Mathematical Modelling and Scientific Computing in the Biosciences

22 May 2007

Lecture 7: Overview

- **Biochemical Oscillations**
  - **Types of Feedback Loops**
  - **Two−Components:**
    - **Substrate−Depletion Oscillator**
    - **Activator−Inhibitor Oscillator**
  - **Three−Components:**
    - **Goodwin Oscillator**

Biochemical Oscillations

A classic example of rhythmic behavior:

cell cycle, periodic growth and division of cells

Crucial events of budding yeast cell:

− Bud emergence

− DNA synthesis

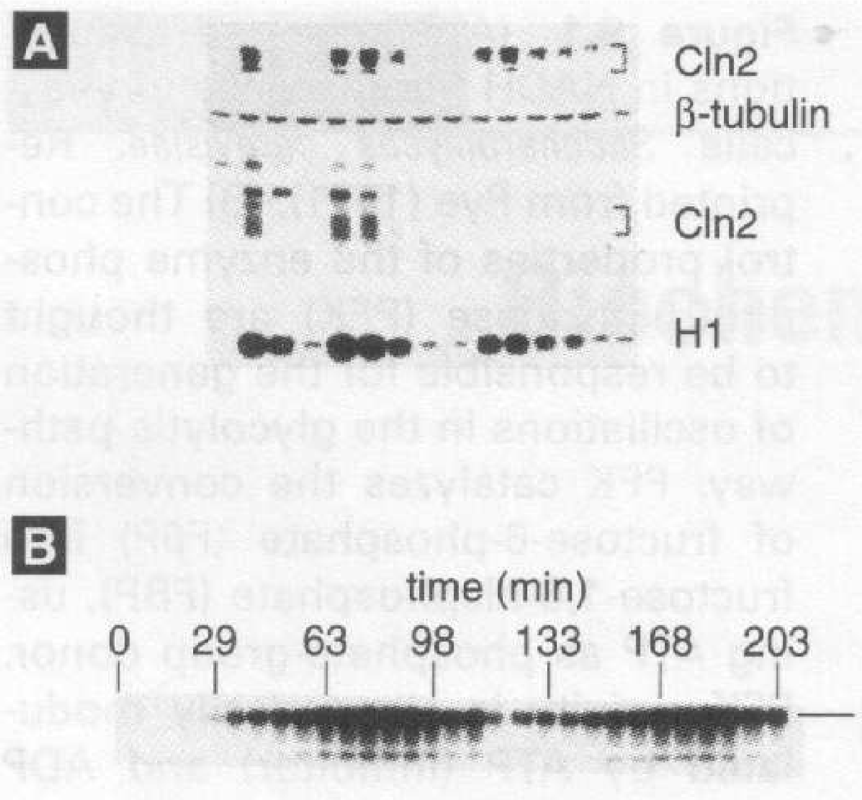
− Mitosis

− Cell division

Biochemical Oscillations

Cyclins: family of proteins involved in cell cycle, which undergo cyclic fluctuations.

Levels of cyclin concentrations observed during cell cycle for budding yeast (M. Tyers, G. Tokiwa et al, Science 260, 2003):

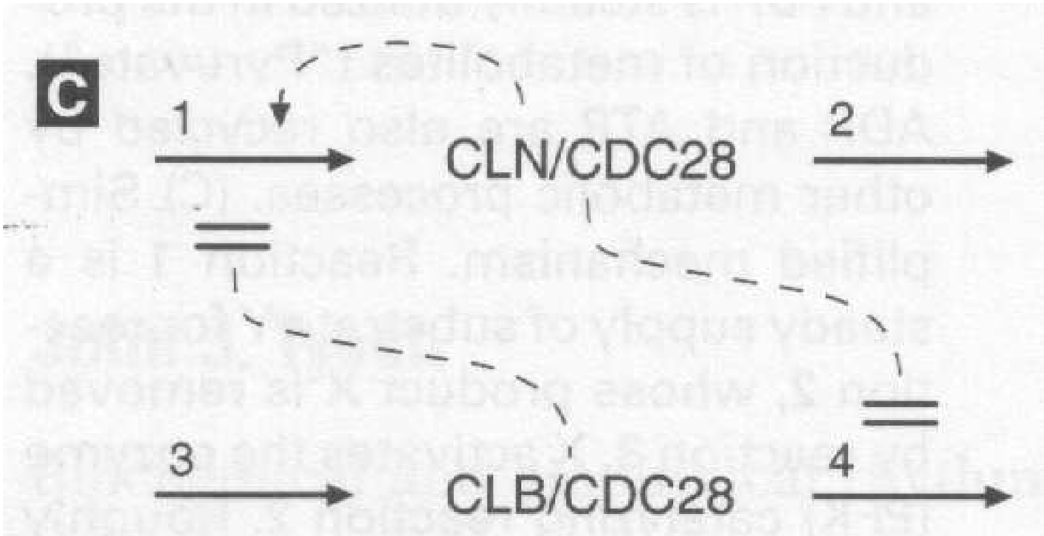


4 of 20

Biochemical Oscillations

Mechanism for cyclin oscillations:

- 2 classes of cyclins: CLN and CLB
- these cyclins combine with a kinase partner, CDC28, to form active dimers.
- since CDC28 is always in excess, oscillations arise from interaction of CLN and CLB



Feedback cycles

− CLN/CDC28

activates transcription factor that promotes CLN synthesis

inhibits degradation of CLB

− CLB/CDC28

inhibits transcription factor that promotes CLB synthesis

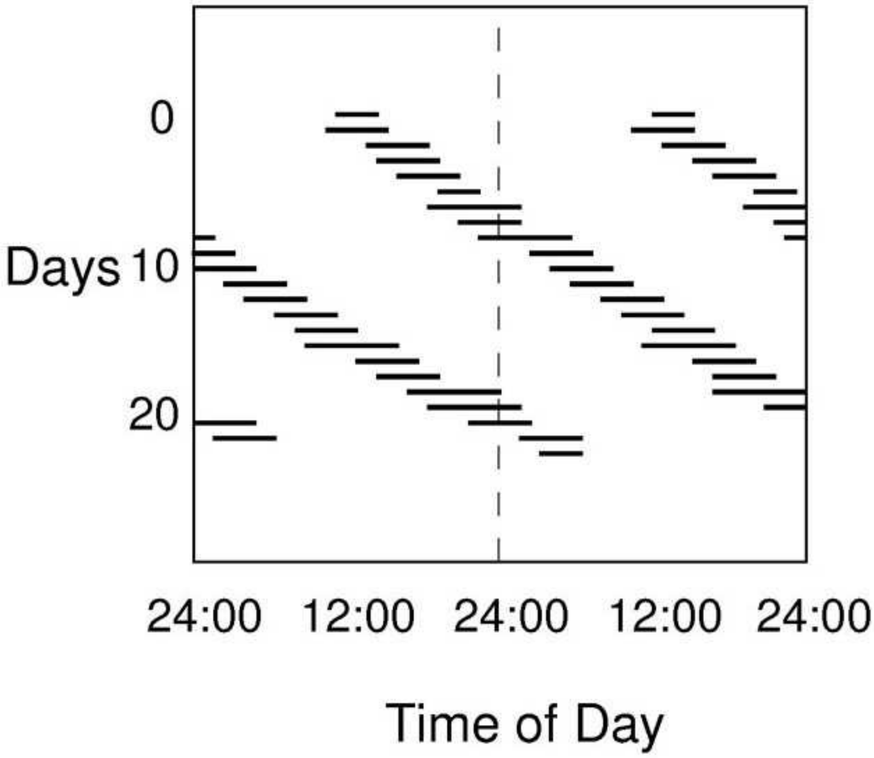
Biochemical Oscillations

Another classic example of biological oscillation is circadian rhythm:

− circadian = close to 24 hr, periodic changes in physiological properties

− endogenous, i.e., not driven by external timekeeper: it persists under constant light and temperature

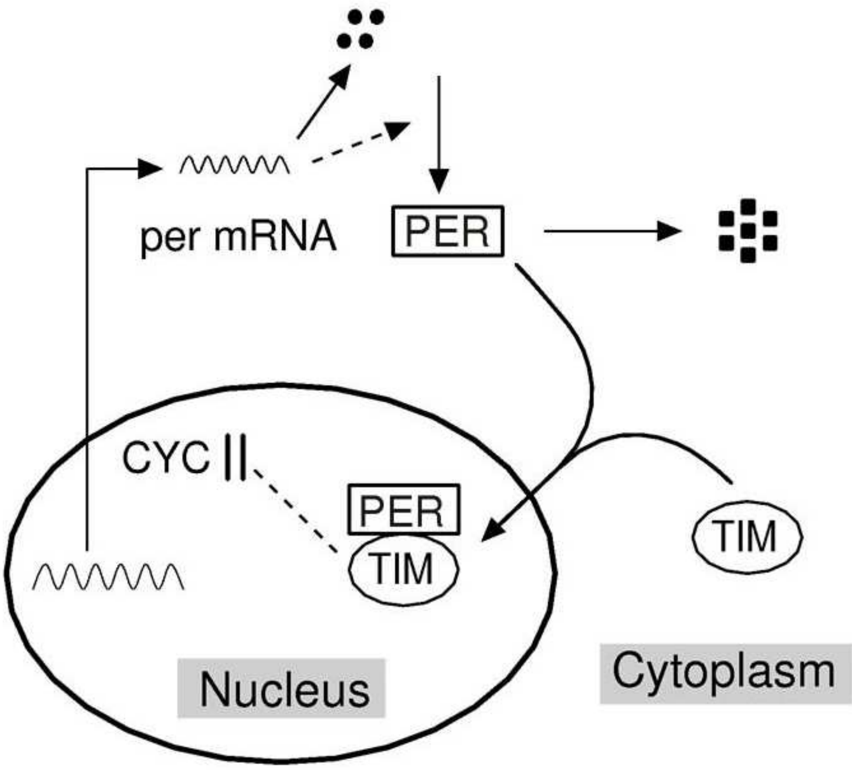
Sleep episodes of human isolated from external cues (e.g., light, temperature):



Biochemical Oscillations

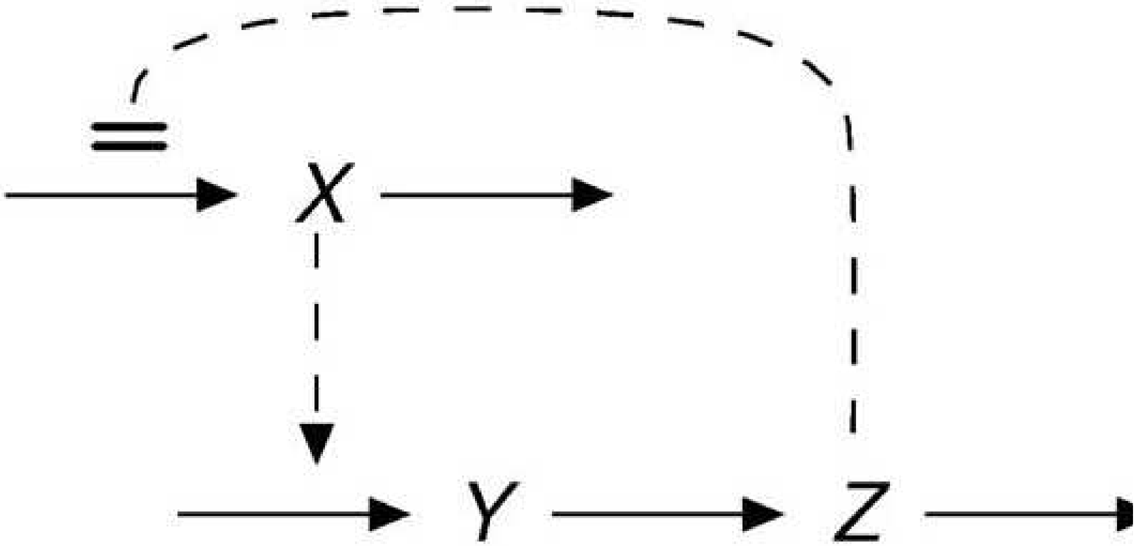
The protein PER plays a crucial role in circadian rhythm:

- *per* gene is transcribed in the nucleus with the help of transcription factor CYC
- *per* mRNA is transported to cytoplasm, where it is translated into PER protein
- PER protein then moves into nucleus, disrupting the binding of CYC and thereby turning off transcription of *per*



Biochemical Oscillations

Representation of feedback−loop: Goodwin oscillator (feedback repression of transcription)



Biochemical Oscillations

Biochemical networks may be described in terms of reactions that produce or consume the species involved:

$$x'(t) = v_{In1}(x(t),\ p) + v_{In2}(x(t),\ p) + \ \ldots\ - v_{Out1}(x(t),\ p) - v_{Out2}(x(t),\ p)\ -\ \ldots$$

$$= f(x,p)$$

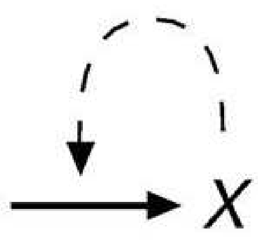
Typically, all species x_j are degraded at some rate, d_j: i.e., $v_{Outj}(x(t),\ p) = d_j\ x_j(t)$ and therefore $d\ v_{Outj}\ /\ dx_j = d_j > 0$.

What is needed to have $d\ f_j\ (x,p)/d\ x_j \equiv a_{jj} > 0$?

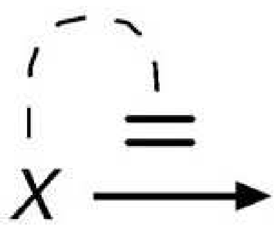
Need autocatalysis: rate−of−production−in−x_j increases as x_j increases.

Biochemical Oscillations: Feedback Loops

• A: Autocatalysis, whereby an increase in X increases its own production rate

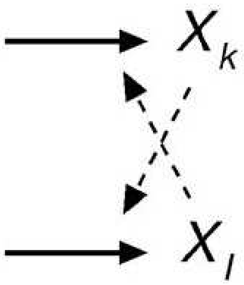


• B: Autocatalysis, whereby an increase in X decreases its own destruction rate

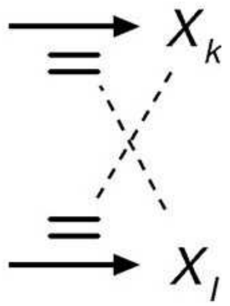


Biochemical Oscillations: Feedback Loops

• C: indirect autocatalysis, whereby an increase in X_k increases the production rate of X_l, and X_l increases X_k in return



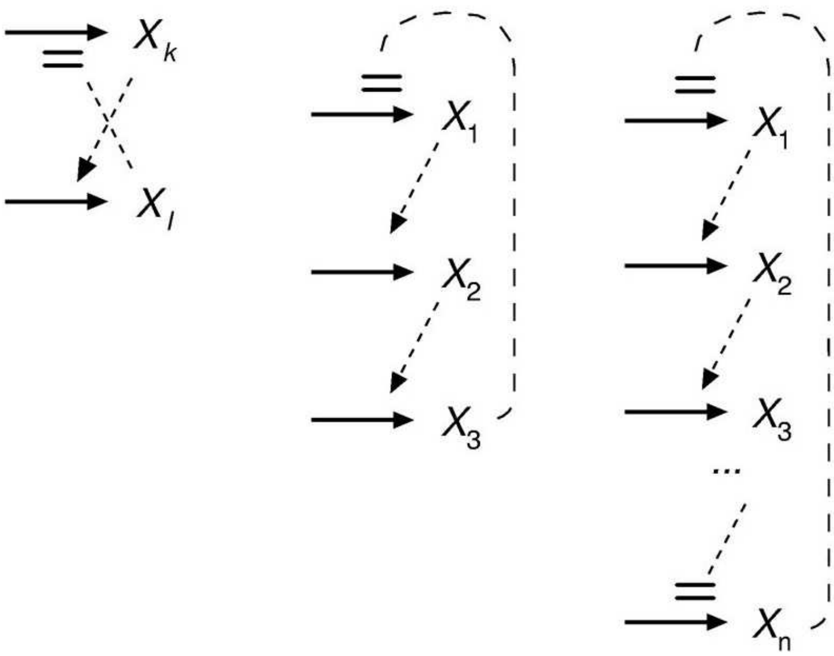
• D: indirect autocatalysis, whereby an increase in X_k decreases the destruction rate of X_l, and X_l decreases the destruction of X_k in return



Biochemical Oscillations: Feedback Loops

• E: 2−component negative feedback loop can be created by having X_k increasing the production of X_l, and X_l inhibiting the production of X_k.

• F, G: longer negative or positive feedback loops are possible, depending on the signs of the products in the regulation function.



Biochemical Oscillations: 2−Dimensional Stability Analysis

Consider the 2−component system:

$$x'(t) = f_1(x(t), y(t), p)$$
$$y'(t) = f_2(x(t), y(t), p)$$

The Jacobian would look like:

$$\begin{pmatrix} f_1^{(1,0,0)}(x(t), y(t), p) & f_1^{(0,1,0)}(x(t), y(t), p) \\ f_2^{(1,0,0)}(x(t), y(t), p) & f_2^{(0,1,0)}(x(t), y(t), p) \end{pmatrix}$$

We use the short−hand, denoting the entries of the Jacobian by a(i,j):

$$\begin{pmatrix} a(1,1) & a(1,2) \\ a(2,1) & a(2,2) \end{pmatrix}$$

Biochemical Oscillations: 2−Dimensional Stability Analysis

Now let’s compute the eigenvalues of the 2x2 system:

$$\lambda_- = \frac{1}{2}\left(a(1,1) + a(2,2) - \sqrt{(a(1,1) - a(2,2))^2 + 4\,a(1,2)\,a(2,1)}\right)$$
$$\lambda_+ = \frac{1}{2}\left(a(1,1) + a(2,2) + \sqrt{(a(1,1) - a(2,2))^2 + 4\,a(1,2)\,a(2,1)}\right)$$

The system is stable if both eigenvalues have negative real component.

This is ensured if both a(1,1), a(2,2) < 0

When does the real component go to zero?

The eigenvalues can zero real component if a(1,1)+a(2,2) = 0. Then:

Out[51]= $\left\{\lambda_- == -\frac{1}{2}\sqrt{4\,a[1,2]\,a[2,1] + 4\,a[2,2]^2},\ \lambda_+ == \frac{1}{2}\sqrt{4\,a[1,2]\,a[2,1] + 4\,a[2,2]^2}\right\}$

That is, if a(1,2) or a(2,1) is sufficiently negative, then λ_- and λ_+ are purely imaginary.

Then the system would undergo a Hopf bifurcation: i.e., show oscillations.

Biochemical Oscillations: 2−Dimensional Stability Analysis

From matrix theory:

− trace of a matrix = sum of eigenvalues

− determinant of matrix = product of eigenvalues

If we would like to have Hopf bifurcation, i.e., $\lambda_- = -i\,\omega$, $\lambda_+ = +i\,\omega$, then:

− trace should be = 0

− determinant should be > 0

Out[57]//TraditionalForm=

$$\begin{pmatrix} a(1,1) & a(1,2) \\ a(2,1) & a(2,2) \end{pmatrix}$$

Zero trace condition: a(1,1)+a(2,2) = 0.

Positive determinant condition:

Out[53]= $-a[1,1]^2 - a[1,2]\,a[2,1]$

In[60]:= **Reduce[-a[1, 1]^2 - a[1, 2] a[2, 1] > 0, {a[1, 2], a[2, 1]}, Reals]**

Out[60]= $\left(a[1,2] < 0\ \&\&\ a[2,1] > -\frac{a[1,1]^2}{a[1,2]}\right)\ ||\ \left(a[1,2] > 0\ \&\&\ a[2,1] < -\frac{a[1,1]^2}{a[1,2]}\right)$

Hence, this is positive if a[1,2] and a[2,1] have opposite signs.

Biochemical Oscillations: 2−Dimensional Stability Analysis

That is, for the simple case of 2−dimensional systems, we have completely characterized sign patterns in the Jacbobian matrix

$$\begin{pmatrix} a(1,1) & a(1,2) \\ a(2,1) & a(2,2) \end{pmatrix}$$

that is necessary for oscillations. In fact, there are 2 distinct patterns:

$$\text{TwoDPattern1} == \begin{pmatrix} + & + \\ - & - \end{pmatrix}$$

The above sign pattern correspond to the Substrate−Depletion Oscillator

$$\text{TwoDPattern2} == \begin{pmatrix} + & - \\ + & - \end{pmatrix}$$

The above sign pattern correspond to the Activator−Inhibitor Oscillator

Biochemical Oscillations: Substrate−Depletion

In a Substrate−Depletion Oscillator, substrate Y is converted into X by an enzyme that is activated by its product. Hence, production of X is autocatalytic, until substrate Y is depleted so much that the reaction stops.

ODE system:

$$X'(t) = \frac{\text{v2}\left(\epsilon^2 + \frac{X(t)^2}{\text{Kn}^2}\right) Y(t)}{\frac{X(t)^2}{\text{Kn}^2} + 1} - \text{k3}\, X(t)$$

$$Y'(t) = \text{k1} - \frac{\text{v2}\left(\epsilon^2 + \frac{X(t)^2}{\text{Kn}^2}\right) Y(t)}{\frac{X(t)^2}{\text{Kn}^2} + 1}$$

After carrying out non−dimensionalization (i.e., x[t] = X[t]/Kn, y[t] = Y[t]/Kn, etc.), we have:

$$x'(t) = -x(t) - \frac{\epsilon^2 + x(t)^2}{x(t)^2 + 1} + v\,(z(t) - x(t))$$

$$z'(t) = k - x(t)$$

Remember that Trace(Jacobian) = 0 is necessary for Hopf bifurcation.

Algebraic calculation shows that this gives rise to condition:

$$\epsilon < k < \frac{1}{\sqrt{1-v}}$$

Biochemical Oscillations: Substrate−Depletion

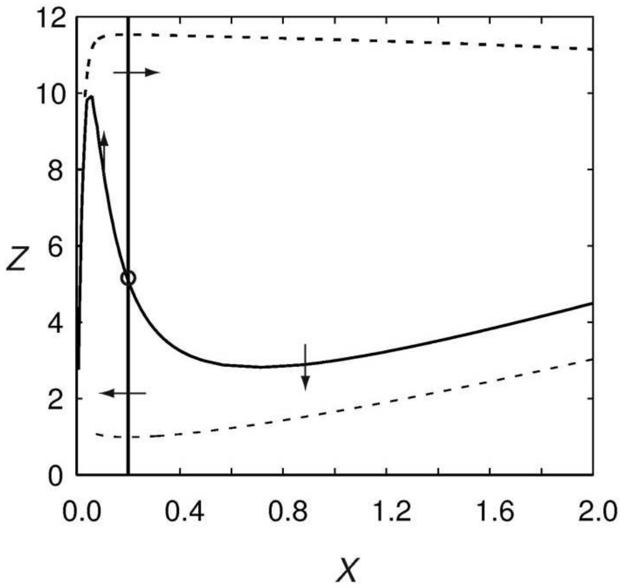
For two−dimensional systems, it is informative to follow the dynamics by plotting the nullclines.

That is, plotting lines in x−z plane to see where x'(t) = 0, and z'(t) = 0, and how they intersect.

$$x'(t) = -x(t) - \frac{\epsilon^2 + x(t)^2}{x(t)^2 + 1} + v\,(z(t) - x(t))$$
$$z'(t) = k - x(t)$$

x−nullcline: $x - \frac{\epsilon^2 + x^2}{x^2 + 1} + v\,(z - x) = 0$

z−nullcline: $x = k$



Biochemical Oscillations: Activator−Inhibitor Oscillator

In an Activator−Inhibitor Oscillator:

−when Y is low, X increases autocatalytically

−X then stimulates an accumulation of Y (by inhibiting degradation of Y)

−large Y causes production of X to be inhibited

−this in turn cases Y to be low, and cycle repeats...

$$X'(t) = \frac{\mathrm{v1}\left(\epsilon^2 + \frac{X(t)^2}{\mathrm{Km}^2}\right)}{\left(\frac{X(t)^2}{\mathrm{Km}^2}+1\right)\left(\frac{Y(t)}{\mathrm{Kn}}+1\right)} - \mathrm{k2}\, X(t)$$

$$Y'(t) = \mathrm{k3} - \frac{\mathrm{k4}\, Y(t)}{\frac{X(t)^2}{\mathrm{Kj}^2}+1}$$

After non−dimensionalization:

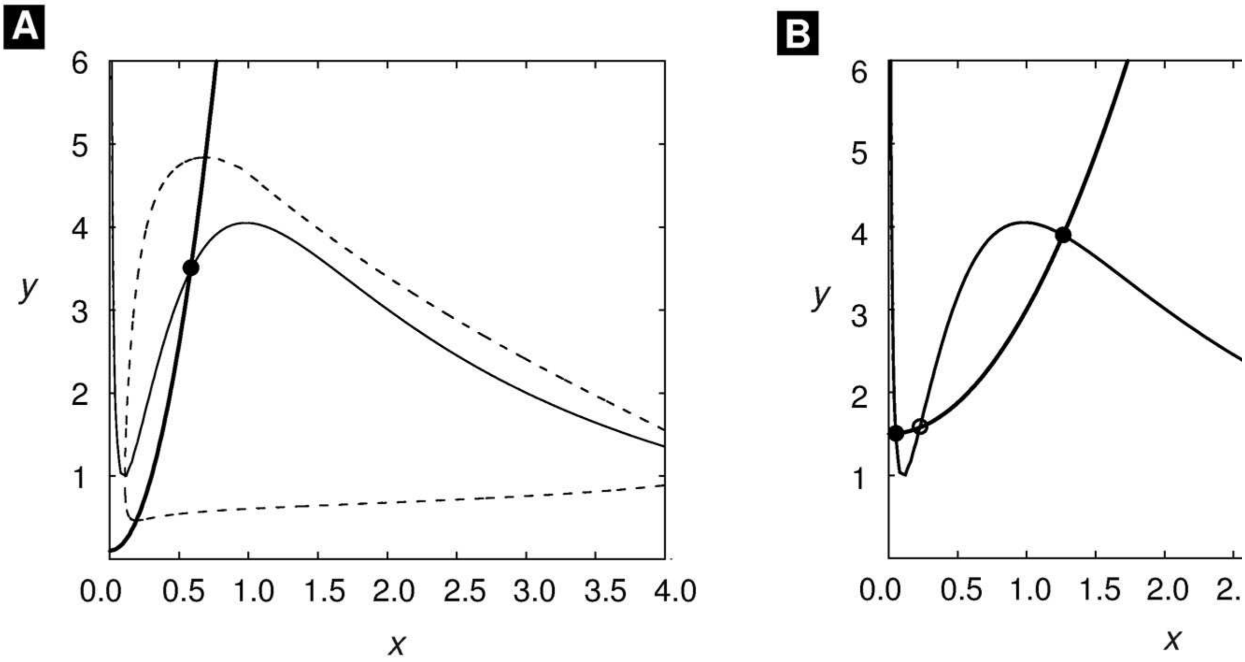
$$x'(t) = \frac{\epsilon^2 + x(t)^2}{\left(x(t)^2+1\right)\left(y(t)+1\right)} - a\, x(t)$$

$$\tau\, y'(t) = \mathrm{k3} - \frac{y(t)}{c\, x(t)^2+1}$$

Biochemical Oscillations: Activator−Inhibitor Oscillator

Two−component A/I system can generate oscillations and bistability.

Plot of possible nullclines



20 of 20

Biochemical Oscillations: 3−Dim, Goodwin Oscillator

Underlying mechanism: negative feedback alone.

End product gene X3 represses gene X1, with co−operativity p:

$$\mathrm{X1}'(t) = \frac{1}{\mathrm{X3}(t)^p + 1} - \mathrm{b1}\,\mathrm{X1}(t)$$

$$\mathrm{X2}'(t) = \mathrm{b2}\,(\mathrm{X1}(t) - \mathrm{X2}(t))$$

$$\mathrm{X3}'(t) = \mathrm{b3}\,(\mathrm{X2}(t) - \mathrm{X3}(t))$$

Stability analysis for higher−than−2 dimensional systems can be rather difficult.

Need to apply Routh−Hurwitz theorem (which gives a sequence of terms whose signs need to be checked) for number of eigenvalues lying in the positive real half−plane.

Analysis shows that co−operativity p needs to be very high > 8.

Thus, the oscillatory potential somewhat limiting.