M1 BBS - EM8BBSEM

# Simulation de Systèmes Biologiques

# (#9)

Georges Czaplicki, UPS / IPBS-CNRS
Tél. : 05.61.17.54.04, email : cgeorge@ipbs.fr

## Adimensionnement

Conversion de variables d'une équation de façon à se libérer des unités (ce qui est équivalent au changement d'échelle).

**Exemple :**

**Equation :** $$A\frac{dx}{dt} + Bx = Cf(t)$$

**Substitution :** $$x = aX$$ $$t = bT$$

**Par conséquent, les dérivées sont :** $$dx = a \cdot dX$$ $$dt = b \cdot dT$$

**Nouvelle forme d'équation :**

$$\left(\frac{Aa}{b}\right)\frac{dX}{dT} + (Ba)X = Cf(bT) \xrightarrow{def} CF(T)$$

**Pour se débarrasser du coefficient du terme dX/dT, on divise tout par (*Aa/b*) :**

$$\boxed{\frac{dX}{dT}+\left(\frac{bB}{A}\right)X=\left(\frac{bC}{Aa}\right)F(T)}$$

**Pour mettre le coefficient du terme X à 1, on choisi :**

$$\boxed{\frac{bB}{A}=1 \quad \Rightarrow \quad b=\frac{A}{B}}$$

**L’équation devient :**

$$\boxed{\frac{dX}{dT}+X=\frac{C}{aB}F(T)}$$

**Il reste à choisir le coefficient *a* pour simplifier l'expression :**

$$\boxed{\frac{C}{aB} = 1 \quad \Rightarrow \quad a = \frac{C}{B}}$$

**Finalement, l'équation initiale prend la forme suivante :**

$$\boxed{\frac{dX}{dT} + X = F(T)}$$

**où**

$$\boxed{\begin{aligned} X &= \frac{B}{C}x \\ T &= \frac{B}{A}t \end{aligned}}$$

**La forme simplifiée permet de se focaliser sur la recherche de propriétés de la solution, indépendamment de l'échelle de variables.**

## Sélection d'une des espèces équivalentes

All living organisms make use of only one of two possible isomers of sugars (***D***, *dextrorotatory*) and amino acids (***L***, *levorotatory*). The other, ‘mirror’ type of isomer, when present in an organism, may not be assimilated or even become harmful. And yet, those ‘mirror’ compounds should exhibit similar properties and thus ‘live’ the same way as their current biological counterparts.

We may argue that at some point in the past both isomers coexisted in a racemic mixture. In the crucial moment of life formation either ***L*** or ***D*** isomers might emerge with equal probability.

We will construct a model describing a process, which results in the survival of one of two equivalent species and the death of the other one. Let ***X*** and ***Y*** be the concentrations of optically active substances, e.g. corresponding to isomers ***L*** and ***D***, respectively. As usual, the growth of each population is proportional to its number, while their antagonistic interaction is modeled by the inclusion of the term ***XY***. The set of equations has the following form:

$$\frac{dX}{dt} = aX - \gamma XY$$
$$\frac{dY}{dt} = aY - \gamma XY$$

The parameter ***a*** balances the reproduction and mortality for each species. The fact that both of the ***XY*** terms are negative means that both objects perish as a result of their antagonistic encounter. The coefficients ***a*** & $\gamma$ are the same for both species, which reflects their equivalence.

To simplify the analysis we will transform the variables to a new dimensionless form, using the following relations:

$$\tau = at, \quad x = \frac{\gamma}{a}X, \quad \mathrm{y} = \frac{\gamma}{\mathrm{a}}Y$$

Here is the new set of equations:

$$\frac{dx}{d\tau} = x - xy$$

$$\frac{dy}{d\tau} = y - xy$$

The stationary points can be found from:

$$0 = x - xy = x(1 - y)$$
$$0 = y - xy = y(1 - x)$$

There are two of them: ***(0,0)*** and ***(1,1)***. Let's take a look at the first one. The theory of perturbations applied to this case gives the following:

$$x(\tau) = 0 + \xi(\tau), \quad \frac{dx}{d\tau} = \frac{d\xi}{d\tau}$$
$$y(\tau) = 0 + \eta(\tau), \quad \frac{dy}{d\tau} = \frac{d\eta}{d\tau}$$

Substituting these expressions into the original set of (dimensionless) equations leads to the following:

$$\frac{d\xi}{d\tau} = \xi - \xi\eta$$
$$\frac{d\eta}{d\tau} = \eta - \xi\eta$$

Linearizing this set of equations gives the following solution:

$$\left.\begin{aligned}\frac{d\xi}{d\tau} &= \xi \\ \frac{d\eta}{d\tau} &= \eta\end{aligned}\right\} \quad \Rightarrow \quad \det\begin{vmatrix}1-\lambda & 0 \\ 0 & 1-\lambda\end{vmatrix} = 0 \quad \Rightarrow \quad \begin{cases}\lambda_1 = 1 \\ \lambda_2 = 1\end{cases} \quad \Rightarrow \quad \begin{cases}\xi = Ae^{\tau} \\ \eta = Be^{\tau}\end{cases}$$

Since both roots are positive, the point ***(0,0)*** is an unstable node (all trajectories leave it permanently).

Now let's analyze the second stationary point ***(1,1)***:

$$x(\tau) = 1 + \xi(\tau), \quad \frac{dx}{d\tau} = \frac{d\xi}{d\tau}$$
$$y(\tau) = 1 + \eta(\tau), \quad \frac{dy}{d\tau} = \frac{d\eta}{d\tau}$$

Substitution and linearization yields:

$$\frac{d\xi}{d\tau} = -\eta$$
$$\frac{d\eta}{d\tau} = -\xi$$

The solution of the characteristic equation is:

$$\left.\begin{aligned} \frac{d\xi}{d\tau} &= -\eta \\ \frac{d\eta}{d\tau} &= -\xi \end{aligned}\right\} \quad \Rightarrow \quad \det\begin{vmatrix} -\lambda & -1 \\ -1 & -\lambda \end{vmatrix} = 0 \quad \Rightarrow \quad \begin{cases} \lambda_1 = 1 \\ \lambda_2 = -1 \end{cases} \quad \Rightarrow \quad \begin{cases} \xi = Ae^{\tau} + Be^{-\tau} \\ \eta = Ce^{\tau} + De^{-\tau} \end{cases}$$

Since the roots have opposite signs, the point ***(1,1)*** is a saddle.

To complete the analysis, let's create a phase portrait of the system. The ***(x,y)*** dependence is obtained by eliminating time from the set of the original equations:

$$\left.\begin{aligned} \frac{dx}{d\tau} &= x - xy \\ \frac{dy}{d\tau} &= y - xy \end{aligned}\right\} \quad \Rightarrow \quad \frac{dy}{dx} = \frac{y(1-x)}{x(1-y)} = \frac{Q(x,y)}{P(x,y)}$$

First, let's find the principal ***isoclines***, i.e. the isoclines of horizontal [***Q(x,y) = 0***] and vertical [***P(x,y) = 0***] adjacent lines:

$$Q(x,y) = 0 \quad \Rightarrow \quad y(1-x) = 0 \quad \Rightarrow \quad \begin{cases} x = 1 \\ y = 0 \end{cases}$$

$$P(x,y) = 0 \quad \Rightarrow \quad x(1-y) = 0 \quad \Rightarrow \quad \begin{cases} x = 0 \\ y = 1 \end{cases}$$

A straight line called ***separator***, which passes through the saddle, separates different attraction basins for the trajectories. Its equation is obtained by assuming that the exponentially growing term is eliminated due to specific initial conditions:

$$\left.\begin{aligned}\xi &= Ae^{\tau} + Be^{-\tau} \\ \eta &= Ce^{\tau} + De^{-\tau}\end{aligned}\right\} \xrightarrow{A=C=0} \frac{\eta}{\xi} = \frac{D}{B} \quad \Rightarrow \quad \eta = \left(\frac{D}{B}\right)\xi$$

As can be seen, the separator passes through the saddle, and also through the origin of the reference frame.

The last element we need to construct the phase portrait of our system is the behaviour of trajectories far from stationary points. Isoclines help us deal with this problem to some extent. However, it is advantageous to know the signs of the ***dy/dx*** derivatives in the phase plane.

$$\frac{dy}{dx} = \frac{y(1-x)}{x(1-y)}$$

In order for the above expression to be positive, the following relationships have to be satisfied:

$$\frac{dy}{dx} > 0 \quad \Rightarrow \quad \frac{y(1-x)}{x(1-y)} > 0 \quad \Rightarrow \quad \left\{ \begin{array}{ccc} 1-x>0 & \text{AND} & 1-y>0 \\ & \text{OR} & \\ 1-x<0 & \text{AND} & 1-y<0 \end{array} \right\}$$

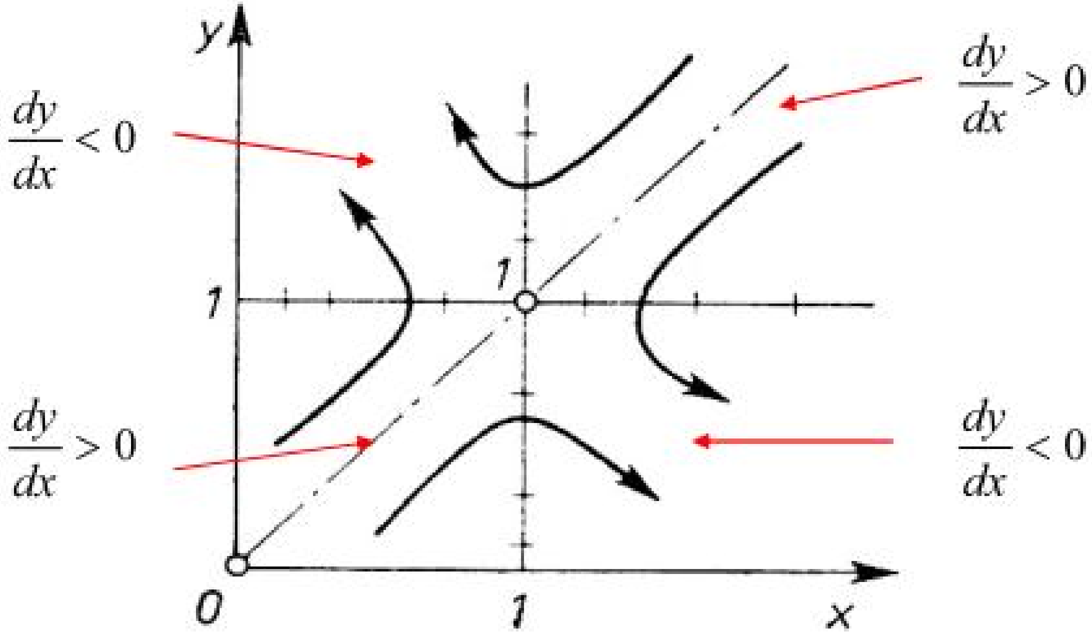
$$\Rightarrow \quad \left\{ \begin{array}{ccc} x<1 & \text{AND} & y<1 \\ & & \\ x>1 & \text{AND} & y>1 \end{array} \right.$$

In order for the derivative to be negative, the following relationships have to be satisfied:

$$\frac{dy}{dx} < 0 \quad \Rightarrow \quad \frac{y(1-x)}{x(1-y)} < 0 \quad \Rightarrow \quad \left\{ \begin{array}{ccc} 1-x>0 & \text{AND} & 1-y<0 \\ & \text{OR} & \\ 1-x<0 & \text{AND} & 1-y>0 \end{array} \right\}$$

$$\Rightarrow \quad \begin{cases} x<1 & \text{AND} \quad y>1 \\ \\ x>1 & \text{AND} \quad y<1 \end{cases}$$

Finally, we are ready to sketch the phase portrait of the system:

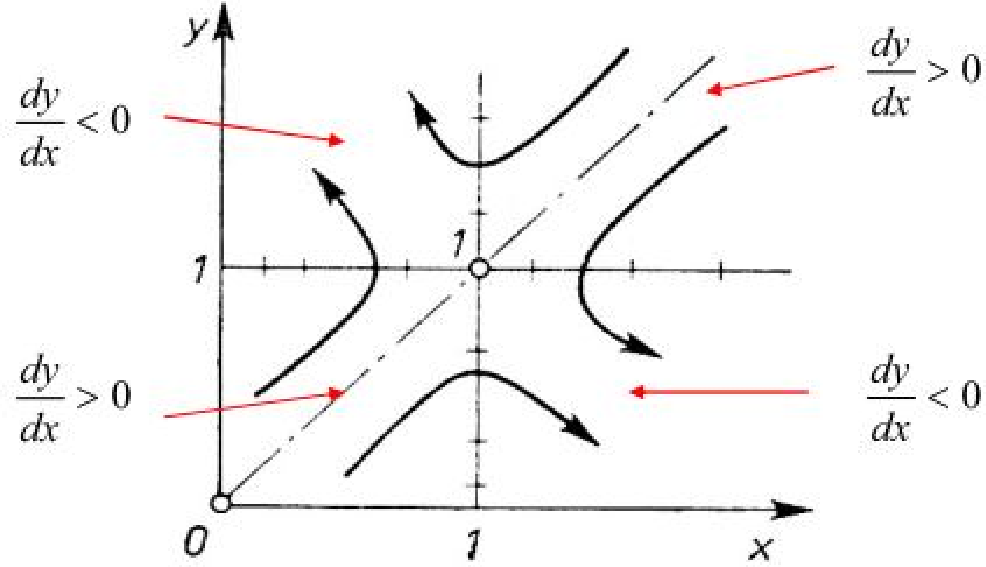



It should be easy to see that this system represents a ***switch*** or a ***trigger***. Depending on the initial conditions the trajectories tend to one of the two stable points located in the infinity:

$$\bar{x} = \infty, \qquad \bar{y} = 0$$

$$\bar{x} = 0, \qquad \bar{y} = \infty$$

The interpretation of this result is straightforward: in our model the food resources are unlimited, hence the populations can grow endlessly.




The fact that the stationary point ***(1,1)*** is a saddle is significant: a racemic mixture of species is unstable and arbitrarily small perturbations will cause either an unlimited growth of ***x*** and disappearance of ***y***, or growth of ***y*** and disappearance of ***x***.

***The lack of stability of a symmetric stationary state is the reason for the biologic asymmetry.***

# Exercice

Suppose there is a small group of individuals who are infected with a contagious disease and who have come into a large population. If the population is divided into three groups, the susceptible (S), the infected (I), and the recovered (R), we have what is known as a **classical S-I-R problem**.

The susceptible class consists of those who are not infected, but who are capable of catching the disease and becoming infected. The probability $\boldsymbol{r}$ of catching a disease upon encountering an infected individual is called the *infection rate*.

The infected class consists of the individuals who are capable of transmitting the disease to others. Their number decreases when they recover. The recovery rate $\boldsymbol{a}$ is called the *removal rate*.

Finally, the recovered class consists of those who have had the disease, but are no longer infectious.

a) Write the equations and analyze the model (stationary points, stability, trajectories…).
b) Draw graphs for solutions. Use $\boldsymbol{r} = \boldsymbol{a} = 1$. What is the behavior of each class?

Equations d'après le modèle :

$$\frac{dS}{dt} = -rSI$$
$$\frac{dI}{dt} = rSI - aI$$
$$\frac{dR}{dt} = aI$$

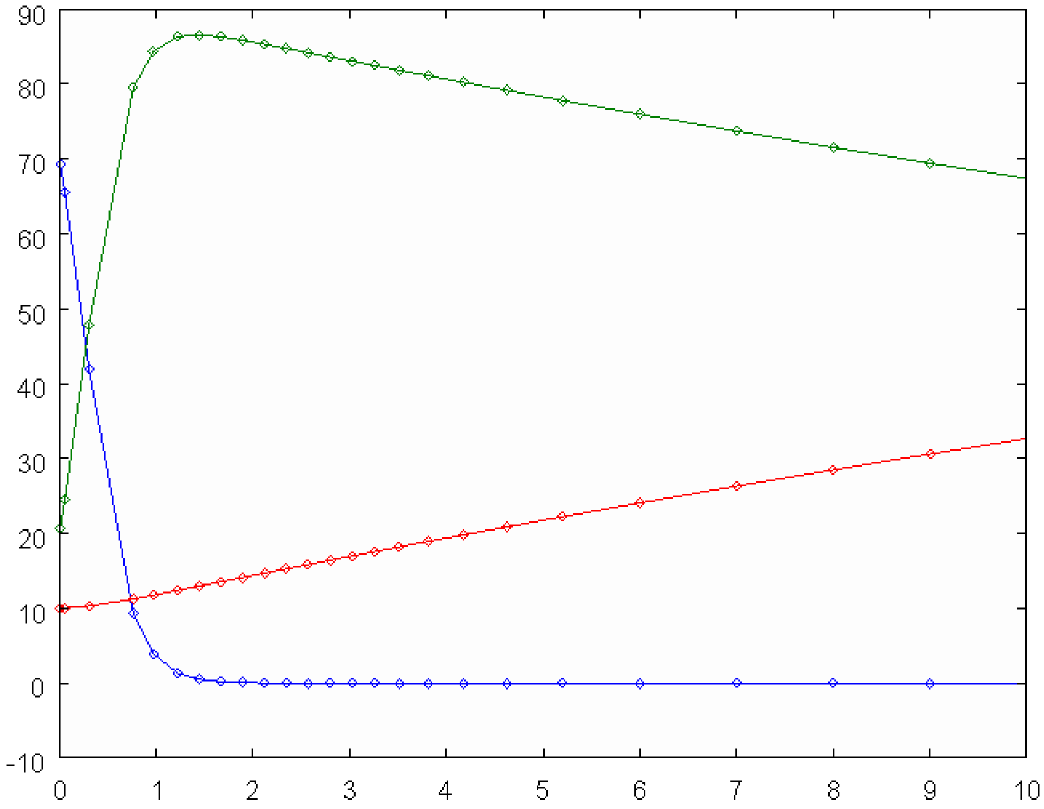
Fonction Matlab/Freemat
qui calcule les trois quations
(avec les paramètres *r* & *a*) :

```
function yp = SIR(t,y,r,a)
yp = zeros(3,1);
yp(1) = -r * y(1) * y(2);
yp(2) =  r * y(1) * y(2) – a * y(2);
yp(3) =  a * y(2);
```

Solution numérique de ce jeu d'équations différentielles :

```
[t,y]=ode45(func,tspan,y0,options,params)
```

```
--> [t,y]=ode45('SIR',[0,10],[70 20 10],['RelTol',1e-6],0.05,0.03);
--> plot(t,y,'-d')
```



## Extrait de commentaires de la commande "ode45" :

```
% The optional argument 'options' is a structure. It may contain any of the
% following fields:
%
% 'AbsTol' - Absolute tolerance, default is 1e-6.
% 'RelTol' - Relative tolerance, default is 1e-3.
% 'MaxStep' - Maximum step size, default is (tspan(2)-tspan(1))/10
% 'InitialStep' - Initial step size, default is maxstep/100
% 'Stepper' - To override the default Fehlberg integrator
% 'Events' - To provide an event function
% 'Projection' - To provide a projection function
```

## Exercice

Montrer que la linéarisation du système :

$$\frac{dx}{dt} = -y + ax \cdot \left(x^2 + y^2\right)$$

$$\frac{dy}{dt} = x + ay \cdot \left(x^2 + y^2\right)$$

prédit que le seul point stationnaire est un centre pour toutes les valeurs du paramètre *a*, mais en réalité c'est une spirale stable si $a < 0$ et une spirale instable si $a > 0$. Tracez les portraits de phase de ce système.

Le point stationnaire peut être obtenu des équations suivantes :

$$0 = -y + ax \cdot \left(x^2 + y^2\right)$$
$$0 = x + ay \cdot \left(x^2 + y^2\right)$$

On regroupant les termes on arrive à :

$$\frac{y}{ax} = \left(x^2 + y^2\right)$$
$$\frac{-x}{ay} = \left(x^2 + y^2\right)$$

En comparant les termes à gauche du "=" on a :

$\boxed{\dfrac{y}{ax} = \dfrac{-x}{ay}}$ d'où on obtient : $ay^2 = -ax^2$

et finalement : $\boxed{a \cdot \left(x^2 + y^2\right) = 0}$ donc : $\boxed{(0,0)}$

## Linéarisation du système :

$$\left.\begin{array}{l} x = 0 + \xi \\ y = 0 + \eta \end{array}\right\} \qquad \begin{array}{l} \dfrac{d\xi}{dt} = -\eta + a\xi\left(\xi^2 + \eta^2\right) \\ \dfrac{d\eta}{dt} = \xi + a\eta\left(\xi^2 + \eta^2\right) \end{array}$$

Si on ne retient que les termes linéaires : $\boxed{\begin{array}{l} \dfrac{d\xi}{dt} = -\eta \\ \dfrac{d\eta}{dt} = \xi \end{array}}$

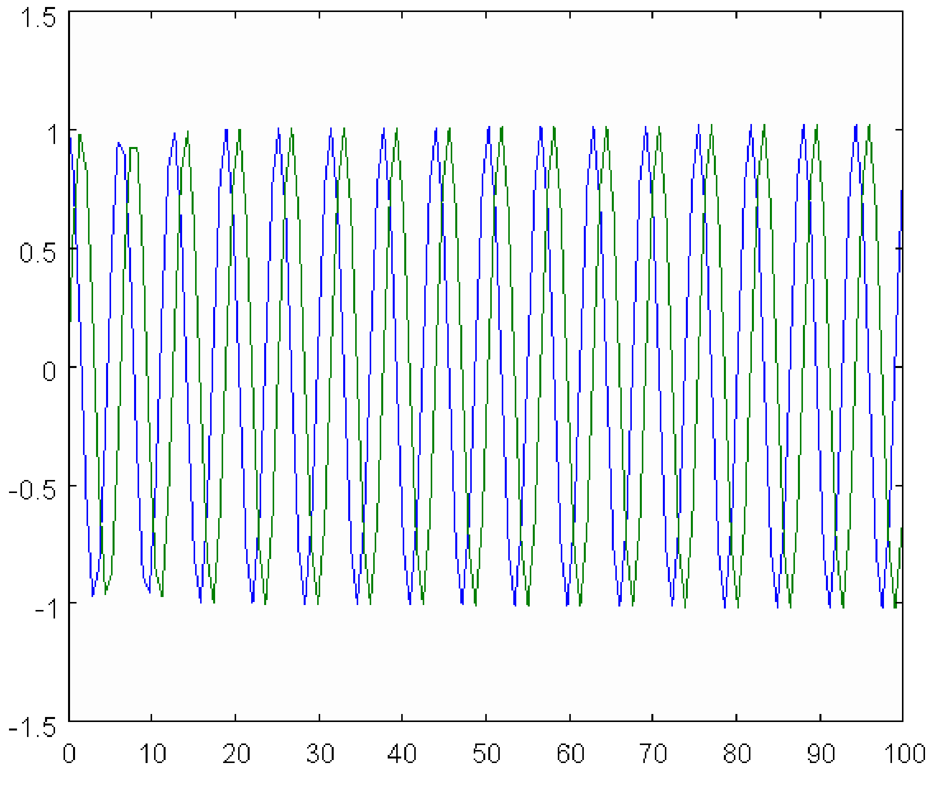
Pour trouver les racines du polynôme caractéristique :

$$A = \begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix} \qquad \det(A - \lambda I) = \begin{bmatrix} -\lambda & -1 \\ 1 & -\lambda \end{bmatrix} = 0 \qquad \left\{\begin{array}{l} \lambda^2 + 1 = 0 \\ \lambda_{1,2} = \pm i \end{array}\right.$$

$$\boxed{\begin{pmatrix} \xi \\ \eta \end{pmatrix} = C_1 e^{it} + C_2 e^{-it} = C_1 \cos(t) + C_2 \sin(t)}$$

```
function yp = myfcn(t,y,a)
yp=zeros(2,1);
yp(1) = -y(2) + a*y(1)*(y(1)^2+y(2)^2);
yp(2) =  y(1) + a*y(2)*(y(1)^2+y(2)^2);
```

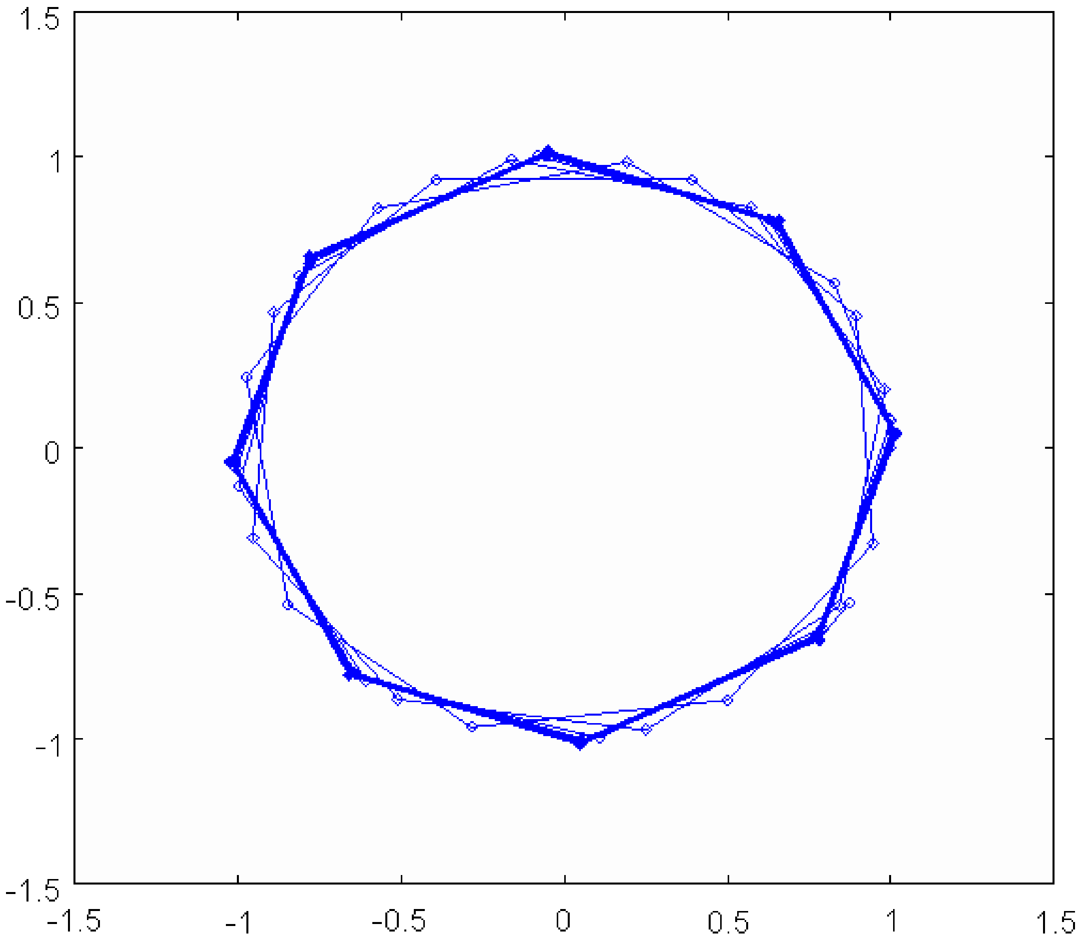
```
--> [t,y]=ode45('myfcn',[0,100],[1,0],[],0);
--> plot(t,y,'-d')
```



```
--> y
ans =
    1.0000         0
    0.9950    0.0998
    0.8253    0.5646
    0.1919    0.9816
   -0.5697    0.8223
   -0.9713    0.2400
   -0.8430   -0.5391
   -0.2816   -0.9604
    0.5006   -0.8668
    0.9448   -0.3310
    0.8933    0.4524
    0.3905    0.9221
   -0.3913    0.9220
   -0.8881    0.4632
   -0.9521   -0.3117
   -0.5075   -0.8640
    0.2497   -0.9705
    0.8424   -0.5431
    0.9822    0.2001
    0.5702    0.8247
   -0.1614    0.9896
   -0.8105    0.5907
   -0.9943   -0.1318
   -0.6060   -0.7995
    0.1094   -0.9974
    0.7912   -0.6174
    0.9994    0.0927
    0.6257    0.7850
   -0.0804    1.0008
   -0.7805    0.6319
```

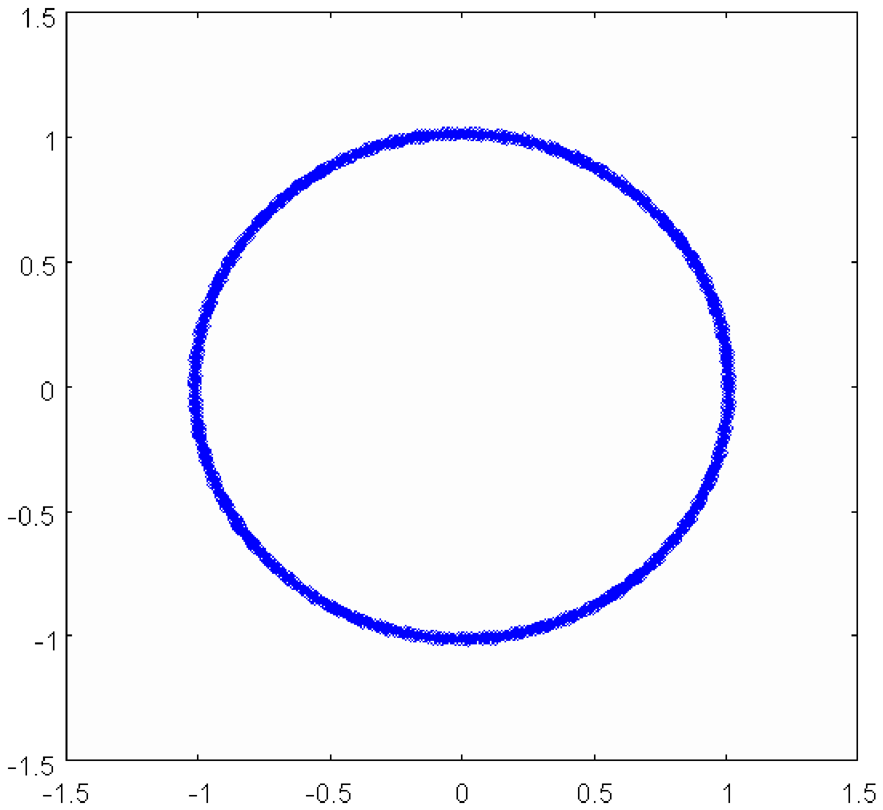
Pour obtenir l'image de phase du système :

```
--> plot(y(:,1),y(:,2),'-d')
```



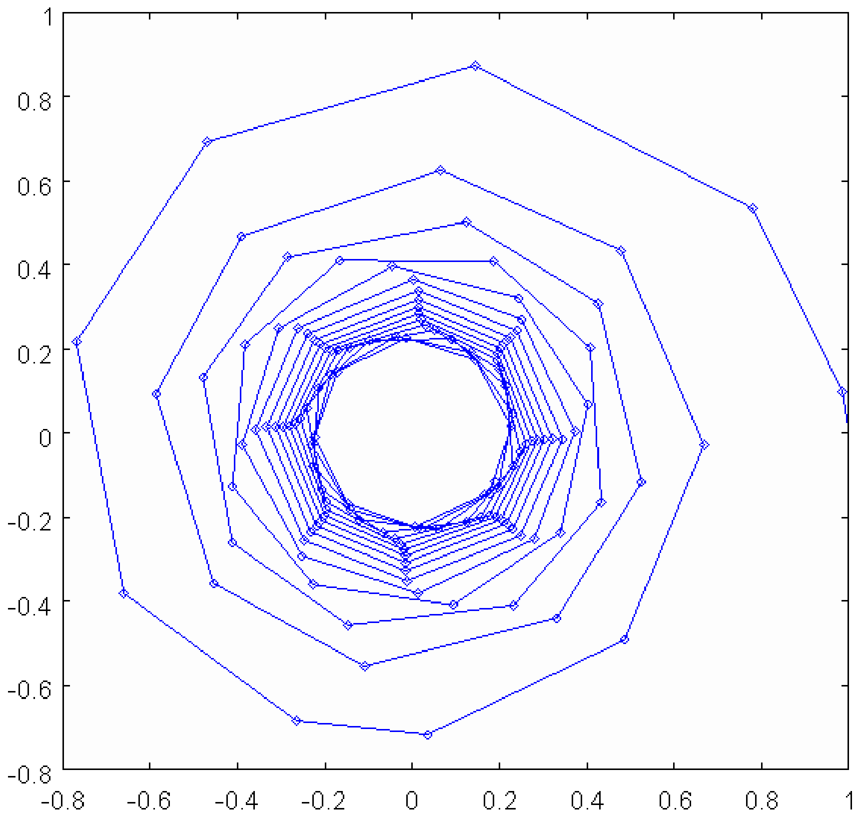
Pour avoir plus de points pour le graphe :

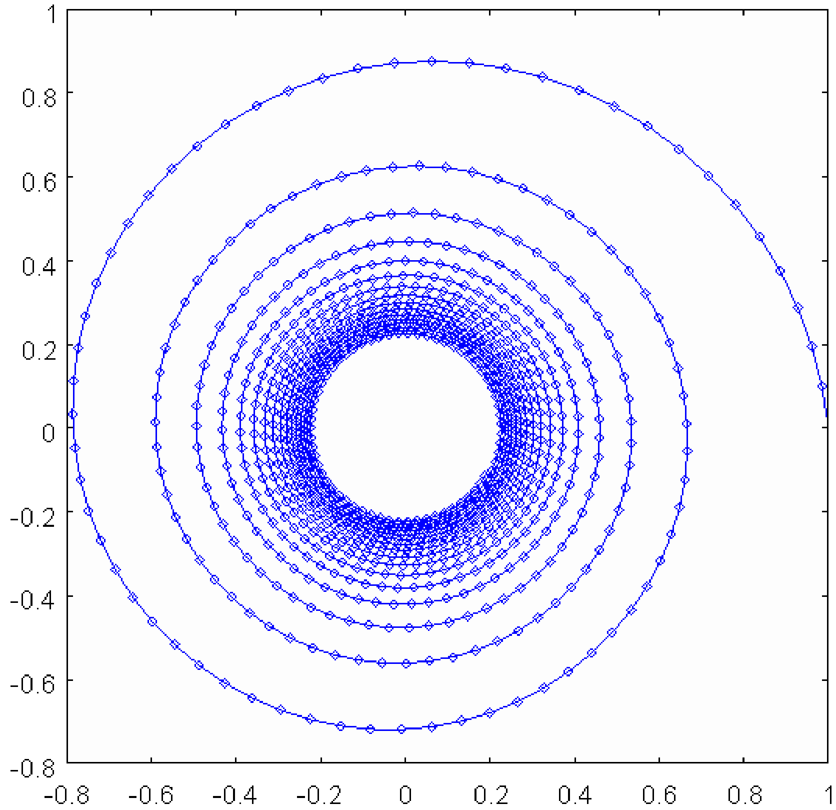
```
--> SOL=ode45('myfcn',[0,100],[1,0],[],0);
--> y=deval(SOL,0:0.1:100);
--> y=y';
--> plot(y(:,1),y(:,2),'-d')
```



Pour voir ce qui se passe quand a < 0 :

```
--> [t,y]=ode45('myfcn',[0,100],[1,0],[],-0.1);
--> plot(y(:,1),y(:,2),'-d')
```

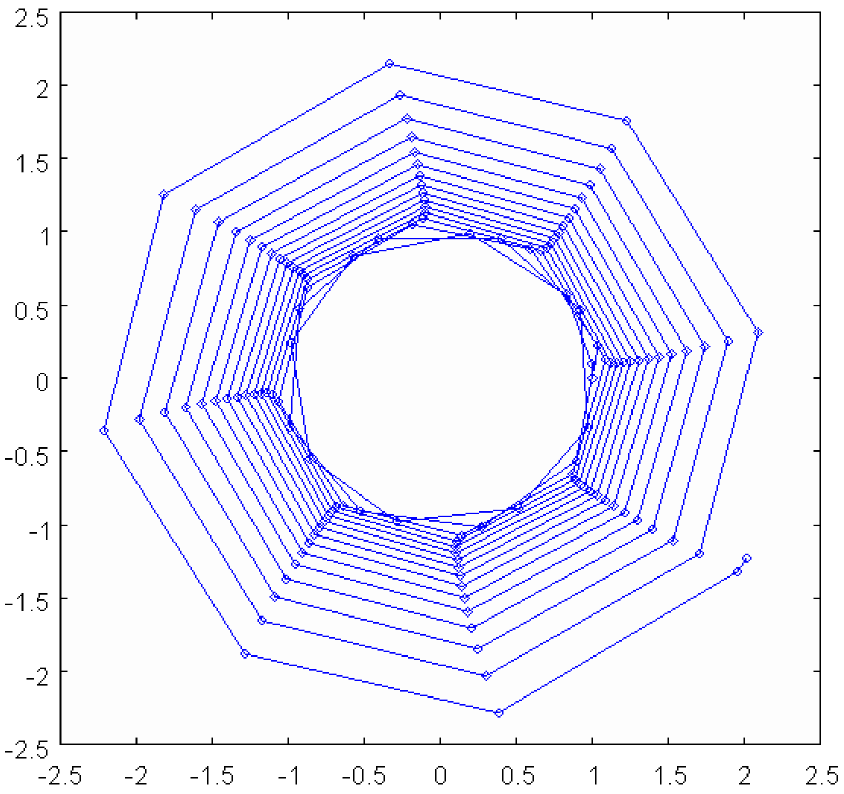


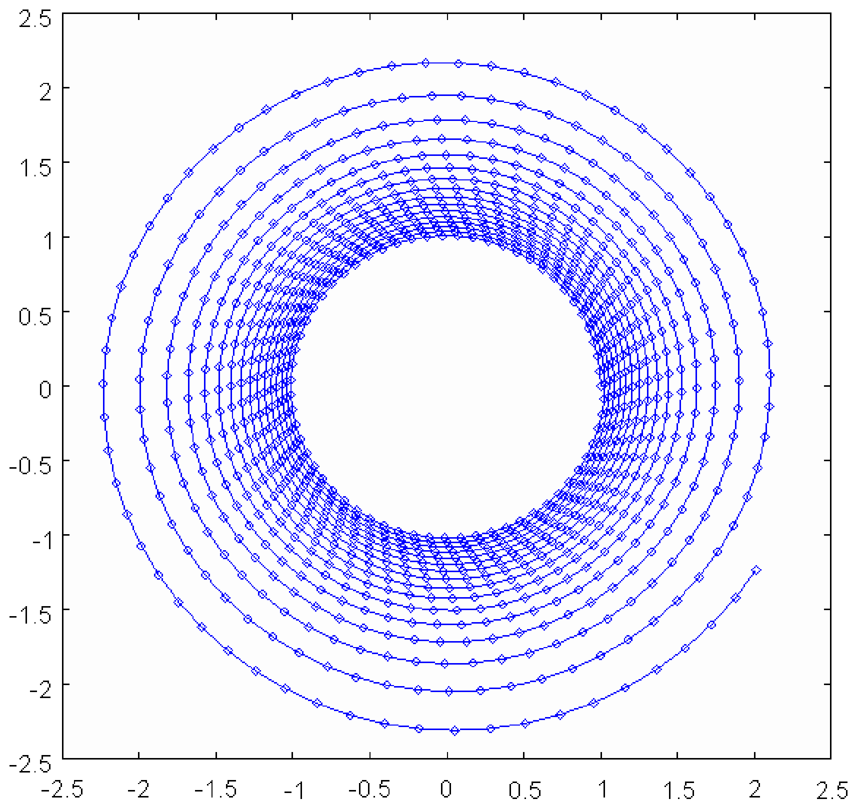




(SOL)

Pour voir ce qui se passe quand a > 0 :

```
--> [t,y]=ode45('myfcn',[0,100],[1,0],[],0.004);
--> plot(y(:,1),y(:,2),'-d')
```

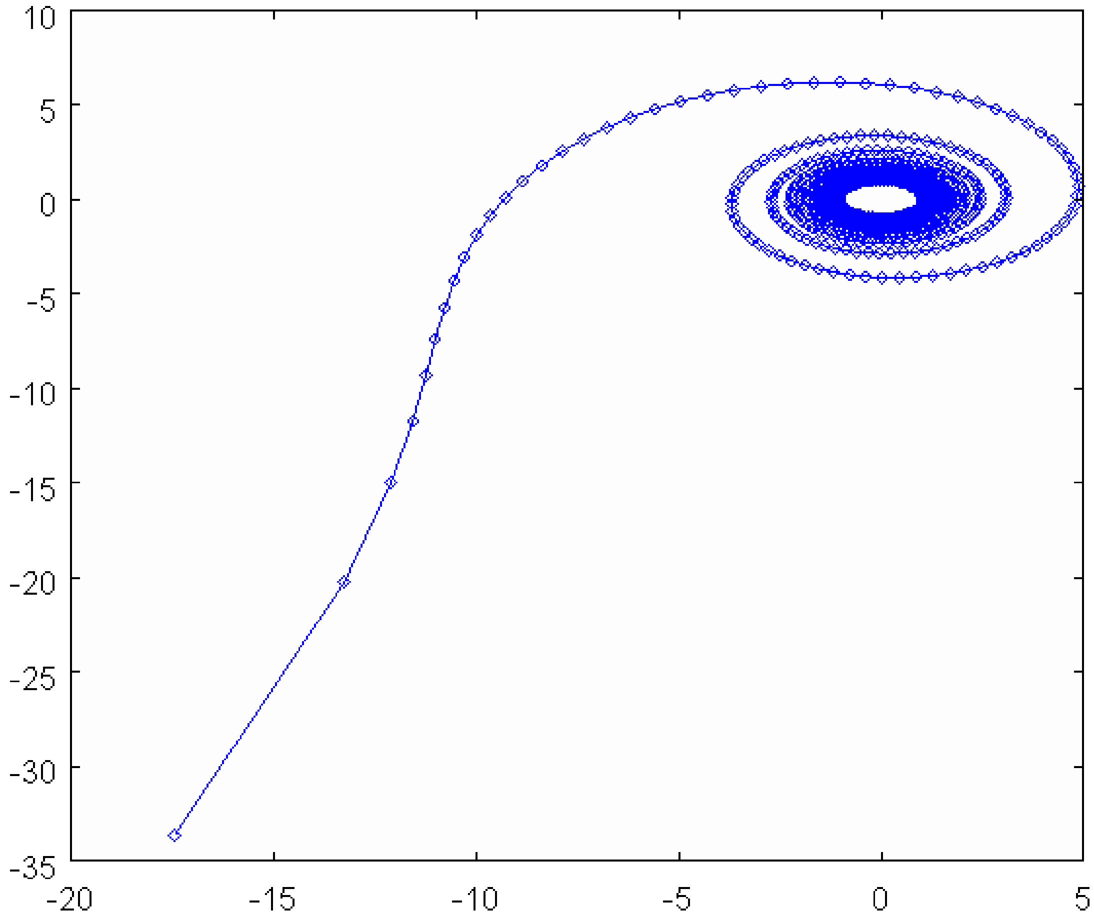



(SOL)

## A cause d'une forte non-linéarité du système, l'intégration numérique peut causer quelques problèmes. Exemple : *a* = 0.005 :

```
--> y
ans =
   1.0e+003 *
    0.0010          0
    0.0010     0.0001
    0.0008     0.0006
    0.0002     0.0010
   -0.0006     0.0008
   -0.0019    -0.0035
    0.0013    -0.0041
    0.0041    -0.0021
    0.0047     0.0017
...
   -0.0208    -0.0428
   -0.0352    -0.0782
   -0.0962    -0.2211
   -0.9499    -2.1944
 -Inf -Inf
 NaN NaN
 NaN NaN
 NaN NaN
 NaN NaN
 NaN NaN
```




(SOL)

# Exercice

The following *competition model* is provided in Reference [9]. Imagine rabbits and sheep competing for the same limited amount of grass. Assume a logistic growth for the two populations, that rabbits reproduce rapidly, and that the sheep will crowd out the rabbits. Assume these conflicts occur at a rate proportional to the size of each population. Further, assume that the conflicts reduce the growth rate for each species, but make the effect more severe for the rabbits by increasing the coefficient for that term. A model that incorporates these assumptions is

$$\frac{dx}{dt} = x(3 - x - 2y)$$

$$\frac{dy}{dt} = y(2 - x - y)$$

where $x(t)$ is the rabbit population and $y$ is the sheep population. (Of course, the coefficients are not realistic, but are chosen to illustrate the possibilities.)