Network Structure and Activity in Boolean Networks

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with

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Boolean Networks (BN)

- A Boolean Network (BN) is a map of the form

$$F = (f_1, \ldots, f_n)\colon \{0,1\}^n \longrightarrow \{0,1\}^n .$$

- There are several types of stability concepts for dynamical systems. Examples:
  - Stability with respect to initial conditions
  - Attractor stability
  - Structural stability

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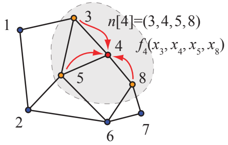
- There are several types of stability concepts for dynamical systems. Examples:
  - Stability with respect to initial conditions
  - Attractor stability
  - Structural stability
- Here: Stability with respect to initial condictions. Specifically:

What is the probability that $F(x)$ and $F(x + e_i)$ are different?

Background, Terminology and Definitions – I

- Associated to F we have the *dependency graph of variables* denoted by X_F. It has *vertex set* $\{1, 2, \ldots, n\}$ and *edges* all (i, j) for which f_j depend non-trivially on x_j.
- We let X denote the undirected version of X_F where loops are omitted.
- More definitions:
  - Ordered 1-neighborhood: $n[i]$
  - System state: $x = (x_1, \ldots, x_n)$
  - Restricted vertex state: $x[i]$



Background, Terminology and Definitions – II

- Define the function $\alpha_{F,i}\colon K^n \longrightarrow \{0,1\}$ by

$$\alpha_{F,i}(x) = \mathbb{I}[F(x+e_i) \neq F(x)]$$

where $\mathbb{I}$ is the indicator function and e_i is the i^{th} unit vector.

Definition

The *activity of F with respect to vertex i* is the expectation value of $\alpha_{F,i}$ using the uniform measure on K^n:

$$\bar{\alpha}_{F,i} = \mathbb{E}[\alpha_{F,i}]\ .$$

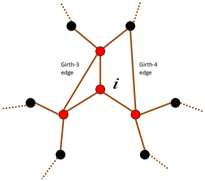
The *activity of F* is the vector

$$\bar{\alpha}_F = (\bar{\alpha}_{F,1}, \bar{\alpha}_{F,2}, \ldots, \bar{\alpha}_{F,n})\ .$$

Comments and Definitions

- Interpretation: For a randomly chosen state $x \in K^n$, the value $\bar{\alpha}_{F,i}$ may be regarded as the probability that perturbing x_i will cause $F(x+e_i) \neq F(x)$ to hold. This activity notion may naturally be regarded as a measure of sensitivity with respect to initial conditions.

  The subgraph $X(i;2)$ of X is induced by vertex i and its distance ≤ 2 neighbors.



- Vertices belonging to the closed 1-neighborhood $n[i]$ of i are marked red. *Type-3 edges* (relative to i) connect neighbors of i, while *type-4* edges connect neighbors of $j \in n'[i]$ through a common neighbor different from i.

- Observation: $\bar{\alpha}_{F_i}(x)$ depends on the vertex states $X(i;2)$ and the vertex functions f_j with $j \in n[i]$ (the set of vertices in the 1-neighborhood of i).

Related Work

- Shmulevich and Kauffman (2003) introduced a notion of activity for regular, random Boolean networks with a common vertex function f (see [3]). Here:

$$\alpha_{f,i} := \mathbb{E}[\frac{\partial f}{\partial x_i}]$$

- May be a reasonable measure for activity for the class of dynamical systems that they studied. However: does not incorporate the impact of network structure.

- Layne et. al. (2012) used the above definition to compute activity for canalyzing functions [2].

- The activity notion introduced here incorporates network structure.

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- Layne et. al. (2012) used the above definition to compute activity for canalyzing functions [2].
- The activity notion introduced here incorporates network structure.
- Why study activity? What are potential uses?

Preliminary Results

- We set $K = \{0,1\}$, write N_i for the size of $X(i;2)$, and $K(i) = K^{N_i}$ for the projection of K^n onto the set of vertex states associated to $X(i;2)$.
- For $j \in n[i]$, define the sets $A_j(i) \subset K(i)$ and $A_j^0, A_j^1 \subset A_j(i)$ by

$$A_j(i) = \{x \in K(i) \mid F(x+e_i)_j \neq F(x)_j\} \quad \text{and} \quad A_j^m(i) = \{x \in A_j(i) \mid x_i = m\}\ , m = 0, 1\ .$$

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Proposition

For any Boolean network we have

$$\mathbb{P}\Big(\bigcup_{j\in n[i]} A_j \mid x_i = 0\Big) = \mathbb{P}\Big(\bigcup_{j\in n[i]} A_j \mid x_i = 1\Big)\ .$$

Proof.

This follows by observing that there is a bijection $\phi_j \colon A_j^0 \longrightarrow A_j^1$ since $x \in A_j^0$ if and only if $x + e_i \in A_j^1$ for all $j \in n[i]$.

Proposition

Let X be a graph and F a Boolean network map over X. The activity of F with respect to vertex i is

$$\bar{\alpha}_{F,i} = \mathbb{P}\Big(\bigcup_{j \in n[i]} A_j \mid x_i = 0 \Big) = \mathbb{P}\Big(\bigcup_{j \in n[i]} \bar{A}_j \Big) .$$

(Here $\bar{A}_j := A_j^0$)

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Proof.

$$\bar{\alpha}_{F,i} = \mathbb{E}[\alpha_{F,i}] = \sum_{x \in K^n} \alpha_{F,i}(x)\mathbb{P}(x) = \sum_{x \in K(i)} \alpha_{F,i}(x)\mathbb{P}(x) = \mathbb{P}\Big[\bigcup_{j \in n[i]} A_j \Big]$$

$$= \sum_{m=0,1} \mathbb{P}\Big[\bigcup_{j \in n[i]} A_j \mid x_i = m \Big] \mathbb{P}(x_i = m) = \mathbb{P}\Big[\bigcup_{j \in n[i]} A_j \mid x_i = 0 \Big] = \mathbb{P}\Big[\bigcup_{j \in n[i]} \bar{A}_j \Big] \ .$$

(Here $\bar{A}_j := A_j^0$)

Examples

Recall that the standard Boolean *threshold function* $\tau_{k,n}\colon K^n \longrightarrow K$ is defined by

$$\tau_{k,n}(x_1,\ldots,x_n) = \begin{cases} 1, & \text{if } \sum_{j=1}^{n} x_j \geq k, \\ 0, & \text{otherwise,} \end{cases}$$

and that the logical nor-function $\mathrm{nor}_m\colon K^m \longrightarrow K$ is defined by

$$\mathrm{nor}_m(x_1,\ldots,x_m) = (1+x_1)\cdot\cdots\cdot(1+x_m)\ ,$$

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Proposition

If F is the BN map induced by the nor*-function over K_n, then*

$$\bar{\alpha}_{F,i} = \frac{1}{2^{n-1}},$$

and if F is induced by the k-threshold function over K_n, then

$$\bar{\alpha}_{F,i} = \binom{n-1}{k-1}\Big/ 2^{n-1}\ .$$

Proof.

For either choice of function, we have $\bar{A}_j = \bar{A}_k$ for all $j, k \in n[i]$.

For threshold functions, and for a state x with $x_i = 0$ to satisfy $\tau_k(x) \neq \tau_k(x + e_i)$, it is necessary and sufficient that x belong to Hamming class $k - 1$.

Since $x_i = 0$, it follows from Proposition 2 that $\mathbb{P}(\bar{A}_j(i)) = \frac{1}{2^{n-1}}|A_j| = \binom{n-1}{k-1}/2^{n-1}$ as stated.

In the case of nor-functions we have $F\left(x + e_i\right)_i \neq F\left(x\right)_i$ precisely when $x_j = 0$ for all $j \in n(i)$ leading to $\mathbb{P}\left(\bar{A}_i\right) = \frac{1}{2^{n-1}}$.

Elementary Cellular Automata

Proposition (Threshold ECA)

The activity of k-threshold ECA for $n \geq 5$ is

$$\bar{\alpha}_{F,i} = \begin{cases} 0, & \text{if } k = 0 \text{ or } k > 3\,, \\ 1/2, & \text{if } k = 1 \text{ or } k = 3\,, \\ 7/8, & \text{if } k = 2\,. \end{cases}$$

For $n = 4$ and $k = 2$, the activity is $3/4$.

Proof (case $k = 1$).

We have

$$\bar{A}_{i-1} = \{(0,0,0,x_{i+1},x_{i+2})\}, \quad \bar{A}_i = \{(x_{i-2},0,0,0,x_{i+2})\}, \text{ and } \bar{A}_{i+1} = \{(x_{i-1},x_{i-1},0,0,0)\} .$$

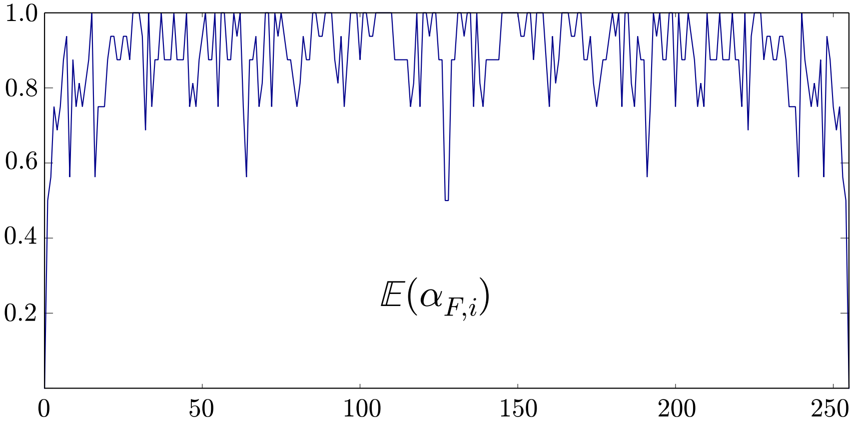
By the inclusion-exclusion principle:

$$\begin{aligned} |\bar{A}_{i-1} \cup \bar{A}_i \cup \bar{A}_{i+1}| &= |\bar{A}_{i-1}| + |\bar{A}_i| + |\bar{A}_{i+1}| \\ &\quad - |\bar{A}_{i-1} \cap \bar{A}_i| - |\bar{A}_{i-1} \cap \bar{A}_{i+1}| - |\bar{A}_i \cap \bar{A}_{i+1}| + |\bar{A}_{i-1} \cap \bar{A}_i \cap \bar{A}_{i+1}| \\ &= 3 \times 4 - 2 - 1 - 2 + 1 = 8 \end{aligned}$$

This yields $\bar{\alpha}_{F,i} = 8/2^4 = 1/2$.

We remark that if we instead use the nor-function, then $\bar{\alpha}_{F,i} = 1/2$ when $n \geq 5$.

Activity of Elementary Cellular Automata



More Elaborate Cases

- The evaluation of activity is more involved with dependencies/overlap among the A_j's (except for at vertex i – of course).
- Will cover two cases here:
  - d-regular trees with threshold and nor-functions
  - Square lattices with nor-functions
- Additional cases covered in the conference paper.

d-regular trees

Proposition

Let X be a d-regular graph of girth ≥ 5 and F the GDS map over X induced by the nor*-function. Then the activity of F with respect to i is given by*

$$\bar{\alpha}_{F,i} = 1 - \left(1 - \frac{1}{2^d}\right)^d + \left(\frac{1}{2} - \frac{1}{2^d}\right)^d \ . \quad (1)$$

Note: let B denote the union of A_j's with $j \neq i$. Then:

$$\mathbb{P}\left[\bigcup_{j \in n[i]} A_j\right] = \mathbb{P}(A_i \cup B) = \mathbb{P}(B) + \mathbb{P}(A_i \cap B^c) = 1 - \mathbb{P}(B^c) + \mathbb{P}(A_i \cap B^c) \ ,$$

where B^c denotes the complement of B.

Proof.

Conditioning on $x_i = 0$ and using independence we have

$$\mathbb{P}\left(\bar{B}^c\right) = \mathbb{P}\left(\bigcap_{j \in n(i)} \bar{A}_j^c\right) = \prod_{j \in n(i)} \mathbb{P}\left(\bar{A}_j\right) \ .$$

For a state x with $x_i = 0$ to be in $\bar{A}_j$ all remaining d states of $\bar{A}_j$ must be zero, leading to $\mathbb{P}\left(\bar{A}_j^c\right) = 1 - \frac{1}{2^d}$ and

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In order to calculate $\mathbb{P}\left(A_i \cap B^c\right)$ we note that $\mathbb{P}\left(A_i \cap B^c\right) = \mathbb{P}\left(A_i\right)\mathbb{P}\left(B^c|A_i\right)$ and again use independence to obtain

$$\mathbb{P}\left(\bar{B}^c|\bar{A}_i\right) = \prod_{j\in n(i)} \mathbb{P}\left(\bar{A}_j^c|\bar{A}_i\right) \ .$$

Note that $\mathbb{P}\left(\bar{A}_j|\bar{A}_i\right) = 1/2^{d-1}$ so that $\mathbb{P}\left(\bar{A}_j^c|\bar{A}_i\right) = 1 - \mathbb{P}\left(\bar{A}_j|\bar{A}_i\right) = 1 - 1/2^{d-1}$ which substituted back in gives

$$\mathbb{P}\left(\bar{B}^c|\bar{A}_i\right) = \left(1 - \frac{1}{2^{d-1}}\right)^d \ .$$

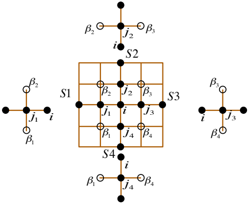
Noting that $\mathbb{P}(\bar{A}_i) = 1/2^d$ we obtain the third term in the proposition statement, finishing the proof

Proposition

If F is the GDS map with k-threshold vertex functions over a d-regular graph of girth ≥ 5, then the activity of F with respect to vertex i is

$$\bar{\alpha}_{F,i} = 1 - \left[\frac{2^d - \binom{d}{k-1}}{2^d}\right]^d + \frac{\binom{d}{k-1}}{2^d}\left[\frac{2^{d-1} - \binom{d-1}{k-2}}{2^{d-1}}\right]^{k-1}\left[\frac{2^{d-1} - \binom{d-1}{k-1}}{2^{d-1}}\right]^{d-(k-1)} .$$

Square lattices (type-4 edge-)



Proposition

Let X be the 2-dimensional lattice (infinite or periodic boundaries) as above where every vertex has degree 4, and let F be the GDS map over X induced by nor-functions. Then the activity of F for any vertex i is $\bar{\alpha}_{F,i} = 1040/2^{12}$.

Proof.

Idea: use inclusion-exclusion and careful book-keeping twice to evaluate $\mathbb{P}(B)$ and $\mathbb{P}(\bar{A}_i \cap \bar{B}^c)$.

Remark

May of course obtain this through brute force evaluation: only 2^{13} state involved for $X(i;2)$.

Questions, Acknowledgements and References

- Computational intractability: in the general case, determination of activity is intractable.
- Are there efficient and accurate methods for estimation?
- Activity only covers 1-step effects. Can something be done for long-term activity (e.g. with comparison of limit sets $\omega_F(x) \neq \omega_F(x + e_i)$?)
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