P versus B:

P Systems as a Formal Framework for Controllability of Boolean Networks

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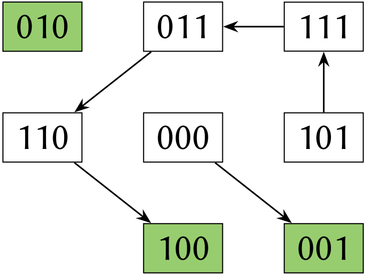
NCMA 2022

Boolean Networks

Boolean variables + Boolean update functions

$$\begin{aligned} f_{x_1} &= (x_1 \wedge \overline{x}_2) \vee (x_1 \wedge \overline{x}_3) \vee (\overline{x}_1 \wedge x_2 \wedge x_3) \\ f_{x_2} &= (x_1 \wedge x_3) \vee (\overline{x}_1 \wedge x_2) \\ f_{x_3} &= (x_1 \wedge x_3) \vee (\overline{x}_1 \wedge \overline{x}_2) \end{aligned}$$

Synchronous dynamics: all variables are always updated

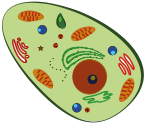


Stable states: 010, 100, 001.

Boolean Networks versus Biology

models

Boolean networks



Controllability of Boolean Networks

Act → Real-world system

Control → Boolean network

Model disease, therapy, environmental hazards, ...

Boolean Control Networks

$$\begin{aligned} f_{x_1} &= (x_1 \wedge \overline{x}_2) \vee (x_1 \wedge \overline{x}_3) \vee (\overline{x}_1 \wedge x_2 \wedge x_3) \\ f_{x_2} &= (x_1 \wedge x_3) \vee (\overline{x}_1 \wedge x_2) \\ f_{x_3} &= \big((x_1 \wedge x_3) \vee (\overline{x}_1 \wedge \overline{x}_2)\big) \wedge u^0 \vee \overline{u^1} \end{aligned}$$

Control inputs:

$u^0 \leftarrow 0$

freezes x_3 to 0

$u^1 \leftarrow 0$

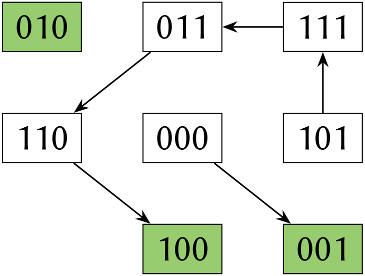
freezes x_3 to 1

Célia Biane, Franck Delaplace. Causal reasoning on Boolean control networks based on abduction: theory and application to Cancer drug discovery. IEEE/ACM Trans. Comput. Biol. Bioinform. (2018).

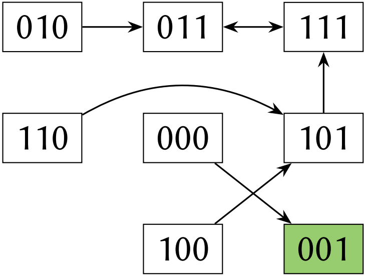
BCN Dynamics

$$
\begin{aligned}
f_{x_1} &= (x_1 \wedge \overline{x}_2) \vee (x_1 \wedge \overline{x}_3) \vee (\overline{x}_1 \wedge x_2 \wedge x_3) \\
f_{x_2} &= (x_1 \wedge x_3) \vee (\overline{x}_1 \wedge x_2) \\
f_{x_3} &= (x_1 \wedge x_3) \vee (\overline{x}_1 \wedge \overline{x}_2)
\end{aligned}
$$

Uncontrolled



x_3 frozen to 1



Sequential Controllability

$$
\begin{aligned}
f_{x_1} &= (x_1 \wedge \overline{x}_2) \vee (x_1 \wedge \overline{x}_3) \vee (\overline{x}_1 \wedge x_2 \wedge x_3) \\
f_{x_2} &= (x_1 \wedge x_3) \vee (\overline{x}_1 \wedge x_2) \\
f_{x_3} &= \big((x_1 \wedge x_3) \vee (\overline{x}_1 \wedge \overline{x}_2)\big) \wedge u^0 \vee \overline{u^1}
\end{aligned}
$$

Control inputs $U = \{u^i\}$

Control $\mu : U \to \{0, 1\}$

Control sequence $\mu_{[k]} = (\mu_1, \ldots, \mu_k)$

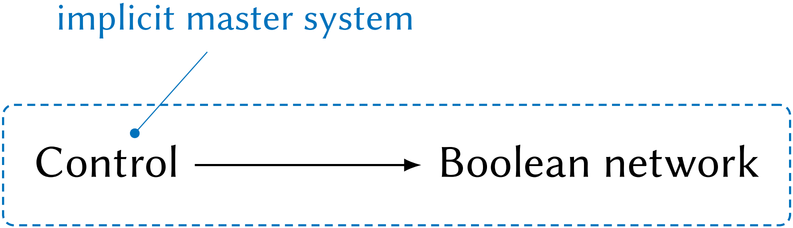
The CoFaSe Inference Problem

Control (cellular) Fate in Sequence

Starting states → control sequence? → Target stable states

Jérémie Pardo, Sergiu Ivanov, Franck Delaplace: Sequential reprogramming of biological network fate. Theor. Comput. Sci. 872: 97-116 (2021)

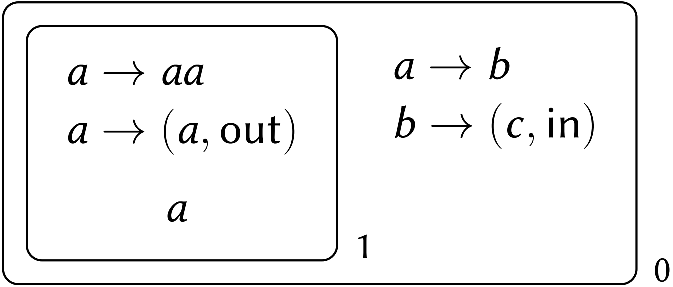
A Framework for Controllability



1. Make the master system explicit.
2. Capture both in a single formalism.

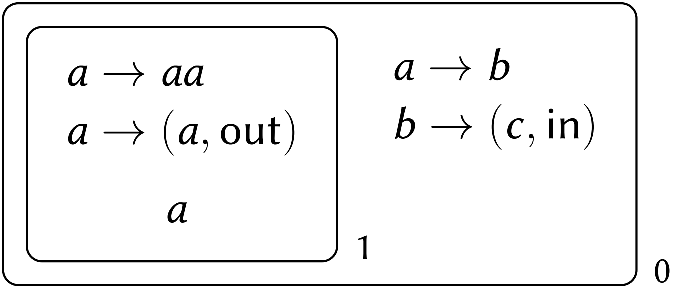
P Systems

Classic P Systems



- hierarchical multiset rewriting
- non-determinism and competition
- communication
- parallelism

P versus B



versus?

$$
\begin{aligned}
f_{x_1} &= (x_1 \wedge \overline{x}_2) \vee (x_1 \wedge \overline{x}_3) \vee (\overline{x}_1 \wedge x_2 \wedge x_3) \\
f_{x_2} &= (x_1 \wedge x_3) \vee (\overline{x}_1 \wedge x_2) \\
f_{x_3} &= \big((x_1 \wedge x_3) \vee (\overline{x}_1 \wedge \overline{x}_2)\big) \wedge u^0 \vee \overline{u^1}
\end{aligned}
$$

P systems are flexible.

Define a specialized P system variant for sequential controllability of Boolean networks.

Boolean P Systems

Boolean P Systems $\Pi = (V, R)$

States: $s : V \to \{0, 1\}$ and the corresponding subset

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

- $A, B \subseteq V$
- φ a propositional formula over V, the guard

---

r is applicable to $W \subseteq V$ if $A \subseteq W$ and $\varphi(W)$

Apply r to $W \mapsto W \setminus A \cup B$

Apply $\{r_i : A_i \to B_i \mid \varphi_i\}$ to $W \mapsto \left(W \setminus \bigcup_i A_i\right) \cup \bigcup_i B_i$

- set rewriting
- no competition

Boolean P systems $\supseteq$ Boolean networks

Let $f_y : \{0,1\}^X \to \{0,1\}$. Simulation:

$$R_y = \{\ \emptyset \to \{y\} \mid f_y,\ \{y\} \to \emptyset \mid \neg f_y\ \}$$

produce y if $f_y(W)$ remove y if not $f_y(W)$

Theorem: Natural extension to whole networks.

Trivial by design

Evolution: Modes versus Quasimodes

P systems:

- A mode tells which rules to apply.

Boolean networks:

- A mode tells which variables to update.
  - all variables can be updated at any step
  - no competition

Boolean P systems:

- A quasimode $\widetilde{M} \subseteq 2^R$ suggests the rules to apply.

The corresponding mode M:

$$M(W) = \{\{r \in m \mid r \text{ applicable to } W\} \mid m \in \widetilde{M}\}$$

Composition of Boolean P Systems

1. Compose the quasimodes:

$$\widetilde{M}_1 \dot{\times} \widetilde{M}_2 = \{m_1 \cup m_2 \mid m_1 \in \widetilde{M}_1, m_2 \in \widetilde{M}_2\}$$

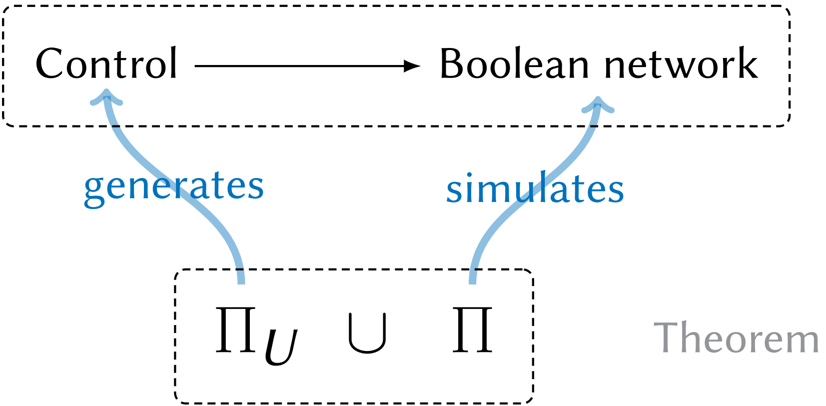
2. Compose the P systems:

$\Pi_1 = (V_1, R_1)$ under $\widetilde{M}_1$

$\Pi_2 = (V_2, R_2)$ under $\widetilde{M}_2$

$\Pi_1 \cup \Pi_2 = (V_1 \cup V_2, R_1 \cup R_2)$ under $\widetilde{M}_1 \dot{\times} \widetilde{M}_2$

A Framework for Controllability



$$\Pi_U = \left(U, R_U^0 \cup R_U^1\right)$$

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

Outlook

Complexity of Controllability

CoFaSe: Starting states —control sequence?→ Target stable states

Work in progress: CoFaSe ∈ PSPACE-complete?

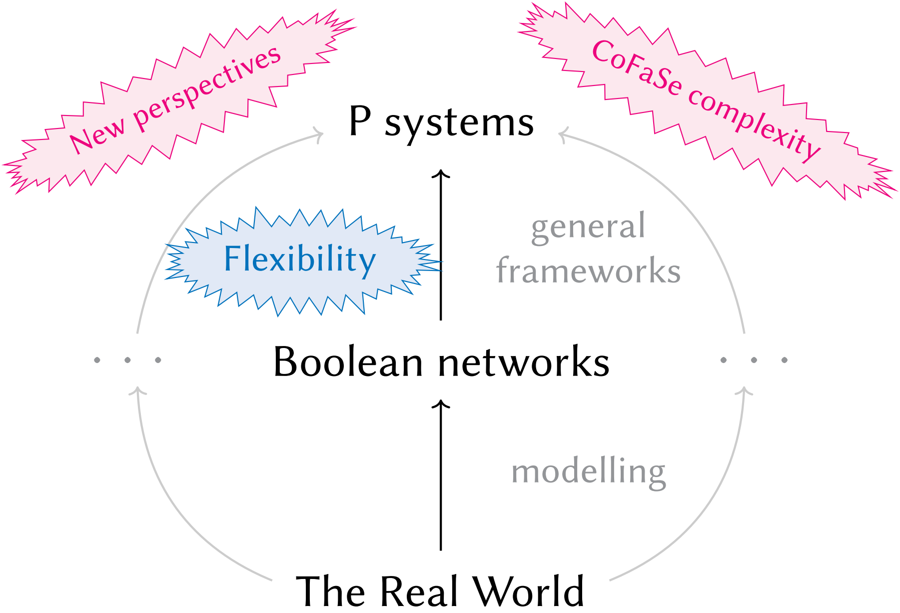
Boolean P systems inside

Beyond CoFaSe

P systems are:

- general
- unifying
- multi-paradigm
- flexible!

P systems = a tool for taking different perspectives.



New perspectives
CoFaSe complexity
P systems
Flexibility
general
frameworks
. . .
Boolean networks
. . .
modelling
The Real World