Biological feedback

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Algebraic Systems Biology

Thomas' rules on biological feedback

In 1981, biologist René Thomas made the following conjectures.

Rule 1 (multistationarity $\Rightarrow$ positive feedback)

A positive cycle in the wiring diagram is necessary for the existence of multiple steady states.

Rule 2 (sustained oscillations $\Rightarrow$ negative feedback)

A negative cycle is a necessary condition for an attractor (stable steady state, limit cycle, or chaotic).

Conversely, when the wiring diagram is acyclic, f^n will be constant. This means that

"*feedback cycles are the engines of complexity*."

These ideas transcend modeling frameworks, and should hold for Boolean and ODE models.

- Thomas, R. (1981). On the relation between the logical structure of systems and their ability to generate multiple steady states and sustained oscillations. *Series in Synergetics* **9**, 180–193.
- Thomas, R. and D'Ari, T. Biological Feedback. *CRC Press*, 1990 (updated 2006).

Thomas' Rule 1 in an ODE framework

Theorem (Cinquin/Demongeot, 2002)

Let $I_f = \int_T \left(\frac{F}{||F||}\right)^* \sigma$, where T is a hypersurface diffeomorphic to the unit sphere, such that $\mathrm{int}(T)$ is in the domain of f and contains all steady-states, and where σ is a volume form compatible with the canonical orientation of T. If f has at least $1 + (-1)^n I_f$ stable steady states, then $\mathcal{G}(f)$ has a positive circuit.

Theorem (Soulé, 2003)

Let $\Omega = \prod_{i=1}^{n} \Omega_i \subseteq \mathbb{R}^n$ be a product of open intervals, and $f \colon \Omega \to \mathbb{R}^n$ a differential map such that for each i, j and any $a \in \Omega$,

$$f_i(x) = f_i(a) + \sum_{j=1}^{n} \frac{\partial f_i}{\partial x_j}(a)(x_j - a_j) + o(||x - a||).$$

If f has ≥ 2 nondegenerate zeros in Ω, then $\exists a \in \Omega$ such that $\mathcal{G}(f)$ has a positive circuit.

- Cinquin, O., & Demongeot, J. (2002). Positive and negative feedback: striking a balance between necessary antagonists. *J. Theor. Biol.* **216**(2), 229-241.
- Soulé, C. (2003). Graphic requirements for multistationarity. *ComPlexUs* **1**(3), 123-133.
- Kaufman, M., Soule, C., & Thomas, R. (2007). A new necessary condition on interaction graphs for multistationarity. *J. Theor. Biol.* **248**(4), 675-685.

Thomas' Rule 2 in an ODE framework

There are partial results of the differential version of Thomas' Rule 2.

Consider a differential equation

$$\frac{dx}{dt} = f(x), \qquad D \subseteq \mathbb{R}^n, \text{ open \& convex}, \qquad f \in \mathcal{C}^1(D).$$

Theorem (Snoussi, 1998)

If $x' = f(x)$ has a stable limit cycle and $\mathcal{G}(f)$ is complete, then $\mathcal{G}(f)$ has a negative loop of length ≥ 2.

Theorem (Gouzé, 1998)

Suppose the semicircuits of length p, for $2 \leq p \leq n$, are non-negative. Then the dynamical system is similar to a cooperative system, and so there is no attracting periodic trajectory.

- Snoussi, E. H. (1998). Necessary conditions for multistationarity and stable periodicity. *J. Biol. Syst.*, **6**(01), 3-9.
- Gouzé, J.L. (1998). Positive and negative circuits in dynamical systems. *J. Biol. Syst.* **6**(01), 11-15.

Local vs. global wiring diagrams

Throughout, let $(f_1, \dots, f_n)$ be a Boolean model with:

- wiring diagram $\mathcal{G}(f)$,
- FDS map $f \colon \mathbb{F}_2^n \to \mathbb{F}_2^n$
- asynchronous automaton $\mathcal{A}(f)$.

The discrete j^{th} partial derivative at $x \in \mathbb{F}_2^n$ is

$$f_{ij}(x) = \frac{\partial f_i(x)}{\partial x_j} = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \{-1, 0, 1\}.$$

For $x \in \mathbb{F}_2^n$, the (signed) local wiring diagram $Gf(x)$ is the graph on $\{1, \dots, n\}$ with:

- A positive edge $x_j \longrightarrow x_i$ if $\frac{\partial f_i(x)}{\partial x_j} = 1$.
- A negative edge $x_j \longrightarrow\!\!\!\!\!\!\;| \; x_i$ if $\frac{\partial f_i(x)}{\partial x_j} = -1$.

The (global) wiring diagram $\mathcal{G}(f)$ is the union of the local wiring diagrams for all $x \in \mathbb{F}_2^n$.

Local vs. global wiring diagrams

Let's compute the local wiring diagram at $x = 011$ of the following Boolean model:

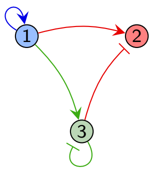
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_2 \wedge \overline{x_3}) \vee (x_1 \wedge \overline{x_2} \wedge \overline{x_3}) \vee (x_1 \wedge x_2 \wedge x_3)\big).$$

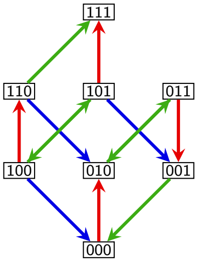
Recall that

$$f_{ij}(x) = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \big\{-1, 0, 1\big\}.$$

- $f_{11}(011) = f_1(\underline{1}11) - f_1(\underline{0}11) = 1 - 0 = 1$
- $f_{12}(011) = f_1(0\underline{1}1) - f_1(0\underline{0}1) = 0 - 0 = 0$
- $f_{13}(011) = f_1(01\underline{1}) - f_1(01\underline{0}) = 0 - 0 = 0$
- $f_{21}(011) = f_2(\underline{1}11) - f_2(\underline{0}11) = 1 - 0 = 1$
- $f_{22}(011) = f_2(0\underline{1}1) - f_2(0\underline{0}1) = 0 - 0 = 0$
- $f_{23}(011) = f_2(01\underline{1}) - f_2(01\underline{0}) = 0 - 1 = -1$
- $f_{31}(011) = f_3(\underline{1}11) - f_3(\underline{0}11) = 1 - 0 = 1$
- $f_{32}(011) = f_3(0\underline{1}1) - f_3(0\underline{0}1) = 0 - 0 = 0$
- $f_{33}(011) = f_3(01\underline{1}) - f_3(01\underline{0}) = 0 - 1 = -1$

$Gf(011)$





In retrospect, note that $f_3 = (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})$.

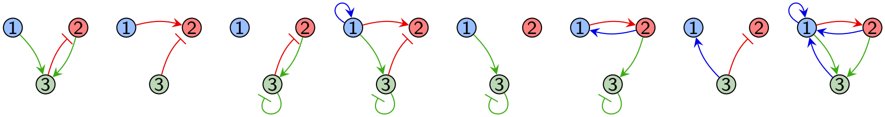
$x_1x_2x_3$	111	110	101	100	011	010	001	000
$f_3(x)$	1	1	0	1	0	1	0	0

Local vs. global wiring diagrams

Consider the following Boolean model:

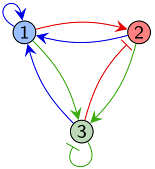
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big)$$

local wiring diagrams



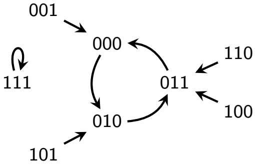
$Gf(000)$ $Gf(001)$ $Gf(010)$ $Gf(011)$ $Gf(100)$ $Gf(101)$ $Gf(110)$ $Gf(111)$

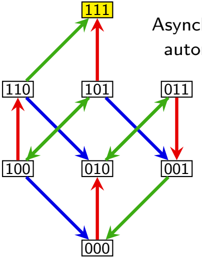
global wiring diagram



$$\mathcal{G}(f) = \bigcup_{x \in \mathbb{F}_2^3} Gf(x)$$

(Synchronous)
state space





Asynchronous
automaton

Thomas' rules on biological feedback in Boolean models

Contrapositives of Thomas' rules give relationships between feedback loops and fixed points.

Theorem 1: multistationarity $\Rightarrow$ positive feedback (Richard/Comet, 2007)

If $\mathcal{G}(f)$ has no positive cycle, then f has at most one fixed point.

Theorem 2: sustained oscillations $\Rightarrow$ negative feedback (Richard, 2010)

If $\mathcal{G}(f)$ has no negative cycle, then f has at least one fixed point.

Corollary

If $\mathcal{G}(f)$ is acyclic, then f has a unique fixed point.

In fact, if $\mathcal{G}(f)$ is acyclic, then we can say a lot more about f.

- Richard, A., & Comet, J.P. (2007). Necessary conditions for multistationarity in discrete dynamical systems. *Discrete Appl. Math.* **155**(18), 2403-2413.
- Richard, A. (2010). Negative circuits and sustained oscillations in asynchronous automata networks. *Adv. Appl. Math.* **44**(4), 378-392.

Acyclic wiring diagrams & nilpotent dynamics

In a geodesic path in the asynchronous automaton, every bit changes at most once.

Theorem (Robert, 1980)

If the wiring diagram $\mathcal{G}(f)$ is acyclic, then

1. f has a unique fixed point, x.
2. $f^n(y) = x$ for all $y \in \mathbb{F}_2^n$.
3. $\mathcal{A}(f)$ is acyclic and has a geodesic path from every state to x.

Boolean models for which $f^k =$ constant, for some k, are said to be nilpotent.

- Robert, F. (1980). Iterations sur des ensembles finis et automates cellulaires contractants. *Linear Algebra Appl.* **29**, 393-412.
- Robert, F. (1986). Discrete Iterations. *Springer Series in Computational Mathematics.*
- Robert, F. (1995). Discrete dynamical systems (Vol. 19). *Springer Science & Business Media.*
- Richard, A. (2019). Nilpotent dynamics on signed interaction graphs and weak converses of Thomas' rules. *Discrete Appl. Math.* **267**, 160-175.

The Jacobian conjecture from algebraic geometry

For polynomials $f_1, \dots, f_n \in \mathbb{F}[x_1, \dots, x_n]$, define the polynomial map

$$f \colon \mathbb{F}^n \longrightarrow \mathbb{F}^n, \qquad f \colon (x_1, \dots, x_n) \longmapsto (f_1(x_1, \dots, x_n), \dots, f_n(x_1, \dots, x_n)).$$

The Jacobian is the matrix

$$J = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \cdots & \frac{\partial f_n}{\partial x_n} \end{bmatrix},$$

and $J_f := \det J$ is its Jacobian determinant.

The following is #16 on Steve Smale's 1998 list of unsolved problems for the 21st century.

Jacobian conjecture (Keller, 1939)

Let $\mathrm{char}(\mathbb{F}) = 0$ and $n > 1$. If J_f is a non-zero constant, then f has an inverse function

$$g \colon \mathbb{F}^n \longrightarrow \mathbb{F}^n, \qquad g \colon (x_1, \dots, x_n) \longmapsto (g_1(x_1, \dots, x_n), \dots, g_n(x_1, \dots, x_n))$$

The Jacobian conjecture from algebraic geometry

Jacobian conjecture, equivalent statement (Cima, Gasull, Mañosas, 1999)

If $f : \mathbb{F}^n \to \mathbb{F}^n$ is a polynomial map such that for each $x \in \mathbb{F}^n$, the spectral radius $\rho(J_f(x)) < 1$, then f has a unique fixed point.

This suggests the following Boolean analogue, first stated by Shih & Ho (1999).

Boolean analogue (Shih & Dong, 2005)

If $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$, and every eigenvalue of J_f is zero, then f has a unique point.

In 2008, Richard extended this to the discrete (non-Boolean) case.

- Shih, M. H., & Ho, J. L. (1999). Solution of the Boolean Markus–Yamabe problem. *Adv. Appl. Math.* **22**(1), 60-102.
- Cima, A., Gasull, A., & Mañosas, F. (1999). The discrete Markus-Yamabe problem. *Nonlinear Anal. Theory Methods Appl.* **35**(3), 343-354.
- Shih, M. H., & Dong, J. L. (2005). A combinatorial analogue of the Jacobian problem in automata networks. *Adv. Appl. Math.* **34**(1), 30-46.
- Richard, A. (2008). An extension of a combinatorial fixed point theorem of Shih and Dong. *Adv. Appl. Math.* **41**(4), 620-627.

Generalizations of Robert's theorem

Robert proved that if the global wiring diagram $\mathcal{G}(f)$ is acyclic, f has a unique fixed point.

This stronger result is equivalent to the Boolean analogue of the Jacobian conjecture.

Theorem (Shih & Dong, 2005)

If the local wiring diagram $Gf(x)$ is acyclic for all $x \in \mathbb{F}_2^n$, then f has a unique fixed point.

Here is a different generalization of Robert's theorem.

Theorem (Richard, 2015)

Suppose that for every $1 \leq \ell \leq n$, there are fewer than 2^ℓ states $x \in \mathbb{F}_2^n$ such that $Gf(x)$ has a cycle of length $\leq \ell$. Then f has a unique fixed point.

- Richard, A. (2015). Fixed point theorems for Boolean networks expressed in terms of forbidden subnetworks. *Theor. Comput. Sci.* **583**, 1-26.

Thomas' Rules for a simple positive cycle

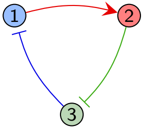
Since Thomas' Rule 1 is about positive feedback, let's first consider the most basic example.

Remark

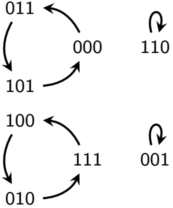
If the wiring diagram $\mathcal{G}(f)$ is a simple chordless cycle, then the asynchronous automaton has two attractors, which are both fixed points.

$$\begin{cases} f_1 = x_2 \\ f_2 = \overline{x_3} \\ f_3 = \overline{x_1} \end{cases}$$

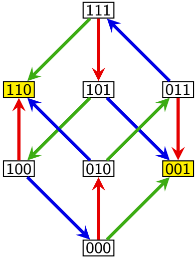
Functions



Wiring diagram



(Synchronous) state space



Asynchronous automaton

- **Rule 1**: multiple fixed points $\Rightarrow$ positive cycle. ✓
- **Rule 2**: no negative cycle $\Rightarrow$ at least one fixed point. ✓

Thomas' Rules for a simple negative cycle

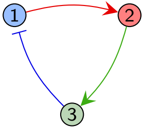
Since Thomas' Rule 2 is about negative feedback, let's first consider the most basic example.

Remark

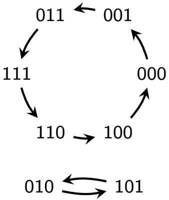
If the wiring diagram $\mathcal{G}(f)$ is a simple chordless cycle, then the asynchronous automaton has one attractor: a $2n$-length cycle.

$$\begin{cases} f_1 = x_2 \\ f_2 = x_3 \\ f_3 = \overline{x_1} \end{cases}$$

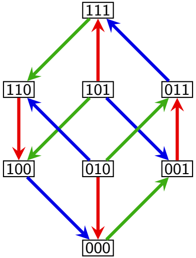
Functions



Wiring diagram



(Synchronous) state space



Asynchronous automaton

- **Rule 1**: no positive cycle $\Rightarrow$ at most one fixed point. ✓
- **Rule 2**: sustained oscillation in $\mathcal{A}(f) \Rightarrow$ negative cycle. ✓

Strengthening Thomas' Rules

Thomas' rules for Boolean models can be strengthened under two extra conditions:

- The wiring diagram $\mathcal{G}(f)$ is strongly connected with a least one arc.
- The functions are unate.

Theorem 1: multistationarity $\Rightarrow$ positive feedback (Aracena, 2008)

If $\mathcal{G}(f)$ has no positive cycle, then f has ~~at most one~~ no fixed point.

Theorem 2: sustained oscillations $\Rightarrow$ negative feedback (Aracena, 2008)

If $\mathcal{G}(f)$ has no negative cycle, then f has at least ~~one~~ two fixed points.

- Aracena, J. (2008). Maximum number of fixed points in regulatory Boolean networks. *Bull. Math. Biol.* **70**, 1398-1409.

Thomas' first rule

Theorem (Aracena, Demongeot, Goles, 2004)

Suppose $(f_1, \ldots, f_n)$ is a Boolean model and $\mathcal{G}(f)$ has no positive cycle. Then f has at most one fixed point.

Corollary

If $\mathcal{G}(f)$ is strongly connected, has at least one arc, and no positive cycle. Then f has no fixed points.

- Aracena, J., Demongeot, J., & Goles, E. (2004). Positive and negative circuits in discrete neural networks. *IEEE Trans. Neural Netw.* **15**(1), 77-83.
- Aracena, J. (2008). Maximum number of fixed points in regulatory Boolean networks. *Bull. Math. Biol.* **70**, 1398-1409.

Theorem

Suppose f has two distinct fixed points, x and y. Then $\mathcal{G}(f)$ has a positive cycle C such that $x_i \neq y_i$ for every vertex i of C.

Thomas' first rule, local versions

Theorem (Remy, Ruet, Thieffry, 2008)

Suppose $(f_1, \ldots, f_n)$ is a Boolean model and $Gf(x)$ has no positive cycle for all $x \in \mathbb{F}_2^n$. Then f has at most one fixed point.

Thus positive cycles are not only necessary for multiple fixed points, but, more generally, for multiple asynchronous attractors.

Theorem (Richard & Comet, 2004)

Suppose $(f_1, \ldots, f_n)$ is a logical model and $Gf(x)$ has no positive cycle for all $x \in \mathbb{F}_2^n$. Then $\mathcal{A}(f)$ has a unique attractor, and every $x \in \mathbb{F}_2^n$ has a geodesic into it.

- Remy, É., Ruet, P., & Thieffry, D. (2008). Graphic requirements for multistability and attractive cycles in a Boolean dynamical framework. *Adv. Appl. Math.* **41**(3), 335-350.
- Richard, A., & Comet, J.P. (2007). Necessary conditions for multistationarity in discrete dynamical systems. *Discrete Appl. Math.* **155**(18), 2403-2413.

Thomas' second rule

Theorem (Richard, 2010)

If $\mathcal{A}(f)$ has a cyclic attractor, then $\mathcal{G}(f)$ has a negative circuit.

This was proven by Remy, Ruet, and Thieffry in special case of $\mathcal{A}(f)$ having a simple cycle.

As a result of Richard's theorem (but *not* Remy/Ruet/Thieffry), we get the following.

Corollary

If $\mathcal{G}(f)$ has no negative circuit, then f has at least one fixed point.

- Remy, É., Ruet, P., & Thieffry, D. (2008). Graphic requirements for multistability and attractive cycles in a Boolean dynamical framework. *Adv. Appl. Math.* **41**(3), 335-350.
- Richard, A. (2010). Negative circuits and sustained oscillations in asynchronous automata networks. *Adv. Appl. Math.* **44**(4), 378-392.

Proof of Thomas' second rule

For each $i = 1, \dots, n$, define the function

$$F_i \colon \mathbb{F}_2^n \longrightarrow \mathbb{F}_2^n, \qquad F_i \colon x \longmapsto (x_1, \dots, x_{i-1}, f_i(x), x_{i+1}, \dots, x_n).$$

The asynchronous dynamics starting from $x(0)$ is defined by a map $\varphi \colon \mathbb{N} \to \{1, \dots, n\}$ called a strategy, where

$$x(t+1) = F_{\varphi(t)}(x(t)), \qquad (t = 0, 1, 2, \dots).$$

A strategy is pseudoperiodic if $|\phi^{-1}(i)| = \infty$, for all $i = 1, \dots, n$.

For each $x \in \mathbb{F}_2^n$, define

$$I_f(x) = \big\{ i \in \{1, \dots, n\} \mid f_i(x) \neq x_i \big\}.$$

A trap domain is a nonempty $D \subseteq \mathbb{F}_2^n$ such that if $x \in D$, then $F_i(x) \in D$, for all i.

An attractor is a minimal trap domain.

A cyclic attractor is a trap domain of size at least 2.

A fixed point is a trap domain of size 1.

A different local wiring diagram

Recall that each edge from j to i in the local wiring diagram has sign

$$f_{ij}(x) = f_i(x_1, \ldots, x_{j-1}, 1, x_{j+1}, \ldots, x_n) - f_i(x_1, \ldots, x_{j-1}, 0, x_{j+1}, \ldots, x_n) \in \{-1, 0, 1\}.$$

Now, we'll define a different local diagram. For each $i = 1, \ldots, n$ define

$$f_i'(x) = \operatorname{sign}\big(f_i(x) - x_i\big) \in \{0, 1, -1\}.$$

Definition

The strong wiring diagram at $x \in X$ is the graph $G'f(x)$ on vertex set $\{1, \ldots, n\}$ that contains an arc from j to i of sign $s \in \{-1, 1\}$ if

$$f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s \in f_j'(x) f_i'\big(F_j(x)\big).$$

Lemma 1 (exercise)

Each local wiring diagram $G'f(x)$ is a subgraph of the global wiring diagram $\mathcal{G}(f)$.

We'll prove these in the Boolean setting, but they hold for any state space $X = \{0, 1, \ldots, r\}$.

A different local wiring diagram

Let's compare both local wiring diagrams at $x = 000$ of the following Boolean model:

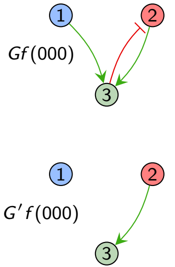
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big).$$

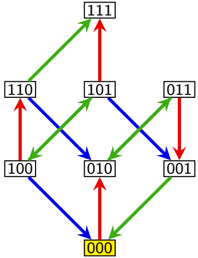
Recall that the edge from j to i has sign $f_{ij}(x)$, or s_{ij}, where

$$f_{ij}(x) = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \{-1, 0, 1\}.$$

$$f_i'(x) = \text{sign}\,\big(f_i(x) - x_i\big) \in \{0, 1, -1\}, \qquad f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

i	j	$f_{ij}(x)$	$f_i'(x)$	$f_j'(x)$	$F_j(x)$	$f_i'(F_j(x))$	$\neq$?	s_{ij}
1	1	0	0	0	000	0	✗	0
1	2	0	0	1	010	0	✗	0
1	3	0	0	0	000	0	✗	0
2	1	0	1	0	000	1	✗	0
2	2	0	1	1	010	0	✓	0
2	3	-1	1	0	000	1	✗	0
3	1	1	0	0	000	0	✗	0
3	2	1	0	1	010	1	✓	1
3	3	0	0	0	000	0	✗	0





A different local wiring diagram

Let's compare both local wiring diagrams at $x = 001$ of the following Boolean model:

$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big).$$

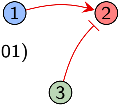
Recall that the edge from j to i has sign $f_{ij}(x)$, or s_{ij}, where

$$f_{ij}(x) = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \{-1, 0, 1\}.$$

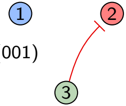
$$f_i'(x) = \operatorname{sign}\big(f_i(x) - x_i\big) \in \{0, 1, -1\}, \qquad f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

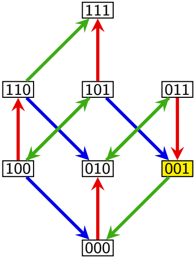
i	j	$f_{ij}(x)$	$f_i'(x)$	$f_j'(x)$	$F_j(x)$	$f_i'(F_j(x))$	$\neq$?	s_{ij}
1	1	0	0	0	$\underline{0}01$	0	✗	0
1	2	0	0	0	$0\underline{0}1$	0	✗	0
1	3	0	0	-1	$00\underline{0}$	0	✗	0
2	1	1	0	0	$\underline{0}01$	0	✗	0
2	2	0	0	0	$0\underline{0}1$	0	✗	0
2	3	-1	0	-1	$00\underline{0}$	1	✓	-1
3	1	0	-1	0	$\underline{0}01$	-1	✗	0
3	2	0	-1	0	$0\underline{0}1$	0	✓	0
3	3	0	-1	-1	$00\underline{0}$	-1	✗	1

$Gf(001)$



$G'f(001)$





A different local wiring diagram

Let's compare both local wiring diagrams at $x = 010$ of the following Boolean model:

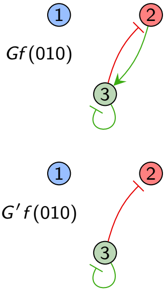
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big).$$

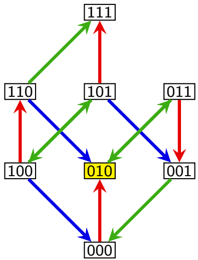
Recall that the edge from j to i has sign $f_{ij}(x)$, or s_{ij}, where

$$f_{ij}(x) = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \big\{-1, 0, 1\big\}.$$

$$f_i'(x) = \text{sign}\,\big(f_i(x) - x_i\big) \in \{0, 1, -1\}, \qquad f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

i	j	$f_{ij}(x)$	$f_i'(x)$	$f_j'(x)$	$F_j(x)$	$f_i'(F_j(x))$	$\neq$?	s_{ij}
1	1	0	0	0	$\underline{0}10$	0	✗	0
1	2	0	0	0	$0\underline{1}0$	0	✗	0
1	3	0	0	1	$01\underline{1}$	0	✗	0
2	1	0	0	0	$\underline{0}10$	0	✗	0
2	2	0	0	0	$0\underline{1}0$	0	✗	0
2	3	-1	0	1	$01\underline{1}$	-1	✓	-1
3	1	0	1	0	$\underline{0}10$	1	✗	0
3	2	1	1	0	$0\underline{1}0$	1	✗	0
3	3	-1	1	1	$01\underline{1}$	-1	✓	-1





A different local wiring diagram

Let's compare both local wiring diagrams at $x = 100$ of the following Boolean model:

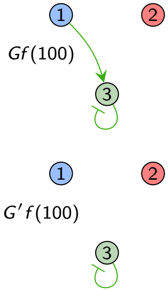
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big).$$

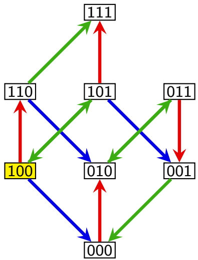
Recall that the edge from j to i has sign $f_{ij}(x)$, or s_{ij}, where

$$f_{ij}(x) = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \big\{-1, 0, 1\big\}.$$

$$f_i'(x) = \operatorname{sign}\big(f_i(x) - x_i\big) \in \{0, 1, -1\}, \qquad f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

i	j	$f_{ij}(x)$	$f_i'(x)$	$f_j'(x)$	$F_j(x)$	$f_i'(F_j(x))$	$\neq$?	s_{ij}
1	1	0	-1	-1	$\underline{0}00$	0	✓	0
1	2	0	-1	1	$1\underline{1}0$	-1	✗	-1
1	3	0	-1	1	$10\underline{1}$	-1	✗	-1
2	1	0	1	-1	$\underline{0}00$	1	✗	-1
2	2	0	1	1	$1\underline{1}0$	0	✓	0
2	3	0	1	1	$10\underline{1}$	1	✗	1
3	1	1	1	-1	$\underline{0}00$	0	✓	0
3	2	0	1	1	$1\underline{1}0$	1	✗	1
3	3	-1	1	1	$10\underline{1}$	-1	✓	-1





A different local wiring diagram

Let's compare both local wiring diagrams at $x = 011$ of the following Boolean model:

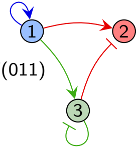
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big).$$

Recall that the edge from j to i has sign $f_{ij}(x)$, or s_{ij}, where

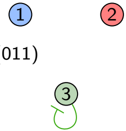
$$f_{ij}(x) = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \big\{-1, 0, 1\big\}.$$

$$f_i'(x) = \operatorname{sign}\big(f_i(x) - x_i\big) \in \{0, 1, -1\}, \qquad f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

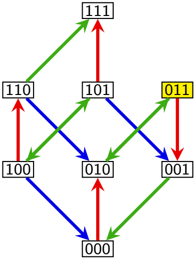
i	j	$f_{ij}(x)$	$f_i'(x)$	$f_j'(x)$	$F_j(x)$	$f_i'(F_j(x))$	$\neq$?	s_{ij}
1	1	1	0	0	$\underline{0}11$	0	✗	0
1	2	0	0	-1	$0\underline{0}1$	0	✗	0
1	3	0	0	-1	$01\underline{0}$	0	✗	0
2	1	1	-1	0	$\underline{0}11$	-1	✗	0
2	2	0	-1	-1	$0\underline{0}1$	0	✓	0
2	3	-1	-1	-1	$01\underline{0}$	0	✓	0
3	1	1	-1	0	$\underline{0}11$	-1	✗	0
3	2	0	-1	-1	$0\underline{0}1$	-1	✗	1
3	3	-1	-1	-1	$01\underline{0}$	1	✓	-1



$Gf(011)$



$G'f(011)$



A different local wiring diagram

Let's compare both local wiring diagrams at $x = 101$ of the following Boolean model:

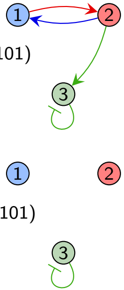
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big).$$

Recall that the edge from j to i has sign $f_{ij}(x)$, or s_{ij}, where

$$f_{ij}(x) = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \{-1, 0, 1\}.$$

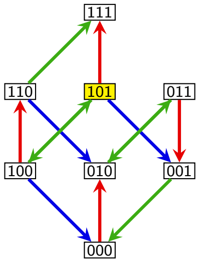
$$f_i'(x) = \operatorname{sign}\big(f_i(x) - x_i\big) \in \{0, 1, -1\}, \qquad f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

i	j	$f_{ij}(x)$	$f_i'(x)$	$f_j'(x)$	$F_j(x)$	$f_i'(F_j(x))$	$\neq$?	s_{ij}
1	1	0	-1	-1	001	0	✓	0
1	2	1	-1	1	111	0	✓	0
1	3	0	-1	-1	100	-1	✗	1
2	1	1	1	-1	001	0	✓	0
2	2	0	1	1	111	0	✓	0
2	3	0	1	-1	100	1	✗	-1
3	1	0	-1	-1	001	-1	✗	1
3	2	1	-1	1	111	0	✓	0
3	3	-1	-1	-1	100	1	✓	-1



$Gf(101)$

$G'f(101)$



A different local wiring diagram

Let's compare both local wiring diagrams at $x = 110$ of the following Boolean model:

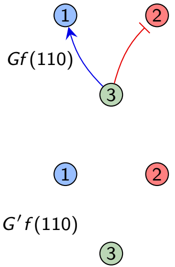
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big).$$

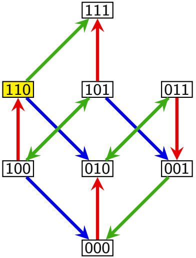
Recall that the edge from j to i has sign $f_{ij}(x)$, or s_{ij}, where

$$f_{ij}(x) = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \big\{-1, 0, 1\big\}.$$

$$f_i'(x) = \text{sign}\,\big(f_i(x) - x_i\big) \in \{0, 1, -1\}, \qquad f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

i	j	$f_{ij}(x)$	$f_i'(x)$	$f_j'(x)$	$F_j(x)$	$f_i'(F_j(x))$	$\neq$?	s_{ij}
1	1	0	-1	-1	$\underline{0}10$	0	✓	0
1	2	0	-1	0	$1\underline{1}0$	-1	✗	0
1	3	1	-1	1	$11\underline{1}$	0	✓	0
2	1	0	0	-1	$\underline{0}10$	0	✗	0
2	2	0	0	0	$1\underline{1}0$	0	✗	0
2	3	1	0	1	$11\underline{1}$	0	✗	0
3	1	0	1	-1	$\underline{0}10$	1	✗	-1
3	2	0	1	0	$1\underline{1}0$	1	✗	0
3	3	0	1	1	$11\underline{1}$	0	✓	0





A different local wiring diagram

Let's compare both local wiring diagrams at $x = 111$ of the following Boolean model:

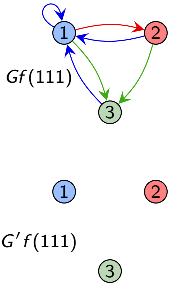
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big).$$

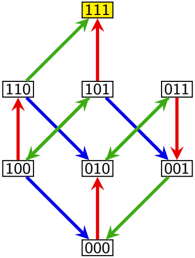
Recall that the edge from j to i has sign $f_{ij}(x)$, or s_{ij}, where

$$f_{ij}(x) = f_i(x_1, \dots, x_{j-1}, 1, x_{j+1}, \dots, x_n) - f_i(x_1, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n) \in \big\{-1, 0, 1\big\}.$$

$$f_i'(x) = \mathrm{sign}\,\big(f_i(x) - x_i\big) \in \{0, 1, -1\}, \qquad f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

i	j	$f_{ij}(x)$	$f_i'(x)$	$f_j'(x)$	$F_j(x)$	$f_i'(F_j(x))$	$\neq$?	s_{ij}
1	1	1	0	0	$\underline{1}11$	0	✗	0
1	2	1	0	0	$1\underline{1}1$	0	✗	0
1	3	1	0	0	$11\underline{1}$	0	✗	0
2	1	1	0	0	$\underline{1}11$	0	✗	0
2	2	0	0	0	$1\underline{1}1$	0	✗	0
2	3	0	0	0	$11\underline{1}$	0	✗	0
3	1	1	0	0	$\underline{1}11$	0	✗	0
3	2	1	0	0	$1\underline{1}1$	0	✗	0
3	3	0	0	0	$11\underline{1}$	0	✗	0



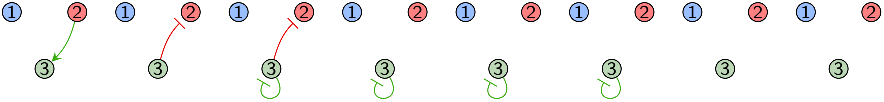


Local vs. global wiring diagrams

Consider the following Boolean model:

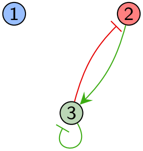
$$(f_1, f_2, f_3) = \big(x_1 \wedge x_2 \wedge x_3, \quad x_1 \vee \overline{x_3}, \quad (x_1 \wedge x_2) \vee (x_1 \wedge \overline{x_3}) \vee (x_2 \wedge \overline{x_3})\big)$$

local strong wiring diagrams



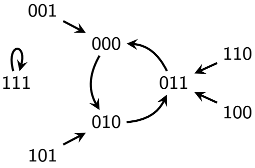
$G'f(000)$ $G'f(001)$ $G'f(010)$ $G'f(011)$ $G'f(100)$ $G'f(101)$ $G'f(110)$ $G'f(111)$

global strong wiring diagram

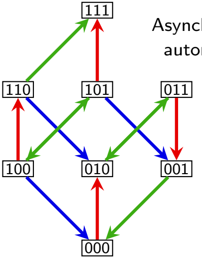


$$\mathcal{G}'(f) = \bigcup_{x \in \mathbb{F}_2^3} G'f(x)$$

(Synchronous) state space



Asynchronous automaton



Steps to prove Thomas' second rule

The graph $G'f(x)$ has an arc from j to i of sign $s_{ij} \in \{-1, 1\}$ if

$$f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

Lemma 1

Each $G'f(x)$ is a subgraph of the local wiring diagram $Gf(x)$.

Proof (sketch)

Suppose that $G'f(x)$ has an arc from j to i of sign s_{ij}.

Case 1 ($i \neq j$): We know $f_j'(x) \neq 0$. First, suppose $f_j'(x) > 0$; the other case is similar.

Subcase 1a ($s_{ij} = 1$). This forces $f_i'(F_j(x)) = 1 \quad \Rightarrow \quad f_i'(x) = 0$ and $x_i = 0$.

$$\begin{array}{llll}
f_i(y) = z_i = 1 & z_j = 1 & z = F_i(y) & \\
 & & \big\uparrow i & \\
y_i = 0 & f_j(x) = y_j = 1 & y = x + e_j = F_j(x) & f_{ij}(x) = f_i(y) - f_i(x) \\
 & & \big\uparrow j & \qquad\quad = 1 - 0 = 1 \\
f_i(x) = x_i = 0 & x_j = 0 & x &
\end{array}$$

Steps to prove Thomas' second rule

The graph $G'f(x)$ has an arc from j to i of sign $s_{ij} \in \{-1, 1\}$ if

$$f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

Lemma 1

Each $G'f(x)$ is a subgraph of the local wiring diagram $Gf(x)$.

Proof (sketch)

Suppose that $G'f(x)$ has an arc from j to i of sign s_{ij}.

Case 1 ($i \neq j$): We know $f_j'(x) \neq 0$. First, suppose $f_j'(x) > 0$; the other case is similar.

Subcase 1b ($s_{ij} = -1$). This forces $f_i'(F_j(x)) = -1 \quad \Rightarrow \quad f_i'(x) = 0$ and $x_i = 1$.

$y_i = 0 \qquad f_j(x) = y_j = 1 \qquad y = x + e_j = F_j(x)$

$$x \xrightarrow{j} y \xrightarrow{i} z$$

$x_i = 0 \qquad x_j = 0 \qquad x \qquad z = F_i(y) \qquad f_i(y) = z_i = 0 \qquad z_j = 1$

This time, we have $f_{ij}(x) = f_i(y) - f_i(x) = 0 - 1 = -1$.

Steps to prove Thomas' second rule

The graph $G'f(x)$ has an arc from j to i of sign $s_{ij} \in \{-1, 1\}$ if

$$f_i'(x) \neq f_i'\big(F_j(x)\big), \qquad s_{ij} = f_j'(x) f_i'\big(F_j(x)\big).$$

Lemma 1

Each $G'f(x)$ is a subgraph of the local wiring diagram $Gf(x)$.

Proof (sketch)

Suppose that $G'f(x)$ has an arc from j to i of sign s_{ij}.

Case 2 ($i = j$): Since $s_{ii} = f_i'(x) f_i'\big(F_i(x)\big)$ and $f_i'(x) \neq f_i'\big(F_i(x)\big)$, we must have $s_{ii} = -1$.

Suppose $f_i'(x) = 1$; the other case is similar. This means $f_i'\big(F_i(x)\big) = -1$ and $x_i = 0$.

$$\begin{tikzcd}
f_i(x) = y_i = 1 & y = x + e_i = F_i(x) \arrow[d, leftrightarrow, "i"'] \\
f_i(y) = x_i = 0 & x = y + e_i = F_i(y)
\end{tikzcd}$$

This time, we have $f_{ii}(x) = f_i(y) - f_i(x) = 0 - 1 = -1$. $\square$

Steps to prove Thomas' second rule

Lemma 2

Let $(x^0, x^1, \ldots, x^r)$ be an elementary path in $\mathcal{A}(f)$ of length $r \geq 1$, and let $i \in I_f(x^r)$. If $f_i'(x^p) \neq f_i'(x^r)$ for all $0 \leq p < r$, then there exists $j \in I_F(x^0)$ such that $\bigcup_{q=0}^{r=1} G'f(x^q)$ has a path from j to i of sign $f_j'(x^0)f_i'(x^r)$.

Lemma 3

Let A be a cyclic attractor of $\mathcal{A}(f)$. If $|I_f(x)| = 1$ for some $x \in A$, then $\bigcup_{x \in A} Gf(x)$ has a negative circuit.

Lemma 4

Let A be a cyclic attractor of $\mathcal{A}(f)$. If $|I_f(x)| > 1$ for all $x \in A$, then:

(i) there exists $h \colon X \to X$ such that $\mathcal{A}(h)$ contains a cyclic attractor attractor $A' \subsetneq A$

(ii) $G'h(x) \subseteq G'f(x)$ for all $x \in X$.

Lemma 5

If A is a cyclic attractor of $\mathcal{A}(f)$, then $\bigcup_{x \in A} G'f(x)$ has a negative circuit.

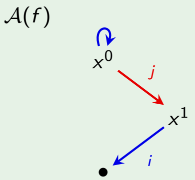
Proof of Thomas' second rule

Lemma 2

Let $(x^0, x^1, \dots, x^r)$ be an elementary path in $\mathcal{A}(f)$ of length $r \geq 1$, and let $i \in I_f(x^r)$. If $f_i'(x^r) \neq f_i'(x^p)$ for all $0 \leq p < r$, then there exists $j \in I_F(x^0)$ such that $\bigcup_{q=0}^{r=1} G'f(x^q)$ has a path from j to i of sign $f_j'(x^0)f_i'(x^r)$.

Proof (induct on r)

Base case $(r = 1)$: We claim that the j satisfying $F_j(x^0) = x^1$ works:



$$f_i'(x^0) \neq f_i'(F_j(x^0)) = f_i'(x^1)$$

$G'f(x^0)$

$$j \xrightarrow{s_{ij}} i$$

By definition, $G'f(x^0)$ has an arc from j to i of sign $s_{ij} = f_j'(x^0)f_i'(F_j(x^0)) = f_j'(x^0)f_i'(x^1)$.

Proof of Thomas' second rule

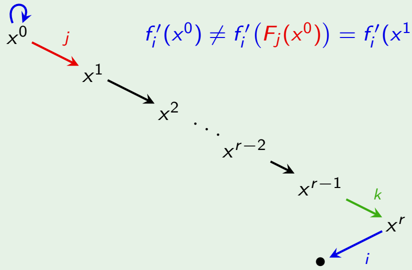
Lemma 2

Let $(x^0, x^1, \ldots, x^r)$ be an elementary path in $\mathcal{A}(f)$ of length $r \geq 1$, and let $i \in I_f(x^r)$. If $f_i'(x^r) \neq f_i'(x^p)$ for all $0 \leq p < r$, then there exists $j \in I_F(x^0)$ such that $\bigcup_{q=0}^{r=1} G'f(x^q)$ has a path from j to i of sign $f_j'(x^0)f_i'(x^r)$.

Proof (induct on r)

Case $(r > 1)$: Let $j \in I_F(r^0)$ satisfy $F_j(x^0) = x^1$, and $k \in I_F(x^{r-1})$ satisfy $F_k(x^{r-1}) = x^r$:

$\mathcal{A}(f)$



$$f_i'(x^0) \neq f_i'(F_j(x^0)) = f_i'(x^1)$$

$G'f(x^0)$

$$\begin{tikzcd} j \arrow[d, "s_{kj} = f_j'(x^0)f_k'(x^{r-1})"] \\ k \arrow[d, "s_{ik} = f_k'(x^{r-1})f_i'(x^r)"] \\ i \end{tikzcd}$$

There is a path from j to i with sign $s_{ji} = s_{kj}s_{ik} = f_j'(x^0)f_i'(x^r)$.

Proof of Thomas' second rule

Lemma 3

Let A be a cyclic attractor of $\mathcal{A}(f)$. If $|I_f(x)| = 1$ for some $x \in A$, then $\bigcup_{x \in A} G'f(x)$ has a negative circuit.

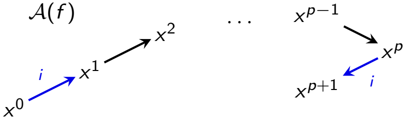
Proof

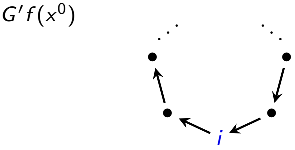
Suppose $|I_F(x^0)| = \{i\}$ and consider an elementary cycle $(x^0, x^1, \dots, x^r = x^0)$.

Suppose $f_i'(x_0) > 1$; the other case is analogous.

Let $p \in \{1, \dots, r-1\}$ be minimal such that $f_i'(x_p) = -1$.

Now, apply Lemma 2 with $j = i$ to the path $(x^0, \dots, x^p)$. $\square$





$s_{ii} = f_i'(x^0) f_i'(x^p) = 1 \cdot (-1) = -1$

Proof of Thomas' second rule

Lemma 4

Let A be a cyclic attractor of $\mathcal{A}(f)$. If $|I_f(x)| > 1$ for all $x \in A$, then:

(i) there exists $h \colon X \to X$ such that $\mathcal{A}(h)$ contains a cyclic attractor attractor $A' \subsetneq A$

(ii) $G'h(x) \subseteq G'f(x)$ for all $x \in X$.

Proof

Pick any $y \in A$, and WLOG, assume $1 \in I_f(y)$. The map we seek is

$$h \colon \mathbb{F}_2^n \longrightarrow \mathbb{F}_2^n, \qquad h \colon x \longmapsto (x_1, f_2(x), \dots, f_n(x)).$$

Claim 1: A is a trap domain of $\mathcal{A}(h)$.

Take any $i \in I_h(x)$. Note that $i \neq 1$, and so $H_i(x) = F_i(x) \in A$. ✓

Let $B \subseteq A$ be an attractor of $\mathcal{A}(h)$. Note that B is *not* a fixed point. (Why?)

Claim 2: $B \subsetneq A$. [Because if $y \in B$, then $F_1(y) \notin B$.]

Claim 3: $G'h(x) \subseteq G'f(x)$ for all $x \in \mathbb{F}_2^n$.

Suppose arc $j \xrightarrow{s_{ij}} i$ in $G'h(x)$ with sign $s_{ij} = h_j'(x)h_i'\big(H_j(x)\big) \neq 0$. Then $i \neq 1$ and $j \neq 1$.

Thus $H_i = F_i$ and $H_j = F_j$, so $s_{ij} = f_j'(x)f_i'\big(F_j(x)\big)$. Hence $j \xrightarrow{s_{ij}} i$ is in $G'f(x)$. □

Proof of Thomas' second rule

Lemma 5

If A is a cyclic attractor of $\mathcal{A}(f)$, then $\bigcup_{x\in A} G'f(x)$ has a negative circuit.

Proof

Consider the following poset

$$P = \big\{(f,A) \mid f\colon \mathbb{F}_2^n \to \mathbb{F}_2^n, \text{ and } A \subseteq \mathbb{F}_2^n \text{ is a cyclic attractor in } \mathcal{A}(f)\big\},$$

where $(h,B) \preceq (f,A)$ if $B \subseteq A$. We will induct over P.

Let $(f,A) \in P$ be minimal. By Lemma 4, $|I_f(x)| = 1$ for some $x \in A$, so apply Lemma 3.

If $(f,A) \in P$ is not minimal, find $(h,B) \prec (f,A)$, and the result follows from induction. $\square$

Corollary (Theorem 2)

If $\mathcal{A}(f)$ has a cyclic attractor, then $\mathcal{G}(f)$ has a negative circuit.

Proof

By Lemma 1, $\bigcup_{x\in A} G'f(x)$ is a subgraph of $\mathcal{G} = \bigcup_{x\in A} Gf(x)$. $\square$