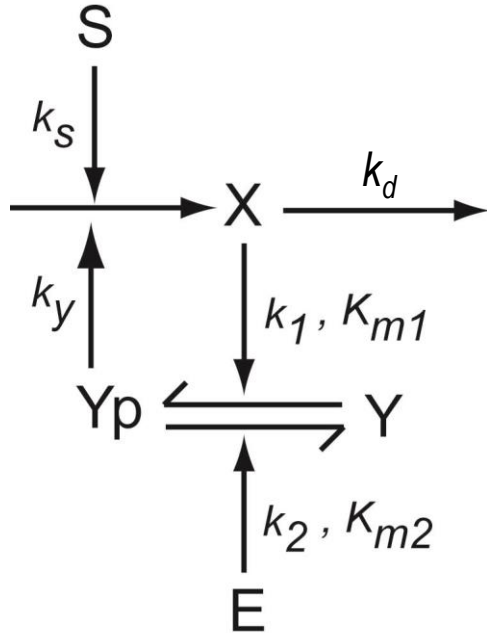# Modeling A Positive Feedback Circuit

A Positive Feedback

Reversible phosphorylation of Y follows Michaelis–Menten kinetics

The model:

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

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

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:

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

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

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

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

Yp nullcline:

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

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

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

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

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

Steady state behavior
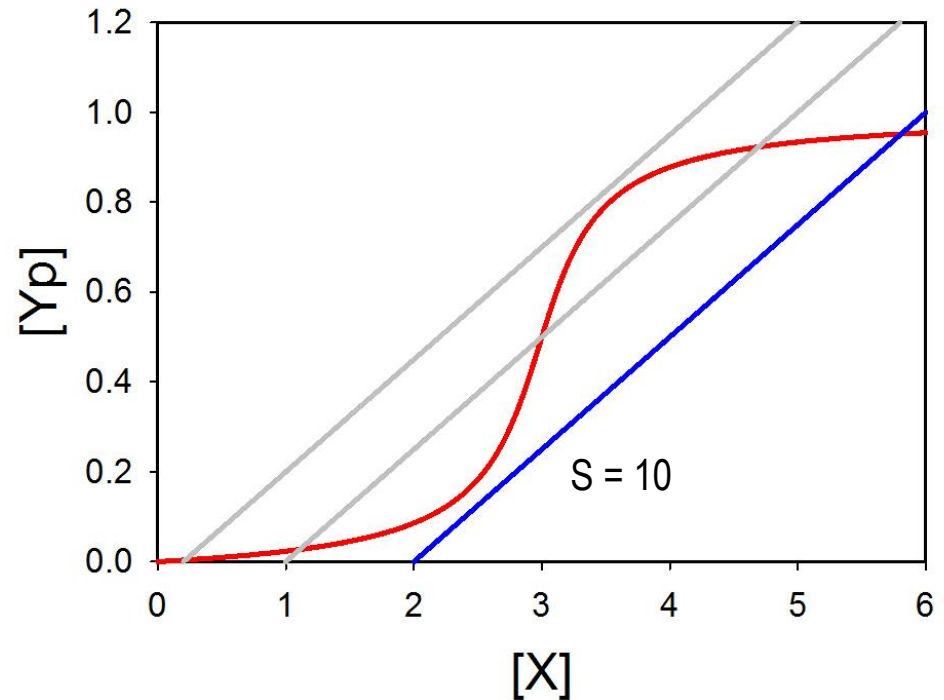
Parameter used for analysis:

$$k_1 = k_2 = 1;$$

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

$$\frac{K_{m1}}{[Y]_T} = \frac{K_{m2}}{[Y]_T} = 0.05$$
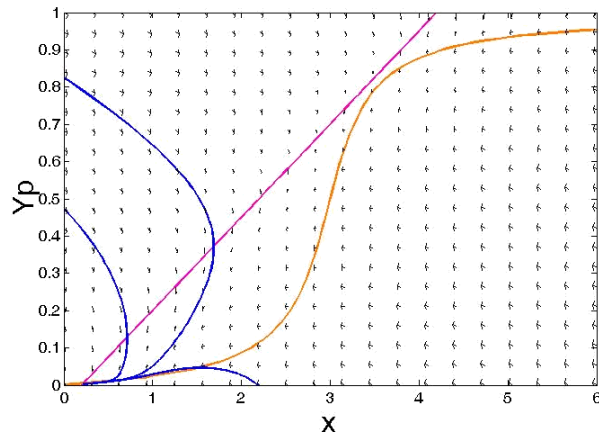
$$k_S = 1 \quad k_y = 20$$

$$k_d = 5$$
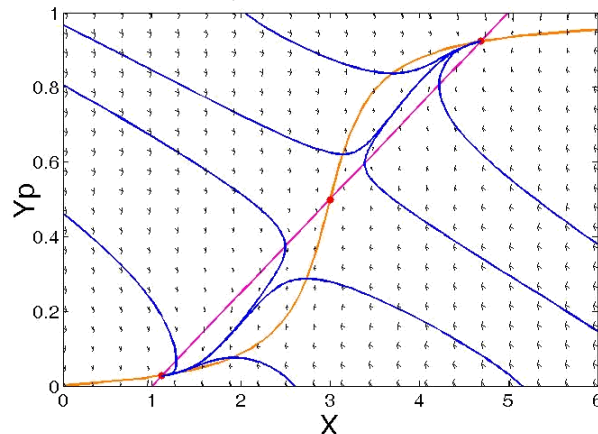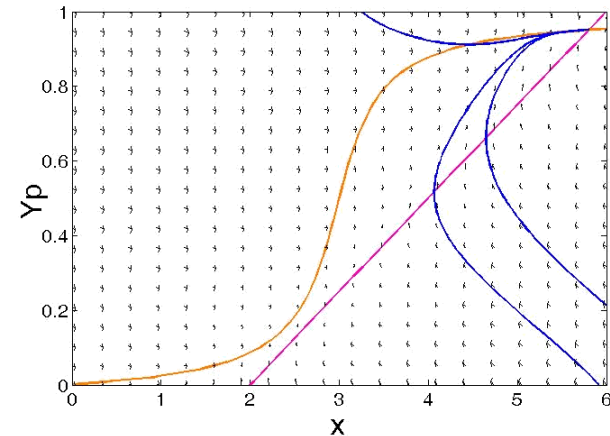
S = 1

One steady state: Nodal Sink

S = 5

Two steady states: Nodal Sink
One steady state: Saddle

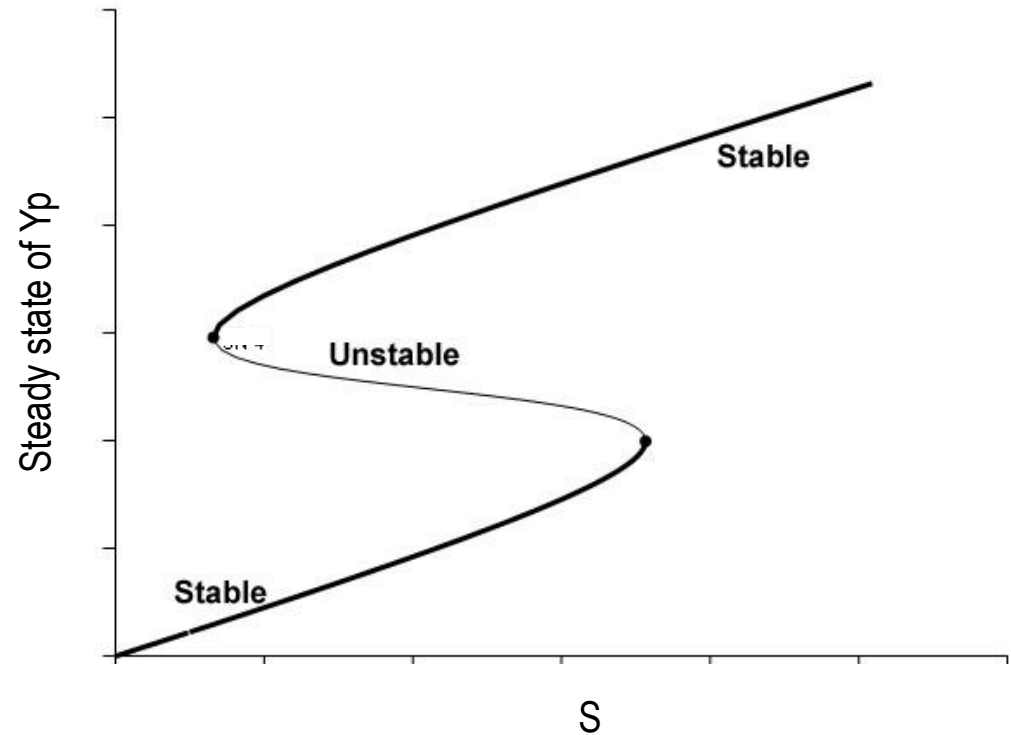
S = 10

One steady state: Nodal Sink

This positive feedback has bifurcation

Number of steady states and their stability
changes with input signal S

Modeling in JSim

```
math PF_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 ky = 20;
        real kd = 5;
        real k1 = 1;
        real k2 = 1;
        real km1 = 0.05;
        real km2 = 0.05;
        real yt =1;
        real e = 3;
```
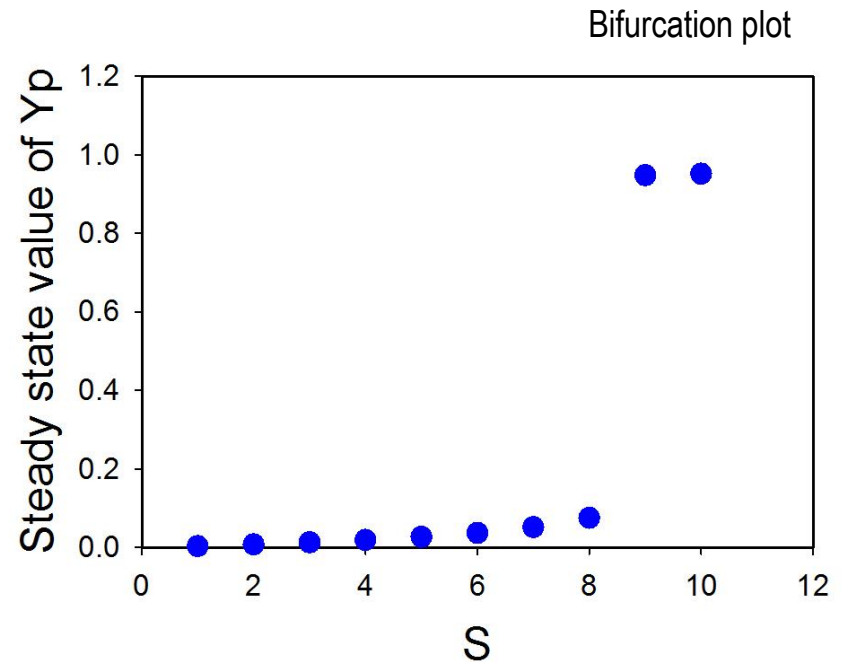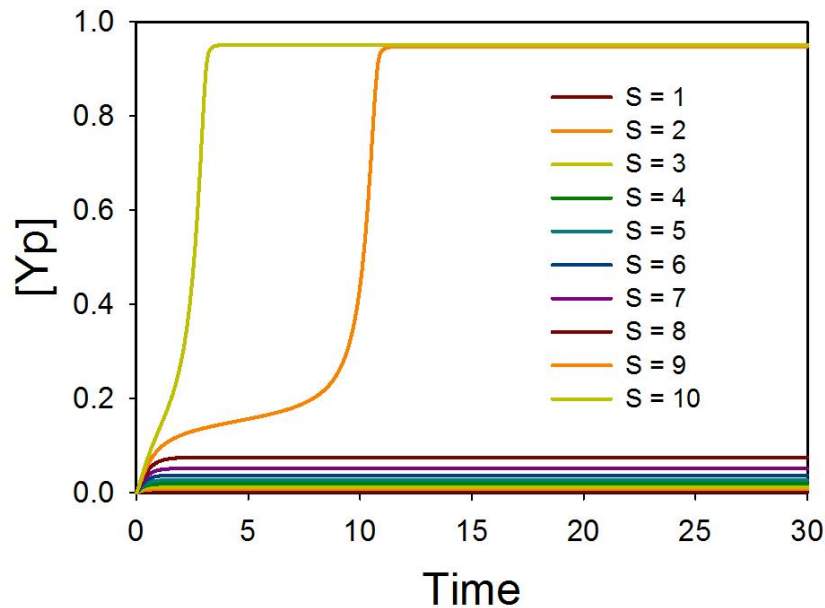
Modeling in JSim

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

  // ODEs
        x:t = ks*s + ky*yp - kd*x;
        yp:t = ((k1*x*(yt-yp))/(km1+(yt-yp)))- (k2*e*yp/(km2+yp));

}
```
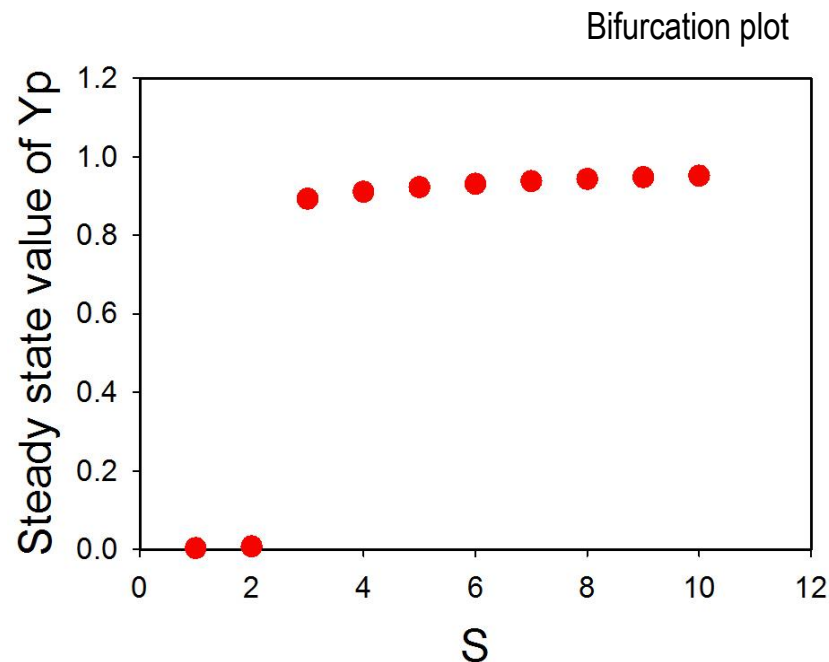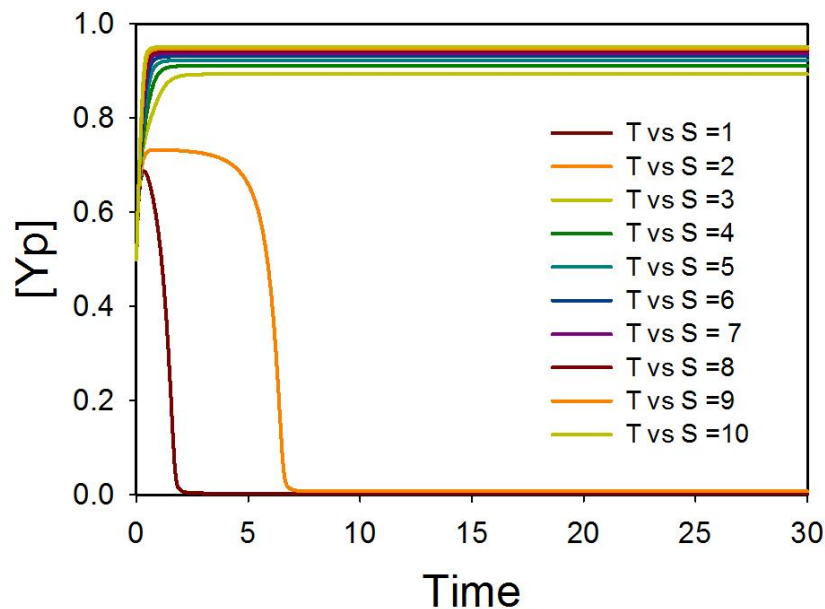
Simulation of JSim model

Initial condition: X = Yp = 0

Bifurcation plot

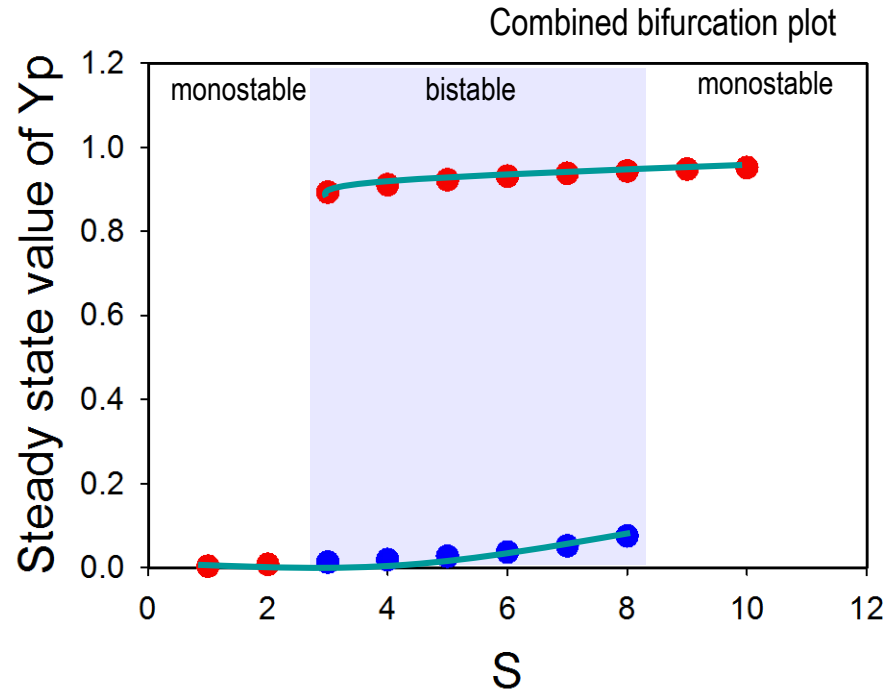Initial condition: X = 5; Yp = 0.5

Bifurcation plot

Simulation of JSim model

Creating a bifurcation diagram:

Plotted together: Steady state values of Yp for different values of S, with different initial conditions.

Those data points can be connected by smooth lines.

By numerical simulation we can get only stable steady states.

Combined bifurcation plot

Key points:

1. We have modeled a positive-feedback circuit with reversible phosphorylation of a protein.
2. The system has bifurcation with respect to input signal S.
3. Depending upon value of S: there can be one stable steady state or two stable with one unstable steady state.
4. Therefore the system is bi-stable
5. The non-linearity in the Yp nullcline is responsible for such bifurcation
6. We can perform bifurcation analysis by numerical simulation too.