University College Dublin

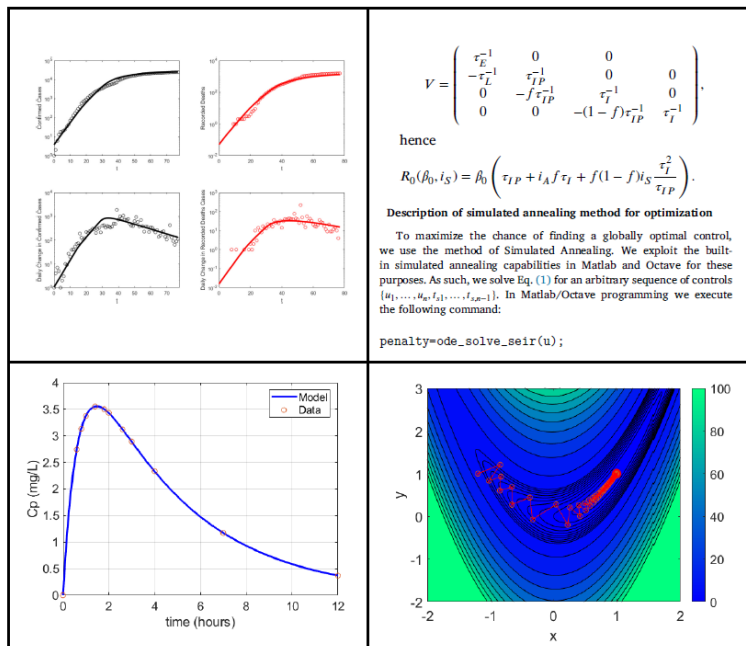An Coláiste Ollscoile, Baile Átha Cliath

School of Mathematics and Statistics
Scoil na Matamaitice agus Staitisticí
Case Studies in Mathematical Modelling

Part of a Course in Applied Statistical Modelling (STAT 40510)

Dr Lennon Ó Náraigh

Contents

Chapter 1

Introduction to Mathematical Modelling

Overview

We give a brief introduction to the rationale of the module.

1.1   Why Mathematical Modelling?

'Traditional' models in Applied Mathematics are deterministic, they typically involve formulating a system of ordinary differential equations to describe a dynamical process, e.g.:

$$\frac{\mathrm{d}\boldsymbol{x}}{\mathrm{d}t} = \boldsymbol{v}(\boldsymbol{x}, t), \tag{1.1}$$

where $\boldsymbol{x} \in \mathbb{R}^n$ and $\boldsymbol{x}(t)$ is a trajectory. The formulation of these models requires physical insights (e.g. 'conservation' laws, mass-action principles, etc.), and helps to place constraints on the model variables. For example, a 'conservation' approach in epidemiological modelling involves adding up different classes of people in a population, measuring how people move from one class to another, and all the while ensuring that the sum of the sub-populations equals the total population. Mathematical models can also help the scientist to understand how and why certain processes occur, in addition to making predictions. Often, 'making predictions' is too big of an 'ask', in which case mathematical modelling can be used to present different **scenarios**. This can also be useful, especially for governments formluating policy.

A kind of idealized flow chart of how mathematical modelling works is shown in Figure 1.1[1].

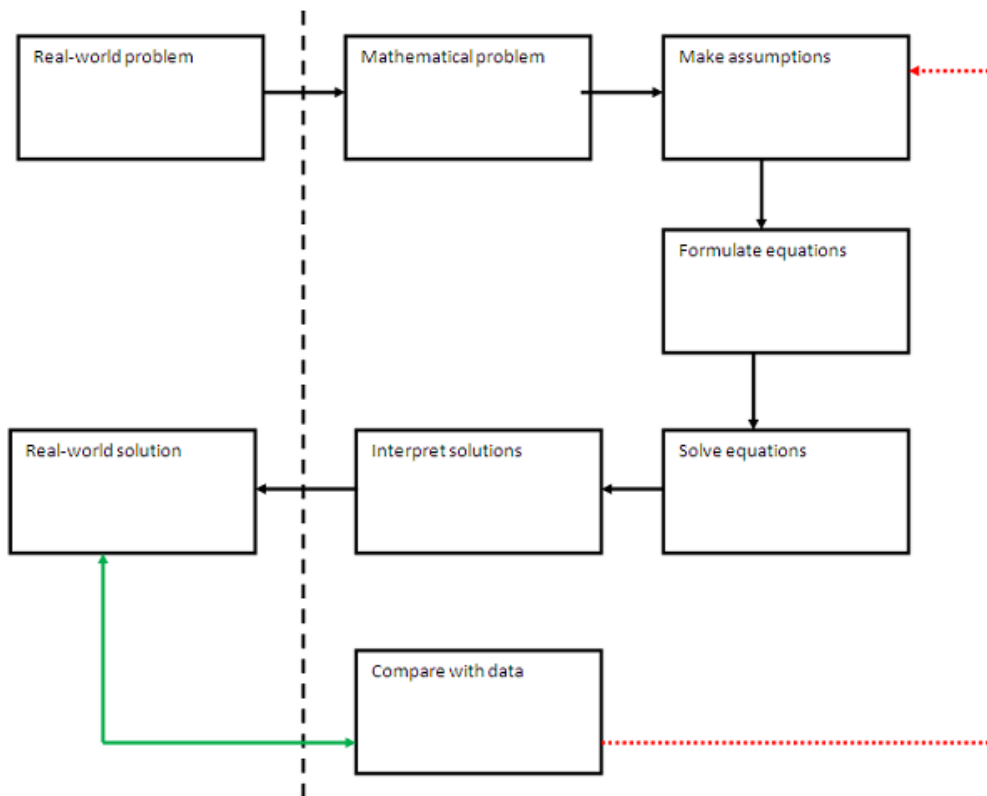[1]It's usually much messier than this.

Figure 1.1: Flowchart showing the modelling process

1.1.1   Example

We look at a very basic example of how the modelling process in Figure 1.1 works. This is a bit of a silly, simplistic example, and it is important to note that the case studies and examples considered in the remainder of these lecture notes are much more detailed, realistic, and complex.

In any case, for the present purposes, consider the population of a fictitious country, Doriath. Let $P(t)$ be the number of people present at time t. We look at an exponential-growth model:
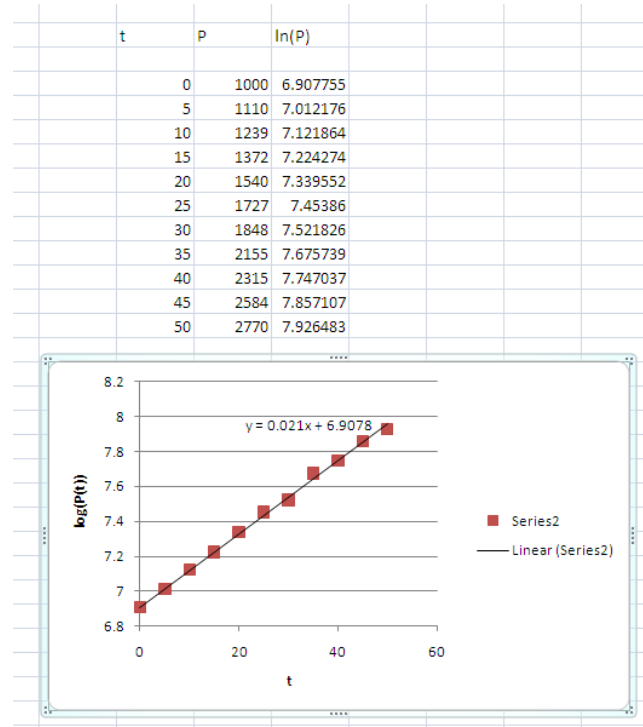
$$P(t) = P(0)e^{kt}, \tag{1.2}$$

where $P(0)$ is the population at time $t = 0$ and k is an unknown constant. Thus, to arrive back at the real-world solution, we need some data to determine k. For a problem involving time-evolution, this will be information about the past. For example, suppose we have the following data for the past fifty years (starting from $t = 0$). We overlay a curve of the kind (1.2) on the data (Figure 1.2) and choose a k-value that best fits the data. The result is $k = 0.021$. The result is not a perfect fit – it never will be. There will be small fluctuations in the population size for reasons unknown to this crude model. Nevertheless, the fit is good.

Suppose now we use the k-value to make a prediction for what the population will be in twenty

t (years)	P	t (years)	P
0	1000	30	1848
5	1110	25	2155
10	1239	40	2315
15	1372	25	2584
20	1540	50	2770
25	1727		

Table 1.1: Population of Doriath over fifty years.

t	P	ln(P)
0	1000	6.907755
5	1110	7.012176
10	1239	7.121864
15	1372	7.224274
20	1540	7.339552
25	1727	7.45386
30	1848	7.521826
35	2155	7.675739
40	2315	7.747037
45	2584	7.857107
50	2770	7.926483

Figure 1.2: Estimating the k-value from the data in Table 1.1.

years' time ($t = 70$):

$$P(t = 70) = 1000\mathrm{e}^{0.021 \times 70} = 4300 \text{ to two significant figures}$$

(our k-value has two significant figures, so we are only allowed to keep two here).

- If, in twenty years' time, the population is close to $P = 4300$, then our model is validated, and we gain confidence in it (broken red line does not need to be followed in Figure 1.1).
- If, however, in twenty years' time, the population prediction is wildly different from $P = 4300$, then we need to revisit the model assumptions in Figure 1.1.

In any event, this example shows a typical (but not essential) property of a mathematical model:

Often, a mathematical model contains free parameters that need to be estimated from data before predictions can be made.

1.2   Deterministic versus statistical modelling

Superficially at least, the mind of model in Section 1.1 this bears little resemblance to a statistical model. We have the following distinctions:

- In deterministic modelling we solve a set of ODEs to make a prediction about the future based on initial conditions.
- In statistical modelling we assume that an output variable depends on
    - An input variable
    - Some additional randomness

    For example, the height of individuals in a population depends on the age of the individual, as well as some random contribution because not all people are the same. The random contribution to the dependence is modelled as a random variable that is drawn from a probability distribution. Statistical modelling involves finding a sensible relationship between the input and output variables, and a sensible probability distribution with which to characterize the random contribution. This is often done with a linear regression analysis.

It is tempting to think that these two approaches constitute two fundamentally different world views. However, this would be wrong. Indeed, as you will notice in this module, many of the deterministic ODE models that we write down depend on parameters (e.g. population growth rates) that are not known *a priori*. An increasingly popular and extremely effective approach to determining these parameters is via statistical modelling. Therefore, the 'best' models are often deterministic ones where the free parameters are determined rigorously via statistical modelling. Thus, at a very high level, these two apparently disparate approaches can be brought together. This is a powerful approach that combines 'the best of both worlds', and the aim of these lectures is to explore some case studies that exemplify this dual approach to modelling, simulation, and prediction.

Chapter 2

A Word of Warning

Overview

We look briefly at some population models and show where they can go wrong. Again, this is not part of the course *per se*, and nor will it form part of the case studies in the course. However, it is included here as a salutary example of what can go wrong when blind faith is placed in a model – especially when human behaviour is being modelled.

2.1 The Malthus model

We model a definite human population (e.g. a country), starting with the following simplifying assumptions:

1. Random fluctuations in the population are ignored (e.g. epidemics);
2. Immigration and emigration are not considered;
3. The environment is assumed to be capable of sustaining any population level;
4. Each individual is assumed to be identical, and has an equal chance of giving birth or dying in a given interval of time.

It follows that only the birth rate and the death rate will affect the population:

- $\beta(t) =$ per-capita birth rate.
- $\alpha(t) =$ per-capita death rate.

Moreover, the characteristics of the population (apart from its level) are assumed to be constant over time, so that α and β are constants. We can now create a mathematical model by dimensional analysis and some ideas about 'conservation'.

- Dimensional analysis tells us that the rate of change of population ([Number]/[Time]) should be equal to

$$\text{Rate of change of population} = \frac{\mathrm{d}P}{\mathrm{d}t}, \tag{2.1}$$

  where $P(t)$ is the population level at time t.
- If $\beta(t)$ is a per-capita rate, it has dimensions of $1/[\text{Time}]$, and the corresponding pure rate is βP, with dimensions of $[\text{Number}]/[\text{Time}]$:

$$\text{Birth rate} = \beta P.$$

- Similarly,

$$\text{Death rate} = -\alpha P.$$

- Now here comes the 'conservation' or 'balance' principle: There is no emigration, immigration, or epidemics. Therefore, the only way for the population to change is through births and deaths. We therefore add the birth rate and the death rate, **with the proper signs**:

$$\text{Total rate of change} = \beta P - \alpha P = (\beta - \alpha)P := kP, \tag{2.2}$$

  where k is some real number that can be positive or negative.

We equate Equations (2.1) and (2.2) to find our mathematical model:

$$\frac{\mathrm{d}P}{\mathrm{d}t} = kP. \tag{2.3}$$

Equation (2.3) is a separable Ordinary Differential Equation (ODE) that can be solved by formally multiplying both sides by $\mathrm{d}t$, and dividing both sides by P:

$$\frac{\mathrm{d}P}{P} = k\mathrm{d}t.$$

Integrate:

$$\int \frac{\mathrm{d}P}{P} = kt + C,$$

where C is a constant of integration. In other words,

$$\log P = D\mathrm{e}^{kt}, \qquad D = \mathrm{e}^{C}.$$

The constant D is determined from initial conditions:

$$P(t=0) = D.$$

Hence, the final form for the solution of the model (2.3) is

$$P(t) = P(0)e^{kt}. \tag{2.4}$$

Remarks:

- The model gives a way of predicting future populations, once the initial population $P(0)$ is known.
- However, it contains an **unknown parameter**, k.
- In practice, to determine k, we would find a historic **time series** of the population and fit a curve of the type (2.4) to the data. This would give us an estimate of k.
- We would then use that estimated value of k to predict future values of the population.
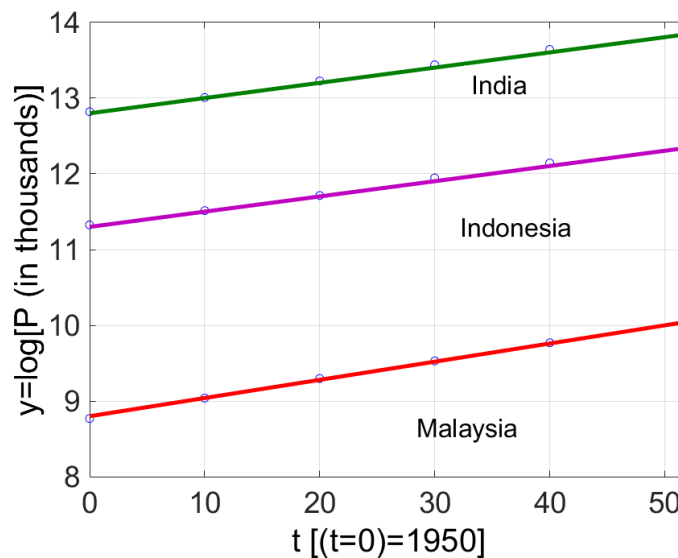
2.1.1 Model validation

Figure 2.1: Census data and the Malthus model

The list of assumptions for the Malthus model does appear long. However, each one can be justified in detail. The things ruled out appear to be one-off events (epidemics and mass migration), and the model can therefore be expected to hold over long periods of time. The carrying capacity of the environment is large, so that again, resource limitations should not affect the population. Even the last point, concerning the sameness of the individuals in the population is not so unreasonable: there may be many atypical individuals in a society, but it is to be expected that there will be a sufficient mass of 'normal' individuals behaving in more-or-less the same way that the outliers can be ignored. Therefore, let us investigate a few human populations to see if they follow the model (2.4).

To validate the model (2.4) we are going to form the auxiliary quantity

$$y = \log(P),$$

such that, within the model,

$$y = kt + \log[P(0)].$$

If a population follows the model, its y-value, plotted against time, will be a straight line. It seems as though at least some populations do follow the Malthus model (Primary source: U.S. Census Bureau) – see Figure 2.1. However, let us look at China's population over the same period (Fig. 2.2). If the population were Malthusian, the 'line of best fit' would coincide with the actual data points.
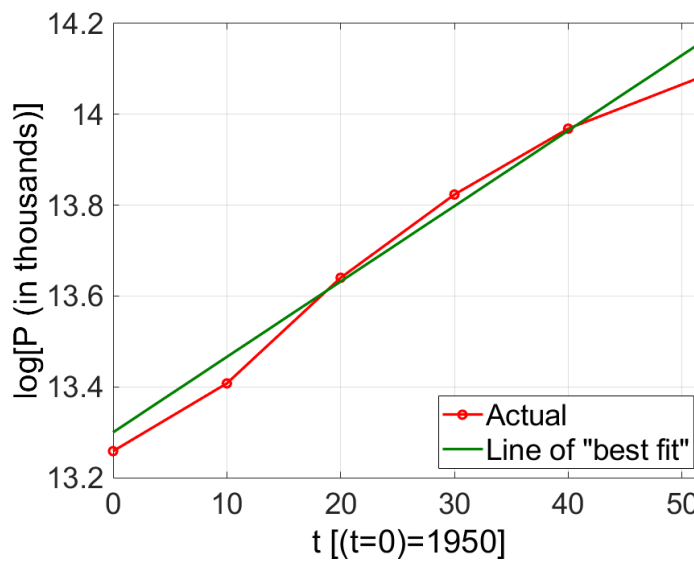

Figure 2.2: Census data for China and the Malthus model

However, the population deviates in a clear and systematic way from a straight line. The population here is not Malthusian.

It is salutary to try to discover where we have gone wrong in Figure 2.2. The dip in the first ten years of the graph could be due to the famine (1958-1961), while the dip in the latter years of the graph could be due to the one-child policy.

- The dip in the early years could be due to an increased death rate – larger α-value;
- The dip in the latter years could be due to a decreased birth rate – smaller β-value.

Both trends conspire to make k a function of time, such that the correct model would be

$$\frac{\mathrm{d}P}{\mathrm{d}t} = k(t)P, \qquad P(t) = P(0)e^{\int_0^t k(t')\mathrm{d}t'}.$$

The moral of this story is that **humans are complicated** and can react to and change their surroundings. Thus, care is needed in applying simple deterministic models to human populations. We will have much better luck in this course when we model the behaviour of drugs in the body in Chapters 5–6.

2.2 Final word

The final words in this chapter is best left to Isaac Newton. Newton had many theories that were less successful than his Laws of Motion and Universal Law of Gravitation (and fluid viscosity and rootfinding method...). He used one of these theories to predict the stock market. He was unsuccessful and lost lots of money. About his spectulations, he said he could:

> calculate the motions of the heavenly bodies, but not the madness of people.

Chapter 3

The SIR Model

Overview

In this Chapter we introduce the most basic compartmental model in epidemiology, the so-called SIR model. We outline the assumptions behind the model, we formulate the model in terms of ordinary differential equations, and we present very basic strategies for the solution. The SIR model is one of the few models in mathematical epidemiology that has an exact analytical solution, this helps with the analysis of the model and with developing understanding. Armed with this understanding, we can then go and look at more complicated models such as the SEIR model, and also, extended SEIR models, which were used to provide scenarios to governments across the world during the Covid-19 pandemic.

3.1 Mathematical Modelling

3.1.1 Assumptions

We consider a human population suffering from an epidemic. The population is divided into three **compartments**:

- Susceptible people, $S(t)$,
- Infectious people, $I(t)$,
- Recovered people, $R(t)$.

The population is then subject to the following assumptions:

- The total population $N = S + I + R$ is constant in size. That is, births, deaths (from non-epidemic-related causes), and migration, are unimportant. This will certainly be the case

when the epidemic moves through the population fast, that is, on a timescale much faster than that of demographic change.

- Once a person is recovered, they do not become susceptible again; people recover at a rate γ.

These assumptions, together with one further assumption (below) suffice to develop our model. The model is now based on a 'conservation law', that is, the total number of people in the population is the same, if a person leaves (say) the susceptible compartment, then they must show up in either the infections compartment or the recovered compartment.

3.1.2   The model

First, imagine that no people recover from the epidemic, $\gamma = 0$. Then, the number of people who become infected is proportional to the probability that an infected person and a susceptible person encounter one another. This in turn is proportional to the product of the population of susceptible and infectious compartments:

Probability of a susceptible person become infections $\propto SI$.

When a susceptible person becomes infectious, this diminishes the susceptible compartment. Thus, we formulate an equation like

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha SI,$$

where the negative sign indicates that the susceptible compartment decreases as more and more people become infectious.

Remember, we have imagined for a minute that the recovery rate is zero. That means that the number of people, $S + I$, is constant, hence

$$\frac{\mathrm{d}}{\mathrm{d}t}(S + I) = 0 \implies \frac{\mathrm{d}I}{\mathrm{d}t} = -\frac{\mathrm{d}S}{\mathrm{d}t} = +\alpha SI.$$

We now have two equations:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha SI, \qquad \frac{\mathrm{d}I}{\mathrm{d}t} = \alpha SI.$$

Now, let us restore the non-zero recovery rate. We have assumed that people recover at a constant rate, γ. The number of people recovering per unit time is thus $-\gamma I$. This will serve to diminish the infectious-population, without affecting the susceptible population directly. We therefore modify the I-equation:

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \alpha SI - \gamma I.$$

Finally, conservation of people now requires that

$$\frac{\mathrm{d}}{\mathrm{d}t}(S + I + R) = 0 \implies \frac{\mathrm{d}R}{\mathrm{d}t} = -\frac{\mathrm{d}S}{\mathrm{d}t} - \frac{\mathrm{d}I}{\mathrm{d}t} = -(-\alpha SI) - (\alpha SI - \gamma I) = +\gamma I.$$

Let us gather up our model equations:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha SI, \tag{3.1a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \alpha SI - \gamma I, \tag{3.1b}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I. \tag{3.1c}$$

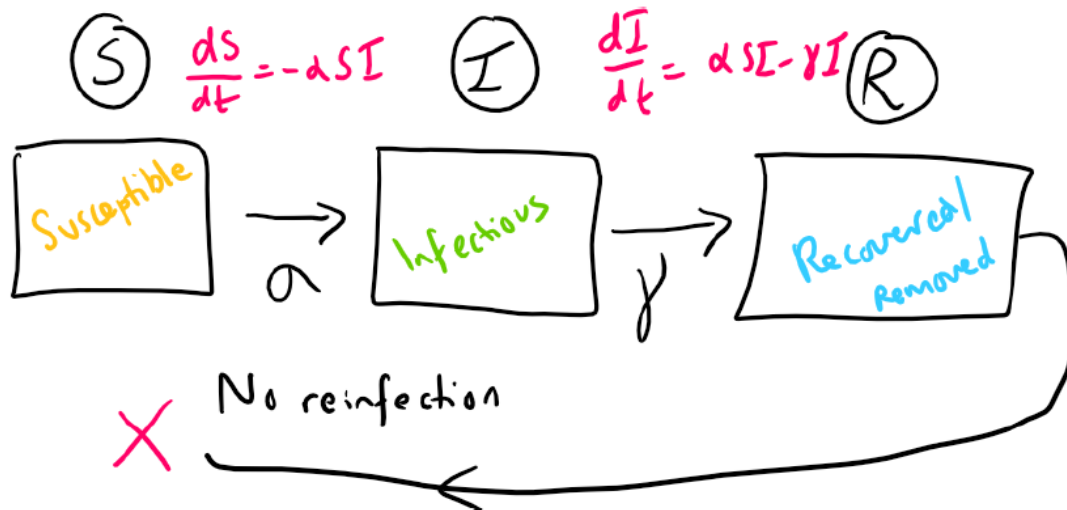The idea behind these equations is summarized in graphical form in Figure 3.1.

Figure 3.1: Schematic description of the 'conservation law' underling the basic SIR model

3.1.3   The parameter β

The constant γ is a rate (1/time). We write $\alpha = \beta/N$ so that β is also a genuine rate, such that Equation (3.1) can be rewritten as:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\frac{\beta}{N}SI, \tag{3.2a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{\beta}{N}SI - \gamma I, \tag{3.2b}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I. \tag{3.2c}$$

The rate β can therefore be decomposed as:

$$\beta = c \times p = (\text{Number of contacts of an individual per unit time})$$

$$\times (\text{Probability that a contact leads to infection}).$$

Thus, the epidemic can in principle be controlled by:

- Reducing contacts ($c \searrow 0$),
- Making contacts safer ($p \searrow 0$).

3.1.4   Initial conditions

Equation (3.2) is valid for $t > 0$. At $t = 0$ we have **initial conditions**, the most obvious of which are:

$$S(t = 0) = S_0, \qquad I(t = 0) = I_0, \qquad R(t = 0) = 0.$$

where $S_0 + I_0 = N$, the total population size. With $S_0 = N - 1$ and $I_0 = 1$ we have the idea of 'patient zero'.

3.2   Mathematical Analysis of the Model

Here, we show that the SIR model (3.2) can be recast as a single ordinary differential equation (ODE). This is an unusual situation: it is rare for **systems** of **coupled** ODEs to reduce to a single form involving a single equation. The reason this works here is because of nice properties enjoyed by the ODE system (3.2). Thereafter, we rescale the single ODE to bring it down to a simple form that can help us to undestand the dynamics of infectious diseases a bit better.

3.2.1   Reduction of Model to a single ODE

Observation 1:   Consider the S- and R-equations alone:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\frac{\beta}{N}SI, \qquad \frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I.$$

In the R-equation, observe that $R = (\mathrm{d}I/\mathrm{d}t)/\gamma$. Substitute this into the first equation to obtain

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\frac{\alpha}{N}S\left(\frac{1}{\gamma}\frac{\mathrm{d}R}{\mathrm{d}t}\right).$$

This looks a little bit like a separation-of-variables problem! First, divide both sides by S:

$$\frac{1}{S}\frac{\mathrm{d}S}{\mathrm{d}t} = -\frac{\beta}{N}\frac{1}{\gamma}\frac{\mathrm{d}R}{\mathrm{d}t}.$$

Now **formally** cancel the $\mathrm{d}t$'s on both sides to obtain

$$\frac{\mathrm{d}S}{S} = -\frac{\beta}{N}\frac{1}{\gamma}\mathrm{d}R.$$

This identity can now be integrated to yield

$$\log S - \log S_0 = -\frac{\beta}{N}\frac{1}{\gamma}[R - R(0)], \qquad S_0 = S(0).$$

However, we assume no recovered people at the onset of the epidemic, so $R(0) = 0$. Exponentiation gives:

$$S = S_0 e^{-(\beta/N)R/\gamma}$$

Here, however, we need to remind ourselves that S and R are in fact functions of time, so the correct form is

$$S(t) = S_0 e^{-(\beta/N)R/\gamma} \tag{3.3}$$

Observation 2: By assumption, the population is constant:

$$\frac{\mathrm{d}}{\mathrm{d}t}(S + I + R) = 0 \implies S + I + R = N = \text{Constant}$$

Thus,

$$I = N - S - R.$$

However, by Equation (3.3), $S = S_0 e^{-(\beta/N)R/\gamma}$, hence

$$y = N - S_0 e^{-(\beta/N)R/\gamma} - R.$$

We substitute this into the R-equation $\mathrm{d}R/\mathrm{d}t = \gamma I$:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma \left[N - S_0 e^{-(\beta/N)R/\gamma} - R \right]. \tag{3.4}$$

Equation (3.4) is a single equation in a single dependent variable – a great simplification compared to Equation (3.2). If we further introduce the scaled variable $u = (\beta/\gamma)(R/N)$, then Equation (3.4) can be re-written as:

$$\frac{1}{\gamma}\frac{\mathrm{d}u}{\mathrm{d}t} = \frac{\beta}{\gamma} - \frac{\beta}{\gamma}\frac{S_0}{N}e^{-u} - u, \qquad u = \frac{\beta}{\gamma}\frac{R}{N}. \tag{3.5}$$

We will analyze this equation further in what follows.

3.2.2 Rescaling the single ODE

We further introduce a rescaled time $\tau = \beta S_0 t/N$, such that:

$$
\begin{aligned}
\frac{1}{\gamma}\left(\frac{\beta S_0/N}{\beta S_0/N}\frac{\mathrm{d}u}{\mathrm{d}t}\right) &= \frac{\beta}{\gamma} - \frac{\beta}{\gamma}\frac{S_0}{N}\mathrm{e}^{-u} - u, \\
\implies \frac{1}{\gamma}(\beta S_0/N)\frac{\mathrm{d}u}{\mathrm{d}\tau} &= \frac{\beta}{\gamma} - \frac{\beta}{\gamma}\frac{S_0}{N}\mathrm{e}^{-u} - u, \\
\implies \frac{1}{\gamma}(\beta S_0/N)\frac{\mathrm{d}u}{\mathrm{d}\tau} &= \frac{\beta}{\gamma} - \frac{\beta}{\gamma}\frac{S_0}{N}\mathrm{e}^{-u} - u.
\end{aligned}
$$

Hence,

$$
\frac{\mathrm{d}u}{\mathrm{d}\tau} = \frac{\beta}{\gamma}\frac{N\gamma}{\beta S_0} - \frac{\beta}{\gamma}\frac{S_0}{N}\frac{N\gamma}{\beta S_0}\mathrm{e}^{-u} - \frac{N\gamma}{\beta S_0}u, \tag{3.6}
$$

From here we identify:

$$
R_0 = \frac{\beta}{\gamma}\frac{S_0}{N}. \tag{3.7}
$$

Hence, Equation (3.6) can be re-written as:

$$
\frac{\mathrm{d}u}{\mathrm{d}\tau} = \frac{N}{S_0} - \frac{1}{R_0}u - \mathrm{e}^{-u}. \tag{3.8}
$$

3.3 Understanding the model

We now try to understand the model in more depth, using Equation (3.8) as the reference point. This is a single autonomous ODE, which can be written generically as:

$$
\frac{\mathrm{d}u}{\mathrm{d}\tau} = f(u), \qquad f(u) = (N/S_0) - (1/R_0)u - \mathrm{e}^{-u}.
$$

The function f depends on the single variable u but also on the parameters N/S_0 and R_0. The equation can be understood by looking at the equilibrium solutions or fixed points where $0 = \mathrm{d}u/\mathrm{d}\tau = 0$, this requires $f(u) = 0$ Thus, the equilibrium solution (or fixed point) is the root of $f(u) = 0$. We examine these roots in detail now.

3.3.1   Rootfinding

Behaviour at zero: We have,

$$f(0) = (N/S_0) - 1.$$

Since $(N/S_0) \geq 1$, $f(0) \geq 0$. Let us consider the case where $N/S_0 > 1$, strictly. Thus, $S_0 > 0$, and there are some infectious people present initially. Then $f(0) > 0$.

Behaviour for large u-values: As $u \to \infty$, the exponential term dies away, and we are left with

$$f(u) \sim -\frac{1}{R_0} u, \qquad u \to \infty.$$

In other words, $f(u)$ becomes large and negative and behaves like a straight line, as $u \to \infty$.

Maxima and minima: We compute $f'(u_0) = 0$ and find

$$-\frac{1}{R_0} + \mathrm{e}^{-u_0} = 0.$$

In other words,

$$u_0 = -\log \frac{1}{R_0} = \log R_0.$$

For $R_0 > 1$, this point exists in the range $u > 0$. The second derivative is

$$f''(u_0) = -\mathrm{e}^{-u_0},$$

and this is always negative. Hence, the point $u_0 = \log R_0$, if it exists, is a **maximum**.

Crossing the u-axis: We have:

- $\lim_{u \to 0} f(u) > 0$,
- $\lim_{u \to \infty} f(u) < 0$,
- $f(u)$ at most has one local maximum on $u > 0$.

Therefore, $f(u)$ has precisely one root on $u > 0$ — one fixed point. Examination of the one-dimensional vector field shows that this is a stable fixed point (Figure 3.2).

3.3.2   The peak of the epidemic

The **peak** of the epidemic occurs when the number of people getting infected is at a maximum:

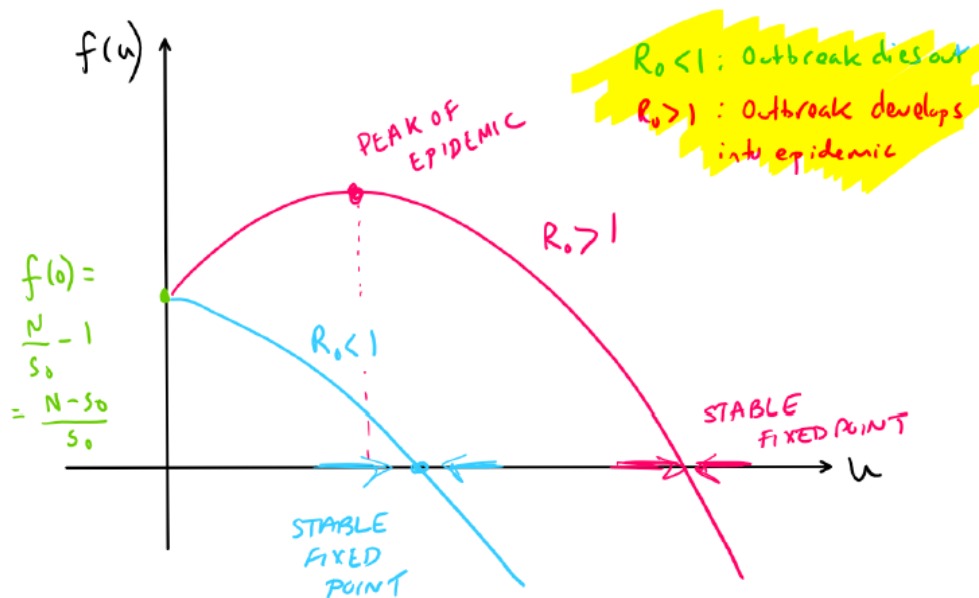$$\frac{\mathrm{d}I}{\mathrm{d}t} = 0 \implies \text{The number of sick people is at a maximum.}$$

Figure 3.2: The function $f(u)$ for the two representative R_0-values.

Note that $\mathrm{d}R/\mathrm{d}t = \gamma I \implies \mathrm{d}^2 R/\mathrm{d}t^2 = \gamma(\mathrm{d}I/\mathrm{d}t)$, so that, at peak,

$$\frac{\mathrm{d}^2 R}{\mathrm{d}t^2} = 0 \text{ at peak.}$$

In other words, **at peak, the number of recoveries stops accelerating**. Since $R \propto u$,

$$\frac{\mathrm{d}^2 u}{\mathrm{d}t^2} = 0 \text{ at peak.}$$

Note further:

$$\frac{\mathrm{d}^2 u}{\mathrm{d}t^2} = \frac{\mathrm{d}}{\mathrm{d}t}\frac{\mathrm{d}u}{\mathrm{d}t} = \frac{\mathrm{d}}{\mathrm{d}t}f(u) = f'(u)\frac{\mathrm{d}u}{\mathrm{d}t} = f'(u)f(u).$$

Thus, peak corresponds to $f'(u) = 0$ of $f(u) = 0$. We do not call $f(u) = 0$ the peak of the epidemic, because this is a fixed point. Therefore,

$$f'(u) = 0 \text{ at peak.}$$

However, by Figure 3.2, this condition is realised only for $R_0 > 1$. **Therefore, the epidemic peaks only when $R_0 > 1$.** Hence:

- For $R_0 > 1$:
    - Starting with an initial condition $u_0 = 0$ (no recovered people at $t = 0$), the number of recovered people accelerates, with $\mathrm{d}^2 u/\mathrm{d}t^2 = f'(u)f(u) > 0$.
    - At peak, the acceleration stops, $f'(u) = 0$.
    - After peak, the number of recovered people decelerates, with $\mathrm{d}^2 u/\mathrm{d}t^2 < 0$.

- For $R_0 < 1$:

    - $\mathrm{d}^2 u/\mathrm{d}t^2 = f'(u)f(u) < 0$ always.
    - The number of recovered people decelerates from the start.

The parameter-value $R_0 = 1$ is therefore called the **threshold** value: If $R_0 > 1$ the epidemic accelerates before slowing down, while if $R_0 < 1$, the epidemic decelerates from the start.

3.3.3   One more way of looking at things

Consider again $R_0 = (\beta/\gamma)(S_0/N)$. For this discussion, take S_0/N to be fixed. Physically, $R \gg 1$ means that $\beta \gg \gamma$. In other words, the rate at which the disease spreads greatly exceeds the recovery rate. Infectious people, before they recover, manage to infect lots of susceptible people. On the other hand, $R_0 \ll 1$ means that $\beta \ll \gamma$. The infectious people recover before they have time to infect too many more people. The faster the recovery rate (or the death rate), the slower the spread!

3.4   The three-equation model revisited

We have already analysed Equation (3.8), and know that there is only ONE stable fixed point u_*, such that

$$f(u_*) = 0.$$

Moreover, $u_* > 0$. But $u = (\beta/\gamma)(R/N)$. Hence, $R_* = (\gamma u_*/\beta)N$ must be part of a fixed point (x_*, y_*, z_*) of the three-equation model (3.2). What are these points? The answer immediately is $S_* = \text{Constant}$, $I_* = 0$, and $R_* = (\gamma u_*/\beta)N$. For, consider again Equation (3.2), with the triple (S, I, R) replaced by the fixed-point triple. We have:

$$0 = -\frac{\beta}{N} S_* \times 0, \tag{3.9a}$$

$$0 = \frac{\beta}{N} S_* \times 0 - \gamma \times 0, \tag{3.9b}$$

$$0 = \gamma \times 0, \tag{3.9c}$$

and these equations are trivially satisfied. Thus, the full system has a fixed point.

3.4.1 Sample numerical results

We want to plot the variables $(S/S_0, I/S_0, R/S_0)$, since such a plot is independent of the initial conditions and depends only on the parameters $a = S_0/N$ and R_0. At the same time, the plot gives complete information about the dynamics. Let's evaluate these re-scaled quantities:

1. S/S_0: From the above:
$$\frac{S}{S_0} = e^{-(\beta/\gamma)(R/N)} = e^{-u(t)}, \tag{3.10}$$

    where $u(t)$.

2. R/S_0: We have, $u = (\beta/\gamma)(R/N)$, hence $R = (\gamma/\beta)Nu$, hence:
$$\begin{aligned} \frac{R}{S_0} &= \frac{\gamma}{\beta}NS_0u, \\ &= \frac{1}{R_0}u. \end{aligned}$$

    Thus,
$$\frac{R}{S_0} = \frac{1}{R_0}u(t). \tag{3.11}$$

3. I/S_0: Since $N = S + I + R$ is a constant, we have
$$\frac{I}{S_0} = \frac{N}{S_0} - \frac{S}{S_0} - \frac{R}{S_0}. \tag{3.12}$$

    It remains to work out N/x_0. We have,
$$N/S_0 = N(0)/S_0 = (S_0 + I_0)/S_0 = 1 + (I_0/S_0) = a, \tag{3.13}$$

    where again, a is prescribed as a parameter. Substitute Equations (3.10), (3.11), and Equation (3.13) into Equation (3.12). The result is
$$\frac{I}{S_0} = a - \frac{1}{R_0}u(t) - e^{-u(t)}.$$

Finally then,
$$\begin{aligned} \frac{du}{d\tau} &= a - \frac{1}{R_0}u - e^{-u}, \qquad u(0) = 0, & \text{(3.14a)} \\ S/S_0 &= e^{-u(t)}, & \text{(3.14b)} \\ I/S_0 &= a - \frac{1}{R_0}u - e^{-u}, & \text{(3.14c)} \\ R/R_0 &= \frac{1}{R_0}u. & \text{(3.14d)} \end{aligned}$$

These equations can be solved numerically. A sample code using Matlab is shown in the following code listings.

```matlab
function [S,I,R,t]=sir_solve_u(a,R0,Tfin)

options = odeset('RelTol',1e-8,'AbsTol',1e-8,'Stats','on','OutputFcn',@odeplot);
[T,u]=ode45(@myfun,[0,Tfin],0,options);

S=exp(-u);
I=a-(1/R0)*u-exp(-u);
R=(1/R0)*u;
t=T;

function dudt=myfun(~,u)
    dudt=a-(1/R0)*u-exp(-u);
end

end
```

Results are shown in Figures 3.3–3.4. Both cases have $a = 9/10$, meaning that $S_0/N = 0.9$, hence $I_0/N = 0.1$, thus 10% of the population is initially susceptible. In the first case, we have $R_0 = 0.9$. Here, the oubreak dies out: there is no characteristic peak in the number of infectious people, and the disease simply does not grow to epidemic size. In the second case, we have $R_0 = 2$. Here, the
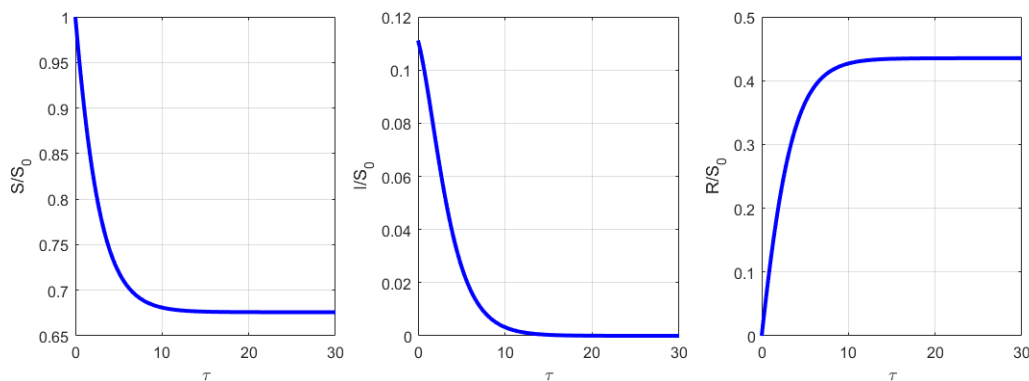

Figure 3.3: Numerical solution of the SIR model, $a = 10/9$, $R_0 = 0.9$

outbreak develops into an epidemic, and there is a characteristic peak in the number of infectious people. Eventually however, the disease dies out, with $S \to \mathrm{Const.}$, $I \to 0$, and $R \to \mathrm{Const.}$, as $\tau \to \infty$.

3.4.2   Another numerical approach

The SIR model has a lot of nice properties which enable its reduction down to a single ODE for the variable u. Many variations of the SIR model do not allow this reduction. In such cases, the numerical solutions are generated by solving a three-equation model (or an N-equation model)
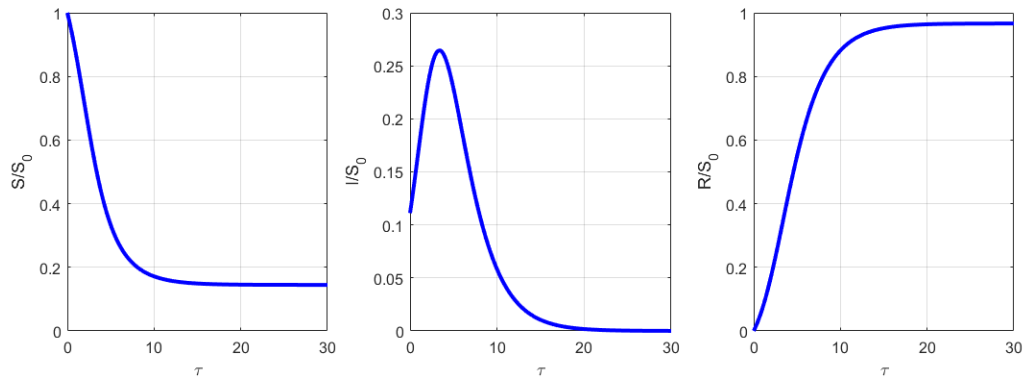
Figure 3.4: Numerical solution of the SIR model, $a = 10/9$, $R_0 = 2$

directly. A code for doing this is shown in the following listings, the numerical resluts generated in this way are identical to those generated previously in Figures 3.3–3.4.

```matlab
function [s,i,r,t]=sir_solve(R0,Tfin)

% Scaled model, variables scaled by S_0. Introduce lower-case variables:
% s=S/S_0, i=I/S_0, r=R/S_0.
% Introduce scaled time tau=beta*S_0*t/N.
% Introduce R0=(beta/gamma)*(S_0/N).
% The scaled SIR model then reads:
%
% ds/d\tau=-s*i
% di/d\tau= s*i-(1/R0)*i
% dr/d\tau=(1/R0)*i

% s=1 at time zero, by definitnion.
s_init=1;

% If 10% of the population are
% infectious initially, then we have:
i_init=1/9;

% Also:
r_init=0;

options = odeset('RelTol',1e-8,'AbsTol',1e-8,'Stats','on','OutputFcn',@odeplot);
[T,Y]=ode45(@myfun,[0,Tfin],[s_init;i_init;r_init],options);

s=Y(:,1);
i=Y(:,2);
r=Y(:,3);
t=T;

function dydtau=myfun(~,y)
    dsdtau=-y(1)*y(2);
    didtau= y(1)*y(2)-(1/R0)*y(2);
    drdtau= (1/R0)*y(2);

    dydtau=[dsdtau;didtau;drdtau];
end

end
```
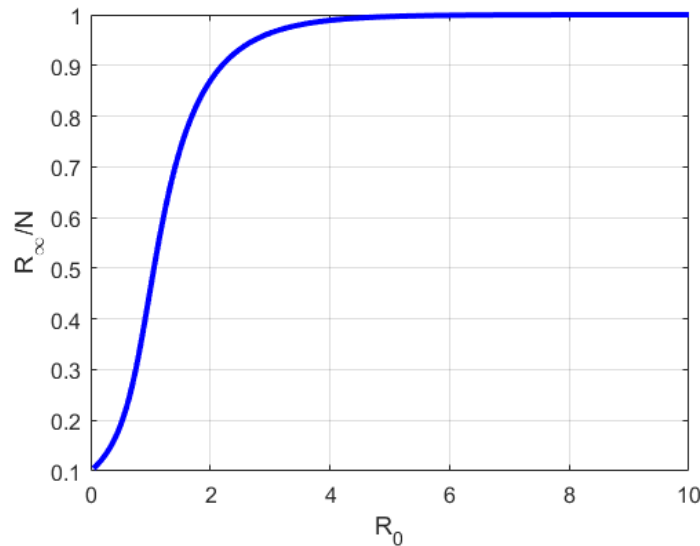
Figure 3.5: Plot showing the idea behind late-stage burnout

3.4.3   Late-stage burnout

In the late stages of the outbreak, there are not very many people left to infect, and the epidemic burns out. This can be seen in Figures 3.3–3.4. Thus, not everybody catches the disease: we have $S_\infty/N = 1 - (R_\infty/N)$, which is strictly greater than zero (some susceptibles left as $\tau \to \infty$).

To understand these ideas in more detail, we study R_∞ carefully, this is defined precisely as:

$$R_\infty = \lim_{\tau \to \infty} R(t),$$

from which we can calculate:

$$\frac{R_\infty}{N} = \frac{u_*}{R_0} \frac{S_0}{N}.$$

Here again, u_* is the fixed of $\mathrm{d}u/\mathrm{d}\tau = a - (1/R_0)u - \mathrm{e}^{-u}$. The fact that not everybody catches the disease can be thought of as 'burn-out'. A plot of R_∞/N as a function of R_0 (with $a = 10/9$) illustrating this phenomenon is shown in Figure 3.5. Clearly, as R_0 gets larger and larger, R_∞ tends to one, meaning that more and more people catch (and recover) from the disease: the bigger the R_0, the more people catch the disease.

3.5   The Herd Immunity Threshold

As a final topic here we look at what happens when a vaccination is available to control the outbreak. In such a scenario, we need to reduce the number of susceptible individuals at time $t = 0$

from $S_0 = N - 1$ to:

$$S_0 = N - \underbrace{1}_{\text{Patient Zero}} - \underbrace{fN}_{\text{Fraction of population vaccinated}}.$$

Here, $0 < f < 1$. We have:

$$R_0 = \frac{\beta}{\gamma}\frac{S_0}{N} = \frac{\beta}{\gamma}\frac{N-1}{N} \approx \beta/\gamma.$$

With an initial cohort fN vaccinated, the 'effective' value of the reproduction number becomes:

$$R_{eff} = \frac{\beta}{\gamma}(1 - f) = R_0(1 - f).$$

To control the disease, we require a threshold value $R_{eff} = 1$. Thus, we require:

$$R_0(1 - f) = 1,$$

which gives the **herd-immunity threshold**

$$f = 1 - \frac{1}{R_0}.$$

Chapter 4

The SIR Model – Workshop

Overview

In this Chapter we show how the SIR model can be fitted to data. The format here is in the style of a workshop, where we work through some sample Matlab codes. Students are invited to reproduce these codes in their choice of programming language (R, Matlab, Python, ...).

4.1 Dataset

A dataset appropriate for the out break of an fast-moving disease is available in the csv file `data1.csv`. The data are plotted in Figure 4.1. We fit an SIR model to the data with the following parameters taken as given:

$$N = 4.9 \times 10^6, \qquad T = \text{Final Time} = 100 \text{ days}.$$

The exact SIR model we fit is as follows:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\frac{\beta}{N}SI, \tag{4.1a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{\beta}{N}SI - \gamma I, \tag{4.1b}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I, \tag{4.1c}$$

which we solve on a time interval $t \in (-t_{offset}, T]$, with the initial condition

$$S(-t_{offset}) = N - 1, \qquad I(t_{offset}) = 1, \qquad R(t_{offset}) = 0.$$
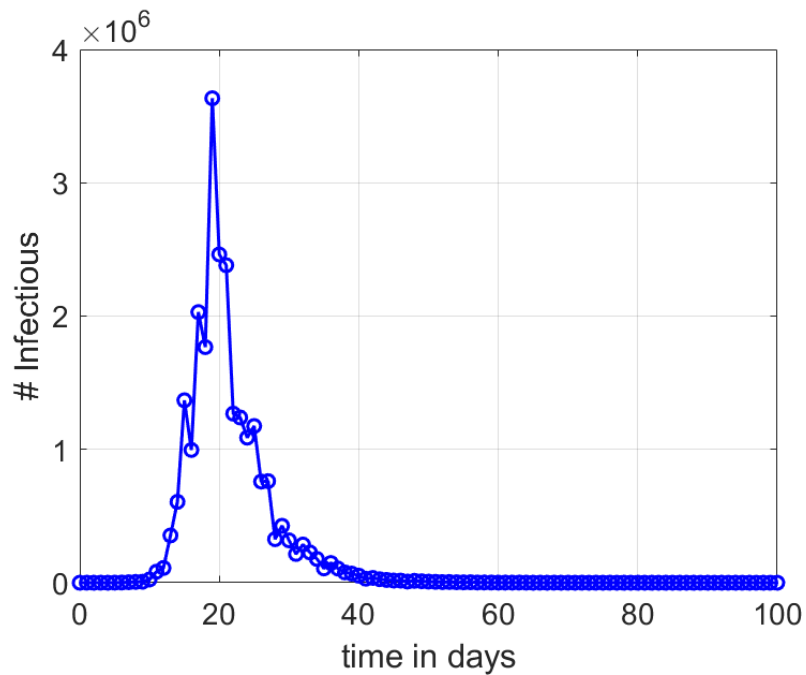
Figure 4.1: Plot of the number of infectious as a function of time (synthetic data set `data1.csv`)

Thus, there are three fitting parameters, $(\beta, \gamma, t_{offset})$. We therefore introduce a cost function,

$$J(\beta, \gamma, t_{offset}) = \sum_{i=0}^{N} \left[\log(I_{model}(t_i) + \epsilon) - \log(I_{data}(t_i) + \epsilon) \right]^2, \tag{4.2}$$

where:

- $I_{model}(t_i)$ is the number of infectious individuals in the model (4.1) on day i,
- $I_{data}(t_i)$ is the number of infectious individuals in the data on day i,
- N is the final day, N can be taken to be equal to T as T is time in days.
- ϵ is a small regularization which corrects for numerical error.

The reason for the numerical error is that in the 'tail' of the curve of $I(t)$, the numerical solution often struggles to distinguish between small positive value and small negative values. This is not important when looking at the graph of $I(t)$, but it certainly is important when taking the logarithm of $I(t)$.

We minimize the cost function in Equation (5.8) using nonlinear least squares, a sample Matlab code for which is shown in the following listings:

```
1  function [beta,gamma,t_offset]=get_params()
2
3  temp=load('data1.mat');
4  I_data=temp.data1.I;
```

Parameter	Value
β	1.0096 days^{-1}
γ	0.1999 days^{-1}
t_{offset}	-2.7439 days

Table 4.1: Estimated values of β, γ, and t_{offset} for the SIR model

```matlab
5    t_data=temp.data1.t;
6
7    % Create an anonymous function handle to the MATLAB file.
8    f = @(x)mycost(x);
9
10   % Initial guess - beta, gamma, t_offset:
11   x0 = [2,1,-2];
12
13   lb=[0,0, -10];
14   ub=[10,10,0];
15
16   options = optimoptions('fmincon','Display','iter');
17   [x, fval] = fmincon(f,x0,[],[],[],[], lb,ub,[], options);
18
19   beta=x(1);
20   gamma=x(2);
21   t_offset=x(3);
22
23   disp('**********************************************')
24   display(strcat('cost function=',num2str(fval)));
25   disp('optimum parameters=')
26   display(strcat('beta=',num2str(beta)));
27   display(strcat('gamma=',num2str(gamma)));
28   display(strcat('t_offset=',num2str(t_offset)));
29   disp('**********************************************')
30
31   [~,I,~,t]=sir_solve(beta,gamma,t_offset,1);
32   semilogy(t,I,t_data,I_data,'o')
33   drawnow
34
35   function y=mycost(x)
36       beta_loc=x(1);
37       gamma_loc=x(2);
38       t_offset_loc=x(3);
39       % Patient zero is introduced at t=t_offset:
40       I_init_loc=1;
41
42       [~,I,~,t]=sir_solve(beta_loc,gamma_loc,t_offset_loc,I_init_loc);
43
44       % semilogy(t,I,t,I_data,'o')
45       % drawnow
46
47       corr=0.1;
48       y=sum( (log(I+corr)-log(I_data+corr)).^2);
49   end
50
51   end
```

The results of applying the optimization algorithm are shown in Figure 4.2: there is close agreement between the model and the data. The optimal value of the model parameters are given in Table 5.2.
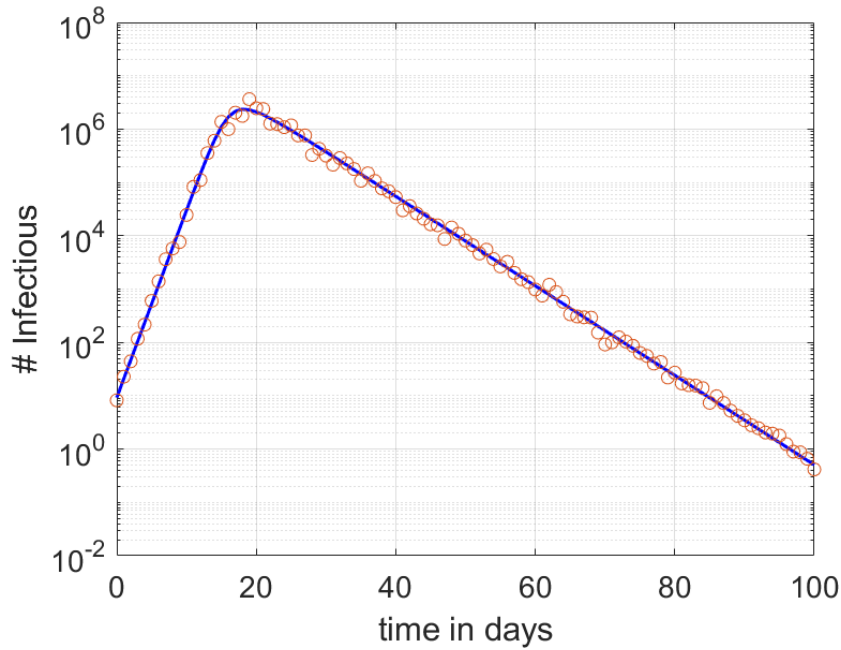
Figure 4.2: The SIR model fitted to the data

4.2 Error Estimation

To quantify the error associated with the estimates in Table 5.2, we perform statistical bootstrapping on the data:

- Compute the residual:

$$r_i = \log(I_{data}(t_i) + \epsilon) - \log(I_{model}(t_i) + \epsilon), \qquad i \in 1, \cdots, N.$$

- Resample the residual $\boldsymbol{r} = (r_1, \cdots, r_N)$ with replacement, to produce a resampled residual $\widetilde{r}$. From this, generate a new, 'synthetic' data set:

$$\widetilde{I}_{data}(t_i) = \mathrm{e}^{\log[I(t_i)+\epsilon]+\widetilde{r}_i}.$$

- Fit the SIR model to the synthetic data set, generate new estimated parameters $\widetilde{\beta}$, $\widetilde{\gamma}$, and $\widetilde{t_{offset}}$.
- Repeat, and generate a histogram of values of β, γ, and t_{offset}.

It is important to note that this is a computationally-intensive task:

- $n_{bootstrap}$ iterations of the bootstrap algorithm.
- Each iteration of the bootstrap algorithm requires a nonlinear optimization step, which requires N_{typ} ODE solves.
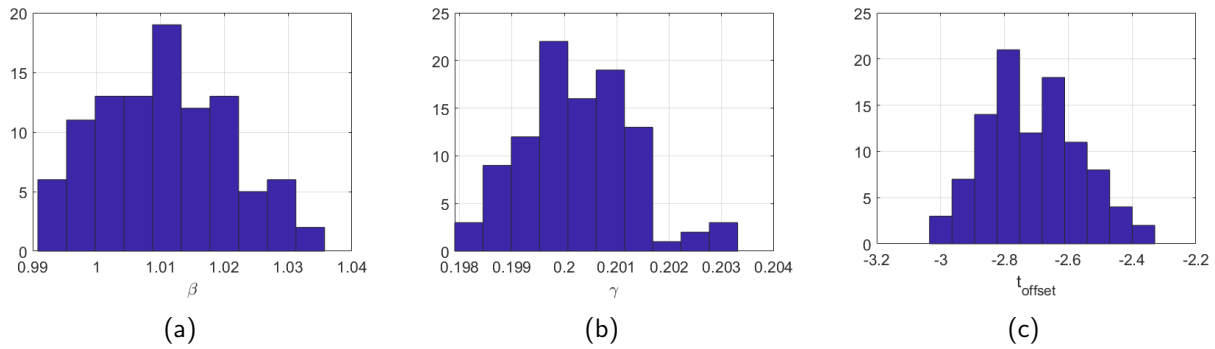
Figure 4.3: Histograms generated by the bootstrap code

Thus, the typical number of ODE solves is $n_{bootstrap} \times N_{typ}$. Here, N_{typ} is not known *a priori*. It is the number of function calls required for the optimization step to converge. From running the code, this is seen to be $N_{typ} \approx 30$. For $n_{bootstrap} = 100$ this amounts to approximately $3,000$ ODE solves.

Sample code to implement the bootstrap method is shown in the following listings.

```
1    function [beta_vec, gamma_vec, t_offset_vec]=my_bootstrap()
2
3    % n_bootstrap=100;
4    n_bootstrap=50;
5
6    temp=load('data1.mat');
7    I_data=temp.data1.I;
8    t_data=temp.data1.t;
9
10   [beta, gamma, t_offset]=get_params();
11   [~, I_model, ~, t]=sir_solve(beta, gamma, t_offset, 1);
12
13   nn=length(t)-length(t_data);
14   corr=0.1;
15   residual= log(I_model(nn+1:end)+corr)-log(I_data+corr);
16
17   beta_vec=0*(1:n_bootstrap);
18   gamma_vec=0*(1:n_bootstrap);
19   t_offset_vec=0*(1:n_bootstrap);
20
21   for i=1:n_bootstrap
22       resampled_residual = randsample(residual, length(residual), 'true');
23       corr=0.1;
24       I_data_resampled=max(exp(log(I_model(nn+1:end)+corr)-resampled_residual)-corr, corr);
25       [beta, gamma, t_offset]=get_params1(t_data, I_data_resampled);
26
27       beta_vec(i)=beta;
28       gamma_vec(i)=gamma;
29       t_offset_vec(i)=t_offset;
30   end
31
32
33   end
```

The histograms generated by running the codes are shown in Figure 4.3. Confidence intervals for the estimated parameters are generated by computing the 2.5 percentile and 97.5 percentiles of the histograms, the results are shown in Table 4.2. Beyond the value $n_{bootstrap} = 50$, the results do not depend on this value, meaning the reported confidence intervals are robust.

Parameter	Value	Lower	Upper
β (days^{-1})	1.00	0.99	1.03
γ (days^{-1})	0.199	0.198	0.202
t_{offset} (days)	-2.7	-2.9	-2.4

Table 4.2: Estimated values of β, γ, and t_{offset} for the SIR model, $n_{bootstrap} = 100$

4.3 Conclusions

In these chapters we have introduced the basics of SIR models, and shown how to fit them to data. In the projects that follow, you will be asked to look at more detailed epidemic models (e.g. SEIR models, age stratification, etc.), as well as looking at other ways of fitting the models to the available data. But the principles will remain the same as those you have encountered here.

Chapter 5

Introduction to Pharmacokinetics

Overview

5.1   Mathematical Modelling

Pharmacokinetics is the study of **what the body does to a drug**. This is in contrast to **Pharmacodynamics**, which is the study of what a drug does to the body. Thus, the fundamentally mathematical problem of Pharmacokinetics is to determine the drug concentration in the plasma:

$$Cp = f_{PK}(\text{Dose}, \text{time}),$$

where Cp is the drug concentration in the plasma, in $\mathrm{mg/L}$, and Dose is the initial dose in mg. whereas, the fundamental mathematical problem of Pharmacodynamics is to determine the drug effect as a function of concentration:

$$E = f_{PD}(Cp).$$

The focus of these lectures is on Pharmacokinetics (PK). It is important to understand that the Lecturer is not an expert on PK, instead, the focus here will be on the modelling using differential equations. For any PK-related questions, the reader is urged to consult the recommended textbook[1].

The basic idea in PK is ADME: a drug administered to the body is:

- Absorbed – the drug is absorbed into the bloodstream;
- Distributed – distribution to the various tissues in the body;
- Metabolized – the breakdown of a drug into other compounds (metabolites) in the liver;
- Excreted – elimination through the liver and/or kidneys.

---

[1]Basic Pharmacokinetics and Pharmacodynamics, Edited by Sara E. Rosenbaum, Wiley, 2017
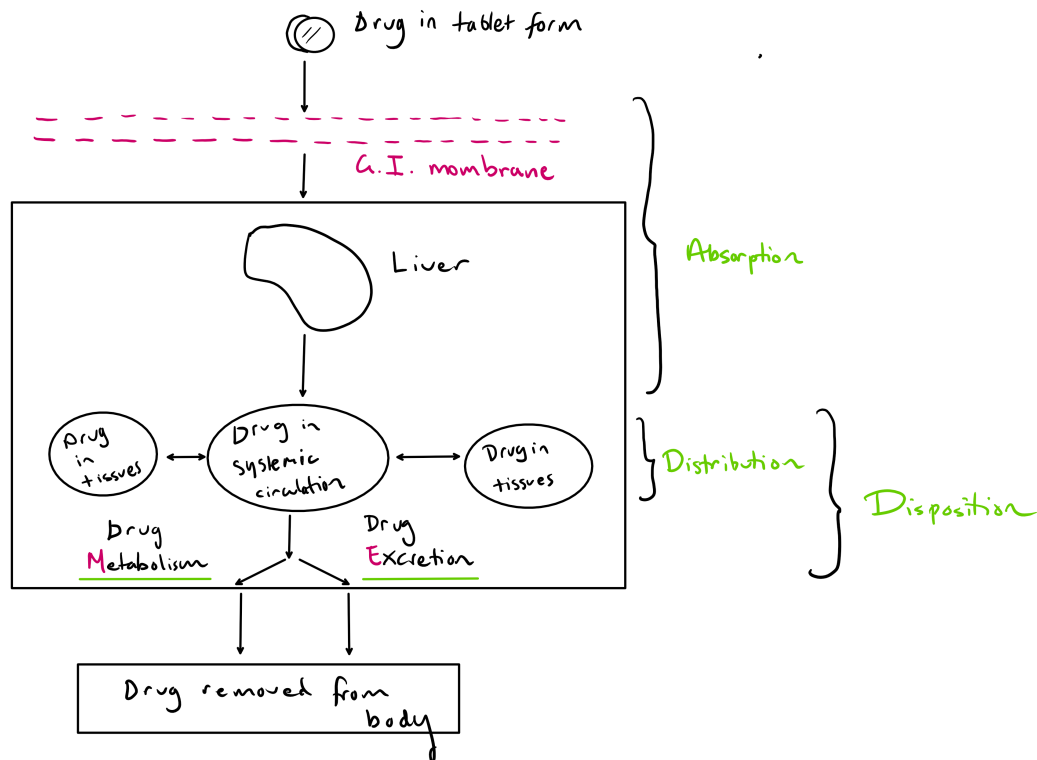
Figure 5.1: The steps in ADME for a drug administered orally

Each step in ADME can be modelled with Ordinary Differential Equations; the steps are further shown schematically in Figure 5.1. This figure refers to drug administration via the oral route.

5.1.1 Plasma Concentration of Drugs

Drug concentrations in the plasma are the main focus of PK. The rationale for this is twofold. First, blood is one of the few body fluids that cna be obtained and analyzed repeatedly for drug concentrations at specified times after the administration of a dose. The concentration of drug in whole blood is not commonly used in PK because blood is a complex physical system that consists of red bloods cells, white blood cells, and platelets suspended in plasma water. Blood with the cellular elements removed, either by centrifucation (plasma) or clotting (serum) is preferred. In these notes, no distinction is made between plasma and serum, and the term **plasma concentration** will be used throughout.

The second rationale for focusing on plasma concentrations in PK is that the circulatory system is the central fluid for the receipt and distribution of drugs. All drug input processes conclude when the drug reaches the plasma and all disposition processes begin once the drug is present in the plasma. Thus, drugs at absorption sites such as the gastrointestinal tract or subcutaneous tissue are absorbed into the circulatory system. Once in the blood, drugs undergo distribution to various tissues in the body and undergo elimination primarily through the liver and/or kidneys.

Plasma or plasma water consists of small dissolved molecules (e.g. glucose, ions, nutrients, and drugs) and suspended substances such as proteins, which are too large to dissolve. Many drugs can bind or associate with plasma proteins. The binding is reversible and may be expressed according the mass-action law:

$$[\text{D}] + [\text{P}] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [\text{DP}] \tag{5.1}$$

where D is the free drug concentration, P is the concentration of the protein not involved in the binding, , DP is the concentration of the drug-protein complex, and k_1 and k_2 are the rate constants for the forward and backward reactions, respectively.

Thus, many drugs exist in the plasma in an equilibrium between two forms: one component dissolved in the plasma water (free drug), and one component associated with or bound to plasma proteins (bound drug). The plasma concentration Cp refers to the total drug concentration of the drug, that is, the bound plus the free drug. Total drug concentrations are reported routinely because they are much easier and less expensive to measure than free drug concentrations. However, the free concentration is the clinically important component: only free unbound drug is able to pass biological membranes, interact with the receptor, and generate a pharmacological response.

5.2   Simplest One-Compartment Model

In a one-compartment model, the body is viewed as a single compartment. All the tissues where the drug goes have a very rapid rate of drug uptake. The distribution of the drug to the tissues is so rapid that there is no evidence of it when plasma concentrations are measured over time. When the drug is administered intravenously, even during the initial period after the injection, the plasma concentrations appear only to be influenced by drug elimination and fall mono-exponentially. Therefore, the simple one-compartment model is appropriate when:

- Drug is administered intravenously;
- Drug is distributed rapidly to the tissues.

In this instance, the amount of drug in the body ($= A_B$, in mg), is governed by first-order kinetics:

$$\frac{\mathrm{d}A_B}{\mathrm{d}t} = -kA_B, \tag{5.2}$$

where k is the overall elimination constant. The solution is of course:

$$A_B(t) = A_{B,0}\mathrm{e}^{-kt}. \tag{5.3}$$

The initial value $A_{B,0}$ is SD, where D is the initial dose and S is the salt factor (many drugs are administered as salts, meaning the dose will consist of pure drug and its conjugate acid or base).

The concentration of the drug in the plasma is thus:

$$Cp = \frac{A_B}{V},$$

where V is the volume of plasma in the body. Equation (5.2) is re-written as:

$$-\frac{dA_B}{dt} = -k\left(\frac{A_B}{V}\right)V = Cp\,\mathrm{Cl},$$

from which we identify the **clearance** $\mathrm{Cl} = kV$. The solution (5.3) can then be fast in proper PK terms as:

$$Cp(t) = \frac{SD}{V}e^{-(\mathrm{Cl}/V)t}.$$

The **half-life** solves $Cp(t_{1/2}) = 0.5Cp(0)$, hence

$$t_{1/2} = \frac{\ln 2}{k}.$$

5.2.1   Worked Example

A 20-mg dose of a drug $S = 1$ was adminstered as an intravenous bolus injection. The drug has the following PK parameters: $k = 0.1\,\mathrm{h}^{-1}$ and $V = 20\,\mathrm{L}$. Calculate Cp_0 and hence calcualte the plsma concentration at $3\,\mathrm{h}$.

Solution: We have:
$$Cp_0 = \frac{S \times D}{V} = \frac{1 \times 20\,\mathrm{mg}}{20\,\mathrm{L}},$$

hence $Cp_0 = 1\,\mathrm{mg/L}$.

After three hours, we have:

$$Cp(t = 3\,\mathrm{h}) = Cp_0\,e^{-k\times(3\,\mathrm{h})} = (1\,\mathrm{mg/L})\,e^{-0.3} = 0.74\,\mathrm{mg/L}.$$

Carrying on with this example, if the therapeutic range is between 5 and $0.3\,\mathrm{mg/}L$, how long are the plasma concentrations in the therapeutic range?

Refer to Figure 5.2. The therapeutic range refers to the maximum therapeutic concentration (MTF, for safety) and the minimum effective concentration (MEC, for effectiveness). Evidently, we require, at time t_*,

$$
\begin{aligned}
Cp(t_*) &= Cp_0 e^{-kt_*}, \\
0.3 &= 1 \times e^{-0.1t_*}, \\
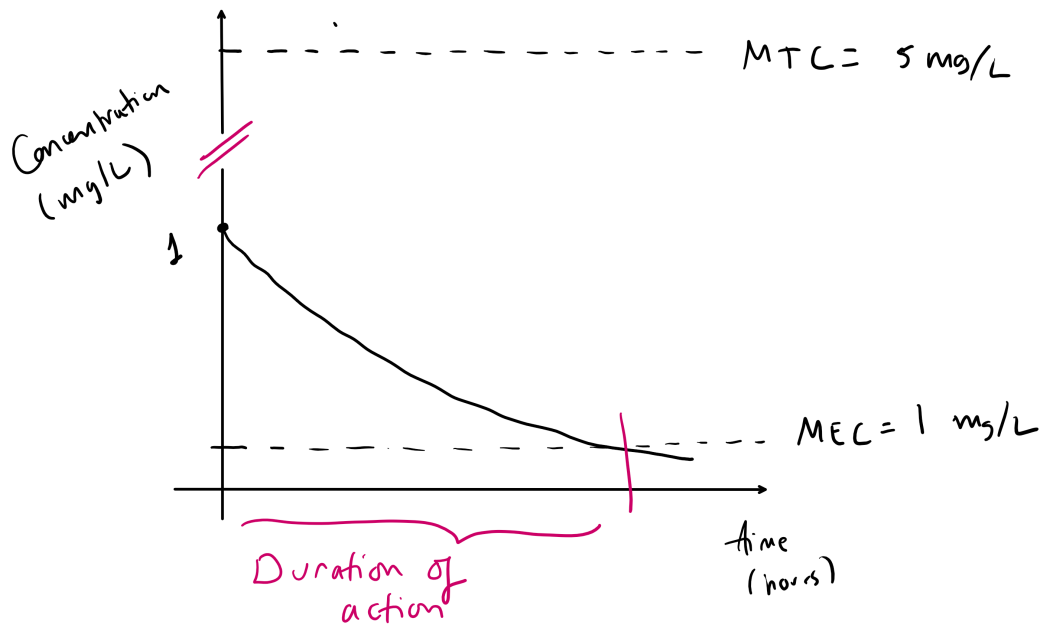\ln(0.3) &= 0.1\,t_*,
\end{aligned}
$$

Figure 5.2: Therapeutic range superimposed over the plasma concentration-time profile

hence

$$t_* = 12.04\,\text{h}.$$

From this example, it can be seen that the initial Cp of $1\,\text{mg/L}$ is unsatisfactory. Therefore, calculate a dose to provide an initial plasma concentration of $5\,\text{mg/L}$.

Solution: We have:

$$
\begin{aligned}
Cp_0 &= \frac{SD}{V}, \\
&= \frac{D}{V}, \\
&= \frac{D}{20\,\text{L}}, \\
&\stackrel{\text{target}}{=} 5\,\text{mg/L}.
\end{aligned}
$$

Hence,

$$D = (5\,\text{mg/L}) \times (20\,\text{L}),$$

hence finally,

$$D = 100\,\text{mg}.$$

5.3   Oral Administration

In oral administration, the drug has to pass through the gastro-intenstinal (GI) tract before making it to the circulation. The drug concentration in the GI tract is governed by first-order kinetics:

$$\frac{\mathrm{d}A_{GI}}{\mathrm{d}t} = -k_a A_{GI},$$

where $A_{GI}(t = 0) = S \cdot F \cdot D$, where:

- S is the salt factor;
- F is the bioavailability – not all of the drug that passes the GI membrane
- D is the dose.

Thus,

$$A_{GI}(t) = (S \cdot F \cdot D)\mathrm{e}^{-k_a t}.$$

This quantity then gets passed into the body – assuming a one-compartment model such as in Section 5.2, the amount of drug in the body at time t now satisfies:

$$\frac{\mathrm{d}A_B}{\mathrm{d}t} = \underbrace{k_a A_{GI}}_{\text{New Term}} - k A_B, \tag{5.4}$$

where the new term represents the rate at which the drug passes from the GI tract into the body (plasma). The appropriate initial condition for Equation (5.4) is now:

$$A_B(0) = 0.$$

5.3.1   Solution

We re-arrange Equation (5.4) to read:

$$\frac{\mathrm{d}A_B}{\mathrm{d}t} + k A_B = k_a (S \cdot F \cdot D)\mathrm{e}^{-k_a t}. \tag{5.5}$$

This can be solved by the integrating-factor technique: the integrating factor is e^{kt}, so we have:

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(A_B \mathrm{e}^{kt}\right) = (S \cdot F \cdot D)\mathrm{e}^{(k - k_a)t},$$

hence

$$A_B \mathrm{e}^{kt} - A_B(0) = k_a (S \cdot F \cdot D)\int_0^t \mathrm{e}^{(k - k_a)t}\mathrm{d}t.$$

Time (h)	Cp (mg/L)
0	0
0.6	2.74
0.8	3.13
1	3.37
1.4	3.55
1.8	3.5
2	3.43
2.6	3.12
3	2.89
4	2.33
7	1.17
12	0.37

Table 5.1: Plasma concentration of a drug at various times after the adminstration of a 100-mg oral dose

But $A_B(0) = 0$, so we have (assuming $k_a > k$):

$$A_B(t) = \frac{k_a}{k_a - k} \left(S \cdot F \cdot D \right) \left(e^{-kt} - e^{-k_a t} \right). \tag{5.6}$$

5.3.2   Worked Example

The plasma concentration-time data for a drug administered to a healthy volunteer are shown in Table 5.1; the dose is $D = 100\,\mathrm{mg}$. Analyze the data and determine k, k_a. Take $S = 1$.

Solution: We need to look at the **apparent volume of distribution** V_d. This is like the 'effective' plasma volume, as we have:

$$\frac{\text{Amount of Drug in Body}}{\text{Effective Volume of Plasma}} = \frac{\text{Amount of Drug in Plasma}}{\text{True Volume of Plasma}}$$

or

$$\frac{A_B}{V_d} = \frac{A_p}{V_p}$$

hence finally,

$$Cp = \frac{A_B}{V_d}.$$

Referring back to Equation (5.6), we have ($S = 1$):

$$Cp(t) = \frac{k_a}{k_a - k} \frac{D}{V_d/F} \left(e^{-kt} - e^{-k_a t} \right). \tag{5.7}$$

As such, we see that the model for Cp as a function of t contains three parameters: $\boldsymbol{x} = (k_a, k, V_d/F)$.

Using nonlinear-least squares, we introduce a penalty function as in Chapter 4 (we use $\phi = V_d/F$:

$$J(k_a, k, \phi) = \sum_{i=0}^{N} \left[\log(Cp_{model}(t_i) + \epsilon) - \log(Cp_{data}(t_i) + \epsilon) \right]^2, \qquad (5.8)$$

Code listings are given below.

```matlab
1   function [ka,k,Vd_F]=get_params()
2
3   [t_data,Cp_data]=get_data();
4   % Dose is given.
5   D=100;
6
7   % Create an anonymous function handle to the MATLAB file.
8   f = @(x)mycost(x);
9
10  % Initial guess - ka,k,Vd_F
11  x0 = [2,0.1,20];
12
13  lb=[0,0,  0];
14  ub=[10,10,200];
15
16  options = optimoptions('fmincon','Display','iter');
17  [x, fval] = fmincon(f,x0,[],[],[],[],lb,ub,[],options);
18
19  ka=x(1);
20  k=x(2);
21  Vd_F=x(3);
22
23  t=0:0.01:t_data(end);
24  Cp_model=(ka/(ka-k))*(D/Vd_F)*(exp(-k*t)-exp(-ka*t));
25  plot(t,Cp_model,t_data,Cp_data,'o')
26  drawnow
27
28  disp('*********************************************')
29  display(strcat('cost function=',num2str(fval)));
30  disp('optimum parameters=')
31  display(strcat('ka=',num2str(ka)));
32  display(strcat('k=',num2str(k)));
33  display(strcat('Vd_F=',num2str(Vd_F)));
34  disp('*********************************************')
35
36  function y=mycost(x)
37      ka_loc=x(1);
38      k_loc=x(2);
39      Vd_F_loc=x(3);
40
41      Cp_model_loc=(ka_loc/(ka_loc-k_loc))*(D/Vd_F_loc)*(exp(-k_loc*t_data)-exp(-ka_loc*t_data));
42
43      corr=0.1;
44      y=sum( (log(Cp_model_loc+corr)-log(Cp_data+corr)).^2);
45      % y=sum( Cp_model_loc-Cp_data).^2;
46  end
47
48  end
```

The results are given in Table 5.2 A plot of Cp versus t is shown in Figure 5.3, it shows the classic shape of such curves in PK. Of relevance also in PK is the area under the curve (AUC):

$$AUC = \int_0^\infty Cp(t)\mathrm{d}t,$$

Parameter	Value
k_a	$1.50\,\text{hours}^{-1}$
k	$0.23\,\text{hours}^{-1}$
V_d/F	$20.0\,\text{L}$

Table 5.2: Estimated values of k_a, k, and V_d/F for the one-compartment model (oral administration)

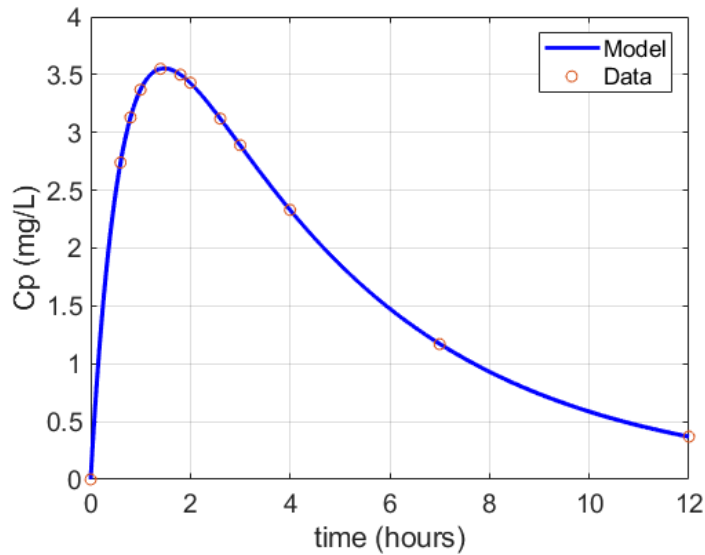
Figure 5.3: Concentration versus time curve

hence

$$AUC = \frac{k_a}{k_a - k}\frac{D}{V_d/F}\left(\frac{1}{k} - \frac{1}{k_a}\right)$$

hence:

$$AUC = 21.6\,\text{mg} \cdot \text{h/L}.$$

As in the case of IV administration, we recognize the clearance as $k \times$ Volume, in this context it is

$$\text{Cl} = kV_d,$$

hence

$$\frac{\text{Cl}}{F} = k(V_d/F),$$

hence

$$\text{Cl}/F = 4.62\,\text{L/h}.$$

5.4 Two-Compartment Model

In a two-compartment model, it is assumed that the body is made up of two compartments:
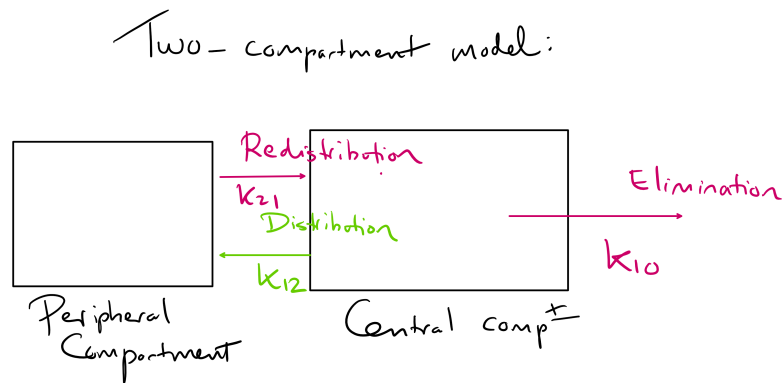
Figure 5.4: Mass balances for the two-compartment model (IV administration)

- The Central Compartment, consisting of the plasma and those tissues that take up the drug rapidly;
- The Peripheral Compartment, consisting of those tissues that take up the drug more slowly.

There are a couple more facts needed to formulate the model:

- The drug concentration measured *in vivo* is that of the central compartment.
- Elimination occurs through the well-perfused tissues, these are a part of the central compartment.

5.4.1 Intravenous Administration

The setup for intravenous (IV) administration is shown in Figure 5.4 The reaction equations are:

$$\frac{\mathrm{d}A_1}{\mathrm{d}t} = -k_{10}A_1 - k_{12}A_1 + k_{21}A_2, \tag{5.9a}$$

$$\frac{\mathrm{d}A_2}{\mathrm{d}t} = k_{12}A_1 - k_{21}A_2, \tag{5.9b}$$

$$\tag{5.9c}$$

with initial conditions

$$A_1(0) = SD, \qquad A_2(0) = 0.$$

5.4.2 Oral Administration

The setup for oral administration is shown in Figure 5.5 The reaction equations are:

$$\frac{\mathrm{d}A_1}{\mathrm{d}t} = \underbrace{k_a A_{GI}}_{} - k_{10}A_1 - k_{12}A_1 + k_{21}A_2, \tag{5.10a}$$

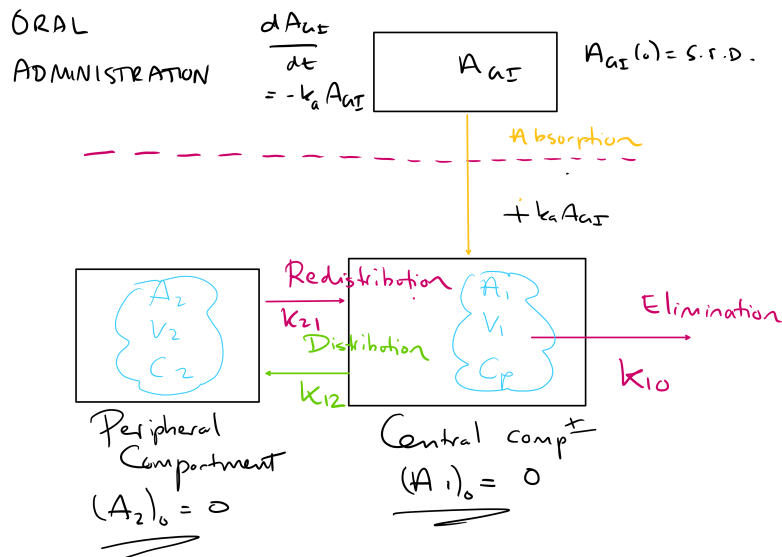$$\frac{\mathrm{d}A_2}{\mathrm{d}t} = k_{12}A_1 - k_{21}A_2. \tag{5.10b}$$

Figure 5.5: Mass balances for the two-compartment model (oral administration)

As before, $A_{GI}(t)$ satisfies $A_{GI}(t) = (S \cdot F \cdot D)\mathrm{e}^{-k_a t}$, and the initial conditions for Equation (5.10) are:

$$A_1(0) = 0, \qquad A_2(0) = 0.$$

5.5 Metabolism Model

Compartmental models can also be used to study the PK of a drug's metabolite. Metabolites are formed primarily by a first-order process inth eliver. Since th eliver is usually part of the central compartment, the ceontral compartment o fth emetabolite is usually attached to the central compartment of the parent drug. As such, a relevant, simple model for metabolism has the following basic features:

- One central compartment, volume V_1, drug amount A_{parent} and plasma concentration $Cp = A_{parent}/V_d$;
- One metabolite compartment, volume V_m, drug amount $A_{metabolite}$, and plasma concentration $Cm = A_{metabolite}/V_m$.

We assume IV administration. Furthermore,

- The parent drug decays at rate k according to first-order kinetics, a fraction $(1 - f)$ of the drug is excreted and a fraction f is converted to metabolite;
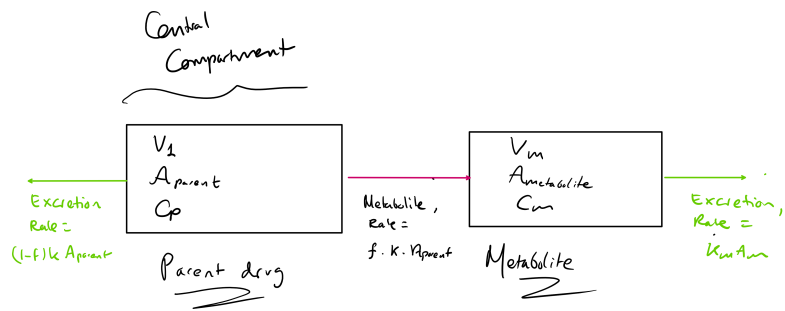- The metabolite is excreted at a rate k_m.

Figure 5.6: Mass balances for the metabolite model (IV administration)

The idea is shown in Figure 5.6, and the corresponding equations are:

$$\frac{\mathrm{d}A_{parent}}{\mathrm{d}t} = -kA_{parent}, \tag{5.11a}$$

$$\frac{\mathrm{d}A_{metabolite}}{\mathrm{d}t} = fkA_{parent} - k_m A_{metabolite}. \tag{5.11b}$$

The initial conditions are:

$$A_{parent}(0) = S \cdot D, \qquad A_{metabolite} = 0.$$

Chapter 6

Pharmacokinetics: Repeated Doses

Overview

In this Chapter we look at PK in the case where multiple doses are administered to a patient. We look at the simplest possible case where the doses are administered intravenously, and where only one compartment is required to describe the drug concentration in the body.

6.1   The model

We assume a single-compartment model with first-order kinetics, the amount of drug in the body as a function of time is therefore given by the following ODE:

$$\frac{\mathrm{d}A_B}{\mathrm{d}t} = -kA_B,$$

where k is the elimination constant. We introduce $C_p = A_B/V_d$, where V_d is the distribution volume, thus the equation we study in this Chapter is:

$$\frac{\mathrm{d}}{\mathrm{d}t}Cp = -kCp.$$

The **first dose** is adminstered at time $t = 0$. Successive doses are adminstered at $t = \tau$, $t = 2\tau$, and so on. Thus, at a later time t after the first dose, but before the second dose, the concentration is:

$$Cp(t) = Cp(0)\mathrm{e}^{-kt}.$$

The initial dose is D, thus,

$$Cp(0) = \frac{S \cdot F \cdot D}{V_d},$$

hence:

$$Cp(t) = \frac{S \cdot F \cdot D}{V_d} e^{-kt}.$$

6.1.1 Successive Doses

Just before the second dose, the concentration is:

$$Cp(\tau - 0) = \frac{S \cdot F \cdot D}{V_d} e^{-k\tau}.$$

Just after the second dose, the concentration is:

$$Cp(\tau - 0) = \frac{S \cdot F \cdot D}{V_d} e^{-k\tau} + \frac{S \cdot F \cdot D}{V_d}.$$

Similarly, just before the third dose, the concentration is

$$Cp(2\tau - 0) = \frac{S \cdot F \cdot D}{V_d} e^{-kt} \left(1 + e^{-kt} \right).$$

Guess the pattern:

$$
\begin{aligned}
Cp(n\tau - 0) &= \frac{S \cdot F \cdot D}{V_d} e^{-kt} \left(\sum_{j=0}^{n-1} e^{-jk\tau} \right), \\
&= \frac{S \cdot F \cdot D}{V_d} e^{-kt} \left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right).
\end{aligned}
$$

Just at $t = n\tau + 0$, a dose is administered, hence:

$$
\begin{aligned}
Cp(n\tau + 0) &= Cp(n\tau - 0) + \frac{S \cdot F \cdot D}{V_d}, \\
&= \frac{S \cdot F \cdot D}{V_d} e^{-kt} \left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right), \\
&= \frac{S \cdot F \cdot D}{V_d} \left(\frac{1 - e^{-(n+1)k\tau}}{1 - e^{-k\tau}} \right).
\end{aligned}
$$

Refer next to Figure 6.1. The concentration just after the Nth dose (with $N = 1, 2, \cdots$) is:

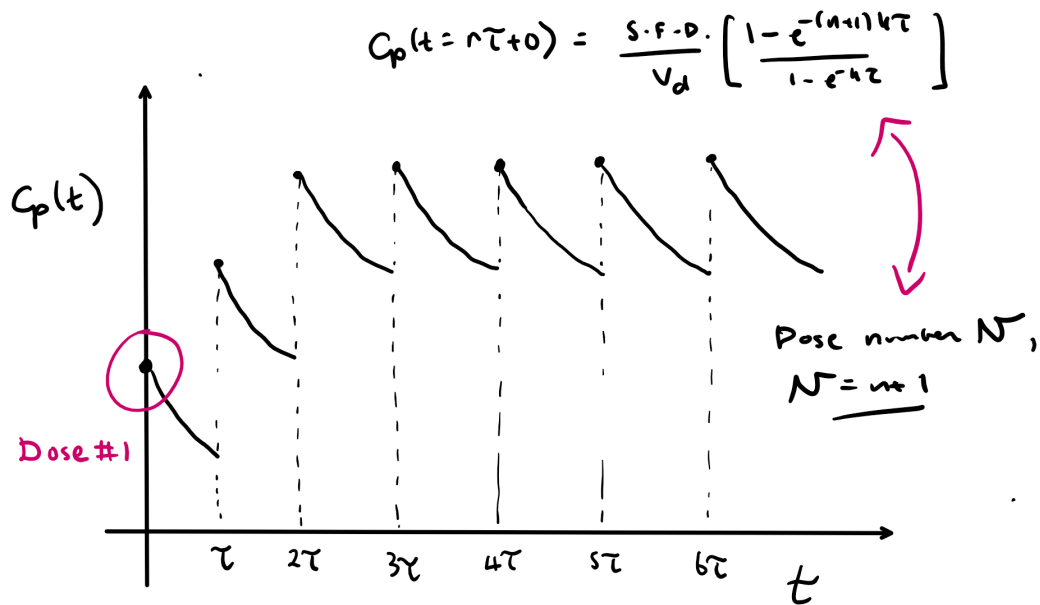$$(Cp)_N^{\max} = \frac{S \cdot F \cdot D}{V_d} \left(\frac{1 - e^{-Nk\tau}}{1 - e^{-k\tau}} \right)$$

$$Cp(t = n\tau + 0) = \frac{S \cdot F \cdot D}{V_d}\left[\frac{1 - e^{-(n+1)k\tau}}{1 - e^{k\tau}}\right]$$

$Cp(t)$

Dose #1

Dose number N, $N = n + 1$

$\tau \quad 2\tau \quad 3\tau \quad 4\tau \quad 5\tau \quad 6\tau$

t

Figure 6.1:

The concentration just before the $(N + 1)^{\text{th}}$ dose is $(Cp)^{\min}$, and we have:

$$
\begin{aligned}
(Cp)_N^{\min} &= (Cp)^{\max}e^{-k\tau}, \\
&= \frac{S \cdot F \cdot D}{V_d}\left(\frac{1 - e^{-(n+1)k\tau}}{1 - e^{-k\tau}}\right)e^{-k\tau}.
\end{aligned}
$$

The Nth dosing interval is the time between the Nth dose and the $(N + 1)^{\text{th}}$ dose.

6.1.2   Worked Example

Multiple intravenous bolus injections ($250\,\text{mg}$) of a drug are adminstered every $8\,\text{h}$. The drug has the following properties: $S = 1$, $Vd = 30\,\text{L}$, $k = 0.1\,\text{h}^{-1}$, and $\tau = 8\,\text{h}$. Calculate:

1. The plasma concentration $3\,\text{h}$ after the second dose.
2. The peak and trough plasma concentrations during this second dosing interval.

After two hours exactly, just after the second dose, the drug concentration is $(Cp)_2^{\max}$, where:

$$(Cp)_2^{\max} = \frac{S \cdot F \cdot D}{V_d}\left(\frac{1 - e^{-2k\tau}}{1 - e^{-k\tau}}\right).$$

Three hours later ($t = 3\,\text{h}$), the concentration is:

$$Cp = \frac{S \cdot F \cdot D}{V_d}\left(\frac{1 - e^{-2k\tau}}{1 - e^{-k\tau}}\right)e^{-kt}.$$

Fill in the numbers ($F = 1$ for intravenous administration):

$$Cp = \frac{250}{30}\left(\frac{1 - e^{-2\times0.1\times2}}{1 - e^{-0.1\times8}}\right)e^{-0.1\times3},$$
$$= 8.96\,\text{mg/L}.$$

For the second part we have:

$$(Cp)_2^{\max} = \frac{S \cdot F \cdot D}{V_d}\left(\frac{1 - e^{-2k\tau}}{1 - e^{-k\tau}}\right),$$
$$= \frac{250}{30}\left(\frac{1 - e^{-2\times0.1\times2}}{1 - e^{-0.1\times8}}\right),$$
$$= 12.1\,\text{mg/L}.$$

Finally,

$$(Cp)_2^{\min} = (Cp)_2^{\max}e^{-k\tau},$$
$$= 12.1\,e^{-0.1\times8},$$
$$= 5.4\,\text{mg/L}.$$

6.2 Steady State

We take $N \to \infty$. We have:
$$(Cp)_N^{\max} \to \frac{S \cdot F \cdot D}{V_d(1 - e^{-k\tau})};$$
this is the maximum concentration in the **steady state**. We therefore introduce the notation:

$$(Cp)_{\text{ss}}^{\max} = \frac{S \cdot F \cdot D}{V_d(1 - e^{-k\tau})}.$$

Similarly,
$$(Cp)_N^{\min} \to \frac{S \cdot F \cdot D}{V_d(1 - e^{-k\tau})}e^{-k\tau} = (Cp)_{\text{ss}}^{\min}.$$

Often, the maximum $(Cp)_{\text{ss}}^{\max}$ will be taken to be the maximum therapeutic concentration, and $(Cp)_{\text{ss}}^{\min}$ will be taken to be the minimum effective concentration. In any case, we have:

$$\frac{(Cp)_{\text{ss}}^{\max}}{(Cp)_{\text{ss}}^{\min}} = e^{k\tau},$$

Hence, the dosing schedule τ and the maximum and minimum steady-state concentrations are related via:
$$\tau = \frac{1}{k}\ln\left(\frac{(Cp)_{\text{ss}}^{\max}}{(Cp)_{\text{ss}}^{\min}}\right).$$

Of interest also is the average concentration in the steady state:

$$
\begin{aligned}
(Cp)_{\text{ss}}^{\text{av}} &= \frac{1}{\tau} \int_0^t Cp(t)\mathrm{d}t, \\
&= \left[\frac{1}{\tau} \int_0^\tau \mathrm{e}^{-kt}\mathrm{d}t \right] \frac{S \cdot F \cdot D}{V_d(1 - \mathrm{e}^{-k\tau})}, \\
&= \frac{1}{k\tau} \frac{S \cdot F \cdot D}{V_d}, \\
&= \frac{S \cdot F \cdot (D/\tau)}{kV_d}, \\
&= \frac{S \cdot F \cdot R_a}{Cl}.
\end{aligned}
$$

Here, $R_a = D/\tau$ is the rate of drug administration. We also define the **accumulation** factor, r:

$$
\begin{aligned}
r &= \frac{Cp_{\text{ss}}}{Cp_1}, \\
&\overset{\text{Peaks}}{=} \frac{(S \cdot F \cdot D/V_d)(1 - \mathrm{e}^{-k\tau})^{-1}}{S \cdot F \cdot D/V_d}, \\
&= \frac{1}{1 - \mathrm{e}^{-k\tau}}.
\end{aligned}
$$

6.2.1   Loading Dose

Call D the **maintenance dose**. The initial dose can be increased so that all of the drug accumulation happens during the first dosing interval. This is the **loading dose**. Referring to Figure 6.2, the
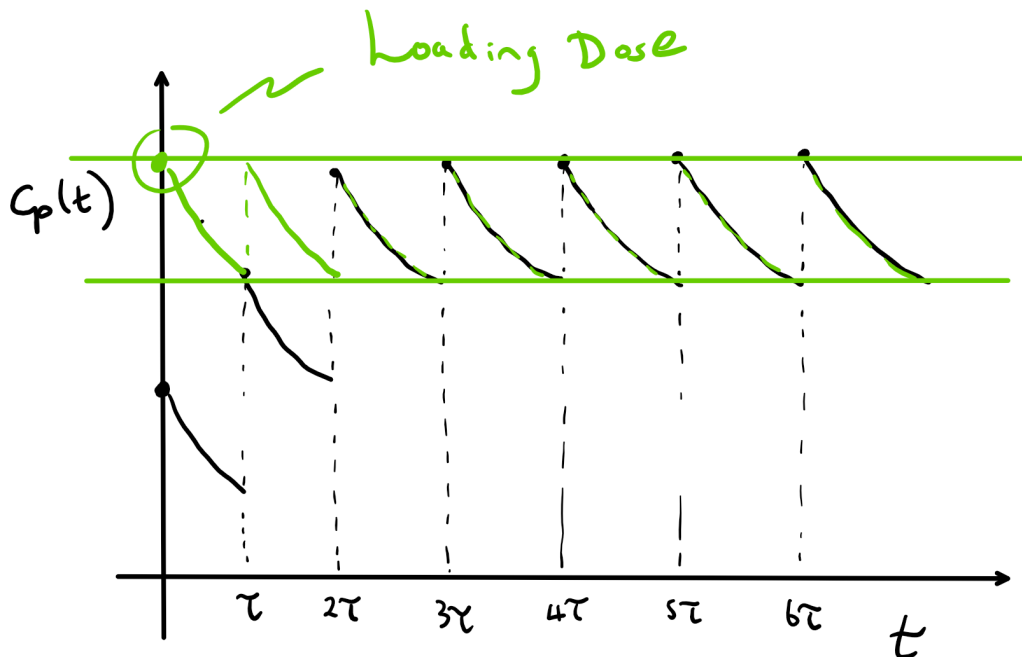

Figure 6.2:

loading dose D_L satisfies:

$$\frac{S \cdot F \cdot D_L}{V_d} \mathrm{e}^{-k\tau} = (Cp)_{\mathrm{ss}}^{\min} = \frac{S \cdot F \cdot M}{V_d} \frac{\mathrm{e}^{-k\tau}}{1 - \mathrm{e}^{-k\tau}}.$$

Effecting cancellations, the loading dose is:

$$D_L = D_M \cdot r.$$

Chapter 7

The Rest of the Module

For the rest of this module, interested students will be working with the lecturer on the main project, based on the materials in these lecture notes. Indeed, the project will be broken up into several tasks; the format will be as follows:

- Follow the recorded lectures based on these notes, attend weekly office hours in Weeks 5-7.
- Over the same time period, complete (in a group) Tasks 1 and 2 to test your knowledge of what you have learned.
- Again over the same time period, you will be assigned your most challenging task, Task 3. You should begin to do background reading to understand what is required here.
- In Week 8, you should present your work to date, the presentation should consist of:

    - The theoretical concepts you have learned in Tasks 1–2;
    - How you will apply these in Task 3.

- The final report (due towards the end of the trimester) will be based entirely on Task 3.