

Discrete dynamic modeling of biological systems

- The functional form of regulatory relationships and kinetic parameters are often unknown
- Increasing evidence for
 - robustness to changes in kinetic parameters.
 - bistability (two steady states)

Hypothesis: *the kinetic details of individual interactions are less important than the organization of the regulatory network*

Discrete dynamic models assume that nodes can be characterized by only a few (minimum two) discrete states.

Discrete models can handle larger networks than continuous models.

Boolean modeling of biological systems

Main assumption: components have two main states :
 Expressed or not expressed, active or inactive, open or closed (ion channel), high or low level. Denote these states by ON (1) or OFF (0)

The changes in state are given by discrete (logical) rules.
 The future state of a regulated node (the output) depends on the current state of its regulators (inputs), which may or may not include its own current state.
 e.g. If transcription factor is active, gene will be transcribed, gene will be expressed in the next time step.

Boole logic: based on the operators NOT, AND, OR
 Can be defined based on set intersection and union, or input-output relations (gates, truth tables)

Truth tables for Boolean operators

NOT

In	Out
0	1
1	0

Out= NOT In

AND

In1	In2	Out
0	0	0
0	1	0
1	0	0
1	1	1

Out= In1 AND In2

OR

In1	In2	Out
0	0	0
0	1	1
1	0	1
1	1	1

Out= In1 OR In2

In	Out
0	1
1	0

Out= NOT In

In1	In2	Out
0	0	0
0	1	0
1	0	0
1	1	1

Out= In1 AND In2

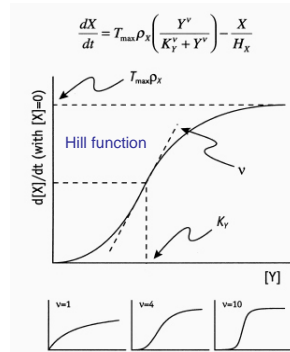
In1	In2	Out
0	0	0
0	1	1
1	0	1
1	1	1

Out= In1 OR In2

Ex. 1 Give examples for the realization of these Boolean rules in a gene regulatory network.

Ex. 2 Consider a transcription event activated by a transcription factor. Compare the continuous and Boolean description of this process.

From dose-response curves to Boolean switches



- X – mRNA
- Y – transcriptional activator

If v is large, the dose-response curve becomes a switch

If $Y > K_Y$ $dX/dt > 0$
 If $Y < K_Y$ $dX/dt < 0$
 The activation threshold is K_Y
 If activation is weak, mRNA can decay.

Boolean simplification:

$X^* = Y$
 Activation:
 If $Y = \text{ON}$ $X^* = \text{ON}$
 Decay:
 If $Y = \text{OFF}$ $X^* = \text{OFF}$

Hybrid models: Boolean regulation combined with continuous decay

- Each node is characterized by both a continuous and a Boolean variable.

$$\frac{d\hat{X}_i}{dt} = B(X_1, X_2, \dots) - \hat{X}_i$$

- X_i is defined by the threshold rule

$$X_i = \begin{cases} 0, & \text{if } \hat{X}_i < 0.5 \\ 1, & \text{if } \hat{X}_i > 0.5 \end{cases}$$

- Compared to $\frac{dX}{dt} = T_{\max} \rho_x \left(\frac{Y^v}{K_Y^v + Y^v} \right) - \frac{X}{H_x}$, this assumes constant activation threshold=0.5, maximal synthesis rate = decay rate= 1

L. Glass, S. Kauffman, J. Theor. Biol. 39:103 1973

Implementing time in discrete models

1. Synchronous models
 - The state of each node is updated simultaneously at multiples of a common timestep.
 - Thus the future state means the state at the next timestep
 - Underlying assumption: the timescales of all synthesis and decay processes are similar

2. Asynchronous models
 The state of each node is updated individually

Implementations:

- Different update time for each node $T_i^k = k\gamma_i$
- Select a random update order in each timestep
 $T_i^{k+1} = Nk + \phi^k(i)$ where ϕ^k is a permutation of the nodes.

Synchronous models have deterministic state transitions, asynchronicity introduces stochasticity (update order dependence) in the dynamics.

Boolean models of signaling networks

- Start with a known or reconstructed network.
- The directed edges in the network indicate regulator – target pairs.
- Assume that the state of each node can be 0 or 1.
- The rule giving the new state of each node is determined by a Boolean function of the states of the nodes that regulate it
- Choose between synchronous/asynchronous update
- Start with a known or assumed initial condition.
- The state of the whole network changes in time. Identify the attracting state(s) or behavior(s) of the system.

Ex. 3

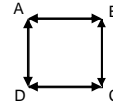
Construct a network of three nodes, such that their in-degree is one or two. Associate a Boolean rule to each node. Assume that each node's state changes at the same time (synchronous update) Start with an initial state, and update the state of the nodes 10 times.

What is happening to the state of the network?

Start from a different initial state. Is the final behavior be the same?

How many different final states/behaviors can the network have?

Example

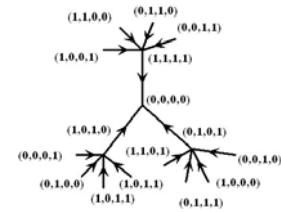


I1	I2	O
0	0	0
0	1	1
1	0	1
1	1	0

States

A	B	C	D
0	0	0	0
0	0	0	1
...
1	1	1	1

Transitions



Concepts in Boolean network dynamics

Attractor – a set of states that repeats itself in a fixed sequence can be **periodic** or a **fixed point**

Fixed point: Future State = Current State = Previous State

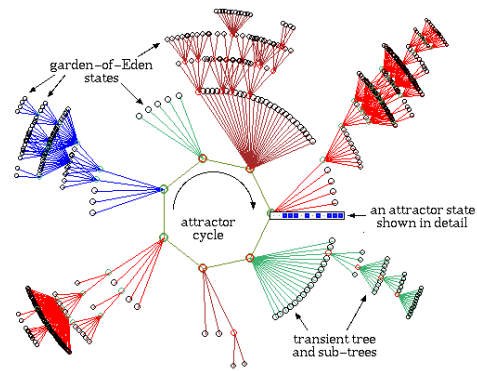
All states lead to or are part of an attractor.

Basin of attraction – all states leading to a given attractor

In a network of N nodes the maximum possible length of a periodic attractor is the total number of states, 2^N

In practice, the period (length) of the attractor is much shorter than this maximum.

Cause: many nodes become **frozen**, due partly to **canalizing functions**.



Andy Wuenche, www.ddlab.com

Canalizing (forcing) functions:

At least one of the inputs has the property that the output is fixed if this input has one particular value.

e.g. $a \text{ AND } b$ is canalizing because $a=0$ implies $a \text{ AND } b = 0$

Ex. 4

How many two-input Boolean functions are there?

How many of them are canalizing?

Ex. 5. Consider a network of four nodes. Node A is the signal, the Boolean rules of the other three nodes are the following:

$B^* = A \text{ or } C$, $C^* = A \text{ and not } D$, $D^* = B \text{ and } C$

Set $A = 0$.

(a) Assume that each node's state changes at the same time (synchronous update). Start with an initial state, and update the state of the nodes 5 times.

What attractor did you find?

(b) Now start from the same initial state, but update the nodes one by one, such that each node is updated in each step in a different order. Is the result the same?

Q. How can you determine the fixed points of a Boolean model without performing updates?

In the fixed point time does not matter, thus the transfer functions become equations

$B = A \text{ or } C$
 $C = A \text{ and not } D$
 $D = B \text{ and } C$

Solution: $A = 0, B = 0, C = 0, D = 0$

Asynchronous models have the same fixed points as synchronous ones.

Ex. 7

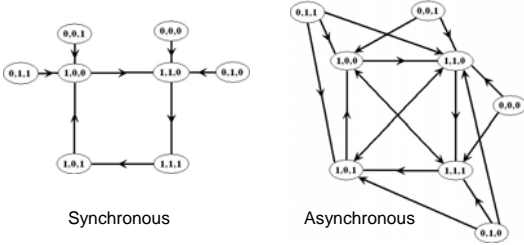
Consider a the same network of four nodes.

$B^* = A \text{ or } C$, $C^* = A \text{ and not } D$, $D^* = B \text{ and } C$

Set $A = 1$. Assume that each node's state changes at the same time (synchronous update)

Start with an initial state, and update the state of the nodes 10 times. What attractor did you find? Is it the same as for $A = 0$?

Attractors for synchronous and asynchronous models



The analog of a periodic orbit in a synchronous model is a strongly connected component in state space in an asynchronous model.

I. Harvey, T. Bossomaier, Proc. ECAL97, 67 1997

Integrating the Boolean rules into the network

- The future expression of a node depends on a combination of the expression of other nodes.

$$hh^* = EN \text{ and not } CIR$$

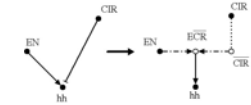
- Introduce "complementary" nodes.

$$\overline{CIR} \equiv \text{not } CIR$$

- Associate pseudo-nodes to node combinations.

$$\overline{ECR} \equiv EN \text{ and } \overline{CIR}$$

- The future expression of nodes depends on the expression of pseudo-nodes. $hh^* = ECR$



Ex. 8: construct the augmented network for Ex. 5. Use different styles for edges ending in pseudo-nodes.

Boolean modeling of gene regulatory networks in the absence of data

Cell differentiation is based on differential gene expression

Genes regulate each other's expression

Stuart Kauffman ~ 1965

Ideas:

genes can be modeled by on-off switches
 the structure of the gene regulatory networks is unknown
 the regulatory functions are unknown
 network states correspond to cell types

The Kauffman (NK) model

- Construct a network where each node's in-degree is K.
- Assume that the state of each node can be 0 or 1.
- The state of each node is updated at each timestep.
- The rule giving the new state of each node is determined by a random Boolean function of the states of its regulators.
- Find the attractors of the network states. The number of attractors corresponds to the number of possible cell types

How does the number and type of attractors change with N and K ?

Attractors in Kauffman networks

- For $K=1$, networks are frozen
 median number of attractors is close to 2^N
 median cycle length close to 1
 - For $K>5$, networks are chaotic
 few attractors
 median cycle length close to 2^N
 - For $K=2$, interesting level of order
 median number and length of attractors both scale as N^α
- This is fairly similar with the number of cell types in different organisms.

Stability of Kauffman networks

What is the effect of a "mutation", changing the state of a randomly selected node?

If the final number of changed nodes is small – frozen network

Percolating changes – chaotic network

The threshold between order and chaos is $K=2$

One can bias the Boolean functions so there are more of 0s or 1s.

Then the threshold varies with the bias Q as $K_c = \frac{1}{2Q(1-Q)}$

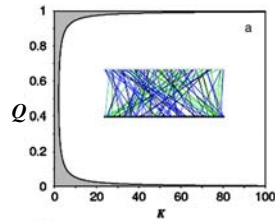
Ordered behavior for $k < K_c$

Does the threshold behavior apply to non-regular networks?

Order: $2Q(1-Q)K < 1$

This relation is maintained if the underlying network is ER with $\langle k_{in} \rangle = K$

Q: How does this compare with the threshold of a large connected component?



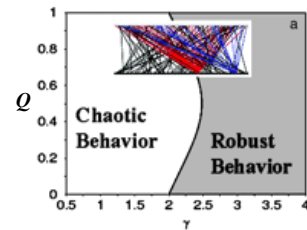
Does the threshold behavior apply to non-regular networks?

For scale-free networks with $P(k) = [Z(\gamma)k^\gamma]^{-1}$

the condition becomes

$$2Q(1-Q) \frac{Z(\gamma-1)}{Z(\gamma)} < 1$$

Scale-free networks with $\gamma > 2.5$ are robust to random perturbations.



M. Aldana, P. Cluzel, PNAS 100, 8711 (2003)

As we find out more about gene regulatory networks, it is not necessary to assume random topologies and regulatory functions anymore.

It is still interesting to see how successful an ON/OFF framework and Boolean logic can be as compared to chemical kinetics-based models.

Example: Boolean modeling of the segment polarity gene network

Continuous: [G. von Dassow et al., Nature 406, 188 \(2000\)](#)

Synchronous Boolean: [R. Albert, H. G. Othmer, Journ. Theor. Biol. 223, 1 \(2003\)](#)

Asynchronous Boolean: [M. Chaves, R. Albert, E. Sontag Journ. Theor. Bio. 235, 431 \(2005\)](#).

Continuous- Boolean hybrid: [M. Chaves, E. Sontag, R. Albert, IEE Proc. Systems Biology \(2006\)](#).