Conditions for cyclic attractors for a class of discrete n-dimensional repressilators

Maxime Folschette

Univ. Lille, CNRS, **Centrale Lille**, UMR 9189 **CRIStAL**, F-59000 Lille, France

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AUTOMATA 2025

Joint work with:
Honlgu Sun (formerly: Centrale Nantes, France)
Morgan Magnin (Centrale Nantes, France)
Elisa Tonello (formerly: Freie Universität Berlin, Germany)

Outline

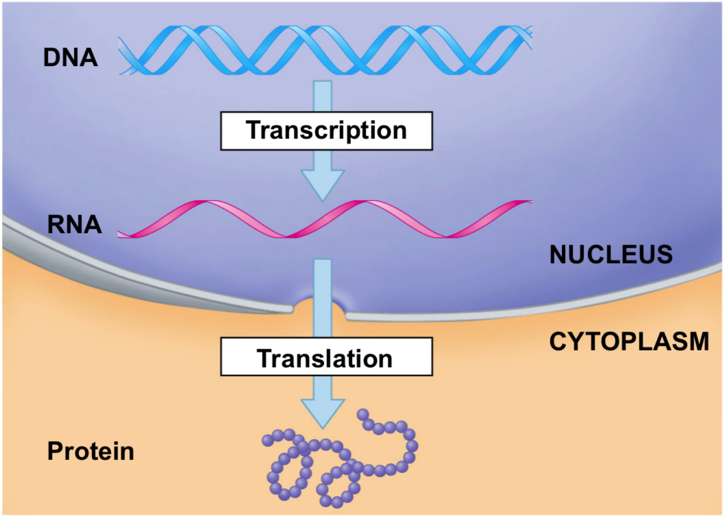
Definitions:

- Discrete networks
- Repressillators
- Static Analysis

Results:

- Necessary and sufficent condition for the existence of a fixed point
- Sufficent conditions for the existence of a cyclic attractor
- Necessary condition in 4 dimensions

Preliminary Abstraction



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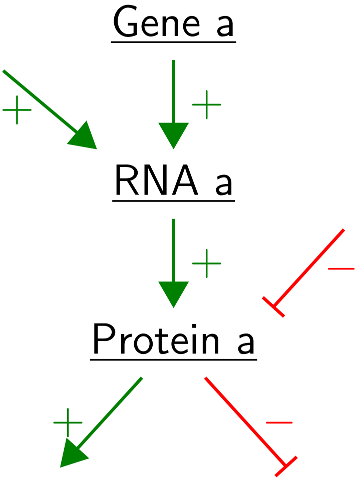

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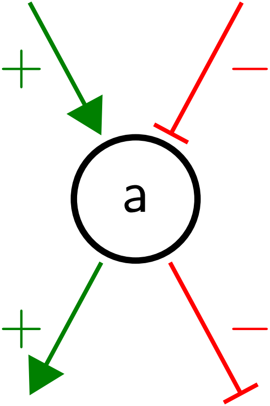

Origin of René Thomas Modeling

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

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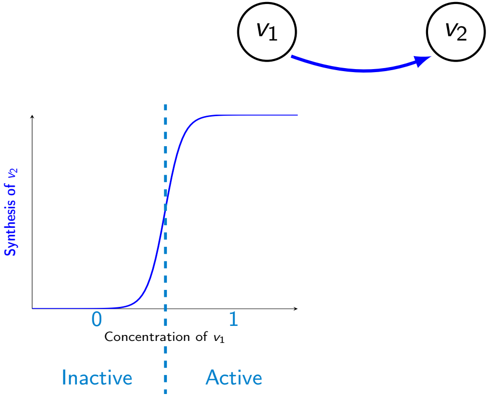

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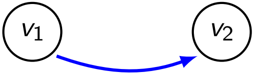

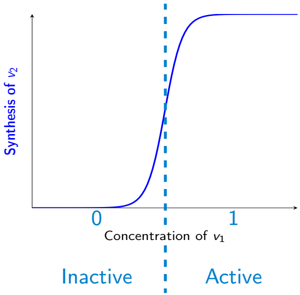

v_1 has no effect on v_2

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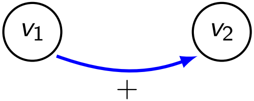

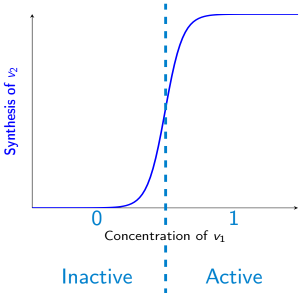

v_1 has no effect on v_2

v_1 triggers synthesis of v_2

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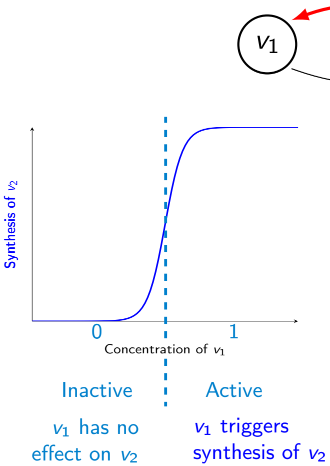

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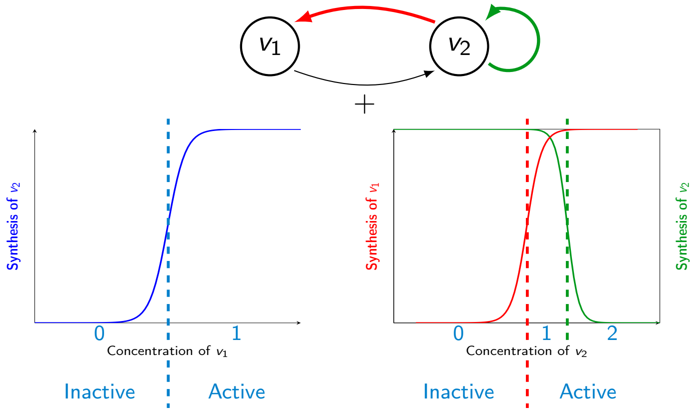

v_1 has no effect on v_2

v_1 triggers synthesis of v_2

v_2 has no effect on v_1 or itself

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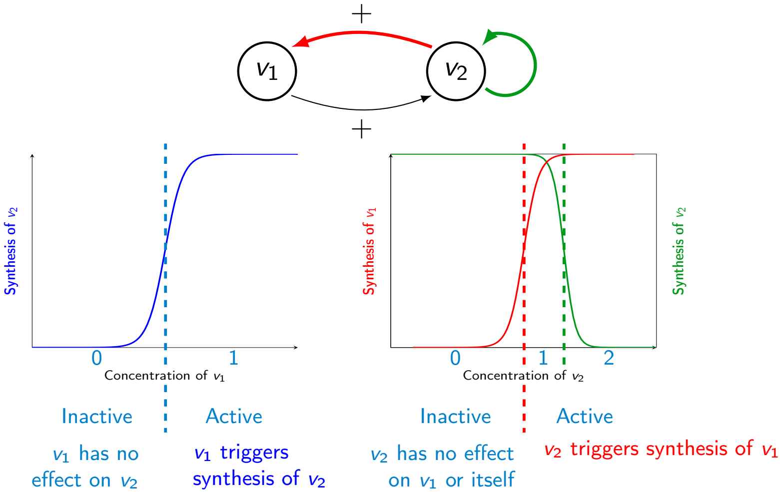

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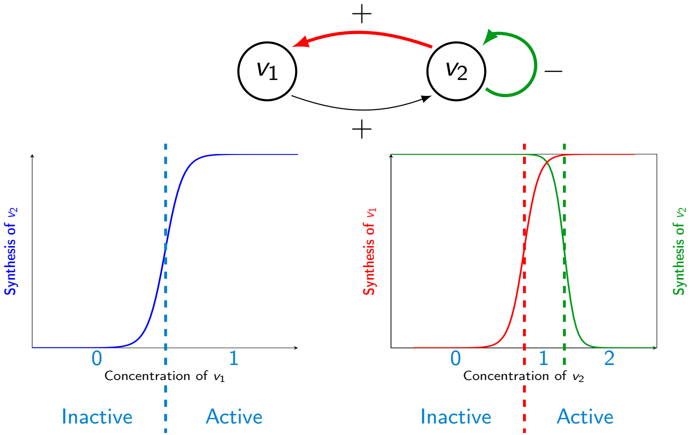

v_1 has no effect on v_2

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

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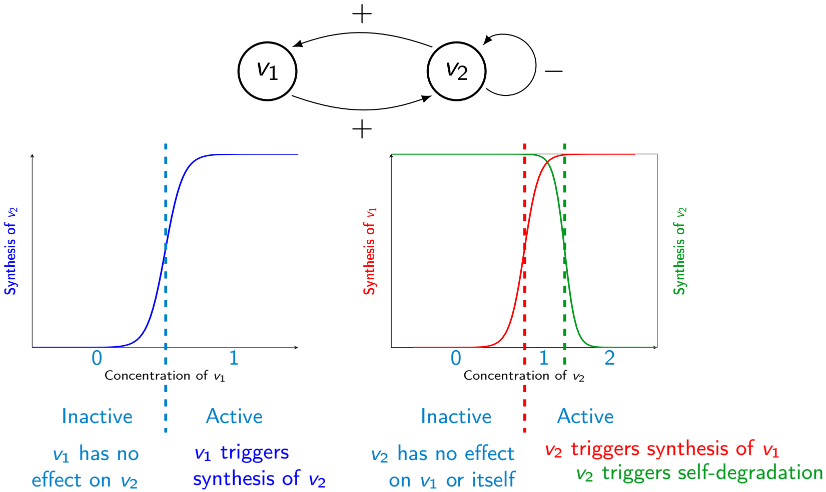

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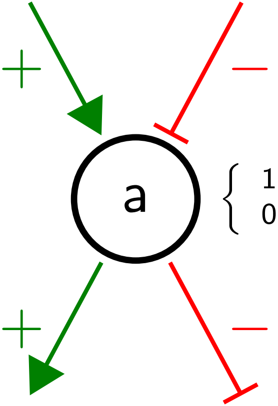
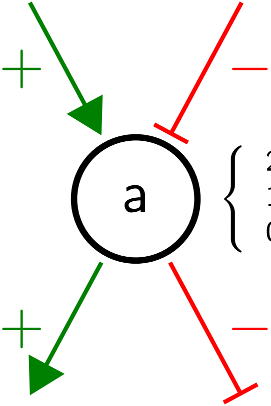


$$\left\{ \begin{array}{l} 1 = \text{active} \\ 0 = \text{inactive} \end{array} \right\}$$

Preliminary Abstraction



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

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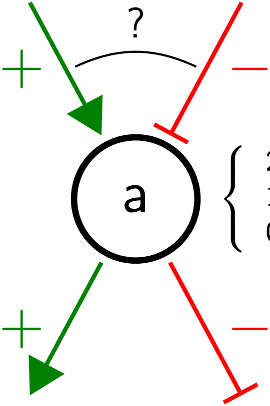

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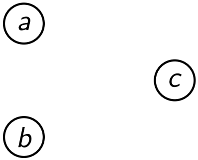
Biological Regulatory Networks

Discrete Networks / Thomas Modeling

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

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



Interaction Graph (IG)

Parameterization

Discrete Networks / Thomas Modeling

[Kauffman, *Journal of Theoretical Biology*, 1969]
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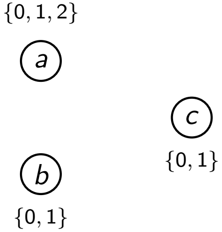
- A set of components $N = \{a, b, c\}$
- A maximum level for each component $\mathrm{m}(a) = 2$



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- A set of components $N = \{a, b, c\}$
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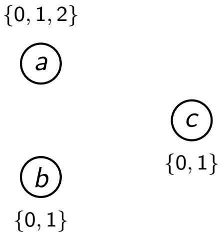
- Discrete parameters / evolution functions $f_a : \mathcal{S} \to \mathrm{dom}(a)$



Interaction Graph (IG)

a	f_b
0	0
1	1
2	1

c	b	f_a
0	0	1
0	1	0
1	0	1
1	1	2

a	b	f_c
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0	1	0
1	0	0
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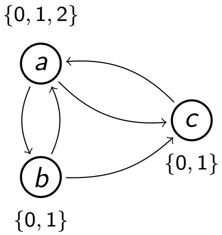

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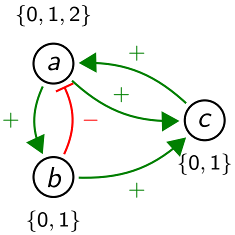

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0	1	0
1	0	0
1	1	0
2	0	0
2	1	1

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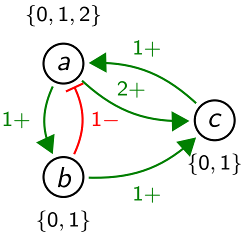

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a	b	f_c
0	0	0
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1	0	0
1	1	0
2	0	0
2	1	1

Parameterization

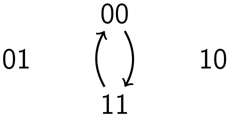
Semantics

$f_a = \neg b$ $f_b = \neg a$

b	f_a
0	1
1	0

a	f_b
0	1
1	0

State transitions differ according to the update semantics used:



Synchronous

- **Synchronous**: all variables are updated

Semantics

$f_a = \neg b$

b	f_a
0	1
1	0

$f_b = \neg a$

a	f_b
0	1
1	0

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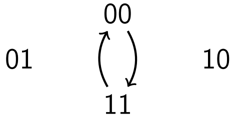
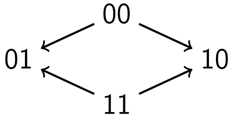


Synchronous



Asynchronous

- **Synchronous**: all variables are updated
- **Asynchronous**: only one variable is updated

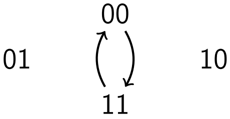
Semantics

$f_a = \neg b$ $\qquad$ $f_b = \neg a$

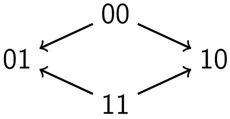
b	f_a
0	1
1	0

a	f_b
0	1
1	0

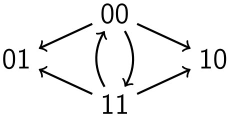
State transitions differ according to the update semantics used:



Synchronous



Asynchronous



General

- **Synchronous**: all variables are updated
- **Asynchronous**: only one variable is updated
- **General**: any number of variables can be updated

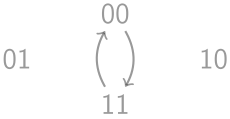
Semantics

$f_a = \neg b$ $\qquad$ $f_b = \neg a$

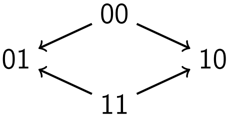
b	f_a
0	1
1	0

a	f_b
0	1
1	0

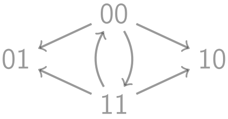
State transitions differ according to the update semantics used:



Synchronous



Asynchronous



General

- **Synchronous**: all variables are updated
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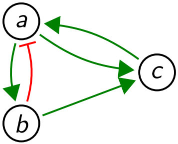
- **General**: any number of variables can be updated

State Graph

The state graph depicts explicitly the dynamics



abz

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

c	b	f_a
0	0	1
0	1	0
1	0	1
1	1	2

a	b	f_c
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

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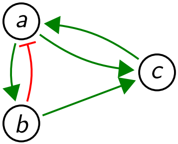

abz

000 010 001 011

100 ⟶ 110 101 111

200 210 201 211

c	b	f_a
0	0	1
0	1	0
1	0	1
1	1	2

a	b	f_c
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

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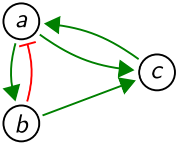

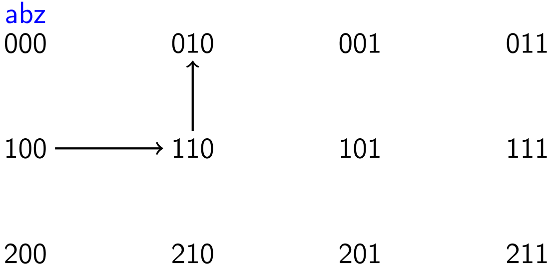

c	b	f_a
0	0	1
0	1	0
1	0	1
1	1	2

a	b	f_c
0	0	0
0	1	0
1	0	0
1	1	0
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a	f_b
0	0
1	1
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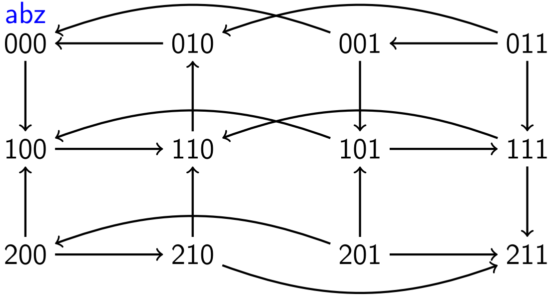

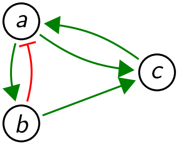

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0	0	1
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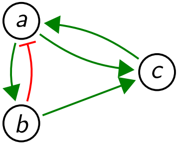
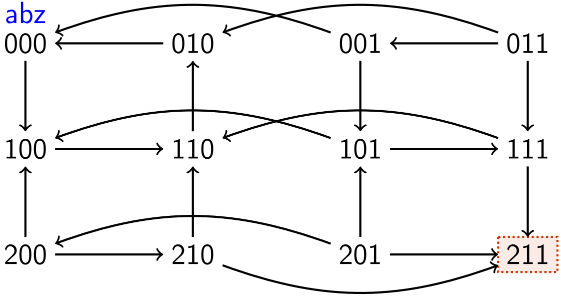
a	b	f_c
0	0	0
0	1	0
1	0	0
1	1	0
2	0	0
2	1	1

a	f_b
0	0
1	1
2	1

State Graph



The state graph depicts explicitly the dynamics



c	b	f_a
0	0	1
0	1	0
1	0	1
1	1	2

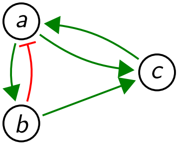
a	b	f_c
0	0	0
0	1	0
1	0	0
1	1	0
2	0	0
2	1	1

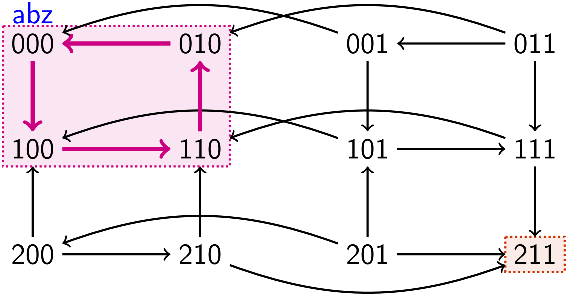
a	f_b
0	0
1	1
2	1

- **Fixed point** = state with no successors

State Graph

The state graph depicts explicitly the dynamics





c	b	f_a
0	0	1
0	1	0
1	0	1
1	1	2

a	b	f_c
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

- **Fixed point** = state with no successors
- **Cyclic attractor** = minimal set of states from which the dynamics cannot escape (always a loop or composition of loops)

Meaning of Edges in the IG

Logic point of view:

- Consider a state
- If increasing only variable a makes variable b change its value in the next state, then a has an influence on b $\quad (a \longrightarrow b)$
- If the change of b is an increase then the influence is positive, otherwise negative

Biological point of view:

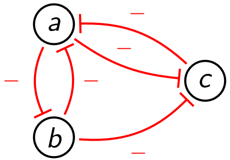
- Species a has been observed to have an increasing/decreasing effect on b
- An edge in the interaction graph ackowledges this information $(a \longrightarrow b)$
- The parameters should reflect this information

Repressilators

Repressilators

Only negative disjunctive influences

- An interaction graph (IG) $G = (N, E)$

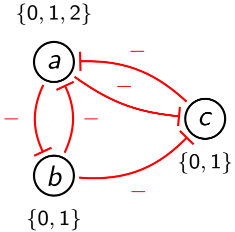


(Only one possible set of parameters)

Repressilators

Only negative disjunctive influences

- An interaction graph (IG) $G = (N, E)$
- A maximum level for each component $\mathrm{m}(a) = 2$

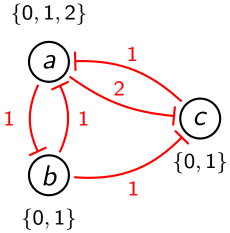


(Only one possible set of parameters)

Repressilators

Only negative disjunctive influences

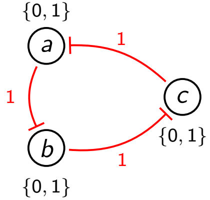
- An interaction graph (IG) $G = (N, E)$
- A maximum level for each component $\mathrm{m}(a) = 2$
- A threshold assignment for the edges $\mathrm{t}(a, b) = 1$

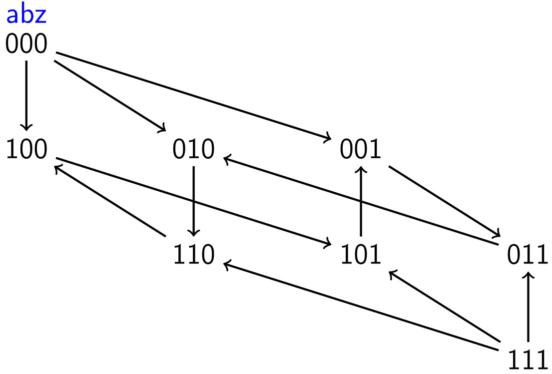


(Only one possible set of parameters)

Repressilator State Graph

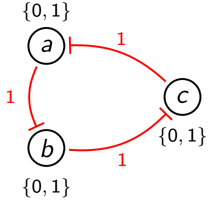
- When all predecessors are below the threshold: increase
- When at least one predecessor is above the threshold: decrease

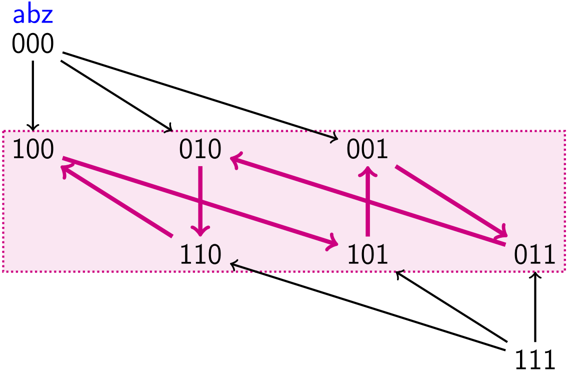




Repressilator State Graph

- When all predecessors are below the threshold: increase
- When at least one predecessor is above the threshold: decrease





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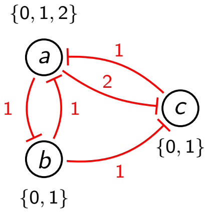

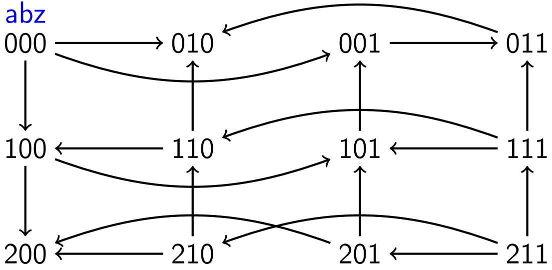

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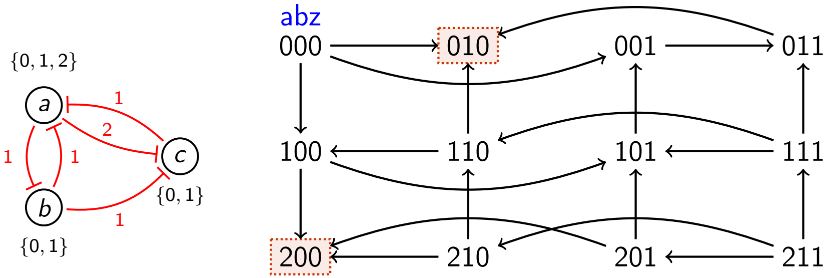
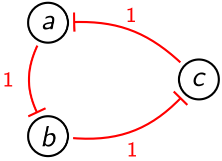


Use of Repressilators in Biology

Deliver a drug at regular time intervals

Repressilators ensure sustained oscillations...



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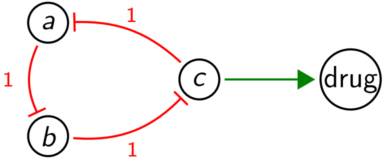

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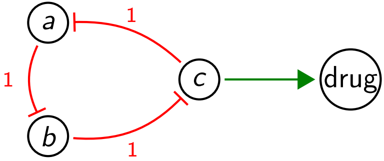
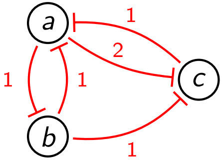


...Hopefully



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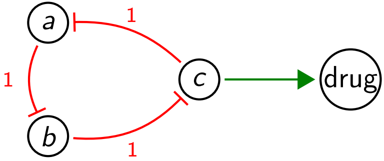

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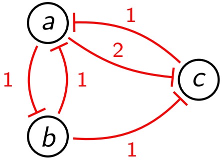
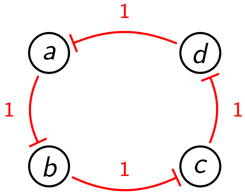




Brute-force enumeration

How to search for repressilators of size n with a cyclic attractor?

Brute-force search:

- Enumerate all possible IG (all combinations of edges)
- Enumerate all maximum level assignments and threshold assignments
- Compute the state graph for each model (**exponential complexity**)

Not tractable for high values of n

Static Analysis

- Enumerate all possible IG (all combinations of edges)
- Enumerate all maximum level assignments and threshold assignments
- ~~Compute the state graph for each model (**exponential complexity**)~~

[Paulevé and Richard, Electronic Notes in Theoretical Computer Science, 2012] gives, based on the IG only, results on:

- the link between cycles in the IG and fixed points/attractors
- bounds on the number of fixed point
- topological fixed points (common to all sets of parameters)

[Gadouleau, Natural Computing, 2020] gives bounds on:

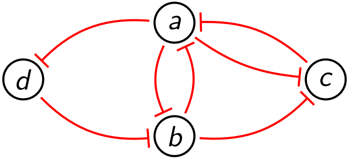
- the rank (number of non-source states)
- the number of states belonging to a cyclic attractor
- the number of fixed points

Stable Dominating Set

$$A \text{ is } \textbf{independent} \overset{\Delta}{\iff} \forall a, b \in A, (a, b) \notin E$$

$$A \text{ is } \textbf{dominating} \overset{\Delta}{\iff} \forall b \in V \setminus A, \exists a \in A, (a, b) \in E$$

$$A \text{ is a } \textbf{stable dominating set} \overset{\Delta}{\iff} A \text{ is independent} \wedge A \text{ is dominating}$$



	Independent	Dominating
$\{a, b, c, d\}$		x

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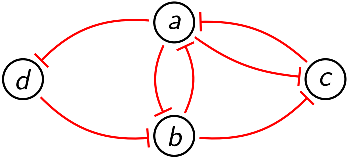

	Independent	Dominating
$\{a, b, c, d\}$		x
$\{d, b\}$		x

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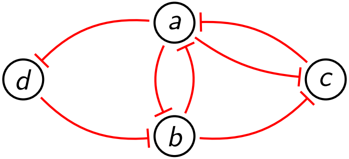

	Independent	Dominating
$\{a, b, c, d\}$		x
$\{d, b\}$		x
$\{b\}$	x	

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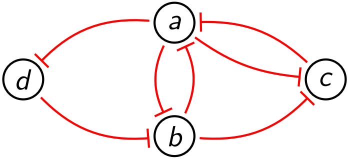

	Independent	Dominating
$\{a, b, c, d\}$		x
$\{d, b\}$		x
$\{b\}$	x	
$\{c, d\}$	x	x

Stable Dominating Set

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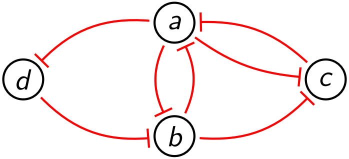


	Independent	Dominating
$\{a, b, c, d\}$		x
$\{d, b\}$		x
$\{b\}$	x	
$\{c, d\}$	x	x
$\{a\}$	x	x

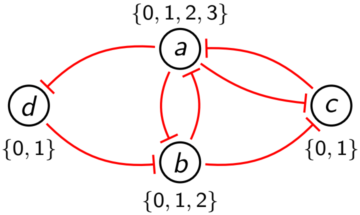
Results

Theorem 1 (Fixed Points)

Theorem 1: A is a stable dominating set $\Longleftrightarrow$ $\phi(A)$ is a fixed point

where $\phi(A) = (1_A(x) \cdot m_x)_{x \in V}$, with 1_A the indicator function of A

Already found by [Richard & Ruet, Discrete Applied Mathematics, 2013] for Boolean networks

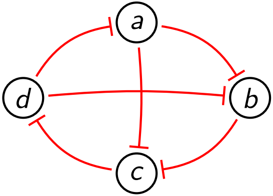


	Independent	Dominating	Associated fixed point
$\{c, d\}$	x	x	$(0, 0, 1, 1)$
$\{a\}$	x	x	$(3, 0, 0, 0)$

Corollary: Sufficient Condition for a Cyclic Attractor

Theorem 1: A is a stable dominating set $\iff \phi(A)$ is a fixed point

Corollary: No stable dominating set $\iff$ There exists no fixed point
$\implies$ There exists a cyclic attractor



Here, there exists a cyclic attractor!

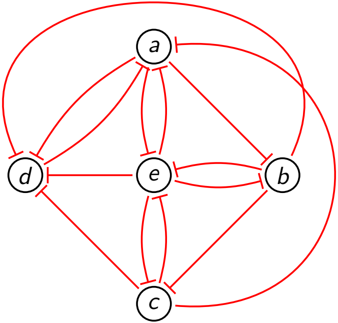
Cyclic Attractor With a Stable Dominating Set

What about the coexistence of a fixed point and a cyclic attractor?

Theorem 2: Suppose that there exists a stable dominating set A such that the subgraph $G[V \setminus A]$ admits no stable dominating set. Take $B \neq \emptyset$ any minimal subset of $V \setminus A$ such that $G[B]$ does not admit a stable dominating set. If all vertices in B inhibit all vertices in $V \setminus B$, then there exist a maximum level assignment and a threshold assignment such that the dynamics admits a cyclic attractor.

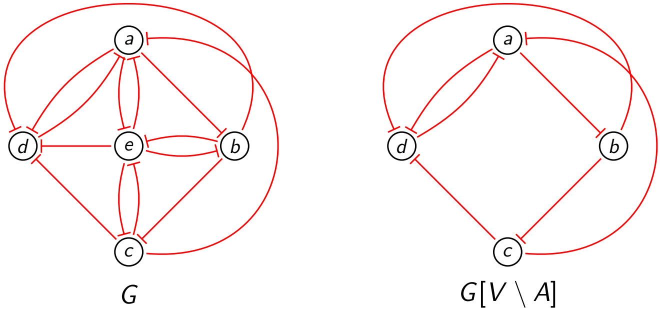
With $G[A]$ the restriction of the IG G to the set of nodes A.

Theorem 2: Suppose that there exists a stable dominating set A such that the subgraph $G[V \setminus A]$ admits no stable dominating set. Take $B \neq \emptyset$ any minimal subset of $V \setminus A$ such that $G[B]$ does not admit a stable dominating set. If all vertices in B inhibit all vertices in $V \setminus B$, then there exist a maximum level assignment and a threshold assignment such that the dynamics admits a cyclic attractor.



$A = \{e\}$

Theorem 2: Suppose that there exists a stable dominating set A such that the subgraph $G[V \setminus A]$ admits no stable dominating set. Take $B \neq \emptyset$ any minimal subset of $V \setminus A$ such that $G[B]$ does not admit a stable dominating set. If all vertices in B inhibit all vertices in $V \setminus B$, then there exist a maximum level assignment and a threshold assignment such that the dynamics admits a cyclic attractor.



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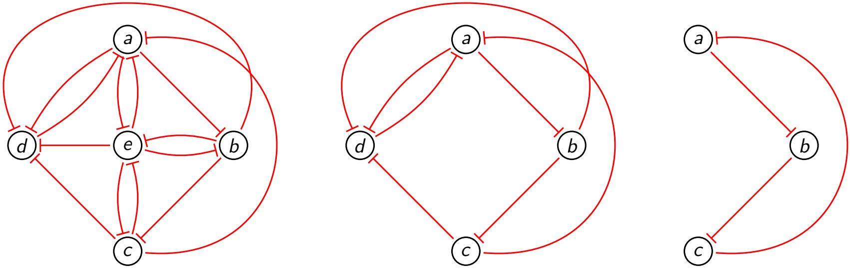

G $\quad$ $G[V \setminus A]$ $\quad$ $G[B]$

$A = \{e\} \qquad B = \{a, b, c\}$

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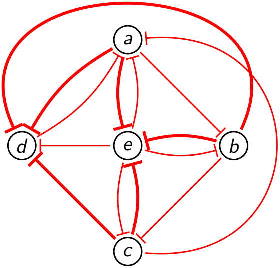
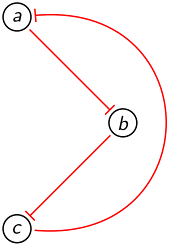


G



$G[B]$

$A = \{e\}$ $\qquad$ $B = \{a, b, c\}$

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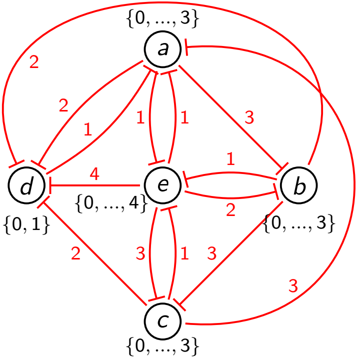

$\{00300, 01300, 02300, 03000, 03100,$
$03200, 03300, 10300, 11300, 12300,$
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$21300, 22300, 23000, 23100, 23200,$
$23300, 30000, 30100, 30200, 30300,$
$31000, 31100, 31200, 31300, 32000,$
$32100, 32200, 32300, 33000, 33100,$
$33200\}$

Case $n = 4$

Theorem 3: In the case $n = 4$, the sufficient condition is also a necessary condition. Moreover, when Theorem 2 applies, there is exacly one fixed point and one cyclic attractor, and the stable dominating set is of size 1.

This allows to characterize exactly the repressillators in dimension 4 that admit both a cyclic attractor and a fixed point

This is compatible with [Sun, Folschette, Magnin, CMSB'2023] where we (almost) found a necessary and sufficient condition for a cyclic attractor in $n = 4$

Case $n = 4$

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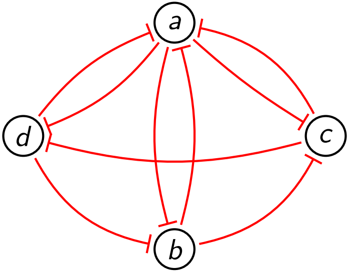

$$A = \{a\}$$

Conclusion

Conclusion

Summary:

- Based on the notion of stable dominating set
- Necessary and sufficient condition for the existence of a fixed point
  - and a characterization of this fixed point
- Sufficient conditions for the existence of a cyclic attractor
  - Necessary condition when $n = 4$

Outlooks:

- If possible, relax the sufficient condition
- Consider also positive interactions
- Explore the links with AND-nets

Thanks

Honglu SUN

Elisa TONELLO

Morgan MAGNIN

And thanks to the reviewers for their useful comments