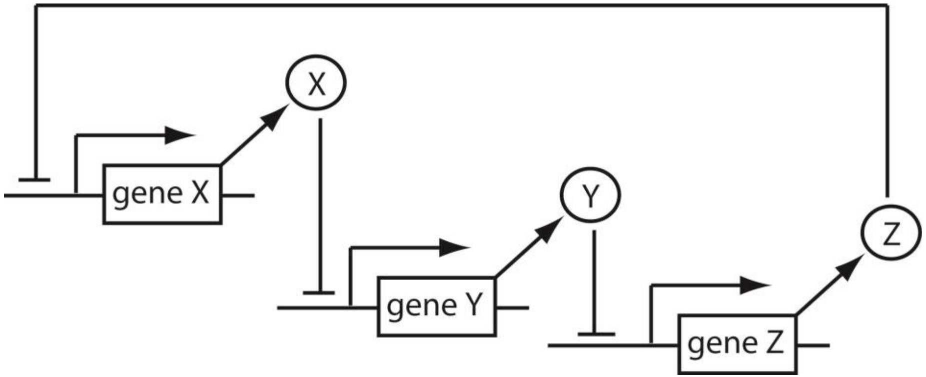
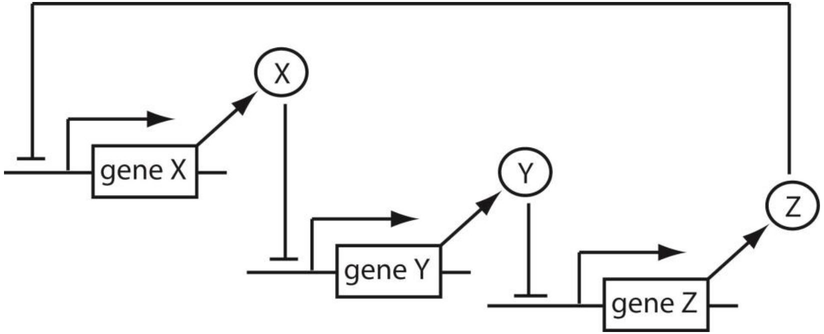


Modeling Transcriptional Circuits - 2

The Repressilator



The Model:

$$\frac{d[m_X]}{dt} = k_0 + k_1 . \frac{1}{1+(\frac{[Z]}{H})^n} - k_2 .[m_X]$$

$$\frac{d[X]}{dt} = k_3[m_X] - k_4 .[X]$$

$$\frac{d[m_Y]}{dt} = k_0 + k_1 . \frac{1}{1+(\frac{[X]}{H})^n} - k_2 .[m_Y]$$

$$\frac{d[m_Z]}{dt} = k_0 + k_1 . \frac{1}{1+(\frac{[Y]}{H})^n} - k_2 .[m_Z]$$

$$\frac{d[Y]}{dt} = k_3[m_Y] - k_4 .[Y]$$

$$\frac{d[Z]}{dt} = k_3[m_Z] - k_4 .[Z]$$

k_0 = basal rate of expression,
k_1 = maximum induced rate of expression
k_3 = rate constant for translation
k_2 & k_4: rate constants for degradation
n = Hill coefficient; H = Hill Constant

Simulation using JSim

```
math repressilator
{ realDomain t ;
        t.min=0;t.delta=0.1;t.max=1000;

  //Define dependent variables
        real mx(t), my(t), mz(t); //mRNAs
        real x(t), y(t), z(t);  //Proteins

  //Define parameters
        real k0 = 0.03;
        real k1 = 30;
        real k2 = 0.35;
        real k3 = 6.93;
        real k4 = 0.07;
        real H = 40;
        real n = 2;
```

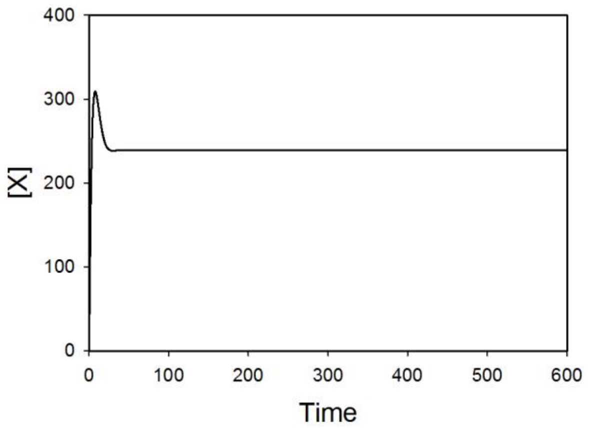
Simulation using JSim

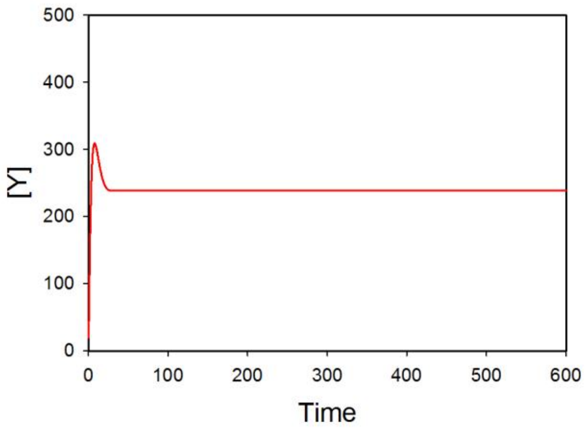
```
// Initial values
        when (t=t.min){mx = 0; my = 0; mz = 0; x=0; y=20; z =0;}

// ODEs
        mx:t = k0 + k1/(1+((z/H)^n)) - k2*mx;
        my:t = k0 + k1/(1+((x/H)^n)) - k2*my;
        mz:t = k0 + k1/(1+((y/H)^n)) - k2*mz;
        x:t = k3*mx - k4*x;
        y:t = k3*my - k4*y;
        z:t = k3*mz - k4*z;

}
```

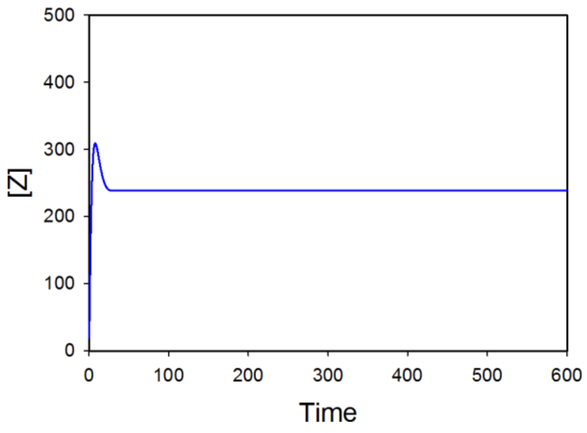
Dynamics of the Repressilator

Initial conditions:

$m_X = m_Y = m_Z = 0$; $\mathbf{X = Y = Z = 20}$

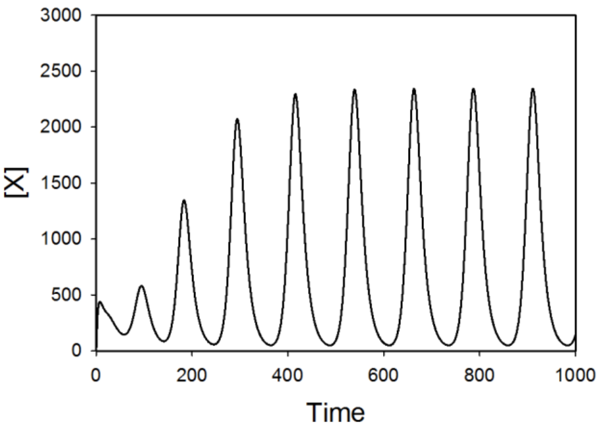


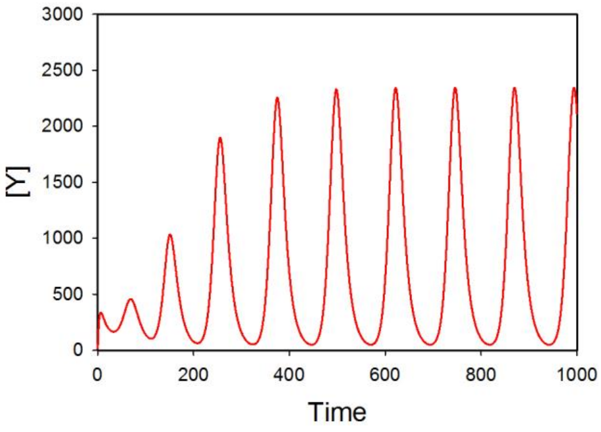


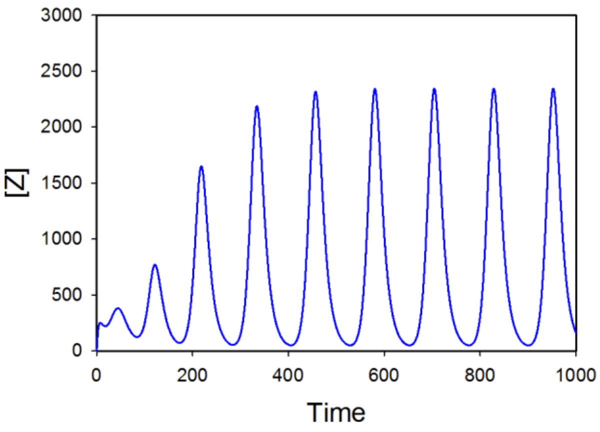


Dynamics of the Repressilator

Initial conditions:
$m_X = m_Y = m_Z = 0$; $X = Z = 0$; **$Y = 20$**





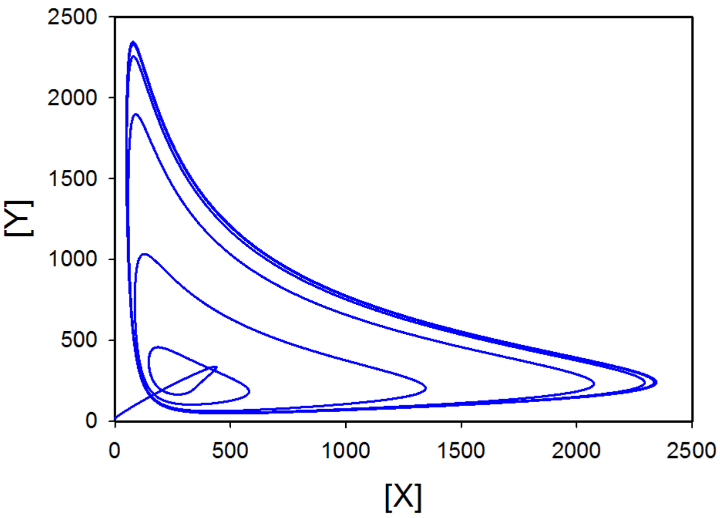


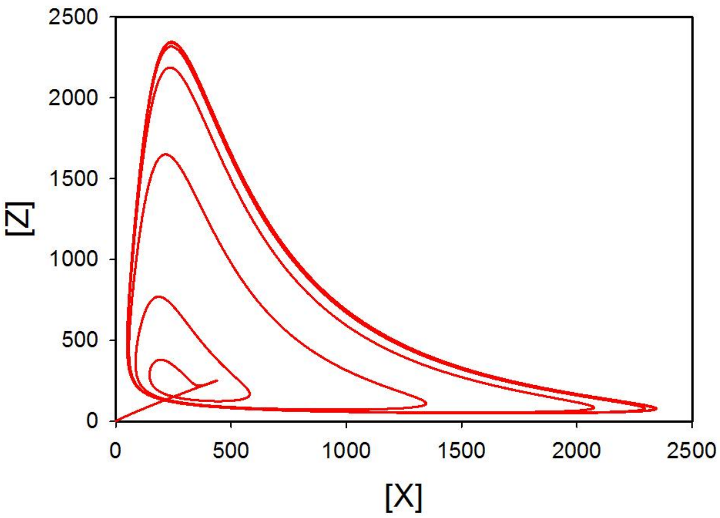
Unequal initial concentrations leads to oscillation

Dynamics of the Repressilator

Initial conditions:

$m_X = m_Y = m_Z = 0$; X = Z = 0; **Y = 20**





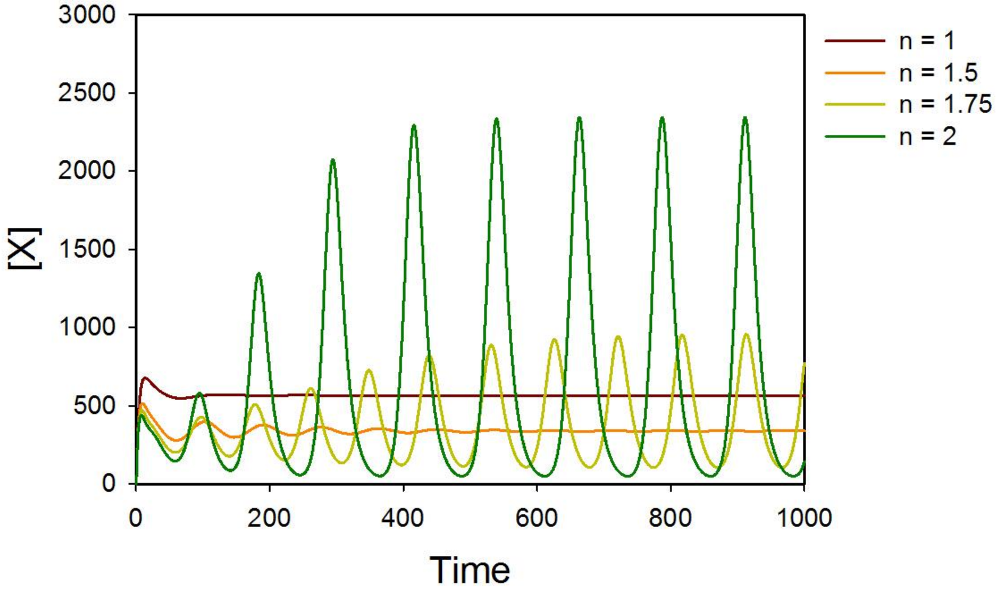
Repressilator shows Stable Limit-Cycle Oscillation: A limit cycle is an isolated closed trajectory. Here it is stable, as trajectories close by it are collapsing on it.

Sigmoidal Promoter Activity is Required for Oscillation

Initial conditions:

$m_X = m_Y = m_Z = 0$; $X = Z = 0$; **$Y = 20$**

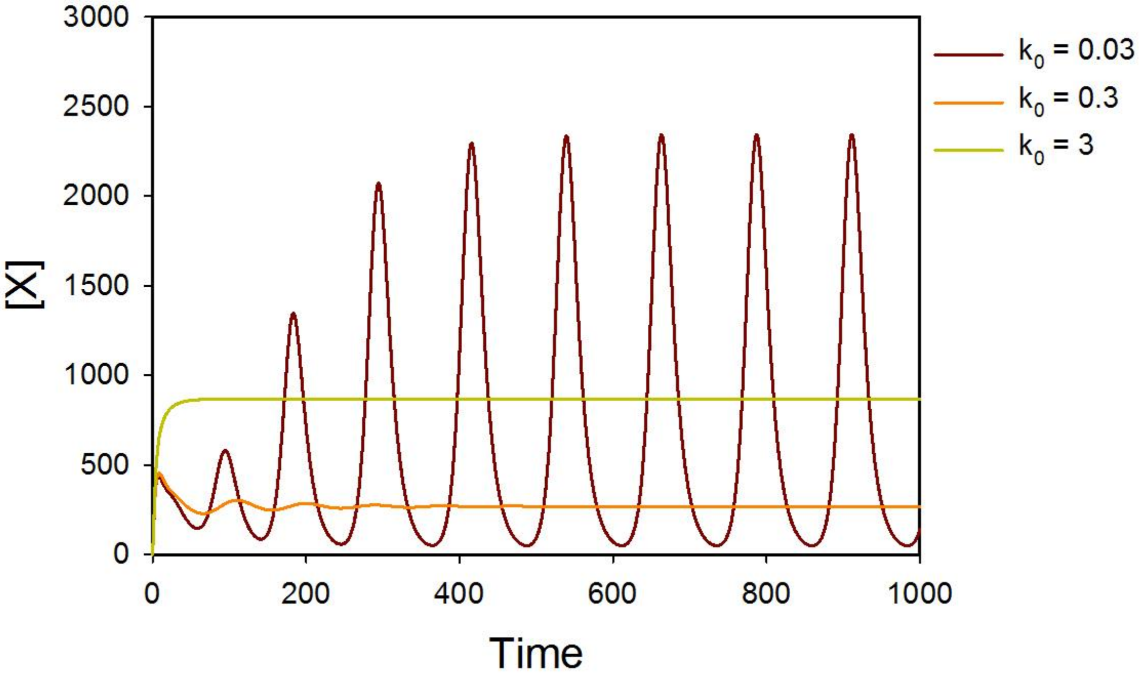
Reduced Hill Coefficient → Loss of oscillation



Effect of Leaky Expression

Initial conditions:
$m_X = m_Y = m_Z = 0$; $X = Z = 0$; **$Y = 20$**

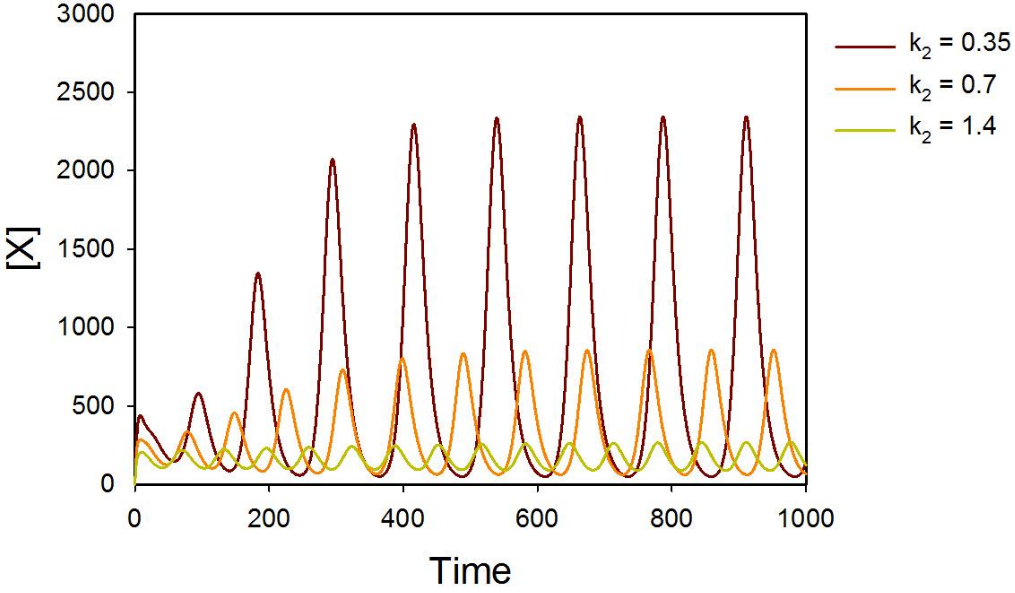
Leaky expression suppress oscillation



Effect of mRNA Stability

Initial conditions:
$m_X = m_Y = m_Z = 0$; $X = Z = 0$; **$Y = 20$**

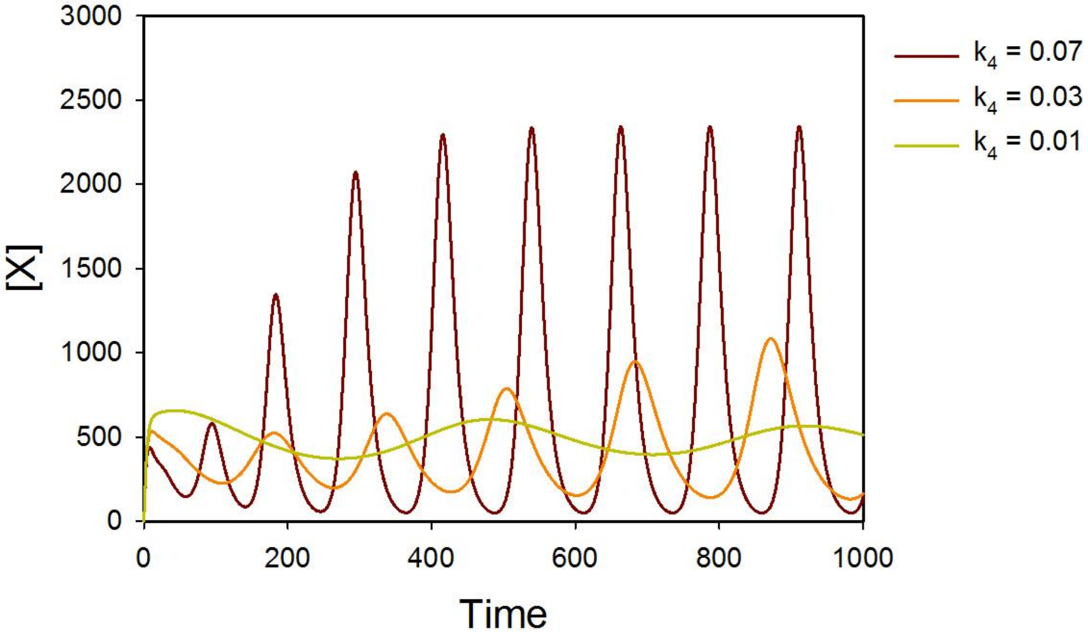
Higher stability → Higher amplitude of oscillation



Effect of Protein Stability

Initial conditions:
$m_X = m_Y = m_Z = 0$; $X = Z = 0$; $\mathbf{Y = 20}$

Higher stability → Lesser oscillation

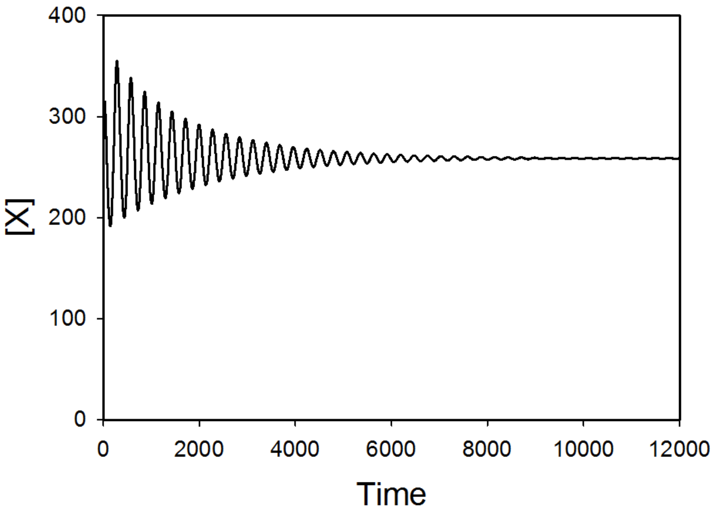


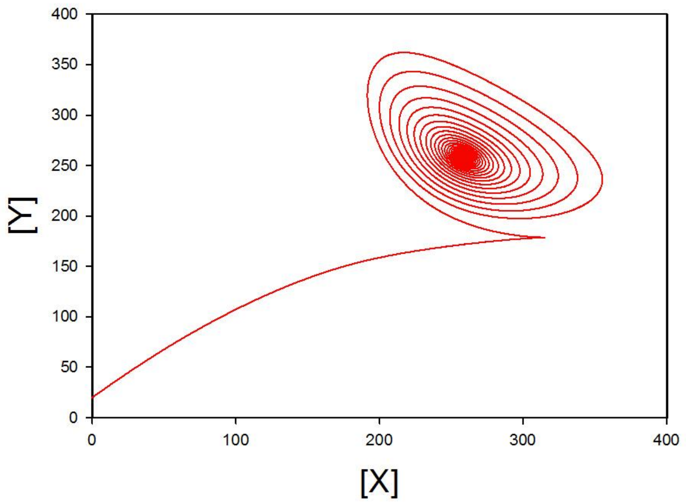
Effect of mRNA & Protein Stability

Initial conditions:
$m_X = m_Y = m_Z = 0$; $X = Z = 0$; **$Y = 20$**

$k_2 = 1.4$; $k_4 = 0.014$; $\beta = k_4/k_2 = 0.01$ (earlier value of $\beta = 0.07/0.35 = 0.2$)

Less stable mRNA & more stable protein → damped oscillation





Key points:

1. Three mutually repressing genes can form a Repressilator
2. Depending on the initial conditions and parameter values, this system can show stable limit cycle oscillation
3. Higher leaky expression does not allow oscillation
4. Oscillation requires non-linear promoter activity
5. Ratio of protein to mRNA stability is a crucial parameter. Based on this ratio the system can have stable limit-cycle oscillation, and damped oscillation