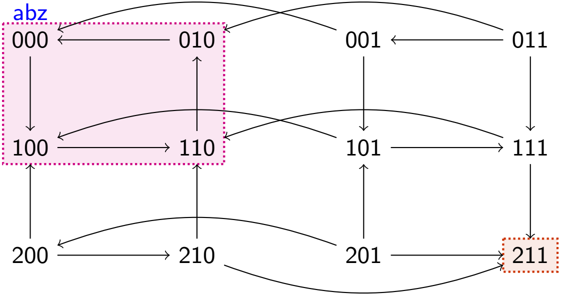

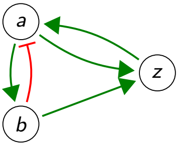

- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape

State Graph

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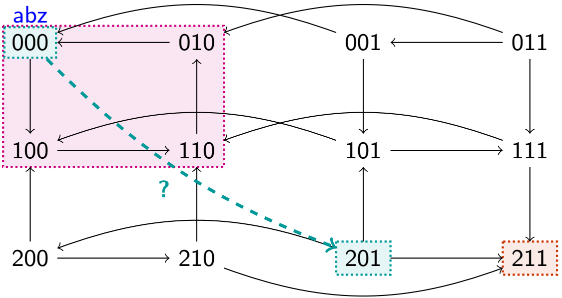
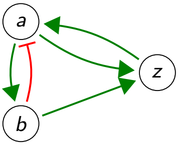
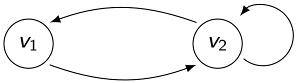




- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape
- **Reachability** = from **000**, can I reach **201**?

Origin of René Thomas Modeling

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



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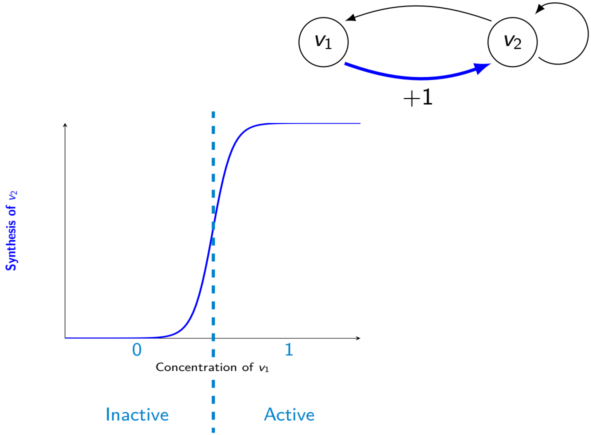

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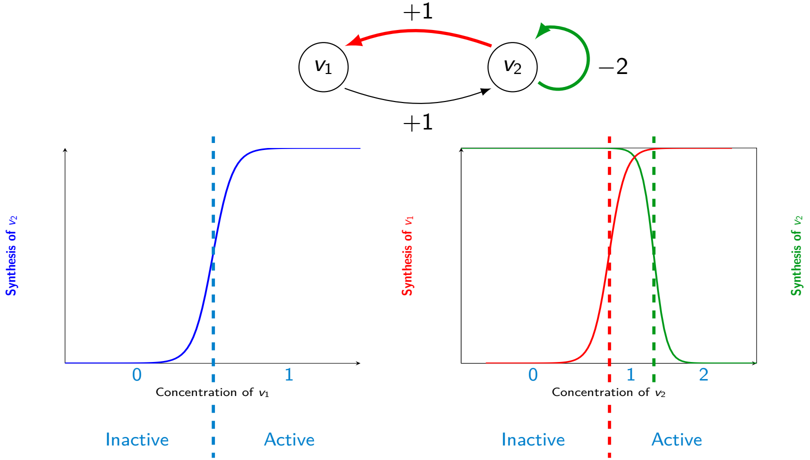

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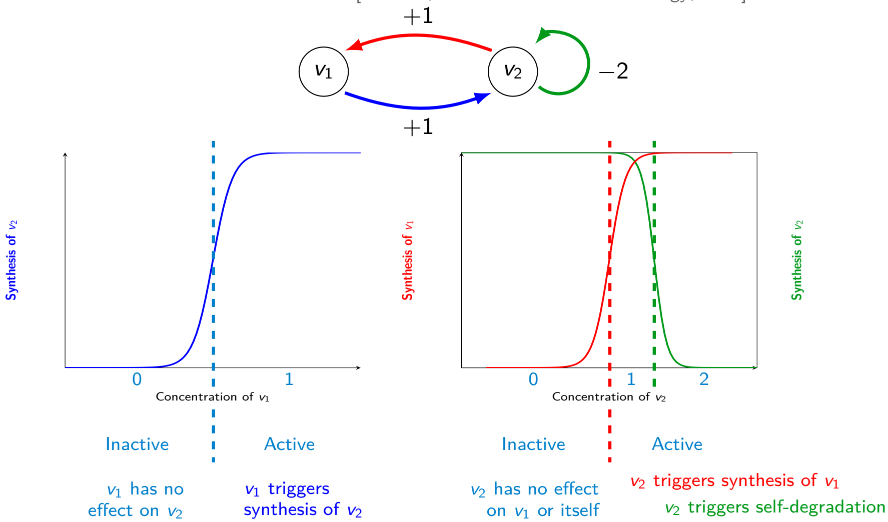

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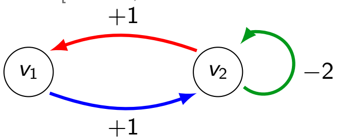
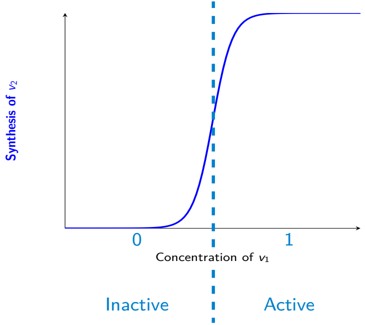
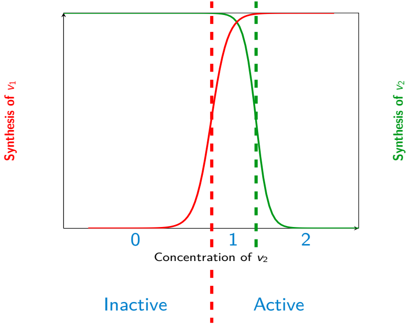






v_1 has no effect on v_2

v_1 triggers synthesis of v_2

v_2 has no effect on v_1 or itself

v_2 triggers synthesis of v_1

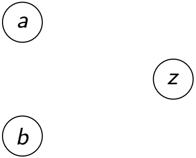
v_2 triggers self-degradation

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

Discrete 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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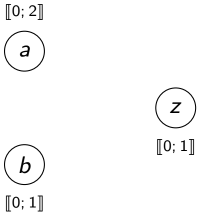

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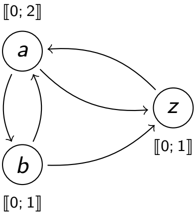
- Discrete parameters / evolution functions $K_{a,\omega}$



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**

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- A set of components $N = \{a, b, z\}$
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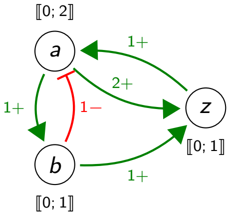
- Signs & thresholds on the edges (redundant) $a \xrightarrow{2+} z$



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

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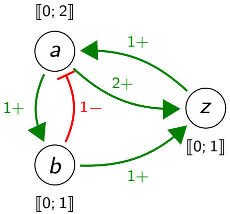

a	$K_{b,\omega}$
0	**0**
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2	**1**

z	b	$K_{a,\omega}$
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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

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

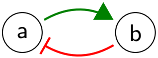
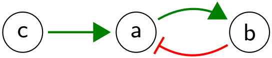
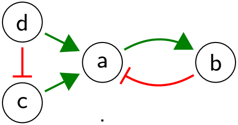
With Boolean variables, $|\text{dom}(v)| = 2$: $\quad \left(2^{\left(2^{|\text{pred}(v)|}\right)}\right)^{|N|}$

- 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
		$\lvert \text{dom}(v) \rvert = 2$
	16	
	128	
	8192	
⋮	⋮	$\lvert \text{pred}(v) \rvert = 1$
(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]

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

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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 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"

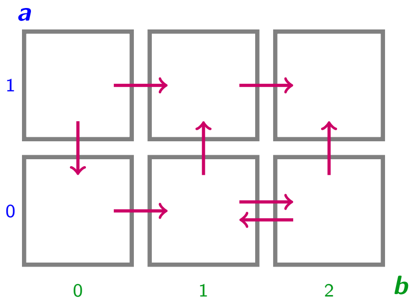
Example: $\{ \ a = 0 \land b = 0 \ \} \ a+ \ ; \ b+ \ \{ \ a = 1 \land b > 0 \ \}$

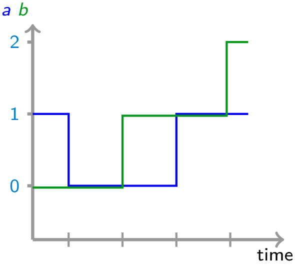
Weakest precondition calculus:
Given p and $Post$, one can compute the weakest (most general) precondition $WPre$ so that $\{ \ WPre \ \} \ p \ \{ \ Post \ \}$ holds
$WPre$ constrains the initial state of the system and the parameters

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

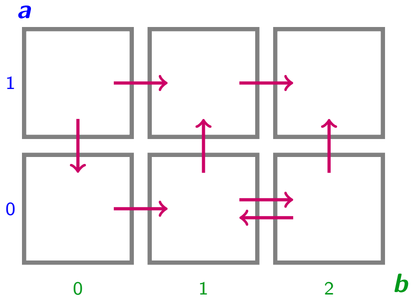
Hybrid Models

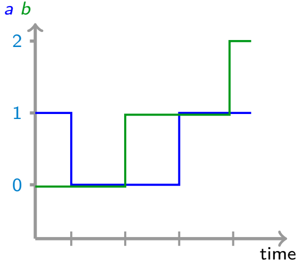
Objective of Hybrid Thomas Modeling

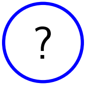


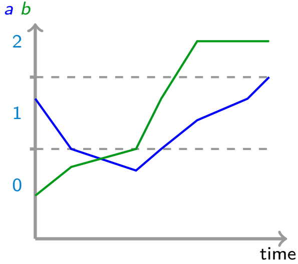


Objective of Hybrid Thomas Modeling



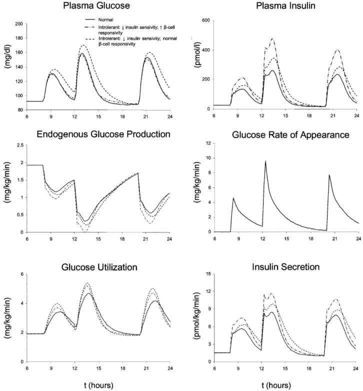






Differential Equations

[Dalla Man *et al.*, *IEEE Trans. Biomed. Eng.*, 2007]



$$\begin{cases} \dot{G}_p(t) = EGP(t) + Ra(t) - U_{\text{ii}}(t) - E(t) - k_1 \cdot G_p(t) + k_2 \cdot G_t(t) & G_p(0) = G_{pb} \\ \dot{G}_t(t) = -U_{\text{id}}(t) + k_1 \cdot G_p(t) - k_2 \cdot G_t(t) & G_t(0) = G_{tb} \\ G(t) = \frac{G_p}{V_G} & G(0) = G_b \end{cases}$$

$$\begin{cases} Q_{\text{sto}}(t) = Q_{\text{sto1}}(t) + Q_{\text{sto2}}(t) & Q_{\text{sto}}(0) = 0 \\ \dot{Q}_{\text{sto1}}(t) = -k_{gri} \cdot Q_{\text{sto1}}(t) + D \cdot d(t) & Q_{\text{sto1}}(0) = 0 \\ \dot{Q}_{\text{sto2}}(t) = -k_{\text{empt}}(Q_{\text{sto}}) \cdot Q_{\text{sto2}}(t) + k_{gri} \cdot Q_{\text{sto1}}(t) & Q_{\text{sto2}}(0) = 0 \\ \dot{Q}_{\text{gut}} = -k_{\text{abs}} \cdot Q_{\text{gut}}(t) + k_{\text{empt}}(Q_{\text{sto}}) \cdot Q_{\text{sto2}}(t) & Q_{\text{gut}}(0) = 0 \\ Ra(t) = \frac{f \cdot k_{\text{abs}} \cdot Q_{\text{gut}}(t)}{\text{BW}} & Ra(0) = 0 \end{cases}$$

$$\begin{cases} \dot{I}_l(t) = -(m_1 + m_3(t)) \cdot I_l(t) + m_2 I_p(t) + S(t) & I_l(0) = I_{lb} \\ \dot{I}_p(t) = -(m_2 + m_4) \cdot I_p(t) + m_1 \cdot I_l(t) & I_p(0) = I_{pb} \\ I(t) = \frac{I_p}{V_I} & I(0) = I_b \end{cases}$$

Comparison of Frameworks

Differential equations

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

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Comparison of Frameworks

Differential equations

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- – Difficult to tune (equations/parameters)
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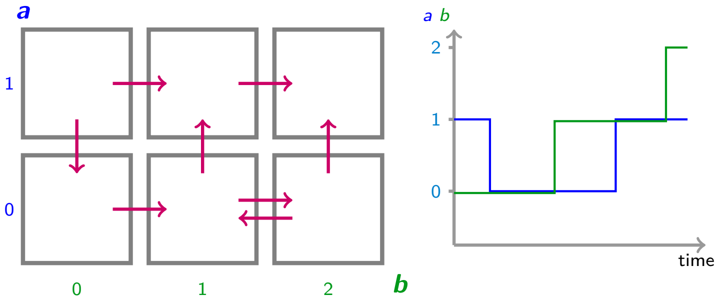
Hybrid models

- \+ 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

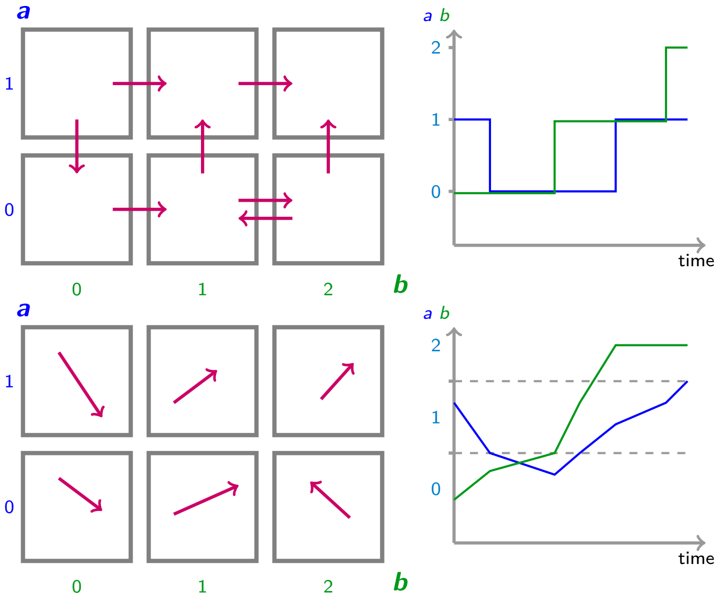
Discrete models

- \+ Abstraction: Much more 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:

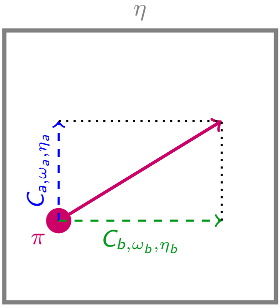
$$\eta = (\eta_a, \eta_b)$$

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

Fractional part in discrete state:

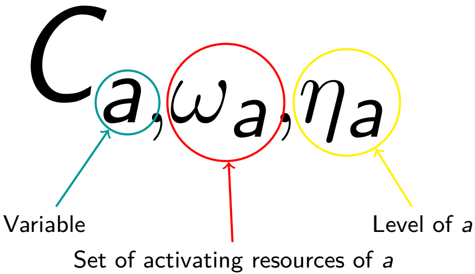
$$\pi = (\pi_a, \pi_b)$$

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



Celerity:

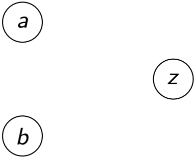
$$C_{a,\omega_a,\eta_a}$$



Hybrid Gene Regulatory Network (HGRN)

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

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



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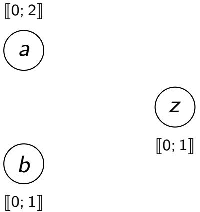

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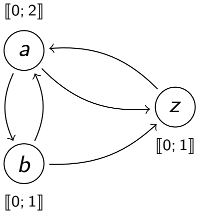
- A discrete domain for each component $\text{dom}(a) = [\![0;2]\!]$
- Real parameters C_{a,ω_a,η_a}



a	b	C_{b,ω_b,η_b}
0	0	$C_{b,\emptyset,0}$
0	1	$C_{b,\emptyset,1}$
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	$C_{a,\emptyset,0}$
1	1	0	$C_{a,\emptyset,1}$
2	1	0	$C_{a,\emptyset,2}$
0	1	1	$C_{a,\{z\},0}$
1	1	1	$C_{a,\{z\},1}$
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…

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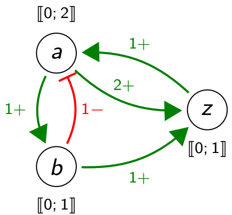

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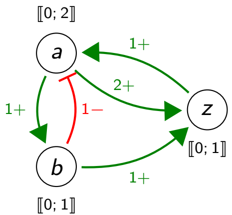

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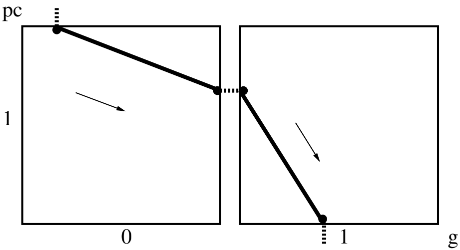
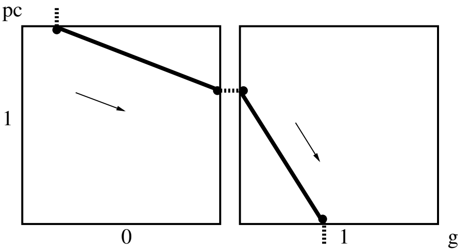
...

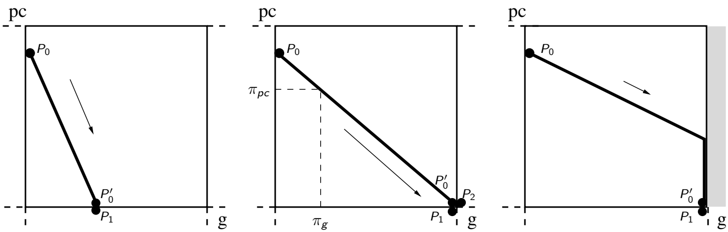
$$C_{a,\omega_a,\eta_a} \in \mathbb{R}$$

Semantics

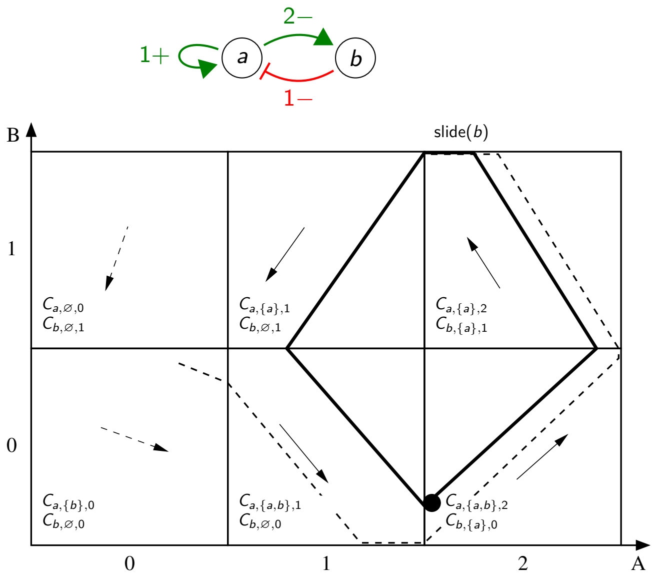


Semantics



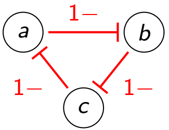


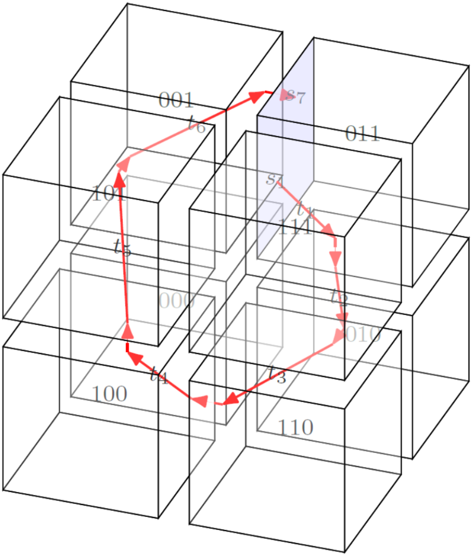
Example (2 dimensions)



Example (3 dimensions)

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





Possible Parametrizations

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

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

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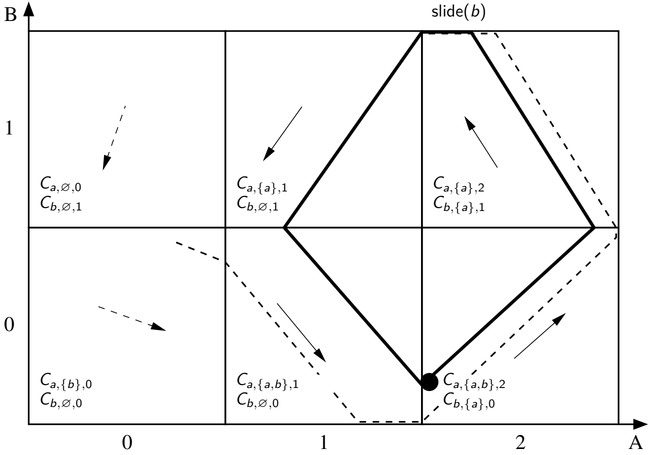
$$\text{Possible parametrizations} = \infty$$

Hybrid Hoare Logic

Hybrid Hoare Logic to Infer Parameters

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



Hybrid Hoare Logic

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

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

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

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

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

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

Weakest Precondition in Hybrid Hoare Logic

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

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

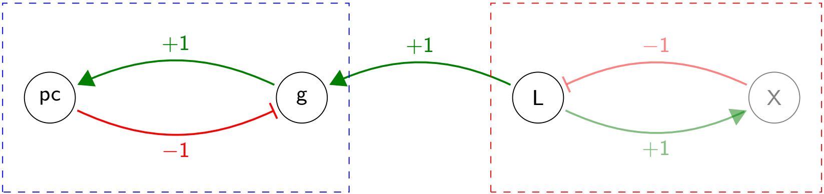
$$\mathrm{WP}(H) \equiv H[\eta_v \setminus \eta_v \pm 1] \land \Phi_v^{\pm}(\Delta t) \land \mathcal{F}_v(\Delta t) \land \neg \mathcal{W}_v^{\pm} \land \mathcal{A}(\Delta t, \mathit{assert}) \land \mathcal{J}_v$$

- $H[\eta_v \setminus \eta_v \pm 1]$ ← 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)

Applications

A Simplified Circadian Cycle Model

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

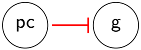


Simplified circadian cycle

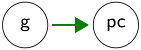
Day/light cycle

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

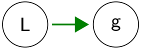
L = light of the day
X = Modeling artifact (clock)



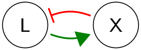
= PER/CRY complex inhibits *per* and *cry*



= transcription and complexation



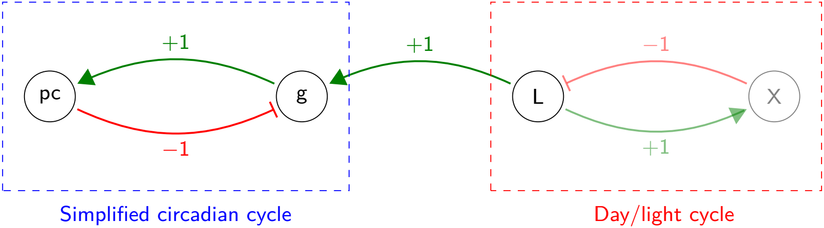
= light makes BMAL1/CLOCK complex activate *per* and *cry*



= 12h day/night oscillation

A Simplified Circadian Cycle Model

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



$$\begin{Bmatrix} D_8 \\ H_8 \end{Bmatrix} \begin{pmatrix} 0.9 \\ \top \\ pc- \end{pmatrix} ; \begin{pmatrix} 4.5 \\ \top \\ g+ \end{pmatrix} ; \begin{pmatrix} 0.6 \\ \top \\ X+ \end{pmatrix} ; \begin{pmatrix} 5.53 \\ \text{slide}^{+}(g) \\ pc+ \end{pmatrix} ; \begin{pmatrix} 0.47 \\ \top \\ L- \end{pmatrix} ; \begin{pmatrix} 5.4 \\ \text{slide}^{+}(pc) \\ g- \end{pmatrix} ; \begin{pmatrix} 0.6 \\ \text{slide}^{-}(L) \\ X- \end{pmatrix} ; \begin{pmatrix} 6 \\ \top \\ L+ \end{pmatrix} \begin{Bmatrix} D_0 \\ H_0 \end{Bmatrix}$$

$$\text{where} \quad \begin{cases} D_0 & \equiv \quad (\eta_g = 0) \wedge (\eta_{pc} = 1) \wedge (\eta_L = 1) \wedge (\eta_X = 0) \\ H_0 & \equiv \quad (\pi_g = 0.12) \wedge (\pi_{pc} = 0.12) \wedge (\pi_L = 0) \wedge (\pi_X = 0) \end{cases}$$

Constraints

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

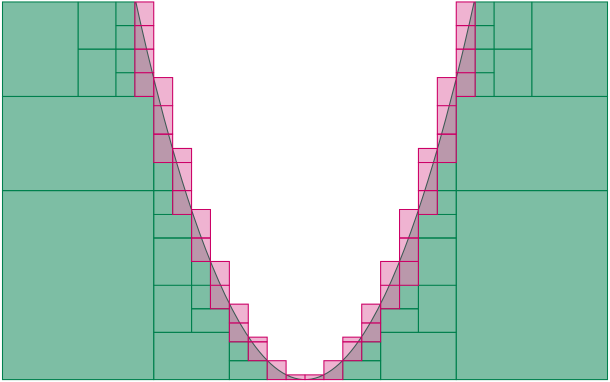
Constraints After Simplification

Constraints After Simplification

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

Nonlinear Solver: AbSolute

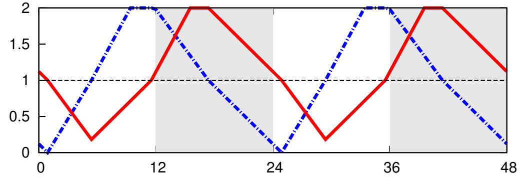
[Pelleau *et al.*, *VMCAI*, 2013]



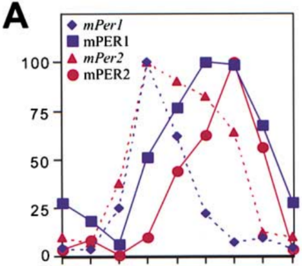
Solving the constraint: $y \leqslant x^2$

Results

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



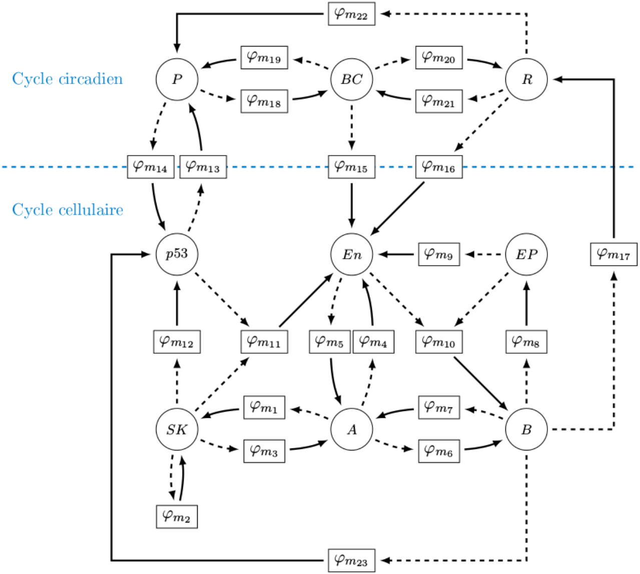
Simulation with 1 set of compatible values



Experiments

Coupling of Cell and Circadian Cycles

[Behaegel, PhD thesis, 2018]



Coupling of Cell and Circadian Cycles

[Behaegel, PhD thesis, 2018]

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

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

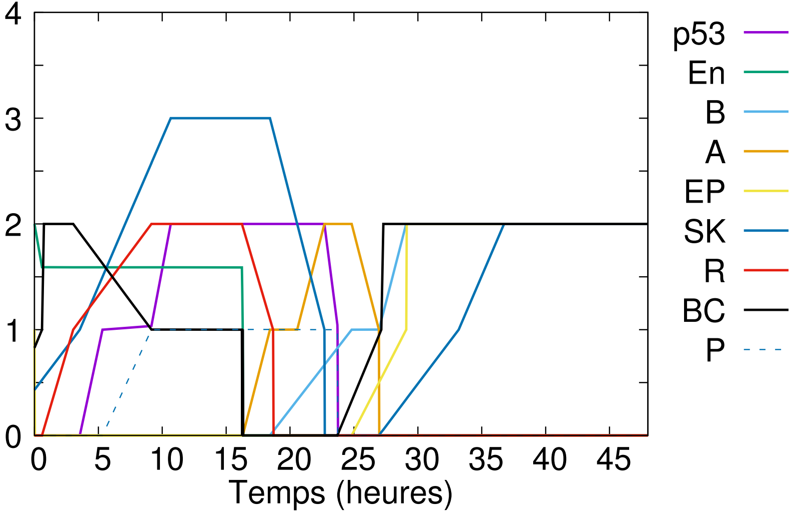
$$\begin{pmatrix} 1.06 \\ \top \\ p53- \end{pmatrix} ; \begin{pmatrix} 1.07 \\ \text{slide}^-(SK) \\ B+ \end{pmatrix} ; \begin{pmatrix} 1.97 \\ \top \\ P- \end{pmatrix} ; \begin{pmatrix} 0.16 \\ \top \\ A- \end{pmatrix} ; \begin{pmatrix} 2.14 \\ \text{slide}^+(B) \\ EP+ \end{pmatrix} ; \begin{pmatrix}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

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

1536 constraints on 152 celerities and 378 fractional parts →
10 minutes → unsure solutions only

Coupling of Cell and Circadian Cycles

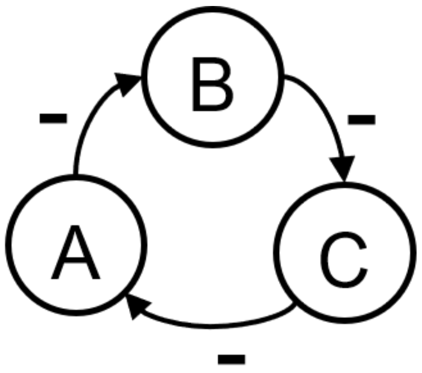
[Behaegel, PhD thesis, 2018]



Inference with Optimization Methods

Problem definition

Parameters identification of a hybrid model of **repressilator**



The influence graph of **repressilator**

All parameters:

$$\begin{matrix} V_{ac0a0} & V_{ba0b0} & V_{cb0c0} \\ V_{ac0a1} & V_{ba0b1} & V_{cb0c1} \\ V_{ac1a0} & V_{ba1b0} & V_{cb1c0} \\ V_{ac1a1} & V_{ba1b1} & V_{cb1c1} \end{matrix}$$

Temporal derivatives (V_i)

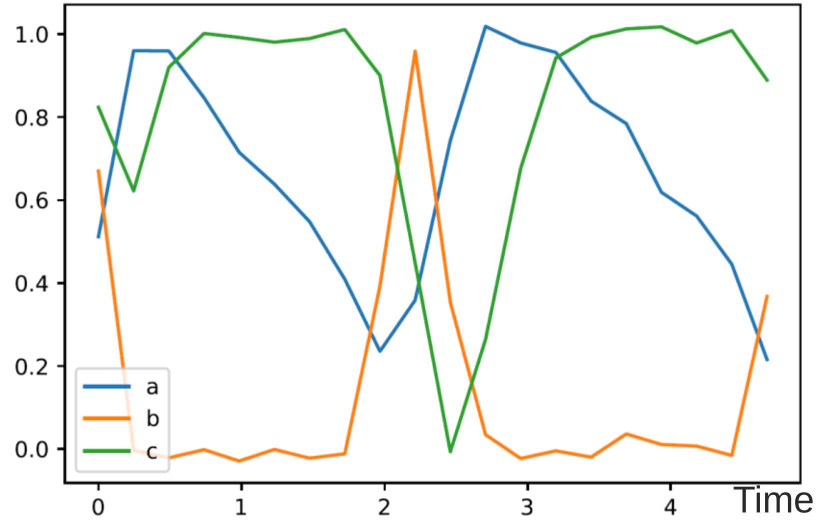
θ_{ab} θ_{bc} θ_{ca}

Thresholds (θ_i)

Problem definition

Parameters identification of a hybrid model of **repressilator**

Expressions of genes



Time series data (by simulation)

Parameters identification

Constraint I (Parameter set)

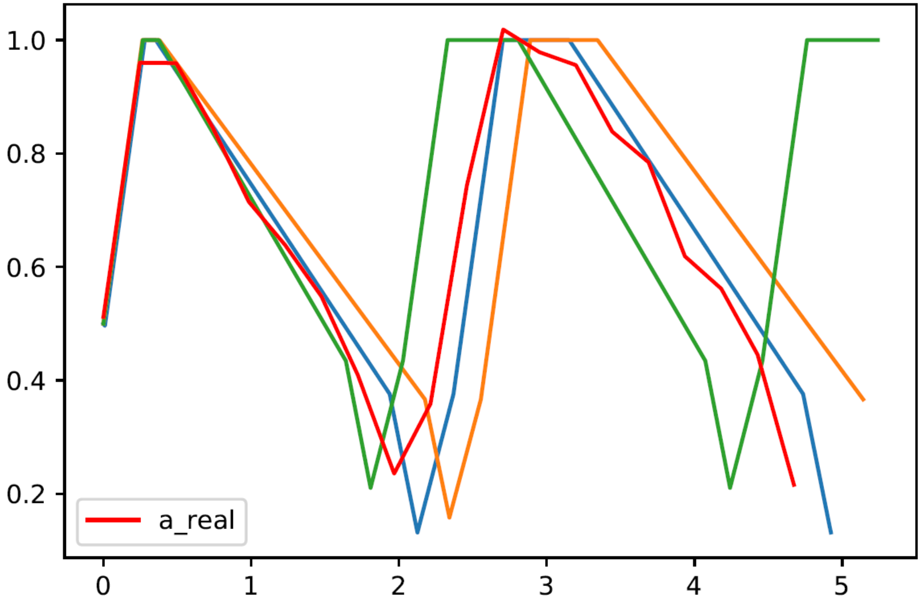
$$V_i \in I_i^v = [\underline{I_i^v}, \overline{I_i^v}]$$

$$\theta_i \in I_i^\theta = [\underline{I_i^\theta}, \overline{I_i^\theta}]$$

Idea of the parameters identification method

Parameters identification by optimization:

Find parameter set which minimizes the difference between simulations and real data



Simulations of several models (model1, model2, model3) in a parameter set

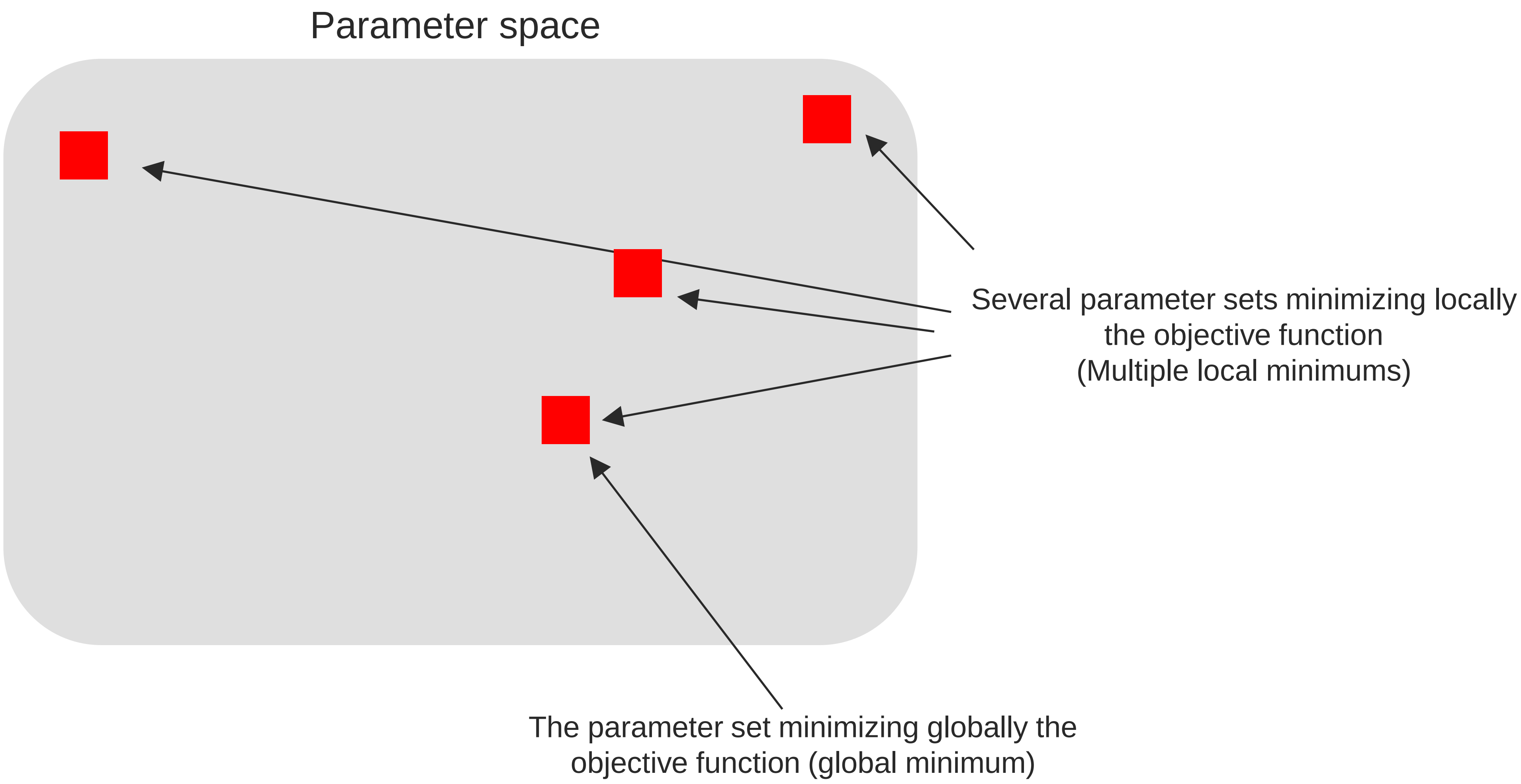
Objective function

Optimize the function:

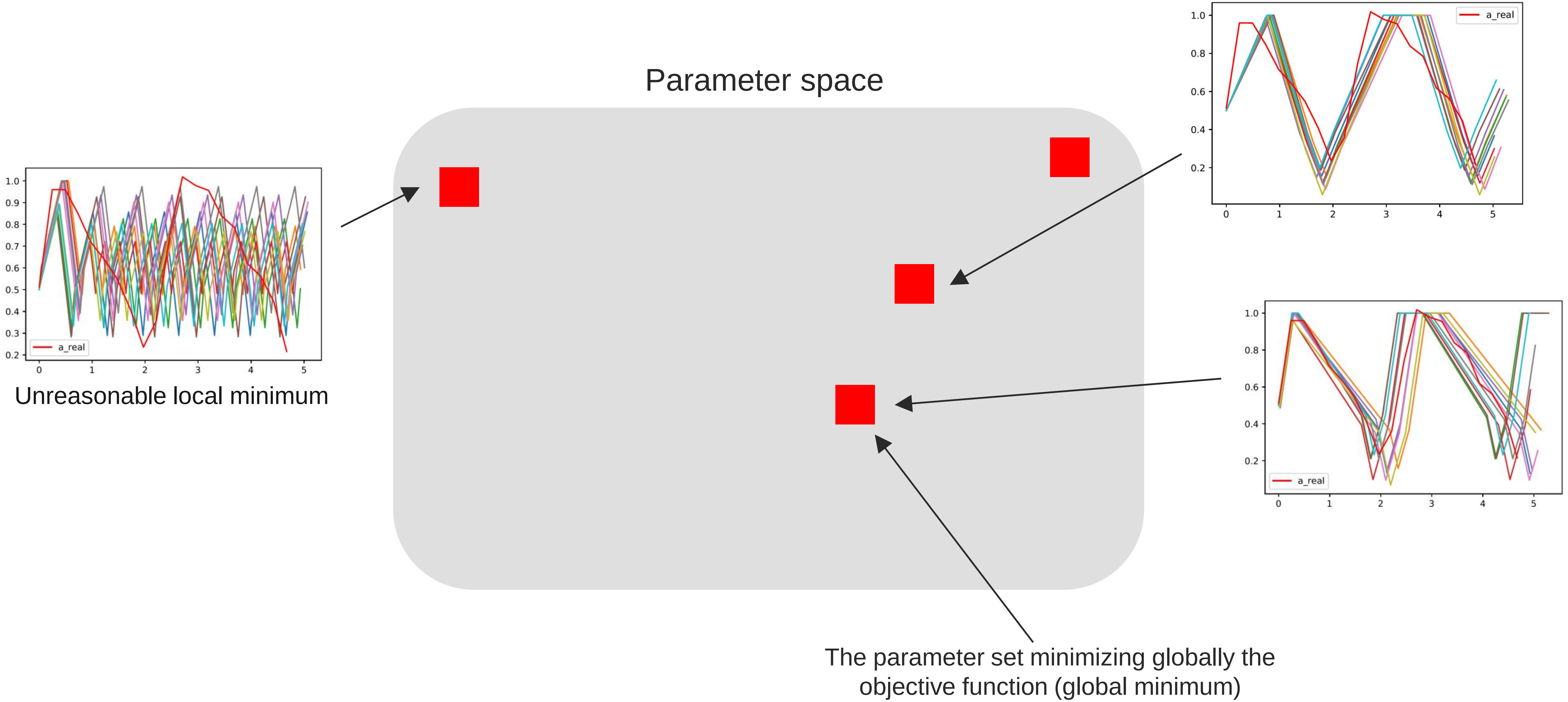
$$\frac{1}{n_1}\sum_{model_i \in M}\frac{1}{n_0}\sum_{j=1}^{n_0} weight^j * (real\ data^j - simulation_i^j)^2$$

M is a set of n_1 models sampled from a parameter set.
$simulation_i$ is the simulation of $model_i$.
n_0 is the number of data.
$weight^j$ is proportional to the estimated temporal derivative.

Optimization based on genetic algorithm

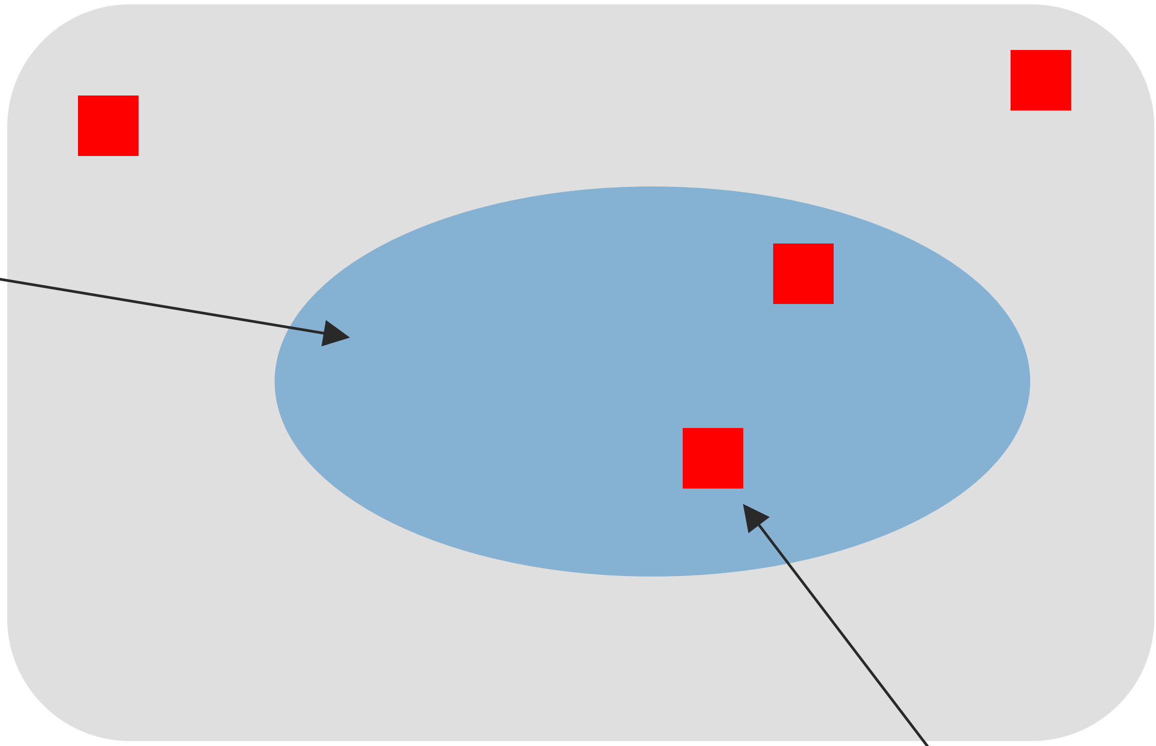


Optimization based on genetic algorithm



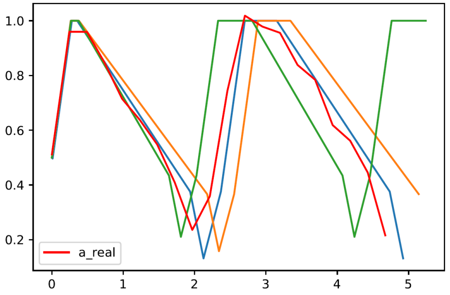
Optimization based on genetic algorithm

Parameter space



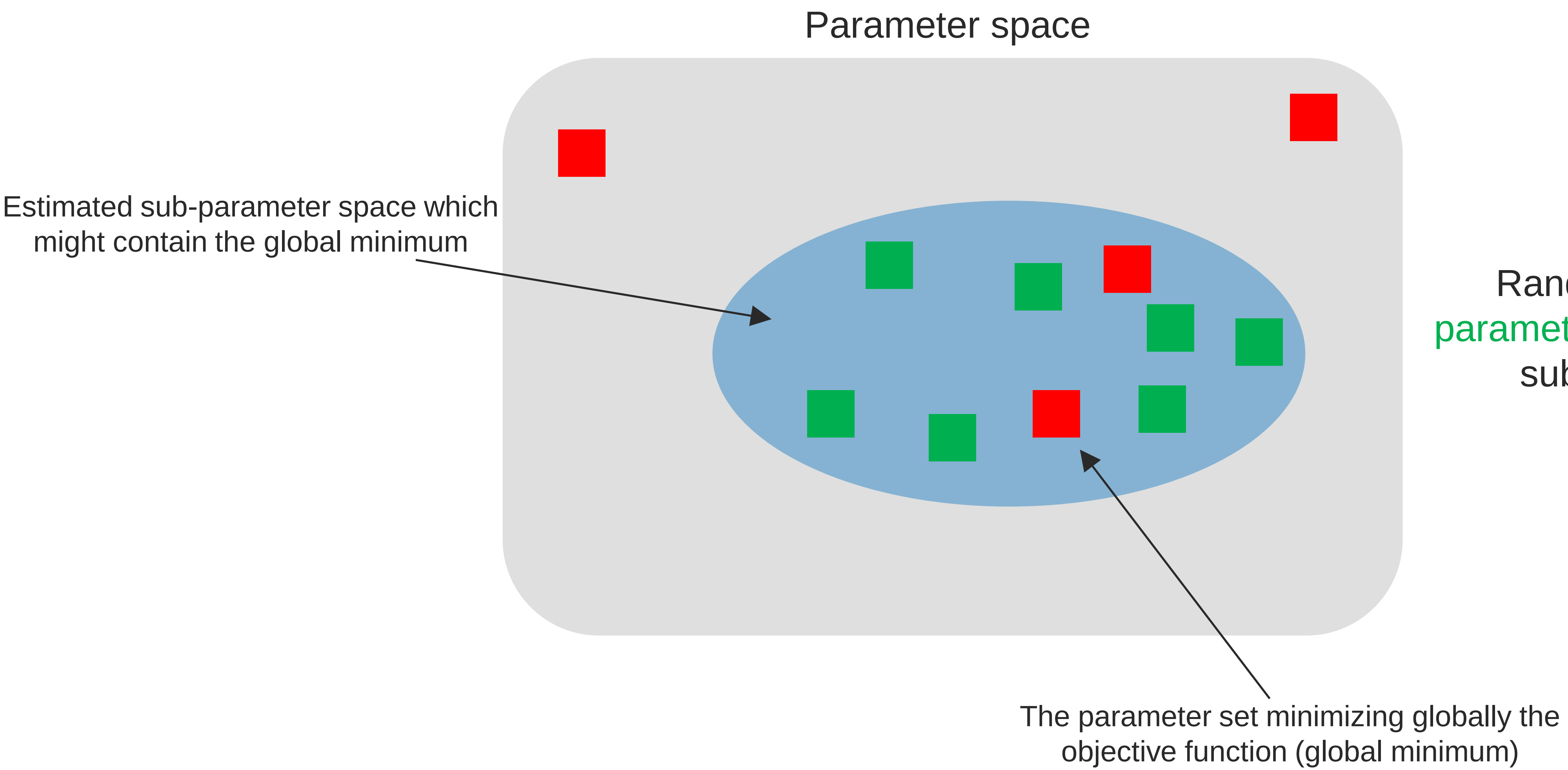
Estimated sub-parameter space which might contain the global minimum

- Based on the estimated temporal derivatives
- Based on biological knowledge (Oscillation? How many periods?)
- Based on symbolic analysis of this model



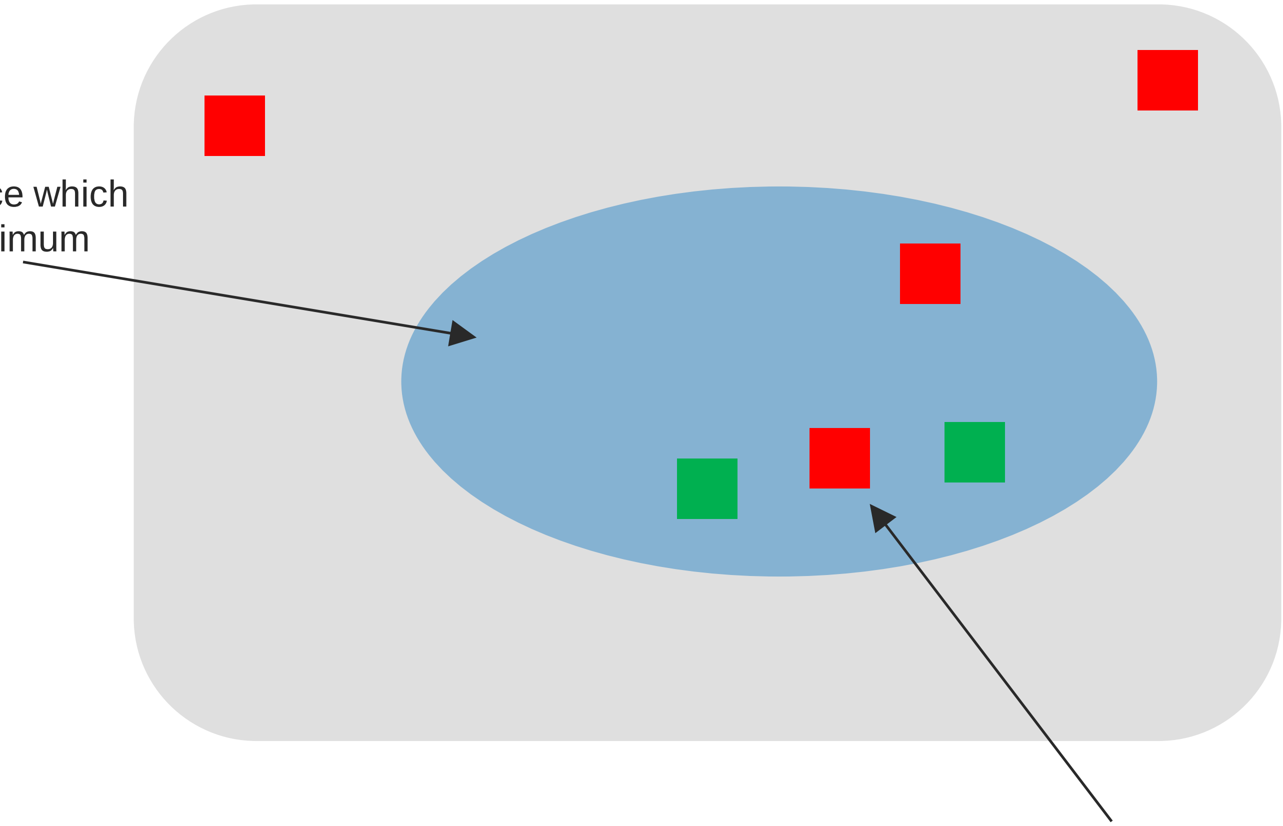
The parameter set minimizing globally the objective function (global minimum)

Optimization based on genetic algorithm



Random generate some parameter sets in the estimated sub-parameter space

Optimization based on genetic algorithm

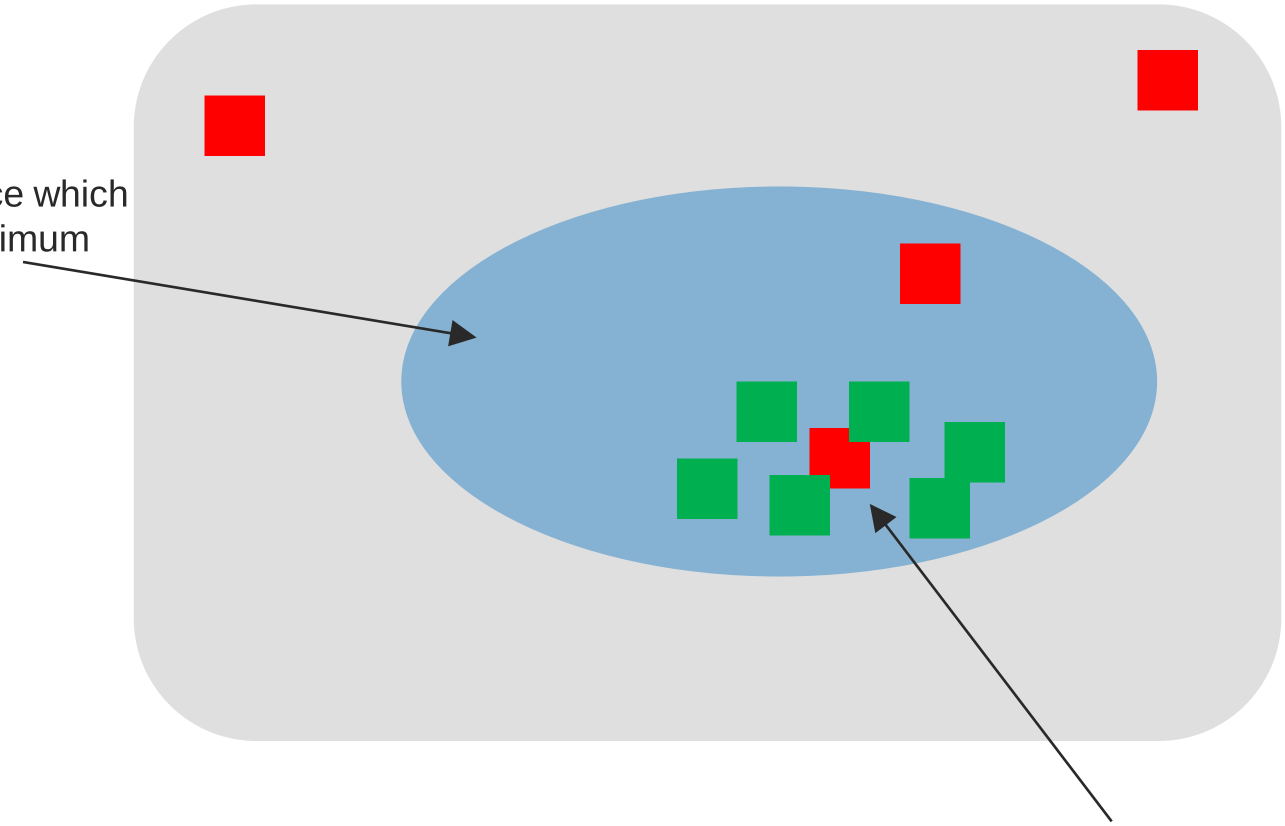


Choose the best parameter sets based on the objective function

Optimization based on genetic algorithm

Parameter space

Estimated sub-parameter space which might contain the global minimum

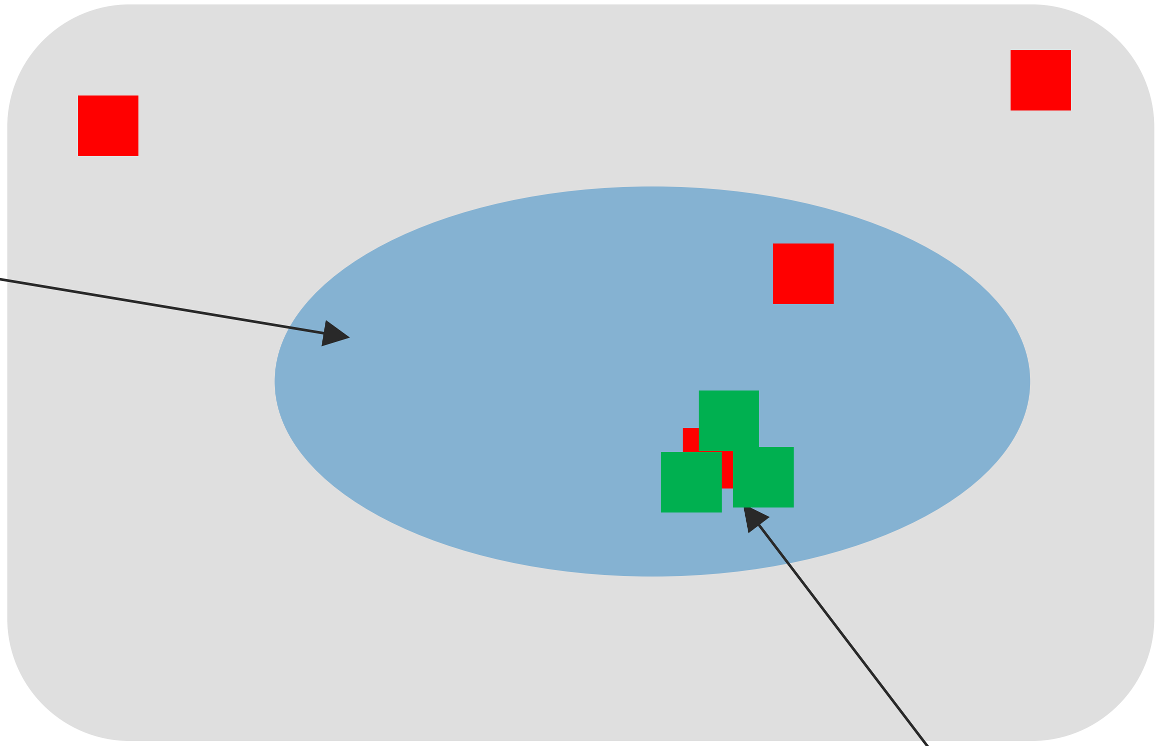


Generate new parameter sets based the best parameter sets

The parameter set minimizing globally the objective function (global minimum)

Optimization based on genetic algorithm

Parameter space



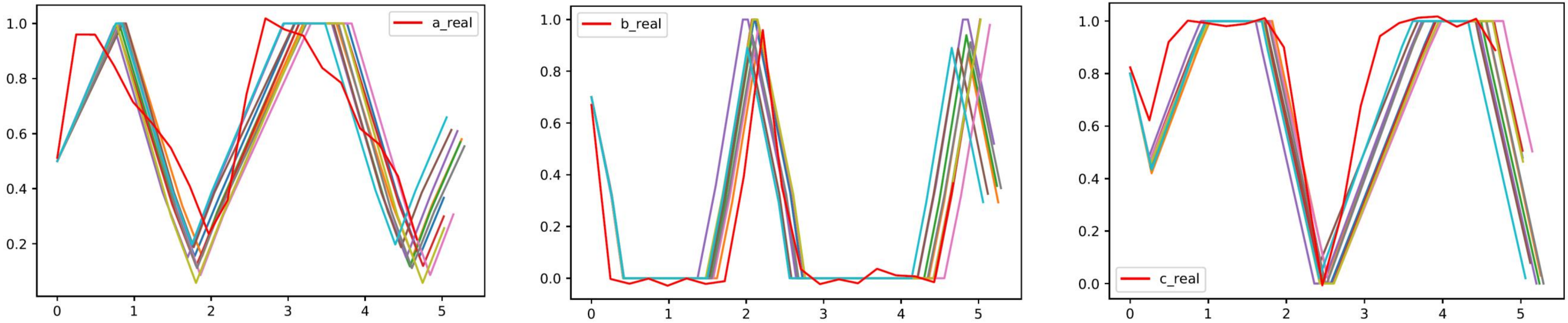
Estimated sub-parameter space which might contain the global minimum

The parameter set minimizing globally the objective function (global minimum)

Repeat this process for a fixed number of times.

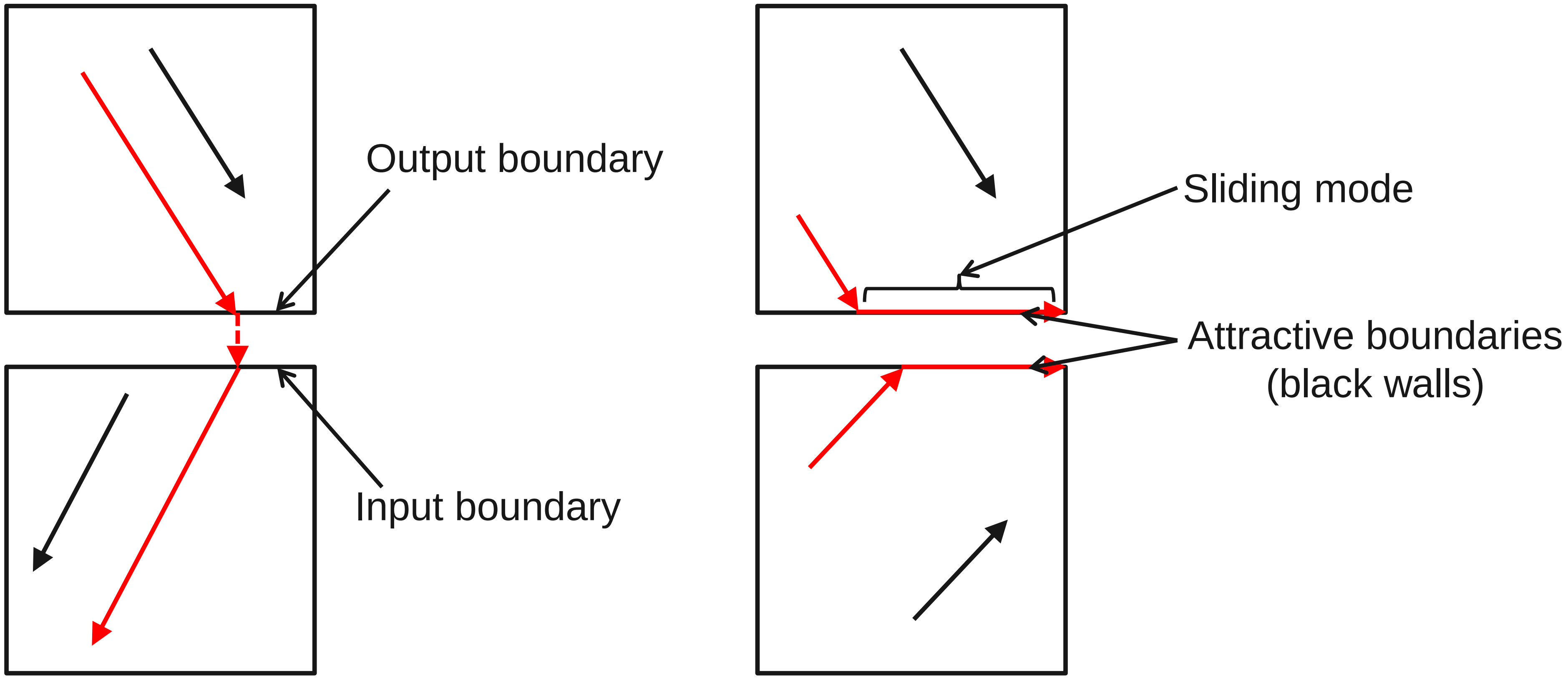
Results

Simulation of the best parameter set found by the algorithm

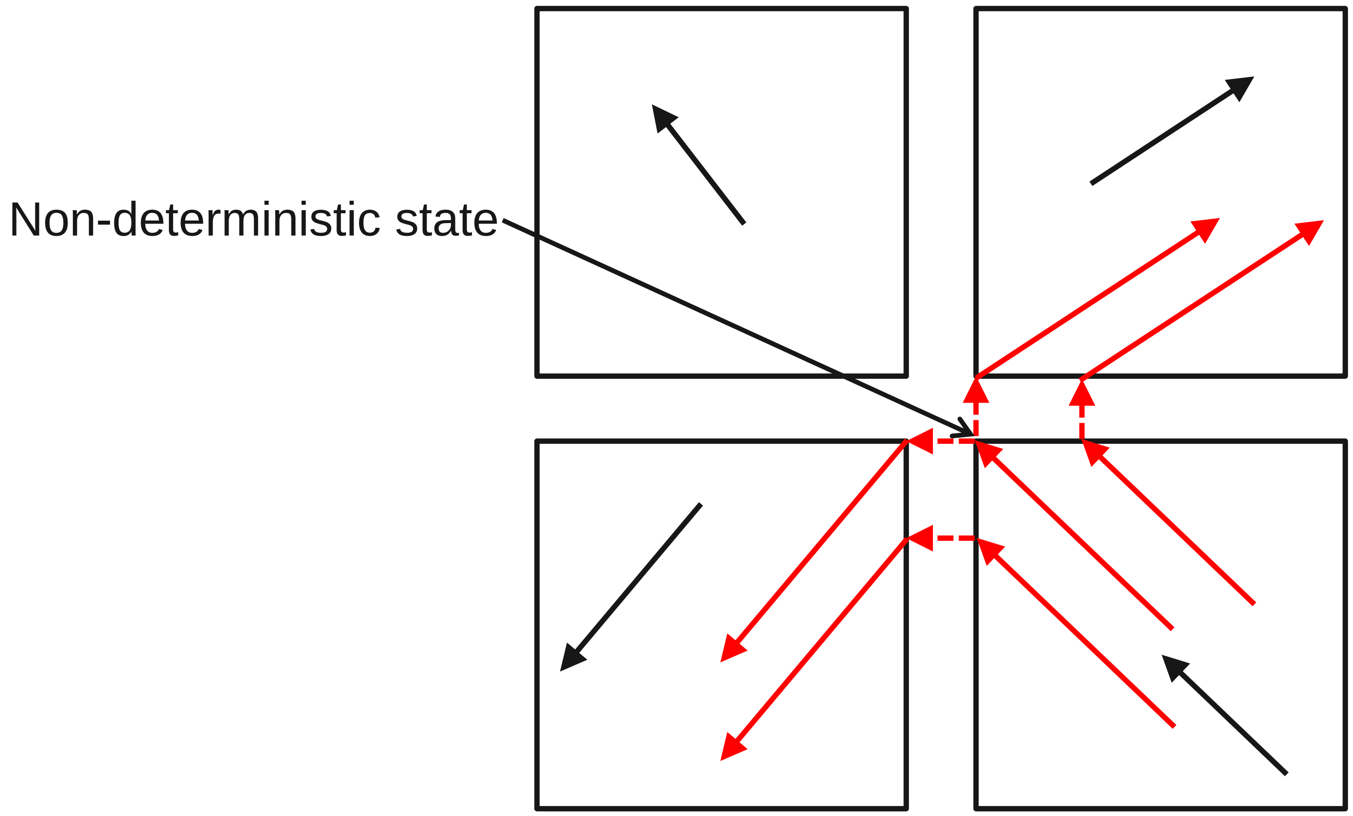


Dynamical Analysis

Boundaries and simulation of HGRN

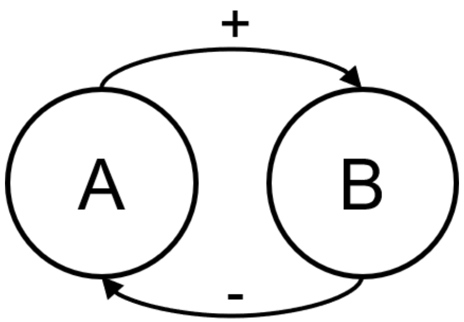


Boundaries and simulation of HGRN

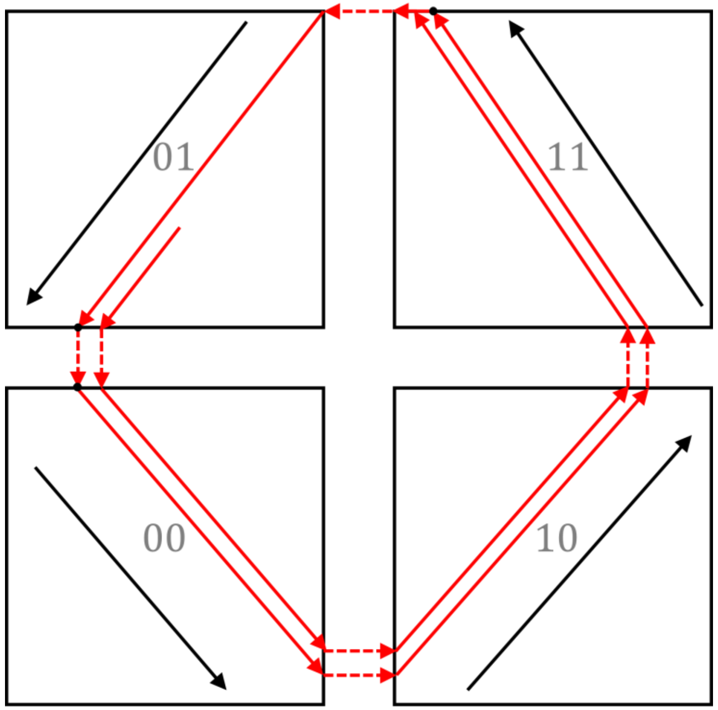


Objective

- Find limit cycles
- Analyze the stability of limit cycles



A	B	C_A	C_B
0	0	0.6	−0.7
0	1	−0.7	−0.9
1	0	0.7	0.8
1	1	−0.6	0.9



Related works:

[Belgacem et al., IEEE Conference on Decision and Control, 2020], [Firippi et al., Chaos: Interdisc. J. Nonlinear Sci., 2020], [Edwards, Physica D: Nonlinear Phenomena, 2000], [Edwards et al., Advances in chemical physics, 2006], etc.

Search for limit cycles

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.

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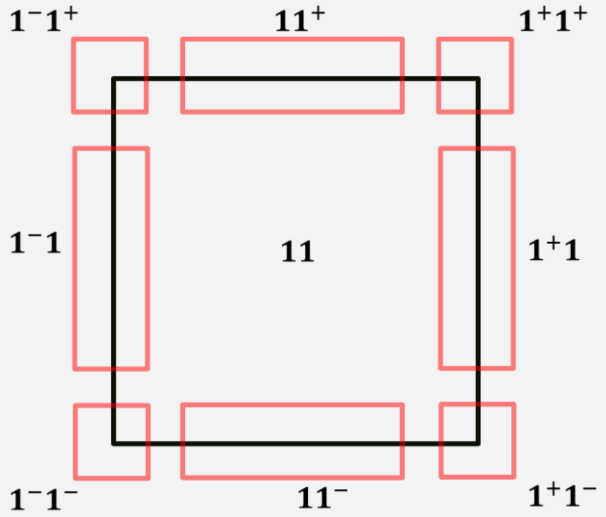
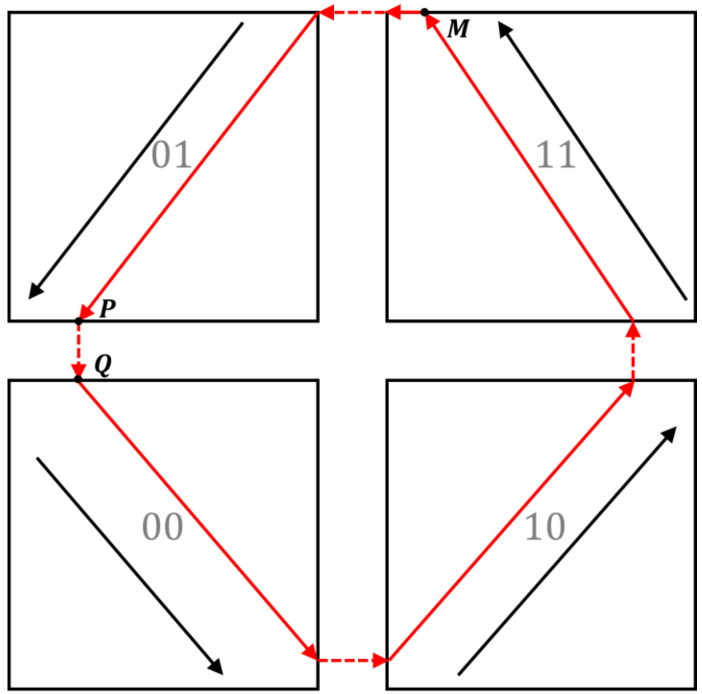


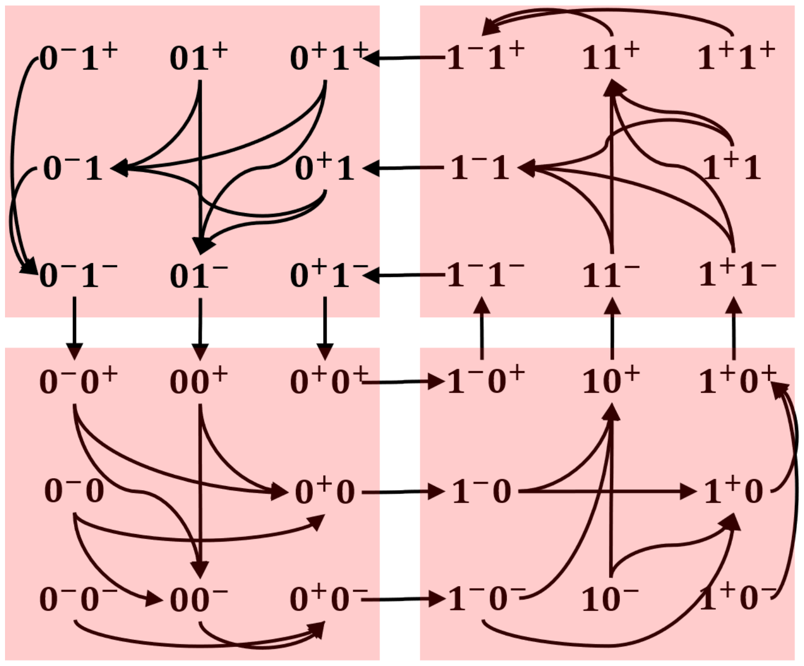
$$(1^+, 1^+) = \{(\pi, 11) |\ \pi^1 = 1, \pi^2 = 1\}$$

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

Examples of **discrete domain**



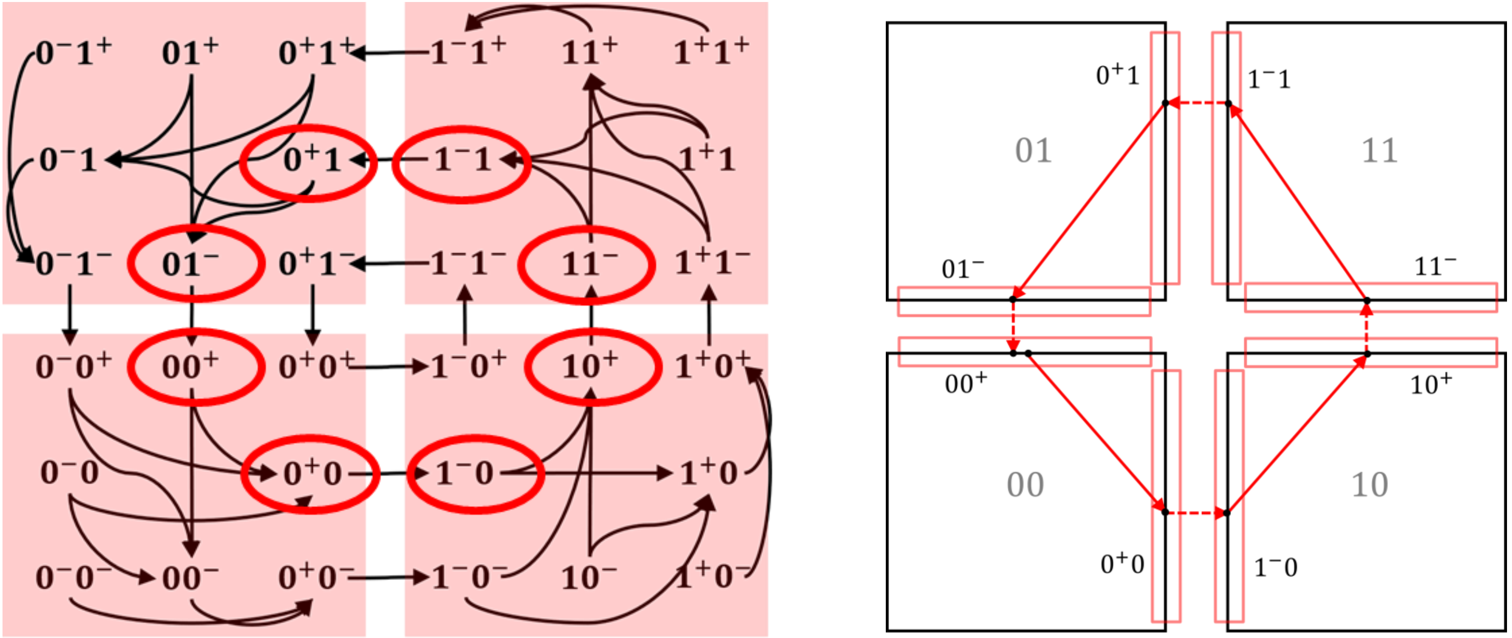
Original system



Graph of discrete domains

Search for limit cycles

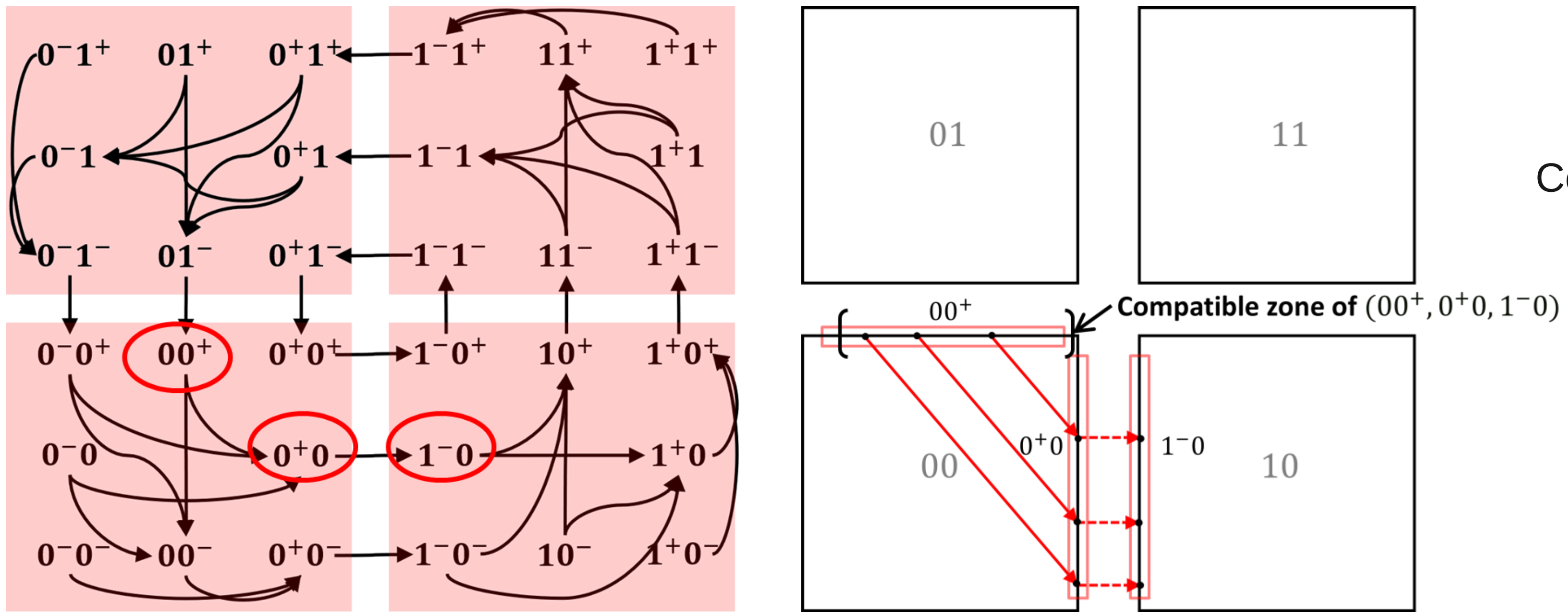
1. Abstraction of the model with discrete domain. ➡ **2. Find cycles of discrete domains which contain continuous trajectories.** ➡ 3. Search for limit cycle(s) inside cycles found in step 2.



Example of a cycle of discrete domains which contains continuous trajectories

Search for limit cycles

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.



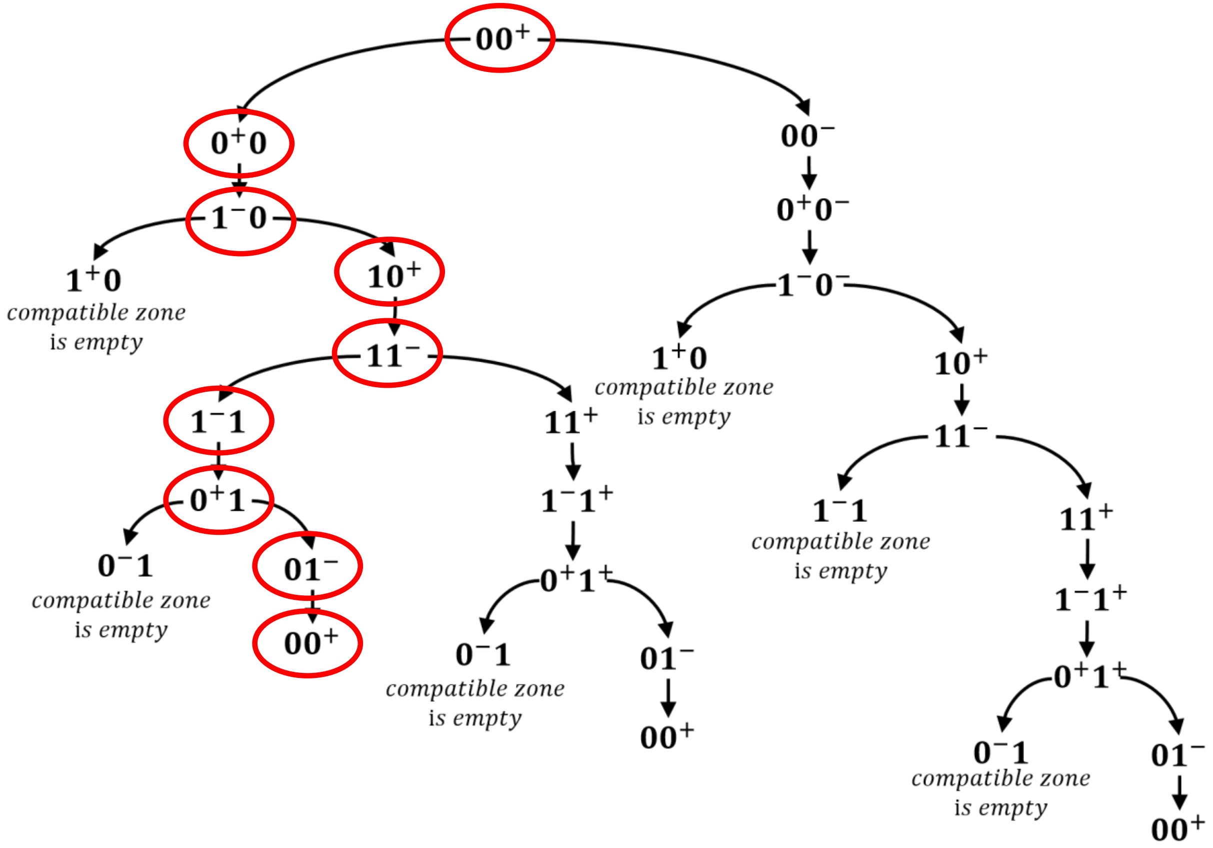
Compatible zone S of $(00^+, 0^+0, 1^-0)$:
$S \subseteq 00^+$ s.t. $\forall h \in S$, any trajectory from h stays inside $(00^+, 0^+0, 1^-0)$.

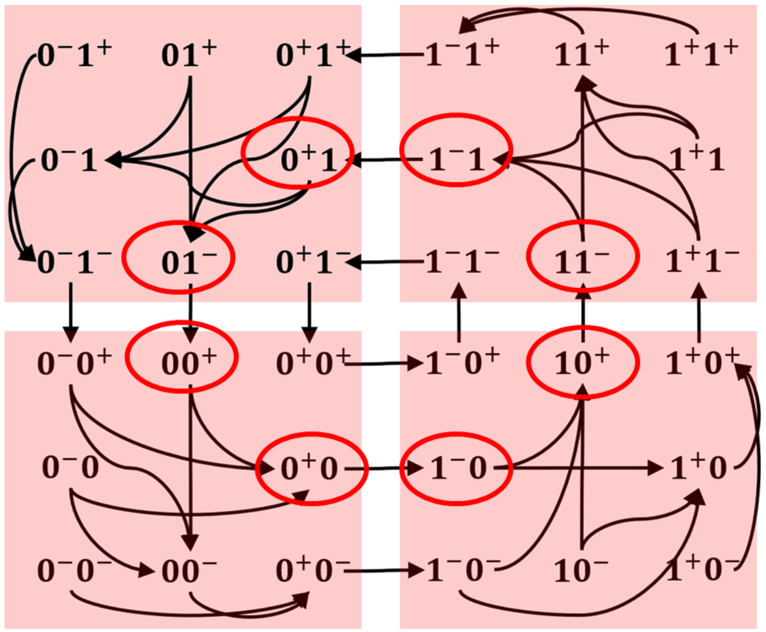
Example of **compatible zone**

Search for limit cycles

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.

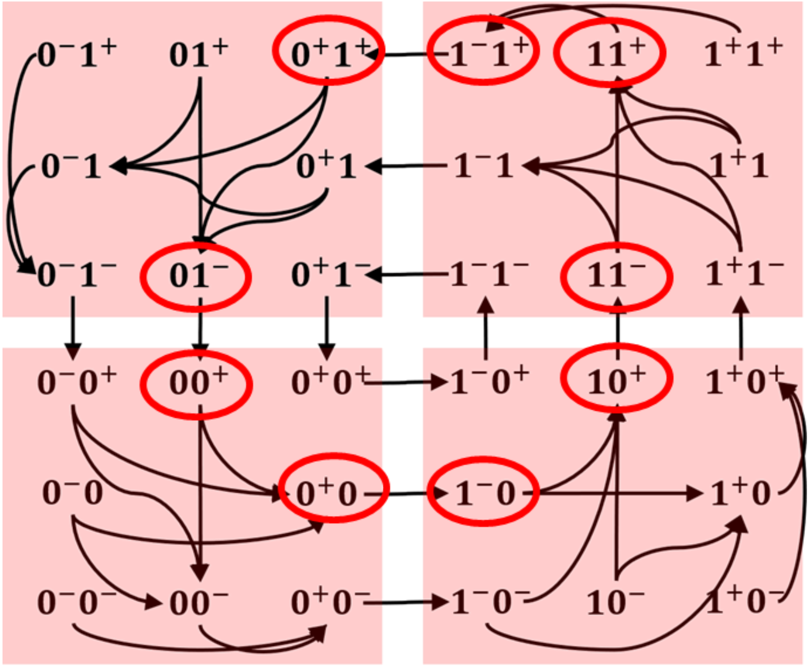
Find cycles of discrete domains of which the **compatible zones** are **not empty**.

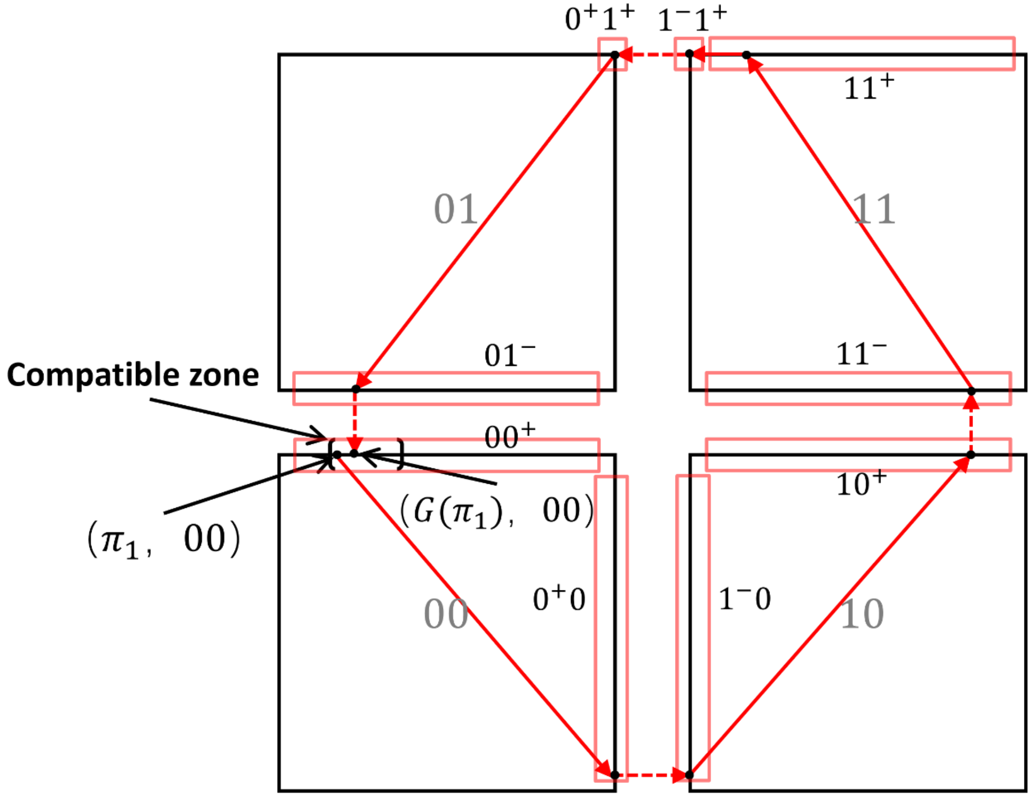




Search for limit cycles

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.**





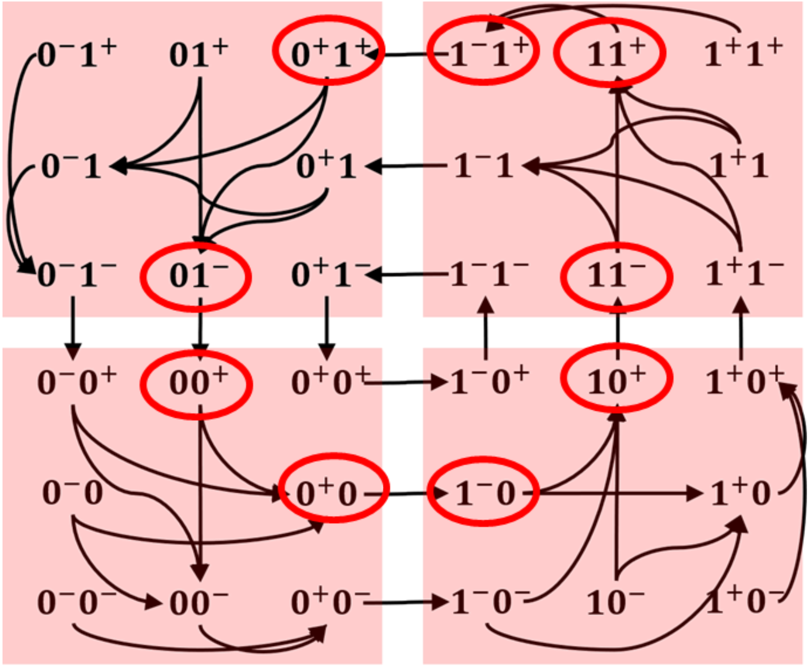
$G(\pi_1) = M \times \pi_1 + b$

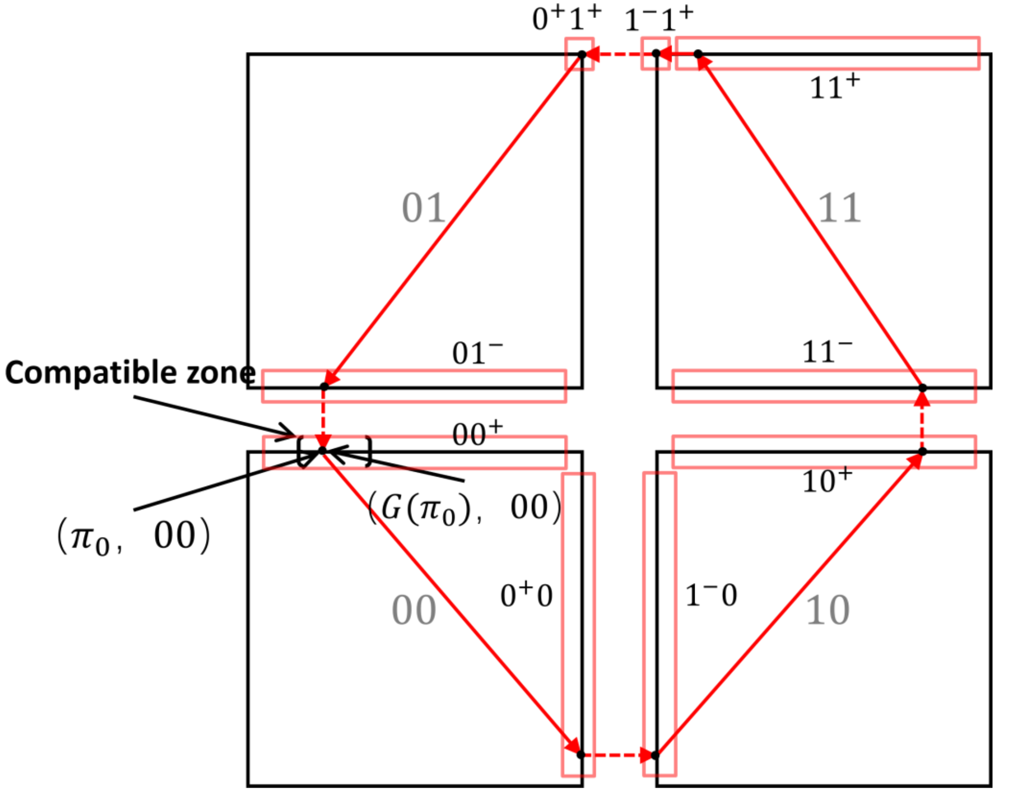
G: Poincaré map

Method: Search $(\pi_0, 00)$ in the compatible zone such that $G(\pi_0) = \pi_0$.

Search for limit cycles

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.**





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

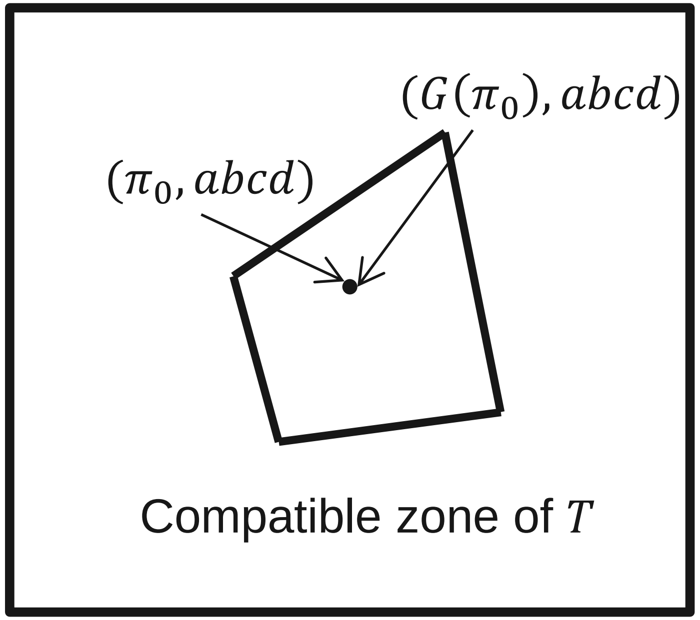
G: Poincaré map

Method: Search $(\pi_0, 00)$ in the compatible zone such that $G(\pi_0) = \pi_0$.

Stability analysis of limit cycle

A cycle of discrete domains T: $a^+b^+c\mathrm{d} \to \cdots \to a^+b^+c\mathrm{d}$

Discrete domain $a^+b^+c\mathrm{d}$



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

$$G(\pi_0) = \pi_0 \Leftrightarrow \begin{pmatrix} x_0 \\ y_0 \end{pmatrix} = A \begin{pmatrix} x_0 \\ y_0 \end{pmatrix} + b$$

Two eigenvalues of A: λ_1, λ_2

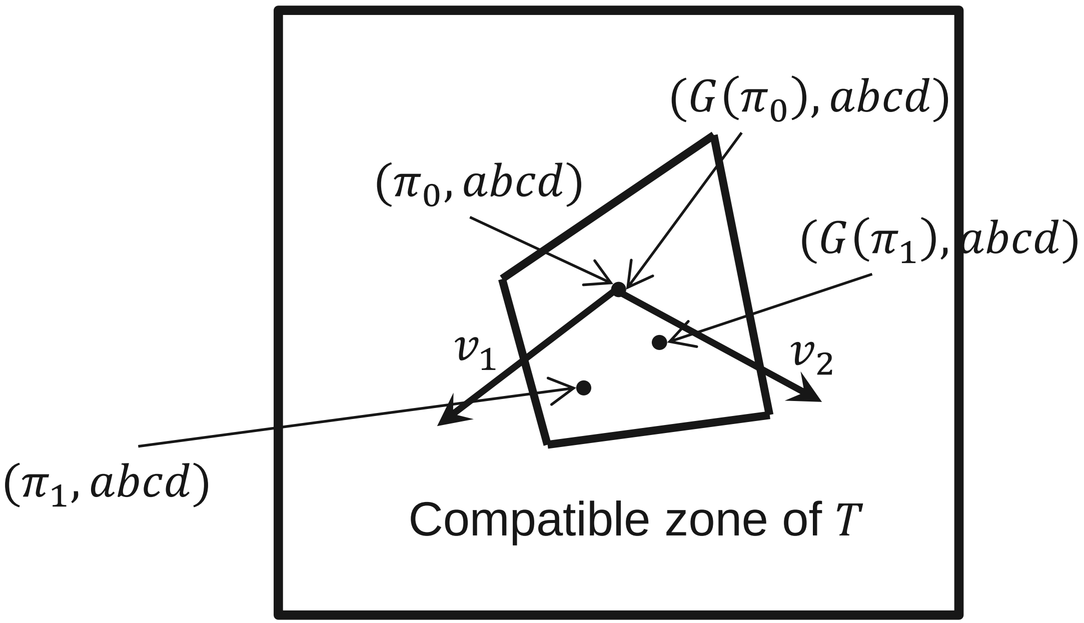
It is a stable limit cycle $\Leftrightarrow |\lambda_i| < 1, i \in \{1,2\}$

Example of stability analysis

Stability analysis of limit cycle

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

Discrete domain a^+b^+cd



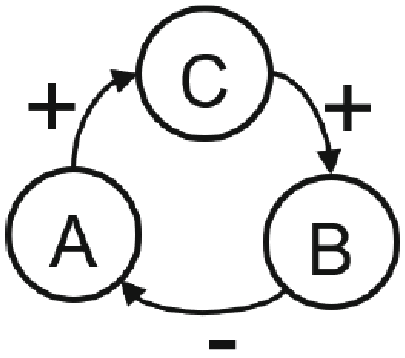
$$\pi_0 = \begin{pmatrix} 1 \\ 1 \\ x_0 \\ y_0 \end{pmatrix}$$

$$G(\pi_0) = \pi_0 \Leftrightarrow \begin{pmatrix} x_0 \\ y_0 \end{pmatrix} = A \begin{pmatrix} x_0 \\ y_0 \end{pmatrix} + b$$

Two eigenvalues of A: $\lambda_1, \lambda_2 \in]0,1[$

Example of stability analysis

Application



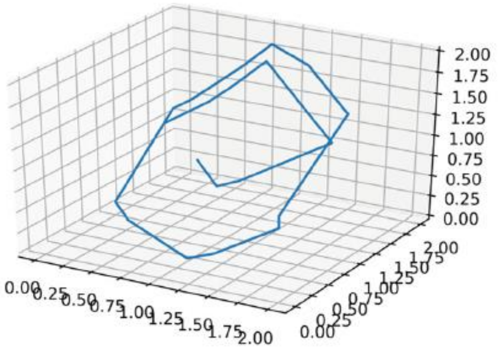
A	B	C	C_A	C_B	C_C
0	0	0	1	-0.6	-0.7
0	0	1	1	0.7	-0.9
0	1	0	-0.8	-0.8	-0.7
0	1	1	-0.8	0.6	-0.9
1	0	0	0.7	-0.6	0.6
1	0	1	0.7	0.7	0.5
1	1	0	-0.9	-0.8	0.6
1	1	1	-0.9	0.6	0.5

A	B	C	C_A	C_B	C_C
0	0	0	3	-0.6	-0.7
0	0	1	3	0.7	-2.9
0	1	0	-2.8	-0.8	-0.7
0	1	1	-2.8	0.6	-2.9
1	0	0	2.7	-0.6	2.6
1	0	1	2.7	0.7	0.5
1	1	0	-2.9	-0.8	2.6
1	1	1	-2.9	0.6	0.5

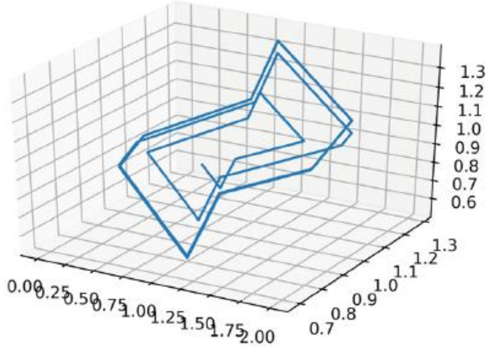
A	B	C	C_A	C_B	C_C
0	0	0	3	-0.6	-0.7
0	0	1	3	0.7	-2.9
0	1	0	-0.8	-0.8	-0.7
0	1	1	-0.8	0.6	-2.9
1	0	0	0.7	-0.6	2.6
1	0	1	0.7	0.7	0.5
1	1	0	-2.9	-0.8	2.6
1	1	1	-2.9	0.6	0.5

Three HGRNs of negative feedback loop in 3 dimensions

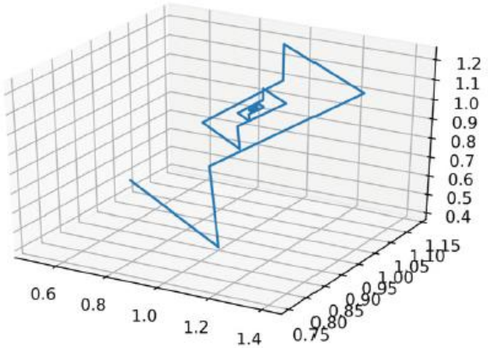
Our analysis method



A stable limit cycle

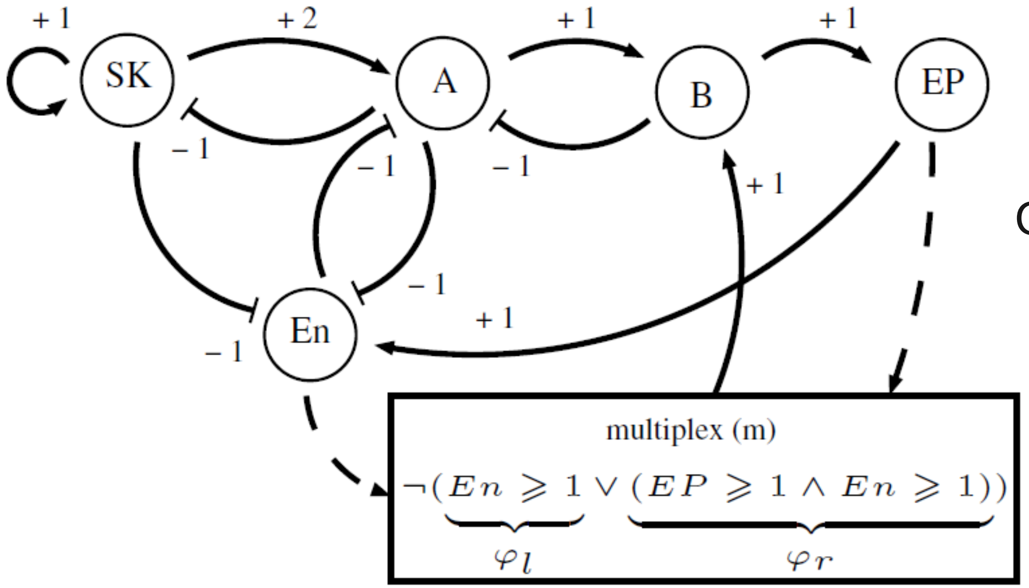


A stable limit cycle



No limit cycle

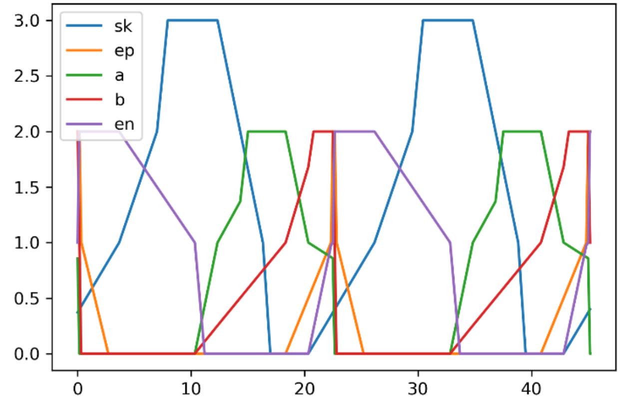
Application



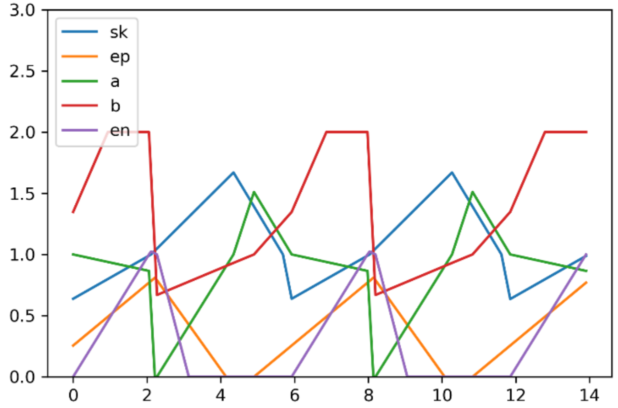
A HGRN of cell cycle

[Behaegel et al., Journal of bioinformatics and computational biology, 2016]

Our analysis method



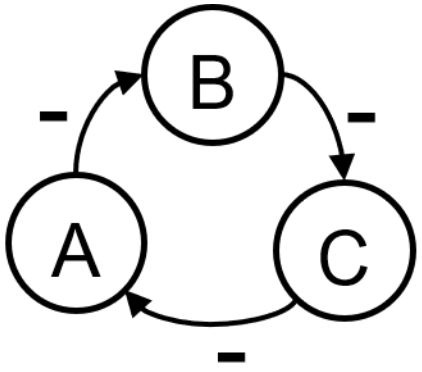
A stable limit cycle



An unstable limit cycle

Repressilator

The specific gene regulatory network studied in this work:

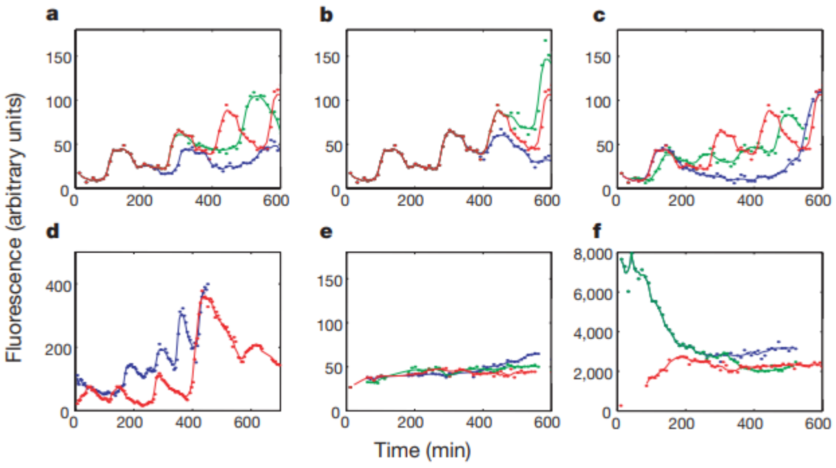


The influence graph of the canonical repressilator

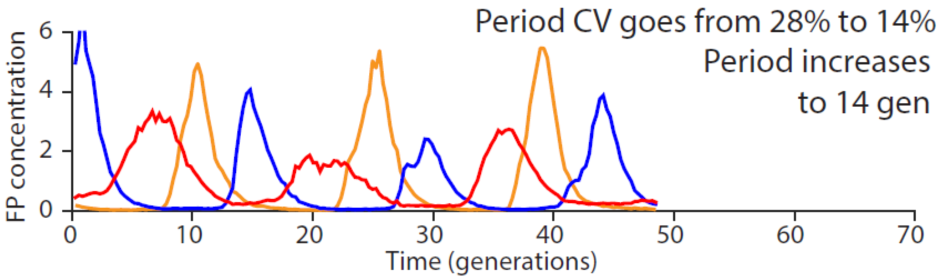
Repressilator

Why study oscillations in repressilator?

- Human-made genetic oscillations have potential medical applications
- Existence of synthetic repressilator with sustained oscillation (but not stable)

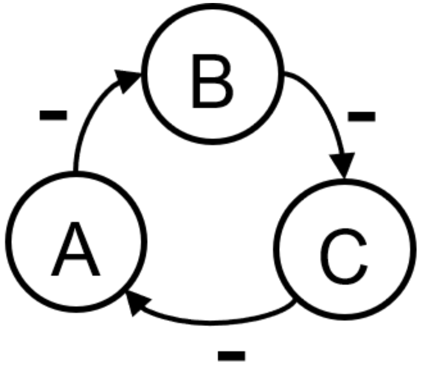


[Elowitz, M. B. et al., Nature, 2000]



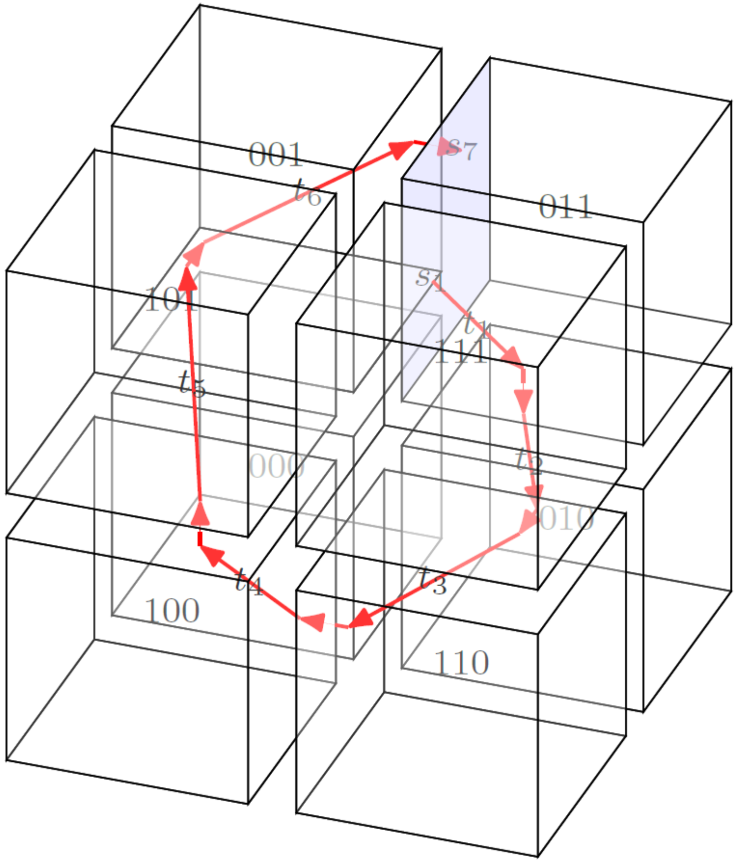
[Potvin-Trottier, L. et al, Nature, 2016]

HGRN of repressilator



A	B	C	C_A	C_B	C_C
0	0	0	C_{ac0a0}	C_{ba0b0}	C_{cb0c0}
0	0	1	$-C_{ac1a0}$	C_{ba0b0}	C_{cb0c1}
0	1	0	C_{ac0a0}	C_{ba0b1}	$-C_{cb1c0}$
0	1	1	$-C_{ac1a0}$	C_{ba0b1}	$-C_{cb1c1}$
1	0	0	C_{ac0a1}	$-C_{ba1b0}$	C_{cb0c0}
1	0	1	$-C_{ac1a1}$	$-C_{ba1b0}$	C_{cb0c1}
1	1	0	C_{ac0a1}	$-C_{ba1b1}$	$-C_{cb1c0}$
1	1	1	$-C_{ac1a1}$	$-C_{ba1b1}$	$-C_{cb1c1}$

All parameters of this HGRN of repressilator



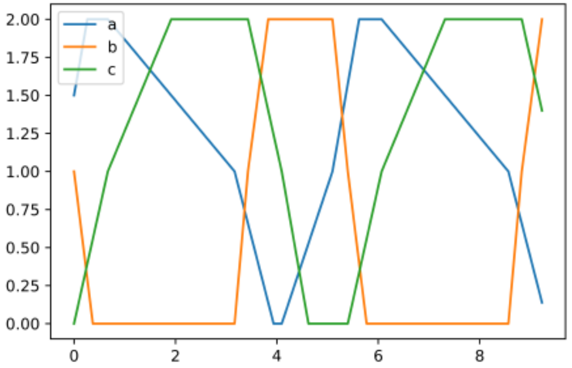
An example of this HGRN of repressilator

Objective of this work

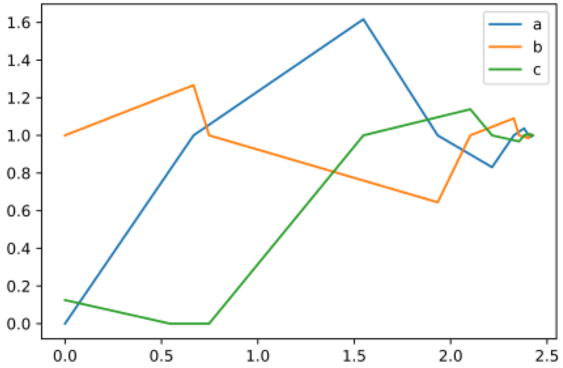
Find constraints on parameters for the existence of sustained oscillations

A	B	C	C_A	C_B	C_C
0	0	0	C_{ac0a0}	C_{ba0b0}	C_{cb0c0}
0	0	1	$-C_{ac1a0}$	C_{ba0b0}	C_{cb0c1}
0	1	0	C_{ac0a0}	C_{ba0b1}	$-C_{cb1c0}$
0	1	1	$-C_{ac1a0}$	C_{ba0b1}	$-C_{cb1c1}$
1	0	0	C_{ac0a1}	$-C_{ba1b0}$	C_{cb0c0}
1	0	1	$-C_{ac1a1}$	$-C_{ba1b0}$	C_{cb0c1}
1	1	0	C_{ac0a1}	$-C_{ba1b1}$	$-C_{cb1c0}$
1	1	1	$-C_{ac1a1}$	$-C_{ba1b1}$	$-C_{cb1c1}$

All parameters of this HGRN of repressilator



A model with sustained oscillations



A model without sustained oscillation

Related work

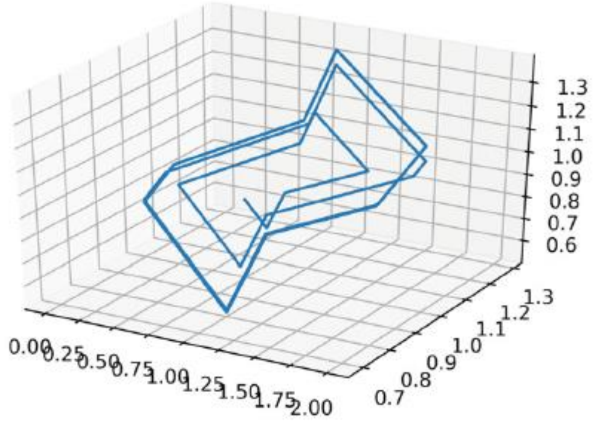
This work relies on our previous work [Sun, H. et al., CMSB, 2022]

Contributions of [Sun, H. et al., CMSB, 2022]:

- Automatic search of limit cycle
- Stability analysis of limit cycle

A	B	C	C_A	C_B	C_C
0	0	0	3	-0.6	-0.7
0	0	1	3	0.7	-2.9
0	1	0	-2.8	-0.8	-0.7
0	1	1	-2.8	0.6	-2.9
1	0	0	2.7	-0.6	2.6
1	0	1	2.7	0.7	0.5
1	1	0	-2.9	-0.8	2.6
1	1	1	-2.9	0.6	0.5

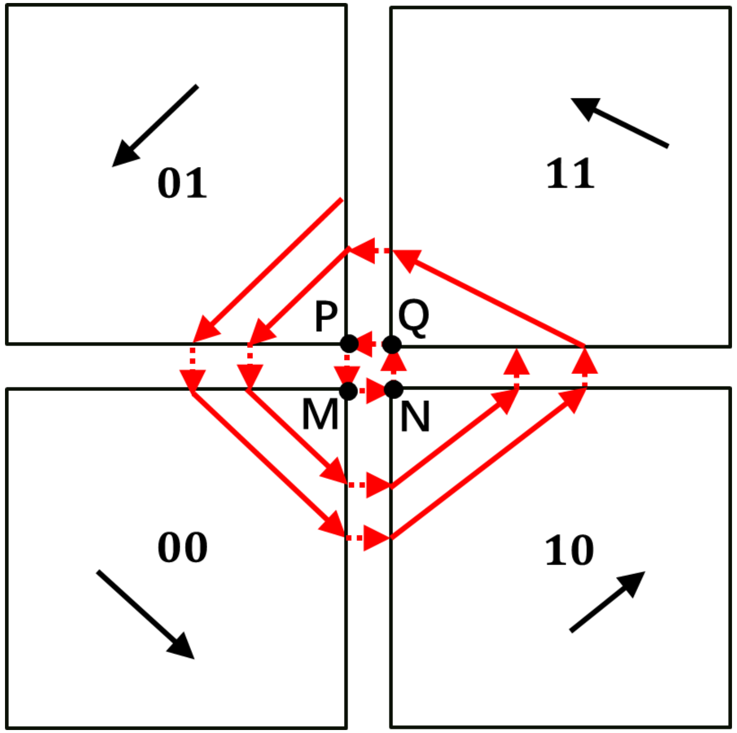
Method of
[Sun, H. et al., CMSB, 2022]



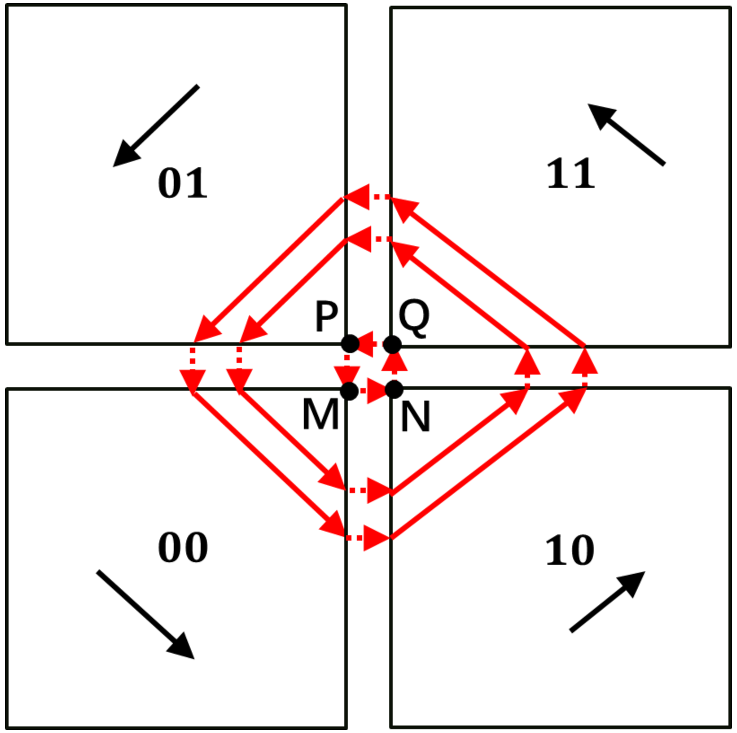
Sun, H., Folschette, M., & Magnin, M. (2022, August). Limit cycle analysis of a class of hybrid gene regulatory networks. In Computational Methods in Systems Biology: 20th International Conference, CMSB 2022, Bucharest, Romania, September 14–16, 2022, Proceedings (pp. 217-236). Cham: Springer International Publishing.

Different qualitative behaviors of this HGRN

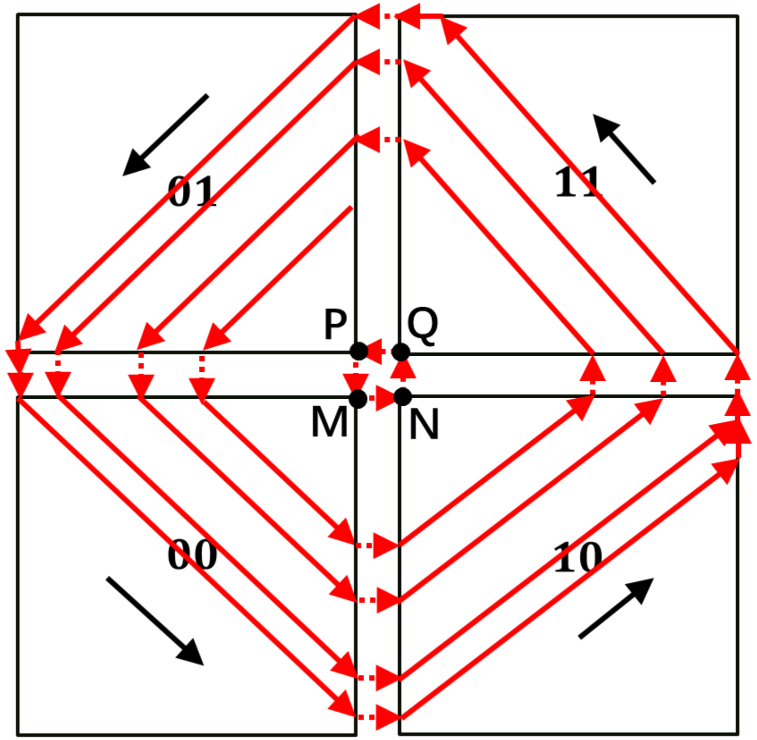
Illustration of different qualitative behaviors by a 2-Dim model



Damped oscillations



Parallel cycles
(special case of sustained oscillations)

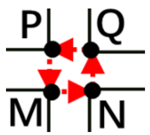


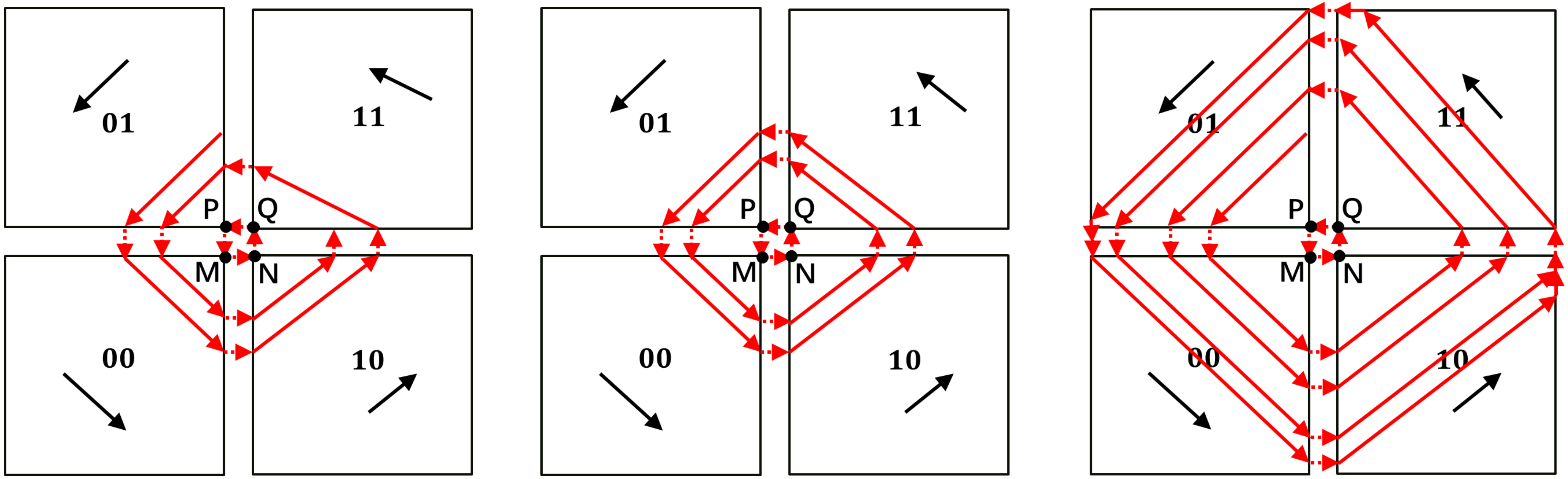
Sustained oscillations

Different qualitative behaviors of this HGRN

How to determine different qualitative behaviors?

Existence of sustained oscillation ⇔ Stability of the characteristic state

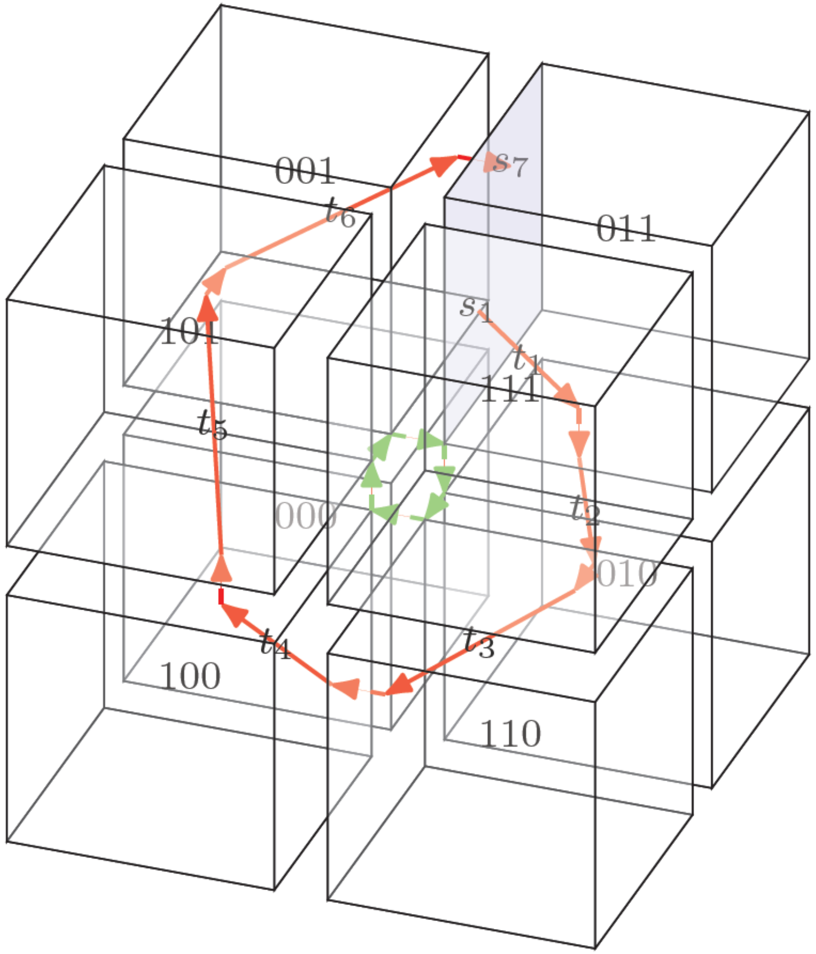


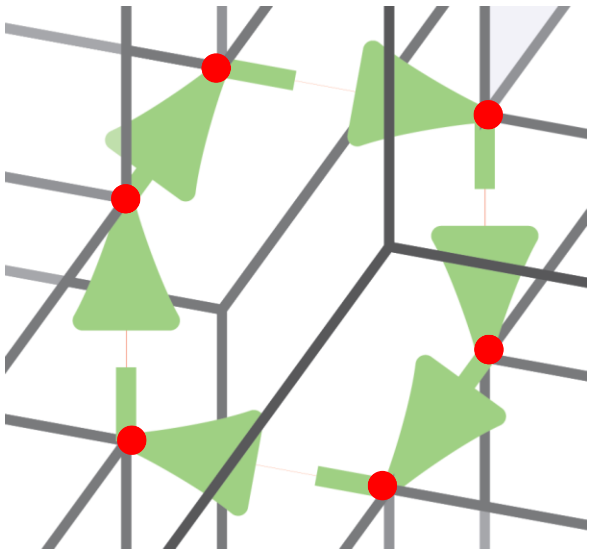


Different qualitative behaviors of this HGRN

How to determine different qualitative behaviors?

Existence of sustained oscillation ⇔ Stability of the characteristic state

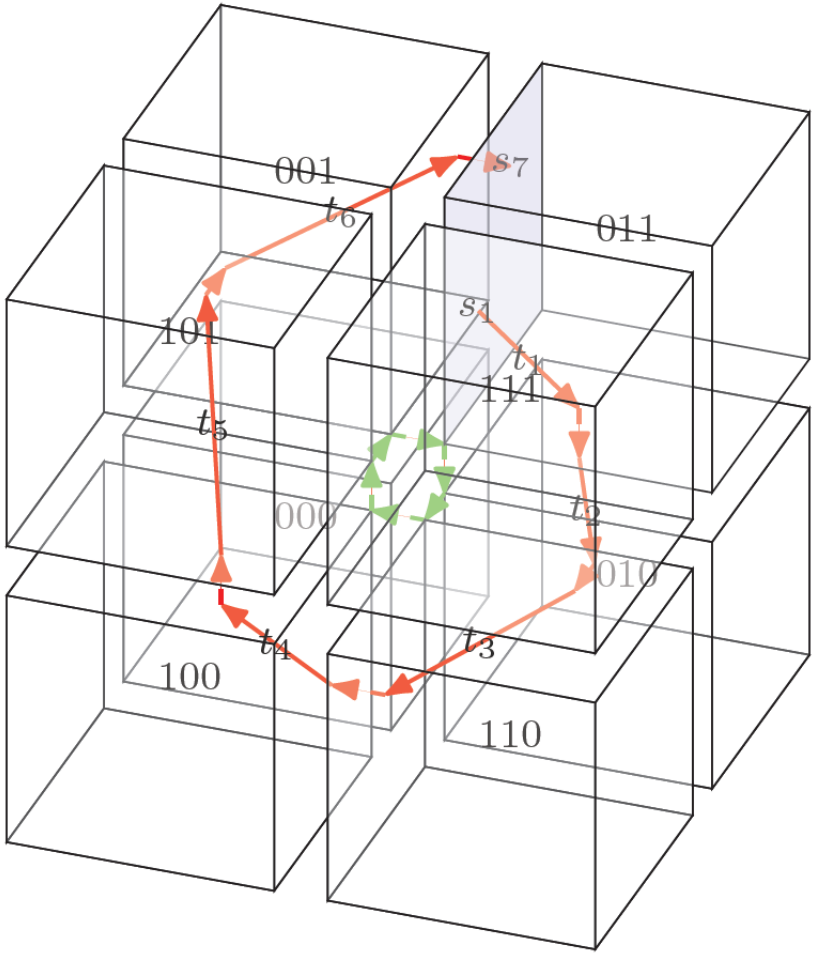


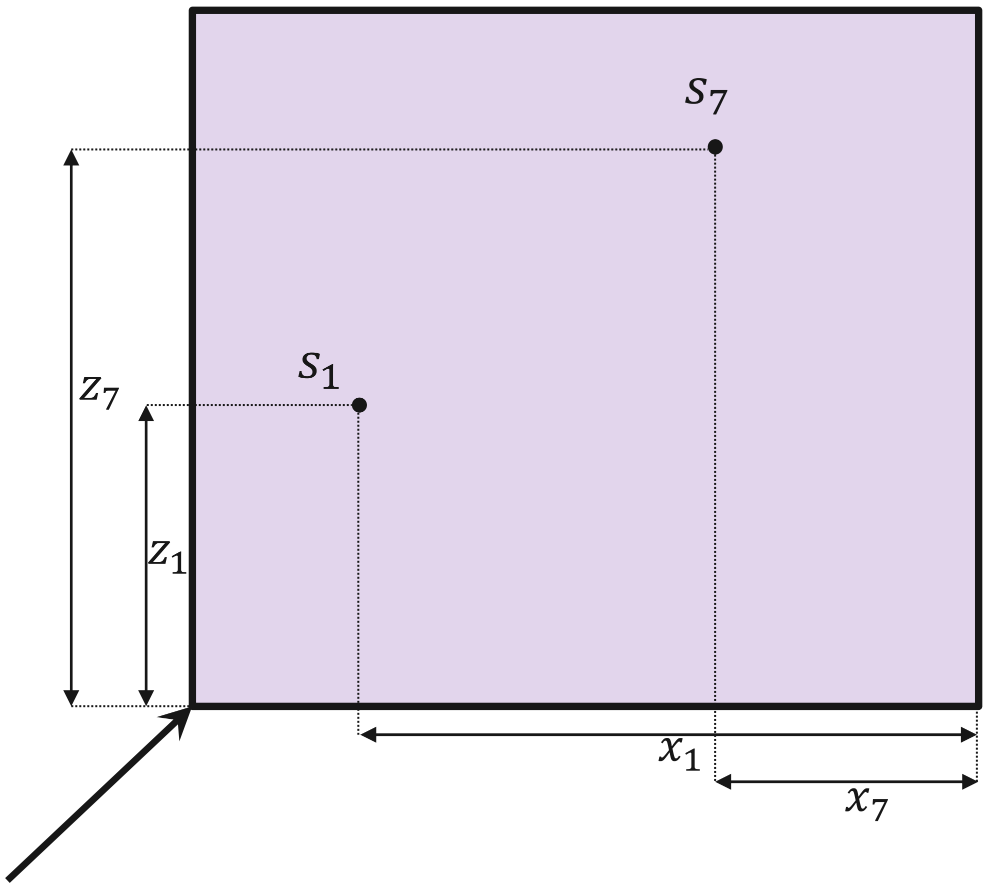


The characteristic state of this HGRN of repressilator

Determine the stability of the characteristics state

Use the Poincaré map (first return map) to determine the stability of the characteristic state





$$\begin{pmatrix} x_7 \\ z_7 \end{pmatrix} = A \begin{pmatrix} x_1 \\ z_1 \end{pmatrix} + b$$

Determine the stability of the characteristics state

Use the Poincaré map (first return map) to determine the stability of the characteristic state

The two eigenvalues of A: λ_1, λ_2 ($\boldsymbol{\lambda_1 > \lambda_2}$)

The characteristic state is unstable $\Leftrightarrow \boldsymbol{\lambda_1 \geq 1}$

Illustration of the case $\boldsymbol{\lambda_1 \geq 1}$

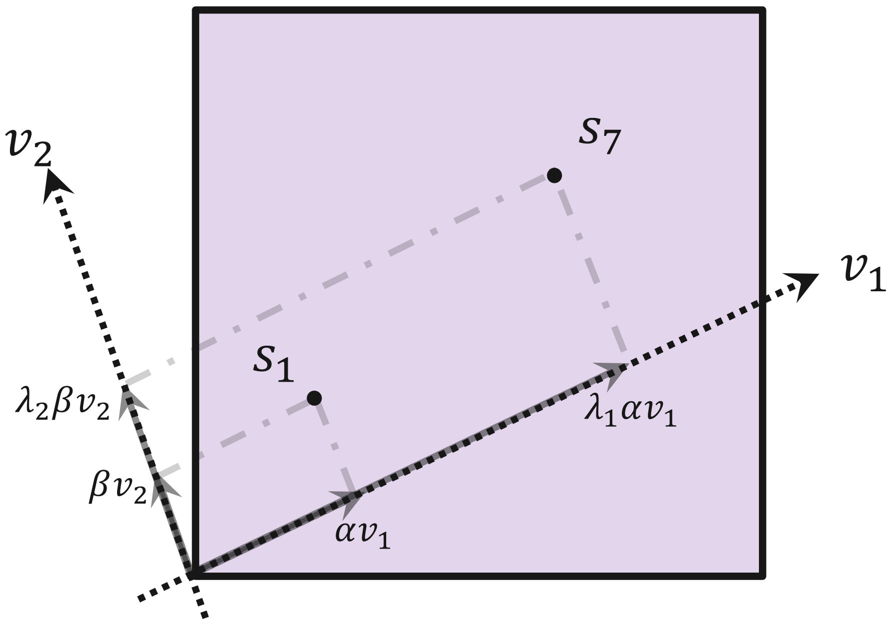
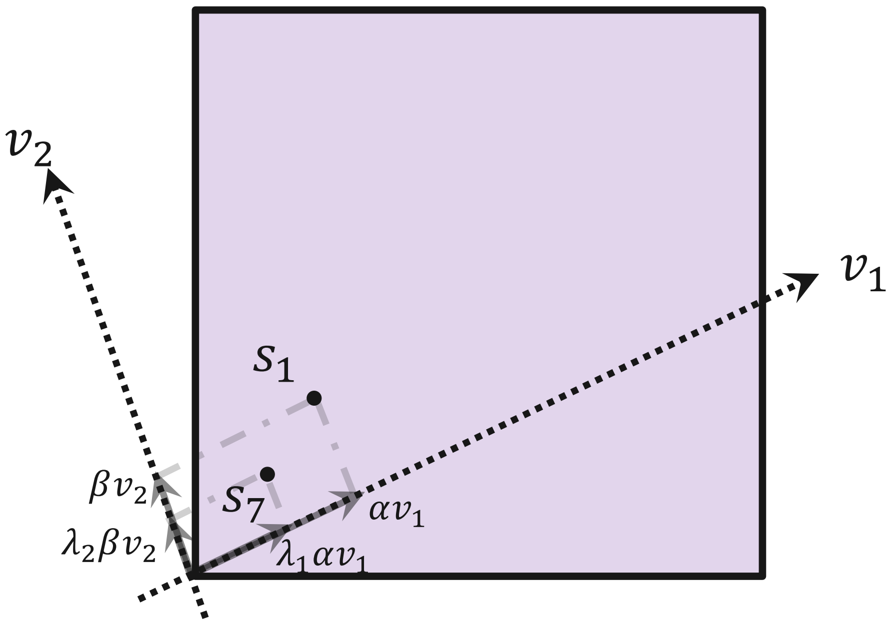


Illustration of the case $\boldsymbol{\lambda_1 < 1}$



Condition for sustained oscillations

Sustained oscillations exist

$\Updownarrow$

The characteristic state is unstable

$\Updownarrow$

$\boldsymbol{\lambda_1 \geq 1}$

$\Updownarrow$ By computing the expression of $\boldsymbol{\lambda_1}$

$(\boldsymbol{P_1} \geq \boldsymbol{0}) \vee (\boldsymbol{P_2} \geq \boldsymbol{0})$

$\boldsymbol{P_1}$ and $\boldsymbol{P_2}$ are polynomials on parameters

Expressions of P_1 and P_2

$$\begin{aligned}
P_1 = {} & C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& - 2C_{ac0a0}C_{ac1a1}C_{ba0b0}C_{ba1b1}C_{cb0c0}C_{cb1c1} \\
& + C_{ac0a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb1c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1} \\
& + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\
& + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1}
\end{aligned}$$

$$\begin{aligned}
P_2 = {} & C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a0}C_{ac0a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& - C_{ac0a0}C_{ac1a1}C_{ba0b0}C_{ba1b1}C_{cb0c0}C_{cb1c1} \\
& + C_{ac0a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba0b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb0c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb0c0}C_{cb1c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\
& + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac0a1}C_{ac1a0}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1} \\
& + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba0b1}C_{ba1b0}C_{cb1c0}C_{cb1c1} \\
& + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb0c1}C_{cb1c0} \\
& + C_{ac1a0}C_{ac1a1}C_{ba1b0}C_{ba1b1}C_{cb1c0}C_{cb1c1}
\end{aligned}$$

Separable constraints on parameters

Separable constraints: $C_{xyixj} \in [\underline{C_{xyixj}}, \overline{C_{xyixj}}]$

The objective is to find separable constraints such that under these constraints $(\boldsymbol{P_1} \geq \boldsymbol{0}) \vee (\boldsymbol{P_2} \geq \boldsymbol{0})$ is always satisfied.

A	B	C	C_A	C_B	C_C
0	0	0	C_{ac0a0}	C_{ba0b0}	C_{cb0c0}
0	0	1	$-C_{ac1a0}$	C_{ba0b0}	C_{cb0c1}
0	1	0	C_{ac0a0}	C_{ba0b1}	$-C_{cb1c0}$
0	1	1	$-C_{ac1a0}$	C_{ba0b1}	$-C_{cb1c1}$
1	0	0	C_{ac0a1}	$-C_{ba1b0}$	C_{cb0c0}
1	0	1	$-C_{ac1a1}$	$-C_{ba1b0}$	C_{cb0c1}
1	1	0	C_{ac0a1}	$-C_{ba1b1}$	$-C_{cb1c0}$
1	1	1	$-C_{ac1a1}$	$-C_{ba1b1}$	$-C_{cb1c1}$

All parameters of this HGRN of repressilator

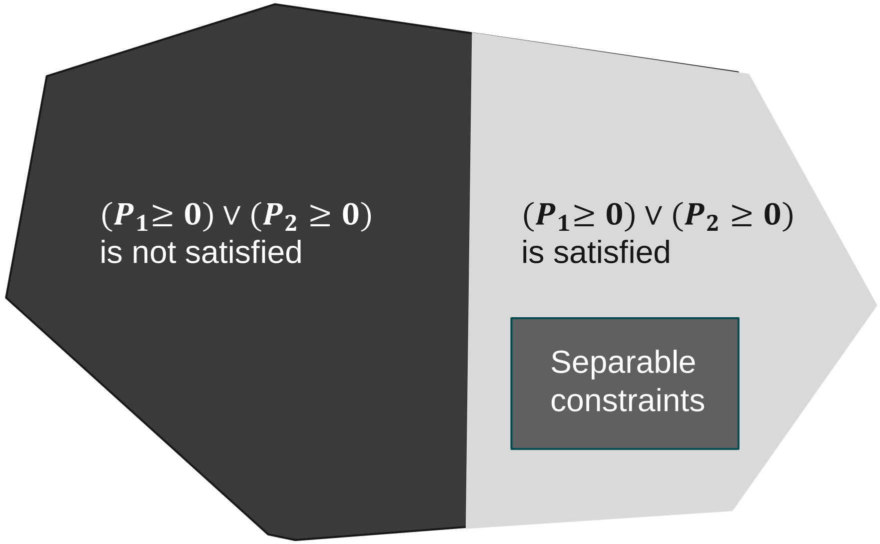


Illustration of separable constraints in the parameter space

Bernstein coefficients

One property of Bernstein coefficients:

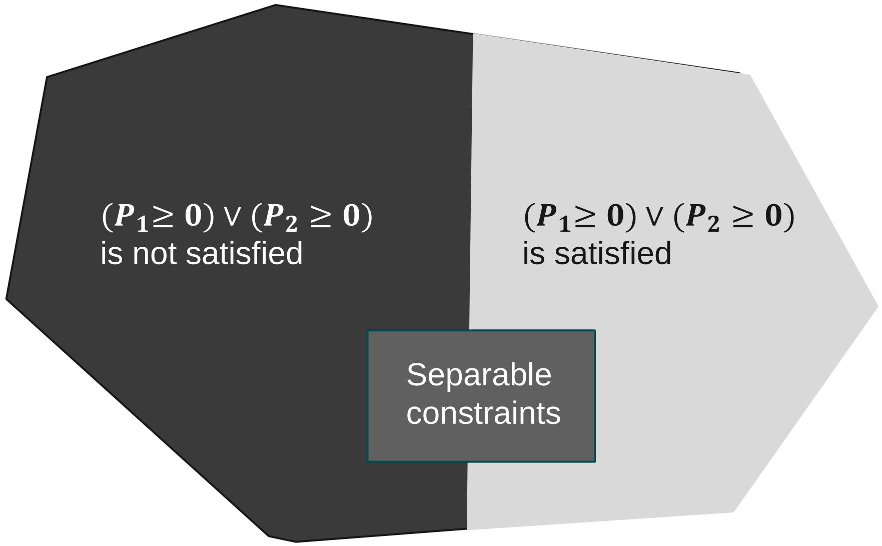
For any polynomial $f\colon \mathbb{R}^n \longrightarrow \mathbb{R}$, we can compute the Bernstein coefficients $\{b_i\}$, $b_i \in \mathbb{R}$, such that:

$$\mathrm{Min}(\{b_i\}) \leq f(x) \leq \mathrm{Max}(\{b_i\}), \forall x \in [0,1]^n$$

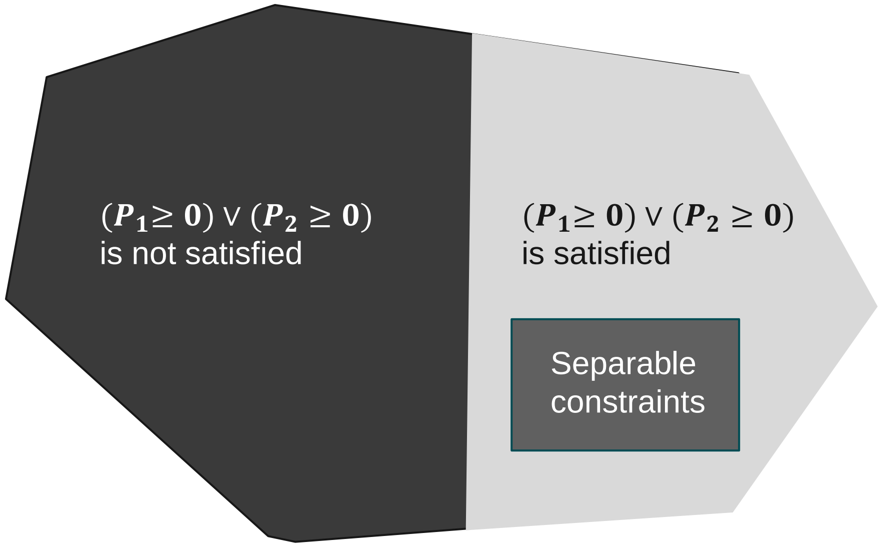
Previous applications of Bernstein coefficients for computing image of polynomial dynamical systems:
[Dang, T. et al., CAV, 2009], [Dang, T. et al., Reliab. Comput., 2012]

Satisfiability under separable constraints

Given separable constraints: $C_{xyixj} \in [\underline{C_{xyixj}}, \overline{C_{xyixj}}]$, $(\boldsymbol{P_1} \geq \mathbf{0}) \vee (\boldsymbol{P_2} \geq \mathbf{0})$ is always satisfied?

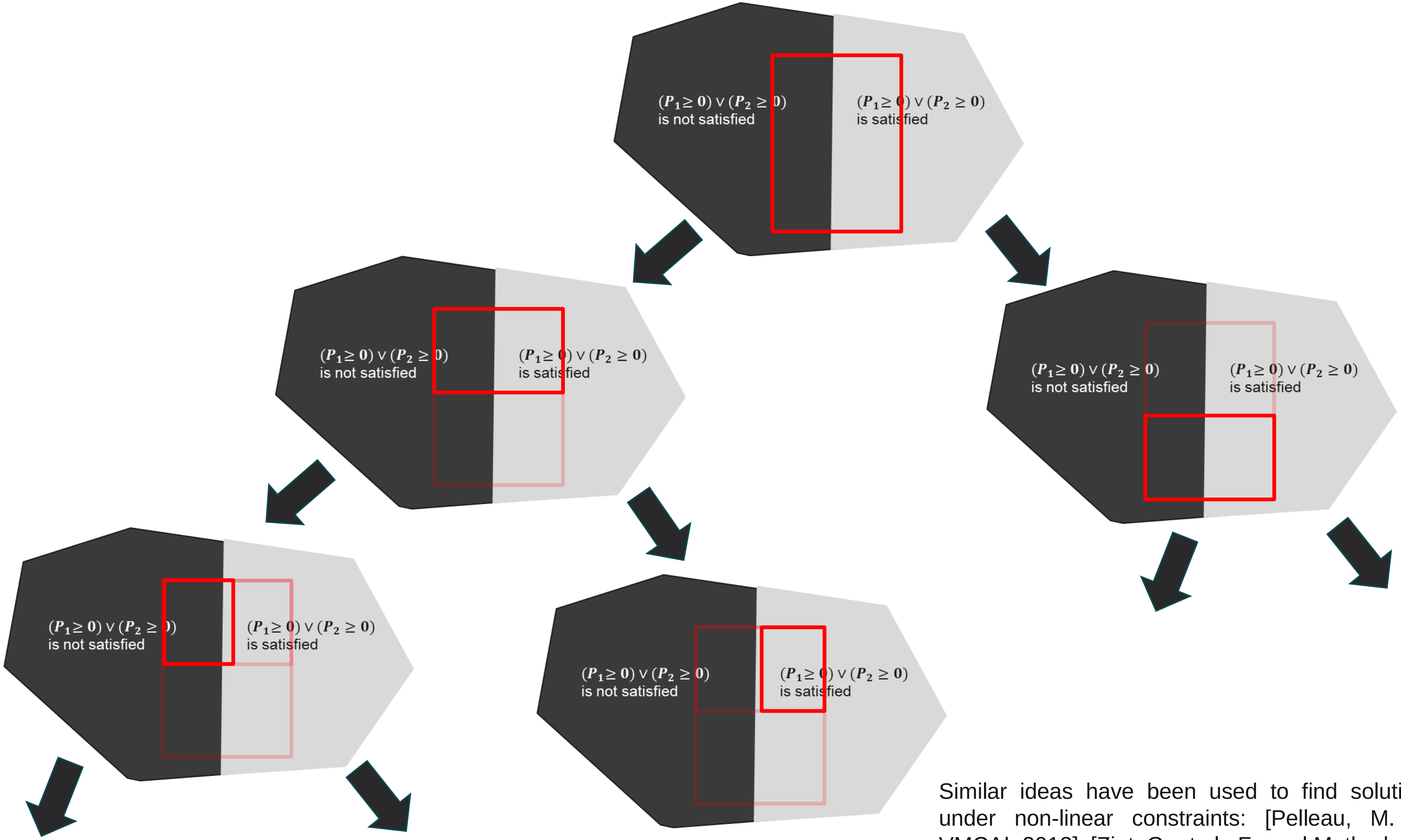


Example of separable constraints which do not satisfy $(\boldsymbol{P_1} \geq \mathbf{0}) \vee (\boldsymbol{P_2} \geq \mathbf{0})$



Example of separable constraints which satisfy $(\boldsymbol{P_1} \geq \mathbf{0}) \vee (\boldsymbol{P_2} \geq \mathbf{0})$

Search of separable constraints by a splitting strategy



Similar ideas have been used to find solution sets under non-linear constraints: [Pelleau, M. et al., VMCAI, 2013], [Ziat, G. et al., Formal Methods, 2019]

An example of separable constraints

A	B	C	C_A	C_B	C_C
0	0	0	C_{ac0a0}	C_{ba0b0}	C_{cb0c0}
0	0	1	$-C_{ac1a0}$	C_{ba0b0}	C_{cb0c1}
0	1	0	C_{ac0a0}	C_{ba0b1}	$-C_{cb1c0}$
0	1	1	$-C_{ac1a0}$	C_{ba0b1}	$-C_{cb1c1}$
1	0	0	C_{ac0a1}	$-C_{ba1b0}$	C_{cb0c0}
1	0	1	$-C_{ac1a1}$	$-C_{ba1b0}$	C_{cb0c1}
1	1	0	C_{ac0a1}	$-C_{ba1b1}$	$-C_{cb1c0}$
1	1	1	$-C_{ac1a1}$	$-C_{ba1b1}$	$-C_{cb1c1}$

All parameters of this HGRN of repressilator

$$C_{ac0a0} \in [0.0, 0.5] \quad C_{ba0b0} \in [0.0, 0.5] \quad C_{cb0c0} \in [0.0, 0.5]$$
$$C_{ac0a1} \in [0.0, 0.5] \quad C_{ba0b1} \in [0.0, 0.5] \quad C_{cb0c1} \in [0.0, 0.5]$$
$$C_{ac1a0} \in [0.5, 1.0] \quad C_{ba1b0} \in [0.5, 1.0] \quad C_{cb1c0} \in [0.5, 1.0]$$
$$C_{ac1a1} \in [0.0, 1.0] \quad C_{ba1b1} \in [0.0, 1.0] \quad C_{cb1c1} \in [0.0, 1.0]$$

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

- Enumeration of simple cycles
- Formal verification of cycle stability with Poincaré map

Collaborations & Bibliography

Jonathan BEHAEGEL

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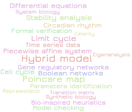

Honglu SUN

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