# On the Link Between Oscillations and Negative Circuits in Discrete Genetic Regulatory Networks

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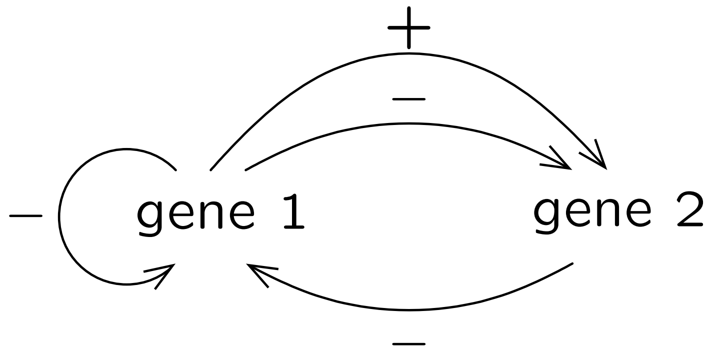
The structure of a gene regulatory network often *known* and represented by an **interaction graph** :




The **dynamics** of the network is often *unknown* and difficile to observe.

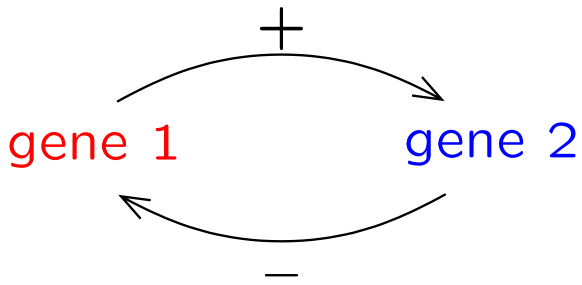
**What dynamical properties of a gene network can be deduced from its interaction graph ?**

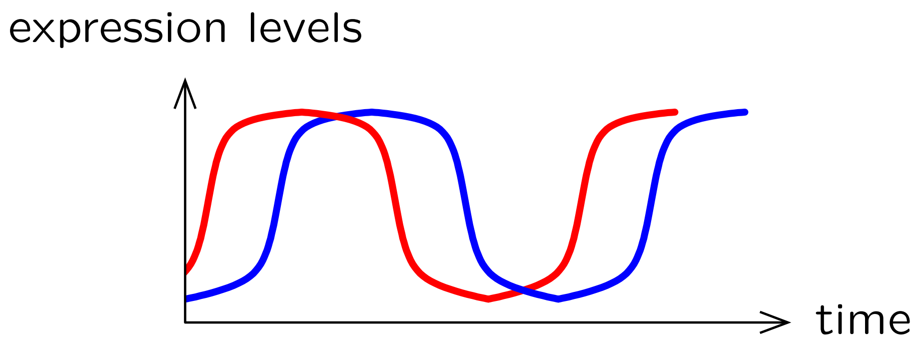
**(Second) Thomas' conjecture (1981) :**

**Without negative circuit (odd number of inhibitions)** in the interaction graph, there is **no sustained oscillations.**

**Equivalent formulation :**

If a network produces sustained oscillations, then its interaction graph has a negative circuit.



In this presentation :

We state the conjecture in a **general discrete framework** which includes the *Generalized Logical Analysis* of Thomas. (The proof is given in the paper.)

**Remark :** Discrete models are a good alternative to continuous models (based on ODEs) which are difficult to use in pratice because of the lack of precise datas about the behavior of genetic regulatory networks.

**Outline :**

1. We describe the dynamics of a network by a **discrete dynamical system** $\Gamma$.

2. We define, from the dynamic $\boldsymbol{\Gamma}$, the **interaction graphe** $G$ of the network.

3. We show that **the presence of sustained oscillations in the dynamics** $\Gamma$ **imply the presence of a negative circuit in** $G$**.**

# Part 1

# Discrete dynamical framework

We consider the evolution of network of $n$ genes :

- The **set of states $X$** is of the form :

$$X = X_1 \times \cdots \times X_n, \qquad X_i = \{0, 1, \ldots, b_i\}, \qquad i = 1, \ldots, n.$$

- To describe the dynamics, we consider a **map $f : X \longrightarrow X$** :

$$x = (x_1, \ldots, x_n) \in X \longrightarrow f(x) = (f_1(x), \ldots, f_n(x)) \in X.$$

Intuitively, at state $x$, the network evolves toward $f(x)$ :

▷ If $x_i < f_i(x)$ the expression level $x_i$ of gene $i$ is increasing.

▷ If $x_i = f_i(x)$ the expression level $x_i$ of gene $i$ is stable.

▷ If $x_i > f_i(x)$ the expression level $x_i$ of gene $i$ is decreasing.

- More precisely, *as in the Thomas' model*, the dynamics is described by the **asynchronous state transition graph of $f$**, denoted $\Gamma(f)$ :

   1. The set of nodes is the set of states $X$.

   2. The set of arcs is defined by : for each state $x$ and gene $i$,

      - if $x_i < f_i(x)$ there is an arc $x \longrightarrow y = (x_1, \dots, x_i + 1, \dots, x_n)$,

      - if $x_i > f_i(x)$ there is an arc $x \longrightarrow y = (x_1, \dots, x_i - 1, \dots, x_n)$.

**Example :** with $n = 2$ and $X = \{0,1,2\} \times \{0,1,2\}$ :

| $x$ | $f(x)$ |
|---|---|
| $(0,0)$ | $(1,2)$ |
| $(0,1)$ | $(1,2)$ |
| $(0,2)$ | $(2,2)$ |
| $(1,0)$ | $(2,2)$ |
| $(1,1)$ | $(2,1)$ |
| $(1,2)$ | $(0,0)$ |
| $(2,0)$ | $(2,0)$ |
| $(2,1)$ | $(2,2)$ |
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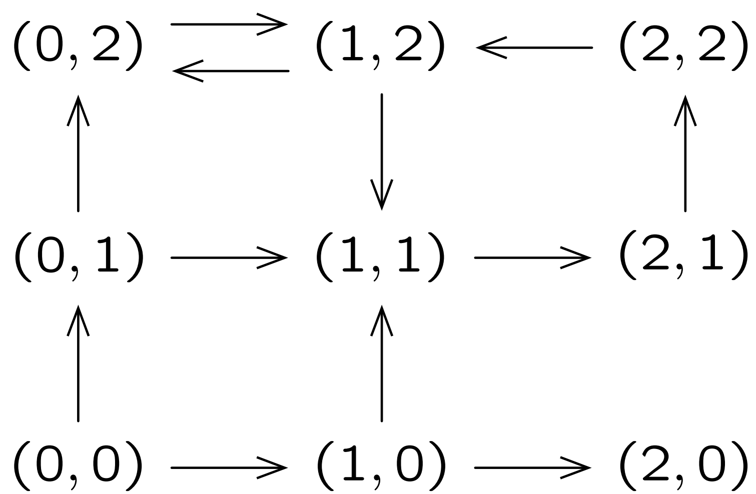
$\Gamma(f)$



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| | $(1,0)$ | $(2,2)$ |
| | $(1,1)$ | $(2,1)$ |
| | $(1,2)$ | $(0,0)$ |
| | $(2,0)$ | $(2,0)$ |
| | $(2,1)$ | $(2,2)$ |
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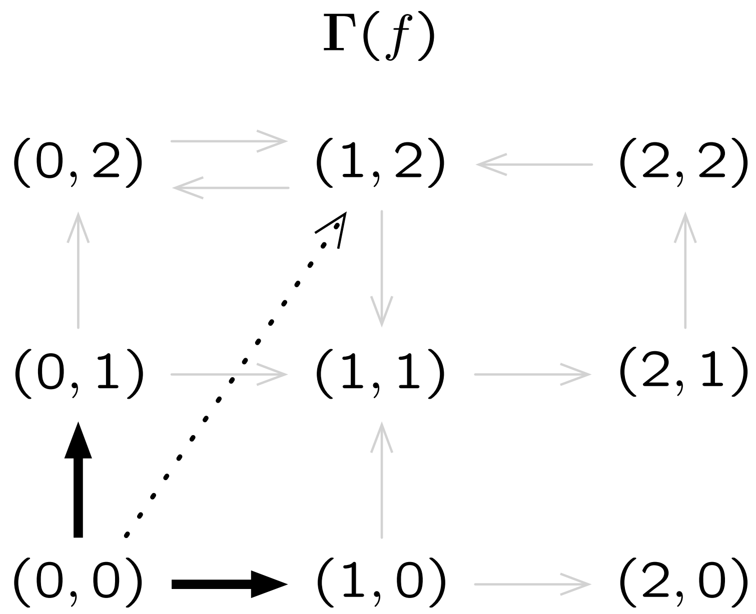

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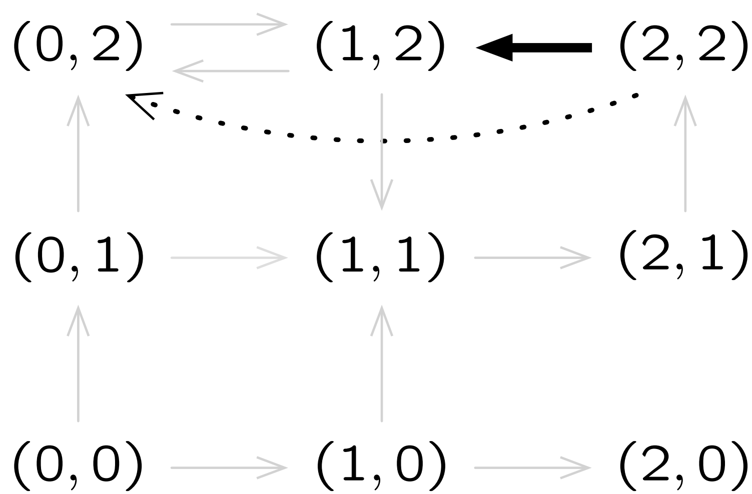
| | $(0,1)$ | $(1,2)$ |
| | $(0,2)$ | $(2,2)$ |
| | $(1,0)$ | $(2,2)$ |
| | $(1,1)$ | $(2,1)$ |
| | $(1,2)$ | $(0,0)$ |
| | $(2,0)$ | $(2,0)$ |
| | $(2,1)$ | $(2,2)$ |
| ▷ | $(2,2)$ | $(0,2)$ |

$\Gamma(f)$



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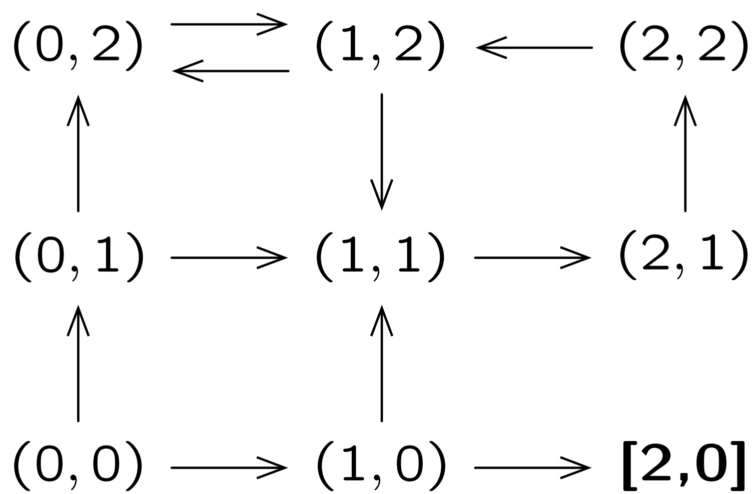
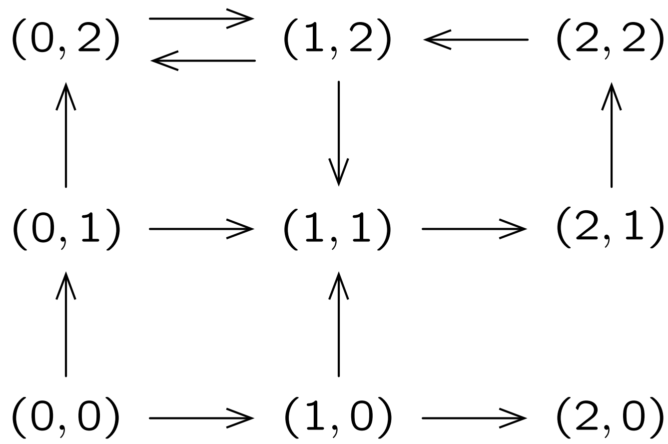
| | $(0,1)$ | $(1,2)$ |
| | $(0,2)$ | $(2,2)$ |
| | $(1,0)$ | $(2,2)$ |
| | $(1,1)$ | $(2,1)$ |
| | $(1,2)$ | $(0,0)$ |
| ▷ | $(2,0)$ | $(2,0)$ |
| | $(2,1)$ | $(2,2)$ |
| | $(2,2)$ | $(0,2)$ |

$\Gamma(f)$



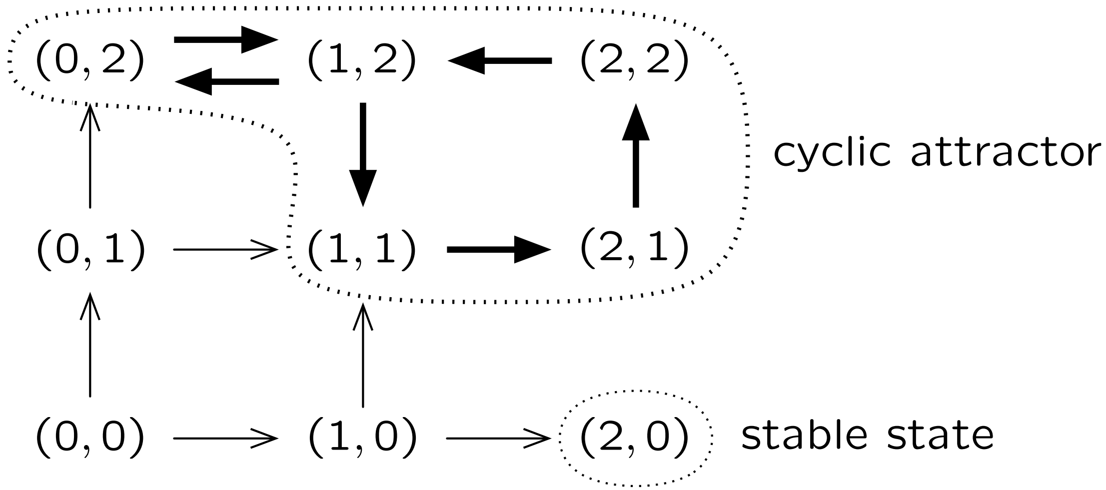
**Remarks :**

1. The dynamics described by $\mathbf{\Gamma}(f)$ is undeterministic.




2. Snoussi and Thomas have showed that this discrete dynamical model is a good approximation of continuous models based on piece-wise differential equations systems.

- An **attractor** of $\Gamma(f)$ is a **smallest** non-empty subset $A$ of $X$ such that all paths of $\Gamma(f)$ starting in $A$ remain in $A$.



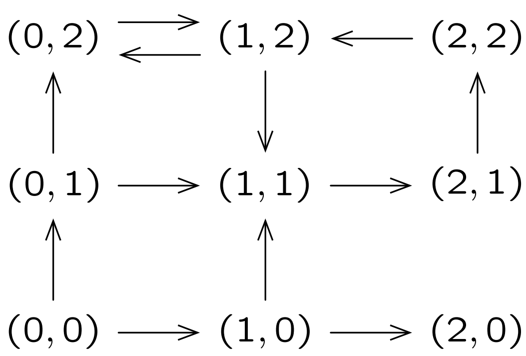

  - ▷ An attractor which contains at least 2 states describes sustained oscillations, and is called **cyclic attractor**.

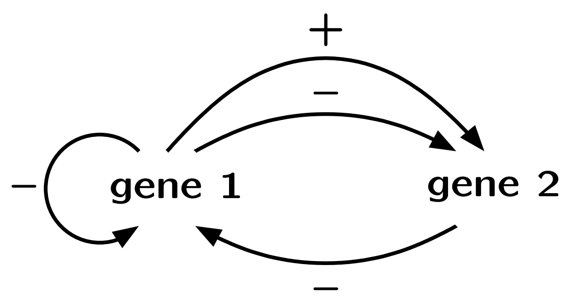
  - ▷ An attractor which contains a unique state is a **stable state**.

**Remark : There is always at least one attractor in $\Gamma(f)$.**

# Part 2

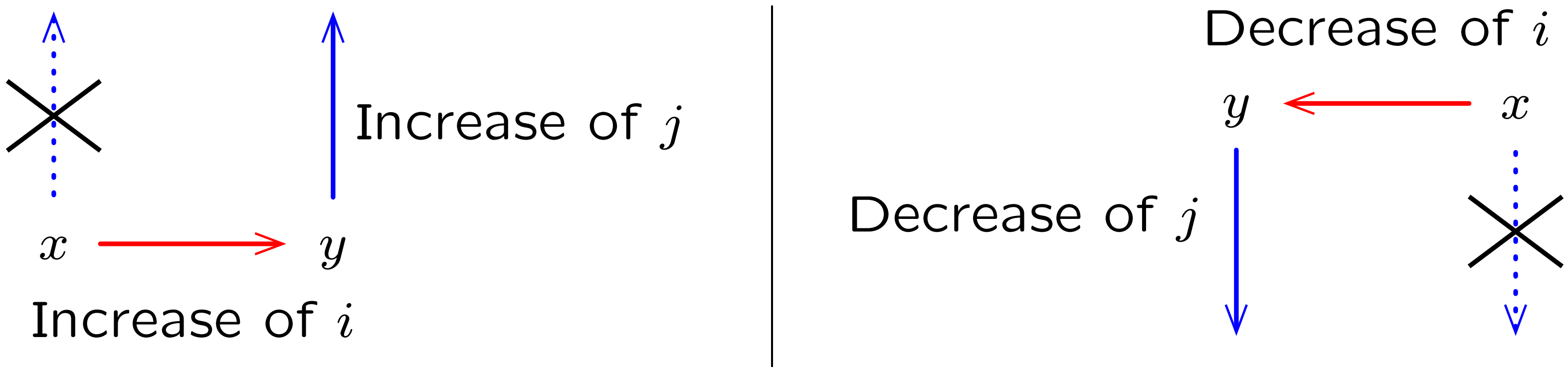
# Interaction graph of $f$



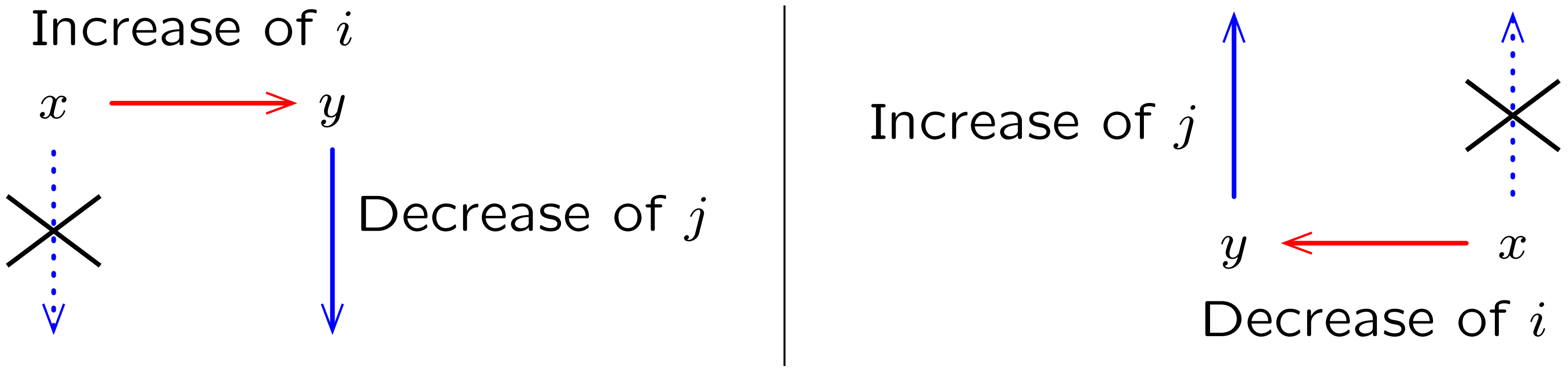



- The **interaction graph $G(f)$ of $f$** is the signed oriented graph whose set of nodes is $\{1,\ldots,n\}$ and such that (3 rules) :

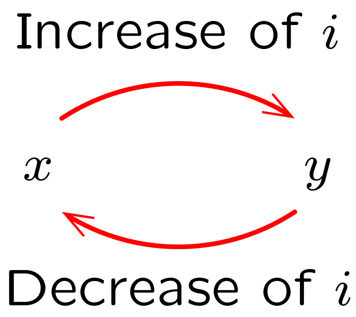
  **1.** There is a **positive interaction $i \longrightarrow j$**, with $i \neq j$, if one of the two following motifs is present in $\Gamma(f)$ :



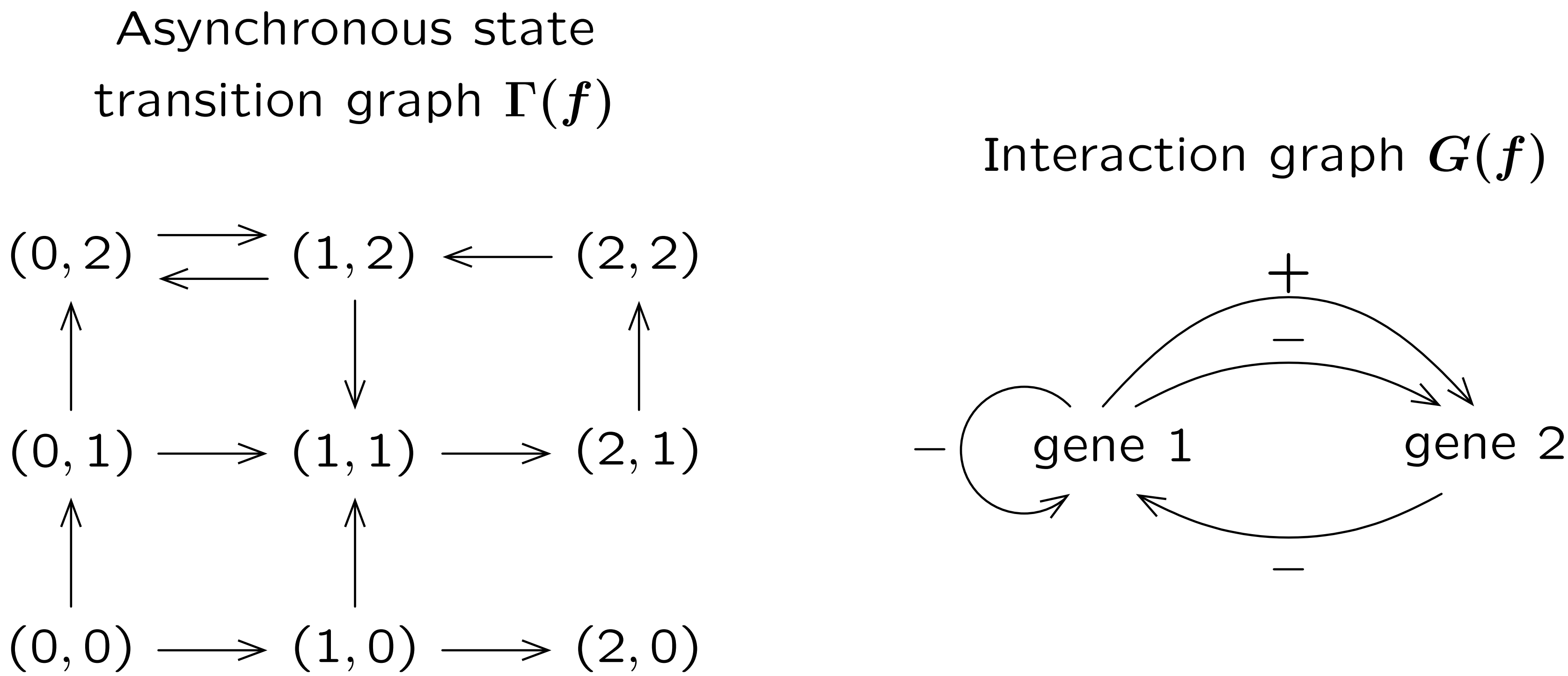
**2.** There is a **negative interaction** $\boldsymbol{i \longrightarrow j}$, with $i \neq j$,
if one of the two following motifs is present in $\mathbf{\Gamma}(f)$ :



**3.** There is a **negative interaction** $\boldsymbol{i \longrightarrow i}$,
if the following motifs is present in $\Gamma(f)$ :

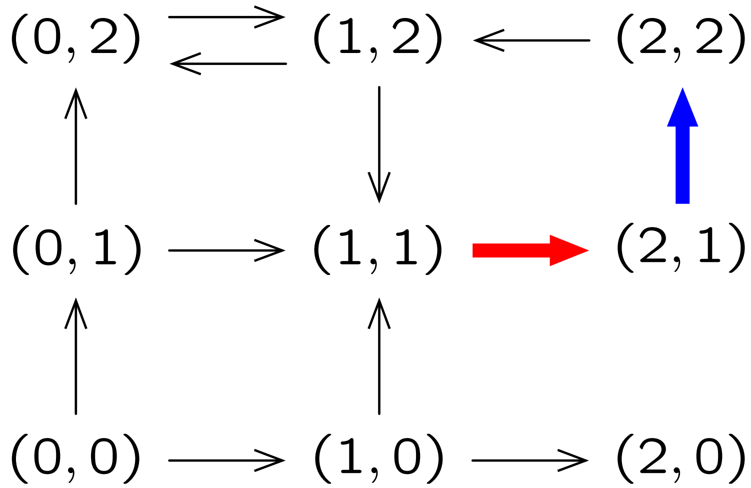



**Remark :** $G(f)$ **is a subgraph of the interaction graphs considered by Thomas and Remy et al.**

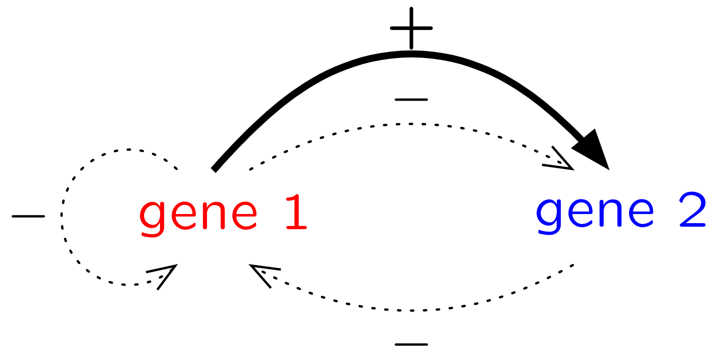


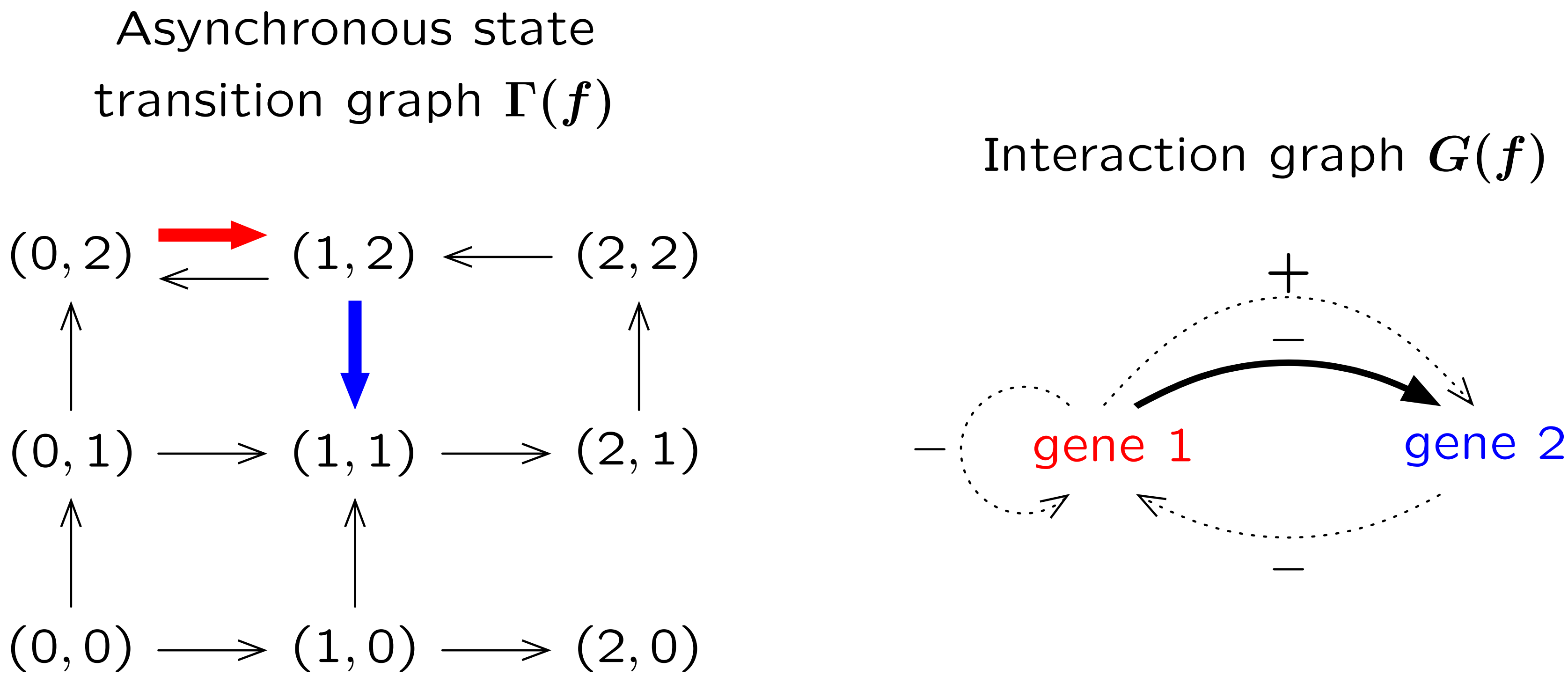
Asynchronous state transition graph $\Gamma(f)$
(0, 2)
(1, 2)
(2, 2)
(0, 1)
(1, 1)
(2, 1)
(0, 0)
(1, 0)
(2, 0)
Interaction graph $G(f)$
+
−
−
gene 1
gene 2
−

Asynchronous state
transition graph $\Gamma(f)$

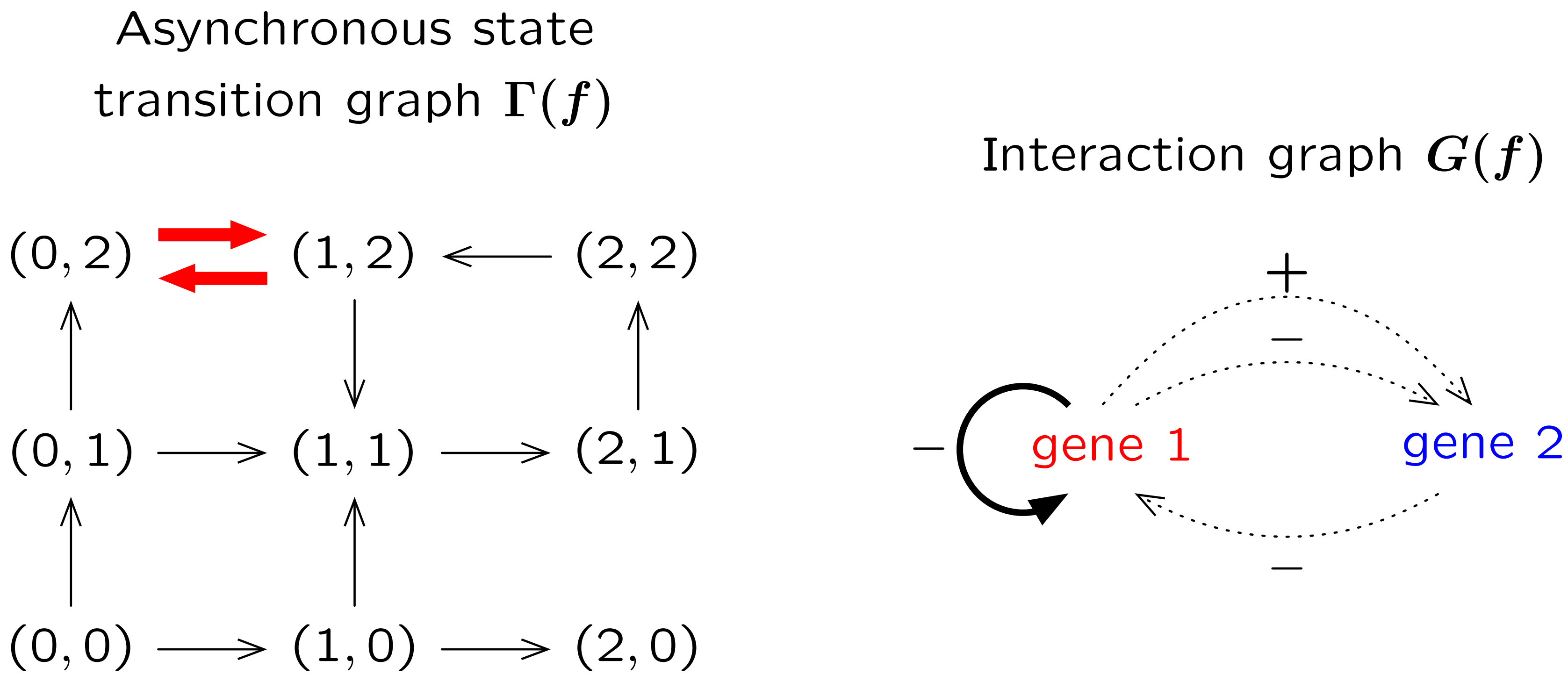



Interaction graph $G(f)$

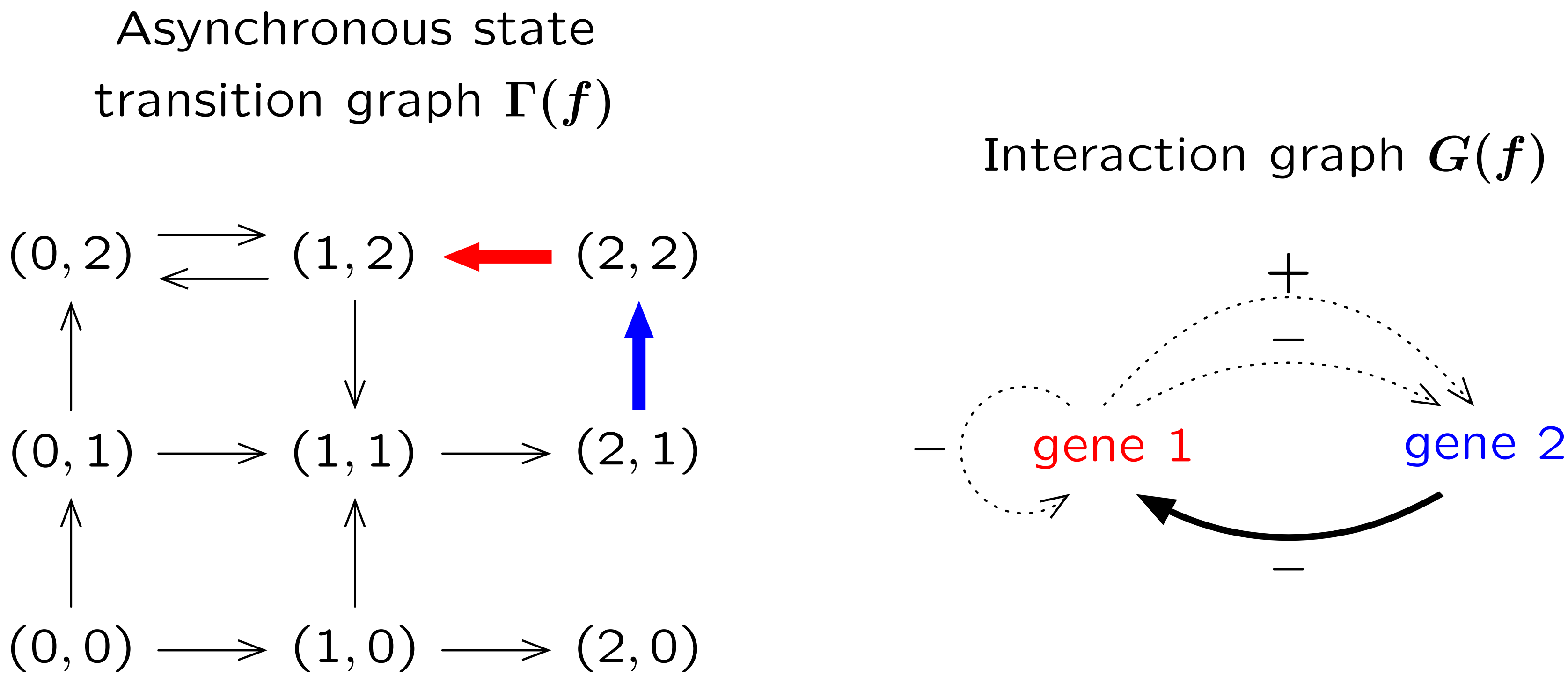




Asynchronous state transition graph $\Gamma(\boldsymbol{f})$
(0, 2)
(1, 2)
(2, 2)
(0, 1)
(1, 1)
(2, 1)
(0, 0)
(1, 0)
(2, 0)
Interaction graph $\boldsymbol{G}(\boldsymbol{f})$
+
−
−
−
gene 1
gene 2



Asynchronous state
transition graph Γ(f)
(0, 2)
(1, 2)
(2, 2)
(0, 1)
(1, 1)
(2, 1)
(0, 0)
(1, 0)
(2, 0)
Interaction graph G(f)
+
−
−
−
gene 1
gene 2


Asynchronous state
transition graph $\Gamma(f)$
(0, 2)
(1, 2)
(2, 2)
(0, 1)
(1, 1)
(2, 1)
(0, 0)
(1, 0)
(2, 0)
Interaction graph $G(f)$
+
−
−
gene 1
gene 2
−

# Part 3

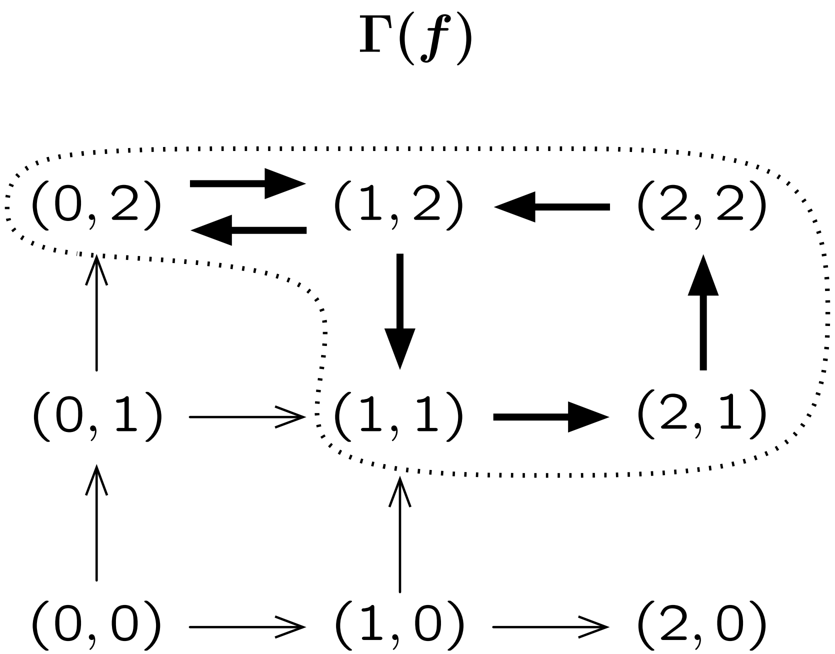
# Result

Let $f : X \to X$, with $X$ the product of $n$ finite intervals of integers.

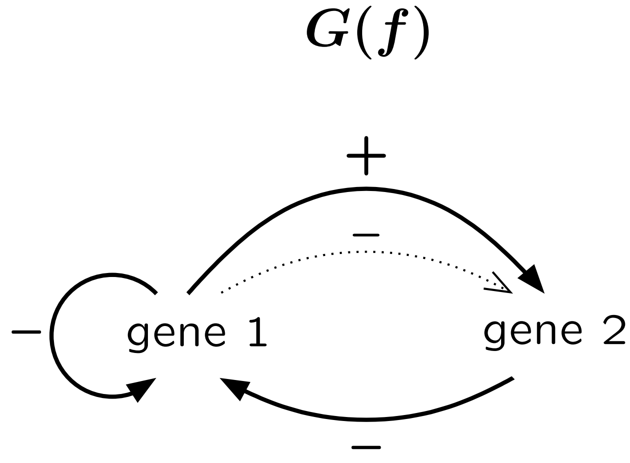
**Theorem (discrete version of the 2nd Thomas' conjecture)** :
If $\Gamma(f)$ has a cyclic attractor, then $G(f)$ has a negative circuit.

To prove the theorem, we reason by induction on the number of transitions in the cyclic attractors ; the base case corresponds to the case where there is a cyclic attractor $A$ containing a state which has a unique successor.

**Remark :** This theorem was proved by Remy *et al.* in the boolean ($X = \{0, 1\}^n$) and under the strong hypothesis that $\Gamma(f)$ contains an attractor $A$ such that *all* the states of $A$ have a unique successor.



Γ(f)
(0,2)
(1,2)
(2,2)
(0,1)
(1,1)
(2,1)
(0,0)
(1,0)
(2,0)

G(f)
+
−
−
gene 1
gene 2
−

**Concluding Remarks :**

**1.** As corollary we have a

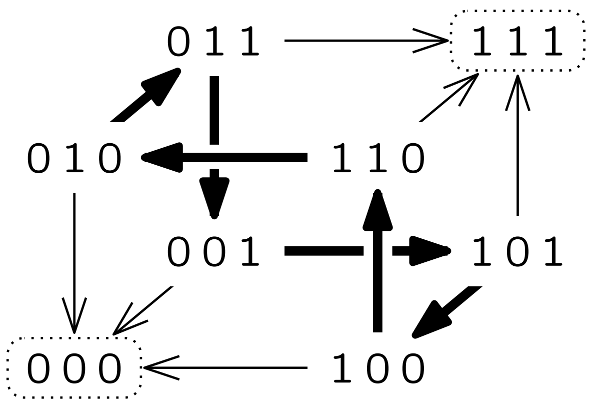
**Fixed point theorem :**
If $G(f)$ has no negative circuit, then $f$ has at least one fixed point.

Indeed, there is always at least one attractor $A$ in $\mathbf{\Gamma}(f)$.
If $G(f)$ has no negative circuit then $A$ is not a cyclic attractor,
so $A$ is reduced to a unique state $x$ which is a fixed point of $f$.

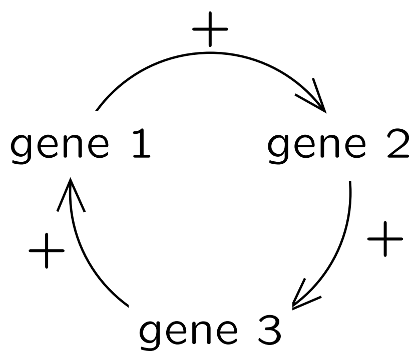
**Concluding remarks :**

**2.** The presence of a cycle in $\mathbf{\Gamma}(f)$ **does not** imply the presence of a negative circuit in $G(f)$.

$\mathbf{\Gamma}(f)$




$G(f)$




It seams difficult to find a form of oscillation in $\mathbf{\Gamma}(f)$ more general than the cyclic attractors and which imply the presence of a negative circuit in $G(f)$.