Ordinary Differential Equations in Pharmacodynamics

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Abstract

Mathematical models in pharmacodynamics often describe the evolution of pharmacological processes in terms of systems of linear or nonlinear ordinary differential equations. The objective of this course is to show how one can "read" these equations and draw conclusions from them about the qualitative behaviour of the pharmacological process that is being modeled. In some cases, in particular when the equations are linear, we shall show how one can obtain explicit expressions for the relevant solutions.

1 First order linear equations

In this course we shall discuss a series of ordinary differential equations which feature in PK/PD models. They usually appear in the context of an **Initial Value Problem**, such as

$$\begin{cases} \dfrac{dx}{dt} = f(t,x), \\ x(0) = \xi, \end{cases}$$

where $f(t,x)$ is a given function of time t and of the dependent variable, which we usually denote by x. It can be a concentration or a temperature, or some other quantity. Given the initial state, which we shall usually call ξ, we expect that the evolution of the system is described by the solution, denoted by $x = x(t,\xi)$. Clearly it depends, not only on time but also on the initial value ξ.

In this course, the existence and the uniqueness of the solution $x(t,\xi)$ – at least for some time period – will be taken for granted. Here we shall focus on:

1. Acquiring as much information about this solution as possible (without actually solving the equation).

2. Finding explicit solutions where possible.

From these perspectives it will be fruitful to view solutions in two ways:

- The solution as a **curve** in state space, parametrized by the time t.

- The solution as a **function** of time t.

Let us give a specific example.

Example 1.1: Consider the problem:

$$\frac{dx}{dt} = ax, \qquad x(0) = \xi, \tag{1.1}$$

where a is a constant.

Before "solving" this problem we ask ourselves the following question about the solution $x = x(t)$:

What will the graph of the solution look like?

Suppose that $x(0) = \xi > 0$. Then inspection readily shows that as long as $x(t)$ remains positive,

$$\begin{array}{lclll} a > 0 & \Longrightarrow & x(t) & \text{is increasing,} & \\ a = 0 & \Longrightarrow & x(t) & \text{is constant} & \Rightarrow \quad x(t) = \xi, \\ a < 0 & \Longrightarrow & x(t) & \text{is decreasing.} & \end{array}$$

Moreover, if $a \neq 0$, whether positive or negative, the graph is **Convex**, i.e.

$$\frac{d^2x}{dt^2} = a\frac{dx}{dt} = a^2x > 0 \qquad \text{for} \qquad 0 \leq t < T,$$

as long as $x(t) > 0$. Here $[0, T)$ is the maximal time interval on which the solution exists. As we shall see, $T = \infty$ for this problem.

One can go on asking questions, such as: If $a < 0$, and the solution is decreasing, will it ever become negative? Or, granted that $T = \infty$, how will $x(t)$ behave as $t \to \infty$. We shall see that these questions can often be answered without the help of an explicit solution.

Remark. If $\xi < 0$ we find that the graph of $x(t)$ is *increasing* when $a < 0$, *decreasing* when $a > 0$ and *concave* for any $a \neq 0$.

In Figure 1 we show graphs of $x(t)$ for $\xi = 1$ and different values of a.

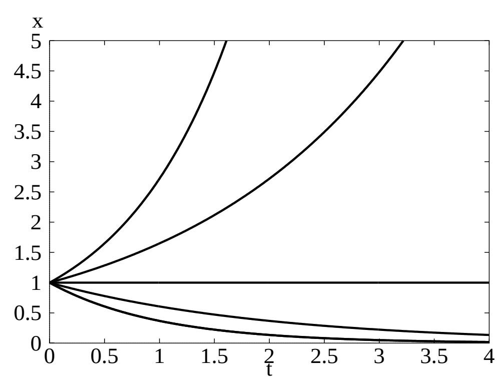


Figure 1: Solution curves $x(t)$ of Problem (1.1) for $a = 1,\ 0.5,\ 0,\ -0.5,\ -1$

For now we call it quits, and solve Problem (1.1) explicitly. We divide by x so that we obtain

$$\frac{1}{x}\frac{dx}{dt} = a,$$

and we realize, using the **Chain Rule**, that

$$\frac{d}{dt}\log\bigl(x(t)\bigr) = \frac{1}{x(t)}\frac{dx(t)}{dt}.$$

Therefore,

$$\frac{d}{dt}\log\bigl(x(t)\bigr) = a$$

and hence, when we integrate over $(0,t)$,

$$\log\bigl(x(t)\bigr) - \log\bigl(x(0)\bigr) = at.$$

Remembering that $x(0) = \xi$, we obtain the solution

$$x(t) = \xi e^{at}. \tag{1.2}$$

Notation: In what follows we shall often denote differentiation with respect to t by a prime, i.e.

$$\frac{dx}{dt} \equiv x'.$$

Next, we add a constant to the right hand side of equation (1.1) and consider the problem

$$x' = ax + b, \qquad x(0) = \xi, \tag{1.3}$$

in which a and b are constants. We assume that $\xi > 0$.

Observations:

• $a > 0$ and $b > 0$: $x(t)$ increases "faster" than the corresponding solution of the homogeneous Problem (1.1).

• $a < 0$ and $b > 0$: In this case there exists a constant positive solution of equation (1.3):

$$x(t) = c^* \stackrel{\text{def}}{=} \frac{b}{|a|}.$$

When we write equation (1.3) as

$$x' = |a|(c^* - x),$$

we readily see that

$$\begin{aligned} x' < 0 \qquad &\text{if} \qquad x > c^*, \\ x' > 0 \qquad &\text{if} \qquad x < c^*. \end{aligned}$$

In Figure 2 we show how solutions of problem (1.3), with $a = -1$ and $b = 1$, converge to $c^* = 1$ as $t \to \infty$.

Exercise 1.1: What happens in the cases $a > 0$, $b < 0$ and $a < 0$, $b < 0$?

We now show how to find an **explicit** solution of Problem (1.3).

Solution: Observe that

$$\frac{d}{dt}\Bigl\{x(t)e^{-at}\Bigr\} = \{x'(t) - ax(t)\}e^{-at}.$$

Hence,

$$\frac{d}{dt}\Bigl\{x(t)e^{-at}\Bigr\} = be^{-at}.$$

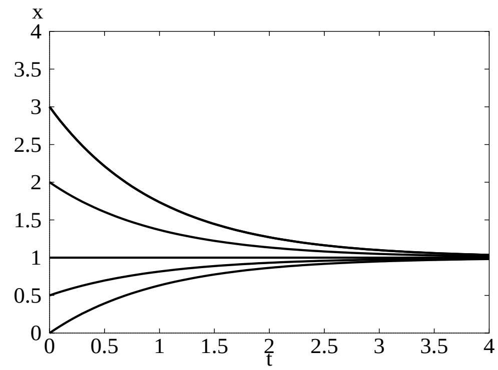


Figure 2: Solution curves $x(t)$ of Problem (1.3) for $a = -1$, $b = 1$ and $\xi = 0,\ 0.5,\ 1,\ 2,\ 3$

This yields upon integration over $(0, t)$,

$$x(t)e^{-at} - x(0) = b \int_0^t e^{-as}\, ds = \frac{b}{a}(1 - e^{-at}),$$

and we obtain

$$x(t) = \xi e^{at} + \frac{b}{a}(e^{at} - 1). \tag{1.4}$$

Remark. The factor e^{-at} is called the **Integrating factor** of equation (1.3).

Exercise 1.2: Solve the problem

$$\frac{dC}{dt} = -\frac{Cl}{V}C, \qquad C(0) = C^0.$$

Exercise 1.3: Show that the solution of the problem

$$\frac{dC}{dt} = \frac{1}{V}(R_{\text{in}} - Cl\, C), \qquad C(0) = 0$$

is given by

$$C(t) = \frac{R_{\text{in}}}{Cl}\big(1 - e^{-Cl\, t/V}\big).$$

Non autonomous equations.

So far, we have considered equations in which the time t did not appear *explicitly*. Such equations are called **Autonomous**. However, many models in PK/PD lead to equations in which time does appear explicitly; so called **Non autonomous** equations.

An important class of such equations arise in **Turnover models** (cf. [ARM], [DGW] and [MWJ]). The fundamental equation of these models is

$$R' = k_{\text{in}} - k_{\text{out}} R, \tag{1.5}$$

in which R denotes the response of the system and k_{in} and k_{out} are (positive) rate constants. When a drug is administered, it may act either on k_{in} or on k_{out}. The action of the drug is modeled by a function $H(C)$, in which C denotes the concentration of the drug: $C = C(t)$. Thus, if the drug acts on the gain term, we are led to an equation of the form

$$R' = k_{\text{in}} H(C(t)) - k_{\text{out}} R, \tag{1.6}$$

and if the drug acts on the loss term, we obtain

$$R' = k_{\text{in}} - k_{\text{out}} H(C(t))R. \tag{1.7}$$

Plainly, both equations are now non autonomous.

The first of these two equations is of the form

$$x' = ax + b(t), \tag{1.8}$$

where a is a constant. Rather than giving the general solution, we discuss an example.

Example 1.2: Consider the problem

$$x' = -x + be^{-\beta t}, \qquad x(0) = \xi, \qquad b,\, \beta > 0 \quad (\beta \neq 1). \tag{1.9}$$

Observations: For definiteness we put $\xi = 0$.

- $x'(0) = b > 0$. Hence, $x(t) > 0$ for $t > 0$ small.
- When t is large, $x' \approx -x$, so that the equation becomes like (1.1), with $a = -1$, and hence $x(t) \to 0$ as $t \to \infty$.
- Consider the graph

$$\Gamma = \{(t, x) : x = be^{-\beta t}\}$$

in the (t, x)-plane along which $x' = 0$, the *Null cline.* It is clear from the differential equation (1.5) that $x' > 0$ below Γ and $x' < 0$ above Γ. Thus the orbit first rises, then intersects Γ, where it levels off and thereafter drops down without however crossing Γ again. In Figure 3 we show a few orbits for different initial values ξ, as well as the null cline Γ.

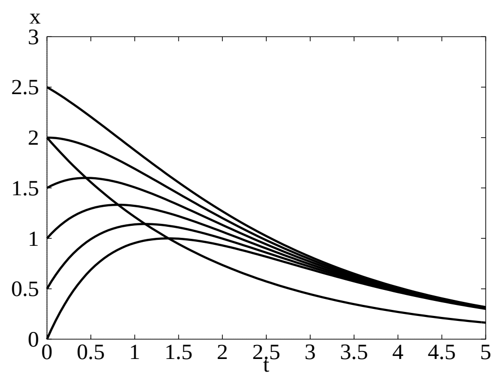


Figure 3: Solution curves $x(t)$ of Problem (1.8) for $b = 2$, $\beta = 0.5$ and $\xi = 0,\ 0.5,\ 1,\ 1.5,\ 2,\ 2.5$, as well as the null cline $\{x' = 0\}$

Solution: We put $\xi = 0$. Note that

$$\big(e^t x(t)\big)' = e^t\{x'(t) + x(t)\} = be^{(1-\beta)t}.$$

This yields upon integration over $(0, t)$,

$$e^t x(t) = b\int_0^t e^{(1-\beta)s}\, ds = \frac{b}{1-\beta}\big(e^{(1-\beta)t} - 1\big).$$

We now divide by e^t to obtain the solution:

$$x(t) = \frac{b}{1-\beta}\big(e^{-\beta t} - e^{-t}\big). \tag{1.10}$$

Exercise 1.4: Show that the solution of the problem (cf. equation (3:19) in [GW])

$$\frac{dC}{dt} = \frac{1}{V}FDe^{-K_a t} - KC, \qquad C(0) = 0, \tag{1.11}$$

in which $K_a \neq K$, is given by

$$C(t) = \frac{K_a FD}{V(K_a - K)}(e^{-Kt} - e^{-K_a t}). \tag{1.12}$$

The second equation, equation (1.7), is of the form

$$x' = a(t)x + b, \qquad x(0) = \xi. \tag{1.13}$$

Here it is more transparent to give a solution for general $a(t)$, b and ξ. Define the integral

$$A(t) = \int_0^t a(s)\,ds.$$

Then

$$\frac{d}{dt}\big\{e^{-A(t)}x(t)\big\} = e^{-A(t)}\big\{x'(t) - a(t)x(t)\big\} = e^{-A(t)}\,b,$$

so that $e^{-A(t)}$ is here the integrating factor. Integration over $(0, t)$ yields

$$e^{-A(t)}x(t) - \xi = b\int_0^t e^{-A(s)}\,ds,$$

or

$$x(t) = e^{A(t)}\left(\xi + b\int_0^t e^{-A(s)}\,ds\right). \tag{1.14}$$

Example 1.3: We consider the problem

$$x' = 1 - (1 + 5e^{-2t})x, \qquad x(0) = 1. \tag{1.15}$$

The differential equation in this problem is a special case of equation (1.7) in which we have put: $k_{\text{in}} = 1$, $k_{\text{out}} = 1$, and

$$H(C) = 1 + C, \qquad C = C(t) = De^{-2t} \quad \text{and} \quad D = 5.$$

Of course we can write down the explicit solution of Problem (1.15) using (1.14). However, that will turn out to be a fairly messy and complicated expression. It therefore pays to begin with a qualitative analysis.

Observations:

• $x(t) > 0$ for all $t > 0$.

<u>Proof:</u> Suppose that the solution touches the line $x = 0$ at some first time $t_0 > 0$. Then,

$$x(t_0) = 0 \qquad \text{and} \qquad x'(t_0) \leq 0.$$

But, by the equation we have $x'(t_0) = 1$ because $x(t_0) = 0$, a contradiction.

• $x(t) < 1$ for all $t > 0$.

Proof: We have $x'(0) = -1 < 0$. Hence $x(t) < 1$ for small values of $t > 0$. Suppose that at some $t_1 > 0$ the orbit first touches the line $x = 1$. Then

$$x(t_1) = 1 \qquad \text{and} \qquad x'(t_1) \geq 0.$$

But, by the equation $x'(t_1) = -5e^{-2t_1} < 0$, a contradiction.

• $x(t) \to 1$ as $t \to \infty$.

Proof: Study the vector field. The orbit first drops, then crosses the null cline

$$\Gamma = \{(t, x) : (1 + 5e^{-2t})x = 1\},$$

and then climbs up again but stays below $x = 1$. Therefore, it must tend to a limit, which can only be 1. The orbit and the null cline are shown in Figure 4.

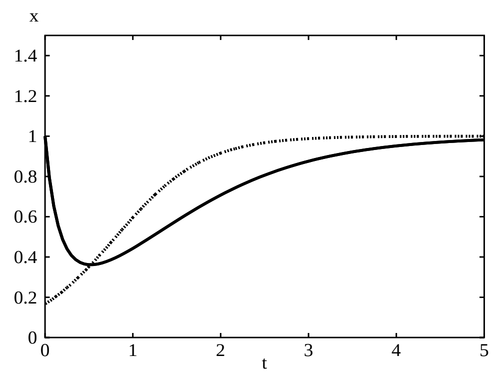


Figure 4: Solution curve $x(t)$ and null cline of Problem (1.15)

Exercise 1.5: Gompertz' equation

$$\frac{dx}{dt} = ae^{-\beta t}x,$$

where a and β are positve constants, is used as a self-limiting growth model for animals and tumors [L]. Show that the solution which starts at $x(0) = \xi$ is given by

$$x(t) = \xi \exp\left(\frac{a}{\beta}(1 - e^{-\beta t})\right),$$

so that

$$x(t) \to \xi e^{a/\beta} \qquad \text{as} \qquad t \to \infty.$$

2 First order nonlinear equations

In this section we discuss Initial Value Problems such as

$$\frac{dx}{dt} = f(t, x), \qquad x(0) = \xi,$$

in which the function $f(t, x)$ is **separable**, i.e. of the form

$$f(t, x) = a(t)g(x).$$

Let us give two examples.

Example 2.1: Consider the problem:

$$\frac{dx}{dt} = x^2, \qquad x(0) = \xi > 0. \tag{2.1}$$

The method we used to solve the linear homogeneous problem also works here. We divide by x^2 to we obtain

$$\frac{1}{x^2}\frac{dx}{dt} = 1.$$

By the Chain Rule,

$$\frac{d}{dt}\left(-\frac{1}{x(t)}\right) = \frac{1}{x^2(t)}\frac{dx(t)}{dt}.$$

Hence

$$\frac{d}{dt}\left(-\frac{1}{x(t)}\right) = 1,$$

and, when we integrate over $(0, t)$,

$$-\frac{1}{x(t)} + \frac{1}{\xi} = t.$$

Thus, the solution of Problem (2.1) is given by

$$x(t, \xi) = \frac{1}{\xi^{-1} - t} = \frac{\xi}{1 - \xi t} \qquad \text{for} \qquad 0 \le t < \frac{1}{\xi}. \tag{2.2}$$

In Figure 5 we show a series of orbits.

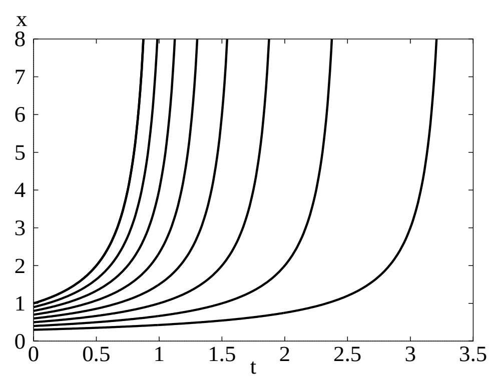


Figure 5: Solution curves $x(t)$ of Problem (2.1) for $\xi = 0.3, 0.4, \ldots, 1$

We see from the exact solution that

(1) The solution of Problem (2.1) only exist up to a **finite** time, $t = \xi^{-1}$, and

$$x(t, \xi) \to \infty \qquad \text{as} \qquad t \to \frac{1}{\xi},$$

i.e. the solution **blows up** at ξ^{-1}. One often writes

$$\beta(\xi) \stackrel{\text{def}}{=} \{t > 0 : x(s, \xi) \text{ exists for } 0 \le s < t\},$$

i.e. $[0, \beta(\xi))$ is the maximal interval in which the solution, which starts at ξ, exists.
(2) $\beta(\xi) \to \infty$ as $\xi \to 0$.
(3) Fix any $t_0 > 0$. Then

$$\lim_{\xi \to 0} x(t_0, \xi) = \lim_{\xi \to 0} \frac{\xi}{1 - \xi t_0} = 0.$$

These last two conclusions can also be deduced from the following general theorem:

Theorem 2.1 *Let $x(t, \xi)$ be the solution of the initial value problem*

$$x' = f(t, x), \qquad x(0) = \xi$$

for $0 \le t < \beta(\xi)$, and let ξ_0 be a fixed constant. Then for any $t_0 \in (0, \beta(\xi_0))$ we have

$$\lim_{\xi \to \xi_0} x(t_0, \xi) = x(t_0, \xi_0).$$

Remark. In Example 2.1, $\xi_0 = 0$ and $x(t, 0) = 0$ for all $t \ge 0$.

Exercise 2.1: Solve the problem

$$\frac{dx}{dt} = 4tx^3, \qquad x(0) = \xi > 0, \tag{2.3}$$

and show that $\beta(\xi) = 1/(4\xi^2)$.
– and we see that

Example 2.2: We consider the problem:

$$\frac{dx}{dt} = x(1 - x), \qquad x(0) = \xi \in (0, 1). \tag{2.4}$$

Remark. This problem involves the *Logistic Equation*, well known from population dynamics, where it models *Verhulst's* growth law:

$$\frac{dp}{dt} = \alpha p - \beta p^2.$$

Here p denotes the population density and α and β are positive constants.

Observations:

• We see that $x' > 0$ when $0 < x < 1$. Since the orbit starts at a point $\xi \in (0, 1)$ it will rise as long as it remains below the level $x = 1$. In particular:

$$x(t) > \xi \quad \text{as long as} \quad x(t) < 1.$$

• The function $y(t) = 1$ is also a solution of the differential equation. Since two orbits cannot cross (see Theorem 2.2),

$$x(t) < y(t) = 1 \qquad \text{for} \qquad 0 < t < \beta(\xi).$$

Thus, we conclude that:

$$x(t) < 1 \quad \text{and} \quad x'(t) > 0 \quad \text{for all} \quad 0 < t < \beta(\xi). \tag{2.5}$$

Suppose that $\beta(\xi) = \infty$, i.e. the solution exists for all $t > 0$. Any increasing function, which is bounded above, is known to have a limit. Hence, this means that

$$\lim_{t\to\infty} x(t) \text{ exists } \stackrel{\text{def}}{=} \ell. \tag{2.6}$$

Plainly, $\xi < \ell \leq 1$.

• Take the limit in the differential equation, and use (2.6). Then we find that

$$\lim_{t\to\infty} \frac{dx}{dt} = \ell(1-\ell). \tag{2.7}$$

If $\ell < 1$, then the limit in (2.7) implies that $x(t) \to \infty$ as $t \to \infty$, which contradicts (2.5). Therefore $\ell = 1$ and (2.6) becomes

$$\lim_{t\to\infty} x(t) = 1.$$

In the second observation, we have used the following theorem:

Theorem 2.2 *Let $\varphi(t)$ and $\psi(t)$ be solutions of the differential equation*

$$x' = f(t,x) \qquad \textit{for} \quad a < t < b,$$

in which $f(t,x)$ is a smooth function of x. Then $\varphi(t) \neq \psi(t)$ for all $a < t < b$.

We can also solve Problem (2.4) explicitly.

Exercise 2.2: Show that the solution of Problem (2.4) is given by

$$x(t,\xi) = \frac{\xi}{\xi + (1-\xi)e^{-t}}.$$

Note that

$$\beta(\xi) = \infty \qquad \text{if} \qquad \xi \geq 0,$$

$$\beta(\xi) = \log\left(1 + \frac{1}{|\xi|}\right) \qquad \text{if} \qquad \xi < 0.$$

In Figure 6 we show graphs of orbits of Problem (2.4) for $\xi > 0$.

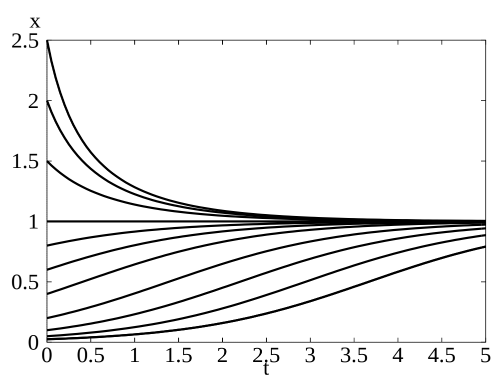


Figure 6: Solution curves $x(t)$ of Problem (2.4)

Exercise 2.3: A system involving first order feeding combined with Michaelis-Menten type clearance leads to the problem

$$\frac{dC}{dt} = k_f C - V_{\max}\frac{C}{K_m + C}, \qquad C(0) = C_0, \tag{2.8}$$

where k_f denotes the feeding rate, $V_{\max}$ the maximal removal rate and K_m the concentration at which the removal rate is $\frac{1}{2}V_{\max}$.

(a) Show that if $k_f = 0$, then, whatever the initial concentration C_0,

$$C(t) \to 0 \qquad \text{as} \qquad t \to \infty.$$

(b) Show that if

$$0 < k_f < \frac{V_{\max}}{K_m},$$

then there exists a positive equilibrium state

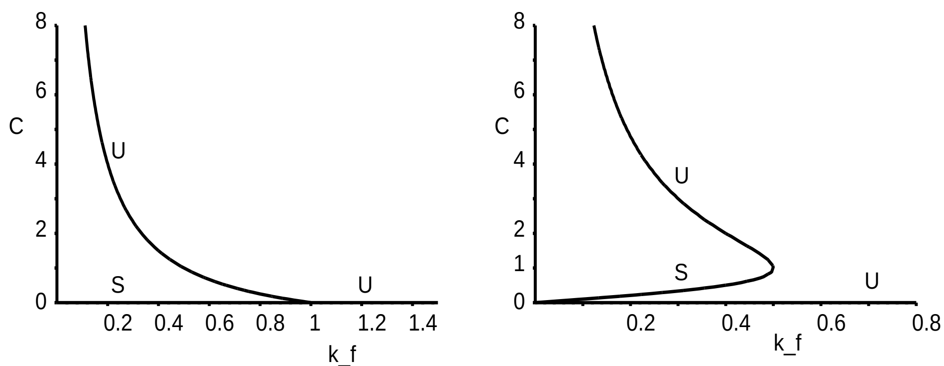
$$C^* = \frac{V_{\max}}{k_f} - K_m. \tag{2.9}$$

Remark. We say that a branch of *nontrivial* equilibrium solutions $C = C^*$ **bifurcates** from the branch of *trivial* equilibrium solutions $C = 0$ at the **bifurcation point** $k_f = V_{\max}/K_m$. This branch is shown in Figure 7(a).

(c) Suppose that $k_f < \frac{V_{\max}}{K_m}$. Discuss the behaviour of $C(t)$ as $t \to \infty$ when

$$(i)\ \ 0 < C_0 < C^* \qquad \text{and} \qquad (ii)\ \ C_0 > C^*.$$

Remark. Note that the stability of the trivial solution changes at the bifurcation point $k_f = V_{\max}/K_m$.



(a) (b)

Figure 7: Bifurcation branches of Problems (2.8) and (2.10); stable branches are marked with S and unstable branches with U

Exercise 2.4: Consider the system

$$\frac{dC}{dt} = k_f C - V_{\max}\frac{C^2}{K_m^2 + C^2}, \qquad C(0) = C_0, \tag{2.10}$$

where k_f denotes the feeding rate, $V_{\max}$ the maximal removal rate and K_m the concentration at which the removal rate is $\frac{1}{2}V_{\max}$.

(a) Show that if $k_f = 0$, then, whatever the initial concentration C_0,

$$C(t) \to 0 \qquad \text{as} \qquad t \to \infty.$$

(b) Show that if

$$0 < k_f < \frac{V_{\max}}{2K_m},$$

then there exists two positive equilibrium states

$$C^*_\pm = \frac{V_{\max}}{2k_f} \pm \sqrt{\frac{V^2_{\max}}{4k_f^2} - K_m^2}. \tag{2.11}$$

The branch of nontrivial solutions is shown in Figure 7(b).

(c) Suppose that $k_f < \frac{V_{\max}}{2K_m}$, and that $C_0 > 0$ is given. Discuss the behaviour of $C(t)$ as $t \to \infty$ when

$$(i) \;\; 0 < C_0 < C^*_- \qquad (ii) \;\; C^*_- < C_0 < C^*_+ \quad \text{and} \quad (iii) \;\; C_0 > C^*_+.$$

3 Second order systems

Frequently, PK/PD models involve not just one but several quantities which evolve simultaneously. For instance, when different substances are involved, or different compartments, or when the temperature plays an important role, either in the dynamics or as a marker. In this chapter we discuss models which involve several quantities and lead to systems of two differential equations. We discuss two types of models:

- **Two-compartment models**
- **Turnover models**

3.1 Two-compartment models

One distinguishes a *central* compartment, sometimes associated with the blood plasma, and a *peripheral* compartment, associated with the tissue. A drug is injected into, as well as cleared from, the central compartment. At the same time it diffuses into and out of the peripheral compartment. Assuming rapid mixing, one can speak of *the concentrations* of the drug in the central compartment, $C_p(t)$, and in the peripheral compartment, $C_t(t)$. For each of the compartments one can write down a conservation law:

$$\begin{cases} V_c \dfrac{dC_p}{dt} = -Cl_d(C_p - C_t) - ClC_p, & \text{(3.1a)} \\ V_t \dfrac{dC_t}{dt} = Cl_d(C_p - C_t). & \text{(3.1b)} \end{cases}$$

Here V_c and V_t denote the volume of each of the compartments and Cl_d and Cl are clearance rates. Typical values are $V_c = 1.4$, $V_t = 0.53$, $Cl_d = 0.25$ and $Cl = 0.05$ ([GW] p. 461).

Before analyzing this system we clean it up a little. We introduce a suitably scaled time on the basis of the situation when there is no peripheral compartment, i.e. $Cl_d = 0$. The equation for the central compartment then becomes:

$$V_c \frac{C_p}{dt} = -ClC_p.$$

This equation is of the form of equation (1.1) and its solution is given by (see (1.2)),

$$C_p(t) = C_p(0)e^{-Cl\,t/V_c}.$$

This suggests we define the new time:

$$t^* = \frac{Cl}{V_c}t \qquad \Longrightarrow \qquad \frac{d}{dt} = \frac{Cl}{V_c}\frac{d}{dt^*}.$$

In addition, we introduce certain combinations of constants and put:

$$\kappa = \frac{Cl_d}{Cl} \qquad \text{and} \qquad \alpha = \frac{V_c}{V_t}\frac{Cl_d}{Cl} = \frac{V_c}{V_t}\kappa.$$

For the values given above we thus find that $\kappa \approx 5$ and $\alpha \approx 15$. Finally, we rename the variables and set:

$$x = C_p \qquad \text{and} \qquad y = C_t.$$

When we divide equation (3.1a) by Cl and equation (3.1b) by ClV_t/V_c, denote the the concentrations by x and y, and omit the asterisk in the scaled time t^*, we obtain the following system

$$\begin{cases} x' = -\kappa(x-y) - x, & (3.2a) \\ y' = \alpha(x-y). & (3.2b) \end{cases}$$

The *State* of the system is now given by the values of x and y, i.e. by a point (x, y) in the xy-plane. This plane is usually referred to as the **Phase Plane**. Since x and y both depend on time, the point $(x(t), y(t))$ describes a curve, or **Orbit**, in the phase plane.

Let us find out what the orbit looks like when initially the central compartment contains a certain amount of the drug, and the peripheral compartment is clear, i.e.,

$$x(0) = x_0 \qquad \text{and} \qquad y(0) = 0,$$

i.e. the initial point lies at the bottom of the first quadrant of the xy-plane. The equations tell us that

$$x'(0) = -(\kappa+1)x_0 < 0 \qquad \text{and} \qquad y'(0) = \alpha x_0 > 0.$$

We can view (x', y') as a *velocity vector*. Clearly, it points into the first quadrant.

In Figure 8 we show a series of orbits which start at points $(x_0, 0)$ on the base line.

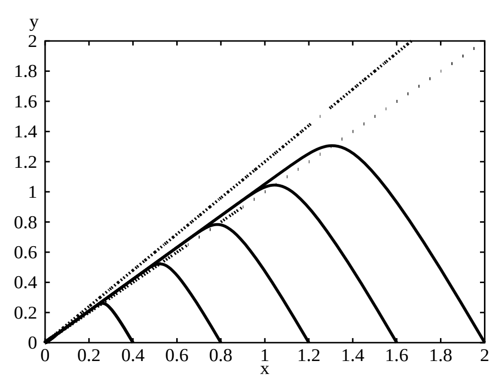


Figure 8: Orbits for $\alpha = 15$ and $\kappa = 5$

We see that initially, they all go up, as expected, but then bend over and come down again. The points where $y' = 0$ lie on a line, a *Null cline*, given by

$$\Gamma_y \stackrel{\text{def}}{=} \{(x, y) : y' = 0\} = \{(x, y) : y = x\}. \qquad (3.3)$$

Similarly, there exists a null cline where $x' = 0$:

$$\Gamma_x \stackrel{\text{def}}{=} \{(x,y) : x' = 0\} = \{(x,y) : y = (1 + \tfrac{1}{\kappa})x\}. \tag{3.4}$$

The null clines divide the first quadrant into three parts:

$$\begin{aligned}
\Omega_1 &= \{(x,y) : x > 0,\ 0 < y < x\}, \\
\Omega_2 &= \{(x,y) : x > 0,\ x < y < (1 + \tfrac{1}{\kappa})x\}, \\
\Omega_3 &= \{(x,y) : x > 0,\ y > (1 + \tfrac{1}{\kappa})x\},
\end{aligned}$$

and in each of these parts, the direction of the vector field (x', y') is different:

$$\begin{array}{lcll}
(x,y) \in \Omega_1 & \Longrightarrow & x' < 0 \text{ and } y' > 0 : & \nwarrow, \\
(x,y) \in \Omega_2 & \Longrightarrow & x' < 0 \text{ and } y' < 0 : & \swarrow, \\
(x,y) \in \Omega_3 & \Longrightarrow & x' > 0 \text{ and } y' < 0 : & \searrow.
\end{array}$$

Thus, when the orbit starts from a point on the x-axis, it enters Ω_1, continues on to Ω_2 and then stays in Ω_2 for all later time. Whilst in Ω_2:

$$\begin{array}{lcl}
x'(t) < 0 \quad \text{and} \quad x(t) > 0 & \Longrightarrow & x(t) \to \overline{x} \geq 0 \quad \text{as} \quad t \to \infty \\
y'(t) < 0 \quad \text{and} \quad y(t) > 0 & \Longrightarrow & y(t) \to \overline{y} \geq 0 \quad \text{as} \quad t \to \infty,
\end{array}$$

and it can be proved that the limit $(\overline{x}, \overline{y})$ must be the origin $(0,0)$, so that

$$\lim_{t\to\infty} (x(t), y(t)) = (0,0).$$

In the following proposition we show that after the orbit has crossed Γ_y, the orbit will "hug" the null cline Γ_y when α is large,.

Proposition 3.1 *Assume that $\alpha > 1 + \kappa$. The orbit of the system (3.2), which starts at any point on the x-axis will always stay below the line*

$$\ell_\alpha \stackrel{\text{def}}{=} \left\{(x,y) : x > 0,\ y = \frac{\alpha}{\alpha - 1}x\right\}.$$

Thus, if the orbit $(x(t), y(t))$ crosses the null cline Γ_y at time T, then

$$x(t) < y(t) < \frac{1}{1-\varepsilon}x(t) \qquad \text{for} \qquad t > T, \qquad \varepsilon = \frac{1}{\alpha},$$

i.e. the orbit lies in a thin wedge, just above Γ_y.

Proof. We compute the vector field on ℓ_α. We readily see that for $\alpha > 1 + \kappa$ the line ℓ_α lies below Γ_x. Therefore $x' < 0$ and $y' < 0$ on ℓ_α. Thus, to show that the vector field points "down", into the wedge between ℓ_α and Γ_y, it suffices to show that

$$\left.\frac{dy}{dx}\right|_{\ell_\alpha} = \frac{y'}{x'} > \frac{\alpha}{\alpha - 1}.$$

The equations (3.2a) and (3.2b) enable us to compute x' and y' on ℓ_α, so that we obtain

$$\left.\frac{dy}{dx}\right|_{\ell_\alpha} = \frac{\alpha(x-y)}{-\kappa(x-y) - x} = \frac{-\dfrac{\alpha}{\alpha-1}}{\dfrac{\kappa}{\alpha-1} - 1} = \frac{\alpha}{\alpha - 1 - \kappa} > \frac{\alpha}{\alpha - 1},$$

as required. □.

When the drug is administered at a constant rate, the model changes, and a positive constant (In) is added to the right hand side of the first equation. Thus, the system (3.1) now becomes:

$$\begin{cases} V_c \dfrac{dC_p}{dt} = In - Cl_d(C_p - C_t) - ClC_p, & (3.5a) \\ V_t \dfrac{dC_t}{dt} = Cl_d(C_p - C_t). & (3.5b) \end{cases}$$

Carrying out the same transformations as in the first system we arrive at the system

$$\begin{cases} x' = v - \kappa(x - y) - x, \qquad v = In/Cl, & (3.6a) \\ y' = \alpha(x - y). & (3.6b) \end{cases}$$

In Figure 9, we show a series of orbits for this system.

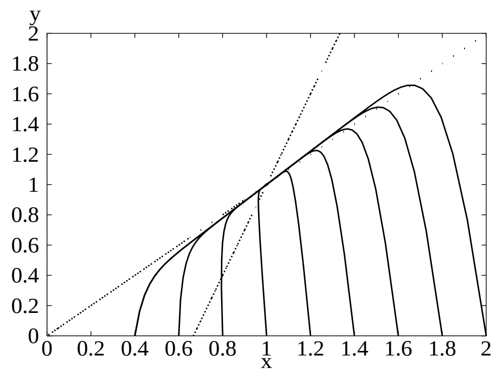


Figure 9: Orbits of system (3.6) for $v = 1$, $\alpha = 10$ and $\kappa = 0.5$

As a **nonlinear** variation on this model, we assume that the clearance is nonlinear, and described by a Michaelis-Menten type rate function. This leads to a system of equations of the form

$$\begin{cases} x' = v - \kappa(x - y) - \dfrac{x}{1 + x}, \\ y' = \alpha(x - y). \end{cases} \qquad (3.7)$$

The null clines now become

$$\Gamma_x : \ y = x + \frac{1}{\kappa}\left(\frac{x}{1+x} - v\right) \qquad \text{and} \qquad \Gamma_y : \ y = x. \qquad (3.8)$$

Exercise 3.1: Study the orbits of the system (3.7) for $\alpha = 10$, $\kappa = 1$ and $v = 0.5,\ 0.8,\ 1.0$ and 2.0.

– Find the null clines in the fist quadrant.

– Find the equilibrium points in the fist quadrant (if any).

– Show what happens to an orbit which starts at a point $(x, y) = (a, 0)$ for different values of $a > 0$.

3.2 Turnover models

In a classical feedback model (cf. [GW]. p. 232) based on the turnover model, the loss of response $R(t)$ is governed by a *modulator* denoted by M:

$$\frac{dR}{dt} = k_{\mathrm{in}} - k_{\mathrm{out}} M, \tag{3.9a}$$

in which k_{in} and k_{out} are positive constants. In turn, the modulator is activated by the response:

$$\frac{dM}{dt} = k_{\mathrm{tol}}(R - M), \tag{3.9b}$$

in which k_{tol} is a positive constant. Here the null clines are given by:

$$\Gamma_R : \quad M = \frac{k_{\mathrm{in}}}{k_{\mathrm{out}}} \qquad \text{and} \qquad \Gamma_M : \quad M = R \qquad (3.10).$$

Clearly, at points where the null clines intersect, and both $R' = 0$ and $M' = 0$, we have an equilibrium point. Thus, here the only equilibrium point is

$$R = \overline{R} \stackrel{\mathrm{def}}{=} \frac{k_{\mathrm{in}}}{k_{\mathrm{out}}} \qquad \text{and} \qquad M = \overline{M} \stackrel{\mathrm{def}}{=} \frac{k_{\mathrm{in}}}{k_{\mathrm{out}}}.$$

In Figures 10 and 11 we show a few orbits of this system.

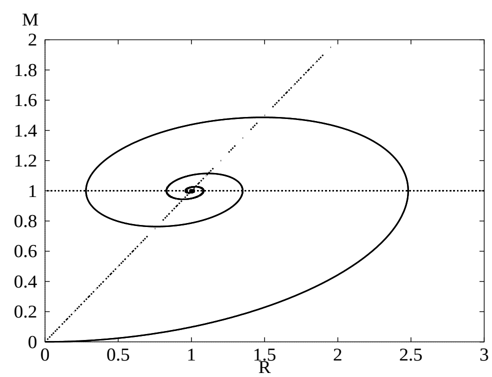


Figure 10: Orbits of system (3.9) for $k_{\mathrm{in}} = 1$, $k_{\mathrm{out}} = 1$ and $k_{\mathrm{tol}} = 0.2$

In both figures the orbits tend to the equilibrium point $(\overline{R}, \overline{M})$ as $t \to \infty$. However, when $k_{\mathrm{tol}} = 0.2$, the orbits spirals around this point whilst if $k_{\mathrm{tol}} = 5$, then it zooms into the equilibrium point "monotonically". To understand what causes this to happen, we need some further mathematical results. We will present these in Section 4.

Exercise 3.2: Analyse the directions of the vector field of the feedback system (3.9) in the first quadrant:

– Find the null clines.

– Find the equilibrium point.

– Sketch the vector field.

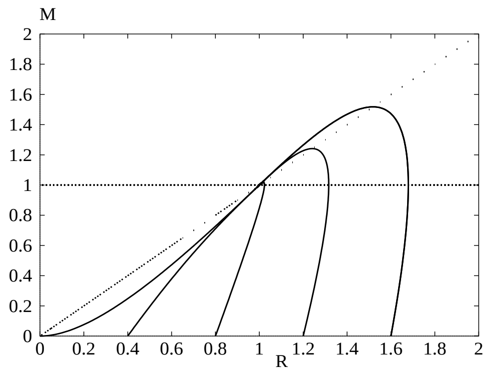


Figure 11: Orbits of system (3.9) for $k_{\text{in}} = 1$, $k_{\text{out}} = 1$ and $k_{\text{tol}} = 5$

Exercise 3.3: Analyse the vector field of the following feedback system (see [GW], p. 235) in the first quadrant:

$$\begin{cases} \dfrac{dR}{dt} = k_{\text{in}} - k_{\text{out}} R(1 + M), & \text{(3.11a)} \\ \dfrac{dM}{dt} = k_{\text{tol}}(R - M). & \text{(3.11b)} \end{cases}$$

In particular, prove that every orbit, which starts in the first quadrant,

(a) stays in the first quadrant;

(b) tends to the unique equilibrium point $(\overline{R}, \overline{M})$ defined by

$$\overline{R} = \overline{M} = \frac{1}{2}\left(\sqrt{1 + \frac{4k_{\text{in}}}{k_{\text{out}}}} - 1\right).$$

Exercise 3.4: Consider the unidirectional **Pool model** (cf. [GW], p. 238) in which R is supplied through a pool. It leads to the system of equations

$$\begin{cases} \dfrac{dP}{dt} = k_{\text{in}} - k_{\text{tol}} P, & \text{(3.12a)} \\ \dfrac{dM}{dt} = k_{\text{tol}} P - k_{\text{out}} R. & \text{(3.12b)} \end{cases}$$

– Find the null clines.

– Find the equilibrium point.

– Sketch the vector field.

– Show that all orbits originating in the first quadrant converge to the unique equilibrium point $(\overline{P}, \overline{R})$, where

$$\overline{P} = \frac{k_{\text{in}}}{k_{\text{tol}}} \qquad \text{and} \qquad \overline{R} = \frac{k_{\text{in}}}{k_{\text{out}}}.$$

– Describe the orbit which starts at the point $(P, R) = (\overline{P}, 0)$.

4 Matrices

In this subsection, and in what follows, we shall write

R = the set of real numbers.

C = the set of complex numbers: $z = x + iy$, where $x, y \in \mathbf{R}$ and $i = \sqrt{-1}$.

Let

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix}, \qquad a, b, c, d \in \mathbf{R}.$$

Definition. The *determinant* of the matrix A is defined by

$$\det(A) \equiv |A| \stackrel{\text{def}}{=} ad - bc.$$

Definition. We say that $\lambda \in \mathbf{C}$ is an eigenvalue of A if there exists a vector $\mathbf{v} \neq 0$ such that

$$A\mathbf{v} = \lambda\mathbf{v}, \qquad \mathbf{v} = \begin{pmatrix} v_1 \\ v_2 \end{pmatrix}. \tag{4.1}$$

The vector $\mathbf{v}$ is called the eigenvector associated with λ.

Theorem 4.1 *Equation (4.1) has a nontrivial solution* $\mathbf{v}$ *if and only if*

$$\det(A - \lambda I) = 0.$$

Corollary 4.1 *The eigenvalues of A are the zeros of the* characteristic polynomial

$$P(\lambda) \stackrel{\text{def}}{=} \lambda^2 - (a + d)\lambda + ad - bc = 0. \tag{4.2}$$

Remark. The *Trace* $\mathrm{tr}(M)$ of a matrix M is defined as the sum of its diagonal elements. Thus,

$$\mathrm{tr}(A) = a + d.$$

Therefore, we can write $P(\lambda)$ also as

$$P(\lambda) = \lambda^2 - \mathrm{tr}(A)\lambda + \det(A).$$

Exercise 4.1: Prove Corollary 4.1.

The roots of equation (4.2) are given by

$$\lambda_\pm = \frac{1}{2}(a + d) \pm \frac{1}{2}\sqrt{(a + d)^2 - 4(ad - bc)}. \tag{4.3}$$

Thus, there exist two different eigenvalues $\lambda_\pm \in \mathbf{C}$, unless

$$(a + d)^2 - 4(ad - bc) = 0,$$

in which case $\lambda_+ = \lambda_- \in \mathbf{R}$.

Consider the system of differential equations

$$\begin{cases} x' = ax + by, \\ y' = cx + dy. \end{cases} \tag{4.4}$$

We write this in matrix notation. Define

$$\mathbf{x} = \begin{pmatrix} x \\ y \end{pmatrix} \qquad \text{and} \qquad \mathbf{x}' = \begin{pmatrix} x' \\ y' \end{pmatrix}.$$

Then the system (4.4) can be written as

$$\mathbf{x}' = A\mathbf{x}. \tag{4.4a}$$

Theorem 4.2 *Suppose that* $\lambda_+ \neq \lambda_-$*. Then the general solution of equation (4.4) (or (4.4a)) is given by*

$$\mathbf{x}(t) = c_+\mathbf{v}_+e^{\lambda_+ t} + c_-\mathbf{v}_-e^{\lambda_- t}, \tag{4.5}$$

where $\mathbf{v}_+$ *and* $\mathbf{v}_-$ *are the eigenvectors associated with, respectively,* λ_+ *and* λ_-*, and* $c_+, c_- \in \mathbf{R}$ *are arbitrary constants.*

Example 4.1: The system (3.9) can be transformed to an equation of the form (4.4a) when we write

$$R = \overline{R} + x \qquad \text{and} \qquad M = \overline{M} + y.$$

Substitution into the system (3.9) then yields

$$\begin{cases} x' = -k_{\text{out}}y, & (4.6\text{a}) \\ y' = k_{\text{tol}}(x - y), & (4.6\text{b}) \end{cases}$$

which can be written in the form of (4.4a) with the matrix

$$A = \begin{pmatrix} 0 & -k_{\text{out}} \\ k_{\text{tol}} & -k_{\text{tol}} \end{pmatrix}.$$

From (4.3) we conclude that the eigenvalues of A are given by

$$\lambda_\pm = -\frac{1}{2}k_{\text{tol}} \pm \frac{1}{2}\sqrt{k_{\text{tol}}^2 - 4k_{\text{tol}}k_{\text{out}}}.$$

We see that the eigenvalues are **complex** if

$$k_{\text{tol}} < 4k_{\text{out}} \qquad \text{as in Figure 10,}$$

and they are **real** if

$$k_{\text{tol}} \geq 4k_{\text{out}} \qquad \text{as in Figure 11.}$$

Plainly, they change from real to complex when

$$k_{\text{tol}} = 4k_{\text{out}} = 4 \qquad \text{if} \quad k_{\text{out}} = 1.$$

5 The Laplace Transform

The Laplace Transform turns differentiation into multiplication by a constant s. Thus, linear differential equations involving $x(t)$ are turned into equations of the form

$$p(s)\overline{x}(s) = q(s),$$

where p is a polynomial functions of s and $\overline{x}(s)$ is the Laplace Transform of $x(t)$. This equation then yields an explicit expression for $\overline{x}(s)$, and it remains to transform back to $x(t)$.

Let $f(t)$ be a function defined for all $t \geq 0$ with algebraic growth, i.e. there exists a constants $C > 0$ and $p \geq 0$ such that

$$|f(t)| \leq Ct^p \qquad \text{for all} \qquad t > 0.$$

Then its **Laplace Transform** $\overline{f}(s)$ is defined by the integral

$$\overline{f}(s) = \mathcal{L}(f)(s) \stackrel{\text{def}}{=} \int_0^\infty f(t)e^{-st}\, dt. \tag{5.1}$$

Plainly, since $f(t) = O(t^p)$, the integral exists for every $s > 0$. In fact, if we allow s to be a complex number, then it exists for every $s \in \mathbf{C}$ such that $\operatorname{Re} s > 0$. In what follows we shall call an function *admissible* if its Laplace Transform exists.

Exercise 5.1: Show that

$$\begin{aligned}
f(t) &= 1 && \Rightarrow && \overline{f}(s) = \frac{1}{s}, \\
f(t) &= t && \Rightarrow && \overline{f}(s) = \frac{1}{s^2}, \\
f(t) &= e^{at} && \Rightarrow && \overline{f}(s) = \frac{1}{s-a}, \\
f(t) &= \sin(at) && \Rightarrow && \overline{f}(s) = \frac{a}{s^2+a^2}, \\
f(t) &= \cos(at) && \Rightarrow && \overline{f}(s) = \frac{s}{s^2+a^2}.
\end{aligned}$$

In the next lemma we formulate a few useful properties of $\mathcal{L}$:

Lemma 5.1 *The Laplace Transform is a* <u>*linear*</u> *operator, i.e. if f and g are two admissible functions, and α and β two complex constants, then*

$$\mathcal{L}(\alpha f + \beta g) = \alpha\mathcal{L}(f) + \beta\mathcal{L}(g). \tag{5.2}$$

The proof is easy and we omit it.

Let us now turn to the solution of differential equations. A pivotal lemma is the following.

Lemma 5.2 *Let f be a differentiable function which has algebraic growth, and let its derivative be denoted by f'. Then*

$$\mathcal{L}(f')(s) = s\mathcal{L}(f)(s) - f(0), \qquad \operatorname{Re} s > 0, \tag{5.3}$$

where $\operatorname{Re} s$ denotes the real part of the complex variable s.

Proof. We have

$$\mathcal{L}(f')(s) = \int_0^\infty f'(t)e^{-st}\, dt.$$

Integrating by parts we find that

$$\int_0^\infty f'(t)e^{-st}\, dt = f(t)e^{-st}\Big|_0^\infty + s\int_0^\infty f(t)e^{-st}\, dt. \tag{5.4}$$

Since f has algebraic growth,

$$f(t)e^{-st} \to 0 \qquad \text{as} \qquad t \to \infty.$$

Hence (5.4) becomes

$$\int_0^\infty f'(t)e^{-st}\,dt = -f(0) + s\int_0^\infty f(t)e^{-st}\,dt,$$

which is the same as (5.3). □

We are now ready to solve some differential equations.

Example 5.1: Solve the initial value problem

$$x' = -ax + b, \qquad x(0) = \xi, \tag{5.5}$$

where a and b are constants, and $a > 0$. We write

$$\overline{x}(s) = \mathcal{L}(x)(s) = \int_0^\infty x(t)e^{-st}\,dt.$$

and take the Laplace Transform of both sides of equation (5.5). Usin Lemma 5.1 on the term involving x', we obtain

$$s\overline{x}(s) - x(0) = -a\overline{x}(s) + b\mathcal{L}(1)(s).$$

As we saw in Exercise 5.1, $\mathcal{L}(1)(s) = 1/s$, so that

$$(s+a)\overline{x}(s) = \xi + \frac{b}{s},$$

and hence

$$\overline{x}(s) = \frac{\xi}{s+a} + \frac{b}{s(s+a)}. \tag{5.6}$$

From this expression for $\overline{x}(s)$ it remains to extract the solution $x(t)$ of Problem (5.5), i.e. we have to perform the **Inverse Laplace Transform**:

$$x(t) = \mathcal{L}^{-1}(\overline{x})(t).$$

Since $\mathcal{L}^{-1}$ is also a linear operator, (5.6) yields

$$x(t) = \mathcal{L}^{-1}\left(\frac{\xi}{s+a}\right) + \mathcal{L}^{-1}\left(\frac{b}{s(s+a)}\right). \tag{5.7}$$

From Exercise 5.1 we know that

$$\mathcal{L}^{-1}\left(\frac{\xi}{s+a}\right) = \xi\mathcal{L}^{-1}\left(\frac{1}{s+a}\right) = \xi e^{-at}. \tag{5.8}$$

To compute the second term, we write it as

$$\frac{b}{s(s+a)} = \frac{b}{a}\left(\frac{1}{s} - \frac{1}{s+a}\right).$$

Thus,

$$\mathcal{L}^{-1}\left(\frac{b}{s(s+a)}\right) = \frac{b}{a}\left\{\mathcal{L}^{-1}\left(\frac{1}{s}\right) - \mathcal{L}^{-1}\left(\frac{1}{s+a}\right)\right\}. \tag{5.9}$$

Since by Exercise 5.1,

$$\mathcal{L}^{-1}\left(\frac{1}{s}\right) = 1 \qquad \text{and} \qquad \mathcal{L}^{-1}\left(\frac{1}{s+a}\right) = e^{-at},$$

it follows that we can write (5.9) as

$$\mathcal{L}^{-1}\left(\frac{b}{s(s+a)}\right) = \frac{b}{a}(1 - e^{-at}). \tag{5.10}$$

Putting (5.8) and (5.10) into (5.7) we find that

$$x(t) = \xi e^{-at} + \frac{b}{a}(1 - e^{-at}) \tag{5.11}$$

is the solution of Problem (5.5).

Example 5.2: We use the Laplace Transform to show that the solution of the problem

$$x' = 1 + 3e^{-2t} - x, \qquad x(0) = 0, \tag{5.12}$$

is given by

$$x(t) = 1 + 2e^{-t} - 3e^{-2t}. \tag{5.13}$$

Note that the equation in (5.12) is a special case of equation (1.11) from the turnover model ($k_{\text{in}} = 1$, $k_{\text{out}} = 1$, $H(C) = 1 + C$ and $C(t) = 3e^{-2t}$).

We multiply equation (5.12) by e^{-st} and integrate over $(0, \infty)$. Since $x(0) = 0$, we obtain, after some rearrangement,

$$(s+1)\overline{x}(s) = \frac{1}{s} + \frac{3}{s+2},$$

so that

$$\begin{aligned}\overline{x}(s) &= \frac{1}{s(s+1)} + \frac{3}{(s+1)(s+2)}, \\ &= \frac{1}{s} - \frac{1}{s+1} + 3\left(\frac{1}{s+1} - \frac{1}{s+2}\right), \\ &= \frac{1}{s} + \frac{2}{s+1} - \frac{3}{s+2}.\end{aligned}$$

Using Exercise 5.1 again we find that

$$x(t) = 1 + 2e^{-t} - 3e^{-2t}.$$

In the next example we solve a second order differential equation.

Example 5.3: We solve the initial value problem

$$x'' + \omega^2 x = 0, \qquad x(0) = 0, \quad x'(0) = 1. \tag{5.14}$$

Of course, the equation in (5.14) is very well known, and we know that the solution of this problem is given by

$$x(t) = \frac{1}{\omega}\sin(\omega t). \tag{5.15}$$

But, here we prove that (5.15) is the solution by means of the Laplace Transform. We first prove a generalisation of Lemma 5.2:

Lemma 5.3 *Let f be a twice differentiable function which has algebraic growth, and let its derivatives be denoted by f' and f''. Then*

$$\mathcal{L}(f'')(s) = s^2\mathcal{L}(f)(s) - f(0)s - f'(0), \qquad \operatorname{Re} s > 0. \tag{5.16}$$

Exercise 5.2: Prove Lemma 5.3.

To solve Problem (5.14) we multiply by e^{-st} and integrate over $(0, \infty)$. Using Lemma 5.3, we find that

$$(s^2 + \omega)\overline{x}(s) = x'(0) = 1,$$

and hence

$$\overline{x}(s) = \frac{1}{s^2 + \omega^2} = \frac{1}{2i\omega}\left(\frac{1}{s - i\omega} - \frac{1}{s + i\omega}\right).$$

For the original function $x(t)$ we thus find

$$x(t) = \frac{1}{2i\omega}(e^{i\omega t} - e^{-i\omega t}) = \frac{1}{\omega}\sin(\omega t).$$

Acknowledgement

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