Asynchronous Boolean models of signaling networks

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Think of it like a big natural Rube Goldberg machine.

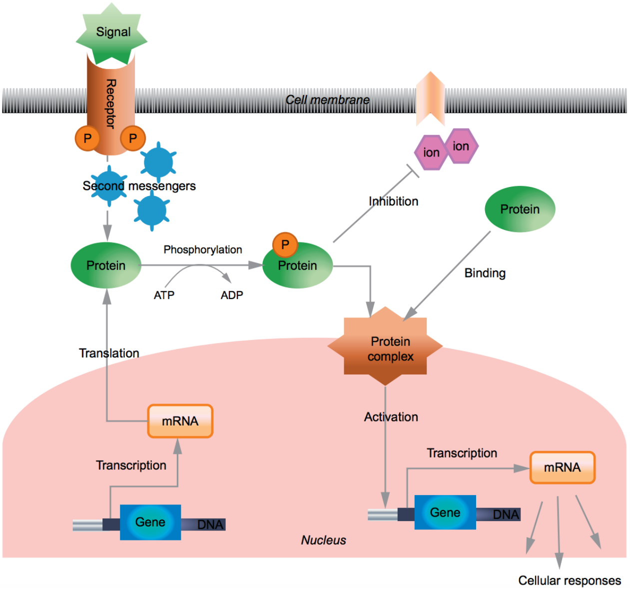

Figure: Scheme of a hypothetical signaling network.

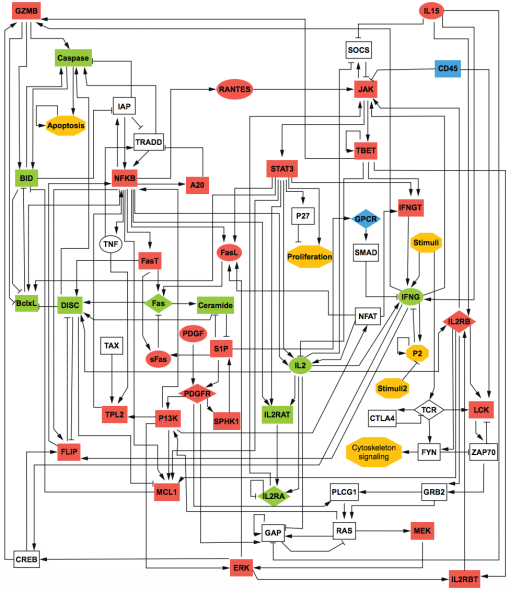

Figure: Signaling network involved in activation-induced cell death of killer T-cells. T-LGL leukemia disrupts this process, causing certain activated T-cells to survive, which later attack healthy cells.

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Rule of thumb

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

Feed-forward loops

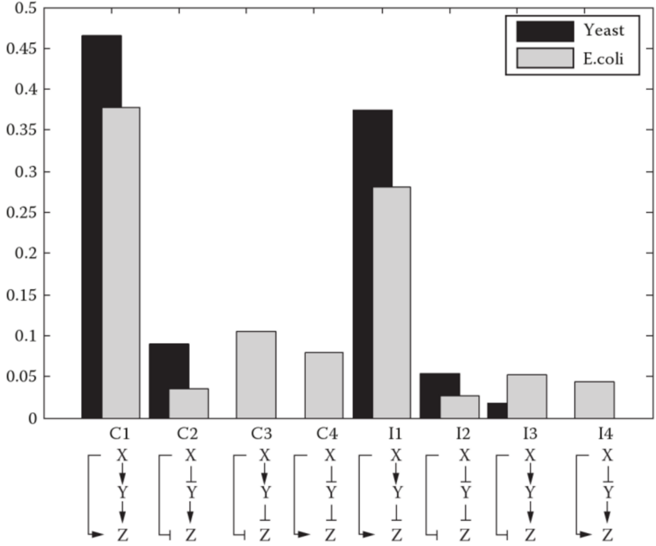

Figure: Relative abundance of the eight types of feed-forward loops in transcription networks (from U. Alon, 2007).

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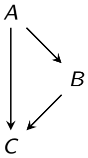

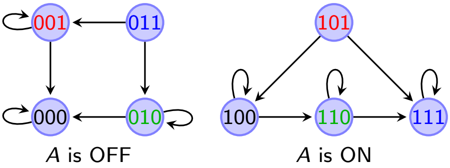

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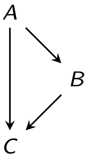

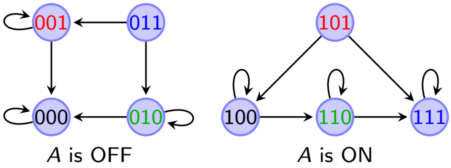

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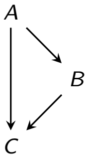

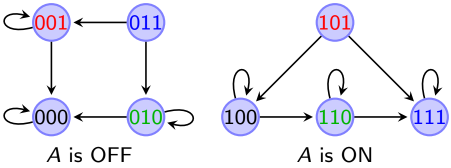

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- What do you the proper analogue of fixed points should be in this setting?

Synchronous vs. general asynchronous update

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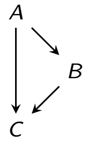

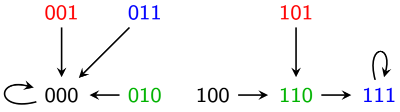

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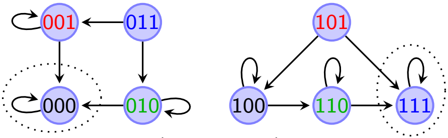

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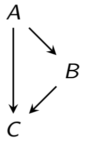

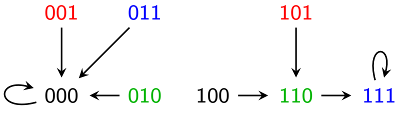

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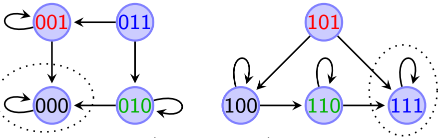

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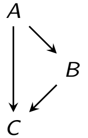

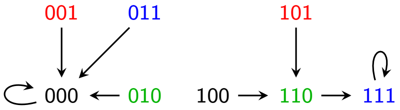

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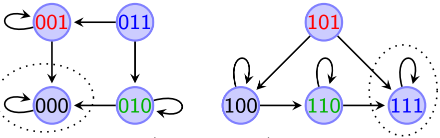

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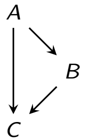

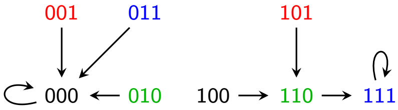

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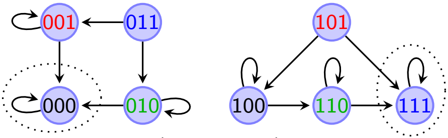

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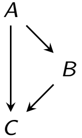
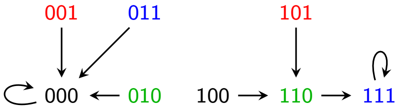
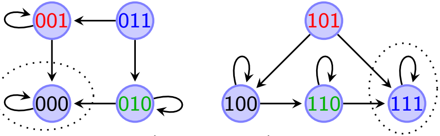




State space as a (synchronous) Boolean network



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

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Remark

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

Excitation–adaptation behavior

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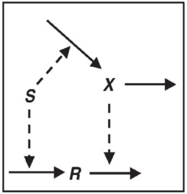
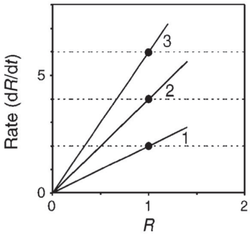
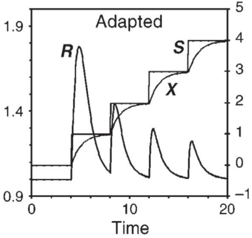
Analytical results

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







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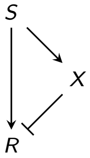

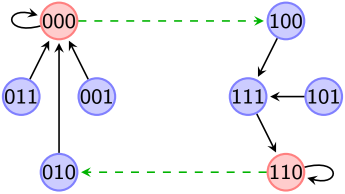

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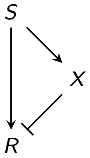

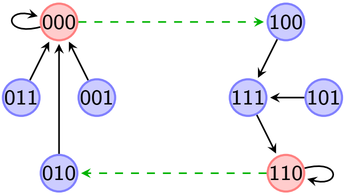

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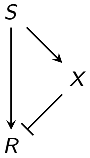

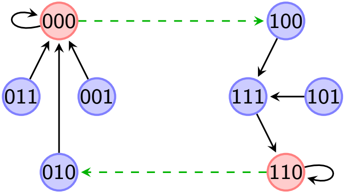

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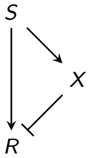

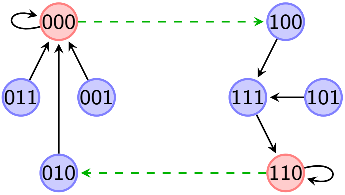

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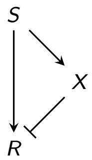

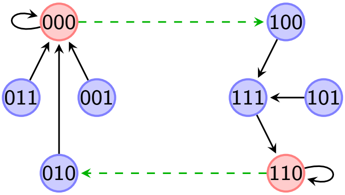

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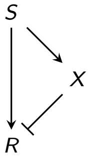

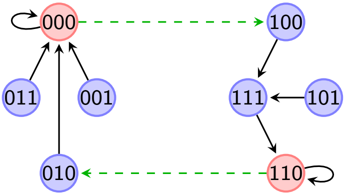

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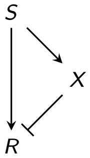

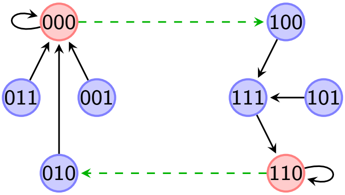

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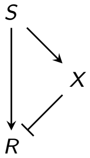

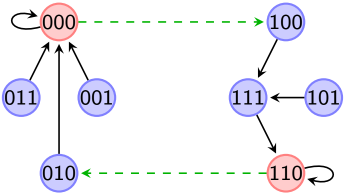

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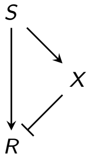

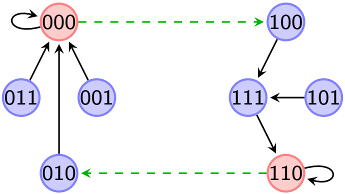

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In summary, the change in x_S drove a transient excitation of x_R: $0 \mapsto 1$ but the steady-state adapted to its original value of $x_R = 0$.

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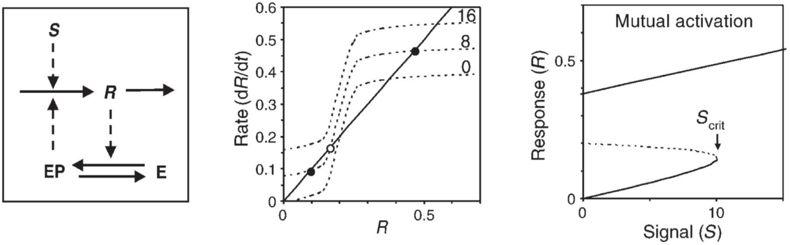

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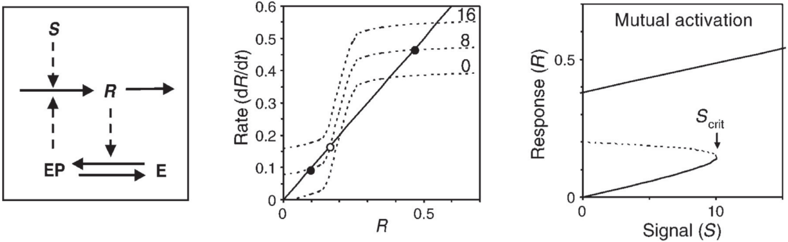

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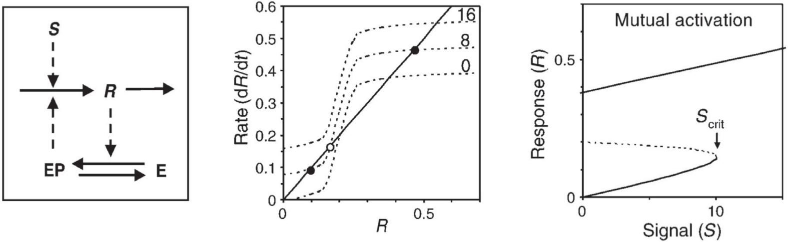

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This ODE exhibits irreversible bistability.

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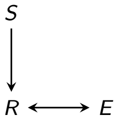

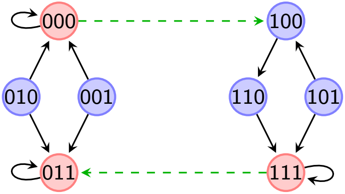

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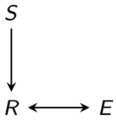

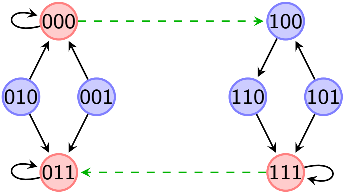

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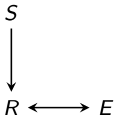

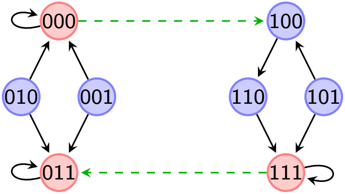

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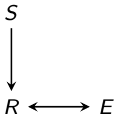

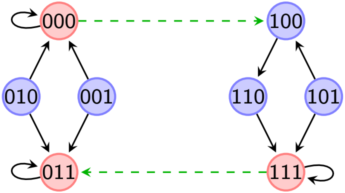

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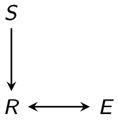
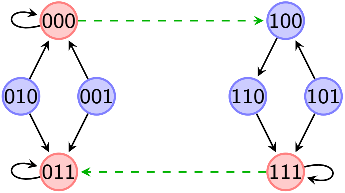




Analysis

(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.

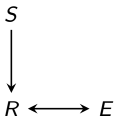
Multistability and hysteresis

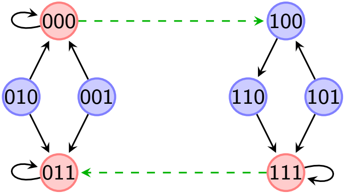
Let's create a Boolean model of this. The nodes will be S, R, E, where $E = 0$ and $E = 1$ are the Boolean approximation of the sigmoidal function $f_E(R)$.

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.

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





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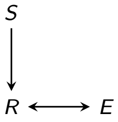

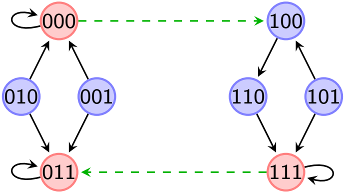

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Exercise. Show that the same behavior occurs under synchronous update.