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 difficult 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 practice because of the lack of precise data 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 $\Gamma$, 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:
  \[
  X = X_1 \times \cdots \times X_n, \quad X_i = \{0, 1, \ldots, b_i\}, \quad i = 1, \ldots, n.
  \]

- To describe the dynamics, we consider a map $f : X \to X$:
  \[
  x = (x_1, \ldots, x_n) \in X \to f(x) = (f_1(x), \ldots, f_n(x)) \in X.
  \]

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

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

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<tr>
<th>$x$</th>
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\( \Gamma(f) \):

- \( (0,2) \rightarrow (1,2) \rightarrow (2,2) \)
- \( (0,1) \rightarrow (1,1) \rightarrow (2,1) \)
- \( (0,0) \rightarrow (1,0) \rightarrow (2,0) \)
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Remarks:

1. The dynamics described by $\Gamma(f)$ 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 $f$

(0,2) ←→ (1,2) ←→ (2,2)
(0,1) → (1,1) → (2,1)
(0,0) → (1,0) → (2,0)

gene 1

gene 2
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** $i \to j$, with $i \neq j$, if one of the two following motifs is present in $\Gamma(f)$:

![Diagram](image)

**Remark:** $G(f)$ is a subgraph of the interaction graphs $\Gamma(f)$.
2. There is a **negative interaction** $i \rightarrow j$, with $i \neq j$, if one of the two following motifs is present in $\Gamma(f)$:

- Increase of $i$
- $x \xrightarrow{} y$
- Decrease of $j$

- Increase of $j$
- $y \xleftarrow{} x$
- Decrease of $i$
3. There is a **negative interaction** \( i \rightarrow i \), if the following motifs is present in \( \Gamma(f) \):

![Diagram](image.png)

**Remark:** \( G(f) \) is a subgraph of the interaction graphs considered by Thomas and Remy et al.
Asynchronous state transition graph $\Gamma(f)$

$$
\begin{align*}
(0, 2) & \leftrightarrow (1, 2) \leftrightarrow (2, 2) \\
(0, 1) & \rightarrow (1, 1) \rightarrow (2, 1) \\
(0, 0) & \rightarrow (1, 0) \rightarrow (2, 0)
\end{align*}
$$

Interaction graph $G(f)$

$$
\begin{align*}
\text{gene 1} & \rightarrow \text{gene 2} \\
\text{gene 1} & \rightarrow \text{gene 2}
\end{align*}
$$
Asynchronous state transition graph $\Gamma(f)$

$\Gamma(f)$

Interaction graph $G(f)$

$G(f)$
Asynchronous state transition graph $\Gamma(f)$

(0, 2) $\leftarrow$ (1, 2) $\rightarrow$ (2, 2)

(0, 1) $\rightarrow$ (1, 1) $\rightarrow$ (2, 1)

(0, 0) $\rightarrow$ (1, 0) $\rightarrow$ (2, 0)

Interaction graph $G(f)$

gene 1

gene 2
Asynchronous state transition graph $\Gamma(f)$

$$
\begin{array}{c}
(0, 2) & \xrightarrow{\text{red}} & (1, 2) & \xleftarrow{\text{red}} & (2, 2) \\
\uparrow & & \downarrow & & \uparrow \\
(0, 1) & \rightarrow & (1, 1) & \rightarrow & (2, 1) \\
\uparrow & & \uparrow & & \\
(0, 0) & \rightarrow & (1, 0) & \rightarrow & (2, 0) \\
\end{array}
$$

Interaction graph $G(f)$

$$
\begin{array}{c}
gene 1 \\
\text{gene 2} \\
\end{array}
$$
Asynchronous state transition graph $\Gamma(f)$

\[
(0, 2) \xleftrightarrow{\text{[red]}} (1, 2) \xrightarrow{\text{[red]}} (2, 2) \\
\uparrow \quad \downarrow \quad \uparrow \\
(0, 1) \rightarrow (1, 1) \rightarrow (2, 1) \\
\uparrow \quad \uparrow \\
(0, 0) \rightarrow (1, 0) \rightarrow (2, 0)
\]

Interaction graph $G(f)$

\[
\text{gene 1} \quad \text{gene 2}
\]

$+$

$-$
Part 3

Result
Let $f : X \rightarrow X$, 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.
$$\Gamma(f)$$

\[
\begin{align*}
(0, 2) & \rightarrow (1, 2) & \leftarrow (2, 2) \\
(0, 1) & \rightarrow (1, 1) & \rightarrow (2, 1) \\
(0, 0) & \rightarrow (1, 0) & \rightarrow (2, 0)
\end{align*}
\]

$$G(f)$$

\[
\begin{align*}
+ & \quad \text{gene 1} \\
- & \quad \text{gene 2}
\end{align*}
\]
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 $\Gamma(f)$. 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 $\Gamma(f)$ **does not** imply the presence of a negative circuit in $G(f)$.

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