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On logical bifurcation diagrams☆

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ABSTRACT

Bifurcation theory provides a powerful framework to analyze the dynamics of differential systems as a function of specific parameters. Abou-Jaoudé et al. (2009) introduced the concept of logical bifurcation diagrams, an analog of bifurcation diagrams for the logical modeling framework. In this work, we propose a formal definition of this concept. Since logical models are inherently discrete, we use the piecewise differential (PWLD) framework to introduce the underlying bifurcation parameters. Given a regulatory graph, a set of PWLD models is mapped to a set of logical models consistent with this graph, thereby linking continuous changes of bifurcation parameters to sequences of valuations of logical parameters. A logical bifurcation diagram corresponds then to a sequence of valuations of the logical parameters (with their associated set of attractors) consistent with at least one bifurcation diagram of the set of PWLD models. Necessary conditions on logical bifurcation diagrams in the general case, as well as a characterization of these diagrams in the Boolean case, exploiting a partial order between the logical parameters, are provided. We also propose a procedure to determine a logical bifurcation diagram of maximum length, starting from an initial valuation of the logical parameters, in the Boolean case. Finally, we apply our methodology to the analysis of a biological model of the p53-Mdm2 network.

1. Introduction

The behavior of biological systems relies on complex regulatory networks which understanding requires the use of computational modeling approaches. Different formalisms, operating at different levels of abstraction, have been used to model complex biological networks. Among these formalisms, the logical framework, initially introduced by Thomas and d'Ari (1990), has proven to be particularly useful to model such networks, in particular when precise quantitative data are lacking, with applications in a wide range of biological systems including cell differentiation in developmental processes (Fauré et al., 2014), haematopoiesis (Collombet et al., 2017), T-cell activation and differentiation (Abou-Jaoudé et al., 2015) or cell cycle control (Faure et al., 2006) (see Abou-Jaoudé et al., 2016 for additional applications).

In the logical modeling formalism, regulatory networks are modeled in terms of a logical regulatory graph, where nodes represent regulatory components, while edges denote regulatory interactions (Thomas and d'Ari, 1990). Each component is associated with a discrete variable representing its (current) functional level of activity. In addition, a logical rule defines the evolution of this level, depending on the values of the regulators of the component. A logical rule can be specified using either a logical function, or logical parameters (Snoussi, 1989; Thomas and d'Ari, 1990). When several component levels are called to update, an updating scheme (*e.g.*, synchronous, asynchronous) has to be specified to define the state successor(s). The resulting dynamics can be represented in terms of a *state transition graph*, where nodes denote states, while directed edges represent state transitions.

Bifurcation theory provides a powerful framework to analyze qualitative changes in the dynamics of ODEs depending on specific parameters. This analysis can be represented in a bifurcation diagram, where the attractors (oscillatory regimes or steady states) and their stability are represented as a function of the parameter(s) of interest (*e.g.*, reaction rate or external stimuli) (Strogatz, 2000). Abou-Jaoudé et al. (2009) introduced the concept of logical bifurcation diagram, an analog to ODE bifurcation diagrams for the logical modeling framework. Given a regulatory graph of a model, a logical bifurcation diagram corresponds to a sequence of valuations of the logical parameters associated with a model component (with its corresponding attractors), upon a change of an implicit parameter

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(*e.g.*, a degradation rate in Abou-Jaoudé et al., 2009). However, a formal definition of this concept is still lacking.

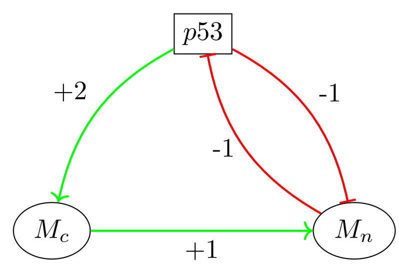
In this work, we propose a formal definition of logical bifurcation diagrams. To do so, we use the piecewise linear differential (PWLD) framework to explicitly introduce the underlying bifurcation parameters and formally associate monotonous and continuous changes of these parameters to sequences of valuations of logical parameters. More precisely, we map a set of piecewise linear differential models associated with a given regulatory graph to the set of the logical models whose logical parameter values are consistent with the regulatory graph. A logical bifurcation diagram then corresponds to a sequence of valuations of the logical parameters (with their associated set of attractors) consistent with at least one bifurcation diagram in the class of PWLD models.

This manuscript is organized as follows. We start in Section 2 by describing the case study of the model of the core of the p53-Mdm2 network, proposed by Abou-Jaoudé et al. (2009). In Section 3, we introduce the class of logical models associated with a regulatory graph, from a partial order defined in the set of the logical parameters. In Section 4, we propose a formal definition of logical bifurcation diagrams associated to a model component, as well as a procedure to compute one logical bifurcation diagram of maximum length, starting from a given valuation of the logical parameters, in the case where the component is Boolean. Finally, Section 5 is devoted to a bifurcation analysis of our case study using our methodology. Details on the building of the set of PWLD models associated to a regulatory graph, and the definition of the pertinent objects to consider in the class of PWLD models for the mappings to the set of logical models are presented in Appendix A. Details on the mappings between the two sets of PWLD and logical models, and the link between their dynamics are presented in Appendix B.

2. A case study: The p53-Mdm2 network

We consider the model of the core of the p53-Mdm2 network, proposed by Abou-Jaoudé et al. (2009), which encompasses the following components: the protein p53; the ubiquitin ligase Mdm2 in the cytoplasm; and the ubiquitin ligase Mdm2 in the nucleus. p53 plays an essential role in the control of cell proliferation in mammals by regulating a large number of genes involved notably in growth arrest, DNA repair or apoptosis. Its level is tightly regulated by the ubiquitin ligase Mdm2. Nuclear Mdm2 down-regulates the level of active p53, both by accelerating p53 degradation through ubiquitination and by blocking the transcriptional activity of p53. In return, p53 activates Mdm2 transcription and down-regulates the level of nuclear Mdm2 by inhibiting Mdm2 nuclear translocation.

These interactions are modeled in the regulatory graph shown in Fig. 1(a), in which we focus on the case where p53 (denoted by $p53$) is active on nuclear Mdm2 (M_n) above its first threshold,



(a)

	Valuation of the logical parameters			
$K_{Mn,\{(p53,1),(M_c,0)\}}$	1	0	0	0
$K_{Mn,\{(p53,0),(M_c,0)\}}$	1	1	0	0
$K_{Mn,\{(p53,1),(M_c,1)\}}$	1	1	1	0
$K_{Mn,\{(p53,0),(M_c,1)\}}$	1	1	1	1,0
Attractors	[001]	[001]	000 → 100 → 200 → 210 → 211 → 111 111 → 011 → 001 → 000 111 → 101 → 001 101 → 100	[210]

Increasing degradation rate of nuclear Mdm2

(b)

Fig. 1. (a) Regulatory graph of the model of the core p53-Mdm2 network, adapted from Fig. 2(a) in Abou-Jaoudé et al. (2009), in the case where p53 (denoted by $p53$) is active on nuclear Mdm2 (denoted by M_n) above its first threshold, and on cytoplasmic Mdm2 (denoted by M_c) above its second threshold. Green edges correspond to activations, whereas red blunt ones denote inhibitions. Ellipses denote Boolean components (0 or 1), whereas the rectangle represents a ternary one (0, 1 or 2). (b) Logical bifurcation diagram, adapted from Fig. 3(a) in Abou-Jaoudé et al. (2009), corresponding to the regulatory graph in (a) in the case where the logical parameters of M_n respect the following constraints: $K_{M_n,\{(p53,1),(M_c,0)\}} \leq K_{M_n,\{(p53,0),(M_c,0)\}} \leq K_{M_n,\{(p53,1),(M_c,1)\}} \leq K_{M_n,\{(p53,0),(M_c,1)\}}$ (see Example 2 for more details on these parameters). The values taken for the logical parameters of $p53$ and M_c are: 0 for $K_{p53,\{(M_n,1)\}}$, 2 for $K_{p53,\{(M_n,0)\}}$, 0 for $K_{M_c,\{(p53,0)\}}$, 1 for $K_{M_c,\{(p53,2)\}}$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and on cytoplasmic Mdm2 (M_c) above its second threshold. To enable a systematic characterization of all the asymptotic behaviors consistent with a given regulatory graph, in the framework of logical modeling, Abou-Jaoudé et al. introduced the concept of logical bifurcation diagram (Abou-Jaoudé et al., 2009), an analog of bifurcation analysis for ODE systems, based on the following two main ideas:

(i) the inference of constraints between the values of the logical parameters of a component (M_n in Abou-Jaoudé et al., 2009) from the regulatory graph, relying on the idea that a negative influence of a component ($p53$) tends to lower the level of its target(s) (M_n) whereas the positive influence of a component (M_c) tends to increase the level of its target(s) (M_n);
(ii) the fact that logical parameters represent discretized ratios of the production and degradation rates of a component, thereby allowing to link changes of the logical parameter values of a component (M_n in Abou-Jaoudé et al., 2009) with the variation of an implicit continuous parameter (the degradation rate of M_n in Abou-Jaoudé et al., 2009), under the inferred constraints.

Fig. 1(b) shows one of the logical bifurcation diagrams derived in Abou-Jaoudé et al. (2009), corresponding to one admissible ordering of the logical parameter values, where the attractors (steady states, limit cycles) of the model are displayed as a function of the degradation rate of M_n. In the following, we propose a formalization of the concept of logical bifurcation diagram introduced in Abou-Jaoudé et al. (2009). We will see that the constraints on the logical parameters values inferred in Abou-Jaoudé et al. (2009) from the regulatory graph, can be formalized in terms of a partial order in the set of the logical parameters (Section 3.2). Regarding the formalization of the link between the implicit bifurcation parameter and the logical parameter values, we will use the piecewise linear differential (PWLD) framework to introduce the underlying bifurcation parameter and link it to sequence of valuations of the logical parameters (Section 4). A class of PWLD models is first associated with the regulatory graph and then formally linked to the set of the logical models consistent with the partial order. We now first recall some key aspects of the logical modeling framework.

3. Logical models

3.1. Regulatory graph and logical parameters

We start by recalling the definition of a regulatory graph, adapted from Chaouiya et al. (2004), in the framework of the logical modeling formalism.

Definition 1. A regulatory graph $(\mathcal{G}, \Gamma, sign, T)$ is defined by:

(i) A set of regulatory components $\mathcal{G} = \{g_1, g_2, \ldots, g_n\}$, where n is the number of components;
(ii) A set of regulatory interactions Γ defined as a subset of the set $\mathcal{G} \times \mathcal{G}$;
(iii) A mapping, sign, from the set Γ to the set $\{-1, 1\}$, defining the sign of the interactions;
(iv) A set $T = \{t_{g,g'}\}_{(g,g')\in\Gamma}$ of sets of thresholds associated with Γ, where, for all $(g, g') \in \Gamma$, $t_{g,g'}$ is a subset of the set of strictly positive integers, which fulfills the following condition: for all $g \in \mathcal{G}$, there exists a strictly positive integer k_g such that:

$$\bigcup_{(g,g')\in\Gamma} t_{g,g'} = [\![1, k_g]\!].$$

We denote by Γ^+ (resp. Γ^-) the subset of Γ defined as follows: $(g, g') \in \Gamma^+$ (resp. $(g, g') \in \Gamma^-$) if and only if $sign((g, g')) = 1$ (resp. $sign((g, g')) = -1$).

For all g of $\mathcal{G}$, we denote by $\mathcal{R}_g$ the subset of $\mathcal{G}$ defined as follows: $g' \in \mathcal{R}_g$ if and only if $(g', g) \in \Gamma$.

In Definition 1, each element (g, g') of Γ represents a regulatory interaction, either positive if $sign((g, g')) = 1$ or negative if $sign((g, g')) = -1$. We thus discard cases of dual interactions. The elements of Γ^+ (resp. Γ^-) are the positive (resp. negative) interactions of the regulatory graph, whereas the elements of $\mathcal{R}_g$ represent the regulators of component g. Note that we account for cases where a regulatory interaction (g, g') has multiple thresholds (that is to say that when the set $t_{g,g'}$ has more than one element).

Example 1. Let us illustrate the definition of a regulatory graph on our case study (Fig. 1). Following Definition 1, its regulatory graph $(\mathcal{G}, \Gamma, sign, T)$ is described as follows:

(i) the set $\mathcal{G}$ of regulatory components is defined as: $\mathcal{G} = \{p53, M_c, M_n\}$;
(ii) the set Γ of regulatory interactions is defined as:

$$\Gamma = \{(p53, M_c), (M_c, M_n), (p53, M_n), (M_n, p53)\};$$

(iii) the mapping, *sign*, from the set Γ to the set $\{-1, 1\}$ is defined as:

$$sign((p53, M_c)) = 1, \;\; sign((M_c, M_n)) = 1,$$
$$sign((p53, M_n)) = -1, \;\; and \; sign((M_n, p53)) = -1;$$

(iv) the set $T = \{t_{p53,M_c}, t_{M_c,M_n}, t_{p53,M_n}, t_{M_n,p53}\}$ of sets of thresholds is defined as:

$$t_{p53,M_c} = \{2\}, \;\; t_{M_c,M_n} = \{1\}, \;\; t_{p53,M_n} = \{1\}, \;\; and \; t_{M_n,p53} = \{1\}.$$

To specify a logical regulatory graph, one has to define a regulatory graph $(\mathcal{G}, \Gamma, sign, T)$, and associate to each component $g \in \mathcal{G}$:

(i) a multivalued discrete variable $X_g \in [\![0, max(X_g)]\!]$ (a Boolean one if $X_g = 1$) and;
(ii) a logical rule defining the target value of the component at each state.

A logical rule can be specified using either a logical function, or logical parameters. In this work, we choose to specify logical rules using logical parameters (Snoussi, 1989; Thomas and d'Ari, 1990). More precisely, to each component is associated a set of logical parameters, each corresponding to a combination of values of its regulators (see Table 1 for an example). The value of a logical parameter defines the target value of the component for the corresponding combination (Thieffry and Romero, 1999; Thomas, 1991). At each state, the state successor(s) are determined from the target values of the components and the chosen updating scheme (*e.g.*, asynchronous, synchronous), thereby defining the dynamics of the model. More formally, we define the logical parameters of a component g as follows:

Definition 2. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph and g a component of $\mathcal{G}$. The set $\mathcal{K}_g$ of the logical parameters associated with g is defined as follows:

$$\mathcal{K}_g = \{K_{g,\alpha} \mid \alpha \in \Omega_g\}$$

where Ω_g is the set of all the combinations of values of the regulators of g, defined as follows:

$$\Omega_g = \prod_{g'\in\mathcal{R}_g} \{(g', l_{g'}) \mid l_{g'} \in \{0 \cup t_{g,g'}\}\}$$

The set $\mathcal{V}_g$ of the valuations of the logical parameters associated with a component g is defined as follows:

$$\mathcal{V}_g = \prod_{\alpha\in\Omega_g} \{(K_{g,\alpha}, l_\alpha) \mid l_\alpha \in [\![0, max(X_g)]\!]\}$$

For all $L \in \mathcal{V}_g$ and all $(K_{g,\alpha}, l_\alpha) \in L$, l_α will be called the value of the logical parameter $K_{g,\alpha}$.

Table 1
Truth table for the regulators of M_n in our case study (Fig. 1), listing the admissible valuations of the logical parameters of M_n (*i.e.* the elements of $\mathcal{V}^a_{M_n}$) with the corresponding logical functions. The symbols ¬, ∧ and ∨ denote the logical operators NOT, AND and OR, respectively.

Logical parameters	Truth table							
	Regulators		Logical functions					
	$p53$	M_c	`false`	$\neg p53 \wedge M_c$	$\neg p53$	M_c	$\neg p53 \vee M_c$	`true`
$K_{M_n,\{(p53,0),(M_c,0)\}}$	0	0	0	0	1	0	1	1
$K_{M_n,\{(p53,0),(M_c,1)\}}$	0	1	0	1	1	1	1	1
$K_{M_n,\{(p53,1),(M_c,0)\}}$	1	0	0	0	0	0	0	1
$K_{M_n,\{(p53,1),(M_c,1)\}}$	1	1	0	0	0	1	1	1

In Definition 2, a logical parameter $K_{g,\alpha} \in \mathcal{K}_g$ of component g is defined by a combination $\alpha \in \Omega_g$ of levels $l_{g'} \in \{0 \cup t_{g,g'}\}$ of the regulators g' of g, where Ω_g is the set of all these combinations. A valuation $L \in \mathcal{V}_g$ of the set $\mathcal{K}_g$ of the logical parameters of g then specifies the discrete target level $l_\alpha \in [\![0, max(X_g)]\!]$ of g for each context $\alpha \in \Omega_g$.

Example 2. Consider our case study (Fig. 1), and let us focus on component M_n. Its regulators are $p53$ and M_c, which interactions on M_n are associated with the following sets of thresholds: $t_{p53,M_n} = \{1\}$ and $t_{M_c,M_n} = \{1\}$. The contexts of regulations of M_n (*i.e.* the elements of the set Ω_{M_n}) are thus:

(i) $\{(p53,\ 1),\ (M_c,\ 0)\}$, for which $p53$ level equals its threshold 1, and M_c level is 0;
(ii) $\{(p53,\ 1),\ (M_c,\ 1)\}$, for which both levels of $p53$ and M_c equal their threshold 1;
(iii) $\{(p53,\ 0),\ (M_c,\ 0)\}$, for which both levels of $p53$ and M_c equal 0;
(iv) $\{(p53,\ 0),\ (M_c,\ 1)\}$, for which $p53$ level is 0, and M_c level equals 1.

Following Definition 2, the set $\mathcal{K}_{M_n}$ of the logical parameters of M_n is:

$$\mathcal{K}_{M_n} = \{K_{M_n,\{(p53,1),(M_c,0)\}}, K_{M_n,\{(p53,1),(M_c,1)\}}, K_{M_n,\{(p53,0),(M_c,0)\}}, K_{M_n,\{(p53,0),(M_c,1)\}}\}.$$

3.2. Partial order and class of logical models associated to a regulatory graph

Let us now assume that a regulatory graph has been defined. To be consistent with this graph, relative values of the logical parameters of a component should be constrained by the sign of the incoming interactions. For example, let us focus on the logical parameters of M_n of our case study. The value of $K_{M_n,\{(p53,0),(M_c,1)\}}$ for which the level of the inhibitor $p53$ equals to 0 and of the activator M_c equals to 1 should be higher than the one of $K_{M_n,\{(p53,0),(M_c,0)\}}$, $K_{M_n,\{(p53,1),(M_c,1)\}}$, and $K_{M_n,\{(p53,1),(M_c,0)\}}$, for which either the level of the activator has been decreased or the level of the inhibitor has been increased. On the contrary, other pairs of logical parameters will not be comparable, as for example $K_{M_n,\{(p53,0),(M_c,0)\}}$ and $K_{M_n,\{(p53,1),(M_c,1)\}}$. We thus see that the sign of the incoming interactions of a component induces a *partial order* in the set of the logical parameters associated to this component.

More formally, given a regulatory graph, the set $\mathcal{K}_g$ of the logical parameters of component g can be equipped with a partial order $\preceq_{\mathcal{K}}$ defined as follows.

Definition 3. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph. Let g be a component of $\mathcal{G}$, and $\mathcal{K}_g$ the set of the logical parameters associated with g. We define the partially ordered set $(\mathcal{K}_g, \preceq_{\mathcal{K}})$ as follows: let $K_{g,\alpha}$ and $K_{g,\alpha'}$ be two elements of $\mathcal{K}_g$ where:

$$\alpha = \{(g', l_{g'})\}_{g' \in \mathcal{R}_g} \text{ and } \alpha' = \{(g', l'_{g'})\}_{g' \in \mathcal{R}_g},$$

with $(l_{g'}, l'_{g'}) \in \{0 \cup t_{g',g}\}^2$ for all $g' \in \mathcal{R}_g$.

Then $K_{g,\alpha} \preceq_{\mathcal{K}} K_{g,\alpha'}$ if and only if the following conditions hold:

(i) for all $g' \in \mathcal{R}_g$ such that $(g', g) \in \Gamma^+$, we have: $l_{g'} \leq l'_{g'}$;
(ii) for all $g' \in \mathcal{R}_g$ such that $(g', g) \in \Gamma^-$, we have: $l_{g'} \geq l'_{g'}$.

According to Definition 3, the logical parameter $K_{g,\alpha}$ is smaller than the logical parameter $K_{g,\alpha'}$ in the partially ordered set $(\mathcal{K}_g, \preceq_{\mathcal{K}})$ of the logical parameters associated to component g (*i.e.* $K_{g,\alpha} \preceq_{\mathcal{K}} K_{g,\alpha'}$), if and only if:

(i) the level of each activator of g is lower in α than in α' (condition (i));
(ii) the level of each inhibitor of g is higher in α than in α' (condition (ii)).

Of note such a way to structure the set of the logical parameters has been previously considered in Thieffry and Romero (1999). The elements of a partially ordered set can be graphically represented by a so-called *Hasse diagram* (Birkhoff, 1948), where nodes represent logical parameters and edges represent the partial order relations. In the Hasse diagram, two logical parameters are said to be *comparable* if there exists an all ascending or an all descending path between the nodes representing these parameters (see Fig. 2 for an example).

Example 3. Let us consider our case study (Fig. 1). Following Definition 3, the partially ordered sets $(\mathcal{K}_{p53}, \preceq_{\mathcal{K}})$, $(\mathcal{K}_{M_c}, \preceq_{\mathcal{K}})$ and $(\mathcal{K}_{M_n}, \preceq_{\mathcal{K}})$ of the logical parameters are represented in the Hasse diagrams shown in Fig. 2.

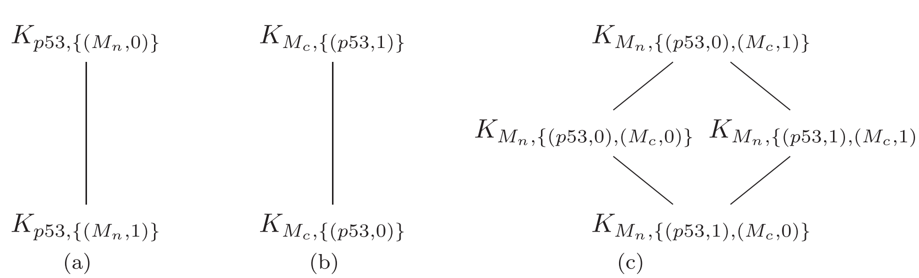


Fig. 2. Hasse diagrams of the partially ordered sets (a) $(\mathcal{K}_{p53}, \preceq_{\mathcal{K}})$, (b) $(\mathcal{K}_{M_c}, \preceq_{\mathcal{K}})$, and (c) $(\mathcal{K}_{M_n}, \preceq_{\mathcal{K}})$, for our case study.

Let us focus on the logical parameters $K_{M_n,\alpha}$ and $K_{M_n,\alpha'}$, associated to M_n, for which:

$\alpha = \{(p53, 1), (M_c, 0)\}$ and $\alpha' = \{(p53, 0), (M_c, 1)\}$.

The level of the activator of M_n, M_c, is smaller in α than in α', while the level of the inhibitor of M_n, $p53$, is higher in α than in α'. Thus $K_{M_n,\alpha}$ and $K_{M_n,\alpha'}$ are comparable and we have $K_{M_n,\alpha} \preceq_{\mathcal{K}} K_{M_n,\alpha'}$. However, in the case where:

$\alpha = \{(p53, 0), (M_c, 0)\}$ and $\alpha' = \{(p53, 1), (M_c, 1)\}$,

the levels of the activator M_c and the inhibitor $p53$ are both smaller in α. Thus $K_{M_n,\alpha}$ and $K_{M_n,\alpha'}$ are not comparable.

Given a regulatory graph, we can then define, from the partial order $\preceq_{\mathcal{K}}$, the set $\mathcal{V}_g^a$ of the admissible valuations of the logical parameters associated to a component g as follows.

Definition 4. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and g a component of $\mathcal{G}$. The set $\mathcal{V}_g^a$ of the admissible valuations of the logical parameters of g is the subset of $\mathcal{V}_g$ defined as follows: let L be an element of $\mathcal{V}_g$, where:

$L = \{(K_{g,\alpha_1}, l_1), \dots, (K_{g,\alpha_{q_g}}, l_{q_g})\}$,

and q_g is the number of elements of $\mathcal{K}_g$.

Then L is an element of $\mathcal{V}_g^a$ if and only if, for all $(j, j') \in [\![1, q_g]\!]^2$ such that $K_{g,\alpha_j} \preceq_{\mathcal{K}} K_{g,\alpha_{j'}}$, we have:

$l_j \le l_{j'}$.

The condition defining the set $\mathcal{V}_g^a$ in Definition 4 states that if a logical parameter K_{g,α_j} is lower than $K_{g,\alpha_{j'}}$, for the partial order $\preceq_{\mathcal{K}}$, then its value l_j should be lower that the value $l_{j'}$ of $K_{g,\alpha_{j'}}$. Of note, the set of the admissible valuations of the logical parameters corresponds to the set of the consistent combinations of logical parameters as defined in Thieffry and Romero (1999), and also to the set of monotone (Boolean or multivalued) logical functions, since a regulator cannot have activator and inhibitor roles on the same target (we discard dual interactions). Note that such constraints do not impede non-functional interactions, and hence do not exclude degenerate logical functions (Crama and Hammer, 2011). The cardinality of the set of all monotone Boolean functions is known as the Dedekind number (Dedekind, 1897), which follows a double exponential growth closely bound to the set of all Boolean functions (2^{2^m}, where m is the number of regulators). Studying this set of functions would quickly become computationally impossible even for small numbers of m. To circumvent this issue, one can use a method proposed in Cury et al. (2018) which exploits a partial order of monotone Boolean functions to locally explore neighboring functions, from a Boolean function of reference.

Example 4. In our case study, let us consider a valuation of the logical parameters of M_n:

$$L = \{\left(K_{M_n,\{(p53,1),(M_c,0)\}}, l_1\right), \left(K_{M_n,\{(p53,1),(M_c,1)\}}, l_2\right), \left(K_{M_n,\{(p53,0),(M_c,0)\}}, l_3\right), \left(K_{M_n,\{(p53,0),(M_c,1)\}}, l_4\right)\}.$$

where the values l_1, l_2, l_3, and l_4 equal to 0 or 1. The logical parameters of the partially ordered set $(\mathcal{K}_{M_n}, \preceq_{\mathcal{K}})$ are ordered as follows:

(i) $K_{M_n,\{(p53,1),(M_c,0)\}} \preceq_{\mathcal{K}} K_{M_n,\{(p53,1),(M_c,1)\}}$,
(ii) $K_{M_n,\{(p53,1),(M_c,0)\}} \preceq_{\mathcal{K}} K_{M_n,\{(p53,0),(M_c,0)\}}$,
(iii) $K_{M_n,\{(p53,1),(M_c,1)\}} \preceq_{\mathcal{K}} K_{M_n,\{(p53,0),(M_c,1)\}}$,
(iv) $K_{M_n,\{(p53,0),(M_c,0)\}} \preceq_{\mathcal{K}} K_{M_n,\{(p53,0),(M_c,1)\}}$,

(see Hasse diagram in Fig. 2(c)). Therefore, following Definition 4, the valuation L is admissible if and only if:

(i) $l_1 \le l_2$, (ii) $l_1 \le l_3$, (iii) $l_2 \le l_4$, and (iv) $l_3 \le l_4$.

The set $\mathcal{V}_{M_n}^a$ of the admissible valuations of the logical parameters of M_n is presented in Table 1.

Finally, we define the class of logical models associated with a regulatory graph as follows.

Definition 5. The class of logical models associated with the regulatory graph $(\mathcal{G}, \Gamma, sign, T)$ is the set of logical models satisfying the following conditions:

(i) their regulatory graph is $(\mathcal{G}, \Gamma, sign, T)$;
(ii) for all components $g_i \in \mathcal{G}$, the valuation of the logical parameters associated with g_i belongs to $\mathcal{V}_{g_i}^a$.

4. Logical bifurcation diagrams

In this section, we propose a formal definition of the concept of logical bifurcation diagram, introduced in Abou-Jaoudé et al. (2009) in the logical modeling framework. To introduce the underlying bifurcation parameters, we take advantage of the piecewise linear differential (PWLD) formalism. Indeed:

(i) this semi-quantitative modeling framework is such that it can be formally linked to logical modeling framework (as we will see in the following);
(ii) its dynamics depends on continuous parameters (contrary to logical modeling which parameters are inherently discrete), which can thus be chosen as bifurcation parameters;
(iii) monotonous and continuous changes of each parameter can be mapped to sequences of valuations of logical parameters (as we will see in the following).

A logical bifurcation diagram would then correspond to a sequence of valuations of the logical parameters (with their associated set of attractors) which can be mapped to a change of at least one bifurcation parameter.

More precisely, we first associate a class PWLD models with a regulatory graph $(\mathcal{G}, \Gamma, sign, T)$. Roughly speaking, each component $g_i \in \mathcal{G}$ is associated with a non-negative variable x_i describing the level of g_i, a basal constant a_i and a degradation rate d_i, while each interaction $(g_i, g_j) \in \Gamma$ of the regulatory graph is associated with a set of step functions of magnitude k_{ij}^l with $l \in t_{g_i,g_j}$ (either increasing or decreasing functions depending on the sign of the interaction), the order between the thresholds of the step functions being consistent with the order between the thresholds of the regulatory graph. The differential equation describing the evolution of x_i is built by summing the step functions associated with the incoming interactions on g_i. Details about the construction of this class of models can be found in Appendix A.1.

We then map this class of PWLD models to the class of logical models associated to $(\mathcal{G}, \Gamma, sign, T)$. More precisely, the ith coordinates of a so-called *focal function* (*i.e.* the elements of the set denoted $\mathcal{F}_i$) are mapped to the logical parameters of component g_i (*i.e.* the elements of $\mathcal{K}_{g_i}$), and a relative position of these ith coordinates with respect to the thresholds (*i.e.* an element of the set denoted $\mathcal{P}_i$) is mapped to an admissible valuation of the logical parameters of g_i (*i.e.* an element of $\mathcal{V}_{g_i}^a$), thereby mapping each model of the class of PWLD models to a specific model of the corresponding class of logical models. Briefly speaking, the focal function describes the values towards which the variables x_i tend according to the relative positions of x_i with the thresholds. A qualitative description of the dynamics of a PWLD model, called *state transition graph*, can be deduced from the positionings of the coordinates of the focal function. We show that the image of the state transition graph of a PWLD model is the asynchronous state transition graph of the image of the PWLD model by the mapping. Details on the definition of the pertinent objects to consider in the class of PWLD models for the mappings (focal function, positioning of the coordinates of the focal function, partial order, state transition graph) can be found in Appendix A. Details on the mapping between the

Table 2
Table of correspondence between the class of logical models and the class of PWLD models, associated with a regulatory graph $(\mathcal{G}, \Gamma, sign, T)$ where $\mathcal{G} = \{g_1, g_2, \ldots, g_n\}$ and $T = \{t_{g_i,g_j}\}_{(g_i,g_j)\in\Gamma}$ (Definition 1). $|t_{g_i,g_j}|$ denotes the number of elements of the set t_{g_i,g_j}. More details on the definitions related to the class of PWLD models can be found in Appendix A.

	Logical models	PWLD models
Components	$\{g_1, g_2, \ldots, g_n\}$	
Variables	$(X_{g_i})_{1\le i\le n} \in \prod_{i=1}^{n} [\![0, \max(X_{g_i})]\!]$	$(x_i)_{1\le i\le n} \in (\mathbb{R}^+)^n$
Thresholds	$t_{g_i,g_j} \subseteq [\![1, \max(X_{g_i})]\!]$	$\left(\theta_{ij}^l\right)_{l\in t_{g_i,g_j}} \in (\mathbb{R}^{+\star})^{\lvert t_{g_i,g_j}\rvert}$
Interactions / Step functions	$(g_i, g_j) \in \Gamma,\ sign((g_i, g_j)) \in \{-1, 1\}$	$\left(s^{sign((g_i,g_j))}(., \theta_{ij}^l)\right)_{l\in t_{g_i,g_j}} \in (\mathbb{R}^+ \mapsto \{0, 1\})^{\lvert t_{g_i,g_j}\rvert}$
Logical parameters/ Coordinates of the focal function	$(\mathcal{K}_{g_1}, \ldots, \mathcal{K}_{g_n})$	$(\mathcal{F}_1, \ldots, \mathcal{F}_n)$
Valuations of logical parameters/ Positioning of the coordinates of the focal function	$\left(\mathcal{V}_{g_1}^a, \ldots, \mathcal{V}_{g_n}^a\right)$	$(\mathcal{P}_1, \ldots, \mathcal{P}_n)$
Partial order in the sets $\mathcal{K}_{g_i}$/ Partial order in the sets $\mathcal{F}_i$	$\preceq_{\mathcal{K}}$	$\preceq_{\mathcal{F}}$
Bifurcation parameters	/	$\{k_{ij}^l\}_{(g_i,g_j)\in\Gamma, l\in t_{g_i,g_j}}$, $(a_i)_{1\le i\le n}$, $(d_i)_{1\le i\le n}$
Dynamics	Asynchronous state transition graph	State transition graph

two classes of models, and the link between their dynamics can be found in Appendix B. A logical bifurcation diagram would then correspond to a sequence of valuations of the logical parameters (with their associated set of attractors) consistent with at least one bifurcation diagram of the class of PWLD models. Of note a given set of attractors can correspond to distinct valuations of the logical parameters. Table 2 summarizes the correspondences between the class of logical models and the class of PWLD models, associated with a regulatory graph.

Let us now define the type of bifurcation analysis in PWLD models that we consider in our work. Generally speaking, a bifurcation analysis of a differential model is the analysis of the attractors as a function of one (or several) parameters. Here, we restrict our study to bifurcation analysis depending on one parameter, called *bifurcation parameter*, and focus on the attractors of the state transition graph of a PWLD model. A bifurcation diagram of a PWLD model then corresponds to the sequence of attractors in the state transition graph of the system upon monotonous (*i.e.* increasing or decreasing) and continuous variation of one bifurcation parameter. Note that the state transition graph depends on the positioning of the coordinates of the focal function (*i.e.* on the sets $\mathcal{P}_i$), and not on the precise values of the parameters of the PWLD model. What matters then is to understand how the positioning of the coordinates of the focal function varies when changing the value of the bifurcation parameter. Actually, the evolution of these positionings is restricted by constraints on the relative positions between the coordinates of the focal function. Part of these constraints can be formalized in the frame of a partial order $\preceq_{\mathcal{F}}$ on the sets of these coordinates (*i.e.* on the sets $\mathcal{F}_i$) (see Appendix A.4).

More formally, given a component g_i, the set $\mathcal{P}_{bd_i}^{pwl}$ of the sequences of positionings of the ith coordinates of the focal function upon monotonous and continuous change of a bifurcation parameter is defined as follows.

Definition 6. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and let us consider the class of PWLD models associated with $(\mathcal{G}, \Gamma, sign, T)$.

Let g_i be a component of $\mathcal{G}$, and $\mathcal{P}_i$ the set of the positionings of the ith coordinates of the focal function for the class of PWLD models.

We define the set $\mathcal{P}_{bd_i}^{pwl} \subseteq \mathcal{P}_i^\star$ as follows: let $(P_j)_{0\le j\le k}$ be an element of $\mathcal{P}_i^\star$ where:

$$P_j = \{\left((f_1, F_1), l_1^j\right), \ldots, \left((f_{q_i}, F_{q_i}), l_{q_i}^j\right)\},$$

with $q_i = |\mathcal{F}_i|$, $\left((f_1, F_1), \ldots, (f_{q_i}, F_{q_i})\right) \in \mathcal{F}_i^{q_i}$, and $(l_1^j, \ldots, l_{q_i}^j) \in [\![0, max(X_{g_i})]\!]^{q_i}$ for all $j \in [\![0, k]\!]$, such that for all $j \in [\![0, k-1]\!]$, there exists $m \in [\![1, q_i]\!]$ satisfying $l_m^j \neq l_m^{j+1}$.

Then $(P_j)_{0\le j\le k} \in \mathcal{P}_{bd_i}^{pwl}$ if and only if there exist:

(i) a parameter p_l;
(ii) a set Θ_i^0 of threshold values of the outgoing interactions of g_i;
(iii) a set $p \setminus p_l^0$ of values of all the parameters except p_l;
(iv) two values p_l^{in} and p_l^{fin} of the parameter p_l;

such that, there exists a continuous and monotonous function γ from the set [0, 1] to the set $\left[p_l^{in}, p_l^{fin}\right]$ satisfying $\gamma(0) = p_l^{in}$ and $\gamma(1) = p_l^{fin}$, and a subdivision $t_0 < t_1 < \ldots < t_{k-1}$ of [0, 1] such that:

(i) $\left(h_i^m([0, t_0[)\right)_{1\le m\le q_i} = \left(l_m^0\right)_{1\le m\le q_i}$,
(ii) $\left(h_i^m\left(]t_{j-1}, t_j[\right)\right)_{1\le m\le q_i} = \left(l_m^j\right)_{1\le m\le q_i}$ for all integers j between 1 and $k-1$,
(iii) $\left(h_i^m\left(]t_{k-1}, +\infty[\right)\right)_{1\le m\le q_i} = \left(l_m^k\right)_{1\le m\le q_i}$,

where h_i^m is the function from the set [0, 1] to the set $[\![0, max(X_{g_i})]\!]$ defined, for all integers m between 1 and q_i, as follows:

$$h_i^m : \begin{cases} [0, 1] \to [\![0, max(X_{g_i})]\!] \\ t \mapsto \alpha_{\mathbb{R}}^{\Theta_i^0}\left(f_m\left(\gamma(t), p \setminus p_l^0\right)\right), \end{cases}$$

where $\alpha_{\mathbb{R}}^{\Theta_i^0}$ is a mapping from the set $\mathbb{R}^+$ to the set $[\![0, max(X_{g_i})]\!]$, defined in Appendix A.2.

Following Definition 6, a sequence $(P_0, P_1, \ldots, P_k)$ belongs to the set $\mathcal{P}_{bd_i}^{pwl}$ if there exists a parameter p_l and a continuous and monotonous change of p_l, from an initial value p_l^{in} to a final value p_l^{fin}, such that the evolution of the relative position l_1^j, ..., $l_{q_i}^j$ of the ith coordinates (f_1, F_1), ..., (f_{q_i}, F_{q_i}) of the focal function with respect to the thresholds Θ_i^0, upon the change of p_l, is the sequence $(P_0, P_1, \ldots, P_k)$, for all integers j from 1 to k. Note that we discard sequences containing identical successive valuations of the logical parameters in the definition of the set $\mathcal{P}_{bd_i}^{pwl}$.

Then using the mappings Ψ_i introduced in Appendix B, we can associate to each positioning of the coordinates of the focal function a valuation of the logical parameters (and thus a logical model) in the corresponding class of logical models. Given a component g_i, a logical bifurcation diagram should now be a sequence of valuations of the logical parameters of g_i (with its associated sets of attractors) which corresponds to at least one bifurcation diagram in the corresponding class of PWLD models (*i.e.* one element of the set $\mathcal{P}_{bd_i}^{pwl}$). More formally, these sequences of valuations of logical parameters are defined by the set $\mathcal{P}^{log}_{bd_{g_i}}$ of sequences of elements of $\mathcal{V}^{a}_{g_i}$, as follows.

Definition 7. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and g_i a component of $\mathcal{G}$.

We define the set $\mathcal{P}^{log}_{bd_{g_i}} \subseteq (\mathcal{V}^{a}_{g_i})^{\star}$ as follows: $\left(L_j\right)_{0 \le j \le k} \in \mathcal{P}^{log}_{bd_{g_i}}$ if and only if:

$$\left(\Psi_i^{-1}(L_j)\right)_{0 \le j \le k} \in \mathcal{P}^{pwl}_{bd_i}.$$

In Definition 7, the sequence $(L_0, L_1, \ldots, L_k)$ of valuations of the logical parameters of a component g_i belongs to the set $\mathcal{P}^{log}_{bd_{g_i}}$ if and only if the sequence $\left(\Psi_i^{-1}(L_0), \Psi_i^{-1}(L_1), \ldots, \Psi_i^{-1}(L_k)\right)$ of positioning of the ith coordinates of the focal function belongs to $\mathcal{P}^{pwl}_{bd_i}$.

The following property holds on the set $\mathcal{P}^{log}_{bd_{g_i}}$, for all components g_i of $\mathcal{G}$:

Property 1. *Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and g_i a component of $\mathcal{G}$. Let $(L_j)_{0 \le j \le k}$ be an element of $\mathcal{P}^{\log}_{bd_{g_i}}$ where, for all integers j between 0 and k:*

$$L_j = \{(K_{g_i,\alpha_1}, l^j_1), \ldots, (K_{g_i,\alpha_{q_{g_i}}}, l^j_{q_{g_i}})\}.$$

Then, the following condition holds:

(i) *either, for all $r \in [\![1, q_{g_i}]\!]$ and for all $j \in [\![0, k-1]\!]$:*

$$l^{j+1}_r - l^j_r = 0 \text{ or } l^{j+1}_r - l^j_r = 1;$$

(ii) *or, for all $r \in [\![1, q_{g_i}]\!]$ and for all $j \in [\![0, k-1]\!]$:*

$$l^{j+1}_r - l^j_r = 0 \text{ or } l^{j+1}_r - l^j_r = -1.$$

The proof of this property is detailed in Appendix D. In Property 1, the condition states that the values l^j_r of the logical parameters K_{g_i,α_r} either all increase (statement (i)), or all decrease (statement (ii)), along a sequence $(L_j)_{0 \le j \le k}$ of the set $\mathcal{P}^{log}_{bd_{g_i}}$ (which results from the monotonic variation of the coordinates of the focal function upon a change of a bifurcation parameter), and that this change cannot exceed 1 (which results from the continuous variation of the coordinates of the focal function upon a change of a bifurcation parameter).

Studying the whole set $\mathcal{P}^{log}_{bd_{g_i}}$ would quickly become computationally intractable even for small numbers of regulators of component g_i. Instead, starting from a given valuation of the logical parameters, one could explore the logical bifurcation diagrams of given length around this valuation, or determine one possible logical bifurcation diagram of maximum length. In the following, we focus on the determination of one possible logical bifurcation diagram of maximum length.

To do so, we first exploit the constraints imposed by the partial order $\preceq_{\mathcal{F}}$ on the relative position of the coordinates of the focal function, upon a continuous and monotonous change of a bifurcation parameter, to determine necessary conditions for a sequence of valuations of the logical parameters of a component g_i to belong to the set $\mathcal{P}^{log}_{bd_{g_i}}$. These constraints can actually be transferred on the partial order $\preceq_{\mathcal{K}}$ operating in the sets of the logical parameters (see Section 3.2), as it is the partial order induced by the mappings Ψ_i from the partial order $\preceq_{\mathcal{F}}$ (see Appendix B).

The following property provides necessary conditions, accounting for the partial order $\preceq_{\mathcal{K}}$, on the elements of $\mathcal{P}^{log}_{bd_{g_i}}$, in the case where the values of the logical parameters increase along a sequence (the other case where the values of the logical parameters decrease can be treated similarly).

Property 2. *Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and g_i a component of $\mathcal{G}$. Let $(L_j)_{0 \le j \le k}$ be an element of $\mathcal{P}^{log}_{bd_{g_i}}$ where, for all integers j between 0 and k:*

$$L_j = \{(K_{g_i,\alpha_1}, l^j_1), \ldots, (K_{g_i,\alpha_{q_{g_i}}}, l^j_{q_{g_i}})\},$$

such that, for all $j \in [\![0, k-1]\!]$ and for all $r \in [\![1, q_{g_i}]\!]$, we have $l^j_r \le l^{j+1}_r$.

Let, for all $m \in [\![0, max(\bigcup_{(g_i,g') \in \Gamma} t_{g_i,g'})]\!]$, $\mathcal{K}^{j,m}_{g_i}$ be the subset of $\mathcal{K}_{g_i}$ for which, for all $j \in [\![0, k-1]\!]$ and for all $r \in [\![1, q_{g_i}]\!]$, $K_{g_i,\alpha_r} \in \mathcal{K}^{j,m}_{g_i}$ if and only if $l^j_r = m$.

Let $\mathcal{K}^{j,m,up}_{g_i}$ be the subset of $\mathcal{K}_{g_i}$ defined, for all integers m from 0 to $max(\bigcup_{(g_i,g') \in \Gamma} t_{g_i,g'}) - 1$, as follows:

$$\mathcal{K}^{j,m,up}_{g_i} = \{K \in \mathcal{K}_{g_i} \mid l^{j+1}_i > l^j_i,\ l^j_i = m\},$$

and $\mathcal{K}^{j,up}_{g_i}$ the union of these sets $\mathcal{K}^{j,m,up}_{g_i}$ for all the integers m from 0 to $max(\bigcup_{(g_i,g') \in \Gamma} t_{g_i,g'}) - 1$:

$$\mathcal{K}^{j,up}_{g_i} = \bigcup_{m \in [\![0, max(\bigcup_{(g_i,g') \in \Gamma} t_{g_i,g'}) - 1]\!]} \mathcal{K}^{j,m,up}_{g_i}.$$

We define the partially ordered sets $(\mathcal{K}_{g_i}, \preceq^j_{\mathcal{K}})$, for all integers j between 0 and $k-1$, as follows:

(i) $(\mathcal{K}_{g_i}, \preceq^0_{\mathcal{K}}) = (\mathcal{K}_{g_i}, \preceq_{\mathcal{K}})$;

(ii) *for all $(K, K') \notin \mathcal{K}^{j,up}_{g_i}$, we have:*

$$K \preceq^j_{\mathcal{K}} K' \Longrightarrow K \preceq^{j+1}_{\mathcal{K}} K';$$

(iii) *for all $m \in [\![0, max(\bigcup_{(g_i,g') \in \Gamma} t_{g_i,g'}) - 1]\!]$, for all $(K, K') \in \mathcal{K}^{j,m,up}_{g_i}$, we have:*

$$K \preceq^{j+1}_{\mathcal{K}} K' \text{ and } K' \preceq^{j+1}_{\mathcal{K}} K;$$

(iv) *for all $m \in [\![0, max(\bigcup_{(g_i,g') \in \Gamma} t_{g_i,g'}) - 1]\!]$, for all $K \in \mathcal{K}^{j,m,up}_{g_i}$, and for all $K' \in \mathcal{K}^{j,m}_{g_i} \cap \overline{\mathcal{K}^{j,up}_{g_i}}$, we have:*

$$K' \preceq^{j+1}_{\mathcal{K}} K.$$

Let M^j_m be the set of the maximal elements of the partially ordered set $(\mathcal{K}^{j,m}_{g_i}, \preceq^j_{\mathcal{K}})$, for all $j \in [\![0, k-1]\!]$ and for all $m \in [\![0, max(\bigcup_{(g_i,g') \in \Gamma} t_{g_i,g'}) - 1]\!]$, and M^j the union of these sets M^j_m for all $m \in [\![0, max(\bigcup_{(g_i,g') \in \Gamma} t_{g_i,g'}) - 1]\!]$, for all $j \in [\![0, k-1]\!]$:

$$M^j = \bigcup_{m \in [\![0, max(\bigcup_{(g_i,g') \in \Gamma} t_{g_i,g'}) - 1]\!]} M^j_m.$$

Then, we have, for all integers j from 0 to $k-1$:

$$\mathcal{K}^{j,up}_{g_i} \subseteq M^j.$$

The proof of this property is detailed in Appendix D. In Property 2, the partial ordered sets $(\mathcal{K}_{g_i}, \preceq^j_{\mathcal{K}})$ are defined by induction on j, starting from the partial order $\preceq_{\mathcal{K}}$. After each transition from the valuation L_j to the valuation L_{j+1} along the sequence, the partial order $\preceq^j_{\mathcal{K}}$ is updated to record the new constraints on the order between the logical parameters appearing after this transition. The condition of the property imposes that the set $\mathcal{K}^{j,up}_{g_i}$ of the logical parameters whose value increases from L_j to L_{j+1} has to belong to the set of the maximal elements M^j of the partially ordered sets $(\mathcal{K}^{j,m}_{g_i}, \preceq^j_{\mathcal{K}})$, for all integers j between 0 and $k-1$. The other case where the values of the logical parameters decrease can be treated similarly by considering the sets of the logical parameters whose values decrease along a sequence, adapting consequently the inequalities in the updating of the partial orders, and considering the sets of the minimal elements of the partially ordered sets.

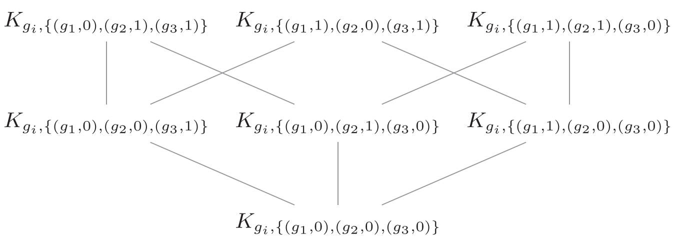


Fig. 3. Hasse diagram of the partially ordered set $(\mathcal{K}^0_{g_i}, \preceq_{\mathcal{K}})$, where $\mathcal{K}^0_{g_i}$ is the set of the logical parameters whose value in L_0 is 0, in the case of Example 5.

As explained above, Property 2 defines necessary conditions accounting for constraints imposed by the partial order $\preceq_{\mathcal{K}}$ but not sufficient ones, regarding the elements of the set $\mathcal{P}^{log}_{bd_{g_i}}$. To illustrate the additional constraints we have to account for, let us consider the following Example 5.

Example 5. We focus on the case of a regulatory graph which contains a Boolean component g_i regulated by three activators g_1, g_2 and g_3, which sets of thresholds are $t_{g_1,g_i} = t_{g_2,g_i} = t_{g_3,g_i} = \{1\}$.

Let us consider the class of logical models associated to the regulatory graph. We start from the valuation:

$$L_0 = \{0, 0, 0, 0, 0, 0, 0, 1\}$$

of the logical parameters associated to component g_i, where the logical parameters are ordered as follows:

(i) $K_{g_i,\{(g_1,0),(g_2,0),(g_3,0)\}}$,
(ii) $K_{g_i,\{(g_1,1),(g_2,0),(g_3,0)\}}$,
(iii) $K_{g_i,\{(g_1,0),(g_2,1),(g_3,0)\}}$,
(iv) $K_{g_i,\{(g_1,0),(g_2,0),(g_3,1)\}}$,
(v) $K_{g_i,\{(g_1,1),(g_2,1),(g_3,0)\}}$,
(vi) $K_{g_i,\{(g_1,1),(g_2,0),(g_3,1)\}}$,
(vii) $K_{g_i,\{(g_1,0),(g_2,1),(g_3,1)\}}$,
(viii) $K_{g_i,\{(g_1,1),(g_2,1),(g_3,1)\}}$.

Let $\mathcal{K}^0_{g_i}$ be the set of logical parameters whose value in L_0 is 0. The maximal elements of the partially ordered set $(\mathcal{K}^0_{g_i}, \preceq_{\mathcal{K}})$ (whose Hasse diagram is shown in Fig. 3) are: $K_{g_i,\{(g_1,1),(g_2,1),(g_3,0)\}}$, $K_{g_i,\{(g_1,1),(g_2,0),(g_3,1)\}}$ and $K_{g_i,\{(g_1,0),(g_2,1),(g_3,1)\}}$.

The set of successors of the valuation L_0, authorized by Property 2, are thus:

(i) $\{0, 0, 0, 0, 1, 0, 0, 1\}$,
(ii) $\{0, 0, 0, 0, 0, 1, 0, 1\}$,
(iii) $\{0, 0, 0, 0, 0, 0, 1, 1\}$,
(iv) $\{0, 0, 0, 0, 1, 1, 0, 1\}$,
(v) $\{0, 0, 0, 0, 1, 0, 1, 1\}$,
(vi) $\{0, 0, 0, 0, 0, 1, 1, 1\}$,
(vii) $\{0, 0, 0, 0, 1, 1, 1, 1\}$.

Let us choose as a successor of L_0 the valuation

$$L_1 = \{0, 0, 0, 0, 1, 0, 0, 1\}.$$

Following Property 2, the partial order $\preceq^0_{\mathcal{K}} = \preceq_{\mathcal{K}}$ is updated to the partial order $\preceq^1_{\mathcal{K}}$ to account for the additional constraints appearing with the transition $L_0 \longrightarrow L_1$, that is to say that:

(i) $K_{g_i,\{(g_1,1),(g_2,0),(g_3,1)\}} \preceq^1_{\mathcal{K}} K_{g_i,\{(g_1,1),(g_2,1),(g_3,0)\}}$,
(ii) $K_{g_i,\{(g_1,0),(g_2,1),(g_3,1)\}} \preceq^1_{\mathcal{K}} K_{g_i,\{(g_1,1),(g_2,1),(g_3,0)\}}$.

Now let us consider the corresponding constraints between the ith coordinates of the focal function, via the mapping χ_i (Appendix B.1), in the class of PWLD models associated to the regulatory graph:

(i) $k^1_{1i} + k^1_{3i} < k^1_{1i} + k^1_{2i}$
(ii) $k^1_{2i} + k^1_{3i} < k^1_{1i} + k^1_{2i}$

holding for all $(k^1_{1i}, k^1_{2i}, k^1_{3i}) \in (\mathbb{R}^{\star+})^3$. It follows after simplification that the following inequalities hold, for all $(k^1_{1i}, k^1_{2i}, k^1_{3i}) \in (\mathbb{R}^{\star+})^3$:

(i) $k^1_{3i} < k^1_{2i}$
(ii) $k^1_{3i} < k^1_{1i}$

that is to say that:

(i) $\chi_i^{-1}(K_{g_i,\{(g_1,0),(g_2,0),(g_3,1)\}})_1(p) < \chi_i^{-1}(K_{g_i,\{(g_1,0),(g_2,1),(g_3,0)\}})_1(p)$
(ii) $\chi_i^{-1}(K_{g_i,\{(g_1,0),(g_2,0),(g_3,1)\}})_1(p) < \chi_i^{-1}(K_{g_i,\{(g_1,1),(g_2,0),(g_3,0)\}})_1(p)$

for all values of the parameter vector p, and thus all along any bifurcation sequence. These last inequalities forbid that the value $K_{g_i,\{(g_1,0),(g_2,0),(g_3,1)\}}$ increases before the value of $K_{g_i,\{(g_1,1),(g_2,0),(g_3,0)\}}$ and $K_{g_i,\{(g_1,0),(g_2,1),(g_3,0)\}}$ along a sequence of valuations belonging to $\mathcal{P}^{log}_{bd_{g_i}}$.

It can then be showed that there exists, from L_1, sequences of valuations respecting Property 2 but which violate this constraint, for example sequences containing the following transition:

$$\{0, 0, 0, 0, 1, 1, 1, 1\} \rightarrow \{0, 0, 0, 1, 1, 1, 1, 1\}.$$

From this example, we see that additional constraints appear from the fact that the coordinates of the focal function are not independent. The following property gives a characterization of the set $\mathcal{P}^{log}_{bd_{g_i}}$, accounting for the dependencies between the coordinates of the focal function, in the case where X_{g_i} is Boolean (*i.e.* $max(X_{g_i}) = 1$) and where the values of the logical parameters increase along a sequence (the other case where the values of the logical parameters decrease can be treated similarly).

Property 3. *Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and g_i a component of $\mathcal{G}$. We assume that $max(X_{g_i}) = 1$ (Boolean case). Let $(L_j)_{0\le j\le k}$ be an element of $(\mathcal{V}^a_{g_i})^\star$, where, for all integers j between 0 and k:*

$$L_j = \{(K_{g_i,\alpha_1}, l^j_1), \ldots, (K_{g_i,\alpha_{q_{g_i}}}, l^j_{q_{g_i}})\},$$

such that, the following conditions hold, for all integers j from 0 to $k-1$:

(i) *for all $r \in [\![1, q_{g_i}]\!]$, we have $l^j_r \le l^{j+1}_r$, and*
(ii) $\mathcal{K}^{j,up}_{g_i} \subseteq M^j$,

where the sets $\mathcal{K}^{j,up}_{g_i}$ and M^j are defined in Property 2.

We define the subset $\mathcal{C}_j$ of the set $(\mathbb{R}^{\star+})^{|\mathcal{DF}_p|-n} \times (\mathbb{R}^+)^n$, where $|\mathcal{DF}_p|$ denotes the number of all the parameters except the thresholds, as follows, for all integers j between 0 and k:

(i) *$p \in C_0$, if and only if, for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l^0_r = 0$ and $l^0_{r'} = 1$, we have:*

$$\chi_i^{-1}(K_{g_i,\alpha_r})_1(p) < \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p);$$

(ii) *$p \in C_j$, for all integers j between 1 and k, if and only if:*
(a) *for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l^{j-1}_r < l^j_r$ and $l^j_{r'} = 0$, we have:*

$$\chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p) < \chi_i^{-1}(K_{g_i,\alpha_r})_1(p);$$

(b) *for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l^{j-1}_r < l^j_r$ and $l^{j-1}_{r'} < l^j_{r'}$, we have:*

$$\chi_i^{-1}(K_{g_i,\alpha_r})_1(p) = \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p);$$

and the set $\mathcal{C}$ as the intersection between the sets C_j for all integers j between 0 and k:

$$\mathcal{C} = \bigcap_{j=0}^{k} C_j.$$

Then, $\left(L_j\right)_{0\le j\le k} \in \mathcal{P}^{log}_{bd_{g_i}}$ *if and only if* $\mathcal{C} \neq \emptyset$.

The proof of this property is detailed in Appendix D. In Property 3, the characterization of the set $\mathcal{P}^{log}_{bd_{g_i}}$ relies on the existence of a solution of a system $\mathcal{C}$ of equalities and inequalities involving the ith coordinates $\chi_i^{-1}(K_{g_i,\alpha_r})$ of the focal function. Roughly speaking, this system gathers the constraints on these coordinates appearing along a sequence $(L_0, L_1, \dots, L_k)$ which already satisfies the necessary conditions stated in Property 2, that is to say that:

- the constraints C_0 at the initial valuation L_0 (condition (i));
- the constraints C_j appearing at each transition (L_{j-1}, L_j), for all integers j from 1 to k (condition (ii));

imposing, at each step j of the sequence, an order between the $\chi_i^{-1}(K_{g_i,\alpha_r})$ which relative positions with the threshold are different. Briefly speaking, proof of Property 3 relies on the fact that the order between the ith coordinates of the focal function which depend on a particular parameter does not change upon a variation of this parameter (Lemma 1 in Appendix D). The case where the values of the logical parameters decrease along a sequence can be treated similarly.

Based on Properties 2 and 3, we propose a procedure to incrementally construct a logical bifurcation diagram of maximum length associated to a component g_i, starting from an initial valuation of the logical parameters, in the case where $max(X_{g_i}) = 1$ (Boolean case). The full procedure is detailed in Appendix E. A generic Java implementation for the multilevel case, accounting for the necessary conditions stated in Property 2, is made publicly available (see section Availability).

The core of the procedure is described in Algorithm 1 which computes a valid successor L_{k+1} (*parentFunc*), if it exists, of an element $(L_0, L_1, \dots, L_k)$ of $\mathcal{P}^{log}_{bd_{g_i}}$, that is to say that a valuation L_{k+1} such that $\left(L_0, L_1, \cdots, L_k, L_{k+1}\right) \in \mathcal{P}^{log}_{bd_{g_i}}$. The main steps of Algorithm 1 are described as follows:

(i) the input *depGraph* of the algorithm represents the updated partially ordered set $(\mathcal{K}_{g_i}, \preceq^k_{\mathcal{K}})$ accounting for the accumulated constraints on the logical parameters along the sequence $(L_0, L_1, \dots, L_k)$, whereas the input *func* represents the valuation L_k of the logical parameters of component g_i;

(ii) in line 4, the algorithm iterates over each logical parameter *lp*, discarding those whose value *lp.state* already reached their maximum *lp.max* (lines 5 to 7);

(iii) in line 8, given a logical parameter *lp*, the set of its immediate parents *lpNeighborList* in the partially ordered set *depGraph* is obtained. If none of the parents equals to the value of *lp* in *func* (lines 10 to 15) (*i.e., lp* belongs to the set of the maximal elements M^j), then *lp* is added to the list *changeLPCand* of the logical parameters whose value can increase (lines 16 to 18). Of note the computation of the immediate parents/children of a logical parameter is inspired by the computation of immediate parents/children of a Boolean function in Cury et al. (2018);

(iv) in line 20, the set of all the combinations of the list *changeLPCand* is generated and shuffled (see Algorithm 3 in Appendix E for more details on the function *getCombinations*);

(v) in line 21, the algorithm iterates over the combinations of the list *changeLPCand*. The first combination which satisfies the following two conditions is selected:
  - the logical parameters which are equal in the partially ordered set *depGraph* are picked together in the selected combination *lpComb* (see Algorithm 3 in Appendix E for more details on the function *isValidLPSet*) (lines 22 to 24);
  - the selected combination satisfies Property 3 (lines 25 to 27);

Algorithm 1 Computation of a valid neighboring function.

```
1: function GETVALIDPARENTFUNCTION(depGraph, func)
2:     changeLPCand ← ∅
3:     funcLPs ← getLPs(func)
4:     for all lp ∈ funcLPs do
5:         if lp.state >= lp.max then
6:             continue
7:         end if
8:         lpNeighborList ← depGraph.getParents(lp)
9:         canChange ← true
10:        for all lpNeighbor ∈ lpNeighborList do
11:            if func.getValueOf(lpNeighbor) == lp.state then
12:                canChange ← false
13:                break
14:            end if
15:        end for
16:        if canChange then
17:            changeLPCand ← changeLPCand ∪ lp
18:        end if
19:    end for
20:    randLPCombList ← random(getCombinations(changeLPCand))
21:    for all lpComb ∈ randLPCombList do
22:        if !isValidLPSet(depGraph, lpComb) then
23:            continue
24:        end if
25:        if !depGraph.satisfiesProp3(lpComb, funcLPs) then
26:            continue
27:        end if
28:        parentFunc ← func.duplicate()
29:        for all lp ∈ lpComb do
30:            parentFunc.increaseLP(lp)
31:        end for
32:        return parentFunc          ▷ Returns a random valid function
33:    end for
34:    return ∅                       ▷ There's no parent function
35: end function
```

(vi) finally, the value of each logical parameter of the selected combination is increased to generate the successor *parentFunc* of *func* (lines 29 to 32).

5. Application

We consider our case study of the model of the core of the p53-Mdm2 network proposed in Abou-Jaoudé et al. (2009), described in Section 2, and focus on the analysis of the logical bifurcation diagrams associated with the component M_n, using our methodology described in the previous section. Table 1 in Section 3.2 lists the logical parameters of M_n, and their admissible valuations in the class of logical models associated to the regulatory graph (Fig. 1(a)). For illustration, we selected three logical bifurcation diagrams, with distinct sequences of attractors, corresponding to the three sequences of valuations of the logical parameters indicated in Fig. 4(a). Correspondence between the classes of logical and PWLD models associated to the regulatory graph, and examples of PWLD bifurcation diagrams corresponding to the logical bifurcation ones are detailed in Appendix C.

In each case, we start from an initial valuation where the values of all the logical parameters are equal to 1, for which the model shows the unique stable state 001, and ends at the valuation where all the logical parameters are equal to 0, for which the model shows the unique stable state 210. Starting from the valuation $L_0 = \{1, 1, 1, 1\}$, the set of the parameters whose value equals

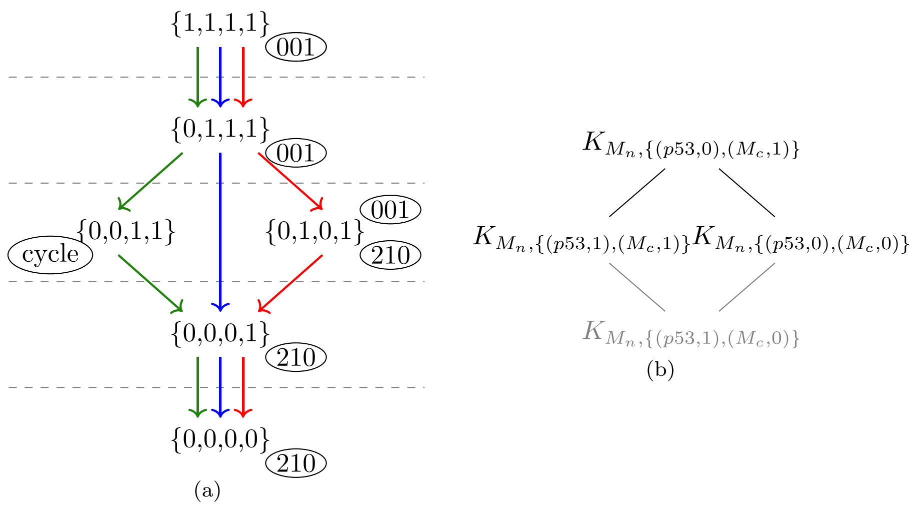


Fig. 4. (a) Figure representing the three logical bifurcation diagrams associated with M_n considered for the bifurcation analysis in Section 5, each represented with a different color. The diagram in green corresponds to the one shown in Fig. 1(b). Ellipses represent the attractors of the model for the corresponding valuation of the logical parameters, where the values of the components are ordered as follows: $p53$, M_c, M_n. The values of the logical parameters of M_n are ordered as follows: $\{K_{M_n,\{(p53,1),(M_c,0)\}}, K_{M_n,\{(p53,1),(M_c,1)\}}, K_{M_n,\{(p53,0),(M_c,0)\}}, K_{M_n,\{(p53,0),(M_c,1)\}}\}$. The values taken for the logical parameters associated to $p53$ and M_c are indicated in caption of Fig. 1. (b) Hasse diagram of the partially ordered set $(\mathcal{K}_{M_n}, \preceq_{\mathcal{K}})$. The subset of $(\mathcal{K}_{M_n}, \preceq_{\mathcal{K}})$ indicated in black corresponds to the partial order in the set of the logical parameters whose value is equal to 1 in the valuation $L_1 = \{0, 1, 1, 1\}$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

1 in L_0 is $\mathcal{K}_{M_n}$, that is to say that:

$$\left\{K_{M_n,\{(p53,1),(M_c,0)\}}, K_{M_n,\{(p53,1),(M_c,1)\}}, K_{M_n,\{(p53,0),(M_c,0)\}}, K_{M_n,\{(p53,0),(M_c,1)\}}\right\}.$$

Therefore, the set of its minimal elements, ordered by $\preceq_{\mathcal{K}}$, is $\{K_{M_n,\{(p53,1),(M_c,0)\}}\}$ (see Fig. 2(c)). Following the necessary conditions stated in Property 2, the only admissible successor of L_0 is then:

$$L_1 = \{0, 1, 1, 1\},$$

for which the value of $K_{M_n,\{(p53,1),(M_c,0)\}}$ has been decreased, leading to the transition $L_0 \longrightarrow L_1$, with no updating of the partial order $\preceq_{\mathcal{K}}$. Focusing on L_1, the set of the minimal elements of the set of the parameters whose value equals 1 in L_1, ordered by $\preceq_{\mathcal{K}}$, is:

$$\{K_{M_n,\{(p53,1),(M_c,1)\}}, K_{M_n,\{(p53,0),(M_c,0)\}}\},$$

(see Fig. 4(b)). According to Property 2, there are now 3 admissible successors:

(i) $L_2 = \{0, 0, 1, 1\}$, (ii) $L_3 = \{0, 1, 0, 1\}$ and (iii) $L_4 = \{0, 0, 0, 1\}$, corresponding to the following 3 possible subsets of the set of the minimal elements:

(i) $\{K_{M_n,\{(p53,1),(M_c,1)\}}\}$, (ii) $\{K_{M_n,\{(p53,0),(M_c,0)\}}\}$ and
(iii) $\{K_{M_n,\{(p53,1),(M_c,1)\}}, K_{M_n,\{(p53,0),(M_c,0)\}}\}$,
respectively, leading to the corresponding transitions, with the following updating of the partial order $\preceq_{\mathcal{K}}$:

$$\text{(i)}\ K_{M_n,\{(p53,1),(M_c,1)\}} \preceq_{\mathcal{K}} K_{M_n,\{(p53,0),(M_c,0)\}},$$
$$\text{(ii)}\ K_{M_n,\{(p53,0),(M_c,0)\}} \preceq_{\mathcal{K}} K_{M_n,\{(p53,1),(M_c,1)\}},$$
$$\text{(iii)}\ K_{M_n,\{(p53,1),(M_c,1)\}} = K_{M_n,\{(p53,0),(M_c,0)\}},$$

respectively. In L_2 (resp. L_3), the set of the minimal elements of the set of the parameters whose value equals to 1, ordered by the updated partial order, is $K_{M_n,\{(p53,0),(M_c,0)\}}$ (resp. $K_{M_n,\{(p53,1),(M_c,1)\}}$), leading to the transition $L_2 \longrightarrow L_4$ (resp. $L_3 \longrightarrow L_4$), with no updating of $\preceq_{\mathcal{K}}$. Finally, the only successor of L_4 is {0, 0, 0, 0}, as there is only one parameter whose value equals to 1 in L_4. It can then be checked that each of these sequences of valuations respects Property 3, thereby proving that these sequences are logical bifurcation diagrams.

Focusing on the attractors shown in the bifurcation diagram in green in Fig. 4(a), the system is characterized by a cyclic attractor, with high amplitude oscillations of $p53$, for the valuation $L_2 = \{0, 0, 1, 1\}$ of the logical parameters. In contrast, in the diagram displayed in red, the system shows instead a bistable behavior, with the coexistence of two stable states (001 and 210), for the valuation $L_3 = \{0, 1, 0, 1\}$. Finally, in the sequence displayed in blue, the system jumps from a monostable behavior to another one, without showing any oscillatory or bistable behavior. As an example, the state transition graphs representing the dynamics corresponding to the sequence showing bistability are described in Fig. 9 in Appendix C.

6. Conclusion

We have proposed a formalization of the concept of logical bifurcation diagrams, an analog of ODE bifurcation diagrams for the logical modeling framework, introduced in Abou-Jaoudé et al. (2009). Moreover, necessary conditions on a sequence of logical parameters valuations to be a logical bifurcation diagrams in the general case, as well as a characterization of these diagrams in the Boolean case, exploiting a partial order between the logical parameters, are provided. We have also designed a procedure to determine one logical bifurcation diagram of maximum length, starting from an initial valuation of the logical parameters, in the case where the component is Boolean. We have illustrated our methodology to the bifurcation analysis of a model of the core network of the p53-Mdm2 network proposed in Abou-Jaoudé et al. (2009), focusing on the case where p53 first activates nuclear Mdm2. Notably, this analysis allowed to recover the two bifurcation diagrams described in Abou-Jaoudé et al. (2009), one showing a bistable behavior, the other displaying an oscillatory regime. Interestingly, our study shows that an additional bifurcation diagram can occur, in which none of these behaviors appears.

It is worth recalling that Property 3 only applies to the case where the component of a logical bifurcation diagram is Boolean. To cope with this limitation, we plan to generalize this property characterizing logical bifurcation diagrams to the multilevel case. Moreover, details on how to implement Property 3 in the designed procedure is still lacking. This property relies on the existence of a solution of a system of equalities and inequalities. One could for example, adapt the Fourier–Motzkin algorithm to this specific problem in order to determine whether a solution of such system exists (Kroening and Strichman, 2008). Apart from the determination of one logical bifurcation diagram of maximum length, our methodology could be also used to explore logical bifurcation diagrams of a given length around an initial valuation of the logical parameters, thereby providing a rational way to assess the sensitivity of an attractor to parameter changes. Another prospect of this work would be to extend the proposed definition of logical bifurcation diagrams to changes of more than one bifurcation parameter in the corresponding class of PWLD models, for example by adapting the approach described in Cummins et al. (2018) to our methodology. Finally, it is known that the functionality of circuits plays a crucial role in the dynamics of regulatory networks (Comet et al., 2013). A future prospect would be to use our methodology to study the functionality of a circuit along logical bifurcation diagrams.

Availability

The software used to compute a bifurcation diagram, given a model and a component, is freely available at https://github.com/ptgm/bifurcation under a GNU General Public License v3.0 (GPL-3.0). This software is expected to be made available as part of the set of software tools made available at http://github.com/colomoto by the http://CoLoMoTo.org (Consortium for Logical Models and Tools) consortium, and integrated into the GINsim modeling and simulation tool (http://ginsim.org).

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Appendix A. Piecewise linear differential models

A1. Class of PWLD models associated with a regulatory graph

Here, we associate a class of piecewise linear differential (PWLD) models to a regulatory graph.

Definition 8. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, as introduced in Definition 1. We proceed as follows to define a class of PWLD models associated with $(\mathcal{G}, \Gamma, sign, T)$:

(i) for all integers i from 1 to n, we associate to each component $g_i \in \mathcal{G}$:
  – a non-negative real variable $x_i \in \mathbb{R}^+$. This variable denotes the level of the component g_i in the PWLD models;
  – a positive real degradation constant $d_i \in \mathbb{R}^{\star+}$;
  – a non-negative real production constant $a_i \in \mathbb{R}^+$.

  We denote by x the vector of variables $(x_1, \ldots, x_n)$.

(ii) To each regulatory interaction $(g_i, g_j) \in \Gamma$, we associate a set of step functions defined, for all integers l in t_{g_i,g_j}, as follows:

$$\begin{cases} s(x_i, \theta_{ij}^l) = 0, & \text{if } x_i < \theta_{ij}^l, \\ s(x_i, \theta_{ij}^l) = k_{ij}^l, & \text{if } x_i > \theta_{ij}^l, \end{cases}$$

  if $sign((g_i, g_j)) = 1$ or:

$$\begin{cases} s(x_i, \theta_{ij}^l) = k_{ij}^l, & \text{if } x_i < \theta_{ij}^l, \\ s(x_i, \theta_{ij}^l) = 0, & \text{if } x_i > \theta_{ij}^l, \end{cases}$$

  if $sign((g_i, g_j)) = -1$, where, the k_{ij}^l and the θ_{ij}^l are positive real constants, such that, for all $((g_i, g_j), (g_i, g_{j'})) \in \Gamma \times \Gamma$ and for all $(l, l') \in t_{g_i,g_j} \times t_{g_i,g_{j'}}$, the following constraints hold:
  – if $l < l'$, then $\theta_{ij}^l < \theta_{ij'}^{l'}$,
  – if $l > l'$, then $\theta_{ij}^l > \theta_{ij'}^{l'}$,
  – if $l = l'$, then $\theta_{ij}^l = \theta_{ij'}^{l'}$.

  k_{ij}^l and θ_{ij}^l will be called the kinetic rate and the threshold of the associated step function, respectively.

(iii) The evolution of the class of PWLD models associated with $(\mathcal{G}, \Gamma, sign, T)$ is described by the following system of piecewise linear differential equations:

$$\frac{dx_i}{dt} = f_i(x) - d_i \cdot x_i, \tag{1}$$

  where:

$$f_i(x) = a_i + \sum_{g_j \in \mathcal{R}_{g_i}} \sum_{l \in t_{g_j,g_i}} s(x_j, \theta_{ji}^l),$$

  for all integers i from 1 to n.

We denote by $\mathcal{DF}_p$ the set of all the parameters except the thresholds, that is to say that:

$$\mathcal{DF}_p = \{k_{ji}^l,\ a_i,\ d_i \mid \forall i \in [\![1, n]\!], \forall (g_j, g_i) \in \Gamma, \forall l \in t_{g_j,g_i}\}.$$

Note that the step functions are not defined at the thresholds (*i.e.* for $x_i = \theta_{ij}^l$) (statement (ii) in Definition 8). Moreover, we opted here for summing the step functions in the differential system describing the evolution of the class of PWLD models (statement (iii) in Definition 8). Such a way to define a class of PWLD models associated to a regulatory graph has also been considered in Cummins et al. (2018).

Example 6. To illustrate Definition 8, let us consider our case study described in Section 2. Following this definition, the evolution of the class of PWLD models associated with the regulatory graph of our case study (Fig. 1) is described by the following piecewise linear differential equations:

$$\begin{cases} \dfrac{dx_1}{dt} = a_1 + k_{31}^1 \cdot s(x_3, \theta_{31}^1) - d_1 \cdot x_1 \\ \dfrac{dx_2}{dt} = a_2 + k_{12}^2 \cdot s(x_1, \theta_{12}^2) - d_2 \cdot x_2 \\ \dfrac{dx_3}{dt} = a_3 + k_{23}^1 \cdot s(x_2, \theta_{23}^1) + k_{13}^1 \cdot s(x_1, \theta_{13}^1) - d_3 \cdot x_3 \end{cases}$$

where x_1, x_2 and x_3 denote the variables associated to the components $p53$, M_c and M_n, respectively, and $\theta_{13}^1 < \theta_{12}^2$ according to the constraints on the definition of the thresholds.

A2. Mapping of values and states

We introduce the following mapping between the set non-negative real numbers and a finite set of integers.

Definition 9. Let p be an integer ≥ 1, and $\Theta = \{\theta_i\}_{1 \leq i \leq p}$ be a set of distinct positive real numbers, ranked by increasing order, *i.e.* $\theta_1 < \theta_2 < \ldots < \theta_p$. We define the mapping of values $\alpha_{\mathbb{R}}^{\Theta}$ from the set $\mathbb{R}^+$ to the set $[\![0, p]\!]$ as follows.

$$\alpha_{\mathbb{R}}^{\Theta} : \begin{cases} \mathbb{R}^+ \to [\![0, p]\!] \\ x \mapsto min\{\{p\} \cup \{k \in [\![0, p-1]\!], x < \theta_{k+1}\}\}. \end{cases}$$

In this mapping, we partition the set of non-negative real numbers into intervals (delimited by the set Θ), and then map each interval to an integer: the interval $[0, \theta_1[$ is mapped to 0, the interval $[\theta_k, \theta_{k+1}[$ is mapped to k, for k from 1 to $p-1$, and the interval $[\theta_p, +\infty[$ to p.

From the mapping defined above, we introduce the mapping α_s^{Θ} between the set of states $(\mathbb{R}^+)^n$ and a finite set of integer vectors as follows.

Definition 10. Let $(p_i)_{1 \leq i \leq n}$ be a vector of integers ≥ 1. Let $\Theta = \{\Theta_i\}_{1 \leq i \leq n}$ be a set of sets of distinct positive real numbers, ranked by increasing order. We define the following mapping of states α_s^{Θ} between the set $(\mathbb{R}^+)^n$ and the set $\prod_{i=1}^n [\![0, p_i]\!]$ as follows:

$$\alpha_s^{\Theta} : \begin{cases} (\mathbb{R}^+)^n \to \prod_{i=1}^n [\![0, p_i]\!] \\ (x_i)_{1 \leq i \leq n} \mapsto (\alpha_{\mathbb{R}}^{\Theta_1}(x_1), \ldots, \alpha_{\mathbb{R}}^{\Theta_n}(x_n)). \end{cases}$$

In this mapping, we partition the state space $(\mathbb{R}^+)^n$ into a set of domains delimited by Θ, and then map each domain to a vector of integers by applying the mappings of values $\alpha_{\mathbb{R}}^{\Theta_i}$ coordinate by coordinate.

A3. Focal function and state transition graph

We now introduce the *focal function* of a class of PWLD models associated with a regulatory graph.

Definition 11. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph. Let us consider the class of PWLD models associated with $(\mathcal{G}, \Gamma, sign, T)$.

For all $i \in [\![1, n]\!]$, let $\Theta_i = \{\theta_{ji}^l\}_{g_j \in \mathcal{R}_{g_i}, l \in t_{g_j, g_i}}$ be the set of thresholds of the step functions associated to the incoming interactions to g_i.

The focal function Φ of the class of PWLD models is a function from the subset of states $\prod_{i=1}^n (\mathbb{R}^+ \diagup \Theta_i)$ to the set of vectors of functions $\left((\mathbb{R}^{\star +})^{|\mathcal{DF}_p|-n} \times (\mathbb{R}^+)^n \to \mathbb{R}^+\right)^n$, defined as follows:

$$\Phi : \begin{cases} \prod_{i=1}^n (\mathbb{R}^+ \diagup \Theta_i) \to \left((\mathbb{R}^{\star +})^{|\mathcal{DF}_p|-n} \times (\mathbb{R}^+)^n \to \mathbb{R}^+\right)^n \\ x \mapsto \left(p \mapsto \dfrac{a_i + \sum_{g_j \in \mathcal{R}_{g_i}} \sum_{l \in t_{g_j, g_i}} s(x_j, \theta_{ji}^l)}{d_i}\right)_{1 \leq i \leq n}, \end{cases}$$

where $p = \left((k_{ij}^l)_{(g_i, g_j) \in \Gamma, l \in t_{g_i, g_j}}, (d_i)_{1 \leq i \leq n}, (a_i)_{1 \leq i \leq n}\right)$ and $|\mathcal{DF}_p|$ is the number of elements of $\mathcal{DF}_p$.

Note that, in Definition 11, we discard the cases where the value of a variable x_i is at a threshold since the step functions are not defined at their threshold. The image of x_0 by the focal function, $\Phi(x_0)$, is a vector of functions defined from the space of parameters $(\mathbb{R}^{\star +})^{|\mathcal{DF}_p|-n} \times (\mathbb{R}^+)^n$ to the set $\mathbb{R}^+$. Actually, $\Phi(x_0)$ defines the point towards which the system tends monotonically, starting from point x_0, for each vector $p^0 = \left((k_{ij}^{l\,0})_{(g_i, g_j) \in \Gamma, l \in t_{g_i, g_j}}, (d_i^0)_{1 \leq i \leq n}, (a_i^0)_{1 \leq i \leq n}\right)$ of parameter values. It is obtained by solving the system of Eq. (1) at the stationary states with the initial conditions x_0, *i.e.* by solving the following equations, for all integers i between 1 and n, considering the initial condition x_0:

$$\frac{dx_i}{dt} = 0,$$

which, from Eq. (1), straightforwardly leads to:

$$\Phi_i(x_0)(p^0) = \frac{a_i^0 + \sum_{g_j \in \mathcal{R}_{g_i}} \sum_{l \in t_{g_j, g_i}} s(x_{0_j}, \theta_{ji}^l)}{d_i^0},$$

for all integers i between 1 and n.

Focusing on the ith coordinate of Φ, we see that $\Phi_i(x)$ only depends on the relative positions of the jth coordinates of x such that $g_j \in \mathcal{R}_{g_i}$, with respect to the set of thresholds $\{\theta_{ji}^l\}_{l \in t_{g_j, g_i}}$. More precisely, we can explicit $\Phi_i(x)$ for all $x \in \prod_{i=1}^n (\mathbb{R}^+) \diagup \Theta_i$ as follows:

$$\Phi_i(x) = \left(p \mapsto \frac{a_i + \sum_{(g_j, g_i) \in \Gamma^+} \sum_{l \in t_{g_j, g_i} \cap [\![1, l_{ji}]\!]} k_{ji}^l}{d_i} + \frac{\sum_{(g_j, g_i) \in \Gamma^-} \sum_{l \in t_{g_j, g_i} \cap [\![l_{ji}+1, max(t_{g_j, g_i})]\!]} k_{ji}^l}{d_i}\right), \quad (2)$$

where for all $i \in [\![1, n]\!]$ and for all $g_j \in \mathcal{R}_{g_i}$, l_{ji} is defined as follows:

$$l_{ji} = max\{0 \cup \{l \in t_{g_j, g_i}, \theta_{ji}^l < x_j\}\},$$

which can also be expressed as follows:

$$l_{ji} = max\left([\![0, \alpha_{\mathbb{R}}^{\Theta_i}(x_j)]\!] \cap \{0 \cup t_{g_j, g_i}\}\right).$$

where $\Theta_i = \{\theta_{ji}^l\}_{g_j \in \mathcal{R}_{g_i}, l \in t_{g_j, g_i}}$ and the mappings $\alpha_{\mathbb{R}}^{\Theta_i}$ have been introduced in Definition 9.

Let us now consider the set of all the functions the ith coordinate of the focal function can take, that is to say that the set of the functions $\Phi_i(x)$ for all $x \in \prod_{i=1}^n (\mathbb{R}^+ \diagup \Theta_i)$.

Before, let us introduce, for all integers i between 1 and n, the mapping β^i from the set $\prod_{g_j \in \mathcal{R}_{g_i}} \{0 \cup t_{g_j, g_i}\}$ to the set of subsets of $\prod_{k=1}^n (\mathbb{R}^+ \diagup \Theta_k)$, defined as follows:

$$\beta^i : \begin{cases} \prod_{g_j \in \mathcal{R}_{g_i}} \{0 \cup t_{g_j, g_i}\} \to \wp\left(\prod_{k=1}^n (\mathbb{R}^+ \diagup \Theta_k)\right) \\ l \mapsto \{x \in (\mathbb{R}^+)^n, \gamma^i(x) = l\}. \end{cases}$$

where γ^i is a mapping from the set $\prod_{k=1}^n (\mathbb{R}^+ \diagup \Theta_k)$ to the set $\prod_{g_j \in \mathcal{R}_{g_i}} \{0 \cup t_{g_j, g_i}\}$, defined as follows:

$$\gamma^i : \begin{cases} \prod_{k=1}^n (\mathbb{R}^+ \diagup \Theta_k) \to \prod_{g_j \in \mathcal{R}_{g_i}} \{0 \cup t_{g_j, g_i}\} \\ (x_i)_{1 \leq i \leq n} \mapsto \left(max\left([\![0, \alpha_{\mathbb{R}}^{\Theta_i}(x_j)]\!] \cap \{0 \cup t_{g_j, g_i}\}\right)\right)_{g_j \in \mathcal{R}_{g_i}}. \end{cases}$$

In the mapping γ_i, we partition the state space $(\mathbb{R}^+)^n$ in a set of subspaces delimited by the set Θ_i of thresholds and then map each of these subspaces (from which we discard the thresholds) to an integer point of the set $\prod_{g_j \in \mathcal{R}_{g_i}} \{0 \cup t_{g_j, g_i}\}$ representing the relative positions of the jth coordinates of x for which $g_j \in \mathcal{R}_{g_i}$, with respect to the thresholds $\{\theta_{ji}^l\}_{l \in t_{g_j, g_i}}$. Inversely, the mapping β_i associates to each integer vector of the set $\prod_{g_j \in \mathcal{R}_{g_i}} \{0 \cup t_{g_j, g_i}\}$ the corresponding subspace as described above.

We can now define the sets $\mathcal{F}_i$ of the functions the ith coordinate of the focal function Φ can take, for all integers i between 1 and n, using the mappings defined above, as follows.

Definition 12. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and let us consider its associated class of PWLD models. Let g_i be a component of $\mathcal{G}$.

We define the set $\mathcal{F}_i$ as follows: $(x, y) \in \mathcal{F}_i$ if and only if there exists a vector of integers $l = (l_{ji})_{g_j \in \mathcal{R}_{g_i}} \in \prod_{g_j \in \mathcal{R}_{g_i}} \{0 \cup t_{g_j, g_i}\}$ such that:

(i) $x = \Phi_i\big(\beta^i(l)\big)$ and,
(ii) $y = \{(g_j, l_{ji})\}_{g_j\in\mathcal{R}_{g_i}}$.

Following Definition 12, each element of the set $\mathcal{F}_i$ is a couple $\big(\Phi_i\big(\beta^i\big((l_{ji})_{g_j\in\mathcal{R}_{g_i}}\big)\big), \{(g_j, l_{ji})\}_{g_j\in\mathcal{R}_{g_i}}\big)$ which:

(i) first coordinate is the function Φ_i takes in the subspace of states $\beta^i\big((l_{ji})_{g_j\in\mathcal{R}_{g_i}}\big)$;
(ii) second coordinate records the corresponding set of positioning l_{ji} of x_j, for all the regulators g_j of g_i.

The following property holds on the sets $\mathcal{F}_i$:

Property 4. *Let* $i\in[\![1, n]\!]$*. Then, for all* $\big((f,F),(f,F')\big)\in\mathcal{F}_i^2$*, we have:*

$F = F' \Longleftrightarrow f = f'$.

Proof. Let $i\in[\![1, n]\!]$, and (f, F) and (f, F') two elements of the set $\mathcal{F}_i$ where:

– $f = \Phi_i\big(\beta^i(l)\big)$, $F = \{(g_j, l_{ji})\}_{g_j\in\mathcal{R}_{g_i}}$, and
– $f' = \Phi_i\big(\beta^i(l')\big)$, $F' = \{(g_j, l'_{ji})\}_{g_j\in\mathcal{R}_{g_i}}$.

Assume that $F\neq F'$. Then, $l\neq l'$. Moreover, by definition of the focal function and of β^i, we have:

$$\Phi_i(\beta^i(l)) = \Bigg(p\to \frac{a_i + \sum_{(g_j,g_i)\in\Gamma^+}\sum_{r\in t_{g_j,g_i}\cap[\![1,l_{ji}]\!]} k^r_{ji}}{d_i} + \frac{\sum_{(g_j,g_i)\in\Gamma^-}\sum_{r\in t_{g_j,g_i}\cap[\![l_{ji}+1,max(t_{g_j,g_i})]\!]} k^r_{ji}}{d_i}\Bigg),$$

and:

$$\Phi_i(\beta^i(l')) = \Bigg(p\to \frac{a_i + \sum_{(g_j,g_i)\in\Gamma^+}\sum_{r\in t_{g_j,g_i}\cap[\![1,l'_{ji}]\!]} k^r_{ji}}{d_i} + \frac{\sum_{(g_j,g_i)\in\Gamma^-}\sum_{r\in t_{g_j,g_i}\cap[\![l'_{ji}+1,max(t_{g_j,g_i})]\!]} k^r_{ji}}{d_i}\Bigg).$$

Since $k^r_{ji}\neq 0$ for all r, j, i (statement (ii) in Definition 8) and $(l,l')\in(\prod_{g_j\in\mathcal{R}_i}\{0\cup t_{g_j,g_i}\})^2$, it follows that $\Phi_i(\beta^i(l))\neq\Phi_i(\beta^i(l'))$, that is to say that:

$f\neq f'$.

Assume now that $F = F'$. Then, $l = l'$, and thus $\beta^i(l) = \beta^i(l')$, that is to say that:

$f = f'$,

which ends the proof. □

Example 7. For illustration, let us consider the class of PWLD models associated with the regulatory graph of our case study (Fig. 1). Following Definition 12, the sets $\mathcal{F}_1$, $\mathcal{F}_2$ and $\mathcal{F}_3$ (corresponding to the components $p53$, M_c and M_n, respectively) are:

$\mathcal{F}_1 = \{f_1, f_2\}$,
$\mathcal{F}_2 = \{f'_1, f'_2\}$,
$\mathcal{F}_3 = \{f''_1, f''_2, f''_3, f''_4\}$,

where:

$$\begin{cases} f_1 = \left(p\mapsto \dfrac{a_1}{d_1}, \{(M_n, 1)\}\right),\\ f_2 = \left(p\mapsto \dfrac{a_1 + k^1_{31}}{d_1}, \{(M_n, 0)\}\right),\end{cases}$$

$$\begin{cases} f'_1 = \left(p\mapsto \dfrac{a_2}{d_2}, \{(p53, 0)\}\right),\\ f'_2 = \left(p\mapsto \dfrac{a_2 + k^2_{12}}{d_2}, \{(p53, 1)\}\right),\end{cases}$$

and:

$$\begin{cases} f''_1 = \left(p\mapsto \dfrac{a_3}{d_3}, \{(p53, 1), (M_c, 0)\}\right),\\ f''_2 = \left(p\mapsto \dfrac{a_3 + k^1_{23}}{d_3}, \{(p53, 1), (M_c, 1)\}\right),\\ f''_3 = \left(p\mapsto \dfrac{a_3 + k^1_{13}}{d_3}, \{(p53, 0), (M_c, 0)\}\right),\\ f''_4 = \left(p\mapsto \dfrac{a_3 + k^1_{13} + k^1_{23}}{d_3}, \{(p53, 0), (M_c, 1)\}\right).\end{cases}$$

We next define the sets $\mathcal{P}_i$ of the positionings of the ith coordinates of the focal function, for all integers i between 1 and n.

Definition 13. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and let us consider its associated class of PWLD models. Let g_i be a component of $\mathcal{G}$, Θ_i the set of thresholds of the outgoing interactions from g_i, ranked by increasing order, and $\mathcal{F}_i = \{(f_j, F_j)\}_{1\le j\le q_i}$, where $q_i = |\mathcal{F}_i|$.

We define the set $\mathcal{P}_i$ as follows:

$\{(x_j, y_j)\}_{1\le j\le q_i}\in\mathcal{P}_i$

if and only if there exists a value $p^0\in(\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n}\times(\mathbb{R}^+)^n$ of the parameter vector such that, for all $j\in[\![1, q_i]\!]$, we have:

(i) $x_j = (f_j, F_j)$ and,
(ii) $y_j = \alpha^{\Theta_i}_{\mathbb{R}}\big(f_j(p^0)\big)$.

In Definition 13, each element of $\mathcal{P}_i$ is a couple $\big((f_j, F_j), \alpha^{\Theta_i}_{\mathbb{R}}\big(f_j(p^0)\big)\big)$ which:

(i) first element (f_j, F_j) is a ith coordinate of the focal function;
(ii) second element $\alpha^{\Theta_i}_{\mathbb{R}}\big(f_j(p^0)\big)$ is the relative position of this coordinate with respect to the thresholds Θ_i of the outgoing interactions from g_i, for the parameter value p^0.

Example 8. For illustration, let us consider the class of PWLD models associated to the regulatory graph our case study (Fig. 1). Following Definition 13, the sets $\mathcal{P}_1$, $\mathcal{P}_2$ and $\mathcal{P}_3$ of positioning of the coordinates of the focal function are:

$$\begin{aligned}\mathcal{P}_1 =\{&\{(f_1,0),(f_2,0)\},\{(f_1,0),(f_2,1)\},\{(f_1,0),(f_2,2)\},\\ &\{(f_1,1),(f_2,1)\},\{(f_1,1),(f_2,2)\},\{(f_1,2),(f_2,2)\}\},\end{aligned}$$

$$\mathcal{P}_2 =\Big\{\{(f'_1,0),(f'_2,0)\},\{(f'_1,0),(f'_2,1)\},\{(f'_1,1),(f'_2,1)\}\Big\},$$

$$\begin{aligned}\mathcal{P}_3 =\{&\{(f''_1,0),(f''_2,0),(f''_3,0),(f''_4,0)\},\\ &\{(f''_1,0),(f''_2,0),(f''_3,0),(f''_4,1)\},\\ &\{(f''_1,0),(f''_2,1),(f''_3,0),(f''_4,1)\},\\ &\{(f''_1,0),(f''_2,0),(f''_3,1),(f''_4,1)\},\\ &\{(f''_1,0),(f''_2,1),(f''_3,1),(f''_4,1)\},\\ &\{(f''_1,1),(f''_2,1),(f''_3,1),(f''_4,1)\}\}.\end{aligned}$$

where $f_1, f_2, f'_1, f'_2, f''_1, f''_2, f''_3$, and f''_4 are defined in Example 7.

From the positionings of the coordinates of the focal function (that is to say that, given an element of $\mathcal{P}_i$, for all integers i between 1 and n), one can build a qualitative representation of the dynamics of a PWLD model, called a *state transition graph* (Glass and Pasternack, 1978; Gouzé and Sari, 2002). In this graph, the nodes represent the domains of the space state delimited by the thresholds of the step functions while the directed edges denote the possible transitions of the trajectories from a domain to the adjacent ones. More formally, a state transition graph $\mathcal{TG}$ of a PWLD model can be defined as follows.

Definition 14. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph and let us consider the associated class of PWLD models.

Let $\Theta = \{\Theta_i\}_{1\leq i\leq n}$, with $\Theta_i = \{\theta_{ij}^l\}_{(g_i,g_j)\in\Gamma, l\in t_{g_i,g_j}}$, be a set of threshold values and $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^+)^n$ a vector of parameter values, thus defining a PWLD model of the considered class.

Let $\mathcal{D}$ be the set of subspaces of $(\mathbb{R}^+)^n$ delimited by Θ, from which we discard the threshold values.

The state transition graph $\mathcal{TG}$ associated with a PWLD model is a couple $(\mathcal{V}, \mathcal{T})$, defined as follows:

(i) $\mathcal{V} = \mathcal{D}$;
(ii) $\mathcal{T}$ is a set of subsets of $\mathcal{D} \times \mathcal{D}$ defined as follows. Let D and D' be two domains of $\mathcal{D}$, then:
   - if D and D' are not adjacent, then $(D, D') \notin \mathcal{T}$;
   - if D and D' are adjacent, let $i^0 \in [\![1, n]\!]$, $j^0 \in [\![1, n]\!]$ and $l^0 \in t_{g_{i^0},g_{j^0}}$ be three integers such that the hyperplane of equation:

     $$x_{i^0} = \theta_{i^0 j^0}^{l^0},$$

     is the hyperplane separating D and D'.
     Let m be the element of $\prod_{g_j\in\mathcal{R}_{g_{i^0}}} \{0 \cup t_{g_j,g_{i^0}}\}$ such that:

     $$D \subseteq \beta^{i^0}(m).$$

     Then:
     (i) if $\alpha_s^{\Theta}(D)_{i^0} < \alpha_s^{\Theta}(D')_{i^0}$, then $(D, D') \in \mathcal{T}$ if and only if:

     $$\alpha_{\mathbb{R}}^{\Theta_{i^0}}\left(\Phi_{i^0}\left(\beta^{i^0}(m)\right)(p^0)\right) \geq \alpha_{\mathbb{R}}^{\Theta_{i^0}}(\theta_{i^0 j^0}^{l^0}),$$

     (ii) if $\alpha_s^{\Theta}(D)_{i^0} > \alpha_s^{\Theta}(D')_{i^0}$, then $(D, D') \in \mathcal{T}$ if and only if:

     $$\alpha_{\mathbb{R}}^{\Theta_{i^0}}\left(\Phi_{i^0}\left(\beta^{i^0}(m)\right)(p^0)\right) \leq \alpha_{\mathbb{R}}^{\Theta_{i^0}}(\theta_{i^0 j^0}^{l^0}).$$

In Definition 14, on can check that a state transition graph does not depend on the precise value of the parameters but on the positioning of the coordinates of the focal function, that is to say that, an element of the set $\prod_{i=1}^n \mathcal{P}_i$ completely defines a state transition graph. The reader can refer to Glass and Pasternack (1978) and Gouzé and Sari (2002) for more details regarding state transition graphs of PWLD models.

Example 9. To illustrate Definition 14, let us consider the class of PWLD models associated with the regulatory graph of our case study (Fig. 1). We focus on the model of this class defined by the following positionings $P_1 \in \mathcal{P}_1$, $P_2 \in \mathcal{P}_2$ and $P_3 \in \mathcal{P}_3$ of the coordinates of the focal function.

$$P_1 = \{(f_1, 0), (f_2, 2)\},$$
$$P_2 = \{(f_1', 0), (f_2', 1)\},$$
$$P_3 = \{(f_1'', 0), (f_2'', 0), (f_3'', 1), (f_4'', 1)\},$$

where f_1, f_2, f_1', f_2', f_1'', f_2'', f_3'', and f_4'' are defined in Example 7.

Let $\mathcal{TG} = (\mathcal{V}, \mathcal{T})$ be the state transition graph of this model. Then, following Definition 14, the set of vertexes $\mathcal{V}$ is:

$$\mathcal{V} = \{D^{000}, D^{001}, D^{010}, D^{011}, D^{100}, D^{101}, D^{110}, D^{111}, D^{200}, D^{201}, D^{210}, D^{211}\}$$

where:

$$\begin{cases} D^{000} = \{x \mid 0 \leq x_1 < \theta_{13}^1,\ 0 \leq x_2 < \theta_{23}^1,\ 0 \leq x_3 < \theta_{31}^1\} \\ D^{001} = \{x \mid 0 \leq x_1 < \theta_{13}^1,\ 0 \leq x_2 < \theta_{23}^1,\ x_3 > \theta_{31}^1\}, \\ D^{010} = \{x \mid 0 \leq x_1 < \theta_{13}^1,\ x_2 > \theta_{23}^1,\ 0 \leq x_3 < \theta_{31}^1\}, \\ D^{011} = \{x \mid 0 \leq x_1 < \theta_{13}^1,\ x_2 > \theta_{23}^1,\ x_3 > \theta_{31}^1\}, \\ D^{100} = \{x \mid \theta_{13}^1 < x_1 < \theta_{12}^2,\ 0 \leq x_2 < \theta_{23}^1,\ 0 \leq x_3 < \theta_{31}^1\}, \\ D^{101} = \{x \mid \theta_{13}^1 < x_1 < \theta_{12}^2,\ 0 \leq x_2 < \theta_{23}^1,\ x_3 > \theta_{31}^1\}, \\ D^{110} = \{x \mid \theta_{13}^1 < x_1 < \theta_{12}^2,\ x_2 > \theta_{23}^1,\ 0 \leq x_3 < \theta_{31}^1\}, \\ D^{111} = \{x \mid \theta_{13}^1 < x_1 < \theta_{12}^2,\ x_2 > \theta_{23}^1,\ x_3 > \theta_{31}^1\}, \\ D^{200} = \{x \mid x_1 > \theta_{12}^2,\ 0 \leq x_2 < \theta_{23}^1,\ 0 \leq x_3 < \theta_{31}^1\}, \\ D^{201} = \{x \mid x_1 > \theta_{12}^2,\ 0 \leq x_2 < \theta_{23}^1,\ x_3 > \theta_{31}^1\}, \\ D^{210} = \{x \mid x_1 > \theta_{12}^2,\ x_2 > \theta_{23}^1,\ 0 \leq x_3 < \theta_{31}^1\}, \\ D^{211} = \{x \mid x_1 > \theta_{12}^2,\ x_2 > \theta_{23}^1,\ x_3 > \theta_{31}^1\}, \end{cases}$$

and the set of transitions $\mathcal{T}$ is:

$$\mathcal{T} = \{(D^{000}, D^{100}),$$
$$(D^{000}, D^{001}), (D^{100}, D^{200}), (D^{200}, D^{210}), (D^{010}, D^{110}),$$
$$(D^{010}, D^{011}), (D^{010}, D^{000}), (D^{110}, D^{210}), (D^{101}, D^{001}), (D^{101}, D^{100}),$$
$$(D^{201}, D^{211}), (D^{201}, D^{200}), (D^{201}, D^{101}), (D^{011}, D^{001}), (D^{111}, D^{011}),$$
$$(D^{111}, D^{110}), (D^{111}, D^{101}), (D^{211}, D^{111}), (D^{211}, D^{210})\}.$$

Fig. 6(a) shows the state transition graph of the considered PWLD model.

A4. Partial order

We now equip the sets $\mathcal{F}_i$ of the ith coordinates of the focal function with the partial order $\preceq_{\mathcal{F}}$, for all integers i between 1 and n, defined as follows.

Definition 15. Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph and let us consider its associated class of PWLD models. Let g_i be a component of $\mathcal{G}$.

We define the partially ordered set $(\mathcal{F}_i, \preceq_{\mathcal{F}})$ as follows: let (f, F) and (f', F') be two elements of $\mathcal{F}_i$.

Then, $(f, F) \preceq_{\mathcal{F}} (f', F')$ if and only if, for all vectors of parameter values $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^+)^n$, we have:

$$f(p^0) \leq f'(p^0).$$

This partial order can be defined from the signs of the incoming interactions of a component g_i according to the following property.

Property 5. *Let g_i be a component of $\mathcal{G}$, and (f, F) and (f', F') two elements of $\mathcal{F}_i$ where:*

$$F = \{(g_j, l_{ji})\}_{g_j\in\mathcal{R}_{g_i}},$$

and:

$$F' = \{(g_j, l'_{ji})\}_{g_j\in\mathcal{R}_{g_i}}.$$

Then, $(f, F) \preceq_{\mathcal{F}} (f', F')$ if and only if the following conditions hold:

(i) *for all $j \in [\![1, |\mathcal{R}_{g_i}|]\!]$ such that $(g_j, g_i) \in \Gamma^+$, we have: $l_{ji} \leq l'_{ji}$, and;*
(ii) *for all $j \in [\![1, |\mathcal{R}_{g_i}|]\!]$ such that $(g_j, g_i) \in \Gamma^-$, we have: $l_{ji} \geq l'_{ji}$.*

Proof. Let $i \in [\![1, n]\!]$, and let (f, F) and (f', F') be two elements of $\mathcal{F}_i$ where:

$$F = \{(g_j, l_{ji})\}_{g_j\in\mathcal{R}_{g_i}},$$

and:

$$F' = \{(g_j, l'_{ji})\}_{g_j\in\mathcal{R}_{g_i}}.$$

Let us first prove the necessary condition of the property. Assume that $(f, F) \preceq_{\mathcal{F}} (f', F')$. Then, by Definition 15, we have, for all vectors of parameter values $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^+)^n$:

$$f(p^0) \leq f'(p^0). \tag{3}$$

It follows, from the expression of f and f' as a function of the parameters (see Eq. (2) in Section A.3), that the following condition holds, for all $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^+)^n$:

$$\begin{aligned}
& d_i\big(f(p^0) - f'(p^0)\big) \\
&= \left(a_i + \sum_{(g_j,g_i)\in\Gamma^+} \sum_{l\in t_{g_j,g_i}\cap[\![1,l_{ji}]\!]} k_{ji}^l + \sum_{(g_j,g_i)\in\Gamma^-} \sum_{l\in t_{g_j,g_i}\cap[\![l_{ji}+1,max(t_{g_j,g_i})]\!]} k_{ji}^l \right) \\
&- \left(a_i + \sum_{(g_j,g_i)\in\Gamma^+} \sum_{l\in t_{g_j,g_i}\cap[\![1,l'_{ji}]\!]} k_{ji}^l + \sum_{(g_j,g_i)\in\Gamma^-} \sum_{l\in t_{g_j,g_i}\cap[\![l'_{ji}+1,max(t_{g_j,g_i})]\!]} k_{ji}^l \right) \\
&= \sum_{(g_j,g_i)\in\Gamma^+} \left(\sum_{l\in t_{g_j,g_i}\cap[\![1,l_{ji}]\!]} k_{ji}^l - \sum_{l\in t_{g_j,g_i}\cap[\![1,l'_{ji}]\!]} k_{ji}^l \right) \\
&+ \sum_{(g_j,g_i)\in\Gamma^-} \left(\sum_{l\in t_{g_j,g_i}\cap[\![l_{ji}+1,max(t_{g_j,g_i})]\!]} k_{ji}^l - \sum_{l\in t_{g_j,g_i}\cap[\![l'_{ji}+1,max(t_{g_j,g_i})]\!]} k_{ji}^l \right) \\
&\leq 0.
\end{aligned} \tag{4}$$

Now let $j^0 \in [\![1, |\mathcal{R}_{g_i}|]\!]$. By tending k_{ji}^l to 0 for all $j \neq j^0$, we get:

(i)
$$\sum_{l\in t_{g_{j^0},g_i}\cap[\![1,l_{j^0i}]\!]} k_{j^0i}^l - \sum_{l\in t_{g_{j^0},g_i}\cap[\![1,l'_{j^0i}]\!]} k_{j^0i}^l \leq 0,$$
if $(g_{j^0}, g_i) \in \Gamma^+$, and:

(ii)
$$\sum_{l\in t_{g_{j^0},g_i}\cap[\![l_{j^0i}+1,max(t_{g_{j^0},g_i})]\!]} k_{j^0i}^l - \sum_{l\in t_{g_{j^0},g_i}\cap[\![l'_{j^0i}+1,max(t_{g_{j^0},g_i})]\!]} k_{j^0i}^l \leq 0,$$
if $(g_{j^0}, g_i) \in \Gamma^-$.

It thus follows, from the previous inequalities, that:

(i) $l_{j^0i} \leq l'_{j^0i}$, if $(g_{j^0}, g_i) \in \Gamma^+$,
(ii) $l_{j^0i} \geq l'_{j^0i}$, if $(g_{j^0}, g_i) \in \Gamma^-$,

which ends the proof of the necessary condition.

Let us now prove the sufficient condition of the property. Assume that:

(i) for all $j \in [\![1, |\mathcal{R}_{g_i}|]\!]$ such that $(g_j, g_i) \in \Gamma^+$, we have: $l_{ji} \leq l'_{ji}$, and;
(ii) for all $j \in [\![1, |\mathcal{R}_{g_i}|]\!]$ such that $(g_j, g_i) \in \Gamma^-$, we have: $l'_{ji} \leq l_{ji}$.

Then, it follows that the inequality in Eq. (4) is satisfied, for all $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^+)^n$, which implies that:

$$f(p^0) \leq f'(p^0), \tag{5}$$

for all $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^+)^n$, that is to say that:

$$(f, F) \preceq_{\mathcal{F}} (f', F'),$$

which ends the proof of the sufficient condition of the property, and thus also the proof of the property. □

The partial order $\preceq_{\mathcal{F}}$ imposes constraints on the relative positions between the coordinates of the focal function. The following property gives necessary conditions on the sets $\mathcal{P}_i$ of the positionings of the coordinates of the focal function, imposed by the partial order $\preceq_{\mathcal{F}}$.

Property 6. *Let $i \in [\![1, n]\!]$, and $\mathcal{F}_i = \{(f_i, F_i)\}_{1\leq i\leq q_i}$, with $q_i = |\mathcal{F}_i|$. Let P be an element of the set $\prod_{i=1}^{q_i}((f_i, F_i) \times \mathbb{N})$ where:*

$$P = \{((f_1, F_1), l_1), \ldots, ((f_{q_i}, F_{q_i}), l_{q_i})\}.$$

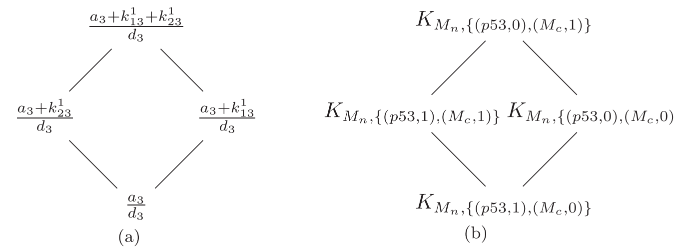

Fig. 5. Hasse diagrams of the partially ordered set $(\mathcal{F}_3, \preceq_{\mathcal{F}})$ (a), and $(\mathcal{K}_{M_n}, \preceq_{\mathcal{K}})$ (b), in the case of Example 1. The Hasse diagrams of $(\mathcal{K}_{M_n}, \preceq_{\mathcal{K}})$ and $(\mathcal{F}_3, \preceq_{\mathcal{F}})$ are linked by the mapping χ_3 (Property 7). For sake of clarity, we omitted the levels of the regulators associated to the coordinates of the focal function in the writing of the elements of $\mathcal{F}_3$.

Assume that $P \in \mathcal{P}_i$. Then the following condition holds, for all $(k, k') \in [\![0, q_i]\!]^2$:

$$(f_k, F_k) \preceq_{\mathcal{F}} (f_{k'}, F_{k'}) \Longrightarrow l_k \leq l_{k'}.$$

Proof. We take the same notations as in the statement of Property 6.

Let $i \in [\![1, n]\!]$, Θ_i the set of the thresholds of the step functions for the outgoing interactions of g_i, and P an element of the set $\prod_{i=1}^{q_i}((f_i, F_i) \times \mathbb{N})$ where:

$$P = \{((f_1, F_1), l_1), \ldots, ((f_{q_i}, F_{q_i}), l_{q_i})\}.$$

Assume that P is an element of $\mathcal{P}_i$, and let k and k' be two integers of $[\![0, q_i]\!]$.

Now assume that $(f_k, F_k) \preceq_{\mathcal{F}} (f_{k'}, F_{k'})$. Then, according to Definition 15, the following condition holds, for all vectors of parameter values $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^+)^n$:

$$f_k(p^0) \leq f_{k'}(p^0).$$

It follows, by definition of the mapping $\alpha_{\mathbb{R}}^{\Theta_i}$, that, for all $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^+)^n$, we have:

$$\alpha_{\mathbb{R}}^{\Theta_i}\big(f_k(p^0)\big) \leq \alpha_{\mathbb{R}}^{\Theta_i}\big(f_{k'}(p^0)\big),$$

that is to say that:

$$l_k \leq l_{k'},$$

by definition of the set $\mathcal{P}_i$ (Definition 13), which ends the proof. □

Example 10. To illustrate the partial order $\preceq_{\mathcal{F}}$ introduced above, let us consider the class of PWLD models associated to the regulatory graph of our case study (Fig. 1). Fig. 5(a) shows the Hasse diagram representing the partially ordered set $(\mathcal{F}_3, \preceq_{\mathcal{F}})$, associated to component M_n, following Definition 15.

Appendix B. From PWLD models to logical models

B1. Mapping between PWLD and logical models

Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph. Let us consider its associated classes of logical models and PWLD models (as defined in Section 3.2 and Appendix A.1). We define the mapping χ_i between the set $\mathcal{F}_i$ of the ith coordinates of the focal function and the set $\mathcal{K}_{g_i}$ of the logical parameters of component g_i, for all integers i between 1 and n, as follows.

Definition 16. Let $i \in [\![1, n]\!]$. We define the mapping χ_i between the set $\mathcal{F}_i$ and the set $\mathcal{K}_{g_i}$ as follows:

$$\chi_i : \begin{cases} \mathcal{F}_i & \to \mathcal{K}_{g_i} \\ (f, F) & \mapsto K_{g_i,F} \end{cases}$$

Let us check that χ_i is well defined, that is to say that:

$$\chi_i(\mathcal{F}_i) \subseteq \mathcal{K}_{g_i}.$$

Let $K \in \chi_i(\mathcal{F}_i)$. Then, there exists $(f, F) \in \mathcal{F}_i$ such that $K = K_{g_i,F}$. By definition of $\mathcal{F}_i$, there exists $(l_{ji})_{g_j \in \mathcal{R}_{g_i}} \in \prod_{g_j \in \mathcal{R}_{g_i}} \{0 \cup t_{g_j,g_i}\}$, such that $F = \{(g_j, l_{ji})\}_{g_j \in \mathcal{R}_{g_i}}$. It follows, from Definition 2, that $F \in \Omega$, which implies that $K = K_{g_i,F} \in \mathcal{K}_{g_i}$.

The following property holds:

Property 7. *Let $i \in [\![1, n]\!]$. Then,*

(i) *χ_i defines a bijection between the sets $\mathcal{F}_i$ and $\mathcal{K}_{g_i}$,*
(ii) *let $(\mathcal{K}_{g_i}, \preceq)$ be the partially ordered set defined as follows: for all $(K, K') \in \mathcal{K}_{g_i} \times \mathcal{K}_{g_i}$, $K \preceq K'$ if and only if:*

$$\chi_i^{-1}(K) \preceq_{\mathcal{F}} \chi_i^{-1}(K').$$

Then we have:

$$(\mathcal{K}_{g_i}, \preceq) = (\mathcal{K}_{g_i}, \preceq_{\mathcal{K}}).$$

Proof. We take the same notations as in the statement of Property 7.

Let $i \in [\![1, n]\!]$. Let us prove statement (i), by first showing that χ_i is injective. Let (f, F) and (f', F') be two elements of $\mathcal{F}_i$, such that:

$$\chi_i(f, F) = \chi_i(f', F').$$

Then, $K_{g_i,F} = K_{g_i,F'}$, and thus $F = F'$. It follows, from Property 4, that $f = f'$. Therefore, χ_i is injective.

Moreover we have $|\mathcal{F}_i| = |\prod_{g_j \in \mathcal{R}_{g_i}} \{0 \cup t_{g_j,g_i}\}| = |\mathcal{K}_{g_i}|$. Thus, χ_i is bijective.

Let us now prove statement (ii). Let $K_{g_i,F}$ and $K_{g_i,F'}$ be two elements of $\mathcal{K}_{g_i}$, and (f, F) and (f', F') the antecedents of $K_{g_i,F}$ and $K_{g_i,F'}$, respectively, by χ_i. By definition of the partial order $\preceq$, the following inequality:

$$K_{g_i,F} \preceq K_{g_i,F'}$$

is equivalent to the following one:

$$(f, F) \preceq_{\mathcal{F}} (f', F'),$$

which, from Property 5 and Definition 3, is equivalent to the following inequality:

$$K_{g_i,F} \preceq_{\mathcal{K}} K_{g_i,F'},$$

which ends the proof. □

Property 7(ii) states that the partial order $\preceq$ in the set $\mathcal{K}_{g_i}$, induced by the mapping χ_i from the partial order $\preceq_{\mathcal{F}}$ in the set $\mathcal{F}_i$, is the partial order $\preceq_{\mathcal{K}}$ in the set $\mathcal{K}_{g_i}$ introduced in Definition 3.

We next define the mapping Ψ_i between the set $\mathcal{P}_i$ of the positionings of the ith coordinates of the focal function, and the set $\mathcal{V}^a_{g_i}$ of the admissible valuations of the logical parameters of component g_i, for all integers i between 1 and n, as follows.

Definition 17. Let $i \in [\![1, n]\!]$. We define the mapping Ψ_i between the set $\mathcal{P}_i$ and the set $\mathcal{V}^a_{g_i}$ as follows:

$$\Psi_i : \begin{cases} \mathcal{P}_i \to \mathcal{V}^a_{g_i} \\ \{\big((f_j, F_j), l_j\big)\}_{1 \le j \le q_i} \mapsto \{\big(\chi_i((f_j, F_j)), l_j\big)\}_{1 \le j \le q_i} \end{cases}$$

where $q_i = |\mathcal{F}_i|$.

In Definition 17, the mappings Ψ_i associate each model of the class of PWLD models (*i.e.* each element of the set $\mathcal{P}_i$) to a specific model of the class of logical models (*i.e.* an element of the set $\mathcal{V}^a_{g_i}$). It is the logical model which value of the logical parameter K_{g_i,F_j} is the positioning l_j of the corresponding ith coordinate (f_j, F_j) of the focal function, for all integers $i \in [\![1, n]\!]$ and $j \in [\![1, q_i]\!]$. Note that Ψ_i does not define a bijection.

Let us check that Ψ_i is well defined, that is to say that:

$$\Psi_i(\mathcal{P}_i) \subseteq \mathcal{V}^a_{g_i}.$$

Let $L \in \Psi_i(\mathcal{P}_i)$. Then, by definition of χ_i, there exists $\{\big((f_j, F_j), l_j\big)\}_{1 \le j \le q_i} \in \mathcal{P}_i$ such that:

$$L = \{\big(\chi_i\big((f_j, F_j)\big), l_j\big)\}_{1 \le j \le q_i}$$
$$= \{\big(K_{g_i,F_j}, l_j\big)\}_{1 \le j \le q_i}.$$

Now let $(K_{g_i,F_j}, K_{g_i,F_k}) \in \mathcal{K}_{g_i} \times \mathcal{K}_{g_i}$, and assume that $K_{g_i,F_j} \preceq_{\mathcal{K}} K_{g_i,F_k}$. From Property 7(ii), it follows that: $(f_j, F_j) \preceq_{\mathcal{F}} (f_k, F_k)$. From Property 6, we then have: $l_j \le l_k$.

We have thus shown that for all $(K_{g_i,F_j}, K_{g_i,F_k}) \in \mathcal{K}_{g_i} \times \mathcal{K}_{g_i}$, if $K_{g_i,F_j} \preceq_{\mathcal{K}} K_{g_i,F_k}$, then $l_j \le l_k$, that is to say that:

$$L \in \mathcal{V}^a_{g_i},$$

by definition of $\mathcal{V}^a_{g_i}$ (Definition 4).

Example 11. To illustrate the mappings χ_i introduced in Definition 16, let us consider our case study (Fig. 1). Following Definition 16, the mappings χ_1, χ_2 and χ_3 between the sets $\mathcal{F}_1$ and $\mathcal{K}_{p53}$, $\mathcal{F}_2$ and $\mathcal{K}_{M_c}$, and $\mathcal{F}_3$ and $\mathcal{K}_{M_n}$ respectively, are defined as follows:

$$\begin{cases} \chi_1(f_1) = K_{p53,\{(M_n,1)\}}, \\ \chi_1(f_2) = K_{p53,\{(M_n,0)\}}, \end{cases}$$

$$\begin{cases} \chi_2\big(f'_1\big) = K_{M_c,\{(p53,0)\}}, \\ \chi_2\big(f'_2\big) = K_{M_c,\{(p53,1)\}}, \end{cases}$$

and:

$$\begin{cases} \chi_3\big(f''_1\big) = K_{M_n,\{(p53,1),(M_c,0)\}}, \\ \chi_3\big(f''_2\big) = K_{M_n,\{(p53,1),(M_c,1)\}}, \\ \chi_3\big(f''_3\big) = K_{M_n,\{(p53,0),(M_c,0)\}}, \\ \chi_3\big(f''_4\big) = K_{M_n,\{(p53,0),(M_c,1)\}}, \end{cases}$$

where f_1, f_2, f'_1, f'_2, f''_1, f''_2, f''_3, and f''_4 are defined in Example 7.

Fig. 5(b) shows the Hasse diagram of the partially ordered set $(\mathcal{K}_{M_n}, \preceq_{\mathcal{K}})$, induced by the mapping χ_3.

Example 12. To illustrate the mappings Ψ_i introduced in Definition 17, let us consider our case study (Fig. 1). Let us focus, as an example, on the component M_c. Following Definition 17, the mapping Ψ_2 between the sets $\mathcal{P}_2$ and $\mathcal{V}^a_{M_c}$, is defined as follows:

$$\begin{cases} \Psi_2(\{(f'_1, 0), (f'_2, 0)\}) = \{(K_{M_c,\{(p53,0)\}}, 0), (K_{M_c,\{(p53,1)\}}, 0)\}, \\ \Psi_2(\{(f'_1, 0), (f'_2, 1)\}) = \{(K_{M_c,\{(p53,0)\}}, 0), (K_{M_c,\{(p53,1)\}}, 1)\}, \\ \Psi_2(\{(f'_1, 1), (f'_2, 1)\}) = \{(K_{M_c,\{(p53,0)\}}, 1), (K_{M_c,\{(p53,1)\}}, 1)\}, \end{cases}$$

where f'_1 and f'_2 are defined in Example 7.

B2. Dynamical analysis

Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and let us consider its associated classes of logical models and PWLD models (as defined in Sections 3.2 and Appendix A.1). We focus in this section on the link between the dynamics of a PWLD model of this class and its corresponding logical model via the mappings Ψ_i defined in Appendix B.1.

The following theorem states a link between the state transition graphs of these two models.

Theorem 1. *Let $(P_i)_{1 \le i \le n}$ be an element of $\prod_{i=1}^{n} \mathcal{P}_i$ in the considered class of PWLD models, and $\mathcal{TG} = (\mathcal{D}, \mathcal{T})$ be the corresponding state transition graph.*

Let us consider the model in the considered class of logical models which valuation of the logical parameters is $\Psi_i(P_i)$, for all integers i between 1 and n, and let $(\mathcal{V}', \mathcal{T}')$ be its asynchronous state transition graph.

We define the graph $(\mathcal{V}'', \mathcal{T}'')$ as follows:

(i) $\mathcal{V}'' = \mathcal{V}'$,

(ii) *$\mathcal{T}''$ is a set of subset of $\mathcal{V}' \times \mathcal{V}'$ defined as follows: let $s = (s_i)_{1 \le i \le n}$ and $s' = (s'_i)_{1 \le i \le n}$ be two elements of $\mathcal{V}'$. Then $(s, s') \in \mathcal{T}''$ if and only if:*

$$\left(\prod_{i=1}^{n} (\alpha_{\mathbb{R}}^{\Theta_i})^{-1}(s_i) / \Theta_i, \prod_{i=1}^{n} (\alpha_{\mathbb{R}}^{\Theta_i})^{-1}(s'_i) / \Theta_i \right) \in \mathcal{T}.$$

where Θ_i is the set of the thresholds of the step functions of the outgoing transitions from g_i, for all $i \in [\![1, n]\!]$.

Then, we have:

$$\mathcal{T}'' = \mathcal{T}'.$$

Proof. We take the same notations as in the statement of Theorem 1.

Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and let us consider its associated classes of logical models and PWLD models.

Let $(P_i)_{1 \le i \le n} \in \prod_{i=1}^{n} \mathcal{P}_i$ in the considered class of PWLD models, and $\mathcal{TG} = (\mathcal{D}, \mathcal{T})$ the corresponding state transition graph.

Let us consider the logical model which valuation L_i of the logical parameters associated to g_i is:

$$L_i = \Psi_i(P_i),$$

for all $i \in [\![1, n]\!]$, and let $(\mathcal{V}', \mathcal{T}')$ be its asynchronous state transition graph.

Let us now prove the following inclusion:

$$\mathcal{T}'' \subseteq \mathcal{T}'. \tag{6}$$

Let $s = (s_i)_{1 \le i \le n}$ and $s' = (s'_i)_{1 \le i \le n}$ be two elements of $\mathcal{V}'$. Assume that $(s, s') \in \mathcal{T}''$. It follows that:

$$\left(D, D'\right) \in \mathcal{T}.$$

where D and D' are defined as follows:

$$D = \prod_{i=1}^{n} (\alpha_{\mathbb{R}}^{\Theta_i})^{-1}(s_i) / \Theta_i \text{ and } D' = \prod_{i=1}^{n} (\alpha_{\mathbb{R}}^{\Theta_i})^{-1}(s'_i) / \Theta_i.$$

By definition of $\mathcal{T}$ (Definition 14), D and D' are adjacent domains, which implies, by definition of D and D', that there exists $i^0 \in [\![1, n]\!]$ such that the following two conditions hold:

(i) either

$$s_{i^0} = s'_{i^0} + 1, \tag{7}$$

or

$$s_{i^0} = s'_{i^0} - 1, \tag{8}$$

(ii)

$$s_i = s'_i \tag{9}$$

for all $i \neq i^0$.

Let i^0 be such an integer. Then there exists $j^0 \in [\![1, n]\!]$ and $l^0 \in t_{g_{i^0}, g_{j^0}}$ such that D and D' are separated by the hyperplane of equation:

$$x_{i^0} = \theta^{l^0}_{i^0 j^0}.$$

Let $m = (m_j)_{g_j \in \mathcal{R}_{g_{i^0}}}$ be the element of $\prod_{g_j \in \mathcal{R}_{i^0}} \{0 \cup t_{g_j, g_{i^0}}\}$ such that:

$$D \subseteq \beta^{i^0}(m).$$

It follows, by definition of D, D' and β^{i^0}, that, for all $g_j \in \mathcal{R}_{g_{i^0}}$, we have:

$$s_j = m_j. \tag{10}$$

Moreover, by definition of $\mathcal{T}$, D and D', the following conditions hold:

Table 3
Correspondence table between the logical parameters and the coordinates of the focal function for the case study (Fig. 1). Logical parameters and coordinates of the focal function are formally linked by the mappings χ_i (Definition 16 in Appendix B.1). For sake of clarity, we omitted to mention the combinations of levels of the regulators in the coordinates of the focal function.

Components	Logical parameters (sets $\mathcal{K}_{g_i}$)	Coordinates of the focal function (sets $\mathcal{F}_i$)
$p53$	$K_{p53,\{(M_n,0)\}}$	$\frac{a_1 + k^1_{31}}{d_1}$
	$K_{p53,\{(M_n,1)\}}$	$\frac{a_1}{d_1}$
M_c	$K_{M_c,\{(p53,0)\}}$	$\frac{a_2}{d_2}$
	$K_{M_c,\{(p53,1)\}}$	$\frac{a_2 + k^2_{12}}{d_2}$
M_n	$K_{M_n,\{(p53,0),(M_c,0)\}}$	$\frac{a_3 + k^1_{13}}{d_3}$
	$K_{M_n,\{(p53,1),(M_c,0)\}}$	$\frac{a_3}{d_3}$
	$K_{M_n,\{(p53,0),(M_c,1)\}}$	$\frac{a_3 + k^1_{13} + k^1_{23}}{d_3}$
	$K_{M_n,\{(p53,1),(M_c,1)\}}$	$\frac{a_3 + k^1_{23}}{d_3}$

(i) if $s_{i^0} < s'_{i^0}$, then:

$$l_k \geq \alpha_{\mathbb{R}}^{\Theta_i}(\theta^{l^0}_{i^0 j^0}), \tag{11}$$

(ii) if $s_{i^0} > s'_{i^0}$, then:

$$l_k \leq \alpha_{\mathbb{R}}^{\Theta_i}(\theta^{l^0}_{i^0 j^0}), \tag{12}$$

where l_k is the integer such that $((f_k, F_k), l_k)$ is the element of P_{i^0} satisfying:

$$F_k = \{(g_j, m_j)\}_{g_j \in \mathcal{R}_{g_i}}.$$

Since $L_{i^0} = \Psi_i(P_{i^0})$, l_k is also the value of the logical parameter $K_{g_{i^0}, F_k}$. It thus follows, from Eqs. (7)–(12), that:

$$(s, s') \in \mathcal{T}',$$

thereby proving the inclusion of Eq. (6).

The proof of the opposite inclusion, that is to say that $\mathcal{T}' \subseteq \mathcal{T}''$, is deduced by proceeding by equivalence, which ends the proof of Theorem 1. □

Example 13. To illustrate Theorem 1, let us consider the classes of PWLD models and logical models associated with the regulatory graph of our case study (Fig. 1).

Let us focus on the PWLD model which positionings $P_1 \in \mathcal{P}_1$, $P_2 \in \mathcal{P}_2$ and $P_3 \in \mathcal{P}_3$ of the coordinates of the focal function are those given in Example 9.

Fig. 6(a) shows the corresponding state transition graph. Then, the state transition graph defined in Theorem 1 (shown in Fig. 6(b)) is the asynchronous state transition graph of the logical model which valuations L_1, L_2 and L_3 of the logical parameters are:

$$L_1 = \Psi_1(P_1), \ L_2 = \Psi_2(P_2) \text{ and } L_3 = \Psi_3(P_3).$$

Appendix C. Correspondence between logical models and PWLD models for the case study

We consider the model of the core of the p53-Mdm2 network, proposed by Abou-Jaoudé et al. (2009), described in Section 2. The evolution of the class of PWLD models associated to its regulatory graph (shown in Fig. 1) is described by the system of differential equations given in Example 6. Table 3 gives the correspondence between the sets $\mathcal{F}_i$ of the coordinates of the focal function and the sets $\mathcal{K}_{g_i}$ of the logical parameters of the class of logical models associated to the regulatory graph, via the mappings χ_i described

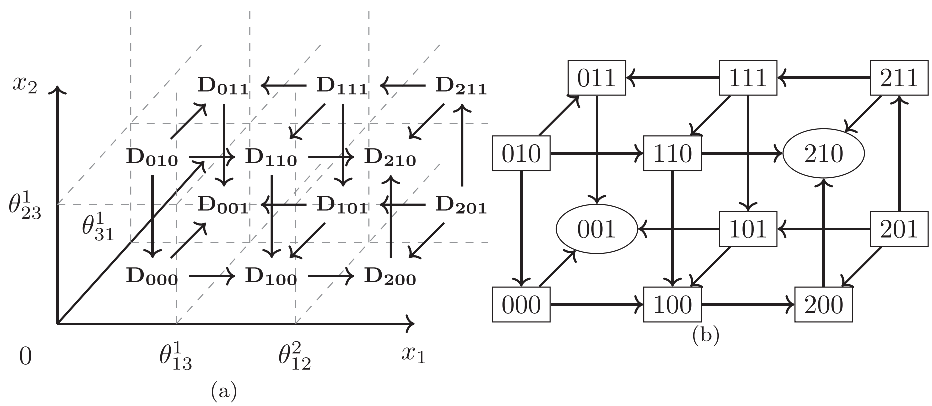

Fig. 6. (a) State transition graph of the PWLD models of the case study (Fig. 1) corresponding to the positionings P_1, P_2 and P_3 of the coordinates of the focal function of Example 9. x_1, x_2 and x_3 denote the variables associated to the components $p53$, M_c and M_n, respectively. (b) Asynchronous state transition graph of the logical model of our case study which valuations of the logical parameters are $\Psi_1(P_1)$, $\Psi_2(P_2)$ and $\Psi_3(P_3)$. The values of the components in each state are ordered as follows: $p53$, M_c, M_n. Ellipses represent the steady states of the model.

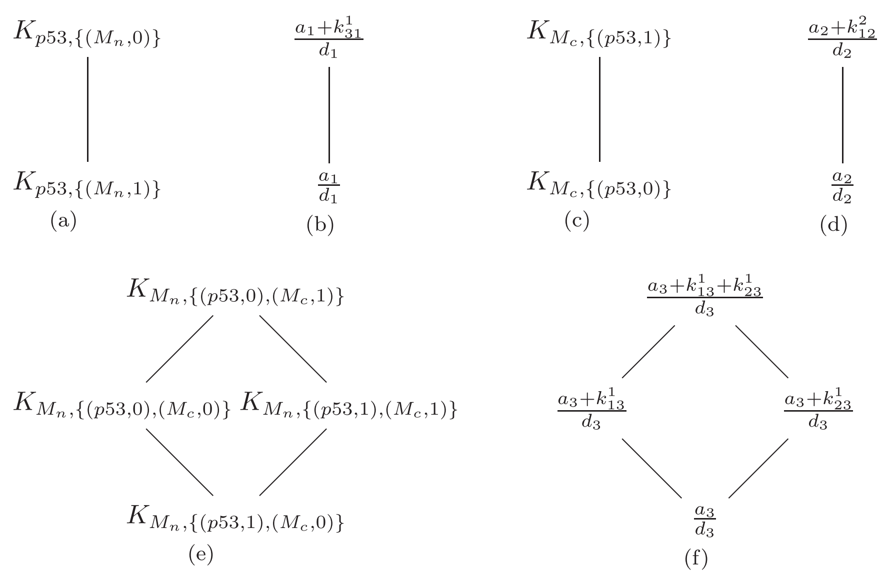

Fig. 7. Hasse diagrams of the partially ordered sets $(\mathcal{K}_{p53}, \preceq_{\mathcal{K}})$ (a), $(\mathcal{F}_1, \preceq_{\mathcal{F}})$ (b), $(\mathcal{K}_{M_c}, \preceq_{\mathcal{K}})$ (c), $(\mathcal{F}_2, \preceq_{\mathcal{F}})$ (d), $(\mathcal{K}_{M_n}, \preceq_{\mathcal{K}})$ (e), $(\mathcal{F}_3, \preceq_{\mathcal{F}})$ (f), for the case study (Fig. 1). For sake of clarity, we omitted to mention the corresponding combination of levels of the regulators in the writing of the elements of the sets $\mathcal{F}_i$.

in the previous section. Fig. 7 shows the Hasse diagrams of the partial order $\preceq_{\mathcal{F}}$ in the sets $\mathcal{F}_i$ with the corresponding Hasse diagrams of the partial order $\preceq_{\mathcal{K}}$ in the sets $\mathcal{K}_{g_i}$.

We now focus on the three logical bifurcation diagrams associated to component M_n considered in Fig. 4. Fig. 8 describes corresponding bifurcation diagrams in the associated class of PWLD models upon an increase of the parameter d_3, chosen as the bifurcation parameter. In each case, we choose:

(i) as initial value of d_3 a value such that all the 3rd coordinates of the focal function are above the threshold θ^1_{31}, which corresponds to the valuation {1, 1, 1, 1} of the logical parameters of M_n; and
(ii) as final value of d_3 a value such that all the 3rd coordinates of the focal function are below the threshold θ^1_{31}, which corresponds to the valuation {0, 0, 0, 0} of the logical parameters of M_n.

The constraints on the values of the PWLD parameters corresponding to the logical bifurcation diagram:

(i) in red is $k^1_{13} < k^1_{23}$. This constraint comes from the transition: $\{0, 1, 1, 1\} \longrightarrow \{0, 1, 0, 1\}$ for which the coordinate $\frac{a_3+k^1_{13}}{d_3}$ of the focal function crosses the threshold before $\frac{a_3+k^1_{23}}{d_3}$;
(ii) in blue is $k^1_{13} = k^1_{23}$. This constraint comes from the transition: $\{0, 1, 1, 1\} \longrightarrow \{0, 0, 0, 1\}$ for which the coordinates $\frac{a_3+k^1_{13}}{d_3}$ and $\frac{a_3+k^1_{23}}{d_3}$ of the focal function cross the threshold at the same time;
(iii) in green is $k^1_{13} > k^1_{23}$. This constraint comes from the transition: $\{0, 1, 1, 1\} \longrightarrow \{0, 0, 1, 1\}$ for which the coordinate $\frac{a_3+k^1_{23}}{d_3}$ of the focal function crosses the threshold before $\frac{a_3+k^1_{13}}{d_3}$.

Appendix D. Proofs

Property 1. *Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and g_i a component of $\mathcal{G}$. Let $(L_j)_{0\le j\le k}$ be an element of $\mathcal{P}^{\log}_{bd_{g_i}}$ where, for all integers j between 0 and k:*

$$L_j = \{(K_{g_i,\alpha_1}, l^j_1), \ldots, (K_{g_i,\alpha_{q_{g_i}}}, l^j_{q_{g_i}})\}.$$

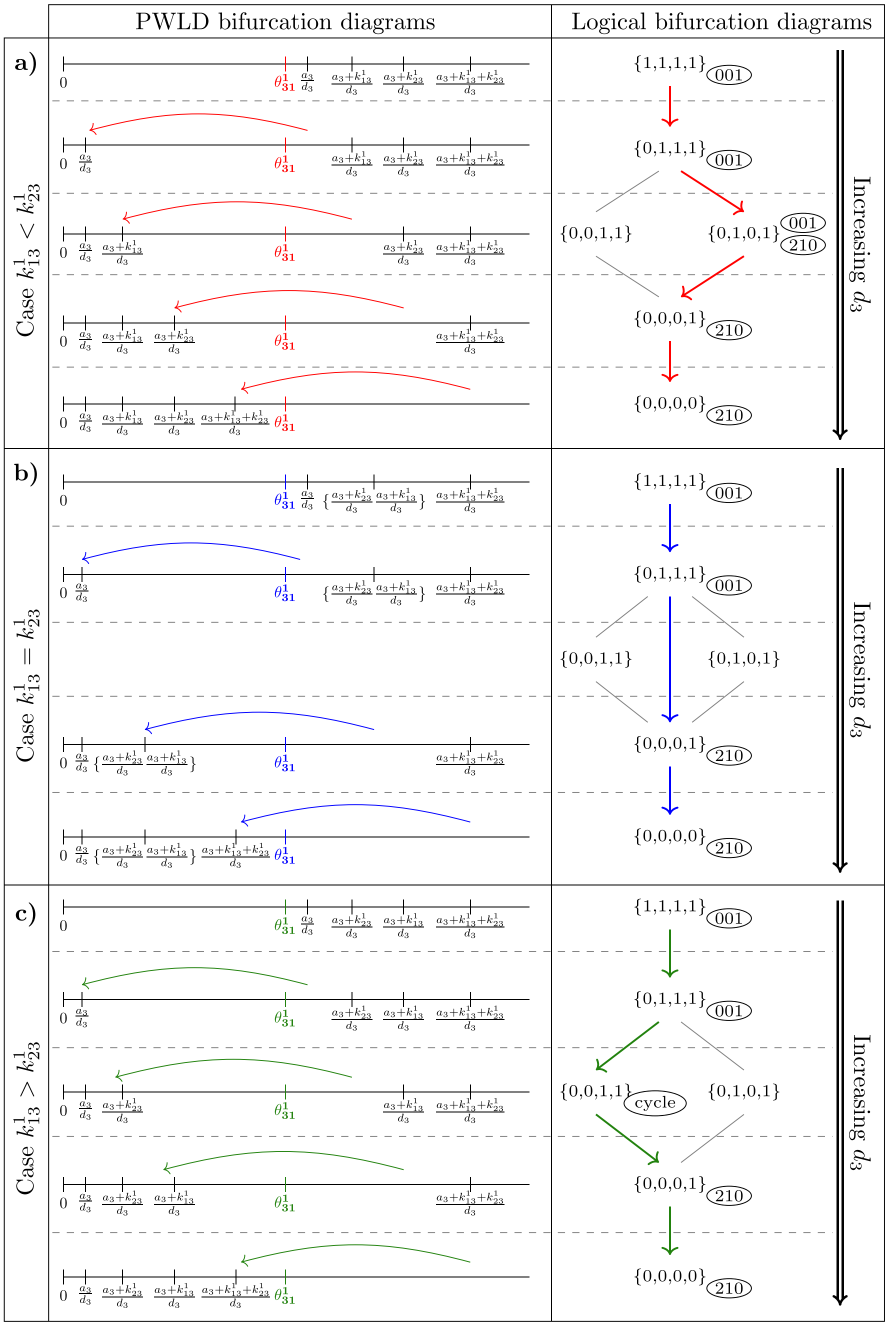

Fig. 8. Logical bifurcation diagrams considered in Fig. 4 for the case study, and corresponding PWLD bifurcation diagrams as a function of the parameter d_3. The PWLD bifurcation diagrams show the successive positionings of the 3rd coordinates of the focal function, relative to the threshold, upon the increase of d_3. Ellipses represent the attractors of the logical model for the corresponding valuation of the logical parameters. The components in the states are ordered as follows: $p53$, M_c, M_n. The logical parameters of M_n in its valuations are ordered as follows: $\{K_{M_n,\{(p53,1),(M_c,0)\}}, K_{M_n,\{(p53,1),(M_c,1)\}}, K_{M_n,\{(p53,0),(M_c,0)\}}, K_{M_n,\{(p53,0),(M_c,1)\}}\}$.

Then, the following condition holds:

(i) *either, for all* $r \in [\![1, q_{g_i}]\!]$ *and for all* $j \in [\![0, k-1]\!]$:

$$l_r^{j+1} - l_r^j = 0 \text{ or } l_r^{j+1} - l_r^j = 1,$$

(ii) *or, for all* $r \in [\![1, q_{g_i}]\!]$ *and for all* $j \in [\![0, k-1]\!]$:

$$l_r^{j+1} - l_r^j = 0 \text{ or } l_r^{j+1} - l_r^j = -1.$$

Proof. Let g_i be a component of $\mathcal{G}$ and $(L_j)_{0 \le j \le k}$ be an element of $\mathcal{P}_{bd_{g_i}}^{\log}$ where, for all integers j between 0 and k:

$$L_j = \{(K_{g_i,\alpha_1}, l_1^j), \ldots, (K_{g_i,\alpha_{q_{g_i}}}, l_{q_{g_i}}^j)\}. \tag{13}$$

Then, according to Definitions 6 and 7, there exists:

(i) a parameter p_l;
(ii) a set Θ_i^0 of threshold values of the outgoing interactions of g_i;
(iii) a set $p \setminus p_l^0$ of values of all the parameters except p_l;
(iv) two values p_l^{in} and p_l^{fin} of the parameter p_l;

such that, there exists a continuous and monotonous function γ from the set [0, 1] to the set $\left[p_l^{in}, p_l^{fin}\right]$ satisfying $\gamma(0) = p_l^{in}$ and $\gamma(1) = p_l^{fin}$, and a subdivision $t_0 < t_1 < \ldots < t_k$ of [0, 1] such that:

(i)

$$h_i^m([0, t_0[) = l_m^0, \tag{14}$$

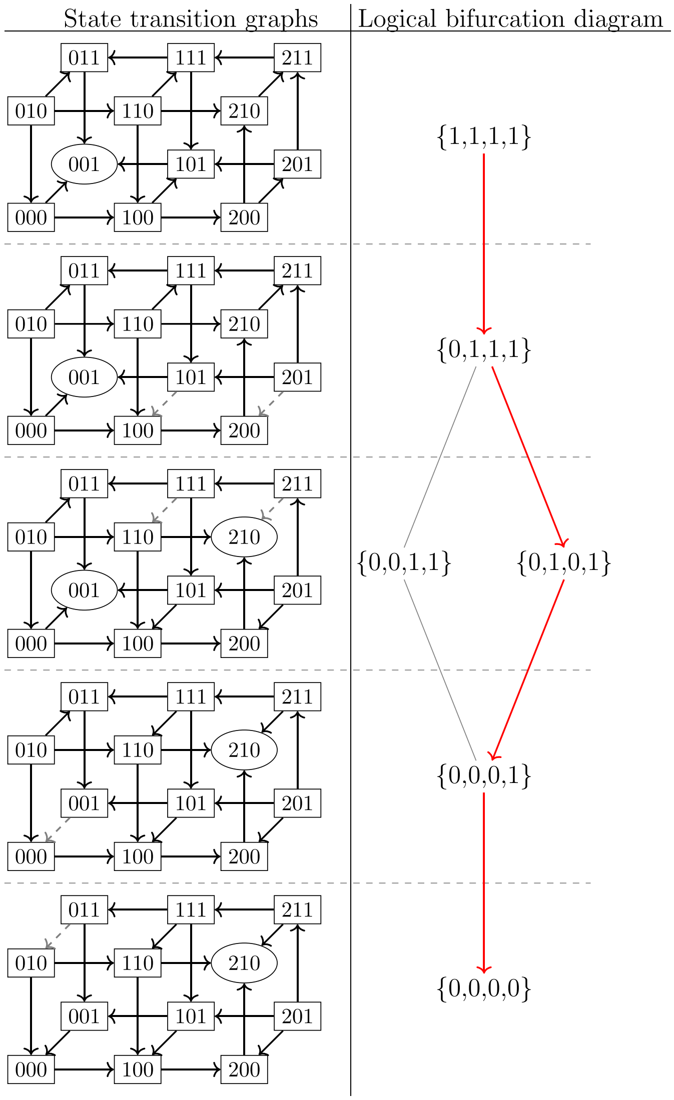

Fig. 9. Sequence of valuations of the logical parameters of M_n corresponding to the logical bifurcation diagram in red in Fig. 4 for our case study, with the corresponding state transition graphs. Gray dashed arrows represent the transitions differing with respect to the preceding graph along the logical bifurcation diagram. The ellipses denote the stable states of the model for each valuation of the logical parameters. The order of the components in the states and of the logical parameters in the valuations are indicated in caption of Fig. 8. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(ii)

$$h_i^m(]t_j, t_{j+1}[) = l_m^j, \tag{15}$$

for all integers j between 0 and $k-1$,

(iii)

$$h_i^m(]t_k, +\infty[) = l_m^k, \tag{16}$$

for all integers m between 1 and q_{g_i}, where h_i^m is the function from the set $[0, 1]$ to the set $[\![0, max(X_{g_i})]\!]$ defined for all integers m between 1 and q_{g_i} as follows:

$$h_i^m : \begin{cases} [0,1] & \rightarrow [\![0, max(X_{g_i})]\!] \\ t & \mapsto \alpha_{\mathbb{R}}^{\Theta_i^0}\left(\chi_i^{-1}(K_{g_i,\alpha_m})_1\left(\gamma(t), p \setminus p_l^0\right)\right). \end{cases}$$

Let γ be a function satisfying the conditions stated above. Then, for all integers m between 1 and q_{g_i}, the function:

$$t \mapsto \chi_i^{-1}(K_{g_i,\alpha_m})_1\left(\gamma(t), p \setminus p_l^0\right)$$

is also continuous and monotonous as the composition of the two continuous and monotonous functions, γ and $x \mapsto \chi_i^{-1}(K_{g_i,\alpha_m})_1\left(x, p \setminus p_l^0\right)$.

By definition of the mapping $\alpha_{\mathbb{R}}^{\Theta_i^0}$ and from the monotony of the function $t \mapsto \chi_i^{-1}(K_{g_i,\alpha_m})_1\left(\gamma(t), p \setminus p_l^0\right)$, it follows that h_i^m is monotonous for all integers m between 1 and q_{g_i}, which implies, from Eqs. (14)–(16), that the following conditions hold:

(i) either, for all $m \in [\![1, q_{g_i}]\!]$ and for all $j \in [\![0, k-1]\!]$:

$$l_m^j \le l_m^{j+1}, \tag{17}$$

(ii) or, for all $m \in [\![1, q_{g_i}]\!]$ and for all $j \in [\![0, k-1]\!]$:

$$l_m^j \ge l_m^{j+1}. \tag{18}$$

Moreover, by definition of the mapping $\alpha_{\mathbb{R}}^{\Theta_i^0}$ and from the continuity of the function $t \mapsto \chi_i^{-1}(K_{g_i,\alpha_m})_1\left(\gamma(t), p \setminus p_l^0\right)$, it follows, from Eqs. (14)–(16), that the following conditions hold, for all $j \in [\![0, k-1]\!]$ and all $m \in [\![1, q_{g_i}]\!]$:

$$|l_m^{j+1} - l_m^j| \le 1. \tag{19}$$

Therefore, from Eqs. (17)–(19), the following conditions hold:

(i) either, for all $r \in [\![1, q_{g_i}]\!]$ and for all $j \in [\![0, k-1]\!]$:

$$l_r^{j+1} - l_r^j = 0 \text{ or } l_r^{j+1} - l_r^j = 1,$$

(ii) or, for all $r \in [\![1, q_{g_i}]\!]$ and for all $j \in [\![0, k-1]\!]$:

$$l_r^{j+1} - l_r^j = 0 \text{ or } l_r^{j+1} - l_r^j = -1,$$

which ends the proof. □

Property 2. *Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and g_i a component of $\mathcal{G}$. Let $(L_j)_{0 \le j \le k}$ be an element of $\mathcal{P}_{bd_{g_i}}^{log}$ where, for all integers j between 0 and k:*

$$L_j = \{(K_{g_i,\alpha_1}, l_1^j), \ldots, (K_{g_i,\alpha_{q_{g_i}}}, l_{q_{g_i}}^j)\},$$

such that, for all $j \in [\![0, k-1]\!]$ and for all $r \in [\![1, q_{g_i}]\!]$, we have $l_r^j \le l_r^{j+1}$.

Let, for all $m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'})]\!]$, $\mathcal{K}_{g_i}^{j,m}$ be the subset of $\mathcal{K}_{g_i}$ for which, for all $j \in [\![0, k-1]\!]$ and for all $K \in \mathcal{K}_{g_i}^{j,m}$, the value of K in L_j is m.

Let $\mathcal{K}_{g_i}^{j,m,up}$ be the subset of $\mathcal{K}_{g_i}$ defined, for all integers m from 0 to $max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1$, as follows:

$$\mathcal{K}_{g_i}^{j,m,up} = \{K \in \mathcal{K}_{g_i} \mid l_i^{j+1} > l_i^j,\ l_i^j = m\},$$

and $\mathcal{K}_{g_i}^{j,up}$ the union of these sets $\mathcal{K}_{g_i}^{j,m,up}$ for all the integers m from 0 to $max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1$:

$$\mathcal{K}_{g_i}^{j,up} = \bigcup_{m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'})-1]\!]} \mathcal{K}_{g_i}^{j,m,up}.$$

We define the partially ordered sets $(\mathcal{K}_{g_i}, \preceq_{\mathcal{K}}^j)$, for all integers j between 0 and $k-1$, as follows:

(i) $(\mathcal{K}_{g_i}, \preceq_{\mathcal{K}}^0) = (\mathcal{K}_{g_i}, \preceq_{\mathcal{K}})$;

(ii) for all $(K, K') \notin \mathcal{K}_{g_i}^{j,up}$, we have:

$$K \preceq_{\mathcal{K}}^j K' \Longrightarrow K \preceq_{\mathcal{K}}^{j+1} K';$$

(iii) for all $m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1]\!]$, for all $(K, K') \in \mathcal{K}_{g_i}^{j,m,up}$, we have:

$$K \preceq_{\mathcal{K}}^{j+1} K' \text{ and } K' \preceq_{\mathcal{K}}^{j+1} K;$$

(iv) *for all* $m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1]\!]$, *for all* $K \in \mathcal{K}_{g_i}^{j,m,up}$, *and for all* $K' \in \mathcal{K}_{g_i}^{j,m} \cap \overline{\mathcal{K}_{g_i}^{j,up}}$, *we have:*

$K' \preceq_{\mathcal{K}}^{j+1} K.$

Let M_m^j *be the set of the maximal elements of the partially ordered set* $(\mathcal{K}_{g_i}^{j,m}, \preceq_{\mathcal{K}}^j)$, *for all* $j \in [\![0, k-1]\!]$ *and for all* $m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1]\!]$, *and* M^j *the union of these sets* M_m^j *for all* $m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1]\!]$, *for all* $j \in [\![0, k-1]\!]$:

$$M^j = \bigcup_{m\in[\![0,max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'})-1]\!]} M_m^j.$$

Then, we have, for all integers j from 0 to $k-1$:

$\mathcal{K}_{g_i}^{j,up} \subseteq M^j.$

Before proving Property 3, we give the following two lemmas:

Lemma 1. *Let* $i \in [\![1, n]\!]$ *and* p_r *a parameter involved in the equation of evolution of* x_i *of a class of PWLD models:*

$$\frac{dx_i}{dt} = a_i + \sum_{g_j\in\mathcal{R}_{g_i}} \sum_{l\in t_{g_j,g_i}} s(x_j, \theta_{ji}^l) - d_i \cdot x_i,$$

where:

$$\begin{cases} s(x_i, \theta_{ij}^l) = 0, & \text{if } x_i < \theta_{ij}^l, \\ s(x_i, \theta_{ij}^l) = k_{ij}^l, & \text{if } x_i > \theta_{ij}^l, \end{cases}$$

or:

$$\begin{cases} s(x_i, \theta_{ij}^l) = k_{ij}^l, & \text{if } x_i < \theta_{ij}^l, \\ s(x_i, \theta_{ij}^l) = 0, & \text{if } x_i > \theta_{ij}^l. \end{cases}$$

Let $p \setminus p_r^0$ *be a vector of values of all the parameters except* p_r.

Let (f, F) *and* (f', F') *be two distinct elements of* $\mathcal{F}_i$, *such that f and f′ depend on* p_j. *Then, the following condition holds:*

(i) *either* $f(p \setminus p_r^0, p_r) < f'(p \setminus p_r^0, p_r)$, *for all* $p_l \in \mathbb{R}^+$ *if* $p_r = a_i$, *or for all* $p_r \in \mathbb{R}^{\star+}$ *if* $p_r = k_{ij}^l$ *or* $p_r = d_i$;
(ii) *or* $f(p \setminus p_r^0, p_r) = f'(p \setminus p_r^0, p_r)$, *for all* $p_r \in \mathbb{R}^+$ *if* $p_r = a_i$, *or for all* $p_r \in \mathbb{R}^{\star+}$ *if* $p_r = k_{ij}^l$ *or* $p_r = d_i$;
(iii) *or* $f(p \setminus p_r^0, p_r) > f'(p \setminus p_r^0, p_r)$, *for all* $p_r \in \mathbb{R}^+$ *if* $p_r = a_i$, *or for all* $p_r \in \mathbb{R}^{\star+}$ *if* $p_r = k_{ij}^l$ *or* $p_r = d_i$.

Lemma 2. *We consider the class of PWLD models associated to a regulatory graph* $(\mathcal{G}, \Gamma, sign, T)$. *Let* g_i *be a component of* $\mathcal{G}$, *and* (f, F) *and* (f', F') *two distinct elements of the set* $\mathcal{F}_i$.

If $(f, F) \preceq_{\mathcal{F}} (f', F')$, *then, for all vectors of parameter values* $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_p|-n} \times (\mathbb{R}^+)^n$ *of the parameter vector, we have:*

$f(p^0) < f'(p^0).$

Proof. We take the same notations as in the statement of Property 2.

Let g_i be a component of $\mathcal{G}$. Let $(L_j)_{0\le j\le k}$ be an element of $\mathcal{P}_{bd_{g_i}}^{log}$, where, for all integers j between 0 and k:

$L_j = \{(K_{g,\alpha_1}, l_1^j), \ldots, (K_{g,\alpha_{q_g}}, l_{q_g}^j)\}.$

Then, according to Definition 6, there exists:

(i) a parameter p_l;
(ii) a set Θ_i^0 of threshold values of the outgoing interactions of g_i;
(iii) a set $p \setminus p_l^0$ of values of all the parameters except p_l;
(iv) two values p_l^{in} and p_l^{fin} of the parameter p_l;

such that the conditions of Definition 6 are satisfied.

Let j be an integer between 0 and $k-1$. Then, $(L_{j'})_{0\le j'\le j}$ is also an element of $\mathcal{P}_{bd_{g_i}}^{log}$, and, for all integers j' between 0 and j, there exists a value $p_l^{j'} \in \mathbb{R}^+$ of parameter p_l, such that:

(i) for all $m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1]\!]$, for all $(K, K') \in \mathcal{K}_{g_i}^{j',m,up}$, we have:

$$\chi_i^{-1}(K)_1(p \setminus p_l^0, p_l^{j'}) = \chi_i^{-1}(K')_1(p \setminus p_l^0, p_l^{j'}), \tag{20}$$

(ii) for all $m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1]\!]$, for all $K \in \mathcal{K}_{g_i}^{j',m,up}$, and for all $K' \in \mathcal{K}_{g_i}^{j',m} \cap \overline{\mathcal{K}_{g_i}^{j',up}}$, we have:

$$\chi_i^{-1}(K')_1(p \setminus p_l^0, p_l^{j'}) < \chi_i^{-1}(K)_1(p \setminus p_l^0, p_l^{j'}). \tag{21}$$

Moreover, by hypothesis, the values of the logical parameters increases along $(L_{j'})_{0\le j'\le j}$. Therefore, $\chi_i^{-1}(K)_1(p \setminus p_l^0, p_l)$ increases along $(L_{j'})_{0\le j'\le j}$ for all $K \in \mathcal{K}_{g_i}$.

It follows, from Lemma 1, that, for all integers j' between 0 and j, and for all values $q \ge max\{p_l^{j'} \mid j' \in [\![0, j]\!]\}$ (resp. for all values $q \le min\{p_l^{j'} \mid j' \in [\![0, j]\!]\}$) of parameter p_l if $p_l \mapsto \chi_i^{-1}(K)_1(p \setminus p_l^0, p_l)$ is an increasing function (resp. if $p_l \mapsto \chi_i^{-1}(K)_1(p \setminus p_l^0, p_l)$ is a decreasing function) for all $K \in \mathcal{K}_{g_i}$, Eqs. (20) and (21) are satisfied, for all integers j' between 0 and j, that is to say that:

(i) for all $m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1]\!]$, for all $(K, K') \in \mathcal{K}_{g_i}^{j',m,up}$, we have:

$$\chi_i^{-1}(K)_1(p \setminus p_l^0, q) = \chi_i^{-1}(K')_1(p \setminus p_l^0, q), \tag{22}$$

(ii) for all $m \in [\![0, max(\bigcup_{(g_i,g')\in\Gamma} t_{g_i,g'}) - 1]\!]$, for all $K \in \mathcal{K}_{g_i}^{j',m,up}$, and for all $K' \in \mathcal{K}_{g_i}^{j',m} \cap \overline{\mathcal{K}_{g_i}^{j',up}}$, we have:

$$\chi_i^{-1}(K')_1(p \setminus p_l^0, q) < \chi_i^{-1}(K)_1(p \setminus p_l^0, q). \tag{23}$$

We can assume without loss of generality that $p_l \mapsto \chi_i^{-1}(K)_1(p \setminus p_l^0, p_l)$ is an increasing function for all $K \in \mathcal{K}_{g_i}$.

Moreover, from Property 7, we have, for all pairs of logical parameters (K, K') such that $K \preceq_{\mathcal{K}} K'$:

$\chi_i^{-1}(K)_1 \preceq_{\mathcal{F}} \chi_i^{-1}(K')_1.$

Since χ_i is bijective (Property 7), it follows, from Lemma 2, that, for all pairs of logical parameters (K, K') such that $K \neq K'$, we have, for all $q > 0$:

$$K \preceq_{\mathcal{K}} K' \Longrightarrow \chi_i^{-1}(K)_1(p \setminus p_l^0, q) < \chi_i^{-1}(K')_1(p \setminus p_l^0, q). \tag{24}$$

Therefore, it follows, from Eqs. (22)–(24), and by definition of $\preceq_{\mathcal{K}}^j$, that the following condition holds, for all pairs of logical parameters (K, K') such that $K \neq K'$:

$$K \preceq_{\mathcal{K}}^j K' \Longrightarrow \chi_i^{-1}(K)_1(p \setminus p_l^0, q) < \chi_i^{-1}(K')_1(p \setminus p_l^0, q) \tag{25}$$

for all $q \ge max\{p_l^{j'} \mid j' \in [\![0, j]\!]\}$.

Now let us prove that $\mathcal{K}_{g_i}^{j,up} \subseteq M^j$ by proving its contraposition. Let K be a logical parameter which does not belong to the set M^j, that is to say that:

$K \notin M^j,$

and let m be the value of K in L_j. Then, by definition of M^j, there exists $K' \neq K$ of value m in L_j such that $K \preceq_{\mathcal{K}}^j K'$. It follows, from Eq. (25), that:

$\chi_i^{-1}(K)_1(p \setminus p_l^0, q) < \chi_i^{-1}(K')_1(p \setminus p_l^0, q),$

for all $q \ge max\{p_l^{j'} \mid j' \in [\![0, j]\!]\}$. Since $p_l \mapsto \chi_i^{-1}(K)_1(p \setminus p_l^0, p_l)$ is an increasing function, it follows that:

(i) either $\alpha_{\mathbb{R}}^{\Theta_i^0}(\chi_i^{-1}(K)_1(p \setminus p_l^0, p_l^j)) = \alpha_{\mathbb{R}}^{\Theta_i^0}(\chi_i^{-1}(K')_1(p \setminus p_l^0, q)),$
(ii) or $\alpha_{\mathbb{R}}^{\Theta_i^0}(\chi_i^{-1}(K)_1(p \setminus p_l^0, p_l^j)) < \alpha_{\mathbb{R}}^{\Theta_i^0}(\chi_i^{-1}(K')_1(p \setminus p_l^0, q)),$

for all $q \geq max\{p_l^{j'} \mid j' \in [\![0, j]\!]\}$.

Therefore, the value of K remains the same from L_j to L_{j+1}. Thus, we have:

$K \notin \mathcal{K}_{g_i}^{j,up}$.

We have thus proved by contraposition that:

$\mathcal{K}_{g_i}^{j,up} \subseteq M^j$.

which ends the proof. □

Property 3. *Let $(\mathcal{G}, \Gamma, sign, T)$ be a regulatory graph, and g_i a component of $\mathcal{G}$. We assume that $max(X_{g_i}) = 1$ (Boolean case). Let $(L_j)_{0 \leq j \leq k}$ be an element of $(\mathcal{V}_{g_i}^a)^\star$, where, for all integers j between 0 and k:*

$$L_j = \{(K_{g_i,\alpha_1}, l_1^j), \ldots, (K_{g_i,\alpha_{q_{g_i}}}, l_{q_{g_i}}^j)\},$$

such that, the following conditions hold, for all integers j from 0 to $k-1$:

(i) *for all $r \in [\![1, q_{g_i}]\!]$, we have $l_r^j \leq l_r^{j+1}$, and*
(ii) $\mathcal{K}_{g_i}^{j,up} \subseteq M^j$,

where the sets $\mathcal{K}_{g_i}^{j,up}$ and M^j are defined in Property 2.

We define the subset C_j of the set $(\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^+)^n$, where $|\mathcal{DF}_P|$ denotes the number of all the parameters except the thresholds, as follows, for all integers j between 0 and k:

(i) *$p \in C_0$, if and only if, for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_r^0 = 0$ and $l_{r'}^0 = 1$, we have:*

$$\chi_i^{-1}(K_{g_i,\alpha_r})_1(p) < \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p);$$

(ii) *$p \in C_j$, for all integers j between 1 and k, if and only if:*
   (a) *for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_r^{j-1} < l_r^j$ and $l_{r'}^j = 0$, we have:*

   $$\chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p) < \chi_i^{-1}(K_{g_i,\alpha_r})_1(p);$$

   (b) *for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_r^{j-1} < l_r^j$ and $l_{r'}^{j-1} < l_{r'}^j$, we have:*

   $$\chi_i^{-1}(K_{g_i,\alpha_r})_1(p) = \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p);$$

and the set $\mathcal{C}$ as the intersection between the sets C_j for all integers j between 0 and k:

$$\mathcal{C} = \bigcap_{j=0}^{k} C_j.$$

Then, $\left(L_j\right)_{0 \leq j \leq k} \in \mathcal{P}_{bd_{g_i}}^{log}$ if and only if $\mathcal{C} \neq \emptyset$.

Proof. We take the same notations as in the statement of Property 3.

Let g_i be a component of $\mathcal{G}$ and let us assume that $max(X_{g_i}) = 1$ (Boolean case). Let $(L_j)_{0 \leq j \leq k}$ be an element of $(\mathcal{V}_{g_i}^a)^\star$, where, for all integers j between 0 and k:

$$L_j = \{(K_{g_i,\alpha_1}, l_1^j), \ldots, (K_{g_i,\alpha_{q_{g_i}}}, l_{q_{g_i}}^j)\}, \tag{26}$$

such that, we have, for all integers j from 0 to $k-1$:

(i) for all $r \in [\![1, q_{g_i}]\!]$, we have $l_r^j \leq l_r^{j+1}$, and
(ii) $\mathcal{K}_{g_i}^{j,up} \subseteq M^j$,

where the sets $\mathcal{K}_{g_i}^{j,up}$ and M^j are defined in Property 2.

We start by first proving the necessary condition of the property, that is to say that:

$$\left(L_j\right)_{0 \leq j \leq k} \in \mathcal{P}_{bd_{g_i}}^{log} \Longrightarrow \mathcal{C} \neq \emptyset. \tag{27}$$

Assume that $\left(L_j\right)_{0 \leq j \leq k} \in \mathcal{P}_{bd_{g_i}}^{log}$. Then, according to Definitions 6 and 7, there exists:

(i) a parameter p_l;
(ii) a set $\Theta_i^0 = \{\theta_i^0\}$ of threshold values of the outgoing interactions of g_i (Θ_i^0 is a singleton since X_{g_i} is Boolean);
(iii) a set $p \setminus p_l^0$ of values of all the parameters except p_l;
(iv) two values p_l^{in} and p_l^{fin} of the parameter p_l;

such that, there exists a continuous and monotonous function γ from the set [0, 1] to the set $\left[p_l^{in}, p_l^{fin}\right]$ satisfying $\gamma(0) = p_l^{in}$ and $\gamma(1) = p_l^{fin}$, and a subdivision $t_0 < t_1 < \ldots < t_{k-1}$ of [0, 1] such that, for all $m \in [\![1, q_{g_i}]\!]$, we have:

(i)
$$h_i^m([0, t_0[) = l_m^0, \tag{28}$$
(ii)
$$h_i^m(]t_{j-1}, t_j[) = l_m^j, \tag{29}$$
for all integers j between 1 and $k-1$,
(iii)
$$h_i^m(]t_{k-1}, +\infty[) = l_m^k, \tag{30}$$

where h_i^m is the function from the set [0, 1] to the set $[\![0, max(X_{g_i})]\!]$ defined for all integers m between 1 and q_{g_i} as follows:

$$h_i^m : \begin{cases} [0,1] \to [\![0, max(X_{g_i})]\!] \\ t \mapsto \alpha_{\mathbb{R}}^{\Theta_i^0}\left(\chi_i^{-1}(K_{g_i,\alpha_m})_1\left(\gamma(t), p \setminus p_l^0\right)\right). \end{cases}$$

Let γ be a function satisfying the conditions stated above. Then, for all integers m between 1 and q_{g_i}, the function:

$$t \mapsto \chi_i^{-1}(K_{g_i,\alpha_m})_1\left(\gamma(t), p \setminus p_l^0\right)$$

is also continuous and monotonous as the composition of the two continuous and monotonous functions, γ and $x \mapsto \chi_i^{-1}(K_{g_i,\alpha_m})_1\left(x, p \setminus p_l^0\right)$.

By definition of the mapping $\alpha_{\mathbb{R}}^{\Theta_i^0}$ and of the functions h_i^m, it follows:

(i) from Eq. (28), that, for all $t \in [0, t_0[$ and for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_r^0 = 0$ and $l_{r'}^0 = 1$, we have:
$$\chi_i^{-1}(K_{g_i,\alpha_r})_1\left(\gamma(t), p \setminus p_l^0\right) < \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1\left(\gamma(t), p \setminus p_l^0\right), \tag{31}$$
(ii) from Eq. (29), that, for all $j \in [\![1, k-1]\!]$, for all $t \in]t_{j-1}, t_j[$, for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_{r'}^{j-1} < l_{r'}^j$ and $l_r^j = 0$, we have:
$$\chi_i^{-1}(K_{g_i,\alpha_r})_1\left(\gamma(t), p \setminus p_l^0\right) < \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1\left(\gamma(t), p \setminus p_l^0\right), \tag{32}$$
(iii) from Eq. (30), that, for all $t \in]t_{k-1}, +\infty[$, for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_{r'}^{j-1} < l_{r'}^j$ and $l_r^j = 0$, we have:
$$\chi_i^{-1}(K_{g_i,\alpha_r})_1\left(\gamma(t), p \setminus p_l^0\right) < \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1\left(\gamma(t), p \setminus p_l^0\right). \tag{33}$$

Now let $j \in [\![1,\ k]\!]$ and $r \in [\![1, q_{g_i}]\!]$ such that $l_r^{j-1} < l_r^j$. From the continuity of the function $t \mapsto \chi_i^{-1}(K_{g_i,\alpha_r})_1\left(\gamma(t), p \setminus p_l^0\right)$, we have:

$$\chi_i^{-1}(K_{g_i,\alpha_r})_1\left(\gamma(t_{j-1}), p \setminus p_l^0\right) = \theta_i^0.$$

It thus follows, for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_r^{j-1} < l_r^j$ and $l_{r'}^{j-1} < l_{r'}^j$, that:

$$\chi_i^{-1}(K_{g_i,\alpha_r})_1\left(\gamma(t_{j-1}), p \setminus p_l^0\right) = \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1\left(\gamma(t_{j-1}), p \setminus p_l^0\right). \tag{34}$$

From Lemma 1, it follows that Eqs. (31)–(34) are satisfied for all $t > t_{k-1}$, that is to say that, by definition of $\mathcal{C}$:

$\gamma(]t_{k-1}, +\infty[) \subseteq \mathcal{C}$, which implies, in particular, that:

$\mathcal{C} \neq \emptyset$,

which ends the proof of the necessary condition of the property.

Let us now prove the sufficient condition of the property, that is to say that:

$$\mathcal{C} \neq \emptyset \Longrightarrow \left(L_j\right)_{0\le j\le k} \in \mathcal{P}^{log}_{bd_{g_i}}. \tag{35}$$

Assume that $\mathcal{C} \neq \emptyset$. Then, by definition of $\mathcal{C}$, there exists a vector $p^0 \in (\mathbb{R}^{\star+})^{|\mathcal{DF}_P|-n} \times (\mathbb{R}^{+})^n$ of the parameter values such that we have:

(i) for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_r^0 = 0$ and $l_{r'}^0 = 1$:

$$\chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0) < \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p^0), \tag{36}$$

(ii) for all integers j between 1 and k, and:
   (a) for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_r^{j-1} < l_r^j$ and $l_{r'}^j = 0$:

$$\chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p^0) < \chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0), \tag{37}$$

   (b) for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_r^{j-1} < l_r^j$ and $l_{r'}^{j-1} < l_{r'}^j$:

$$\chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0) = \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p^0). \tag{38}$$

Let us choose such a value p^0. Let us further choose:

(i) d_i as the parameter of bifurcation;
(ii) a positive threshold value θ_i^0; and
(iii) the vector of values $p^0\backslash d_i$ for the values of all the parameters except d_i.

By definition of the set $\mathcal{F}_i$, $\chi_i^{-1}(K)$ depends on d_i for all $K \in \mathcal{K}_{g_i}$. It follows, from Lemma 1, that Eqs. (36)–(38) are satisfied for all $d_i \in \mathbb{R}^{\star+}$, that is to say that, the following conditions hold, for all $d_i \in \mathbb{R}^{\star+}$:

(i) for all $(r, r') \in [\![1, q_{g_i}]\!]^2$ such that $l_r^0 = 0$ and $l_{r'}^0 = 1$:

$$\chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0 \setminus d_i, d_i) < \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p^0 \setminus d_i, d_i), \tag{39}$$

(ii) for all integers j between 1 and k, and:
   (a) for all $(r, r') \in [\![1, g_i]\!]^2$ such that $l_r^{j-1} < l_r^j$ and $l_{r'}^j = 0$:

$$\chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p^0 \setminus d_i, d_i) < \chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0 \setminus d_i, d_i), \tag{40}$$

   (b) for all $(r, r') \in [\![1, g_i]\!]^2$ such that $l_r^{j-1} < l_r^j$ and $l_{r'}^{j-1} < l_{r'}^j$:

$$\chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0 \setminus d_i, d_i) = \chi_i^{-1}(K_{g_i,\alpha_{r'}})_1(p^0 \setminus d_i, d_i). \tag{41}$$

Moreover, the function $d_i \mapsto \chi_i^{-1}(K)_1(p^0 \setminus d_i, d_i)$ is continuous and decreasing from the set $\mathbb{R}^{\star+}$ to the set $\mathbb{R}^{\star+}$, for all $K \in \mathcal{K}_{g_i}$, as it is inversely proportional to d_i by definition of the set $\mathcal{F}_i$.

It follows, from the continuity of the function $d_i \mapsto \chi_i^{-1}(K)_1(p^0 \setminus d_i, d_i)$ over the sets $\mathbb{R}^{\star+}$, and:

(i) from Eq. (39), that there exists a value d_i^{in} of d_i such that:
   (a) $\chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0 \setminus d_i, d_i^{in}) < \theta_i^0$, for all r such that $l_r^0 = 0$,
   (b) $\chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0 \setminus d_i, d_i^{in}) > \theta_i^0$ for all r such that $l_r^0 = 1$,
(ii) from Eqs. (39)–(41), that there exists a value d_i^{fin} of d_i such that:
   (a) $\chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0 \setminus d_i, d_i^{fin}) < \theta_i^0$, for all r such that $l_r^0 = 0$,
   (b) $\chi_i^{-1}(K_{g_i,\alpha_r})_1(p^0 \setminus d_i, d_i^{fin}) > \theta_i^0$ for all r such that $l_r^0 = 1$.

Now let γ be the function defined for all $t \in [0, 1]$ as follows:

$$\gamma(t) = (d_i^{fin} - d_i^{in})t + d_i^{in}.$$

We have $\gamma(0) = d_i^{in}$, $\gamma(1) = d_i^{fin}$ and γ is straightforwardly continuous and monotonous (decreasing) over [0, 1].

From the continuity of $t \mapsto \chi_i^{-1}(K)_1(p^0 \setminus d_i, \gamma(t))$ for all $K \in \mathcal{K}_{g_i}$, and from Eqs. (39)–(41), it follows that for all $j \in [\![0, k-1]\!]$ and for all m such that $l_m^j < l_m^{j+1}$, there exists $t_j \in [0, 1]$ such that:

$$\chi_i^{-1}(K_{g_i,\alpha_m})_1\big(p^0 \setminus d_i, \gamma(t_j)\big) = \theta_i^0. \tag{42}$$

Let us choose such a subdivision $t_0 < t_1 < \ldots < t_{k-1}$ of [0, 1]. It follows, by definition of $\alpha_{\mathbb{R}}^{\Theta_i^0}$ and from the monotonicity of $t \mapsto \chi_i^{-1}(K)_1(p^0 \setminus d_i, \gamma(t))$ for all $K \in \mathcal{K}_{g_i}$, that the following conditions hold, for all integers m between 1 and q_{g_i}:

(i)

$$h_i^m([0, t_0[) = l_m^0, \tag{43}$$

(ii)

$$h_i^m(]t_{j-1}, t_j[) = l_m^j, \tag{44}$$

for all integers j between 1 and $k-1$,

(iii)

$$h_i^m(]t_{k-1}, +\infty[) = l_m^k. \tag{45}$$

where h_i^m is the function from the set [0, 1] to the set $[\![0, max(X_{g_i})]\!]$ defined for all integers m between 1 and q_{g_i} as follows:

$$h_i^m : \begin{cases} [0,1] \to [\![0, max(X_{g_i})]\!] \\ t \mapsto \alpha_{\mathbb{R}}^{\Theta_i^0}\big(\chi_i^{-1}(K_{g_i,\alpha_m})_1\big(\gamma(t), p \setminus p_j^0\big)\big). \end{cases}$$

Therefore, by Definition 6, we have:

$$\left(L_j\right)_{0\le j\le k} \in \mathcal{P}^{log}_{bd_{g_i}},$$

thus proving the sufficient condition of the property. □

Appendix E. Algorithms

The high level procedure computing a logical bifurcation diagram of maximum length starting from an initial valuation of the logical parameters is described in Algorithm 2. Given a logical model (*model*), and a component g_i (*node*):

(i) the algorithm first constructs, with the procedure genBifurcationPath, a sequence $\left(L_0, \ldots, L_{j_0}, \ldots, L_k\right)$ of valuations of the logical parameters associated to *node* (*bifurcPath*) which:
   (a) belongs to the set $\mathcal{P}^{log}_{bd_{g_i}}$,
   (b) contains the valuation of the logical parameter L_{j_0} of *model*,
   (c) is of maximum length,
   (lines 1 and 2);
(ii) then, for each valuation L_j (*function*) of the sequence, the attractors of the corresponding logical model are computed (lines 3–8);
(iii) finally, the algorithm returns the corresponding sequence of pairs (*function*, associated model attractors) (*attractorList*).

The structure *bifurcDiag* contains information relative to *model*. The procedure genBifurcationPath receives *bifurcDiag* and a component g_i (*node*), and returns a sequence $(L_0, L_1, \ldots, L_k)$ of valuations of the logical parameters associated to *node* (*bifurcPath*) as follows:

(i) the procedure first gets the set of regulators (*regList*) of the component *node*, and the valuation L_{j_0} of the logical parameters associated to the component *node* (*funcRef*) of the logical model defined in *bifurcDiag* (lines 12–13);
(ii) it then verifies if the valuation *funcRef* is consistent with the signs of the incoming interactions on *node* (lines 14–16);
(iii) if it is, it constructs the partial order $\preceq_{\mathcal{K}}$ in the set $\mathcal{K}_{g_i}$ of the logical parameters associated to *node* (*depGraph*) and verifies if the valuation *funcRef* satisfies Property 3 (lines 17–20);
(iv) if it does, the partial order *depGraph* is updated with the constraints imposed by *funcRef* (line 21);
(v) it then initializes the bifurcation diagram (*bifurcPath*) with *funcRef* (line 22), and:

Algorithm 2 Computation of a logical bifurcation diagram and its attractors.

```
Input: model, node
1: bifurcDiag ← buildBifurcationDiagram(model)
2: bifurcPath ← genBifurcationPath(bifurcDiag, node)
3: attractorList ← ∅
4: for all function ∈ bifurcPath do
5:     newModel ← bifurcDiag.getModel(node, function)
6:                 ▷ model manipulation relies on the bioLQM library
7:     pair ← (function, computeAttractors(newModel))
8:                 ▷ model attractors relies on the bioLQM library
9:     attractorList ← attractorList + pair
10: end for
Output: attractorList
11: function GENBIFURCATIONPATH(bifurcDiag, node)
12:     regList ← regulators(bifurcDiag, node)
13:     funcRef ← referenceFunction(bifurcDiag, node)
14:     if !consistent(funcRef, regList) then
15:         return ∅
16:     end if
17:     depGraph ← buildLogicParamDepGraph(len(regList))
18:     if !depGraph.satisfiesProp3(∅, getLPs(funcRef)) then
19:         return ∅            ▷ If funcRef does not satisfy Property 3
20:     end if
21:     depGraph.initRestrictions(funcRef)
22:     bifurcPath ← funcRef   ▷ new list to keep function ordering
23:     f ← funcRef            ▷ compute functions above funcRef
24:     while (f ← getParentFunction(depGraph, f)) ≠ ∅ do
25:         bifurcPath ← bifurcPath + f          ▷ list push back
26:     end while
27:     f ← funcRef            ▷ Compute functions bellow funcRef
28:     while (f ← getChildFunction(depGraph, f)) ≠ ∅ do
29:         bifurcPath ← f + bifurcPath          ▷ list push front
30:     end while
31:     return bifurcPath
32: end function
```

(a) calls the procedure GETPARENTFUNCTION which, considering the current *depGraph* and the current valuation of the logical parameters L_j (*f*), returns a valid valuation L_{j+1} (*i.e.* a valuation such that $(L_{j_0}, \ldots, L_j, L_{j+1}) \in \mathcal{P}^{log}_{bdg_i}$), for which logical parameter values have been increased from L_j to L_{j+1}, and updates *depGraph* accordingly (lines 24–26);

(b) analogously calls the procedure GETCHILDFUNCTION to return a valid valuation L_{j-1} (*i.e.* a valuation such that $(L_{j-1}, L_j, \ldots, L_{j_0}) \in \mathcal{P}^{log}_{bdg_i}$), for which logical parameter values have been decreased from L_j to L_{j-1}, and updates *depGraph* accordingly (lines 27–30);

until the bifurcation diagram has reached its maximum length.

Algorithm 3 describes three auxiliary procedures used in Algorithms 1 and 2. The first one, GETPARENTFUNCTION, proceeds as follows:

(i) it calls the procedure GETVALIDPARENTFUNCTION, described in Algorithm 1, to compute a valid successor (*func*) if it exists (line 2);
(ii) the set of the logical parameters whose values have increased (*changingLPs*) is retrieved (line 4);
(iii) the partial order *depGraph* is updated with the constraints imposed by *changingLPs* (lines 5–6).

The second procedure, GETCOMBINATIONS, computes all the subsets of a given set of logical parameters.

Algorithm 3 Auxiliary functions.

```
1: function GETPARENTFUNCTION(depGraph, lastFunc)
2:     func ← getValidParentFunction(depGraph, lastFunc)
3:     if func ≠ ∅ then
4:         changingLPs ← getChangingLPs(lastFunc, func)
5:         depGraph.updateEqualLPs(func, changingLPs)
6:         depGraph.updateInequalLPs(func, changingLPs)
7:     end if
8:     return func
9: end function
10: function GETCOMBINATIONS(listLPs)
11:     listOfCombs ← ∅
12:     for all lp ∈ listLPs do
13:         for all comb ∈ listOfCombs do
14:             newComb ← comb ∪ lp
15:             listOfCombs ← listOfCombs ∪ newComb
16:         end for
17:         listOfCombs ← lp
18:     end for
19: end function
20: function ISVALIDLPSET(depGraph, listLPs)
21:     for all lp ∈ listLPs do
22:         equalLPset ← depGraph.getEqualLPs(lp)
23:         if equalLPset ≠ ∅ ∧ equalLPset ⊈ listLPs then
24:             return false
25:         end if
26:     end for
27:     return true
28: end function
```

The third procedure, ISVALIDLPSET takes as inputs a partial order (*depGraph*) and a list of logical parameters (*listLPs*), and proceeds as follows:

(i) for each logical parameter in *listLPs*, it gets the set of logical parameters which are equal for the partial order *depGraph* (*equalLPset*) (lines 21–22);
(ii) then, if *equalLPset* is not empty and is not a subset of *listLPs*, the procedure returns *false* (line 24);
(iii) if, for each element of *listLPs*, *equalLPset* is either empty or is a subset of *listLPs*, the procedure returns *true* (line 26).

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