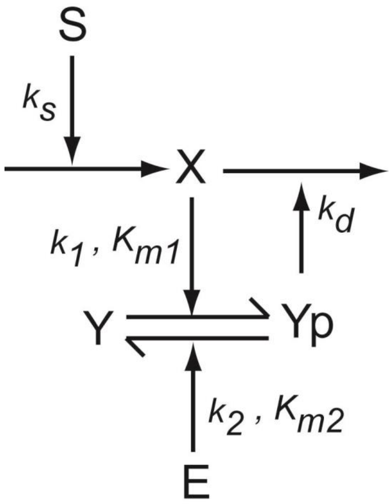
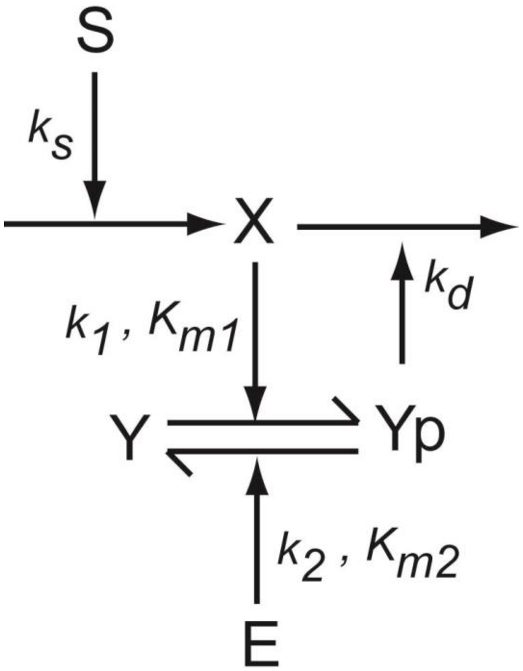


Modeling A Signal Transduction Circuit

A Negative Feedback



Reversible phosphorylation of Y follows Michaelis–Menten kinetics

The model:

$$\frac{d[X]}{dt} = k_S.S - k_d.[X].[Yp]$$

$$\frac{d[Yp]}{dt} = \frac{k_1.[X][Y]}{K_{m1} + [Y]} - \frac{k_2.[E][Yp]}{K_{m2} + [Yp]}$$

Considering conservation, $[Y]_T = [Y] + [Yp]$

$$\frac{d[Yp]}{dt} = \frac{k_1.[X]([Y]_T - [Yp])}{K_{m1} + ([Y]_T - [Yp])} - \frac{k_2.[E][Yp]}{K_{m2} + [Yp]}$$

Analyzing nullclines

X nullcline:

$$\frac{d[X]}{dt} = k_S.S - k_d.[X].[Yp]$$

$$\frac{d[X]}{dt} = 0$$

$$\therefore\ k_S.S - k_d.[X].[Yp] = 0$$

$$\Rightarrow [Yp] = \frac{k_S.S}{k_d[X]}$$

Yp nullcline:

$$\frac{d[Yp]}{dt} = \frac{k_1.[X]([Y]_T - [Yp])}{K_{m1} + ([Y]_T - [Yp])} - \frac{k_2.[E][Yp]}{K_{m2} + [Yp]}$$

$$\frac{d[Yp]}{dt} = 0$$

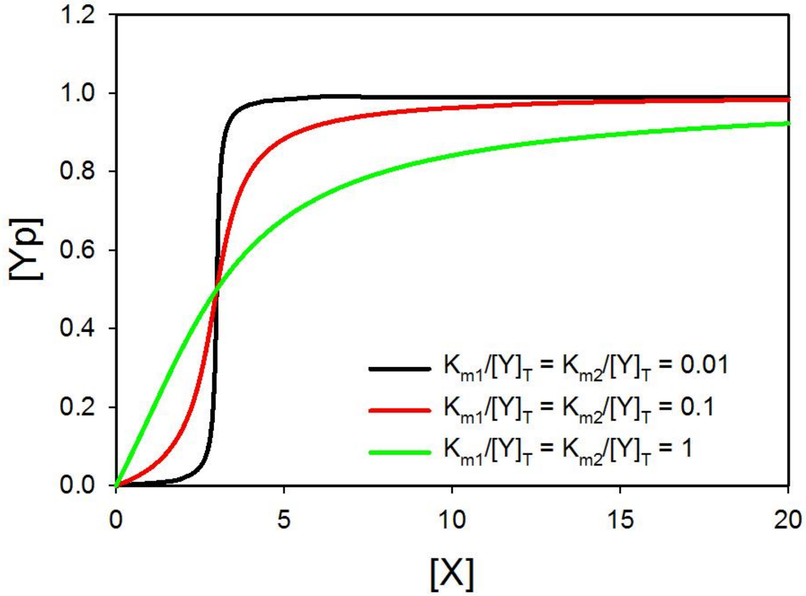
$$\therefore\ \frac{k_1.[X]([Y]_T - [Yp])}{K_{m1} + ([Y]_T - [Yp])} - \frac{k_2.[E][Yp]}{K_{m2} + [Yp]} = 0$$

$$[X] = \frac{1}{k_1}.\frac{k_2.[E].\frac{[Yp]}{[Y]_T}}{\frac{K_{m2}}{[Y]_T} + \frac{[Yp]}{[Y]_T}}.\frac{\frac{K_{m1}}{[Y]_T} + (1 - \frac{[Yp]}{[Y]_T})}{(1 - \frac{[Yp]}{[Y]_T})}$$

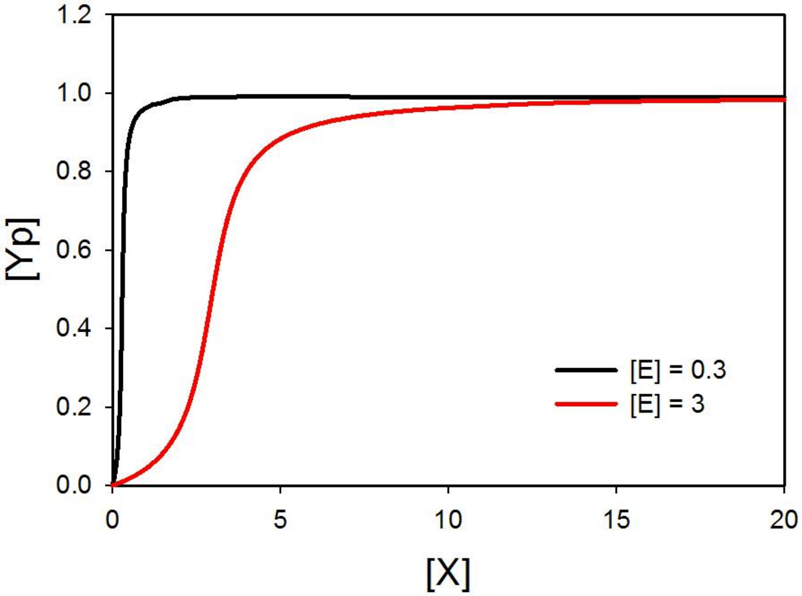
This is a sigmoid function & shape of it depends upon $K_{m1}/[Y]_T$, $K_{m2}/[Y]_T$, [E]

Behavior of Yp nullcline

$$k_1 = k_2 = 1;\ [Y]_T = 1;\ [E] = 3$$



$$k_1 = k_2 = 1;\ [Y]_T = 1;\ \frac{K_{m1}}{[Y]_T} = \frac{K_{m2}}{[Y]_T} = 0.1$$

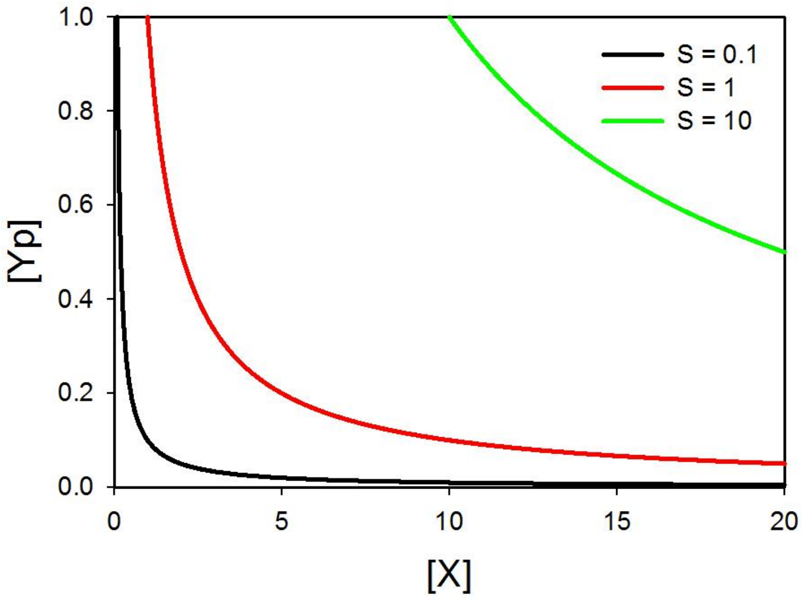


Behavior of X nullcline

Input signal S controls X nullcline

$$[Yp] = \frac{k_S . S}{k_d [X]}$$

$$k_S = k_d = 1$$

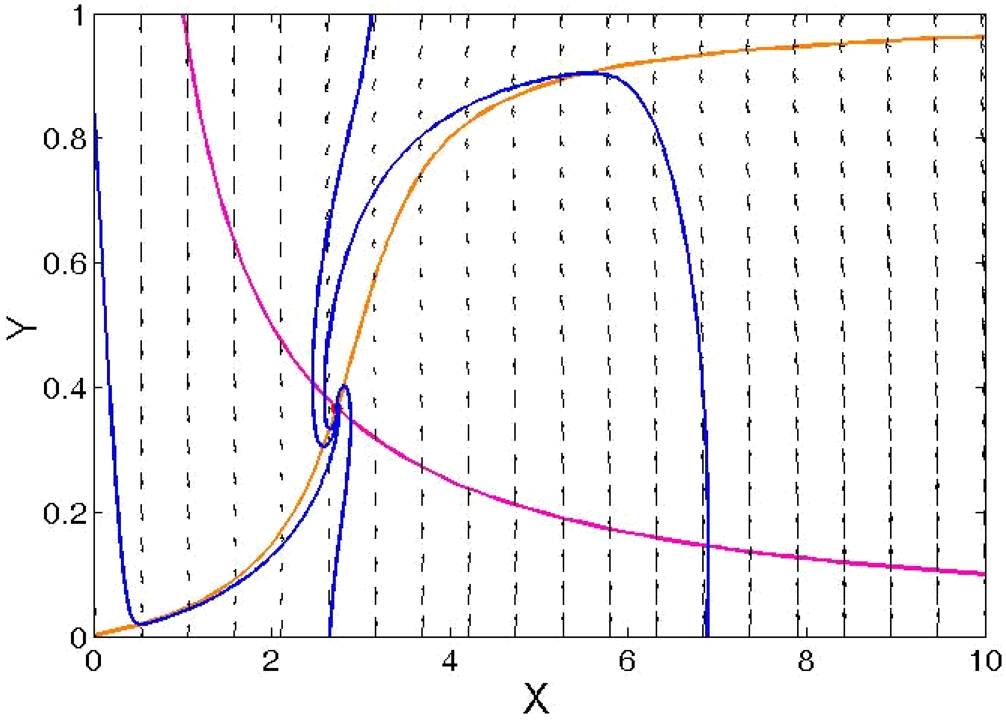


Steady state behavior

Parameter used for analysis:

$$k_1 = k_2 = 1;$$
$$[Y]_T = 1;\ [E]=3;$$
$$\frac{K_{m1}}{[Y]_T} = \frac{K_{m2}}{[Y]_T} = 0.1$$
$$k_S = k_d = 1$$
$$S = 1$$

Steady state → Spiral sink (stable)



Input-output behavior

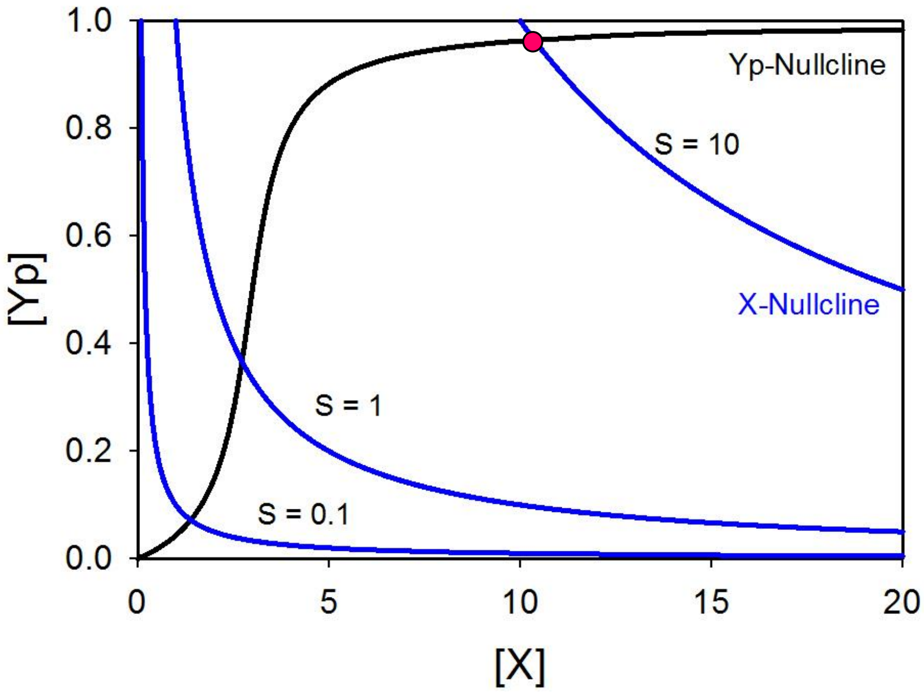
In this system,

S → Input

Steady state [Yp] → Output

Parameter used for analysis:

$$k_1 = k_2 = 1;$$
$$[Y]_T = 1;\ [\mathrm{E}]=3;$$
$$\frac{K_{m1}}{[Y]_T} = \frac{K_{m2}}{[Y]_T} = 0.1$$
$$k_S = k_d = 1$$



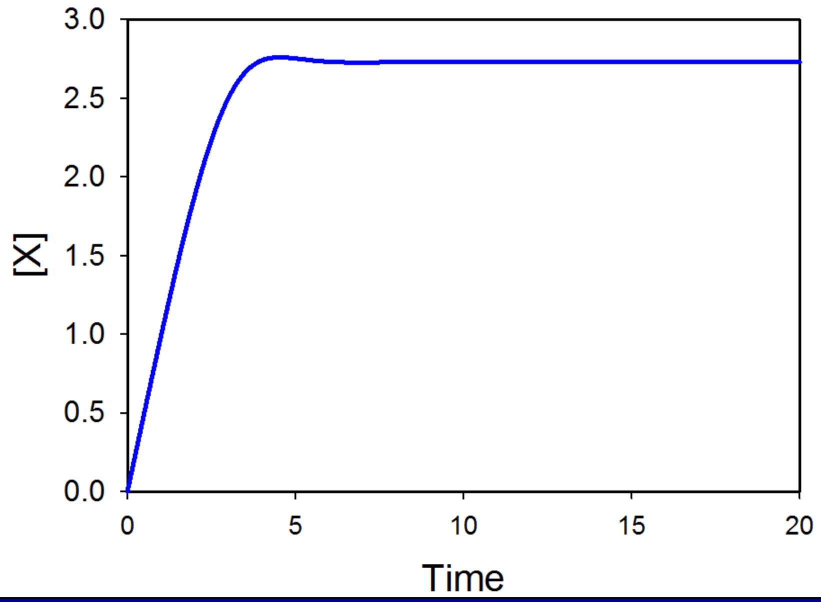
Modeling in JSim

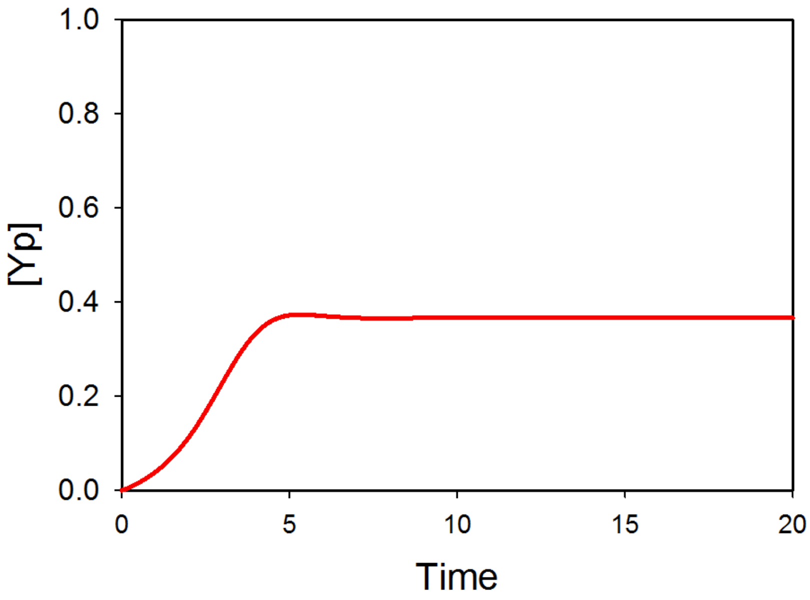
```
math NF_enzyme
{ realDomain t ;
          t.min=0;t.delta=0.1;t.max=50;

  //Define dependent variables
          real x(t), yp(t);
  //Define parameters
          real s = 1;
          real ks = 1;
          real kd = 1;
          real k1 = 1;
          real k2 = 1;
          real km1 = 0.1;
          real km2 = 0.1;
          real yt =1;
          real e = 3;
  // Initial values
          when (t=t.min){x=0; yp=0;}
  // ODEs
          x:t = ks*s - kd*yp*x;
          yp:t = ((k1*x*(yt-yp))/(km1+(yt-yp)))- (k2*e*yp/(km2+yp));
    }
```

Simulation: Dynamics of X and Yp

Parameter values used:

$$k_1 = k_2 = 1;\ [Y]_T = 1;\ [E]=3;\ \frac{K_{m1}}{[Y]_T} = \frac{K_{m2}}{[Y]_T} = 0.1;\ k_S = k_d = 1;\quad S = 1$$





Simulation: Input-output relation

Simulated using JSim

Parameter values used:

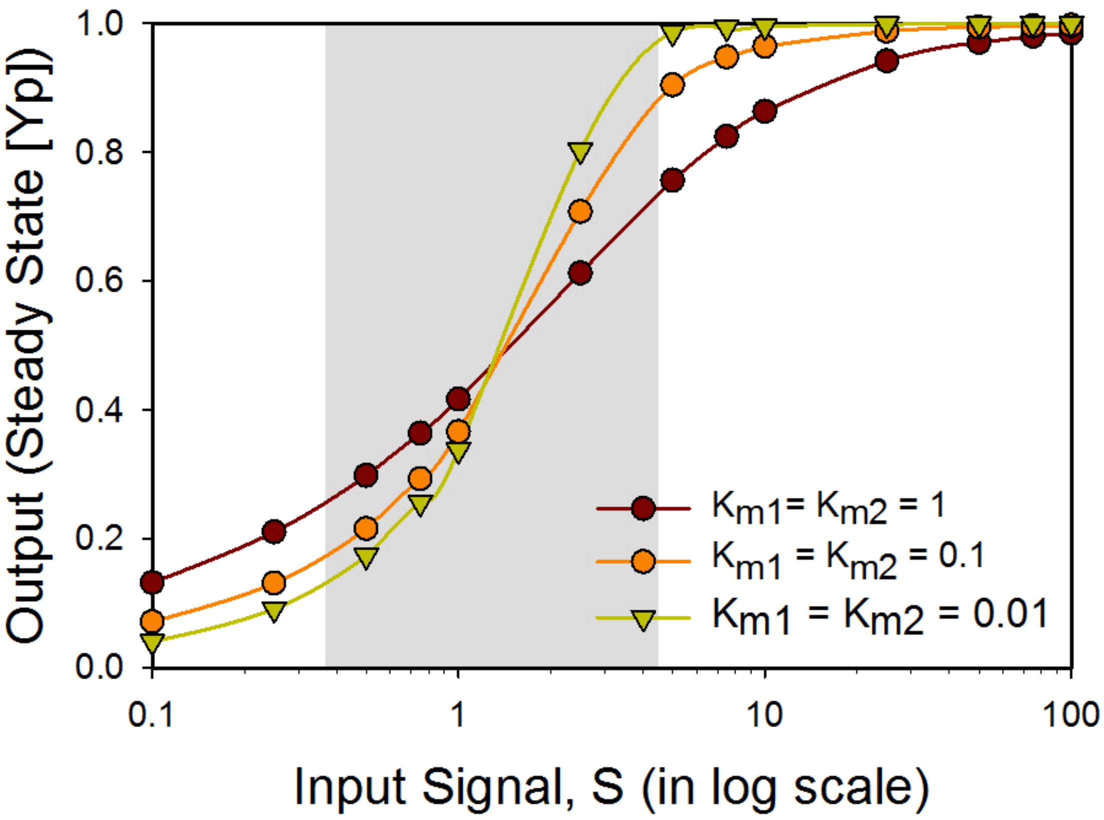
$$k_1 = k_2 = 1;$$

$$[Y]_T = 1;\ [E]=3;$$

$$k_S = k_d = 1$$

$$\frac{K_{m1}}{[Y]_T} = \frac{K_{m2}}{[Y]_T} = \text{ varied}$$

$$S = \text{ varied}$$



Key points:

1. We have modeled a negative-feedback circuit with reversible phosphorylation of a protein
2. The system is monostable with Spiral sink type steady state
3. Steady state position depends on input signal S, and Michaelies Menten parameters of reversible phosphorylation switch
4. When $Km/[Y]_T$ are close to 1, for kinase (X) and phosphatase (E): Input-output relation is close to linear
5. When $Km/[Y]_T$ are much smaller than 1, for kinase (X) and phosphatase (E): Input-output relation is ultra-sensitive and sigmoidal, with lack of sensitivity at higher and lower inputs.