SYSTEM BIOLOGY: BELOUSOV-ZHABOTINSKY REACTION

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Construction of the kinetic model

The Belousov-Zhabotinsky reaction system represents in a minimal way the basic attributes of an autocatalytic oscillating reaction system. It consist in the following reactions:

$$A \rightarrow X$$

$$B + X \rightarrow Y + D$$

$$X + Y \rightarrow 3X$$

$$X \rightarrow E$$

For this case all reactions are considered irreversible and present values of kinetic constants equal to 1.

1. How many variable does this model have? What will be the dimension of the phase space?

   According to this model, the number of variables are 2; therefore, the dimension of the phase space is 2.

2. Write the set of differential epuations that describes this model. What is its dimension? Are they ordinary differential equations or not? Are they linear or non-linear?

   According to the set of chemical reactions described above, the differential equations are the following:

$$\frac{dX}{dt} = A - BX + X^2Y - X$$

$$\frac{dY}{dt} = BX - X^2Y$$

   Since there is one independent variable (X) in this set of differential equations, these are ordinary differential equations (ODEs). Futhermore, these equations are non-linear, meaning that the output is not proportional to the change in the input. The dimension of this set of equations is 2.

Calculation of steady states

1. Calculate the stationary solution or steady state symbolically. How many steady states are there?

   Steady states are described as the states at which the behaviour of the system or process are unchanging in time, so that $\frac{dX}{dt} = 0$ and $\frac{dY}{dt} = 0$. From this equalities, the variables values X^{ss} and Y^{ss} can be determined:

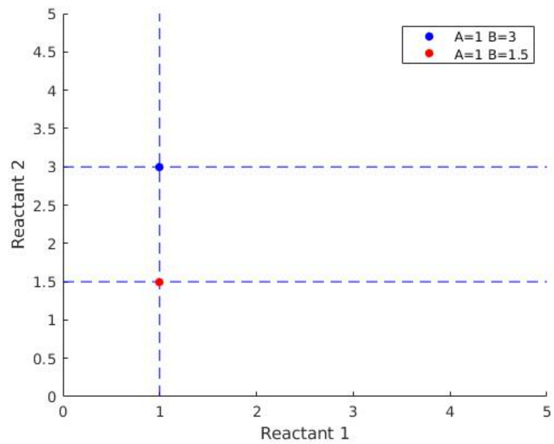
$$\frac{dX}{dt} = A - BX^{ss} + X^{ss2}Y^{ss} - X^{ss} = 0 \qquad X^{ss} = A$$

$$\frac{dY}{dt} = BX^{ss} + X^{ss2}Y^{ss} = 0 \qquad Y^{ss} = B/A$$

2. Represent the particular steady state values found for :

   a. A = 1 mM and B = 1.5 mM.

   b. A = 1 mM and B = 3 mM.



Numerical integration experiments

In order to numerically solve the dynamics of the Belousov-Zhabotinski, the following programm was built, where A = 1 mM and B = 1.5 mM and the initial conditions are x_0= 2 mM and y_0 = 2 mM :

belousov_zhabotinski_ODEset.m:

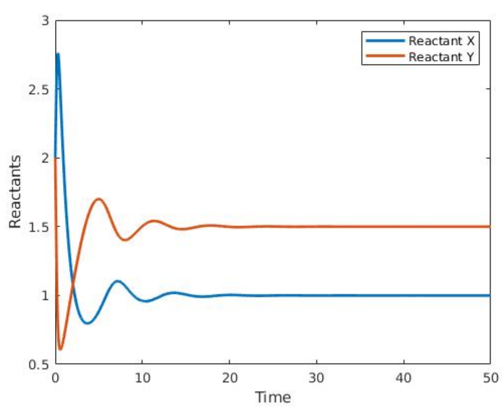
```
function [f]=belousov_zhabotinsky_ODEset(t,x)

%PARAMETER VALUES:
%values of kinetic constants:1

%constant values of parameters
A =1;
B =1.5;

%KINETIC EQUATIONS TO BE INTEGRATED: f=zeros(2,1); f(1)= A - B*x(1) + x(1)*x(1)*x(2) - x(1); f(2)= B*x(1) - x(1)*x(1)*x(2);
```

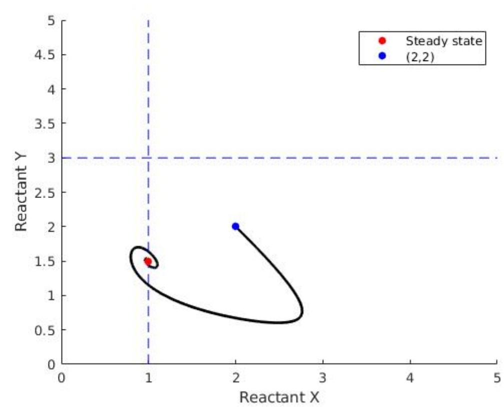
belousov_zhabotinski_numerical_integration.m:

```
clear all;
clc;
disp('NUMERICAL INTEGRATION – BELOUSOV-ZHABOTINSKY');

%SETTINGS:
%initial values of variables at time=0:
```

```
x0 = [2 2];
options=odeset('RelTol',1e-12,'AbsTol',1e-12);
%NUMERICAL INTEGRATION

[t,u]=ode15s(@belousov_zhabotinsky_ODEset,[0 50],x0,options);

%FIGURES
%time course of variables:
figure(1)
plot(t,u,'LineWidth',2);
xlabel('Time')
ylabel('Reactants');
legend('Reactant X','Reactant Y')
%Orbits
figure(3)
hold on
plot(u(:,1),u(:,2),'k','LineWidth',2)
xlabel('Reactant X')
ylabel('Reactant Y')
%GRAPHICS
line([1 1],[05],'LineStyle','–','Color','b','HandleVisibility','off')
line([0 5],[1.5 1.5],'LineStyle','–','Color','b')
plot([0 0],[0 0],'MarkerSize',20,'MarkerEdgeColor','r')
h1 = plot([1 1],[1.5 1.5],'.','MarkerSize',20,'MarkerEdgeColor','r')
h2 = plot([2 2],[2 2],'.','MarkerSize',20,'MarkerEdgeColor','b')
h3 = plot([1 1],[3 3],'.','MarkerSize',20,'MarkerEdgeColor','g')
h4 = plot([0 0],[1 1],'.','MarkerSize',20,'MarkerEdgeColor','c')
h5 = plot([1 1],[0 0],'.','MarkerSize',20,'MarkerEdgeColor','m')
h6 = plot([3 3],[0 0],'.','MarkerSize',20,'MarkerEdgeColor','y')
legend([h1 h2 h3 h4 h5 h6],'Steady state','(2,2)','(1,3)','(0,1)','(1,0)','(3,0)','Location','NorthEast')
```

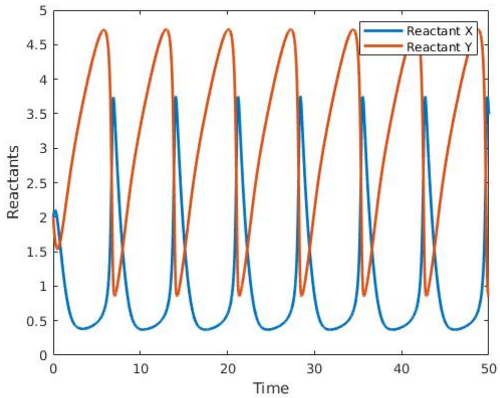
When the programm is ran, we obtain the following trayectories and phase space:

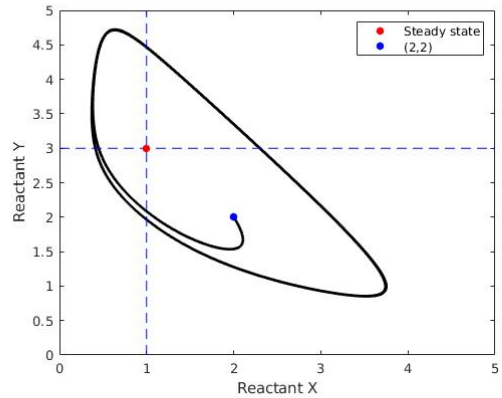




The trajectory of the variables x and y change in time so that they achive the steady state values, 1 and 1.5, respectively, in an oscillatory way. The representation of phase space shows the orbit from the initial state to the steady state. Based on the trend of the orbit (a spiral type orbit) it can be envisaged that it is a focus.

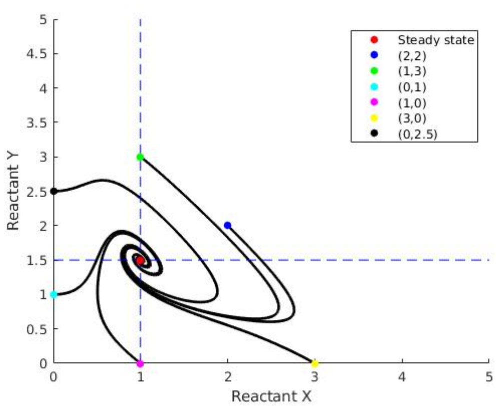
When the parameter values are fixed at A = 1 mM and B = 3 mM and the initial conditions are x_0= 2 mM and y_0 = 2 mM, the following representations are obtained:

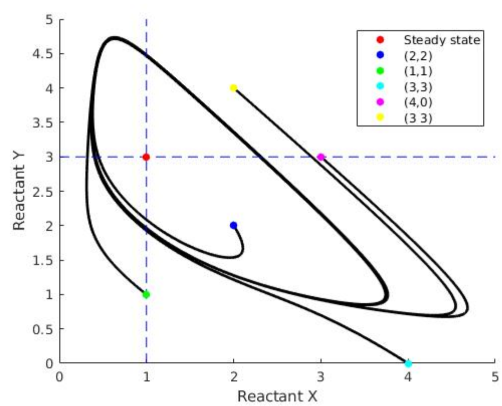




In this case, the trajectories are periodic both for x and y. As a consequence, the orbit in phase space is a closed orbit; therefore, it can be envisaged that its a limit cycle. This results are in agreement with the initial calculations of the steady states; in fact, the center of the limit cycle is (1,3)

In the following phase space representation, orbits are shown for different initial conditions for both cases. Interestingly, orbits do not cross each other, but they are all directed to the same steady state or limit cycle. According to this results, the destination of the orbits do not change depending on the initial concentrations.





In this case, the final destination is different to the previous conditions (A = 1 mM and B = 1.5 mM). Just like in the previous case, changing the initial condition affect the orbits in phase space, but the final destination remains constant. Furthermore, the stability apparently differs depending on the parameters.

To summarize, the qualitative behaviour (final destination and trajectories) depend on the values of the parameters. In fact, the steady states are defined as a function of the parameters. Because little changes in the parameters cause large perturbations in the variable trajectories and orbits, we conclude that the system is not stable. In other words, the stability of the system depends directly on the parameters.

Stability analysis of steady states

1. Symbolically calculate the Jacobian matrix, the variational system particularized over the steady state, as well as the eigenvalues as the function of the parametres of the model.

   The Jacobian matrix is defined as the matrix of all fisrt order partial derivatives of a vector-valued function. From equations 1 and 2:

$$J = \begin{pmatrix} \frac{\partial dX}{dX} & \frac{\partial dX}{dY} \\ \frac{\partial dY}{dX} & \frac{\partial dY}{dY} \end{pmatrix} = \begin{pmatrix} -B + 2XY - 1 & X^2 \\ B - Y - 2XY & -X^2 \end{pmatrix}$$

   If stationary states are considered, we obtain the resulting Jacobian matrix:

$$J = \begin{pmatrix} B - 1 & A^2 \\ -B & -A^2 \end{pmatrix}$$

   Therefore the Jacobian matrix determinant and trace are, $\Delta = A^2$ and $\mathrm{T} = -A^2 - B - 1$.

2. Could you determine from the expression of the eigenvalues which will be the sign and nature (whether real, complex or imaginary) of the eigenvalues when A = 1 mM and B = 1.5 mM? And when A = 1 mM and B = 3 mM? Complementarily, check with a program in matlab whichh are the numerical values of the eigen values in these two cases.

   According to the expression of the eigenvalues (ω), when A = 1 mM and B = 1.5 mM, T < 0 and $(T^2 - 4\Delta) < 0$. Therefore, $\omega = Re(\omega) + Im(\omega)i$ and it sign is negative. When A = 1 mM and B = 3 mM, the nature and sign of eigenvalues are the same as in the previous case.

   The program required for the calculation of the eigenvalues:

```
clear all
clc
disp('STABILITY ANALYSIS OF STEADY STATES – BELOUSOV-ZHABOTINSKY MODEL');

%PARAMETER VALUES:
A =1;
B =1.5;
```

```
%STEADY STATE CONCENTRATION VALUES:
x(1) = 1;
x(2) = 1.5;
%JACOBIAN MATRIX:
%matrix elements:
a11 = -B + 2x(1)*x(2) - 1;
a12 = x(1)*x(1);
a21 = B - 2x(1)*x(2);
a22 = -x(1)*x(1);
%Jacobian matrix:
J=[a11, a12;
a21, a22]

%CALCULUS FOR THE EIGENVALUES AND EIGENVECTORS:
%eig function gives eigenvectors and eigenvalues
eigvec,eigval =eig(J)
```

Result:

```
STABILITY ANALYSIS OF STEADY STATES – BELOUSOV-ZHABOTINSKY MODEL

J =

0.5000 1.0000
-1.5000 -1.0000

eigvec =

-0.3873 - 0.5000i -0.3873 + 0.5000i
0.7746 + 0.0000i 0.7746 + 0.0000i

eigval =

-0.2500 + 0.9682i 0.0000 + 0.0000i
0.0000 + 0.0000i -0.2500 - 0.9682i
```

The eigenvalues correspond to the stable focus, which agrees with the previous conclusions. Therefore, the phase space portraits a spiral toward, and converge to the critical point. The trajectories have elliptical traces, but with each revolution, the distance from the critical decay exponentially.

When A = 1 mM and B = 3 mM, the resulting eigenvalues are the following:

STABILITY ANALYSIS OF STEADY STATES – BELOUSOV-ZHABOTINSKY MODEL

J =

2 1
-3 -1

eigvec =

-0.4330 - 0.2500i -0.4330 + 0.2500i
0.8660 + 0.0000i 0.8660 + 0.0000i

eigval =

0.5000 + 0.8660i 0.0000 + 0.0000i
0.0000 + 0.0000i 0.5000 - 0.8660i

Therefore the eigenvalues correspond to the unstable focus, because eigenvalues are composed of real and imaginary numbers and the trace is negative. Because it is unstable, the phase space should represent a orbit outward, to infinit. This results do not agree with the orbit in the previous phase space, which shows a limit cycle.

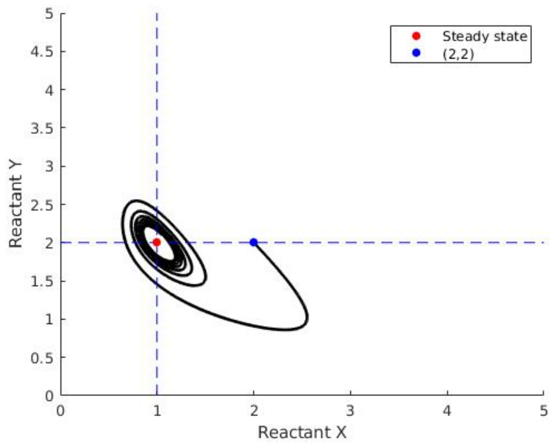
3. Could you directly determine from the expression of the eigenvalues what are the requirements (in terms of the parameters A and B) to get a stable steady state or an unstable one?

   Given that the steady states are functions of the parameters, the steady state stability will depend in the parameters.

   - When B -1 < A^2 the focus is stable, i.e. the steady state is an attractor
   - When B -1 > A^2 the focus is unstable, i.e. the steady state is an repellor.

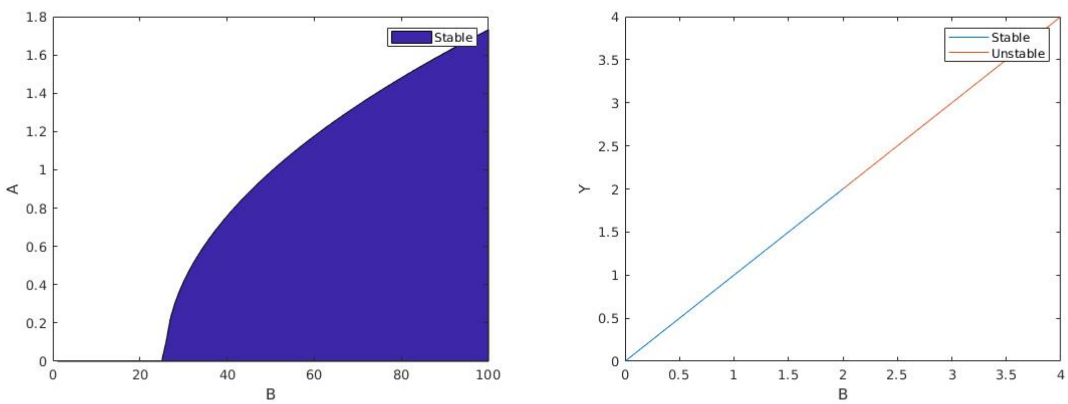
4. Could you also say if this model accepts other types of steady states? For instace, determine the parameter conditions needed to get a center. Check it by numerical integration. Are there any other types of steady state?

   In order to get a center-type critical point, T must be equal to 0. Therefore the parameter conditions needed to get a center are B - 1 = A^2, as shown in the phase space below. Because, the determinant is always positive $\Delta = A^2 > 0$, the stability is never going to be a saddle point. Other type of stabilities cannot be discarded.



5. Could tou try to draw a 2D bifurcation diagram?

   The following images represent the limit for parameters A and B to be stable and unstable (left), and the bifurcation diagram for Y and B. In the bifurcation diagram, the A parameter was fixed at A = 1 mM and the stabilty was studied depending on B.



Limit cycle and isoclines

Isoclines are defined as the set of points which attains a given slope. According to this definition, nullclines are the curves that associate the points with slope 0 and ∞. The mathematical deffinition of isoclines is given by

$$\frac{dy}{dx} = \frac{f_y(x, y, \{\lambda\})}{f_x(x, y, \{\lambda\})} = s$$

For s = 0, f_y = BX - X^2Y = 0 ;therefore, the nullcline is described by the curves

$$Y = B/X and X = 0$$

For s = ∞, f_x = A + BX + X^2Y = 0; therefore, the nullcline is describes by the curves

$$Y = \frac{X - BX - A}{X^2}$$

For the case of A = 1 mM and B = 3 mM the resulting nullclines are represented in the following graphic. Note that the nullclines cross the orbit when the slope is 0 or ∞, which agrees with the interpretation of nullclines.