Isometries of the hypercube: a tool for Boolean regulatory networks analysis

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July 2021

WAN - CIRM
Workshop on Automatas Networks

Introduction

Team MABioS

Biological and medical motivation: to develop tools for the analysis of regulatory networks controlling the cellular processes

- ↪ To get a better understanding of these processes
- ↪ To understand and predict the impact of given perturbations, such as disease-induced perturbations

Necessity of in-depth understanding of mathematical objects we use: Finite Dynamical Systems

Outline

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Isometries of the hypercube

Geometrical point of view:

↪ Hypercube embedded in n dimensional euclidian space $\mathbb{R}^n$

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Isometries of $\mathcal{H}_n = [0,1]^n \subset \mathbb{R}^n$

Form a group $\Gamma(\mathcal{H}_n)$ whose elements are composed of

- $\hookrightarrow$ a permutation of axes
- $\hookrightarrow$ hyperplane symmetries exchanging parallel hyperfaces

From geometrical to symbolic point of view

Isometries of $\mathcal{H}_n = [0,1]^n$ are isometries of $\{0,1\}^n$

Given $f \in \Gamma(\mathcal{H}_n)$ and $x = (x_1, \ldots, x_n) \in \{0,1\}^n$,

$f(x) = (x_{\sigma^{-1}(1)}^{\varepsilon_1}, \ldots, x_{\sigma^{-1}(n)}^{\varepsilon_n})$ (where $a^{-1} = 1 - a$, for $a \in \{0,1\}$)

$\hookrightarrow$ σ codes for the permutation of axes

$\hookrightarrow$ $(\varepsilon_1, \ldots, \varepsilon_n) \in \{-1,+1\}^n$ codes for the hyperplane symmetries

Outline

Boolean FDS

Boolean FDS: a map $S : X = \{0,1\}^n \to X$

n underlying components g_1, ... , g_n

$\hookrightarrow$ "processors"

$\hookrightarrow$ "genes"

Associated dynamics

$S : X = \{0,1\}^n \to X$

States: elements $x = (x_1, \ldots, x_n)$ of X

- Synchronous dynamics: iteration of S
  x has one successor $S(x)$ (deterministic)
- (Fully) asynchronous dynamics
  one coordinate changes at a time (underlying delays, non-deterministic)

State Transition Graphs (STG)

STG give successors of the states

- Synchronous STG
  vertices = states x, edges give the successor $S(x)$
- Asynchronous STG
  vertices = states x, edges give $Upd(x)$ successors

$$S(000) = 110$$

$$000 \longrightarrow 110$$

In the synchronous STG

$$\overset{++}{000} \rightarrow 010$$
$$\overset{++}{000} \rightarrow 100$$

In the asynchronous STG

Regulatory Graph associated to S

g_1, g_2, ... , g_n are regulated through the dynamics:
at state x, coordinate x_k = level of g_k

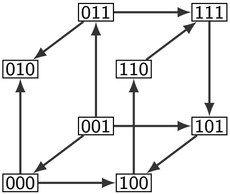
Given $x = (x_1, \ldots, x_n)$ and $S(x) = (y_1, \ldots, y_n)$

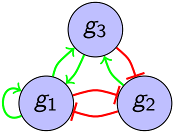
- ↪ if switching x_i implies that y_j switches in the same sense, g_i activates g_j (locally)
- ↪ if switching x_i implies that y_j switches in the other sense, g_i inhibites g_j (locally)

Regulatory Graph $\mathcal{RG}(S)$:
Obtained by superimposing local Regulatory Graphs
Signs of interactions may be undetermined

Example: S, asynchronous STG, Regulatory Graph (RG)

x	$S(x)$
$\overset{+}{0}\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ \overset{+}{0}\ \overset{-}{1}$	1 1 0
0 1 0	0 1 0
$1\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ 1\ \overset{-}{1}$	1 1 0
$1\ 0\ \overset{-}{1}$	1 0 0
$1\ 1\ \overset{+}{0}$	1 1 1
$1\ \overset{-}{1}\ 1$	1 0 1





↪ Same information in S and in the asynchronous STG

↪ Information lost in the Regulatory Graph

Logical formalism

Logical formulas

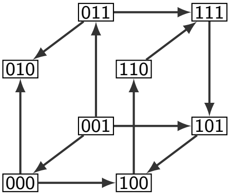
Give necessary and sufficient conditions for the level of g_i to become equal to 1 under S

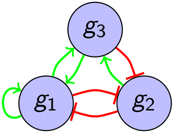
$\hookrightarrow$ In a disjunctive normal form

$\hookrightarrow$ Involving only regulators

Example: S, asynchronous STG, RG, logical formulas

x	$S(x)$
$\overset{+}{0}\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ \overset{+}{0}\ \overset{-}{1}$	1 1 0
0 1 0	0 1 0
$1\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ 1\ \overset{-}{1}$	1 1 0
$1\ 0\ \overset{-}{1}$	1 0 0
$1\ 1\ \overset{+}{0}$	1 1 1
$1\ \overset{-}{1}\ 1$	1 0 1





- $\hookrightarrow$ $S(x)_1 = 1$ *iff* $(x_1 = 1) \vee (x_2 = 0) \vee (x_3 = 1)$
- $\hookrightarrow$ $S(x)_2 = 1$ *iff* $(x_1 = 0) \vee (x_3 = 0)$
- $\hookrightarrow$ $S(x)_3 = 1$ *iff* $(x_2 = 1) \wedge (x_2 = 1)$

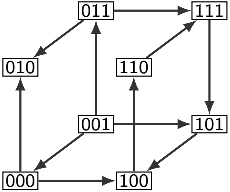
Outline

Problematic

Main problematic:
determination of the attractors of the asynchronous STG

Attractors: terminal strongly connected components of the STG

- Stable states: attractors reduced to a single state
- Complex attractors: attractors with at least 2 states



Runways

Difficulty: combinatorial explosion of STG

Some runways:

- To reduce the number of components
- To find links between the dynamics and the Regulatory Graph (Thomas's rules)
- To focus on circuits (an acyclic RG implies a degenerated dynamics - F.Roberts)
- To analyze the functionality of circuits (isolated: positive 2 stable states, negative one complex attractor)
- To focus on more complex motifs and their functionality
- To use probabilistic methods (Monte Carlo)
- Other classical mathematical approaches: to transform, to classify

Runways

Difficulty: combinatorial explosion of STG

Some runways:

- To reduce the number of components
- To find links between the dynamics and the Regulatory Graph (Thomas's rules)
- To focus on circuits
  (no circuit implies degenerated dynamics - F.Roberts)
- To analyze the functionality of circuits
  (isolated: positive 2 stable states, negative one complex attractor)
- To focus on more complex motifs and their functionality
- To use probabilistic methods (Monte Carlo)
- Other classical mathematical approaches:
  to transform, to classify

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Action of the group $\Gamma(\mathcal{H}_n)$ of isometries of the hypercube on asynchronous STG

A natural idea:

Asynchronous STG are embedded in the hypercube

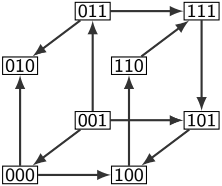
- Isometric STG introduced by dynamicist Leon Glass
- Recent works of Franck Delaplace, Elisa Tonello

Particular interest on the combinatorial tools of group action theory (Burnside formula for counting of "configurations")

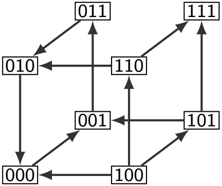
Jean Fabre-Monplaisir, Brigitte Mossé, and Elisabeth Remy. Isometries of the hypercube: a tool for boolean regulatory networks analysis. Physica D: Nonlinear Phenomena, 2021 (in press).

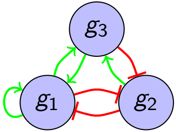
Action of the group $\Gamma(\mathcal{H}_n)$ on Boolean FDS giving "isometric" dynamics

S Boolean FDS, f isometry of the hypercube

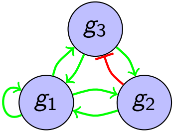


S becomes $f \circ S \circ f^{-1}$





Same topology, signs of circuits



For instance the central symmetry switches *vee* and *wedge* in all formulas

Some remarks

- Isometric is more than isomorphic (in the sense of graph theory).

- Two Boolean FDS such that their asynchronous graphs involve all the edges of $\mathcal{H}_n$ are isometric iff they are isomorphic.

Idea of rigidity...

Outline

To transform and to classify

Main ideas:

$\hookrightarrow$ To define classes gathering all isometric Boolean FDS

$\hookrightarrow$ To choose in each class a representative - the most appropriate

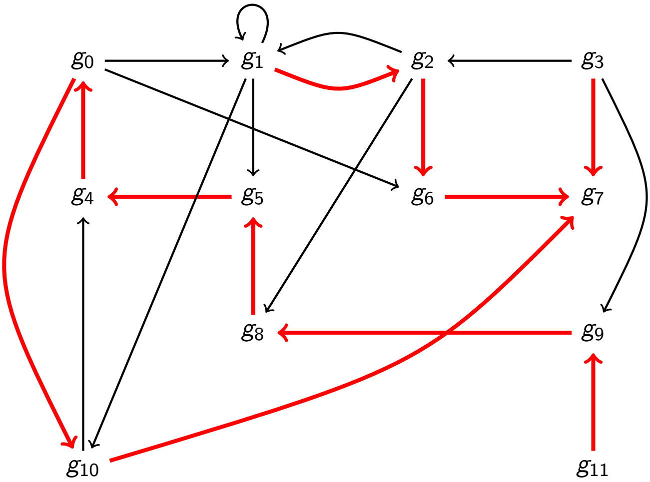
$\hookrightarrow$ To prioritise activations in this representative for mathematical questions

Major benefit of activations: rewriting

Typically, in the case of a positive circuit with only activations, S is simply the shift $S(x_1, \ldots, x_n) = (x_n, x_1, \ldots, x_{n-1})$

A key tool for the choice of representative

A way of identifying subgraphs of a RG, on which it is possible to choose the signs of the interactions after the action of some isometry



The red subgraph is "tree-supported"

Outline

About Robert's theorem on acyclic RG

Robert's theorem

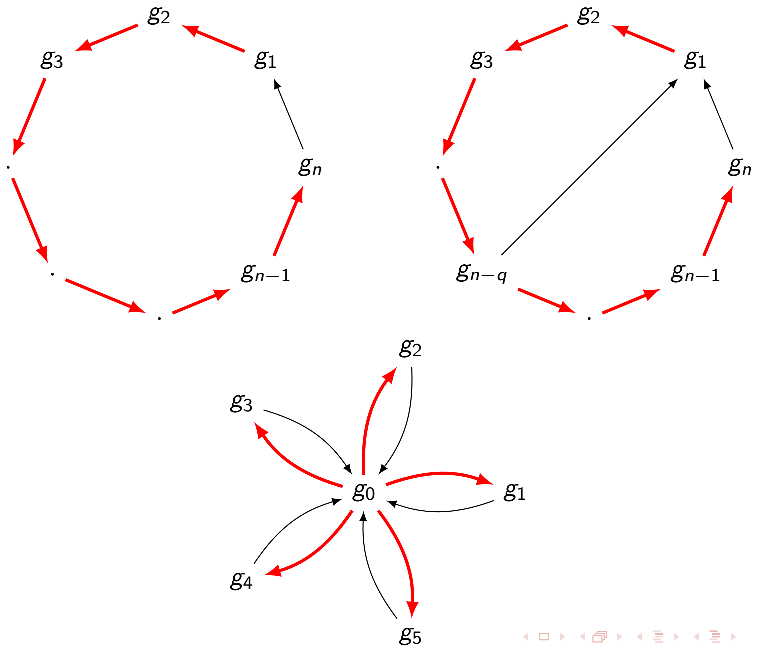
If $\mathcal{RG}(S)$ is acyclic and admits r genes without regulator g_1, ..., g_r, then for each input the lonely related attractor in the asynchronous STG is a stable state.

Robert's proof via isometries

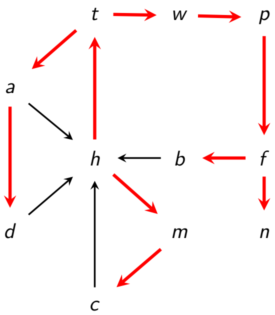
- Consider an isometry f reduced to a permutation σ of axes producing a topological sorting of the RG.
- Under f, the adjacency matrix $\mathcal{M}(S)$ of the RG is conjugated in $P_\sigma \mathcal{M}(S) P_\sigma^t =$ a nilpotent upper triangular matrix.
  Consequence: $\mathcal{M}(S)$ is nilpotent.
- A basic inequality gives the proof: for x and y with same input

$$d(S^n(x), S^n(y)) \leq [\mathcal{M}(S)^t]^n \, d(x,y) = (0, \ldots, 0)^t$$

Special motifs: circuits, chorded circuits, flower-graphs



Special motifs: Hub-graphs



Three types

1 stable state, 2 stable states, 1 cyclic attractor

Interpretation of the types

in terms of concurrences /cooperations of regulators of the hub

The negative Thomas's rule

New proof of this rule: "Given $S : X \to X$ a boolean FDS such that the asynchronous dynamics of S displays a cyclic attractor, then the Regulatory Graph of S contains a negative circuit."

Sketch of proof (by contraposition)

- Let $S : X \to X$ be a Boolean FDS such that all the interactions of $\mathcal{RG}(S)$ are activations (colaborative FDS). Then for any state x, there exists a stable state y such that $x \rightsquigarrow y$ in $\mathcal{G}_a(S)$.

- Cooperative system -

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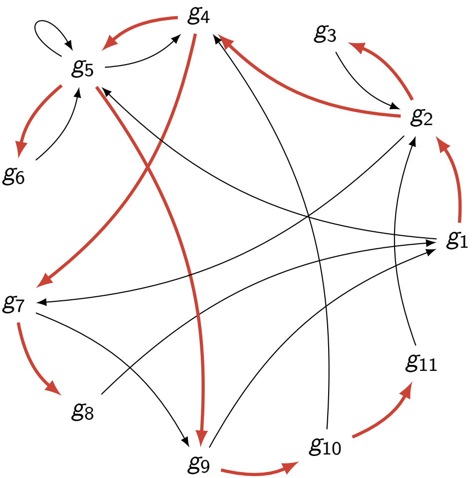
- Let $S : X \to X$ be a Boolean FDS whose regulatory graph $\mathcal{RG}(S)$ is strongly connected, all the signs of the interactions are determined, and all the circuits are positive. There exists an isometry $f \in \Gamma(\mathcal{H}_n)$ such that all the interactions of $\mathcal{RG}(S)$ become activations under the conjugation by f.

- Key tool -



g_1
g_2
g_3
g_4
g_5
g_6
g_7
g_8
g_9
g_{10}
g_{11}

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- A topological sorting of the graph of the strongly connected components of $\mathcal{RG}(S)$ gives the conclusion.

Thanks for your attention !

Acknowledgements

INSTITUT de MATHÉMATIQUES de MARSEILLE

MABioS

- C. Chaouiya
- B. Mossé
- É. Remy
- L. Tichit
- L. Pio-Lopez
- S. Chapman
- M. Lucas
- D. Courtine
- L. Hérault
- S. Pankaew
- E. Novoa

ENS ÉCOLE NORMALE SUPÉRIEURE

- J. Fabre-Monplaisir

IBENS

- D. Thieffry

Marseille Medical Genetics

- A. Baudot
- O. Ozisik
- M. Térézol
- J. Lambert