Asynchronous Boolean models of signaling networks

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Motivation

Signal transduction

Living cells receive various external stimuli which trigger intracellular responses.

Signal transduction is a crucial part of how a cell communicates and reacts with its surroundings.

Signal transduction is needed to maintain cellular homeostatis and to carry out necessary cell behavior.

Many disease processes such as cancer, developmental disorders, diabetes, vascular diseases, and autoimmunity, arise from problems in signal tranductions.

Such problems could arise from mutations, or from alterations in expression of signal transduction pathway components.

A signal transduction network, or signaling network can be represented as a graph: the nodes are the components (e.g., biomolecules), and the edges represent interactions.

Think of it like a big natural Rube Goldberg machine.

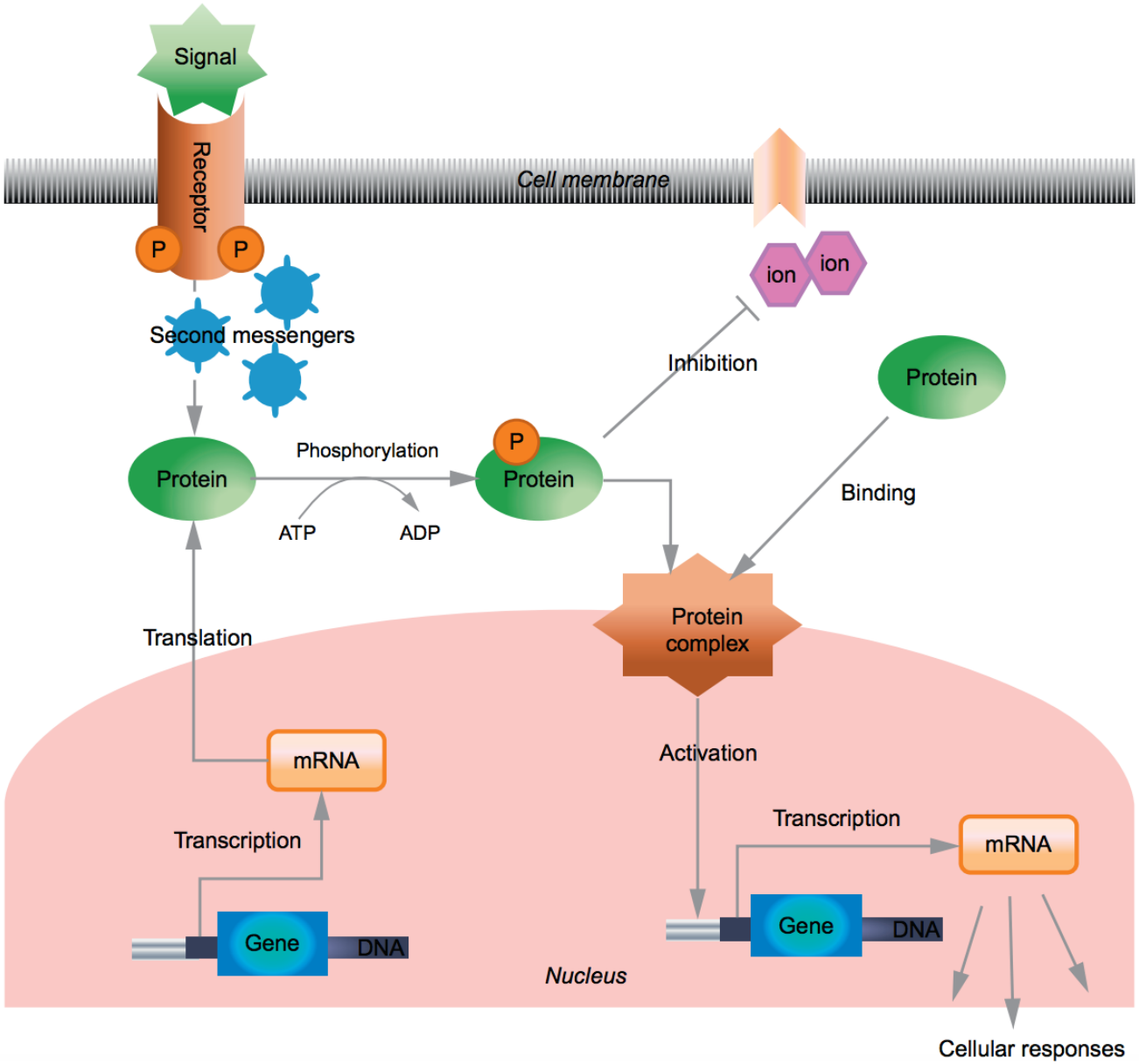


Figure: Scheme of a hypothetical signaling network.

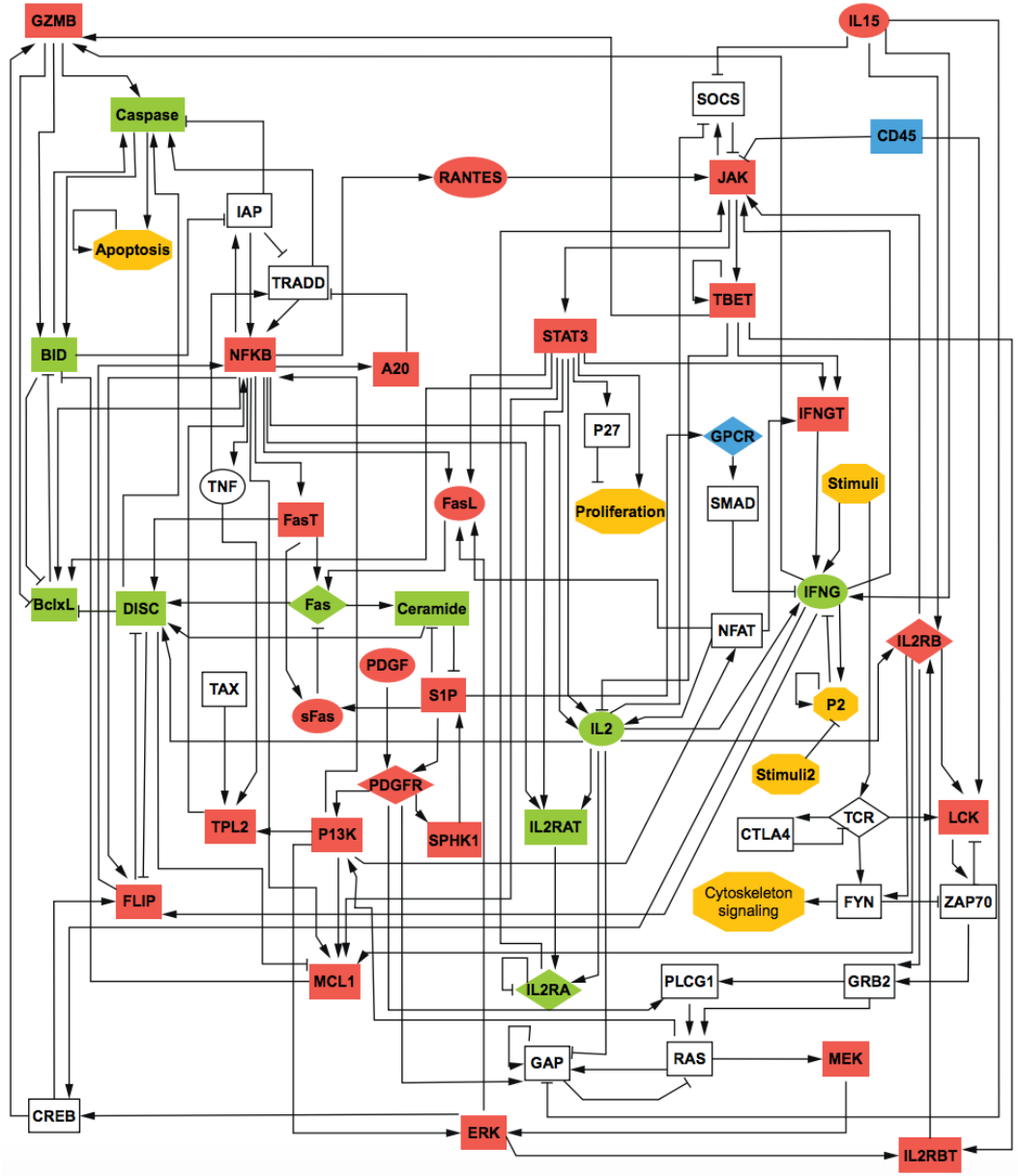


Figure: Signaling network involved in activation-induced cell death of killer T-cells. T-LGL leukemia disrupts this process, causing certain activated T-cells to survive, which later attack healthy cells.

Network topology

Analysis of the network topology of signaling networks includes graph-theretic measures such as *centrality*, *network motifs*, and *shortest paths*.

Nodes can be categorized as *sources* (signals), *sinks* (outcomes), or neither.

Centrality measures describe the importance of individual nodes in the network. Examples include:

- degree (or in-degree, or out-degree),
- clustering coefficient.
- betweenness,

Network motifs are recurring patterns (subgraphs) with well-defined topologies. Common examples include:

- Feed-forward loops (coherent and incoherent)
- Feedback loops (positive and negative)

Feed forward loops tend to arise with greater frequency than in random networks.

Rule of thumb

Positive feedback loops tend to support multistability while negative feedback loops lead to oscillations.

Feed-forward loops

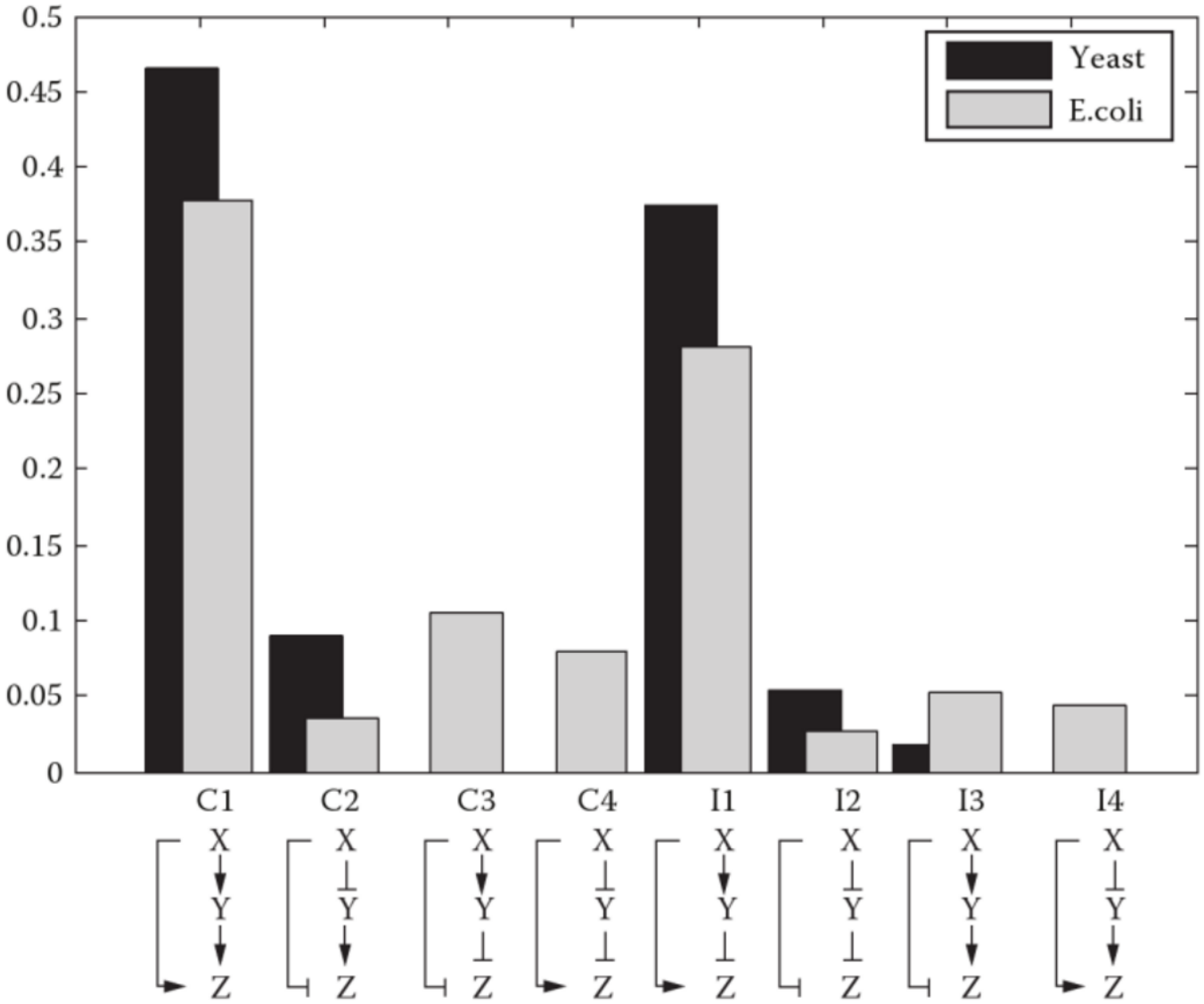


Figure: Relative abundance of the eight types of feed-forward loops in transcription networks (from U. Alon, 2007).

Strongly connected components

Definition

A directed graph is strongly connected if for every two nodes u and v, there is a (directed) path from u to v.

In any directed graph, the strongly connected components form a equivalence relation.

Moreover, there strongly connected components form a directed acyclic graph (i.e., are partially ordered): *add an edge from C_i to C_j if there is a directed path from some $x \in C_i$ to $y \in C_j$ in the original graph.*

Nodes in a strongly connected component tend to have a common task.

Signaling networks tend to have a large strongly connected core. For example, the previous T-cell network has a core of 44 nodes (75% total).

Question

Can Boolean models be used as realistic qualitative approximations of signal transduction networks in biology? Can they capture complex dynamic behavior such as:

- filtering of noisy input signals (coherent feed-forward loops)
- excitation–adaptation (incoherent feed-forward loops, or negative feedback loops)
- multistability (positive feedback loops)

An example

Consider a 3-node network with a signal A that activates B, which in turn, activates C.

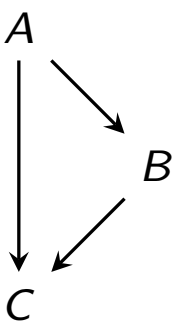
Suppose that C is active as long as both A and B are.

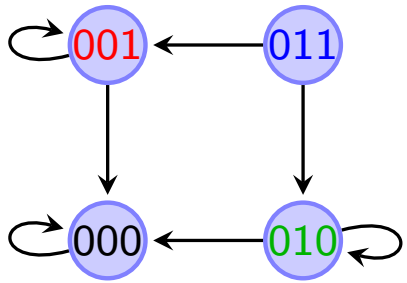
Here's what might happen biologically:

- A turns on. This activates B and then C, and the system settles in the ON steady-state, 111.
- Eventually, A turns off. This de-activates B and then C, and the system flips to the OFF steady-state, 000.

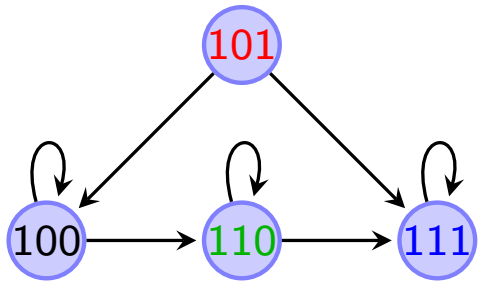
This can be visualized by the following *wiring diagram* and state space:

$$f_A = x_A$$
$$f_B = x_A$$
$$f_C = x_A \wedge x_B$$





A is OFF



A is ON

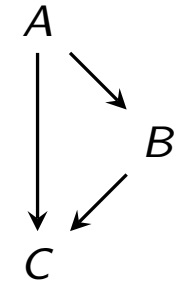
Remarks

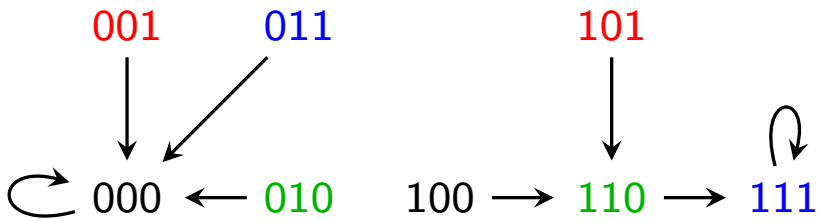
- Unlike synchronous Boolean networks, state space nodes can have multiple out-edges.
- What do you the proper analogue of fixed points should be in this setting?

Synchronous vs. general asynchronous update

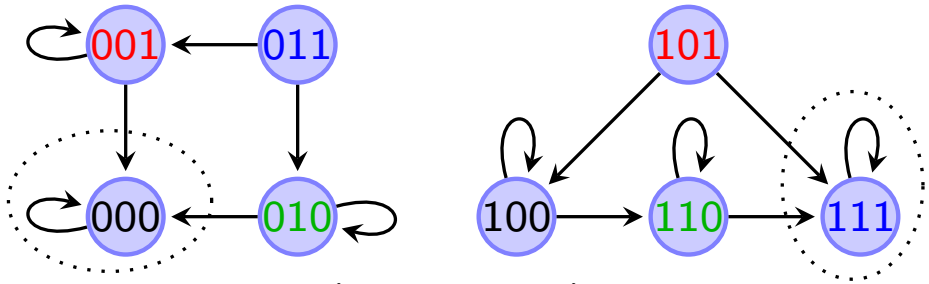
Let's compare the state space of the previous example as a Boolean network vs. an (asynchronous) signaling network.

$$f_A = x_A$$
$$f_B = x_A$$
$$f_C = x_A \wedge x_B$$





State space as a (synchronous) Boolean network



State space as an (asynchronous) signaling network

In actual biological networks, events and updates might occur randomly and unexpectedly.

Thus, one can think of the evolution of the network state as general asynchonrous update:

- a random walk along the state space, and
- (optional) occasionally "flipping" the bits of a variable (e.g., turning a signal on/off).

In the signaling network above, note that there's no way to leave the states 000 or 111 because they are sinks of the directed graph.

Synchronous vs. general asynchronous update

Under a synchronous update, the recurring states fall into two categories:

- fixed points
- periodic cycles

Under asynchronous update, there is one more type complex attractors.

Fixed-point attractors usually correspond to the steady activation states of components (e.g., ON or OFF) or to cellular phenotypes (e.g., cancerous, non-cancerous) in signaling networks.

Proposition

The set of fixed points of a Boolean or signaling network is independent of update scheme (synchronous, asynchronous, stochastic, etc.)

Remark

Under synchronous update, multiple nodes can change state across a single (edge) transition. This is impossible under general asynchronous update.

Excitation–adaptation behavior

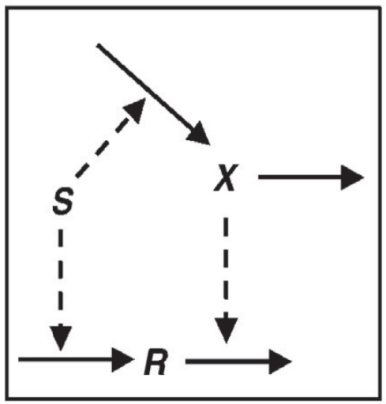
Chemotaxis is the movement of a cell in response to a chemical stimulus (the signal).

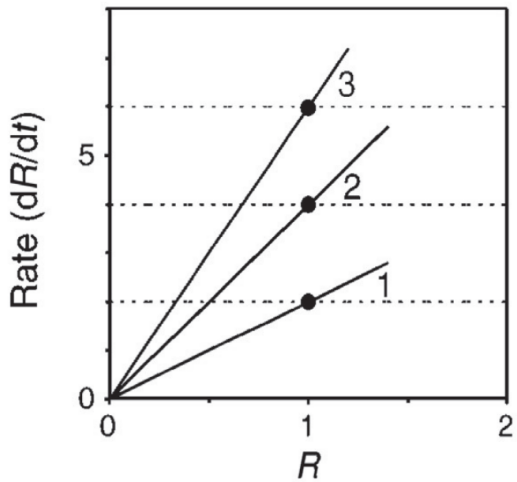
Consider the following system of ODEs, where X and R be concentrations of proteins, k_i ($i = 1, \ldots, 4$) are rate constants, and S be the value of the signal (a parameter):

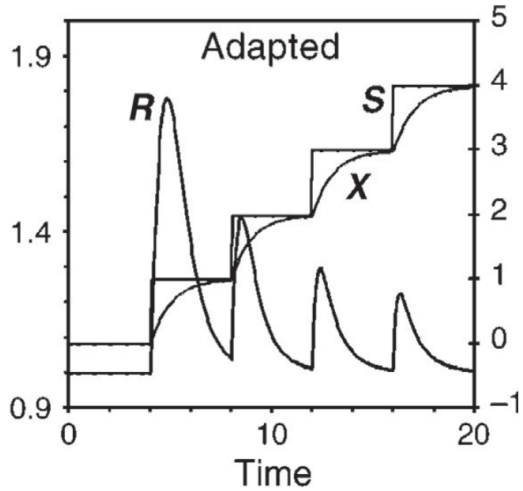
$$\frac{dR}{dt} = k_1 S - k_2 XR$$
$$\frac{dX}{dt} = k_3 S - k_4 X$$

Analytical results

The (steady-state) concentration R^* does not depend on S.





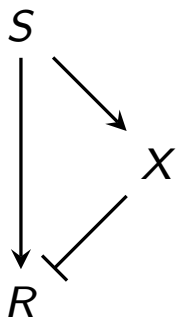


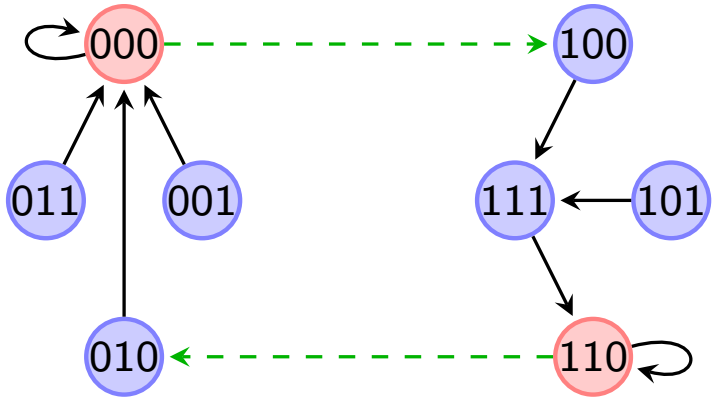
Excitation–adaptation behavior

Let's create a Boolean model of this. The nodes will be S, X, R. Assume X and R have similar timescales and use synchronous update.

Here are the Boolean functions, wiring diagram, and state space:

$$f_S = x_S$$
$$f_X = x_S$$
$$f_R = x_S \wedge \overline{x_X}$$





The dashed lines describe a step-wise increase in the signal S (i.e., $0 \to 1$ or $1 \to 0$).

Analysis

(i) Start with $x_S = 0$. The system goes into 000 in one step.

(ii) Now set $x_S = 1$, which leads to 100.

(iii) The system transitions $100 \to 111$ excitation for R.

(iv) In the next step $111 \to 110$ adaptation for R.

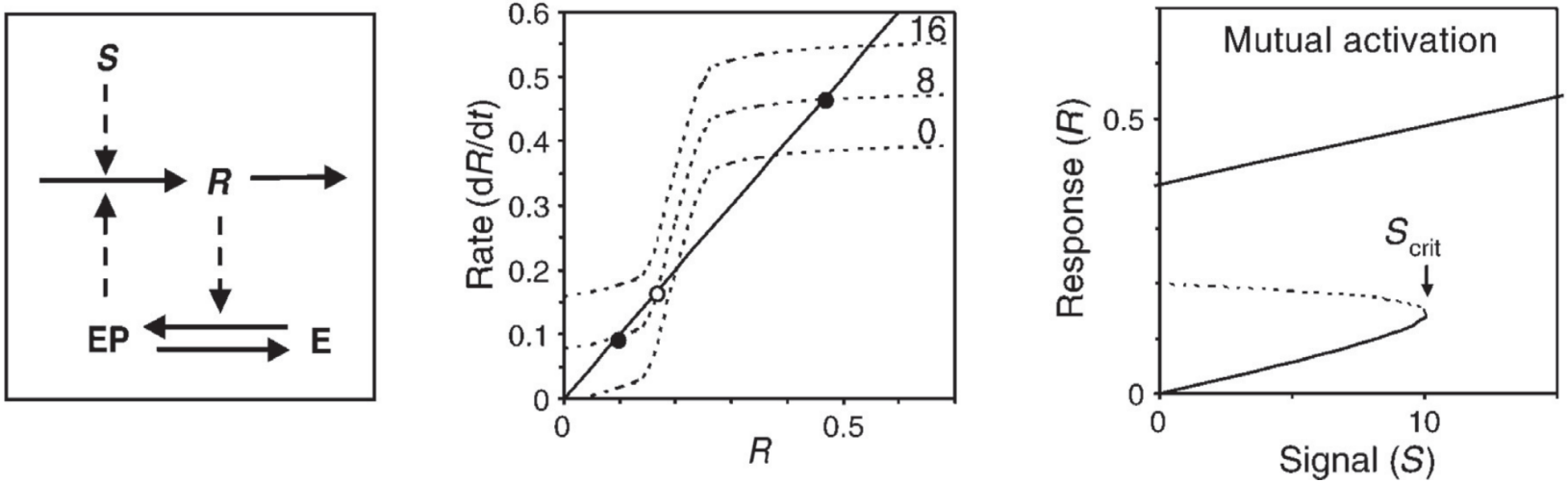
In summary, the change in x_S drove a transient excitation of $x_R : 0 \mapsto 1$ but the steady-state adapted to its original value of $x_R = 0$.

Multistability and hysteresis

Recall the phenomenon of multistability that open arises in physica, biology, and chemistry. It is the ability of a system to achieve multipe steady-states under the same external conditions.

Consider the following ODE, where S and P are concentrations of proteins, k_i $(i = 0, \ldots, 2)$ are rate constants, and f_E is a sigmoidal ("*Hill-like*") function:

$$\frac{dR}{dt} = k_0 f_E(R(t)) + k_1 S(t) - k_2 P(t)$$



Phosphorylation of a protein (adding of a phosphoryl group (PO_3^{2-}) changes its function, e.g., like an ON/OFF switch. The $EP \leftrightarrow E$ represents a phosphorylation–dephosphorylation cycle in which concentration of P is constant.

This ODE exhibits irreversible bistability.

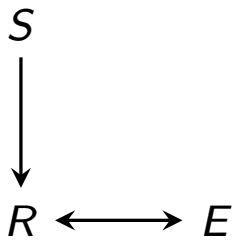
Multistability and hysteresis

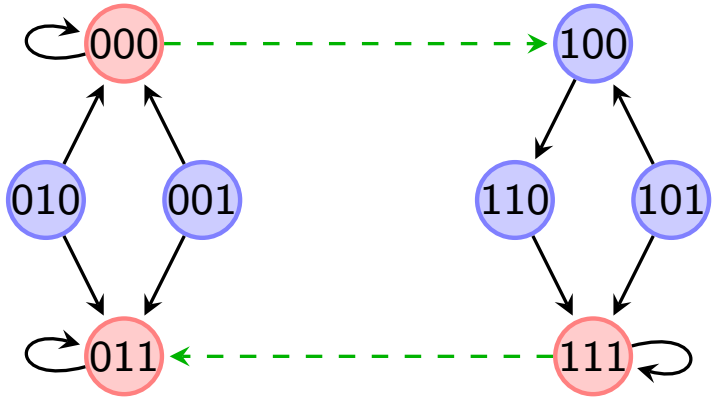
Let's create a Boolean model of this. The nodes will be S, R, E, where $E = 0$ and $E = 1$ are the Boolean approximation of the sigmoidal function $f_E(R)$.

In $R' = k_0 f_E(R(t)) + k_1 S(t) - k_2 P(t)$, synthesis of R is catalyzed *independently* by E and S.

Use general asynchronous update.

$$f_S = x_S$$
$$f_R = x_S \vee x_E$$
$$f_E = x_R$$





Analysis

(i) Start at 000 (OFF). Increase x_S to 1, which leads to 100.

(ii) The system settles to the ON steady-state 111.

(iii) Now, decrease x_S to 0, which leads to the steady-state 011. However, R is still 1.

Exercise. Show that the same behavior occurs under synchronous update.