Content: Linear systems, linearisation and some pharmacokinetics

4.7-4.10, part of 4.11, 5.2-5.8

In drug development the study of what happens to a drug when it has entered the body is of paramount importance. In this lecture we will indicate both how to model this using physiological principles, and how it is done in real life. The study of how a drug affects the body is a related subject, called pharmacodynamics, which we will return to.

Linear systems

A linear system of differential equations with constant coefficients can be written

\[ u'(t) = Au(t), \quad u(0) = u_0 \]

and solved by matrix methods. The key observation is that if we take an eigenvector \( v \) and write \( u(t) = f(t)v \) with \( f(0) = 1 \), then

\[ f'(t)v = u'(t) = Au(t) = f(t)Av = \lambda f(t)v, \]

so \( f'(t) = \lambda f(t) \) and therefore \( f(t) = e^{\lambda t} \). Linearity now explains why the method in the next example works. It will work as long as we have a basis of eigenvectors with different eigenvalues (including complex ones).

Example Consider the system

\[
\begin{align*}
x' &= 3x - 4y, \\
y' &= 2x + 9y
\end{align*}
\]

with \( x(0) = 1 \) \quad \( y(0) = 0 \).

1. Determine the eigenvalues \( \lambda_1 = 5, \lambda_2 = 7 \).
2. Determine the corresponding eigenvectors \( v_1 = (2, -1) \), \( v_2 = (-1, 1) \).
3. Write \( u_0 = c_1v_1 + c_2v_2 \) and determine \( c_1 = 1, c_2 = -1 \).
4. From above we now have that

\[ (x(t), y(t)) = e^{5t}(2, -1) - e^{7t}(-1, 1). \]

To solve the (affine linear) system

\[ u'(t) = Au(t) + m, \quad u(0) = u_0, \]

We first solve for the equilibrium \( u^* : 0 = Au^* + m \Rightarrow u^* = -A^{-1}m \). We then write \( u(t) = u^* + e(t) \) to get \( e'(t) = Ae(t) \), \( e(0) = u_0 - u^* \). Which we solve. The question on whether we will approach the equilibrium or not is settled by the eigenvalues of \( A \): if the real part is negative for all eigenvalues it will be an asymptotically stable equilibrium. If one eigenvalue has a positive real part it will be unstable.

Basic principles of pharmacokinetics

When a drug molecule is taken up by the body it first enters the blood circulation, from which it may leave to be either temporarily stored in an organ or, in the case of the liver and kidney mainly, possibly eliminated from the body. To derive equations describing the dynamics we first note that there are two conservation laws we need to adhere to:

1. the sum of blood flow entering must equal the sum of blood flows leaving a point (conservation of volume – does not quite apply to kidneys - why?)
2. the amount of drug leaving must equal what entered minus what was lost (mass balance).

We assume that organs contain no internal barrier to the drug, which is well-mixed concentration \( C_T \) in the organ. The organ has volume \( V_T \), and we assume that the blood flow is \( Q \) over the organ. The amount of drug in the organ is then \( M_T = V_T C_T \), and we have

\[ QC_{out} = QC_{in} - M_T. \]

We also assume that equilibrium on the venous side is very quick, so that \( C_{out} = C_T/K_p \), where the constant \( K_p \) is called the tissue partition coefficient. In all this means that

\[ V_T C_T'(t) = Q(C_{in}(t) - C_T(t)/K_p). \]

The modifications needed if the organ is eliminating depends on the details, and will be discussed in more detail later. We will assume that the elimination rate is proportional to the tissue concentration.

Note that expressed in terms of the venous blood concentration the equation above is

\[ V_T K_p C_{out}'(t) = Q(C_{in}(t) - C_{out}(t)), \]

which is the version we use below for a physiological model.

A perfusion limited physiological model

From the figure to the right we can build a system of ODEs describing the pharmacokinetics of a drug we assume is eliminated only from the liver:

For a non-eliminating organ (except the lungs) we have an equation

\[ V_i K_p C_i'(t) = Q_i(C_a - C_i), \]

for the liver we have the rhs

\[ Q_1 (C_a - C_l) + Q_2 (C_{GI} - C_l) - CLC_l. \]

For the artery and vein concentrations we have

\[ V_a C_a' = \sum_{i \in I} Q_i C_i - Q_c C_v, \]

where \( I \) is a list of organs feeding into the venous circulation and \( Q_c = \sum_{i \in I} Q_i \) is the cardiac output, and

\[ V_a C_v' = Q_c (C_{lungs} - C_a). \]

In addition to this we need to add a term to account for how the drug is given. This can be as a nonzero value of \( C_0(0) \) (bolus dose) or an input term to the equation for \( C_v \).

For detailed modeling such a system is huge, but linear, and can therefore be solved if we have all the data. In general many organs can be lumped together without any real loss of information.

Example To model the pharmacokinetics of lead, we consider three compartments: bone, blood and soft tissue. Lead enters the system by ingestion and through the skin and lungs. These intake paths usher the substance to the blood, from which it is taken up by bone and soft tissue. However, especially for bone, lead’s half-life in that tissue
is very long. Lead can be shed from the body via the kidneys from the blood and to a lesser extent, through hair. We have the following system, where lead is measured in μg and time in days:

\[
\begin{align*}
\dot{x}_1 &= -(0.0211 + 0.0111 + 0.0039)x_1 + 0.0124x_2 + 0.000035x_3 + 49.3 \\
\dot{x}_2 &= 0.0111x_1 - (0.0162 + 0.0124)x_2 \\
\dot{x}_3 &= 0.0039x_1 - 0.000035x_3
\end{align*}
\]

(The 49.3 represent the amount that enters the body; uptake is assumed to occur continuously at a fixed rate.) This system has the eigenvalues

\[
\lambda_1 = -0.447, \quad \lambda_2 = -0.02, \quad \lambda_3 = -0.00003
\]

so we see that the equilibrium \(-A^{-1}m = (1800, 698, 200582)\) is stable. The model therefore predicts that the level of lead in the blood will rise to about 1800 μg, in soft tissue to a level of about 700 μg but in the bones to a level of almost 1/5 kg. But the latter will take some time, as the following graph of the first year of accumulation shows.

Practical pharmacokinetics

In real life the data necessary to do the physiological modeling is not available. What we have at best is the blood concentration profile and a knowledge of how much drug we gave. We therefore base our analysis on the overall differential equation

\[
M'(t) = a(t) - CLC(t),
\]

where \(M(t) = V_aC_a + V_cC_c + \sum V_iK_{pi}C_i\) is the total amount of drug in the body and \(C = C_v\) is the venous blood concentration. \(a(t)\) is the rate of uptake in the blood of drug. Integrating we find that if all drug is eventually eliminated from the body,

\[
CL = \frac{D}{\int_0^\infty C(t)dt},
\]

which means that we can compute this constant (called the clearance) from data alone. In addition to this we also introduce an apparent volume \(V(t)\) by the formula \(M(t) = V(t)C(t)\), which is used to describe the distribution of the drug in the body.

Nonlinear equations

For a nonlinear (system) of differential equation

\[
x'(t) = F(x(t))
\]

a value \(x_0\) such that \(F(x_0) = 0\) is a solution, called an equilibrium point. Such a point can be stable or unstable, and which is determined by looking at the linearised equation: let \(u(t) = x(t) - x_0\). Then

\[
F(x(t)) = F(x_0 + u(t)) \approx F(x_0) + F'(x_0)u(t) = F'(x_0)u(t).
\]

If follows that insight into \(u(t)\) should be gained by looking at the linear equation

\[
u'(t) = Au(t) \quad \text{where} \quad A = F'(x_0)
\]

with start values close to zero. The key observation is now

1. If the eigenvalues of the linearised system all have negative real part, the equilibrium is (asymptotically) stable
2. If the linearised system has at least one eigenvalue with a positive real part, the equilibrium is unstable.

It is also true that the trajectories of the nonlinear system looks much like the trajectories of the linearised system close to the equilibrium, provided that none of the eigenvalues have real part zero.

An outbreak of cholera in Bari, Italy

Example Consider the system

\[
\begin{align*}
x' &= -x + y \\
y' &= \theta h(x) - y
\end{align*}
\]

where \(\theta\) is a positive constant. The important point about \(h(x)\) is that it is increasing, continuous, approximately \(x\) for small \(x\) and has a limit as \(x\) increases to infinity.

The equilibrium points are determined by \(x = \theta h(x)\) and \(y = x\). With our choice of \(h\) this has two solutions: \(x = 0\) and \(x = \theta - 1 = x^*\); the latter is positive only if \(\theta > 1\). The derivative of the function is

\[
\frac{-1}{\theta(1 + x)^2} \cdot \frac{1}{1} = \frac{1}{1 - \theta}
\]

so we see that at the equilibrium \((0, 0)\) the eigenvalues are \(-1 \pm \sqrt{\theta}\). It is therefore stable when \(\theta < 1\) and unstable when \(\theta > 1\). At the equilibrium \((x^*, x^*)\) the eigenvalues are \(-1 \pm \frac{1}{\sqrt{\theta}}\), which is stable when it exist \((\theta > 1)\).

The usefulness of this analysis is illustrated by a discussion about where the system originates. In the mediterranean region there was an outbreak of cholera in the summer 1973, including the port town Bari. The two main factors contributing to the epidemic were

1. Garbage was in this region flushed directly into the sea (also from hospitals). Drinking water was, however, chlorinated, so the disease did not spread that way
2. In these regions food from the sea is eat raw, especially clams. Living clams were sprinkled with sea water.

Person-to-person spread was negligible, because of the high living standards.

To model the situation we introduce

1. \(B(t)\) as the concentration of cholera bacteria in the waters around Bari
2. \(N(t)\) the number of infected individuals in the community.

The simplest equation for \(B\) is

\[
B' = a(N - bB)
\]

\((b > 0)\) since cholera is not usually present in the sea around Bari). The equation for the infected individuals is

\[
N' = g(B) - rN,
\]

where we assume that new infectives occur as a result of consumption of raw, contaminated sea food. We assume that

\[
g(B) = Not p\beta f(B),
\]

where \(Not\) is the number of raw clams consumed, \(p\) is the proportion of clams containing bacteria, and \(\beta\) is the rate at which this leads to infection.
What actually was done was to chlorinate garbage water, prohibit sea food on a single day, $\beta$ the fraction that is not immune to cholera and $f(B)$ the fraction of non-immune individuals that eat raw sea food and get cholera if the sea concentration is $B$. It is reasonable to assume that $g(B)$ is approximately $cB$ when bacteria are scarce in sea water, and approaches one asymptotically as $B$ increases.

A nondimensional version of the model reads

\[
\begin{align*}
  s' &= -x + y \\
  y' &= \sigma(h(x) - y)
\end{align*}
\]

where $\sigma = r/b$ and $h(x)$ is an increasing function that is approximately $b x$, $\theta = ac/br$ when $x$ is small and approaches $N_{tot}/\sigma$ as $x$ increases. From the example we now learn that we need to introduce measures that guarantees that

\[
\theta = \frac{ac}{br} < 1.
\]

These are the options:

1. reduce $a$, which means to reduce the contribution to the sea from infected individuals. One might for example cholera garbage water in order to later introduce a sewage plant
2. reduce $c = N_{tot} \beta' f'(0)$: to reduce $p$ is a propaganda-thing and usually ineffective, to reduce $\beta$ can be done by vaccination but is slow and costly. The function $f$ cannot be tempered with.
3. to increase $b$ can be done, but is expensive
4. increase $1/r$, which is the length of the infections period – cannot be done.

What actually was done was to chlorinate garbage water, prohibit sales of raw sea food, and vaccinate the population.

Analysis of the Chemostat

As our model system we use the chemostat equation in nondimensional form:

\[
\begin{align*}
  s' &= (s_0 - s) - \frac{sb}{1 + s} \\
  b' &= \frac{asb}{1 + s} - b
\end{align*}
\]

The analysis goes in three steps:

- determine possible equilibrium points
- determine the stability of these
- try to sketch the trajectories in a $sb$-plane.

We will do the first two of these today.

Equilibrium points

are the solution to the equations

\[
\begin{align*}
  (s_0 - s) - \frac{sb}{1 + s} &= 0 \\
  \frac{asb}{1 + s} - b &= 0
\end{align*}
\]

The second equations have to solutions:

\[
b = 0 \quad \text{and} \quad s = 1/(a - 1).
\]

If $b = 0$ the first equations requires $s = s_0$. In the second case we get

\[
b = a(s_0 - \frac{1}{a - 1}).
\]

We therefore have two equilibrium points:

\[(s_0,0), \quad \text{and} \quad (\frac{1}{a - 1}, a(s_0 - \frac{1}{a - 1})).\]

Stability considerations

The derivative of the system is

\[
\begin{pmatrix}
-1 - \frac{b}{1 + s} & -\frac{c}{1 + s} \\
\frac{ab}{1 + s} & \frac{ac}{1 + s} - 1
\end{pmatrix}.
\]

In the equilibrium point $(s_0,0)$ this becomes

\[
\begin{pmatrix}
-1 & -\frac{s_0}{s_0} \\
0 & \frac{s_0}{s_0} - 1
\end{pmatrix}.
\]

This has eigenvalues $-1$ and $\frac{a(s_0 - 1)}{s_0}$, which means that it is stable if $s_0 < 1/(a - 1)$. In other words, it is only stable when the other equilibrium does not exist (biologically).

At the other equilibrium point we note that $s/(1 + s) = 1/a$, and that

\[
\frac{b}{(1 + s)^2} = b(1 - \frac{s}{1 + s})^2 = b(\frac{a - 1}{a})^2 = (s_0 - \frac{s_0 + 1}{a})(a - 1).
\]

If we denote this number by $A$ we get the matrix

\[
\begin{pmatrix}
-1 - A & -\frac{1}{a} \\
\frac{1}{a}A & 0
\end{pmatrix}.
\]

We see that the sum of the eigenvalues is $-(A + 1)$ and that their product is $A$ and that the eigenvalues are both real and negative. The equilibrium is therefore always stable when it exists.

Exercises

Exercise 1 Assume that the concentration $C_{in}$ of a drug entering a non-eliminating organ is constant.

1. Calculate the tissue concentration $C_{in}$. What parameters does it depend on?
2. If the tissue is filled with drug, and it is cleared from the blood, which is the time scale on which it disappears from the organ?

Exercise 2 Find the general solution of the system $x' = Ax$ with the choises of $A$ below, and sketch how the trajectories look in the $x_1 x_2$-plane:

\[
a) \quad \begin{pmatrix}
-1 & 0 \\
0 & 1
\end{pmatrix}, \quad b) \quad \begin{pmatrix}
3 & 1 \\
1 & 3
\end{pmatrix}, \quad c) \quad \begin{pmatrix}
-2 & 7 \\
2 & 3
\end{pmatrix}, \\
\quad d) \quad \begin{pmatrix}
-1 & 4 \\
-2 & 5
\end{pmatrix}, \quad e) \quad \begin{pmatrix}
2 & -3 \\
1 & -2
\end{pmatrix}, \quad f) \quad \begin{pmatrix}
-4 & 1 \\
3 & 0
\end{pmatrix}
\]

Exercise 3 In this problem we examine a plant-herbivore model in which the herbivore is a small insect (such as scale bugs) and which is such that the plant quality if enhanced when the vegetation is subjected to a low to moderate level of herbivory and declines when herbivory is extensive. Let $q$ denote the chemical state of the plant and $I$ the density of herbivores. First explain the assumptions behind the following model:

\[
q' = K_3 - K_2 q I (1 - I_0), \quad I' = K_3 I (1 - K_4 I/q).
\]

Then derive the nondimensional version of the system:

\[
q' = 1 - K_4 I (1 - I), \quad I' = a I (1 - I/q),
\]

and determine its steady states and their stabilities.

Exercise 4 Now we want to formulate a continuous time version of the simple model for CO$_2$-controlled breathing. Deduce the model

\[
C' = -\beta V C + m, \quad V' = \frac{V_m C}{K + C} - \epsilon V.
\]

What is $\epsilon$? Determine its steady states and their stability.