VII Biological Oscillators

During class we consider the following two coupled differential equations:

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

From the phase plane analysis (see L9_notes.pdf) 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:

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

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

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

The matrix A is (using [V.4] and [V.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:

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

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. 10.

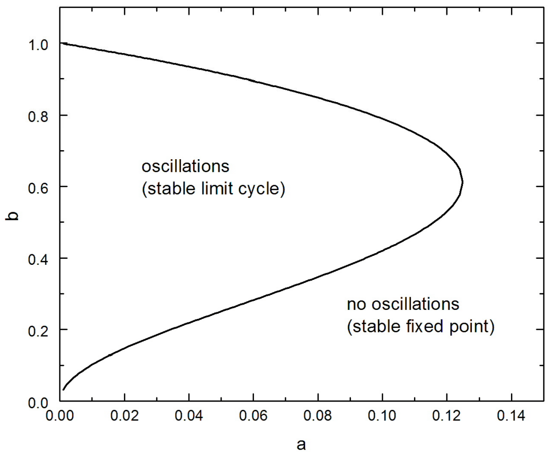

Figure 11. a-b-parameter space indicating for which values of a and b the system exhibits stable oscillations and a stable fixed point

MATLAB code 5: 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));
```

Recently Elowitz et al. constructed a genetic oscillator 'from scratch' in the bacterium *Escherichia coli.* Details of these experiments can be found in:

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):

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

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:

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

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 section V):

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

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 [V.8] 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:

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