Limit cycles and update schedules in Boolean networks: Inverse Problem.
(Results of Luis Gómez’s Ph.D. Thesis)

Advisors: L. Salinas(UdeC), J. Demongeot (UG) and J. Aracena (UdeC).

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Summary

1 Definition and Notation

2 Limit Cycle Existence problem

3 Limit Cycle Non Existence problem

4 Feasible Limit Cycle problem
A Boolean network is $N = (F, s)$, where

- $F = (f_v)_{v \in V} : \{0, 1\}^n \rightarrow \{0, 1\}^n$, global transition function,
- $V$ a set of $n$ elements.
- $f_v(x) := F(x)_v$, $\forall v \in V$, local activation functions.
- $s : V \rightarrow \{1, \ldots, n\}$ a deterministic update schedule (parallel, sequential, block-sequential).
Definition and Notation

Limit Cycle Existence problem
Limit Cycle Non Existence problem
Feasible Limit Cycle problem

Interaction Digraph

$G^F = (V, A)$ interaction digraph associated to a Boolean Network.

$(u, v) \in A$ if and only if $f_v$ depends on $x_u$. 

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Limit cycles and update schedules in Boolean networks
Interaction Digraph

$G^F = (V, A)$ interaction digraph associated to a Boolean Network.

$(u, v) \in A$ if an only if $f_v$ depends on $x_u$. 
Example 1

- $F: \{0, 1\}^4 \rightarrow \{0, 1\}^4$
- $f_1(x) := x_3 \land x_4$
- $f_2(x) := x_1 \land x_3$
- $f_3(x) := (x_1 \land x_2) \lor \overline{x}_4$
- $f_4(x) := \overline{x}_2$
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Update Schedule

\[ s: V \to \{1, \ldots, n\}, \text{ function.} \]
Definition and Notation

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Update Schedule

\[ s : V \rightarrow \{1, \ldots, n\}, \text{ function.} \]

\[ s(V) = \{1\}, \text{ parallel.} \]
Definition and Notation

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Update Schedule

$s: V \rightarrow \{1, \ldots, n\}, \text{ function.}$

$s(V) = \{1\}, \text{ parallel.}$

$s(V) = \{1, \ldots, n\}, \text{ sequential.}$
Update Schedule

\(s: V \rightarrow \{1, \ldots, n\}, \text{ function.}\)

\(s(V) = \{1\}, \text{ parallel.}\)

\(s(V) = \{1, \ldots, n\}, \text{ sequential.}\)

\(s(V) = \{1, \ldots, m\}, 1 < m < n, \text{ block-sequential.}\)
Given $x = (x_v)_{v \in V} \in \{0, 1\}^n$, the $(k + 1)$-iteration of $x$ by $F$ according to $s$ is given by:

$$x^{k+1}_v = f_v(x^{l_u}_u : u \in V)$$

Where:

$$l_u = \begin{cases} 
  k & \text{if } s(v) \leq s(u) \\
  k + 1 & \text{if } s(v) > s(u)
\end{cases}$$
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Limit cycles and update schedules in Boolean networks
Dynamical Behavior

- We can define $f_v^s(x) = f_v(g_v^s(u)(x): u \in V)$

  Where:

  $$g_{v,u}^s(x) = \begin{cases} 
  x_u & \text{if } s(v) \leq s(u) \\
  f_u^s(x) & \text{if } s(v) > s(u)
  \end{cases}$$

- $F^s$ is the dynamical behavior of $N = (F, s)$. 
Dynamical Behavior

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- $F^s$ is the dynamical behavior of $N = (F, s)$. 
Dynamical Behavior

- We can define $f_v^s(x) = f_v(g_{v,u}^s(x); u \in V)$
- Where:

  $g_{v,u}^s(x) = \begin{cases} 
  x_u & \text{if } s(v) \leq s(u) \\
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  \end{cases}$

- $F^s$ is the dynamical behavior of $N = (F, s)$. 
Limit Behavior

Fixed point: \( x \in \{0, 1\}^n : F^s(x) = x \)

Limit Cycles: \( C = \left[ x^k \right]_{k=0}^{p} , x^k \in \{0, 1\}^n, p > 1 : \)

\[ x^{k+1} = F^s(x^k) \land x^p \equiv x^0 \]

\( LC(N) : \) set of limit cycles of \( N. \)
Definition and Notation

**Limit Cycle Existence problem**

**Limit Cycle Non Existance problem**

**Feasible Limit Cycle problem**

**Limit Behavior**

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Definition and Notation

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Limit Behavior

Fixed point: \( x \in \{0, 1\}^n : F^s(x) = x \)

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\[
    x^{k+1} = F^s(x^k) \quad \wedge \quad x^p \equiv x^0
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\( LC(N) \): set of limit cycles of \( N \).
Given a Boolean network \((F, s)\), we define the associated labeled digraph \(G^F_s = (G^F, \text{lab}_s)\), called update digraph, where \(\text{lab}_s : A(G^F) \to \{\ominus, \oplus\}\) is defined as:

\[
\text{lab}_s(u, v) = \begin{cases} 
\oplus & \text{if } s(u) \geq s(v) \\
\ominus & \text{if } s(u) < s(v)
\end{cases}
\]

Example:

\[
\begin{array}{c}
1 \\
2 \\
3 \\
4
\end{array}
\]

\[
s(i) = i, \quad \forall i \in \{1, \ldots, n\}.
\]

It was proven in (Aracena, J., Goles, E., Moreira, A., Salinas, L., 2009. Biosystems 97, 1-8) that if two different update schedules have the same update digraph, then they also have the same dynamical behavior.
Given a Boolean network \((F, s)\), we define the associated labeled digraph \(G_s^F = (G^F, \text{lab}_s)\), called *update digraph*, where \(\text{lab}_s : A(G^F) \rightarrow \{\ominus, ⊕\}\) is defined as:

\[
\text{lab}_s(u, v) = \begin{cases} 
⊕ & \text{if } s(u) \geq s(v) \\
\ominus & \text{if } s(u) < s(v)
\end{cases}
\]

Example: \[
\begin{array}{cccc}
2 & \rightarrow & 1 & \leftarrow & 3 \\
| & ⊕ & | & ⊕ & \ominus \\
\ominus & | & ⊕ & & \\
1 & \leftarrow & 4 & \rightarrow & 2
\end{array}
\]

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Summary

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2. Limit Cycle Existence problem
3. Limit Cycle Non Existence problem
4. Feasible Limit Cycle problem
Inverse problems of update schedules

General problem

Given $F = (f_v)_{v \in V} : \{0, 1\}^n \rightarrow \{0, 1\}^n$. Does there exists an update schedule $s$ such that $(F, s)$ has a given dynamical property?

Particular cases:

- Limit Cycle Existence problem (LCE)
- Limit Cycle Non Existence problem (LCNE)
- Feasible Limit Cycle (FLC)
Inverse problems of update schedules

General problem

Given $F = (f_v)_{v \in V} : \{0, 1\}^n \rightarrow \{0, 1\}^n$. Does there exists an update schedule $s$ such that $(F, s)$ has a given dynamical property?

Particular cases:

- Limit Cycle Existence problem (LCE)
- Limit Cycle Non Existence problem (LCNE)
- Feasible Limit Cycle (FLC)
Limit Cycle Existence problem (LCE)

Given $F = (f_v)_{v \in V} : \{0, 1\}^n \to \{0, 1\}^n$. Does there exists an update schedule $s$ such that $LC(F, s) \neq \emptyset$?

Previous works: The specific problem of determining the existence of limit cycles of a Boolean network with parallel update is known to be NP-Hard (Just, W., 2006. The steady state system problem is NP-Hard even for monotone quadratic Boolean dynamical systems. pre-print).
Limit Cycle Existence problem (LCE)

Given $F = (f_v)_{v \in V} : \{0, 1\}^n \rightarrow \{0, 1\}^n$. Does there exists an update schedule $s$ such that $LC(F, s) \neq \emptyset$?

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Theorem

**AND-OR LCE** is NP-hard.

Proof (idea): SAT \(\leq_p\) AND-OR LCE.
Definition and Notation

Limit Cycle Existence problem
Limit Cycle Non Existence problem
Feasible Limit Cycle problem

Limit Cycle Existence problem

Theorem

**AND-OR LCE** is NP-hard.

Proof (idea): \( \text{SAT} \leq_p \text{AND-OR LCE} \).
Remark: AND-OR LCE is NP-Hard even in the following cases:

I.- Restricted to the parallel update schedule. (In this case we remove the vertex $z_3$ and we add an arc from $z_1$ to $z_2$.)

II.- Restricted to sequential update schedules.

III.- Restricted to limit cycles of length 2.

IV.- Restricted to maximum in-degree equal to 2.
Theorem

**SYMmetric LCE is NP-Hard.**

Proof: The proof is similar with the following local activation functions: $\forall i \in \{1, \ldots, n\}$,

\[
\begin{align*}
    f_{v_i}(x) &= x_{v_i} \land x_{v_\phi} \\
    f_{v_\phi}(x) &= \phi(x_{v_i}) \land (x_{z_1} \lor x_{z_2}) \\
    f_{z_1}(x) &= x_{v_\phi} \land x_{z_2} \\
    f_{z_2}(x) &= x_{v_\phi} \land x_{z_1}
\end{align*}
\]
Limit Cycle Existence problem

Theorem

SYMMETRIC LCE is NP-Hard.

Proof: The proof is similar with the following local activation functions: \( \forall i \in \{1, \ldots, n\}, \)

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    f_{z_1}(x) &= x_{v\phi} \land x_{z_2} \\
    f_{z_2}(x) &= x_{v\phi} \land x_{z_1}
\end{align*}
\]
Limit cycles in symmetric AND-OR networks

**Defn:** Given $F$ an AND-OR function with symmetric $G^F$.

- Let $G_1^{\text{OR}}, \ldots, G_k^{\text{OR}}$ be the non trivial connected components of $G[V_{\text{OR}}(F)]$.
- Let $G_1^{\text{AND}}, \ldots, G_k^{\text{AND}}$ be the non trivial connected components of $G[V_{\text{AND}}(F)]$.
- We define the alternated nodes as

$$V_{\text{AO}} = V \setminus \left( \bigcup_{i=1}^{k_{\text{OR}}} V(G_i^{\text{OR}}) \cup \bigcup_{i=1}^{k_{\text{AND}}} V(G_i^{\text{AND}}) \right)$$

and we denote by $G_1^{\text{AO}}, \ldots, G_k^{\text{AO}}$, to the connected component of $G[V_{\text{AO}}]$.

- $\{ G_1^{\text{OR}}, \ldots, G_k^{\text{OR}}, G_1^{\text{AND}}, \ldots, G_k^{\text{AND}}, G_1^{\text{AO}}, \ldots, G_k^{\text{AO}} \}$ is an AOA (AND-OR ALTERNATED) decomposition of $G^F$. 
Limit Cycles in AND-OR symmetric networks

**Theorem**

Given $F$ an AND-OR function with symmetric $G^F$. There exists an update schedule $s$ such that, $LC(F, s) \neq \emptyset$ if and only if there exists a bipartite element (without loops) in the AOA decomposition of $G^F$.

**Corollary**

SYMMETRIC AND-OR LCE is polynomial.

Remark: In AND-OR networks with symmetric $G^F$ with block-sequential update there are limit cycles of length super-polynomial.
Limit Cycles in AND-OR symmetric networks

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Limit Cycle Non Existence problem (LCNE)

Given $F = (f_v)_{v \in V} : \{0, 1\}^n \rightarrow \{0, 1\}^n$. Does there exists an update schedule $s$ such that: $LC (F, s) = \emptyset$?

Previous works:


Definition and Notation

Limit Cycle Non Existence problem

Given $F = (f_v)_{v \in V} : \{0, 1\}^n \rightarrow \{0, 1\}^n$. Does there exists an update schedule $s$ such that: $LC(F, s) = \emptyset$?

Previous works:


Limit Cycle Non Existence problem

Theorem

LCNE is NP-Hard.

Proof (idea):
Theorem

LCNE is NP-Hard.

Proof (idea):

[Diagram of a network with nodes 1, 2, 3, ..., v_n, showing connections between nodes.]
Theorem

Let $F$ be an OR (AND) function. Then, there exists a sequential update schedule $s$ such that $N = (F, s)$ has only have fixed points as attractors.

Proof: Let $V'$ be a minimum FVS of the cycles of $G^F = (V, A)$ and let consider $N = (F, s)$, with $s = s_{V'}$, defined by:

$$s_{V'}(u, v) = \begin{cases} \oplus & \text{if } (u, v) \in A_{V'} \\ \ominus & \text{otherwise} \end{cases}$$

where $A_{V'}$ is a minimal FAS from $N^+(V')$. 

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Remark: The previous Theorem is not valid in the case of AND-OR networks as shown in the following example:

\[
\begin{align*}
  f_1(x) &= x_6 \lor x_9 \lor x_{11} \\
  f_2(x) &= x_6 \lor x_7 \lor x_{12} \\
  f_3(x) &= x_6 \lor x_8 \lor x_{10} \\
  f_4(x) &= x_4 \\
  f_5(x) &= x_5 \\
  f_6(x) &= x_4 \land x_5 \\
  f_7(x) &= x_1 \land x_4 \\
  f_8(x) &= x_2 \land x_4 \\
  f_9(x) &= x_3 \land x_4 \\
  f_{10}(x) &= x_1 \land x_5 \\
  f_{11}(x) &= x_2 \land x_5 \\
  f_{12}(x) &= x_3 \land x_5
\end{align*}
\]
Summary

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Feasible Limit Cycle problem (FLC)

Given a set $V$ of $n$ elements and $F = (f_v)_{v \in V} : \{0, 1\}^n \to \{0, 1\}^n$ and a sequence $C = [x^k]_{k=0}^p$ such that $x^k \in \{0, 1\}^n$, $x^k$ are pairwise distinct and $x^p \equiv x^0$. Does there exist an update schedule $s$ such that $C \in LC(F, s)$?
Definition and Notation
Limit Cycle Existence problem
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Feasible Limit Cycle problem

Feasible Limit Cycle problem

Theorem

OR FLC is NP-Complete.

Proof (idea):

\[
\begin{align*}
C_0^0 & \rightarrow C_0^1 \\
C_1^0 & \rightarrow C_1^1 \\
C_2^0 & \rightarrow C_2^1 \\
C_3^0 & \rightarrow C_3^1 \\
& \vdots \\
C_0^2 & \rightarrow C_2^2 \\
\end{align*}
\]
### Feasible Limit Cycle problem

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$\phi(w) = (w_1 \lor w_2 \lor \neg w_3 \lor w_4) \land (\neg w_2 \lor w_3 \lor \neg w_4) \land (\neg w_1 \lor \neg w_3)$. 
Theorem

FLC is polynomial in the following cases:

- OR Symmetric
- OR and cycle of length two.
- AND-OR and cycle of length two.
Merci