Boolean models for genetic regulatory networks

Cynthia Olson Reichhardt
T-12
Los Alamos National Laboratory

Kevin Bassler
Department of Physics
University of Houston
Outline

• Introduction: Cell cycles, genetic regulatory networks, and phenotypic development
• Phenotypes, mutations, and genetic variation. The canalization concept
• Representations of genetic logic: Boolean network models
• Cell type and cycle length in Kauffman network models
• Mapping of the gene strategy tables to Ising hypercubes
• Group theoretic concepts (brief review)
• Symmetry properties of strategies for combinatoric enumeration
• Preserving the phenotype through network interactions
• Summary
Cell cycle in *Saccharomyces cerevisiae*
The brain of yeast
Gene-gene interactions

Gene 1
- Produces protein A
- Activated by protein C
- Suppressed by protein B

Gene 2
- Activated by protein A
- Suppressed by protein C
- Produces protein B

Gene 3
- Activated by protein B
- Suppressed by protein A
- Produces protein C

Current state of cell
Gene-gene interaction network

Cell cycle (temporal)

1 - A

2 - B

3 - C

Interaction network (logical)

1

2

3
Genetic regulation of *S. cerevisiae*

Temporal states and logical network both shown

Gene regulation in *Escherichia coli*
What about multicellular organisms?

*Strongylocentrotus purpuratus* (Purple sea urchin)
Genetic logic for multiple cells

D.A. Kleinjan et al.
76, 8 (2005)
Tissue differentiation: Phenotype expression

Development of the sea urchin embryo from a mass of undifferentiated cells (blastula)

Each cell type has its own genetic regulatory cycle

The DNA must contain one possible cycle per cell type

More complex organisms = More complex DNA
Genetic regulation during development

Endomesoderm genetic regulatory network for *S. Purpuratus*

Xenopus laevis (African clawed frog)

Mesodermal genetic regulatory network
T. Koide et al, PNAS 102, 4943 (2005)
Arabidopsis thaliana

Figure 4. Gene Network Architecture for the Arabidopsis Floral Organ Fate Determination.

Resistance to phenotype mutation

Drosophila sp.

Canalization: A biologist’s view

“Canalization and the inheritance of acquired characters”

“Once the developmental path has been canalized, it is to be expected that many different agents, including a number of mutations available in the germplasm of the species, will be able to switch development into it. By such a series of steps, then, it is possible that an adaptive response can be fixed without waiting for the occurrence of a mutation.”

Canalization is mediated by “developmental reactions [that] are adjusted so as to bring about one definite end result regardless of minor variations in conditions during the course of the reaction.”
Canalization: Allowing evolution to work offline?

Fixed phenotype

Expression of new phenotype due to changing conditions

Mating display (Lethal) Camouflage Better hunting ?
Genetic interactions in the eyes of a physicist

Kauffman’s genetic logic model


- Replace each gene with a Boolean logic element having two states, “off (0)” and “on (1)”
- Genes are randomly connected to k other input genes in a network
- The response of each gene to its k inputs is given by a randomly chosen Boolean strategy table

```
<table>
<thead>
<tr>
<th>i_1</th>
<th>i_2</th>
<th>i_3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
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<td>1</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
```

k=3
Gene-gene interaction network

Cell cycle (temporal)

1 - A
2 - B
3 - C

Interaction network (logical)

Current state of system
100 -> 010 -> 001 -> 100
Cycles in a random Boolean network

N=5, k=3

<table>
<thead>
<tr>
<th>$f_1$</th>
<th>$f_2$</th>
<th>$f_3$</th>
<th>$f_4$</th>
<th>$f_5$</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
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<td>1</td>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

$\begin{array}{cccc}
 j_1 & 5 & 3 & 3 & 3 & 5 \\
 j_2 & 2 & 5 & 1 & 4 & 4 \\
 j_3 & 4 & 4 & 5 & 4 & 1 \\
\end{array}$
Cycles in a random Boolean network

Kauffman: Each attractor corresponds to a cell type

Internal homogeneity

Avg period increases exponentially with $N$ in chaotic regime; as a power of $N$ in the ordered regime; intermediate at boundary.

$K = \frac{1}{2p(1-p)}$.

Values of k in real genetic networks: *E. coli*


Small values of k and much autoregulation

Yeast transcription regulatory network structure
Classifying strategies

Number of strategies: $2^{2^k}$

<table>
<thead>
<tr>
<th>$k$</th>
<th>$N_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>256</td>
</tr>
<tr>
<td>5</td>
<td>65536</td>
</tr>
<tr>
<td>6</td>
<td>4294967296</td>
</tr>
<tr>
<td>7</td>
<td>18446744073709551616</td>
</tr>
<tr>
<td>8</td>
<td>Much larger than Avogadro’s number</td>
</tr>
</tbody>
</table>

Due to combinatoric explosion, it is not possible to reach $k=10$ by direct inspection.
Classifying $k=2$ strategies

<table>
<thead>
<tr>
<th>In</th>
<th>$\mathcal{F}$</th>
<th>$C_1$</th>
<th>$C_2$</th>
<th>$R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td>1</td>
<td>0 1 0 1</td>
<td>1 0 0 0</td>
<td>1 1 1 1</td>
</tr>
<tr>
<td>01</td>
<td>1</td>
<td>0 1 1 0</td>
<td>0 1 0 0</td>
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<td>10</td>
<td>1</td>
<td>1 0 0 1</td>
<td>0 0 1 0</td>
<td>1 1 0 1</td>
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<tr>
<td>11</td>
<td>1</td>
<td>1 0 1 0</td>
<td>0 0 0 1</td>
<td>1 1 1 0</td>
</tr>
</tbody>
</table>

Fixed

- Sensitive to only one input
  
  *(Acts like $k=1)*

| $p$ = 1 | $p$ = 0.5 | $p$ = 0.75 | $p$ = 0.5 |

V. Kaufman et al, PRE 72, 046124 (2005)
Minority game for an evolving N-K network

- System of N nodes is initialized with fixed K. All nodes are assigned an unbiased strategy (equal number of 0s and 1s).
- Repeatedly update the network until the attractor is reached.
- For each update on the attractor, determine whether “0” or “1” is the output of the majority of the nodes.
- Assign a “point” +1 to all nodes in the majority on each update.
- The node which is in the majority most often (has the most “points”) loses the game and is assigned a new randomly chosen unbiased strategy. This completes an “epoch.”
- Repeat the procedure for the new network.

Fourteen $k=3$ classes of strategies with equal evolutionary advantage

FIG. 3 (color online). Selection for canalization. The average relative probability of occurrence of the 256 different $K = 3$ Boolean strategies shown at different stages in the evolutionary process. The strategies are grouped according to the classification in Table I, and the groups are ordered with decreasing canalization. Results are the average of 10,000 different realizations.

Classifying $k=3$ strategies


<table>
<thead>
<tr>
<th>Class</th>
<th>A</th>
<th>B</th>
<th>$C_a$</th>
<th>$C_b$</th>
<th>D</th>
<th>E</th>
<th>$F_a$</th>
<th>$F_b$</th>
<th>$F_c$</th>
<th>G</th>
<th>$H_a$</th>
<th>$H_b$</th>
<th>I</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>2</td>
<td>16</td>
<td>24</td>
<td>6</td>
<td>48</td>
<td>24</td>
<td>8</td>
<td>8</td>
<td>24</td>
<td>48</td>
<td>6</td>
<td>24</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>$P_0$</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_1$</td>
<td>1</td>
<td>1/2</td>
<td>1/3</td>
<td>1/6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_2$</td>
<td>1</td>
<td>3/4</td>
<td>2/3</td>
<td>7/12</td>
<td>1/2</td>
<td>1/2</td>
<td></td>
<td></td>
<td>1/2</td>
<td>5/12</td>
<td>1/3</td>
<td>1/4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>1</td>
<td>7/8</td>
<td>3/4</td>
<td>1/2</td>
<td>5/8</td>
<td>3/4</td>
<td>3/4</td>
<td>1/2</td>
<td>5/8</td>
<td>1/2</td>
<td>5/8</td>
<td>1/2</td>
<td>1/2</td>
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</tr>
<tr>
<td>Sym</td>
<td>S</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>A</td>
<td>N</td>
<td>S</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Classification of the 256 $K = 3$ Boolean functions according to their canalization properties, internal homogeneity, and parity symmetry. ($S$ indicates symmetric, $A$ indicates anti-symmetric, and $N$ indicates neither, or non-symmetric.)

Strategies in the same class have the same evolutionary advantage when the network is allowed to evolve under some rule.

How to identify classes? What about $k>3$?
Map strategies to Ising k-hypercubes

$k=2$

$k=3$

$k=4$
Example: $k=2$

Each strategy group contains all objects in a particular group orbit of the Ising hypercube symmetry group plus parity.
Counting strategy classes

All strategies correspond to all states of the k-hypercube.

We can identify the total number of strategy classes by counting the number of group orbits that exist for the k-hypercube.

\[
\begin{array}{ccc}
N_c & k & N_s \\
- & 2 & 2 \\
4 & 3 & 16 \\
14 & 4 & 256 \\
5 & 65536 \\
6 & 4294967296 \\
7 & 18446744073709551616 \\
\end{array}
\]
Permutations and Cyclic Decomposition

Given an ordered set of elements, a permutation is a reordering of that set where each element occurs only once.

“game”  “emag”  “ameg”  “eagm”
{1,2,3,4}  {4,3,2,1}  {2,3,4,1}  {4,2,1,3}

Cyclic decomposition: Consider the permutation {4,2,1,3} of {1,2,3,4}. Repeated applications of this permutation result in a cycle:

game -> eagm -> maeg -> game

The permutation can be written in terms of cycles of elements:

(2)(143)
Definition 1.1. A group \((G, \cdot)\) is a set \(G\) with a binary operation
\[
\cdot : G \times G \rightarrow G,
\]
and a unit \(e \in G\), possessing the following properties.

1. Unital: for \(g \in G\), we have \(g \cdot e = e \cdot g = g\).
2. Associative: for \(g_1, g_2, g_3 \in G\), we have \((g_1 \cdot g_2) \cdot g_3 = g_1 \cdot (g_2 \cdot g_3)\).
3. Inverses: for \(g \in G\), there exists \(g^{-1} \in G\) so that \(g \cdot g^{-1} = g^{-1} \cdot g = e\).

A set of elements \(S\) of \(G\) is said to generate \(G\) if every element of \(G\) may be expressed as a product of elements of \(S\), and inverses of elements of \(S\). That is to say, given \(g \in G\), there exists \(s_i \in S\) and \(\epsilon_i \in \{\pm 1\}\) so that
\[
g = s_1^{\epsilon_1} \cdots s_n^{\epsilon_n}.
\]

If a group \(G\) is a generated by a single element, it is said to be cyclic. Every element of a cyclic group \(G\) is of the form \(g^n\) for some \(n \in \mathbb{Z}\).
Orbit-counting theorem

Total number of classes \( P_G \)

\[
P_G(x_1, x_2, \ldots) = \frac{1}{|G|} \sum_{g \in G} |X^g|
\]

- \(|G|\): number of symmetry operators (generators) \( g \)
- \(X^g\): the set of elements in \( X\) that are left invariant by \( g\)

Counting the number of classes for higher \( k\):
- Identify the symmetry operators of the \( k\)-hypercube with parity
- Write these symmetry operators in terms of cycles
- Find the number of fixed points for each symmetry operator

The symmetry group for the \( k\)-hypercube is isomorphic to the hyperoctahedral group \( O_n \) with \( n=k\), which has \( n!2^n \) symmetry operations
Example: k=2

- Identify the symmetry operators of the k-hypercube with parity
- Write these symmetry operators in terms of cycles
- Find the number of fixed points for each symmetry operator

\[ k!2^k = 8 \text{ for } k=2 \]

<table>
<thead>
<tr>
<th>Operator</th>
<th>Fixed Points</th>
<th>Parity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1243) E</td>
<td>2</td>
<td>(1243) P 2</td>
</tr>
<tr>
<td>(3421) E</td>
<td>2</td>
<td>(3421) P 2</td>
</tr>
<tr>
<td>(14)(23) E</td>
<td>2^2</td>
<td>(14)(23) P 2^2</td>
</tr>
<tr>
<td>(12)(34) E</td>
<td>2^2</td>
<td>(12)(34) P 2^2</td>
</tr>
<tr>
<td>(13)(24) E</td>
<td>2^2</td>
<td>(13)(24) P 2^2</td>
</tr>
<tr>
<td>(14)(2)(3) E</td>
<td>2^3</td>
<td>(14)(2)(3) P 0</td>
</tr>
<tr>
<td>(23)(1)(4) E</td>
<td>2^3</td>
<td>(23)(1)(4) P 0</td>
</tr>
</tbody>
</table>

48/16 = 4 classes

Identifying generators by inspection is difficult for k>3
Arbitrarily high k: Cycle representation of the Zyklenzeiger group

\[ Z_{\Theta_n} = \frac{1}{n!2^n} \sum_{\{i\}} \frac{n!2^n}{\prod_{i} i!(2i)^{j_i}} \chi_{\frac{1}{d_i}} \left( \prod_{d|2^i} f_d^{(2^i)} + \prod_{d|2^i} f_d^{(2^i)} \times \epsilon \right) \]

where the sum is over all solutions of

\[ \sum_{i=1}^{n} ij_i = n; \]

where

\[ \epsilon(k) = \frac{1}{k} \sum_{d|k} 2^d \mu \left( \frac{k}{d} \right) \]

and

\[ g(2k) = \frac{1}{2k} \sum_{d|2k} 2^{d/2} \mu \left( \frac{2k}{d} \right) \]

where \( \mu(n) \) is the Möbius function.

M.A. Harrison, J. SIAM 11, 806 (1963)
Example: $k=2$

\[ x_1^4 + 3x_2^2 + 2x_1^2x_2 + 2x_4 \]

<table>
<thead>
<tr>
<th>Operator</th>
<th>$E$</th>
<th>$P$</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x_2^4$</td>
<td>(1243) E</td>
<td>2</td>
<td>(1243) P</td>
</tr>
<tr>
<td>$x_4^2$</td>
<td>(3421) E</td>
<td>2</td>
<td>(3421) P</td>
</tr>
<tr>
<td>$x_2^2$</td>
<td>(14)(23) E</td>
<td>$2^2$</td>
<td>(14)(23) P</td>
</tr>
<tr>
<td>$x_2^2$</td>
<td>(12)(34) E</td>
<td>$2^2$</td>
<td>(12)(34) P</td>
</tr>
<tr>
<td>$x_2^2$</td>
<td>(13)(24) E</td>
<td>$2^2$</td>
<td>(13)(24) P</td>
</tr>
<tr>
<td>$x_2^2$</td>
<td>(14)(2)(3) E</td>
<td>$2^3$</td>
<td>(14)(2)(3) P</td>
</tr>
<tr>
<td>$x_1^2x_2$</td>
<td>(23)(1)(4) E</td>
<td>$2^3$</td>
<td>(23)(1)(4) P</td>
</tr>
</tbody>
</table>

For each operator without parity, the number of functions left invariant is equal to $2^{N_c}$, where $N_c = \sum_{i=1}^{k} b_i$ is the total number of cycles in the operator. Parity must be treated separately; no functions are left invariant by the parity operator with any $k$-hypercube operator containing at least one cycle of length 1. Thus there are $2^{N_p}$ functions left invariant for the eight operators which include parity, where $N_p = (1 - \Theta(b_1)) \sum_{i=1}^{k} b_i$ and $\Theta$ is the Heaviside step function.
Generating polynomials through $k=5$

<table>
<thead>
<tr>
<th>$k$</th>
<th>Cycle polynomial</th>
<th>$P_G$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$(1/2) \left( x_1^2 + x_2 \right)$</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>$(1/8) \left( x_1^4 + 3x_2^2 + 2x_1^2x_2 + 2x_4 \right)$</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>$(1/48) \left( x_1^8 + 13x_2^4 + 8x_1^2x_3^2 + 8x_2x_6 + 6x_1^4x_2^2 + 12x_4^2 \right)$</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>$(1/384) \left( x_1^{16} + 12x_1^8x_2^4 + 51x_2^8 + 12x_1^4x_6^4 + 32x_1^4x_3^4 + 48x_1^2x_2x_4^3 + 84x_4^4 + 96x_2^2x_6^2 + 48x_8^2 \right)$</td>
<td>238</td>
</tr>
<tr>
<td>5</td>
<td>$(1/3840) \left( x_1^{32} + 384x_1^{16}x_2 + 20x_1^{16}x_8 + 60x_1^8x_2^12 + 231x_1^{16} + 80x_1^8x_3^8 + 320x_1^2x_4^8 + 240x_1^4x_2^3x_4^6 + 240x_2^4x_4^6 + 520x_4^8 + 384x_1^2x_5^6 + 160x_1^4x_3^4x_6^2 + 720x_2^4x_6^4 + 480x_8^4 \right)$</td>
<td>698 635</td>
</tr>
</tbody>
</table>
Class structure: Isomer chemistry

Substitute a term of the form $A^a + B^a$ for each $x_a$

### Table 4. Class structure for $k = 2$

<table>
<thead>
<tr>
<th>Class type</th>
<th>$N_h$</th>
<th>$\langle S_c \rangle$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A^4$</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>$A^3B$</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>$A^2B^2$</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

$k = 2$ (max 16)

### Table 5. Class structure for $k = 3$

<table>
<thead>
<tr>
<th>Class type</th>
<th>$N_h$</th>
<th>$\langle S_c \rangle$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A^8$</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>$A^7B$</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>$A^6B^2$</td>
<td>3</td>
<td>18.667</td>
</tr>
<tr>
<td>$A^5B^3$</td>
<td>3</td>
<td>37.333</td>
</tr>
<tr>
<td>$A^4B^4$</td>
<td>6</td>
<td>11.667</td>
</tr>
</tbody>
</table>

$K = 3$ (max 96)

### Table 6. Class structure for $k = 4$

<table>
<thead>
<tr>
<th>Class type</th>
<th>$N_h$</th>
<th>$\langle S_c \rangle$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A^{16}$</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>$A^{15}B$</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>$A^{14}B^2$</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>$A^{13}B^3$</td>
<td>6</td>
<td>186.667</td>
</tr>
<tr>
<td>$A^{12}B^4$</td>
<td>19</td>
<td>191.58</td>
</tr>
<tr>
<td>$A^{11}B^5$</td>
<td>27</td>
<td>323.56</td>
</tr>
<tr>
<td>$A^{10}B^6$</td>
<td>50</td>
<td>320.32</td>
</tr>
<tr>
<td>$A^{9}B^7$</td>
<td>56</td>
<td>408.57</td>
</tr>
<tr>
<td>$A^{8}B^8$</td>
<td>74</td>
<td>173.9</td>
</tr>
</tbody>
</table>

$K = 4$ (max 768)

$\langle S_c \rangle = N_f / N_h$

$N_f(m, n) = (2 - \delta_{m,n})(2^k)!/(m!n!), \text{ where } m + n = 2^k$.

$S_c^{max} = k! 2^{k+1}$. 

Los Alamos
Class structure for \( k=5 \)

<table>
<thead>
<tr>
<th>Class type</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A^{32} )</td>
</tr>
<tr>
<td>( A^{31}B )</td>
</tr>
<tr>
<td>( A^{30}B^2 )</td>
</tr>
<tr>
<td>( A^{29}B^3 )</td>
</tr>
<tr>
<td>( A^{28}B^4 )</td>
</tr>
<tr>
<td>( A^{27}B^5 )</td>
</tr>
<tr>
<td>( A^{26}B^6 )</td>
</tr>
<tr>
<td>( A^{25}B^7 )</td>
</tr>
<tr>
<td>( A^{24}B^8 )</td>
</tr>
<tr>
<td>( A^{23}B^9 )</td>
</tr>
<tr>
<td>( A^{22}B^{10} )</td>
</tr>
<tr>
<td>( A^{21}B^{11} )</td>
</tr>
<tr>
<td>( A^{20}B^{12} )</td>
</tr>
<tr>
<td>( A^{19}B^{13} )</td>
</tr>
<tr>
<td>( A^{18}B^{14} )</td>
</tr>
<tr>
<td>( A^{17}B^{15} )</td>
</tr>
<tr>
<td>( A^{16}B^{16} )</td>
</tr>
</tbody>
</table>

\[ K=5 \ (7680) \]
Characteristic polynomials

Do two randomly chosen strategies belong to the same class?

Each class has a unique characteristic polynomial.

Construct the adjacency matrix: $A_{ij} = 1$ if link, 0 if no link
Place the strategy on the diagonal
Find the determinant

\[
\begin{array}{ccc}
1 & 1 & 0 \\
1 & b & 0 \\
1 & 0 & c \\
0 & 1 & 1 \\
d & & \\
\end{array}
\]

Det: $-ab-ac-bd-cd-abcd$

$-4A^2+A^4$

$-4AB+A^2B^2$

$-A^2-2AB-B^2+A^2B^2$

Geometric strategy classification

We classify a given strategy depending on the number of edges, faces, and higher dimensional objects having all entries the same, \( p(d,k), \ d \leq k \). This represents varying degrees of canalization.

- \( h=1 \):
  - \( p(1,2)=4 \)
  - \( p(2,2)=1 \)

- \( h=0.5 \):
  - \( p(1,2)=2 \)
  - \( p(2,2)=0 \)

- \( h=0.75 \):
  - \( p(1,2)=2 \)
  - \( p(2,2)=0 \)

- \( h=0.5 \):
  - \( p(1,2)=0 \)
  - \( p(2,2)=0 \)
Recursion relations

We can think of a $k+1$ strategy as being assembled out of two $k$ strategies

\[
\begin{align*}
\begin{array}{cccc}
00 & 1 & 00 & 0 \\
01 & 1 & 01 & 0 \\
10 & 1 & 10 & 0 \\
11 & 1 & 11 & 0 \\
p(1,2)=4 & p(1,2)=4 & p(2,2)=1 & p(2,2)=1 \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{cccc}
000 & 1 & 000 & 1 \\
001 & 1 & 001 & 1 \\
010 & 1 & 010 & 1 \\
011 & 1 & 011 & 1 \\
p(1,3)=8 & p(1,3)=8 & p(2,3)=2 & p(3,3)=0 \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
h(k + 1) &= \sum_{i=1}^{2} h_i(k) \\
p(d, k + 1) &\geq \sum_{i=1}^{2} p_i(d, k) \\
N_d(k) &= \frac{2^{k-d}k!}{(k-d)!d!} \\
N_d(k + 1) &\geq p(d, k + 1) \geq \sum_{i=1}^{2} p_i(d, k) \\
\frac{N_d(k)}{N_d(k - 1)} &= \frac{2k}{k - d}
\end{align*}
\]
Recursion relations

Improving on the maximum bound

\[ p(d, k + 1) \geq \sum_{i=1}^{2} p_i(d, k) \]

\[ p(d, k + 1) \leq \sum_{i=1}^{2} p_i(d, k) + \min(p_1(d, k), p_2(d, k)) \]

\(6 \leq p(1,3) \leq 8\)

\[ p(1,2) = 4 \quad p(2,2) = 1 \]
\[ p(1,3) = 7 \]
\[ p(2,3) = 1 \]
\[ p(3,3) = 0\]
Lower symmetry cases

4 \leq p(1,3) \leq 6

\begin{align*}
\text{OR} & \quad \text{+ all possible rotations} \\
001 & \quad 001 \\
011 & \quad 010 \\
100 & \quad 100 \\
111 & \quad 110 \\
p(1,2)=2 & \quad p(1,2)=2 \\
p(2,2)=0 & \quad p(2,2)=0
\end{align*}

\begin{align*}
\text{symmetric} & \\
p(1,3)=6 & \\
p(2,3)=0 & \\
p(3,3)=0 & \\
\text{asymmetric} & \\
p(1,3)=6 & \\
p(2,3)=0 & \\
p(3,3)=0
\end{align*}
Bounding canalization

Although the fraction of fully canalizing functions drops rapidly with $k$, the fraction of partially canalizing functions remains large.

*Figure 4.* Average fraction $c_d$ of homogeneous $d$-dimensional sides in randomly selected Boolean functions versus $k$ for (a) $d = 1$, (b) $d = 2$, (c) $d = 3$ and (d) $d = 4$. 

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Effective k may be lower than actual k

Fig. 5. A large network of protein–protein interactions among kinases and phosphatases in yeast. (a) Kinases and phosphatases are very well connected in a large protein–protein interaction network. (b) Transcription factors, a functional class similar in size to the kinase/phosphatase class, are not. This is an example of an unanticipated result that is completely unobtainable without genome-wide studies. Loops indicate self-interactions.

Summary

- Boolean network models can be used to represent genetic regulatory networks.
- The number of possible strategies grows rapidly with connection degree \( k \); the number of network states grows rapidly with network size \( N \).
- Nodes which respond to only a fraction of their inputs have an effectively reduced \( k \), which reduces the available phase space.
- Mapping of the gene strategy tables to Ising hypercubes allows us to use symmetry properties to enumerate strategy classes.
- By assembling \( k+1 \) strategies out of \( k \) strategies recursively, we can put bounds on the amount of canalization present in the \( k+1 \) strategies.
- A significant fraction of strategies are at least partially canalized, reducing the complexity and cycle length of the logical network.