

Qualitative 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

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

Network topology: identity of nodes, edge attributes (direction, sign)

Topological features such as **path redundancy** and **feedback loops** constrain network dynamics.

First step - pseudo-dynamics: propagation of reactions in chemical (interaction) space, starting from a source (signal)

Ma'ayan et al, Science 309, 1078 (2005)

Qualitative models are most closely based on the network topology.

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

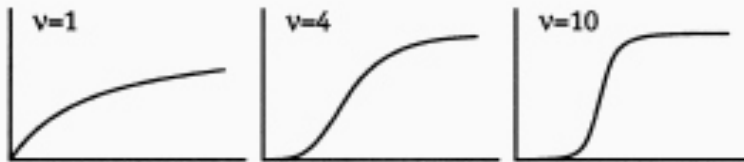
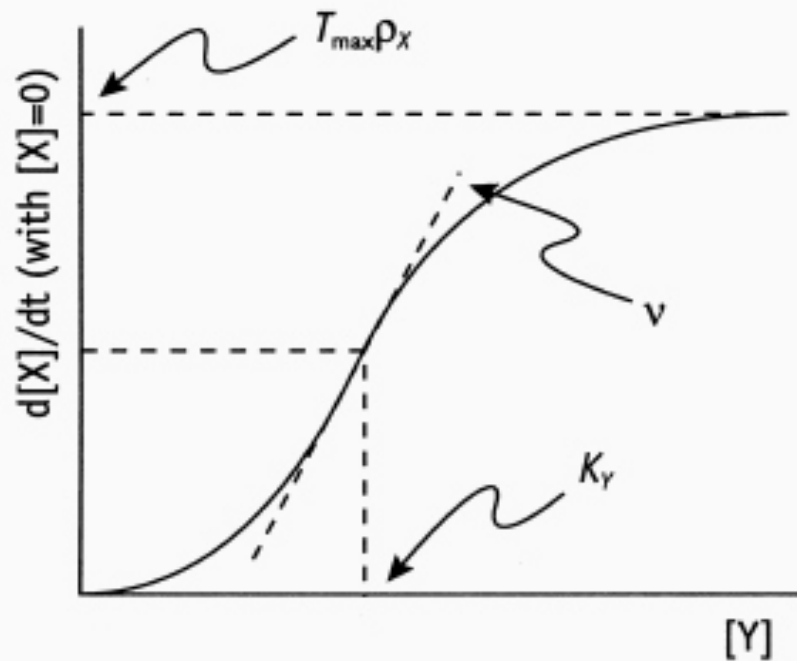
Out= In1 OR In2

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.

Dose-response curves and Boolean switches

$$\frac{dX}{dt} = T_{\max} \rho_X \left(\frac{Y^v}{K_Y^v + Y^v} \right) - \frac{X}{H_X}$$



- 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, protein can decay.

Boolean simplification:

$X(t+1) = Y(t)$

Activation:

If $Y(t) = \text{ON}$ $X(t+1) = \text{ON}$

Decay:

If $Y(t) = \text{OFF}$ $X(t+1) = \text{OFF}$

Random Boolean networks

- Construct a network where each node is connected randomly to K other nodes. Assume that edges are bidirectional (not undirected!)
- 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 Boolean function of the states of the nodes that regulate it
- The Boolean function is selected randomly from all possible K -input Boolean functions.
- The state of the whole network changes in time.

Ex. 3

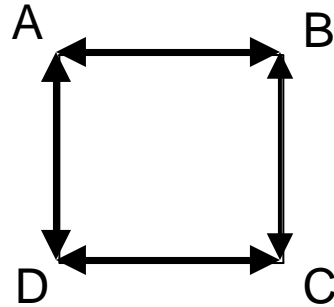
Construct a network of three nodes, such that their in-degree is one or two. Associate a Boolean rule to each node. Assume that each node's state changes at the same time (synchronous update)
Start with an initial state, and update the state of the nodes 10 times.

What is happening to the state of the network?

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

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

Example

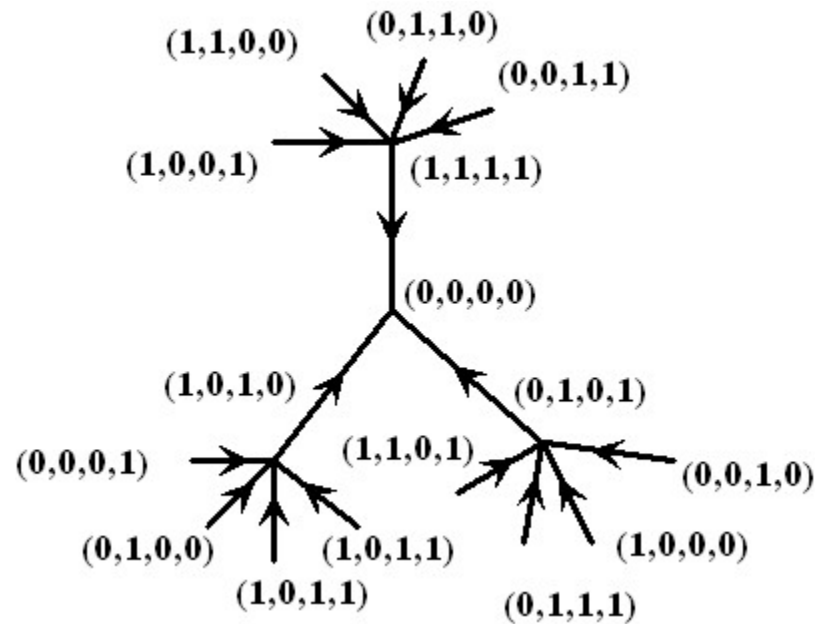


I1	I2	O
0	0	0
0	1	1
1	0	1
1	1	0

States

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

Transitions



Concepts in RBN

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

Fixed point: $\text{State}(t+1) = \text{State}(t)$

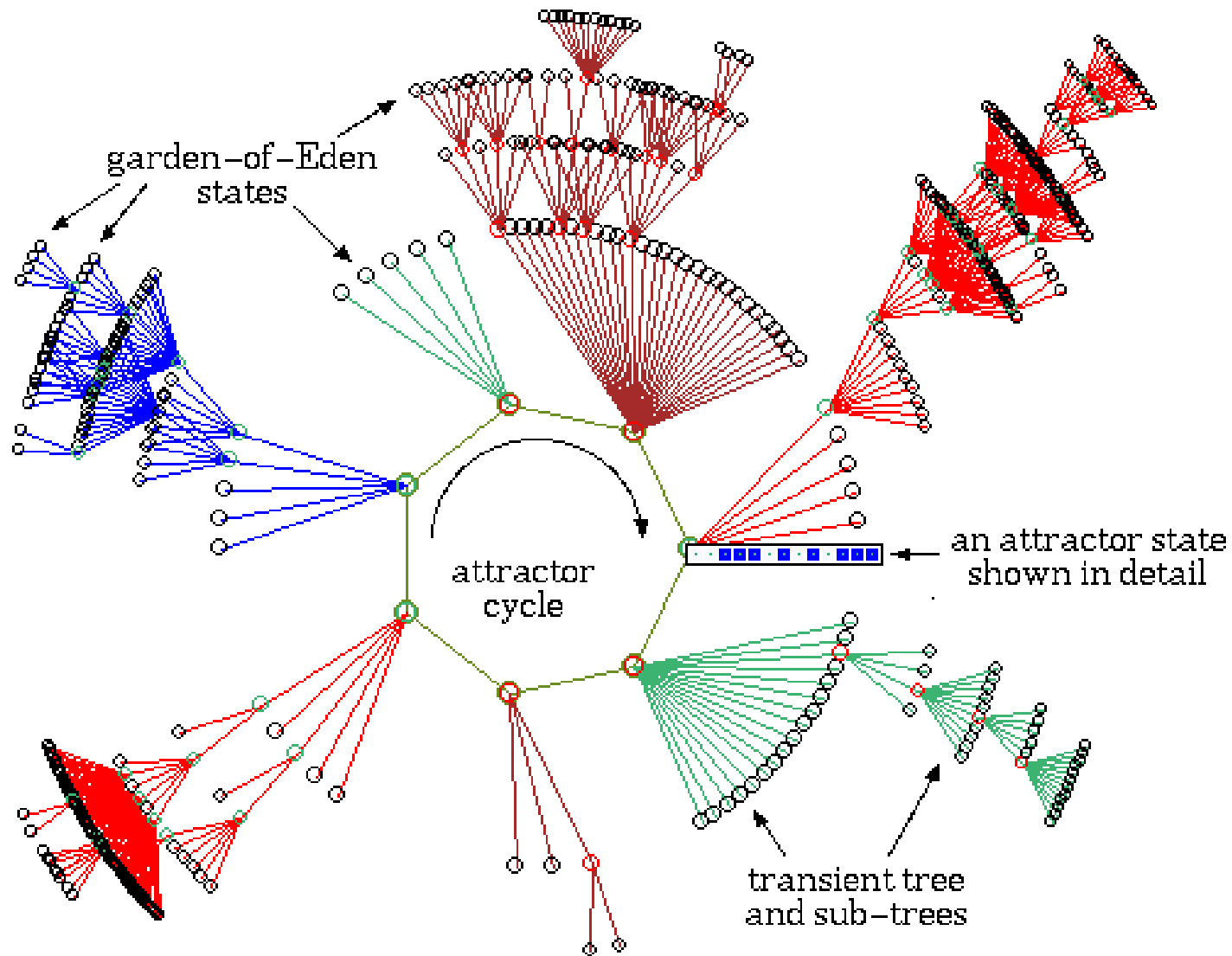
All states lead to or are part of an attractor.

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

How would you determine the fixed points of a Boolean network?

Boolean modeling of gene regulatory networks

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
$$K_c = \frac{1}{2Q(1-Q)}$$

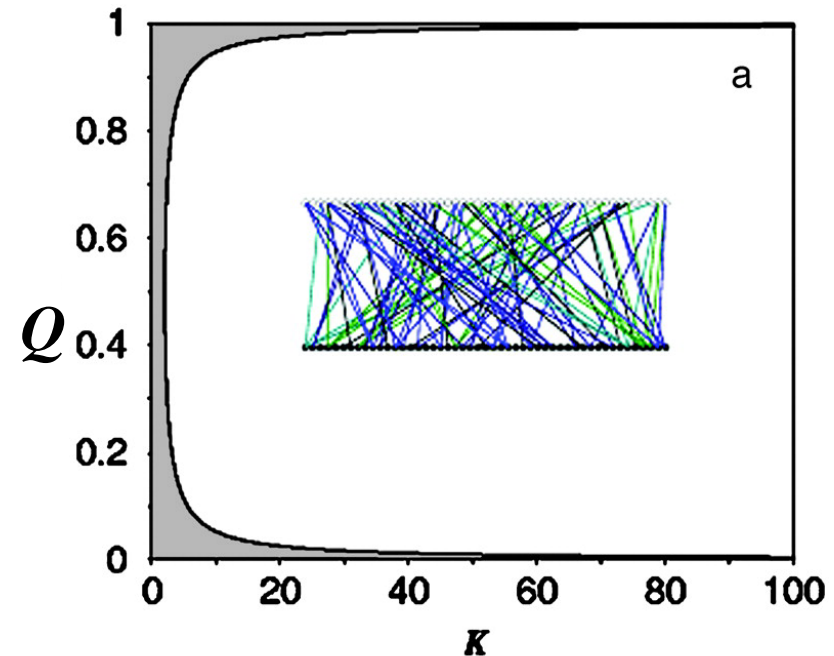
Ordered behavior for $k < K_c$

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 $\langle k_{in} \rangle = K$

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



Does the threshold behavior apply to non-regular networks?

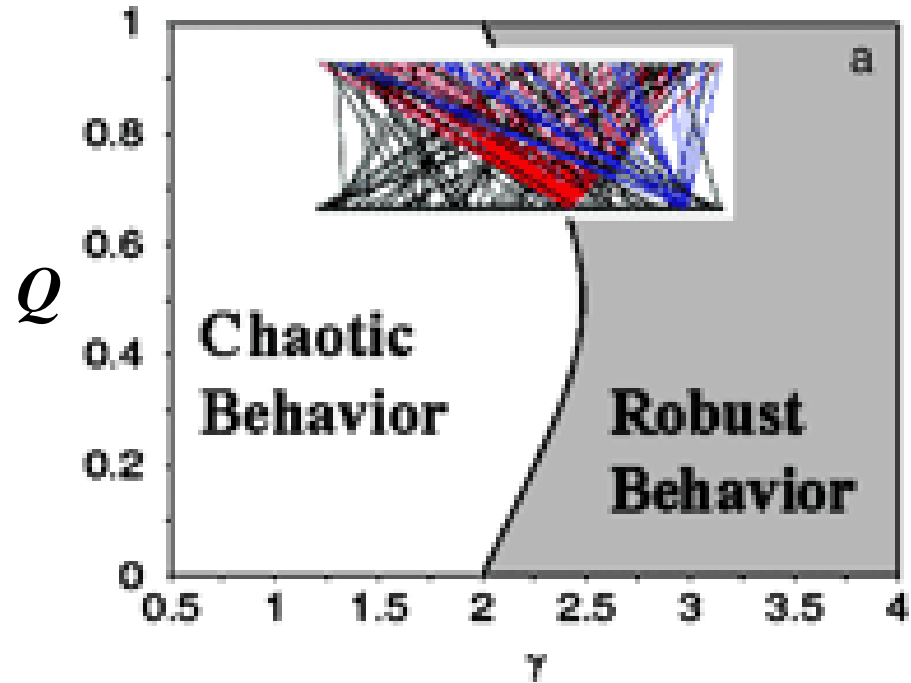
For scale-free networks

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)