VII Biological Oscillators

VII. 1. Limit cycles

During class we consider the following two coupled differential equations:

$$\begin{aligned}\dot{x} &= -x + ay + x^2 y \\ \dot{y} &= b - ay - x^2 y\end{aligned} \qquad \textbf{[VII.1]}$$

From the phase plane analysis it was clear that for certain values of a and b this system exhibits periodic oscillations as a function of time. Let us analyze [VII.1] in more detail. The nullclines are:

$$\begin{aligned}y &= \frac{x}{a + x^2} \\ y &= \frac{b}{a + x^2}\end{aligned} \qquad \textbf{[VII.2]}$$

There is only one fixed point (x^*, y^*):

$$\begin{aligned}x^* &= b \\ y^* &= \frac{b}{a + b^2}\end{aligned} \qquad \textbf{[VII.3]}$$

The matrix A is (using [VI.4] and [VI.5]):

$$A = \begin{bmatrix} -1 + 2x^* y^* & a + (x^*)^2 \\ -2x^* y^* & -(a + (x^*)^2) \end{bmatrix} \qquad \textbf{[VII.4]}$$

The determinant and trace are:

$$\begin{aligned}\Delta &= a + b^2 > 0 \\ \tau &= -\frac{b^4 + (2a-1)b^2 + (a + a^2)}{a + b^2}\end{aligned} \qquad \textbf{[VII.5]}$$

The fixed point is stable when $\tau < 0$. The region in a-b-parameter space where the system is oscillating (stable limit cycle) and is not oscillating (stable fixed point) is illustrated in Fig. 14.

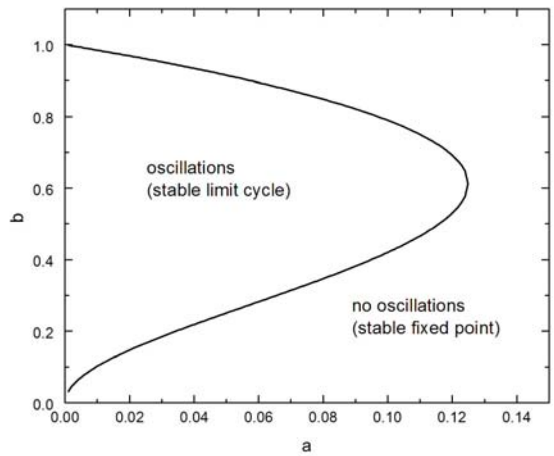

Figure 14. *a*-*b*-parameter space indicating for which values of a and b the system exhibits stable oscillations and a stable fixed point.

MATLAB code 3: Limit cycle

```
% filename: cyclefunc.m

function dydt = f(t,y,flag,a,b)

dydt = [-y(1)+a*y(2)+y(1)*y(1)*y(2);
         b-a*y(2)-y(1)*y(1)*y(2)];

plot(y(1),y(2),'.');
drawnow;
hold on;
axis([0 2 0 2]);
```

```
% filename: limitcycle.m
close;
clear;

a=0.1;
b=0.5;

options=[];

[t y]=ode23('cyclefunc',[0 50],[0.6 1.4],options,a,b);

plot(y(:,1),y(:,2));
```

VII.2 Synthetic genetic oscillators

The first synthetic genetic oscillator was constructed by Elowitz *et al.* in the bacterium *Escherichia coli.* Details of these experiments can be found in:

Reference:

1. M. B. Elowitz and S. Leibler. A synthetic oscillatory network of transcriptional regulators. *Nature* **403**, 335-338 (2000).

In class we derived the conditions under which the network exhibits oscillations. The chemical reactions describing the concentration of mRNA *m* and protein concentration *p* are (see Box):

$$\begin{aligned} \frac{dm_i}{dt} &= -m_i + \frac{\alpha}{(1+p_j^n)} + \alpha_o \\ \frac{dp_i}{dt} &= -\beta(p_i - m_i) \end{aligned} \qquad \textbf{[VII.6]}$$

where the index i=[lacI,tetR,cI] and the index j=[cI,lacI,tetR]. Below will we use numerical indices to represent the repressors. Let us assume that we can ignore the intermediate step of mRNA synthesis. This leads to the following three equations:

$$\begin{aligned} \frac{dp_1}{dt} &= -p_1 + \frac{\alpha}{1+p_3^n} + \alpha_o \\ \frac{dp_2}{dt} &= -p_2 + \frac{\alpha}{1+p_1^n} + \alpha_o \\ \frac{dp_3}{dt} &= -p_3 + \frac{\alpha}{1+p_2^n} + \alpha_o \end{aligned} \qquad \textbf{[VII.7]}$$

In the analysis below we will assume that all three genes have the same basal synthesis rate α_o, maximum synthesis rate α, and Hill coefficient n. Note that time is measured with respect to protein decay rate. As all three genes have the same properties, the steady-state values of the mRNA and protein concentrations will be:

$$p \equiv p_1 = p_2 = p_3 \qquad \textbf{[VII.8]}$$

therefore in steady-state,

$$p = \frac{\alpha}{1+p^n} + \alpha_o \qquad \textbf{[VII.9]}$$

For the stability analysis we have to determine the matrix A (Jacobian) as described before (see chapter VI):

$$A = \begin{bmatrix} -1 & 0 & X \\ X & -1 & 0 \\ 0 & X & -1 \end{bmatrix} \qquad \textbf{[VII.10]}$$

where

$$X \equiv -\frac{\alpha n p^{n-1}}{(1+p^n)^2} \qquad \textbf{[VII.11]}$$

For the steady state to be stable, the real part of the eigenvalues of matrix A have to be negative. As mentioned in chapter VI the eigenvalues can be found by solving:

$$\det \begin{bmatrix} -1-\lambda & 0 & X \\ X & -1-\lambda & 0 \\ 0 & X & -1-\lambda \end{bmatrix} = 0 \qquad \textbf{[VII.12]}$$

Leading to

$$-(1+\lambda)^3 + X^3 = 0 \qquad \textbf{[VII.13]}$$

This equation has three solutions, one real and two complex:

$$\begin{aligned} \lambda_1 &= X - 1 \\ \lambda_2 &= -1 - \frac{1}{2}X + i\frac{\sqrt{3}}{2}X \\ \lambda_3 &= -1 - \frac{1}{2}X - i\frac{\sqrt{3}}{2}X \end{aligned} \qquad \textbf{[VII.14]}$$

For a stable fixed point the real part of all eigenvalues should be negative. Therefore the system is stable for:

$$-2 < X < 1 \qquad \textbf{[VII.15]}$$

X is negative by definition (see [VII.11]) so the final stability condition is:

$$\frac{\alpha n p^{n-1}}{(1+p^n)^2} < 2 \qquad \textbf{[VII.16]}$$