R. Thomas' logical method

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1 Introduction

To face the frequent lack of quantitative data on the behavior of gene networks, Thomas introduced in the 70's a boolean method allowing to capture the main qualitative features of the dynamics of such systems [48]. He proved its usefulness in the context of lambda phage genetic switch [48, 55, 50, 49, 54, 47]. The boolean idealization being frequently too caricatural to give realistic dynamical models, later on, he generalized his formalism to multivalued levels of expression [54, 52, 56]. The Thomas' method has been used to model a number of genetic systems, for instance involved in the embryonic development of *Drosophila melanogaster* [40, 38, 39], the flowers morphogenesis in *Arabidopsis thaliana* [22], or the immune response [19, 18, 54, 23, 21].

Thomas describes gene networks in terms of graphs. On one hand, the *topology* of a network is described by an *interaction graph*: nodes correspond to genes, and arcs to their interactions (either positive or negative). On the other hand, the *dynamics* of the network is described by a *state transition graph*: the set of nodes (which is finite) corresponds to the possible states for the network, and the edges correspond to transitions of state which can occur with time. In practice, the dynamics are derived from the interaction graph thanks to *logical parameters* describing the strength of the interactions.

In this note, we briefly present the Thomas' logical method, using mostly the definitions of [5]. We then focus on the problem of the determination of the value of the logical parameters. These are indeed most often unknown and difficult to extract from experimental data. First, we show that some information about the dynamics of a network can be inferred from its interaction graph, in the absence of information on the value of parameters. Then, we present a computational approach, based on formal methods, for the determination of parameters which define dynamics coherent with the known or hypothetical behaviors of the system.

2 Generalized logical method

We are interested by the evolution of a gene network containing n genes. These are identified to integers from 1 to n.

2.1 Interaction graph and sigmoidal regulations

The topology of the network is described by an *interaction graph* G: the nodes correspond to the genes, and each edge $a \to b$ is labelled by a sign s_{ab}. A positive (resp. negative) sign means a is an *activator* (resp. *inhibitor*) of b. Figure 1 gives an example of interaction graph.

If a is an activator of b, then an increase of the concentration of the protein A encoded by gene a induces, generally following a sigmoidal curve, an increasing of the rate of synthesis of the protein encoded by b [58, 54, 10]. So A has a quasi null effect on gene b if the concentration of A is below a threshold θ_{ab} (corresponding to the inflection point of the sigmoid) and a quasi saturated effect above it. If a is an inhibitor of b, the sigmoid is decreasing. The presence of thresholds leads to a natural discretization of concentrations described in Figure 2. This discretization is at the basis of the logical method.

2.2 States and thresholds

Because of the sigmoidal nature of genetic regulations and the resulting discretization, we associate to each gene a a finite interval of integers

$$X_a = \{0, \ldots, b_a\}$$

which corresponds to the possible discrete *levels* of concentration for the protein A. In the following, we just say that X_a is the set of possible levels for a. The set of possible *states* for the network is then $X = X_1 \times \cdots \times X_n$. The level of a at state $x = (x_1, \ldots, x_n) \in X$ is given by the component $x_a \in X_a$. In the boolean case, $b_a = 1$ so a is either present ($x_a = 1$) or absent ($x_a = 0$).

We also associate to each interaction $a \to b$ a *logical threshold*

$$\theta_{ab} \in \{1, \ldots, b_a\}.$$

At state x, the interaction $a \to b$ is *effective* if and only if $x_a \geq \theta_{ab}$. The set of *effective regulators* of a at state x is then

$$\omega_a(x) = \{b \in G_a : x_b \geq \theta_{ba}\},$$

where G_a denotes the set of predecessors of a in the interaction graph G.

The interaction graph G together with the bounds b_a and the thresholds θ_{ab} forms a *regulatory graph* $\mathcal{G}$ (see Figure 3). Given such a graph, we know the set of states of the network (thanks to the bounds), and we know, at each state, which are the effective regulators (thanks to G and the thresholds).

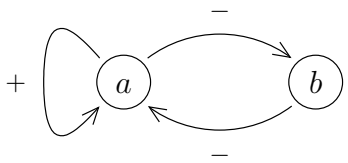


Figure 1: An interaction graph G.

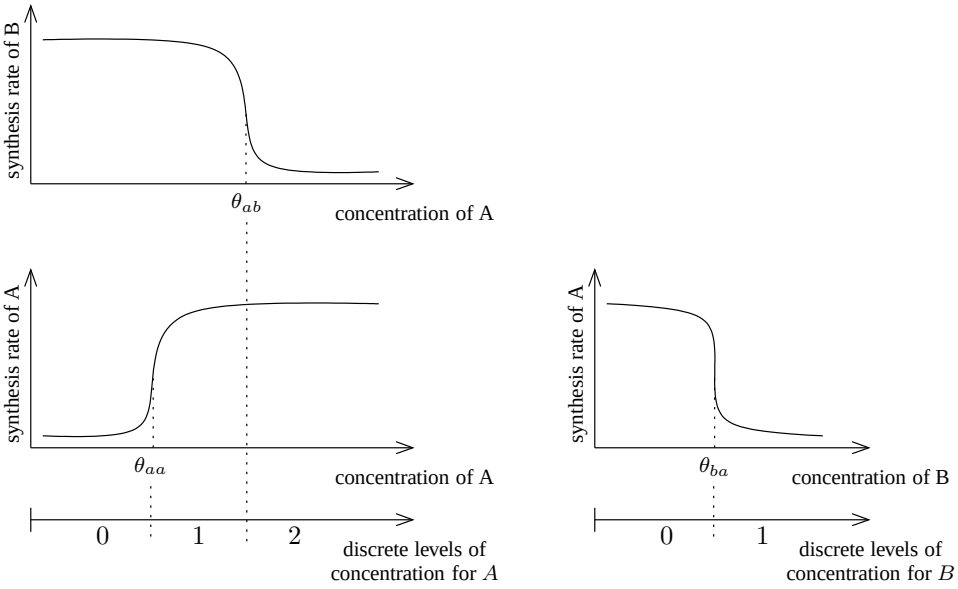


Figure 2: Sigmoid regulations for the interaction graph of Figure 1 and the corresponding discretization of concentrations. The alternative case where $\theta_{ab} < \theta_{aa}$ leads also to three possible discrete levels of concentration for A. The singular case where $\theta_{aa} = \theta_{ab}$ leads to only two possible discrete levels of concentration for A (0 and 1).

2.3 Logical parameters

At state $x \in X$, the evolution of the level x_a only depends on the set of effective regulators $\omega_a(x)$. The effect of $\omega_a(x)$ on the evolution of x_a is described by a *logical parameter*

$$k_a(\omega_a(x)) \in X_a.$$

This parameter corresponds to the level toward which x_a evolves:

1. If $x_a < k_a(\omega_a(x))$ then x_a is increasing.
2. If $x_a > k_a(\omega_a(x))$ then x_a is decreasing.
3. If $x_a = k_a(\omega_a(x))$ then x_a is stable.

A *parameterization* of $\mathcal{G}$ is then a map k which associates to each gene a and to each set of predecessors $R \subseteq G_a$ an integer $k_a(R) \in X_a$. Figure 4 gives an example of parameterization.

Activatory and inhibitory effects are encoded by *constraints on parameters*:

1. If b is an activator of a, we must have:

$$\forall R \subseteq G_a, \qquad k_a(R) \leq k_a(R \cup \{b\});$$

2. If b is an inhibitor of a we must have:

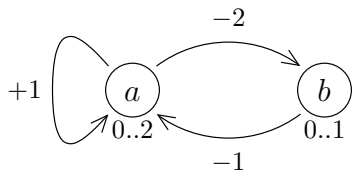
$$\forall R \subseteq G_a, \qquad k_a(R) \geq k_a(R \cup \{b\}).$$

These constraints mean that *the effectiveness of an activator of a cannot decrease the level toward which x_a evolves*, and that *the effectiveness of an inhibitor of a cannot increase the level toward which x_a evolves*. A parameterization satisfying these natural constraints is said *coherent* (see Figure 5).

2.4 Asynchronous state graph

Given a coherent parameterization k of $\mathcal{G}$, the dynamics of the network is finally explicitly described under the form of a directed graph on X called *asynchronous state graph* and denoted $\Gamma(\mathcal{G}, k)$: the set of nodes is the set of states X, and there is a *transition* (an edge) $x \to y$ if there exists a gene a such that $x_a \neq k_a(\omega_a(x))$ and such that:

$$\begin{aligned} y &= (x_1, \ldots, x_a + 1, \ldots, x_n) \quad \text{if } x_a < k_i(\omega_a(x)), \\ y &= (x_1, \ldots, x_a - 1, \ldots, x_n) \quad \text{if } x_a > k_i(\omega_a(x)). \end{aligned}$$



x_a	x_b	$\omega_a(x)$	$\omega_b(x)$
0	0	$\emptyset$	$\emptyset$
0	1	$\{b\}$	$\emptyset$
1	0	$\{a\}$	$\emptyset$
1	1	$\{a,b\}$	$\emptyset$
2	0	$\{a\}$	$\{a\}$
2	1	$\{a,b\}$	$\{a\}$

Figure 3: A regulatory graph $\mathcal{G}$ derived from the interaction graph G of Figure 1 (the bounds are $b_a = 2$ and $b_b = 1$; the thresholds are $\theta_{aa} = 1$, $\theta_{ab} = 2$ and $\theta_{ba} = 1$). The table gives the set of effective regulators of a and b according to the state $x = (x_a, x_b)$ of the network.

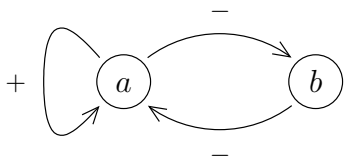
Parameterization k

$$k_a(\emptyset) = 2$$
$$k_a(\{a\}) = 2 \qquad k_b(\emptyset) = 1$$
$$k_a(\{b\}) = 0 \qquad k_b(\{a\}) = 0$$
$$k_a(\{a,b\}) = 0$$

Corresponding tendencies

x_a	x_b	$k_a(\omega_a(x))$	$k_b(\omega_b(x))$
0+	0+	$k_a(\emptyset) = 2$	$k_b(\emptyset) = 1$
0	1	$k_a(\{b\}) = 0$	$k_b(\emptyset) = 1$
1+	0+	$k_a(\{a\}) = 2$	$k_b(\emptyset) = 1$
1−	1	$k_a(\{a,b\}) = 0$	$k_b(\emptyset) = 1$
2	0	$k_a(\{a\}) = 2$	$k_b(\{a\}) = 0$
2−	1−	$k_a(\{a,b\}) = 0$	$k_b(\{a\}) = 0$

Figure 4: A parameterization k for the regulatory graph $\mathcal{G}$ of Figure 3. In the table, a sign $+$ (resp. $-$) is associated to expression levels which are increasing (resp. decreasing). The absence of sign denotes the stability.



$$k_a(\{b\}) \leq k_a(\emptyset) \leq k_a(\{a\})$$
$$k_a(\{b\}) \leq k_a(\{a,b\}) \leq k_a(\{a\})$$
$$k_b(\{a\}) \leq k_b(\emptyset)$$

Figure 5: Constraints on the parameters induced by the sign of the interactions. The parameterization of Figure 4 satisfies these constraints.

This description of the dynamics is based on the fact that evolution of each expression level needs a delay since it involves complex biological phenomena which are not instantaneous. These delays are most often unknown, but they are a priori mutually distinct. In these conditions, if $x_a \neq k_a(\omega_a(x))$, the delay that x_a needs to evolve may be the smallest, and this case is taken into account through the presence of a transition from x to

$$(x_1, \ldots, x_a + 1, \ldots, x_n) \quad \text{or} \quad (x_1, \ldots, x_a - 1, \ldots, x_n)$$

according to whether $x_a < k_a(\omega_a(x))$ or $x_a > k_a(\omega_a(x))$. Since delays are supposed distinct, at each step, there is only one gene whose expression level evolves. This is why the state graph is said asynchronous. (The fact that expression levels evolve per unit is inspired from continuous descriptions.) Figure 6 gives an example of asynchronous state graph.

2.5 Stable states and attractors

The states x without successor in $\Gamma(\mathcal{G}, k)$ are of particular interest: they correspond to the *stable states* of the network. In Figure 6, there are two stable states, and all the paths lead to one of them. This describes a simple epigenetic switch. The genes a and b inhibit each other. If a "wins" the system reaches the stable state 20, and if b "wins" the system reaches the stable state 01. If these stable stables correspond to different cellular behaviors, the dynamics mays describe a simple differentiation process.

There are other interesting regions of stability in $\Gamma(\mathcal{G}, k)$ called trap domain and attractors. A *trap domains* is a subset of states $T \subseteq X$ such that, for all transitions $x \to y$, if $x \in T$ then $y \in T$. A trap domain is thus a set of states that we cannot leave. An *attractor* is a smallest trap domain with respect to the inclusion relation (see Figures 7 and 8).

The notion of attractor extends the notion of stable state since x is a stable state if and only if $\{x\}$ is an attractor. Other easy observations follow (the second show why, in a weak sense, attractors perform an attraction):

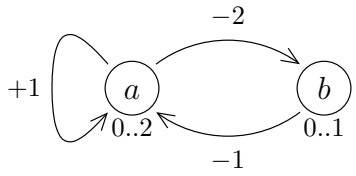
1. There is always at least one attractor (since X is itself a trap domain).

2. From each state, there is at least one path which leads to an attractor.

3. Attractors are strongly connected components (if x and y belong to the same attractor, then there is a path from x to y and a path from y to x).

4. Attractors are mutually disjointed.

Regulatory graph $\mathcal{G}$



Coherent parameterization k

$k_a(\emptyset) = 2$
$k_a(\{a\}) = 2$ $\quad$ $k_b(\emptyset) = 1$
$k_a(\{b\}) = 0$ $\quad$ $k_b(\{a\}) = 0$
$k_a(\{a,b\}) = 0$

Corresponding tendencies

x_a	x_b	$k_a(\omega_a(x))$	$k_b(\omega_b(x))$
$0+$	$0+$	$k_a(\emptyset) = 2$	$k_b(\emptyset) = 1$
0	1	$k_a(\{b\}) = 0$	$k_b(\emptyset) = 1$
$1+$	$0+$	$k_a(\{a\}) = 2$	$k_b(\emptyset) = 1$
$1-$	1	$k_a(\{a,b\}) = 0$	$k_b(\emptyset) = 1$
2	0	$k_a(\{a\}) = 2$	$k_b(\{a\}) = 0$
$2-$	$1-$	$k_a(\{a,b\}) = 0$	$k_b(\{a\}) = 0$

Corresponding asynchronous state graph $\Gamma(\mathcal{G}, k)$

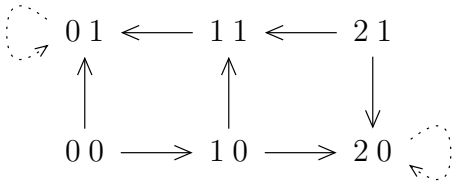


Figure 6: Asynchronous state graph $\Gamma(\mathcal{G}, k)$ associated to the regulatory graph $\mathcal{G}$ and the coherent parameterization k (which is the one of Figure 4).

In Figure 7, the asynchronous state graph contains two attractors, and this situation may also described an epigenetic switch. Note that one of the attractor is not a stable state. Such an attractor is said *cyclic* since it necessarily contains cycles (according to the third point). When the system is in a cyclic attractor, it never reaches a stable state and describes sustained oscillations by following, ad infinitum, the cycles of the attractors. Such oscillations are observed in homeostatis phenomena [53].

Summing up, the main properties of the dynamics often concern the attractors, their number, their relative positions, their nature (stable state, cyclic), and their reachability from a set of potential initial states.

3 "Theoretical" and "computational" tools

3.1 Positive and negative circuits

In practice, the logical parameters (and the logical thresholds) are most often unknown. An interesting question is then: which dynamical properties of a gene network can be inferred from its interaction graph, in the absence of information on the value of parameters? This question can be partially solved by studying positive and negative circuits of the interaction graph G.

A circuit in G is *positive* if it contains an even number of inhibitions, and *negative* otherwise. The sign of a circuit is thus the product of the sign of its edges. For instance, the interaction graph of Figure 1 has two positive circuits, and the one of figure 7 has one positive circuit and two negative circuits.

René Thomas highlighted the predominant dynamical role of positive and negative circuits by stating the following two conjectures [51]:

1. A necessary condition for the presence of *several stable states* is the presence of a *positive circuit* in G.

2. A necessary condition for the presence of *sustained oscillations* is the presence of a *negative* circuit in G.

These conjectures are transversal to the considered framework in the sense that they have been proved in differential frameworks [24, 14, 43, 8, 45, 46, 17], in boolean frameworks [25, 2, 29] and discrete frameworks [46, 28, 30, 34, 31]. The obvious interest of these two rules is that they relate the rather simple information contained in the interaction graph G of a network to its much more complex dynamical behaviors.

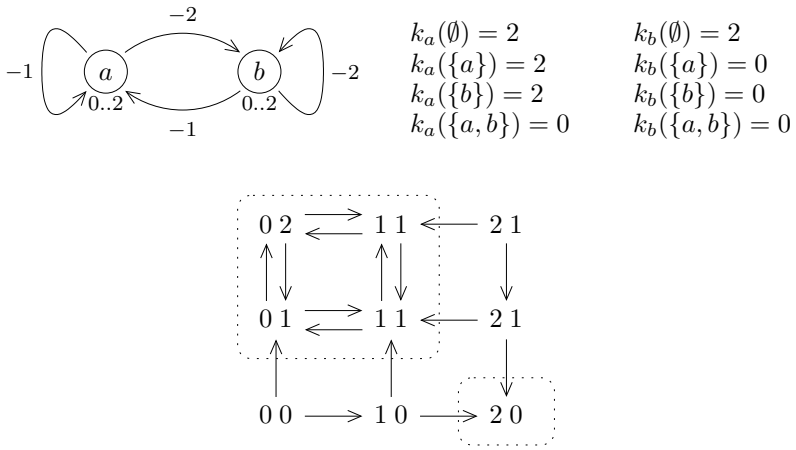


Figure 7: An asynchronous state graph with two attractors.

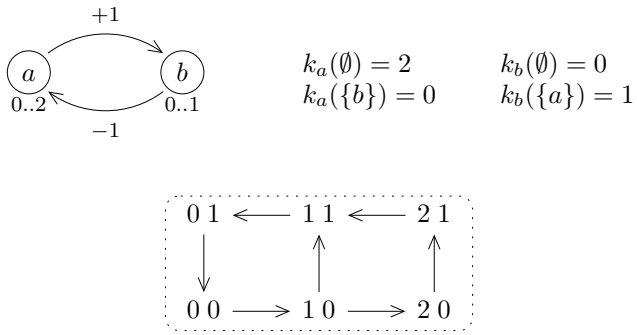


Figure 8: An asynchronous state graph with one cyclic attractor.

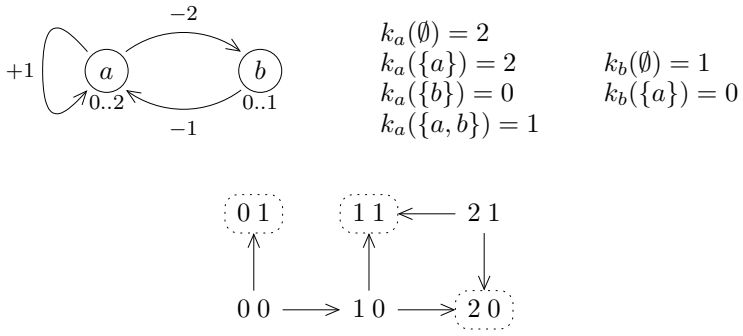


Figure 9: An asynchronous state graph with 3 stable states.

With our notations, the Thomas' conjectures take the following form:

Theorem [34, 31]: *For all interaction graph G, for all regulatory graph $\mathcal{G}$ built from G, and for all coherent parameterization k of $\mathcal{G}$:*

1. *If G has no positive circuit, then $\Gamma(\mathcal{G}, k)$ has at most one attractor.*
2. *If G has no negative circuit, then $\Gamma(\mathcal{G}, k)$ has no cyclic attractor.*

In fact, if G has no positive circuit, then $\Gamma(\mathcal{G}, k)$ contains a *unique* attractor, since $\Gamma(\mathcal{G}, k)$ always contains an attractor (see the first point in the previous section). We also deduce from this theorem that if G has no circuit, then $\Gamma(\mathcal{G}, k)$ has a unique attractor which is a stable state (conditions for the presence of a unique stable state are studied in [36, 37, 41, 32]).

The previous theorem is obviously satisfied by the given examples. In Figure 8, the interaction graph has no positive circuit, and there is indeed a unique attractor. In Figure 6, the interaction graph has no negative circuit, and there is no cyclic attractor. The interaction graph of Figure 7 contains positive and negative circuits. It is thus a priori possible to have several attractors and cyclic attractors.

It is also possible to extract from the interaction graph G information about the total number of attractors [1, 2, 33]. For instance, in the boolean case (all the bounds are equal to 1), if G has p positive circuits, it is known that $\Gamma(\mathcal{G}, k)$ has at most 2^p attractors. This bound can be significantly improved by taken into account *connections* between positive circuits. Roughly speaking, a high level of connection between the positive circuits leads to a small number of attractors. More precisely:

Theorem [33]: *If S is a set of genes such that all the positive circuits of G have a node in S, then $\Gamma(\mathcal{G}, k)$ has at most*

$$\prod_{a \in S} |X_a|$$

attractors.

So, for example, if all the positive circuits of G share a common node a, then $\Gamma(\mathcal{G}, k)$ has at most $|X_a| = b_a + 1$ attractors.

In Figure 7, there is one positive circuit in G. Since b is a node of this circuit, $\Gamma(\mathcal{G}, k)$ has at most $|X_b| = 2$ attractors. This bound is reached for the asynchronous state graph given in the figure. In Figure 6, all the positive circuits share the gene a, thus $\Gamma(\mathcal{G}, k)$ has at most $|X_a| = 3$ attractors. In the given asynchronous state graph there is only two attractors, but it there is a coherent parameterization k which leads to 3 attractors, as shown in Figure 9.

3.2 Temporal logic and model checking

The previous theorems only gives *necessary conditions* for the presence of several attractors and/or cyclic attractors. Given a regulatory graph $\mathcal{G}$, they do not give solution to find coherent parameterizations k such that $\Gamma(\mathcal{G}, k)$ presents these dynamical properties. In order to find such parameterizations, Thomas and coworkers introduced the *circuit functionality constraints* [44, 57, 56, 27, 26]. When these constraints are applied on the logical parameters associated with variables of some positive (resp. negative) circuits, the resulting dynamics often contain several attractors (resp. cyclic attractors). These constraints have been used to model several genetic systems [47, 40, 22, 38].

In this section, we present a complementary (and less technical) approach to constrain the logical parameters according to observed (or hypothetical) dynamical properties. It is a computational approach proposed in [5] which is based on formal methods. First, the observed properties Φ are translated into a *temporal formula* thanks to the use of a *temporal logic*. Next, given a regulatory graph $\mathcal{G}$ for the network, the coherent parameterizations k of $\mathcal{G}$ are enumerated. Each resulting asynchronous state graph $\Gamma(\mathcal{G}, k)$ is then studied by *model checking* to check if the temporal formula is satisfied (i.e if the observed properties Φ are present). If there is not any parameterization selected by this verification process, it means that the regulatory graph $\mathcal{G}$ and the observations Φ are inconsistent (and have to be revisited). Otherwise, the selected parameterizations define consistent dynamics which can be useful to elaborate predictions and new experiments.

The obvious limitation of this modeling method is that the number of parameterizations to enumerate is often too huge to consider networks with more than ten or so genes, even if some functionality constraints are applied (however, the dynamics of a lot of important networks with less than ten genes remains globally unknown). The obvious interest is that temporal logic and model checking allows us to handle automatically rather complex dynamical properties, and that the method is exhaustive: *all* the parameterizations of $\mathcal{G}$ consistent with Φ are given as output.

The previous modeling method has been implemented in the tool SMBIONET [5] with the *Computational Tree Logic* (CTL) as temporal logic [12] (the verification step is performed by the model checker NUSMV [7]). This logic is well suited for the formulation of properties present in undeterministic state graphs, such as the asynchronous state graphs considered here (a state graph is undeterministic if some states have several successors). The following gives an idea on the properties that can be expressed with this logic.

The *syntax* of CTL is inductively defined by:

1. For all genes a and positive integers l,

$$a = l, \quad a < l, \quad a > l, \quad a \leq l, \quad a \geq l,$$

   are *atomic* CTL formulas,

2. If ϕ and ψ are two CTL formulas then

$$\begin{array}{llll} \neg\phi, & \phi \wedge \psi, & \phi \vee \psi, & \phi \Rightarrow \psi, \\ \mathrm{EX}(\phi), & \mathrm{EF}(\phi), & \mathrm{EG}(\phi), & \mathrm{E}(\phi \,\mathrm{U}\, \psi), \\ \mathrm{AX}(\phi), & \mathrm{AF}(\phi), & \mathrm{AG}(\phi), & \mathrm{A}(\phi \,\mathrm{U}\, \psi), \end{array}$$

   are CTL formulas.

The *semantic* is given by the satisfactory relation $\models$ between the states x of a given asynchronous state graphs $\Gamma(\mathcal{G}, k)$ and the CTL formulas ϕ. If $x \models \phi$ we say that x satisfies ϕ or that ϕ is true at state x. The semantic of atomic formulas is obvious: for instance, $x \models (a = l)$ if and only if $x_a = l$. The semantic of the logical connectives $\neg$ (negation), $\wedge$ (conjunction), $\vee$ (disjunction), and $\Rightarrow$ (implication) is also obvious: for instance, $x \models \phi \wedge \psi$ if and only if $x \models \phi$ and $x \models \psi$. The other connectives, made with two letters, lead to formulas which are satisfied by a state x according to the set of infinite paths of $\Gamma(G, k)$ starting from x [1]:

1. $x \models \mathrm{EX}(\phi)$ if and only if there exists a successor of x satisfying ϕ.
   $x \models \mathrm{AX}(\phi)$ if and only if all the successors of x satisfy ϕ.

2. $x \models \mathrm{EF}(\phi)$ if and only if there exists an infinite path starting from x which contains a state satisfying ϕ.
   $x \models \mathrm{AF}(\phi)$ if and only if all the infinite paths starting from x contain a state satisfying ϕ.

3. $x \models \mathrm{EG}(\phi)$ if and only if there exists an infinite path starting from x which only contains states satisfying ϕ.
   $x \models \mathrm{AG}(\phi)$ if and only if all the infinite paths starting from x only contain states satisfying ϕ.

4. $x \models \mathrm{E}(\psi \,\mathrm{U}\, \phi)$ if and only if there exists both an infinite path $x^0x^1x^2\ldots$ with $x = x^0$ and $i \in \mathbb{N}$ such that $x^i \models \phi$ and $x^j \models \psi$ for all $j < i$.
   $x \models \mathrm{A}(\psi \,\mathrm{U}\, \phi)$ if and only if, for all infinite paths $x^0x^1x^2\ldots$ with $x = x^0$, there exists $i \in \mathbb{N}$ such that $x^i \models \phi$ and $x^j \models \psi$ for all $j < i$.

[1] An infinite path of $\Gamma(\mathcal{G}, k)$ is an infinite sequence of states $x^0x^1x^2, \ldots$ such that, for all $k \in \mathbb{N}$, (x^k, x^{k+1}) is an edge of $\Gamma(\mathcal{G}, k)$ if x^k has a successor, and $x^k = x^{k+1}$ otherwise.

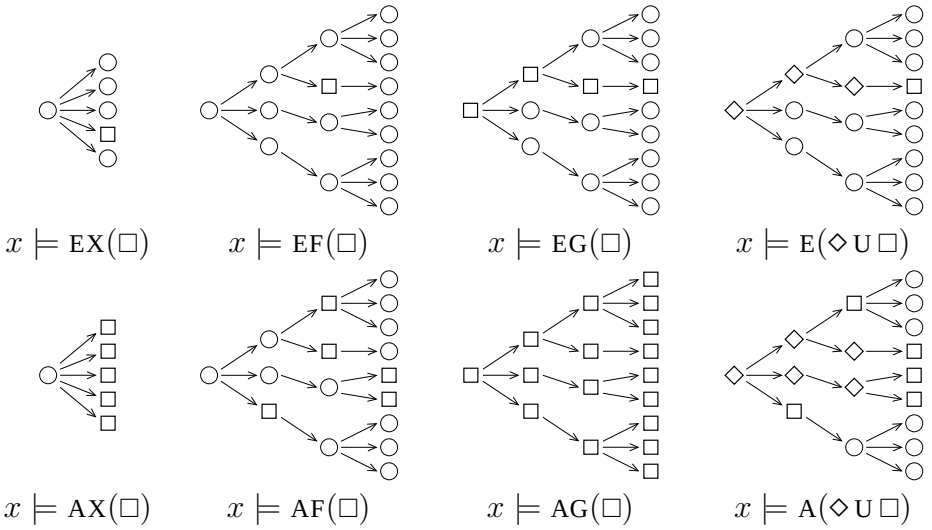
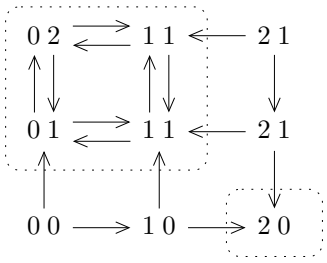


Figure 10: Semantic of temporal connectives (trees regroup the infinite paths starting from x).

So E and A correspond to existential and universal quantifiers respectively: E means "for at least one path" and A "for all paths". The other letters express properties along the paths: $\mathrm{X}(\phi)$ means that ϕ is true at the neXt step, $\mathrm{F}(\phi)$ means that ϕ is Finally true; $\mathrm{G}(\phi)$ means that ϕ is Globally true, and $(\psi \,\mathrm{U}\, \phi)$ means that ψ is always true Until that ϕ becomes true (see Figure 10). If all the states of an asynchronous state graph $\Gamma(\mathcal{G}, k)$ satisfy a given formula, we said that $\Gamma(\mathcal{G}, k)$ satisfies this formula.

For instance, the asynchronous state graph



satisfies the the formula

$$\mathrm{EF}(\mathrm{AG}(a = 2 \wedge b = 0) \vee \mathrm{AG}(a < 2 \wedge b > 1)) \qquad (\phi)$$

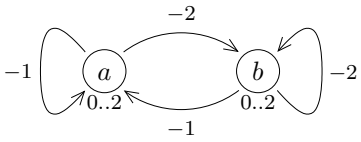
which states that, for all initial state, the system can reach (EF) a state from which $(a = 2 \wedge b = 0)$ or $(a < 2 \wedge b > 1)$ is always true (AG). So if this formula is true, then 20 is a stable state and the set of states satisfying

$(a < 2 \wedge b > 1)$ is a trap domain. The previous asynchronous state graph also satisfies the formula

$$(a = 1 \wedge b = 1) \Rightarrow \text{AG}(\text{EF}(a = 1 \wedge b = 1)) \qquad (\psi)$$

which states that, from initial state 11, all the future states (AG) are states from which 11 can be reached (EF). This formula is true if and only if state 11 belongs to an attractor.

Now, consider the regulatory graph $\mathcal{G}$ of Figure 7 from which the previous asynchronous state graph has been obtained:



There are 400 coherent parameterizations k for $\mathcal{G}$ which lead to 100 different asynchronous state graphs $\Gamma(\mathcal{G}, k)$. When the regulatory graph $\mathcal{G}$ and the formula (ϕ) are given as input of the SMBIONET soft, then 100 parameterizations k are enumerated, one for each asynchronous state graph, and 88 of them are selected since defining an asynchronous state graph $\Gamma(\mathcal{G}, k)$ which satisfies the formula (ϕ). If $\mathcal{G}$ and the formula $(\phi) \wedge (\psi)$ are given as input, then 50 parameterizations are selected. Obviously, one of them leads to the asynchronous state graph given above. Such an automatic method has been used to test hypothesis on the behavior of gene networks in *Pseudomonas aeruginoza* [5, 15]. It has also been used to automatically regain a dynamical model of a gene network in bacteriophage lambda proposed by Thieffry and Thomas [47, 35]. For other applications of formal methods to the modeling of gene networks or other biological systems, one can see [4, 3, 13, 16, 6, 9, 20].

4 Conclusion

Gene networks are often symbolically described by biologists under the form of interaction graphs. These graphs are then taken as main support to reason about the behavior of the corresponding networks. It is however difficult to understand intuitively how the dynamical properties of a network emerge from its interaction graph, especially when several intertwined feedback circuits are involved.

By focusing on the logic of genetic interactions, the Thomas' method offers a simple modeling framework to reason on the dynamics of gene networks. The precision level of the resulting dynamics, defined on a finite set of states, is well suited to observations which remain, in a first time, mostly qualitative

and expressed in natural language.

The fact that dynamics are defined on a finite set of states allows the use of powerful formal methods inherited from computer science. For instance, temporal logic and model checking techniques can be used to automatically prove that a given dynamical model has the (formally translated) observed properties. As we have seen, these methods can be used for the automatic determination of appropriate logical parameters.

Finally, discrete approach of Thomas can be taken as a first step towards more accurate descriptions, as those given by piecewise-linear differential equations systems. Indeed, both approaches are based on the approximation of sigmoid regulations by step functions. As a result, there exists a discretization map which associates to each piecewise linear differential system, an asynchronous state graph that extracts the main dynamical properties of this system [42, 44] (see also [11] for a more sophisticated discretization). The logical parameters then correspond to the discretization of kinetic parameters and gives precious information about them.

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