# P versus B: P Systems as a Formal Framework for Controllability of Boolean Networks

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Membrane computing and P systems are a paradigm of massively parallel natural computing introduced by Gheorghe Păun in 1999, inspired by the structure of the living cell and by its biochemical reactions. In spite of this explicit biological motivation, P systems have not been extensively used in modelling real-world systems. To confirm this intuition, we establish a state of the art investigation comparing the use of P systems to that of Boolean networks in this line of research. We then propose to use P systems as a tool for setting up formal frameworks to reason about other formalisms, and we introduce Boolean P systems, specifically tailored for capturing sequential controllability of Boolean networks. We show how to tackle some technical challenges and prove that sequential controllability properly embeds in the framework of Boolean P systems.

**Keywords:** Boolean networks, controllability, formal framework

## 1 Introduction

Membrane computing and P systems are a paradigm of massively parallel computing introduced more than two decades ago by Gheorghe Păun [19], and inspired by the structure and function of the biological cell. Following the example of the cell, a membrane (P) system is a hierarchical membrane structure defining compartments containing multisets of objects, representing the biochemical species in an abstract sense. 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 [13, 20].

Even though P systems resemble the organisation of a "fundamental unit" of modern life, their use in representing actual biological knowledge has historically been scarce. Furthermore, one of the salient examples of P systems in modelling are the works by the Sevillan team (e.g. [3, 4, 6, 7, 12, 23, 24]), in which P systems represent ecosystems, an undeniably biological structure, but far removed from the organisation of a cell.

To give more substance to this impression of underuse, we performed a comparative bibliographic study of the literature using P systems to represent any biological knowledge on the one hand, and on the

H. Bordihn, G. Horváth, G. Vaszil (Eds.): 12th International Workshop on
Non-Classical Models of Automata and Applications (NCMA 2022)
EPTCS 367, 2022, pp. 28–48, doi:10.4204/EPTCS.367.3

other hand the publications in the conference Computational Methods in Systems Biology (e.g. [5]) using Boolean networks to represent biological knowledge. 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. While Boolean networks represent well gene regulatory networks (e.g. [25]), their structure arguably resembles less the actual organisation of cellular processes. Our study suggests nonetheless that Boolean networks tend to be considerably more popular than P systems for representing these processes. We give the details of this comparison in the appendix.

The main message of this paper is that the potential of P systems to represent biological knowledge seems to remain relatively unexplored, but that one can already rely on P systems as a flexible formal framework providing powerful tools for studying other abstract structures. As an example, we show how to construct a P system variant which naturally captures the semantics of sequentially controlled Boolean networks. In the future, this construction will allow for more straightforward proofs of some properties of interest.

This paper is structured as follows. Sections 2 and 3 recall the notions of P systems as well as Boolean networks, Boolean control networks, and sequential controllability. Section 4 introduces Boolean P systems. Section 5 introduces quasimodes to bridge between the dynamics of Boolean networks and Boolean P systems, and Section 6 formally proves that Boolean P systems capture Boolean networks. Finally, Sections 7 and 8 show how Boolean P systems explicitly embed sequential controllability of Boolean networks.

## 2 Preliminaries

To ensure unambiguous notation, in this section we briefly recall some basic notions and concepts of formal language theory and membrane computing. For a detailed reference on both, we suggest [20].

For any alphabet $V$, $V^\circ$ is the set of multisets over $V$, and $V^*$ denotes the set of all strings over $V$. For any $u \in V^*$ and any $u \in V^\circ$, $|u|$ is the *length* of the string $u$ and the number of elements in the multiset $u$, respectively. For $V^\circ$ and $V^*$ we use $\varepsilon$ to denote the empty multiset and empty string, respectively.

We use $2^V$ to denote the set of all subsets of $V$ (the power set of $V$). Given two sets $A$ and $B$, by $B^A$ we denote the set of all functions $f : A \to B$.

An *indicator function* of a subset $U \subseteq V$ is the function $i_U : V \to \{0,1\}$ with the property that $U = \{a \mid i_U(a) = 1\}$. In this paper, we will often use the same symbol to refer to a subset and to its indicator function.

A *Boolean variable* is a variable which may only have values in the Boolean domain $\{0,1\}$.

### 2.1 P Systems

**Definition 1.** *A* P system *is a construct*

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

*where $O$ is the alphabet of objects, $T \subseteq O$ is the alphabet of terminal objects, $\mu$ is the membrane structure injectively labelled by the numbers from $\{1,\ldots,n\}$ 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 $u \to v$, with $u \in O^\circ \setminus \{\varepsilon\}$ and $v \in O^\circ$. If $|u| = 1$, the rule $u \to v$ 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 often are 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 the P system choosing non-determinstically between the maximal collections of rules applicable in one step. Yet rules may also be applied in a *sequential* way, i.e. in every derivation step one rule which is applicable to the current configuration is carried out. Moreover, when any multiset of applicable rules may be applied, we speak of the *asynchronous* derivation mode.

A computation of a P system is traditionally considered to be a sequence of configurations it can successively visit by applying the applicable rules in the given derivation mode (maximally parallel, sequential, asynchronous), stopping at a 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* in a P system $\Pi$ 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*

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

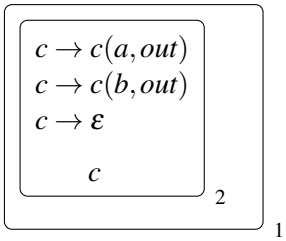



Figure 1: An example of a simple P system.

*In any derivation mode (maximally parallel, sequential, asynchronous),* $\Pi$ *may apply one of the rules* $c \to c(a,out)$ *or* $c \to c(b,out)$*, thereby keeping the object* $c$ *in membrane* 2 *and at the same time sending out to membrane* 1 *one object* $a$ *or* $b$*, respectively.*

*After* $k$ *such derivation steps, in membrane* 1 *a multiset* $u \in \{a,b\}^\circ$ *with* $|u| = k$ *has been obtained. Now applying the final rule* $c \to \varepsilon$*, we obtain the halting configuration with no objects in membrane* 2 *and the multiset* $u$ *in membrane* 1 *as the result of the computation in* $\Pi$*.* □

# 3 Sequential Controllability of Boolean Networks

In this section we briefly recall the definition of Boolean networks, the extension of the formalism with control inputs, and the problem of sequential controllability. For a more in-depth coverage of these definitions and problems, as well as the underlying biomedical motivations, we refer the reader to [18].

## 3.1 Boolean Networks

**Definition 2.** *Let $X$ be a finite alphabet of Boolean variables. A* state *of these variables is any function $s$ in $\{0,1\}^X$, i.e., $s : X \to \{0,1\}$, assigning a Boolean value to every single variable in $X$. By $S_X$ we denote the set of all states $s$ in $\{0,1\}^X$.*

*An* update function *is a Boolean function computing a Boolean value from a state: $f : s \to \{0,1\}$. A* Boolean network *over $X$ is a function $F : S_X \to S_X$, 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 may 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 $\tau$ of a Boolean network under a given mode $M$ is any finite sequence of states $\tau = (s_i)_{0 \le i \le n}$ such that $F$ can derive $s_{i+1}$ from $s_i$ under the mode $M$.

An *attractor* is a set of mutually reachable states $A \subseteq S_X$ of $F$ with the property that $F$ cannot escape from $A$. Since the set of states $S_X$ is finite, any run of a Boolean network, under any mode, must end up in an attractor. These are called the asymptotic behaviors.

**Remark 1.** *These definitions are quite different from similar definitions generally used in P systems. 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 considered in Boolean networks, and the asymptotic behavior is often looked at as the important part of the dynamics.* □

**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 represented as pairs of binary digits, e.g.* 01 *stands for the state in which $x = 0$ and $y = 1$.*


Figure 2: The synchnronous (left) and the asynchnronous (right) dynamics of the Boolean network in Example 2.

*We notice that, under the synchronous mode, this network exhibits two kinds of behaviors. If initialized in the state* 00 *or* 11*, it will stay in the initial state forever—these two are stable states. If it is initialized in any one of the states* 01 *or* 10*, it will oscillate between them. The behavior of the network therefore is deterministic under the synchronous update mode.*

*The state transitions are quite different under the asynchronous mode, under which only one variable may be updated at a time. While the states* 00 *and* 11 *remain stable, two possible transitions are now from the states* 01 *and* 10*, and there are no transitions leading from* 01 *to* 10 *or vice versa.* □

### 3.2 Boolean Control Networks

Boolean networks are often used to represent biological networks in the presence of external perturbations: environmental hazards, drug treatments, etc. (e.g., [1, 2, 18]). To represent network reprogramming, an extension of Boolean networks can be considered: Boolean control networks (BCN) [2]. 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 $F_U : S_U \to (S_X \to S_X)$, 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 $\mu$ of $F_U$ is any Boolean assignment to the control inputs: $\mu : U \to \{0,1\}$.

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.

When Boolean update functions are written as propositional formulae, freeze control inputs can be written directly in the formulae of the update functions. For example, consider 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 $x_1$, we introduce the control variables $U = \{u_1^0, u_1^1\}$ into the Boolean formula of $f_1$ in the following way: $f_1' = (x_1 \wedge x_2) \wedge u_1^0 \vee \bar{u}_1^1$. 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 (or 0) freezes $x_1$ to 1.

### 3.3 Sequential Controllability of Boolean Control Networks

In many situations, perturbations of biological networks do not happen once, but rather accumulate or evolve over time [9, 15, 18]. In the language of Boolean control networks, this corresponds to considering sequences of controls $(\mu_1, \ldots, \mu_n)$. More precisely, take a BCN $F_U$ with the variables $X$ and the control inputs $U$, as well as a sequence of controls $\mu_{[n]} = (\mu_1, \ldots, \mu_n)$, $\mu_i : U \to \{0,1\} \in S_U$. This gives rise to a sequence of Boolean networks $(F_U(\mu_1), \ldots, F_U(\mu_n))$. Fix a mode $M$ and consider a sequence of trajectories $(\tau_1, \ldots, \tau_n)$ 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 $\tau_i$ is the first state of $\tau_{i+1}$. 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 $\tau_i$, in which the last state of every single $\tau_i$ is glued together with the first state of $\tau_{i+1}$.

The problem of inference of control sequences (the CoFaSe problem) was extensively studied in [18]. Given the 3-tuple $(F_U, S_\alpha, S_\omega)$, where $F_U$ is a BCN, $S_\alpha$ is a set of starting states, and $S_\omega$ is a set of target states, the CoFaSe problem consists in inferring a control sequence driving $F_U$ from any state in $S_\alpha$ to any state in $S_\omega$. Deciding the existence of such a sequence is PSPACE-hard.

**Example 3.** *While the framework of Boolean control networks allows for considering arbitrary kinds of control actions, it has been extensively used (e.g. [18]) for capturing freezing, i.e. setting and maintaining specific variables at specific values. These actions mean to model gene knock-ins and knock-outs.*

*Consider again the Boolean network from Example 2, with* $X = \{x, y\}$ *and the update functions* $f_x = \bar{x} \wedge y$ *and* $f_y = x \wedge \bar{y}$*. A convenient way to express freezing controls is by explicitly including the*

*control inputs into the update functions in the following way:*

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

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

*Consider now the following 3 controls:*

$$\begin{aligned} \mu_1 &= \{u^0_x \leftarrow 0, u^1_x \leftarrow 0, u^0_y \leftarrow 0, u^1_y \leftarrow 0\}, \\ \mu_2 &= \{\underline{u^0_x \leftarrow 1}, u^1_x \leftarrow 0, u^0_y \leftarrow 0, u^1_y \leftarrow 0\}, \\ \mu_3 &= \{u^0_x \leftarrow 0, u^1_x \leftarrow 0, u^0_y \leftarrow 0, \underline{u^1_y \leftarrow 1}\}. \end{aligned}$$

*Informally $\mu_1$ does not freeze any variables, $\mu_2$ freezes x to 0, and $\mu_3$ 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 $\mu_1$—i.e. a trajectory of $F_U(\mu_1)$—is $\tau_1 : 01 \to 10 \to 01$. A trajectory of $F_U(\mu_2)$ is $\tau_2 : 01 \to 00 \to 00$; remark that 00 is still a stable state of $F_U(\mu_2)$. A trajectory of $F_U(\mu_3)$ is $\tau_3 : 00 \to 01 \to 11$. We can now glue together the trajectories $\tau_1$, $\tau_2$, and $\tau_3$ by identifying their respective ending and starting states, and we will obtain the following trajectory of the BCN $F_U$ under the control sequence $\mu_{[3]} = (\mu_1, \mu_2, \mu_3)$:*

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

*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 in the uncontrolled case, as Figure 2 illustrates.* □

## 4 Boolean P Systems

In this section we introduce a new variant of P systems—Boolean P systems—tailored specifically to capture sequential control of Boolean networks with as little descriptional overhead as possible. Rather than trying to be faithful to the original model as recalled in Section 2, we here invoke the intrinsic flexibility of the domain to design a variant fitting to our specific use case.

We construct Boolean P systems as set rewriting systems. A Boolean state $s : X \to \{0,1\}$ will be 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 a construct

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

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

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

where $A, B \subseteq X$ and $\varphi$ 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 $\varphi$ to indicate the set of subsets of $V$ which satisfy $\varphi$. Formally, for $W \subseteq V$, by $\varphi(W)$ we denote the truth value of the formula obtained by replacing all variables appearing in $W$ by 1 in $\varphi$, and by 0 all variables

from $V \setminus W$. Then the set of subsets satisfying $\varphi$ is $\varphi = \{W \subseteq V \mid \varphi(W) \equiv \mathbf{1}\}$, where $\mathbf{1}$ is the Boolean tautology.

Applying the rule $r : A \to B \mid \varphi$ to a set $W$ results in the set $(W \setminus A) \cup B$. Applying a set of separately applicable rules $\{r_i : A_i \to B_i \mid \varphi_i\}$ 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 $\Pi$ 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 $\Pi$ will then be a function assigning to any configuration $W$ of $\Pi$ a set of sets of rules applicable to $W$, i.e.,

$$M : 2^V \to 2^R \text{ such that } M(W) \subseteq Appl(\Pi, W).$$

If $|M(W)| \leq 1$ for any $W \subseteq V$, the mode $M$ is called deterministic. Otherwise it is called non-deterministic.

An evolution of $\Pi$ 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 the state $W_i$. This is usually written as $W_i \xrightarrow{R'} W_{i+1}$. If no rules are applicable to the state $W_k$, $W_k$ is called *halting state*, and $(W_i)_{0 \leq i \leq k}$ is called a halting evolution.

Finally, we remark that the starting state is not part of this definition of a Boolean P system. We make this choice to better parallel the way in which Boolean networks are defined.

**Example 4.** *Take $V = \{a, b\}$ and consider the following rules $r_1 : \{a, b\} \to \{a\} \mid \mathbf{1}$ and $r_2 : \{a\} \to \emptyset \mid \bar{b}$, 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 $\Pi$ under the maximally parallel mode—which applies non-extendable applicable sets of rules—is $\{a, b\} \to \{a\} \to \emptyset$. Note that only $r_1$ is applicable in the first step, since $r_2$ requires the configuration to not contain b.* □

**Remark 2.** *Boolean P systems as defined here are very close to other set rewriting formalisms, and in particular to reaction systems [8]. A reaction system $\mathscr{A}$ 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 such a good 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.* □

**Remark 3.** *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. We refer to [14] for an in-depth discussion of controllability of reaction systems.* □

## 5 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:

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

Given a configuration $W$ of $\Pi$, $M$ 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 $\Pi$ under the quasimode $\tilde{M}$" to mean "evolution of $\Pi$ under the mode derived from the quasimode $\tilde{M}$".

## 6 Boolean P Systems Capture 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 rules corresponding to setting $x$ to 1, i.e. introducing $x$ into the configuration, and the rules corresponding to setting $x$ to 0, i.e. erasing $x$ from the configuration:

$$R_x = \{\ \emptyset \to \{x\} \mid f_x,\ \ \{x\} \to \emptyset \mid \neg f_x\ \}.$$

Now consider 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.* Consider two arbitrary states $s$ and $s'$ of $F$ such that $s'$ is reachable from $s$ by the update prescribed by an element $m \in M$. Now consider the subsets of variables $W, W' \subseteq X$ defined by $s$ and $s'$ taken as 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 $\tilde{m} = \bigcup_{x \in m} R_x$. Now take the indicator functions $s, s' : X \to \{0,1\}$ 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. □

The above proof stresses the original motivation behind the introduction of Boolean P systems as a framework for direct and easy generalization of Boolean networks: Boolean P systems were designed to make the simulation of Boolean networks as easy as possible.

**Remark 4.** *Incidentally, Boolean P systems also capture reaction systems (see also Remarks 2 and 3). 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 $\emptyset \to P_a \mid \varphi_a$, 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 is simulated by adding a rule $x \to \emptyset \mid \mathbf{1}$ for every species $x$, where $\mathbf{1}$ is the Boolean tautology.* □

## 7 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 $\Pi_1$ and $\Pi_2$ 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 $B$, which consists in taking the union of the elements of the pairs: $A \dot{\times} B = \{a \cup b \mid a \in A, b \in B\}$. 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 $\Pi_1$ to a configuration $W$ is independent of the applicability of a set of rules of $\Pi_2$ to $W$.

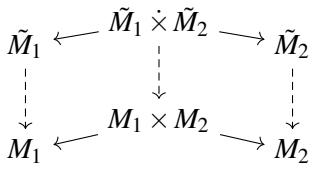
For a mode $M_1$ of $\Pi_1$ and a mode $M_2$ of $\Pi_2$, we define their product as follows:

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

The union of Boolean P systems $\Pi_1 \cup \Pi_2$ together with the product mode $M_1 \times M_2$ implements parallel composition of the two P systems. In particular, if the alphabets of $\Pi_1$ and $\Pi_2$ 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 $\Pi_1$ under $M_1$ (modulo some repeated states), while the projection on $V_2$ will yield a valid evolution of $\Pi_2$ under the mode $M_2$ (modulo some repeated states). Note 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 $\tilde{M}_1 \dot{\times} \tilde{M}_2$:*




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

*Proof.* Pick a state $W \subseteq X$ and recall that the mode $M_{12}$ derived from $\tilde{M}_1 \dot{\times} \tilde{M}_2$ is defined as follows:

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

Consider 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 $m_1 \in \tilde{M}_1 \cap Appl(\Pi, W)$ and $m_2 \in \tilde{M}_2 \cap Appl(\Pi, W)$, implying that

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

On the other hand, consider arbitrary $m_1 \in \tilde{M}_1 \cap Appl(\Pi, W)$ and arbitrary $m_2 \in \tilde{M}_2 \cap Appl(\Pi, W)$. 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 $m_1 \cup m_2 \in Appl(\Pi, W)$. Combining this observation with the reasoning from the previous paragraph we finally derive:

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

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

# 8 Boolean P Systems Capture Sequential Controllability

Underlying sequential controllability of Boolean control networks (Section 3.3) is the implicit presence of a master dynamical system emitting the control inputs of 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 $F_U : S_U \to (S_X \to S_X)$ can be written as a set of propositional formulae over $X \cup U$. Indeed, any control $\mu \in S_U$ can be translated into the conjuction $\bigwedge_{u \in \mu} u \wedge \bigwedge_{v \in U \setminus \mu} \bar{v}$. Now fix an $x \in X$ and consider the formula

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

in which $\mu$ enumerates all the conjuctions corresponding to the controls in $S_U$ and $F(\mu)_x$ is the propositional formula of the update function which $F$ associates to $x$ under the control $\mu$. With the formulae (1), we can translate any BCN $F_U : S_U \to (S_X \to S_X)$ into $F' : S_{X \cup U} \to S_X$ and use the set $R_x$ from Section 6 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. Finally, construct the Boolean P system $\Pi_U(U, R_U)$ with the following rules whose guards are always true:

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

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 of $\tilde{M}_U$ is a union of $R_U^0$ and a subset of $R_U^1$. 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 $\mu$ as indicator functions. Then, as in Theorem 1, there exists an $\tilde{m} \in \tilde{M}$ such that $\Pi$ reaches $W' \cup W_U$ from $W \cup W_U$ in one step. This follows directly from the construction of the rules in $\Pi$ and from the fact that $W_U$ contains exactly the symbols corresponding to the control inputs activated by $\mu$.

Now take $\tilde{M} \dot{\times} \tilde{M}_U$ and remark that it contains an element $\tilde{m} \cup \tilde{m}_U$, where $\tilde{m}_U = \tilde{m}_U^1 \cup R_U^0$ and $\tilde{m}_U^1 \subseteq R_U^1$. Under this 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 the elements of $W_U$ are always erased by the rules $R_U^0$, but may be reintroduced by $m_U^1$.

Suppose that $F_U(\mu)$ reaches $s'$ from $s$ in multiple steps. Then $\Pi$ 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 activates 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 $\mu_0$ 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 $\mu$ 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 $F_U$. □

The component $\Pi_U$ in the composite P system of Theorem 2 is an explicit implementation of the master dynamical system driving the evolution of the controlled system $\Pi$. The setting of this theorem captures the situation in which the control can change at any moment, but $\Pi_U$ can be designed to implement other kinds of control sequences. We give the construction ideas for the kinds of sequences introduced in [18]:

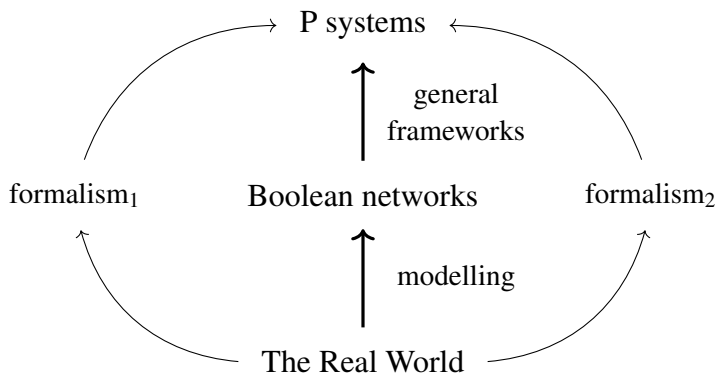



Figure 3: A graphical summary of our methodological conclusion: P systems are a powerful tool for constructing formal frameworks for other formalisms.

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

  The quasimode of $\Pi_U$ will be correspondingly defined to always freeze the controlled variables: $\tilde{M}_U = \{R_U^0\} \dot{\times} 2^{P_U^1}$, 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 its value may change.

  The rules of $\Pi_U$ 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:

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

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

# 9 Conclusion

The motivation of this work stems from the relative underuse of P systems in representing biological knowledge, in spite of its obvious biological inspiration. To informally confirm this intuition of underuse, we established a state of the art comparing the numbers of publications using P systems and Boolean networks to represent any kind of biological knowledge. Our conclusion is that Boolean networks tend to be more popular in this line of research. We speculate that the reason behind this relative popularity of Boolean networks is the greater simplicity of the formalism and original interest on the part of the biological community.

We therefore propose that P systems should be used as a tool for setting up general frameworks for reasoning about other formalisms, which are more popular in biological modelling. We give an example of such a general framework—Boolean P systems—which capture Boolean networks and in particular provide a homogeneous language for sequential controllability. Indeed, sequential controllability of Boolean networks implicitly supposes the presence of a master dynamical system emitting the control

inputs. Our Boolean P system framework makes this master system explicit, as well as its interactions with the controlled Boolean network.

The immediate future research direction which we have already started is actually showing how Boolean P systems facilitate proving some properties of sequential controllability of Boolean networks. Another challenge would be capturing and reasoning about the ConEvs dynamics of the control sequence [18]. Under ConEvs, the control is only allowed to evolve in a stable state, meaning that the master dynamical system is not unilaterally acting on the Boolean network any more, but both of them are part of feedback loop.

The main conclusion of our work is methodological: we believe that the intrinsic flexibility and richness of P systems makes them an excellent tool for constructing formal frameworks for other models of computing.

## References

[1] Albert-László Barabási, Natali Gulbahce & Joseph Loscalzo (2011): *Network medicine: a network-based approach to human disease*. Nature reviews. Genetics 12, pp. 56–68, doi:10.1038/nrg2918.

[2] Célia Biane & Franck Delaplace (2019): *Causal Reasoning on Boolean Control Networks Based on Abduction: Theory and Application to Cancer Drug Discovery*. IEEE ACM Transactions on Computational Biology and Bioinformatics 16(5), pp. 1574–1585, doi:10.1109/TCBB.2018.2889102.

[3] Mónica Cardona, M. Angels Colomer, Antoni Margalida, Antoni Palau, Ignacio Pérez-Hurtado, Mario J. Pérez-Jiménez & Delfí Sanuy (2011): *A computational modeling for real ecosystems based on P systems*. Natural Computing 10, pp. 39–53, doi:10.1007/s11047-010-9191-3.

[4] Mónica Cardona, M. Angels Colomer, Antoni Margalida, Ignacio Pérez-Hurtado, Mario J. Pérez-Jiménez & Delfí Sanuy (2010): *A P system based model of an ecosystem of some scavenger birds*. Lecture Notes in Computer Science 5957, pp. 182–195, doi:10.1007/978-3-642-11467-0_14. Membrane Computing, 10th International Workshop, WMC 2009, Curtea de Argeş, Romania, August 24-27, 2009, Revised Selected and Invited Papers.

[5] Eugenio Cinquemani & Loïc Paulevé, editors (2021): *Computational Methods in Systems Biology - 19th International Conference, CMSB 2021, Bordeaux, France, September 22-24, 2021, Proceedings*. Lecture Notes in Computer Science 12881, Springer, doi:10.1007/978-3-030-85633-5.

[6] M. Angels Colomer, Santiago Lavín, Ignasi Marco, Antoni Margalida, Ignacio Pérez-Hurtado, Mario J. Pérez-Jiménez, Delfí Sanuy, Eduardo Serrano & Luis Valencia-Cabrera (2011): *Modeling population growth of Pyrenean Chamois (Rupicapra p. pyrenaica) by using P systems*. Lecture Notes in Computer Science 6501, pp. 144–159, doi:10.1007/978-3-642-18123-8_13. Available at `http://springerlink.com/content/y87522j29m145434`.

[7] M. Angels Colomer, Antoni Margalida, Luís Valencia & Antoni Palau (2014): *Application of a computational model for complex fluvial ecosystems: The population dynamics of zebra mussel Dreissena polymorpha as a case study*. Ecological Complexity 20, pp. 116–126, doi:10.1016/j.ecocom.2014.09.006. Available at `http://www.sciencedirect.com/science/article/pii/S1476945X14000981`.

[8] Andrzej Ehrenfeucht & Grzegorz Rozenberg (2007): *Reaction Systems*. Fundamenta Informaticae 75(1-4), pp. 263–280. Available at `http://content.iospress.com/articles/fundamenta-informaticae/fi75-1-4-15`.

[9] Eric R. Fearon & Bert Vogelstein (1990): *A genetic model for colorectal tumorigenesis*. Cell 61(5), pp. 759–767, doi:10.1016/0092-8674(90)90186-i.

[10] Rudolf Freund, Tseren-Onolt Ishdorj, Grzegorz Rozenberg, Arto Salomaa & Claudio Zandron, editors (2020): *21st International Conference, CMC 2020, Virtual Event, September 14–18, 2020, Revised Selected Papers*. Springer, doi:10.1007/978-3-030-77102-7.

[11] Rudolf Freund & Sergey Verlan (2007): *A Formal Framework for Static (Tissue) P Systems*. In George Eleftherakis, Petros Kefalas, Gheorghe Păun, Grzegorz Rozenberg & Arto Salomaa, editors: *Membrane Computing, Lecture Notes in Computer Science* 4860, Springer, pp. 271–284, doi:10.1007/978-3-540-77312-2_17.

[12] Manuel García-Quismondo, Carmen Graciani & Agustín Riscos-Núñez (2018): *Membrane Computing as a Modelling Tool: Looking Back and Forward from Sevilla*. *Enjoying Natural Computing: Essays Dedicated to Mario de Jesús Pérez-Jiménez on the Occasion of His 70th Birthday*, pp. 114–129, doi:10.1007/978-3-030-00265-7_10.

[13] *Bulletin of the International Membrane Computing Society (IMCS)*. `http://membranecomputing.net/IMCSBulletin/index.php`.

[14] Sergiu Ivanov & Ion Petre (2020): *Controllability of reaction systems*. *Journal of Membrane Computing* 2(4), pp. 290–302, doi:10.1007/s41965-020-00055-x.

[15] Michael Lee, Albert S. Ye, Alexandra K. Gardino, Anne Heijink, Peter Sorger, Gavin Macbeath & Michael Yaffe (2012): *Sequential Application of Anti-Cancer Drugs Enhances Cell Death by Re-wiring Apoptotic Signaling Networks*. *Cell* 149, pp. 780–794, doi:10.1016/j.cell.2012.03.031.

[16] David Orellana-Martín, Gheorghe Păun, Agustín Riscos-Núñez & Ignacio Pérez-Hurtado, editors (2020): *Proceedings of the 18th Brainstorming Week on Membrane Computing, BWMC 2020*. Fénix Editora, Sevilla, Spain.

[17] Linqiang Pan & Gheorghe Păun, editors (March 2022): *Journal of Membrane Computing*. 4 issue 1, Springer.

[18] Jérémie Pardo, Sergiu Ivanov & Franck Delaplace (2021): *Sequential reprogramming of biological network fate*. *Theoretical Computer Science* 872, pp. 97–116, doi:10.1016/j.tcs.2021.03.013.

[19] Gheorghe Păun (2000): *Computing With Membranes*. *Journal of Computer and System Sciences* 61(1), pp. 108–143, doi:10.1006/jcss.1999.1693.

[20] Gheorghe Păun, Grzegorz Rozenberg & Arto Salomaa, editors (2010): *The Oxford Handbook of Membrane Computing*. Oxford University Press.

[21] *Bibliography of the Research Group on Natural Computing, University of Seville, Spain*. `http://www.gcn.us.es/?q=biblio`.

[22] René Thomas (1973): *Boolean formalization of genetic control circuits*. *Journal of Theoretical Biology* 42(3), pp. 563–585, doi:10.1016/0022-5193(73)90247-6.

[23] Luis Valencia-Cabrera, Manuel García-Quismondo, Mario J. Pérez-Jiménez, Yansen Su, Hui Yu & Linqiang Pan (2013): *Analysing Gene Networks with PDP Systems. Arabidopsis thaliana, a Case Study*. *Eleventh Brainstorming Week on Membrane Computing (11BWMC)*, pp. 257–272. Available at `http://www.gcn.us.es/files/11bwmc/257_valencia_cabrera.pdf`.

[24] Luis Valencia-Cabrera, Carmen Graciani, Ignacio Pérez-Hurtado, Mario J. Pérez-Jiménez & Agustín Riscos-Núñez (2018): *A Decade of Ecological Membrane Computing Applications*. *Bulletin of the International Membrane Computing Society* 6, pp. 39–50. Available at `http://membranecomputing.net/IMCSBulletin/pdf/BulletinDec2018.pdf`.

[25] Jorge G. T. Zañudo, Steven N. Steinway & Réka Albert (2018): *Discrete dynamic network modeling of oncogenic signaling: Mechanistic insights for personalized treatment of cancer*. *Current Opinion in Systems Biology* 9, pp. 1–10, doi:10.1016/j.coisb.2018.02.002.

[26] *11th Asian Conference on Membrane Computing, ACMC 2022*. `https://aclab.dcs.upd.edu.ph/acmc`.

## Appendix 1: A Quantitative Study

To establish a comparative state of the art, we fixed the period between years 2010 and 2021 and counted the publications using P systems and Boolean networks for representing any kind of biological knowledge. Our choice

of the time interval has a double motivation. On the one hand, in 2010 P systems became a fully mature domain, and the first international Conference on Membrane Computing was organized. On the other hand, Boolean networks started gaining popularity in modelling and analysis over the same period of time.

For P systems, we focused mostly on the following sources, representing the major bibliographical references of the domain:

- the bibliography of the Research Group on Natural Computing [21],
- the proceedings of the Brainstorming Weeks on Membrane Computing in Seville (BWMC), e.g. [16],
- the proceedings of the Conference on Membrane Computing (CMC), e.g. [10],
- the Journal of Membrane Computing, e.g. [17],
- the proceedings of the Asian Conference on Membrane Computing (ACMC), e.g. [26].

A quantitative synthesis of the relevant publications in these sources is shown in Figure 4. This histogram indexes 33 publications. The category "Other" refers to the papers which we found cited in the indexed sources, and is not exhaustive.

For Boolean networks, we only focused on the publications in the conference Computational Methods in Systems Biology, e.g. [5], concerned with using Boolean networks to represent any kind of biological knowledge. We found 18 publications, as shown in Figure 5.

Full lists of indexed publications are given in the following appendices.

The informal conclusion which we draw from this bibliographic study comparing the number of publications in many major membrane computing sources to the number of publications in a single systems biology conference confirms the intuition from the introduction: Boolean networks enjoy more success in biological modelling and analysis.

Even though explaining the deep reasons behind this disparity is beyond the scope of our work, we speculate that the ultimate simplicity of Boolean models and finiteness of the state space may play a role. Furthermore, the interest in Boolean modelling may be traced back to the biological research (e.g., [22]), and has developed in tight connection with biology (e.g., [1, 25]).

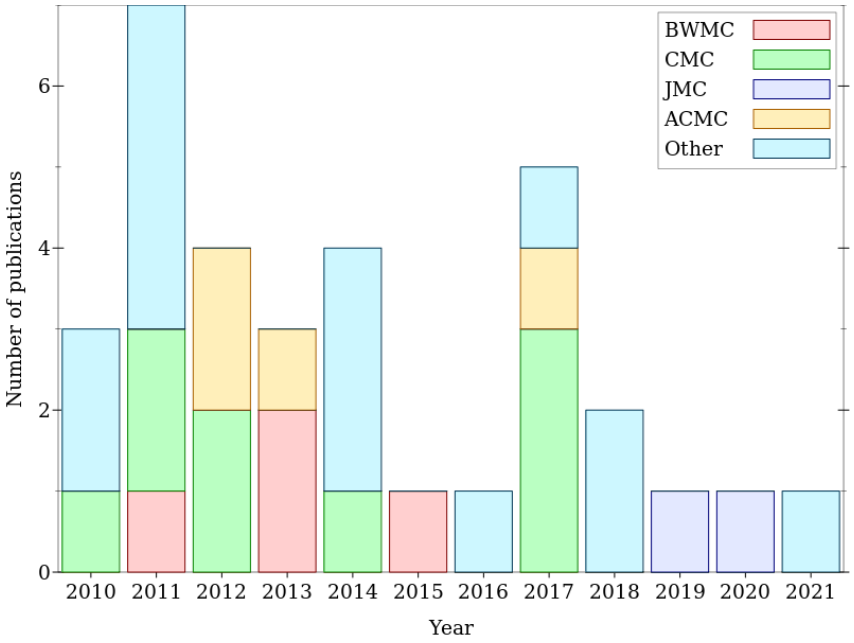



Figure 4: A breakdown by source of the 33 publications concerned with using P systems to represent any kind of biological knowledge between years 2010 and 2021. The bibliography behind the source "Other" is not exhaustive.

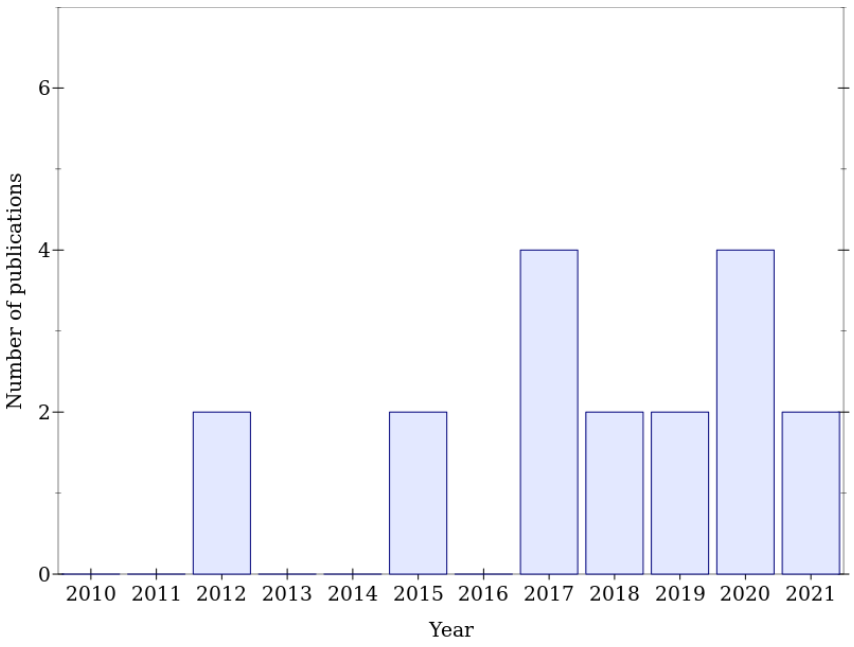



Figure 5: The distribution over the period 2010–2021 of the 18 publications in the proceedings of the international conference Computational Methods in Systems Biology (CMSB) using Boolean networks to represent any kind of biological knowledge.

## Appendix 2

In this appendix, we list the 33 papers using P systems to represent any kind of biological knowledge published between years 2010 and 2021 which were counted in Figure 4. The publications are annotated by tags, representing the source:

- rgnc: the bibliography of the Research Group on Natural Computing,
- bwmc: the proceedings of the Brainstorming Weeks on Membrane Computing in Seville,
- cmc: the proceedings of the Conference on Membrane Computing,
- jmc: the Journal of Membrane Computing,
- acmc: the proceedings of the Asian Conference on Membrane Computing.

### 2021

1. García-Quismondo, M., Hintz W. D., Schuler M. S., & Relyea R. A. (2021): Modeling Diel Vertical Migration with Membrane Computing. Journal of Membrane Computing 3, 35–50. rgnc cmc

### 2020

1. Barbuti, R., Gori, R., Milazzo, P. et al. (2020): A survey of gene regulatory networks modelling methods: from differential equations, to Boolean and qualitative bioinspired models. Journal of Membrane Computing 2, 207–226.
   https://doi.org/10.1007/s41965-020-00046-y jmc

**2019**

1. Nash, A., Kalvala, S. (2019): A P system model of swarming and aggregation in a Myxobacterial colony. Journal of Membrane Computing 1, 103–111.
   https://doi.org/10.1007/s41965-019-00015-0 jmc

**2018**

1. Valencia-Cabrera, L., Graciani C., Pérez-Hurtado I., Pérez-Jiménez M. J., & Riscos-Núñez A. (2018): A Decade of Ecological Membrane Computing Applications. Bulletin of the International Membrane Computing Society. 6, 39–50. rgnc
2. García-Quismondo, M., Graciani C., & Riscos-Núñez A. (2018): Membrane Computing as a Modelling Tool: Looking Back and Forward from Sevilla. In: Carmen Graciani, Agustín Riscos-Núñez, Gheorghe Păun, Gregorz Rozenberg, Arto Salomaa, editors: Enjoying Natural Computing: Essays Dedicated to Mario de Jesús Pérez-Jiménez on the Occasion of His 70th Birthday. 114–129. rgnc

**2017**

1. Cavaliere M., Sanchez A. (2017): The Evolutionary Resilience of Distributed Cellular Computing. In: Leporati A., Rozenberg G., Salomaa A., Zandron C., editors: Membrane Computing. CMC 2016. Lecture Notes in Computer Science, vol. 10105. Springer, Cham.
   https://doi.org/10.1007/978-3-319-54072-6_1 cmc
2. Hinze T.: Coping with Dynamical Structures for Interdisciplinary Applications of Membrane Computing (2017). In: Leporati A., Rozenberg G., Salomaa A., Zandron C., editors: Membrane Computing. CMC 2016. Lecture Notes in Computer Science, vol. 10105. Springer, Cham.
   https://doi.org/10.1007/978-3-319-54072-6_2 cmc
3. Barbuti R., Bove P., Milazzo P., Pardini G. (2017): Applications of P Systems in Population Biology and Ecology: The Cases of MPP and APP Systems. In: Leporati A., Rozenberg G., Salomaa A., Zandron C., editors: Membrane Computing. CMC 2016. Lecture Notes in Computer Science, vol. 10105. Springer, Cham.
   https://doi.org/10.1007/978-3-319-54072-6_3 cmc
4. Zhang G., Pérez-Jiménez M.J., Gheorghe M. (2017): Data Modeling with Membrane Systems: Applications to Real Ecosystems. In: Real-life Applications with Membrane Computing. Emergence, Complexity and Computation, vol. 25. Springer, Cham.
   https://doi.org/10.1007/978-3-319-55989-6_7
5. Mario J. Pérez-Jiménez (2017): Modelling the dynamics of complex systems: A membrane computing based framework, Proceedings of the 6th Asian Conference on Membrane Computing, 2017. acmc

**2016**

1. Cristian Fondevilla, M. Àngels Colomer, Federico Fillat, Ulrike Tappeiner (2016): Using a new PDP modelling approach for land-use and land-cover change predictions: A case study in the Stubai Valley (Central Alps), Ecological Modelling, vol. 322, pp. 101–114, ISSN 0304-3800,
   https://doi.org/10.1016/j.ecolmodel.2015.11.016.

**2015**

1. Gheorghe Păun (2011): Looking for Computer in the Biological Cell. After Twenty Years, Proceedings of the Ninth Brainstorming Week on Membrane Computing, 251–300. bwmc

**2014**

1. Colomer, A. M., Margalida A., Valencia-Cabrera L., & Palau A. (2014): Application of a computational model for complex fluvial ecosystems: The population dynamics of zebra mussel Dreissena polymorpha as a case study. Ecological Complexity 20, 116–126. rgnc

2. Frisco, P., Gheorghe M., & Pérez-Jiménez M. J. (2014): Applications of Membrane Computing in Systems and Synthetic Biology. Emergence, Complexity and Computation. 7, 266. rgnc

3. Blakes, J., Twycross J., Konur S., Romero-Campero F. J., Krasnogor N., & Gheorghe M.(2014): Infobiotics Workbench: A P Systems Based Tool for Systems and Synthetic Biology. Applications of Membrane Computing in Systems and Synthetic Biology 7, 1–42 . rgnc

4. Pérez-Jiménez M.J. (2014): A Bioinspired Computing Approach to Model Complex Systems. In: Gheorghe M., Rozenberg G., Salomaa A., Sosík P., Zandron C., editors: Membrane Computing. CMC 2014. Lecture Notes in Computer Science, vol. 8961. Springer, Cham.
https://doi.org/10.1007/978-3-319-14370-5_2 cmc

**2013**

1. Ardelean, I., Díaz-Pernil D., Gutiérrez-Naranjo M. A., Peña-Cantillana F., & Sarchizian I. (2013): Studying the Chlorophyll Fluorescence in Cyanobacteria with Membrane Computing Techniques. Eleventh Brainstorming Week on Membrane Computing (11BWMC), 9–24. rgnc bwmc

2. L. Valencia-Cabrera, M. García-Quismondo, M.J. Pérez-Jiménez, Y. Su, H. Yu, L. Pan (2011): Analysing Gene Networks with PDP Systems. Arabidopsis thaliana, a Case Study. Proceedings of the Ninth Brainstorming Week on Membrane Computing, 257–272. bwmc

3. Colomer M.À., Margalida A., Pérez-Jiménez M.J. (2013): Population Dynamics P system (PDP) models: a standardized protocol for describing and applying novel bio-inspired computing tools. Plos one. 8(4):e60698.
DOI: 10.1371/journal.pone.0060698. PMID: 23593284; PMCID: PMC3622025. acmc

**2012**

1. García-Quismondo, M., Valencia-Cabrera L., Su Y., Pérez-Jiménez M. J., Pan L., & Yu H. (2012): Modeling logic gene networks by means of probabilistic dynamic P systems. In: Linqiang Pan, Gheorghe Paun, Tao Song, editors. Asian Conference on Membrane Computing. 30–60 (2012). rgnc acmc

2. Romero-Campero, F. J., & Pérez-Jiménez M.J. (2012): P systems as a modeling framework for molecular Systems Biology. In: Linqiang Pan, Gheorghe Paun, Tao Song, editors: Asian Conference on Membrane Computing. 8–10. rgnc acmc

3. Martínez-del-Amor M.A. et al. (2013): DCBA: Simulating Population Dynamics P Systems with Proportional Object Distribution. In: Csuhaj-Varjú E., Gheorghe M., Rozenberg G., Salomaa A., Vaszil G., editors: Membrane Computing. CMC 2012. Lecture Notes in Computer Science, vol. 7762. Springer, Berlin, Heidelberg.
https://doi.org/10.1007/978-3-642-36751-9_18 rgnc cmc

4. Ramón P., Troina A. (2013): Modelling Ecological Systems with the Calculus of Wrapped Compartments. In: Csuhaj-Varjú E., Gheorghe M., Rozenberg G., Salomaa A., Vaszil G., editors: Membrane Computing. CMC 2012. Lecture Notes in Computer Science, vol. 7762. Springer, Berlin, Heidelberg.
https://doi.org/10.1007/978-3-642-36751-9_24 cmc

**2011**

1. Colomer, A. M., Lavín S., Marco I., Margalida A., Pérez-Hurtado I., Pérez-Jiménez M. J., et al. (2011): Modeling population growth of Pyrenean Chamois (Rupicapra p. pyrenaica) by using P systems. Lecture Notes in Computer Science. 6501, 144–159. rgnc
2. Gheorghe, M., Manca V., & Romero-Campero F. J. (2011): Deterministic and stochastic P systems for modelling cellular processes. Natural Computing. 9(2), 457–473. rgnc
3. Colomer, A. M., Pérez-Hurtado I., Riscos-Núñez A., & Pérez-Jiménez M. J. (2011): Comparing simulation algorithms for multienvironment probabilistic P system over a standard virtual ecosystem. Natural Computing 11, 369–379. rgnc
4. Cardona, M., Colomer M. A., Margalida A., Palau A., Pérez-Hurtado I., Pérez-Jiménez M. J., et al. (2011): A computational modeling for real ecosystems based on P systems. Natural Computing 10(1), 39–53. rgnc
5. M.A. Colomer, C. Fondevilla, L. Valencia-Cabrera (2011): A New P System to Model the Subalpine and Alpine Plant Communities, Proceedings of the Ninth Brainstorming Week on Membrane Computing, 91–112. bwmc
6. Beal J.: Bridging Biology and Engineering Together with Spatial Computing (2012). In: Gheorghe M., Păun Gh., Rozenberg G., Salomaa A., Verlan S., editors Membrane Computing. CMC 2011. Lecture Notes in Computer Science, vol. 7184. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-28024-5_2 cmc
7. Giavitto J.L. (2012): The Modeling and the Simulation of the Fluid Machines of Synthetic Biology. In: Gheorghe M., Păun Gh., Rozenberg G., Salomaa A., Verlan S., editors: Membrane Computing. CMC 2011. Lecture Notes in Computer Science, vol. 7184. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-28024-5_3 cmc

**2010**

1. Colomer, A. M., Lavín S., Marco I., Margalida A., Pérez-Hurtado I., Pérez-Jiménez M. J., et al. (2010): Modeling population growth of Pyrenean Chamois (Rupicapra p. pyrenayca) by using P systems. In: Marian Gheorghe, Thomas Hinze, Gheorghe Păun, editors: Eleventh International Conference on Membrane Computing (CMC11). 121–135. rgnc cmc
2. Cardona, M., Colomer A. M., Margalida A., Pérez-Hurtado I., Pérez-Jiménez M. J., & Sanuy D. (2010): A P system based model of an ecosystem of some scavenger birds. Lecture Notes in Computer Science, vol. 5957, 182–195. rgnc
3. Besozzi D., Cazzaniga P., Mauri G., Pescini D. (2010): BioSimWare: A Software for the Modeling, Simulation and Analysis of Biological Systems. In: Gheorghe M., Hinze T., Păun Gh., Rozenberg G., Salomaa A., editors: Membrane Computing. CMC 2010. Lecture Notes in Computer Science, vol. 6501. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-18123-8_12 cmc

## Appendix 3

In this appendix, we list the 18 papers using Boolean networks to represent any kind of biological knowledge, published between the years 2010 and 2021 in the proceedings of the international conference on Computational Methods in Systems Biology (CMSB), and which were counted in Figure 5.

**2021**

1. Biswas A., Gupta A., Missula M., Thattai M. (2021): Automated Inference of Production Rules for Glycans. In: Cinquemani E., Paulevé L., editors: Computational Methods in Systems Biology. CMSB 2021. Lecture Notes in Computer Science, vol. 12881. Springer, Cham.
https://doi.org/10.1007/978-3-030-85633-5_4

2. Thuillier K., Baroukh C., Bockmayr A., Cottret L., Paulevé L., Siegel A. (2021): Learning Boolean Controls in Regulated Metabolic Networks: A Case-Study. In: Cinquemani E., Paulevé L., editors: Computational Methods in Systems Biology. CMSB 2021. Lecture Notes in Computer Science, vol. 12881. Springer, Cham.
https://doi.org/10.1007/978-3-030-85633-5_10

**2020**

1. Cifuentes Fontanals L., Tonello E., Siebert H. (2020): Control Strategy Identification via Trap Spaces in Boolean Networks. In: Abate A., Petrov T., Wolf V., editors: Computational Methods in Systems Biology. CMSB 2020. Lecture Notes in Computer Science, vol. 12314. Springer, Cham.
https://doi.org/10.1007/978-3-030-60327-4_9

2. Diop O., Chaves M., Tournier L. (2020): Qualitative Analysis of Mammalian Circadian Oscillations: Cycle Dynamics and Robustness. In: Abate A., Petrov T., Wolf V., editors: Computational Methods in Systems Biology. CMSB 2020. Lecture Notes in Computer Science, vol. 12314. Springer, Cham.
https://doi.org/10.1007/978-3-030-60327-4_10

3. Chevalier S., Noël V., Calzone L., Zinovyev A., Paulevé L. (2020): Synthesis and Simulation of Ensembles of Boolean Networks for Cell Fate Decision. In: Abate A., Petrov T., Wolf V., editors: Computational Methods in Systems Biology. CMSB 2020. Lecture Notes in Computer Science, vol. 12314. Springer, Cham.
https://doi.org/10.1007/978-3-030-60327-4_11

4. Su C., Pang J. (2020): Sequential Temporary and Permanent Control of Boolean Networks. In: Abate A., Petrov T., Wolf V., editors: Computational Methods in Systems Biology. CMSB 2020. Lecture Notes in Computer Science, vol. 12314. Springer, Cham.
https://doi.org/10.1007/978-3-030-60327-4_13

**2019**

1. Mandon H., Su C., Haar S., Pang J., Paulevé L. (2019): Sequential Reprogramming of Boolean Networks Made Practical. In: Bortolussi L., Sanguinetti G., editors: Computational Methods in Systems Biology. CMSB 2019. Lecture Notes in Computer Science, vol. 11773. Springer, Cham.
https://doi.org/10.1007/978-3-030-31304-3_1

2. Pardo J., Ivanov S., Delaplace F. (2019): Sequential Reprogramming of Biological Network Fate. In: Bortolussi L., Sanguinetti G., editors: Computational Methods in Systems Biology. CMSB 2019. Lecture Notes in Computer Science, vol. 11773. Springer, Cham.
https://doi.org/10.1007/978-3-030-31304-3_2

**2018**

1. Razzaq M., Kaminski R., Romero J., Schaub T., Bourdon J., Guziolowski C. (2018): Computing Diverse Boolean Networks from Phosphoproteomic Time Series Data. In: Češka M., Šafránek D., editors: Computational Methods in Systems Biology. CMSB 2018. Lecture Notes in Computer Science, vol. 11095. Springer, Cham.
https://doi.org/10.1007/978-3-319-99429-1_4

2. Paul S., Pang J., Su C. (2018): On the Full Control of Boolean Networks. In: Češka M., Šafránek D., editors: Computational Methods in Systems Biology. CMSB 2018. Lecture Notes in Computer Science, vol. 11095. Springer, Cham.
https://doi.org/10.1007/978-3-319-99429-1_21

**2017**

1. Biane C., Delaplace F. (2017): Abduction Based Drug Target Discovery Using Boolean Control Network. In: Feret J., Koeppl H., editors: Computational Methods in Systems Biology. CMSB 2017. Lecture Notes in Computer Science, vol. 10545. Springer, Cham.
https://doi.org/10.1007/978-3-319-67471-1_4

2. Carcano A., Fages F., Soliman S. (2017): Probably Approximately Correct Learning of Regulatory Networks from Time-Series Data. In: Feret J., Koeppl H., editors: Computational Methods in Systems Biology. CMSB 2017. Lecture Notes in Computer Science, vol. 10545. Springer, Cham.
https://doi.org/10.1007/978-3-319-67471-1_5

3. Mandon H., Haar S., Paulevé L. (2017): Temporal Reprogramming of Boolean Networks. In: Feret J., Koeppl H., editors: Computational Methods in Systems Biology. CMSB 2017. Lecture Notes in Computer Science, vol. 10545. Springer, Cham.
https://doi.org/10.1007/978-3-319-67471-1_11

4. Paulevé L. (2017): Pint: A Static Analyzer for Transient Dynamics of Qualitative Networks with IPython Interface. In: Feret J., Koeppl H., editors: Computational Methods in Systems Biology. CMSB 2017. Lecture Notes in Computer Science, vol. 10545. Springer, Cham.
https://doi.org/10.1007/978-3-319-67471-1_20

**2015**

1. Ostrowski M., Paulevé L., Schaub T., Siegel A., Guziolowski C. (2015): Boolean Network Identification from Multiplex Time Series Data. In: Roux O., Bourdon J., editors: Computational Methods in Systems Biology. CMSB 2015. Lecture Notes in Computer Science, vol. 9308. Springer, Cham.
https://doi.org/10.1007/978-3-319-23401-4_15

2. Abou-Jaoudé W., Feret J., Thieffry D. (2015): Derivation of Qualitative Dynamical Models from Biochemical Networks. In: Roux O., Bourdon J., editors: Computational Methods in Systems Biology. CMSB 2015. Lecture Notes in Computer Science, vol. 9308. Springer, Cham.
https://doi.org/10.1007/978-3-319-23401-4_17

**2012**

1. Folschette M., Paulevé L., Inoue K., Magnin M., Roux O. (2012): Concretizing the Process Hitting into Biological Regulatory Networks. In: Gilbert D., Heiner M. (eds) Computational Methods in Systems Biology. CMSB 2012. Lecture Notes in Computer Science, vol. 7605. Springer, Berlin.
Heidelberg. https://doi.org/10.1007/978-3-642-33636-2_11

2. Naldi A., Monteiro P.T., Chaouiya C. (2012): Efficient Handling of Large Signalling-Regulatory Networks by Focusing on Their Core Control. In: Gilbert D., Heiner M., editors: Computational Methods in Systems Biology. CMSB 2012. Lecture Notes in Computer Science, vol. 7605. Springer, Berlin, Heidelberg .
https://doi.org/10.1007/978-3-642-33636-2_17