Positive and Negative Circuits in Discrete Gene Networks

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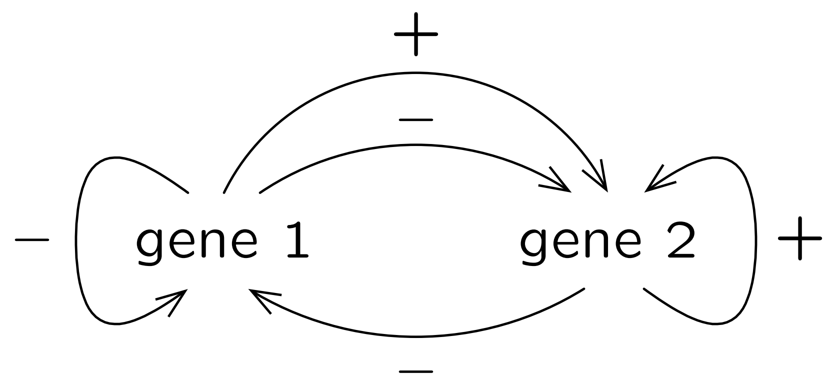
Introduction

Gene networks are often described in terms of **interaction graph**:



Generally, very little is known about the strength of the interactions:

Which dynamical properties of a gene network can be inferred from its interaction graph ?

We study this question in a **discrete modeling framework**.

Summary

1. Discrete modeling framework

- Asynchronous state graph
- Interaction graph

2. Results

- Positive circuit and multistationarity - 1st Thomas' conjecture
- Negative circuit and oscillations - 2nd Thomas' conjecture
- Boolean converses of the Thomas' conjectures

We consider a network of n genes.

Each gene i evolves inside a finite interval of integers

$$\boldsymbol{X_i = \{0, 1, \ldots, b_i\}}$$

The **set of states** of the network is

$$\boldsymbol{X = X_1 \times \cdots \times X_n}$$

The **dynamics** of the network is described from a map

$$\begin{aligned} \boldsymbol{f} : \boldsymbol{X} &\longrightarrow \boldsymbol{X} \\ \boldsymbol{x = (x_1, \ldots, x_n)} &\longmapsto \boldsymbol{f(x) = (f_1(x), \ldots, f_n(x))} \end{aligned}$$

More precisely, the dynamics of the network is described by the **asynchronous state graph of f** that we denote $\Gamma(f)$.

x	$f(x)$
$(0,0)$	$(2,2)$
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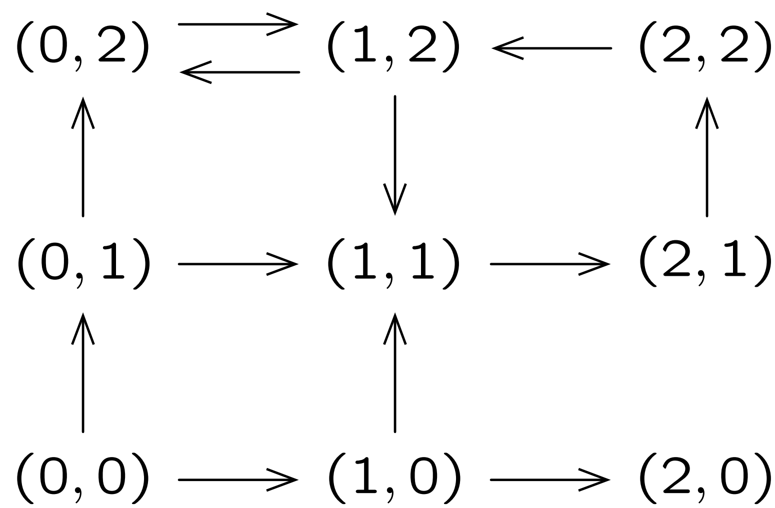
$\boldsymbol{\Gamma(f)}$



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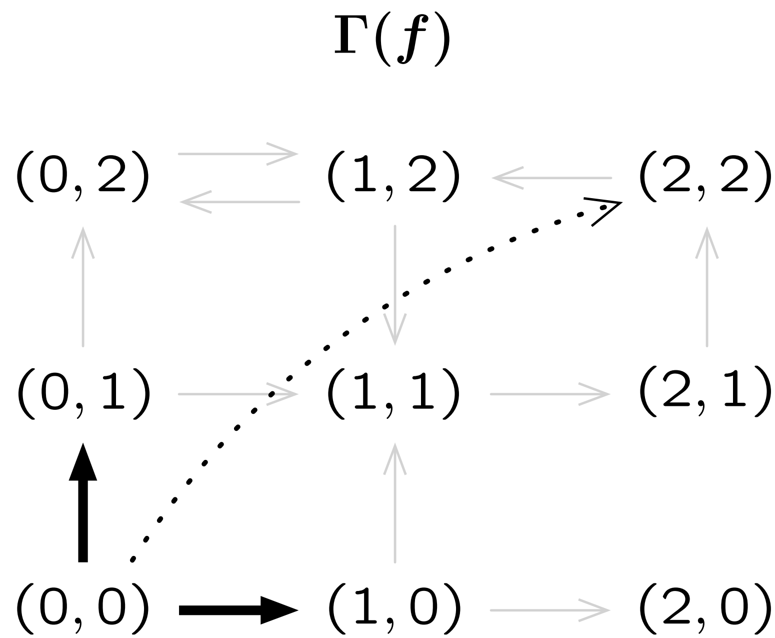

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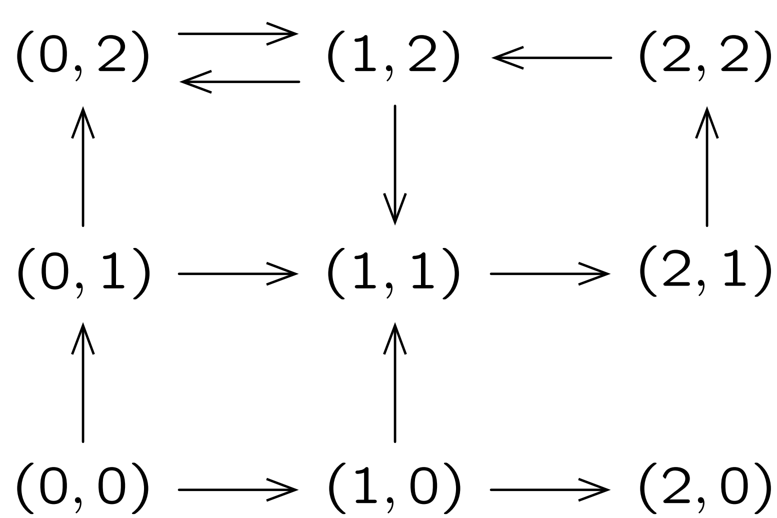
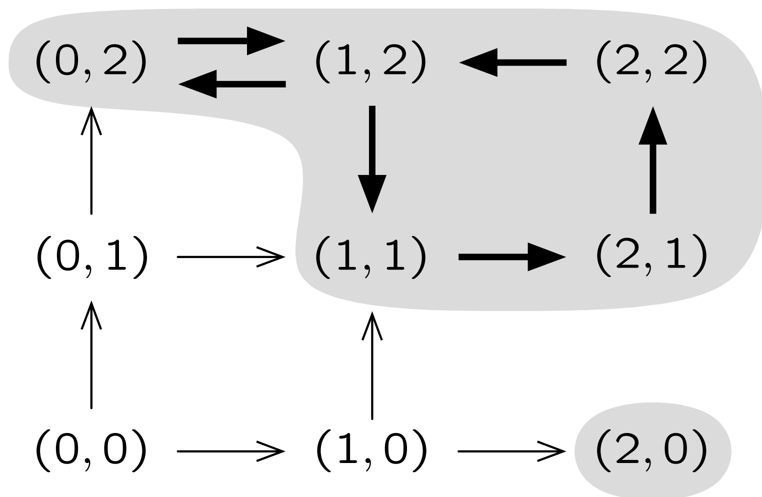


We call **attractors** the *smallest* subsets of states that we cannot leave.



Remarks

- Attractors are strongly connected components.
- From any state, there always exists a path leading to an attractor.

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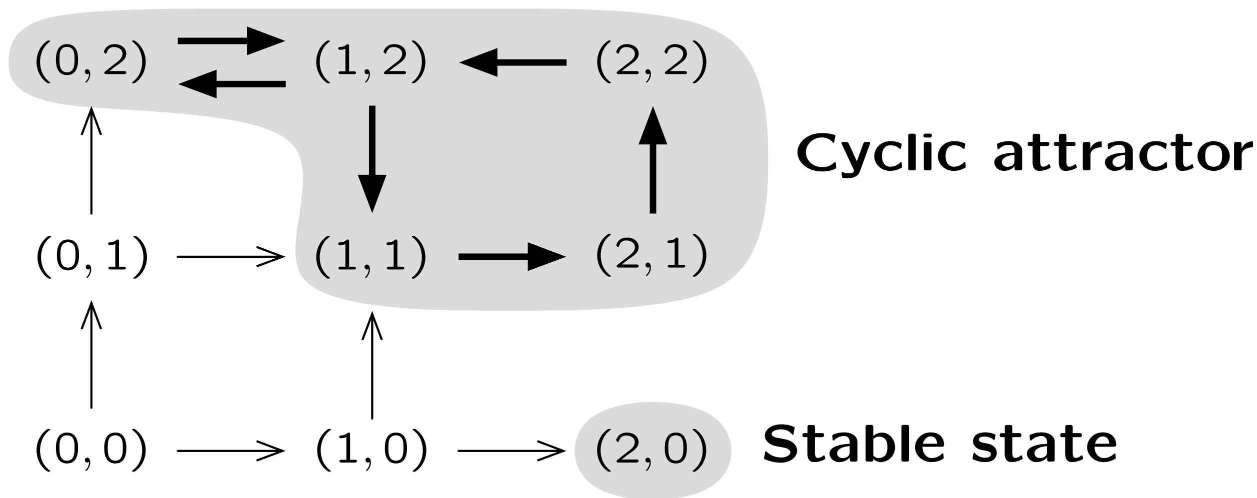

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Summary

1. Discrete modeling framework

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- **Interaction graph**

2. Results

- Positive circuit and multistationarity - 1st Thomas' conjecture
- Negative circuit and oscillations - 2nd Thomas' conjecture
- Boolean converses of the Thomas' conjectures

The topology of the network is described by the **interaction graph of** $\boldsymbol{f}$ denoted $\boldsymbol{G(f)}$:

- The set of nodes is $\{1, \dots, n\}$.

- There is a **positive edge** $\boldsymbol{j \to i}$ if there exists $x \in X$ such that:

$$\boldsymbol{f_i(x_1, \dots, x_j, \dots, x_n) < f_i(x_1, \dots, x_j{+}1, \dots, x_n)}$$

- There is a **negative edge** $\boldsymbol{j \to i}$ if there exists $x \in X$ such that:

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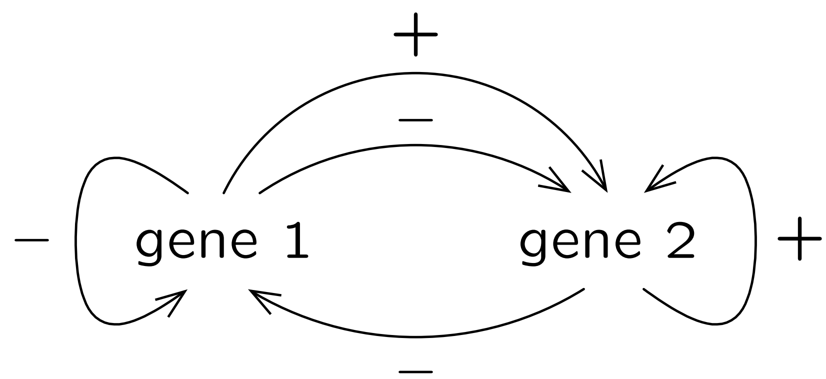

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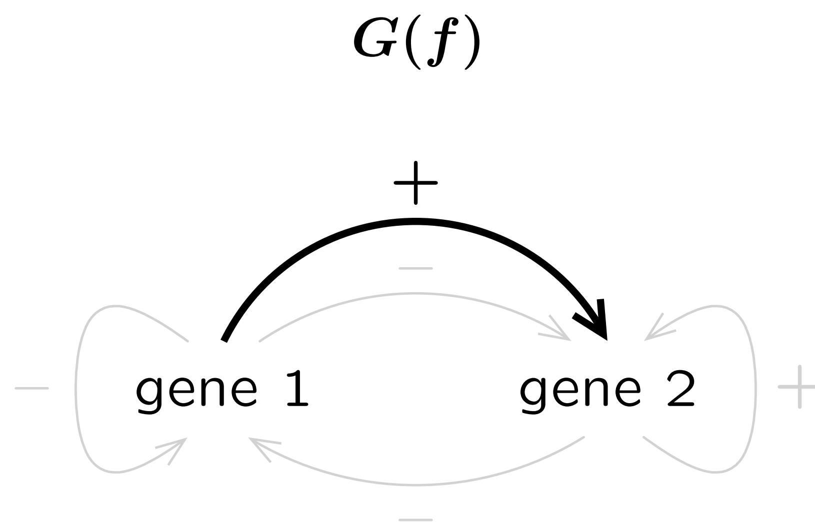

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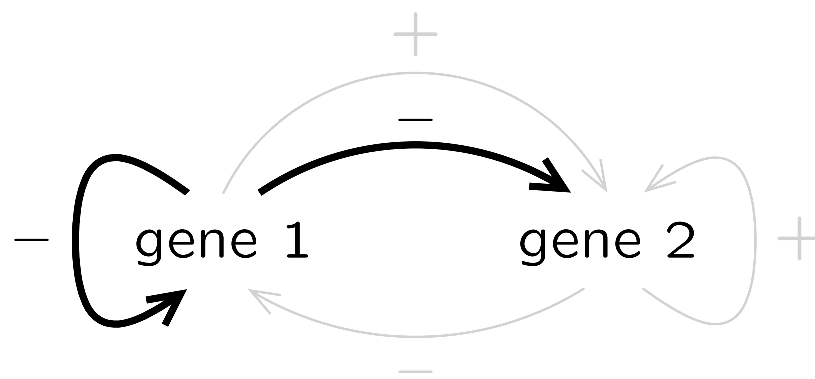

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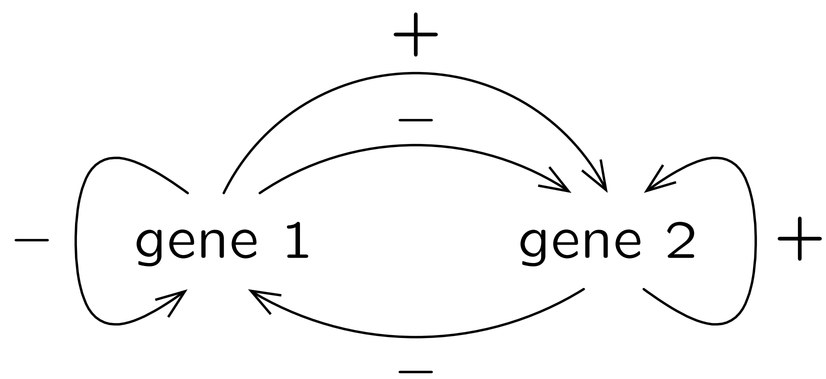

Remark

$\boldsymbol{G}(f)$ does not only depends on the asynchronous state graph $\boldsymbol{\Gamma}(f)$.

The natural definition of $\boldsymbol{G}[\boldsymbol{\Gamma}(f)]$ is slightly more technical.

All the incoming results are valid and more strong
when the considered interaction graph is $\boldsymbol{G}[\boldsymbol{\Gamma}(f)]$.

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   - **Positive circuit and multistationarity -1st Thomas' conjecture**
   - Negative circuit and oscillations - 2nd Thomas' conjecture
   - Boolean converses of the Thomas' conjectures

Theorem 1 (discrete version of the 1st Thomas' conjecture)
If $G(f)$ has no positive circuit then f has at most one fixed point.

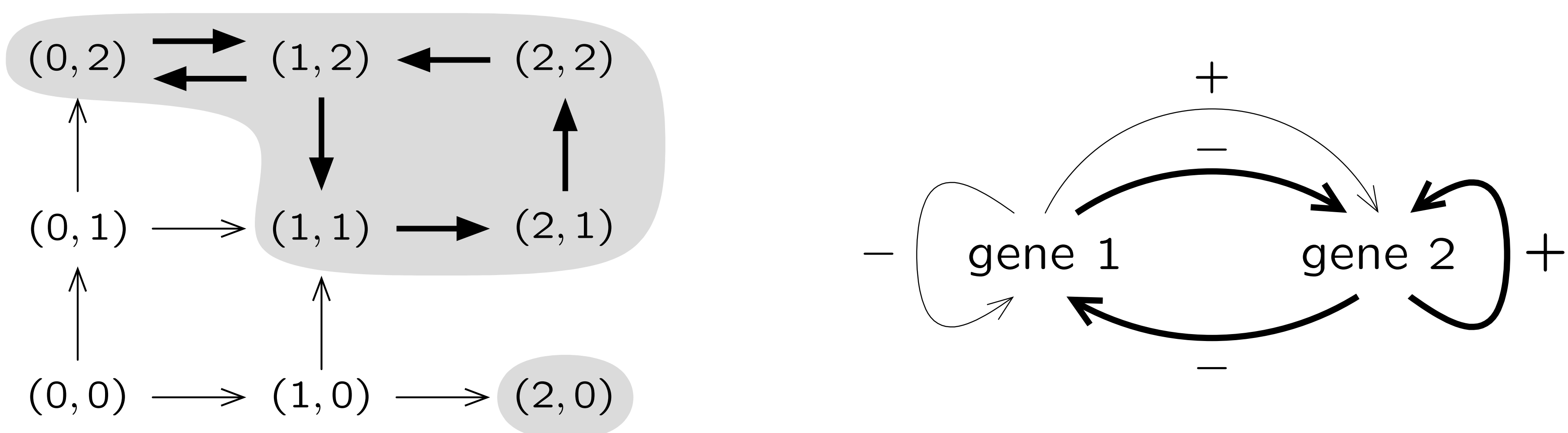
Remarks

- With J.P. Comet, we have proved a *local version* of this theorem.
- In the *boolean case*, this local version have been proved by E. Remy, P. Ruet and D. Thieffry (2005).

Theorem 1'

If $\boldsymbol{G}(f)$ has no positive circuit then $\Gamma(f)$ has a unique attractor.

Several attractors $\Rightarrow$ Positive circuit(s)



Theorem 1" (upper bound for the number of attractors)

Let $\boldsymbol{I} \subseteq \{1, \ldots, n\}$ be any set of genes such that

each positive circuit of $\boldsymbol{G}(f)$ *has at least one node in* $\boldsymbol{I}$*.*

The number of attractors in $\boldsymbol{\Gamma}(f)$ is less than

$$\prod_{\boldsymbol{i} \in \boldsymbol{I}} |\boldsymbol{X}_{\boldsymbol{i}}|$$

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Remarks

- None hypothesis is maded on $\boldsymbol{G}(f)$.
- Proved in the context of *boolean neural networks* by J. Aracena, J. Demongeot and E. Goles (2004).
- The bound is small when positive circuits are "highly" connected.

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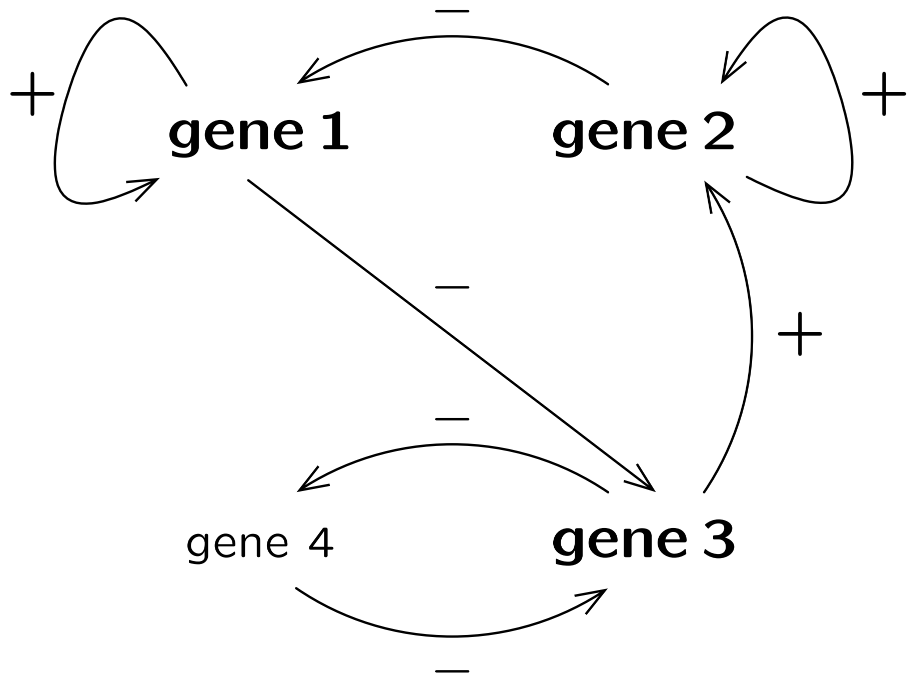
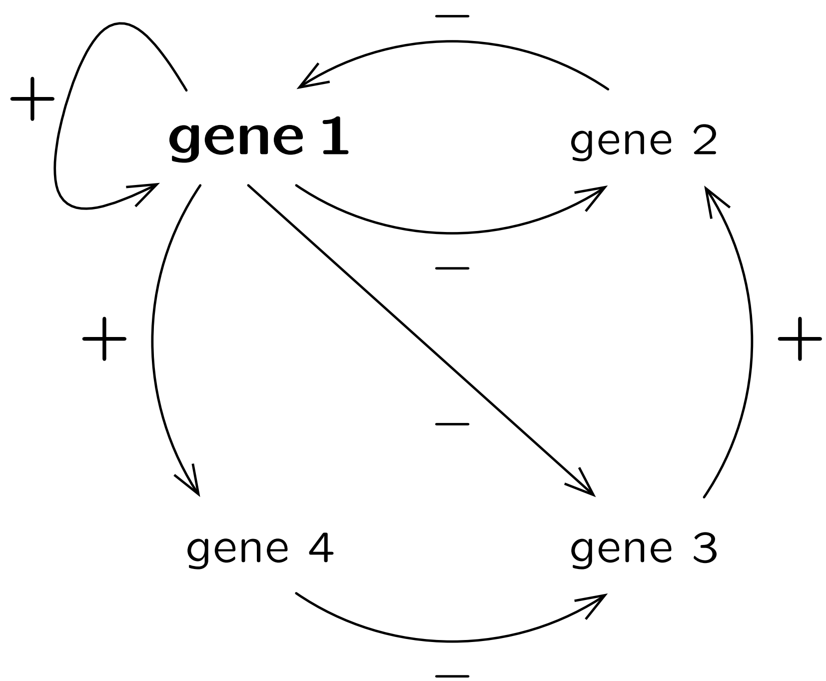


4 positives circuits

At most $|X_1||X_2||X_3|$ **attractors** (2^3 in the boolean case)



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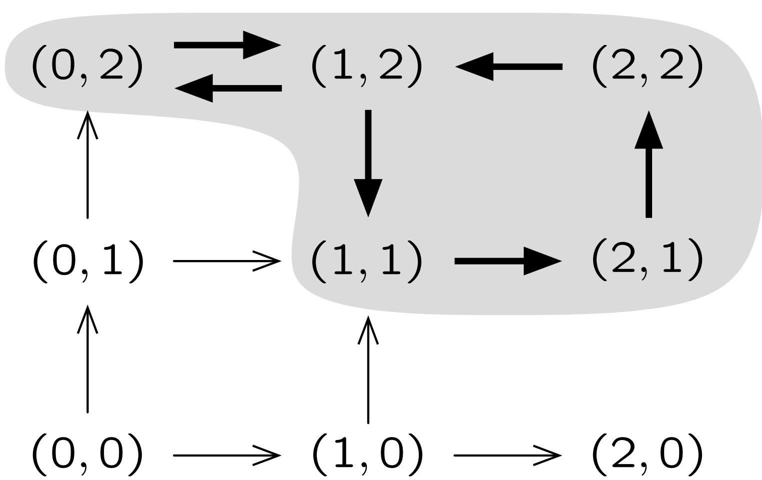
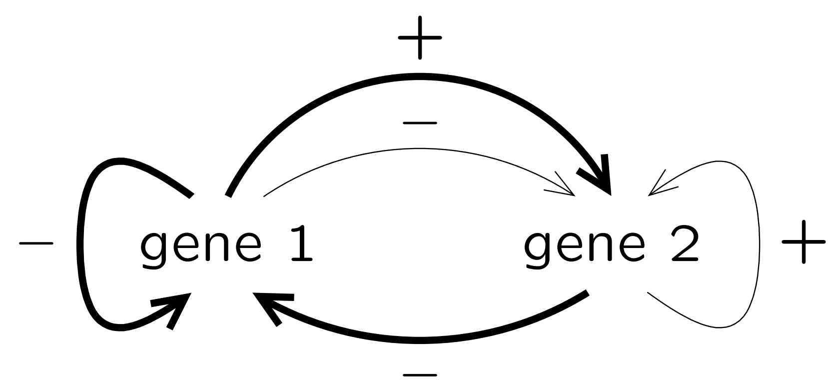
Theorem 2 (discrete version of the 2nd Thomas' conjecture)

If $\boldsymbol{G}(f)$ has no negative circuit then $\Gamma(f)$ has no cyclic attractor.

Cyclic attractor(s) $\Rightarrow$ Negative circuit(s)





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Remarks

- The condition "$\boldsymbol{G}(f)$ has no negative circuit" does not ensure the absence of cycle in $\Gamma(f)$.

  It seems not easy to find a more general form of oscillation needing the presence of a negative circuit.

- The question of a (pure) local version of this theorem is open.

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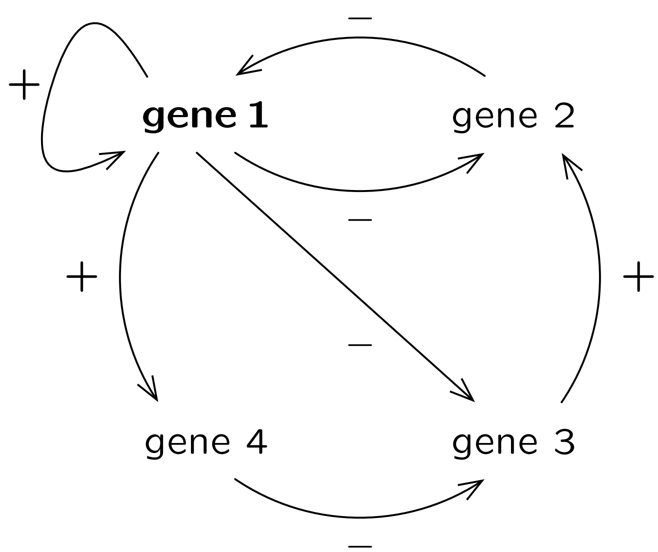
Theorem 3 (boolean converses of the Thomas' conjectures)

Let $f : \{0,1\}^n \to \{0,1\}^n$ and assume that $f_i \neq$ cst for $i = 1, \ldots, n$.

1. If $\boldsymbol{G}(f)$ only contains positive circuits then f has two fixed points.
2. If $\boldsymbol{G}(f)$ only contains negative circuits then f has no fixed point.

Remark: This theorem has been proved under additional assumptions, for boolean neural networks, by Aracena, Demongeot and Goles (2004).



(only positive circuits)

In the boolean case:

- At least 2 fixed points (Theorem 3)
- At most 2 fixed points (Theorem 1")
- No other attractor (Theorem 2)
- Since the interaction graph is *strongly connected* the two fixed points x and y are such that $\bar{x} = y$

Conclusion

The Thomas' conjectures take natural statements in the discrete case and the proofs are elementary.

The discrete case is a natural framework to study the dynamical influence of networks' topology.