Mathematical Modeling in Genetic Networks: Relationships Between the Genetic Expression and Both Chromosomic Breakage and Positive Circuits

J. Aracena, S. Ben Lamine, M. A. Mermet, O. Cohen, and J. Demongeot

***Abstract*—The genome has evolved since a primitive genome until the present state of the human genome dispatched along the 23 pairs of chromosomes. This evolution has been ruled by the mutation process and also by the physiological and pathological reorganization of the genomic material inside or between the chromosomes, which are conditioning the genomic variability. This reorganization is starting at singular points on the short or long chromosomic arms, called crossing-over, or translocations, insertions, break points. In this paper, we will show that these points, also called weak points or hot spots of the genome are correlated, independently of their origin. In addition, we will give some properties of the genetic interaction matrices in terms of attractors of the genetic expression dynamics.**

***Index Terms*—Genetics, interaction matrix, positive and negative circuit, regulatory network, translocation.**

I. Introduction

THE GENOME has evolved since a primitive genome [1] until the present state of the human genome dispatched along the 23 pairs of chromosomes. This evolution has been ruled by the mutation process and also by the physiological (crossing-over mechanism) and pathological (translocations, inversions, insertions, deletions, fusions, etc.) re-organization of the genomic material inside or between the chromosomes, which are conditioning the genomic variability. This reorganization is starting at singular points on the short or long chromosomic arms, called crossing-over, or deletions, translocations, insertions, inversions, and fusions break points. In Section I, we will show that these points, also called weak (chromosomic break) point or hot spots of the genome are correlated, independently of their origin (physiological crossing-over, pathological constitutional or acquired chromosomic abnormal breakage). One of the mechanisms involved in the weakness of certain parts of the chromosomes is the presence of ubiquitory genes expressed during the whole cell cycle at methylated parts of the chromosome causing locally decoiling and opening of the DNA double strand, hence, causing a local fragility of the genome. In order to give arguments in favor of this hypothesis, we will partly randomly choose interaction matrices giving the relations existing between the ubiquitory genes and we will calculate the attractor configurations of expression of these genes. Then, we will be able to calculate the probability of expression, compare the location of the high expressed parts to the location of the weak genomic points and find for certain chromosomes a high correlation between these locations. Finally, we will give some properties of the interaction matrices in terms of the number of their possible attractors (generalizing some results obtained in [2]–[6] to the discrete case). Two main results are emerging from the present study. 1) The positive circuits of the interaction matrix are necessary for observing multiple attractors as conjectured by Delbrück [7] and Thomas [8], and 2) the number of attractors is of order of magnitude $\sqrt{\mathrm{n}}$, if the number n of genes is great and if the number of interactions is equal to $2\mathrm{n}$, as conjectured by Kauffman [9].

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II. Genetic Data Description

A. Review Stage

First, we will present the central hypothesis concerning the presence of correlated weak points in the human genome, based on a similarity between the distributions of translocation points, crossing-over locations and ubiquitory (i.e., expressed during the whole cell cycle) genes expression sites. This co-occurrence is probably due to the fragility of chromosomes at the transcriptionally active regions of the DNA, which are correlated to those involved in physiological crossing-over break points and in pathologic translocation breakpoints. The data used provided from genetic papers and from unpublished data provided by human genetic centers: They have been brought together in a dedicated database named HC FORUM [1] which is available on http://www.HCForum.imag.fr/ [10]. A previous study [11] has pointed out the potential pit-falls due to recruitment bias as well as the heterogeneous distribution of the different kinds of chromosomal bands. For example, translocations published in the literature are mainly those responsible for imbalances at birth that are more observed in relation to distal break points. Furthermore R bands are more often located in the distal regions of chromosomes.

III. Comparison Between Chromosomal Hot Spots of Different Origin

We give in Fig. 1 data collected in crossing-over distributions, calculated from http://www.genetics.soton.ac.uk/ and

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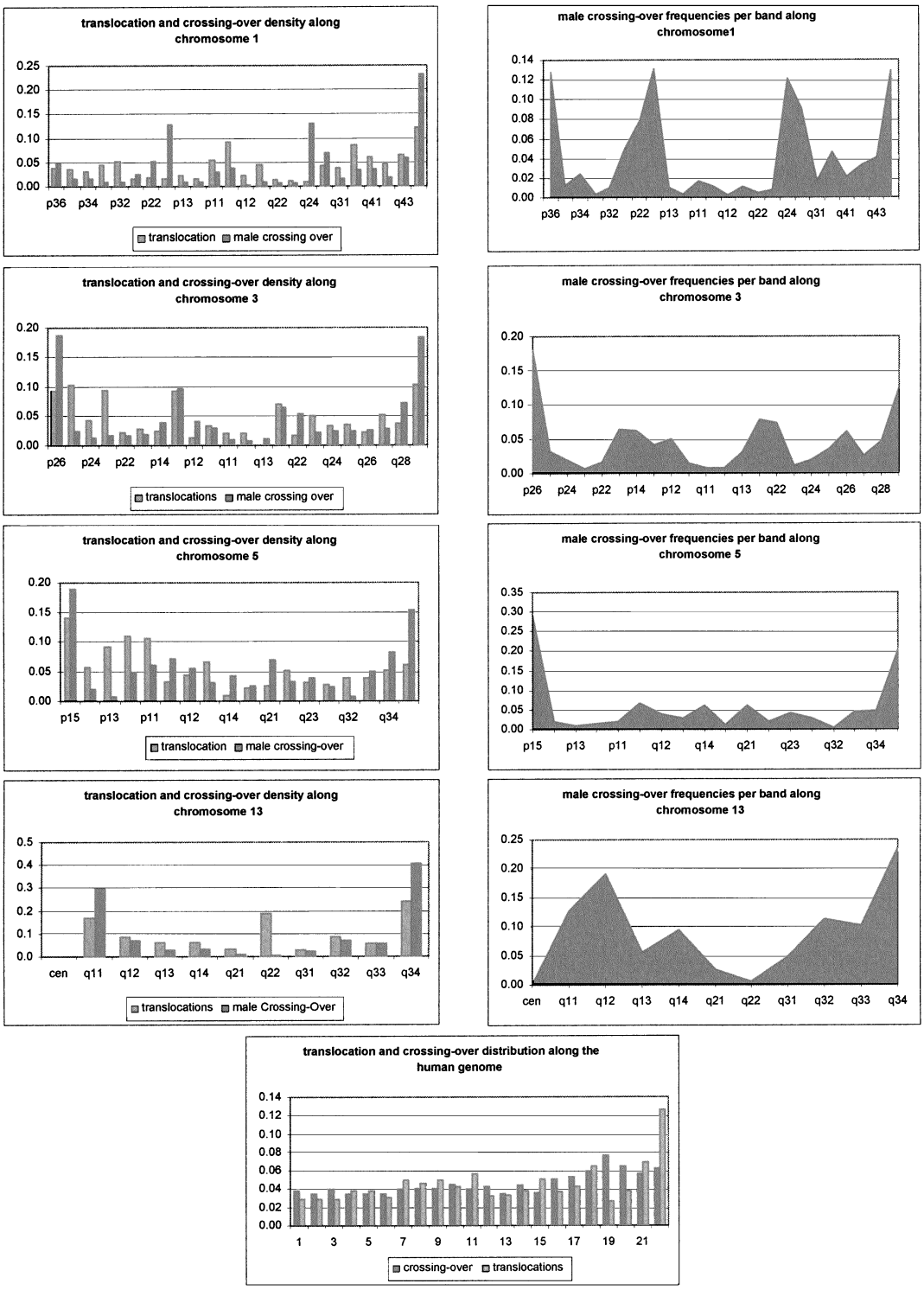

Fig. 1. Translocations and crossing-over distributions along the chromosomes 1, 3, 5, and 13 and the global histogram (bottom) along 22 autosomes of the human genome.

in constitutional translocation distributions, calculated from http://www.HCForum.imag.fr/.

We call monotony signs of a distribution the succession of signs $=$ if the consecutive bars of the distribution histogram are not significantly different, $+$ if the consecutive bars are significantly increasing and $-$ if they are significantly decreasing. For example, in Fig. 1 top left below, the monotony signs are successively $= - + + - + = + - + + - + - == + - + - - + +$. We have compared this monotony signature of the chromosome 1 translocations histogram to the monotony signature of the crossing-over histogram of the same chromosome on the first line of the Table I.

Let us define by X the random variable equal to the number of differences between monotony signs of the translocation (T) and of the crossing-over (C) break points distributions: in the Table I, we give in the second column the succession of the

TABLE I
MONOTONY SIGNS OF THE TRANSLOCATION (T) AND CROSSING-OVER (C) DISTRIBUTIONS

Ch	Monotony signs T/C	x/N	Pr(X≤x) X~B(N,1/2)
1	=-++-+=+-++-+-==+-+--++ -=-=+++-=++-+-=+--+=-++	4/23	.005
2	=+-+-+-+--+-+-+-+-+=+-=-+ --++-+---++-==+---+-+-=++	6/25	.007
3	+-+- +=+-+-=-+-+-=- +-+ =-+==+---=+--====++	3/21	.001
4	-+-+ - - - -+=+-+-+-+--+ --++==++ - - -+-+-+---+	12/2	NS
5	-++ =-++-+=+- =+=++ - -+++- -+- +-+ - -+++	9/17	NS
6	-+ -=+ -==+-+ -+- +- + -+++ - -=++ - -+ -+-+==++= -+++	6/21	.05
7	- --+ -+ --+-+ -+ -++ - -+-=++++--=+== -++	8/17	NS
8	=++ - -++== -+-+==+ - - = -=++ - -+==-++=++	4/17	.025
9	+--=+-+- +- +=+-+ - --- -===+=+-+=+	2/15	.004
10	-+-+-=+-+-+ -- --=++-+-+	2/11	.03
11	-+=-+ -+=+ -+-+ -+- -=+==+=-++	3/13	.05
12	+=-+=+ -+====+ - - -+ -+ -=++ -+==+	5/14	NS
13	--=-+ -+-+ --=-=++-+	1/9	.002
14	-+-++=- -+ -+ +-- -+-=++++	5/11	NS
15	+-+=+--++-++ -+-=++--=++	5/12	NS
16	+-++-=+ -++- -++ - -- =-- ===+-+++	3/14	.03
17	+--=+- +++-+ +--+==+-=++	2/11	.03
18	-+--+- +=+ -- --==+++	1/9	.002
19	+-+++- -+ - - --=-==++=+	4/10	NS
20	-+ -++- -+ - -==-==+++	3/9	NS
21	- + -+ +=++	2/4	NS
22	+ -+ - - =+ -++	4/5	NS

monotony signs for these distributions (+ if the distribution function is increasing, − if it is decreasing and = if it is constant). The third column gives the percentage of observed differences and the last column gives the significantly level (i.e., the risk α) of the test having as H_0 hypothesis the difference between the two distributions is due to chance between the two distributions, equal to the probability that X be less than x (or $N - X$ be more than $N - x$), where N is the number of bands of the considered chromosome (column 1) and x the observed number of differences. This probability can be calculated by remarking that X (or $N - X$), under H_0 hypothesis, is a binomial random variable following the distribution B (N, 1/2).

We remark on Table I that (except for the four last acrocentric chromosomes which are too small) we reject 12 times over 18 the hypothesis of the difference (due to the chance) between translocation and crossing-over distributions. Hence we can conclude that our central hypothesis about a common etiology for chromosome hot spots distribution is not falsified. When there is no significantly similarity for sufficiently long chromosomes (superior or equal to 12 bands) with large values of α superior or equal to 0.15), i.e., for chromosomes 4, 5, 7, and 15, then that corresponds to a small level of crossing-over with respect to the number of translocations (see histogram for chromosome 5 and also the global histogram on Fig. 1 above).

IV. USE OF THE GENETIC INTERACTION MATRIX

A major problem a genetician has presently to face since the introduction of the bio-array imaging is the estimation of the intergenic interaction matrix W which rules the observed genes expression [9], [12]–[14]. This interaction matrix is similar to the synaptic weight matrix, which rules the relationships between neurons in a neural network (cf. [15]–[17]). Hence, it is in general of a great biological interest and relevance to determine matrices having characteristics like: 1) a minimal number of nonzero coefficients for a given set of stationary behaviors (fixed points or cycles), 2) a minimal number of positive or negative circuits, controlling the number of attractors and their stability. In this paper we give two general results about the relationships between the positive and negative circuits in the graph of the interaction matrix W and the existence of fixed points. This permits us to characterize minimal matrices given dynamical behaviors and therefore partly solve the first problem. Finally, we constructed a bound for the number of fixed points in terms of the number of positive circuits in the graph of the interaction matrix W. So we partly solve the second problem too.

In general, it is very difficult to have exhaustively the interaction matrices: in the genetic literature and also by observing co-expressions through bio-arrays imaging, it is possible to qualitatively, or even quantitatively estimate the inhibitory (in case of repression by a protein obtained by the expression of a gene) or activatory (in case of induction or promotion) coefficients of the interaction matrix. If we have no information, we can randomly choose the matrix by respecting certain basic rules, e.g., by respecting certain proportions of activatory or inhibitory interactions. We can for example obtain the location density of expressed ubiquitory genes (calculated from http://www.citi2.fr/GENATLAS/) and then randomly simulate the interaction matrix and the initial conditions of the gene expression, by sampling them 100 000 times, the interaction matrices respecting the constraint to have 10% (resp. 10%) of negative (resp. positive) interactions, like in the *Arabidopsis* thaliana genome [13]. The Fig. 2 below gives the distribution of the co-expression of the ubiquitory genes calculated from the expected stationary behavior corresponding to a random choice of the interaction matrix and the initial conditions: we have systematically calculated attractors (fixed points or limit cycles) corresponding to an initial condition and an interaction matrix, and then we have calculated the frequency of observing the expression of each ubiquitory gene in these attractors. In absence of complementary information about the localization of the inhibitory or activatory interactions between ubiquitory genes, the obtained co-expression distribution is just

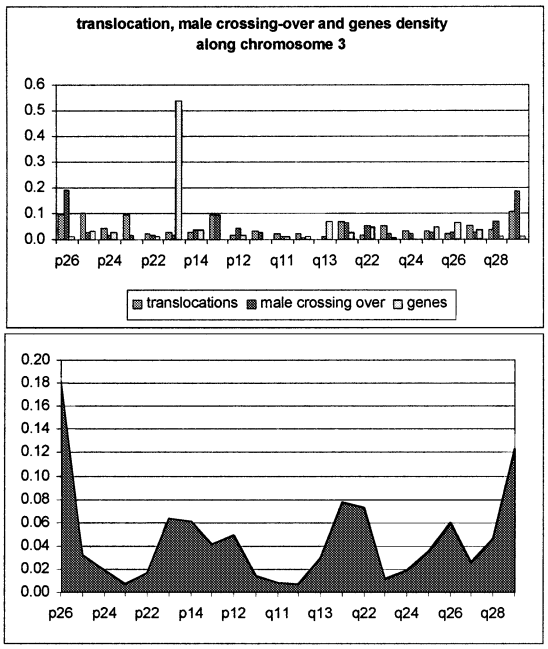

Fig. 2. Distributions of ubiquitory genes (below), all genes (right above) crossing-over (middle above) and translocation (left above) along the chromosome 3.

TABLE II
MONOTONY SIGNS OF THE HISTOGRAMS OF FIG. 2.

Ubiquitory genes distribution:	- - - ++=- + - ==++=- +++- ++	3/21
All genes distribution:	+=- ++- - + - +=+ - + - =++- - +	9/21
Crossing-over distribution:	- ====++- - - =++- - ===+++	0/21
Translocation distribution:	=- + - ==+ - + - ==+ - + - ==+ - +	3/21

a reflection of the spatial distribution of these ubiquitory genes along the human chromosome 3.

If we now determine the signed vectors corresponding to the monotonic variations of the histograms of Fig. 2 and, after, the number of differences between these signed vectors, we obtain as shown in Table II.

By comparing the vectors giving the succession of monotonic increasing $(+)$, decreasing $(-)$ and constant $(=)$ parts of the histograms of Fig. 2, it is easy to prove that we reject the hypothesis that ubiquitory and translocation distributions are different of the crossing-over distributions $(\mathrm{p} < 0.001)$, but we cannot reject the hypothesis of difference between the all genes and the crossing over distribution. It has to be noted, however, that the predisposition to chromosomal breakage cannot be explained solely by gene expression since breakpoints are also observed in heterochromatic regions with a lack of genes (for example the short arm of acrocentric chromosomes) (cf. also [19] and [20]).

V. MATHEMATICAL PROPERTIES OF THE INTERACTION MATRIX

Here we give some properties for minimal interaction matrices representing the inhibitory or activatory relationships existing between the ubiquitory genes, confirming the role of interaction coefficients: their presence in the interaction matrix causes the occurrence of positive and negative circuits very involved in the existence of several asymptotic configurations. For example, in [13], it is shown that the number of these asymptotic configurations for *Arabidopsis* thaliana flower morphogenesis control is equal to 4: this result can be predicted from [9], where it is shown by simulations that, if the Kauffman connectivity coefficient (equal to the number of nonzero interactions, here 22, divided by the number of genes, here 11) is equal to 2, then the number of possible genes expression asymptotic configurations is of the magnitude order of the square root of the number of genes ($3 < \sqrt{11} < 4$). Another result suggested in [9] confirms that genetic networks definitively have mathematically predictable behaviors: the human genome is made from about 45.000 genes and we have about $250 \cong \sqrt{45.000}$ different tissues in the human body, each tissue corresponding to a specific asymptotic expression of the nuclear material.

The interaction matrix is similar to the synaptic weight matrix, which rules the relationships between neurons in a neural network. The general coefficient $\mathrm{w_{ij}}$ of such an interaction matrix W is equal to $+1$ if the gene $\mathrm{G_j}$ activates the gene $\mathrm{G_i}$, equal to -1 if the gene $\mathrm{G_j}$ inhibits the gene $\mathrm{G_i}$ and equal to 0 if $\mathrm{G_j}$ and $\mathrm{G_i}$ have non interaction, $\mathrm{G_i}$ being equal to $+1$ (resp. -1), if it is (resp. not) expressed. In the case of small regulatory genetic systems (called operons), the knowledge of such a matrix W permits to explicit all possible stationary behaviors of the organizms having the corresponding genome: for example, in the operon which regulates the *Arabidopsis* thaliana flower morphogenesis, the interaction matrix is a (11,11)-matrix with only 22 non zero coefficients. This matrix presents a certain number of positive and negative circuits and only four observed attractors [13]. Hence it is general of a great biological interest and relevance to determine matrices having characteristic properties like 1) a minimal number of non-zero coefficients for a given set of stationary behaviors (fixed points or cycles) or 2) a minimal number of positive or negative circuits controlling the number of attractors and their stability (cf. [2], [5], [12] in the continuous case). In the following, we intend to partly solve the problems described above by giving necessary and sufficient conditions to obtain the properties 1) and 2).

A. Definitions and Notations

Let $\mathrm{G} = (\mathrm{V}, \mathrm{E})$ be a directed graph, where $\mathrm{V} = \{1, \ldots, \mathrm{n}\}$ is the set of nodes or vertices and $\mathrm{E} \subseteq \mathrm{V} \times \mathrm{V}$ is the set of arcs. Let $\mathrm{W} = (\mathrm{w_{ij}})$ be a (n, n)-real matrix. We call G the *incidence graph* of W if for all nodes i, j the arc going from i (*initial node*) to j (*terminal node*) (i, j) belongs to E if and only if $\mathrm{w_{ji}} \neq 0$. By extension, W will also be called the *incidence matrix* of G. We define the sign of an arc (i, j), denoted by $\mathrm{sign}((i, j))$, as the sign of $\mathrm{w_{ij}}$. Let us denote by $\Gamma_{\mathrm{G}}^{-}(i)$ $(\Gamma_{\mathrm{G}}^{+}(\mathrm{i}))$ the set of nodes $\mathrm{i_j}$ such that $(\mathrm{i_j}, \mathrm{i})$ $((\mathrm{i}, \mathrm{i_j}))$ belongs to E. We say that a set of arcs $\mathrm{C} = \{\mathrm{e_1}, \mathrm{e_2}, \ldots, \mathrm{e_r}\}$ is a *chain* if each arc $\mathrm{e_k}$ in C has a node belonging to $\mathrm{e_{k-1}}$ and the other one belonging to $\mathrm{e_{k+1}}$. We say that C is a *simple* (*elementary*) chain if the arcs (nodes) are different. In the sequel we will understand by chain a simple and elementary chain. In the same way we call C a *path* if the for each $\mathrm{e_k} = (\mathrm{i_k}, \mathrm{i_{k+1}})$, $\mathrm{e_{k+1}} = (\mathrm{i_{k+1}}, \mathrm{i_{k+2}})$ for every $\mathrm{k} = 1, \ldots, \mathrm{r}$,

that is to say, the final node of each arc is the beginning node of the next arc in C. The *sign of a path* or a chain C [denoted by sign (C)] is positive if the number of negative arcs of C is even and negative otherwise. A *cycle* $C = \{e_1, e_2, \ldots, e_r\}$ is defined as a chain, that is, where the initial node of e_1 and the terminal node or the initial node of e_r coincide. In the particular case where the initial node of e_1 and the terminal node of e_r coincide, we say that C is a *circuit*. For simplicity of notation, we say that a node i belongs to a cycle C if there exists a node j such that, (i, j) or (j, i) belongs to C. Every other definition of graph theory will be consistent with that in [21], [22]. A circuit or cycle C is negative (positive) if the sign(C) is negative (positive). Define now a *discrete state regulatory network* (DSRN), acting on the set of states $\{-1, 1\}$, here and subsequently denoted by N, as the 4-tuple $N = (G, W, b, \text{sign})$, where G is the incidence graph of W, b is a threshold real vector and for each node i is defined a local transition function f_i, depending on the values x_j of the nodes, as follows:

$$f_i(x) = \text{sign}\left(\sum_{j=1,\ldots,n} w_{ij}x_j - b_i\right),\ x \in \{-1,1\}^n$$
$$\text{where sign}\,(u) = 1,\ \text{if}\ u \geq 0$$
$$\text{and sign}(u) = -1,\ \text{otherwise.}$$

A DSRN has associated a discrete updating rule of the nodes' values, normally synchronous iteration or sequential iteration (see [15]). We shall say that a vector x is a fixed point if it is invariant under the application of the complete sequence of updates. Observe that the type of iteration does not change the set of fixed points, but only change their attraction basins. In the following we will use systematically the parallel iteration consists in updating all the nodes synchronously, i.e.,

$$x(t+1) = \text{sign}\left(\sum_{j=1,\ldots,n} w_{ij}x_j(t) - b_i\right),$$
$$\text{for } \textit{all } i = 1, \ldots, n,$$

with $x(0)$ in $\{-1, 1\}^n$.

B. Relations Between Positive and Negative Cycles and Fixed Points

In the sequel, we will assume that the directed graph G is connected, since otherwise one can apply the results to each of connected components of G. In addition, we will suppose, with not loss of generality, that $|\Gamma_G^-(i)| > 0$, for all $i \in V$, since otherwise if there exists a node $i \in V$, such that, $\Gamma_G^-(i)$ is empty, then its local transition function f_i would be constant, and therefore uninteresting. It follows directly from this property that there exists at least one circuit C in G [it can even be a circuit of the form (i, i) called *loop*]. Finally, we suppose that the directed graph G and the matrix W have a *quasiminimal structure*, that is, for all arc (i, j) in E, $i \neq j$, there exists $x \in \{-1, 1\}^n$, such that

$$\text{sign}\left(\sum_k w_{jk}x_k(t) - b_i\right) \neq \text{sign}\left(\sum_{k\neq i} w_{jk}x_k(t) - b_i\right).$$

Hence, we have the following necessary condition to have a quasiminimal structure:

$$-\sum_k |w_{ik}| < b_i \leq \sum_k |w_{ik}| \qquad \forall i = 1, \ldots, n$$

The following property will be very useful in the sequel for characterizing a cycle.

Proposition 1: A cycle C is positive if and only if there exists a vector $x \in \{-1, 1\}^n$ such that for all $(i, j) \in C$, $\text{sign}(w_{ji}) = x_i \cdot x_j$ or equivalently for all $(i, j) \in C$

$$x_i = \text{sign}(w_{ji})x_j. \tag{1}$$

Proof: Let C be a positive cycle and $i(0)$ a fixed node belonging to C. Let us enumerate the nodes belonging to C by $i(0), i(1), \ldots, i(k)$, such that, for all $j = 0, \ldots, k$, $(i(j), i(j-1)) \in C$ or $(i(j-1), i(j)) \in C$. Finally, let us define the vector x as follows:

—$x_{i(0)} = 1$ and
—$x_{i(j)} = \text{sign}(w_{i(j)i(j-1)})x_{i(j-1)}$ if $(i(j-1), i(j)) \in C$ or $x_{i(j)} = \text{sign}(w_{i(j-1)i(j)}) \cdot \text{sign}(x_{i(j-1)})$ if $(i(j), i(j-1)) \in C, \forall j = 1, \ldots, k$.

Obviously, x is satisfying (1). Hence $-x$ satisfies (1) too. Finally, it is direct that there does not exist another vector $y \notin \{x, -x\}$ that satisfies (1).

Let C be now a negative cycle, and let us suppose that (1) is true, then

$$\prod_{(i,j)\in C} \text{sign}(w_{ij}) = \prod_j x_j \prod_i x_i = \left(\prod_j x_j\right)^2.$$

but $\text{sign}(C) = \prod_{(i,j)\in C} \text{sign}(w_{ij}) < 0$, which is a contradiction. ■

Theorem 1: Given N, if all cycles of incidence graph G are positive, then there exists a vector $x = (x_1, \ldots, x_n) \in \{-1, 1\}^n$ such that x and $-x = (-x_1, \ldots, -x_n)$ are fixed points of N.

Proof: Let T be an arbitrary spanning tree of G, that is to say, $\forall i, j \in V, \exists!$ chain between i and j belonging to T (see example in Fig. 3). Let us now construct x as follows:

—Fix the value 1 to x_1, and —)
—Take $x_i = \text{sign}(C_{1i})$, where C_{1i} is the chain between node 1 and node i in T.

Observe that the value of x_i does not depend on T. In effect, let T' be another spanning tree of G, and C'_{1i} the chain in T' between the node 1 and i. If C'_{1i} is different of C1i, then by hypothesis all subcycles of the chain made of the concatenation of C_{1i} and C'_{1i} are positive, hence $\text{sign}(C_{1i}) = \text{sign}(C'_{1i})$, which ensures that the value x_i is well defined. If C'_{1i} is equal to C_{1i}, the same result is trivial. Because this result is available for each i, the value x is well defined.

We can also note that the values x_is are independent of the choice of the first component x_1.

Let us now prove that x so defined is a fixed point of N.

It is easily to check that x satisfies (1) of the proposition 1. It shows that, $\forall j \in V, \forall j(1), \ldots, j(n) \in \Gamma_G^-(j)$, $w_{jj(l)}x_{j(l)} > 0$ if and only if $x_j = 1$, and then that

$$\left(\sum_k w_{jk}x_k = \sum_k |w_{ik}| \geq b_j\right) \Leftrightarrow x_j = 1.$$

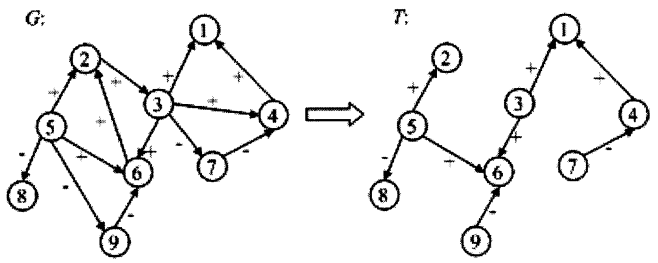

Fig. 3. Example of spanning tree. G corresponds to a graph where all cycles are positive and T is a spanning tree of G. In this case $x = (1, 1, 1, 1, 1, 1, -1, -1, -1)$.

Hence, $\text{sign}(\sum_k w_{jk}x_k - b_j) = 1$ if and only if $x_j = 1$, $\forall j \in V$. Therefore, x is a fixed point of N. The same procedure we can apply to prove that $-x$ is a fixed point of N too. ■

Remark: For a DSRN satisfying the hypothesis of Theorem 1, there exists two remarkable fixed points; they possess by construction a non frustration property, that is on each cycle of G the sign changes of the x_is are identical to the sign changes of the arcs of the cycle. For the other eventual fixed points, there is at least one cycle in G for which they are frustrated.

Theorem 2: Given N, if all circuits of the incidence graph G are negative, then N has no fixed points.

Proof: Let $x \in \{-1, 1\}^n$ be a fixed point of N and C a circuit, by hypothesis negative. By Proposition 1 there exists $(i, j) \in C$ such that $\text{sign}(w_{ji}x_i) \neq x_j$. Let us denoted by E^- the set of such arcs, i.e.,

$$E^- = \{(i, j) \in E \,|\, \text{sign}(w_{ji}x_i) \neq x_j\},$$

which is not empty. Let us define $N' = (G', W', b, \text{sign})$ by

- $G' = (V', E')$, $V' = V$, $E' = E \backslash E'$;
- $W' = (w'_{ij})$, $w'_{ij} = w_{ij}$ if $(j, i) \notin E^-$ and $w'_{ij} = 0$ otherwise;
- $b' = b$.

If for all $j \in V'$, $|\Gamma^-_{G'}(j)| > 0$, then there exists a circuit (it can even be a loop) in G′ what is by hypothesis negative. This is impossible by construction of G′, hence there exists one node l such that, $\Gamma^-_{G'}(l) = \phi$ which means that $\text{sign}(w_{lk}x_k) \neq x_l$, for all $k \in \Gamma^-_G(l)$ and therefore if $x_l = 1$, then

$$\sum_k w_{lk}x_k = -\sum_k |w_{jk}|$$

which implies that $\sum_k w_{lk}x_k - b_l < 0$. Hence, x_l is not a fixed component on x, which is a contradiction. The same argument we can apply if $x_l = -1$. Therefore, the vector x is not a fixed point of N. ■

C. Minimal Regulatory Networks

The previous results allow us to characterize some minimal regulatory networks. The following propositions constitute one example.

Proposition 2: Let N be a DSRN with n nodes and n connections, a necessary and sufficient condition for the existence of a fixed point x is the existence of a positive circuit. In this case, x and $-x$ are both fixed points.

Proof: The proof is an immediate consequence of Theorems 1 and 2, and the fact that G has only one circuit.

In this way, given a vector x, we can characterize the set of minimal N's having x as fixed point. ■

Proposition 3: Given a vector x, the set of DSRNs $N = (G, W, b, \text{sign})$ with $|V| = |E| = n$, having x as fixed point is given by the following conditions:

1) $w_{ij} = \alpha_{ij}x_ix_j$, where $\alpha_{ij} \geq 0$ and, for all i, there exists a unique j(i) such that $\alpha_{ij(i)} \neq 0$;
2) $-|\alpha_{ij(i)}| < b_i \leq |\alpha_{ij(i)}|$.

Proof: The proof is straightforward of Theorems 1 and 2 and the hypothesis of quasiminimal structure of G. ■

D. Fixed Points Bounds in Regulatory Networks

Theorem 3: If m is the total number of positive circuits of N, then the number of fixed points of N is less or equal than 2^m. And this upper bound is reached.

Proof: Let us denote by $C^+ = \{C1, C2, \ldots Cm\}$ the set of positive circuits of G. Let $f: \{x \,|\, x \text{ is a fixed point of } N\} \rightarrow \{-1, 1\}^{|C+|}$ be a function defined by

$$f(x) = \left(x_{i(C1)}, x_{i(C2)}, \ldots, x_{i(Cm)}\right)$$

where $i(Ck) = \min\{i \,|\, i \in Ck\}$ for all $k = 1, \ldots, m$.

Let us prove that the function f is injective.

Let $x^1, x^2 \in \{-1, 1\}^n$ be two fixed points of N such that $f(x^1) = f(x^2)$.

Let us define the partition V1, V2 of V as follows:

$$V1 = \{j \in V \,|\, x^1_j = x^2_j\}, \qquad V2 = \{j \in V \,|\, x^1_j \neq x^2_j\}.$$

Let us observe that all nodes $i(Ck)$, $k = 1, \ldots, m$, are in V1. Let us suppose that $V2 \neq \phi$. Fix $j(0) \in V2$ and let us assume with not loss of generality that $x^1_{j(0)} = 1$ and therefore $x^2_{j(0)} = -1$. Hence, there exists $j(1) \in \Gamma^-_G(j(0))$, such that $\text{sign}(w_{j(0)j(1)}x^1_{j(1)}) = 1$, but in addition we can choose $j(1) \in V2$. In this case that $x^1_{j(0)} = -1$ and therefore $x^2_{j(0)} = 1$. We can use analogous arguments to prove that there exists $j(1) \in \Gamma^-_G(j(0)) \cap V2$, such that $\text{sign}(w_{j(0)j(1)}x^1_{j(1)}) = x^1_{j(0)}$.

In this way, we can construct inductively a sequence (eventually constant) of nodes $j(0), j(1), \ldots$ belonging to V2 such that $\text{sign}(w_{j(k-1)j(k)}x^1_{j(k)}) = \text{sign}(x^1_{j(k-1)})$ for all k, therefore there exsts a circuit C in C^+ with nodes in V2, such that $x^1_{i(C)} \neq x^2_{i(C)}$, which is a contradiction with the fact that the node i(C) is in V1. Therefore, the function f is injective and $|\{x \,|\, x \text{ is fixed point of } N\}| \leq |\{-1, 1\}|^m = 2^m$.

Let us now see one family of DSRN where the bound is reached.

Let $N_n = (G_n, W_n, b_n, \text{sign})$ be a DSRN defined by

— $G_n = (V_n, E_n)$, $V_n = \{1, 2, \ldots, n\}$ and
— $E_n = \bigcup_{k=1}^{(n-1)/2}\{(2k-1, 2k)\} \cup \{(2k, 2k-1)\} \cup \{(2k, n)\}$;
— $W_n = (w_{ij})_{i,j=1,\ldots,n}$ $w_{ij} = 1$, if $(j, i) \in E_n$, and $w_{ij} = 0$ otherwise;
— $b_n = 0$.

It is easy to check that N_n has $2^{(n-1)/2}$ fixed points and the number of positive circuits is equal to $(n-1)/2$, so the bound is reached. ■

Remark: We have to notice that the condition concerns the number of circuits and not of cycles, these last being in general very more numerous.

E. Asymptotic Mean Value for the Number of Attractors in Case of Connectivity Coefficient K *Equal to 2*

Let us consider now a network N having n nodes and 2n connections such as its Kauffman's connectivity coefficient $K = 2$ (K being just the ratio between the number of connections and the number of nodes). We will now search for a mean value of the number of attractors of N, when n is growing to infinity.

Lemma 1: For any graph G having m non oriented arcs, the mean number of oriented arcs we can define on G from the nonoriented configuration is equal to $4m/3$.

Proof: Let us note $\langle o \rangle$ the mean number of oriented arcs we can construct from a configuration of m non oriented arcs; then, if exactly k from the m non oriented arcs are decomposed into two oriented opposite connections, we have $C_m^{m-k}2^{m-k}$ different ways to dispatch the not double connections into the $(m-k)$ other nonoriented arcs; hence we can write

$$\langle o \rangle = \sum_{k=0}^{m} (k+m) C_m^{m-k} 2^{m-k} \Bigg/ \sum_{k=0}^{m} C_m^{m-k} 2^{m-k} = 4m/3$$

Theorem 4: If the network N has n nodes and Kn connections, with $K = 2$, then the expectation of the number attractors of N is $O(n^{1/2})$, if n is sufficiently large.

Proof: Following [22], if the connections of N are random, and if the mean number c of non oriented arcs per node is equal to 3/2, then the random variables X_i equal to the number of disjoint cycles of length i of N are independent and Poissonnian with parameter $\lambda(i) = 2^{i-1}/i$, if n is sufficiently large. From Lemma 1, we are just in this case, because we have $2n = 4m/3$ connections, hence we have $m = 3n/2$ and $c = m/n = 3/2$. Then we have, for the mean number $\langle f \rangle$ of the attractors of N

$$\langle f \rangle = \sum_{s=0}^{n} \sum_{k=s}^{n} \sum_{\sigma \in \Omega(s,k)} A(\sigma) \Pi_\sigma$$

where

$$\Omega(s,k) = \left\{ \sigma = (s(1), \ldots, s(n))/s(i) \geq 0 \; \sum_{i=1}^{n} s(i) = s, \sum_{i=1}^{n} i s(i) = k \right\}$$

$$\Pi_\sigma = P\left(\left\{ X_i = s(i), s(i) \geq 0, \sum_{i=1}^{n} s(i) = s \; \sum_{i=1}^{n} i s(i) = k \right\} \right)$$

$$= e^{\Sigma\lambda(i)} \prod_{i=1}^{n} \lambda(i)^{s(i)}/s(i)!$$

is the probability to have the X_i's equal each to s(i), and $A(\sigma)$ is the mean number of attractors, when the X_i's equal each to s(i).

We will now evaluate the expectation $A(\sigma)$. Each disjoint positive circuit bringing 2 fixed points (Theorem 3 above), an isolated positive noncircuit cycle bringing also 2 fixed points and a isolated negative circuit bringing one cyclic attractor, we can first calculate $A(0, \sigma)$, the expected number of attractors in the case where we have only disjoint positive circuits C's, the rest of the nodes being in $\Gamma_G^+(i)$, $i \in C$'s (and hence their states being fixed by the states of the circuit):

— $A(0, \sigma) = B(0, \sigma)/D(\sigma)$, where

— $B(0, \sigma) = 2^s$ [number of fixed points of $s = \sum_{i=1}^{n} s(i)$ disjoint positive circuits, from Theorem 3 above] $\times 2^k$ [number of different signs for each of the $k = \sum_{i=1}^{n}$ is (i) connections] $\times$ [2^s (number of different directions—left or right—for each of the s circuits)/2^s (reduction factor for having only positive circuits)] $\times N(\sigma)$,

— $D(\sigma) = 2^k$ (number of different directions for each of the k connections) $\times 2^k$ (number of different signs for each of the k connections) $\times N(\sigma)$, where $N(\sigma)$ is the number of choices for the s disjoint cycles:

$$N(\sigma) = \left(C_n^{s(1)1 \cdots s(n)n} \prod_{i=1}^{n} (i-1)!^{s(i)} \right) \Bigg/ 2^s.$$

$N(\sigma)$ is just equal to the number of choices of k nodes dispatched in s(1) subsets of size 1, …, and s(n) subsets of size n multiplied by the number of choices of different loops (without multiple points) connecting the vertices inside each of these subsets.

In the same way, we can calculate $A(1, \sigma)$ [resp. $A(j, \sigma)$] the expected number of attractors of N in the case where we have among the s disjoint cycles 1 (resp. j) isolated positive noncircuit cycles (bringing 2 attractors) or isolated negative circuits (bringing 1 attractor).

We have

$$A(1, \sigma) = B(1, \sigma)/D(\sigma)$$

where

$$\begin{aligned} B(1, \sigma) = {} & 2^{s-1}(2^{s-1}/2^{s-1})N(\sigma) \\ & \cdot [2^{k-1}s(1)(2^1 2^1 2^1 + 2^1 2^1 - 2^1 2^1 2^1)/2^1 \\ & + \cdots + 2^{k-i}s(i)(2^1 2^i 2^i + 2^i 2^1 - 2^1 2^i 2^1)/2^1 \\ & + \cdots + 2^{k-n}s(n)(2^1 2^n 2^n + 2^n 2^1 - 2^1 2^n 2^1)/2^1] \end{aligned}$$

where $s(i)2^1 2^i 2^i/2^1$ is just the number (2^1) of fixed points of 1 positive cycle (circuit or not) of length i times the number of such configurations $s(i)2^i 2^i/2^1$, $s(i)2^i 2^1/2^1$ is the number (1) of attractors of 1 isolated negative circuit of length i times the number of such configurations $s(i)(2^i 2^1/2^1)$ and $-s(i)2^1 2^i 2^1/2^1$ is the number (2^1) of fixed points of 1 positive circuit [already counted in $B(0, \sigma)$] times the number of such configurations $s(i)(2^i 2^1/2^1)$; $2^{s-1}(2^{s-1}/2^{s-1})N(\sigma)2^{k-i}$ is equal to the number of configurations of $s-1$ positive circuits with s(1) of length 1, …, $s(i)-1$ of length i, …, s(n) of length n. Then we have:

$$A(2, \sigma) = B(2, \sigma)/D(\sigma)$$

where

$$\begin{aligned} B(2, \sigma) = {} & 2^{s-2}(2^{s-2}/2^{s-2})N(\sigma)[2^{k-2}s(1)^2 \\ & \cdot (2^2 2^2 2^2 - 2(2^2 2^2 2^1 - 2^1 2^2 2^1) + 2^2 2^1)/2^2 \\ & + \cdots + 2^{k-i-j}s(i)s(j)(2^2 2^{i+j} 2^{i+j} - (2^2 2^{i+j} 2^i 2^1 \\ & - 2^1 2^{i+j} 2^i 2^1) - (2^2 2^{i+j} 2^j 2^1 \\ & - 2^1 2^{i+j} 2^j 2^1) + 2^{i+j} 2^2)/2^2 \\ & + \cdots + 2^{k-2n}s(n)^2(2^2 2^{2n} 2^{2n} - 2(2^2 2^{2n} 2^n 2^2 \\ & - 2^1 2^{2n} 2^n 2^2) + 2^{2n} 2^2)/2^2], \end{aligned}$$

where

$$s(i)s(j)(2^2 2^{i+j} 2^{i+j} - (2^2 2^{i+j} 2^i 2^2 - 2^1 2^{i+j} 2^i 2^2) - (2^2 2^{i+j} 2^j 2^2 - 2^1 2^{i+j} 2^j 2^2) + 2^{i+j} 2^2)/2^2$$

is just the number of attractors of a couple made of positive not circuit cycles or negative circuits, the $s-2$ remaining cycles being positive circuits, by paying attention to the fact the attractors of the couples of a positive not-circuit cycle combined with a positive circuit [in number equal to $s(i)s(j)2^2 2^{i+j}(2^i + 2^j)2^2$] have been already counted both in $B(1, \sigma)$ and in $B(0, \sigma)$ and hence have to be taken away (by using the sign $-$) from the sum $s(i)s(j)(2^2 2^{i+j} 2^{i+j} + 2^1 2^{i+j} 2^i 2^1 + 2^1 2^{i+j} 2^j 2^1 + 2^{i+j} 2^2)/2^2$.

Finally, more generally, we have

$$A(j, \sigma) = B(j, \sigma)/D(\sigma)$$

where

$$\begin{aligned} &B(j, \sigma) \\ &= 2^{s-j}(2^{s-j}/2^{s-j})N(\sigma) \Big/ \sum_{\xi \in I} 2^{k-r(\zeta)} \\ &\quad \cdot \Bigg[2^j 2^{r(\zeta)} 2^{r(\zeta)} + \sum_{m=1}^{j} 2^{j-1} 2^{r(\zeta)-i(m)} 2^{r(\zeta)-i(m)} \\ &\quad \cdot \left(2^{i(m)} 2^1 - 2^1 2^{i(m)} 2^1 \right) + \cdots + \sum_{\xi=(m(1),\ldots,m(v)) \in \{1,\ldots,n\}^v} \\ &\quad \cdot 2^{j-v} 2^{r(\zeta)-r(\xi)} 2^{r(\zeta)-r(\xi)} \\ &\quad \cdot \left(2^{r(\xi)} 2^v - v \left(2^{v-1} 2^{r(\xi)} 2^v - 2^{v-2} 2^{r(\xi)} 2^v \right) + v(v-1) \right. \\ &\quad \cdot \left(2^{v-2} 2^{r(\xi)} 2^v - 2.2^{v-3} 2^{r(\xi)} 2^v + 2^{v-4} 2^{r(\xi)} 2^v \right) \Big/ 2 \\ &\quad \left. + \cdots + (-1)^v 2^v 2^{r(\xi)} 2^v \right) + \cdots + (-1)^j 2^j 2^{r(\zeta)} \Big) \Big/ 2^j \Bigg] \\ &= 2^{s-j}(2^{s-j}/2^{s-j})N(\sigma) \sum_{I} \prod_{t=1}^{j} \left(2^{i(t)-1} - 1/2 \right)^{u(i(t))} \end{aligned}$$

where $I = \{\zeta = (i(1), \ldots, i(j)) \in \{1, \ldots, n\}^j / \forall t = 1, \ldots, j$, the number $u(i(t))$ of cycles of size $i(t)$ satisfies: $0 < u(i(t)) \leq s(i(t))$, and $j = \sum_{t=1}^{j} u(i(t))\}$, and $r(\zeta) = \sum_{t=1}^{j} i(t)$, and $2^j 2^{r(\zeta)} 2^{r(\zeta)}/2^j$ is just the number (2^j) of fixed points of j positive cycles (circuits or not) of lengths $i(1), \ldots, i(j)$ multiplied by the number of such configurations of j positive cycles $(2^{r(\zeta)} 2^{i(1)+\cdots i(j)}/2^j)$, and

$$\sum_{m=1}^{j} 2^{j-1} 2^{r(\zeta)-i(m)} 2^{r(\zeta)-i(m)} \left(2^{i(m)} 2^1 - 2^1 2^{i(m)} 2^1 \right) \Big/ 2^j$$

being just the number of attractors in a configuration where we have 1 negative circuit of length $i(m)$ among the $(j-1)$ other positive cycles (circuits or not) diminished by the number of the configurations having $(j-1)$ positive non circuit cycles and $(k-j+1)$ positive circuits [already counted in $B(j-1, \sigma)$]. The other terms of $B(j, \sigma)$ correspond to the number of attractors of the configurations having $(k-j)$ positive circuits and j either positive non circuit cycles or negative circuits, diminished by the number of already counted attractors in the $B(m, \sigma)$'s, for $m < j-1$, and not yet taken away. To finish the calculation of $B(j, \sigma)$

$$\begin{aligned} &2^{k-r(\zeta)} \Bigg[\sum_{\xi=(m(1),\ldots,m(v)) \in \{1,\ldots,n\}^v} 2^{j-v} 2^{r(\zeta)-r(\xi)} 2^{r(\zeta)-r(\xi)} \\ &\quad \cdot \left(2^{r(\xi)} 2^v - v \left(2^1 2^{r(\xi)} 2^v - 2^{r(\xi)} 2^v \right) \right. \\ &\quad \left. + v(v-1) \left(2^2 2^{r(\xi)} 2^v - 2^1 2^{r(\xi)} 2^v + 2^{r(\xi)} 2^v \right) \Big/ 2 \right. \\ &\quad \left. + \cdots + (-1)^v 2^v 2^{r(\xi)} 2^v \right) \Bigg] \Big/ 2^j \\ &= \sum_{\xi=(m(1),\ldots,m(v)) \in \{1,\ldots,n\}^v} 2^v 2^k 2^{r(\zeta)-r(\xi)} (1/2 - 1)^v \\ &= \sum_{\xi=(m(1),\ldots,m(v)) \in \{1,\ldots,n\}^v} 2^k 2^{r(\zeta)-r(\xi)} (-1)^v. \end{aligned}$$

By summing the $A(j, \sigma)$'s and after the $A(\sigma).\Pi_\sigma$'s, it is then possible to show that $\langle f$ is of the order of $n^{1/2}$

$$\begin{aligned} \langle f \rangle &= \sum_{\sigma=0}^{n} \sum_{k=s}^{n} \sum_{\sigma \in \Omega(s,k)} e^{-\Sigma\lambda(i)} \prod_{i=1}^{n} \lambda(i)^{s(i)}/s(i)! \\ &\quad \cdot \sum_{j=0}^{n} A(j, \sigma) \\ &= \sum_{\sigma=0}^{n} \sum_{k=s}^{n} \sum_{\sigma \in \Omega(s,k)} e^{-\Sigma\lambda(i)}/s! \left(s! \Big/ \prod_{i=1}^{n} s(i)! \right) K_\sigma \end{aligned}$$

where

$$\begin{aligned} K_\sigma &= 2^{s-k} \prod_{i=1}^{n} \lambda(i)^{s(i)} (2^{i-1} - 1/2 + 1)^{s(i)} \\ &= \prod_{i=1}^{n} (2^i/i)^{s(i)} (1 + 1/2^i)^{s(i)} \end{aligned}$$

and

$$\begin{aligned} \sum_{i=1}^{n} \lambda(i) &= \left(\sum_{i=1}^{n} 2^i \Big/ i \right)/2 \\ &= \sum_{i=1}^{n} \int_0^2 x^{i-1}\, dx/2 = O(2^{n-1}). \end{aligned}$$

Then, we have

$$\begin{aligned} \langle f \rangle &\sim \sum_{s=0}^{n} e^{-\Sigma\lambda(i)} \left(\sum_{i=1}^{n} \lambda(i) + \mathrm{Log} n/2 \right)^s \Big/ s! \\ &= O\left(\sqrt{n}\right). \end{aligned}$$

■

Remark: We have to notice that the Theorem 4 corresponds to the proof of the Kauffman's conjecture [16], approximately verified as we have already said for the human genome and for the *Arabidopsis* genome.

VI. Conclusion

By introducing interaction matrices expressing negative (repression) and positive (promotion) relationships between genes, we have shown that ubiquitory genes can play a role in the weak part (hot spot) configurations along human chromosomes. This role can be crucial, because the environment can cause the ex-

pression of ubiquitory genes responsible for the control of basic metabolisms (mitochondrial respiration, glycolytic and lipidic control, membrane, and cyto-skeleton formation). Certain previous arguments (like the richness of chromosomic hot spots in Alu G-C sequences and methylated parts of the genome) already pushed in the same direction. We have now to confirm this hypothesis by systematically exploring all possible genes interactions and after by calculating all asymptotic behaviors permitted by the interaction matrices for expression configurations, allowing the determination of the ubiquitory genes expression histograms. By refining also the location of the chromosomic break points, we will be able to confront more precisely these histograms with all weak points histograms in order to reinforce or falsify the central hypothesis of our paper.

An other important conclusion we have made explicit in this paper concerns the relationship between the number F of fixed points and the number S of interaction circuits of the interaction matrix W: the problem is in fact to find the best upper bound for F for a given interaction matrix W. This question is the discrete translation of the famous XVIth Hilbert's problem (the VIIIth problem of the recent Smale classification) of determining an efficient upper bound for the number of limit cycles of a polynomial differential system. Let us summarize the role of the architecture of positive and negative circuits of W on the occurrence of multiple stationary behaviors as obtained above: if the number of nodes and the number of arcs are the same, there is only one isolated interaction circuit $(S = 1)$ in W and either this circuit is negative and the lowest bound (0) for F is reached, or this circuit is positive and the upper bound (2^1) for F is reached. If the number of nodes is n and the number of arcs is $n + 1$, there is two interaction circuits $(S = 2)$ with the following structure: if both circuits are negative, $F = 0$; if there is a positive circuit and a negative circuit disjoint, $F = 0$; if there is a positive circuit intersecting a negative circuit, $F = 1$; if there is a positive circuit intersecting a positive circuit, $F = 1$; if there is two disjoint positive circuits, $F = 2^2$. If more generally the number S of interaction circuits of W is m, then: if all circuits are negative, $F = 0$; if all circuits are positive, $2 \leq F \leq 2^m$ and if, and only if, all circuits are positive and disjoint, $F = 2^m$.

An interesting open problem is now to make exhaustive the determination of F and S and in particular to find the circumstances (related to the circuits structure) in which we can relate the number of intersecting and isolated circuits to F. The approach for solving this open problem could consist first in finding coherent relationships between analogous properties discovered for continuous versions of the regulatory networks and for general Boolean networks. The second conclusion concerns the practical use of the presented results; a genetician can for example exploit the minimality results in the following sense, i.e., we have shown in the paper that it would be possible to characterize the minimal interaction matrices having certain state vectors as fixed points. The determination of these matrices is not unique, but permits to focus on certain important equivalence classes in which the expected matrix has to belong. This considerably restricts the choice of the possible interaction matrices compatible with observed fixed points, when it is impossible to directly get from experiments all interaction coefficients, but when it is only possible to observe the phenomenology of fixed points or limit cycles. This corresponds in genetics to the phenotypic observation of stationary expression behaviors without experimental measure of all the inhibitory and activatory coefficients of promoters and repressors. The possibility to obtain (even in an equivalence class) a sketch of the interaction matrix permits to construct (by randomizing in a Bayesian way the unknown coefficients of W) more complicated interaction matrices than the observed one, then to test if they still have the observed states as fixed points and finally keep or reject definitively the so tested matrices and propose further experimental strategies (e.g., using the bio-arrays instrumentation [23] and [24] for refining the knowledge about the interaction structure of the genetic regulatory network (see [25]).

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