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A P Systems Variant for Reasoning about Sequential Controllability of Boolean Networks^{*}

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Abstract. A Boolean network is a discrete dynamical system operating on vectors of Boolean variables. The action of a Boolean network can be conveniently expressed as a system of Boolean update functions, computing the new values for each component of the Boolean vector as a function of the other components. Boolean networks are widely used in modelling biological systems that can be seen as consisting of entities which can be activated or deactivated, expressed or inhibited, on or off. P systems on the other hand are classically introduced as a model of hierarchical multiset rewriting. However, over the years the community has proposed a wide range of P system variants including diverse ingredients suited for various needs. In this work, we propose a new variant—Boolean P systems—specifically designed for reasoning about sequential controllability of Boolean networks, and use it to first establish a crisp formalization of the problem, and then to prove that the problem of sequential controllability is PSPACE-complete. We further claim that Boolean P systems are a demonstration of how P systems can be used to construct ad hoc formalisms, custom-tailored for reasoning about specific problems, and providing new advantageous points of view.

^{*} This is a revised and extended version of [1].

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1 Introduction

Membrane computing and P systems are a paradigm of massively parallel computing introduced more than two decades ago by Gh. Păun [27], and inspired by the structure and the functioning of the biological cell. Following the example of the cell, a membrane (P) system is a hierarchical membrane structure with compartments containing multisets of objects, representing in an abstract sense the biochemical species. Multiset rewriting rules are attached to every membrane to represent the reactions. Over the last two decades, a considerable number of variants of P systems have been introduced, inspired by various aspects of cellular life, or capturing specific computing properties. For comprehensive overviews we refer the reader to [14,28].

Even though P systems are directly inspired by the biological cell, their use for actual cellular modelling has encountered relatively little success. On the other hand, Boolean networks have been quite successful recently, despite their relative dissimilarity to biological structures—a Boolean network is a set of Boolean variables equipped with Boolean update functions, describing how to compute the new value of the variables from their current values. We refer the reader to [1] for a more detailed impression.

One application of interest of Boolean networks is controllability—the problem of deciding whether externally modifying some parameters of a system can make it reach a particular state, and finding the necessary modifications [6,12,25,30,31]. A variant of this problem which has attracted particular attention is sequential controllability: instead of looking for a particular combination of control inputs, find a *sequence* of control inputs to guide the system to a given state [17,18,19,20,22,24]. Sequential controllability is promising because it may allow reducing the total number of control actions, or may even drive the Boolean network along trajectories which would otherwise be inaccessible. On the other hand, sequential controllability is PSPACE-hard [24], making it a difficult problem to tackle.

The goal of this paper is to show how to combine the modelling power of Boolean networks with the richness of P systems to reason about and prove some properties of sequential controllability of Boolean networks. We construct a P system variant to satisfy the following two properties simultaneously:

1. represent sequential controllability of Boolean control networks via simple syntax transformations,
2. have PSPACE-complete reachability.

This formalization of sequential controllability allows us to complete the complexity result from [24] by proving that this problem is PSPACE-complete. We would like to use this construction to promote P system variants as a general tool for building ad hoc formalisms specifically tailored for tackling particular problems.

This paper is structured as follows. Section 2 briefly recalls all the necessary preliminaries: linear bounded automata, P systems, Boolean networks, sequential controllability. Section 3 introduces the specific P system variant for tackling sequential controllability: Boolean P systems. Section 4 shows how Boolean

P systems can directly simulate Boolean networks. Section 5 introduces composition of Boolean P systems in the spirit of automata theory, and Section 6 shows how composite Boolean P systems can capture a Boolean network together with the master dynamical system emitting the control inputs. In Section 7, we show that the reachability problem for Boolean P systems is PSPACE-complete, and we use this result in Section 8 to show that sequential controllability of Boolean networks is PSPACE-complete as well. Finally, in Section 9 we extensively discuss the obtained technical results concerning sequential controllability, the features of Boolean P systems, and the general methodology of designing ad hoc formalisms custom-tailored to specific problems.

2 Preliminaries

In this section, we briefly recall the necessary preliminaries, in particular deterministic bounded automata, P systems, Boolean networks, Boolean Control Networks (BCN), and sequential controllability of BCN.

Given two sets A and B , we denote by B^A the set of all functions $f : A \rightarrow B$. We denote by 2^A the set of all subsets of A (the power set of A) and by $|A|$ the cardinal of the set A . An indicator function of a subset $C \subseteq A$ is the function $i_C : A \rightarrow \{0, 1\}$ with the property that $C = \{a \mid i_C(a) = 1\}$. In this paper, we will often use the same symbol to refer to a subset and to its indicator function.

2.1 Deterministic Linear Bounded Automata (LBA)

A deterministic linear bounded automaton (deterministic LBA or simply LBA) \mathcal{M} is a construct

$$\mathcal{M} = (Q, V, T_1, T_2, \delta, q_0, q_1, Z_l, B, Z_r),$$

where:

- Q is a finite set of states,
- V is the finite tape alphabet,
- $T_1 \subseteq V \setminus \{Z_l, B, Z_r\}$ is the input alphabet,
- $T_2 \subseteq V \setminus \{Z_l, B, Z_r\}$ is the output alphabet,
- $\delta : Q \times V \rightarrow Q \times V \times \{L, R, S\}$ is the transition function,
- q_0 is the initial state,
- q_1 is the final state,
- $Z_l \in V$ is the left boundary marker,
- $B \in V$ is the blank symbol,
- $Z_r \in V$ is the right boundary marker,

We restrict the transition function such that the automaton can never write over the boundary markers or exceed them, more precisely:

$$\begin{aligned} \forall q \in Q : \delta(q, Z_l) &\in Q \times \{Z_l\} \times \{R, S\}, \text{ and} \\ \forall q \in Q : \delta(q, Z_r) &\in Q \times \{Z_r\} \times \{L, S\}. \end{aligned}$$

A configuration of the automaton will be written as $Z_l u \underline{q a} v Z_r$, where $a \in V \setminus \{Z_l, Z_r\}$, $u, v \in (V \setminus \{Z_l, Z_r\})^*$. The state q is written to the left of the underlined tape symbol a on which the head of the automaton currently stands.

Suppose the LBA is in state q and reads the symbol a on the tape. If $\delta(q, a) = (p, b, D)$, one of the following transitions occurs, depending on the value of $D \in \{L, R, S\}$:

$$\begin{aligned} Z_l u c \underline{q a} v Z_r &\Rightarrow Z_l u p \underline{c b} v Z_r, & \text{if } D = L, \text{ where } c \in V, \\ Z_l u \underline{q a} c v Z_r &\Rightarrow Z_l u b p \underline{c} v Z_r, & \text{if } D = R, \text{ where } c \in V, \\ Z_l u \underline{q a} v Z_r &\Rightarrow Z_l u p \underline{b} v Z_r, & \text{if } D = S. \end{aligned}$$

Due to the restriction of the transition function, the accessible part of the tape is limited to the input plus the two delimiters Z_l and Z_r . Another model of LBA consists in restricting the size of the accessible part of the tape to a linear function of the input, which is the origin of the name *linear* bounded automaton. The two models have the same computational power [13].

An LBA accepts the input $x \in V^*$ if starting with the configuration $Z_l q_0 x Z_r$ it reaches a configuration of the form $Z_l q_1 \{B\}^* Z_r$. Given an LBA \mathcal{M} and an input x , the LBA-ACCEPTANCE problem consists in deciding whether \mathcal{M} accepts x . This problem is PSPACE-complete [13].

2.2 P Systems

In this subsection, we give a general overview of P systems. For more details, we refer the reader to [14,28]. A P system is a construct

$$\Pi = (O, T, \mu, w_1, \dots, w_n, R_1, \dots, R_n, h_i, h_o),$$

where O is the alphabet of objects, $T \subseteq O$ is the alphabet of terminal objects, μ is the membrane structure injectively labelled by the numbers from $\{1, \dots, n\}$ and usually given by a sequence of correctly nested brackets, w_i are the multisets giving the initial contents of each membrane i ($1 \leq i \leq n$), R_i is the finite set of rules associated with membrane i ($1 \leq i \leq n$), and h_i and h_o are the labels of the input and the output membranes, respectively ($1 \leq h_i \leq n$, $1 \leq h_o \leq n$).

Quite often, the rules associated with membranes are multiset rewriting rules (or special cases of such rules). Multiset rewriting rules have the form $u \rightarrow v$, with $u \in O^\circ \setminus \{\mathbf{0}\}$ and $v \in O^\circ$, where O° is the set of multisets over O , and $\mathbf{0}(a) = 0$, for all $a \in O$. If $|u| = 1$, the rule $u \rightarrow v$ is called non-cooperative; otherwise it is called cooperative. In communication P systems, rules are additionally allowed to send symbols to the neighbouring membranes. In this case, for rules in R_i , $v \in (O \times Tar_i)^\circ$, where Tar_i contains the symbols *out* (corresponding to sending the symbol to the parent membrane), *here* (indicating that the symbol should be kept in membrane i), and *in_h* (indicating that the symbol should be sent into the child membrane h of membrane i). When writing out the multisets over $O \times Tar_i$, the indication *here* is often omitted.

In P systems, rules are often applied in a maximally parallel way: in one derivation step, only a non-extendable multiset of rules can be applied. The rules are not allowed to consume the same instance of a symbol twice, which creates competition for objects and may lead to non-deterministic choice between the maximal collections of rules applicable in one step.

A computation of a P system is traditionally considered to be a sequence of configurations it can successively visit, stopping at the halting configuration. A halting configuration is a configuration in which no rule can be applied any more, in any membrane. The result of a computation of a P system Π as defined above is the contents of the output membrane h_o projected over the terminal alphabet T .

Example 1. Figure 1 shows the graphical representation of the P system formally given by

$$\begin{aligned} \Pi &= (\{a, b, c, d\}, \{a, d\}, [1[2]_2]_1, R_1, R_2, 1, 1), \\ R_2 &= \{a \rightarrow aa, b \rightarrow b(c, out)\}, \\ R_1 &= \emptyset. \end{aligned}$$

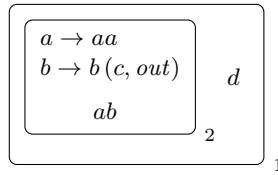


Fig. 1. An example of a simple P system.

In the maximally parallel mode, the inner membrane 2 of Π will apply as many instances of the rules as possible, thereby doubling the number of a , and ejecting a copy of c into the surrounding (skin) membrane at each step. The symbol d in the skin membrane is not used. Therefore, after k steps of evolution, membrane 2 will contain the multiset $a^{2^k} b$ and membrane 1 the multiset $c^k d$. Since all rules are always applicable in Π , this P system never halts. \square

2.3 Boolean Networks

A Boolean variable is a variable which may only have values in the Boolean domain $\{0, 1\}$. Let X be a finite set of Boolean variables. A state of these variables is any function $s : X \rightarrow \{0, 1\}$, $s \in \{0, 1\}^X = S_X$ assigning a Boolean value to every single variable. An update function is a Boolean function computing a Boolean value from a state: $f : S_X \rightarrow \{0, 1\}$. A Boolean network over X is a function $F : S_X \rightarrow S_X$, in which the update function for a variable $x \in X$ is computed as a projection of F : $f_x(s) = F(s)_x$.

A Boolean network F computes trajectories on states by updating its variables according to a (Boolean) mode $M \subseteq 2^X$, defining the variables which

should be updated together in a step. Typical examples of modes are the synchronous mode $syn = \{X\}$ and the asynchronous mode $asyn = \{\{x\} \mid x \in X\}$. A trajectory τ of a Boolean network under a given mode M is any finite sequence of states $\tau = (s_i)_{0 \leq i \leq n}$ such that F can derive s_{i+1} from s_i under the mode M .

Remark 1. The definition of modes and evolution are quite different in P systems and Boolean networks. The asynchronous mode in Boolean networks only allows updating one variable at a time, while the asynchronous mode in P systems generally allows any combinations of updates. Furthermore, no halting conditions are generally considered in Boolean networks, and the asymptotic behavior is often looked at as the important part of the dynamics. \square

Example 2. Consider the set of variables $X = \{x, y\}$ with the corresponding update functions $f_x(x, y) = \bar{x} \wedge y$ and $f_y(x, y) = x \wedge \bar{y}$. Figure 2 shows the possible state transitions of this network under the synchronous and the asynchronous modes. The states are represent as pairs of binary digits, e.g. 01 stands for the state in which $x = 0$ and $y = 1$.



Fig. 2. The synchronous (left) and the asynchronous (right) dynamics of the Boolean network in Example 2.

We notice that, under the synchronous mode, this network exhibits three kinds of behaviors. If initialized to 00, it will stay in this state forever—00 is a stable state. If initialized to 11, the network will directly converge to 00. Finally, if it is initialized to any one of the states 01 or 10, it will oscillate between them. The synchronous mode yields deterministic behavior.

The state transitions are quite different under the asynchronous mode, under which only one variable may be updated at a time. While state 00 remains stable, states 01 and 10 can now oscillate to 11, but not directly between them. Moreover, these states can also converge to 00, but 11 cannot anymore. \square

2.4 Boolean Control Networks (BCN)

Boolean networks are often used to represent biological networks in the presence of external perturbations: environmental hazards, drug treatments, etc. (e.g., [5,6,24]). To represent network reprogramming, an extension of Boolean networks can be considered: Boolean control networks (BCN) [6]. Informally, a BCN is a parameterized Boolean network template; assigning a Boolean value to every single one of its parameters yields a Boolean network.

Formally, a Boolean control network is a function $F_U : S_U \rightarrow (S_X \rightarrow S_X)$, where the elements of U , $U \cap X = \emptyset$, are called the control inputs. To every

valuation of control inputs, F_U associates a Boolean network. A control μ of F_U is any Boolean assignment to the control inputs: $\mu : U \rightarrow \{0, 1\}$.

While this definition of BCNs is very general, in practice one restricts the impact the control inputs may have on the BCN to some biologically relevant classes. One particularly useful class are freeze perturbations, in which a variable in X is temporarily frozen to 0 or to 1, independently of its normal update function. These actions mean to model gene knock-outs and knock-ins.

When Boolean update functions are written as propositional formulae, freeze control inputs can be written directly in the formulae. Consider for example a Boolean network F over $X = \{x_1, x_2\}$ with the update functions $f_1 = x_1 \wedge x_2$ and $f_2 = x_2$. To allow for freezing of x_1 , we introduce the control variables $U = \{u_1^0, u_1^1\}$ into the Boolean formula of f_1 in the following way: $f'_1 = (x_1 \wedge x_2) \wedge u_1^0 \vee \overline{u_1^1}$. Setting u_1^0 to 0 and u_1^1 to 1 freezes x_1 to 0, independently of the values of x_1 and x_2 . Symmetrically, setting u_1^1 to 0 and u_1^0 to 1 freezes x_1 to 1. Setting both u_1^0 and u_1^1 to 0 is generally disallowed.

In this paper, we will use two notations to indicate which control inputs correspond to which controlled variable. In the simplest examples in which the variables have no indices, e.g. x or y , we will directly specify the name of the variable in the subscript of the corresponding control inputs, like so: u_x^0 , u_x^1 , u_y^0 , or u_y^1 . In more general cases, we will refer to the variables by indexed names x_i , and we will only specify the respective index as the subscript of the corresponding control inputs: u_i^0 and u_i^1 .

2.5 Sequential Controllability of BCN

In many situations, perturbations of biological networks do not happen once, but rather accumulate or evolve over time [9,16,24]. In the language of Boolean control networks, this accumulation can be represented by sequences of controls (μ_1, \dots, μ_n) . More precisely, take a BCN F_U with the variables X and the control inputs U , as well as a sequence of controls $\mu_{[n]} = (\mu_1, \dots, \mu_n)$, $\mu_i : U \rightarrow \{0, 1\} \in S_U$. This gives rise to a sequence of Boolean networks $(F_U(\mu_1), \dots, F_U(\mu_n))$. Fix a mode M and consider a sequence of trajectories (τ_1, \dots, τ_n) of these Boolean networks. Such a sequence is an evolution of F_U under the sequence of controls $\mu_{[n]}$ if the last state of every τ_i is the first state of τ_{i+1} . In this case we can speak of the trajectory of the BCN F_U under the control sequence $\mu_{[n]}$ as the concatenation of the individual trajectories τ_i , in which the last state of every single τ_i is glued together with the first state of τ_{i+1} .

Given the 3-tuple $(F_U, S_\alpha, S_\omega)$, where F_U is a BCN, S_α is a set of starting states, and S_ω is a set of target states, the sequence inference problem is the problem of inferring a control sequence driving F_U from each state in S_α to any state in S_ω . This problem was called the CoFaSe problem in [24] and was extensively studied. In particular, it was shown that CoFaSe is PSPACE-hard.

Example 3. Consider again the Boolean network from Example 2, with $X = \{x, y\}$ and the update functions $f_x = \bar{x} \wedge y$ and $f_y = x \wedge \bar{y}$. As mentioned before,

a convenient way to express freezing controls is by explicitly including the control inputs into the update functions in the following way:

$$\begin{aligned} f'_x &= (\bar{x} \wedge y) \wedge u_x^0 \vee \overline{u_x^1}, \\ f'_y &= (x \wedge \bar{y}) \wedge u_y^0 \vee \overline{u_y^1}. \end{aligned}$$

Notice how setting u_x^0 to 0 essentially sets $f'_x = 0$, and setting u_x^1 to 0 essentially sets $f'_x = 1$, independently of the actual value of x or y .

Consider now the following 3 controls:

$$\begin{aligned} \mu_1 &= \{u_x^0 \leftarrow 1, u_x^1 \leftarrow 1, u_y^0 \leftarrow 1, u_y^1 \leftarrow 1\}, \\ \mu_2 &= \{\underline{u_x^0 \leftarrow 0}, u_x^1 \leftarrow 1, u_y^0 \leftarrow 1, u_y^1 \leftarrow 1\}, \\ \mu_3 &= \{u_x^0 \leftarrow 1, u_x^1 \leftarrow 1, u_y^0 \leftarrow 1, \underline{u_y^1 \leftarrow 0}\}. \end{aligned}$$

Informally μ_1 does not freeze any variables, μ_2 freezes x to 0, and μ_3 freezes y to 1. Consider now the BCN F_U with the variables $X = \{x, y\}$ and the controlled update functions f'_x and f'_y . Fix the synchronous update mode. A trajectory of this BCN under the control μ_1 —i.e. a trajectory of $F_U(\mu_1)$ —is $\tau_1 : 01 \rightarrow 10 \rightarrow 01$. A trajectory of $F_U(\mu_2)$ is $\tau_2 : 01 \rightarrow 00 \rightarrow 00$; remark that 00 is still a stable state of $F_U(\mu_2)$. A trajectory of $F_U(\mu_3)$ is $\tau_3 : 00 \rightarrow 01 \rightarrow 11$. We can now glue together the trajectories τ_1 , τ_2 , and τ_3 by identifying their respective ending and starting states, and we obtain the following trajectory of the BCN F_U under the control sequence $\mu_{[3]} = (\mu_1, \mu_2, \mu_3)$:

$$\tau : 01 \rightarrow 10 \rightarrow 01 \rightarrow 00 \rightarrow 00 \rightarrow 01 \rightarrow 11.$$

It follows from this construction that $\mu_{[3]}$ is a solution for the CoFaSe problem $(F_U, \{01\}, \{11\})$. Remark that 11 is not reachable from 01 under the synchronous mode in the uncontrolled case, as Figure 2 illustrates. \square

Remark 2. We follow the approach from [24] which decorrelates the length of the control sequence from the length of the trajectories it yields. Thus, $\mu_{[3]}$ can yield trajectories of different lengths greater or equal to 3. From the modeling standpoint, this represents the fact that the time scale on which control inputs are emitted is not necessarily the same as the time scale of the controlled system.

3 Boolean P Systems

In this section we introduce a new variant of P systems—Boolean P systems—tailored specifically to capture sequential controllability of Boolean networks with as little descriptive overhead as possible. We further tackle the differences between evolution modes in Boolean networks and P systems by introducing quasimodes.

Rather than trying to be faithful to the original model of P systems as recalled in Section 2, we here invoke the intrinsic flexibility of the domain to design a variant fitting to our specific use case.

3.1 Formalism

Boolean P systems are set rewriting systems. A Boolean state $s : X \rightarrow \{0, 1\}$ is represented as the subset of X obtained by considering s as an indicator function: $\{x \in X \mid s(x) = 1\}$. By abuse of notation, we will sometimes use the symbol s to refer both to the Boolean state and to the corresponding subset of X .

A Boolean P system is the following construct:

$$\Pi = (V, R),$$

where V is the alphabet of symbols, and R is a set of rewriting rules with propositional guards. A rule $r \in R$ is of the form

$$r : A \rightarrow B \mid \varphi,$$

where $A, B \subseteq X$ and φ is the guard—a propositional formula with variables from V . The rule r is applicable to a set $W \subseteq V$ if $A \subseteq W$ and $W \in \varphi$, where by abuse of notation we use the same symbol φ to indicate the set of subsets of V which satisfy φ . Formally, for $W \subseteq V$, we denote by $\varphi(W)$ the truth value of the formula obtained by replacing all variables appearing in W by 1 in φ , and by 0 all variables from $V \setminus W$. Then the set of subsets satisfying φ is $\varphi = \{W \subseteq V \mid \varphi(W) \equiv 1\}$.

Applying the rule $r : A \rightarrow B \mid \varphi$ to a set W results in the set $(W \setminus A) \cup B$. Applying a finite set of separately applicable rules $\{r_i : A_i \rightarrow B_i \mid \varphi_i\}$ to W results in the new set

$$\left(W \setminus \bigcup_i A_i \right) \cup \bigcup_i B_i.$$

Note how this definition excludes competition between the rules, as only individual applicability is checked. Further note that applying a rule multiple times to the same configuration has exactly the same effect as applying it once.

In P systems, the set of multisets of rules of Π applicable to a given configuration W is usually denoted by $Appl(\Pi, W)$ [11]. Since in Boolean P systems multiple applications of rules need not be considered, we will only look at the set of *sets* of rules applicable to a given configuration W of a Boolean P system $\Pi = (V, R)$, and use the same notation $Appl(\Pi, W)$. A mode M of Π will then be a function assigning to any configuration W of Π a set of sets of rules applicable to W : $M(W) \subseteq Appl(\Pi, W)$. If $|M(W)| \leq 1$ for any $W \subseteq V$, the mode M is called deterministic⁶. Otherwise it is called non-deterministic.

An evolution of Π under the mode M is a sequence of states $(W_i)_{0 \leq i \leq k}$ with the property that W_{i+1} is obtained from W_i by applying one of the sets of rules $R' \in M(W_i)$ prescribed by the mode M in state W_i . This is usually written as $W_i \xrightarrow{R'} W_{i+1}$. If no rules are applicable in state W_k , it is called the halting state, and $(W_i)_{0 \leq i \leq k}$ is called a halting evolution.

⁶ More precisely, this is the definition of strong determinism, see [3].

Example 4. Take $V = \{a, b\}$ and consider the following rules $r_1 : \{a, b\} \rightarrow \{a\} \mid \mathbf{1}$ and $r_2 : \{a\} \rightarrow \emptyset \mid \bar{b}$, where $\mathbf{1}$ is the Boolean tautology. Construct the Boolean P system $\Pi = (V, \{r_1, r_2\})$. Informally, r_1 removes b from a configuration which contains a and b , and r_2 removes a from the configuration which does not already contain b . A possible trajectory of Π under the maximally parallel mode—which applies non-extendable applicable sets of rules—is $\{a, b\} \rightarrow \{a\} \rightarrow \emptyset$. Note that only r_1 is applicable in the first step, since r_2 requires the configuration to not contain b . \square

Remark 3. Boolean P systems as defined here are very close to other set rewriting formalisms, and in particular to reaction systems [8]. A reaction system \mathcal{A} over a set of species S is a set of reactions (rules) of the form $a : (R_a, I_a, P_a)$, in which $R_a \subseteq S$ is called the set of reactants, $I_a \subseteq S$ the set of inhibitors, and $P_a \subseteq S$ the set of products. For a to be applicable to a set W , it must hold that $R_a \subseteq W$ and $I_a \cap W = \emptyset$. Applying such a reaction to W yields P_a , i.e. the species which are not explicitly sustained by the reactions disappear.

We claim that despite their apparent similarity and tight relationship with Boolean functions, reaction systems are not so good a fit for reasoning about Boolean networks as Boolean P systems. In particular:

1. Reaction systems lack modes and therefore non-determinism, which may appear in Boolean networks under the asynchronous Boolean mode.
2. The rule applicability condition is more powerful in Boolean P systems, and closer to Boolean functions than in reaction systems.
3. Symbols in reaction systems disappear unless sustained by a rule, which represents the degradation of species in biochemistry, but which makes reaction systems harder to use to directly reason about Boolean networks.

We recall that our main goal behind introducing Boolean P systems is reasoning about Boolean networks in a more expressive framework. This means that zero-overhead representation of concepts from Boolean networks is paramount. \square

Remark 4. Reaction systems [8] are intrinsically interesting for discussing controllability, because they are defined as open systems from the start, via the explicit introduction of context. Note however that contexts only allow adding symbols to the configuration, not removing them. We refer to [15] for an in-depth discussion of controllability of reaction systems. \square

3.2 Quasimodes

An update function in a Boolean network can always be computed, but a rule in a Boolean P system need not always be applicable. This is the reason behind the difference in the way modes are defined in the two formalisms: in Boolean networks a mode is essentially a set of subsets of update functions, while in Boolean P systems a mode is a function incorporating applicability checks. This means in particular that Boolean network modes are not directly transposable to Boolean P systems.

To better bridge the two different notions of modes, we introduce quasimodes. A *quasimode* \tilde{M} of a P system $\Pi = (V, R)$ is any set of sets of rules: $\tilde{M} \subseteq 2^R$. The mode M corresponding to the quasimode \tilde{M} is derived in the following way:

$$M(W) = \tilde{M} \cap \text{Appl}(\Pi, W).$$

Given a configuration W of Π , M picks only those sets of rules from \tilde{M} which are also applicable to W . Thus, instead of explicitly giving the rules to be applied to a given configuration of a P system W , a quasimode advises the rules to be applied.

In the rest of the paper, we will say “evolution of Π under the quasimode \tilde{M} ” to mean “evolution of Π under the mode derived from the quasimode \tilde{M} ”.

4 Boolean P Systems Simulate Boolean Networks

Consider a Boolean network F over the set of variables X , and take a variable $x \in X$ with its corresponding update function f_x . The update function f_x can be simulated by two Boolean P systems rules: the rule corresponding to setting x to 1, i.e. introducing x into the configuration, and the rule corresponding to setting x to 0, i.e. erasing x from the configuration:

$$R_x = \{ \emptyset \rightarrow \{x\} \mid f_x, \{x\} \rightarrow \emptyset \mid \overline{f_x} \}.$$

Consider now the following Boolean P system:

$$\Pi(F) = \left(X, \bigcup_{x \in X} R_x \right).$$

We claim that $\Pi(F)$ faithfully simulates F .

Theorem 1. *Take a Boolean network F and a Boolean mode M . Then the Boolean P system $\Pi(F)$ constructed as above and working under the quasimode $\tilde{M} = \{ \bigcup_{x \in m} R_x \mid m \in M \}$ faithfully simulates F : for any evolution of F under M there exists an equivalent evolution of $\Pi(F)$ under \tilde{M} , and conversely, for any evolution of $\Pi(F)$ under \tilde{M} there exists an equivalent evolution of F under M .*

Proof. Take two arbitrary states s and s' of F such that s' is reachable from s by the update prescribed by an element $m \in M$. Consider now the subsets of variables $W, W' \subseteq X$ defined by s and s' taken as the respective indicator functions. It follows from the construction of \tilde{M} that it contains an element \tilde{m} including the update rules for all the variables of m : $\tilde{m} = \bigcup_{x \in m} R_x$. Therefore, $\Pi(F)$ can derive W' from W under the quasimode \tilde{M} .

Conversely, consider two subsets of variables $W, W' \subseteq X$ such that $\Pi(F)$ can derive W' from W under the update prescribed by an element $\tilde{m} \in \tilde{M}$. By construction of \tilde{M} , there exists a subset $m \subseteq X$ such that $\tilde{m} = \bigcup_{x \in m} R_x$. Take now the indicator functions $s, s' : X \rightarrow \{0, 1\}$ describing W and W' respectively. Then F can derive s' from s by updating the variables in m .

We conclude that the transitions of $\Pi(F)$ exactly correspond to the transitions of F , which proves the statement of the theorem. \square

Example 5. Consider the Boolean network F_U from Example 2:

$$\begin{aligned} f_x &= \bar{x} \wedge y, \\ f_y &= x \wedge \bar{y}. \end{aligned}$$

This Boolean network can be translated to the Boolean P system $\Pi = (V, R)$ with $V = \{x, y\}$ and the following rules:

$$\begin{aligned} R &= R_x \cup R_y, \\ R_x &= \{ \emptyset \rightarrow \{x\} \mid \bar{x} \wedge y, \{x\} \rightarrow \emptyset \mid \overline{\bar{x} \wedge y} \}, \\ R_y &= \{ \emptyset \rightarrow \{y\} \mid x \wedge \bar{y}, \{y\} \rightarrow \emptyset \mid \overline{x \wedge \bar{y}} \}. \end{aligned}$$

The first rule in R_x ensures that x is introduced whenever the current state satisfies $\bar{x} \wedge y = f_x$, and the second rule ensures that x is removed whenever the current state does not satisfy $\bar{x} \wedge y$. Similarly, the rules in R_y introduce or remove y depending on whether the current state satisfies f_y .

To simulate F_U under the Boolean synchronous mode, Π should run under the quasimode $\tilde{M}_{syn} = \{R\}$, i.e. the quasimode allowing all rules in R to be applied at all times. To simulate F_U under the Boolean asynchronous mode, Π should run under the quasimode $\tilde{M}_{asyn} = \{R_x, R_y\}$, i.e. the quasimode allowing the application of either both rules in R_x , or both rules in R_y , but not all 4 rules at a time. \square

Remark 5. Incidentally, Boolean P systems also capture reaction systems (see also Remarks 3 and 4). Indeed, consider a reaction $a = (R_a, I_a, P_a)$ with the reactants R_a , inhibitors I_a , and products P_a . It can be directly simulated by the Boolean P system rule $\emptyset \rightarrow P_a \mid \varphi_a$, where $\varphi_a = \bigwedge_{x \in R_a} x \wedge \bigwedge_{y \in I_a} \bar{y}$. The degradation of the species in reaction systems can be simulated by adding a rule $\{x\} \rightarrow \emptyset \mid \mathbf{1}$ for every species x , where $\mathbf{1}$ is the Boolean tautology. \square

5 Composition of Boolean P Systems

In this section, we define the composition of Boolean P systems in the spirit of automata theory. Consider two Boolean P systems $\Pi_1 = (V_1, R_1)$ and $\Pi_2 = (V_2, R_2)$. We will call the union of Π_1 and Π_2 the Boolean P system $\Pi_1 \cup \Pi_2 = (V_1 \cup V_2, R_1 \cup R_2)$. Note that the alphabets V_1 and V_2 , as well as the rules R_1 and R_2 are not necessarily disjoint.

To talk about the evolution of $\Pi_1 \cup \Pi_2$, we first define a variant of Cartesian product of two sets of sets A and B : $A \dot{\times} B = \{a \cup b \mid a \in A, b \in B\}$. We remark now that

$$\forall W \subseteq V_1 \cup V_2 : Appl(\Pi_1 \cup \Pi_2, W) = Appl(\Pi_1, W) \dot{\times} Appl(\Pi_2, W).$$

Indeed, since the rules of Boolean P systems do not compete for resources among them, the applicability of any individual rule is independent of the applicability of the other rules. Therefore, the applicability of a set of rules of Π_1 to a configuration W is independent of the applicability of a set of rules of Π_2 to W .

For a mode M_1 of Π_1 and a mode M_2 of Π_2 , we define their product as follows:

$$(M_1 \times M_2)(W) = M_1(W) \dot{\times} M_2(W).$$

The union of Boolean P systems $\Pi_1 \cup \Pi_2$ together with the product mode $M_1 \times M_2$ implement parallel composition of the two P systems. In particular, if the alphabets of Π_1 and Π_2 are disjoint, the projection of any evolution of $\Pi_1 \cup \Pi_2$ under the mode $M_1 \times M_2$ on the alphabet V_1 will yield a valid evolution of Π_1 under M_1 (modulo some repeated states), while the projection on V_2 will yield a valid evolution of Π_2 under the mode M_2 (modulo some repeated states). Note that this property may not be true if the two alphabets intersect $V_1 \cap V_2 \neq \emptyset$.

Quasimodes fit naturally with the composition of modes, as the following lemma shows.

Lemma 1. *If the mode M_1 can be derived from the quasimode \tilde{M}_1 and M_2 from the quasimode \tilde{M}_2 , then the product mode $M_1 \times M_2$ can be derived from $\tilde{M}_1 \dot{\times} \tilde{M}_2$:*

$$\begin{array}{ccccc} & & \tilde{M}_1 \dot{\times} \tilde{M}_2 & & \\ & \swarrow & \downarrow & \searrow & \\ \tilde{M}_1 & & & & \tilde{M}_2 \\ & \downarrow & & & \downarrow \\ & \swarrow & M_1 \times M_2 & \searrow & \\ M_1 & & & & M_2 \end{array}$$

where a dashed arrow $--\rightarrow$ from a quasimode to a mode indicates that the mode is derived from the quasimode, and the arrows \rightarrow are the respective projections.

Proof. Consider the mode M_{12} derived from $\tilde{M}_1 \dot{\times} \tilde{M}_2$:

$$M_{12}(W) = \left(\tilde{M}_1 \dot{\times} \tilde{M}_2 \right) \cap \text{Appl}(\Pi, W).$$

Pick an arbitrary element $m_{12} \in M_{12}(W)$ and remark that it can be seen as a union $m = m_1 \cup m_2$ where m_1 is a subset of applicable rules with the property that $m_1 \in \tilde{M}_1$, and m_2 is a subset of applicable rules with the property that $m_2 \in \tilde{M}_2$. Thus $m_1 \in \tilde{M}_1 \cap \text{Appl}(\Pi, W)$ and $m_2 \in \tilde{M}_2 \cap \text{Appl}(\Pi, W)$, implying that

$$M_{12}(W) \subseteq \left(\tilde{M}_1 \cap \text{Appl}(\Pi, W) \right) \dot{\times} \left(\tilde{M}_2 \cap \text{Appl}(\Pi, W) \right).$$

Consider on the other hand an arbitrary $m_1 \in \tilde{M}_1 \cap \text{Appl}(\Pi, W)$ and an arbitrary $m_2 \in \tilde{M}_2 \cap \text{Appl}(\Pi, W)$. By definition of $\dot{\times}$, $m_1 \cup m_2 \in \tilde{M}_1 \dot{\times} \tilde{M}_2$. Remark that every rule in m_1 and m_2 is individually applicable, meaning that they are also applicable together and that $m_1 \cup m_2 \in \text{Appl}(\Pi, W)$. Combining this observation with the reasoning from the previous paragraph we finally derive:

$$M_{12}(W) = \left(\tilde{M}_1 \cap \text{Appl}(\Pi, W) \right) \dot{\times} \left(\tilde{M}_2 \cap \text{Appl}(\Pi, W) \right) = M_1(W) \dot{\times} M_2(W),$$

which implies that $M_{12} = M_1 \times M_2$ and concludes the proof. \square

6 Boolean P Systems for Sequential Controllability

Underlying sequential controllability of Boolean control networks (Section 2.5) is the implicit presence of a master dynamical system emitting the control inputs to the network and thereby driving it. This master system is external with respect to the controlled BCN. The framework of Boolean P systems is sufficiently general to capture both the master system and the controlled BCN in a single homogeneous formalism. In this section, we show how to construct such Boolean P systems for dealing with questions of controllability.

Any BCN $F_U : S_U \rightarrow (S_X \rightarrow S_X)$ can be written as a system of propositional formulae over $X \cup U$. First, note that a control $\mu \in S_U$ can be described by the conjunction $\bigwedge_{u \in \mu} u \wedge \bigwedge_{v \in U \setminus \mu} \bar{v}$. Now fix an $x \in X$ and consider the formula

$$\bigvee_{\mu \in S_U} \mu \wedge F(\mu)_x, \quad (1)$$

in which μ enumerates all the conjunctions corresponding to the controls in S_U and $F(\mu)_x$ is the propositional formula of the update function which $F(\mu)$ associates to x . Using (1), we can translate any BCN $F_U : S_U \rightarrow (S_X \rightarrow S_X)$ into the system of Boolean functions $F' : S_{X \cup U} \rightarrow S_X$ and use the set R_x from Section 4 to further translate the individual components of F' to pairs of Boolean P system rules. Denote $\Pi = (X \cup U, R)$ the Boolean P system whose set of rules is precisely the union of the sets R_x mentioned above, for $x \in X$. Finally, construct the Boolean P system $\Pi_U(U, R_U)$ with the following rules whose guards are always true:

$$\begin{aligned} R_U &= R_U^0 \cup R_U^1, \\ R_U^0 &= \{ \{u\} \rightarrow \emptyset \mid \mathbf{1} \mid u \in U \}, \\ R_U^1 &= \{ \emptyset \rightarrow \{u\} \mid \mathbf{1} \mid u \in U \}. \end{aligned}$$

Suppose now that the original BCN F_U runs under the mode M , and consider the corresponding quasimode $\tilde{M} = \{ \bigcup_{x \in m} R_x \mid m \in M \}$, as well as the quasimode

$$\tilde{M}_U = \{ R_U^0 \} \dot{\times} 2^{R_U^1}.$$

Every element $m_U \in \tilde{M}_U$ is a union of R_U^0 and a subset of R_U^1 , meaning that m_U enables all rules removing the control inputs, and enables *some* of the rules adding back control inputs.

We claim that the Boolean P system $\Pi \cup \Pi_U$ running under the quasimode $\tilde{M} \dot{\times} \tilde{M}_U$ faithfully simulates the BCN F_U running under the mode M . The following theorem formalizes this claim.

Theorem 2. *Consider a BCN F_U running under the mode M . Then the Boolean P system $\Pi \cup \Pi_U$ constructed as above and running under the quasimode $\tilde{M} \dot{\times} \tilde{M}_U$ faithfully simulates F_U :*

1. *For any evolution of F_U under M there exists an equivalent evolution of $\Pi \cup \Pi_U$ under $\tilde{M} \dot{\times} \tilde{M}_U$.*

2. For any evolution of $\Pi \cup \Pi_U$ under $\tilde{M} \dot{\times} \tilde{M}_U$ there exists an equivalent evolution of F_U under M .

Proof. (1) Consider two states $s, s' \in S_X$ and a control $\mu \in S_U$ such that $F_U(\mu)$ reaches s' from s in one step. Take $W, W' \subseteq X$ and $W_U \subseteq U$ by respectively taking s, s' , and μ as indicator functions. Then, as in Theorem 1, there exists an $\tilde{m} \in \tilde{M}$ such that Π reaches $W' \cup W_U$ from $W \cup W_U$ in one step. This follows directly from the construction of the rules in Π and from the fact that W_U contains exactly the symbols corresponding to the control inputs activated by μ .

Take now $\tilde{M} \dot{\times} \tilde{M}_U$ and remark that its elements are of the form $\tilde{m} \cup \tilde{m}_U$, where $\tilde{m}_U = \tilde{m}_U^1 \cup R_U^0$ and $\tilde{m}_U^1 \subseteq R_U^1$. Under such an element $\tilde{m} \cup \tilde{m}_U$, $\Pi \cup \Pi_U$ reaches a state $W' \cup W'_U$ from $W \cup W_U$ in one step, where W'_U contains the symbols from U introduced by the rules selected by \tilde{m}_U^1 . Further note that all elements of W_U are always erased by the rules R_U^0 , but may be immediately reintroduced by m_U^1 .

Suppose now that $F_U(\mu)$ reaches s' from s in multiple steps. Then Π reaches $W' \cup W_U$ from $W \cup W_U$ in the same number of steps, provided that \tilde{m}_U^1 is always chosen such that the rules it selects reintroduce exactly the subset W_U . If F_U reaches s' from s in multiple steps, but the control evolves as well, it suffices to choose \tilde{m}_U^1 such that it introduces the correct control inputs before each step. Finally, the control μ_0 applied in the first step of a trajectory of F_U must be introduced by setting the starting state of $\Pi \cup \Pi_U$ to $W \cup W_U^0$, where W corresponds to the initial state of the trajectory of F_U .

(2) The converse construction is symmetric. A state $W \cup W_U$ of $\Pi \cup \Pi_U$ is translated into the state $s \in S_X$ and the control $\mu \in S_U$ corresponding to W_U . A step of $\Pi \cup \Pi_U$ under $\tilde{m} \cup \tilde{m}_U$ is translated to applying μ to F_U and updating the variables corresponding to the rules activated by \tilde{m} . In this way, for any trajectory of $\Pi \cup \Pi_U$ under the quasimode $\tilde{M} \dot{\times} \tilde{M}_U$ there exists a corresponding trajectory in the controlled dynamics of F_U . \square

We now give an extensive example showing how the composite system $\Pi \cup \Pi_U$ from the proof above is constructed for a concrete BCN, and detailing how $\Pi \cup \Pi_U$ simulates its sequentially controlled trajectories.

Example 6. Consider the BCN F_U from Example 3 with the following update functions modified to include the control inputs:

$$\begin{aligned} f'_x &= (\bar{x} \wedge y) \wedge u_x^0 \vee \overline{u_x^1}, \\ f'_y &= (x \wedge \bar{y}) \wedge u_y^0 \vee \overline{u_y^1}, \end{aligned}$$

and recall that $X = \{x, y\}$ and $U = \{u_x^0, u_x^1, u_y^0, u_y^1\}$. Since the control inputs are already explicitly present in the propositional formulae, we can put these together directly to obtain $F' : S_{X \cup U} \rightarrow S_X$, bypassing equation 1.

Construction of $\Pi \cup \Pi_U$. First construct the Boolean P system $\Pi = (X \cup U, R)$ with the following rules:

$$\begin{aligned} R &= R_x \cup R_y, \\ R_x &= \{ \emptyset \rightarrow \{x\} \mid f'_x, \{x\} \rightarrow \emptyset \mid \overline{f'_x} \}, \\ R_y &= \{ \emptyset \rightarrow \{y\} \mid f'_y, \{y\} \rightarrow \emptyset \mid \overline{f'_y} \}. \end{aligned}$$

Now, define $\Pi_U = (U, R_U)$ with the following rules:

$$\begin{aligned} R_U &= R_U^0 \cup R_U^1, \\ R_U^0 &= \{ \{u_x^0\} \rightarrow \emptyset \mid \mathbf{1}, \{u_x^1\} \rightarrow \emptyset \mid \mathbf{1}, \{u_y^0\} \rightarrow \emptyset \mid \mathbf{1}, \{u_y^1\} \rightarrow \emptyset \mid \mathbf{1} \}, \\ R_U^1 &= \{ \emptyset \rightarrow \{u_x^0\} \mid \mathbf{1}, \emptyset \rightarrow \{u_x^1\} \mid \mathbf{1}, \emptyset \rightarrow \{u_y^0\} \mid \mathbf{1}, \emptyset \rightarrow \{u_y^1\} \mid \mathbf{1} \}. \end{aligned}$$

Suppose that F_U runs under the synchronous mode. This is translated into the quasimode $\tilde{M}_{syn} = \{R\}$ for the Boolean P system Π . The quasimode \tilde{M}_U for Π_U will be as follows:

$$\tilde{M}_U = \{R_U^0 \cup \tilde{m}_U^1 \mid \tilde{m}_U^1 \subseteq R_U^1\}.$$

Finally, the composite P system $\Pi \cup \Pi_U$ will run under the following quasimode:

$$\tilde{M} \dot{\times} \tilde{M}_U = \{R \cup R_U^0 \cup \tilde{m}_U^1 \mid \tilde{m}_U^1 \subseteq R_U^1\}.$$

Simulation of sequential control. The 3 controls introduced in Example 3 can be written as sets in the following way:

$$\begin{aligned} \mu_1 &= \{u_x^0, u_x^1, u_y^0, u_y^1\}, \\ \mu_2 &= \{u_x^1, u_y^0, u_y^1\}, \\ \mu_3 &= \{u_x^0, u_x^1, u_y^0\}. \end{aligned}$$

The trajectory $\tau_1 : 01 \rightarrow 10 \rightarrow 01$ of $F_U(\mu_1)$ will be simulated as the following evolution of $\Pi \cup \Pi_U$:

$$\{y\} \cup \mu_1 \rightarrow \{x\} \cup \mu_1 \rightarrow \{y\} \cup \mu_1,$$

where the rules to be applied in each transition are picked from the set $R \cup R_U^0 \cup R_U^1 \in \tilde{M} \dot{\times} \tilde{M}_U$. Note how μ_1 is explicitly included as a set of symbols in the configuration of the composite Boolean P system $\Pi \cup \Pi_U$.

Similarly, the trajectory $\tau_2 : 01 \rightarrow 00 \rightarrow 00$ of $F_U(\mu_2)$ will be simulated as follows:

$$\{y\} \cup \mu_2 \rightarrow \emptyset \cup \mu_2 \rightarrow \emptyset \cup \mu_2,$$

where the rules to be applied in each transition are picked from the set $R \cup R_U^0 \cup \{\emptyset \rightarrow \{u\} \mid \mathbf{1} \mid u \in \mu_2\} \in \tilde{M} \dot{\times} \tilde{M}_U$. Note how all symbols corresponding to control inputs are removed at every step, and then specifically the control inputs from μ_2 are reintroduced.

Finally, the trajectory $\tau_3 : 00 \rightarrow 01 \rightarrow 11$ of $F_U(\mu_3)$ will be simulated as follows by $\Pi \cup \Pi_U$:

$$\emptyset \cup \mu_3 \rightarrow \{y\} \cup \mu_3 \rightarrow \{x, y\} \cup \mu_3.$$

To simulate the final trajectory under the control sequence $\mu_{[3]} = (\mu_1, \mu_2, \mu_3)$, we glue together the final and the initial states of the above simulations, always anticipating the control from the subsequent simulation:

$$\{y\} \cup \mu_1 \rightarrow \{x\} \cup \mu_1 \rightarrow \underline{\{y\} \cup \mu_2} \rightarrow \emptyset \cup \mu_2 \rightarrow \underline{\emptyset \cup \mu_3} \rightarrow \{y\} \cup \mu_3 \rightarrow \{x, y\} \cup \mu_3.$$

Underlined elements are the states in which the control inputs change. Thus, the transition $\{x\} \cup \mu_1 \rightarrow \underline{\{y\} \cup \mu_2}$ for example is governed by the set of rules $R \cup R_U^0 \cup \{\emptyset \rightarrow \{u\} \mid \mathbf{1} \mid u \in \mu_2\} \in \tilde{M} \dot{\times} \tilde{M}_U$ already, instead of $R \cup R_U^0 \cup R_U^1$ which was used in the first step. \square

The component Π_U in the composite P system of Theorem 2 and Example 6 is an explicit implementation of the master dynamical system driving the evolution of the controlled system Π . The setting of this theorem captures the situation in which the control can change at any moment, but Π_U can be designed to implement other kinds of control sequences. We give the construction ideas for the kinds of sequences introduced in [24]:

- *Total Control Sequence (TCS)*: all controllable variables are controlled at all times.

The quasimode of Π_U will be correspondingly defined to always freeze the controlled variables: $\tilde{M}_U = \{R_U^0\} \dot{\times} 2^{P^1}$, where $P_U^1 \subseteq R_U^1$ with the property that for every $x_i \in X$ every set $p \in P_U^1$ either introduces u_i^0 or u_i^1 , but not both.

- *Abiding Control Sequence (ACS)*: once controlled, a variable stays controlled forever, but the value to which it is controlled may change.

The rules of Π_U will be constructed to never erase the control symbols which have already been introduced, but will be allowed to change the value to which the corresponding controlled variable will be frozen: $R_U = R_U^1 \cup P_U$, with the new set of rules defined as follows:

$$P_U = \{ \{u_i^a\} \rightarrow \{u_i^b\} \mid \mathbf{1} \mid x_i \in X, a, b \in \{0, 1\} \}.$$

Π_U will be able to rewrite some of the control symbols, or to introduce new control symbols: $\tilde{M}_U = 2^{R_U}$.

7 Reachability in Boolean P Systems

In this section we focus on reachability in Boolean P systems, which we define in the following way: given a Boolean P system Π , a mode M (or a quasimode \tilde{M}), a set of starting states S_α and a set of target states S_ω , decide whether an

evolution of Π exists under the mode M (or the quasimode \tilde{M}) driving it from each state in S_α to some state in S_ω . We refer to such a decision problem by the 4-tuple $(\Pi, M^\dagger, S_\alpha, S_\omega)$, where M^\dagger may be a mode or a quasimode. In the rest of the paper, we will mainly deal with reachability under quasimodes.

Remark 6. Unlike the CoFaSe problem in which the synchronous mode is implicitly assumed, we explicitly include here the mode or the quasimode into the reachability problem. Indeed, the size of the quasimode may be as much as exponential in the number of symbols, while the complexity of a mode may be even bigger, since it depends on the current configuration. Furthermore, the mode choice impacts the answer of the problem. For example the problem under the quasimode $\tilde{M} = \emptyset$ has a solution if and only if $S_\alpha \subseteq S_\omega$.

In this section we will show that the reachability problem for Boolean P systems is PSPACE-complete. We start by showing that this reachability problem is at least as hard as LBA-ACCEPTANCE.

Lemma 2. *LBA-ACCEPTANCE is reducible in polynomial time to reachability for Boolean P systems.*

Proof. We will first show how to construct a Boolean P system simulating a given LBA, and will then evaluate the size complexity of the construction.

Construction. Let $\mathcal{M} = (Q, V, T_1, T_2, \delta, q_0, q_1, Z_l, B, Z_r)$ be an LBA and $x \in T_1^*$ an input word of length n . We construct in polynomial time a Boolean P system $\Pi = (\tilde{V}, R)$ that simulates the computation of \mathcal{M} on the input x . The alphabet of Π contains the following symbols

$$\tilde{V} = \{A_{v,j} \mid v \in V, 0 \leq j \leq n+1\} \cup \{C_{q,j} \mid q \in Q, 0 \leq j \leq n+1\},$$

where the symbols $A_{v,j}$ describe which symbols appear in which tape cells of \mathcal{M} and $C_{q,j}$ describes the position and the state of the LBA head. More precisely:

- $A_{v,j}$ represents the situation in which cell j contains the symbol v ,
- $C_{q,j}$ represents the situation in which the head is on cell j and in state q .

We construct the rules of Π as the union $R = \bigcup_{\rho \in \delta} R_\rho$, where each instruction $\rho = (q, X; p, Y, D)$ of \mathcal{M} is simulated by a set of Boolean P system rules in the following way, depending on the direction of the movement of the head:

$$\begin{aligned} D = R : R_{(q,X;p,Y,R)} &= \{ \{A_{X,j}, C_{q,j}\} \rightarrow \{A_{Y,j}, C_{p,j+1}\} \mid \mathbf{1} \mid 0 \leq j \leq n \}, \\ D = S : R_{(q,X;p,Y,S)} &= \{ \{A_{X,j}, C_{q,j}\} \rightarrow \{A_{Y,j}, C_{p,j}\} \mid \mathbf{1} \mid 0 \leq j \leq n+1 \}, \\ D = L : R_{(q,X;p,Y,L)} &= \{ \{A_{X,j}, C_{q,j}\} \rightarrow \{A_{Y,j}, C_{p,j-1}\} \mid \mathbf{1} \mid 1 \leq j \leq n+1 \}. \end{aligned}$$

The evolution of Π is governed by the quasimode $\tilde{M} = \{R\}$. Due the form of the left-hand sides of the rules above, if the current state contains exactly one state symbol of the form $C_{q,j}$, at most one rule in R will be applicable.

We finally define the singleton set of target states:

$$S_\omega = \{ \{A_{B,j} \mid 1 \leq j \leq n\} \cup \{C_{q_1,0}, A_{Z_l,0}, A_{Z_r,n+1}\} \}.$$

The only state appearing in S_ω therefore corresponds to the halting configuration of \mathcal{M} in which all tape cells are blank except cells 0 and $n + 1$ which contain the left and right end delimiters Z_l and Z_r respectively, and the head is on cell 0 and in state q_1 .

It is a direct consequence of the definition of the rules in R that the LBA \mathcal{M} accepts a word $x = v_1 v_2 \dots v_n$ of length n if and only if the reachability problem $(\Pi, \tilde{M}, \{s_x\}, S_\omega)$ has a solution, where $s_x = \{A_{v_j, j} \mid 1 \leq j \leq n\} \cup \{C_{q_0, 1}\}$.

Complexity. The number of symbols in Π is $|\tilde{V}| = (n + 2)(|V| + |Q|)$ and the number of rules is $|R| = \mathcal{O}(n|V||Q|)$, so the Boolean P system Π can be constructed in time $\mathcal{O}(n|V||Q|)$.

Since \tilde{M} is a singleton and its only element is of cardinal $|R| = \mathcal{O}(n|V||Q|)$, the quasimode can be constructed in time $\mathcal{O}(n|V||Q| \cdot \log(n|V||Q|))$ —roughly, the number of rules times the number of bits necessary to describe a rule. Because there is only one starting state and one target state, and since a state can be described by a sequence of $n + 3$ symbols ($n + 2$ for the tape and 1 for the state of the head), the whole description $(\Pi, \tilde{M}, S_\alpha, S_\omega)$ can be constructed in the following time:

$$\mathcal{O}(n|V||Q| \cdot \log(n|V||Q|)) = \mathcal{O}((n|V||Q|)^2).$$

This expression is polynomial in the size of the specification of \mathcal{M} and in the length n of the input x , which concludes the proof. \square

We will now show the symmetrical statement that reachability in Boolean P systems is at most as hard as LBA-ACCEPTANCE.

Lemma 3. *Reachability for Boolean P systems is in PSPACE.*

Proof. We will prove that reachability for Boolean P systems is in NPSpace, which implies the required statement by Savitch's theorem [29].

Let $(\Pi, \tilde{M}, S_\alpha, S_\omega)$, with $\Pi = (V, R)$, be an instance of the reachability problem. Algorithm 1 is a non-deterministic algorithm that solves this problem in polynomial space. The function $UPDATE_\Pi$ takes a state s of Π and an element of a quasimode $m \in \tilde{M}$, and returns the state updated according to the rules R of Π and the chosen element of the quasimode, as defined in Section 3.2.

Since the number of possible states of Π is $2^{|V|}$, the shortest evolution between two states is of length at most $2^{|V|}$, if it exists. Algorithm 1 therefore non-deterministically tests all possible evolutions of length at most $2^{|V|}$, starting from all states in S_α . At the end $Reachable$ gets the value *true* if and only if a state in S_ω can be reached from every state in S_α , which ensures the correctness of the algorithm.

This algorithm runs in polynomial space in the size of the reachability problem. Note that several states, a counter up to $2^{|V|}$, and $|S_\alpha|$ Boolean flags are stored, all of which takes up $\mathcal{O}(|V| + |S_\alpha|)$ space. Furthermore, the function $UPDATE_\Pi$ can be evaluated in polynomial space. Indeed, to determine the set

Algorithm 1 Solving reachability for Boolean P systems in NPSPACE

Require: $(\Pi, \tilde{M}, S_\alpha, S_\omega)$, $\Pi = (V, R)$

Ensure: $Reachable = true \iff (\Pi, \tilde{M}, S_\alpha, S_\omega)$ has a solution

```
for all  $x \in S_\alpha$  do
   $i \leftarrow 0$ 
   $s \leftarrow x$ 
   $Reachable_x \leftarrow false$ 
  while  $i < 2^{|V|}$  do
     $i \leftarrow i + 1$ 
    if  $s \in S_\omega$  then
       $Reachable_x \leftarrow true$ 
    end if
    Pick non-deterministically  $m \in \tilde{M}$ 
     $s \leftarrow UPDATE_\Pi(s, m)$ 
  end while
end for
 $Reachable \leftarrow \bigwedge_{x \in S_\alpha} Reachable_x$ 
```

of applicable rules in a state s , one needs to check for each rule if the guard is true and if the left part of the rule is present in s . Both operations, the evaluation of a Boolean function and a comparison, can be carried out in polynomial space with respect to $|V|$. Only the rules in m are then applied, and these applications can be carried out in polynomial space with respect to $|V|$ and $|R|$. \square

Remark 7. The argument of Lemma 3 focuses on reachability under quasimodes. This argument can be trivially extended to modes derivable from quasimodes, and more generally to any mode for which non-deterministically picking a set m of rules to apply can be done in polynomial space.

The following theorem brings together Lemmas 2 and 3 to show the main result with respect to the complexity of reachability.

Theorem 3. *Reachability for Boolean P systems is PSPACE-complete*

8 Complexity of Sequential Controllability

In this section we first extend the CoFaSe problem with some additional details necessary to properly reason about its complexity, and then show that sequential controllability of BCN is PSPACE-complete.

8.1 CoFaSe and Control Modes

Theorem 2 shows that Boolean P systems can directly simulate Boolean networks together with the master control system, and Theorem 3 shows that reachability

for Boolean P systems is PSPACE-complete. Nevertheless, we cannot immediately conclude that CoFaSe is PSPACE-complete because of the role modes and quasimodes play in evaluating the size of the problem.

Consider a BCN F_U with the variables X and the control inputs U , and recall that the CoFaSe problem is given by the triple $(F_U, S_\alpha, S_\omega)$, where $S_\alpha, S_\omega \subseteq S_X$ are the sets of starting and target states respectively. The simulating Boolean P system $\Pi \cup \Pi_U$ constructed in Theorem 2 uses the quasimode

$$\tilde{M}_U = \{R_U^0\} \dot{\times} 2^{R_U^1},$$

for which $|\tilde{M}_U| = 2^{|U|}$, meaning that size of the reachability problem for $\Pi \cup \Pi_U$ is always exponential in the size of U , independently of the sizes of the individual elements of the triple $(F_U, S_\alpha, S_\omega)$ ⁷. As a consequence, directly combining Theorems 2 and 3 is not guaranteed to yield a polynomial bound on space in terms of the size of the CoFaSe problem $(F_U, S_\alpha, S_\omega)$.

We believe that the correct way to deal with this issue is to include a specification of the master system emitting the controls into the description of the problem of sequential controllability. Indeed, CoFaSe is formulated for the situation in which the control can change at any moment [24], and this information is not explicitly included in its definition, while it is explicitly present in the P system $\Pi \cup \Pi_U$ from Theorem 2.

We propose to describe the possible changes in controls by defining a relation on 2^U —the control mode. A *control mode* for a BCN F_U is a relation $\mathcal{R}_U \subseteq 2^U \times 2^U$ describing the possible evolutions of control inputs. More precisely, consider the following trajectory of the BCN F_U :

$$s_1 \xrightarrow{F_U(\mu_1)} s_2 \xrightarrow{F_U(\mu_2)} s_3 \xrightarrow{F_U(\mu_3)} \dots \xrightarrow{F_U(\mu_n)} s_{n+1}.$$

This trajectory complies with the control mode \mathcal{R}_U if and only if $(\mu_i, \mu_{i+1}) \in \mathcal{R}_U$, for every $1 \leq i \leq n$.

Example 7. Control modes naturally capture the types of control sequences given at the end of Section 6 and initially discussed in [23]. To streamline the definitions of the corresponding control modes, we introduce the following helper function:

$$idx : 2^U \rightarrow 2^{\{1, \dots, |U|\}}, \quad idx(\mu) = \{i \mid u_i^* \in \mu, \star \in \{0, 1\}\}.$$

In other words, *idx* produces the set of control input indices appearing in a control μ , irrespectively of the nature of the control input (freeze to 0 or freeze to 1).

We can now define the control mode \mathcal{R}_U^{TCS} capturing Total Control Sequences (TCS) as follows:

$$\forall \mu, \nu \in 2^U : (\mu, \nu) \in \mathcal{R}_U^{TCS} \iff idx(\mu) = idx(\nu) = idx(U).$$

⁷ In general, the description of F_U is of size $\mathcal{O}(2^{|X||U|})$, because some Boolean functions may require an exponential number of Boolean connectors $\wedge, \vee, \bar{\cdot}$ to be represented. S_α and S_ω are of size $\mathcal{O}(|X|)$ by their definition. In practice, however, the sizes of these entities are often well under the respective upper bounds [6,24].

Informally, \mathcal{R}_U^{TCS} includes all those pairs of controls which act on every single controlled variable by activating one of the corresponding control inputs.

Similarly, in the case of Abiding Control Sequences (ACS), the control mode \mathcal{R}_U^{ACS} can be defined as follows:

$$\forall \mu, \nu \in 2^U : (\mu, \nu) \in \mathcal{R}_U^{TCS} \iff idx(\mu) \subseteq idx(\nu).$$

Thus, \mathcal{R}_U^{ACS} only allows to transition from μ to ν if ν acts at least on the same controlled variables as μ . Note that ν is allowed to change the value to which a controlled variable x_i is frozen by replacing u_i^0 by u_i^1 or vice versa. \square

We now define an extension of CoFaSe to capture sequential controllability of BCN in a more general framework. The **SEQ-CONTROL** problem is given by the 5-tuple $(F_U, M, \mathcal{R}_U, S_\alpha, S_\omega)$ and consists in deciding whether for every starting state in S_α there exists an initial control μ_0 and a trajectory of the BCN F_U under the mode M and the control mode \mathcal{R}_U ending up in a target state from S_ω . μ_0 must appear as a the first term in at least a pair of \mathcal{R}_U : $\exists \nu \subseteq U : (\mu_0, \nu) \in \mathcal{R}_U$.

Example 8. Consider the Boolean network F_U described in Figure 3, as well as the controls $\mu_{110} = \{u_1^1, u_2^1\}$, freezing both x_1 and x_2 to 1, and $\mu_\emptyset = \emptyset$. If $(\mu_{110}, \mu_{110}), (\mu_{110}, \mu_\emptyset) \in \mathcal{R}_U$ then the following trajectory is possible:

$$000 \xrightarrow{F_U(\mu_{110})} 110 \xrightarrow{F_U(\mu_{110})} 111 \xrightarrow{F_U(\mu_\emptyset)} 001.$$

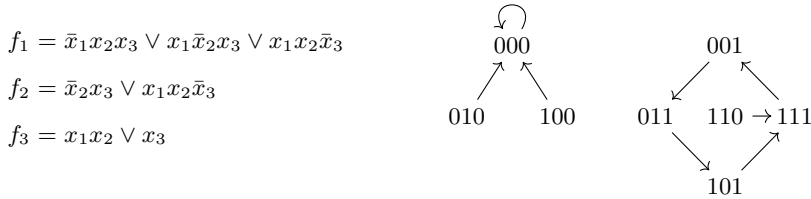


Fig. 3. The update functions of the Boolean network from Example 8 (left) as well as its uncontrolled synchronous dynamics (right).

Suppose now that only freezing x_1 or x_2 separately is permitted, i.e. $i \in idx(\mu) \cap \{1, 2\} \implies idx(\mu) = \{i\}$, for any μ appearing in a pair in \mathcal{R}_U . In this case, F_U can reach 100 or 010 from 000 by respectively controlling x_1 or x_2 to 1. The following 3 scenarios are possible afterwards:

1. maintain the control of x_1 or x_2 and stay in the same state;
2. freeze the other variable— x_2 if x_1 was controlled or x_1 if x_2 was controlled, and switch to the other state—010 or 100 respectively;
3. release all controls and go back to 000.

In any of these cases, F_U is not able to reach 001 with the above restriction on the control mode.

Finally, suppose that once μ_{110} is employed, it must be maintained for the rest of the trajectory, i.e. $(\mu_{110}, \nu) \in \mathcal{R}_U \implies \nu = \mu_{110}$. The previous paragraph shows that the only way for F_U to leave the connected component consisting of the states $\{000, 100, 010\}$ while starting from 000 is to apply μ_{110} . On the other hand, since μ_{110} cannot be deactivated once applied, this means that F_U cannot reach 001 from 000 with this restriction on the control mode. \square

8.2 SEQ-CONTROL and CoFaSe Are PSPACE-complete

We start by combining Theorems 2 and 3 to characterize the complexity of SEQ-CONTROL.

Theorem 4. *SEQ-CONTROL is PSPACE-complete.*

Proof. SEQ-CONTROL is PSPACE-hard, since by taking $U = \emptyset$ it is reduced to the problem of reachability for Boolean networks, known to be PSPACE-complete [7,23].

Let now $(F_U, M, \mathcal{R}_U, S_\alpha, S_\omega)$ be an instance of SEQ-CONTROL and consider the following set of rules:

$$R_U = \{ \mu_1 \rightarrow \mu_2 \mid \mathbf{1} \mid (\mu_1, \mu_2) \in \mathcal{R}_U \},$$

as well as the quasimode $\tilde{M}_U = \{r \mid r \in R_U\}$. The Boolean P system $\Pi_U = (U, R_U)$ running under the quasimode \tilde{M}_U will therefore simulate the changes in controls allowed by the control mode \mathcal{R}_U .

We can now construct the reachability problem $(\Pi \cup \Pi_U, \tilde{M} \dot{\times} \tilde{M}_U, S_\alpha, S_\omega)$ in the same way as in Theorem 2. The entire construction, including that of R_U , happens in polynomial time with respect to the size of the initial instance of SEQ-CONTROL. This allows us to conclude the proof by invoking the fact that reachability in Boolean P systems is PSPACE-complete (Theorem 3). \square

As explained in the previous section, SEQ-CONTROL being PSPACE-complete does not immediately imply that CoFaSe is PSPACE-complete, since translating from CoFaSe to SEQ-CONTROL may require exponential increase in space. However, it is possible to directly prove that CoFaSe is in PSPACE by using a variation of Algorithm 1 from Lemma 3.

Theorem 5. *CoFaSe is PSPACE-complete.*

Proof. Similarly to the proof of Lemma 3, we show here a non-deterministic polynomial-space algorithm solving the instance of CoFaSe given by the triple $(F_U, S_\alpha, S_\omega)$: Algorithm 2.

Algorithm 2 has very similar properties to Algorithm 1. Note that no requirements on the values of control inputs are imposed in the CoFaSe problem,

Algorithm 2 Solving CoFaSe in NPSPACE

Require: $(F_U, S_\alpha, S_\omega)$ **Ensure:** $Reachable = true \iff (F_U, S_\alpha, S_\omega)$ has a solution

```
for all  $x \in S_\alpha$  do
   $i \leftarrow 0$ 
   $s \leftarrow x$ 
   $Reachable_x \leftarrow false$ 
  while  $i < 2^{|X|}$  do
     $i \leftarrow i + 1$ 
    if  $s \in S_\omega$  then
       $Reachable_x \leftarrow true$ 
    end if
    Pick non-deterministically  $\mu \in S_U$ 
     $s \leftarrow F_U(\mu)(s)$ 
  end while
end for
 $Reachable \leftarrow \bigwedge_{x \in S_\alpha} Reachable_x$ 
```

meaning that only the state space S_X needs to be explored, excluding the control inputs. Since $|S_X| = 2^{|X|}$, exploring trajectories of length at most $2^{|X|}$ is sufficient to conclude about the reachability of a state in S_ω for all states in S_α .

Algorithm 2 stores a constant number of intermediate states and controls, a counter up to $2^{|X|}$, and $|S_\alpha|$ Boolean flags, all of which takes up $\mathcal{O}(|V| + |U| + |S_\alpha|)$ space. Furthermore, F_U can be computed in polynomial space in $|X|$ and $|U|$, meaning that Algorithm 2 requires polynomial space in the size of the triple $(F_U, S_\alpha, S_\omega)$. Finally, we conclude the proof by invoking Savitch's theorem [29], stating that $\text{NPSPACE} = \text{PSPACE}$. \square

9 Conclusion and Discussion

We structure the conclusion into three subsections, focusing on three main takeaways and future research directions stemming from this paper.

9.1 Complexity of Sequential Controllability

The central technical result of this work is proving that sequential controllability of Boolean control networks (BCN) is PSPACE -complete, thereby closing the question left open in [24]. One important intuition that this result yields is that sequential controllability of BCN is not in fact harder computationally speaking than simple reachability, in spite of the much heftier two-level setup with a master dynamical system driving the Boolean network. While no explicit construction is given, it is to be expected that the evolution of a BCN under a control sequence may be simulated by a Boolean network, modulo a polynomial transformation. This implies that reasoning about sequential controllability is as hard as reasoning about pure reachability in Boolean networks,

opening a promising direction of future work about using the most permissive semantics [26] for sequential controllability of BCN.

We stress nevertheless that sequential controllability and reachability being in the same complexity class does not necessarily imply that the techniques for efficiently solving reachability in practical situations can be immediately transposed to controllability. Exploring such possibilities is an important direction for future research on sequential controllability of BCN.

While we extensively deal with CoFaSe in this work, it should be noted that the ConEvs semantics explored in [24] is not treated. The ConEvs semantics of the control sequence constraints the moments at which the control may change to the stable states of the driven Boolean network. This places the master system in a feedback loop with the driven network and changes the architecture substantially. In particular, the computational complexity of sequential controllability under the ConEvs semantics still remains to be characterized.

9.2 Boolean P Systems

Most of the technical results presented in this paper are obtained via Boolean P systems, a framework specifically designed for dealing with sequential controllability in Boolean networks. We particularly emphasize one of our central goals: designing ad hoc formalisms very tightly suited for a specific problem and thereby giving new relevant viewpoints.

One of the advantages in relying on Boolean P systems is that the language of individual rules is more flexible than that of propositional formulae in Boolean networks. In particular, having set rewriting directly available allows for naturally expressing the notions of adding, removing, or depending on resources, while the propositional guards allow for easy checking of Boolean conditions whenever necessary. These two ingredients shine in Section 6, in which we show how a Boolean P system can capture both the BCN and the master dynamical system emitting the control inputs. On the other hand, we construct Boolean P systems without indulging too much into computationally expensive ingredients, which keeps the complexity of reachability in PSPACE.

We would like to dwell specifically on the difference between Theorems 4 and 5, in particular on the fact that the latter directly shows that CoFaSe is in PSPACE, completely eliding Boolean P systems. First, remark that Theorem 4 showing that SEQ-CONTROL is PSPACE-complete is in fact more general, as it holds for any mode and for any control mode, incorporating *en passant* different kinds of control sequences such as TCS, ACS, etc. Secondly, remark that Algorithm 2 in Theorem 4 is directly derived from (and is a special case of) Algorithm 1 in Lemma 3, which arguably needed some general framework like Boolean P systems to be conceived.

Going back to the ConEvs semantics mentioned in the previous subsection, we expect that considering it in the framework of Boolean P systems will bring new valuable insight both concerning the characterization of its complexity and its other properties, as well as possible optimizations for specific use cases. Observe that ConEvs cannot be captured as a control mode, because it introduces a

backward dependency of the control sequence on the state of the BCN. Boolean P systems on the other hand should allow to express this feedback elegantly, since the master system Π_U and the driven system Π are both part of the same composite system $\Pi \cup \Pi_U$ (Theorem 2), and can therefore communicate both ways. In fact, just from this informal reasoning we can make a conjecture with respect to the upper bound on the complexity of sequential controllability under the ConEvs semantics.

Conjecture 1. Sequential controllability of BCN under the ConEvs semantics is in PSPACE.

Finally, we stress once again the point of Remark 3: while Boolean P systems are very closely related to reaction systems [8], they have distinctive features which make them a much better fit for reasoning about sequential controllability—specifically, explicit Boolean guards and permanency of the resources.

9.3 Lineage of (Polymorphic) P Systems, Homoiconicity, and Lisp

As we have already insisted, one central point that we bring forward with this work is conceiving ad hoc formalisms specialized for solving particular problems. This approach is partially inspired by the venerable Lisp family of programming languages, and more particularly by language-oriented programming—a methodology proposing to start solving problems by developing specifically-tailored programming languages—domain-specific languages or DSLs [10,32].

When adopting this approach, it is important that such bespoke constructions be done within a particular general framework, lest the design costs grow too high and the new formalisms too obscure. In this paper, we promote P systems as such a general framework. The community around this model of computing has been producing a wide spectrum of variants, a far-from-exhaustive glimpse of which can be seen in [2,14,21,28]. The rich body of literature provides many ingredients and various tools for easily assembling different new formalisms. This is why we believe that P systems are particularly well suited for the ad hoc formalism methodology.

We conclude this work by underlining that Boolean P systems are far from being a frontier of how far one can go in designing specialized formalisms. We recall as an example polymorphic P systems [4], in which the rules are given by pairs of membranes rather than being part of the static description of the system, as is classically done in automata and language theory. Polymorphic P systems thus implement a form of homoiconicity—code-as-data, similarly to the Lisp languages. A lot more can be done in terms of customizing P systems, and we expect to see and invest further effort into the ad hoc formalism methodology.

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