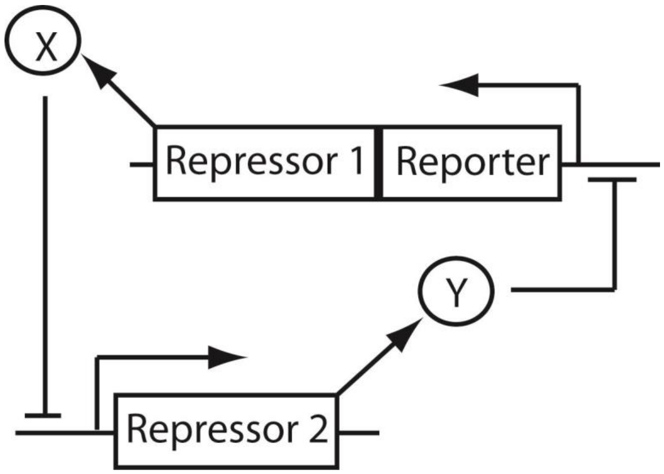
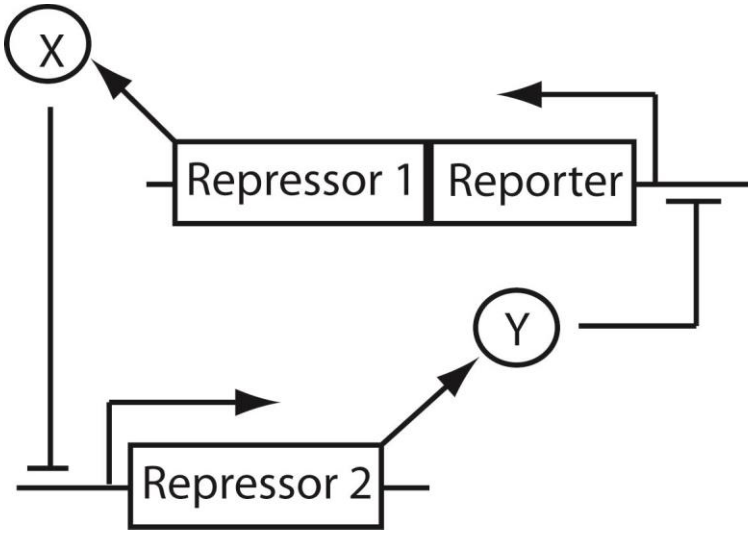


Modeling Transcriptional Circuits - 1

Mutual Repression

Repression of repressor : Equivalent to positive feedback



Considered faster transcription and steady state for mRNA

$$\frac{d[x]}{dt} = k_1 . \frac{1}{1 + (\frac{[y]}{H_1})^{n_1}} - k_{d1} . [x]$$

$$\frac{d[y]}{dt} = k_2 . \frac{1}{1 + (\frac{[x]}{H_2})^{n_2}} - k_{d2} . [y]$$

k_1, k_2: maximum rate of production

H_1, H_2: Hill constants

n_1, n_2: Hill coefficients

k_{d1}, k_{d2}: rate constants for degradation

Simplifying ODEs

$$\frac{d[x]}{dt} = k_1 . \frac{1}{1 + (\frac{[y]}{H_1})^{n_1}} - k_{d1} . [x]$$

$$\frac{d[x]}{dt} = k_1 . \frac{1}{1 + [y]^{n_1}} - [x]$$

$$\frac{d[y]}{dt} = k_2 . \frac{1}{1 + (\frac{[x]}{H_2})^{n_2}} - k_{d2} . [y]$$

$$\frac{d[y]}{dt} = k_2 . \frac{1}{1 + [x]^{n_2}} - [y]$$

For simplifications, assume

$H_1 = H_2 = 1$

$K_{d1} = k_{d2} = 1$

Analyzing nullclines

x nullclines:

$$\frac{d[x]}{dt} = k_1 . \frac{1}{1+[y]^{n_1}} - [x]$$

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

$$\therefore \; k_1 . \frac{1}{1+[y]^{n_1}} - [x] = 0$$

$$\Rightarrow [x] = k_1 . \frac{1}{1+[y]^{n_1}}$$

y nullclines:

$$\frac{d[y]}{dt} = k_2 . \frac{1}{1+[x]^{n_2}} - [y]$$

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

$$\therefore \; k_2 . \frac{1}{1+[x]^{n_2}} - [y] = 0$$

$$\Rightarrow [y] = k_2 . \frac{1}{1+[x]^{n_2}}$$

Analyzing nullclines

x nullcline:

$$[x] = k_1 \cdot \frac{1}{1+[y]^{n_1}}$$

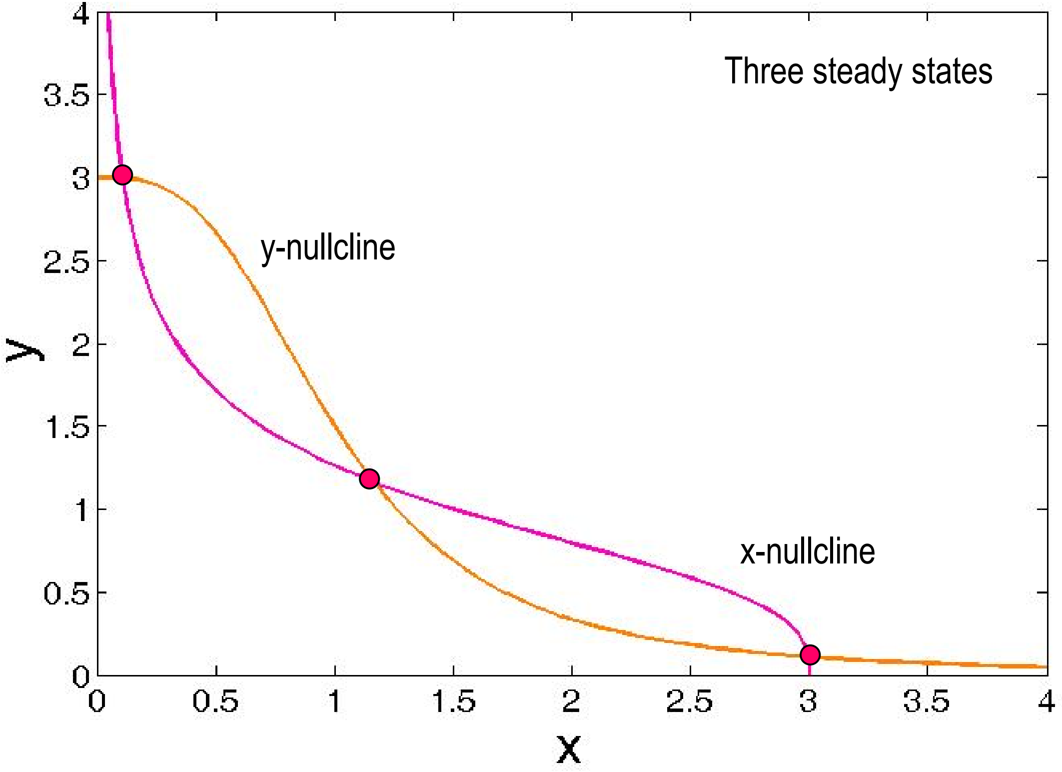
y nullcline

$$[y] = k_2 \cdot \frac{1}{1+[x]^{n_2}}$$

For

$k_1 = k_2 = 3$

$n_1 = n_2 = 3$



Analyzing nullclines

x nullcline:

$$[x] = k_1 . \frac{1}{1+[y]^{n_1}}$$

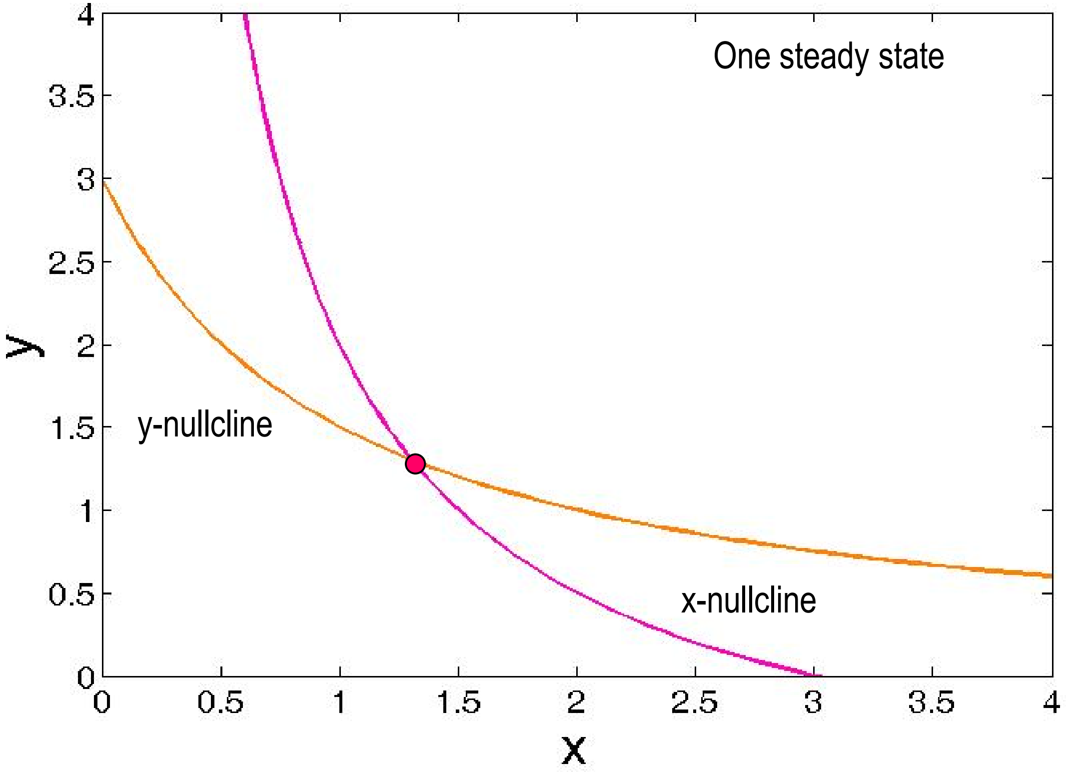
y nullcline

$$[y] = k_2 . \frac{1}{1+[x]^{n_2}}$$

For

k_1 = k_2 = 3

n_1 = n_2 = 1



Analyzing nullclines

x nullcline:

$$[x] = k_1 \cdot \frac{1}{1+[y]^{n_1}}$$

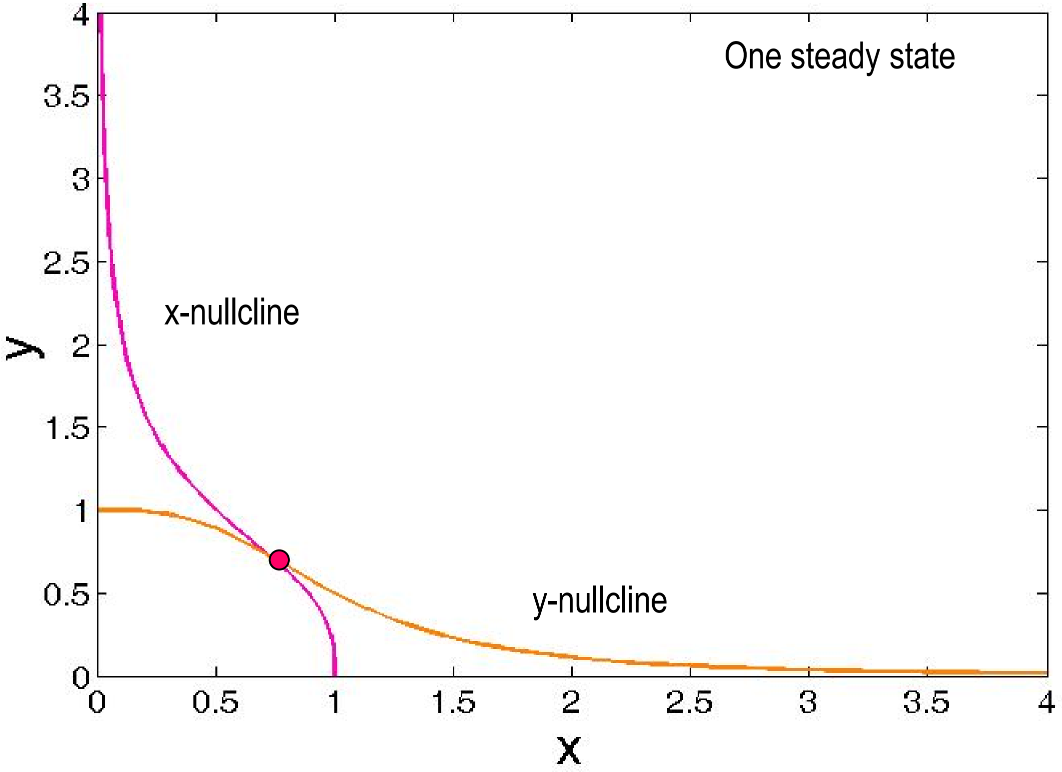
y nullcline

$$[y] = k_2 \cdot \frac{1}{1+[x]^{n_2}}$$

For

$k_1 = k_2 = 1$

$n_1 = n_2 = 3$



Analyzing nullclines

x nullcline:

$$[x] = k_1 . \frac{1}{1+[y]^{n_1}}$$

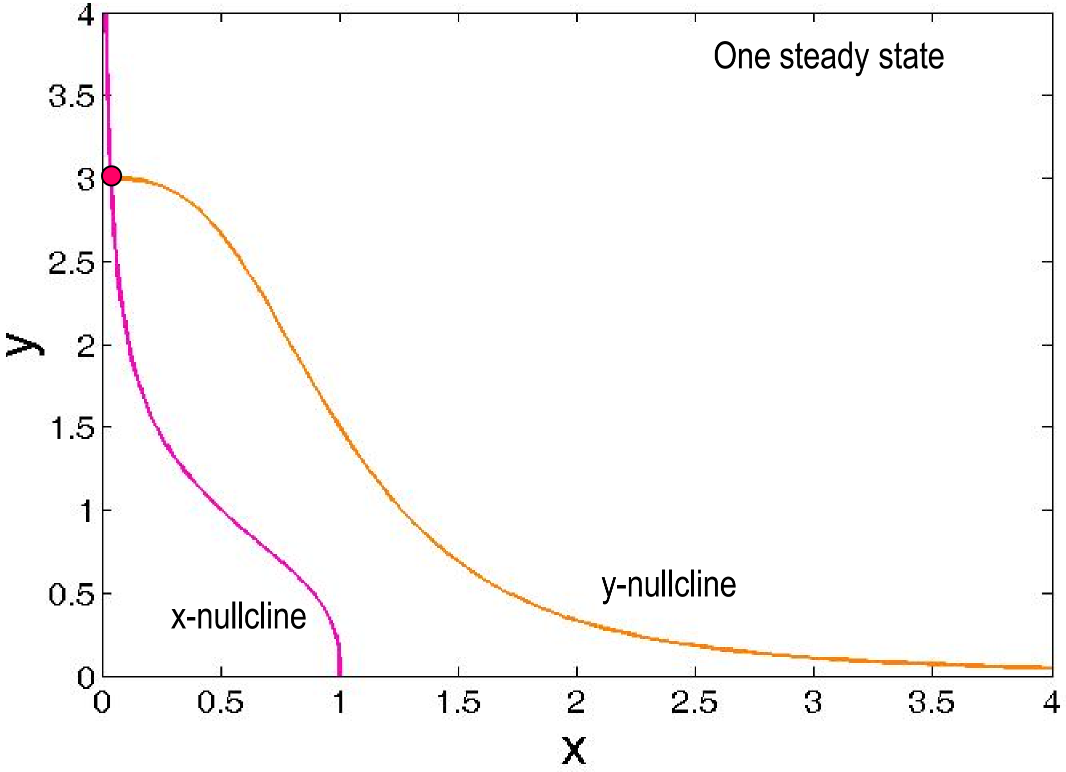
y nullcline

$$[y] = k_2 . \frac{1}{1+[x]^{n_2}}$$

For

k_1 = 1, k_2 = 3

n_1 = n_2 = 3



Analyzing Stability

Bistable

x nullcline:

$$[x] = k_1 . \frac{1}{1+[y]^{n_1}}$$

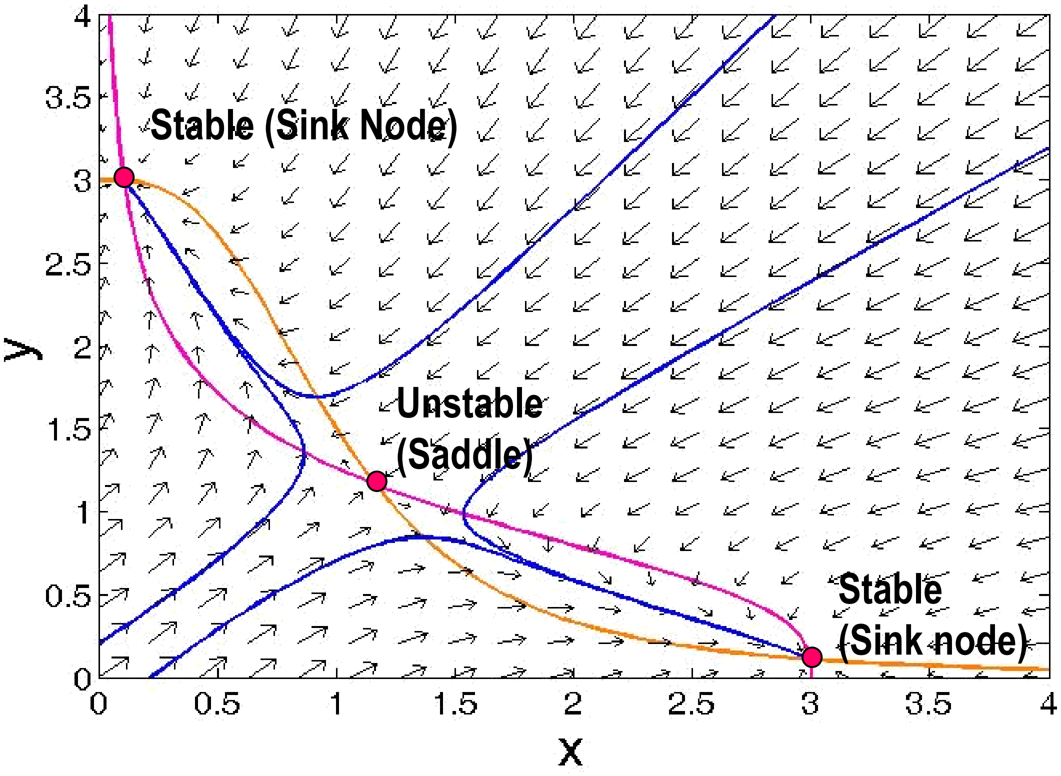
y nullcline

$$[y] = k_2 . \frac{1}{1+[x]^{n_2}}$$

For

k_1 = k_2 = 3

n_1 = n_2 = 3



Analyzing Stability

Mono-stable

x nullcline:

$$[x] = k_1 . \frac{1}{1+[y]^{n_1}}$$

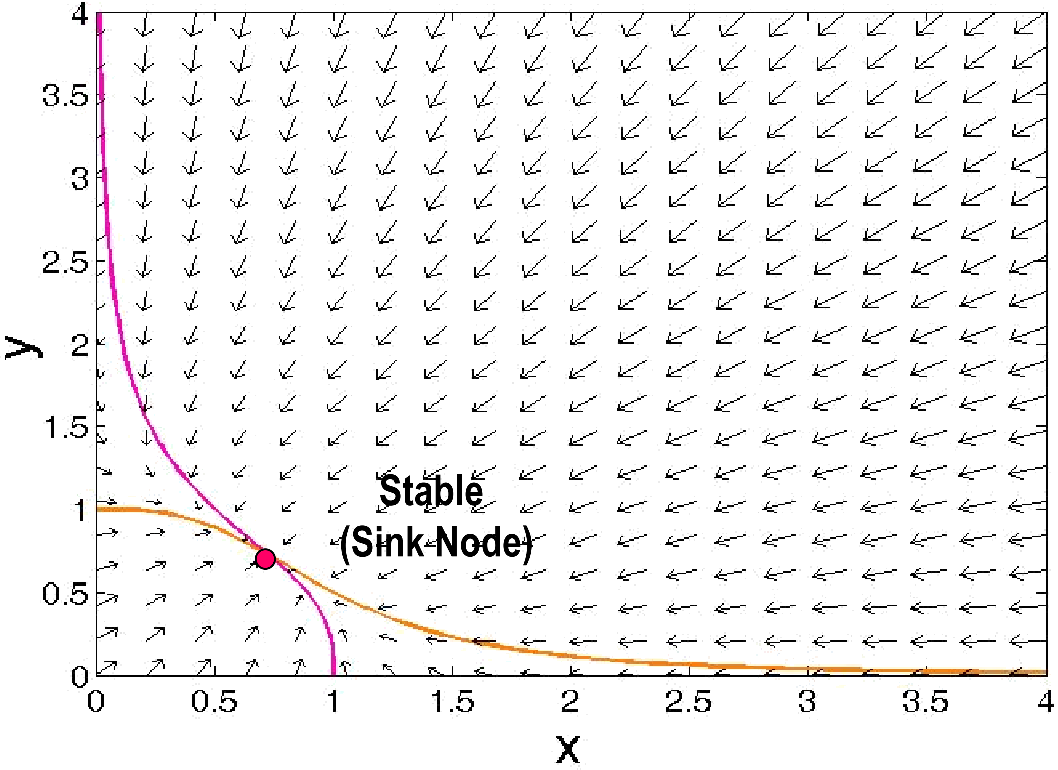
y nullcline

$$[y] = k_2 . \frac{1}{1+[x]^{n_2}}$$

For

$k_1 = k_2 = 1$

$n_1 = n_2 = 3$



Analyzing Stability

Mono-stable

x nullcline:

$$[x] = k_1 \cdot \frac{1}{1+[y]^{n_1}}$$

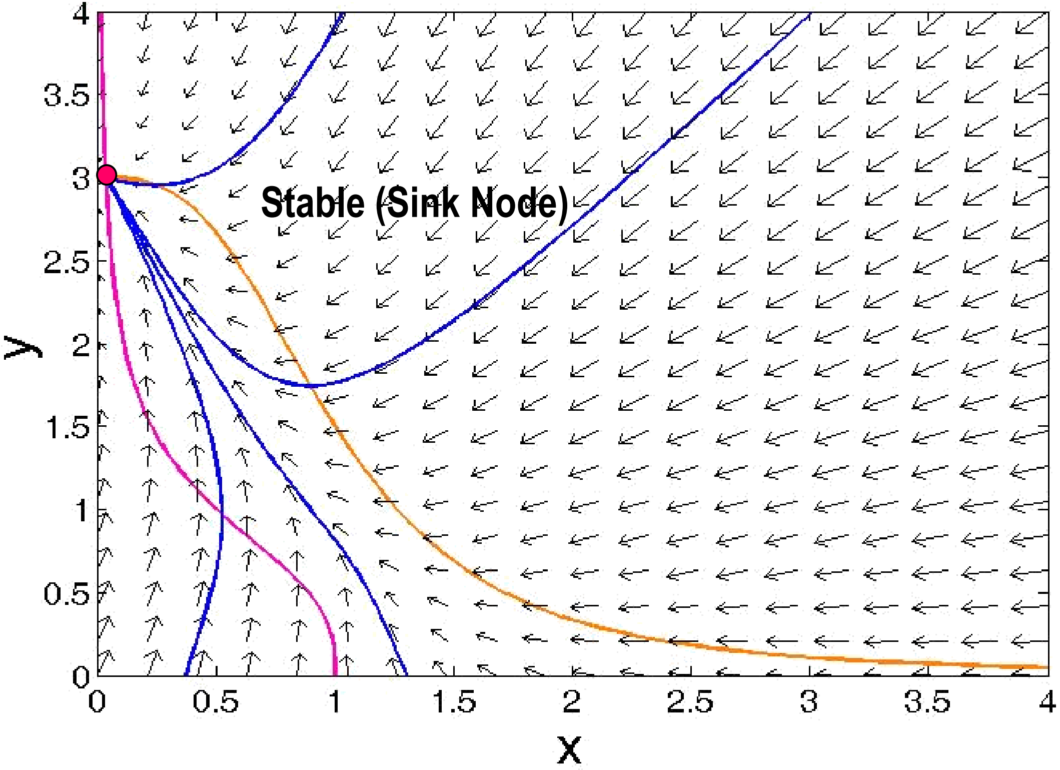
y nullcline

$$[y] = k_2 \cdot \frac{1}{1+[x]^{n_2}}$$

For

k_1 = 1, k_2 = 3

n_1 = n_2 = 3



Modeling in JSim

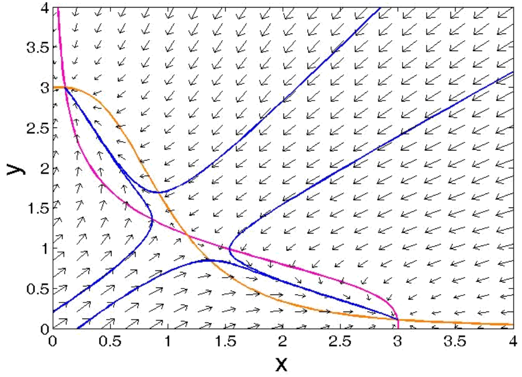
```
math mutual_inhibition
{ realDomain t ;
        t.min=0;t.delta=0.1;t.max=40;

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

  //Define parameters
        real k1 = 3;
        real k2 = 3;
        real n1 = 3;
        real n2 = 3;


  // Initial values
        when (t=t.min){x=1; y=0;}
  // ODEs
        x:t =  k1*1/(1+y^n1) - x;
        y:t = k2*1/(1+x^n2) - y;
}
```

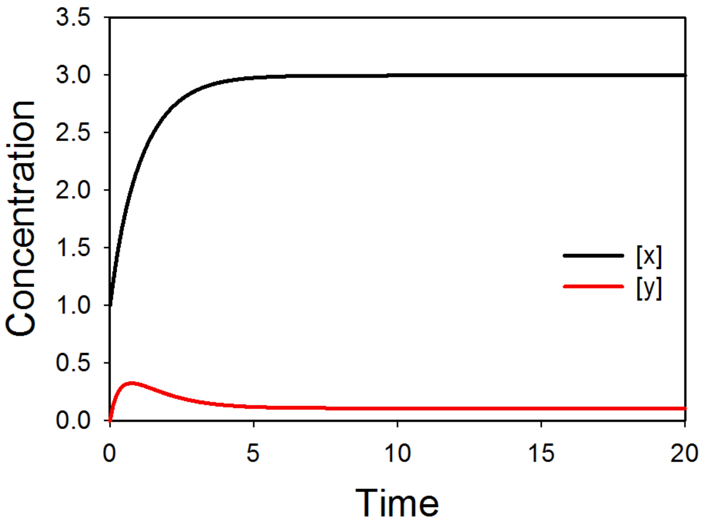
Results of simulation

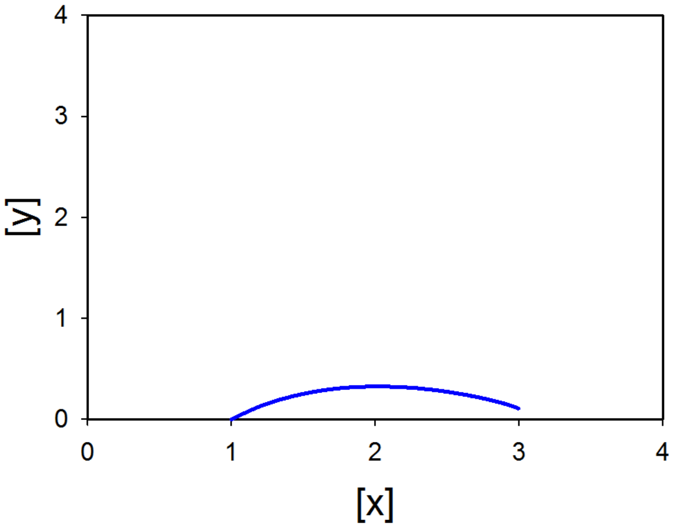
$k_1 = 3,\ k_2 = 3$

$n_1 = n_2 = 3$

Initial condition: x = 1, y = 0





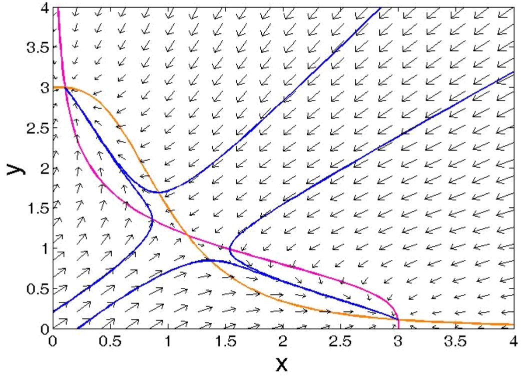


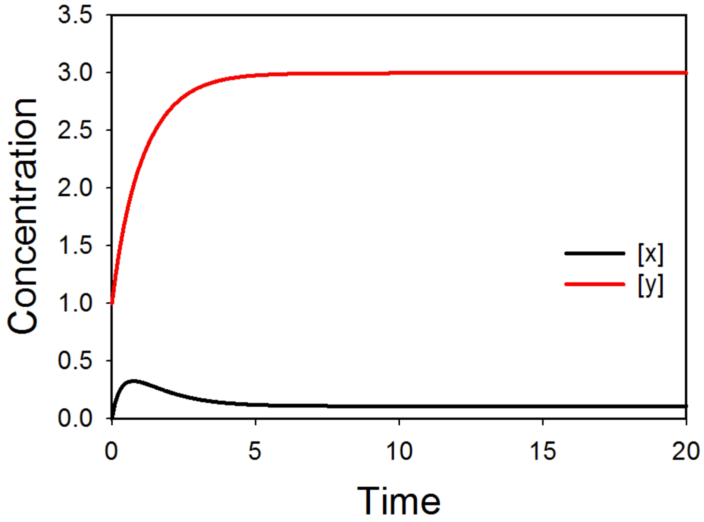
Results of simulation

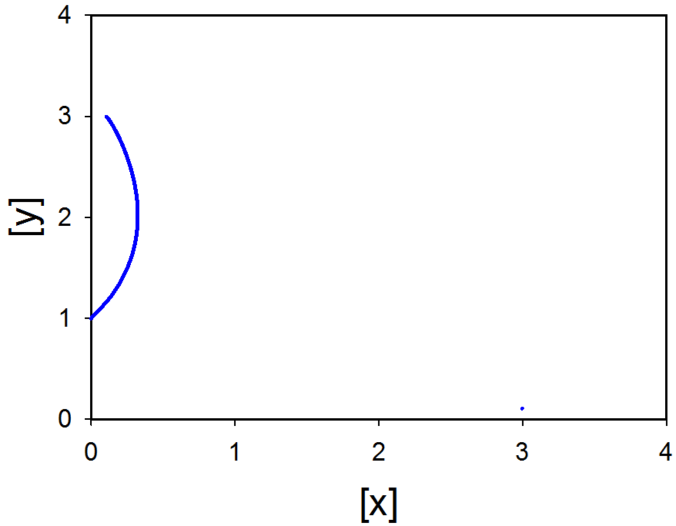
$k_1 = 3, \; k_2 = 3$

$n_1 = n_2 = 3$

Initial condition: x = 0, y = 1







Key points:

1. A mutual-inhibition circuit with non-linear promoter control can have bifurcation
2. Such system can give rise to bistability
3. Mono-stability and bi-stability depends upon maximum rate of production and hill coefficients
4. Such system can give rise to population heterogeneity
5. We can analyse such system by phase-plane analysis as well by numerical simulation