Number of different dynamics in particular families of Boolean networks

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Workshop: Desafíos matemáticos e informáticos para la construcción y análisis de redes de regulación biológica
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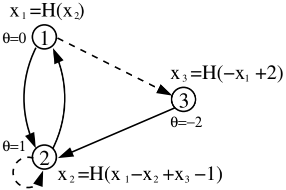
UNIVERSIDAD ADOLFO IBÁÑEZ

Boolean Network (BN): Definition



Definition

A BN $N = (G, F, s)$ is defined by:

- A graph $G = (V, A)$
- A global transition function $F = (f_1, \ldots, f_n) : \{0,1\}^n \to \{0,1\}^n$. f_i local activation function.
- An update schedule $s : \{1, \ldots, n\} \to \{1, \ldots, n\}$.

→ $x_i(t) \in \{0,1\}$ is the node state i on time t (1= active, 0= inhibite).

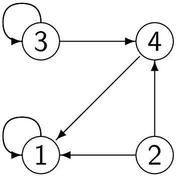
Connection graph

The connection graph of $N = (G, F, s)$ is $G^F = (V, A)$:

- $V = \{1, ..., n\}$,
- $(i, j) \in A \iff f_j$ depends on x_i,

$$f_j(x_1, \ldots, x_{i-1}, 0, x_{i+1}, \ldots, x_n) \neq f_j(x_1, \ldots, x_{i-1}, 1, x_{i+1}, \ldots, x_n)$$

$$\begin{aligned}
f_1(x) &= (x_1 \wedge x_2) \vee x_4 \\
f_2(x) &= 0 \\
f_3(x) &= x_3 \wedge (x_4 \vee \bar{x}_4) \\
f_4(x) &= x_2 \wedge \bar{x}_3
\end{aligned}$$



(Deterministic) Update Schedule

An update schedule is a function $s : \{1, \dots, n\} \to \{1, \dots, n\}$ such that $s(\{1, \dots, n\}) = \{1, \dots, m\},\ m \leq n$.

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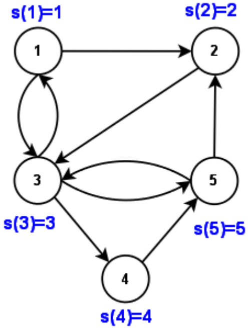

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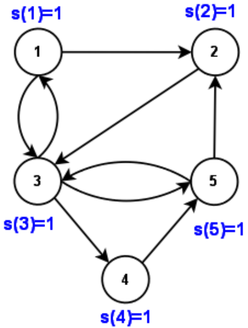
  $s(\{1, \ldots, n\}) = \{1\}$



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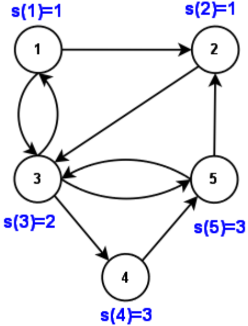

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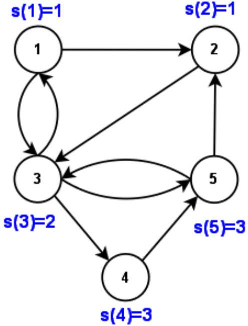
$\rightarrow$ $|S_n| = T_n = \sum_{k=0}^{n-1} \binom{n}{k} T_k$ ($|S_5| = 541$)



BN Dynamic

The iteration of the Boolean network $N = (G, F, s)$ is:

$$x_i(t+1) = f_i(x_1(t_1), ..., x_j(t_j), ..., x_n(t_n)),$$

where $t_j = \begin{cases} t & ; \quad s(i) \leq s(j) \\ t+1 & ; \quad s(i) > s(j) \end{cases}$

Thus, there exists function $F^s : \{0,1\}^n \to \{0,1\}^n$, with $F^s(x) = (f_1^s(x), \ldots, f_n^s(x))$ such that: $x(t+1) = F^s(x(t))$.

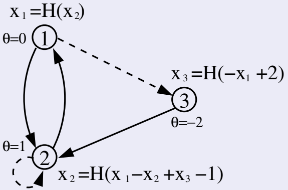
Definition (Iteration Graph):

Given $N = (G, F, s)$ a BN, we define the iteration graph $G_I = (V_I, A_I)$ by:

- $V_I = \{0,1\}^n$.
- $\forall x, y \in V_I,\ (x, y) \in A_I \Leftrightarrow F^s(x) = y$.

EXAMPLE: two dynamics of a BN

Network N



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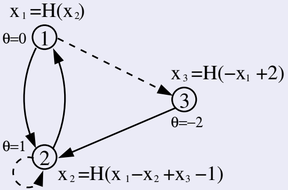
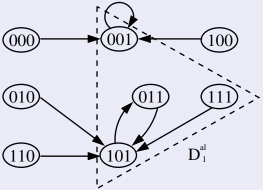


Parallel, $s_p = (1, 2, 3)$



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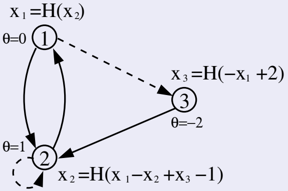

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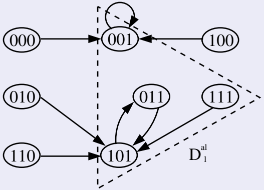

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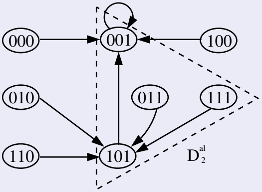

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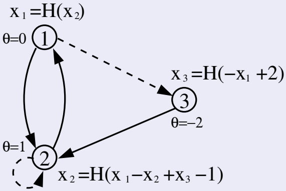

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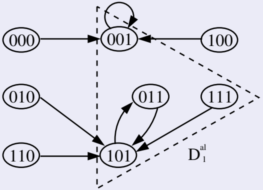

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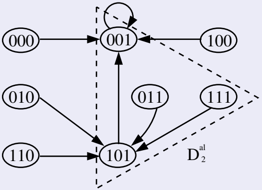

Attractors

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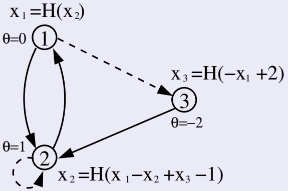

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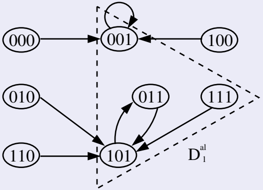

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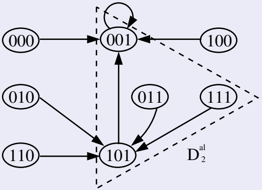

Attractors

- For N with s_p: 001 (fixed point) and 101 $\leftrightarrow$ 011 (limit cycle)

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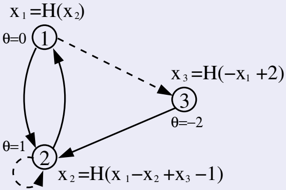

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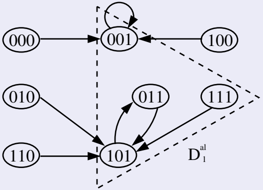

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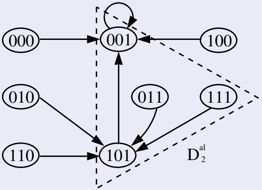

Attractors

- For N with s_p: 001 (fixed point) and 101 $\leftrightarrow$ 011 (limit cycle)
- For N with s_q: only 001 (fixed point)

Update Digraph (UD)

Given $N = (G, F, s)$ a BN, we say that:

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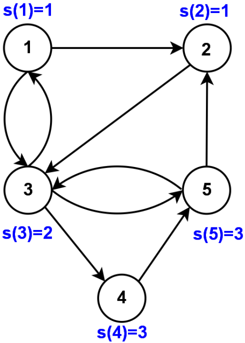

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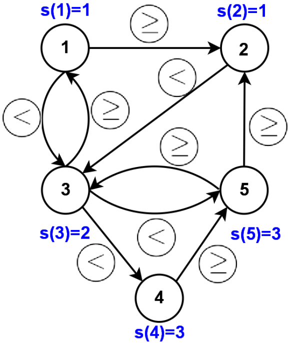

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★ (G, lab) is an UD $\Rightarrow$ (G, lab) is a labeled digraph ($\Leftarrow$ is false).

Equivalent update schedules

The following result[1] allows grouping updates that have exactly the same dynamic.

Theorem (Aracena et al.,2009)

Let $N_1 = (G, F, s_1)$ and $N_2 = (G, F, s_2)$ be two Boolean networks which are different only in the update schedule. If $G^F_{s_1} = G^F_{s_2}$, then both dynamical behaviors are equal.

We define the equivalence relation between update schedules:

$$s_1 \sim_N s_2 \iff G^F_{s_1} = G^F_{s_2}.$$

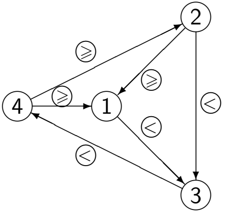
Hence, we denote $[s]_N = \{s' : s \sim_N s'\}$.

[1] J. Aracena, E. Goles, A. Moreira, L. Salinas: *On the robustness of update schedules in Boolean networks*. Biosystems, vol. 97, 1, pp. 1-8, (2009).

Example

$s_1 = (1)(2)(3)(4)$

$G^F_{s_1}$



$s_2 = (1,2)(3)(4)$

$G^F_{s_2}$

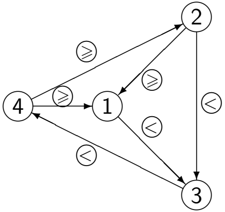


Figure: OR-Boolean Network with two equivalent schedules that yield the same dynamical behavior.

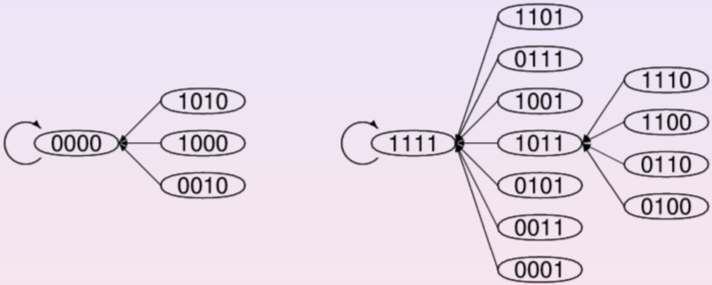


Figure: Dynamical behavior of both OR-Boolean networks.

The converse of previous theorem is not true.

$s_1 = (1)(2)(3)(4)$ $s_3 = (1)(3)(2)(4)$

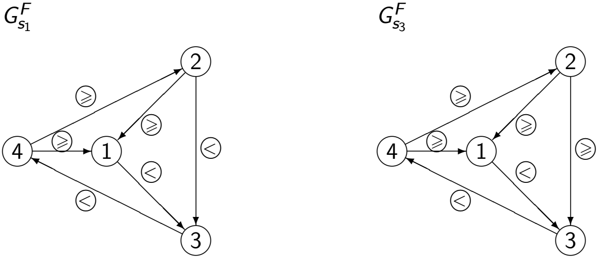


Figure: OR-Boolean Networks with two non-equivalent schedules that have the same dynamic.

OPEN PROBLEM: Which are the conditions to have the converse of the previous theorem?

Some questions/answers on UD

(q1) Let (G, lab) be a labeled digraph. Is (G, lab) an UD?

[2] J. Aracena, E. Fanchon, M.M., M. Noual: *Combinatorics on update digraphs in Boolean networks*. Discret. Appl. Math., 159, pp. 401-409, (2011).

[3] J. Aracena, J. Demongeot, E. Fanchon, M.M.: *On the number of update digraphs and its relation with the feedback arc sets and tournaments*. Discret. Appl. Math., 161(10-11), pp. 1345-1355, (2013).

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R: For (q2) and (q3) some bounds and exact formulas for particular graphs (complete, acyclic tournaments, etc) can be found in [2] and [3].

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Algorithm to determine all $[s]_G$

The following Algorithm 2 must be executed with DigraphUD$(e, \emptyset, V)$[4].

Algorithm 2 DigraphUD(s, A, B)

Input: A, B subsets of vertices of a digraph G, and s a partial update schedule of a subdigraph of G
Output: UD, a set of partial update schedules for G

```
begin
  UD ← ∅;
  U ← B_{nb(s)};
  if U = A = ∅ then
    UD = UD ∪ {s_B = (j ∈ B)};
    for all A_0 ⊂ B such that A_0 ≠ ∅ with decreasing size do
      B_0 = B − A_0;
      UD = UD ∪ DigraphUD(s_e, A_0, B_0);
    end
  else
    if MoveTest(U, A) = 0 then
      if MoveTest(A, B) = 0 then
        UD = UD ∪ {(s ∗ A) ∗ B};
      if |B| > 1 then
        for all A_1 ⊂ B such that A_1 ≠ ∅ with decreasing size do
          B_1 = B − A_1;
          UD = UD ∪ DigraphUD(s ∗ A, A_1, B_1);
        end
      end
    end
  end
  return (UD);
end
```

Algorithm 3: MoveTest(C, D)

Input: C, D subsets of vertices of a digraph G
bf Output: An index 1 if it is possible to move nodes from D to C without changing the update digraph induced by $C \cup D$, an index 0 otherwise

```
begin
  if C = ∅ then
    return (0);
  else
    if ∃H ⊆ D such that
    (G_(C,D), lab_(C,D)) = (G_(C∪H,D−H), lab_(C∪H,D−H))
    then
      return (1);
    else
      return (0);
    end
  end
end
```

[4] J. Aracena, J. Demongeot, E. Fanchon, M.M.: *On the number of different dynamics in Boolean networks with deterministic update schedules*. Mathematical Biosciences, 242(2), 188-194, (2013).

Given a BN, how many dynamics can exist?

n	2^{n-1}	$2^n - 1$	$n!$	T_n
3	4	7	6	13
4	8	15	24	75
5	16	31	120	541
6	32	63	720	4.683
7	64	127	5.040	47.293
8	128	255	40.320	545.835
9	256	511	362.880	7.087.261

- 2^{n-1}, $2^n - 1$, $n!$ and T_n are the number of UDs ($= \{[s]_G\}$) when the digraph: is connected with $n-1$ arcs, is a single cycle, is an acyclic tournament and is a complete digraph, respectively.

  OPEN PROBLEM: Exact formulas for the number of UDs in particular families of BN, for example, CAs?

Elementary cellular automata

Definition

An **elementary cellular automata** (ECA) is a circle graph of n vertices (cells) where the same Boolean function $f\colon \{0,1\}^3 \to \{0,1\}$ is applied on each vertex synchronously.

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Configuration
000
001
010
011
100
101
110
111

These configurations define $2^8 = 256$ possible functions, sometimes called **Wolfram[5] rules**. They are numbered from 0 to 255 as it follows:

Configurations	Rule	Factor	
000	0	2^0	0
001	0	2^1	0
010	0	2^2	0
011	1	2^3	+8
100	1	2^4	+16
101	1	2^5	+32
110	0	2^6	0
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[5] Stephen Wolfram. A New Kind of Science, Wolfram Media (2002).

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Preliminary simulations show that 146 of these 256 wolfram rules have exactly $|U(G)|$ different dynamics. Specifically:

n	$\|U(G)\|$	$\|S_n\|$
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	$\lvert D(n)\rvert = 3^n + 2 - 2^{n+1}$	

$D(n)$: set of different dynamics of the ECA of size n.

Example: Rule 110

- Boolean expression: $f(x,y,z) = \overline{x}y + y\overline{z} + \overline{y}z$
- Attractors with the parallel update: only 000.
- Attractors with the sequential update $s = (1)(2)(3)$: 000 and the limit cycle composed by the configurations 011 (3), 101 (5), 110 (6), 111 (7)
- Attractors with the block sequential update $s = (1)(2,3)$: 000 and the limit cycle composed by 011 (3), 100 (4), 101 (5), 111 (7)

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- Validate/refuse $|D(n)| = 3^n + 2 - 2^{n+1}$

Muchas Gracias!!