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Unfolding of Parametric Logical Regulatory Networks

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Abstract

In systems biology, models of cellular regulatory processes such as gene regulatory networks or signalling pathways are crucial to understanding the behaviour of living cells. Available biological data are however often insufficient for full model specification. In this paper, we focus on partially specified models where the missing information is abstracted in the form of parameters. We introduce a novel approach to analysis of parametric logical regulatory networks addressing both sources of combinatoric explosion native to the model. First, we introduce a new compact representation of admissible parameters using Boolean lattices. Then, we define the unfolding of parametric regulatory networks. The resulting structure provides a partial-order reduction of concurrent transitions, and factorises the common transitions among the concrete models. A comparison is performed against state-of-the-art approaches to parametric model analysis.

Keywords: logical networks, parameters identification, asynchronous systems, concurrency, systems biology

1 Introduction

One of the main problems studied in computational systems biology is understanding of intracellular molecular interactions, often represented as networks. Two particular classes of processes are predominantly modelled, gene expression regulation (gene regulatory networks) and cell signalling [12].

The prime interests of gene regulatory networks are gene-protein and gene-gene interactions, the latter are generally facilitated by the proteins they encode. Cell signalling models usually consist of one or several signalling pathways. In simple terms chains of proteins providing information flow by means of sequential phosphorylation until some cellular process (such as gene expression) is influenced.

Although both of the described processes are quantitative in their nature, it is often the case that precise kinetic parameters of the reactions are unknown in

biological context. As such, it is common to model genetic regulatory networks and signalling pathways by discrete models (logical regulatory networks) [1,6,14,18,19].

In the context of gene regulatory networks and signalling pathways it is often the case that one-to-one influences between species are known from *in vitro* experiments. The results of combinations of those influences are, however, largely unknown. In other words, it may be known that two species have both positive influence on the activity/population of a third species. However, it is rarely known if both of the activators must be present to activate the target or if just one is sufficient. In general, an arbitrary logical function may govern the joint influences. To cope with the problem technically, the individual target values of a species in possible combinations of their regulators activity are considered as unknown *parameters*.

The analysis of *parametric regulatory networks* (PRNs) is hindered by dual combinatorial explosion. Not only is the state space exponential in size of the networks, but the number of parametrisations is in the worst case double exponential in number of species. Combination of those factors often leads to the fact that analysis techniques of PRNs do not scale to larger networks.

Our Contribution. We introduce a new analysis framework for parametric logical regulatory networks addressing combinatorial explosion on two levels. First, we propose *a novel encoding of parametrisations utilising the inner structure of parametrisations*. The encoding is applied to mitigate the combinatorial explosion induced by parametrisations. Accompanying methods are provided allowing for efficient use of the encoding. Second, we *extend Petri net unfoldings to accommodate for the parametric setting*. The unfoldings are coupled with the encoding method for parametrisations to allow for compact representation of state space of the PRNs thanks to their ability to exploit concurrency. Finally, a prototype implementation is provided to compute the introduced unfoldings. Experiments are conducted comparing the results of our methods against state-of-the-art methods in parametric regulatory network analysis.

Related Work. The analysis of logical regulatory networks under parameter uncertainty is a field not yet largely explored. Recently, it is gaining popularity thanks to the importance and great promise to the field of systems biology. Computational Tree Logic (CTL) [2] has been used to enumerate all possible temporal properties (parametrisations) of Thomas networks, by Bernot et al. [4]. Methods based on LTL model checking [2] have also been introduced for Thomas networks [13,10]. In [13] the method called coloured model checking first introduced in [3] is used to capitalise on many parametrisations sharing some parts of their behaviour. The parametrisations are represented by colours (bits) in a binary vector and the model checking is extended to binary vector operations to keep track of the satisfying behaviours.

The approach in [10] explores the state space represented symbolically in form of execution trees. This approach is closest to our work since the symbolical representation of state space employed in [10] is acyclic similarly to unfoldings. Furthermore, encoding of parametrisations is also performed in [10] utilising logical formulas. Contrary to our fixed-size encoding, however, the formula used in [10] continues to expand during the exploration as more detailed encoding of parametrisations is required.

Work was also done using constraint logic programming for parameter identification [5,9], again using Thomas networks. The approach in [5] encodes all available biological knowledge into logical constraints on the behaviour of the network while in [9] the constraint logic programming is used to pre-process the initial set of behaviours to filter out those in conflict with the constraints. Model checking is used on the smaller (filtered) set afterwards.

Ostrowski et al. [16] also introduce a method for restricting the initial set of possible behaviours for Boolean networks. Logical constraints are derived from time series data and answer set programming (ASP) is applied to compute a set of transient dynamics (parametrisations) best fitted to the measurements.

Paper Structure. In Section 2 we introduce the parametric regulatory networks including their semantics and parametrisation. Section 3 further expands the model by labels on the influences used to incorporate prior knowledge into the model. In Section 4 we address the potentially double exponential number of parametrisations by introducing a new encoding of parametrisations. This encoding is subsequently applied for unfoldings of parametric regulatory networks in Section 5. Section 6 features experimental results using the parametric unfoldings and comparison against methods relying on execution trees [10] is provided.

2 Parametric Regulatory Networks

In this section we introduce *parametric regulatory networks* (PRN). Informally one can consider PRN as a standard regulatory network with unknown dynamics, namely transition relation. We can therefore capture the topology of a PRN using a directed graph, so-called Influence Graph, $G = (V, I)$ where V is the set of n vertices (components) and $I \subseteq V \times V$ is the set of directed edges (influences). We denote the set of all in-neighbours (regulators) of some $v \in V$ as $n^-(v) = \{u \in V | (u, v) \in I\}$ and the set of all out-neighbours (targets) as $n^+(v) = \{u \in V | (v, u) \in I\}$. The influence graph of our running example can be seen in Figure 1.

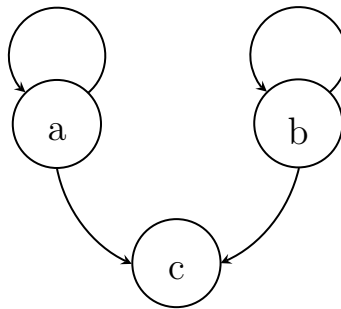


Figure 1. The influence graph of a simple three node regulatory network. We will further use this influence graph for our running example.

Generally, every component $v \in V$ is considered as a variable with a finite discrete domain (multivalued). In the scope of this article we limit ourselves to Boolean setting for the sake of simplicity. However, natural extension to any multivalued variables is considered. In the case that every variable $v \in V$ is Boolean we denote the PRN as a *parametric Boolean network* (PBN).

a	a
0	P_{\emptyset}^a
1	$P_{\{a\}}^a$

b	b
0	P_{\emptyset}^b
1	$P_{\{b\}}^b$

a	b	c
0	0	P_{\emptyset}^c
0	1	$P_{\{b\}}^c$
1	0	$P_{\{a\}}^c$
1	1	$P_{\{a,b\}}^c$

Table 1

The truth tables for the nodes of the running example influence graph depicted in Figure 1. Truth tables for all three nodes: a, b and c are listed left to right.

Viewing the components of the interaction graph as variables allows for a natural definition of a state of the PBN. By a state X of $G = (V, I)$ we understand any subset of V ($X \subseteq V$). We say that any component $v \in V$ is *active* (has value 1) in state X if $v \in X$ and, respectively, v is *inactive* (has value 0) if $v \notin X$. We denote the set of all possible states as $\mathcal{X} = 2^V$.

The nature of the interactions depends on the activity levels of the components in a given state. However, it is often the case in biology that exact effects of regulators on their targets are unknown. We therefore abstract these values by means of parameters.

A *parameter* represents a value of the target assigned to a given combination of active and inactive regulators as determined in the particular state. Naturally, there exists a parameter for any such combination of regulators. We denote such a combination as *regulatory context* (RC). Formal definition follows.

Definition 2.1 A regulatory context ω of component $v \in V$ is an arbitrary subset of the regulators of v . Formally, $\omega \subseteq n^-(v)$. Just as with the states of PBN we say that all components $u \in \omega$ are active and all components $u \in n^-(v) \setminus \omega$ are inactive.

The set of all combinatorially possible regulatory contexts of v will be further denoted as $\Omega_v = 2^{n^-(v)}$.

It can be shown that RCs correspond to the rows of the truth table for each component. The truth tables with the RCs and parameters for our running example can be seen in Table 1.

Every parameter (RC) can be assigned a target value 0 or 1. We denote such an assignment for all RCs as *parametrisation*.

Definition 2.2 A parametrisation assigns every RC of every component a target value. Formally, a parametrisation P is defined as $P \subseteq \Omega$ where $\Omega = \bigcup_{v \in V} \{v\} \times \Omega_v$ represents all regulatory context of all components. In other words, parametrisation is a subset of pairs of a component v and a RC ω of the component v . We say that the target value of RC ω of component v under parametrisation P is 1 if $(v, \omega) \in P$. We write simply $\omega \in P$ instead of $(v, \omega) \in P$ whenever the target v is known from the context.

We denote the set of all possible parametrisations of an influence graph $G = (V, I)$ as $\mathcal{P}_G = 2^\Omega$

A PBN \mathcal{B} is thus an influence graph G equipped with a set of possible parame-

trisations $\mathcal{P} \subseteq \mathcal{P}_G$ ($\mathcal{B} = (G, \mathcal{P})$). Shall $\mathcal{P} = \mathcal{P}_G$ we say that \mathcal{B} is fully parametric. On the other hand, shall $|\mathcal{P}| = 1$ \mathcal{B} is a simple Boolean network.

Finally we can define the dynamics of the PBN. As we have already mentioned the dynamics of a PBN equipped with a single parametrisation is identical to standard Boolean networks. There are, however, several ways to define dynamics of a Boolean network from the synchrony perspective. In the biological setting the individual reactions are often temporally independent and no explicit synchrony exists. In the scope of this paper, we consider the asynchronous dynamics.

The asynchronous dynamics are generally nondeterministic, however, it can be easily captured by means of so-called *state transition graph* (STG) $S = (\mathcal{X}, \delta)$ where $\delta \subseteq \mathcal{X} \times \mathcal{X}$ is the state transition relation given by target values of RCs. Intuitively, the STG of a PBN $\mathcal{B} = (G, \mathcal{P})$ can be considered a natural composition (union on transitions) of STGs of Boolean networks $(G, \{P\})$ for every $P \in \mathcal{P}$. More formally, due to the asynchrony we only consider transitions between states that differ in exactly one element. As such, for $X_1, X_2 \in \mathcal{X}$ such that $X_1 \setminus X_2 = \{v\}$ (respectively $X_2 \setminus X_1 = \{v\}$) for some $v \in V$ there exists a transition $(X_1, X_2) \in \delta$ iff $\exists P \in \mathcal{P} : (n^-(v) \cap X_1) \notin P$ (respectively $\exists P \in \mathcal{P} : (n^-(v) \cap X_1) \in P$).

The dynamics and parametrisation definitions can be easily extended to general PRNs. An example of such an extension can be found in [13] where a further capability is introduced to allow for an interval of values of regulators to share behaviour. In the general case PRNs each parametrisation defines a unique Thomas network instead of a Boolean network.

3 Labels on Edges of Influence Graphs

In the previous section we have introduced the PBNs and mentioned that the cause of parameter uncertainty comes from the lack of information on biological interaction. The information is, however, often partially available. Most of the biological knowledge can be compiled into two types of conditions on the edges of the influence graph: *monotonicity* and *observability*.

Monotonicity comes in two forms, either as *plus-monotonicity* or the dual *minus-monotonicity*. An edge $(u, v) \in I$ is plus-monotonous under parametrisation P iff $\forall \omega \in \Omega_v : u \in \omega \Rightarrow (\omega \in P \vee \omega \setminus \{u\} \notin P)$. Analogically, an edge $(u, v) \in I$ is minus-monotonous under P iff $\forall \omega \in \Omega_v : u \in \omega \Rightarrow (\omega \notin P \vee \omega \setminus \{u\} \in P)$. In other words, an edge is plus-monotonous if the increase in the activity of the source cannot cause a decrease in the activity of the target and minus-monotonous if the increase in the activity of source cannot cause an increase in the target activity.

On the other hand, an edge $(u, v) \in I$ is observable under parametrisation P if $\exists \omega \in \Omega_v : |\{\omega \setminus \{u\}, \omega \cup \{u\}\} \cap P| = 1$. In other words, an edge is observable if there exists a combination of regulators such that the change in the activity of the source causes a change in the activity of the target.

Naturally, monotonicity and observability may be used to restrict possible parametrisations. We therefore equip the influence graph with a labelling function $\gamma : I \rightarrow 2^{\{+, -, o\}}$ specifying the conditions imposed on every edge. A *Labelled Influence Graph* (LIG) is thus a tuple $\mathcal{G} = (V, I, \gamma)$. The set of possible parametrisations of \mathcal{G} is $\{P \in \mathcal{P}_{(V, I)} \mid \forall i \in I : P \text{ satisfies the conditions imposed by } \gamma(i)\}$. An example

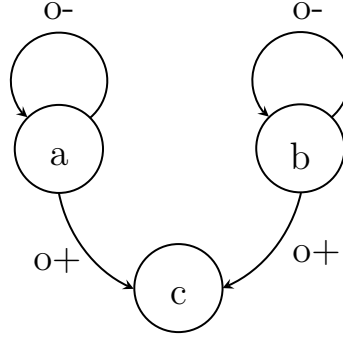


Figure 2. An example of a labelled influence graph (LIG) obtained by introducing a labelling function $\gamma = \{((a, a), \{-, o\}), ((b, b), \{-, o\}), ((a, c), \{+, o\}), ((b, c), \{+, o\})\}$. Only one possible parametrisation is available to govern the self-regulation of a and b after the labelling. In fact, from the initial $2^8 = 256$ parametrisations of the running example, only two parametrisations are possible with the labelling. Also notice that with the labelling γ every influence of the running example is both observable and monotonous. We refer to such labelling function as full labelling and to LIG with full labelling as fully labelled.

of a labelling function and a LIG is given in Figure 2 using the running example as the original influence graph.

The concept of monotonicity and observability can again be straightforwardly extended to multivalued variables.

4 Parametrisation Encoding

In previous sections we have introduced the concept of parametrisation of Boolean networks and natural constraints to implement partial knowledge about the model. In practice, however, known methods are not scalable when applied to PBNs as introduced due to combinatorial explosion. In fact, the combinatorial explosion occurs for PBNs in two instances. First the state space is exponential in the number of components (note $\mathcal{X} = 2^V$). The state space explosion also affects standard Boolean networks and equivalent models (this is addressed more closely in Section 5). In this section we dedicate ourselves to the second cause of combinatorial explosion, the parametrisations themselves (recall $\mathcal{P}_G = 2^\Omega$). Here we introduce a novel approach to encode some special sets of parametrisations relevant for our application.

The need to encode parametrisations is required especially for generating processes (possible behaviours) of the PBN. Although processes may be infinite, any reachable state is reachable by at least one finite process. We therefore only require finite processes to be reachability-complete. Formal definition follows.

Definition 4.1 Let $(\mathcal{G}, \mathcal{P})$ be a PBN with STG (\mathcal{X}, δ) . A process of length $k \in \mathbb{N}$ is a sequence of states $\pi = (X_1, \dots, X_k) \in \mathcal{X}^k$ where $\forall i \in \{1, \dots, k-1\} : (X_i, X_{i+1}) \in \delta$.

Let $\pi = (X_1, \dots, X_k)$ be a process and $X \in \mathcal{X}$ state such that $(X_k, X) \in \delta$. Then $\pi' = \pi \cdot X$ is a process of length $k+1$ and we say π' is an extension of π .

PBNs represent several different model possibilities introduced by individual parametrisations. The parametrisations are in fact mutually exclusive. The dynamics given by STG, however, do not distinguish between individual parametrisations and allow for their combinations. As such, there may exist processes that cannot be reproduced by any single parametrisation. It is useless to explore such processes and it is therefore imperative to assign every process (set of transitions) a set of feasible parametrisations.

Let (G, \mathcal{P}_G) be a PBN and $(X_1, X_2) \in \delta$ a transition of the respective STG such that $X_1 \setminus X_2 = \{v\}$ for some $v \in V$. We call such transition the *inhibition* of v . Every parametrisation that allows the inhibition of v in state X_1 must necessarily assign the target value of $X_1 \cap n^-(v)$ to 0. Furthermore, it is sufficient for the target value of $X_1 \cap n^-(v)$ to be fixed to 0 for the parametrisation to allow transition (X_1, X_2) . We can apply similar reasoning to *activations* ($X_2 \setminus X_1 = \{v\}$ for some $v \in V$). An activation requires the associated RC $X_1 \cap n^-(v)$ to have target value 1. As such, we can define an associated regulatory context of a transition $d = (X, X') \in \delta$ as $\omega_d = n^-(v) \cap X$ where $\{v\} = X \triangle X'$ (by \triangle we understand symmetric difference).

Any transition changes the value of exactly one component. Thus any transition is either exclusively an activation or an inhibition of some component. Arbitrary set of transitions $D \subseteq \delta$ is therefore uniquely given as union of set of inhibitions D_I and set of activations D_A ($D = D_A \cup D_I$). We now formalise the notion of feasible parametrisations of any set of transitions under the notion of *parameter context* (PC).

Definition 4.2 Let (G, \mathcal{P}) be a PBN with STG (\mathcal{X}, δ) . We define a function $p : 2^\delta \rightarrow 2^\mathcal{P}$ that assigns every set of transitions the set of parametrisations that allow all of the transitions. Formally, given any $D \subseteq \delta$ we set $p(D) = \{P \in \mathcal{P} \mid \forall d \in D_A : (\omega_d \in P) \wedge \forall d \in D_I : (\omega_d \notin P)\}$ where D_A and D_I are sets of activations and inhibitions (respectively) such that $D_A \cup D_I = D$. We call $p(D)$ the parameter context of D for any $D \subseteq \delta$. One can remark that $p(D) = \bigcap_{d \in D} p(\{d\})$.

We extend the definition to processes in natural fashion. Let $\pi = (X_1, \dots, X_k)$ be a process. By PC of π we understand $p(\pi) = p(\{(X_i, X_{i+1}) \mid i \in \{1, \dots, k-1\}\})$.

A naive approach to computing the PC as defined above could be to enumerate all exponentially many parametrisations. It is, however, precisely thanks to $\mathcal{P}_G = 2^\Omega$ that by introducing set inclusion order to parametrisations we obtain a Boolean lattice $(\mathcal{P}_G, \subseteq)$. We now provide intuition behind the use of lattices for PC encoding.

Let us consider a fully parametric PBN (G, \mathcal{P}_G) . As was mentioned above, the PC of arbitrary single transition d only contains parametrisations that set target value of ω_d to the same value. Shall d be an inhibition of some $v \in V$ we thus know $\forall P \in p(\{d\}) : \omega_d \notin P$. Keeping the set inclusion order in mind the largest parametrisation in $p(\{d\})$ is $\Omega \setminus \{(v, \omega_d)\}$. In fact, $p(\{d\})$ is a prime ideal of the lattice $(\mathcal{P}_G, \subseteq)$ with sole principal (maximal) element $\Omega \setminus \{(v, \omega_d)\}$. Analogically, shall d be an activation of some $v \in V$ the PC $p(\{d\}) = \{P \in \mathcal{P}_G \mid \omega_d \in P\}$ is a prime filter of $(\mathcal{P}_G, \subseteq)$ with sole principal (minimal) element $\{(v, \omega_d)\}$.

Since $p(D \cup D') = p(D) \cap p(D')$, one can remark that PC of any set $D_I \subseteq \delta$ such that $\forall d \in D_I : d$ is an inhibition is an ideal of $(\mathcal{P}_G, \subseteq)$. Respectively, PC of any set of activations $D_A \subseteq \delta$ is a filter. It is well known that the intersection of an arbitrary ideal and filter is either empty or a convex sub-lattice. Moreover, any convex sub-lattice can be uniquely represented by intersection of an ideal and a filter [11]. This allows us to represent any convex sub-lattice of $(\mathcal{P}_G, \subseteq)$ by only the maximal element (ideal) and minimal element (filter). As any set of transitions can be split into set of inhibitions and set of activations it is clear that any PC can be encoded by minimal and maximal elements. An example of the PCs represented as convex sub-lattices is visualised in Figure 3.

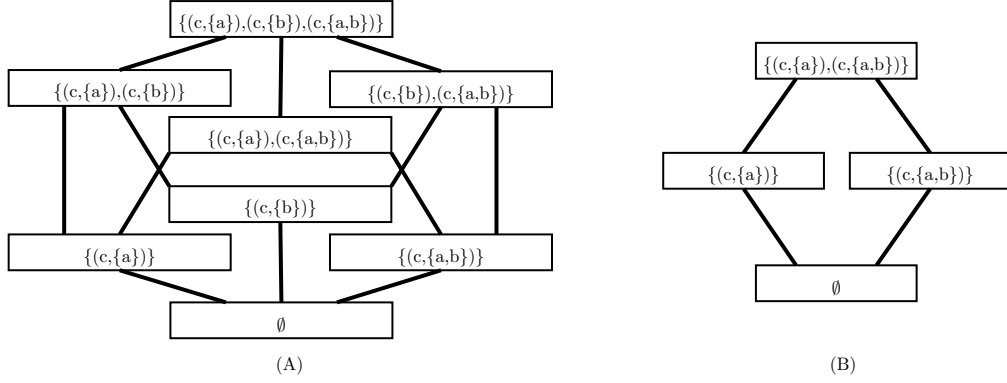


Figure 3. Hasse diagrams of the lattices representing parameter contexts for the regulation of component c in the unlabelled running example. **(A)** The PC of transition $(\{c\}, \emptyset)$ ($p(\{\{c\}, \emptyset\})$). **(B)** The restricted PC after transition $(\{b, c\}, \{b\})$ is included ($p(\{\{c\}, \emptyset\}, \{\{b, c\}, \{b\}\})$).

The results we have provided hold for fully parametric PBN (G, \mathcal{P}_G) . However, considering a LIB \mathcal{G} the lattice $(\mathcal{P}_G, \subseteq)$ is no longer guaranteed to exist. We therefore propose an over-approximation of a PBN $\mathcal{B} = (\mathcal{G}, \mathcal{P}_G)$ constructed as $\mathcal{B}' = (\mathcal{G}, [\mathcal{P}_G])$ where we use $[\mathcal{P}]$ to denote the smallest convex sub-lattice such that $\mathcal{P} \subseteq [\mathcal{P}]$. On similar note we introduce an over-approximative PC $p' : 2^\delta \rightarrow 2^{\mathcal{P}_G}$ such that $p'(D) = [p(D)]$ or $p'(D) = \emptyset$ if $p(D) = \emptyset$. The labelling function γ introduces dependencies between target values of individual RCs and therefore computing $p'(D) \cap p'(D')$ may not be sufficient to obtain the correct $p'(D \cup D')$ contrary to p . However, a method to resolve the issue for our purposes exists.

The method relies on knowledge of $p'(\pi)$ for some process $\pi = (X_1, \dots, X_k)$ to compute the PC of an arbitrary extension $\pi \cdot X$ where $X \in \mathcal{X}$ is a compatible state. Since we know that $p(\pi \cdot X) \subseteq p(\pi)$ and in conjecture $p'(\pi \cdot X) \subseteq p'(\pi)$ the PC of the extension can only be smaller than the PC of π . The method thus continuously removes elements from $p'(\pi)$ until $[p(\pi \cdot X)]$ is reached. The elements are removed in steps we refer to as *restriction*. By restriction we understand a combination of a regulatory context $\omega \in \Omega_v$ for some $v \in V$ and a value $i \in \{0, 1\}$. A restricted PC is then a PC \mathcal{P} such that $\forall P \in \mathcal{P} : \omega \in P$ if $i = 1$ and $\omega \notin P$ if $i = 0$. In other words, a restriction ensures all parametrisations in the restricted PC to have the same target value for a given RC.

The method recognises two causes of restriction. First, the extension itself requires the transition (X_k, X) to be allowed. Second, the edge labels introduce dependencies between target values of individual RCs. The method detects those dependencies and restricts the PC accordingly. For a more detailed explanation of the method see Appendix A.1.

One of the most important properties of the method is preservation of reachability. Since the method guarantees that $p'(\pi \times X) = [p(\pi \times X)]$ and namely $p'(\pi \times X) = \emptyset$ if $p(\pi \times X) = \emptyset$, any process π such that $p'(\pi) \neq \emptyset$ is guaranteed to also have $p(\pi) \neq \emptyset$ and vice versa. This property becomes important in Section 5 where we construct a compact representation of reachable state space. Thanks to the reachability being preserved any state reached by the over-approximation p' is guaranteed to be also reachable by p and vice versa. This allows us to compute the reachable states within the over-approximation p' . Reachability is, however, only

guaranteed to be preserved if the input $p'(\pi)$ of the method is correct. Cases exist where the initial $[\mathcal{P}_G] \neq \mathcal{P}_G$. A pre-computation is therefore necessary to determine $[\mathcal{P}_G]$. The pre-computation itself is detailed in Appendix A.3.

The lattice encoding and over-approximation of PCs can be extended to cover general multivalued PRNs. As multivalued parametrisations can no longer be expressed as sets, the lattice obtained is not a Boolean lattice. Instead an instance of vector lattice (also known as Riesz space) with product order of integer orders for each RC is obtained in the general case. The method for computing PCs of extensions also requires several adjustments discussed in detail in Appendix A.2.

5 Parametric Unfolding

Previously we have introduced an encoding of parametrisations to alleviate the combinatorial explosion induced by all possible combinations of RCs. In this section we address the combinatorial explosion of the state space of PBNs and standard Boolean networks for that matter. Biological networks are often considerably sparse in nature and contain a high amount of concurrent interactions. Partial order reduction approaches are therefore meaningful for dealing with the state space explosion in case of standard networks. Petri Net unfoldings are a prime example of a structure exploiting the concurrency of transitions. This section is therefore dedicated to application of unfoldings to PBNs and parametric setting in general.

We will now introduce unfoldings for PBNs utilising the PCs given by p' . Intuitively, the unfolding is an acyclic (tree-like) representation of all the processes of the PBN starting in a given initial state. Albeit an equivalent Petri net can be constructed for any PBN we do not require this Petri net explicitly to be able to unfold the PBN. We define (parametric) unfolding of a PBN as an event structure. Hence, our construction is similar to Petri net unfoldings [8,7], at the difference that the events are generated from the PBN.

In general, an event structure is a triplet $\mathcal{E} = (E, \leq, \#)$ where E is the set of events, $\leq \subseteq E \times E$ is a partial order relation on E called *causality relation* and $\# \subseteq E \times E$ is an antisymmetric, irreflexive relation called *conflict relation* satisfying:

- (i) $\forall e \in E : \{e' \in E \mid e' \leq e\}$ is finite.
- (ii) $\forall e, e', e'' \in E : (e \# e' \wedge e' \leq e'') \Rightarrow e \# e''$.

For our purposes we extend the event structure by a set of conditions B (we adopt Petri net unfolding notation here) to provide better intuition behind causality and conflict relations in our setting. First let us define the set of all events \overline{E} and conditions \overline{B} possible for a given PBN. As the definitions of events and conditions are interdependent, we define a hierarchy of sets E_i and B_i . First let $B_0 = \{(\perp, v, j) \mid v \in V \wedge j \in \{0, 1\}\}$. We then define $E_i = \{(\beta, v) \mid v \in V \wedge \beta \subseteq \bigcup_{j \in \{0, \dots, i-1\}} B_j \wedge \beta \cap B_{i-1} \neq \emptyset\}$ and $B_i = \{(e, v, j) \mid v \in V \wedge j \in \{0, 1\} \wedge e \in E_i\}$ for all $i \in \mathbb{N}$. The coveted $\overline{E} = \bigcup_{i \in \mathbb{N}} E_i$ and $\overline{B} = \bigcup_{i \in \mathbb{N}_0} B_i$ thus become the infinite unions.

Every condition $b \in \overline{B}$ is of the form $b = (e, v, i)$ where $e \in \overline{E} \cup \{\perp\}$ is a predecessor (parent) event of b if it exists, or \perp , otherwise, $v \in V$ is the component of PBN represented by condition b and $i \in \{0, 1\}$ is the value of v in b . Intuitively, a condition represents the possibility of a process reaching state where component

v has value i by following event e . Analogically, every event $e \in E$ is of the form $e = (\beta, v)$ where $\beta \subseteq \overline{B}$ is the set of predecessors (*preset*) of e and $v \in V$ is the component whose value changes by firing e . Intuitively, an event e represents the possibility of component v changing value under influence of regulators in β .

Events very closely resemble the transitions of the STG (δ). In fact, if the event $e = (\beta, v)$ is *well-formed* (satisfies $n^-(v) \cup \{v\} = \{u \mid (e', u, i) \in \beta\}$ and $|n^-(v) \cup \{v\}| = |\beta|$) we can define an associated RC $\omega_e = \{u \in n^-(v) \mid \exists (e', u, i) \in \beta : i = 1\}$ much like for transitions. We can also make a distinction between activations and inhibitions among the events. We say an event $e = (\beta, v)$ is an activation of v if $\exists (e', v, 0) \in \beta$ and analogically, e is an inhibition of v if $\exists (e', v, 1) \in \beta$. Any well-formed event is exclusively either activation or inhibition. This allows us to extend the PC function p and in turn also p' to well-formed events in the natural fashion. Formally, let $E \subseteq \overline{E}$ be a set of well-formed events. Then $p(E) = \{P \in \mathcal{P} \mid \forall e \in E_A : (\omega_e \in P) \wedge \forall e \in E_I : (\omega_e \notin P)\}$ where E_A is a set of activations and E_I is a set of inhibitions such that $E = E_A \cup E_I$.

We can now define causality and conflict relations. Let $e, e' \in E$ be arbitrary. We say that event $e = (\beta, v)$ is causally dependent on event $e' = (\beta', u)$ ($e' \leq e$) if $e = e'$ or there exists $b = (e'', w, i) \in \beta$ such that $e' \leq e''$. In other words, e is causally dependent on e' if there exists a directed path from e to e' defined by the parents and presets of conditions and events. If $\neg(e \leq e')$ and $\neg(e' \leq e)$ we say that e and e' are causally independent. Similarly, e is in conflict with e' ($e \# e'$) if there exist events $(\beta, v), (\beta', u) \in E$ such that $(\beta, v) \neq (\beta', u)$, $(\beta, v) \leq e$, $(\beta', u) \leq e'$ and $\beta \cap \beta' \neq \emptyset$. In other words, two events are in conflict if they (or their causal predecessors) use the same condition by two different events.

We can also naturally extend the relations of causality and conflict to conditions simply by setting $\forall (\beta, v) \in \overline{E} : \forall b \in \beta : b < (\beta, v)$ and $\forall (e, v, i) \in \overline{B} : e < (e, v, i)$ and computing the reflexive and transitive closure. The conflict relation is adjusted extending its domain to $\overline{E} \cup \overline{B}$. Additionally, let $x, y \in \overline{E} \cup \overline{B}$ such that x and y are causally independent and not in conflict. We then say x and y are concurrent.

One can notice that $(\overline{B}, \overline{E}, \leq, \#)$ may not be an extended event structure as it is not guaranteed to satisfy the constraints on the causality and conflict relations. We therefore construct the unfolding using subsets of $B \subseteq \overline{B}$ and $E \subseteq \overline{E}$ on which the relations \leq and $\#$ satisfy the coveted properties. Let $(\mathcal{G}, \mathcal{P}_{\mathcal{G}})$ be a PBN with STG (\mathcal{X}, δ) and $X_0 \in \mathcal{X}$ an initial state. Then the unfolding $\mathcal{U} = (B, E, \leq, \#)$ of $(\mathcal{G}, [\mathcal{P}_{\mathcal{G}}])$ in state X_0 is constructed as follows.

- (i) Start with empty $B = \emptyset$ and $E = \emptyset$.
- (ii) For every $v \in V$ add a condition (\perp, v, i) to B such that $i = 1$ if $v \in X_0$ and $i = 0$ otherwise.
- (iii) For every $v \in V$ find all sets $\mathcal{C} \subseteq B$ of concurrent conditions (*cosets*) such that $\{u \mid (e, u, i) \in \mathcal{C}\} = n^-(v) \cup \{v\}$ and $|\mathcal{C}| = |n^-(v) \cup \{v\}|$. For every such \mathcal{C} create an event $e = (\mathcal{C}, v)$. If $e \notin E$ then compute $p'(e)$ using the algorithm in Appendix A.1. If $p'(e) \neq \emptyset$ add e to the set E and for every $(e', u, i) \in \mathcal{C}$ add new condition $b = (e, u, j)$ to B where $j = i$ if $u \neq v$ and $j = (1 - i)$ for $u = v$. If at least one event was added to E repeat step (iii).

Although B and E are subsets of \overline{B} and \overline{E} it is apparent from the construction

of the unfolding that they are infinite in the general case. We have mentioned in Section 4 that any reachable state is reachable by a finite process. As the unfolding is a representation of all the processes of the network and the number of states is finite, there exists finite prefixes of the unfolding from which all the reachable states can be recovered. We refer to such a prefix as a *complete finite prefix* (CFP), and show hereafter a possible construction. First, we define an equivalent of a process within the unfolding traditionally denoted as configuration.

Definition 5.1 A set $C \subseteq E$ is a configuration if it is conflict free ($\nexists e, e' \in C : e \# e'$) and causally closed $\forall : e \in C, e' \in E : e' \leq e \Rightarrow e' \in C$.

By $[e]$ we denote a special configuration called local configuration of e , $[e] = \{e' \in E \mid e' \leq e\}$.

Any configuration C corresponds to at least one process of the PBN given by completing the partial order on the transitions equivalent to events in C . We can therefore assign every finite configuration a terminal (final) state $X_C = X_0 \Delta \{v_1\} \Delta \dots \Delta \{v_k\}$ where $C = \{e_1 = (\beta_1, v_1), \dots, e_k = (\beta_k, v_k)\}$ and $k \in \mathbb{N}_0$.

Let C be a configuration and $F \subseteq E$ such that $C \cap F = \emptyset$. We say that F is an extension of C if $C \cup F$ is a configuration. Let us now consider all possible extensions of C . Any extension of C corresponds to a process in the original PBN starting in state X_C and every such process is represented by an extension. As such, we can see that all extensions of C define an unfolding of the PBN in state X_C and initial parametrisation $p'(C)$. Furthermore, any extension possible in $\mathcal{P} \subseteq p'(C)$ is also possible under $p'(C)$.

Let us now consider two configurations $C, C' \subseteq E$ such that $X_C = X_{C'}$ and $p'(C) \subseteq p'(C')$ and an extension $F \subseteq E$ of C . Since F is an extension of C it surely belongs to the unfolding of the PBN in state X_C with $p'(C)$ and namely it also belongs to the unfolding in X_C with $p'(C')$. Unfolding of a PBN is given uniquely by initial state and set of feasible parametrisations. The unfolding in X_C with $p'(C')$ must therefore be isomorphic to the unfolding in $X_{C'}$ with $p'(C')$. And especially, there must be an extension $F' \subseteq E$ of C' isomorphic to F . This holds for any extension of C meaning any information captured by the extensions of C is already covered by extensions of C' and is redundant from the reachability point of view.

This result is interesting especially for local configurations. Let $e, e' \in E$ be such that $X_{[e]} = X_{[e']}$ and $p'([e]) \subseteq p'([e'])$. As there is no need to explore extensions of $[e]$ we omit them from the CFP. We formalise this by the notion of *cut-off* events. Once an event e is marked as cut-off event, no other event $e' \in E$ such that $e < e'$ is added to the CFP. Esparza et al. [8] show for Petri net unfoldings that a specific order on the configurations called adequate order is required to guarantee that no reachability is lost by cut-offs. As our unfolding notion is equivalent to Petri net unfoldings we have the same requirement on the order. By \prec we will further understand the total adequate order as defined in [8] adjusted for our definition of unfolding (see Appendix B for details). Formal definition of a cut-off event follows.

Definition 5.2 An event $e \in E$ is considered a cut-off event if there exists a different event $e' \in E$ such that $X_{[e]} = X_{[e']}$, $[e'] \prec [e]$ and $p'([e]) \subseteq p'([e'])$.

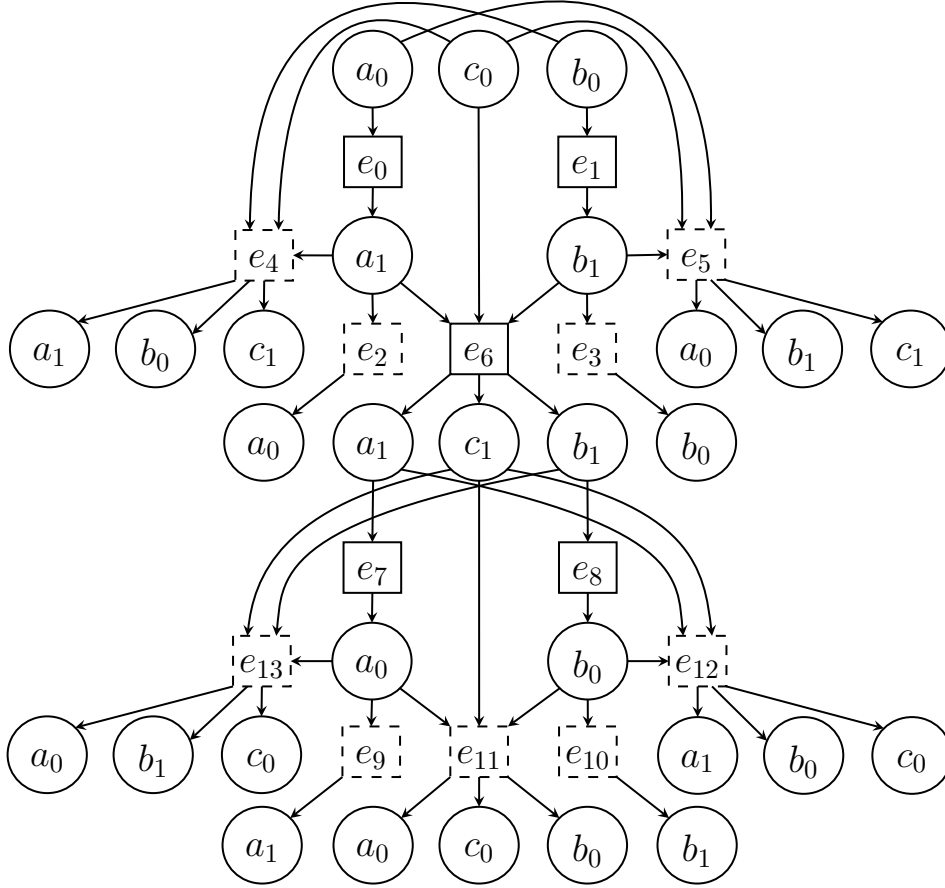


Figure 4. The complete finite prefix of the running example equipped with full labelling function as illustrated in Figure 2. The conditions are labelled by the component they represent and the value of the component $(v_i$ for (e, v, i)) while events are simply numbered. Cut-off events are marked with dashed borders. Notice that the order of concurrent activation/inhibition of species a and b is abstracted.

The total adequate order \prec , however, does not correlate with inclusion order over PCs. In other words, $C \prec C'$ does not guarantee $p(C') \subseteq p(C)$ and vice versa. As such a situation may occur where local configurations of two events $e, e' \in E$ lead to the same state $X_{[e]} = X_{[e']}$ and $p([e]) \subseteq p([e'])$ also holds, however, due to $[e] \prec [e']$ the event e would not be designed as a cut-off event. Although we do not currently possess the means to prevent such a situation, we can resolve it by marking e cut-off upon adding e' into the prefix. Naturally, a situation may arise where there exists $e'' \in E$ such that $e < e''$ by the time e' is reached. Any such e'' is removed from the prefix upon marking e as a cut-off and was therefore explored uselessly.

It is proven for Petri net unfoldings that the number of non-cut-off events does not exceed the size of the marking graph (state space) of the Petri net [8]. As the parametric unfolding relies on the PC for cut-offs, however, the claim cannot be extended to our setting. It is intuitively clear, however, that the number of traces in the CFP is surely smaller than in the STG. The CFP computed for the fully labelled version of the running example is shown in Figure 4.

6 Experiments

In this section we present some initial results on biological models and compare against the symbolic representation employed in [10]. The results have been obtained by a prototype implementation in Python of a **parametric unfolder** named *Pawn*.¹

The comparison is done regarding the size of the structure representing all the possible traces. We therefore compare the size of the unfolding – typically represented as the number of non-cut-off events with the number of states in the complete symbolic execution tree, obtained with the tool **SPuTNIk** [10]. Therefore, the difference accounts for the partial-order reduction implicitly achieved by the unfolding, in the scope of Parametric Biological Regulatory Networks.

The experiments were conducted for two different biological models. First we use the common biological example of the bacteriophage λ life cycle genetic regulatory network [17] also analysed in [10,13]. The model is depicted in Figure 5 (A). The reachable state space has been explored from initial state with all species inactive ($X = \emptyset$). The model has been considered in two configurations, with and without the Min/Max constraint as introduced and employed in [10].

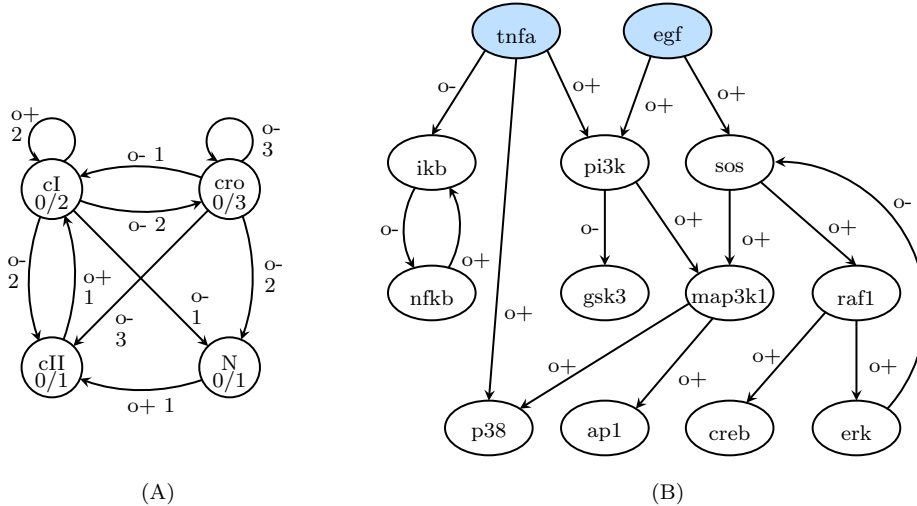


Figure 5. **(A)** A genetic regulatory network controlling the bacteriophage λ life cycle. Notice that the network is not Boolean. The numbers in the nodes represent the initial state slash maximal value. The numbers next to the edges represent the thresholds in the same fashion as in [10]. **(B)** Model of signalling pathway of EGF-TNF α . In this case, we consider only compatible Boolean networks and therefore no specification of maximal values and edge thresholds is necessary. The only two states that start with initial value 1 are marked in blue.

The second model is a signalling pathway, EGF-TNF α , as studied in [15,16] (Figure 5 (B)). In this case the initial state was with every specie inactive save for the two input species, *tnfa* and *egf*, which were active ($X = \{tnfs, egf\}$). The results are summarised in Table 2. The execution times for *Pawn* were less than a second ($\sim 0.4s$) and around 8.5 seconds for the bacteriophage λ (both variants) and EGF-TNF α respectively. **SPuTNIk** on the other hand took $\sim 1m$ and $\sim 10m$ for the bacteriophage λ with and without Min/Max respectively, and $\sim 30m$ for EGF-TNF α .

¹ *Pawn* is available online: <https://github.com/GeorgeKolcak/Pawn>

Model	Unfolding Events	Unfolding Events (with cut-offs)	Symbolic Execution Size
Lambda Switch	170	575	68,011
LS (with Min/Max)	170	569	15,139
EGF-TNF α	1,057	2,658	534,498

Table 2
Comparison of the size of the obtained structures between unfolding and the symbolic representation for different models.

Although no theoretical estimate on the size of the parametric unfolding can be given it is apparent from the results that exploiting the concurrency allows for considerably small representations of the parametric state space in practice. The difference in size is derived especially from the capability of the unfoldings to exploit concurrency. Therefore, shall there be n different concurrent transitions firing, unfolding does not distinguish the order in which they are fired and only explores one possibility. The symbolic execution on the other hand explores all $n!$ possible firing sequences only to obtain the same result each time. This is especially apparent in sparse networks that contain high amount of concurrent transitions.

The compact size of the unfolding allows for analysis of larger models. It was mentioned in Section 4, however, that only over-approximation is given in case of LIGs. Therefore, in the unfolding of an LIG based PBN, the PC of an arbitrary process may contain parametrisations that do not allow the said process. It may thus be required to filter out these false positives before further application. Reachability model checking on the obtained PC may be considered for such a filtering.

7 Conclusion

We offer a new platform for parameter identification of logical regulatory networks based on Petri net unfoldings. Our contribution addresses several issues. First, we introduce a novel approach to encoding parametrisations allowing for efficient analysis of parametric regulatory networks. We employ the encoding in practice for computing feasible parametrisations for all possible behaviours of the system. Accompanying methods are also presented for efficiently computing the feasible parametrisations of extensions of behaviours within the encoding. Although only over-approximation of the set of feasible parametrisations is given in the general case, reachability preservation is guaranteed by the methods. The refinement of the overapproximation is considered for future work.

Next we analyse the possibility of using Petri net unfoldings to exploit concurrency in parametric models of biological networks. We present a modification to allow for unfolding of parametric regulatory networks and couple the unfoldings with the encoding of parametrisations to neutralise both sources of combinatorial explosion in parametric regulatory networks.

Last but not least, we provide a prototype implementation of the introduced methods and compare against existing methods on relevant biological examples. The comparison proves our methods capable of representing the reachable state space of parametric regulatory networks in much smaller structure than previous approaches. This compression opens the possibilities of efficient further analysis of parametric networks via the parametric unfoldings.

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Appendices

A Parameter Context of Extensions

Here we present in detail the method to compute the overapproximation PC p' of process extensions expanding on the intuition given in Section 4. Precomputation of $[\mathcal{P}_G]$ is also provided and the case with multivalued PRNs is discussed.

A.1 Method for Parameter Context Restriction

Let us first fix a notation for minimum and maximum of the PCs. For $[\mathcal{P}]$ we denote the minimum as $0_{\mathcal{P}} = \bigcap_{P \in \mathcal{P}} P$ and the maximum as $1_{\mathcal{P}} = \bigcup_{P \in \mathcal{P}} P$. Next we define restriction formally and denote some special relationships between PCs and RCs.

Definition A.1 A restriction is a tuple $r = (v, \omega, i)$ where $\omega \in \Omega_v$ is RC of $v \in V$ and $i \in \{0, 1\}$ is the new target value of ω .

Let \mathcal{P} be a PC (convex lattice). \mathcal{P} can be restricted by restriction $r = (v, \omega, i)$ to obtain a restricted PC $\mathcal{P}' = \{P \in \mathcal{P} \mid \omega \in P \text{ if } i = 1 \text{ or } \omega \notin P \text{ if } i = 0\}$

Using the notation with minimal and maximal element a restriction $(v, \omega, 0)$ results in $\omega \notin 1_{\mathcal{P}'}$ and $(v, \omega, 1)$ leads to $\omega \in 0_{\mathcal{P}'}$. As long as $0_{\mathcal{P}'} \subseteq 1_{\mathcal{P}'}$ holds ($\mathcal{P}' \neq \emptyset$) the above constraints enforce $\omega \notin 0_{\mathcal{P}'} \Delta 1_{\mathcal{P}'}$.

Definition A.2 Let $\omega \in \Omega_v$ be RC of some $v \in V$ and let $u \in n^-(v)$ be an arbitrary regulator of v . We say that $\omega' \in \Omega_v$ such that $\omega' = \omega \Delta \{u\}$ is a u -pair regulatory context (u -pair) of ω . In other words, two RCs of v are reciprocal u -pairs of each other if they differ only in activity of regulator u . We will denote the u -pair of ω as ω^u .

Let $[\mathcal{P}]$ be some PC. We say that ω is restricted under $[\mathcal{P}]$ iff $\omega \notin 0_{\mathcal{P}} \Delta 1_{\mathcal{P}}$. In other words, ω is said to be restricted under $[\mathcal{P}]$ if all parametrisations in \mathcal{P} assign ω the same target value. In such case we say $[\mathcal{P}]$ fixes the target value of ω . On the other hand, shall the target values for ω differ we say ω is free under $[\mathcal{P}]$.

Additionally, if both ω and the u -pair of ω are restricted under some $[\mathcal{P}]$ we say that ω and the u -pair are u -restricted under $[\mathcal{P}]$.

As mentioned in Section 4 the method works with two causes of restrictions. In fact, the first cause – the transition itself is always the first restriction to happen. Let $\pi = (X_1, \dots, X_k)$ be a process and transition (X_k, X) an inhibition of v . If there is indeed no restriction necessary for all parametrisations to allow the transition then we know that $X_k \cap n^-(v) \notin 1_{p'(\pi)}$ and thus especially $X_k \cap n^-(v) \notin 1_{p(\pi)}$. Surely then $p((X_k, X)) \subseteq p(\pi)$ must hold leading to $p(\pi \cdot X) = p(\pi)$. We may even extend this reasoning as it can be shown that any edge label based restriction is a result of a prior restriction and dependency introduced by labelling function.

Let us first consider a case when a restriction occurs due to monotonicity requirement. Let $(u, v) \in I$ be an interaction such that $+$ $\in \gamma((u, v))$. (Once again we assume plus-monotonicity without loss of generality as the reasoning is analogical for minus-monotonicity.) We now define necessary and sufficient conditions for the monotonicity of interaction (u, v) to introduce a restriction $(v, \omega, 1)$: $u \in \omega$ and

$\omega^u \in 0_{p(\pi \cdot X)}$. Clearly these conditions are sufficient as using the definition of monotonicity we have $u \in \omega \Rightarrow (\omega \in P \vee \omega^u \notin P)$ thus obviously $\omega \in P$. In fact, the given conditions are not necessary strictly speaking. However, under the assumption that it was indeed the monotonicity of the (u, v) interaction that requires the restriction $(v, \omega, 1)$, it becomes easy to see that they are indeed necessary. In other words, those are the necessary conditions for a plus-monotonicity criterion to introduce a new restriction. Let us therefore assume restriction $(v, \omega, 1)$ was required. As we are working with plus-monotonicity, the only way to enforce restriction on ω is when $u \in \omega$. Moreover, the restriction with value 1 can only be imposed if $\omega^u \in P$ for all P giving us $\omega^u \in 0_{p(\pi \cdot X)}$. Clearly then restriction $(v, \omega, 1)$ enforced by plus-monotonicity requires a prior restriction $(v, \omega^u, 1)$ to occur.

Similarly we may consider restriction enforced by observability. Let $(u, v) \in I$ be an interaction such that $o \in \gamma((u, v))$. Just as in the monotonicity case we define necessary and sufficient conditions for the observability of interaction (u, v) to introduce restriction $(v, \omega, 1)$: $\forall \omega' \in \Omega_v \setminus \{\omega, \omega^u\} : (\omega' \in 0_{p(\pi \cdot X)} \wedge \omega'^u \in 0_{p(\pi \cdot X)}) \vee (\omega' \notin 1_{p(\pi \cdot X)} \wedge \omega'^u \notin 1_{p(\pi \cdot X)})$ and $\omega^u \notin 1_{p(\pi \cdot X)}$. Albeit the conditions are more complex to formalise compared to monotonicity, they are fundamentally very straightforward, the first condition requires any u -pair of regulatory contexts other than ω to be u -restricted to the same value in $p(\pi \cdot X)$ while the second condition simply requires the u -pair of ω to have target value fixed to 0. Again we show the given conditions are sufficient. As any $\omega' \in \Omega_v$ except ω and ω^u has target value equal to the u -pair ω'^u it is apparent that to satisfy the existential condition in the definition of observability we need target values of ω and ω^u to differ. Thus $\omega \in 0_{p(\pi \cdot X)}$ as the value of ω^u is fixed to 0 and the coveted restriction happened. The conditions again, are not necessary in the general sense, however it can be shown they are necessary if the restriction $(v, \omega, 1)$ is imposed by the observability of (u, v) . Let therefore $\omega \in 0_{p(\pi \cdot X)}$ be enforced by observability of (u, v) . For ω and the u -pair of ω to be able to satisfy observability is clearly necessary that their target values differ and as ω is fixed to 1 we get $\omega^u \notin 1_{p(\pi \cdot X_{k+1})}$. Moreover for observability to strictly determine the target value of ω it must hold for all the other u -pairs that they do not satisfy observability of (u, v) giving us the first criterion $(\forall \omega' \in \Omega_v \setminus \{\omega, \omega^u\} : (\omega' \in 0_{p(\pi \cdot X)} \wedge \omega'^u \in 0_{p(\pi \cdot X)}) \vee (\omega' \notin 1_{p(\pi \cdot X)} \wedge \omega'^u \notin 1_{p(\pi \cdot X)}))$ as if any of those u -pairs differed in target value the observability would be satisfied with arbitrary target value of ω . Again we can draw the conclusion that there must have been a prior restriction that allowed the sufficient and necessary conditions to become true before the restriction $(v, \omega, 1)$ was enforced by observability.

We can conduct analogical reasoning for restrictions with target values 0. As any restriction with the exception of the first one imposed by the transition itself has a one prior restriction acting as a cause, we can define a causal partial order on the restrictions. It is easy to see, that such a partial order defines a tree topology on the restrictions. We will now proceed with the definition of the method itself. Let $\pi = (X_0, \dots, X_k)$ be a process and $X \in \mathcal{X}$ a state such that $(X_k, X) \in \delta$. The following method computes $p'(\pi \cdot X)$ using $p'(\pi)$.

- (i) Set $0_{p(\pi \cdot X)} = 0_{p(\pi)}$ and $1_{p(\pi \cdot X)} = 1_{p(\pi)}$ and initialise an empty FIFO queue of restrictions.
- (ii) Push $(v, X_k \cap n^-(v), i)$ where $i = 0$ if (X_k, X) is inhibition of v or $i = 1$ if

- (X_k, X) is activation of v to the queue of restrictions.
- (iii) While the queue of restrictions is not empty, pop (v, ω, i) from the queue and execute the following:
- (a) If $i = 0$ set $1_{p(\pi \cdot X)} = 1_{p(\pi \cdot X)} \setminus \{\omega\}$ else $0_{p(\pi \cdot X)} = 0_{p(\pi \cdot X)} \cup \{\omega\}$. If no change occurred by the previous operation skip to next element in the queue of restrictions.
 - (b) For every monotonous influence $(u, v) \in I$ push (v, ω_u, i) where ω_u is the u -pair of ω to the queue of restrictions if one of the following is true:
 - $i = 0, + \in \gamma((u, v))$ and $u \in \omega$.
 - $i = 1, + \in \gamma((u, v))$ and $u \notin \omega$.
 - $i = 0, - \in \gamma((u, v))$ and $u \notin \omega$.
 - $i = 1, - \in \gamma((u, v))$ and $u \in \omega$.
 - (c) If there exists only one regulatory context $\omega' \in \Omega_v$ such that ω' is open under $p'(\pi \cdot X)$ as defined by $0_{\pi \cdot X}$ and $1_{\pi \cdot X}$ then for every observable influence $(u, v) \in I$ such that there does not exist an u -closed pair of regulatory contexts with different target values push $(v, \omega', 1 - j)$ where j is the fixed target value of u -pair of ω' to the queue of restrictions.
- (iv) Output $0_{\pi \cdot X}$ and $1_{\pi \cdot X}$ as minimum and maximum of $p'(\pi \cdot X)$ respectively. If $0_{\pi \cdot X} \leq 1_{\pi \cdot X}$ does not hold we consider the result to be empty ($p'(\pi \cdot X) = \emptyset$) in accordance with the definition as intersection of ideal and filter.

In simpler terms, the aforementioned method traverses the tree of restrictions with a breadth first search while constructing it on the run. Monotonocity (point (iii)(b)) is enforced straightforwardly as the universal quantifier in the definition requires every u -pair to satisfy the condition. Observability (point (iii)(c)) definition contains an existential quantifier and is therefore enforced only if no other u -pair can satisfy the condition. The method always terminates and has a polynomial complexity of $\mathcal{O}(\Omega^2)$ in the worst case as every RC can have it's value restricted at most twice.

Assuming the input is correct ($p'(\pi) = [p(\pi)]$) the method computes correct $p'(\pi \cdot X) = [p(\pi \cdot X)]$ ($p(\pi \cdot X) = \emptyset \Rightarrow p'(\pi \cdot X) = \emptyset$). Let us first assume $p(\pi \cdot X) \neq \emptyset$. As $[p(\pi \cdot X)]$ is by definition the smallest convex sub-lattice containing $p(\pi \cdot X)$ it is enough to prove $p(\pi \cdot X) \subseteq p'(\pi \cdot X) \subseteq [p(\pi \cdot X)]$.

Let us first show $p(\pi \cdot X) \subseteq p'(\pi \cdot X)$. Let (v, ω, i) be an arbitrary restriction that gets added to the restriction queue during the algorithm. If the restriction does not change $0_{p'(\pi \cdot X)}$ and $1_{p'(\pi \cdot X)}$ within the algorithm then $p'(\pi \cdot X) = p'(\pi)$ and the condition is trivially satisfied since we know $p(\pi \cdot X) \subseteq p(\pi) \subseteq [p(\pi)] = p'(\pi)$. Let us therefore expect that the restriction (v, ω, i) had an effect on $p'(\pi \cdot X)$. Thanks to the self-duality of the Boolean matrix, the duality of plus-/minus-monotonocity and symmetry of observability it is enough to consider $i = 1$ without loss of generality. Thus we get that $0_{p(\pi \cdot X)}$ gets extended by ω by the restriction. Now let us create a discussion as to the cause of the restriction.

- (i) The restriction $(v, \omega, 1)$ is added to the queue due to transition (X_k, X) such that $\{v\} = X \setminus X_k$ and $n^-(v) \cap X_k = \omega$. By definition $p((X_k, X)) = \{P \in \mathcal{P}_{\mathcal{G}} | \omega \in P\}$ and $p(\pi \cdot X) = p(\pi) \cap p((X_k, X))$ it thus follows that $\forall P \in p(\pi \cdot X) : \omega \in P$ and therefore $\omega \in 0_{p(\pi \cdot X)}$.

- (ii) The restriction $(v, \omega, 1)$ is enforced by some prior restriction r and monotonicity of $(u, v) \in I$ (plus-monotonicity without loss of generality). If we apply this reasoning to restriction in the partial order given by the restriction tree we can assume r does not break the desired $p(\pi \cdot X) \subseteq p'(\pi \cdot X)$ ($0_{p'(\pi \cdot X)} \subseteq 0_{p(\pi \cdot X)}$ is enough to consider for the case $i = 1$). We can now use the sufficient and necessary conditions for restriction $(v, \omega, 1)$ to happen. Thus we get $u \in \omega$ and $\omega^u \in 0_{p'(\pi \cdot X)}$ (by extension $\omega^u \in 0_{p(\pi \cdot X)}$). Since $p(\pi \cdot X) \subseteq \mathcal{P}_{\mathcal{G}}$ the monotonicity restrictions must hold for every $P \in p(\pi \cdot X)$. Thus namely for any $P \in p(\pi \cdot X)$ such that $\omega^u \in P$ is must also hold $\omega \in P$ giving us the coveted $\omega \in 0_{p(\pi \cdot X)}$.
- (iii) The restriction $(v, \omega, 1)$ is enforced by some prior restriction r and observability of $(u, v) \in I$. Just as in the previous case we can assume r does not break the coveted $0_{p'(\pi \cdot X)} \subseteq 0_{p(\pi \cdot X)}$. Again, we use the sufficient and necessary conditions for $(v, \omega, 1)$ giving us $\forall \omega' \in \Omega_v \setminus \{\omega, \omega^u\} : (\omega' \in 0_{p(\pi \cdot X)} \wedge \omega'^u \in 0_{p(\pi \cdot X)}) \vee (\omega' \notin 1_{p(\pi \cdot X)} \wedge \omega'^u \notin 1_{p(\pi \cdot X)})$ and $\omega^u \notin 1_{p(\pi \cdot X)}$. Applying the same reasoning and $p(\pi \cdot X) \subseteq \mathcal{P}_{\mathcal{G}}$ we know the target value of ω must be different from ω^u for every parametrisation in $p(\pi \cdot X)$.

We will now show $p'(\pi \cdot X) \subseteq [p(\pi \cdot X)]$. Shall $[p(\pi)] = [p(\pi \cdot X)]$ we know $p'(\pi \cdot X) \subseteq p'(\pi) = [p(\pi)] = [p(\pi \cdot X)]$ and the result is trivial. Let us thus assume $[p(\pi \cdot X)] \subseteq [p(\pi)]$. This clearly means there exists at least one regulatory context ω such that $\omega \in 0_{p(\pi \cdot X) \setminus 0_{p(\pi)}}$ or $\omega \in 1_{p(\pi)} \setminus 1_{p(\pi \cdot X)}$. Just as in the previous case we can assume $\omega \in 0_{p(\pi \cdot X)} \setminus 0_{p(\pi)}$ without loss of generality thanks to the duality and symmetry properties. We will now show, that for any such ω the algorithm definitely adds restriction $(v, \omega, 1)$ to the restriction queue where $v \in V$ is such that $\omega \in \Omega_v$. Analogically to the above discussion on the restriction we do a discussion on the nature of ω . Since we know that any parametrisation with target value of ω equal to 0 does not belong to $p(\pi \cdot X)$ despite belonging to $p(\pi)$ there are only few possible explanations of this occurrence (we once again use the sufficient and necessary conditions for monotonicity and observability enforcement).

- (i) $\omega = X_k \cap n^-(v)$ is the regulatory context used by the activation (X_k, X) . The corresponding restriction $(v, \omega, 1)$ is always added to the restriction queue. Thus $p'(\pi \cdot X)$ is restricted appropriately thus retaining the coveted $0_{p(\pi \cdot X)} \subseteq 0_{p'(\pi \cdot X)}$.
- (ii) $u \in \omega$ and ω^u also belongs to $0_{p(\pi \cdot X)} \setminus 0_{p(\pi)}$ and $(u, v) \in I$ is plus-monotonous (without loss of generality). We may assume that restriction $(v, \omega^u, 1)$ is in the queue by conducting this discussion on ω^u . By restriction tree we are guaranteed to eventually have $X_k \cap n^-(v)$ as the cause RC. Since $(v, \omega^u, 1)$ is in the restriction queue it will eventually be handled by the algorithm. Since $\omega^u \notin 0_{p'(\pi)}$ the restriction will make a difference leading to monotonicity and observability check. By the plus-monotonicity of (u, v) the restriction $(v, \omega, 1)$ will be enqueued.
- (iii) There exists some $\omega' \in 0_{p(\pi \cdot X)} \subseteq 0_{p'(\pi \cdot X)}$ (without loss of generality although it could also belong to $1_{p(\pi)} \setminus 1_{p(\pi \cdot X)}$) such that $\omega \neq \omega'$ and $\omega' \in \Omega_v$ and $(u, v) \in I$ is observable. In this case we have two different possibilities for how the sufficient and necessary conditions are satisfied.

- (a) $\omega' = \omega^u$. In this case we get $\forall \omega'' \in \Omega_v \setminus \{\omega, \omega^u\} : (\omega'' \in 0_{p(\pi \cdot X)} \wedge \omega''^u \in 0_{p(\pi \cdot X)}) \vee (\omega'' \notin 1_{p(\pi \cdot X)} \wedge \omega''^u \notin 1_{p(\pi \cdot X)})$ and $\omega^u \notin 1_{p(\pi \cdot X)}$. We can thus assume $(v, \omega^u, 0)$ to be in the restriction queue. From the first condition we know that every RC is u -restricted under $p'(\pi \cdot X)$ by the time restriction $(v, \omega^u, 0)$ is handled and the observability of (u, v) is yet to be satisfied. As such ω is left as the last free context by restriction of ω^u and to ensure observability the algorithm adds $(v, \omega, 1)$ to the restriction queue.
- (b) Otherwise we get $\forall \omega'' \in \Omega_v \setminus \{\omega, \omega^u, \omega', \omega'^u\} : (\omega'' \in 0_{p(\pi \cdot X)} \wedge \omega''^u \in 0_{p(\pi \cdot X)}) \vee (\omega'' \notin 1_{p(\pi \cdot X)} \wedge \omega''^u \notin 1_{p(\pi \cdot X)})$, $\omega'^u \notin 1_{p(\pi \cdot X)}$ and $\omega^u \notin 1_{p(\pi \cdot X)}$. And our assumption becomes existence of restriction $(v, \omega', 1)$ in the restriction queue. As we know $\omega' \notin 0_{p(\pi)}$ the restriction will make a difference and as it leaves behind ω as the last free RC and (u, v) with still unfulfilled observability requirement the $(v, \omega, 1)$ restriction must be added to the restriction queue.

Finally, let us assume $p(\pi \cdot X) = \emptyset$ (and $p(\pi) \neq \emptyset$). We now show that in such a case the algorithm computes $\neg(0_{p'(\pi \cdot X)} \subseteq 1_{p'(\pi \cdot X)})$ we interpret as $p'(\pi \cdot X) = \emptyset$. It is easy to see, as $0_{p'(\pi \cdot X)}$ is only extended and $1_{p'(\pi \cdot X)}$ only reduced that the method cannot recover from such a malformed state.

Let us again assume (X_k, X) to be activation of some $v \in V$ without loss of generality. We know $p(\pi \cdot X) = p(\pi) \cap p((X_k, X)) = \emptyset$. Since $p((X_k, X))$ contains all parametrisations $P \in \mathcal{P}_{\mathcal{G}}$ such that $X_k \cap n^-(v) \in P$ and $p(\pi) \subseteq \mathcal{P}_{\mathcal{G}}$ it must hold that $\forall P \in p(\pi) : X_k \cap n^-(v) \notin P$ and by extension $X_k \cap n^-(v) \notin 1_{p(\pi)}$. $p'(\pi) = [p(\pi)]$ further gives us $\forall P \in p'(\pi) : X_k \cap n^-(v) \notin P$. By the structure for the algorithm $1_{p'(\pi \cdot X)} \subseteq 1_{p'(\pi)}$ and therefore $X_k \cap n^-(v) \notin 1_{p'(\pi \cdot X)}$. Furthermore the algorithm will for sure handle restriction $(v, X_k \cap n^-(v), 1)$ due to the transition (X_k, X) resulting in $X_k \cap n^-(v) \in 0_{p'(\pi \cdot X)}$ giving us $\neg(0_{p'(\pi \cdot X)} \subseteq 1_{p'(\pi \cdot X)})$.

A.2 Multivalued Case

In the case of multivalued PRNs a restriction does not necessarily close the RC and there no longer exist u -pairs. Each RC instead has several u -supercontexts and u -subcontexts. The monotonicity enforcement can be extended straightforwardly, however, observability poses a slight problem. Let $v \in V$ be a component with maximal activity value 2 and $(u, v) \in I$ be an observable influence. Consider a PC such that all but one RCs of v have target value fixed to 1. As there is an observable influence it is apparent that the last open context cannot have value 1, however, the lattice encoding lacks the expressive power as it can only control minimum and maximum, which is still 0 and 2 respectively. Although the coveted $p'(\pi) = [p(\pi)]$ is breached in such a rare situation it is easy to detect the observability not being satisfied shall a further restriction fix the target value of the last open RC to 1 and the PC can thus be set to \emptyset .

A.3 The Initial Parameter Context Overapproximation

As the method relies on the knowledge of $p'(\pi)$ to compute $p(\pi \cdot X)$ it is necessary to be able to compute the initial $p'(\emptyset) = [\mathcal{P}_{\mathcal{G}}]$. Although $[\mathcal{P}_{\mathcal{G}}] = \mathcal{P}_{\mathcal{G}}$ often holds, there are some cases when a restriction is viable.

As regulations of individual components are independent (note that both monotonicity and observability only speak about RCs of the same component) it is enough to consider restrictions for regulation of each component separately. Let thus $v \in V$ be an arbitrary component. Let $A = \{u \in n^-(v) \mid + \in \gamma((u, v))\}$ be the set of all regulators of v with plus-monotonous interaction and $I = \{u \in n^-(v) \mid - \in \gamma((u, v))\}$ be the set of all regulators of v with minus-monotonous interaction. We now consider two parametrisations $P_s = \Omega \setminus \{I\}$ and $P_i = \{A\}$. We can show easily that any monotonicity criterion on interaction with v is satisfied by both P_s and P_i . Monotonicity for (u, v) is satisfied by default if both ω and u -pair of ω have the same target value. As such only the context I has to be analysed. Let $u \in A$ be arbitrary. We get $u \in I_u$ by definition and $I \notin P_s$ as well as $I \notin P_i$ thus monotonicity of (u, v) is satisfied by both P_s and P_i . Now let $u \in I$ be arbitrary. By definition $u \in I$ and thus by $I \notin P_s$ and $I \notin P_i$ we again satisfy monotonicity of (u, v) for both P_s and P_i . Let us now discuss observability. For any $u \in A$ observability is trivially satisfied under both P_s and P_i as $I \notin P_s$ and $I \cup \{u\} \in P_s$ and similarly $A \in P_i$ and $A \setminus \{u\} \notin P_i$. Similarly let $u \in I$ be arbitrary then $I \notin P_s$ and $I \setminus \{u\} \in P_s$ make (u, v) observable under P_s and $A \in P_i$ and $A \cup \{u\} \notin P_i$ makes (u, v) observable also under P_i . Finally, observability is also satisfied for any other $u \in (n^-(v) \setminus A) \setminus I$ as $I \notin P_s$ and $I \cup \{u\} \in P_s$ and $A \in P_i$ and $A \cup \{u\} \notin P_i$. It thus becomes clear that P_s and P_i satisfy both monotonicity and observability for arbitrary labelling function γ . As such, edge labelling cannot reduce the initial lattice beyond the maximum P_s and minimum P_i for each $v \in V$ ($\forall v \in V : [\{P_s, P_i\}] \subseteq [\mathcal{P}_G \cap (\{v\} \times \Omega_v)]$).

Let us now consider a set of regulators $N \subseteq n^-(v)$ such that $N \cap A = \emptyset$ and $N \cap I = \emptyset$ and parametrisations $P_{ns} = \Omega \setminus \{N \cup I\}$ and $P_{ni} = \{A \cup N\}$. It is easy to see that both P_{ns} and P_{ni} have the same properties as P_s and P_i and thus satisfy arbitrary γ . In fact, shall $N = \emptyset$ we trivially get $P_{ns} = P_s$ and $P_{ni} = P_i$. Let us now consider $N \neq \emptyset$. Then clearly both P_s and P_{ns} are valid parametrisations. Moreover the supremum of P_{ns} and P_s according to the set inclusion order is $P_{ns} \cup P_s = \Omega$. Similarly both P_i and P_{ni} are also valid and their infimum $P_{ni} \cap P_i = \emptyset$. Thus, shall there exist any interaction (u, v) such that $+ \notin \gamma((u, v))$ and $- \notin \gamma((u, v))$ then the initial lattice of parametrisations for regulations of v is equal to the fully parametrised case ($[\mathcal{P}_G \cap (\{v\} \times \Omega_v)] = \mathcal{P}_G \cap (\{v\} \times \Omega_v)$). And we can safely conclude that for $[\mathcal{P}_G] \subset \mathcal{P}_G$ there must exist at least one $v \in V$ such that $\forall u \in n^-(v) : + \in \gamma((u, v)) \vee - \in \gamma((u, v))$.

Since the parametrisations Ω and \emptyset are both plus-monotonous and minus-monotonous for all interactions it is obvious that just monotonicity is not enough for $[\mathcal{P}_G] \subset \mathcal{P}_G$. In fact, Ω and \emptyset are not observable for any interaction (An interaction that is both plus and minus-monotonous is anti-observable) and thus a single observable interaction (u, v) is sufficient to remove Ω and \emptyset from the set of feasible parametrisation. In fact, shall every interaction $(u, v) \in I$ be monotonic for some $v \in V$ and at least one of them also observable, the initial PC can be restricted to maximum P_s and minimum P_i ($[\mathcal{P}_G \cap (\{v\} \times \Omega_v)] = [P_s, P_i]$). To prove this let us consider any parametrisation P such that $I \in P$. Since (u, v) is minus-monotonous for every $u \in I$ every RC of the form $I \setminus \{u\}$ must also belong to P and by iterative application of the minus-monotonicity condition $\forall J \subseteq I : J \in P$. Similarly (u, v) is plus-monotonous for any other $u \in A$. As such, for any $J \subseteq I$ we get $J \cup \{u\} \in P$

and by iterative application $P = \Omega$ and the observability is not satisfied. Thus we may conclude that no parametrisation P such that $I \in P$ is feasible. An analogical construction can be conducted for P such that $A \notin P$ reaching $P = \emptyset$.

The construction of the initial PC $p'(\emptyset) = [\mathcal{P}_G]$ can thus be done algorithmically as follows.

- (i) Start with $[\mathcal{P}_G] = \mathcal{P}_G$.
- (ii) Find all components $v \in V$ such that $\forall u \in n^-(v) : + \in \gamma((u, v)) \vee - \in \gamma((u, v))$ and $\exists u \in n^-(v) : o \in \gamma((u, v))$.
- (iii) For every such v construct the sets $A = \{u \in n^-(v) | + \in \gamma((u, v))\}$ and $I = \{u \in n^-(v) | - \in \gamma((u, v))\}$ and restrict the minimum by $(v, A) \in 0_{\mathcal{P}_G}$ and the maximum by $(v, I) \notin 1_{\mathcal{P}_G}$.

The computation of the initial PC is very similar in the general case of multivalued PRNs. The only difference is the target value limitation for I for every suitable component $v \in V$ (target value of A is still set to be at least 1). Instead of setting target value of I to 0, in general the value is limited to be at most $k_v - 1$ where $k_v \in \mathbb{N}$ is the maximum value of component v .

B Total Adequate Order

Here we extend the total adequate order \prec_F introduced in [8] to our formalism of unfoldings as introduced in section 5. Let $\mathcal{U} = (B, E, \leq, \#)$ be an unfolding of some PRN and let $C_1, C_2 \subseteq E$ be two finite configurations of \mathcal{U} .

Let \ll be an arbitrary total order on all RCs $(v, \omega) \in \Omega$. We can always find such an order as Ω is finite. Then we define a function φ such that for every finite configuration C , $\varphi(C) = (\omega_{e_1}, \dots, \omega_{e_k})$ is a vector of regulatory contexts such that $C = \{e_1, \dots, e_k\}$ ordered by \ll . $\varphi(C)$ is thus a variant of a Parikh vector of associated RCs of C . We extend the order \ll to ordered vectors as a lexicographical order. Essentially the same construction has been used for Petri net unfoldings in [8] using transitions of the original Petri net instead of RCs.

Furthermore let us define Foata normal form of configuration C , $FC(C)$ as follows.

- (i) $FC_1(C) = \varphi(\{e \in C | \forall e' \in C : \neg(e' < e)\})$ is the φ of all events in C minimal in respect to the causality relation.
- (ii) For $1 < i \in \mathbb{N} : FC_i(C) = \varphi(\{e \in C | \forall e' \in C : e' < e \Rightarrow e' \in \bigcup_{j < i-1} FC_j(C)\})$ is the φ of all events in C without all the previous $FC_j(C)$ minimal in respect to the causality relation.
- (iii) $FC(C) = (FC_1(C), \dots, FC_k(C))$ where $k \in \mathbb{N}$ is the largest natural number such that $FC_k(C) \neq \emptyset$. Such k is guaranteed to exist as C is finite.

Intuitively, the Foata normal form $FC(C)$ is a layered representation of C in respect to causality relation and represents steps in which events of C can fire if all concurrent events fire synchronously. We again extend \ll to Foata normal forms as a lexicographical order on the vectors of $FC(C)$. The construction is again equivalent to the one proposed in [8] for Petri net unfoldings. Finally, the order \prec as used in Section 5 is defined as follows.

Definition B.1 Let $\mathcal{U} = (B, E, \leq, \#)$ be an unfolding of some PRN and $C_1, C_2 \subseteq E$ two finite configurations of \mathcal{U} . We say that $C_1 \prec C_2$ if one of the following conditions holds.

- $|C_1| < |C_2|$
- $|C_1| = |C_2| \wedge \varphi(C_1) \ll \varphi(C_2)$
- $|C_1| = |C_2| \wedge \varphi(C_1) = \varphi(C_2) \wedge FC(C_1) \ll FC(C_2)$