Aix-Marseille Université Master CMB-Bio
2019-2020

Continuous dynamical systems and modeling
Nonlinear ODEs

Exercise 1 [Cell population]
We consider for $K_* > 0$ the following differential system:

$$\begin{cases} x'(t) = x(t)(K(t) - x(t)) & \text{(1a)} \\ K'(t) = (K_* - K(t))x(t) & \text{(1b)} \end{cases}$$

The variable $x(t)$ denotes the size of the cell population at time t while and $K(t)$ is an indicator of the amount of resources available at time t. We complete the system with the initial condition

$$x(0) = x_0, \quad K(0) = K_0 \quad \text{with} \quad 0 \leq x_0 \leq K_0. \tag{2}$$

1. Determine the solution in the case $K_0 = K_*$.
2. Determine the equilibrium points of the system.
3. For each equilibrium point, determine the associated linearized system. What can you say about their stability ?
4. (**) Asymptotic behavior. Assume that initially

$$0 < x_0 < K_0 < K_*.$$

   (a) Prove that x is an increasing function upper-bounded and that for all $t \in \mathbb{R}^+$, $x_0 \leq x(t) \leq K_*$.
   (b) Given $v(t) = K_* - K(t)$. Prove that for all $t \in \mathbb{R}^+$

$$v(t) = (K_* - K_0)e^{-\int_0^t x(s)\,ds}$$

   (c) Deduce that $v(t)$ converges exponentially towards 0 when $t \to +\infty$ and thus that the function K converges to K_* when t goes to infinity.
   (d) Deduce the convergence of x toward K_*.

Correction.

1. Assume that $K(0) = K_0 = K_*$. Then $K'(t) = 0$ and therefore $K(t) = K_*$ for any time t. As a consequence, the variable x satisfies the logistic equation

$$x'(t) = (K_* - x(t))x(t).$$

To solve this nonlinear equation, one can use the method of separation of variables. First, if $x_0 \in]0, K_*[$ we ensure that for t sufficiently small $x(t) \in]0, K_*[$. We can then write

$$\frac{x'(t)}{x(t)(K - x(t))} = 1$$

which can be rewritten as

$$\frac{x'(t)}{Kx(t)} + \frac{x'(t)}{K(K - x(t))} = 1.$$

Integrating between 0 and t we get

$$\frac{1}{K} \ln\left(\frac{x(t)}{x_0}\right) - \frac{1}{K} \ln\left(\frac{K - x(t)}{K - x_0}\right) = t$$

and thus

$$\ln\left(\frac{x(t)}{K - x(t)}\right) = \ln\left(\frac{x_0}{K - x_0}\right) + Kt.$$

Composing by the exponential, we infer that

$$\frac{x(t)}{K - x(t)} = \frac{x_0}{K - x_0} e^{Kt}$$

which can be rewritten as

$$x(t)\Big[1 + \frac{x_0}{K - x_0} e^{Kt}\Big] = \frac{Kx_0}{K - x_0} e^{Kt}.$$

Finally the solution reads

$$x(t) = \frac{\frac{Kx_0}{K - x_0} e^{Kt}}{1 + \frac{x_0}{K - x_0} e^{Kt}} = \frac{Kx_0 e^{Kt}}{K - x_0 + x_0 e^{Kt}}.$$

2. Let us set

$$f_1(x, K) := x(K - x) \qquad f_2(x, K) := (K_* - K)x$$

The i-nullcline is the set of points (x, K) such that $f_i(x, K) = 0$:

$$f_1(x, K) = 0 \iff x = 0 \text{ or } K = x$$

$$f_2(x, K) = 0 \iff x = 0 \text{ or } K = K_*$$

An equilibrium point is a point belonging to both nullclines (i.e. in the intersection). The equilibrium points are then $\{(0, K), K \in \mathbb{R}\}$ (we can restrict this set to the set $\{(0, K), K \in \mathbb{R}_+\}$ for the biological application that we consider) and the point (K_*, K_*).

3. To determine the nature of the equilibrium points, let us first calculate the Jacobian matrix of $f = (f_1, f_2)$ at a given point (x_e, K_e):

$$Df(x_e, K_e) = \begin{pmatrix} \frac{\partial f_1}{\partial x}(x_e, K_e) & \frac{\partial f_1}{\partial K}(x_e, K_e) \\ \frac{\partial f_2}{\partial x}(x_e, K_e) & \frac{\partial f_2}{\partial K}(x_e, K_e) \end{pmatrix} = \begin{pmatrix} K_e - 2x_e & x_e \\ K_* - K_e & -x_e \end{pmatrix}$$

The linearized system at the equilibrium point (x_e, K_e) writes

$$z'(t) = Df(x_e, K_e).z(t) \quad \text{where} \quad z(t) = \begin{pmatrix} x(t) - x_e \\ K(t) - K_e \end{pmatrix}.$$

- at $(0, K)$, the Jacobian matrix $Df(0, K)$ is

$$Df(0, K) = \begin{pmatrix} K & 0 \\ K_* - K & 0 \end{pmatrix}$$

whose eigenvalues are 0 and K. As a consequence, for $K > 0$, the equilibrium point $(0, K)$ is locally unstable.

- at (K_*, K_*), the Jacobian matrix $Df(K_*, K_*)$ is

$$Df(K_*, K_*) = \begin{pmatrix} -K_* & K_* \\ 0 & -K_* \end{pmatrix}.$$

This matrix admits one (double) eigenvalue $-K^*$ which is negative. The equilibrium point is thus locally asymptotically stable.

4. Sketch of correction.

(a) While $x(t) \in]0, K(t)[$, we ensure that

$$x'(t) = x(t)(K(t) - x(t)) > 0$$

and therefore x is increasing. Since the system is autonomous, the trajectory associated to the initial datum (x_0, K_0) with $x_0 \in]0, K_0[$and $K_0 < K_*$, can then never cross the trajectory starting from the equilibrium point $(x_e, K_e) = (K_*, K_*)$. Hence x is an increasing function upper-bounded by K^*.

(b) using the separation of variables (valid as long as $K < K_*$) we have

$$\frac{K'(t)}{K_* - K(t)} = x(t)$$

Integrating both sides of the equality between $t_0 = 0$ and t we get

$$\ln \frac{K_* - K_0}{K_* - K(t)} = \int_0^t x(s)ds$$

and therefore

$$\frac{K_* - K_0}{K_* - K(t)} = e^{\int_0^t x(s)ds}.$$

Finally, we obtain

$$v(t) = K_* - K(t) = (K_* - K_0)e^{-\int_0^t x(s)ds}.$$

(c) since $x_0 \leq x(t)$ we deduce from the previous question that

$$|v(t)| = (K_* - K_0)e^{-\int_0^t x(s)ds} \leq (K_* - K_0)e^{-x_0 t} \longrightarrow 0 \text{ as } t \to +\infty$$

and thus

$$K(t) \longrightarrow K^* \text{ as } t \to +\infty$$

(d) since x is increasing and upper-bounded, then x converges to a limit $l \leq K^*$.Coming back to equation (1a) and using the fact that $K(t)$ tends to K^*, it means that l has to satisfy

$$l(K_* - l) = 0 \quad \text{i.e.} \quad l = 0 \text{ or } l = K_*.$$

Since $x_0 > 0$ and x is increasing, we deduce that

$$x(t) \longrightarrow K_* \quad \text{as } t \to +\infty.$$

Exercise 2 [Epidemiology. SI-SIS models]
The SI model is one the simplest model in epidemiology. In the considered population, individuals are born with no immunity, there are *susceptible* to infection. Once infected and with no treatment, individuals remain infected and infectious throughout their life for the rest of the susceptible population. This model is relevant for diseases like cytomegalovirus (CMV) or herpes. The model takes the form

$$\begin{cases} \dfrac{dS}{dt}(t) = -\beta S(t)I(t) & \text{(3a)} \\ \dfrac{dI}{dt}(t) = \beta S(t)I(t) & \text{(3b)} \end{cases}$$

where we assume that $\beta > 0$ and

- $S(t)$ denotes the number of *susceptible* (nonimmune) individuals at time t,
- $I(t)$ denotes the number of infected individuals at time t,

Initially we assume that $S(0) = S_0,\ I(0) = I_0$ and we denote $N_0 = S_0 + I_0$.

1. Verify that the size of the total population is constant in time and that the function I is solution to a logistic equation.

We now consider the case where the infected individuals return to the susceptible state after infection. This model is appropriate for diseases that have repeated infections, for example, the common cold (rhinoviruses).

$$\begin{cases} \dfrac{dS}{dt}(t) = -\beta S(t)I(t) + \gamma(N_0 - S(t) - I(t)) & \text{(4a)} \\ \dfrac{dI}{dt}(t) = \beta S(t)I(t) - \delta I(t) & \text{(4b)} \end{cases}$$

with $\beta,\ \gamma,\ \delta > 0$.

2. Comment on the different terms appearing in model (4).
3. Determine the equilibrium points of the system.
4. Determine the linearized system associated to each equilibrium point and study their stability according to the value of the parameter $R_0 = \frac{\beta N_0}{\delta}$.

Correction.

1. Let us denote $N(t) = S(t) + I(t)$ the total population at time t. Using Equation (3), we have

$$\frac{dN}{dt}(t) = \frac{dS}{dt}(t) + \frac{dI}{dt}(t) = -\beta S(t)I(t) + \beta S(t)I(t) = 0 \quad \forall\, t \geq 0.$$

Therefore the total population is constant over time and

$$N(t) = N_0 \quad \forall\, t \geq 0.$$

As a consequence, we also deduce that

$$S(t) = N(t) - I(t) = N_0 - I(t) \quad \forall\, t \geq 0$$

and thus Eq (3b) rewrites

$$\frac{dI}{dt}(t) = \beta S(t)I(t) = \beta(N_0 - I(t))I(t) \quad \forall\, t \geq 0$$

which corresponds to a logistic equation. One can calculate explicitly the solution (see previous exercise):

$$I(t) = \frac{N_0 I_0 e^{\beta N_0 t}}{N_0 - I_0 + I_0 e^{\beta N_0 t}}.$$

As $t \to +\infty$, $I(t) \to N_0$ (and thus $S(t) \to 0$), which means that the whole population is infected.

2. In model (4), we now take into account a third category of individuals: the recovered individuals that no more infected and not yet susceptible. The full system (called SIR) reads

$$\begin{cases} \dfrac{dS}{dt}(t) = -\beta S(t)I(t) + \gamma R(t) & \text{(5a)} \\ \dfrac{dI}{dt}(t) = \beta S(t)I(t) - \delta I(t) & \text{(5b)} \\ \dfrac{dR}{dt}(t) = \delta I(t) - \gamma R(t) & \text{(5c)} \end{cases}$$

Infected individuals recover with a rate of recovery δ and recovered individuals become susceptible with a rate γ. As before, we check that the total population $N = S + I + R$ is constant (the sum of terms in the right-hand side of the previous system is equal to 0). Replacing in Eq (5) $R(t)$ by $N_0 - S(t) - I(t)$, we get system (4).

3. Let us rewrite system (4) as

$$\begin{cases} S'(t) = f_1(S(t), I(t)) \\ I'(t) = f_2(s(t), I(t)) \end{cases} \quad \text{with} \quad \begin{cases} f_1(S, I) = -\beta SI + \gamma(N_0 - S - I) \\ f_2(S, I) = \beta SI - \delta I \end{cases}$$

We have (excluding here the case $S < 0$ which is not relevant for our application, so $\beta S + \gamma > 0$)

$$f_1(S, I) = 0 \quad \Longleftrightarrow \quad I = \frac{N_0 - S}{\beta S + \gamma}$$

and

$$f_2(S,I)=0 \quad \Longleftrightarrow \quad I=0 \text{ or } S=\frac{\delta}{\beta}.$$

As a consequence, the equilibrium points are

- $(S_1^*, I_1^*) = (N_0, 0)$;
- $(S_2^*, I_2^*) = (\frac{\delta}{\beta}, \frac{\gamma}{\beta}\frac{\beta N_0 - \delta}{\gamma+\delta})$ if $N_0 > \frac{\delta}{\beta}$ (i.e. $R_0 > 1$).
  If $N_0 < \frac{\delta}{\beta}$ (i.e. $R_0 < 1$) then $I_2^* = \frac{\gamma}{\beta}\frac{\beta N_0 - \delta}{\gamma+\delta} = \frac{\gamma}{\gamma+\delta}\frac{N_0(R_0-1)}{R_0} < 0$ which is irrelevant for our application (I is supposed to represent the number of infected people, it should be thus non-negative).

4. To determine the nature of the equilibrium points, let us first calculate the Jacobian matrix of $f = (f_1, f_2)$ at a given point (S^*, I^*):

$$\begin{aligned} Df(S^*,I^*) &= \begin{pmatrix} \dfrac{\partial f_1}{\partial S}(S^*,I^*) & \dfrac{\partial f_1}{\partial I}(S^*,I^*) \\ \dfrac{\partial f_2}{\partial S}(S^*,I^*) & \dfrac{\partial f_2}{\partial I}(S^*,I^*) \end{pmatrix} \\ &= \begin{pmatrix} -\beta I^* - \gamma & -\beta S^* \\ \beta I^* & \beta S^* - \delta \end{pmatrix} \end{aligned}$$

The linearized system at the equilibrium point (S^*, I^*) writes

$$z'(t) = Df(S^*,I^*).z(t) \quad \text{where} \quad z(t) = \begin{pmatrix} S(t) - S^* \\ I(t) - I^* \end{pmatrix}.$$

- at $(S_1^*, I_1^*) = (N_0, 0)$, the Jacobian matrix $Df(N_0, 0)$ is

$$Df(N_0,0) = \begin{pmatrix} -\gamma & -\beta N_0 \\ 0 & \beta N_0 - \delta \end{pmatrix}$$

  whose eigenvalues are $-\gamma$ and $\beta N_0 - \delta$. Therefore (S_1^*, I_1^*) is (locally) asymptotically stable when $\beta N_0 - \delta < 0$, and (locally) unstable when $\beta N_0 - \delta > 0$.
- at $(S_2^*, I_2^*) = (\frac{\delta}{\beta}, \frac{\gamma}{\beta}\frac{\beta N_0 - \delta}{\gamma+\delta})$, the Jacobian matrix $Df(S_2^*, I_2^*)$ is

$$Df(S_2^*,I_2^*) = \begin{pmatrix} -\gamma\frac{\beta N_0 - \delta}{\gamma+\delta} - \gamma & -\delta \\ \gamma\frac{\beta N_0 - \delta}{\gamma+\delta} & 0 \end{pmatrix}.$$

  Let us determine its eigenvalues, λ_1, λ_2: we have

$$\begin{aligned} \text{Tr } Df(S_2^*,I_2^*) &= -\gamma\frac{\beta N_0 - \delta}{\gamma+\delta} - \gamma \\ \det Df(S_2^*,I_2^*) &= \delta\gamma\frac{\beta N_0 - \delta}{\gamma+\delta} \end{aligned}$$

  The equilibrium is relevant only in the case where $I_2^* \geq 0$, i.e. $\beta N_0 - \delta \geq 0$. In the case $\beta N_0 - \delta > 0$, since $\det Df(S_2^*, I_2^*) > 0$ and since $\det Df(S_2^*, I_2^*) = \lambda_1\lambda_2$, we infer that both eigenvalues have the same sign. On the other hand, since $\text{Tr } Df(S_2^*, I_2^*) < 0$ and $\text{Tr } Df(S_2^*, I_2^*) = \lambda_1 + \lambda_2$, we deduce that both eigenvalues are negative. Hence the equilibrium point (S_2^*, I_2^*) is locally asymptotically stable.

Let us summarize the results

- for $R_0 < 1$ the equilibrium point $(N_0, 0)$ is asymptotically stable which means that the epidemic tends to extinct for large times;
- for $R_0 > 1$ the equilibrium point $(N_0, 0)$ is unstable whereas the point $(S_2^*, I_2^*) = (\frac{N_0}{R_0}, \frac{\gamma}{\gamma+\delta}\frac{N_0(R_0-1)}{R_0})$ is asymptotically stable, which means that for large times the epidemic persists within the population;
- if $R_0 = 1$, then the linearization theorem does not allow us to conclude to the stability or the unstability of the equilibrium point $(S_1^*, I_1^*) = (S_2^*, I_2^*) = (N_0, 0)$.

The number R_0, usually called *basic reproduction number* of an infection, can be thought of as the number of infected individuals one single infected person generates on average over the course of its infectious period. The larger the value of R0, the harder it is to control the epidemic