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POSITIVE CIRCUITS AND MAXIMAL NUMBER OF FIXED POINTS IN DISCRETE DYNAMICAL SYSTEMS

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RÉSUMÉ :

On considère un système dynamique discret dont l'espace des états est le produit X de n intervalles finis d'entiers. L'évolution du système est décrite par les itérations successives d'une application f de X dans lui-même, et la structure du système est décrite par un graphe d'interaction G . Ce graphe a n sommets, notés de 1 à n , et ses arcs sont définis, comme dans le cas différentiel, à partir du signe des entrées de la matrice Jacobienne de f : il y a un arc positif (négatif) de i sur j si, quelque part dans l'espace des phases, l'analogue discret de $\partial f_i / \partial x_j$ est positif (négatif).

G donne une image très grossière, mais très pertinente, du système. Il est tentant d'essayer d'extraire de G les propriétés dynamiques principales du système. Ici, on s'intéresse à la relation entre le nombre d'états stables, i.e. le nombre de points fixes pour f , et les circuits positifs du graphe d'interaction, i.e. les circuits contenant un nombre pair d'inhibitions. On établit une borne supérieure sur le nombre de points fixes pour f qui ne dépend que de la topologie des circuits positifs de G (et de X). Cette borne supérieure généralise une preuve récente d'une version discrète de la conjecture de Thomas, qui affirme que si G est sans circuit positif alors f admet au plus un point fixe. Cette borne généralise aussi une borne supérieure sur le nombre de points fixes établie par Aracena, Demongeot et Goles dans le contexte des réseaux de neurones booléens.

Ce travail est motivé par des considérations biologiques: les réseaux de régulation génétique sont souvent décrits par les biologistes en termes de graphes d'interaction, et la présence de plusieurs points fixes dans ces systèmes est reliée à un phénomène biologique important: la différenciation cellulaire. De plus, les approches discrètes sont de plus en plus utilisées en biologie du fait du manque de données expérimentales précises, et du caractère sigmoïdal des régulations génétiques.

MOTS CLÉS :

Système dynamique discret, réseau booléen, Dérivée discrète, Matrice Jacobienne Discrète, Graphe d'interaction, Circuit positif, Multistationnarité, Réseaux de régulation génétique

ABSTRACT:

We consider a discrete dynamical system whose set of states is the product X of n finite intervals of integers. The evolution of the system is described by the successive iterations of a map f from X to itself, and the structure of the system is described by an interaction graph G . This graph has n nodes, denoted from 1 to n , and its edges are defined, as in the differential case, from the sign of the entries of the Jacobian matrix of f : there is positive (negative) edge from j to i if, somewhere in the state space, the discrete analogue of $\partial f_i / \partial x_j$ is positive (negative).

G gives a rather simple picture of the system. It is then tempting to relate it to the main dynamical properties of the system. Here, we focus on the relationships between the number of stable states, i.e. the number of fixed points for f , and the positive circuits of G , i.e. the circuits with an even number of negative edges. We establish an upper bound on the number of fixed points for f which only depends on the topology of the positive circuits of G (and on X). This upper bound generalizes a recent proof of a discrete version of the Thomas' conjecture, stating that if G has no positive circuit then f has at most one fixed point. It also generalizes an upper bound on the number of fixed points established by Aracena, Demongeot and Goles in the context of boolean neural networks.

This work is motivated by biological considerations: genetic regulatory networks are often described by biologists in terms of interaction graphs, and the presence of several fixed points in these systems is related to an important biological phenomena, namely, the cell differentiation process. Furthermore, discrete approaches are increasingly used in biology because of the qualitative nature of most experimental data and the sigmoidal character of genetic regulations.

KEY WORDS :

Discrete dynamical system, Boolean network, Discrete derivative, Discrete Jacobian Matrix, Interaction graph, Positive circuit, Fixed point, Multistationarity, Genetic regulatory network

Positive circuits and maximal number of fixed points in discrete dynamical systems

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Abstract

We consider a discrete dynamical system whose set of states is the product X of n finite intervals of integers. The evolution of the system is described by the successive iterations of a map f from X to itself, and the structure of the system is described by an interaction graph G . This graph has n nodes, denoted from 1 to n , and its edges are defined, as in the differential case, from the sign of the entries of the Jacobian matrix of f : there is positive (negative) edge from j to i if, somewhere in the state space, the discrete analogue of $\partial f_i / \partial x_j$ is positive (negative). G gives a rather simple picture of the system. It is then tempting to relate it to the main dynamical properties of the system. Here, we focus on the relationships between the number of stable states, i.e. the number of fixed points for f , and the positive circuits of G , i.e. the circuits with an even number of negative edges. We establish an upper bound on the number of fixed points for f which only depends on the topology of the positive circuits of G (and on X). This upper bound generalizes a recent proof of a discrete version of the Thomas' conjecture, stating that if G has no positive circuit then f has at most one fixed point. It also generalizes an upper bound on the number of fixed points established by Aracena, Demongeot and Goles in the context of boolean neural networks. This work is motivated by biological considerations: genetic regulatory networks are often described by biologists in terms of interaction graphs, and the presence of several fixed points in these systems is related to an important biological phenomena, namely, the cell differentiation process. Furthermore, discrete approaches are increasingly used in biology because of the qualitative nature of most experimental data and the sigmoidal character of genetic regulations.

Keywords: Discrete dynamical system, Boolean network, Discrete derivative, Discrete Jacobian Matrix, Interaction graph, Positive circuit, Fixed point, Multistationarity, Genetic regulatory network.

1 Introduction

Let X be the Cartesian product of n finite intervals of integers. We see X as the set of states of a discrete dynamical system with n discrete variables. The evolution of the system is described by the successive iterations of a map $f : X \rightarrow X$. Several modes of iteration are possible: parallel, serial, chaotic, asynchronous (see [9,10] for a definition and a comparison of these iterations). In all cases, the fixed points of f correspond to the *stable states* of the system and are thus of particular interest.

The dynamics described by f may be very complex. A coarse but pertinent information is contained in the structure of the system. It is usually represented

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under the form of a signed directed graph called *interaction graph*: the set of nodes is $\{1, \dots, n\}$, and there is an edge from j to i if the evolution of the i th variable depends on the evolution of the j th one. Furthermore, edges are labelled with a sign, $+$ or $-$, to denote activatory versus inhibitory effects.

We are interested by the relationships between the number of stable states and the *positive circuits* of the interaction graph, i.e. the circuits with an even number of negative edges. About this relation, the biologist René Thomas conjectured that *the presence of a positive circuit in the interaction graph is a necessary condition for the presence of several stable states* [16]. The so called Thomas' conjecture have been proved in differential frameworks [3,2,11,12,15]. More recently, it has been proved in the boolean framework [1,4,5] and in the discrete framework considered here [6,7]. The obvious interest of these works is that they relate the rather simple information contained in the interaction graph to a non trivial property on the dynamics: the presence of several stable states.

The Thomas conjecture gives an upper bound on the number of stable state under the strong hypothesis that the interaction graph has no positive circuit. In the context of boolean neural networks, Aracena, Demongeot and Goles [1], established, without any condition on the interaction graph, an upper bound for the number of stable states which only depends on the positive circuits of the graph. In this paper, we establish an upper bound on the number of stable states which generalizes both upper bound given by Aracena *et al* and the discrete version of the Thomas conjecture proved in [6,7]. This upper bound only depends on the topology of the positive circuits of the interaction graph (and on X). It formally shows that a high level of connection between positive circuits leads to a small number of stable states.

This work is motivated by biological consideration: genetic regulatory networks are often described by the biologists in terms of interaction graphs, and the presence of several stable states in these systems is related to an important biological phenomena, namely, the cell differentiation process [16,18,19]. Moreover, discrete approaches are increasingly used in biology because of the qualitative nature of most experimental data and the switch-like character of genetic regulations.

The paper is organized as follow. In Section 2 we introduce a notion of *discrete derivative*, or *discrete Jacobian matrix*, for maps $f : X \rightarrow X$. Then, we use it to define the interaction graph $G(f)$, as in the differential framework [11,2,12,15]: there is a positive (resp. negative) edge node from the j th variable to the i th one if, somewhere in the phase space, (the discrete analogue of) $\partial f_i / \partial x_j$ is positive (resp. negative). In Section 3 we express an upper bound for the number of fixed points for f which only depends on the positive circuits of $G(f)$ and on X . In Section 4, we adapt and improve the bound by focusing on the discrete approach that Thomas used to model the behavior of gene networks. Thomas described the evolution of gene networks with a particular kind of asynchronous iterations [17,19]. These iterations are visualized under the form of a directed graph on X called *asynchronous state graph* and denoted $\Gamma(f)$. We extend the notion of stable state of f to the notion of attractor of $\Gamma(f)$, and we show that the established upper bound for the number of fixed points is, more generally, an upper bound for the number of attractors in $\Gamma(f)$. Finally, we improve this upper bound by expressing it from the interaction graph of $\Gamma(f)$ which is naturally defined to be the intersection

of all the interaction graphs $G(h)$ such that $\Gamma(h) = \Gamma(f)$.

2 Discrete Jacobian matrix and interaction graph

Let $X = \prod_{i=1}^n X_i$ be the product of n finite intervals of integers of cardinality ≥ 2 , and consider a map f from X to itself:

$$x = (x_1, \dots, x_n) \in X \mapsto f(x) = (f_1(x), \dots, f_n(x)) \in X.$$

In this section, we introduce a Jacobian matrix for f based on a notion of directional discrete derivative. We then use it to define the interaction graph of f , as in [11,2,12,7,5] for example.

Let us start with preliminary notations. For $i = 1, \dots, n$, we denote by e_i the n -tuple whose i th component is 1 and whose other components are 0. Then, we denote by X' the set of couples (x, v) such that

$$x \in X, \quad v \in \{-1, 1\}^n \quad \text{and} \quad x + v \in X.$$

So, if $(x, v) \in X'$ then

$$x + v_i e_i = (x_1, \dots, x_i + v_i, \dots, x_n) \in X.$$

Definition 2.1 For all $(x, v) \in X'$, we call *Jacobian matrix* of f evaluated at x with the directional vector v , the $n \times n$ matrix $f'(x, v) = (f'_{ij}(x, v))$ defined by:

$$f'_{ij}(x, v) = \frac{f_i(x + v_j e_j) - f_i(x)}{v_j} \quad (i, j = 1, \dots, n).$$

If v_j is positive (resp. negative), then $f'_{ij}(x, v)$ may be seen as the right (resp. left) partial derivative of f_i with respect to the j th variable evaluated at x . In both cases, $f'_{ij}(x, v)$ is a natural discrete analogue of $(\partial f_i / \partial x_j)(x)$.

Remark 2.2 The notion of discrete derivative was first introduced by Robert in the boolean case, i.e. when X is the n -cube $\{0, 1\}^n$ [8,9,10]. In this case, there is a unique directional vector v attached to each point x so the Jacobian matrix only depends on x and can be written $f'(x) = (f'_{ij}(x))$. The Robert's Jacobian matrix is then the $n \times n$ *boolean* matrix whose entry at (i, j) is $|f'_{ij}(x)|$.

An *interaction graph* is a directed graph whose set of nodes is $\{1, \dots, n\}$ and whose set of edges is a subset of $\{1, \dots, n\} \times \{-1, 1\} \times \{1, \dots, n\}$. An edge (j, s, i) is said positive if $s = 1$ and negative otherwise. Note that such a graph can contain both a positive and a negative edge from one node to another.

Definition 2.3 We call *n-interaction graph* of f , and we denoted by $G(f)$, the n -interaction graph which contains a positive (resp. negative) edge from j to i if there exists $(x, v) \in X'$ such that $f'_{ij}(x, v)$ is positive (resp. negative).

So, there is an edge from j to i if and only if f_i depends on the j th variable. More precisely, there is a positive (resp. negative) edge from j to i if, somewhere in X , an increase of the j th variable induces an increase (resp. decrease) of f_i .

Note that $G(f)$ gives a very coarse information about f : it contains only n nodes whereas f is defined on at least 2^n points.

3 Positive circuits and fixed points

We are interested in the relationships between the fixed points of f and the positive circuits of the interaction graph $G(f)$. In order to remove any ambiguity about positive circuits, we formally define them as follow:

Definition 3.1 Let G be a n -interaction graph. A *positive circuit* of G is a nonempty sequence of edges, say

$$(j_1, s_1, i_1), (j_2, s_2, i_2), \dots, (j_r, s_r, i_r),$$

such that: $i_k = j_{k+1}$ for $k = 1, \dots, r - 1$ (the sequence is a path); $i_r = j_1$ (the path is a circuit); the nodes j_k are mutually distinct (the circuit is elementary); the product of the signs s_k is positive.

3.1 Previous works

Thomas stated a well known conjecture about the link between fixed points and positive circuits [16]. This conjecture has been proved in differential frameworks [3,2,11,12,15], and more recently in discrete frameworks [4,7,5]. In the following, we use a weak statement of the discrete version of Thomas' conjecture proved in [6,7]:

Theorem 3.2 (discrete version of the Thomas' conjecture [7])

If $G(f)$ is without positive circuit, then f has at most one fixed point.

This theorem gives an upper bound for the number of fixed points for f under the strong hypothesis that $G(f)$ has no positive circuit. In the context of boolean neural networks, Aracena, Demongeot and Goles [1], established, *without any condition on the interaction graph*, a non trivial upper bound for the number of fixed points which only depends on the positive circuits of the graph. In order to express this upper bound, they introduce the concept of positive feedback vertex set (that we will use in the following):

Definition 3.3 [1] Let G be a n -interaction graph. A *positive feedback vertex set* of G is a subset I of $\{1, \dots, n\}$ such that each positive circuit of G has a node in I .

Remark 3.4 The set of all the nodes of G is always a positive feedback vertex set of G . Oppositely, \emptyset is a positive feedback vertex set of G if and only if G has no positive circuit.

A more precise idea about the result of Aracena *et al* can now be given: in [1], they proved that if f is a map from $\{0, 1\}^n$ obtained according to the boolean neural networks formalism², and if I is a positive feedback vertex set of $G(f)$, then f has at most $2^{|I|}$ fixed points.

3.2 Upper bound on the number of fixed points

Here, we give an upper bound for the number of fixed points for all maps $f : X \rightarrow X$. This bound generalizes the one given by Aracena *et al* for boolean neural networks and the discrete version of the Thomas' conjecture.

² This implies that $G(f)$ cannot have both a positive and a negative edge between two given nodes.

Theorem 3.5 *Let $f : X \rightarrow X$. If I is positive feedback vertex set of $G(f)$, then f has at most*

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

fixed points.

(The above product is naturally equal to 1 if I is empty.)

Proof. We reason by induction on I . Suppose I to be a positive feedback vertex set of $G(f)$.

Base case. If $I = \emptyset$ then $G(f)$ is without positive circuit and, following the discrete version of the Thomas' conjecture, f has at most one fixed point.

Induction step. Suppose that $I \neq \emptyset$. The induction hypothesis is:

Let $\bar{f} : X \rightarrow X$. If \bar{I} is a positive feedback vertex set of $G(\bar{f})$, and if \bar{I} is strictly included in I , then \bar{f} has at most $\prod_{i \in \bar{I}} |X_i|$ fixed points.

Without loss of generality, suppose that $1 \in I$. Let a be any element of X_1 and consider the map \bar{f} from X to itself defined by:

$$\bar{f} = (\bar{f}_1, \bar{f}_2, \dots, \bar{f}_n) = (a, f_2, \dots, f_n).$$

Since $\bar{f}_1 = \text{cst} = a$, we have $\bar{f}_{1j} = \text{cst} = 0$ for $j = 1, \dots, n$. So, node 1 has no predecessor in $G(\bar{f})$ has no edge with a final node equals to 1. In addition, if $i \neq 1$ then $\bar{f}_{ij} = f_{ij}$ for $j = 1, \dots, n$. Consequently all the edges of $G(\bar{f})$ are edges of $G(f)$, i.e. $G(\bar{f})$ is a subgraph of $G(f)$.

Thus, $\bar{I} = I \setminus \{1\}$ is a positive feedback vertex set of $G(\bar{f})$. Indeed, if C is a positive circuit of $G(\bar{f})$, then C is also a positive circuit of $G(f)$ so it has a node $i \in I$, and since node 1 has no predecessor in $G(\bar{f})$, $i \in \bar{I}$. Thus, by induction hypothesis, \bar{f} has at most $\prod_{i \in \bar{I}} |X_i|$ fixed points.

Now, suppose x to be a fixed point of f such that $x_1 = a$. Then

$$\bar{f}(x) = (a, f_2(x), \dots, f_n(x)) = (a, x_2, \dots, x_n) = x$$

so x is also a fixed point of \bar{f} . Consequently, f has at most $\prod_{i \in \bar{I}} |X_i|$ fixed points x such that $x_1 = a$. Since this holds for each $a \in X_1$, we deduce that f has at most

$$|X_1| \prod_{i \in \bar{I}} |X_i| = \prod_{i \in I} |X_i|$$

fixed points. □

3.3 Comments

In order to comment the previous result, we need a definition.

Definition 3.6 When X is given, for all n -interaction graph G , we set:

$$\mu(G) = \min \left\{ \prod_{i \in I} |X_i|, I \text{ is a positive feedback vertex set of } G \right\}.$$

$\mu(G(f))$ is obviously the best upper bound on the number of fixed point for f given by the previous theorem. This bound *only depends on $G(f)$ and on X* and

reveals an interesting property about the influence of connections between positive circuits (two circuits are connected if they share a common node).

Roughly speaking, *connections between positive circuits decrease the number of fixed points*. This property being more clear when intervals X_i have the same cardinality, suppose that $|X_i| = q$ for $i = 1, \dots, n$. Then, for each positive feedback vertex set I of minimal cardinality, we have $\mu(G(f)) = q^{|I|}$. Let us compare $q^{|I|}$ with q^p where p is the number of positive circuits in $G(f)$. It is clear that $|I| \leq p$, and that the more the positive circuits of $G(f)$ are connected, the more $|I|$ is less than p . For instance, $|I| < p$ whenever $G(f)$ has connected positive circuits, and if all the positive circuits of $G(f)$ share a same node, then $|I| = 1$ (so f has at most q fixed points). Observe also that $|I|$ is always greater than or equals to the number of disjoint positive circuits (two circuits are disjoint if they are not connected).

Remark 3.7 Given two n -interaction graphs G and H : *If all the positive circuits of G are positive circuits of H , then $\mu(G) \leq \mu(H)$* . Indeed, suppose I to be a positive feedback vertex set of H . If C is a positive circuit of G then C is a positive circuit of H and, by definition, C has a node in I . Thus I is a positive feedback vertex set of G and we deduce that $\mu(G) \leq \mu(H)$. A fortiori, if G is a *subgraph* of H , i.e. if all the edges of G are edges of H , then $\mu(G) \leq \mu(H)$.

4 Asynchronous state graph and attractors

In this section, we adapt and improve the previous theorem to the context of gene regulatory networks. We focus on the called *logical approach* that Thomas proposed to study the qualitative behavior of gene regulatory networks (see [17,19] for instance).

4.1 Asynchronous state graph

In the logical approach of Thomas, X is seen as the set of states of a genetic regulatory network with n genes, and the dynamics of the network is described, given a map $f : X \rightarrow X$, under the form of a directed graph on X called asynchronous state graph.

Definition 4.1 The *asynchronous state graph* of f is the directed graph $\Gamma(f)$ whose set of nodes is X and which contains an edge from x to y if there exists $i \in \{1, \dots, n\}$ such that

$$f_i(x) \neq x_i \quad \text{and} \quad y = \begin{cases} x + e_i & \text{if } x_i < f_i(x), \\ x - e_i & \text{if } x_i > f_i(x). \end{cases}$$

The interpretation of f and $\Gamma(f)$ in terms of gene networks is the following. At state $x \in X$, x_i is the expression level of the i th gene, and $f_i(x)$ is the level toward which x_i evolves. The asynchronous state graph $\Gamma(f)$ is built, from this interpretation of f , by taking into account the fact that evolution of expression levels involve complex biological phenomena and thus need delay. Without any information on these delays, if $x_i \neq f_i(x)$, the delay that x_i needs to evolve may be the smallest. This case is taken into account through the presence, in $\Gamma(f)$, of an

edge from x to $x + e_i$, or from x to $x - e_i$, according to whether $x_i < f_i(x)$ or $x_i > f_i(x)$. Since delays are a priori mutually distinct, at each step, there is a unique gene whose level evolves. This is why the state graph is said asynchronous. The fact that expression levels evolve of per unit is inspired from continuous descriptions. Note that continuous models of gene networks are often based on piece-wise differential equation systems, and that there are strong links between these differential systems and asynchronous state graphs [13,17,14,15].

4.2 Attractors

The fixed points of f are of particular interest: they have no successor in $\Gamma(f)$ and correspond to the *stable states* of the system. In the following definition, we introduce the notion of *attractor* which is a natural extension of the notion of stable state.

Definition 4.2 A *trap domain* of $\Gamma(f)$ is a nonempty subset A of X such that, for all edges (x, y) of $\Gamma(f)$, if $x \in A$ then $y \in A$. An *attractor* of $\Gamma(f)$ is a smallest trap domain with respect to the inclusion relation.

In other words, the attractors of $\Gamma(f)$ are the smallest set of states that we cannot leave. They extend the notion of stable state in the sense that *x is a fixed points of f if and only if $\{x\}$ is an attractor of $\Gamma(f)$* . Note also that there always exists at least one attractor (since X is itself a trap domain). The following proposition gives other easy observations about attractors. The first one shows why, in weak sense, attractors perform an attraction.

Proposition 4.3

- (i) *From each state $x \in X$, there is a path which leads to an attractor of $\Gamma(f)$.*
- (ii) *Attractors are strongly connected components of $\Gamma(f)$.*
- (iii) *Attractors of $\Gamma(f)$ are mutually disjointed.*

Proof. For all $x \in X$, let P_x be the set of y such that there is a path from x to y in $\Gamma(f)$ (by convention, $x \in P_x$). (i) Since P_x is a trap domain, there is at least one attractors $A \subseteq P_x$. (ii) Let A be an attractor of $\Gamma(f)$ and let $x, y \in A$. Then, $P_x \subseteq A$ and $P_y \subseteq A$. Since there is no trap domain strictly included in A , we deduce that $P_x = P_y = A$. Thus there is a path from x to y and a path from y to x . (iii) Let A and B be two attractors and suppose that $x \in A \cap B$. We show as previously that $P_x = A$ and that $P_x = B$. Thus if $A \neq B$ then $A \cap B = \emptyset$. \square

4.3 Upper bound on the number of attractors

Consider the following extension of the discrete version of the Thomas' conjecture proved in [6,7].

Theorem 4.4 [7] *If $G(f)$ is without positive circuit, then $\Gamma(f)$ has a unique attractor.*

Using this theorem, we prove that the upper bound for the number of fixed points for f given by Theorem 3.5 is, more generally, an upper bound for the number of

attractors in $\Gamma(f)$.

Theorem 4.5 *Let $f : X \rightarrow X$. If I is positive feedback vertex set of $G(f)$, then $\Gamma(f)$ has at most*

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

attractors.

Proof. The structure of the proof is similar to the one of Theorem 3.5. We reason by induction on I . Suppose I to be a positive feedback vertex set of $G(f)$.

Base case. If $I = \emptyset$ then $G(f)$ is without positive circuit and, following Theorem 4.4, $\Gamma(f)$ has at most one attractors.

Induction step. Suppose that $I \neq \emptyset$. The induction hypothesis is:

Let $\bar{f} : X \rightarrow X$. If \bar{I} is a positive feedback vertex set of $G(\bar{f})$, and if \bar{I} is strictly included in I , then $\Gamma(\bar{f})$ has at most $\prod_{i \in \bar{I}} |X_i|$ attractors.

Without loss of generality, suppose that $1 \in I$. Fix $a \in X_1$, and consider the map \bar{f} from X to itself defined by:

$$\bar{f} = (\bar{f}_1, \bar{f}_2, \dots, \bar{f}_n) = (a, f_2, \dots, f_n).$$

We show, as in the proof of Theorem 3.5, that $\bar{I} = I \setminus \{1\}$ that is a positive feedback vertex set of $G(\bar{f})$. Let $\bar{\mathbb{A}}$ be the set of attractors of $\Gamma(\bar{f})$. Since \bar{I} is strictly included in I , by induction hypothesis:

$$(1) \quad |\bar{\mathbb{A}}| \leq \prod_{i \in \bar{I}} |X_i|$$

Now, consider the set \mathbb{A} of attractors of $\Gamma(f)$. Let \mathbb{A}_a be set of $A \in \mathbb{A}$ such that there exists $x \in A$ with $x_1 = a$. We want to show that

$$(2) \quad |\mathbb{A}_a| \leq |\bar{\mathbb{A}}|.$$

Let $A \in \mathbb{A}_a$ and let B be the set of $x \in A$ such that $x_1 = a$. We claim that B is a trap domain of $\Gamma(\bar{f})$. Suppose that (x, y) is an edge of $\Gamma(\bar{f})$ such that $x \in B$. Then, there exists i such that:

$$\bar{f}_i(x) \neq x_i \quad \text{and} \quad y = \begin{cases} x + e_i & \text{if } x_i < \bar{f}_i(x), \\ x - e_i & \text{if } x_i > \bar{f}_i(x). \end{cases}$$

Since $x_1 = a$ and $f_1 = \text{cst} = a$, $i \neq 1$ so $f_i = \bar{f}_i$. Hence, (x, y) is an edge of $\Gamma(f)$, and since $x \in A$, by definition, $y \in A$. We deduce from $x_1 = a$ and $i \neq 1$ that $y \in B$. Hence, B is a trap domain of $\Gamma(\bar{f})$. Thus, there exists at least one attractor $\bar{A} \in \bar{\mathbb{A}}$ such that $\bar{A} \subseteq B \subseteq A$. Since this holds for all $A \in \mathbb{A}_a$, there exists a map H from \mathbb{A}_a to $\bar{\mathbb{A}}$ such that

$$\forall A \in \mathbb{A}_a, \quad H(A) \subseteq A.$$

Then, following Proposition 4.3, for all $A, B \in \mathbb{A}_a$, we have

$$A \neq B \Rightarrow A \cap B = \emptyset \Rightarrow H(A) \cap H(B) = \emptyset \Rightarrow H(A) \neq H(B).$$

Thus H is injective and (2) is proved.

From (1) and (2) we deduce that

$$|\mathbb{A}_a| \leq \prod_{i \in \bar{I}} |X_i|.$$

Since this holds for all $a \in X_1$, and since $\mathbb{A} = \cup_{a \in X_1} \mathbb{A}_a$, we deduce that

$$|\mathbb{A}| \leq \sum_{a \in X_1} |\mathbb{A}_a| \leq |X_1| \prod_{i \in \bar{I}} |X_i| = \prod_{i \in I} |X_i|.$$

□

4.4 Interaction graph of an asynchronous dynamics

In our biological context, f is just an intermediate step to define the dynamics of a gene network under the form of the asynchronous state graph $\Gamma(f)$. It is tempting to see $G(f)$ as the interaction graph of the networks of dynamics $\Gamma(f)$. However, $G(f)$ cannot be seen as *the* interaction graph of $\Gamma(f)$ since $G(f)$ does not only depends on $\Gamma(f)$.

This lead us to define an interaction graph which only depends on $\Gamma(f)$, and which is minimal in the sense that it corresponds to the intersection of all the interaction graphs associated to the maps from which $\Gamma(f)$ can be obtained. Let us say that Γ is an asynchronous state graph if there exists a map f such that $\Gamma(f) = \Gamma$.

Definition 4.6 Let Γ be an asynchronous state graph. We call *interaction graph of Γ* , and we denote by $G[\Gamma]$, the n -interaction graph which contains an edge e if and only if, for all maps f such that $\Gamma(f) = \Gamma$, e is an edge of $G(f)$.

The interpretation is that e is an edge of $G[\Gamma]$ if and only if e is *necessary* to produce the dynamics Γ . It seems us to be a natural definition of $G[\Gamma]$.

Remark 4.7 $G[\Gamma(f)]$ is a subgraph of $G(f)$. Note also that, in the boolean case, $G[\Gamma(f)] = G(f)$ since, in this case, distinct maps lead to distinct asynchronous state graphs.

Recall that the smallest upper bound for the number of fixed points for f given by Theorem 3.5 is $\mu(G(f))$ (see Section 3.3). Recall also that, following the previous theorem, this bound is, more generally, an upper bound on the number of attractors in $\Gamma(f)$. Let Γ be an asynchronous state graph. For all map f such that $\Gamma(f) = \Gamma$, since $G[\Gamma]$ is a subgraph of $G(f)$, we have

$$\mu(G[\Gamma]) \leq \mu(G(f)).$$

In other words:

$$\mu(G[\Gamma]) \leq \min\{ \mu(G(f)), f \text{ is such that } \Gamma(f) = \Gamma \}.$$

The right member of this inequality is clearly an upper bound for the number of attractors in Γ . But *is $\mu(G[\Gamma])$ an upper bound on the number of attractors in Γ ?* This is not obvious a priori. The answer is positive since, in fact:

$$\mu(G[\Gamma]) = \min\{ \mu(G(f)), f \text{ is such that } \Gamma(f) = \Gamma \}.$$

To prove this, we use a supplementary definition and two lemmas.

Definition 4.8 We call *min-max version* of $f : X \rightarrow X$, and we denote by \tilde{f} the map from X to itself defined by:

$$\tilde{f}_i(x) = \begin{cases} \max(X_i) & \text{if } f_i(x) > x_i \\ x_i & \text{if } f_i(x) = x_i \\ \min(X_i) & \text{if } f_i(x) < x_i \end{cases} \quad (i = 1, \dots, n).$$

Remark 4.9 \tilde{f} only depends on $\Gamma(f)$ and $\Gamma(\tilde{f}) = \Gamma(f)$.

Lemma 4.10 *All the positive circuits of $G(\tilde{f})$ are positive circuits of $G(f)$.*

Proof. We first show that, for all $x, y \in X$:

$$x_i \leq y_i \text{ and } \tilde{f}_i(x) < \tilde{f}_i(y) \Rightarrow f_i(x) < f_i(y).$$

If $x_i \leq y_i$ and $\tilde{f}_i(x) < \tilde{f}_i(y)$ then $\tilde{f}_i(x) < \max(X_i)$ and $\min(X_i) < \tilde{f}_i(y)$ thus

$$f_i(x) \leq x_i \leq y_i \leq f_i(y).$$

We deduce that $f_i(x) < f_i(y)$ because if not then

$$f_i(x) = x_i = y_i = f_i(y),$$

and it follows that

$$\tilde{f}_i(x) = x_i = y_i = \tilde{f}_i(y),$$

a contradiction.

Now, we show that the positive circuits of $G(\tilde{f})$ of length ≥ 2 (i.e. involving at least two nodes) are positive circuits of $G(f)$. To show this, it is sufficient to prove that an edge (j, s, i) of $G(\tilde{f})$ with $j \neq i$ is an edge of $G(f)$. So let (j, s, i) be an edge of $G(\tilde{f})$ with $j \neq i$. Then, there exists $(x, v) \in X'$ such that $\tilde{f}_{ij}(x, v)$ and s have the same sign, i.e such that:

$$\begin{cases} \tilde{f}_i(x) < \tilde{f}_i(x + e_j) & \text{if } s = v_j, \\ \tilde{f}_i(x) > \tilde{f}_i(x - e_j) & \text{if } s \neq v_j. \end{cases}$$

Since $i \neq j$, we have $x_i = (x + v_j e_j)_i$, and it follows from (2) that:

$$\begin{cases} f_i(x) < f_i(x + e_j) & \text{if } s = v_j, \\ f_i(x) > f_i(x - e_j) & \text{if } s \neq v_j. \end{cases}$$

So $f_{ij}(x, v)$ and s have the same sign, and we deduce that (j, s, i) is an edge of $G(f)$.

It remains to prove that the positive circuits of $G(\tilde{f})$ of length 1 are also positive circuits of $G(f)$. So suppose $(i, 1, i)$ to be an edge of $G(\tilde{f})$. Then, there exists $(x, v) \in X'$ such that $f_{ii}(x, v) > 0$, i.e such that:

$$\begin{cases} \tilde{f}_i(x) < \tilde{f}_i(x + e_i) & \text{if } v_j = 1, \\ \tilde{f}_i(x) > \tilde{f}_i(x - e_i) & \text{if } v_j = -1. \end{cases}$$

Since $x_i < (x + e_i)_i$ and $x_i > (x - e_i)_i$, it follows from (2) that

$$\begin{cases} f_i(x) < f_i(x + e_i) & \text{if } v_j = 1, \\ f_i(x) > f_i(x - e_i) & \text{if } v_j = -1. \end{cases}$$

Hence $f_{ii}(x, v) > 0$ so $(i, 1, i)$ is an edge of $G(f)$. \square

Remark 4.11 We have proved a property quite stronger than the one stated. Let us said that a negative edge from a node to itself is a *negative loop*. We have proved that $G(\tilde{f})$ without its negative loops is a subgraph of $G(f)$.

Lemma 4.12 $G(\tilde{f})$ and $G[\Gamma(f)]$ have the same positive circuits.

Proof. Let \preceq be the partial order on n -interaction graphs defined by $G \preceq H$ if and only if all the positive circuits of G are positive circuits of H . Since $\Gamma(\tilde{f}) = \Gamma(f)$, $G[\Gamma(f)]$ is a subgraph of $G(\tilde{f})$. So $G[\Gamma(f)] \preceq G(\tilde{f})$ and it remains to prove that $G(\tilde{f}) \preceq G[\Gamma(f)]$, i.e. that $G(\tilde{f}) \preceq G(h)$ for all map h such that $\Gamma(h) = \Gamma(f)$. Let h be such that $\Gamma(h) = \Gamma(f)$. Since $\Gamma(h) = \Gamma(f)$, $\tilde{h} = \tilde{f}$ and thus, following Lemma 4.10, $G(\tilde{f}) = G(\tilde{h}) \preceq G(h)$. \square

It is no clear that

$$\mu(G[\Gamma]) = \min\{ \mu(G(f)), f \text{ is such that } \Gamma(f) = \Gamma \},$$

Indeed, we know that $\mu(G[\Gamma])$ is less than the right member of the above equality and, according to the previous lemmas, for all maps f such that $\Gamma(f) = \Gamma$, we have

$$\Gamma(\tilde{f}) = \Gamma \quad \text{and} \quad \mu(G[\Gamma]) = \mu(G(\tilde{f})) \leq \mu(G(f)).$$

Thus $\mu(G[\Gamma])$ is an upper bound for the number of attractors in Γ . In other words, we have the following stronger version of Theorem 4.5.

Theorem 4.13 Let Γ be an asynchronous state graph. If I is a positive feedback vertex set of $G[\Gamma]$ then Γ has at most

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

attractors.

The following example show that $\mu(G(\tilde{f}))$ can be significantly less than $\mu(G(f))$.

Example 4.14 Consider the map f from $\{0, \dots, q\}^n$ to itself defined by:

$$f_i(x) = \begin{cases} x_i + 1 & \text{if } x_i < q \\ x_i & \text{otherwise} \end{cases} \quad (i = 1, \dots, n).$$

For $i = 1, \dots, n$, $(i, 1, i)$ is an edge of $G(f)$. In other words, there is a positive circuit of length one on each node. The unique positive feedback vertex set of $G(f)$ is thus $\{1, \dots, n\}$. So, $\mu(G(f))$ is the trivial upper bound on the number of attractors:

$$\mu(G(f)) = (q + 1)^n = |X|.$$

On the other hand, $\tilde{f}_i = \text{cst} = q$ so $G(\tilde{f})$ has no edge, and we deduce that $\Gamma(\tilde{f}) = \Gamma(f)$ has at most

$$\mu(G(\tilde{f})) = \mu(G[\Gamma(f)]) = 1$$

attractors.

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