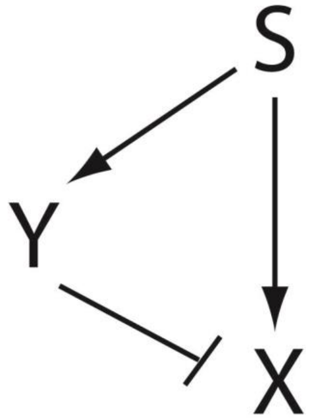
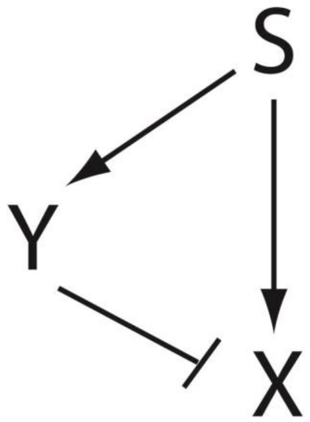


Modeling An Incoherent Feedforward Motif

A Incoherent Feedforwad



A simplified IFF: X and Y are active molecules.
Both are activated by S
Y inactivates X

The model:

$$\frac{dx}{dt} = k_1 * S * (1 - x) - k_2 * x * y$$

$$\frac{dy}{dt} = k_3 * S * \frac{(1 - y)}{Km + (1 - y)} - k_4 * y$$

Two path starting from same node, converge at same node.

These two paths are carrying opposing signals.

Analyzing the IFF

Consider, the system is saturated with total Y.

In other words, $Km << 1$

$$\frac{dy}{dt} = k_3 * S * \frac{(1-y)}{Km + (1-y)} - k_4 * y$$

$$\Rightarrow \frac{dy}{dt} = k_3 * S * \frac{(1-y)}{(1-y)} - k_4 * y$$

$$\Rightarrow \frac{dy}{dt} = k_3 * S - k_4 * y$$

Y nullcline:

$$\frac{dy}{dt} = 0$$

$$\therefore k_3 * S - k_4 * y = 0$$

$$\Rightarrow y = \frac{k_3}{k_4} * S$$

Analyzing the IFF

X nullcline:

$$\frac{dx}{dt} = 0$$

$$\therefore k_1 * S * (1 - x) - k_2 * x * y = 0$$

$$\Rightarrow y = \frac{k_1 * S * (1 - x)}{k_2 * x}$$

$$\Rightarrow y = \frac{k_1}{k_2} . S . (\frac{1}{x} - 1)$$

At steady state $\frac{dx}{dt} = 0 \quad \frac{dy}{dt} = 0$

X nullcline: $y = \frac{k_1}{k_2} . S . (\frac{1}{x} - 1)$ Y nullcline: $y = \frac{k_3}{k_4} * S$

So, at steady state,

$$\frac{k_1}{k_2} . S . (\frac{1}{x} - 1) = \frac{k_3}{k_4} . S$$

$$\Rightarrow (\frac{1}{x} - 1) = \frac{k_3}{k_4} . \frac{k_2}{k_1}$$

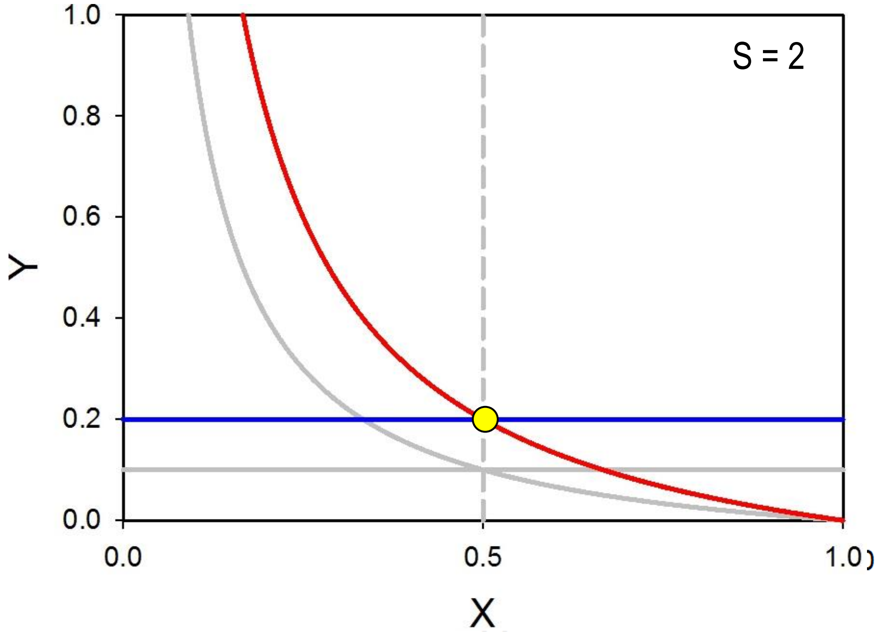
$$\Rightarrow x = \frac{1}{1 + \frac{k_3}{k_4} . \frac{k_2}{k_1}}$$

Steady state value of X is independent of input S

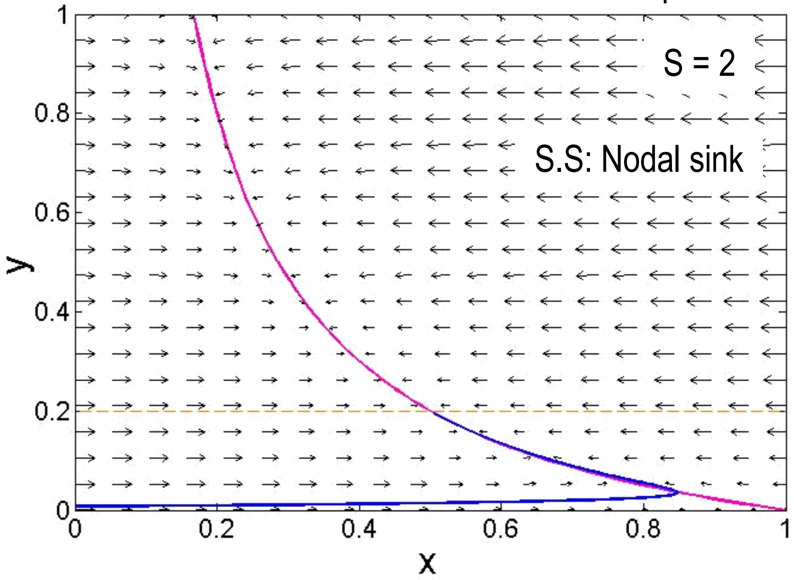
Steady state behavior

X nullcline: $y = \frac{k_1}{k_2}.S.(\frac{1}{x} - 1)$ Y nullcline: $y = \frac{k_3}{k_4} * S$

$k_1 = 10;\ k_2 = 100;\ k_3 = 0.1;\ k_4 = 1$



Phase portrait



Modeling in JSim

```
math IFF1
{ realDomain t ;
          t.min=0;t.delta=0.1;t.max=10;

  //Define dependent variables
          real x(t), y(t);

  //Define parameters
          real s = 1;
          real k1 = 10;
          real k2 = 100;
          real k3 = 0.1;
          real k4 = 1;
          real km = 0.001;

  // Initial values
          when (t=t.min){x=0; y=0;}

  // ODEs
          x:t = k1*s*(1-x) -k2*x*y;
          y:t = k3*s*(1-y)/(km+1-y) -k4*y;
 }
```

Simulation of JSim model

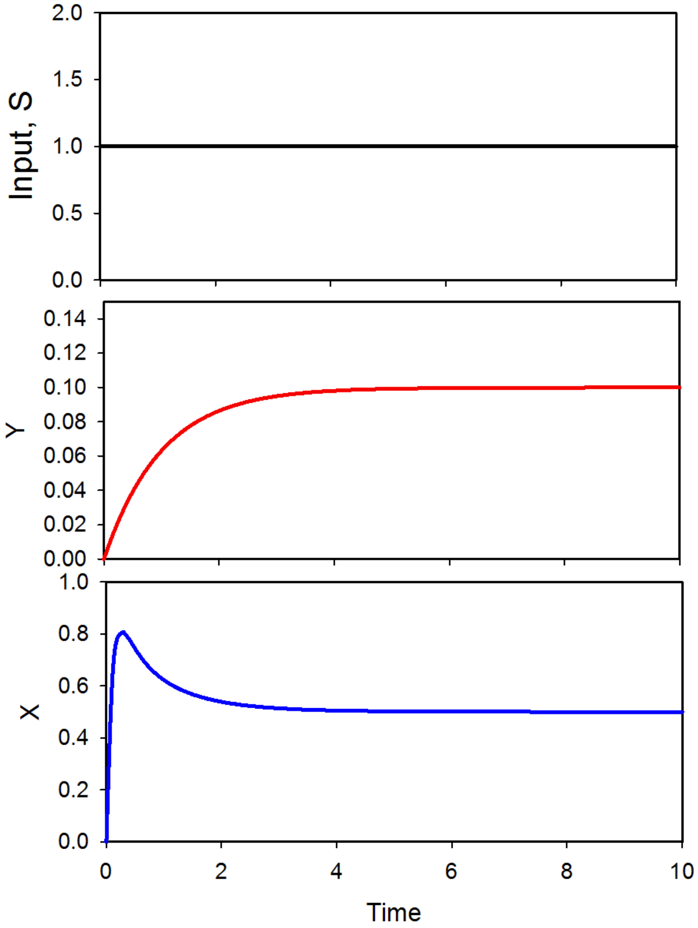
The path through Y is slower than direct activation of X by S.

This causes fast rise of X at the initial time points.

Y increases slowly with a hyperbolic time course

Subsequently the inhibition by Y, balances activation by S.

X reaches stable steady state after initial spike.

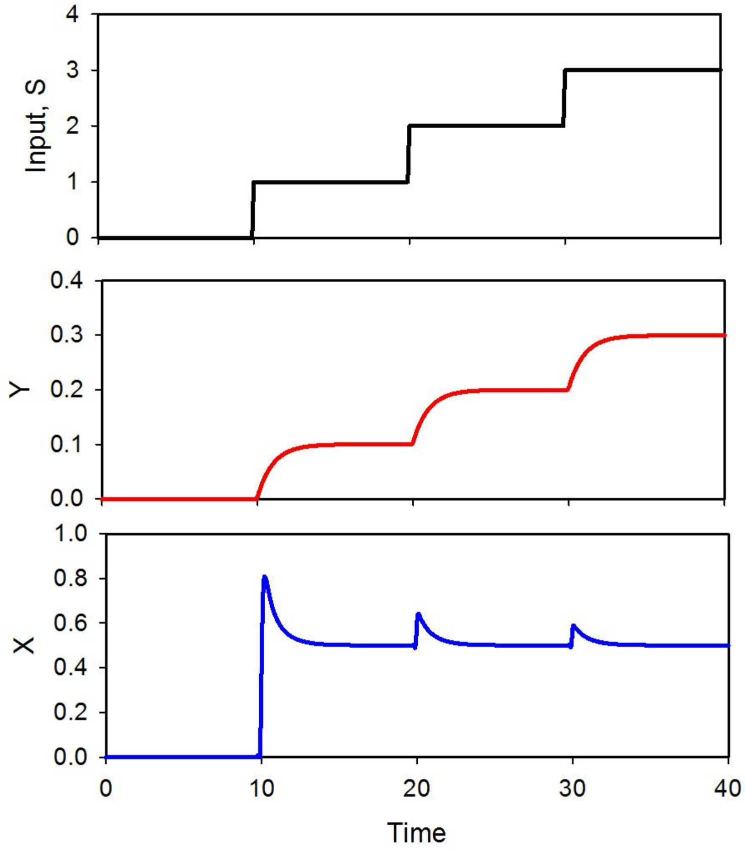


The IFF works as an adaptive motif

Input: Consecutive and with increasing amplitude

Output: Steady state value of X. After initial transient spike, X reaches same steady state value.

The system is sensitive to ON and OFF states of input. Adapts for any ON value of input to same output.



Key points:

1. We have modeled a simple IFF.
2. We have investigated the steady state using nullclines.
3. When the system is saturated with total Y, or Y nullcline gives linear relation between Y and input S, the output of the system (steady state value of X) is independent of the input, S.
4. We have performed simulation of the system using JSim
5. This IFF have adaptive behavior: It discriminates between ON and OFF state of the input. However, for any non-zero input the output of the system (steady state value of X) is same.
6. Negative feedback and IFF are known to have this type of adaptive behavior.