Advances in Applied Mathematics 44 (2010) 378–392

Contents lists available at ScienceDirect

Advances in Applied Mathematics

www.elsevier.com/locate/yaama

Negative circuits and sustained oscillations in asynchronous automata networks

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ARTICLE INFO

Article history:
Received 29 July 2009
Accepted 21 September 2009
Available online 4 December 2009

MSC:
14R15
37B99
68R05
92D99
94C10

Keywords:
Discrete dynamical system
Automata network
Boolean network
Genetic regulatory network
Interaction graph
Discrete Jacobian matrix
Feedback circuit
Negative circuit
Oscillation
Fixed point

ABSTRACT

The biologist René Thomas conjectured, twenty years ago, that the presence of a negative feedback circuit in the interaction graph of a dynamical system is a necessary condition for this system to produce sustained oscillations. In this paper, we state and prove this conjecture for asynchronous automata networks, a class of discrete dynamical systems extensively used to model the behaviors of gene networks. As a corollary, we obtain the following fixed point theorem: given a product X of n finite intervals of integers, and a map F from X to itself, if the interaction graph associated with F has no negative circuit, then F has at least one fixed point.

1. Introduction

We are interested in a class of discrete dynamical systems used to model gene networks. The biological context is the following. Gene networks are often described by Biologists under the form of *interaction graphs*. These are directed graphs where vertices correspond to genes and where arcs are

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0196-8858/$ – see front matter
doi:10.1016/j.aam.2009.11.011

labeled with a sign: a positive (negative) arc from a gene j to a gene i means that the protein encoded by the gene j activates (represses) the synthesis of the protein encoded by the gene i. These very coarse descriptions of gene networks are then taken as a basis to design much more complex *dynamical models* that describe the temporal evolution of the concentration of the encoded proteins [7]. Unfortunately, these models require, in most cases, unavailable informations on the strength of the interactions. In this context, a difficult and interesting question is: *which dynamical properties of a gene network can be deduced from its interaction graph*?

The biologist René Thomas stated two well-known conjectures that partially answer this question. These conjectures can be informally stated as follows [25,9]:

1. The presence of a *positive circuit* in the interaction graph of a network (*i.e.* a circuit with an *even* number of negative arcs) is a necessary condition for the presence of *multiple stable states* in the dynamics of the network.
2. The presence of a *negative circuit* in the interaction graph of a network (*i.e.* a circuit with an *odd* number of negative arcs) is a necessary condition for the presence of *sustained oscillations* in the dynamics of the network.

It is worth noting that multistationarity and sustained oscillations are, from a biological point of view, important dynamical properties often related to differentiation processes and homeostasis phenomena respectively [25,26,28].

The first conjecture has been formally stated and proved by several authors in continuous frameworks [10,6,21,4,22,23], in which the concentration of each protein evolves continuously, generally following an ordinary differential equation system. The first conjecture has been more recently stated and proved in discrete frameworks [1,2,13,11,15], in which the concentration level of each protein evolves inside a finite interval of integers, which is $\{0,1\}$ in the Boolean case. Studies of the second conjecture are fewer: a Boolean version of the second conjecture has been stated and proved by Remy, Ruet and Thieffry [11], and there are only partial results in the continuous case [6,21].

In this paper, we state and prove the second Thomas' conjecture for asynchronous automata networks (Theorem 1). Our interest for these discrete dynamical systems comes from the fact that they have been proposed by Thomas as model for the dynamics of gene networks more than thirty years ago [24,26–28]. They are still extensively used because of the qualitative nature of most reliable experimental data, and the fact that the sigmoidal shape of genetic regulations leads to a natural discretization of concentrations [5,19,26,20,8].

The discrete version of Thomas' conjecture we establish generalizes in several ways the one established by Remy, Ruet and Thieffry [11] in the Boolean case: both the discrete dynamical framework and the considered class of sustained oscillations are more general. Furthermore, the class of sustained oscillations we consider allows us to obtain, as an immediate consequence, the fixed point theorem mentioned in the abstract (Corollary 1).

The paper is organized as follows. Section 2 presents definitions related to asynchronous automata networks. In Section 3, the second Thomas' conjecture is stated and proved for these networks. In Section 4, we establish a variant of the second Thomas' conjecture more suited to the modeling of gene networks. Counter examples to natural extension of the established results are given in Section 5.

2. Definitions

We consider a network of n interacting automata, denoted from 1 to n. The set of possible states for automaton i is a finite intervals of integers X_i of cardinality at least two. The set of possible states for the network is the Cartesian product $X=\prod_{i=1}^n X_i$. The dynamics of the network is then described by a map $F: X\to X$,

$$x=(x_1,\dots,x_n)\in X\mapsto F(x)=\big(f_1(x),\dots,f_n(x)\big)\in X,$$

with which we associate the maps $F_i: X\to X$ defined by

$$F_i(x)=\big(x_1,\dots,x_{i-1},f_i(x),x_{i+1},\dots,x_n\big)\quad(i=1,\dots,n).$$

More precisely, given an initial point $x^0 \in X$ and a map φ from $\mathbb{N}$ to $\{1, \ldots, n\}$, the dynamics of the network is described by the following recurrence, that we call the *asynchronous iteration of F induced by the strategy φ from initial point x^0*:

$$x^{t+1} = F_{\varphi(t)}(x^t) \quad (t = 0, 1, 2, \ldots). \tag{1}$$

Generally, one only considers the asynchronous iterations induced by *pseudo-periodic strategies*, *i.e.* strategies φ such that $|\varphi^{-1}(i)| = \infty$ for $i = 1, \ldots, n$ [17,3].

In this paper, we will study the asynchronous iterations of F through a directed graph on X called the asynchronous state transition graph of F. Before defining this graph, let us set, for all $x \in X$,

$$I_F(x) = \{ i \in \{1, \ldots, n\} \mid f_i(x) \neq x_i \}.$$

Definition 1. The *asynchronous state transition graph of F*, denoted $\Gamma(F)$, is the directed graph whose set of vertices is X and whose set of arcs is

$$\{ (x, F_i(x)) \mid x \in X,\ i \in I_F(x) \}.$$

Remark 1. $|I_F(x)|$ is the number of successors of x in $\Gamma(F)$, and $|I_F(x)| = 0$ if and only if x is a fixed point of F. Also, $\Gamma(F)$ has no arc from a vertex to itself, and in the following, we assume, by convention, that $\Gamma(F)$ has a path of length zero from each vertex to itself.

The relation between $\Gamma(F)$ and the asynchronous iterations of F is clear: there is a path from x to y in $\Gamma(F)$ if and only if there exists a strategy φ such that the asynchronous iteration of F induced by φ from x reaches y.

In this context, the fixed points of F are of particular interest: they correspond to the stable states of the system. More precisely, if φ is a pseudo-periodic strategy, then the asynchronous iteration (1) stabilizes on a point ξ (*i.e.* there exists t such that $x^t = x^{t+1} = \xi$) *if and only if* ξ is a fixed point of F. In the following definition, we introduce a notion of an attractor, which extends in a natural way the one of a stable state.

Definition 2. A *trap domain* of $\Gamma(F)$ is a non-empty subset $D \subseteq X$ such that for every arc (x, y) of $\Gamma(F)$, if $x \in D$ then $y \in D$. An *attractor* of $\Gamma(F)$ is a smallest trap domain with respect to the inclusion. A *cyclic attractor* is an attractor of cardinality at least two.

Remark 2. One has the three following basic properties: (1) x is a fixed point of F if and only if $\{x\}$ is an attractor of $\Gamma(F)$; (2) attractors perform an attraction in the weak sense that, from any state, there always exists a path leading to one of them; (3) if x and y belong to the same attractor, then there exists a path from x to y.

The third point highlights the fact that inside a cyclic attractor, each state has at least one successor. So, when the network is inside a cyclic attractor, it cannot reach a fixed point, and thus, it describes sustained oscillations. More precisely, *if x^0 belongs to a cyclic attractor A, then for all pseudo-periodic strategy φ, the asynchronous iteration of F induced by φ from x^0 never leaves A and never stabilizes, and since A is finite, it necessarily describes sustained oscillations.* In the following, we are interested in the relationship between sustained oscillations produced by cyclic attractors and negative circuits of the interaction graph of the network.

An *interaction graph* is here defined to be a directed graph whose set of vertices is $\{1, \ldots, n\}$ and where each arc is provided with a sign. Formally, each arc is characterized by a triple (j, s, i) where j (i) is the initial (final) vertex, and where $s \in \{-1, 1\}$ is the sign of the arc. An interaction graph can then have both a positive and a negative arc from one vertex to another.

In the following definition, we attach to F an interaction graph $G(F)$ that is nothing but the interaction graph of the network whose dynamics is described by the asynchronous iterations of F.

Definition 3. The *interaction graph of* F, denoted $G(F)$, is the interaction graph defined by: for all $i, j \in \{1, \dots, n\}$, there is a positive (negative) arc from j to i if there exists $x \in X$ with $x_j + 1 \in X_j$ such that

$$f_i(x_1, \dots, x_j + 1, \dots, x_n) - f_i(x_1, \dots, x_j, \dots, x_n)$$

is positive (negative).

Remark 3. $G(F)$ has at least one arc from j to i if and only if the value of f_i depends on the value of x_j.

Definition 4. A *path of* $G(F)$ of length $r \geqslant 1$ is a sequence of r arcs of $G(F)$, say $(j_1, s_1, i_1), (j_2, s_2, i_2), \dots, (j_r, s_r, i_r)$, such that $i_q = j_{q+1}$ for all $1 \leqslant q < r$. Such a path is a path *from* j_1 *to* i_r of *sign* $s = \prod_{q=1}^{r} s_q$. It is a *circuit* if $i_r = j_1$ and it is an *elementary circuit* if, in addition, the vertices i_q are mutually distinct.

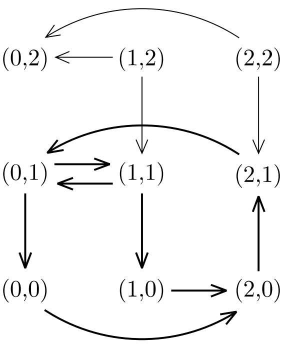
Remark 4. If $G(F)$ has a negative circuit, then it has an elementary negative circuit (this is false for positive circuits). So, in order to prove that $G(F)$ has an elementary negative circuit, it is sufficient to prove that $G(F)$ has a negative circuit.

Example 1. $n = 2$, $X = \{0, 1, 2\}^2$ and F is defined by the following table:

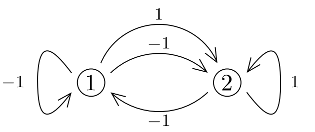
x	$(0,0)$	$(0,1)$	$(0,2)$	$(1,0)$	$(1,1)$	$(1,2)$	$(2,0)$	$(2,1)$	$(2,2)$
$F(x)$	$(2,0)$	$(1,0)$	$(0,2)$	$(2,0)$	$(0,0)$	$(0,1)$	$(2,1)$	$(0,1)$	$(0,1)$

The asynchronous state transition graph and the interaction graph of F are as follows:

$\Gamma(F)$



$G(F)$



We see that $\Gamma(F)$ has two attractors: the stable state $(0, 2)$ and the cyclic attractor $\{0, 1, 2\} \times \{0, 1\}$. We also see that $G(F)$ has two elementary positive circuits, and two elementary negative circuits.

3. Main result

In this section, we prove the following discrete version of the second Thomas' conjecture:

Theorem 1. *If $\Gamma(F)$ has a cyclic attractor, then $G(F)$ has a negative circuit.*

Remark 5. This theorem has been proved by Remy, Ruet and Thieffry [11] in the Boolean case (*i.e.* when X is the n-dimensional hypercube $\{0,1\}^n$) and under the rather strong hypothesis that $\Gamma(F)$ contains a *stable cycle*, that is, a cyclic attractor A in which each state has a unique successor (*i.e.* $|I_F(x)| = 1$ for all $x \in A$).

Remark 6. For continuous models the second Thomas' conjecture states that "The presence of a negative circuit of length at least two (somewhere in phase space) is a necessary condition for stable periodicity." (see [9]). And this is the statement that Gouzé and Snoussi have proved in some cases [6,21]. Theorem 1 does not impose any restriction on the length of the negative circuit, since it can be of length one. For instance, if F is the map from $\{0,1\}^n$ to itself defined by $f_1(x) = 1 - x_1$ and $f_i(x) = x_1$ for $i = 2, \dots, n$, then $\{0,1\}^n$ is a cyclic attractor of $\Gamma(F)$ and $G(F)$ has only one circuit, which is negative and of length one.

Before proving Theorem 1, let us point out that it has, as immediate consequence, the following fixed point theorem (which cannot be deduced, in the Boolean case, from the theorem of Remy, Ruet and Thieffry mentioned above):

Corollary 1. *If $G(F)$ has no negative circuit, then F has at least one fixed point.*

Proof. Indeed, if F has no fixed point, then $\Gamma(F)$ has clearly at least one cyclic attractor, and following Theorem 1, $G(F)$ has a negative circuit. □

Remark 7. In [17, Chapter 13] (see also [3]), Robert proves the following convergence result: if $G(F)$ has no circuit, then F has a unique fixed point ξ, and, for all initial point x^0 and for all pseudo-periodic strategy φ, the asynchronous iteration of F induced by φ from x^0 reaches the fixed point ξ. From Theorem 1 and the second point of Remark 2, one obtains a convergence result that has a weaker conclusion under a weaker condition: if $G(F)$ has no negative circuit, then F has at least one fixed point, and for all initial point x^0, there exists a strategy φ for which the asynchronous iteration (1) reaches a fixed point of F.

The proof of Theorem 1 needs few additional definitions and notations. Let $\mathcal{G}$ and $\mathcal{G}'$ be two interaction graphs with arc-set E and E', respectively. We say that $\mathcal{G}$ is a *subgraph* of $\mathcal{G}'$ if $E \subseteq E'$. We denote by $\mathcal{G} \cup \mathcal{G}'$ the interaction graph whose set of arcs is $E \cup E'$. Next, for all $x \in X$, we set

$$f'_i(x) = \operatorname{sign}\big(f_i(x) - x_i\big) \quad (i = 1, \dots, n),$$

where sign is the usual sign function ($\operatorname{sign}(a) = a/|a|$ for all $a \neq 0$, and $\operatorname{sign}(0) = 0$). The main tool used in the proof of Theorem 1 is the following notion of local interaction graph:

Definition 5. For all $x \in X$, we denote by $\mathscr{G}_F(x)$ the interaction graph that contains an arc from j to i of sign $s \in \{-1, 1\}$ if

$$f'_i(x) \neq f'_i\big(F_j(x)\big) \quad \text{and} \quad s = f'_j(x) f'_i\big(F_j(x)\big).$$

Lemma 1. *For all $x \in X$, $\mathscr{G}_F(x)$ is a subgraph of $G(F)$.*

Proof. Let $x \in X$, and suppose that $\mathscr{G}_F(x)$ has an arc from j to i of sign s. For every integer p, we set

$$x^p = (x_1, \dots, x_{j-1}, x_j + p, x_{j+1}, \dots, x_n).$$

Case *($j \neq i$).* By definition, $f'_j(x) \neq 0$. We suppose $f'_j(x) > 0$ the other case being similar. Setting $q = f_j(x) - x_j$, we have $q > 0$ and $x^q = F_j(x)$. So $s = f'_i(x^q)$ and $f'_i(x) = f'_i(x^0) \neq f'_i(x^q)$. Consider the smallest $0 \leqslant p \leqslant q$ such that $f'_i(x^p) = f'_i(x^q)$. Clearly, $p > 0$ and $f'_i(x^{p-1}) \neq f'_i(x^p) = s$. So if $s = 1$ then $f_i(x^{p-1}) \leqslant x_i < f_i(x^p)$ and we deduce that $G(F)$ has a positive arc from j to i. Similarly, if $s = -1$ then $f_i(x^{p-1}) \geqslant x_i > f_i(x^p)$ and we deduce that $G(F)$ has a negative arc from j to i.

Case *($j = i$).* By definition, $s = f'_i(x) f'_i(F_i(x))$ and $f'_i(x) \neq f'_i(F_i(x))$ thus $s = -1$. Suppose that $f'_i(x) > 0$, the other case being similar. Then $q = f_i(x) - x_i > 0$ and $f'_i(F_i(x)) < 0$. Since $x^0 = x$ and $x^q = F_i(x)$, we deduce that $x^0_i < f_i(x^0) = x^q_i$ and $f_i(x^q) < x^q_i$. Thus, there exists a smallest $0 \leqslant p \leqslant q$ such that $f_i(x^p) < x^q_i$. Clearly, $p > 0$ and $x^q_i \leqslant f_i(x^{p-1})$. Thus $f_i(x^p) < f_i(x^{p-1})$ and we deduce that $G(F)$ has a negative arc from i to itself. □

Lemma 2. *Let $(x^0, x^1, \ldots, x^r)$ be an elementary path of $\Gamma(F)$ of length $r \geqslant 1$, and let $i \in I_F(x^r)$. If $f'_i(x^p) \neq f'_i(x^r)$ for all $0 \leqslant p < r$, then there exists $j \in I_F(x^0)$ such that $\bigcup_{q=0}^{r-1} \mathscr{G}_F(x^q)$ has a path from j to i of sign $f'_j(x^0) f'_i(x^r)$.*

Proof. We proceed by induction on the length r of the path.

Case *($r = 1$).* Since (x^0, x^1) is an arc of $\Gamma(F)$ there exists $j \in I_F(x^0)$ such that $x^1 = F_j(x^0)$. Following the conditions of the lemma $f'_i(x^0) \neq f'_i(x^1)$, and thus, by definition, $\mathscr{G}_F(x^0)$ has an arc from j to i of sign $f'_j(x^0) f'_i(x^1)$.

Case *($r > 1$).* Since (x^{r-1}, x^r) is a path of $\Gamma(F)$ of length 1 satisfying the conditions of the lemma for $i \in I_F(x^r)$, following the base case, there exists $k \in I_F(x^{r-1})$ such that $\mathscr{G}_F(x^{r-1})$ has a path from k to i of sign

$$s_{ki} = f'_k\big(x^{r-1}\big) f'_i\big(x^r\big).$$

Now, consider the smallest $0 \leqslant p < r$ such that $f'_k(x^p) = f'_k(x^{r-1})$. First, suppose that $p = 0$. Then $k \in I_F(x^0)$ and $f'_k(x^0) f'_i(x^r)$ is equals to sign s_{ki} of the path of $\mathscr{G}_F(x^{r-1})$ from k to i mentioned above, so that the lemma holds. Now, suppose that $p > 0$. Then, by the choice of p, for all $0 \leqslant l < p$, we have $f'_k(x^l) \neq f'_k(x^p)$. Thus, the path $(x^0, \ldots, x^p)$ satisfies the conditions of the lemma for $k \in I_F(x^p)$. Since $p < r$, by induction hypothesis, there exists $j \in I_F(x^0)$ such that $\bigcup_{q=0}^{p-1} \mathscr{G}_F(x^q)$ has a path from j to k of sign

$$s_{jk} = f'_j\big(x^0\big) f'_k\big(x^p\big).$$

Since $\mathscr{G}_F(x^{r-1})$ contains a path from k to i of sign s_{ki}, we deduce that $\bigcup_{q=0}^{r-1} \mathscr{G}_F(x^q)$ contains a path from j to i of sign

$$s_{ji} = s_{jk} s_{ki} = f'_j\big(x^0\big) f'_k\big(x^p\big) f'_k\big(x^{r-1}\big) f'_i\big(x^r\big),$$

and since $f'_k(x^p) = f'_k(x^{r-1})$, we deduce that $s_{ji} = f'_j(x^0) f'_i(x^r)$. □

Lemma 3. *Let A be a cyclic attractor of $\Gamma(F)$. If there exists $x \in A$ such that $|I_F(x)| = 1$ then $\bigcup_{x \in A} \mathscr{G}_F(x)$ has a negative circuit.*

Proof. Suppose that there exists $x^0 \in A$ such that $|I_F(x^0)| = 1$, and let i be the unique element of $I_F(x^0)$. Suppose that $f'_i(x^0) > 0$, the other case being similar. Let $x^1 = F_i(x)$. Then $\Gamma(F)$ has an arc from x^0 to x^1 and we have $x_i^0 < x_i^1$. Since $x^0 \in A$, we have $x^1 \in A$, and we deduce that $\Gamma(F)$ has an elementary path $(x^1, x^2, \dots, x^r)$ from x^1 to $x^r = x^0$, all the vertices of which belong to A. If $f'_i(x^p) \geqslant 0$ for all $0 < p < r$, then $x_i^p \leqslant x_i^{p+1}$ for all $0 < p < r$, and we deduce that $x_i^1 \leqslant x_i^r = x_i^0$, a contradiction. Thus, there exists a smallest $0 < p < r$ such that $f'_i(x^p) < 0$. Then, $(x^0, x^1, \dots, x^p)$ is an elementary path where $i \in I_F(x^p)$ and by the choice of p, we have $f'_i(x^l) \neq f'_i(x^p)$ for all $0 \leqslant l < p$. So, according to Lemma 2, there exists $j \in I_F(x^0)$ such that $\bigcup_{q=0}^{p-1} \mathcal{G}_F(x^q)$ contains a path from j to i of sign $f'_j(x^0) f'_i(x^p)$. Since $I_F(x^0) = \{i\}$, we have $j = i$ and consequently, $\bigcup_{q=0}^{p-1} \mathcal{G}_F(x^q)$ contains a path from i to itself, and thus a circuit, of sign $f'_i(x^0) f'_i(x^p)$. By construction, $f'_i(x^0) f'_i(x^p) < 0$, thus this circuit is negative, and since $\{x^0, \dots, x^{p-1}\} \subseteq A$, it is contained in $\bigcup_{x \in A} \mathcal{G}_F(x)$. □

Lemma 4. *Let A be a cyclic attractor of $\Gamma(F)$. If $|I_F(x)| > 1$ for all $x \in A$, then there exists $H : X \to X$ such that $\Gamma(H)$ contains a cyclic attractor strictly included in A, and such that $\mathcal{G}_H(x)$ is a subgraph of $\mathcal{G}_F(x)$ for all $x \in X$.*

Proof. Suppose A to be a cyclic attractor of $\Gamma(F)$ such that $|I_F(x)| > 1$ for all $x \in A$. Let y be any state of A. Then $I_F(y)$ contains at least two elements, and without loss of generality, we can suppose that $1 \in I_F(y)$. Consider the map $H : X \to X$ defined by:

$$\forall x \in X, \quad H(x) = \big(h_1(x), h_2(x), \dots, h_n(x)\big) = \big(x_1, f_2(x), \dots, f_n(x)\big).$$

We first prove that A is a trap domain of $\Gamma(H)$. For that, it is sufficient to prove that, given any $x \in A$ and $i \in I_H(x)$, we have $H_i(x) \in A$. Since $h_1(x) = x_1$, $1 \notin I_H(x)$, so $i \neq 1$. Thus $F_i(x) = H_i(x)$, and since A is a trap domain of $\Gamma(F)$, we have $F_i(x) \in A$ and we deduce that $H_i(x) \in A$ as expected. So A is a trap domain of $\Gamma(H)$ and, by definition, $\Gamma(H)$ contains at least one attractor $B \subseteq A$.

We claim that B is a cyclic attractor of $\Gamma(H)$. Let $x \in B$. Then $x \in A$ so $|I_F(x)| > 1$ and we deduce that $I_F(x)$ contains an index $i \neq 1$. Then, $x_i \neq f_i(x) = h_i(x)$ so $x \neq H_i(x)$. Since $x \in B$ we have $H_i(x) \in B$. So $|B| \geqslant 2$, *i.e.* B is a cyclic attractor of $\Gamma(H)$.

We now prove that $B \subset A$ (strict inclusion). Suppose, by contradiction, that $B = A$. Since $1 \in I_F(y)$ and $y \in A$, we have $y \neq F_1(y) \in A = B$. Since B is an attractor of $\Gamma(H)$, we deduce that $\Gamma(H)$ has a path $(x^0, x^1, \dots, x^r)$ from $x^0 = y$ to $x^r = F_1(y)$. Since $h_1(x) = x_1$ for all $x \in X$, we have $x_1^0 = x_1^1 = \dots = x_1^r$. So $y_1 = f_1(y)$, a contradiction.

It remains to prove that $\mathcal{G}_H(x)$ is a subgraph of $\mathcal{G}_F(x)$ for all $x \in X$. If (j, s, i) is an arc of $\mathcal{G}_H(x)$, then by definition, $h'_j(x) \neq 0$ and $h'_i(H_j(x)) \neq 0$. So $j \neq 1$ and $i \neq 1$. Thus $f_j = h_j$ and $f_i = h_i$. It is then clear that (i, s, j) is an arc of $G_F(x)$. □

Lemma 5. *If A is a cyclic attractor of $\Gamma(F)$, then $\bigcup_{x \in A} \mathcal{G}_F(x)$ has a negative circuit.*

Proof. Let U be the set of couples (F, A) such that F is a map from X to itself, and such that A is a cyclic attractor of $\Gamma(F)$. Let $\prec$ be the well-funded strict order on U defined by $(H, B) \prec (F, A)$ if and only if B is strictly included in A. Proceeding by induction on the set U ordered by $\prec$, we show that, for all $(F, A) \in U$, $\bigcup_{x \in A} \mathcal{G}_F(x)$ has a negative circuit.

Base case. Let (F, A) be a minimal element of $(U, \prec)$. If $|I_F(x)| > 1$ for all $x \in A$, then, following Lemma 4, there exists $(H, B) \in U$ such that $(H, B) \prec (F, A)$, and this contradict the minimality of (F, A). So there exists $x \in A$ such that $|I_F(x)| = 1$ and, following Lemma 3, $\bigcup_{x \in A} \mathcal{G}_F(x)$ has a negative circuit.

Induction step. Let (F, A) be a non-minimal element of $(U, \prec)$. By induction hypothesis, for all $(H, B) \prec (F, A)$, $\bigcup_{x \in B} \mathcal{G}_H(x)$ has a negative circuit. If, for all $x \in A$, we have $|I_F(x)| > 1$, then following Lemma 4, there exists $(H, B) \prec (F, A)$ such that $\mathcal{G}_H(x)$ is a subgraph of $\mathcal{G}_F(x)$ for all $x \in X$. Since $B \subset A$, we deduce that $\bigcup_{x\in B} \mathcal{G}_H(x)$ is a subgraph of $\bigcup_{x\in A} \mathcal{G}_F(x)$, and since, by induction hypothesis, $\bigcup_{x\in B} \mathcal{G}_H(x)$ has a negative circuit, we deduce that $\bigcup_{x\in A} \mathcal{G}_F(x)$ has a negative circuit. Otherwise, there exists $x \in A$ such that $|I_F(x)| = 1$, and following Lemma 3, $\bigcup_{x\in A} \mathcal{G}_F(x)$ has again a negative circuit. □

Proof of Theorem 1. If A is a cyclic attractor of $\Gamma(F)$, then by Lemma 5, $\bigcup_{x\in A} \mathcal{G}_F(x)$ has a negative circuit. By Lemma 1, $\bigcup_{x\in A} \mathcal{G}_F(x)$ is a subgraph of $G(F)$ and we deduce that $G(F)$ has a negative circuit. □

Remark 8. The key lemma is clearly Lemma 5, which shows that it is sufficient to consider the restriction of F to a cyclic attractor A in order to obtain a negative circuit.

4. A variant for gene regulatory networks

In this section, we establish a variant of Theorem 1 that is more suited to the modeling of gene networks. To model the behaviors of a network of n genes, Thomas [24,26,28] proposes to consider a "unitary" asynchronous state transition graph $\Gamma[F]$ that is slightly different than $\Gamma(F)$. In $\Gamma[F]$, each transition starting from a given state x involves, as in $\Gamma(F)$, the evolution of the state x_i of at most one component $i \in I_F(x)$, but in $\Gamma[F]$, this state x_i is not updated to $f_i(x)$: it is increased or decreased by a unit depending on whether $x_i < f_i(x)$ or $x_i > f_i(x)$. Thanks to this updating rule, unitary asynchronous state transition graphs can be seen as discretizations of piece-wise linear differential equation systems [19,20].

Definition 6. The *unitary* asynchronous state transition graph of F, denoted $\Gamma[F]$, is the asynchronous state transition graph $\Gamma(\tilde{F})$ of the map $\tilde{F} : X \to X$ defined by

$$\tilde{F}(x) = \big(\tilde{f}_1(x), \dots, \tilde{f}_n(x)\big), \qquad \tilde{f}_i(x) = x_i + f'_i(x) \quad (i = 1, \dots, n).$$

Remark 9. In the Boolean case, $\Gamma[F] = \Gamma(F)$.

We are now confronted to the following problem: $G(F)$ cannot be seen as *the* interaction graph of the network whose dynamics is described by $\Gamma[F]$, since maps H such that $G(H) \neq G(F)$ and $\Gamma[H] = \Gamma[F]$ may exist. In addition, it is not satisfactory to see $G(\tilde{F})$ as the interaction graph of the network whose dynamics is described by $\Gamma[F]$, since maps H such that $G(H)$ is a *strict* subgraph of $G(\tilde{F})$ and such that $\Gamma[H] = \Gamma[F]$ may also exist.

To solve this problem, Richard and Comet [13] define a subgraph $G[F]$ of $G(F)$ that only depends on $\Gamma[F]$ and provide, in this way, a natural and non-ambiguous definition of the interaction graph of the network whose dynamics is described by $\Gamma[F]$. Furthermore, one can show that $G[F]$ is, with respect to the subgraph relation, the smallest interaction graph from which one can obtain $\Gamma[F]$ by following the logical method developed by Thomas to model gene networks [12].

Definition 7. We denote by $G[F]$ the interaction graph that contains a positive arc from j to i if there exists $x \in X$ with $x_j + 1 \in X_j$ such that

$$f_i(x_1, \dots, x_j, \dots, x_n) \leqslant x_i < f_i(x_1, \dots, x_j + 1, \dots, x_n),$$

and that contains a negative arc from j to i if there exists $x \in X$ with $x_j + 1 \in X_j$ such that

$$f_i(x_1, \dots, x_j, \dots, x_n) > x_i \geqslant f_i(x_1, \dots, x_j + 1, \dots, x_n).$$

Remark 10. $G[F]$ is a subgraph of $G(F)$, and in the Boolean case, $G[F] = G(F)$.

We now establish, in this setting, the following discrete version of the second Thomas' conjecture (which is, as Theorem 1, an immediate consequence of Lemma 5):

Theorem 2. *If $\Gamma[F]$ has a cyclic attractor, then $G[F]$ has a negative circuit.*

Lemma 6. *For all $x \in X$, $\mathscr{G}_{\tilde{F}}(x)$ is a subgraph of $G[F]$.*

Proof. First observe that $f_i'(x) = \tilde{f}_i'(x)$ for all $x \in X$ and $i \in \{1, \dots, n\}$. Furthermore, if $\tilde{f}_i(x) \leqslant x_i$ (resp. $\tilde{f}_i(x) \geqslant x_i$) then $f_i(x) \leqslant \tilde{f}_i(x)$ (resp. $f_i(x) \geqslant \tilde{f}_i(x)$).

Now, suppose that $\mathscr{G}_{\tilde{F}}(x)$ has an arc from j to i of sign s with $j \neq i$. Let

$$y = \big(x_1, \dots, x_j + \tilde{f}_j'(x), \dots, x_n\big)$$

and observe that $y = \tilde{F}_j(x)$. Suppose that $\tilde{f}_i'(y) > 0$, the other case being similar. Then, by definition, $\tilde{f}_j'(x) = s$ and $\tilde{f}_i'(x) \leqslant 0$. Thus $\tilde{f}_i(x) \leqslant x_i = y_i < \tilde{f}_i(y)$ and we deduce that

$$f_i(x) \leqslant \tilde{f}_i(x) \leqslant x_i = y_i < \tilde{f}_i(y) \leqslant f_i(y).$$

So if $\tilde{f}_j'(x) = s$ is positive then

$$f_i(x) \leqslant x_i < f_i(y) = f_i(x_1, \dots, x_j + 1, \dots, x_n)$$

and we deduce that $G[F]$ has a positive arc from j to i, and if $\tilde{f}_j'(x) = s$ is negative then

$$f_i(y_1, \dots, y_j + 1, \dots, y_n) = f_i(x) \leqslant y_i < f_i(y)$$

and we deduce that $G[F]$ has a negative edge from j to i.

Suppose now that $\mathscr{G}_{\tilde{F}}(x)$ has an arc from i to itself of sign s. By definition, we have $s = \tilde{f}_i'(x)\tilde{f}_i'(\tilde{F}_i(x))$ and $\tilde{f}_i'(x) \neq \tilde{f}_i'(\tilde{F}_i(x))$ so that s is negative. Suppose that $\tilde{f}_i'(x) > 0$, the other case being similar. Then, $\tilde{F}_i(x) = (x_1, \dots, x_i + 1, \dots, x_n)$ and $\tilde{f}_i'(\tilde{F}_i(x)) < 0$. Thus

$$\tilde{f}_i(x_1, \dots, x_i + 1, \dots, x_n) \leqslant x_i < \tilde{f}_i(x)$$

and we deduce that

$$f_i(x_1, \dots, x_i + 1, \dots, x_n) \leqslant \tilde{f}_i(x_1, \dots, x_i + 1, \dots, x_n) \leqslant x_i < \tilde{f}_i(x) \leqslant f_i(x).$$

Consequently, $G[F]$ has a negative arc from i to itself. □

Proof of Theorem 2. Since $\Gamma[F] = \Gamma(\tilde{F})$, if $\Gamma[F]$ has a cyclic attractor A, then by Lemma 5, $\bigcup_{x \in X} \mathscr{G}_{\tilde{F}}(x)$ has a negative circuit. Following the previous lemma, $\bigcup_{x \in X} \mathscr{G}_{\tilde{F}}(x)$ is a subgraph of $G[F]$, and we deduce that $G[F]$ has a negative circuit. □

Corollary 2. *If $G[F]$ has a no negative circuit, then F has at least one fixed point.*

Proof. If F has no fixed point, then $\Gamma[F]$ has at least one cyclic attractor, and following Theorem 2, $G[F]$ has a negative circuit. □

Remark 11. Since $G[F]$ is a subgraph of $G(F)$, Corollary 2 is stronger than Corollary 1 (the same conclusion is obtained under a weaker condition). In addition, from Theorems 1 and 2, it is clear that: *if $\Gamma(F)$ or $\Gamma[F]$ has a cyclic attractor, then $G(F)$ has a negative circuit*. This generalizes Theorem 1 (the same conclusion is obtained under a weaker condition). Indeed, as showed by the following two examples, the presence of a cyclic attractor in $\Gamma(F)$ ($\Gamma[F]$) does not imply the presence of a cyclic attractor in $\Gamma[F]$ ($\Gamma(F)$).

Example 2. $n = 1$, $X = \{0, 1, 2\}$ and F defined by $F(0) = 2$, $F(1) = 1$ and $F(2) = 0$. The state transitions graphs $\Gamma(F)$ and $\Gamma[F]$ are the following:

We see that $\Gamma(F)$ has a cyclic attractor and that $\Gamma[F]$ has no cyclic attractor. The interaction graph $G(F)$ is the interaction graph with one vertex and a negative arc from this vertex to itself: it has thus a negative circuit. The interaction graph $G[F]$ is the interaction graph with one vertex and no arc (it is a strict subgraph of $G(F)$). This shows that the presence of a cyclic attractor in $\Gamma(F)$ does not imply the presence of a negative circuit in $G[F]$.

Example 3. $n = 1$, $X = \{0, 1, 2\}$ and F defined by $F(0) = 0$, $F(1) = 2$ and $F(2) = 0$. The state transitions graphs $\Gamma(F)$ and $\Gamma(F)$ are the following:

We see that $\Gamma[F]$ has a cyclic attractor and that $\Gamma(F)$ has no cyclic attractor. The interaction graphs $G(F)$ and $G[F]$ are equal to the interaction graph with one vertex and both a positive and a negative arc from this vertex to itself ($G(F)$ and $G[F]$ have thus a negative circuit).

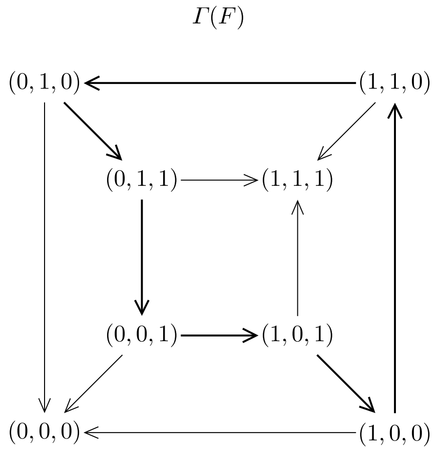
5. Concluding remarks

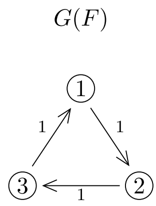
The weakest condition allowing the asynchronous iterations of F to describe sustained oscillations is the presence of a directed cycle in $\Gamma(F)$. However, as showed by the following example, the presence of a directed cycle in $\Gamma(F)$ does not imply the presence of a negative circuit in $G(F)$ (one can only show that it implies the presence of a circuit in $G(F)$). This shows that structures in $\Gamma(F)$ stronger than directed cycles (such as cyclic attractors) are needed to obtain a negative circuit.

Example 4. $n = 3$, $X = \{0, 1\}^3$ and F is defined by

$$f_1(x) = x_3,$$
$$f_2(x) = x_1,$$
$$f_3(x) = x_2.$$

The asynchronous state transition graph $\Gamma(F)$ (which is here equal to $\Gamma[F]$) and the interaction graph $G(F)$ (which is here equal to $G[F]$) are the following:





We see that $\Gamma(F)$ has a directed cycle and that $G(F)$ has no negative circuit.

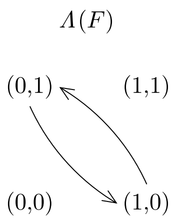
A second remark is that it is not easy to find other classes of iterations for which Theorem 1 remains valid. Consider for instance the *synchronous state transition graph* $\Lambda(F)$ that encodes the behaviors of the iteration $x^{t+1} = F(x^t)$: the set of vertices of $\Lambda(F)$ is X and the set of its arcs is $\{(x, F(x)) \mid x \in X,\ x \neq F(x)\}$. The cyclic attractors of such a (deterministic) state transition graph $\Lambda(F)$ are naturally defined to be the directed cycles of $\Lambda(F)$. However, the following example shows that the presence of a directed cycle in $\Lambda(F)$ does not imply the presence of a negative circuit in $G(F)$ (Robert [16,17] proves only that it implies the presence of a circuit in $G(F)$).

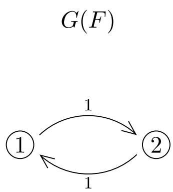
Example 5. $n = 2$, $X = \{0, 1\}^2$ and F is defined by

$$f_1(x) = x_2,$$

$$f_2(x) = x_1.$$

The synchronous state transition graph $\Lambda(F)$ and the interaction graph $G(F)$ are as follows:





We see that $\Lambda(F)$ has a cyclic attractor and that $G(F)$ has no negative circuit.

Finally, we can ask if, under the condition that $\Gamma(F)$ has a cyclic attractor, a conclusion stronger than "$G(F)$ has a negative circuit" could be obtained. Following Example 2, the presence of a cyclic attractor in $\Gamma(F)$ does not imply the presence of a negative circuit in the subgraph $G[F]$ of $G(F)$. So, another direction has to be taken. As showed below, previous results on the links between the interaction graph and the dynamical properties of automata networks suggest to improve the conclusion of Theorem 1 by studying if the presence of a cyclic attractor in $\Gamma(F)$ implies the presence of a negative circuit in a *local interaction graph* associated with F.

Definition 8. For all $x \in X$, the *local interaction graph of F evaluated at state x* is the interaction graph $G_F(x)$ that contains a positive (negative) arc from j to i if $x_j + 1 \in X_j$ and

$$f_i(x_1, \dots, x_j + 1, \dots, x_n) - f_i(x_1, \dots, x_j, \dots, x_n)$$

is positive (negative), or if $x_j - 1 \in X_j$ and

$$f_i(x_1, \dots, x_j, \dots, x_n) - f_i(x_1, \dots, x_j - 1, \dots, x_n)$$

is positive (negative).

Remark 12. $G_F(x)$ is a subgraph of $G(F)$. More precisely, $G(F) = \bigcup_{x \in X} G_F(x)$.

With this material, Richard and Comet [13] prove the following local version of first Thomas' conjecture:

Theorem 3. *(See [13].) If $\Gamma[F]$ has several attractors, and in particular if F has several fixed points, then there exists $x \in X$ such that $G_F(x)$ has a positive circuit.*

Let us also mention the following fixed point theorem proved by Richard [14] (and previously proved by Shih and Dong [18] in the Boolean case):

Theorem 4. *(See [14].) If $G_F(x)$ has no circuit for all $x \in X$, then F has a unique fixed point.*

The proof of Theorem 4 done in [14] reveals that if $G_F(x)$ has no circuit for all $x \in X$, then F has a unique fixed point ξ, and, in addition, for all $x \in X$, $\Gamma[F]$ has a path from x to ξ. It is then clear that the presence of a cyclic attractor in $\Gamma[F]$ implies the presence of a circuit in $G_F(x)$ for at least one $x \in X$. We then arrive to the following natural question:

Question 1. Does the presence of a cyclic attractor in $\Gamma[F]$ or $\Gamma(F)$ implies the presence of a negative circuit in $G_F(x)$ for at least one $x \in X$?

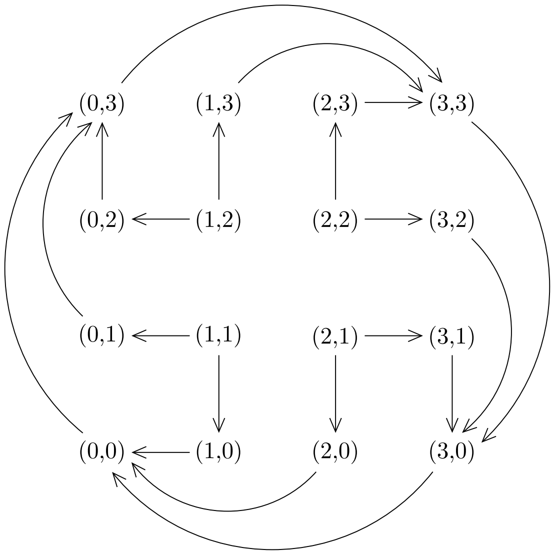
Clearly, a positive answer would improve significantly Theorem 1 or 2 by providing a local version of the second Thomas' conjecture. However, the following example shows that the answer is negative. This highlights the fact that it is necessary to take a union of local interaction graphs in order to obtain, from a cyclic attractor, a negative circuit.

Example 6. $n = 2$, $X = \{0, 1, 2, 3\}^2$ and F is defined by:

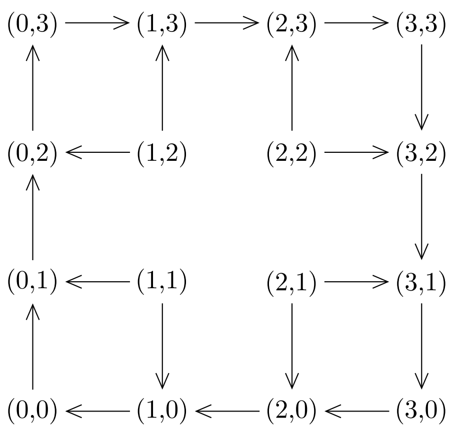
$$f_1(x) = \begin{cases} 3 & \text{if } x_2 = 3 \text{ or if } x_2 > 0 \text{ and } x_1 \geqslant 2, \\ 0 & \text{otherwise,} \end{cases}$$

$$f_2(x) = \begin{cases} 3 & \text{if } x_1 = 0 \text{ or if } x_1 < 3 \text{ and } x_2 \geqslant 2, \\ 0 & \text{otherwise.} \end{cases}$$

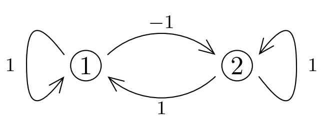
The asynchronous state transition graph $\Gamma(F)$ is the following:



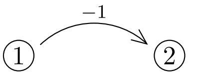
The unitary asynchronous state transition graph $\Gamma[F]$ is the following:



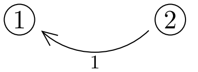
The interaction graph $G(F)$, which is here equal to $G[F]$, is the following:



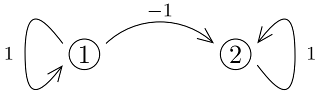
We see that $\{(0,0),(0,3),(3,3),(3,0)\}$ is a cyclic attractor of $\Gamma(F)$ and that $G(F)$ has a negative circuit. We see also that $\{(0,0),(0,1),(0,2),(0,3),(1,3),(2,3),(3,3),(3,2),(3,1)(3,0)\}$ is a cyclic attractor of $\Gamma[F]$ and that $G[F]$ has a negative circuit. However, for all $x \in X$, the local interaction graph $G_F(x)$ has no negative circuit. Indeed, for $x \in \{(1,0),(0,0),(0,1)\}$ and $x \in \{(2,3),(3,3),(3,2)\}$, $G_F(x)$ is as follows:



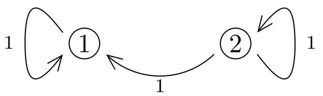
for $x \in \{(3,1),(3,0),(2,0)\}$ and $x \in \{(0,2),(0,3),(1,3)\}$, $G_F(x)$ is as follows:



for $x = (1,1)$ and $x = (2,2)$, $G_F(x)$ is as follows:



and for $x = (1,2)$ and $x = (2,1)$, $G_F(x)$ is as follows:



The fact that Theorem 3 establishes the uniqueness of a fixed point for F under the condition that $G_F(x)$ has no positive circuit suggests the following weaker version of Question 1:

Question 2. Does the absence of a negative circuit in $G_F(x)$ for all $x \in X$ implies the presence of at least one fixed point for F?

A positive answer would improve significantly Corollary 1, and would give, together with Theorem 3, a very nice proof by dichotomy of Theorem 4. However, the previous example shows that Question 2 has also a negative answer. Nevertheless,

Questions 1 *and* 2 *remain open in the Boolean case*.

Acknowledgments

Example 6 has been obtained with Jean-Paul Comet that I gratefully thank. I also thank Bruno Soubeyran for stimulating discussions.

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