Positive and Negative Circuits in Discrete Models of Gene Networks

Adrien Richard, Équipe BioInfo
Introduction

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

The dynamics is complex: **non-linearities and feedback circuits**.
Several **dynamical models** have been proposed:

- Ordinary Diff. Equa. (Tyson, Soulé)
- Piece-wise Linear Diff. Equa. (Glass, de Jong)
- **Discrete Networks (Thomas’ Logical Method)**
- Boolean Networks (Kaufman, Thomas)

These models needed parameters whose value is generally unknown:

Which dynamical properties of a gene network can be deduced from its interaction graph?
The main properties of a dynamical system are often described in terms of **attractors** (stable state, limit cycle...).
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Biological interpretation: attractors \(\sim\) cell types
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Biological interpretation: attractors ~ cell types
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Which properties on the attractors of a network can be deduced from its interaction graph?

René Thomas’ conjectures:
Relations between the attractors of the network and the positive and negative circuits of the interaction graph.
Positive circuit: Even number of negative edges

Negative circuit: Odd number of negative edges
Conjectures of René Thomas (1981):

1. The presence of a **positive circuit** is a necessary condition for the presence of **several stable states (differentiation)**.

2. The presence of a **negative circuit** is a necessary condition for the presence of **sustained oscillations (cyclic attractors)**.
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[Diagram of a positive circuit with gene 1 and gene 2]

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![Positive Circuit Diagram]

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   ![Diagram of positive circuit](gene_1 -> gene_2)

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   ![Diagram of negative circuit](gene_1 <- gene_2)
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   ![Diagram of gene expression](image)

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   ![Positive Circuit Diagram]

   gene 1  gene 2

   +

2. The presence of a **negative circuit** is a necessary condition for the presence of **sustained oscillations** (cyclic attractors).

   ![Negative Circuit Diagram]

   gene 1  gene 2

   -

   Time

   Expression
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![Negative circuit diagram]
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1. The presence of a **positive circuit** is a necessary condition for the presence of **several stable states** (differentiation).

   ![Diagram of a positive circuit]

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2. The presence of a **negative circuit** is a necessary condition for the presence of **sustained oscillations** (cyclic attractors).

   ![Diagram of a negative circuit]

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Proofs of the first Thomas’ conjecture

- *In differential frameworks*

- *In discrete frameworks*

Proofs of the second Thomas’ conjecture

- *In differential frameworks*
  Open (see however Gouzé 1998, Snoussi 1998)

- *In discrete frameworks*
Interesting features of discrete frameworks

1. Adapted to the qualitative nature of observations.

2. State space and parameters space are finite.

3. Based on a natural approximation of the sigmoidal shape of genetic regulations.
Discretization comes from the sigmoidal shape of genetic regulations:

The boolean approximation may be too caricatural.
Summary

1. Discrete modeling framework
   - Asynchronous state graph
   - Interaction graph

2. Results
   - Positive circuit and multistationarity
   - Extension of Shih-Dong’s fixed point theorem
   - Negative circuit and oscillations
We consider a network of $n$ genes.

Each gene $i$ evolves inside a finite interval of integers

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

The set of states of the network is

$$X = X_1 \times \cdots \times X_n$$

The dynamics of the network is described given a map

$$f : X \rightarrow X$$

$$x = (x_1, \ldots, x_n) \mapsto f(x) = (f_1(x), \ldots, f_n(x))$$
More precisely, the dynamics of the network is described by the **asynchronous state graph of** $f$ that we denote $\Gamma(f)$.

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$\Gamma(f)$

- $(0,2) \leftrightarrow (1,2) \leftarrow (2,2)$
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\begin{align*}
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\end{align*}
\]
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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2. Results
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1. Set of states $X$ and function $f : X \to X$

2. Asynchronous state graph $\Gamma(f)$

3. Interaction graph $G(f)$
We proceed in two steps:

1. We associate to each state $x \in X$, a **local interaction graph** $G(x)$ that is based on a notion of **discrete derivative** for $f$.

2. We define the **global interaction graph** $G(f)$ of the network described by $f$ as the union of all the local interaction graphs.
1. The **local interaction graph** $G(x)$ is defined by:

- $G(x)$ contains a **positive edge** $j \xrightarrow{+} i$ if
  \[
  f_i(x) < f_i(x_1, \ldots, x_j + 1, \ldots, x_n)
  \]
  or
  \[
  f_i(x) > f_i(x_1, \ldots, x_j - 1, \ldots, x_n)
  \]

- $G(x)$ contains a **negative edge** $j \xrightarrow{-} i$ if
  \[
  f_i(x) > f_i(x_1, \ldots, x_j + 1, \ldots, x_n)
  \]
  or
  \[
  f_i(x) < f_i(x_1, \ldots, x_j - 1, \ldots, x_n)
  \]
2. The **global interaction graph** $G(f)$ of the network is defined by:

$$G(f) = \bigcup_{x \in X} G(x)$$

(each local interaction graph $G(x)$ is a *subgraph* of $G(f)$)
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$G(0, 1)$

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![Diagram showing gene 1 and gene 2 with a direction from gene 1 to gene 2 labeled $G(1, 0)$](image)
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Diagram:

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<td>$(1,1)$</td>
<td>$(2,1)$</td>
</tr>
<tr>
<td>$(1,2)$</td>
<td>$(0,1)$</td>
</tr>
<tr>
<td>$(2,0)$</td>
<td>$(2,0)$</td>
</tr>
<tr>
<td>$(2,1)$</td>
<td>$(2,2)$</td>
</tr>
<tr>
<td>$(2,2)$</td>
<td>$(0,2)$</td>
</tr>
</tbody>
</table>

\[G(2, 1)\]

```
+  
\(\text{gene 1}\)  \(\text{gene 2}\)  +
```

-
\[
\begin{array}{c|c}
  x & f(x) \\
  \hline
  (0, 0) & (2, 2) \\
  (0, 1) & (2, 2) \\
  (0, 2) & (1, 2) \\
  (1, 0) & (2, 1) \\
  (1, 1) & (2, 1) \\
  (1, 2) & (0, 1) \\
  (2, 0) & (2, 0) \\
  (2, 1) & (2, 2) \\
  [2, 2] & (0, 2) \\
\end{array}
\]

\[
G(2, 2)
\]

\[
\begin{aligned}
gene 1 & \quad gene 2 \\
\end{aligned}
\]

\[
\begin{aligned}
+ & \\
- & \\
\end{aligned}
\]

\[
\begin{aligned}
\text{gene 1} & \quad \text{gene 2} \\
\end{aligned}
\]

\[
\begin{aligned}
+ & \\
- & \\
\end{aligned}
\]
<table>
<thead>
<tr>
<th>$x$</th>
<th>$f(x)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0, 0)</td>
<td>(2, 2)</td>
</tr>
<tr>
<td>(0, 1)</td>
<td>(2, 2)</td>
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<tr>
<td>(0, 2)</td>
<td>(1, 2)</td>
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<td>(2, 2)</td>
</tr>
<tr>
<td>(2, 2)</td>
<td>(0, 2)</td>
</tr>
</tbody>
</table>

$G(f)$

- [ gene 1 ]
- [ gene 2 ]

- [ + ]
- [ - ]
Summary

1. Discrete modeling framework
   - Asynchronous state graph
   - Interaction graph

2. Results
   - Positive circuit and multistationarity
   - Extension of Shih-Dong’s fixed point theorem
   - Negative circuit and oscillations
Let $X$ be the product of $n$ finite intervals of integers, and let $f : X \to X$.

**Path Lemma**

*Suppose that $G(x)$ has no positive circuit for all $x \in X$, and let $x, y \in X$. If “$x$ is between $f(x)$ and $y$”, that is

$$f_i(x) \leq x_i \leq y_i \quad \text{or} \quad y_i \leq x_i \leq f_i(x) \quad \text{for all } i$$

then the asynchronous state graph $\Gamma(f)$ has a shortest path from $y$ to $x$.***
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then the asynchronous state graph $\Gamma(f)$ has a shortest path from $y$ to $x$. 
Theorem 1 (discrete version of the 1st Thomas’ conjecture)

If $G(x)$ has no positive circuit $\forall x \in X$, then $f$ has at most one fixed point.

Corollary

Remark

Theorem 1 has been proved in the boolean case by E. Remy, P. Ruet and D. Thiery (2005).
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Theorem 1 has been proved in the boolean case by E. Remy, P. Ruet and D. Thieffry (2005).
Theorem 1'
If $G(x)$ has no positive circuit $\forall x \in X$, then $\Gamma(f)$ has a unique attractor.

The existence is obvious. The uniqueness comes from the path lemma.
**Theorem 1’**

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*If $G(x)$ has no positive circuit $\forall x \in X$, then $\Gamma(f)$ has a unique attractor.*

**Corollary**

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

Several attractors \(\Rightarrow\) Positive circuit(s)

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

\[
\begin{align*}
gene 1 & \rightarrow + \\
gene 2 & \rightarrow +
\end{align*}
\]
Theorem 1" (upper bound for the number of attractors)

If $I$ is a set of genes such that $G(x) \setminus I$ has no positive circuit $\forall x \in X$, then the number of attractors in $\Gamma(f)$ is at most

$$\prod_{i \in I} |X_i|$$
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Remarks

- If \( G(x) \) has no positive circuit for all \( x \in X \), then \( I = \emptyset \) satisfies the conditions of the statement, so the upper bound is 1 and Theorem 1’ is recovered.
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**Remarks**

- If $G(x)$ has no positive circuit for all $x \in X$, then $I = \emptyset$ satisfies the conditions of the statement, so the upper bound is 1 and Theorem 1’ is recovered.

- The bound can be significantly improved by replacing $|X_i|$ by a number $T_i \leq |X_i|$ which only depends on the local positive circuits that contain the gene $i$. 
Corollary

If $I$ is a set of genes such that $G(f) \setminus I$ has no positive circuit, then the number of attractors in $\Gamma(f)$ is at most

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Remarks

- This corollary has been proved for fixed points of monotonous boolean networks, by J. Aracena, J. Demongeot and E. Goles (2004).

- None hypothesis on $G(f)$.

- The bound is small when positive circuits are “highly” connected.
At most $|X_1| |X_2| |X_3|$ attractors  ($2^3$ in the boolean case)
At most $|X_1||X_3|$ attractors \ (2^2 \text{ in the boolean case})
At most $|X_1|$ attractors (2 in the boolean case)
Summary

1. Discrete modeling framework
   - Asynchronous state graph
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2. Results
   - Positive circuit and multistationarity
   - Extension of Shih-Dong’s fixed point theorem
   - Negative circuit and oscillations
Theorem [Shi and Dong 2005] for $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$.

If $G(x)$ has no circuit $\forall x \in \{0, 1\}^n$, then $f$ has a unique fixed point.

According to Shih and Ho (1999), this theorem is a boolean analogue of the Jacobian conjecture in algebraic geometry.
Let $f : X \to X$ with $X$ the product of $n$ finite intervals of integers.

**Lemma** If $G(x)$ has no circuit $\forall x \in X$, then each hyper-rectangular region $P$ of $X$ contains a unique $P$-fixed point.
Let $f : X \rightarrow X$ with $X$ the product of $n$ finite intervals of integers.

**Lemma** If $G(x)$ has no circuit $\forall x \in X$, then each hyper-rectangular region $P$ of $X$ contains a unique $P$-fixed point.
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**Lemma** If $G(x)$ has no circuit $\forall x \in X$, then each hyper-rectangular region $P$ of $X$ contains a unique $P$-fixed point.

1. If $P$ is a cube, the lemma is given by Shih and Dong.
Let \( f : X \to X \) with \( X \) the product of \( n \) finite intervals of integers.

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**Theorem 2** (extension of the Shih-Dong’ fixed point theorem)

If $G(x)$ has no circuit $\forall x \in X$, then $f$ has a unique fixed point.
Remark

If $G(x)$ has no circuit $\forall x \in X$, then $f$ has a unique fixed points $x$,

\[ \text{and} \]

for all $y \in X$, there is a shorted path from $y$ to $x$ in $\Gamma(f)$. 
Remark
If $G(x)$ has no circuit $\forall x \in X$, then $f$ has a unique fixed points $x$,

and

for all $y \in X$, there is a shorted path from $y$ to $x$ in $\Gamma(f)$.

However, all the paths starting from $y$ does not lead necessarily to $x$ since $\Gamma(f)$ can contains cycles.
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\[ G(x) \text{ has no circuit for all } x \in X \]
Which additional conditions ensure an asynchronous convergence?

**Theorem**

If $G(x)$ has no circuit $\forall x \in X$ and if $G(f)$ has no negative circuit, then $\Gamma(f)$ describes an asynchronous convergence.
Which additional conditions ensure an asynchronous convergence?

**Theorem**

*If* $G(x)$ *has no circuit* $\forall x \in X$ *and if* $G(f)$ *has no negative circuit, then* $\Gamma(f)$ *describes an asynchronous convergence.*

**Corollary [Robert 1995]**

*If* $G(f)$ *has no circuit then* $\Gamma(f)$ *describes an asynchronous convergence*
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*If* \( G(f) \) *has no circuit then* \( \Gamma(f) \) *describes an asynchronous convergence*

**Theorem** *for* \( f : \{0, 1\}^n \rightarrow \{0, 1\}^n \).

*If* \( G(x) \) *has no circuit* \( \forall x \in \{0, 1\}^n \) *and if* \( G(f) \) *has no negative circuit or no positive circuit, then* \( \Gamma(f) \) *describes an asynchronous convergence.*
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If $G(x)$ has no circuit $\forall x \in X$ and if $G(f)$ has no negative circuit, then $\Gamma(f)$ describes an asynchronous convergence.

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**Theorem** for $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$.

If $G(x)$ has no circuit $\forall x \in \{0, 1\}^n$ and if $G(f)$ has no negative circuit or no positive circuit, then $\Gamma(f)$ describes an asynchronous convergence.

**Question** for $f : X \rightarrow X$.

If $G(x)$ has no circuit $\forall x \in X$ and if $G(f)$ has no positive circuit, then $\Gamma(f)$ describes an asynchronous convergence?
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Theorem 3 (discrete version of the 2nd Thomas’ conjecture)

If the asynchronous state graph $\Gamma(f)$ contains a cyclic attractor $A$, then

$$\bigcup_{x \in A} G(x)$$

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If \( G(f) \) has no negative circuit then \( \Gamma(f) \) has no cyclic attractor.
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**Corollary**

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

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

Cyclic attractor:

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

Negative circuit:

- $\rightarrow$ gene 1
- $\rightarrow$ gene 2
- $\rightarrow$
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**Corollary**
If $G(f)$ has no negative circuit then $\Gamma(f)$ has no cyclic attractor.

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

If $G(f)$ has no negative circuit then $f$ has at least one fixed point.

Remark 1

Theorem 3 has been prove by Remy, Ruet and Thieffry (2005) in the boolean case, and under the hypothesis that the cyclic attractor $A$ is a stable cycle (each state of $A$ has a unique successor in $\Gamma(f)$).
Remark 2

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

It is necessary to consider a cyclic attractor to obtain a negative circuit.
Remark 3

The presence of a cyclic attractor does not imply the presence of a negative circuit in a local interaction graph $G(x)$.

$G(x)$ has no negative circuit for all $x \in X$
Remark 3

The presence of a cyclic attractor does not imply the presence of a negative circuit in a local interaction graph $G(x)$.

$\Gamma(f)$

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

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

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

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

$G(f)$

$G(x)$ has no negative circuit for all $x \in X$

It is necessary to take a union of local graphs to obtain a negative circuit.
Remark 4

By Theorem 1, Theorem 2 and Theorem 3:

If \( G(x) \) has no positive circuit \( \forall x \in X \), then \( f \) has at most one fixed point.
If \( G(x) \) has no circuit \( \forall x \in X \), then \( f \) has a unique fixed point.
If \( G(f) \) has no negative circuit, then \( f \) has at least one fixed point.
Remark 4

By Theorem 1, Theorem 2 and Theorem 3:
If $G(x)$ has no positive circuit $\forall x \in X$, then $f$ has at most one fixed point.
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Question
If $G(x)$ has no negative circuit $\forall x \in X$, then $f$ has at least one fixed point?
\[\Gamma(f)\]

(0, 2) \leftrightarrow (1, 2) \leftrightarrow (2, 2) \leftrightarrow (2, 2)

G(x) has no negative circuit for all \(x \in X\).

..and \(f\) has no fixed point
Remark 4

By Theorem 1, Theorem 2 and Theorem 3:

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If $G(x)$ has no circuit $\forall x \in X$, then $f$ has a unique fixed point.
If $G(f)$ has no negative circuit, then $f$ has at least one fixed point.

Question

If $G(x)$ has no negative circuit $\forall x \in X$, then $f$ has at least one fixed point?

$\leftarrow$ false in the discrete case, but open in the boolean case
Remark 4

By Theorem 1, Theorem 2 and Theorem 3: 
If \( G(x) \) has no positive circuit \( \forall x \in X \), then \( f \) has at most one fixed point. 
If \( G(x) \) has no circuit \( \forall x \in X \), then \( f \) has a unique fixed point. 
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If \( G(x) \) has no negative circuit \( \forall x \in X \), then \( f \) has at least one fixed point? 
\( \rightarrow \) false in the discrete case, but open in the boolean case

Preliminary result
If \( G(x) \) has no negative circuit \( \forall x \in \{0,1\}^n \), and if 
\[ d(x, y) = 1 \Rightarrow d(F(x), F(y)) \leq 1, \]
then \( f \) has at least one fixed point.
Conclusion

Discrete approaches are well adapted to the modeling of gene network (qualitative data, sigmoidal regulations).

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.
Asynchronous state graphs can be seen as discretizations of Piecewise Linear Differential Systems.

In a PLD system, the set of states is $\mathbb{R}^n$ and is partitioned into rectangular regions $R$. In each rectangular regions $R$, the dynamics obeys a linear differential equations system which monotonically converges toward a focal point $\mathcal{F}(R) \in \mathbb{R}^n$. 
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\[
\mathcal{F}(R)
\]
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\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\end{figure}
Idea of the proof

1. We consider the graph \( G(x, v) \) where \( v \) allows variations toward \( y \).
2. We show that \( G(x, v) \) has no negative circuit (technical point), and we deduce that \( G(x, v) \) has no circuit.
3. There exists a gene \( i \) without successor in \( G(x, v) \); let \( z = x + v_i e_i \).
4. There is a transition \( z \to x \), and since \( z \) is between \( f(z) \) and \( y \), by induction hypothesis, there exists a shortest path \( y \leadsto z \).
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![Diagram of graph and transition](image-url)
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![Graph Diagram]

\[ F(x) \quad \downarrow \quad F(z) \]

\[ s_j \quad \downarrow \quad s_i \]

\[ x - e_j \quad \leftarrow \quad z \quad \rightarrow \quad y \]
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Theorem 4 (Boolean converses of the Thomas’ conjectures)

Let \( f : \{0, 1\}^n \rightarrow \{0, 1\}^n \) be such that \( f_i \) is not a constant for all \( i \).

1. If \( G(f) \) has no negative circuit then \( f \) has at least two fixed points.
2. If \( G(f) \) has no positive circuit then \( f \) has none fixed point.

Remarks

This theorem has been proved for monotonous boolean networks by Aracena et al (2004), and is false in the discrete case.
Let \( f : \{0,1\}^n \rightarrow \{0,1\}^n \) be such that \( f_i \) is not a constant for all \( i \).

**Lemma 1.** Let \( i \) be a node of \( G(F) \).

1. If at state \( x \)
   all the activators of \( i \) are present (if \( j \xrightarrow{+} i \) then \( x_j = 1 \)) and
   all the inhibitors of \( i \) are absent (if \( j \xrightarrow{-} i \) then \( x_j = 0 \))
then \( f_i(x) = 1 \).

2. If at state \( x \)
   all the activators of \( i \) are absent (if \( j \xrightarrow{+} i \) then \( x_j = 0 \)) and
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then \( f_i(x) = 0 \).
Lemma 2

If $G(F)$ has a negative closed path, then $G(F)$ has a negative circuit.

Lemma 3

Suppose that $G(F)$ is strongly connected and without negative circuit. Let $i, j$ be nodes of $G(F)$. Then all the paths $j \leadsto i$ have the same sign.
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$$x_k = 1; \quad x_i = \begin{cases} 1 & \text{if the paths } k \leadsto i \text{ are positives} \\ 0 & \text{if the paths } k \leadsto i \text{ are negatives} \end{cases} \quad \text{for all } i \neq k.$$
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If $j \longrightarrow i$ then $x_j = 1$ since $x_j = 0 \Rightarrow k \bar{\rightsquigarrow} j \Rightarrow k \bar{\rightsquigarrow} j \longrightarrow i \Rightarrow x_i = 0$. 
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So $F(x) = x$, and we show similarly that $F(\overline{x}) = \overline{x}$. 
Let $F : \{0, 1\}^n \to \{0, 1\}^n$ be such that $f_i$ is not constant for all $i$.

**First point of Theorem 4**  
*If $G(F)$ has no negative circuit, then $F$ has at least two fixed points.*

**Sketch of proof**  
We consider a strongly connected component $C$ of $G(F)$ without input edges. By Lemma 4, there exists two points $x$ and $\bar{x}$ such that

$$f_i(x) = x_i \quad \text{and} \quad f_i(\bar{x}) = \bar{x}_i \quad \text{for all } i \in C.$$

These two points lead to the following disjointed trap domains of $\Gamma(F)$:

$$T = \{ y \in \{0, 1\}^n \mid y_i = x_i \text{ for all } i \in C \},$$

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We deduce that $\Gamma(F)$ has at least two attractors (one in $T$, one in $\bar{T}$). Since $G(F)$ has no negative circuit, by Theorem 3, these two attractors are fixed points of $F$. 
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Example In the boolean case, what can been say on the dynamics of the networks whose interaction graph is

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\begin{aligned}
gene 1 & \rightarrow - & gene 2 \\
gene 4 & \rightarrow - & gene 3 \\
\end{aligned}
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- At least 2 fixed points (Theorem 4)
- At most 2 fixed points (Theorem 1)
- No cyclic attractor (Theorem 3)

So the dynamics contains exactly 2 attractors, which are fixed points.
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